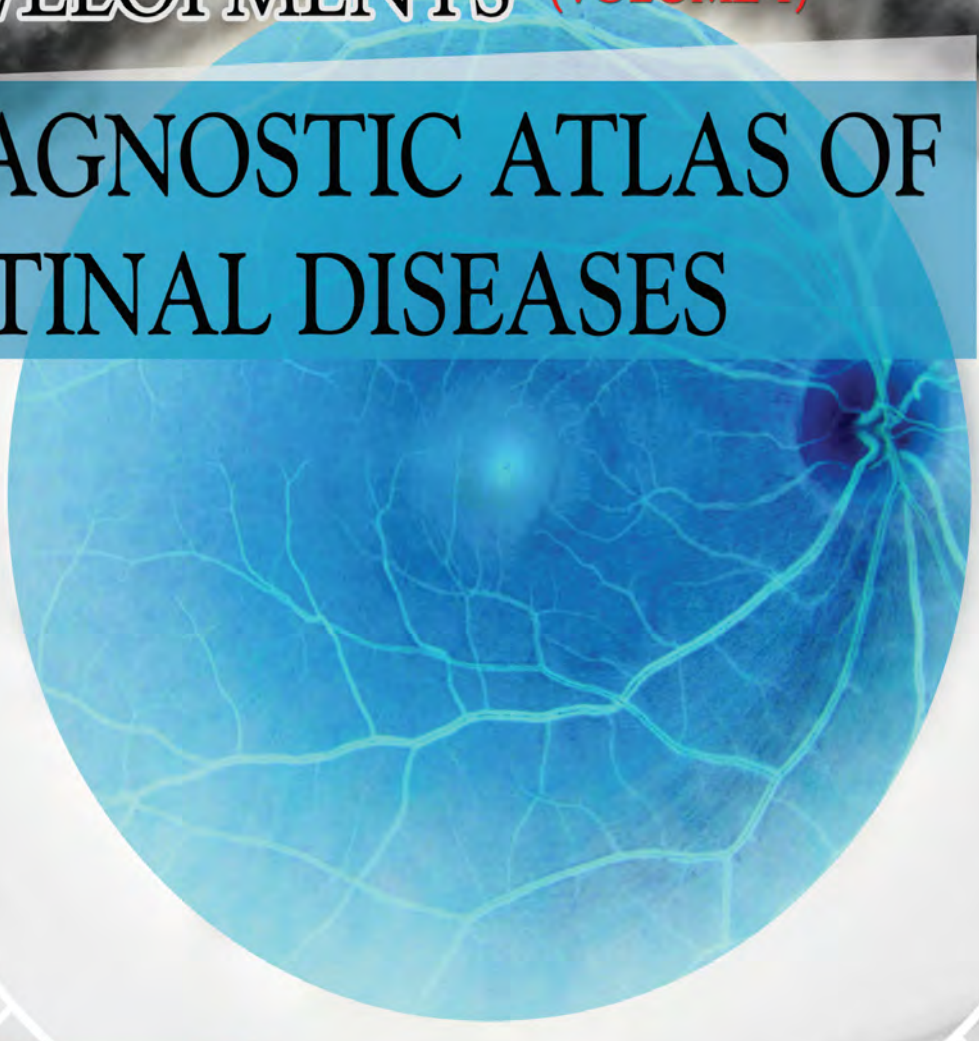
eISBN: 978-1-68108-357-5
ISBN: 978-1-68108-358-2

eISSN: 2468-7170
ISSN: 2468-7162

OPHTHALMOLOGY
CURRENT AND FUTURE DEVELOPMENTS (VOLUME 1)

DIAGNOSTIC ATLAS OF RETINAL DISEASES



Editors:
Mitzy E. Torres Soriano
Gerardo García Aguirre
Maximiliano Gordon
Veronica Kon Graversen

Bentham Books

Ophthalmology: Current and Future Developments

Diagnostic Atlas of Retinal Diseases

(Volume 1)

Editors

Mitzy E. Torres Soriano
Unidad Oftalmológica "Dr. Torres López". Centro Médico Cagua, Aragua, Venezuela

Gerardo García Aguirre
Retina Department, Asociación para Evitar la Ceguera en Mexico, Mexico City, Mexico

Co-Editors

Maximiliano Gordon
Centro de la Visión Gordon Manavella, Rosario, Santa Fe, Argentina

Veronica Kon Graversen
University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Ophthalmology: Current and Future Developments

Volume # 1

Diagnostic Atlas of Retinal Diseases

Editors: Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen

ISSN (Print): 2468-7162

eISSN (Online): 2468-7170

eISBN (Online): 978-1-68108-357-5

ISBN (Print): 978-1-68108-358-2

Published by Bentham Science Publishers – Sharjah, UAE.

© 2011 by the Editor / Authors. Chapters in this eBook are Open Access and distributed under the Creative Commons Attribution (CC BY 4.0) license, which allows users to download, copy and build upon published chapters, as long as the author and publisher are properly credited, which ensures maximum dissemination and a wider impact of our publications.
The book taken as a whole is © 2011 Bentham Science Publishers under the terms and conditions of the Creative Commons license CC BY-NC-ND.

CONTENTS

FOREWORD

Drs. Torres, García, Gordon and Kon deliver a very useful and practical work that contains, in this volume, a collection of images of retinal vascular diseases and macular diseases. The editors have recruited a vast array of retina specialists from four continents to write the different chapters that constitute this volume. The chapters are structured in such a way that the reader may easily find pearls about the diagnosis, differential and treatment, accompanied by beautiful pictures using different imaging modalities. Our subspecialty has had tremendous advances in recent years regarding diagnostic imaging, and I'm sure ophthalmologists and residents will find this compilation really useful and enjoyable.

Dr. Hugo Quiroz-Mercado
Retina Department
Asociación para evitar la Ceguera en Mexico
Mexico City
Mexico
E-mail: hugoquiroz@yahoo.com

PREFACE

We are honored to contribute to the information and education of ophthalmology students around the world. We have attempted to distill the current knowledge of medical practice and basic science retina research into a diagnostic atlas of retinal diseases. This is a quick-reference atlas eBook of the retina, edited by specialists in the field, essential to any practicing ophthalmologist or resident who has more than a passing interest in diseases and treatment of the retina.

This e-book includes contributors from Mexico, Venezuela, Argentina, Brazil, United States, Denmark, Spain, Italy, Costa Rica and Peru. It is divided into three volumes: Volume I, retinal vascular diseases, choroidal neovascularization related diseases, vitreomacular interface, and other macular disorders; Volume II, traumatic retinopathies, diseases of vitreous, peripheral degenerations, retinal detachment, pediatric retinal diseases, and retinal dystrophies; and Volume III, posterior uveitis, tumors of the retina, and choroid.

This diagnostic atlas eBook of retinal diseases contains full-color, high quality images of the most frequent retinal pathologies with a brief and comprehensive review of retinal diseases. Each chapter includes essentials of diagnosis, differential diagnosis and treatment. The format is concise, well organized, and didactic, without being exhaustive.

We hope and expect that our atlas of retina will facilitate in providing patients with the best possible care.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Judy Soriano, who provided support with english composition and edition.

To our friends and colleagues without whose contribution would not have been possible to realize this project.

We also want to thank the staff of Bentham Science for their help and support and give us the opportunity to publish this eBook.

DEDICATION

This e-book is specially dedicated to Guillermo Manuel Gordon, MD. He inspired us to always work hard and try our best. He was a friend and a recognized ophthalmologist of Rosario-Argentina, who died on May 2nd, 2015.

Dr. Mitzy E. Torres Soriano
Unidad Oftalmológica “Dr. Torres López”,
Centro Médico Cagua,
Aragua,
Venezuela

Dr. Gerardo García Aguirre
Retina Department,
Asociación para Evitar la Ceguera en Mexico,
Mexico City,
Mexico

Dr. Maximiliano Gordon
Centro de la Visión Gordon Manavella,
Rosario, Santa Fe,
Argentina

Dr. Veronica Kon Graversen
University of North Carolina at Chapel Hill,
Chapel Hill, NC,
USA

List of Contributors

Andrés Bastien	Universidad de Buenos Aires-Universidad del Salvador, Retina and Vitreous, Argentina
Aristides J. Mendoza	Retina Department, Centro Oftalmológico de Valencia (CEOVAL), Valencia, Venezuela Retina Department, OftalmoSalud, Arequipa, Peru
Ana Domínguez Yates	Retina Consultants of Charleston, Charleston, South Carolina, USA
Aziz A. Khanifar	Retina Group of Washington, Washington DC, USA
Daniela Roca	Ophthalmology Department, Clínica Ricardo Palma, Lima, Peru
Diego Fernando Mojica	Centro Oftalmológico de Valencia (CEOVAL), Valencia, Venezuela
Daniel D. Kim	Department of Ophthalmology, Henry Ford Health Systems, Detroit, MI, USA
Eleonora Lavaque	Retina Deparmeant, Hospital Oftalmológico Santa Lucia, Buenos Aires, Argentina
Federico Furno Sola	Ophthalmology Service, Sanatorio Mapaci, Rosario, Argentina Grupo Laser Visión, Rosario, Santa Fe, Argentina
Gerardo García Aguirre	Retina Department, Asociación para Evitar la Ceguera en Mexico, Mexico City, Mexico
Guillermo Gordon	Died
Hugo Luglio	Macula D&T, Lima, Peru
Jans Fromow Guerra	Retina Department, Asociación para Evitar la Ceguera en México, IAP, México City, México
Jose A. Roca	Ophthalmology Department, Clínica Ricardo Palma, Lima, Peru
Luis Felipe Rivero	Centro Clínico, de Ojos Maracay, Maracay, Venezuela Centro Oftalmológico Regional Aragua "Filippo Sindoni", Maracay, Venezuela
Luis A. Acabá	Sidney Kimmel College of Medicine, Philadelphia, PA, USA
Liriany Arrieta Ruiz	Unidad Popular de Ojos (UPO), Maracay, Venezuela
Luke B. Lindsell	Retina Group of Washington, Washington DC, USA
Luz Elena Concha del Río	Uveitis Department, Asociación para Evitar la Ceguera en México. I.A.P, Mexico
Luis M. Suarez-Tata	Retina & Vitreous Service, Clínica Oftalmológica El Viñedo, Valencia, Venezuela

Maximiliano Gordon	Centro de la Visión Gordon-Manavella, Rosario, Santa Fe, Argentina
Maria H. Berrocal	Berrocal & Asociados, San Juan, Puerto Rico
Mitzy E. Torres Soriano	Centro de la Visión Gordon-Manavella, Rosario, Santa Fe, Argentina Unidad Oftalmológica "Dr Torres López", Centro Médico Cagua, Aragua, Venezuela
Michael D. Ober	Department of Ophthalmology, Henry Ford Health System, Detroit, MI, USA Retina Consultants of Michigan, Southfield, MI, USA
Michael Larsen	Department of Ophthalmology, Glostrup Hospital and Faculty of Health Sciences, University of Copenhagen, Denmark
Mette K.G. Andersen	Department of Ophthalmology, Glostrup Hospital and Faculty of Health Sciences, University of Copenhagen, Denmark
Manuel Garza León	Department of Medical Sciences, Division of Health Sciences, Universidad de Monterrey, Monterrey, Nuevo León, México
Miguel Pedroza Seres	Uveitis and Ocular Inmunology Department, Instituto de Oftalmología Conde de Valenciana, México, DF. Clínica de Retina, Guadalajara, Jalisco, Mexico
Moravia B. Suarez-Tata	Retina & Vitreous Service, Clínica Oftalmológica El Viñedo, Valencia, Venezuela
Naresh Mandava	Department of Ophthalmology, University of Colorado School of Medicine, Aurora, CO, USA
Nelson Segovia Rodríguez	Retina Department, Grupo de Clínicas IDB, Centro Profesional Arca, Barquisimeto, Venezuela
Paul Baciu	Department of Ophthalmology, Henry Ford Health Systems, Detroit, MI, USA
Raul Velez-Montoya	Retina Department, Asociación para Evitar la Ceguera en México, IAP, Mexico City, Mexico
Rafael Muci Mendoza	Universidad Central de Venezuela, Unidad de Neurooftalmología, Hospital Vargas de Caracas, Venezuela
Rodrigo Lechuga Perezanta	Asociación para Evitar la Ceguera en Mexico, Mexico City, Mexico
Richard Hwang	Vitreoreitnal Disease and Surgery, Department of Ophthalmology, University of Colorado School of Medicine, Aurora, CO, USA
Reinaldo García	Retina & Vitreous Service, Clínica Oftalmológica El Viñedo, Valencia, Venezuela
Silvia Mendoza	Retina Department, Centro Oftalmológico de Valencia (CEOVAL), Valencia, Venezuela

Sandra Zambrano	Centro Oftalmológico de Valencia (CEOVAL), Valencia, Venezuela
Virgilio Morales Cantón	Retina Department, Asociación para Evitar la Ceguera en Mexico, Mexico City, Mexico
Veronica Kon Graversen	University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Virgil Alfaro	Retina Consultants of Charleston, Charleston, South Carolina, USA
Yogin Patel	Department of Ophthalmology, Henry Ford Health System, Detroit, MI, USA

CHAPTER 1

Non-Proliferative Diabetic Retinopathy

Luis Felipe Rivero[1,2,*] and **Maximiliano Gordon**[3]

[1] *Centro Clínico de Ojos Maracay, Maracay, Venezuela*

[2] *Centro Oftalmológico Regional Aragua "Filippo Sindoni", Maracay, Venezuela*

[3] *Centro de la Visión Gordon-Manavella, Rosario, Santa Fe, Argentina*

Diabetic retinopathy (DR) is the most frequent ocular complication in patients with diabetes mellitus. Its early and moderate stages are called non-proliferative diabetic retinopathy (NPDR). It is characterized clinically by the presence of one or more of the following signs: microaneurysms, intraretinal hemorrhages, intraretinal microvascular anomalies (IRMA), cotton-wool spots (CWS), hard exudates, and venous beading.

ESSENTIALS OF DIAGNOSIS

The hallmark of DR is the development of microaneurysms, which are small dilations of the capillaries due to weakening of their walls and the loss of pericytes [1]. They appear clinically as tiny red dots in the retinal stroma, predominantly in and around the posterior pole. Eventually they may break, leading to the formation of intraretinal hemorrhages. When the broken microaneurysms are located in the most superficial layers of the retina, the hemorrhage will take a flame or splinter-like appearance, oriented along the nerve fiber layer. When they are located in the deeper layers, the hemorrhage will look like a red dot or blot. Clinically, microaneurysms and dot hemorrhages are indistinguishable (Fig. **1**), so they are referred to as hemorrhages and/or microaneurysms (H/Ma). Unless clotted, microaneurysms will show as hyperfluorescent points in a fluorescein angiogram (FA). They may or may not

* **Corresponding author Luis Felipe Rivero:** Centro Clínico de Ojos Maracay, Av. José María Vargas N° 18, Maracay 2101, Edo. Aragua, Venezuela; Tel: +58(243) 241-8324/5243; E-mail: luife2020@hotmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

leak dye depending on the integrity of their walls (Fig. **2**). In an optic coherence tomography (OCT), they appear as hyperreflective rings usually located in the middle retinal layers [2] (Fig. **3**). The smaller intraretinal hemorrhages will hardly show in the FA, while the larger ones block the dye (Fig. **4**). The largest intraretinal hemorrhages may be seen in an OCT as moderately hyperreflective masses located in the inner retinal layers.

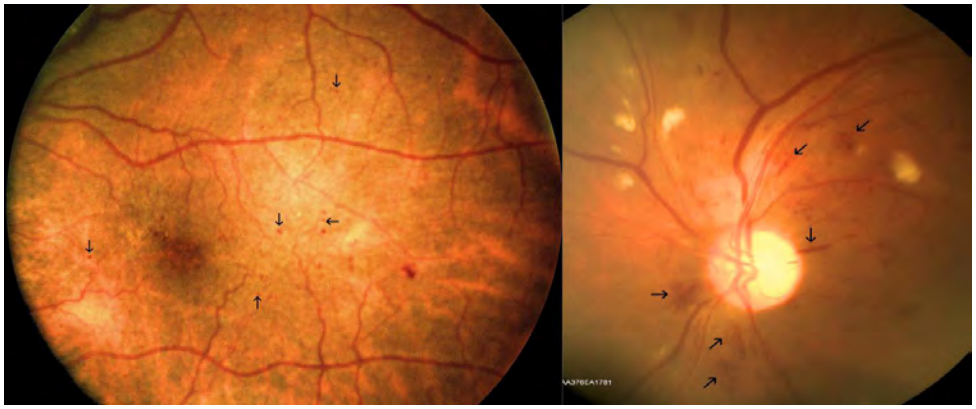


Fig. (1). Intraretinal hemorrhages and microaneurysms. **Left**: Both deep intraretinal hemorrhages and microaneurysms (H/Ma) appear as small red points and dots. Some of them are pointed with arrows. **Right**: Superficial intraretinal hemorrhages have a splinter or flame shape (some of them are pointed with arrows). Note that superficial hemorrhages as well as CWS follow the striations of the nerve fiber layer.

Capillary wall damage will lead to leakage of fluids and macromolecules. These will accumulate in the retinal stroma producing macular edema, which can be observed as areas of thickening of the retina. Lipoproteins diffusing from microaneurysms or weakened capillaries will be trapped at the outer plexiform layer forming the so-called hard exudates. They are irregularly shaped yellow-white spots located slightly deeper in the retina and may coalesce with each other, forming streaks, clusters or a circinate pattern centered on the leaking structure (Fig. **5**). They may accumulate in the center of the fovea forming a dense plaque, which carries a very bad visual prognosis [3]. They are not usually seen on a FA, except when they are extremely dense, causing minimum blockage of the dye. On the OCT they appear as markedly hyperreflective and irregular interstitial images with posterior shadowing (Fig. **6**).

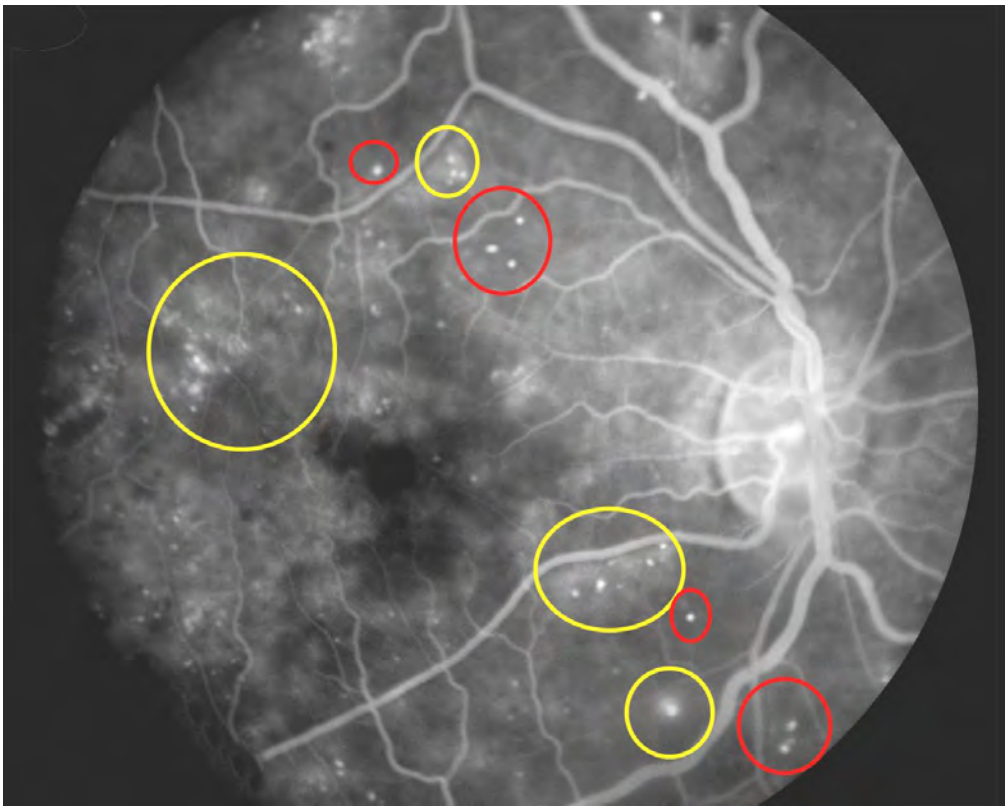


Fig. (2). Fluorescein angiogram showing microaneurysms. They can be observed as well-defined hyperfluorescent (white) dots, appearing in the early phases of the study. Non-leaking microaneurysms will remain as well-defined dots throughout the angiogram (some are circled in red). Leaking microaneurysms develop a hazy area around them that increases along the study (some are circled in yellow).

As diabetic retinopathy progresses, there will be further damage to the arterioles and capillaries, leading to progressive ischemia. Focal ischemia in the inner layers will result in the arrest of the axoplasmic flow with the subsequent dilation of the axons, constituting the so-called CWS [4]. Clinically they present as small superficial grey-white fluffy spots with feathery borders (Fig. **7**). They are usually located near the temporal arcades and near the disc in the nasal retina. They look hypofluorescent in the FA (Fig. **4**). In an OCT they appear as more or less pronounced focal thickenings of the nerve fiber layer with enhanced hyperreflectivity (Fig. **8**). Over some 6 to 12 months CWS will eventually fade, leaving almost no signs of their former presence but relative scotomata [5] and nicks in the inner retinal layers [6].

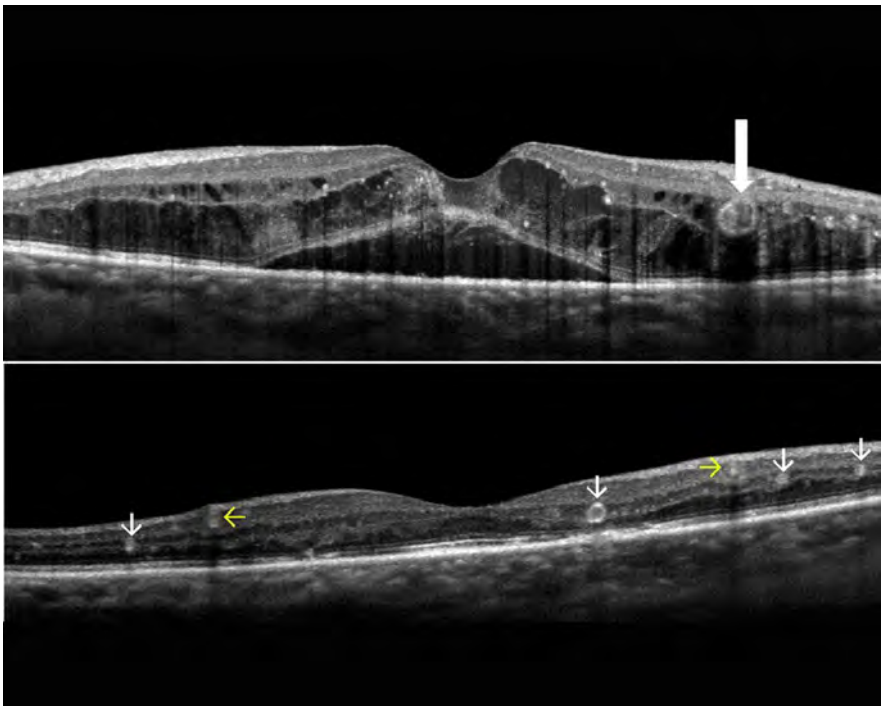


Fig. (3). OCT showing microaneurysms. Top: a large microaneurysm (white arrow) in the setting of a severe (center involving) macular edema. Bottom: note that normal vessels (yellow arrows) look very similar to microaneurysms (white arrows). However, normal vessels are usually found in the inner retinal layers (nerve fiber layer or ganglion cell layer), while microaneurysms are usually located in the middle retinal layers. In this case, they are all seen in the inner nuclear layer. The only way to positively differentiate one from the other is to see where the B scan passes in comparison with the fundus image.

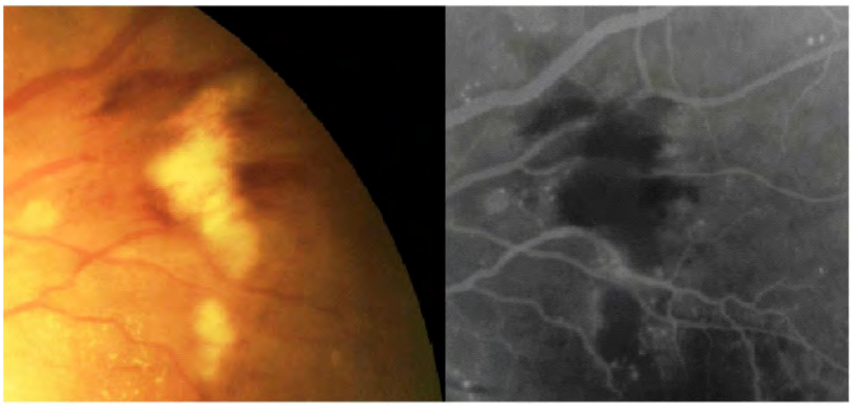


Fig. (4). Fluorescein angiogram of both CWS and flame hemorrhages. Note that both produce blockage of the dye, although the hemorrhage does so more intensely.

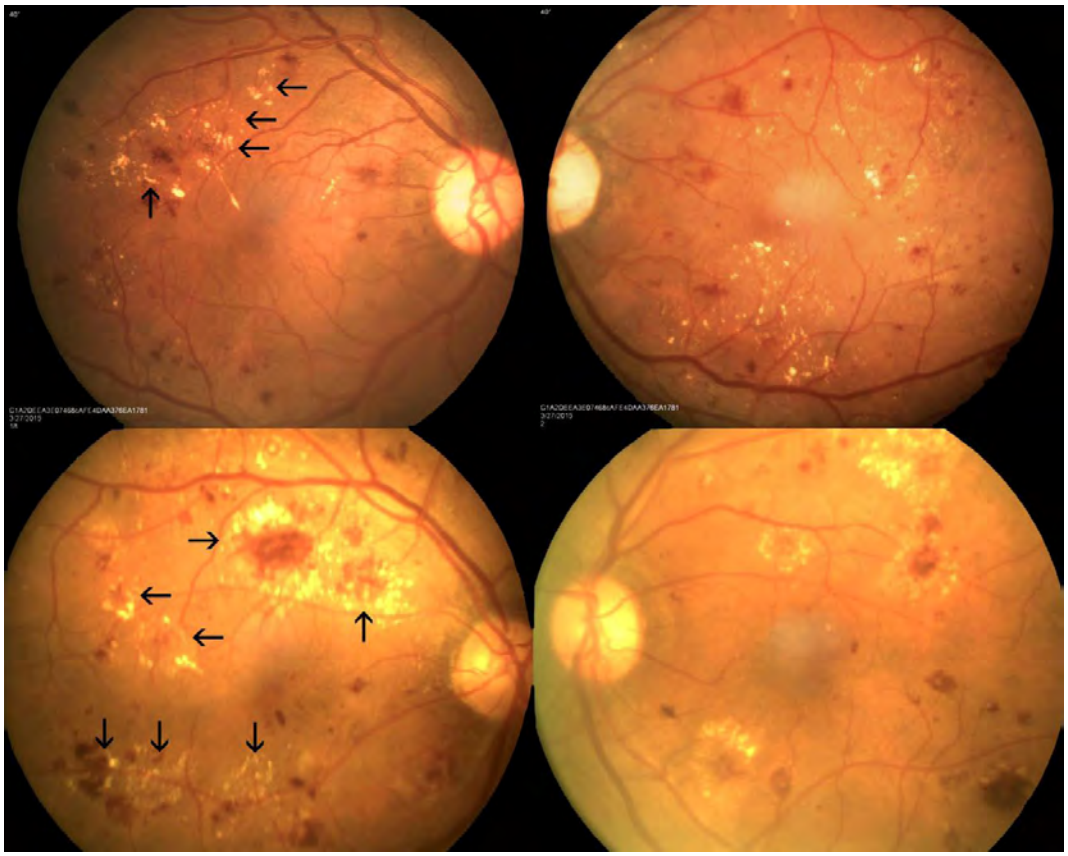


Fig. (5). Hard exudates. Note that they usually form circinate patterns surrounding a group of micro-aneurysms and that they tend to coalesce.

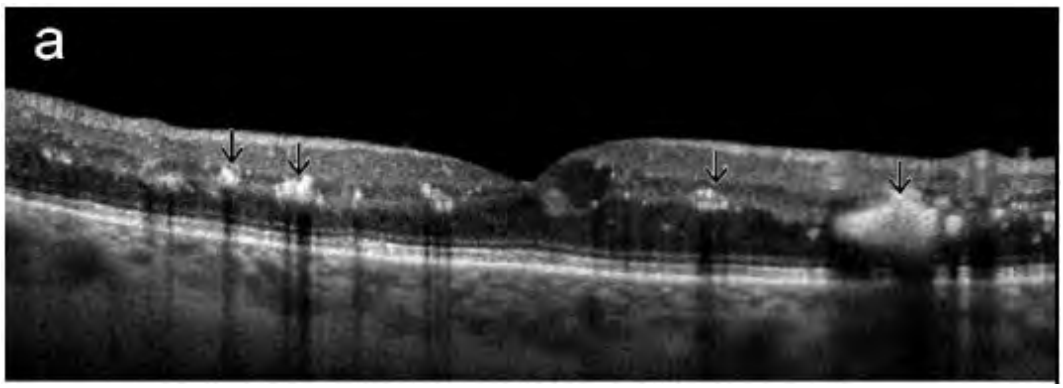


Fig. 6 contd.....

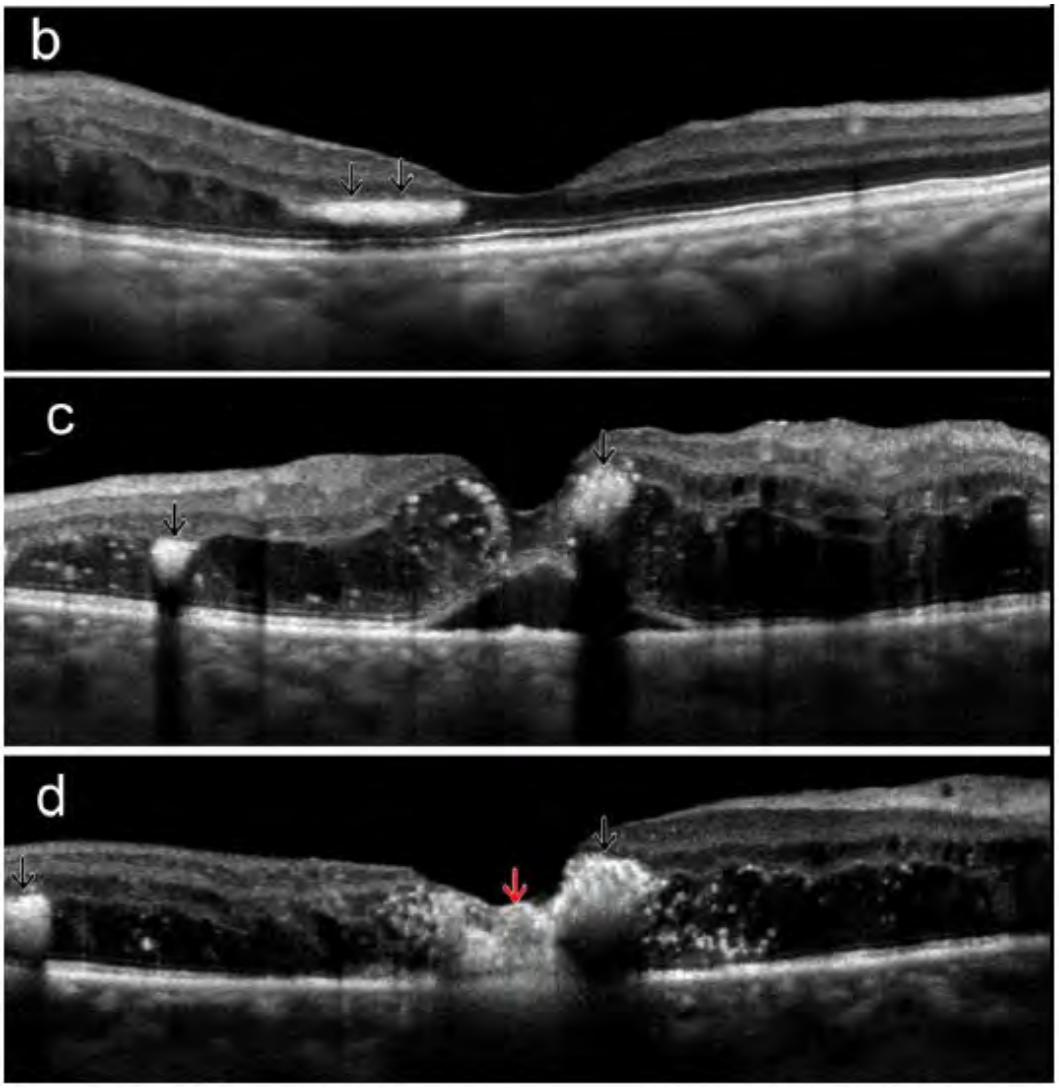


Fig. (6). a) In an OCT, hard exudates (black arrows) appear as highly hyperreflective and irregular images with posterior shadowing, usually located by the outer plexiform layer; **b**) In some cases they form streaks, especially around the fovea, in what constitutes a macular star (arrow shows one such streak); **c**) Hard exudates may migrate and accumulate in the center of the fovea, forming plaques. This case shows early migration of the lipids; **d**) These plaques may initiate an inflammatory response, leading to a retinal epithelial detachment with subjacent fibrosis (red arrow), which carries a very poor visual prognosis.

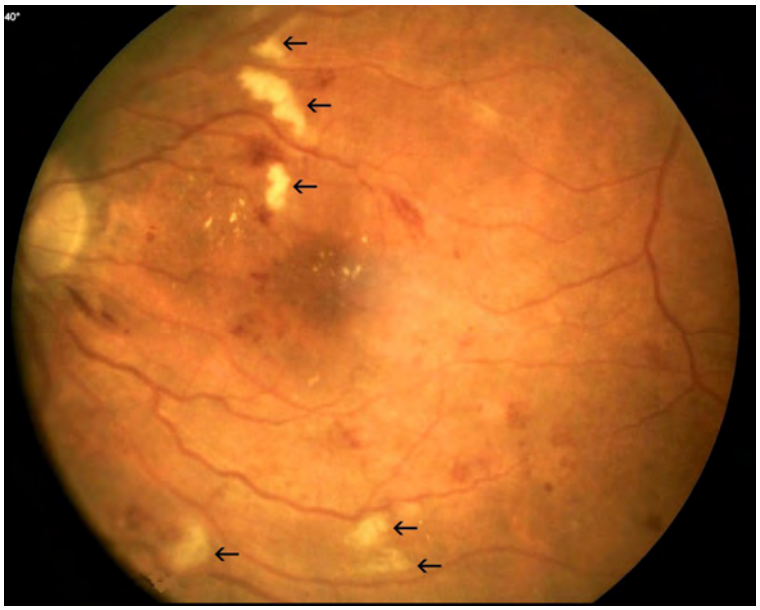


Fig. (7). Cotton wool spots (arrows). Note their feathery borders and their distribution along the nerve fiber layer bundle.

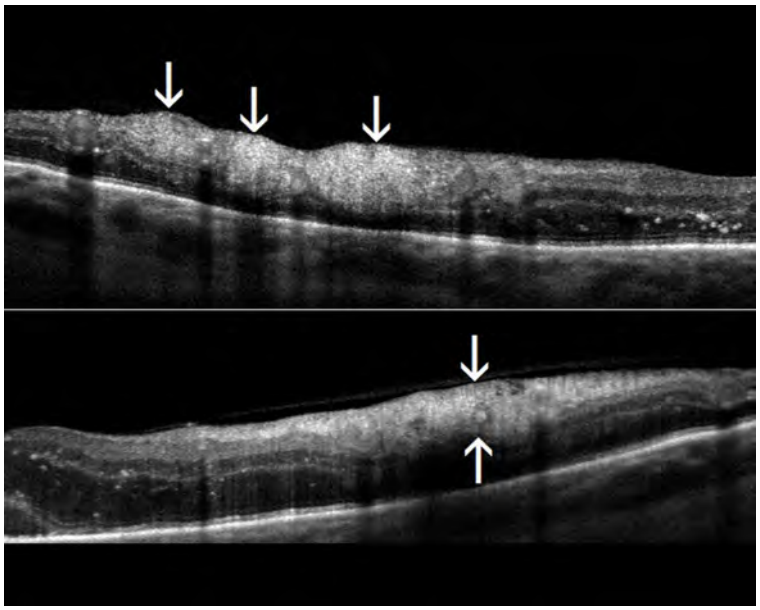


Fig. (8). OCT of CWS. Note the severe thickening and reflectivity enhancement of the nerve fiber layer. Some vessels are seen passing through them. **Top**: Three adjacent CWS. **Bottom**: A single large CWS. They are typically located in the perifoveal area.

In some cases, very small tortuous vessels may develop in the proximity of prior CWS or in other ischemic areas. These are called IRMA, and are very difficult to see clinically (Fig. **9**). It is not clear what their nature is, but they are probably intraretinal new vessels or perhaps intraretinal shunts bypassing non perfused areas [7].

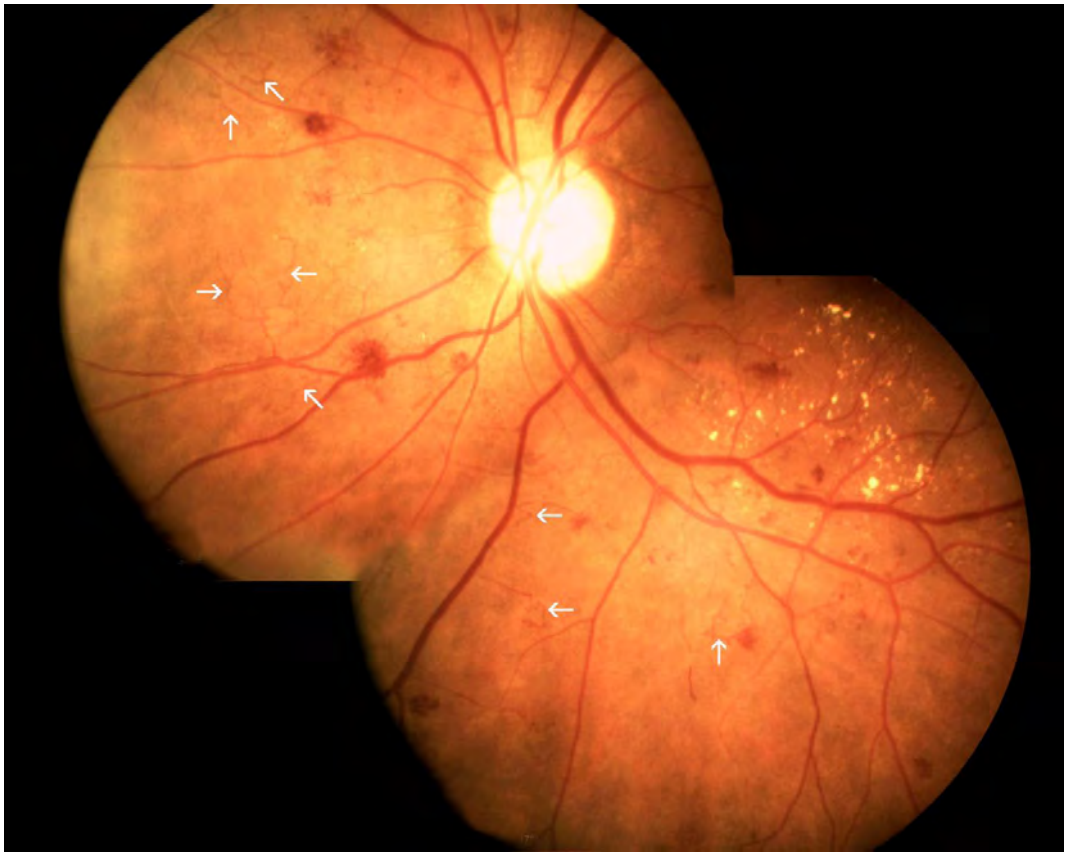


Fig. (9). IRMAs appear clinically as very small, tortuous and hard to see thread-like vessels. This patient has multiple IRMAs in the inferior and nasal quadrants. Some of them are pointed with arrows.

The last sign of NPDR is venous beading, which is a succession of constrictions and thickenings of the vein walls and translates significant ischemia (Fig. **10**). This is the feature most strongly associated with progression to proliferative diabetic retinopathy [8]. As the capillary dropout increases it induces progressive venous dilatation followed by the appearance of small bumps on the veins, and finally, strictures will develop. Venous loops and sheathing may also appear.

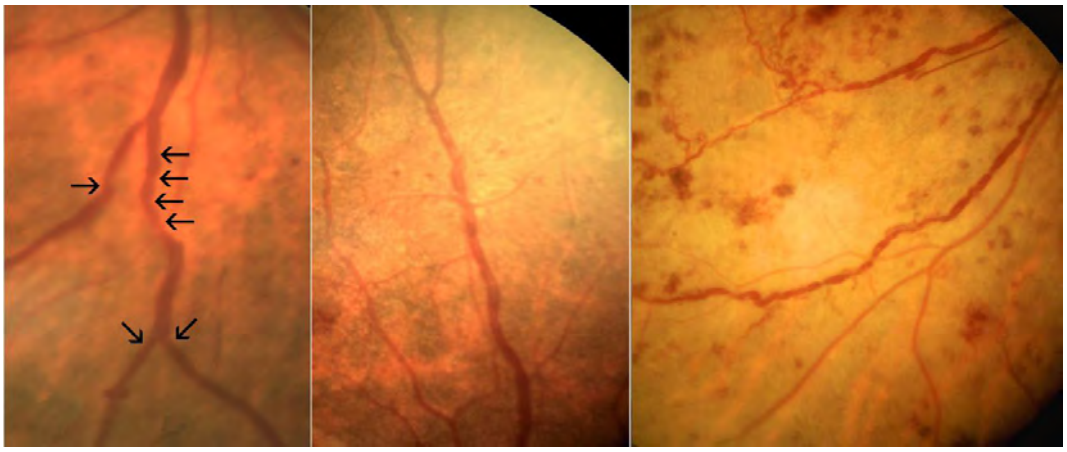


Fig. (10). Left: Moderate, but significant venous beading. Arrows point to several constrictions. Center: Severe venous beading with several successive constrictions and dilations of the vein walls. **Right**: Very severe venous beading.

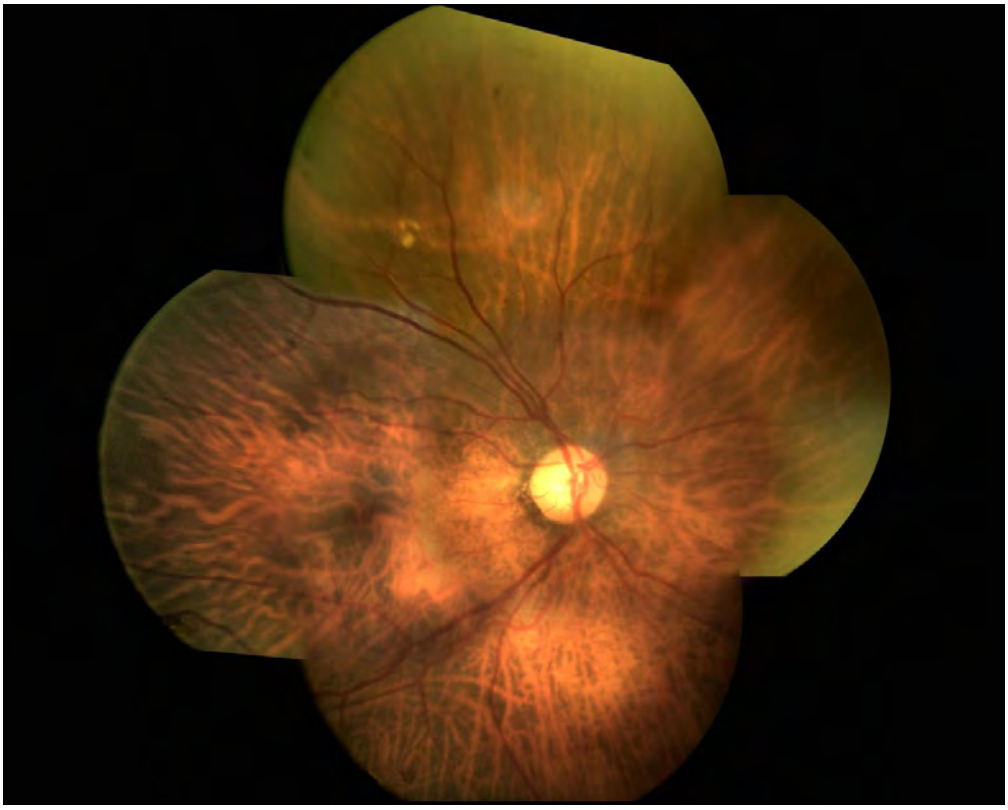


Fig. (11). Mild NPDR. Note that only a few microaneurysms can be seen in all four quadrants.

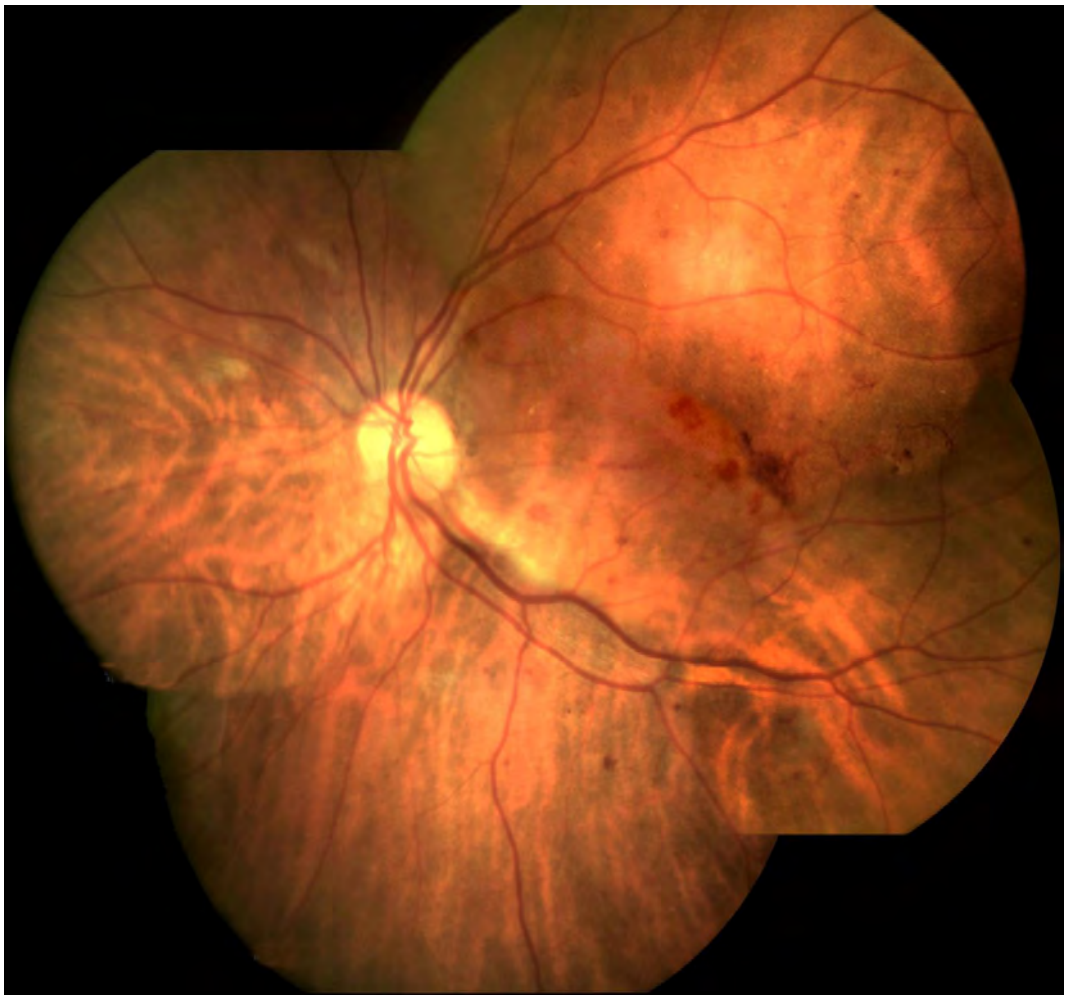


Fig. (12). Moderate NPDR. H/Ma, CWS, venous beading and hard exudates may be present, but do not meet severity criteria. Note that all four quadrants must be examined to establish the degree of severity.

Classification

A simplified classification, the International Clinical Diabetic Retinopathy Disease Severity Scale, was published in 2003 to facilitate the staging in the clinical setting [9]. The part of the scale pertaining NPDR is shown in the following table (Table **1**).

Table 1. International clinical diabetic retinopathy disease severity scale.

Proposed Disease Severity Level	Findings Observable with Dilated Ophthalmoscopy
No apparent DR	No abnormalities
Mild nonproliferative DR (Fig. **11**)	Microaneurysms only
Moderate nonproliferative DR (Fig. **12**)	More than "mild" but less than "severe"
Severe nonproliferative DR (Fig. **13**)	Any of the following: 20 or more intraretinal hemorrhages in each of the 4 quadrants Definite venous beading in 2 or more quadrants Prominent IRMA in 1 or more quadrants and no neovascularization

Proposed by the Global Diabetic Retinopathy Project Group [9].

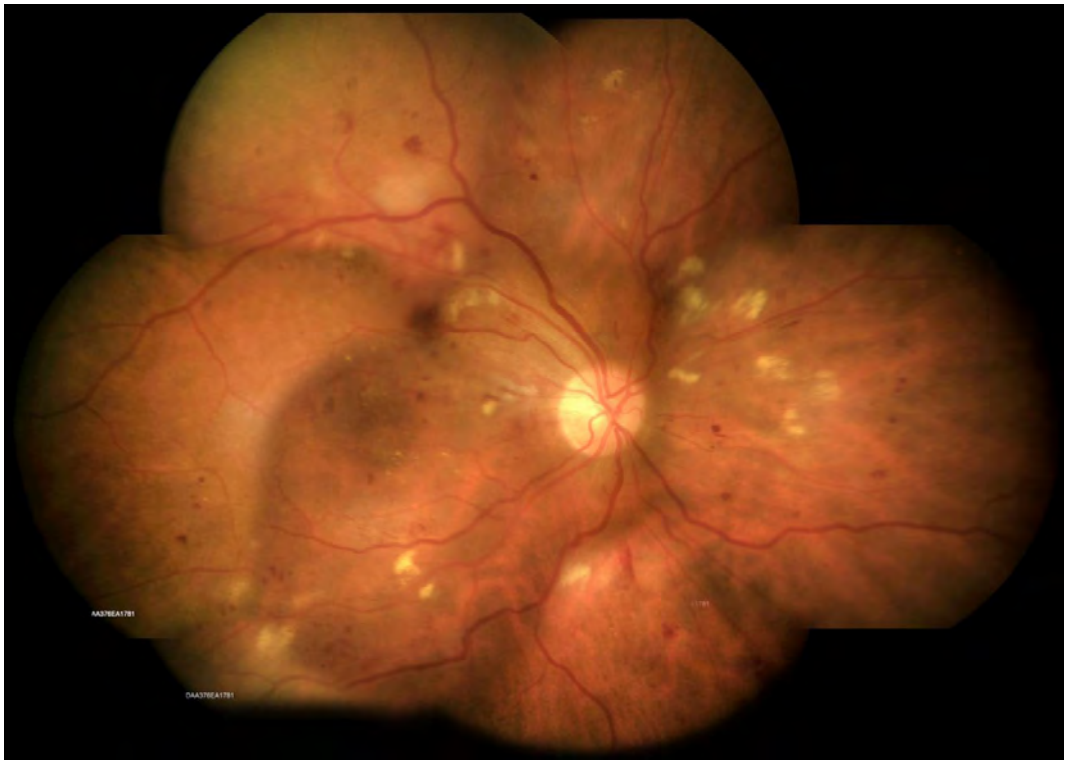


Fig. (13). Severe NPDR. In this case, more than 20 H/Ma can be counted in each of the four quadrants, along with several CWS and some hard exudates.

DIFFERENTIAL DIAGNOSIS

Most ischemic diseases may mimic diabetic retinopathy. Especially important are those pathologies that frequently concur with it, such as vein occlusions [10]

(Fig. **14**), hypertensive retinopathy [11], ocular ischemic syndrome [12] and subretinal neovascular membranes [13].

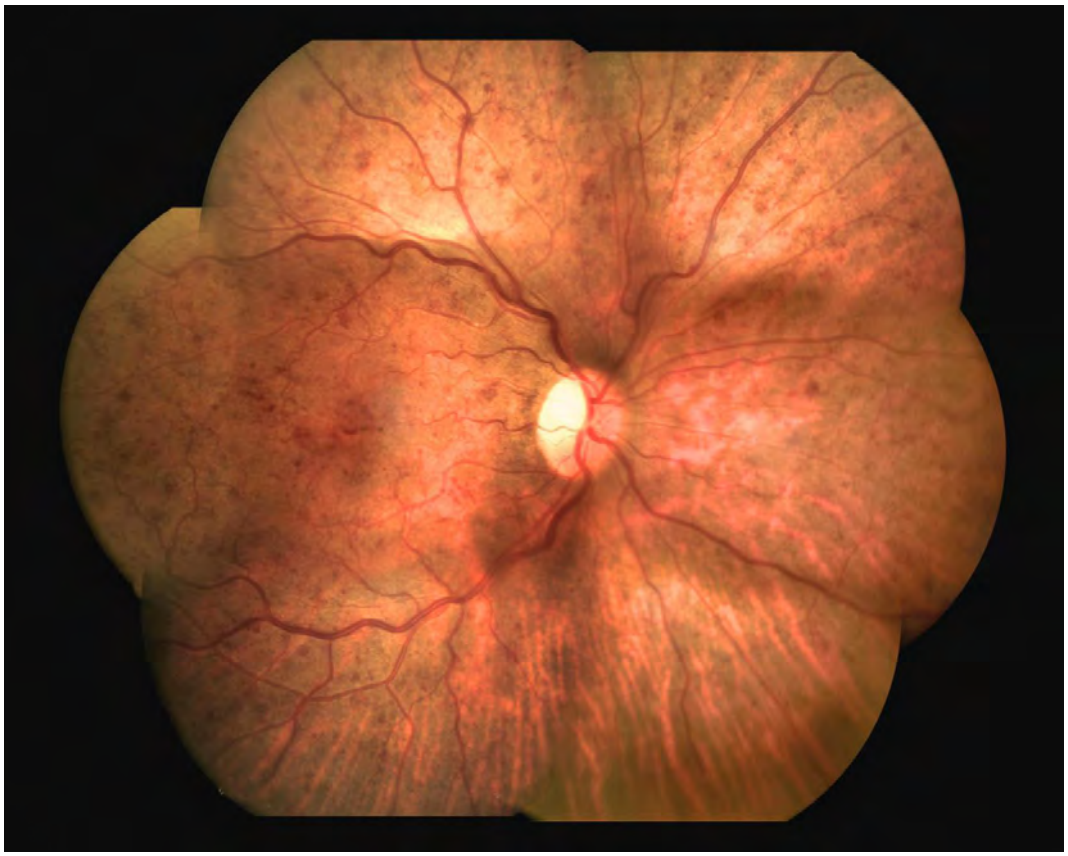


Fig. (14). Central vein occlusion simulating a severe NPDR in a diabetic patient. Venous tortuosity and asymmetry with the other eye helped determine the right diagnosis.

Other diseases that should be considered include retinal macro aneurysms, macular telangiectasias [14], radiation retinopathy [15], autoimmune retinopathies (such as systemic lupus erythematosus and antiphospholipid syndrome) [16], neoplasms (leukemia, lymphomas), HIV retinopathy, sickle cell disease [17], Eales disease and CMV retinitis [18]. Usually the differential diagnosis is straightforward when the patient is not diabetic or it is based on an examination of the patient's past medical history.

MANAGEMENT

The most important measure to prevent the appearance or to slow down the progression of diabetic retinopathy is to optimize the metabolic control of the patient [19 - 21]. This includes keeping both fasting and postprandial glycemic levels within normal limits, hemoglobin A1c below 7%, normal serum lipids, and a good, though not necessarily strict [22] control of blood pressure. Frequent exercise, a healthy diet, a normal body mass index and avoiding tobacco may also aid in maintaining a good metabolic control [23, 24]. Fenofibrate at 200 mg/d has been shown to slow the progression of DR and should be considered to treat it [22, 25].

Periodic controls are warranted to assess the evolution of the disease and to determine the development of macular edema or proliferative retinopathy, which would require treatment. Mild NPDR should be followed once a year, moderate every six to 12 months, and severe quarterly [26].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Moore J, Bagley S, Ireland G, McLeod D, Boulton ME. Three dimensional analysis of microaneurysms in the human diabetic retina. J Anat 1999; 194(Pt 1): 89-100. [http://dx.doi.org/10.1046/j.1469-7580.1999.19410089.x] [PMID: 10227670]

[2] Wang H, Chhablani J, Freeman WR, *et al.* Characterization of diabetic microaneurysms by simultaneous fluorescein angiography and spectral-domain optical coherence tomography. Am J Ophthalmol 2012; 153(5): 861-867.e1. [http://dx.doi.org/10.1016/j.ajo.2011.10.005] [PMID: 22300473]

[3] Fong DS, Segal PP, Myers F, Ferris FL, Hubbard LD, Davis MD. Subretinal fibrosis in diabetic macular edema. ETDRS report 23. Arch Ophthalmol 1997; 115(7): 873-7. [http://dx.doi.org/10.1001/archopht.1997.01100160043006] [PMID: 9230827]

[4] McLeod D, Marshall J, Kohner EM, Bird AC. The role of axoplasmic transport in the pathogenesis of retinal cotton-wool spots. Br J Ophthalmol 1977; 61(3): 177-91. [http://dx.doi.org/10.1136/bjo.61.3.177] [PMID: 66930]

[5] Kim JS, Maheshwary AS, Bartsch DU, *et al.* The microperimetry of resolved cotton-wool spots in eyes of patients with hypertension and diabetes mellitus. Arch Ophthalmol 2011; 129(7): 879-84. [http://dx.doi.org/10.1001/archophthalmol.2011.51] [PMID: 21746978]

[6] Gomez ML, Mojana F, Bartsch DU, Freeman WR. Imaging of long-term retinal damage after resolved cotton wool spots. Ophthalmology 2009; 116(12): 2407-14. [http://dx.doi.org/10.1016/j.ophtha.2009.05.012] [PMID: 19815278]

[7] Campochiaro PA. Ocular neovascularization. J Mol Med 2013; 91(3): 311-21. [http://dx.doi.org/10.1007/s00109-013-0993-5] [PMID: 23329331]

[8] ETDRS Report Number 12: Fundus photographic risk factors for progression of diabetic retinopathy. Ophthalmology 1991; 98: 823-33. [http://dx.doi.org/10.1016/S0161-6420(13)38014-2] [PMID: 2062515]

[9] Wilkinson CP, Ferris FL III, Klein RE, *et al.* Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003; 110(9): 1677-82. [http://dx.doi.org/10.1016/S0161-6420(03)00475-5] [PMID: 13129861]

[10] Jaulim A, Ahmed B, Khanam T, Chatziralli IP. Branch retinal vein occlusion: epidemiology, pathogenesis, risk factors, clinical features, diagnosis, and complications. An update of the literature. Retina 2013; 33(5): 901-10. [http://dx.doi.org/10.1097/IAE.0b013e3182870c15] [PMID: 23609064]

[11] Ojaimi E, Nguyen TT, Klein R, *et al.* Retinopathy signs in people without diabetes: the multi-ethnic study of atherosclerosis. Ophthalmology 2011; 118(4): 656-62. [http://dx.doi.org/10.1016/j.ophtha.2010.08.007] [PMID: 21055817]

[12] Niestrata-Ortiz M, Li JP, Davies N. Rubeosis iridis in patients with diabetes: not forgetting oculoischaemic syndrome as a differential. BMJ Case Rep 2014. [http://dx.doi.org/10.1136/bcr-2014-207236]

[13] Hahn P, Acquah K, Cousins SW, Lee PP, Sloan FA. Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among medicare beneficiaries. Retina 2013; 33(5): 911-9. [http://dx.doi.org/10.1097/IAE.0b013e3182831248] [PMID: 23407352]

[14] Díaz-Rodríguez EJ. Telangiectasias parafoveales idiopáticas tipo 2A. Arch Soc Esp Oftalmol 2005; 80(9): 541-5. [http://dx.doi.org/10.4321/S0365-66912005000900010] [PMID: 16193439]

[15] Zamber RW, Kinyoun JL. Radiation retinopathy. West J Med 1992; 157(5): 530-3. [PMID: 1441494]

[16] Sivaraj RR, Durrani OM, Denniston AK, Murray PI, Gordon C. Ocular manifestations of systemic lupus erythematosus. Rheumatology (Oxford) 2007; 46(12): 1757-62. [http://dx.doi.org/10.1093/rheumatology/kem173] [PMID: 17681981]

[17] Bonanomi MT, Lavezzo MM. Sickle cell retinopathy: diagnosis and treatment. Arq Bras Oftalmol 2013; 76(5): 320-7. [http://dx.doi.org/10.1590/S0004-27492013000500016] [PMID: 24232951]

[18] Takayama K, Ogawa M, Mochizuki M, Takeuchi M. Cytomegalovirus retinitis in a patient with proliferative diabetes retinopathy. Ocul Immunol Inflamm 2013; 21(3): 225-6.
[http://dx.doi.org/10.3109/09273948.2012.762983] [PMID: 23480605]

[19] The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14): 977-86.
[http://dx.doi.org/10.1056/NEJM199309303291401] [PMID: 8366922]

[20] Progression of retinopathy with intensive *versus* conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 1995; 102(4): 647-61.
[http://dx.doi.org/10.1016/S0161-6420(95)30973-6] [PMID: 7724182]

[21] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131): 837-53.
[http://dx.doi.org/10.1016/S0140-6736(98)07019-6] [PMID: 9742976]

[22] Chew EY, Davis MD, Danis RP, *et al.* Action to control cardiovascular risk in diabetes. Eye study research group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Ophthalmology 2014; 121(12): 2443-51.

[23] Sumamo E, Ha C, Korownyk C, Vandermeer B, Dryden DM. Lifestyle interventions for four conditions: type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer [Internet].Fuente: Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 May. Report No.: LFST1209. AHRQ Technology Assessments.

[24] Boretsky A, Gupta P, Tirgan N, *et al.* Nicotine accelerates diabetes-induced retinal changes. Curr Eye Res 2015; 40(4): 368-77.
[PMID: 24911405]

[25] Keech AC, Mitchell P, Summanen PA, *et al.* Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007; 370(9600): 1687-97.
[http://dx.doi.org/10.1016/S0140-6736(07)61607-9] [PMID: 17988728]

[26] American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern® Guidelines. Comprehensive Adult Medical Eye Evaluation. San Francisco, CA: American Academy of Ophthalmology; 2014. Available at: www.aao.org/ppp.

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 2

Proliferative Diabetic Retinopathy (PDR)

Maria H. Berrocal[1,*] and **Luis A. Acabá**[2]

[1] *Berrocal & Asociados, San Juan, Puerto Rico*

[2] *Sidney Kimmel College of Medicine, Philadelphia, PA, USA*

ESSENTIALS OF DIAGNOSIS

Proliferative diabetic retinopathy (PDR) occurs as a progression of severe diabetic vascular damage and includes intraretinal capillary closure with resultant ischemia and the formation of new vessels (Figs. **1-3**). Severe non-proliferative diabetic retinopathy is the precursor of PDR. It includes diffuse intraretinal hemorrhages in 4 quadrants, venous beading in 2 quadrants or more and intra-retinal microvascular abnormalities (IRMA) in 1 quadrant. The chance of progression to PDR in 1 year is between 15% and 45% [1, 2].

Severe NPDR can be confused with PDR. Fluorescein angiography is the best way to differentiate IRMA from neovascularization as the latter shows significant leakage throughout the study. The evolution of new vessels starts with fine vessels with minimal fibrosis, then an increase in vessel size and fibrous tissue, and then the end stage of PDR which includes regressed vessels and significant fibrovascular proliferation on the posterior hyaloid. Vitreous hemorrhage and sub-hyaloid hemorrhage can result from PDR.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes NPDR particularly when many IRMAs are present, other retinovascular diseases like vein occlusions, sickle cell retinopathy,

[*] **Corresponding author Maria H. Berrocal:** 150 Ave De Diego Ste 404, San Juan, 00907, Puerto Rico; Tel: (787) 725-9315; E-mail: mariahberrocal@hotmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

leukemic retinopathy, hypertensive retinopathy, radiation retinopathy, retinal vasculitis, sarcoidosis, and ocular ischemic syndrome. Differences in the clinical picture and fluorescein angiographic appearance are usually sufficient to discriminate bet-ween these entities.

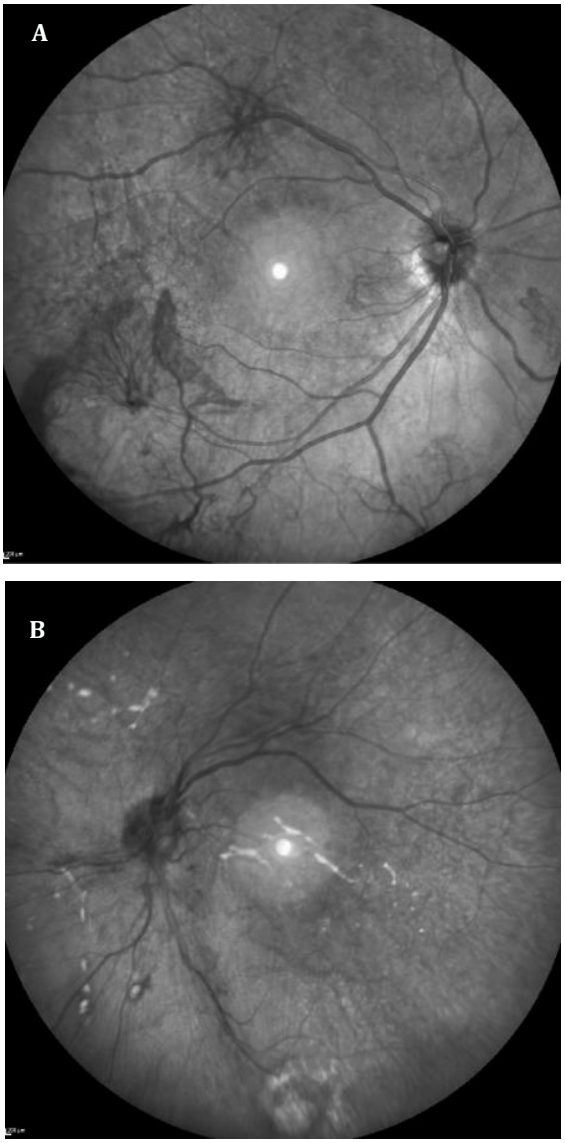


Fig. (1). A. Red-free image of the right eye of a 35 year-old male with prominent neovascularization in the posterior pole; **B**. Red-free image of the left eye in the same patient, showing neovascularization and exudates.

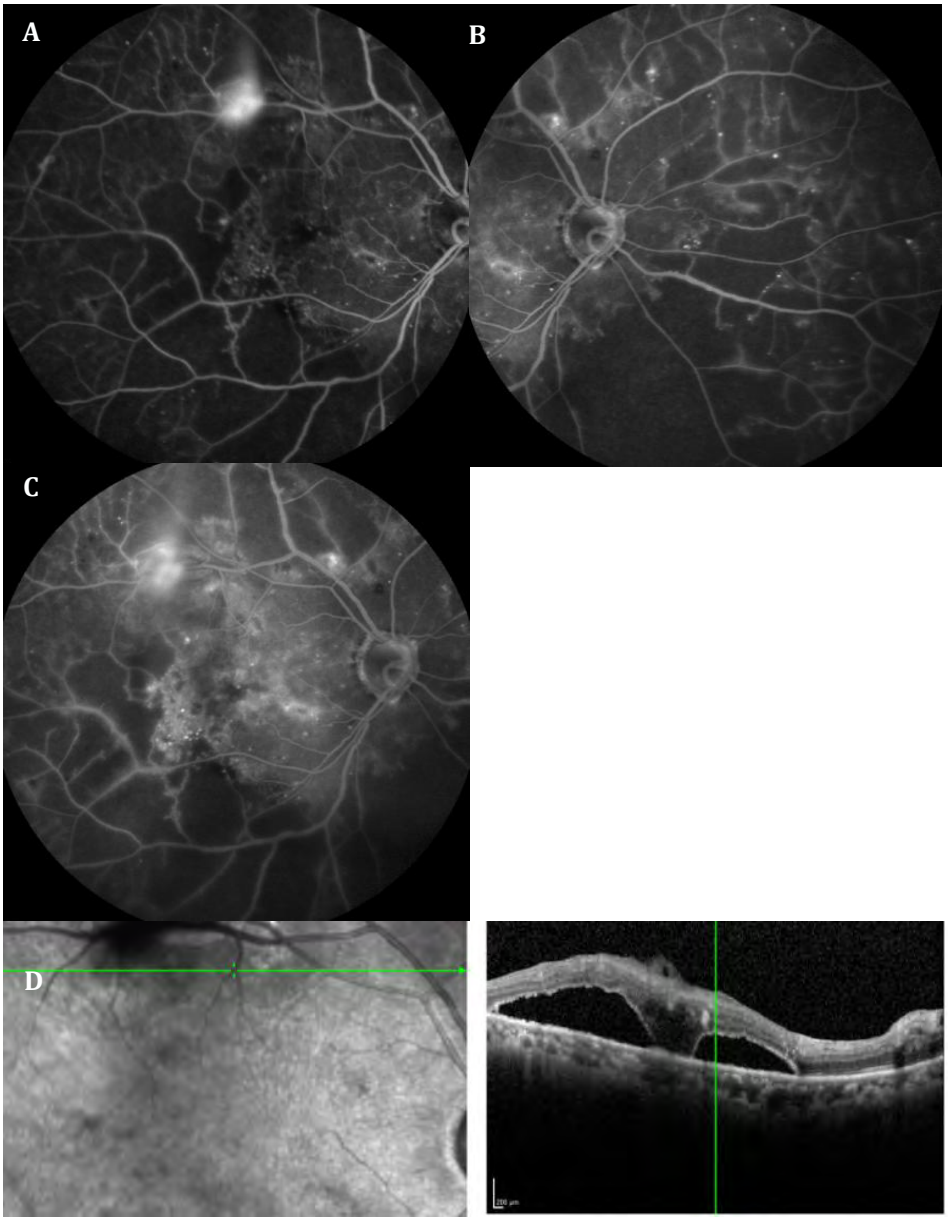


Fig. (2-I). 66-year-old male with type 1 diabetes mellitus and proliferative diabetic retinopathy. **A**. Early fluorescein angiography (FA) of the right eye showing multiple areas of capillary dropout and ischemia, including the foveal area with enlarged foveal avascular zone. One area of NVE is present in the superotemporal arcade; **B**. FA of the nasal retina with severe ischemia and capillary leakage; **C**. Late FA of the same eye, showing diffused leakage in the posterior pole; **D**. OCT of retinal area near neovascularization showing areas of localized tractional retinal detachment.

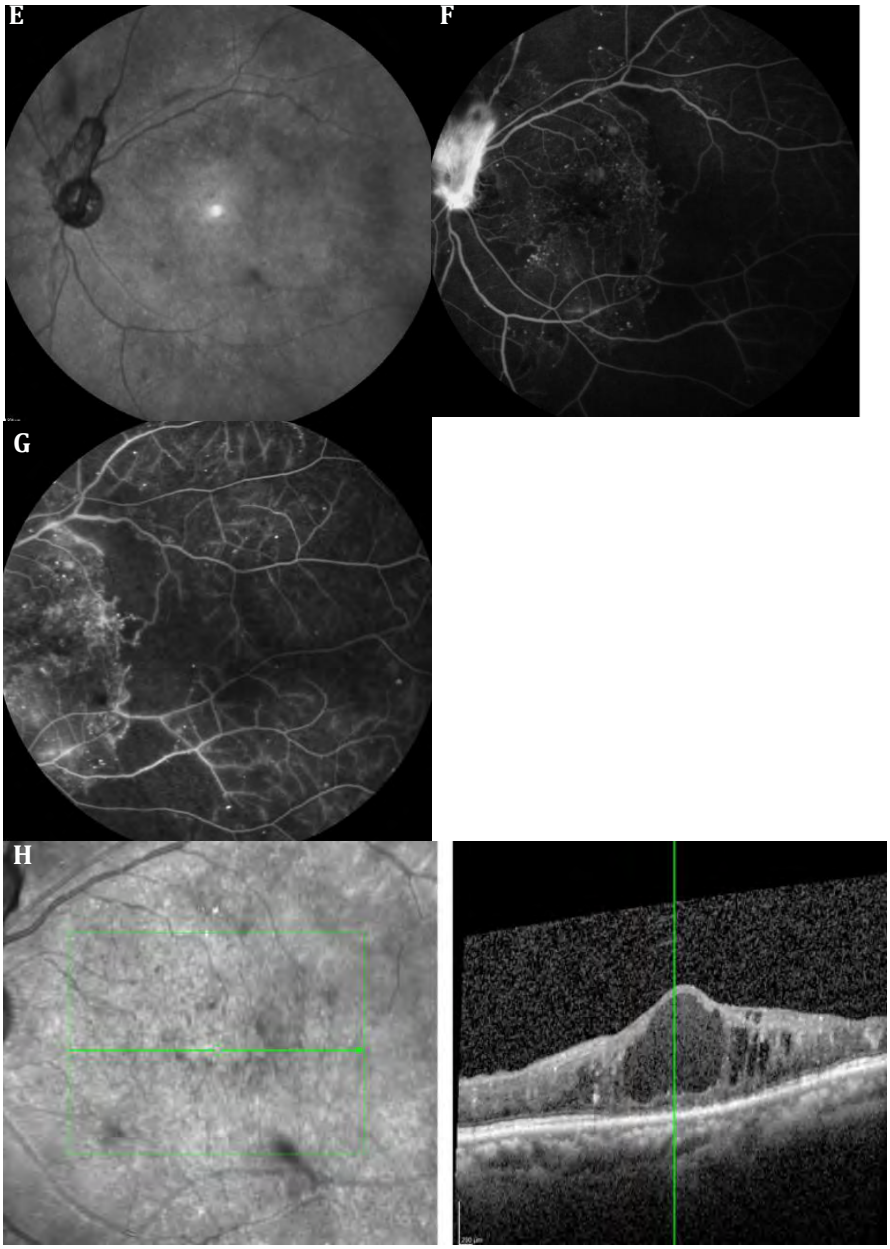


Fig. (2-II). **E**. Image of the left eye, with prominent neovascularization in the disc; **F**. Early FA showing intense staining of the neovascularization in the disc; **G**. FA of the temporal retina, showing severe capillary dropout throughout the retina with diffused staining and microaneurysms; **H**. OCT of the fovea showing macular edema with a large cyst.

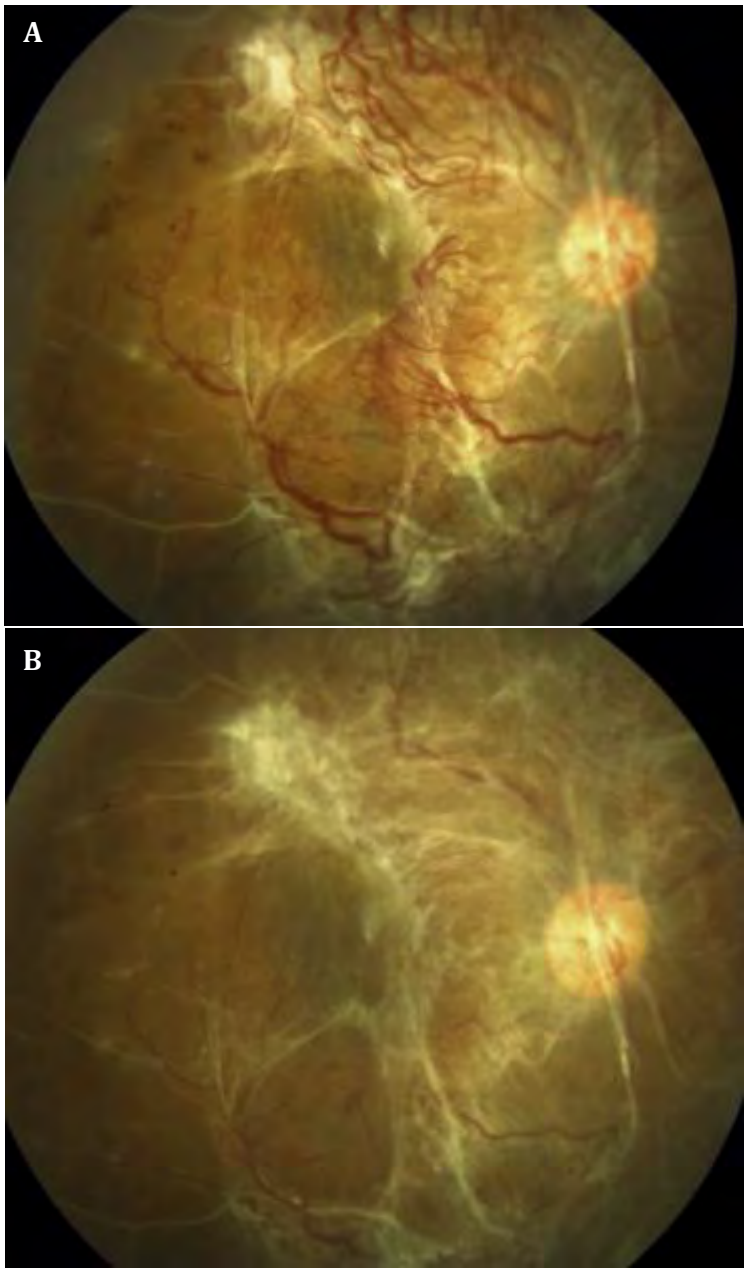


Fig. (3). 35-year-old female with type 1 diabetes mellitus. **A**. Fundus photograph showing very prominent neovascularization throughout the posterior pole; **B**. Same eye one week after 1.25 mg intravitreal bevacizumab, with marked regression of neovascularization.

MANAGEMENT

Medical management includes optimizing diabetic control to prevent progression. Conditions that can cause worsening of PDR include hypertension, anemia, pregnancy and renal disease [1 - 4]. The Diabetes Control and Complications trial (DCCT) showed that intensive glycemic control reduces the progression of PDR [2].

The mainstay of treatment for high-risk PDR is scatter laser photocoagulation in a pan retinal distribution (Figs. **4** and **5**). This results in regression of neovascular vessels and prevents progression of the disease [5, 6]. High risk PDR includes any of these: 1. -mild neovascularization of the disc (NVD) with vitreous hemorrhage (VH); 2. -moderate to severe NVD with or without hemorrhage; 3. -moderate (1/2 disc area) neovascularization elsewhere (NVE) with VH. Another definition of high risk includes any three of: 1.-vitreous or pre-retinal hemorrhage; 2.- presence of new vessels; 3.- new vessels on or near optic nerve (ON); 4.-moderate or severe neovascularization.

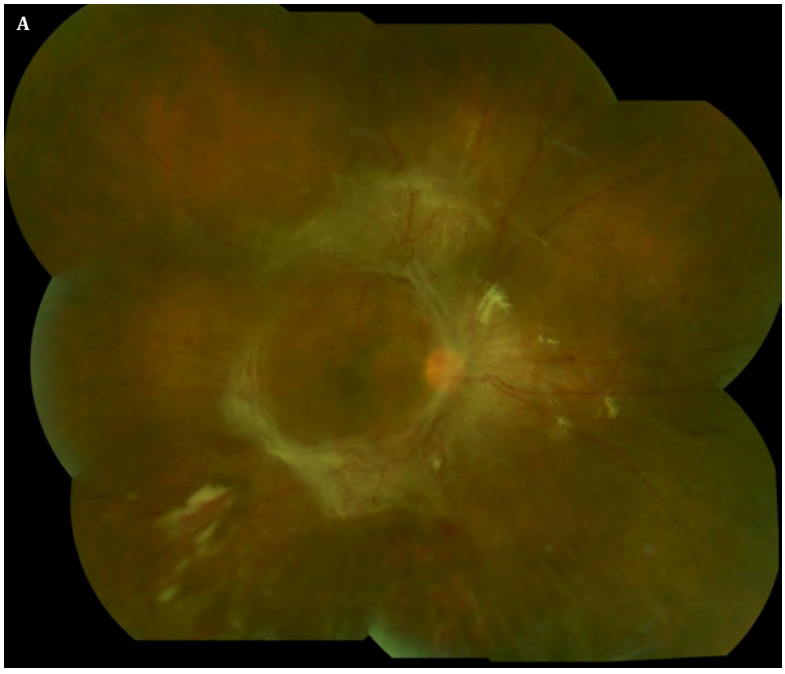


Fig. (4A). 40-year-old female with tractional retinal detachment. **A**. Preoperative image showing fibrovascular tissue throughout the arcades.

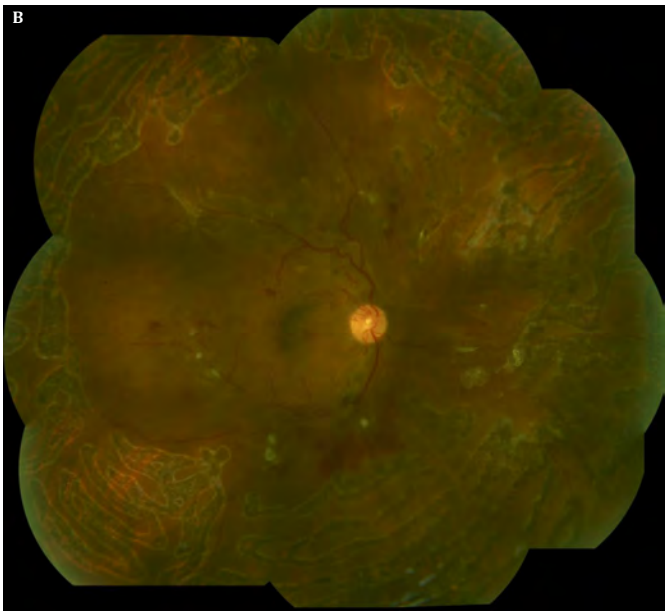


Fig. (4B). Postoperative image showing flattened retina, laser photocoagulation scars in the periphery and residual hemorrhage in the inferior arcade.

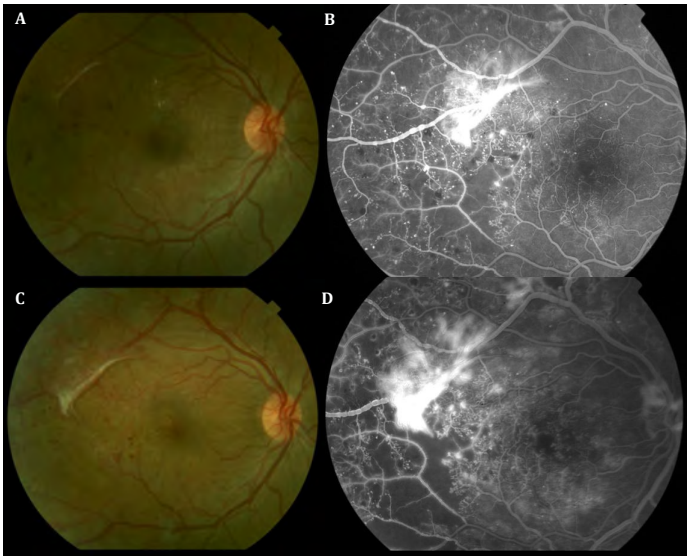


Fig. (5). 27 year-old female with type 1 diabetes mellitus. **A**. Fundus photograph of the right eye showing neovascularization in the superotemporal arcade, hard exudates and microaneurysms in the posterior pole; **B**. FA showing neovascularization with leakage, venous beading and capillary dropout; **C**. Fundus photograph of the same eye 8 months later, after panretinal photocoagulation was applied, with some fibrosis in the superotemporal arcade; **D**. FA showing increased neovascularization, venous beading and capillary closure.

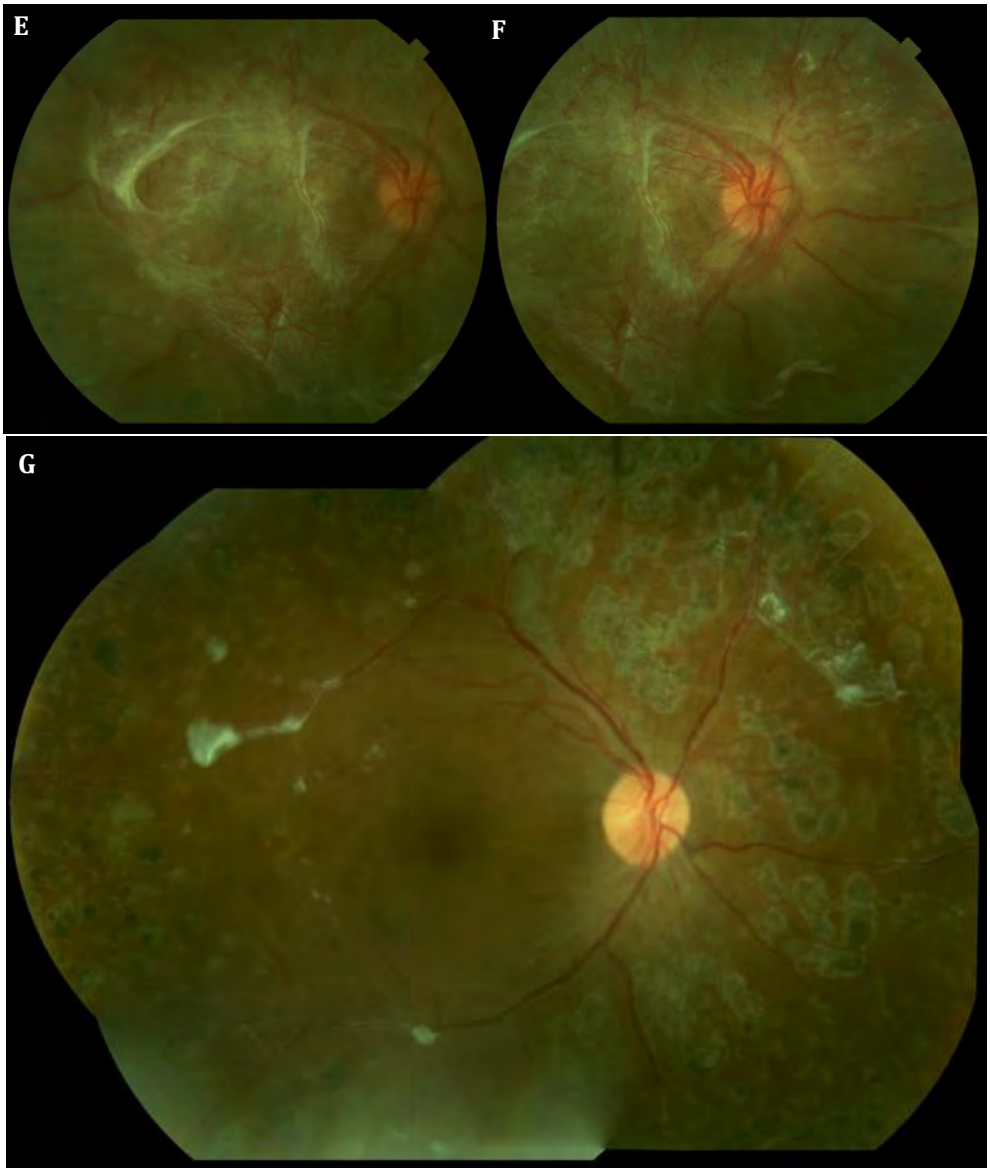


Fig. (5). E. Fundus photograph of the same eye 11 months after photocoagulation, with a tractional retinal detachment and massive neovascularization throughout the posterior pole; **F**. Nasal view of the same eye; **G**. Fundus photograph 3 months after vitrectomy with preoperative bevacizumab.

Full PRP is defined as 1,200 or more 500µm spots separated by 1/2 burn width and 0.1s duration. This can be performed in 1 or 2 sessions.

Surgical management of PDR is performed when there is persistent or severe VH and or traction retinal detachment threatening the fovea. The Diabetic Retinopathy Vitrectomy Study (DRVS) results showed a greater benefit of early vitrectomy in VH eyes in type 1 diabetics, and in very severe PDR (Figs. **4**-**7**) [7].

The advent of VEGF inhibitor therapy for many conditions has made its use appealing in the treatment of diabetic retinopathy (Fig. **3**). Although the benefit of these agents has been validated for the treatment of diabetic macular edema, panretinal photocoagulation remains the mainstay of treatment of PDR.

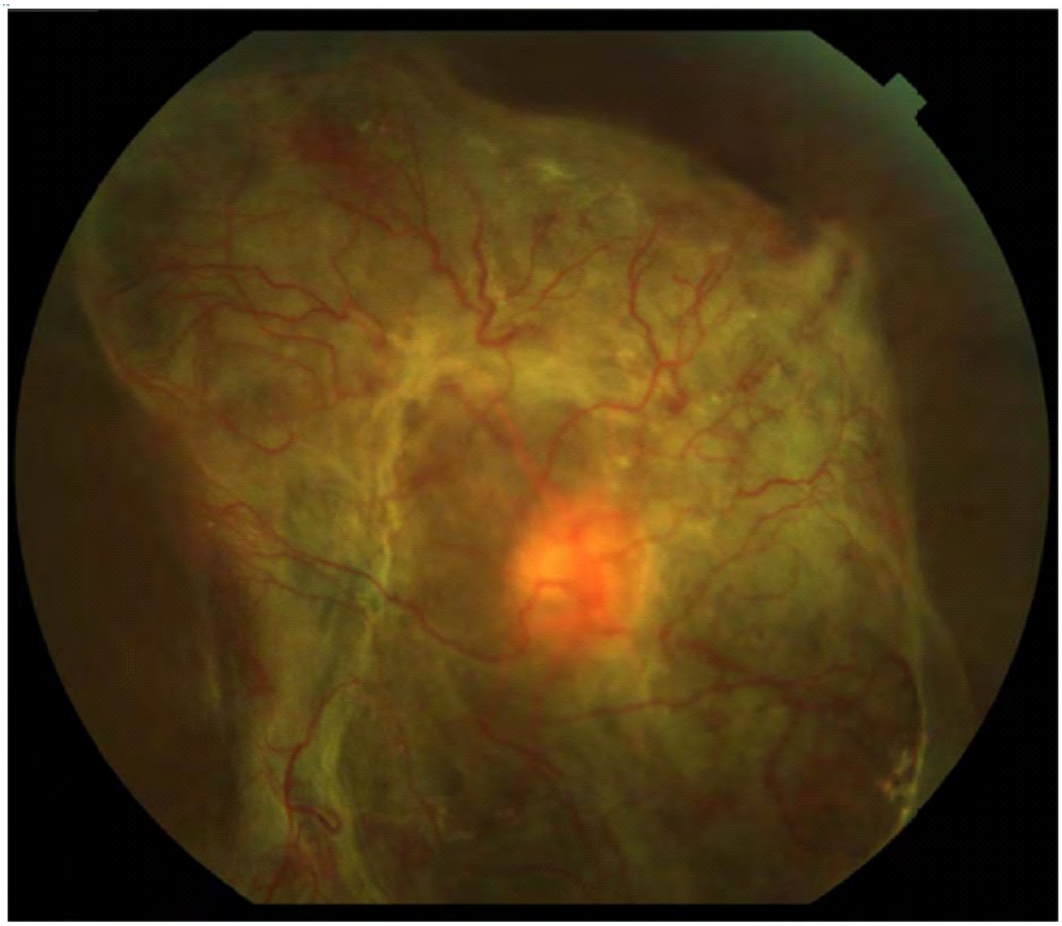


Fig. (6). Tabletop neovascular fibrovascular proliferation in an eye with a tractional retinal detachment.

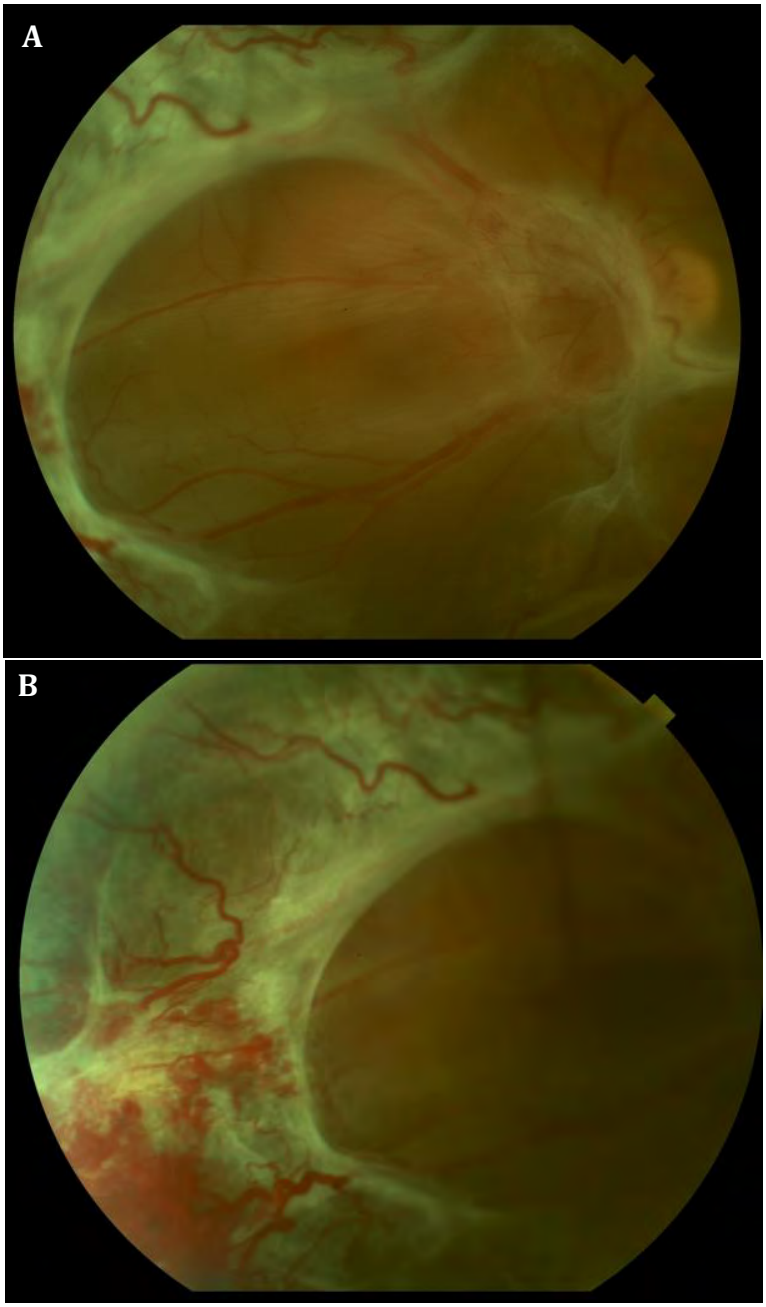


Fig. (7). 36-year-old with type 1 diabetes mellitus and no prior laser photocoagulation. **A**. Massive fibrovascular proliferation causing circumferential traction and a combined rhegmatogenous-tractional retinal detachment: **B**. Peripheral view of fibrovascular sheet with very large neovascular vessels.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Davis MD, Fisher MR, Gangnon RE, *et al.* Risk factors of high-risk proliferative diabetic retinopathy and severe visual loss: ETDRS Report 18. Invest Ophthalmol Vis Sci 1998; 39: 233-52. [PMID: 9477980]

[2] Progression of retinopathy with intensive *versus* conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 1995; 102(4): 647-61. [http://dx.doi.org/10.1016/S0161-6420(95)30973-6] [PMID: 7724182]

[3] Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317(7160): 703-13. [http://dx.doi.org/10.1136/bmj.317.7160.703] [PMID: 9732337]

[4] Davis MD, Fisher MR, Gangnon RE, *et al.* Risk factors of high-risk proliferative diabetic retinopathy and severe visual loss: ETDRS Report 18. Invest Ophthalmol Vis Sci 1998; 39: 233-52. [PMID: 9477980]

[5] Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology 1991; 98(5) (Suppl.): 766-85. [http://dx.doi.org/10.1016/S0161-6420(13)38011-7] [PMID: 2062512]

[6] Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. Ophthalmology 1981; 88(7): 583-600. [PMID: 7196564]

[7] Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision: results of a randomized trial. DRVS report 3. Diabetic Retinopathy Vitrectomy Study Research Group. Ophthalmology 1988; 95: 1307-20. [http://dx.doi.org/10.1016/S0161-6420(88)33015-0] [PMID: 2465517]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 3

Diabetic Macular Edema

Maximiliano Gordon[1,2,*] and **Mitzy E. Torres Soriano**[1,2,3]

[1] *Centro de la Visión Gordon-Manavella, Rosario, Santa Fe, Argentina*

[2] *Retina Department, Ophthalmology Service, Hospital Provincial del Centenario, Rosario, Santa Fe, Argentina*

[3] *Unidad Oftalmológica "Dr Torres López", Centro Médico Cagua, Aragua, Venezuela*

Diabetic macular edema (DME) is the main cause of visual loss in diabetic patients. It may present at every stage of diabetic retinopathy.

The systemic risk factors identified for DME are hyperglycemia, arterial hypertension, hyperlipidemia, kidney failure and anemia [1, 2].

ESSENTIALS OF DIAGNOSIS

Diabetic macular edema is diagnosed with a detailed bio-microscopic examination with the slit lamp and indirect ophthalmoscopy.

The Early Treatment Diabetic Retinopathy Study (ETDRS) described DME as retinal thickening or hard exudates (consisting of lipoproteins) within 1 disk diameter of the center of the macula (Figs. **1**, **2**, **4a**, **5a-b**, **6a**, **8**, **11a**).

The term clinically significant macular edema (CSME) indicates the severity of macular edema and is used for treatment guidelines. CSME is characterized by: 1) thickening of the retina within 500 μm of the macular center; 2) hard exudates at the center of the retina or within 500 μm with thickening of adjacent retina; and 3) one or more disc diameters of retinal thickening, part of which is within one disc diameter of the center of the macula [3].

[*] **Corresponding author Maximiliano Gordon:** Centro de la Vision Gordon - Manavella, Montevideo 763, CP 2000, Rosario - Santa Fe, Argentina; Tel: +54 (0341) 4 400 239; E-mail: maximilianogordon19@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

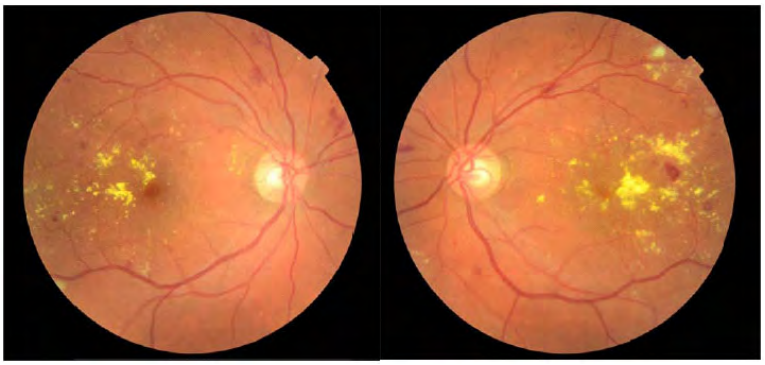


Fig. (1). Fundus photograph of CSME in both eyes. Microaneurysms, hard exudates and retinal hemorrhages are shown.

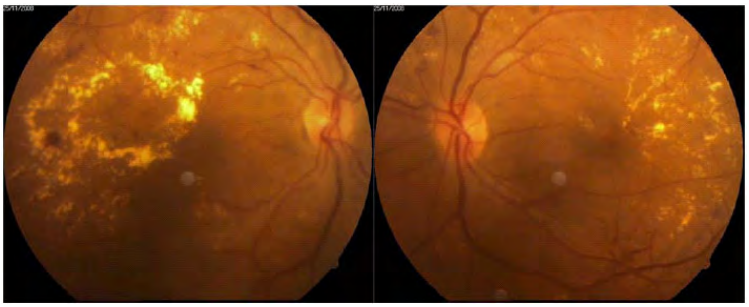


Fig. (2). Fundus photograph of severe and clinically significant diabetic macular edema in both eyes.

In 2002, the American Academy of Ophthalmology proposed an international classification of DME (Table **1**): DME absent: absence of retinal thickening or hard exudates in the posterior pole. DME present: some retinal thickening or hard exudates in the posterior pole.

Table 1. International clinical diabetic macular edema (DME) disease severity scale.

Proposed Disease Severity Level	**Findings observable on Dilated Ophthalmoscopy**
Mild DME	Some retinal thickening or hard exudates in posterior pole but far from the macula center
Moderate DME	Retinal thickening or hard exudates that approach the macular center but without involving it
Severe DME	Retinal thickening or hard exudates involving the macula center

Program and abstracts of the American Academy of Ophthalmology 2002 [4].

Classically, three different types of DME can be observed in fluorescein angiography (FA): 1) focal leakage: well-defined focal area of leakage from micro-aneurysms or dilated capillaries (Figs. **3**-**6**); 2) diffuse leakage: wide-spread leakage from IRMA, retinal capillary bed (Fig. **7**); and 3) diffuse cystoid leakage: diffuse leakage and pooling of dye in the cystic spaces of the macula in the late phase of the angiogram [5]. However, one of the most important utilities of the angiography is to roll out macular ischemia (Fig. **7**). It has long been considered that ischemic changes and microvascular pathologies are key in the development of DME. In diabetic retinopathy, peripheral ischemia leads to an increased production of vascular endothelial growth factor (VEGF), which can result in the breakdown of blood-retinal barriers, thus increasing retinal vessel permeability and causing DME. These areas can be detected using ultra-wide field fluorescein angiography [6].

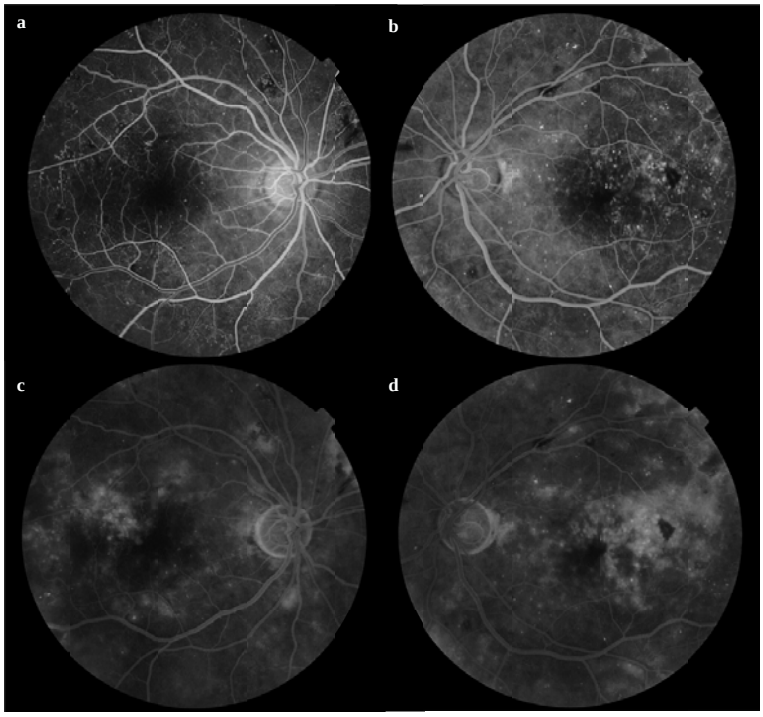


Fig. (3). FA of the same patient as shown in Fig. (**1**). (**a-b**) Multiple hyperfluorescent points due to mycroaneurisms with mild leakage in late phases (**c-d**).

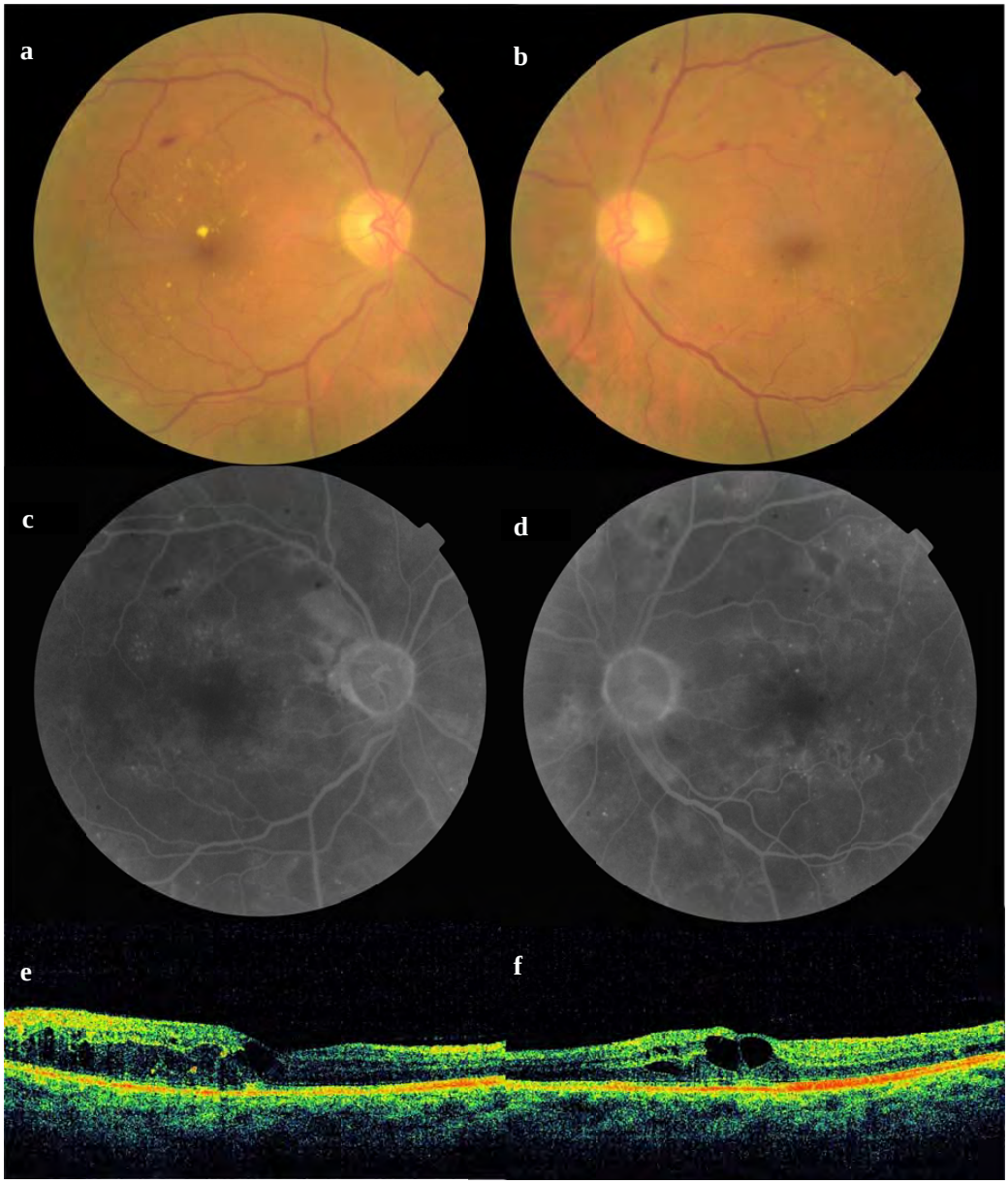


Fig. (4). Fundus photograph (**a-b**) and FA (**c-d**) of focal diabetic macular edema. OCT showing focal increased macular thickness and cystoid macular edema (**e-f**).

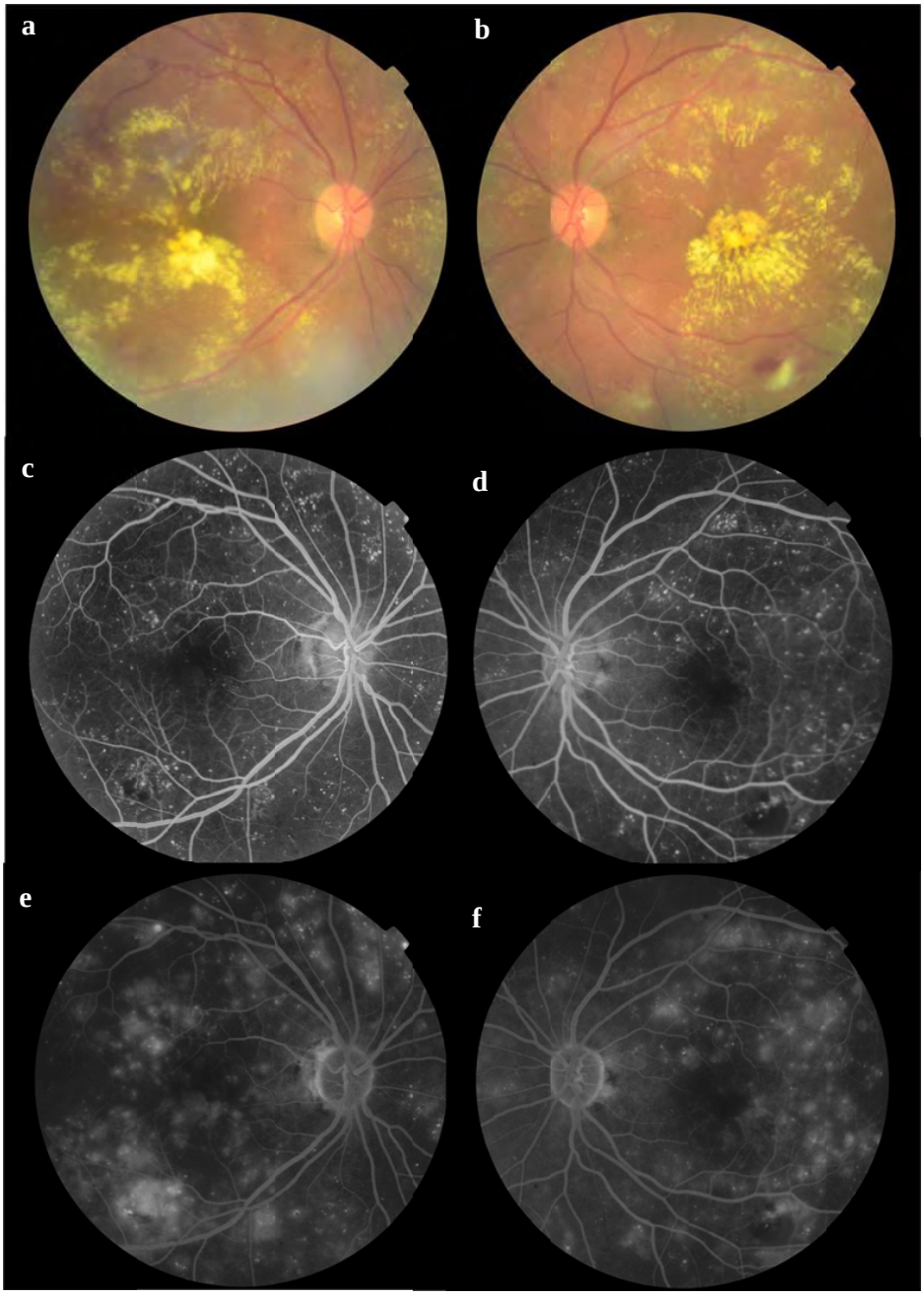


Fig. (5). (**a-b**) CSME with abundant and confluent hard exudates involving fovea. (**c-d**) FA shows multiple hyperfluorescent points due to microaneurysms with mild leakage in late phases (**e-f**).

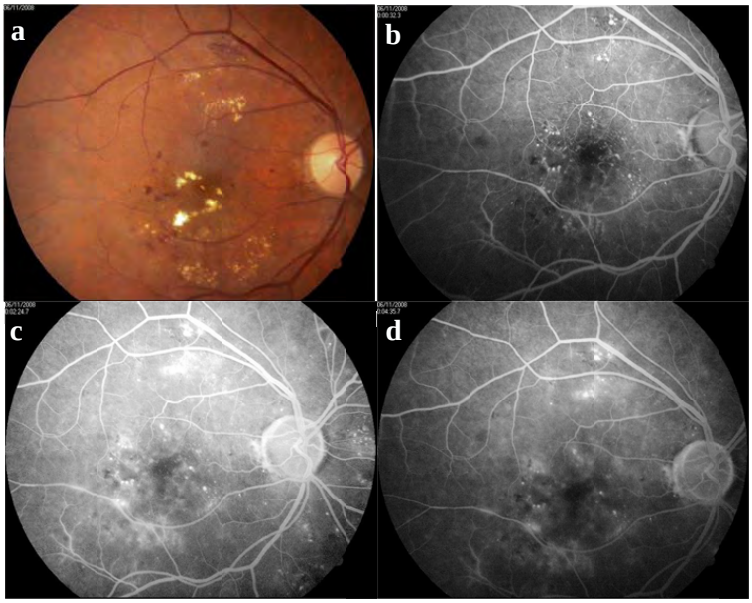


Fig. (6). (**a**) Fundus photograph of DME in right eye. (**b-d**) FA shows hyperfluorescent points with mild leakage in late phases.

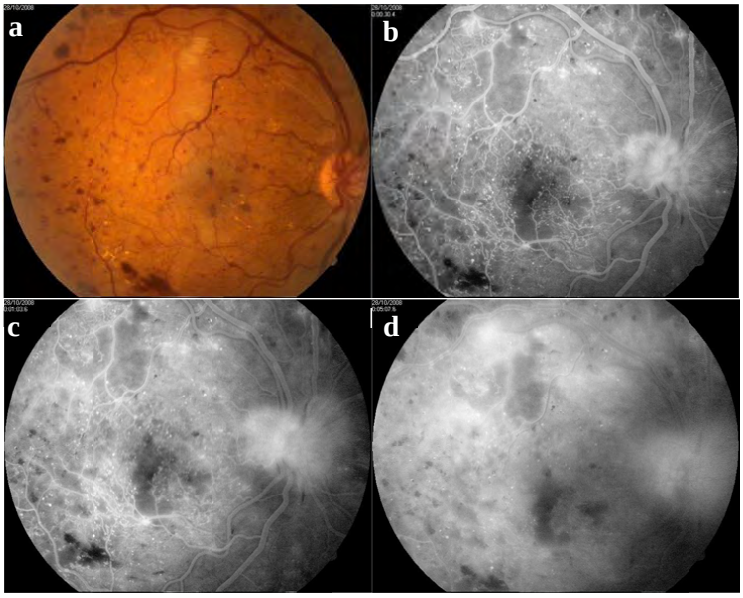


Fig. (7). (**a**) Fundus photograph reveals retinal round hemorrhages and hard exudates in a diabetic female patient. (**b-c**) FA shows hypofluorescence from capillary dropout, typical of ischemic diabetic maculopathy and (**d**) late hyperfluorescence due to diffuse perivascular leakage.

OCT has shown four important changes in neurosensory retinal structure: cystoid macular edema (CME) (Figs. **4e-f**, **8** and **10**), swelling of the retina (Figs. **9** and **10**), serous retinal detachment (Fig. **11b**), and retinal traction (Fig. **12**) [5].

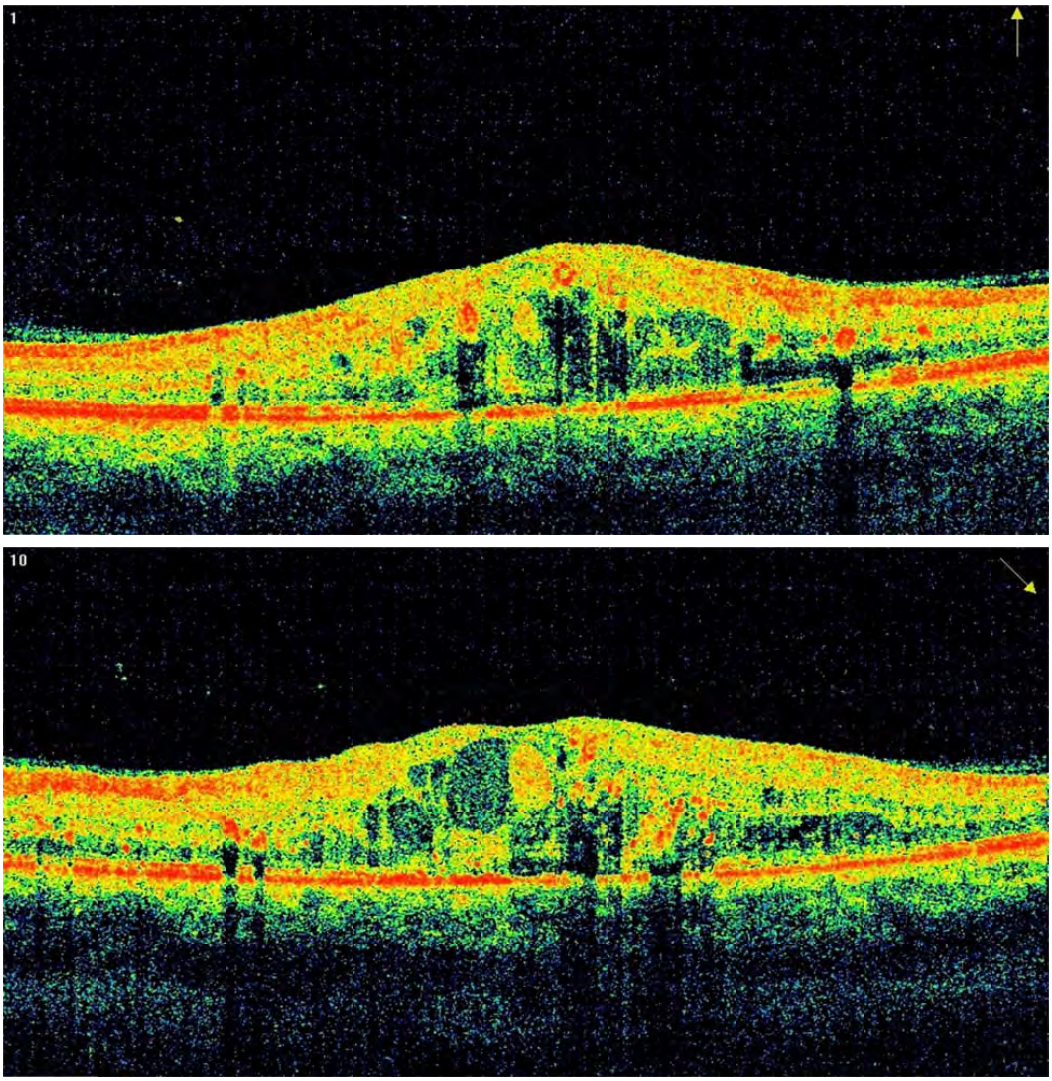


Fig. (8). Cystoid diabetic macular edema with a significant amount of hypereflective foci that correspond to hard exudates.

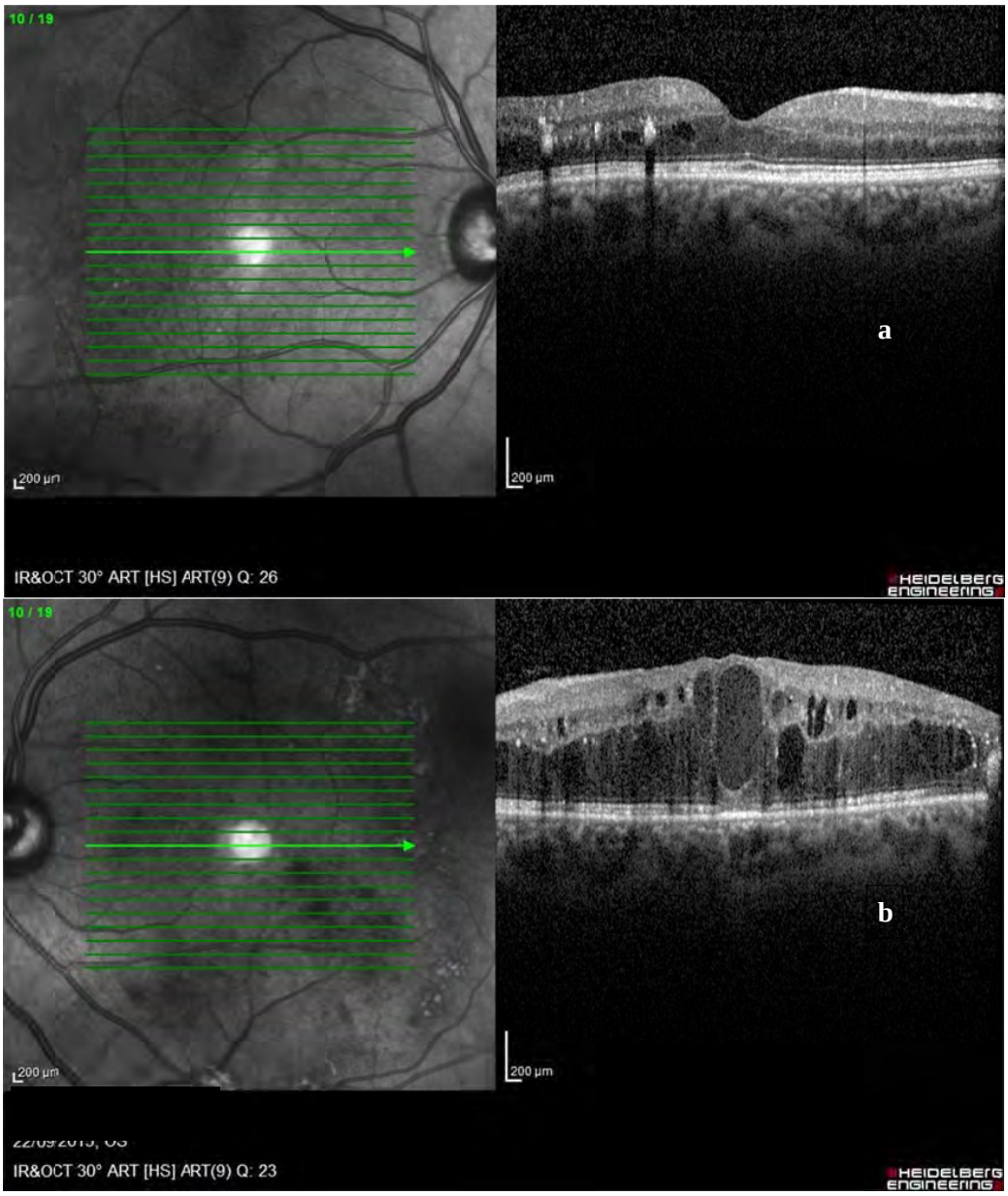


Fig. (9). 59 year-old male patient with insulin dependent diabetes mellitus and diabetic retinopathy. Spectral domain-optical coherence tomography showing (**a**) focal cystoid diabetic macular edema in his right eye; and (**b**) diffuse diabetic macular edema showing retinal swelling and cystoid spaces in his left eye. Visual Acuity: OD 20/25 OS 20/200.

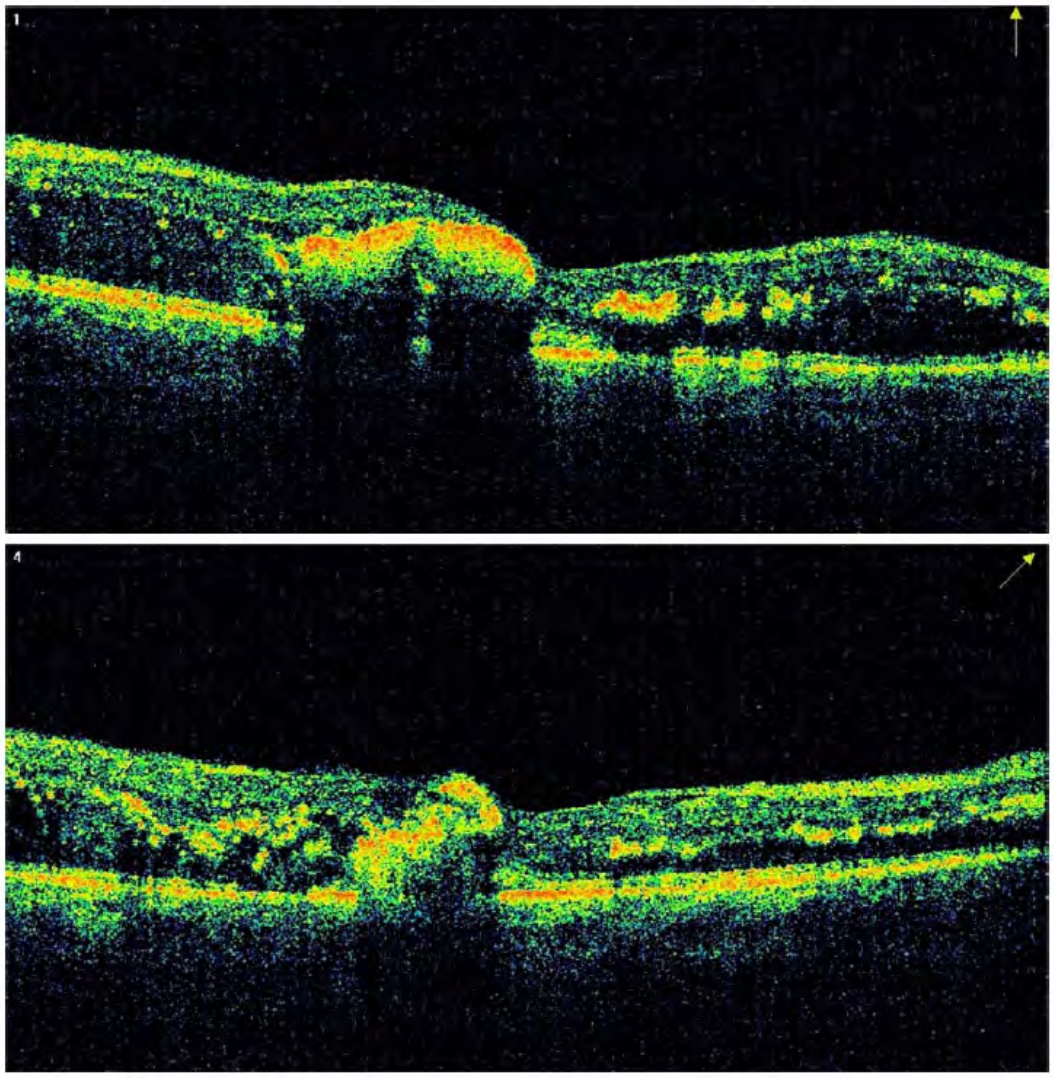


Fig. (10). Spectral domain-optical coherence tomography showing diffuse diabetic macular edema, intraretinal dense hard exudates with posterior shadow and hypo-reflective outer retinal layers.

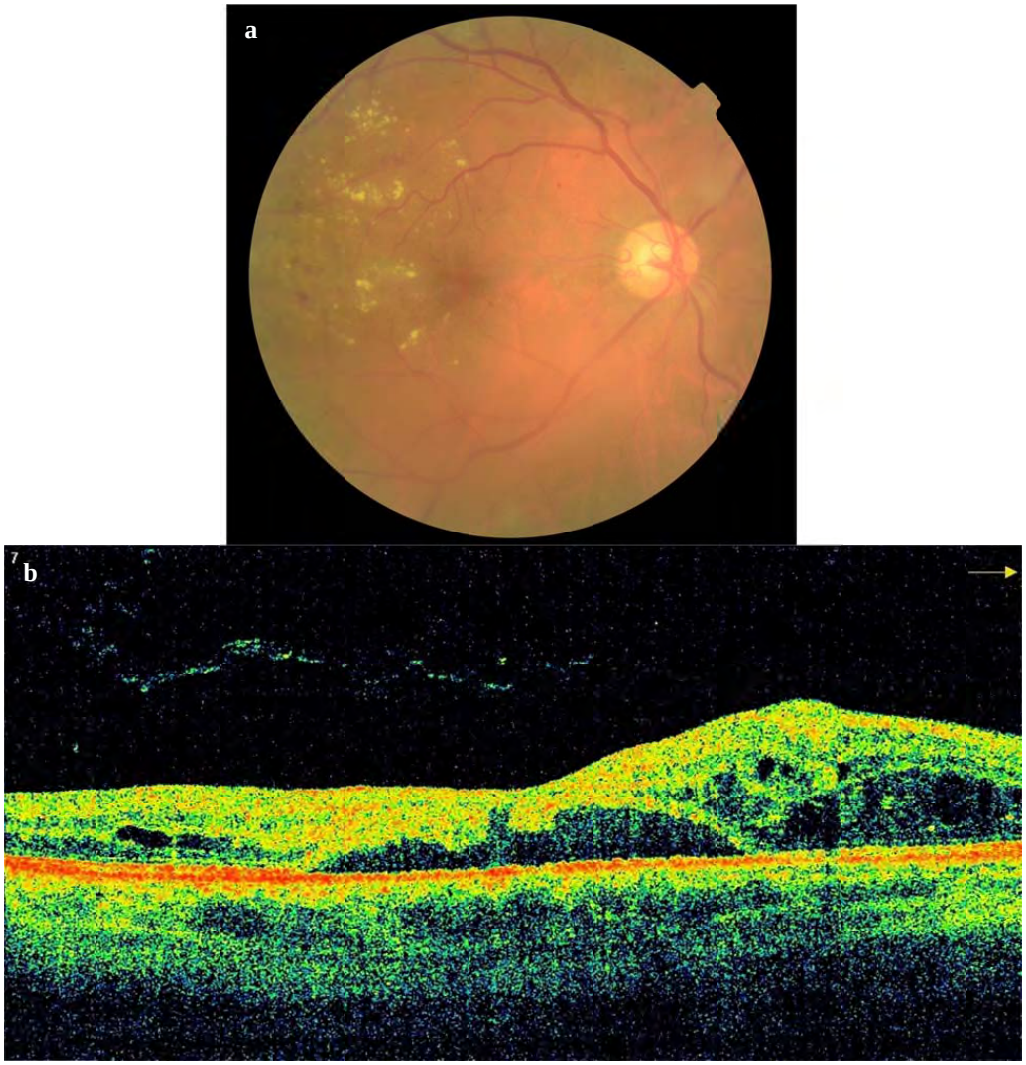


Fig. (11). (**a**) Fundus photograph of CSME; (**b**) OCT shows small and medium cystoid intraretinal spaces and subretinal serous detachment.

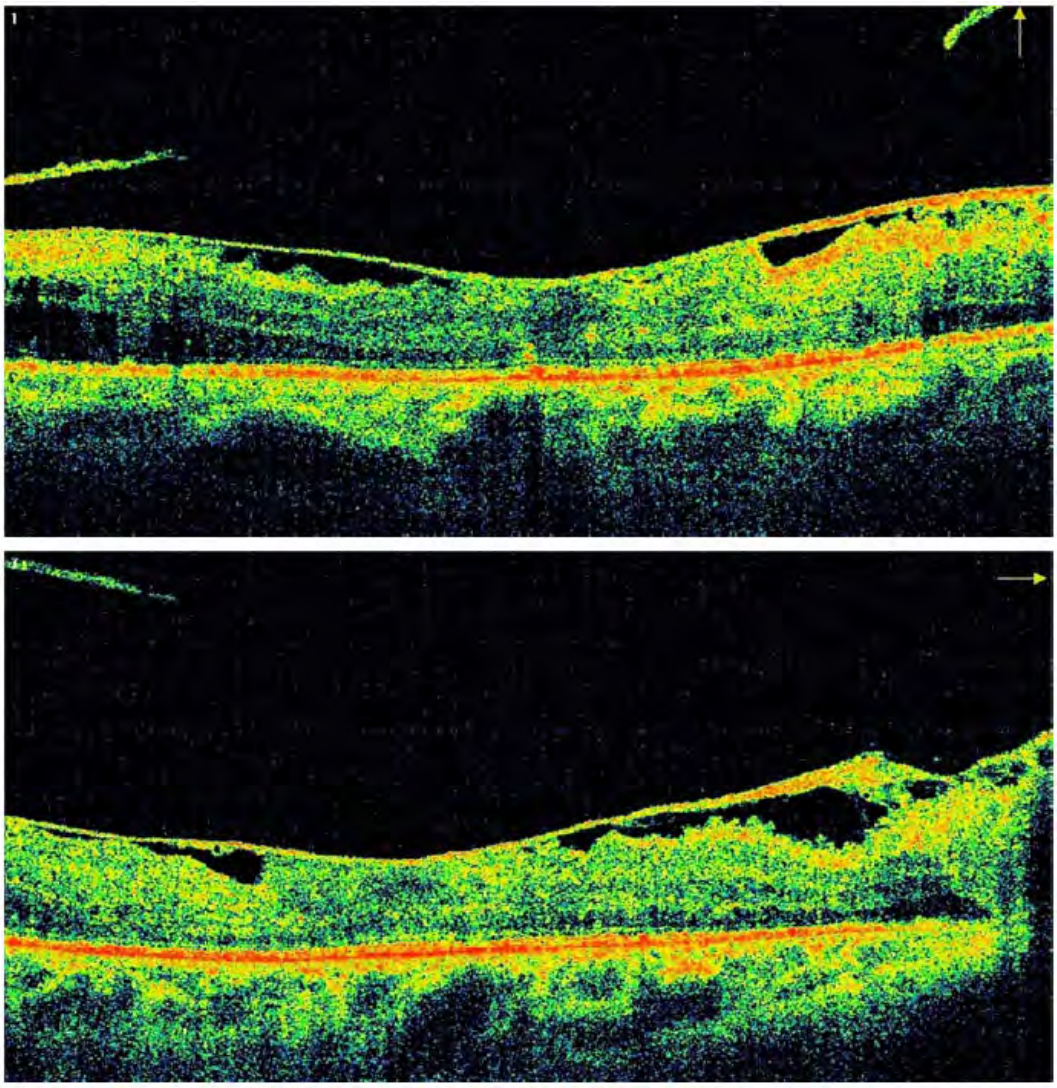


Fig. (12). Spectral domain-optical coherence tomography showing diabetic macular edema with vitreoretinal traction component.

DIFFERENTIAL DIAGNOSIS

Other causes of macular edema may be hypertensive retinopathy (it can coexist), vein occlusion (central vein or branch), pseudophakic macular edema, uveitis (anterior or posterior), radiation retinopathy, and active choroidal neovascularization.

MANAGEMENT

Of the utmost necessity is the strict control of diabetes, hypertension, and hypercholesterolemia.

Diabetic macular edema is usually a chronic disease. Although sometimes spontaneous recovery is possible, patients that do not receive treatment will experience a moderate visual loss (15 or more letters on the ETDRS chart) within 3 years in 24% of CSME cases and in 33% of center-involving CSME cases [7 - 9].

Laser Photocoagulation: In the ETDRS, grid laser treatment in diffuse macular edema revealed that treated eyes showed improved visual acuity in 16% of cases, remained unchanged in 77% of cases, and worsened in 7% of cases, while these results changed to 11%, 73%, and 16%, respectively, after 2 years of follow-up [3]. Therefore, these results did not show substantial benefit in treated eyes [10]. However, in patients with focal DME, a focal laser pattern is used for the treatment of leaking micro-aneurysms revealed by the FA.

Steroids: Some reports suggest the beneficial effects of subtenon or peribulbar steroid injection therapy for DM [11, 12]. Intravitreal injection of triamcinolone acetonide is a treatment option for patients with DME who do not respond to laser photocoagulation. The most frequent ocular adverse effects associated to corticosteroids are glaucoma and cataract. Actually, some fluocinolone acetonide implants and dexamethasone long standing delivered intravitreal implants were approved for DME treatment [5, 10, 13, 14].

Anti-VEGF therapy: Blockage of VEGF has shown to reduce vascular permeability [5]. Intra-vitreous injection of anti-VEGF agents has been proven to be a relatively safe treatment option for diabetic edema (Fig. **13**) and more effective than laser photocoagulation of the macula. The most commonly used VEGF inhibitors are aflibercept (Eylea, Regeneron Pharmaceuticals), ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) [15]. The first two are approved for intraocular use by the FDA. Bevacizumab is not approved for intraocular treatment, but it is used as an off-label therapy.

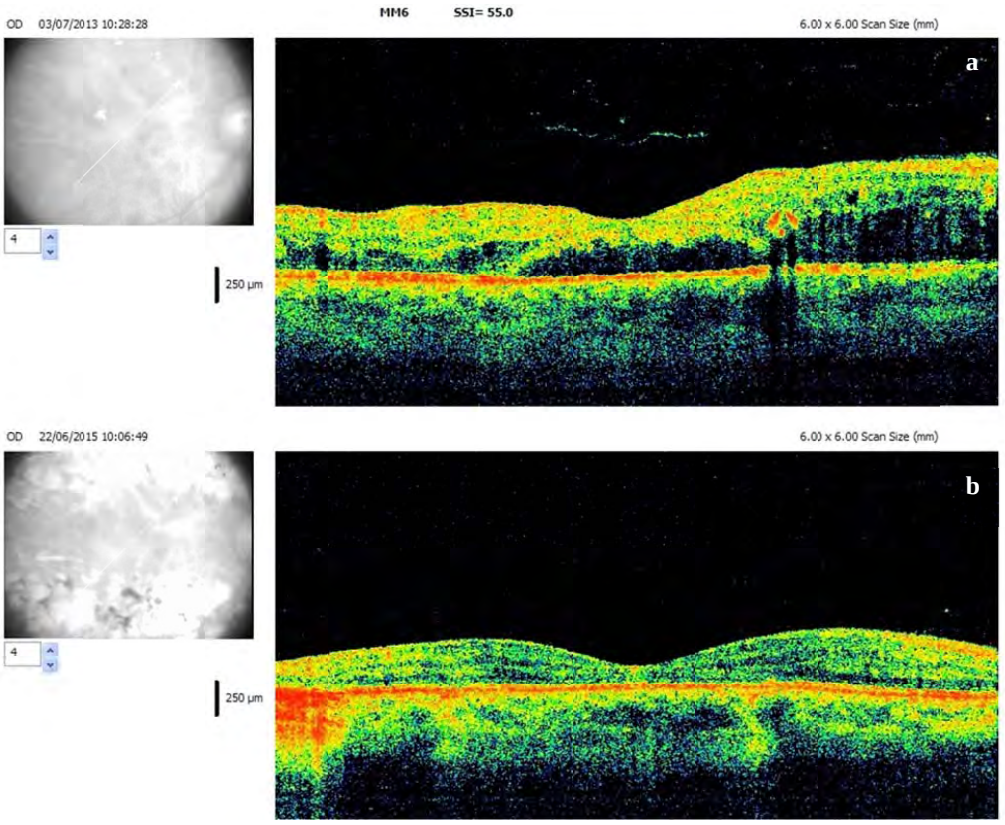


Fig. (13). 60 year-old male patient with diabetic retinopathy. Spectral domain-optical coherence tomography showing (**a**) diabetic macular edema; and (**b**) resolution after repeated intravitreal bevacizumab in his right eye. Retinal thickness is significantly decreased.

Micro-pulse laser is a treatment option for DME [16 - 18] that produces multiple short exposure burns localized to the apical portion of the RPE, with minimal effects to the surrounding structures [5].

Pars plana vitrectomy may be used to remove vitreomacular traction, which can reduce the concentration of DME-promoting factors and also improve the fluid currents and thus the inner retinal oxygenation [5].

The management of DME remains complex, so a combined treatment approach is often necessary in order to address the persistence of fluid within the macular region.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Klein R, Klein BE, Moss SE. The epidemiology of ocular problems in diabetes mellitus. In: Feman SS, Ed. Ocular problems in diabetes mellitus. Boston: Blackwell Scientific Publications 1991; pp. 1-51.

[2] Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy. XV. The long-term incidence of macular edema. Ophthalmology 1995; 102(1): 7-16. [http://dx.doi.org/10.1016/S0161-6420(95)31052-4] [PMID: 7831044]

[3] Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group. Arch Ophthalmol 1985; 103(12): 1796-806. [http://dx.doi.org/10.1001/archopht.1985.01050120030015] [PMID: 2866759]

[4] Wilkinson CP. Achieving consensus on an international clinical classification for diabetic retinopathy. Annual Meeting. October 20-23, 2002; Orlando, Florida.

[5] Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol 2009; 54(1): 1-32. [http://dx.doi.org/10.1016/j.survophthal.2008.10.001] [PMID: 19171208]

[6] Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. Br J Ophthalmol 2012; 96(5): 694-8. [http://dx.doi.org/10.1136/bjophthalmol-2011-300774] [PMID: 22423055]

[7] Early treatment diabetic retinopathy study R. photocoag-ulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group. Arch Ophthalmol 1985; 103(12): 1796-806. [http://dx.doi.org/10.1001/archopht.1985.01050120030015] [PMID: 2866759]

[8] Ferris FL, Podgor MJ, Davis MD. Macular edema in diabetic retinopathy study patients. Diabetic retinopathy study report number 12. Ophthalmology 1987; 94(7): 754-60. [http://dx.doi.org/10.1016/S0161-6420(87)33526-2]

[9] Ferris FL III, Patz A. Macular edema. A complication of diabetic retinopathy. Surv Ophthalmol 1984; 28 (Suppl.): 452-61. [http://dx.doi.org/10.1016/0039-6257(84)90227-3] [PMID: 6379946]

[10] Yaseri M, Zeraati H, Mohammad K, *et al.* Intravitreal bevacizumab injection alone or combined with triamcinolone *versus* macular photocoagulation in bilateral diabetic macular edema; application of bivariate generalized linear mixed model with asymmetric random effects in a subgroup of a clinical

trial. J Ophthalmic Vis Res 2014; 9(4): 453-60.
[http://dx.doi.org/10.4103/2008-322X.150818] [PMID: 25709771]

[11] Bakri SJ, Kaiser PK. Posterior subtenon triamcinolone acetonide for refractory diabetic macular edema. Am J Ophthalmol 2005; 139(2): 290-4.
[http://dx.doi.org/10.1016/j.ajo.2004.09.038] [PMID: 15733990]

[12] Entezari M, Ahmadieh H, Dehghan MH, Ramezani A, Bassirnia N, Anissian A. Posterior sub-tenon triamcinolone for refractory diabetic macular edema: a randomized clinical trial. Eur J Ophthalmol 2005; 15(6): 746-50.
[PMID: 16329060]

[13] Panozzo G, Gusson E, Panozzo G, Dalla Mura G. Dexamethasone intravitreal implant for diabetic macular edema: indications for a PRN regimen of treatment. Eur J Ophthalmol 2015; 25(4): 347-51.
[http://dx.doi.org/10.5301/ejo.5000563] [PMID: 25633618]

[14] A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008; 115(9): 1447-1449, 1449.e1-1449.e10.
[http://dx.doi.org/10.1016/j.ophtha.2008.06.015] [PMID: 18662829]

[15] Wells JA, Glassman AR, Ayala AR, *et al.* Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015; 372(13): 1193-203.
[http://dx.doi.org/10.1056/NEJMoa1414264] [PMID: 25692915]

[16] Friberg TR, Karatza EC. The treatment of macular disease using a micropulsed and continuous wave 810-nm diode laser. Ophthalmology 1997; 104(12): 2030-8.
[http://dx.doi.org/10.1016/S0161-6420(97)30061-X] [PMID: 9400762]

[17] Moorman CM, Hamilton AM. Clinical applications of the MicroPulse diode laser. Eye (Lond) 1999; 13(Pt 2): 145-50.
[http://dx.doi.org/10.1038/eye.1999.41] [PMID: 10450372]

[18] Stanga PE, Reck AC, Hamilton AM. Micropulse laser in the treatment of diabetic macular edema. Semin Ophthalmol 1999; 14(4): 210-3.
[http://dx.doi.org/10.3109/08820539909069539] [PMID: 10758221]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 4

Central Retinal Vein Occlusion

Nelson Segovia Rodríguez*

Retina Department, Grupo de Clínicas IDB, Centro Profesional Arca, Barquisimeto, Venezuela

Central retinal vein occlusion (CRVO), a member of the group of vascular retinal diseases, is a sight-threatening condition that needs to be correctly diagnosed and treated in order to diminish its consequences, which can lead to painful blindness if neovascular glaucoma (NVG) develops. CRVO occurs predominantly in adults of 65 years old and over [1]; the prevalence does not differ by gender [2], and it is predominantly unilateral [3]. Some described systemic risk factors are end-organ damage from hypertension or diabetes, a hypercoagulable state, and a diagnosis of stroke or obstructive sleep apnea [4, 5]. The most described ocular risk factor is glaucoma. Patients with CRVO also show an increased (almost two-fold) incidence in cerebrovascular accidents compared with age and sex-matched controls in a US population [6].

ESSENTIALS OF DIAGNOSIS

Fortunately, this is a relatively easy condition to diagnose based mostly on its clinical features. CRVO commonly presents as a sudden and painless loss of vision. Occasionally, the vision loss occurs gradually, mostly happens at night time in the recumbent position probably by low blood pressure and/or high central venous pressure. The typical fundoscopic features appear in all the four quadrants of the fundus: venous tortuosity and dilation, retinal hemorrhages (scattered superficial and deep), and cotton wool spots (Figs. **1**-**3**). Macular edema and optic disc swelling are also present. All these features are present in varying degrees depending on the severity of the occlusion. Long-standing CRVO should be

* **Corresponding author Nelson Segovia Rodríguez:** Retina Department, Grupo de Clínicas IDB, Centro Profesional Arca, Barquisimeto, Venezuela; Tel: +57(315)5929618; Email: nelsegovia@yahoo.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

suspected if occluded or sheathed retinal veins are observed, or if vascular anastomoses (known as optociliary collaterals) at the optic disc are detected (Fig. **4**).

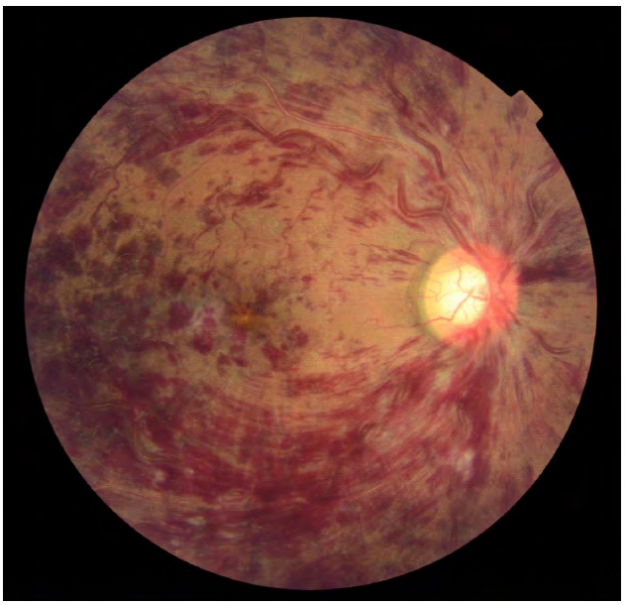


Fig. (1). Central Retinal Vein Occlusion. Fundus photograph shows tortuosity and dilatation of all branches of the central retinal vein, dot and flame-shaped hemorrhages, macular edema and optic nerve head cupping is noted. (Courtesy of Mitzy E. Torres Soriano).

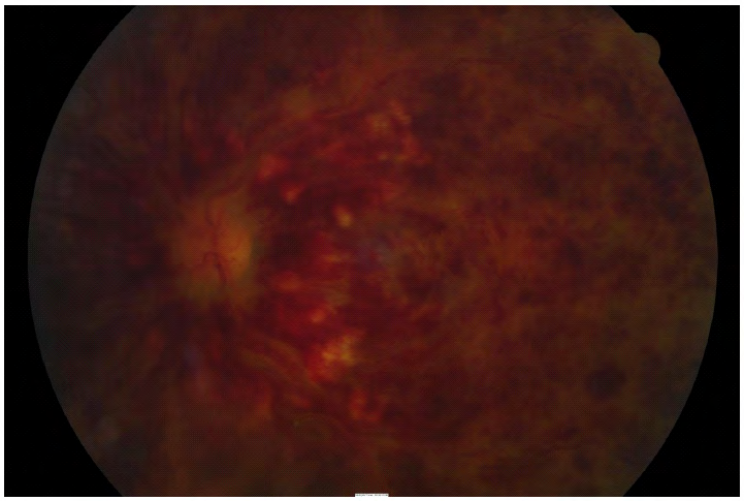


Fig. (2). Fundus photograph showing massive intraretinal hemorrhages, venular tortuosity, cotton wool spots and macular edema, corresponding to an ischemic CRVO.

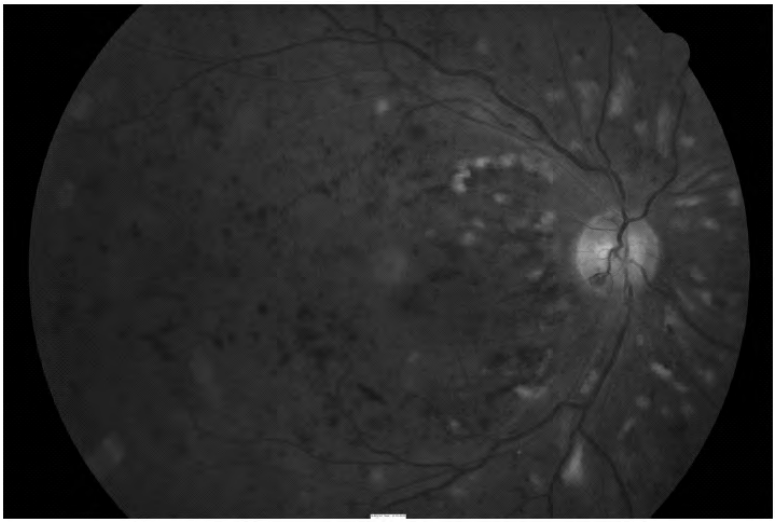


Fig. (3). Red-free photograph shows the typical features of CRVO, corresponding to a non-ischemic CRVO.

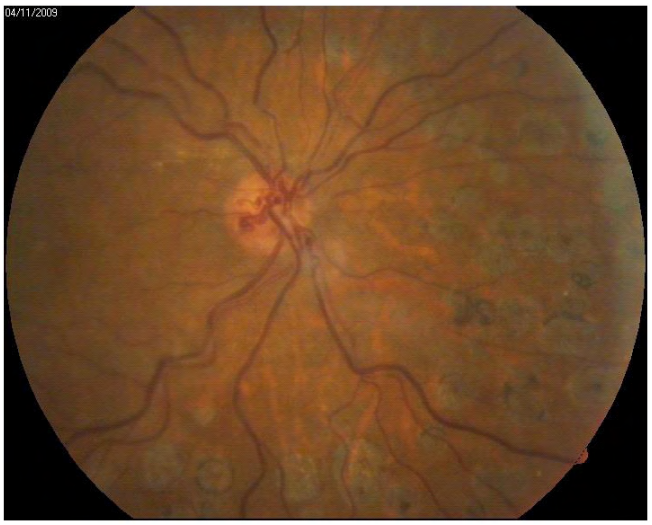


Fig. (4). Eye fundus of a patient with long standing CRVO demonstrating optociliary shunts vessels (optociliary collaterals) in the optic nerve head, and panretinal photocoagulation.

CRVO can be divided into 2 clinical types, ischemic and non-ischemic. Non-ischemic CRVO (Figs. **3**, **5**, **6**) is the most common type, accounting for about 75% CRVO cases. Non-ischemic CRVO is characterized by mild to moderate loss of acuity, usually 20/200 or better, and an absent or mild relative afferent pupillary defect. Conversion to ischemic CRVO occurs in 15% of cases within 4

months and 34% within 3 years. Ischemic CRVO (Figs. **2**, **7**, **8**) is characterized by severe visual loss (20/200 or worse), a marked afferent pupillary defect, extensive typical fundoscopic features (Fig. **7**), poor perfusion to retina, and presence of severe electroretinographic changes [7].

In addition to the general clinical assessment made by the patient's physician, including a complete blood count, renal function (serum levels of urea and creatinine), fasting serum lipids and fasting serum levels of glucose and glycated hemoglobin, a complete evaluation should include:

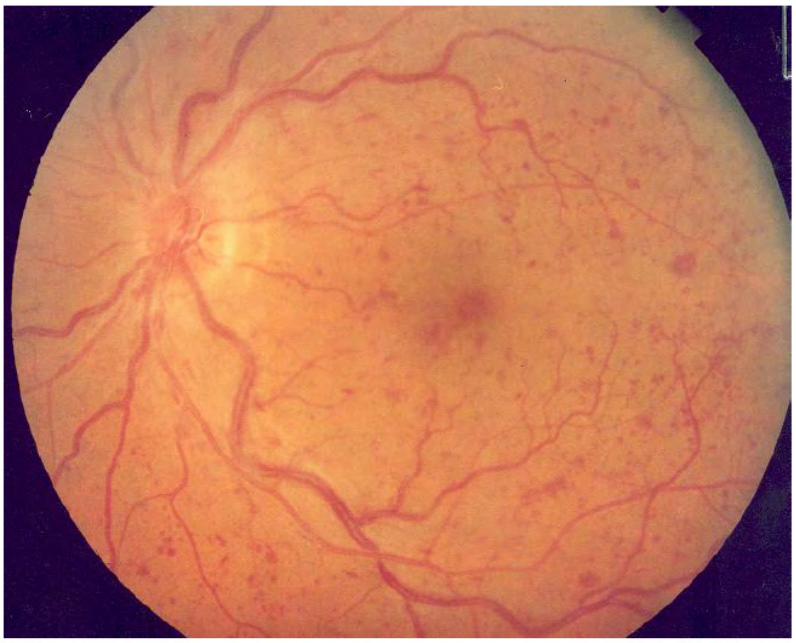


Fig. (5). Non-ischemic CRVO. Fundoscopy shows tortuosity and dilatation of all branches of the central retinal vein, dot/blot and flame-shaped hemorrhages, throughout all four quadrants. (Courtesy of Mitzy E. Torres Soriano).

Fluorescein Angiography (FA): Fluorescein angiography (FA) reveals marked delay in arteriovenous transit time, which is longer than 20 seconds, masking by retinal hemorrhages, vessel wall staining, leakage and perfusion status (greater than 10 disc areas of retinal capillary non-perfusion is the ischemic form) [7, 8] (Figs. **6**, **8-11**).

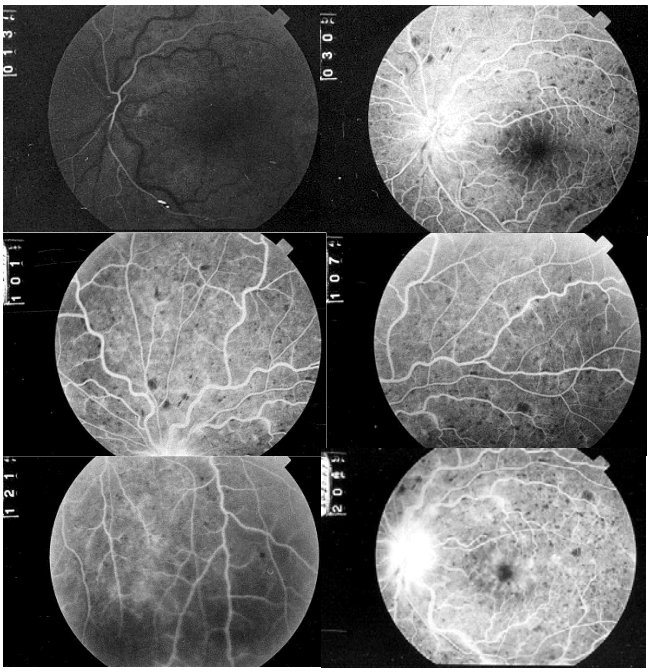


Fig. (6). Fluorescein angiography of (Fig. **5**). It reveals delay in arteriovenous transit time, blockage from retinal hemorrhages, vessel wall staining; in late phases cystoid macular edema (petalloid appearance) and optic nerve staining. (Courtesy of Mitzy E. Torres Soriano).

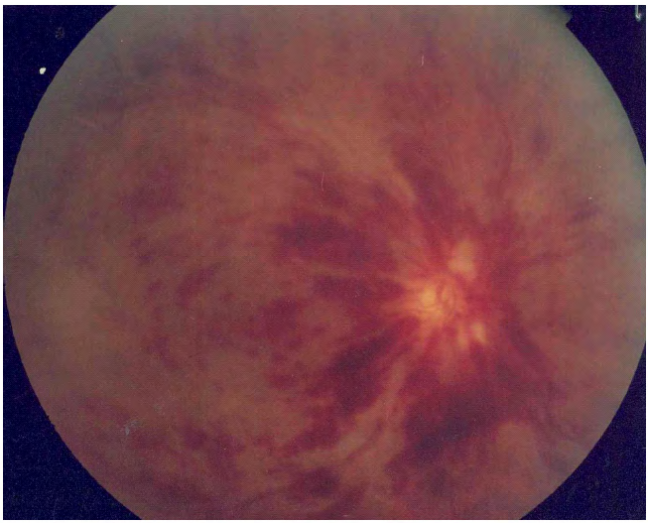


Fig. (7). Ischemic CRVO. Fundoscopy showing extensive hemorrhages in the posterior pole and giving the "blood and thunder appearance". (Courtesy of Mitzy E. Torres Soriano).

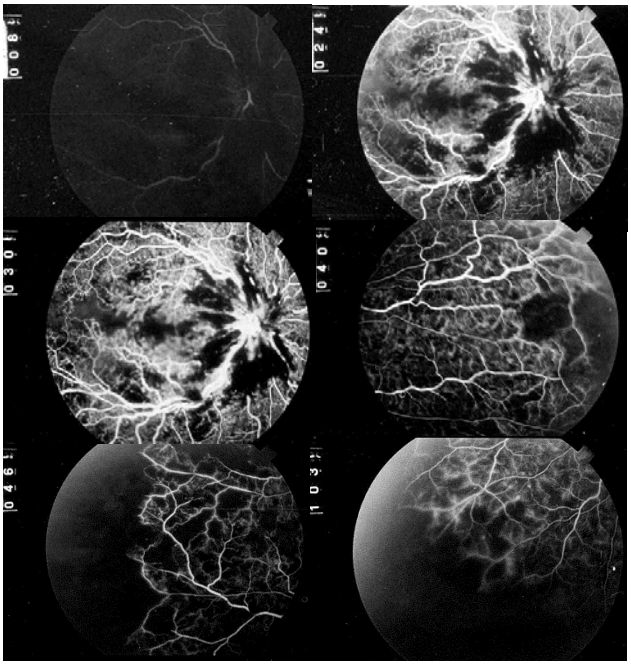


Fig. (8). Fluorescein angiography of the eye showing in Fig. (**7**), showing hypofluorescence due to blockage from hemorrhages in the retina, capillary non perfusion and areas of capillary leakage. (Courtesy of Mitzy E. Torres Soriano).

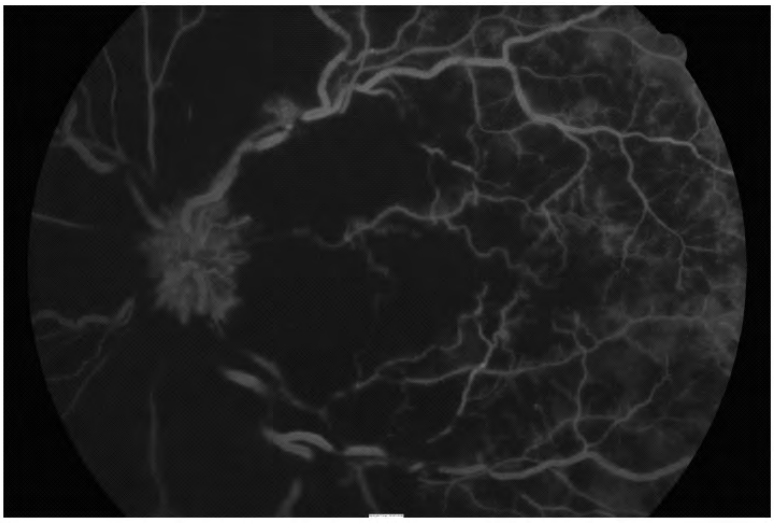


Fig. (9). Fluorescein angiography (FA) image showing optic nerve head swelling, engorged venules, hypofluorescence by blockage and capillary non-perfusion.

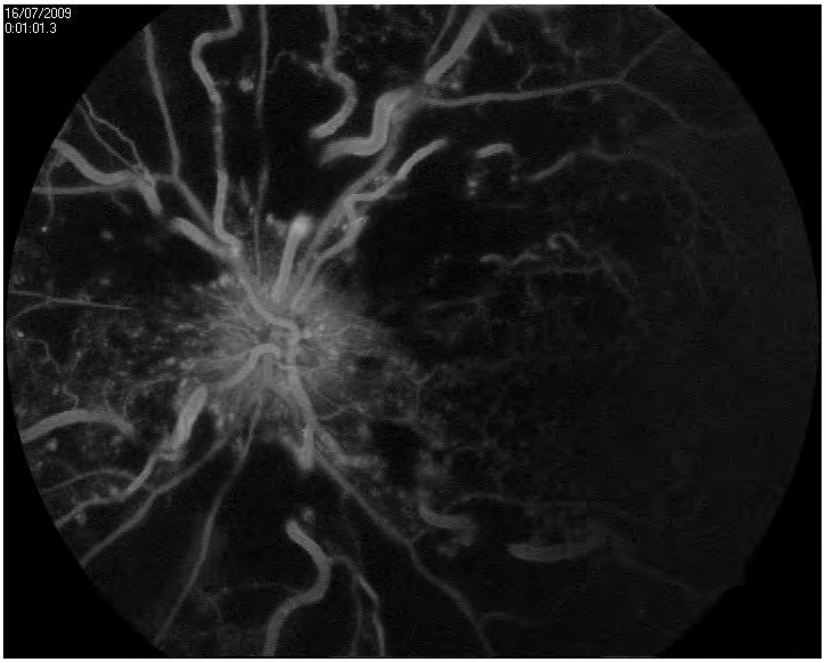


Fig. (10). FA image shows closely the capillary dilation in the optic nerve head and vessel wall staining.

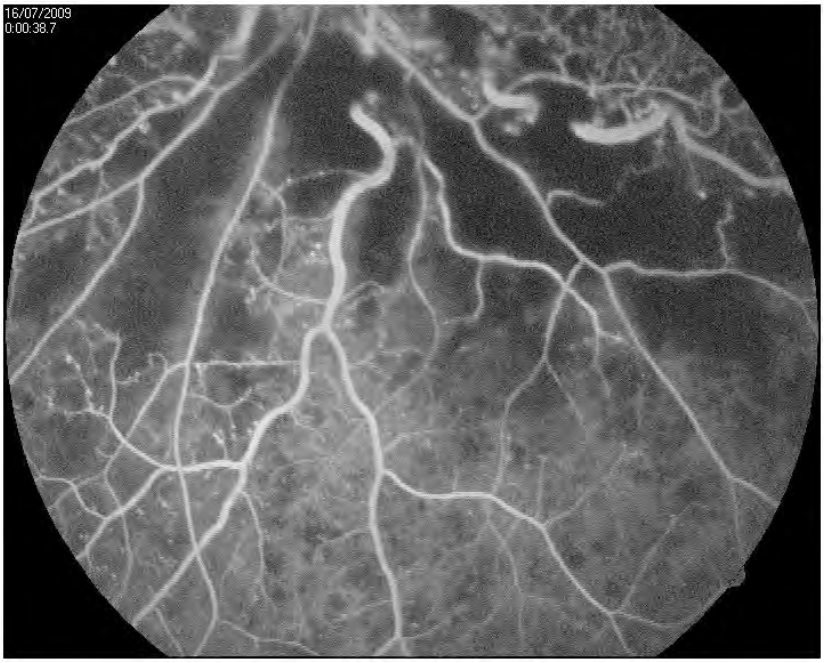


Fig. (11). FA of the mid-periphery showing zones of non-perfusion and capillary abnormalities.

Optical Coherence Tomography (OCT): Optical Coherence Tomography (OCT) images reveal that the increased retinal thickness is caused mostly by large cystoid spaces in the inner nerve layer of the foveal region and diffuse intraretinal edema of the foveal and perifoveal areas [7, 9] (Figs. **12**, **13**).

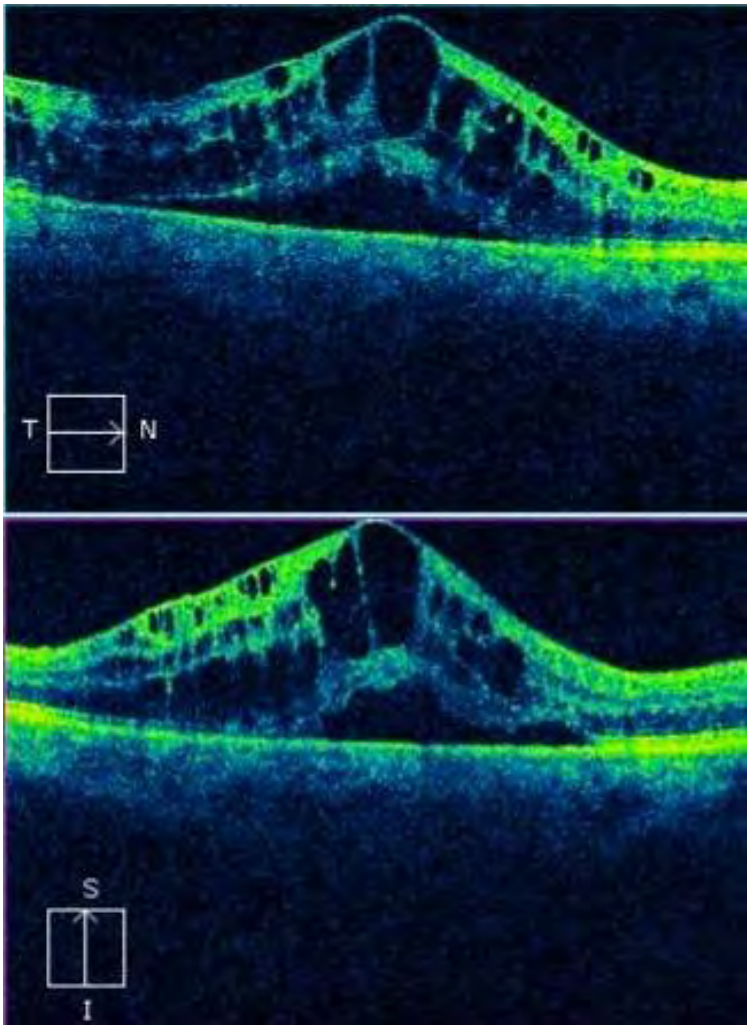


Fig. (12). Optical coherence tomography (OCT) of a patient with CRVO and associated macular edema showing a central field retinal thickness of 794 microns.

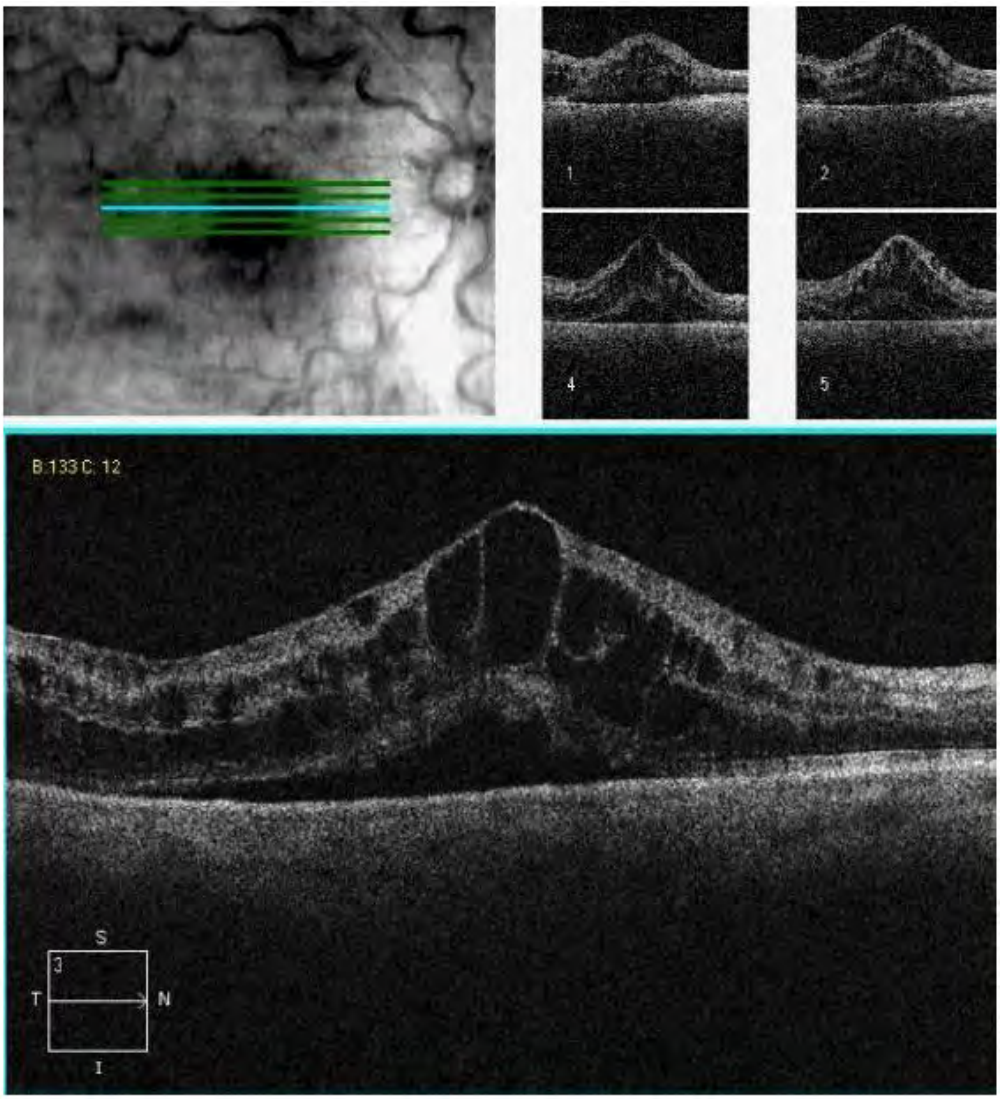


Fig. (13). OCT report of the same patient of Fig. (**12**) shows some clinical features of CRVO like intra retinal hemorrhages and venous tortuosity. In the OCT image, increased retinal thickness, intra retinal cystoid spaces of different sizes and neurosensory retina detached from retinal pigment epithelium can be observed (serous retinal detachment or subretinal fluid).

Electroretinogram (ERG): Electroretinogram (ERG) shows reduced scotopic and photopic b-wave amplitude in the ischemic form. Another important predictor of neovascularization is a delayed implicit time in the photopic 30Hz flicker ERG.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of CRVO is not a difficult task. Other pathologies such as diabetic retinopathy, hypertensive retinopathy, and hyperviscosity syndromes occur bilaterally. If CRVO occurs bilaterally, a careful clinical systemic examination should be done. Other entities that should be ruled out are anterior ischemic neuropathy and ocular ischemia with venous stasis retinopathy [10] caused by severe carotid artery obstructive disease. Most difficulties in the differential diagnosis are encountered with early, mild non-ischemic CRVO and late forms and complications that can mimic other conditions.

MANAGEMENT

Treatment of CRVO is mainly focused on macular edema and also on NVG. Many treatment options have been tried through the years from systemic, local (ocular medication) to surgical ones. The objective of this chapter is only to name a few of them, focusing on the actual trends.

Panretinal photocoagulation (PRP) (Fig. **4**) is indicated in the case of iris or angle neovascularization. In the case of optic disc neovascularization or neovascularization elsewhere, PRP also should be performed in order to avoid anterior segment neovascularization and the consequent NVG. It has been fully established in the CVOS Study that prophylactic treatment does not prevent iris and angle neovascularization. Furthermore, regression of iris and angle neovascularization in response to PRP is more likely to occur in eyes that have not been treated previously [11]. The main treatments for macular edema are intravitreal injections of ranibizumab, aflibercept, dexamethasone intravitreal implant, and off-label use of bevacizumab and triamcinolone. Ranibizumab showed to be effective, improving the best corrected visual acuity (BCVA) by 15 letters compared to placebo injections at six months [12, 13]. This improvement was also true with the use of bevacizumab [14]. Aflibercept also showed an improvement of BCVA, and this result was largely maintained between 6 to 12 months [15]. This evidence, based on randomized clinical trials, shows the important role of anti-vascular endothelial grow factor (anti-VEGF) in the treatment of CRVO (Fig. **14**). Dexamethasone intravitreal implants improved

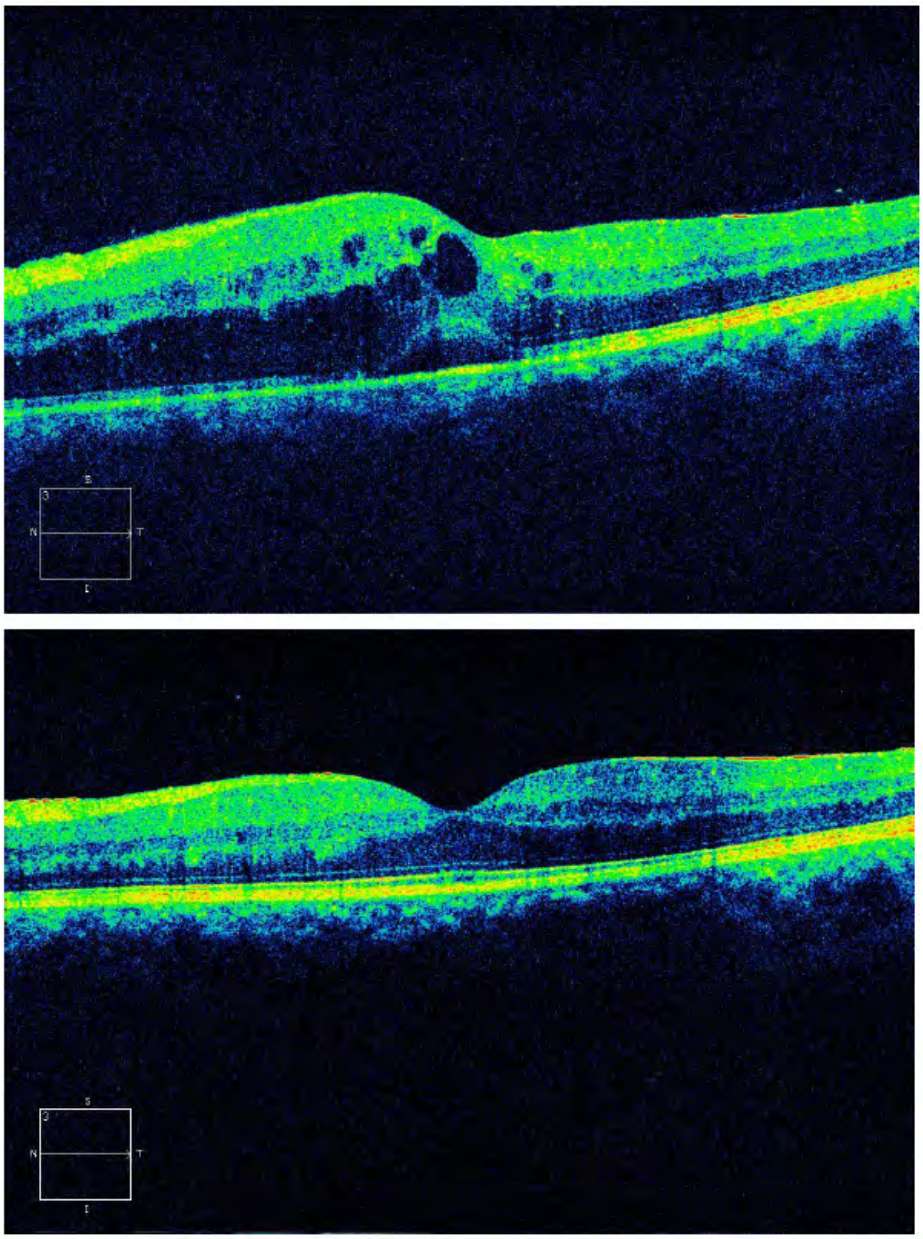


Fig. (14). Response to anti-VEGF treatment for macular edema secondary to CRVO. Top: OCT of an eye with non-ischemic CRVO, showing accumulation of intraretinal fluid and a subfoveal serous retinal detachment. Visual acuity was 20/40 Bottom: OCT of the same eye, after four doses of 1.25 mg intravitreal bevacizumab, showing resolution of intra and subretinal fluid. Visual acuity improved to 20/20. (Images courtesy of Gerardo Garcia-Aguirre, MD).

mean BCVA at 1, 2 and 3 months, but not at six months compared to placebo [16]. With the use of triamcinolone, the percentage of patients with a gain of BCVA of 15 letters or more was 26.5%, 25.6% and 6.8% for triamcinolone 1 mg, 4 mg and placebo, respectively. Both triamcinolone concentrations stabilized visual acuity at month 12 [17]. By comparing the issues of secondary effects between the use of anti-VEGF drugs and steroids, it has been observed that in the latter group the rise in intraocular pressure and rate of cataract progression were higher than in control groups [16, 17]. A study from the European Vitreoretinal Society also suggests that vitrectomy with internal limiting membrane peeling may be a good treatment for macular edema due to CRVO. In this study, the improvement of vision was better than other therapies at every time point in time [18]. In future, randomized clinical trials are needed to verify these results and establish a standard of care for the treatment of macular edema secondary to CRVO.

Follow up: Patients with CRVO should be seen monthly for 6 months to detect the onset of anterior segment neovascularization and to establish prompt treatment.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Mruthyunjaya P, Fekrat S. Central Retinal Vein Occlusion. In: Stephen J Ryan RETINA. Fourth Edition. Medical Retina: Elsevier 2006; II: pp. 1339-48. [http://dx.doi.org/10.1016/B978-0-323-02598-0.50076-8]

[2] Rogers S, McIntosh RL, Cheung N, *et al.* The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology 2010; 117(2): 313-9.e1. [http://dx.doi.org/10.1016/j.ophtha.2009.07.017] [PMID: 20022117]

[3] Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc 2000; 98: 133-41.

[PMID: 11190017]

[4] Stem MS, Talwar N, Comer GM, Stein JD. A longitudinal analysis of risk factors associated with central retinal vein occlusion. Ophthalmology 2013; 120(2): 362-70.
[http://dx.doi.org/10.1016/j.ophtha.2012.07.080] [PMID: 23177364]

[5] Risk factors for central retinal vein occlusion. Arch Ophthalmol 1996; 114(5): 545-54.
[http://dx.doi.org/10.1001/archopht.1996.01100130537006] [PMID: 8619763]

[6] Werther W, Chu L, Holekamp N, Do DV, Rubio RG. Myocardial infarction and cerebrovascular accident in patients with retinal vein occlusion. Arch Ophthalmol 2011; 129(3): 326-31.
[http://dx.doi.org/10.1001/archophthalmol.2011.2] [PMID: 21402990]

[7] Hayreh SS. Classification of central retinal vein occlusion. Ophthalmology 1983; 90(5): 458-74.
[http://dx.doi.org/10.1016/S0161-6420(83)34530-9] [PMID: 6877778]

[8] Wong T, Scott I. Clinical practice. Retinal-vein occlusion. N Engl J Med 2010; 363(22): 2135-44.

[9] Ko TH, Fujimoto JG, Schuman JS, *et al.* Comparison of ultrahigh- and standard-resolution optical coherence tomography for imaging macular pathology. Ophthalmology 2005; 112(11): 1922.e1-1922.e15.
[http://dx.doi.org/10.1016/j.ophtha.2005.05.027] [PMID: 16183127]

[10] Kearns TP, Hollenhorst RW. Venous-stasis retinopathy of occlusive disease of the artery. Proc Staff Meet Mayo Clin 1963; 38: 304-12.
[PMID: 14043286]

[11] A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The central vein occlusion study group N report. Ophthalmology 1995; 102(10): 1434-44.
[http://dx.doi.org/10.1016/S0161-6420(95)30848-2] [PMID: 9097789]

[12] Brown DM, Campochiaro PA, Singh RP, *et al.* Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010; 117(6): 1124-1133.e1.
[http://dx.doi.org/10.1016/j.ophtha.2010.02.022] [PMID: 20381871]

[13] Kinge B, Stordahl PB, Forsaa V, *et al.* Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study. Am J Ophthalmol 2010; 150(3): 310-4.
[http://dx.doi.org/10.1016/j.ajo.2010.03.028] [PMID: 20591399]

[14] Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. Ophthalmology 2012; 119(12): 2587-91.
[http://dx.doi.org/10.1016/j.ophtha.2012.06.037] [PMID: 22902212]

[15] Brown DM, Heier JS, Clark WL, *et al.* Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol 2013; 155(3): 429-437.e7.
[http://dx.doi.org/10.1016/j.ajo.2012.09.026] [PMID: 23218699]

[16] Haller JA, Bandello F, Belfort R Jr, *et al.* Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology

2010; 117(6): 1134-1146.e3.
[http://dx.doi.org/10.1016/j.ophtha.2010.03.032] [PMID: 20417567]

[17] Ip MS, Scott IU, VanVeldhuisen PC, *et al.* A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care *vs* Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. Arch Ophthalmol 2009; 127(9): 1101-14.
[http://dx.doi.org/10.1001/archophthalmol.2009.234] [PMID: 19752419]

[18] Adelman R, Parnes A, Bopp S, Saad I, Ducournau D. 2015; Strategy for the management of macular edema in retinal vein occlusion: The European vitreo retinal society macular edema study. Biomed Res Int 2015; 2015: 870987.

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 5

Branch Retinal Vein Occlusion

Liriany Arrieta Ruiz[1] and **Gerardo García Aguirre**[2,*]

[1] *Unidad Popular de Ojos (UPO), Maracay, Venezuela*

[2] *Retina Department, Asociación para Evitar la Ceguera en Mexico, Mexico City, Mexico*

Branch Retinal Vein Occlusion (BRVO) is a common retinal vascular disease caused by the occlusion of one of the branches of the central retinal vein, affecting only a portion, typically a quadrant, of the posterior pole [1]. It is three times more common than the central retinal vein occlusion, and onset usually occurs in the elderly. There are some risks factors for its development: hypertension, cardiovascular disease, obesity and open angle glaucoma.

ESSENTIALS OF DIAGNOSIS

Patients usually complain of a sudden onset of blurred vision or central visual field defect.

Upon ophthalmologic examination, typical findings include superficial hemorrhages, which are usually flame-shaped, retinal edema, and cotton-wool spots in a sector of retina drained by the affected vein (Figs. **1**-**3**). The horizontal raphe is respected.

In the chronic stage (Fig. **4**), hemorrhages may be absent and macular edema with telangiectatic vessels can be observed, extending across the horizontal raphe. The quadrant most commonly affected is the superotemporal (63%) [2].

* **Corresponding author Gerardo García Aguirre:** Retina Department, Asociación para Evitar la Ceguera en Mexico, Vicente García Torres 46, San Lucas Coyoacan, Mexico City 04030, Mexico; Tel: +52 (55) 10841400; Email: jerry_gar_md@yahoo.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

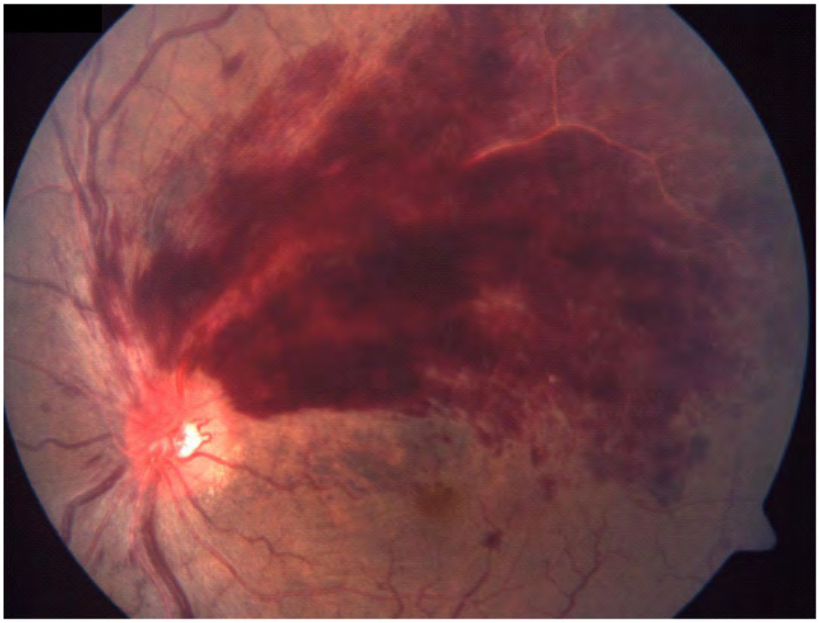


Fig. (1). Flamed-shaped hemorrhages and retinal edema in superior macular area. (Courtesy of Gerardo Garcia Aguirre (Mexico)).

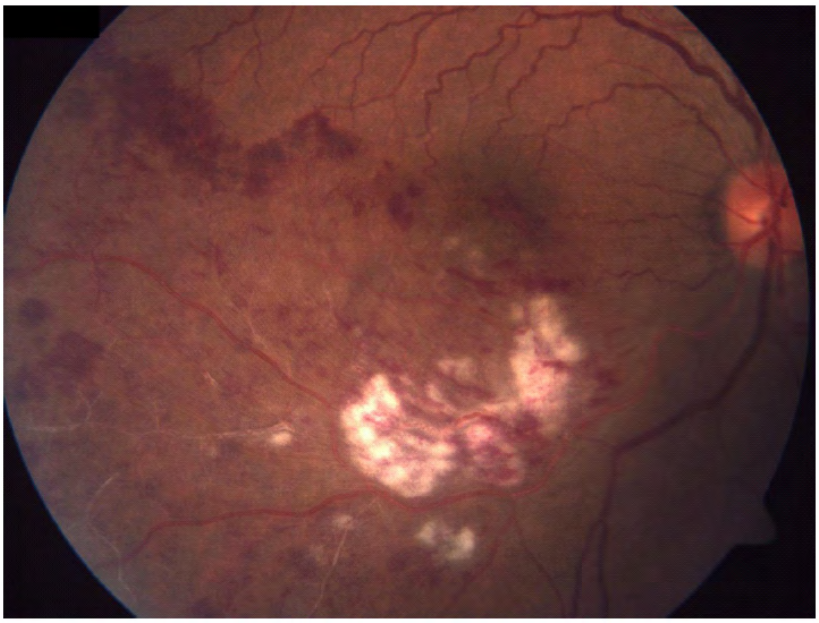


Fig. (2). Retinal hemorrhages, cotton-wool spots and sclerotic vessels in inferotemporal BRVO. (Courtesy of Gerardo Garcia Aguirre (Mexico)).

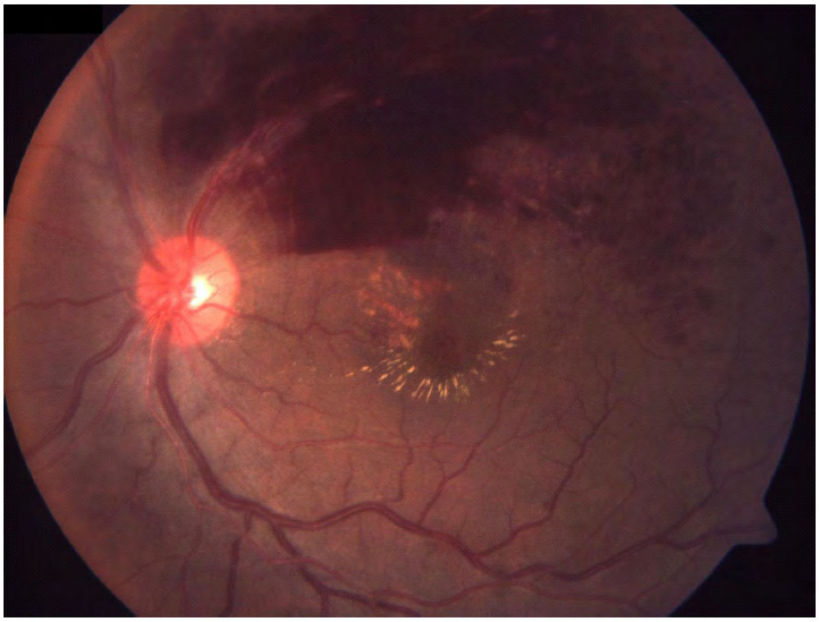


Fig. (3). Intraretinal hemorrhages in the superotemporal area and macular edema. (Courtesy of Gerardo Garcia Aguirre (Mexico)).

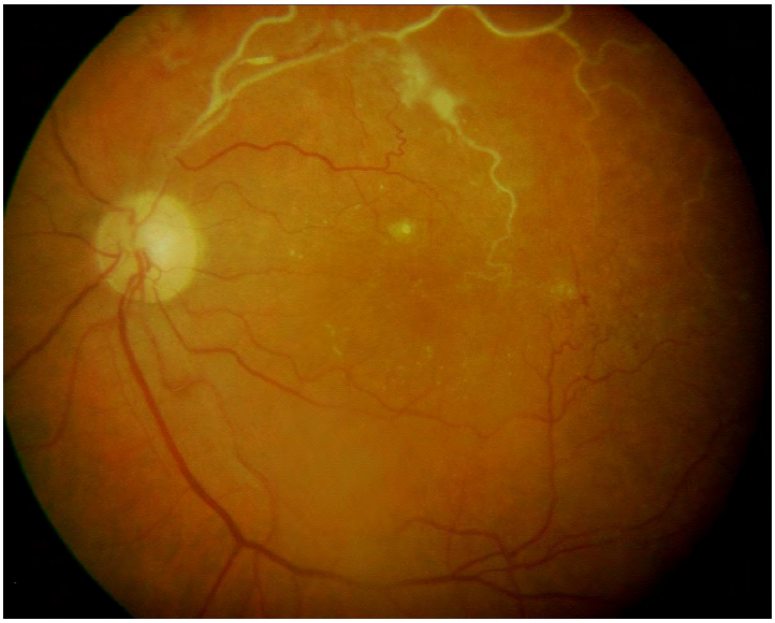


Fig. (4). Left eye: Chronic superior temporal branch retinal vein occlusion, sclerotic vessels and neovascularization. Courtesy of Luis Miguel Suarez Tata MD (Venezuela).

BRVO can be subdivided as ischemic or non-ischemic; the non-ischemic type is associated with a more favorable prognosis. This classification is based on findings observed in a fluorescein angiogram (FA). Non-ischemic BRVO is defined as the absence of retinal neovascularization and areas of capillary non-perfusion that amount to less than 5 disc areas. Ischemic BRVO is characterized by 5 or more disc areas of capillary non-perfusion and/or the presence of retinal neovascularization. Retinal neovascularization may lead to vitreous hemorrhage.

FA and optical coherence tomography (OCT) are helpful diagnostic tools. Findings in FA include delayed venous filling, hypofluorescence caused by hemorrhages and capillary non-perfusion, dilation and tortuosity of veins, leakage in case of neovascularization and macular edema (Figs. **5**-**8**). OCT is used as a rapid and noninvasive way of monitoring macular edema (Fig. **9**). Eyes may present cystoid macular edema and serous retinal detachment extending into the fovea.

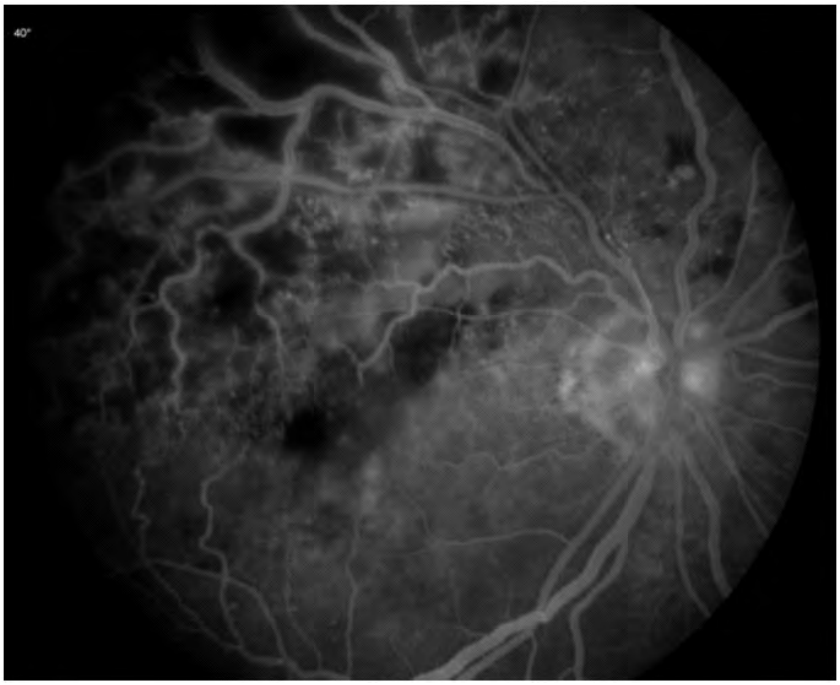


Fig. (5). FA shows hypofluorescence caused by hemorrhages and areas of capillary non-perfusion (*Courtesy by Claudia Arrieta).

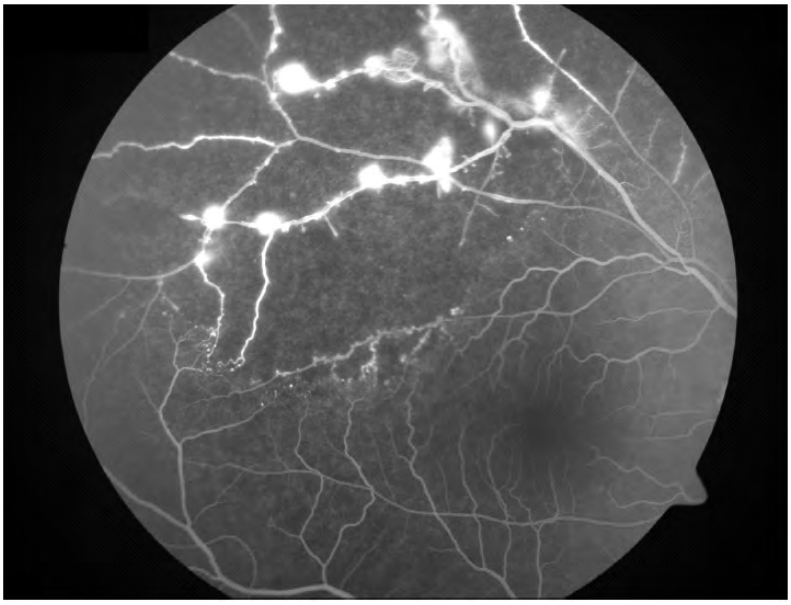


Fig. (6). FA shows areas of capillary non-perfusion, dilatation of veins, retinal telangiectasias and neovascularization. Courtesy of Gerardo Garcia Aguirre (Mexico).

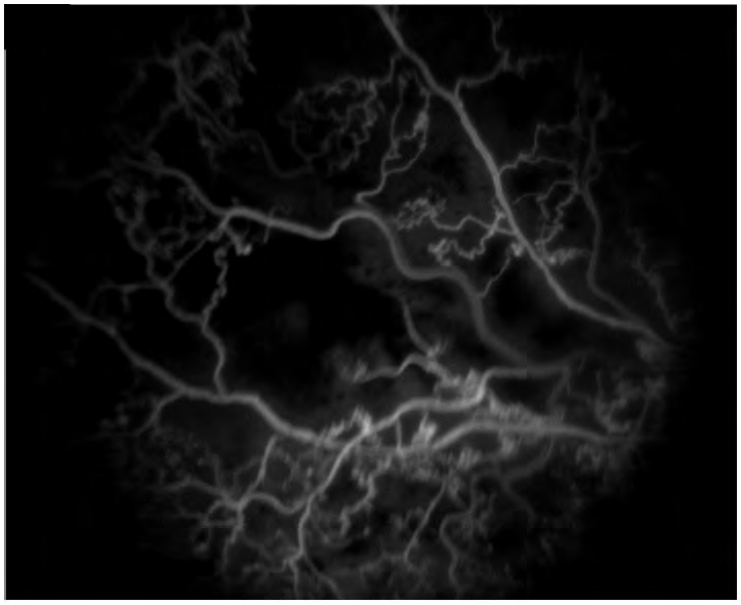


Fig. (7). FA: Ischemic BRVO. Hypoflourescence caused by hemorrhages, capillary non perfusion and delayed venous filling, dilatation and tortuosity of veins. Areas of non-perfusion exceed 5 disc areas (*Courtesy by Claudia Arrieta).

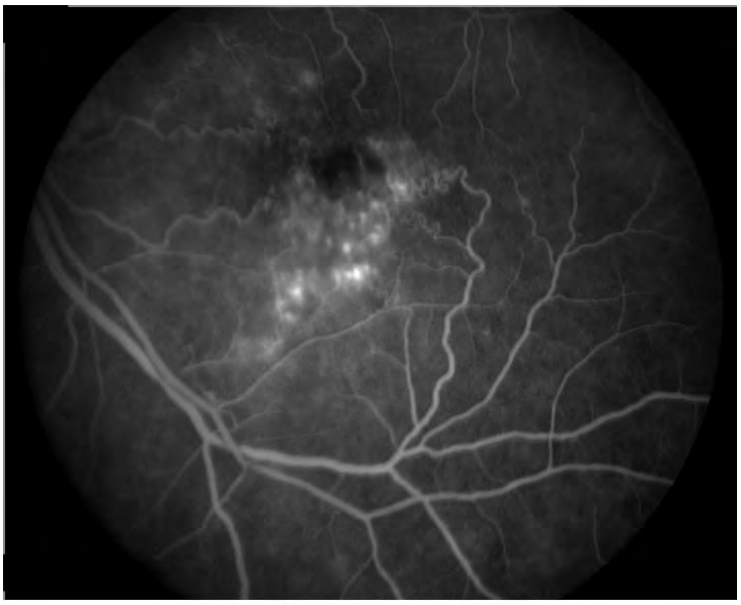


Fig. (8). Secondary retinal telangiectasias in an eye with history of inferotemporal BRVO (*Courtesy by Claudia Arrieta).

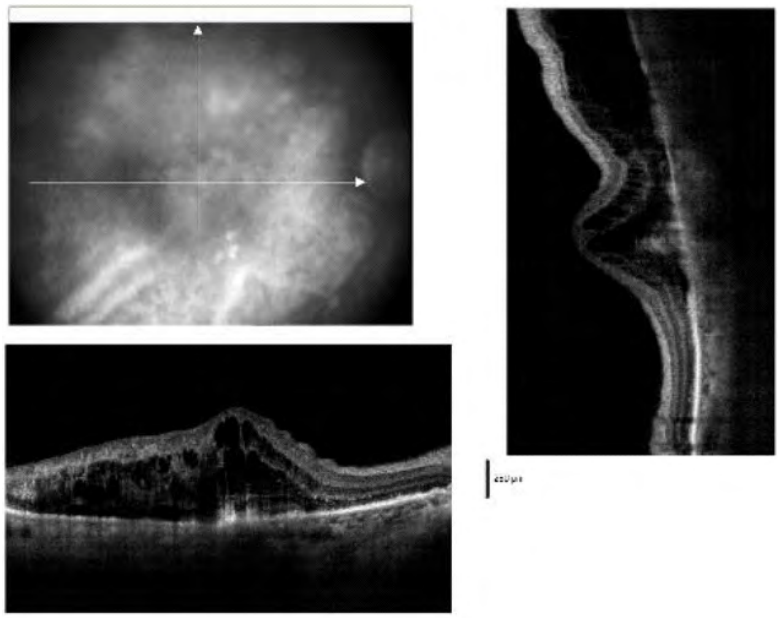


Fig. (9). OCT: Cystoid macular edema and serous retinal detachment secondary to BRVO (*Courtesy by Claudia Arrieta). (*) FA and OCT were performed by Claudia Arrieta MD (Venezuela).

DIFFERENTIAL DIAGNOSIS

The principal differential diagnoses are diabetic retinopathy and hypertensive retinopathy.

MANAGEMENT

Management is directed towards the most significant complications of BRVO: macular edema and retinal neovascularization [3].

Macular edema may be managed expectantly for a short period of time (usually up to 30 days), since some cases may regress spontaneously. The BVOS study demonstrated that macular grid laser photocoagulation was helpful for eyes with vision of 20/40 or worse [4, 5]. The current gold-standard for treatment, however, is the injection of intravitreal anti-VEGF agents. All three available agents (ranibizumab [6, 7], aflibercept [8] and bevacizumab [9]) have proven to be safe and effective for the treatment of macular edema, with significant reduction of macular thickness and improvement in visual acuity (Fig. **10**). Intravitreal steroids such as triamcinolone [10] or dexamethasone [11] have also proven to reduce macular edema secondary to BRVO, although results are not as favorable as the ones obtained with anti-VEGF agents, with the additional concern of side effects such as cataract or intraocular pressure elevation.

Eyes with retinal neovascularization should be treated with retinal laser photocoagulation directed toward areas of capillary non-perfusion observed in FA, to decrease the risk of vitreous hemorrhage and tractional retinal detachment [5].

Pars-plana vitrectomy should be considered in eyes with persistent vitreous hemorrhage, tractional retinal detachment or epiretinal membrane.

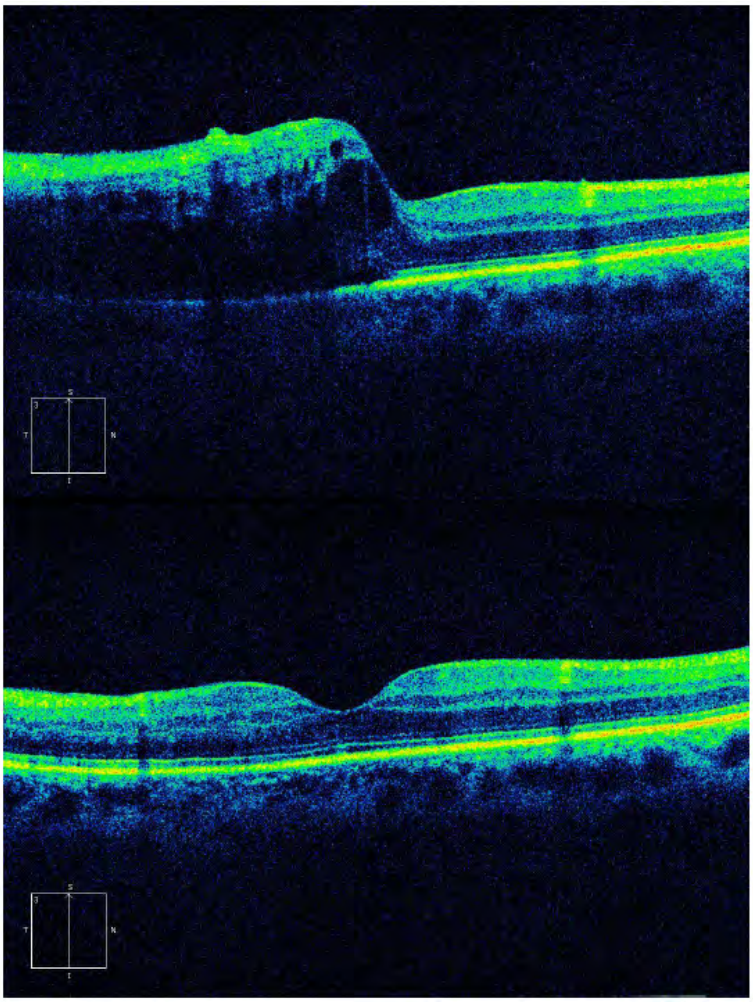


Fig. (10). Response to anti-VEGF treatment for macular edema secondary to an inferotemporal BRVO. Top: OCT of an eye with non-ischemic BRVO, showing accumulation of intraretinal fluid and a subfoveal serous retinal detachment Note the sparing of the superior macula (right side of the image). Visual acuity was 20/60 Bottom: OCT of the same eye, after three doses of 1.25 mg intravitreal aflibercept, showing resolution of intra and subretinal fluid. Visual acuity improved to 20/20 (Images courtesy of Gerardo Garcia-Aguirre, MD).

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Jay SD. Ophthalmology. 3rd ed., Mosby Elsevier 2009.

[2] Rogers S, McIntosh RL, Cheung N, *et al.* The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology 2010; 117(2): 313-9.e1.
[http://dx.doi.org/10.1016/j.ophtha.2009.07.017] [PMID: 20022117]

[3] Karia N. Retinal vein occlusion: pathophysiology and treatment options. Clin Ophthalmol 2010; 4: 809-16.
[http://dx.doi.org/10.2147/OPTH.S7631] [PMID: 20689798]

[4] Guyer DR, Lampert R, *et al.* Retina-Vitreous-Macula: Branch Retinal Vein Occlusion. W.B. Saunders Company 1999; pp. 308-15.

[5] The branch vein occlusion study group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol 1984; 98(3): 271-82.
[http://dx.doi.org/10.1016/0002-9394(84)90316-7] [PMID: 6383055]

[6] Campochiaro PA, Heier JS, Feiner L, *et al.* Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010; 117(6): 1102-1112.e1.
[http://dx.doi.org/10.1016/j.ophtha.2010.02.021] [PMID: 20398941]

[7] Heier JS, Campochiaro PA, Yau L, *et al.* Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology 2012; 119(4): 802-9.
[http://dx.doi.org/10.1016/j.ophtha.2011.12.005] [PMID: 22301066]

[8] Campochiaro PA, Clark WL, Boyer DS, *et al.* Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. Ophthalmology 2015; 122(3): 538-44.
[http://dx.doi.org/10.1016/j.ophtha.2014.08.031] [PMID: 25315663]

[9] Wu L, Arevalo JF, Roca JA, *et al.* Comparison of two doses of intravitreal bevacizumab (Avastin) for treatment of macular edema secondary to branch retinal vein occlusion: results from the Pan-American Collaborative Retina Study Group at 6 months of follow-up. Retina 2008; 28(2): 212-9.
[http://dx.doi.org/10.1097/IAE.0b013e3181619bee] [PMID: 18301025]

[10] Scott IU, Ip MS, VanVeldhuisen PC, *et al.* A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care *vs* Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. Arch Ophthalmol 2009; 127(9): 1115-28.
[http://dx.doi.org/10.1001/archophthalmol.2009.233] [PMID: 19752420]

[11] Haller JA, Bandello F, Belfort R Jr, *et al.* Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology 2011; 118(12): 2453-60.
[http://dx.doi.org/10.1016/j.ophtha.2011.05.014] [PMID: 21764136]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 6

A Three-Dimensional Look into Hypertensive Retinopathy

Rafael Muci Mendoza*

Universidad Central de Venezuela, Unidad de Neurooftalmología, Hospital Vargas de Caracas, Venezuela

ESSENTIALS OF DIAGNOSIS

The amount of arteriolar damage signals the individual prognosis of a hypertensive subject; therefore, any information about its severity will be extremely helpful in a practical way. Arteriolosclerosis is the hardening and narrowing of the arterioles secondary to systemic arterial hypertension [1]. Fundoscopic changes reflect the duration, severity, and the right way to control hypertension, so monitoring the changes in the retina, the choroid, and the optic nerve will help the physician determine the best course of care of the hypertensive patient. "Essential" or "primary" hypertension is a pathological condition characterized by endothelial dysfunction that affects vessel structure and tone, thus causing constriction of blood vessels and narrowing of small arteries and arterioles in the peripheral vascular bed. It is a silent disease and its injurious effect begins many years before organic damage becomes clinically apparent [2, 3]. Arteriosclerosis follows chronic arterial hypertension like a shadow [4]. The amount of arteriolar damage is the essential piece of information that signals the individual prognosis of a hypertensive subject [5, 6]. Retinal arterioles share similar anatomical, physiological and embryological characteristics with cerebral, coronary and renal arterioles. Thus, the ocular fundus and the retina are like doors open to medical curiosity that enable noninvasive, *in vivo* testing of circulation,

* **Corresponding author Rafael Muci Mendoza:** Universidad Central de Venezuela, Unidad de Neurooftalmología, Hospital Vargas de Caracas, Venezuela; Email: rafalemuci@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

since a direct fundoscopy allows for easy and bedside observation of the arterioles. This can lead to extremely important data when the resulting information is applied to other arterial territories [2].

When considered individually, the fundoscopic technique gains more importance than a blood pressure check. The reason is that it provides first-hand knowledge to the trained eye about past and future events in the disease natural history, thus providing a *three dimensional look into hypertensive patients*: 1) The acute or insidious damage to the arteries in the past, since the chronic form causes progressive arteriolosclerotic changes, unlike recently diagnosed hypertension; 2) "*Here and now*": the current situation of arteriolar and retinal damage, manifestation of the process activity, probable diastolic blood pressure readings, and, especially, which phase of the evolution process the patient is going through: incorrectly called benign hypertension *vs.* accelerated-malignant hypertension; 3) The possibility of differentiating "secondary" forms of hypertension and primary hypertension, and even the possibility of going deeper into the etiologic diagnosis; 4) Prognosis of the disease in untreated patients; and 5) Objective assessment of the response to different invasive and noninvasive treatments [4].

We consider the following fundoscopic changes of hypertension, which depend on diastolic blood pressure readings:

- Arteriolar signs typical of chronic hypertension. 1) Diffuse constriction that is difficult to observe if it is not in youthful vessels with normal auto regulation (pregnancy toxemia, acute diffuse glomerulonephritis). It is reversible. 2) Focal or localized constriction: apparent notches along the arterioles where caliber narrows and axial reflex is less bright. They are easily visible and constitute morphological wall changes that cannot be reversed with treatment. A significant number of them suggest left ventricular hypertrophy (Fig. **1**). 3) Irreversible generalized arteriolosclerosis: This means long-standing hypertension. It manifests as exaggerated axial reflex over arterioles, copper wiring and silver wiring of arterioles, sheathing of arterioles, and arteriolovenous crossing changes in its four grades of progressive severity: concealment, tapering, deflection with depression and compression (Figs. **1**-**8**).

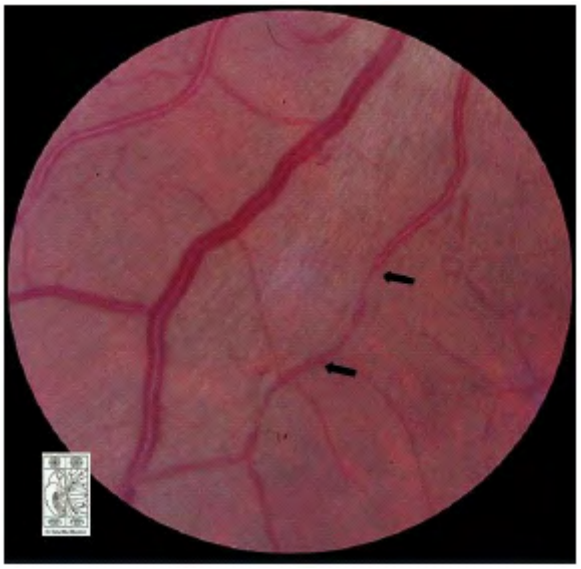


Fig. (1). Hypertensive arteriolosclerosis – time function: Arteriolar narrowing and focal narrowing.

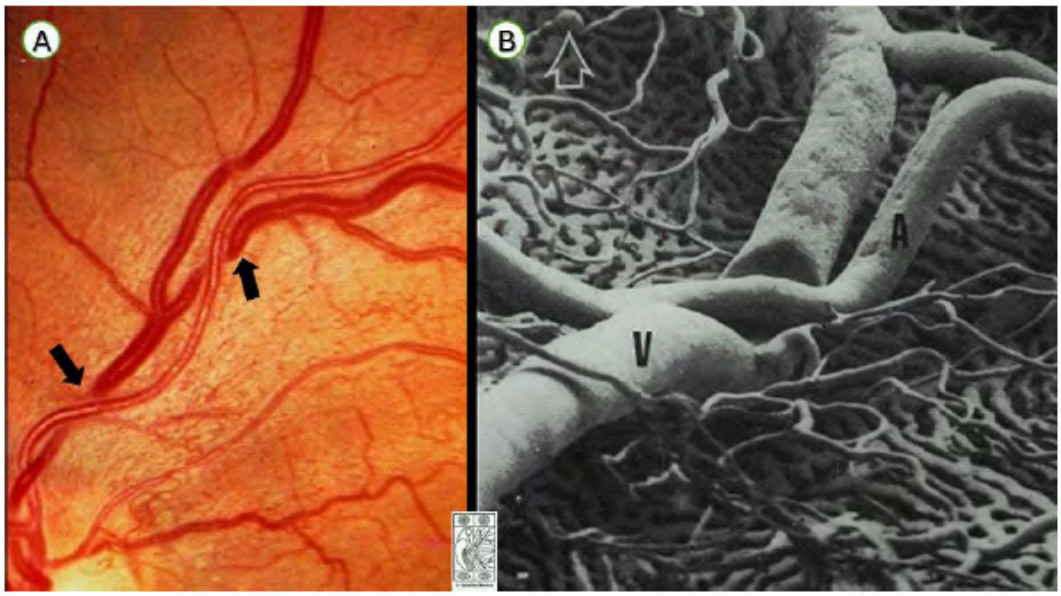


Fig. (2). (**A**) Chronic hypertensive arteriolosclerosis: Copper wiring of arteriole. Abnormal arteriolovenous crossing of higher grade. Notice that the end that is distal from the crossing is wider than the proximal end, which denotes compression. A thin layer of collateral vessels can be seen adjacent to the optic disc. (**B**) Abnormal crossing (scanning microscopy).

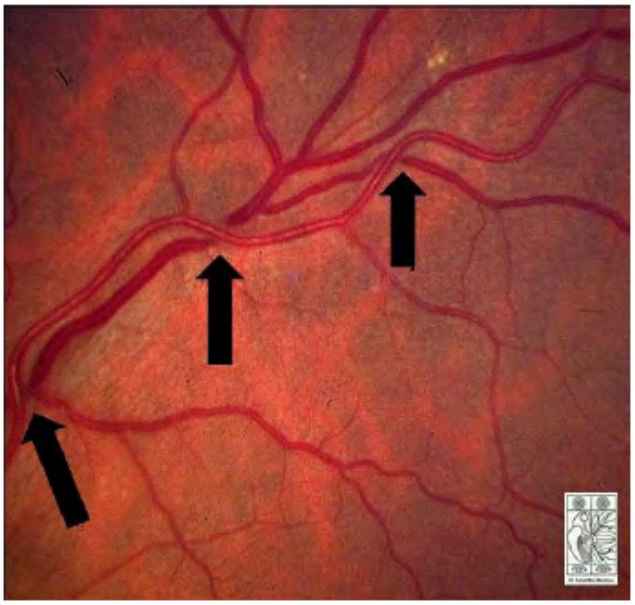


Fig. (3). Chronic arterial hypertension: copper wiring of arterioles and arteriolovenous crossing of higher grade.

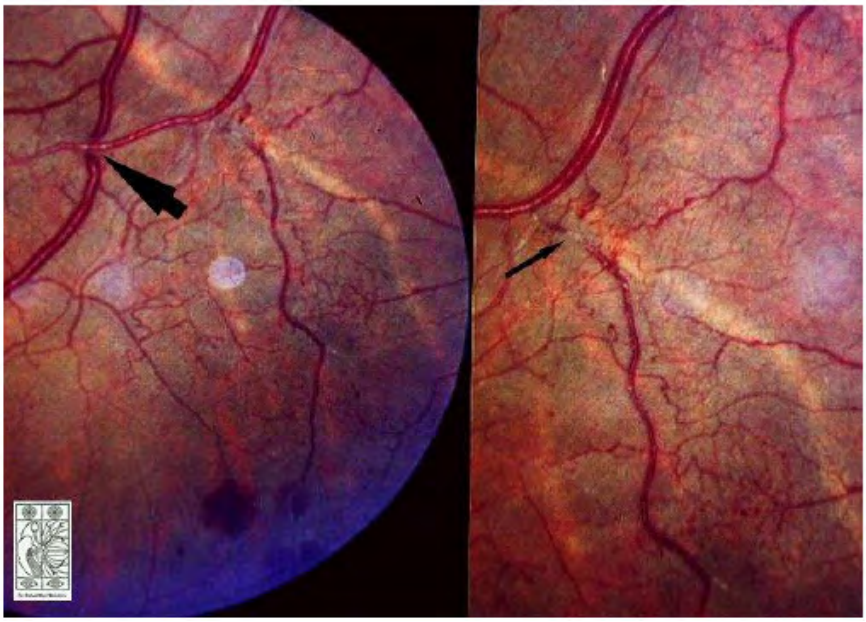


Fig. (4). Chronic arterial hypertension: copper wiring of arterioles and abnormal arteriolovenous crossings; venous collateral network and deep hemorrhages (manifestation of retinal ischemia); Silver wiring of one segment of the arteriole.

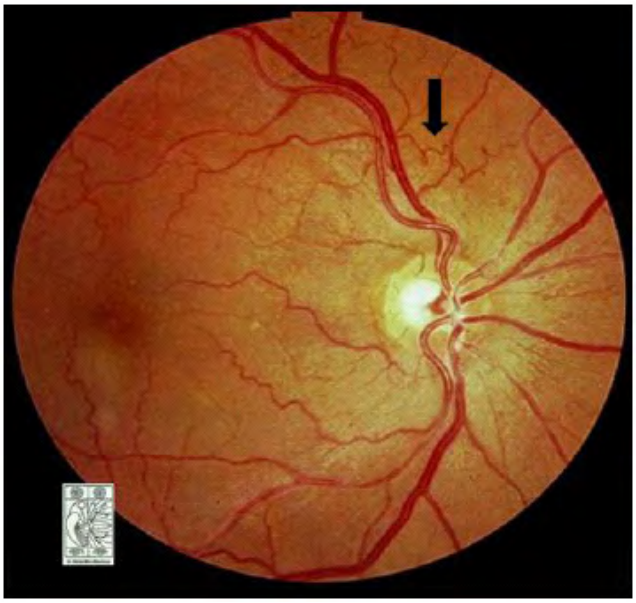


Fig. (5). Chronic arterial hypertension: copper wiring of arterioles and abnormal arteriolovenous crossings; Arteriolovenous communication.

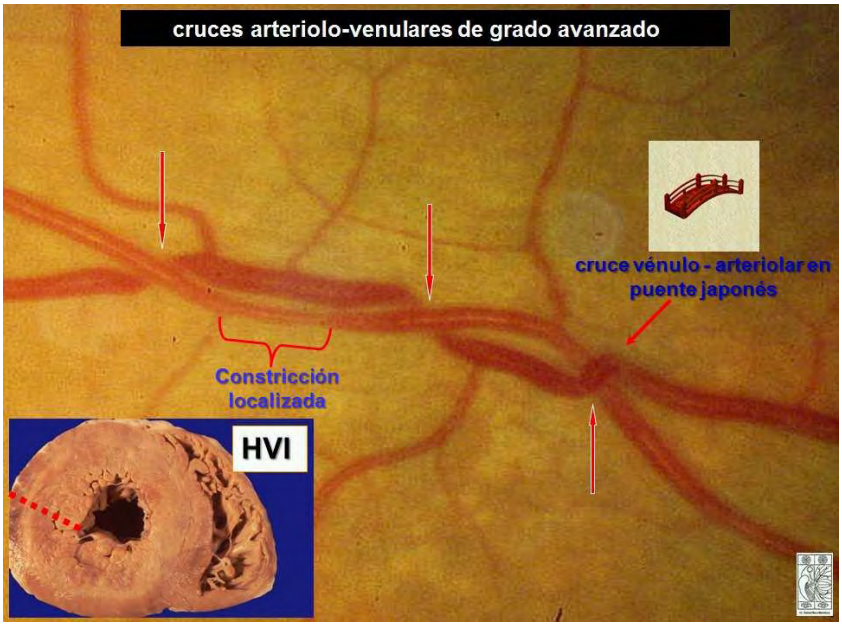


Fig. (6). Advanced retinal arteriolosclerosis: Copper wiring, segmental constriction, arteriolovenous crossings of higher grade; arteriolovenous and venoule-arteriolar –similarity with a Japanese bridge; Systemic correlation of left ventricular hypertrophy.

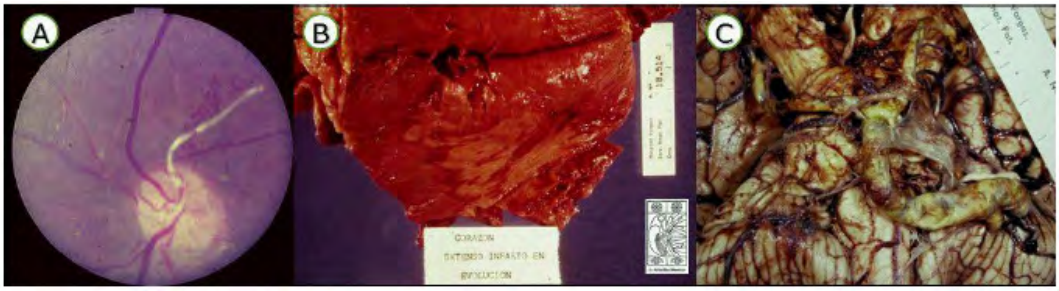


Fig. (7). (**A**) Old occlusion of superior temporal artery –silver wiring of arteriole– with superfluous collateral vessels; (**B**) Acute myocardial infarction in evolution; (**C**) Basilar artery atherosclerosis.

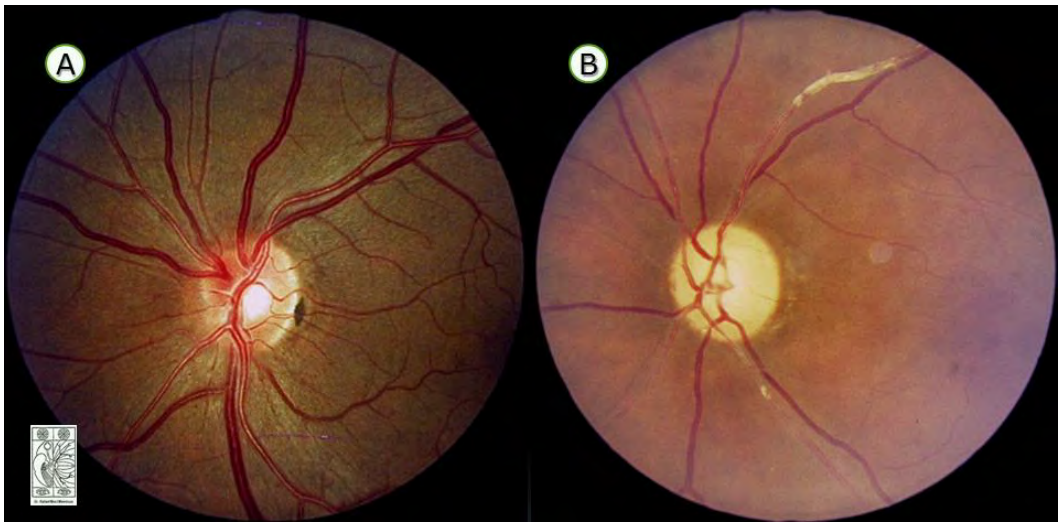


Fig. (8). (**A**) Chronic hypertensive arteriolosclerosis; (**B**) Embolic occlusion of the central retinal artery and its branch arterioles.

- Retinal signs are typical of accelerated-malignant retinopathy. It is associated with the presence of fibrinoid necrosis in the kidney and includes retinal edema, cotton wool spots (accumulation of axoplasmic material) that are characteristic of this acute phase and are an invaluable sign of alarm because it is the way the retina "complains" when diastolic pressure exceeds 130 mmHg.

Light microscopy reveals the presence of so-called "cytoid bodies" because of its similarity with cells; hard exudates in the deeper retinal layers. Its pathogenesis combines alteration of the retinal capillary network and changes in the choriocapillaris of the choroid. When they are located in the macular area, they

arrange in a star-shaped pattern around the fovea (macular star or stellar retinopathy); optic disc edema (a manifestation of hypertensive optic neuropathy) [2] (Figs. **9-18**).

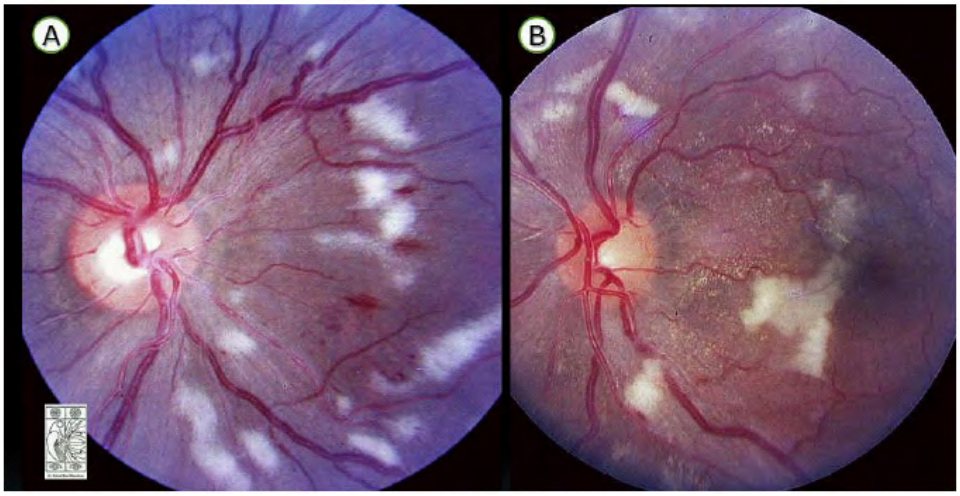


Fig. (9). (**A**) Accelerated-malignant hypertension: cotton wool spots – axoplasmic material accumulations – a typical sign of alarm that indicates the severity of the disease; (**B**) Chronic malignant hypertension: hard exudates in the shape of small dots with waxy appearance.

Complications of Hypertensive Retinopathy

Chronic hypertension, because of concomitant arteriolosclerosis, is responsible for vascular occlusions, whether arteriolar or venous. Arteriolar obstructions are associated with thrombotic occlusion or atheromatous embolism. On the other hand, vein occlusions, central or peripheral branch, the latter related to abnormal arteriolovenous crossing of higher grade, make it compulsory to carry out an assessment of the patient's coronary status. For its part, accelerated-malignant hypertension can be associated with exudative retinal detachment due to the presence of fibrinoid necrosis of the choroid (Figs. **19-25**).

Classification

We favor Lip and collaborator's classification system (1994) [5] because it is simple and it allows the classification of hypertension quickly on different phases of evolution. Grade I: Non accelerated-malignant; and Grade II: Accelerated-malignant (Fig. **26**).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for hypertensive retinopathy with diffuse retinal hemorrhage, cotton wool spots, and hard exudates includes most notably diabetic retinopathy. Diabetic retinopathy can be distinguished from hypertensive retinopathy by evaluation for the individual systemic diseases. Other conditions with diffuse retinal hemorrhage that can resemble hypertensive retinopathy include radiation retinopathy, anemia and other blood dyscrasias, ocular ischemic syndrome, and retinal vein occlusion.

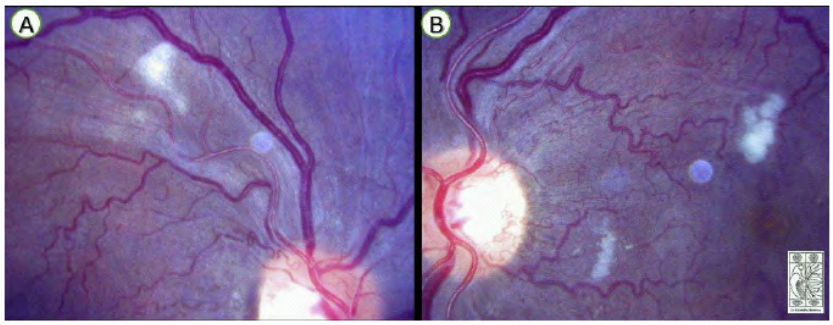


Fig. (10). Chronic secondary accelerated hypertension. (**A**) 58-year-old male patient; and (**B**) 60-year-old male patient. Signs of chronic hypertensive arteriolosclerosis, plus cotton wool spots, which are manifestations of acceleration-malignancy.

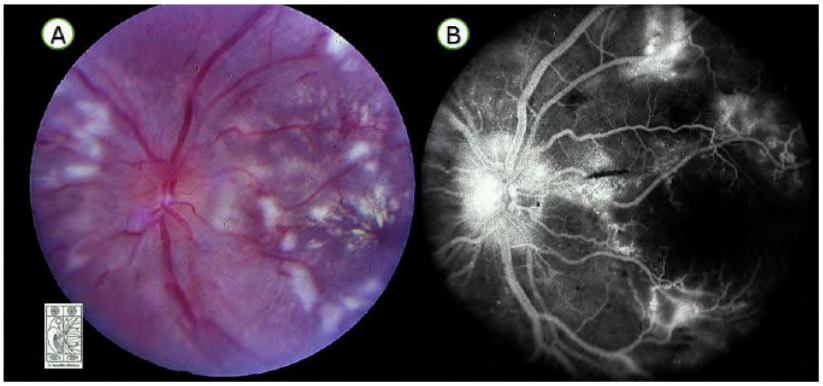


Fig. (11). Accelerated-malignant hypertension. 18-year-old male patient. Rapidly progressive glomerul-onephritis. (**A**) Multiple cotton wool spots and macular star. (**B**) Hyperfluorescence in the optic disc and around cotton wool spots that put pressure in the retina and capillary closure, and perilesional leakage due to blood-ocular barrier breakdown. No fluorescence on hard exudates.

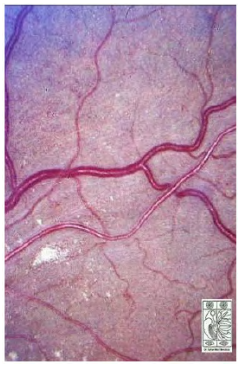


Fig. (12). A partial image of the retina showing (**A**) arteriolosclerotic changes that are typical of long-standing hypertension: Copper wiring of arteriole with bright axial reflex, irregular caliber and an arteriolovenous crossing of higher grade; and (**B**) involutional cotton wool spot and the presence of scattered hard exudates (a manifestation of acceleration-malignancy).

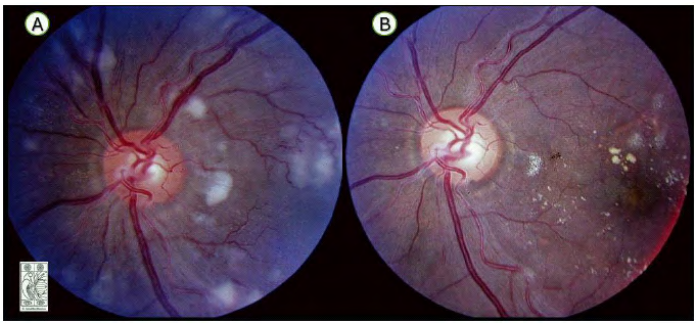


Fig. (13). Renovascular hypertension in a 59-year-old male patient. (**A**) Chronic secondary accelerated hypertension: multiple cotton wool spots; (**B**) After treatment, retinal signs tend to disappear, leaving hard exudates in the central area but without modifying arteriolosclerosis (arteriolar wall changes that cannot be reversed).

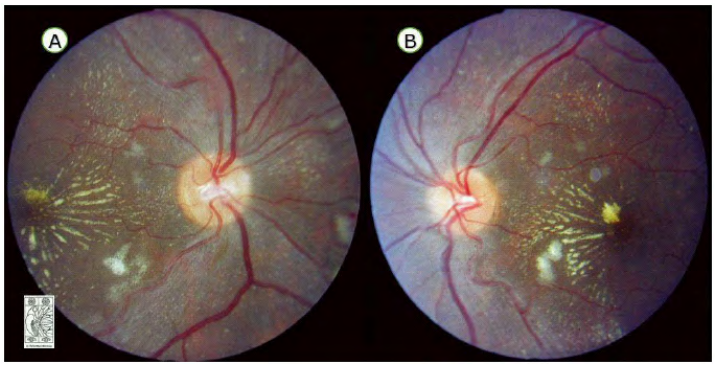


Fig. (14). Accelerated-malignant hypertension in a 48-year-old male patient with chronic secondary malignant hypertension: Macular hard exudates due to retinal edema.

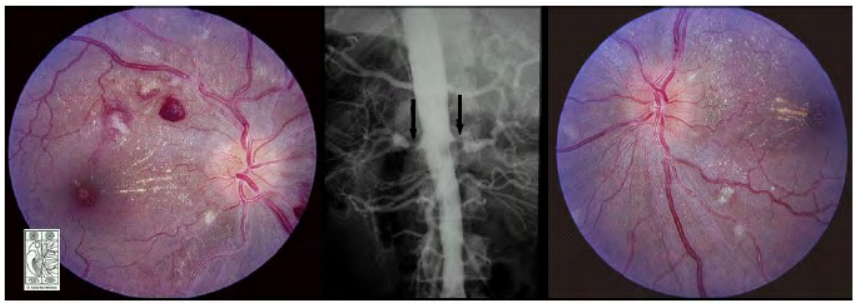


Fig. (15). Accelerated-malignant hypertension in a 62-year-old male patient with atherosclerotic stenosis of both renal arteries.

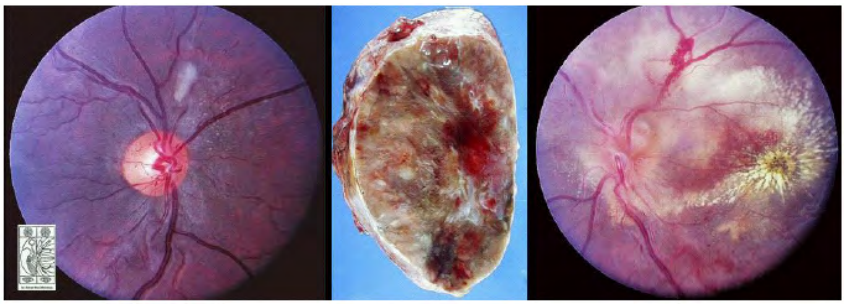


Fig. (16). Asymmetric accelerated-malignant hypertension in a 22-year-old female patient with pheochromocytoma.

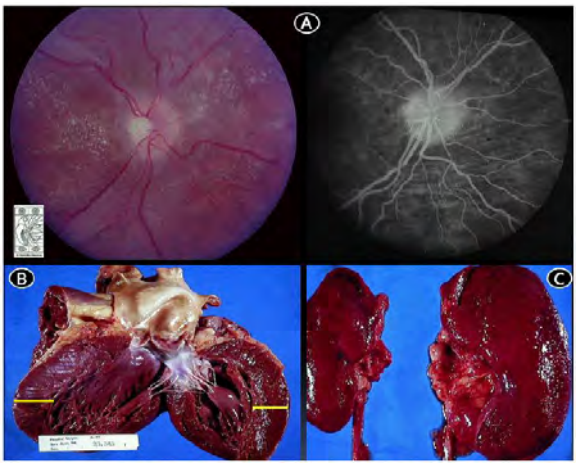


Fig. (17). (**A**) Accelerated-malignant hypertension, optic disc edema; fluorescein angiography: hyperfluorescence in the optic disc and choroidal scars; (**B**) Left ventricular hypertrophy; (**C**) Left renal atrophy.

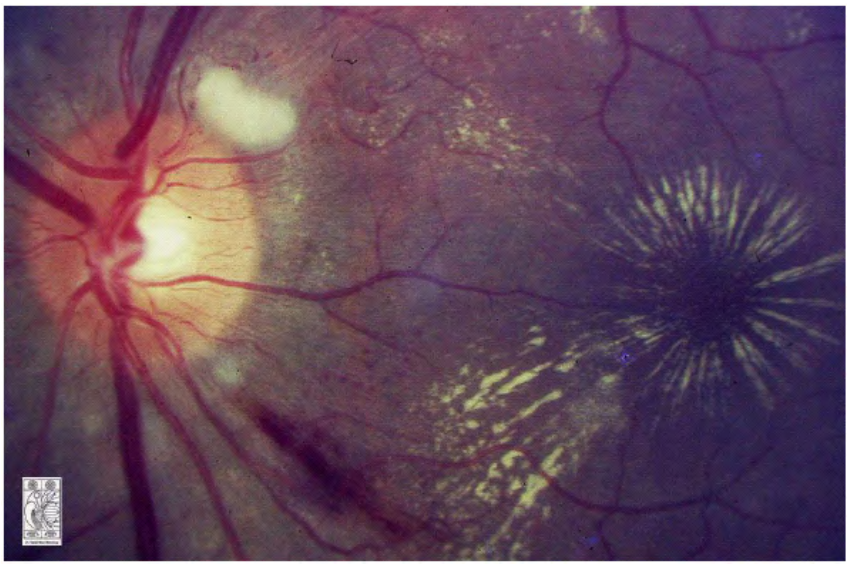


Fig. (18). Typical condition of accelerated-malignant hypertension: Optic disc congestion, cotton wool spots – accumulations of axoplasmic material – macular star image in a 20-year-old patient with rapidly progressive glomerulonephritis.

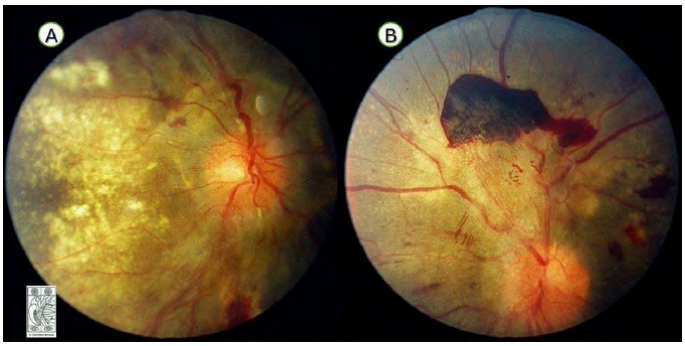


Fig. (19). Accelerated-malignant hypertension. (**A**) Bilateral optic disc edema; (**B**) Subhyaloid hemorrhage.

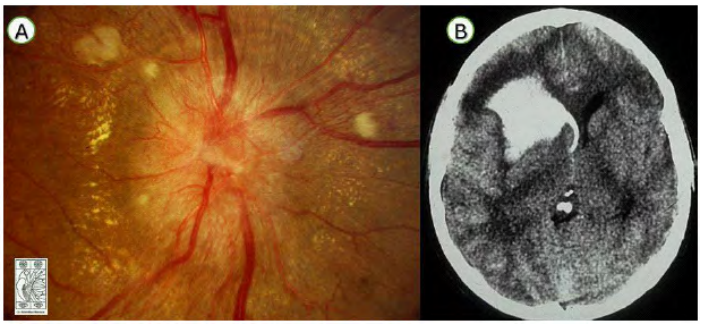


Fig. (20). (**A**) Accelerated-malignant hypertension and papilledema. (**B**) Hypertensive intracerebral

hematoma. Such development of disc edema is unusual.

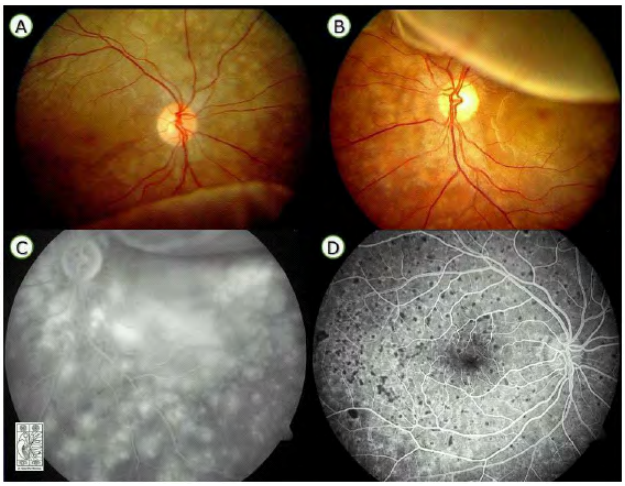


Fig. (21). (**A** and **B**) Eclampsia: 22-year-old patient with bilateral serous retinal detachment and macular edema; Choroidal infarctions (acute Elschnig spots); (**C**) Fluorescein angiography: Choroidal hyperfluorescence in patches and macular edema; (**D**) Two months later: Scattered hypofluorescent spots: related to choroidal infarctions (chronic Elschnig spots).

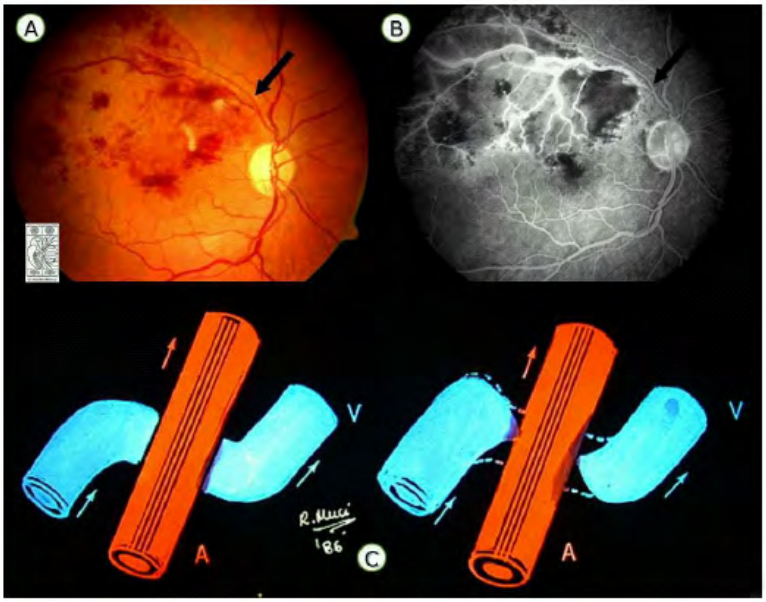


Fig. (22). Chronic arterial hypertension. (**A** and **B**) Superior temporal branch vein occlusion: retinography and fluorescein angiography: Triangular pattern of deep and superficial hemorrhages and cotton wool spots; (**C**) Scheme of abnormal arteriolovenous crossings of higher grade.

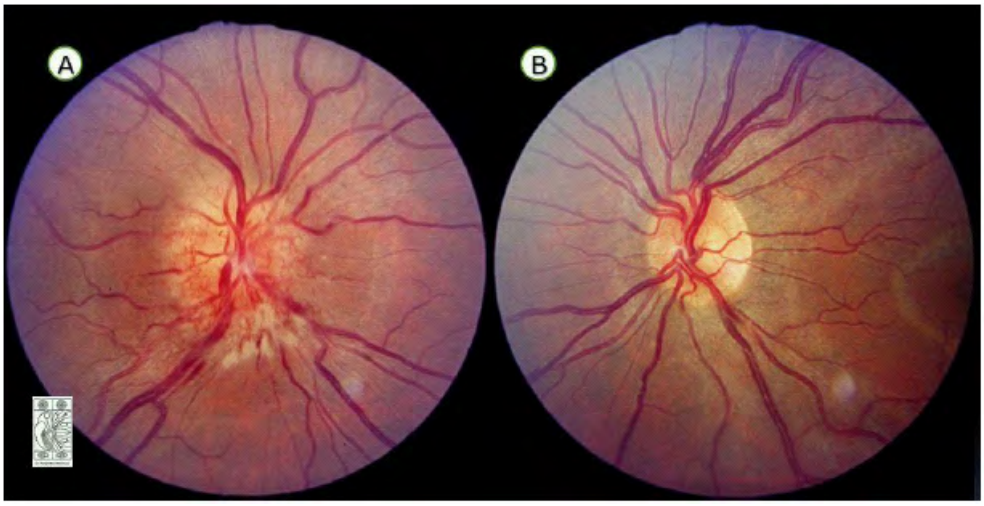


Fig. (23). (**A**) Non-arteritic anterior ischemic optic neuropathy; (**B**) Left disc at risk.

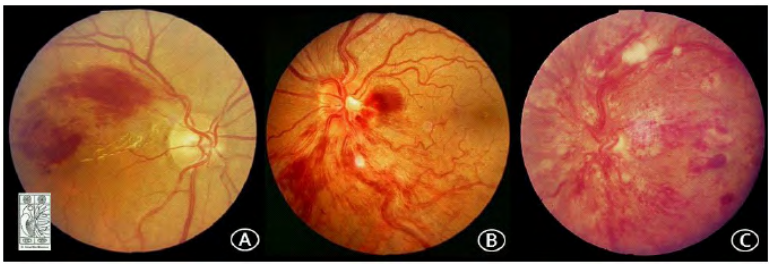


Fig. (24). Examples of venous occlusions in hypertensive patients. (**A**) Superior temporal branch occlusion; (**B**) Hemispheric occlusion; (**C**) Ischemic occlusion of the central retinal vein.

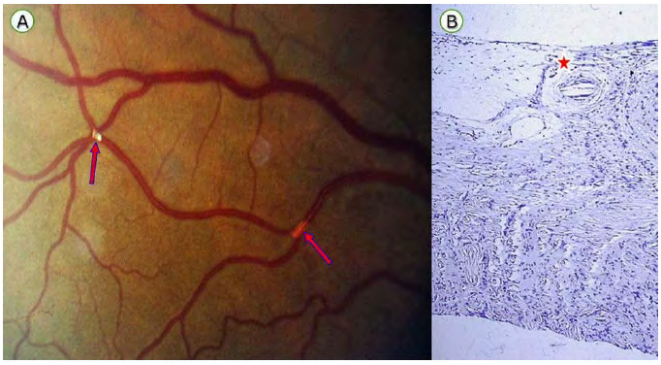


Fig. (25). Chronic hypertension. (**A**) Systemic atheromatous embolism (Hollenhorst plaques) at two arteriolar bifurcations; (**B**) Histological appearance in posterior capsule of an eye. Visually empty space that was occupied by cholesterol emboli before tissue dehydration (*). A dreadful clinical sign that anticipates a vascular catastrophe (myocardial infarction, stroke, aortic dissection or rapidly progressive renal failure).

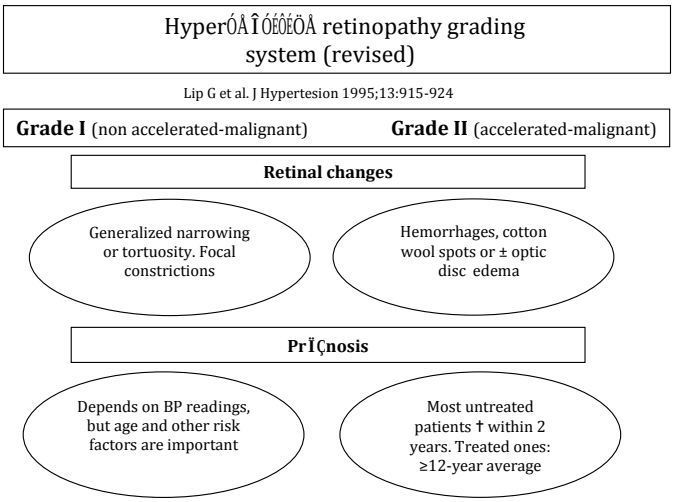


Fig. (26). Lip's classification – recommended due to its simplicity.

MANAGEMENT

The treatment for hypertensive retinopathy is primarily focused on reducing blood pressure.

Antihypertensive medication may reverse hypertensive retinopathy signs, with clinical case series [6, 7] showing regression of some retinopathy signs (*e.g.*, hemorrhages, cotton wool spots) with control of blood pressure.

If complications have occurred, surgery or laser may be required to help heal a hemorrhage or other resulting condition.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Blandeiner C. Patología cardiovascular adquirida de las principales enfermedades en nuestro medio. Colección estudios: Universidad central de Venezuel. Consejo de Desarrollo Científico y Humanístico 1998.

[2] Muci-Mendoza R. Retinopatía hipertensiva: Un factor de riesgo Clasificación y valor de la oftalmoscopia en el tratamiento Clemente-Heimerdinger A, Briceño-Iragorri L, editores Academia Nacional de Medicina, Venezuela Colección Razetti Volumen VII. Caracas: Editorial Ateproca 2009; pp. 259-98.

[3] Wong TY, Mitchell P. Hypertensive retinopathy. N Engl J Med 2004; 351(22): 2310-7.
[http://dx.doi.org/10.1056/NEJMra032865] [PMID: 15564546]

[4] Muci-Mendoza R. El fondo del ojo en la hipertensión arterial. el punto de vista del internista. Acta Cient Venez 1979; 30(5): 429-39.
[PMID: 545973]

[5] Lip GY, Beevers M, Beevers G. The failure of malignant hypertension to decline: a survey of 24 years' experience in a multiracial population in England. J Hypertens 1994; 12(11): 1297-305.
[http://dx.doi.org/10.1097/00004872-199411000-00013] [PMID: 7868878]

[6] Bock KD. Regression of retinal vascular changes by antihypertensive therapy. Hypertension 1984; 6(6 Pt 2): III158-62.
[PMID: 6519755]

[7] Dahlöf B, Stenkula S, Hansson L. Hypertensive retinal vascular changes: relationship to left ventricular hypertrophy and arteriolar changes before and after treatment. Blood Press 1992; 1(1): 35-44.
[http://dx.doi.org/10.3109/08037059209065122] [PMID: 1345141]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 7

Central Retinal Artery Occlusion

Silvia Mendoza[1], Sandra Zambrano[2], Diego Fernando Mojica[2] and **Mitzy E. Torres Soriano[3,*]**

[1] *Retina Department, Centro Oftalmológico de Valencia (CEOVAL), Valencia, Venezuela*

[2] *Centro Oftalmológico de Valencia (CEOVAL), Valencia, Venezuela*

[3] *Centro de la Visión Gordon-Manavella, Rosario-Santa Fe, Argentina*

Central retinal artery occlusion is a vaso-occlusive ischemic disease that causes a sudden painless loss of vision usually irreversible and unilateral. Incidence is 1 to 15 cases per 10,000 it generally occurs in the elderly, and is usually accompanied by an afferent pupillary defect [1 - 3].

The most frequent causes of obstruction of blood flow are:

1. Atherosclerosis: The deposits of cholesterol and other particles form atherosclerotic plaques. They slowly thicken towards the artery lumen causing obliteration or even complete obstruction.
2. Embolism: The ophthalmic artery is the first branch of the internal carotid artery. When the artery lumen narrows by plaques containing cholesterol or other particles, some pieces can break off, blocking the flow of the ophthalmic artery, central retinal artery or one of its branches. The severity of vision loss depends on the area of obstruction.
3. Collagenosis and coagulopathy [3 - 5].

Risk factors: Hypertension, hypercholesterolemia, blood dyscrasias, vasculitis.

[*] **Corresponding author Mitzy E. Torres Soriano:** Centro de la Visión Gordon-Manavella, Montevideo 763, CP 2000, Rosario - Santa Fe, Argentina; Tel: +54 (0341) 4400239; E-mail: mitzytorres@yahoo.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

ESSENTIALS OF DIAGNOSIS

Symptoms

- Sudden painless loss of vision can last for seconds, minutes or be permanent.
- Usually unilateral.
- Loss of the entire visual field if the central retinal artery is affected or partial loss if a branch is affected.
- Most patients have a history of previous episodes of amaurosis fugax.

Fundus Findings

- Whitish discoloration of the retina, due to edema of the inner retinal layers, especially at the posterior pole where the nerve fiber layer and ganglion cell layer are thickest (Figs. **1**-**4**) [1 - 6].

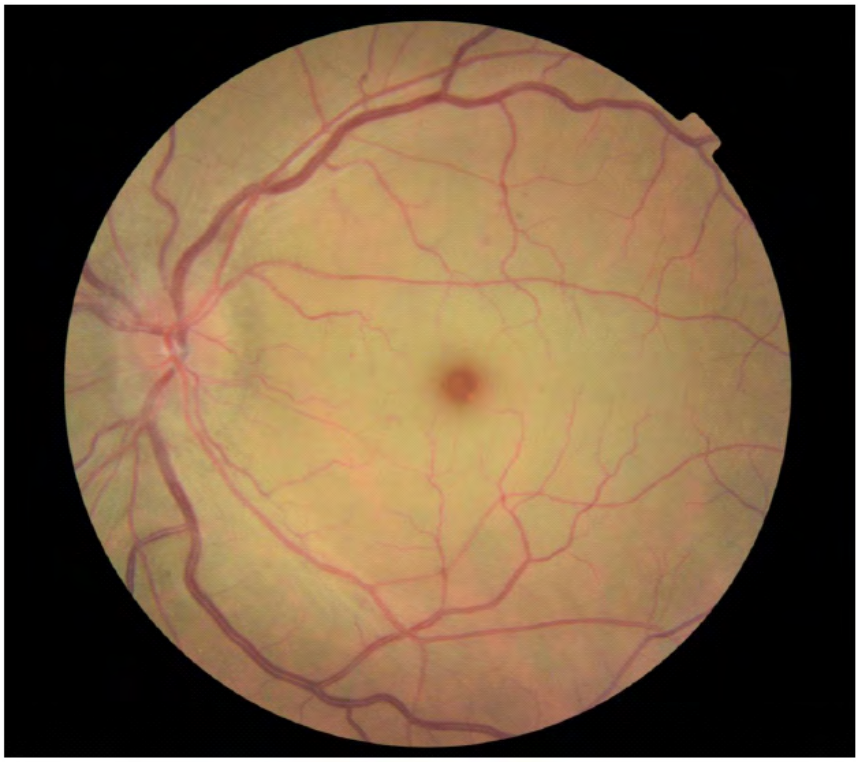


Fig. (1). Central retinal artery occlusion: Note pale retina, narrowed arterioles and “cherry red spot” in macula.

- Cherry-red spot. Visualization of the choroid and retinal pigment epithelium with xanthophyll pigment in the foveal area, surrounded by edematous retina (Figs. **1**-**4**) [1 - 5].
- Retinal arterial attenuation [4].
- Optic disc edema and pallor [4].
- At later stages, fundoscopic findings include optic atrophy, retinal arterial attenuation, cilioretinal collaterals, and macular retinal pigment epithelial changes [4].

Complementary Exams

- Fluorescein angiography: to assess if the arterial obstruction is complete or partial and to determine if there is reperfusion (Figs. **2**, **4**).

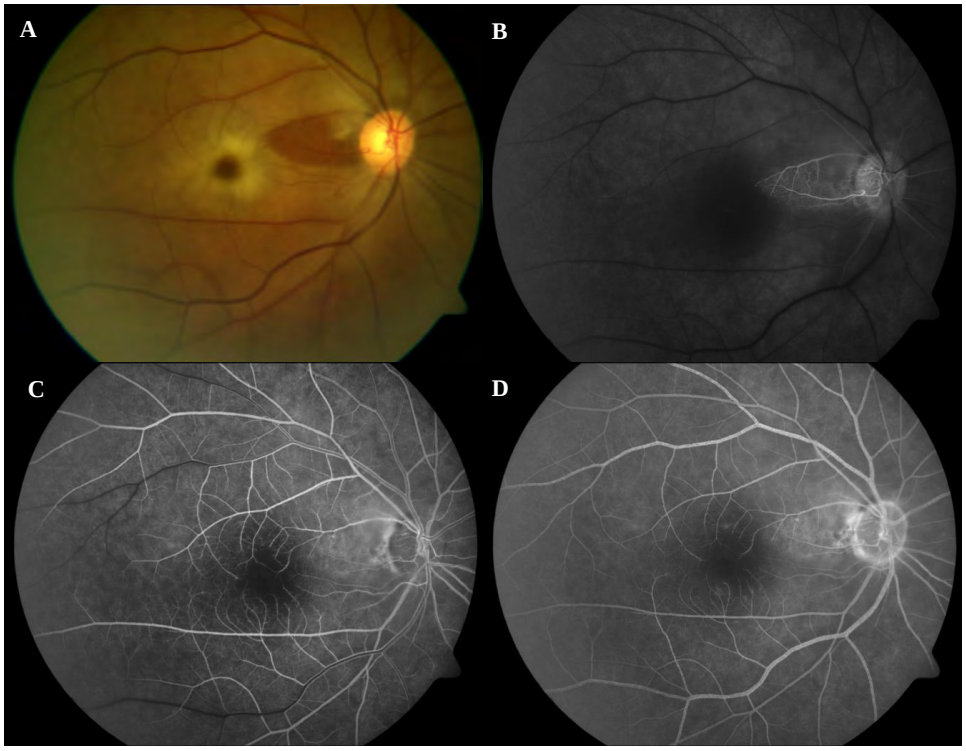


Fig. (2). A. Fundus photograph showing retinal pallor and a cherry-red spot. **B** and **C**. Early to mid stages of the fluorescein angiogram showing significant delay in the vascular filling. There is a small area adjacent to the optic disc that is still perfused by a cilioretinal artery. **D**. Late Phase of the Angiogram.

- Optical coherence tomography may show increased inner retinal layer thickness (Fig. **3B**) in the acute stage of CRAO, due to retinal edema and optic nerve swelling [5].

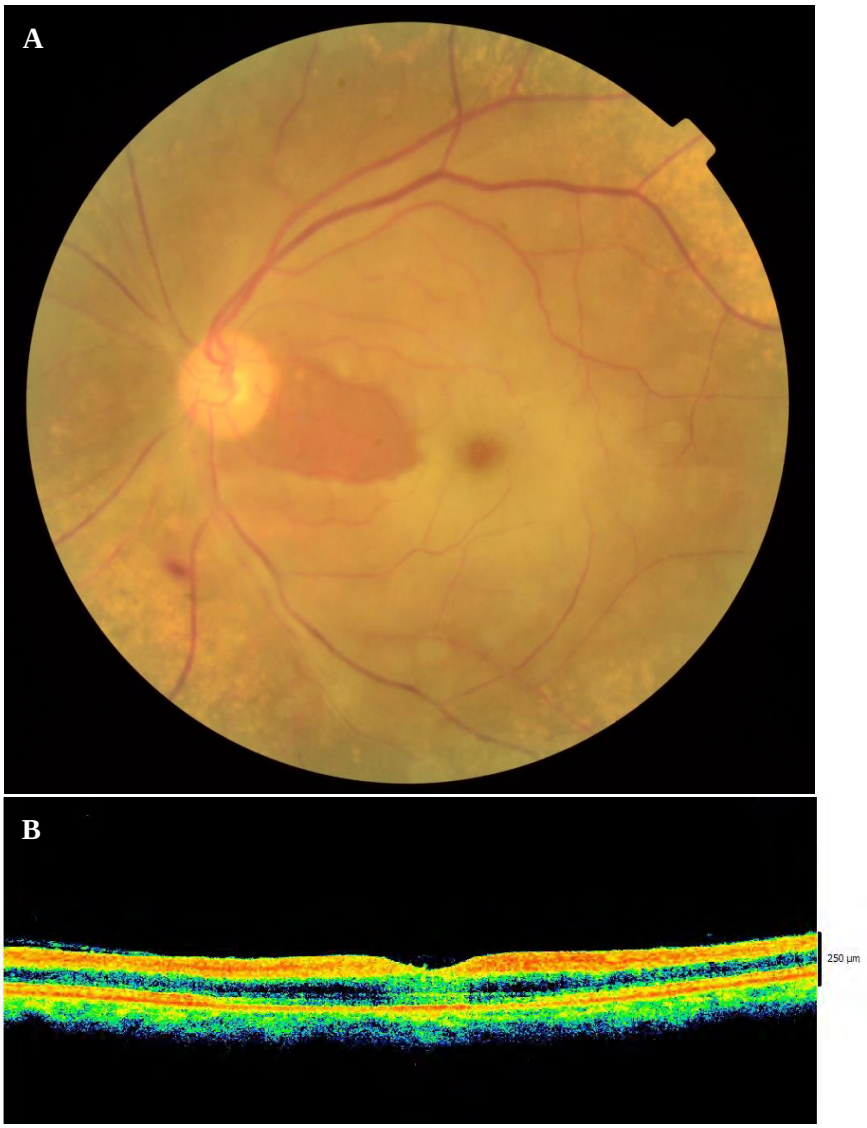


Fig. (3). A. Color photograph of the left fundus showing diffuse retinal whitening with a classic cherry-red spot. This patient has an area of perfused retina supplied by a cilioretinal artery located just temporal to the disc. **B**. Optical coherence tomography shows hyperreflectance of inner retinal layers. (Courtesy of Manuel Torres MD, Cagua, Venezuela).

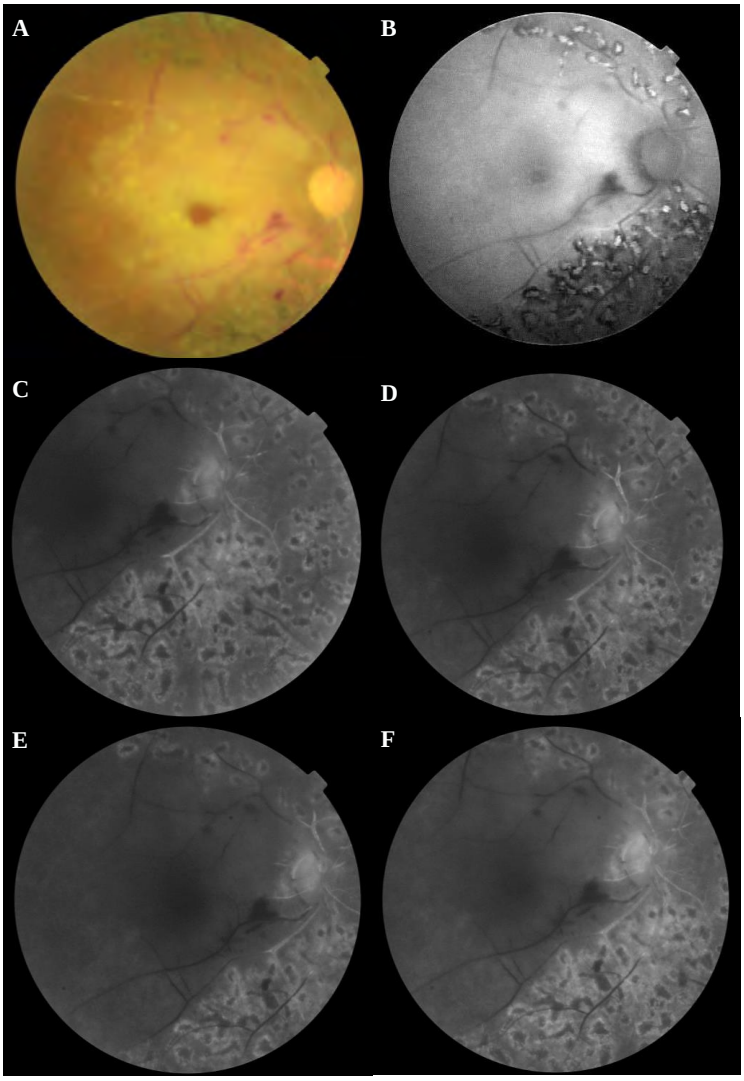


Fig. (4). A. Central retinal artery occlusion in a patient with diabetic retinopathy, **B**. Fundus autofluorescence. **C-F**. FA shows non-perfusion of the retinal vasculature from early to late phases. (Courtesy of Manuel Torres MD, Cagua, Venezuela).

- Visual field: useful for follow-up.
- Electroretinogram: there is a reduction in the b-wave amplitude, due to selective damage of inner retinal layers (Fig. **5**) [5].

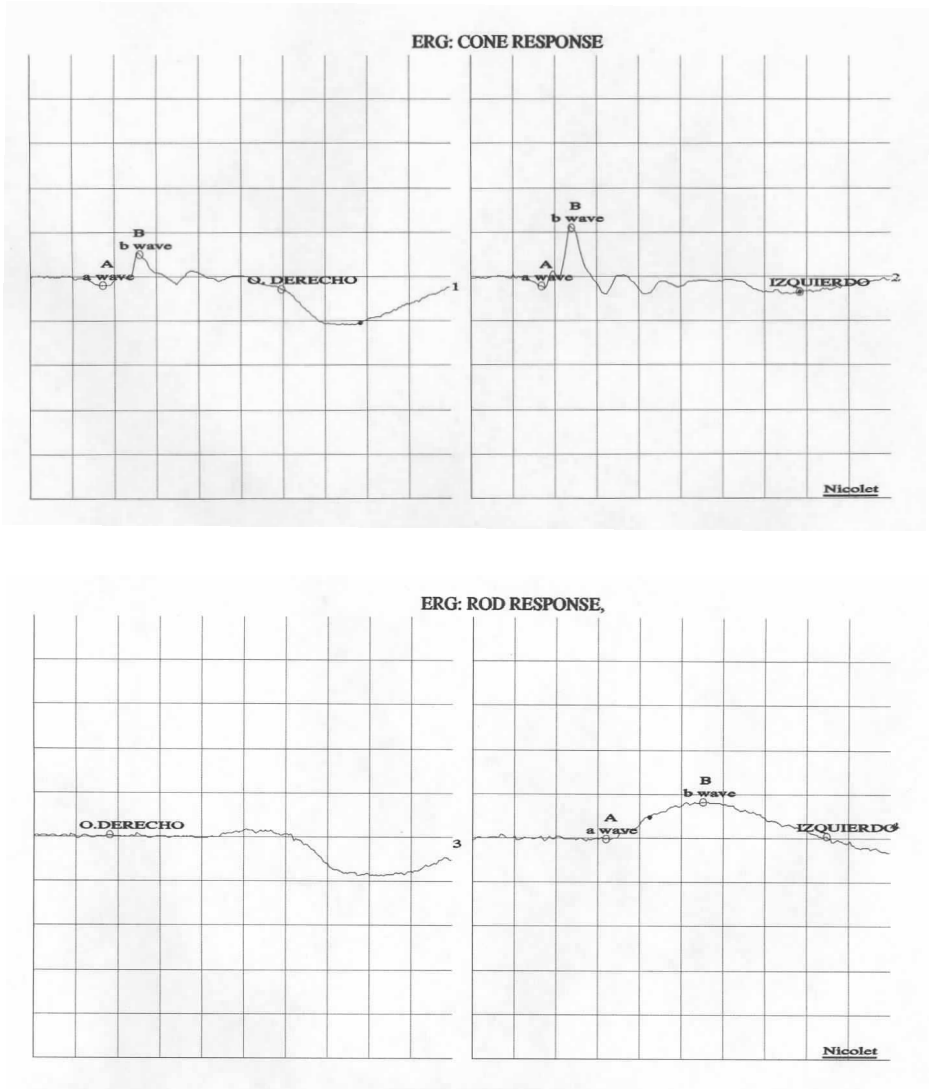


Fig. (5). Electroretinogram of the same patient of Fig. (**2**). There is a reduction in the b-wave amplitude in cone and rod response of right eye (left side of the image) due to a CRAO.

DIFFERENTIAL DIAGNOSIS

Although the cherry-red spot is a fairly specific clinical sign, it is not pathognomonic, since it may also be observed in traumatic *commotio retinae*, and in metabolic diseases such as Niemann-Pick disease, Farber disease, Tay-Sach disease, and Sandhoff disease among others.

MANAGEMENT

Once it ensues, there is no proven treatment for this disease. Retinal tissue can survive for up to 240 minutes without oxygen before damage is permanent and irreversible. Therefore the aim of treatment is to restore retinal circulation as soon as possible.

Treatment strategies include:

- Ocular massage.
- Topic beta-blockers.
- Anterior chamber paracentesis.
- Intravenous or oral acetazolamide.
- Hemodilution.
- Retrobulbar injection of vasodilators such as papaverine.
- Anticoagulation.
- Hyperbaric chamber.

Other therapeutic options are:

- Systemic fibrinolysis: in cases of arterial thrombotic occlusion or fibrin platelet emboli less than 6 hours of evolution [7 - 13].
- Intra-arterial fibrinolysis: injected into the ophthalmic artery, it may be effective in the early hours of ischemia. It needs specialized equipment and is not devoid of complications [7 - 13].
- In cases of ophthalmic artery embolic obstruction, direct removal of the embolus might be attempted, cutting the affected artery wall with a 20G lancet.

All these therapeutic measures have to be attempted within the first six hours of the occlusion, and have a very low success rate.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Gil MA, Ortigosa L, Civancos E, Mesa MC, Delgado JL, Abreu P. Mácula rojo cereza: a propósito de un caso. St Ophthal 1999; 17: 239-41.

[2] Piñero Bustamante A. Aparato ocular. Barcelona: Pharma Consult, S.A; 1992; 41.

[3] Sharma S, Brown M, Brown G. Retinal artery occlusions. Ophthalmol Clin North Am 1998; 11: 591-600.
[http://dx.doi.org/10.1016/S0896-1549(05)70080-8]

[4] Hayreh SS, Zimmerman MB. Fundus changes in central retinal artery occlusion. Retina 2007; 27(3): 276-89.
[http://dx.doi.org/10.1097/01.iae.0000238095.97104.9b] [PMID: 17460582]

[5] Shinoda K, Yamada K, Matsumoto CS, Kimoto K, Nakatsuka K. Changes in retinal thickness are correlated with alterations of electroretinogram in eyes with central retinal artery occlusion. Graefes Arch Clin Exp Ophthalmol 2008; 246(7): 949-54.
[http://dx.doi.org/10.1007/s00417-008-0791-x] [PMID: 18425524]

[6] Conolly BP, Krishnan A, Shah GK, *et al.* Characteristics of patients presenting with CRAO with and without giant cell arteritis. Can J Ophthalmol 2000; 35: 379-84.
[http://dx.doi.org/10.1016/S0008-4182(00)80125-8] [PMID: 11192446]

[7] Schmidt P, Schulte-Mönting J, Schumacher M. Prognosis of CRAO: local intraarterial fibrinolysis *versus* conservative treatment. Am J Neurorad 2002; 23: 1301-7.

[8] Beatty S, Au Eong KG. Local intra-arterial fibrinolysis for acute occlusion of the central retinal artery: a meta-analysis of the published data. Br J Ophthalmol 2000; 84(8): 914-6.
[http://dx.doi.org/10.1136/bjo.84.8.914] [PMID: 10906103]

[9] Cilveti Puche A, Lapeira Andraca M, García Campos J. Fibrinolisis sistémica con rTPA en OACR. Arch Soc Esp Oftalmol 2000; 4: 9.

[10] Neubauer AS, Mueller AJ, Schriever S, Gruterich M, Ulbig M, Kampik A. Minimally invasive therapy for clinically complete CRAO results and meta-analysis of literature. Klin Mbl Augenheilkd; 217: 30-36.

[11] Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawas S, Ohsumi Y. Intravenous rTPA in acute carotid artery territory stroke. Neurology 1992; 42: 976-82.
[http://dx.doi.org/10.1212/WNL.42.5.976] [PMID: 1579252]

[12] Schumacher M, Schmidt D, Wakhloo AK. Intra-arterial fibrinolytic therapy in CRAO. Neuroradiology 1993; 35: 600-5.
[http://dx.doi.org/10.1007/BF00588405] [PMID: 8278042]

[13] Fernández FJ, Guelbenzu S, Barrena C, *et al.* Fibrinolisis selectiva de arteria oftálmica en la OACR. Arch Soc Esp Oftalmol 2002; 2: 7.

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 8

Branch Retinal Artery Occlusion and Cilioretinal Artery Occlusion

Raul Velez-Montoya*

Retina Department, Asociación para Evitar la Ceguera en México, IAP. Mexico City, Mexico

Branch retinal artery occlusion (BRAO) is an arterial occlusive disease in which the obstruction of blood flow is located after the bifurcation of the central retinal artery in its major branches. The severity of the clinical manifestations will depend on the exact localization of the obstruction which can be found anywhere from the emergence of the major temporal or nasal arcades to the small capillary arterioles [1, 2].

BRAOs are thought to represent 38% of all acute retinal artery obstructions [3]. It is classified according to its visual outcome in *transient* and *permanent* BRAO [2, 4, 5]. Diabetes mellitus, arterial hypertension, ischemic heart disease, and transient ischemic attacks/cerebrovascular accidents are more prevalent in patients with BRAO than the matched US population ($p<0.001$) [2]. Smoking prevalence in female patients with BRAO is higher; although this association has not been proven in male patients. When comparing BRAO with central retinal artery occlusion (CRAO), only diabetes mellitus has a slightly higher prevalence among patients with CRAO [2].

Embolism is the most common cause of BRAO [5, 7]. There are three main types or retinal emboli: calcific (10.5%), cholesterol (74%), and platelet-fibrin (15.5%) [6, 7]. The most common sources of emboli are the carotid artery (plaque) and the heart (valvular lesions, atrial fibrillation, patent foramen ovale, tumors in left

* **Corresponding author Raul Velez-Montoya:** Retina Department, Asociación para Evitar la Ceguera en México, Vicente García Torres, 46. San Lucas Coyoacán, México DF.04030; México; Tel: +52.55.10841400; Fax: +52.55.10841404; Email: rvelezmx@yahoo.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

atrium and myxoma) [8]. Due to the fact that microemboli are responsible for most BRAO, and the major source of microemboli is an arterial plaque, the absence of an abnormal carotid doppler does not rule out the carotid artery as the source of microemboli [7, 9].

ESSENTIALS OF DIAGNOSIS

Conversely to CRAO patients, in which visual loss can be severe (light perception) at presentation, more than 70% of patients with *permanent* BRAO, seen within 7 days of onset, will have 20/40 or better at the initial visit especially if the affected vessel is the inferior temporal artery. Furthermore, 80% of patients with decreased visual acuity (VA) at presentation (worse than 20/40) will experience an improvement of VA within 1 week after onset. Final VA of 20/40 or better is seen in 89% of patients, and only 3% of eyes experience a worsening of VA during follow-up. The most frequently reported visual field defects are a central scotoma (20%) and inferior central altitudinal defect (13%), which tend to improve in 47% of the cases within 1 week of onset. In patients with *transient* BRAO, VA at presentation of 20/40 or better is seen in more than 90% of cases. The central and peripheral visual field remains normal. Final VA tends to be 20/40 or better in virtually all cases, regardless of VA at onset (even if it was worse than 20/40) [1, 5].

During the acute phase of the disease, an area of retinal pallor corresponding to the area of compromised blood flow and oncotic damage (swelling) can be identified on fundus examination (Figs. **1**, **2**) [10 - 12]. However, the initial pallor is replaced by the normal sheen of the fundus in long-standing cases, making it more difficult to diagnose [10]. If there is enough ischemia, cotton-wool spots will develop 6 to 18 hours after onset, especially if the affected vessel is large enough and close to the posterior pole where the nerve fiber layer is thicker [13, 14]. A retinal emboli is seen in 47% of cases. However, its absence does not rule out an embolic case because it may have disintegrated, migrated and disappeared by the time the eye is examined [15, 16].

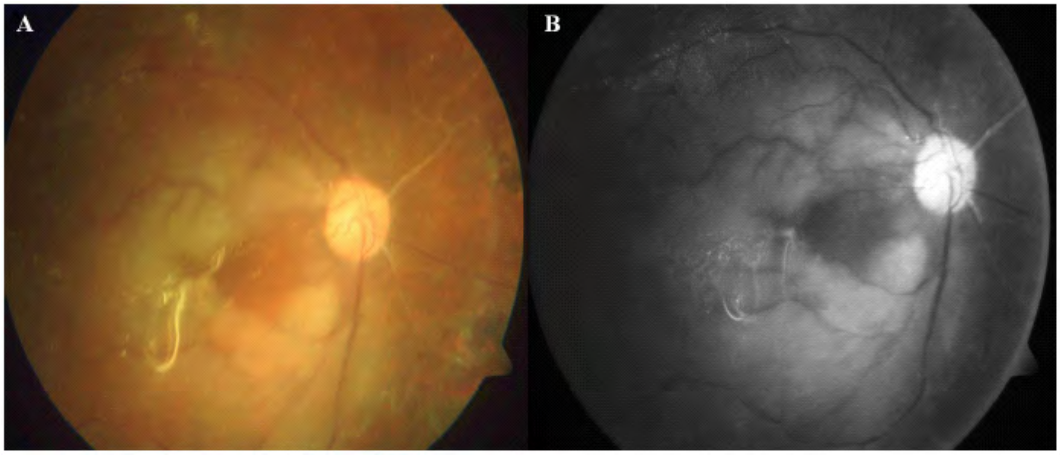


Fig. (1). BRAO on a diabetic patient after pars plana vitrectomy and silicon oil. **A**) Color photograph shows whitening of the posterior pole with normal color of the papillomacular bundle. **B**) Red-free photograph shows more clearly the territory supplied by the cilioretinal artery on the same patient.

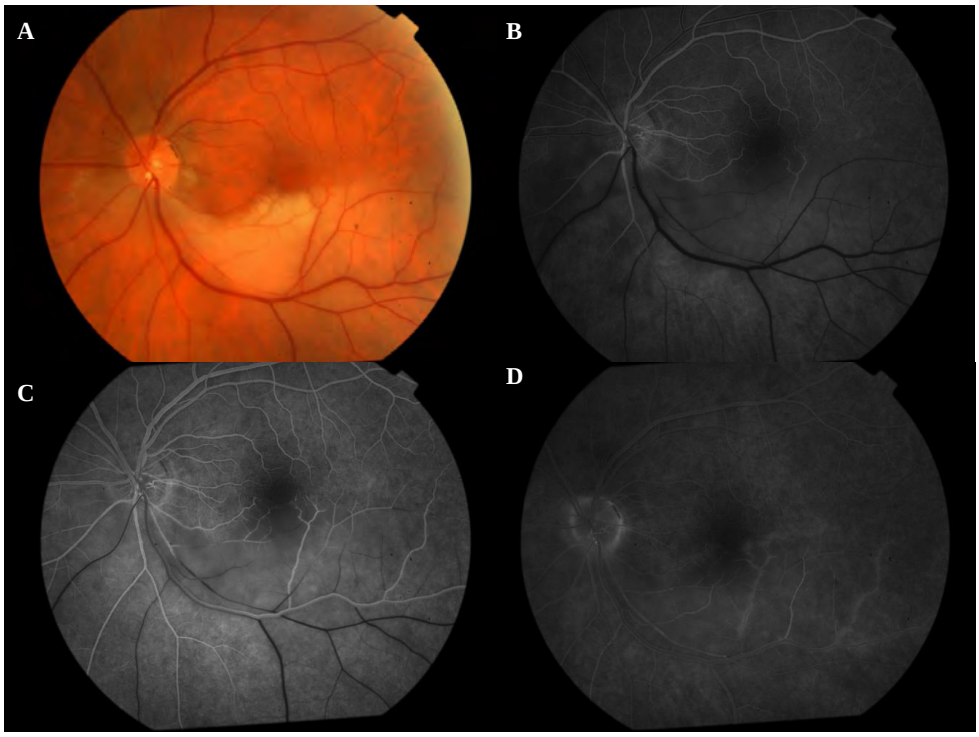


Fig. (2). Acute phase of inferotemporal BRAO. **A**) Fundus photograph shows retinal pallor in inferior macular area. **B** and **C**) FA shows a delay on the vessel filling and transit time. **D**) Cattle trucking and staining of the vessels walls (Courtesy of Natalia Pecce MD, Argentina).

Fluorescein angiogram (FA) may show delayed filling, reduced arterial caliber, "cattle trucking" of the arterial blood column (Figs. **2**, **3**), and increased transit time on the affected vessels as well as capillary dropout and collateral vessels development on the area of the retina affected by compromised blood flow (Fig. **4**) [4, 17, 18]. Optical coherence tomography (OCT) of the ischemic areas will show marked thickening and hyper-reflectivity of the inner retina during the acute phase (Fig. **5**) [10, 13, 19]. A decrease in retinal thickness may be noticed after resolution [10, 13]. Fundus autofluorescence of the area supplied by the occluded retinal artery will show decreased autofluorescence due to blockage of the normal autofluorescence of the retinal pigment epithelium by the thickened retina with normal autofluorescence over the rest of the retina [10, 12]. After resolution, an increase in autofluorescence due to a very thin retina may also be visualized [10].

Cilioretinal Artery Occlusion (CLRAO): The cilioretinal artery originates from the short posterior ciliary arteries or from the choroid, and emerges directly from the optic disc or disc margins, and not from the central retinal artery [5, 16]. It is usually present in 49.5% of the eyes and supplies the papillomacular bundle [4, 20]. Clinically evident CLRAO is a rare event, since it only comprises between 5.3 to 7.1% of all cases or retinal artery occlusions [16]. It occurs in three clinical settings: as non-arteritic CLRAO alone; as an arteritic CLRAO associated with giant cell arteritis; and as CLRAO associated with central/hemicentral retinal vein occlusions [2, 5]. The clinical presentation at onset will depend on the clinical setting in which CLRAO occurred. Patients with non-arteritic CLRAO can have decreased VA (20/40 or worse) and central visual field defects (mostly central and centrocecal scotomas) which tend to improve during the follow-up [5]. Such presentations are due to the high variability in size of the cilioretinal artery and the area it supplies [1]. Translucent, pale gray swelling of the papillomacular bundle is typically present [21, 22]. The presence of a CLRAO with a white optic disc edema, posterior ciliary artery occlusion on fluorescein angiography, headache and jaw claudication in a patient of 50 years of age or older might signify an association with giant cell arteritis [2, 5]. In this scenario, prompt treatment should begin to prevent severe bilateral visual loss [22]. When associated with central or hemicentral retinal vein occlusion, VA at onset as well as VA improve-

ment during follow-up will depend on the type of vein occlusion (ischemic or no

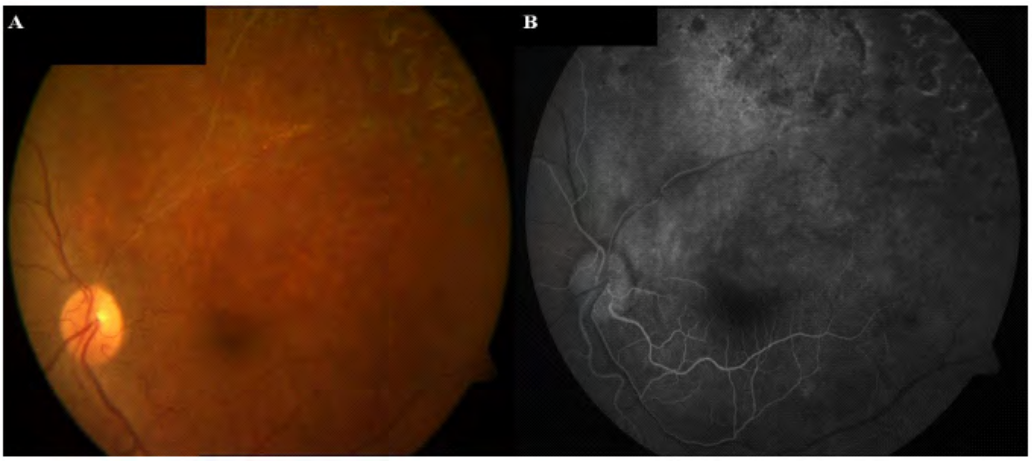


Fig. (3). A) BRAO of the superotemporal arcade on a patient with diabetic retinopathy, previously treated with panretinal photocoagulation. Color photographs shows a severe decrease in the caliber of the vessels. **B**) FA shows a delay on the transit time and a thinner dye column inside the affected vessels.

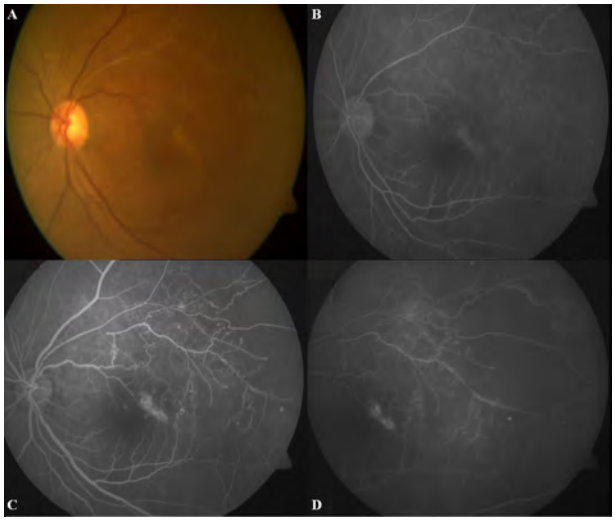


Fig. (4). A) BRAO of the superotemporal arcade. **B** to **D**) FA show a filling defect with extensive capillary dropout and collateral vessel formations.

ischemic), macular ischemia due to the CLRAO, and the existence of macular edema [5, 21]. Central visual field defects are usually due to CLRAO [5]. On fundus examination, CLRAO is accompanied by superficial and intraretinal hemorrhages [16].

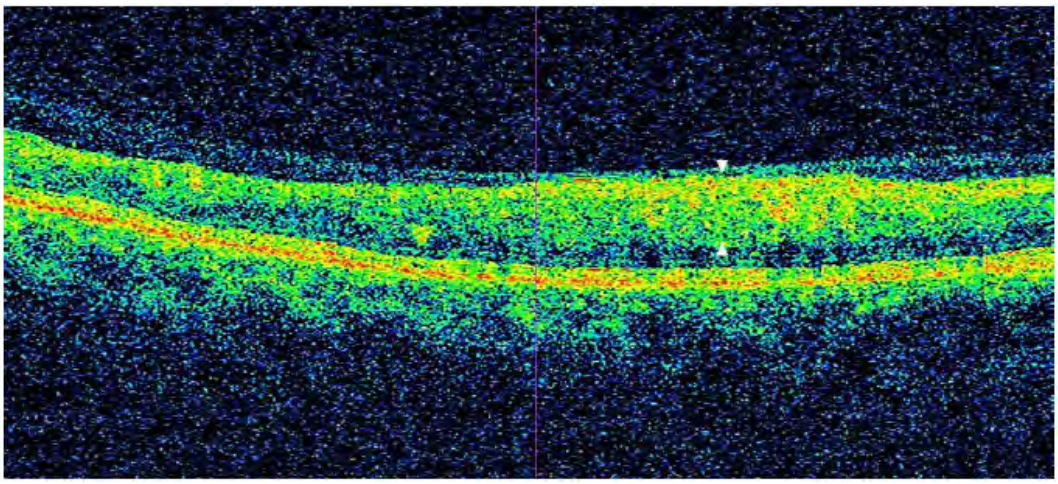


Fig. (5). Spectral domain OCT in a patient with acute BRAO. There is an increase in the thickness of the inner retinal and increased reflectivity (area between arrow heads).

DIFFERENTIAL DIAGNOSIS

Although diagnosis of BRAO is mostly clinical and straightforward during the acute phases, it can prove to be difficult on long-standing cases. Differential must be done with other entities causing whitening of the retina like commotion retina, persistence of myelinated nerve fiber layer, central/hemicentral retinal artery occlusion, and shallow retinal detachment, among others. There are multiple anecdotal associations of BRAO with various diseases including systemic lupus erythematosus, polyarteritis nodosa, dengue fever, West Nile virus, AIDS, toxoplasmosis, herpes zoster, sickle cell disease, Takayasu's arteritis, post-smallpox vaccination, Churg-Strauss syndrome, ocular Behçet's disease, Fabry's disease, head injury, and migraine [5].

Susac´s syndrome is a pathology characterized by the clinical triad of encephalopathy, hearing loss, and BRAO, mostly in young women, and is thought to be due to microangiopathy [24].

MANAGEMENT

A wise man once said, "A disease without treatment has many treatments." This is the case of the arterial occlusive disease [25]. Although most of BRAO cases with impaired VA or visual field defects will improve regardless of whether it is

transient, permanent, or level of VA at onset, it is nearly impossible to identify which will improve and which will not, based on purely clinical evidence at presentation. Current options include the standard non-invasive therapies: the use of vasodilator to increase blood oxygen content and dilate arteries (sublingual isosorbide, systemic pentoxifylline, inhalation of carbogen and hyperbaric oxygen); ocular massage to attempt to dislodge the emboli [4]; lowering of intraocular pressure to increase retinal artery perfusion pressure (intravenous acetazolamide and mannitol, anterior chamber paracentesis) [4]; methylprednisolone [4]; oral acetylsalicylic acid [26]; and the combination of some or all of the above in a multimodal stepwise approach. None of these therapies has been shown to be better than a placebo in clinical trials in the treatment of BRAO. More invasive therapies include isovolemic hemodilution, anticoagulation with heparin, and local intra-arterial fibrinolysis with tissue plasminogen activator (*t*PA). However, the latter has proven to be of doubtful utility since major randomized clinical trials had found no greater benefit than non-invasive standard treatments but with higher rate of adverse reactions [26]. There are reports of the successful destruction of the emboli using an Nd:YAG laser. Nevertheless, there is still concern about the safety and efficacy of the treatment [27, 28]. In cases of CLRAO associated with giant cell arteritis, intensive corticosteroid therapy can prevent further visual loss [23].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Hayreh SS, Podhajsky PA, Zimmerman MB. Branch retinal artery occlusion: natural history of visual outcome. Ophthalmology 2009; 116(6): 1188-94. [http://dx.doi.org/10.1016/j.ophtha.2009.01.015]

[2] Hayreh SS, Podhajsky PA, Zimmerman MB. Retinal artery occlusion: associated systemic and ophthalmic abnormalities. Ophthalmology 2009; 116(10): 1928-36. [http://dx.doi.org/10.1016/j.ophtha.2009.03.006] [PMID: 19577305]

[3] Brown GC, Shields JA. Cilioretinal arteries and retinal arterial occlusion. Arch Ophthalmol 1979; 97(1): 84-92.
[http://dx.doi.org/10.1001/archopht.1979.01020010024006] [PMID: 758898]

[4] Varma DD, Cugati S, Lee AW, Chen CS. A review of central retinal artery occlusion: clinical presentation and management. Eye (Lond) 2013; 27(6): 688-97.
[http://dx.doi.org/10.1038/eye.2013.25] [PMID: 23470793]

[5] Hayreh SS. Ocular vascular occlusive disorders: natural history of visual outcome. Prog Retin Eye Res 2014; 41: 1-25.
[http://dx.doi.org/10.1016/j.preteyeres.2014.04.001] [PMID: 24769221]

[6] Arruga J, Sanders MD. Ophthalmologic findings in 70 patients with evidence of retinal embolism. Ophthalmology 1982; 89(12): 1336-47.
[http://dx.doi.org/10.1016/S0161-6420(82)34626-6] [PMID: 7162779]

[7] Klein R, Klein BE, Jensen SC, Moss SE, Meuer SM. Retinal emboli and stroke: the Beaver Dam Eye Study. Arch Ophthalmol 1999; 117(8): 1063-8.
[http://dx.doi.org/10.1001/archopht.117.8.1063] [PMID: 10448750]

[8] Schmidt D, Hetzel A, Geibel-Zehender A. Retinal arterial occlusion due to embolism of suspected cardiac tumors -- report on two patients and review of the topic. Eur J Med Res 2005; 10(7): 296-304.
[PMID: 16055401]

[9] Grigg MJ, Papadakis K, Nicolaides AN, *et al.* The significance of cerebral infarction and atrophy in patients with amaurosis fugax and transient ischemic attacks in relation to internal carotid artery stenosis: a preliminary report. J Vasc Surg 1988; 7(2): 215-22.
[http://dx.doi.org/10.1016/0741-5214(88)90139-5] [PMID: 3339768]

[10] Mathew R, Papavasileiou E, Sivaprasad S. Autofluorescence and high-definition optical coherence tomography of retinal artery occlusions. Clin Ophthalmol 2010; 4: 1159-63.
[http://dx.doi.org/10.2147/OPTH.S13592] [PMID: 21060665]

[11] Hafidi Z, Handor H, Laghmari M, Daoudi R. Cilioretinal artery and central retinal vein occlusion after sildenafil use. Emerg Med J 2013; (Aug): 16.
[PMID: 23956320]

[12] Munk MR, Mirza RG, Jampol LM. Imaging of a cilioretinal artery embolisation. Int J Mol Sci 2014; 15(9): 15734-40.
[http://dx.doi.org/10.3390/ijms150915734] [PMID: 25192292]

[13] Coady PA, Cunningham ET Jr, Vora RA, *et al.* Spectral domain optical coherence tomography findings in eyes with acute ischaemic retinal whitening. Br J Ophthalmol 2014; (Jul): 3.
[PMID: 24993106]

[14] McLeod D. Why cotton wool spots should not be regarded as retinal nerve fibre layer infarcts. Br J Ophthalmol 2005; 89(2): 229-37.
[http://dx.doi.org/10.1136/bjo.2004.058347] [PMID: 15665358]

[15] Schmidt D, Schumacher M, Feltgen N. Circadian incidence of non-inflammatory retinal artery occlusions. Graefes Arch Clin Exp Ophthalmol 2009; 247(4): 491-4.
[http://dx.doi.org/10.1007/s00417-008-0989-y] [PMID: 18989688]

[16] Makino S, Ohkawara Y, Sato Y. A case of cilioretinal artery occlusion resembling hemicentral retinal artery occlusion. Clin Ophthalmol 2012; 6: 1945-7.
[http://dx.doi.org/10.2147/OPTH.S37991] [PMID: 23225997]

[17] Beatty S, Au Eong KG. Acute occlusion of the retinal arteries: current concepts and recent advances in diagnosis and management. J Accid Emerg Med 2000; 17(5): 324-9.
[http://dx.doi.org/10.1136/emj.17.5.324] [PMID: 11005400]

[18] Shinoda K, Yamada K, Matsumoto CS, Kimoto K, Nakatsuka K. Changes in retinal thickness are correlated with alterations of electroretinogram in eyes with central retinal artery occlusion. Graefes Arch Clin Exp Ophthalmol 2008; 246(7): 949-54.
[http://dx.doi.org/10.1007/s00417-008-0791-x] [PMID: 18425524]

[19] Yu S, Pang CE, Gong Y, *et al.* The spectrum of superficial and deep capillary ischemia in retinal artery occlusion. Am J Ophthalmol 2015; 159(1): 53-63. e51-52
[http://dx.doi.org/10.1016/j.ajo.2014.09.027]

[20] Justice J Jr, Lehmann RP. Cilioretinal arteries. A study based on review of stereo fundus photographs and fluorescein angiographic findings. Arch Ophthalmol 1976; 94(8): 1355-8.
[http://dx.doi.org/10.1001/archopht.1976.03910040227015] [PMID: 949278]

[21] McLeod D. Central retinal vein occlusion with cilioretinal infarction from branch flow exclusion and choroidal arterial steal. Retina 2009; 29(10): 1381-95.
[http://dx.doi.org/10.1097/IAE.0b013e3181b85f41] [PMID: 19898176]

[22] Park SU, Lee SJ, Kim M. Isolated cilioretinal artery occlusion in a patient with hypertensive crisis. BMJ Case Rep 2014.
[http://dx.doi.org/10.1136/bcr-2013-202890]

[23] Hayreh SS, Zimmerman B. Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. Ophthalmologica 2003; 217(4): 239-59.
[http://dx.doi.org/10.1159/000070631] [PMID: 12792130]

[24] Bitra RK, Eggenberger E. Review of Susac syndrome. Curr Opin Ophthalmol 2011; 22(6): 472-6.
[http://dx.doi.org/10.1097/ICU.0b013e32834bbfeb] [PMID: 21897238]

[25] Hayreh SS. Intra-arterial thrombolysis for central retinal artery occlusion. Br J Ophthalmol 2008; 92(5): 585-7.
[http://dx.doi.org/10.1136/bjo.2007.136481] [PMID: 18441165]

[26] Schumacher M, Schmidt D, Jurklies B, *et al.* Central retinal artery occlusion: local intra-arterial fibrinolysis *versus* conservative treatment, a multicenter randomized trial. Ophthalmology 2010; 117(7): 1367-1375 e1361.

[27] Mason JO III, Nixon PA, Albert MA Jr. Trans-luminal nd:YAG laser embolysis for branch retinal artery occlusion. Retina 2007; 27(5): 573-7.
[http://dx.doi.org/10.1097/IAE.0b013e3180546c4d] [PMID: 17558318]

[28] Lim JY, Lee JY, Chung HW, Yoon YH, Kim JG. Treatment of branch retinal artery occlusion with transluminal Nd:YAG laser embolysis. Korean J Ophthalmol 2009; 23(4): 315-7.
[http://dx.doi.org/10.3341/kjo.2009.23.4.315] [PMID: 20046697]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 9

Retinal Arterial Macroaneurysm

Rodrigo Lechuga Perezanta[1] and **Virgilio Morales Cantón**[2,*]

[1] *Asociación para Evitar la Ceguera en Mexico, Mexico City, Mexico*

[2] *Retina Department, Asociación para Evitar la Ceguera en Mexico, Mexico City, Mexico*

The term macroaneurysm was first coined by Robertson, in 1973 making reference to arterial retinal lesions with saccular or fusiform swelling, localized on the first three orders of the retinal arterial tree found mainly at arterial bifurcations [1]. Saccular arterial macroaneurysms are more likely to burst and develop closer to the optic nerve where perfusion pressure is higher. Retinal arterial macroaneurysms are more frequent in women (60 – 80% probably due to hormonal and hereditary factors) with an average age of 69 years and have a strong association with systemic diseases such as arterial hypertension, aterosclerotic disease, hyperlipidemia, polycythemia and cerebrovascular disease. Retinal arterial macroaneurysms have been described in Leber´s miliary aneurysms, Coats´ disease, branch retinal artery occlusion and Eales´ disease among others [1, 2].

Systemic arterial hypertension causes an increase in hydrostatic pressure and may lead to hyaline degeneration of the vascular wall, loss of autoregulation tone and arterial dilatation [2].

Another theory to support that systemic arterial hypertension is a risk factor to the formation of arterial macroaneurysms is Laplace equation, which states that an increase in the transmural pressure is directly proportional to the increased tension of the wall.

Focal embolic damage to the arterial wall is considered to be a part of the

* **Corresponding author Virgilio Morales Cantón:** Retina Department, Asociación para Evitar la Ceguera en Mexico, Vicente García Torres 46, San Lucas Coyoacan, Mexico City, 04030; Mexico; Tel +52 (55) 10841400, Email: vmoralesc@mac.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

mechanism for lesion formation, which may result in localized ischemia.

ESSENTIALS OF DIAGNOSIS

Most of these lesions appear on the superotemporal arterial branch (51%), followed by the inferotemporal branch (28%). Macroaneurysms affecting the nasal arterial branches may be less frequently diagnosed because patients may not notice the loss of visual acuity until the macula is affected, which could not happen, or a vitreous hemorrhage develops. Usually one macroaneurysm is present, but more lesions have been described affecting the same eye and 10% may be bilateral.

The main symptom is decreased visual acuity as a consequence of exudation, edema or hemorrhage. A characteristic finding is the presence of hemorrhage in different layers including subretinal, intraretinal, sub internal limiting membrane (Figs. **1A**, **2A** and **3A**) or in the vitreous cavity [1, 3]. Hourglass hemorrhages are also a typical finding.

These lesions may develop symptoms when acute or chronic decompensation occurs. Acute decompensation is typically associated with rupture and hemorrhage of the macroaneurysm while chronic decompensation is due to abnormal leakage of plasma constituents across the aneurysmal wall leading to the accumulation of yellow perianeurysmal intraretinal exudates [4].

When the arterial macroaneurysm is visible during fundus examination, the correct diagnosis can be achieved without much trouble, but when massive hemorrhage, exudation or retinal edema are present they suppose a diagnostic challenge. Fluorescein angiography (Figs. **1B**, **2B** and **3B**) is useful to locate the lesion when dense hemorrhage is absent so hyperfluorescence is visible. Macroaneurysm typically shows hyperfluorescence during the early arterial phase of the angiogram but late phase varies from little staining of the vessel wall to marked leakage. The absorption and emission spectrum of indocyanine green are close to infrared range and this allows the dye to be seen through hemorrhage. This makes indocyanine green a good alternative when diagnostic dilemma is present due to dense hemorrhage or exudates [5, 6].

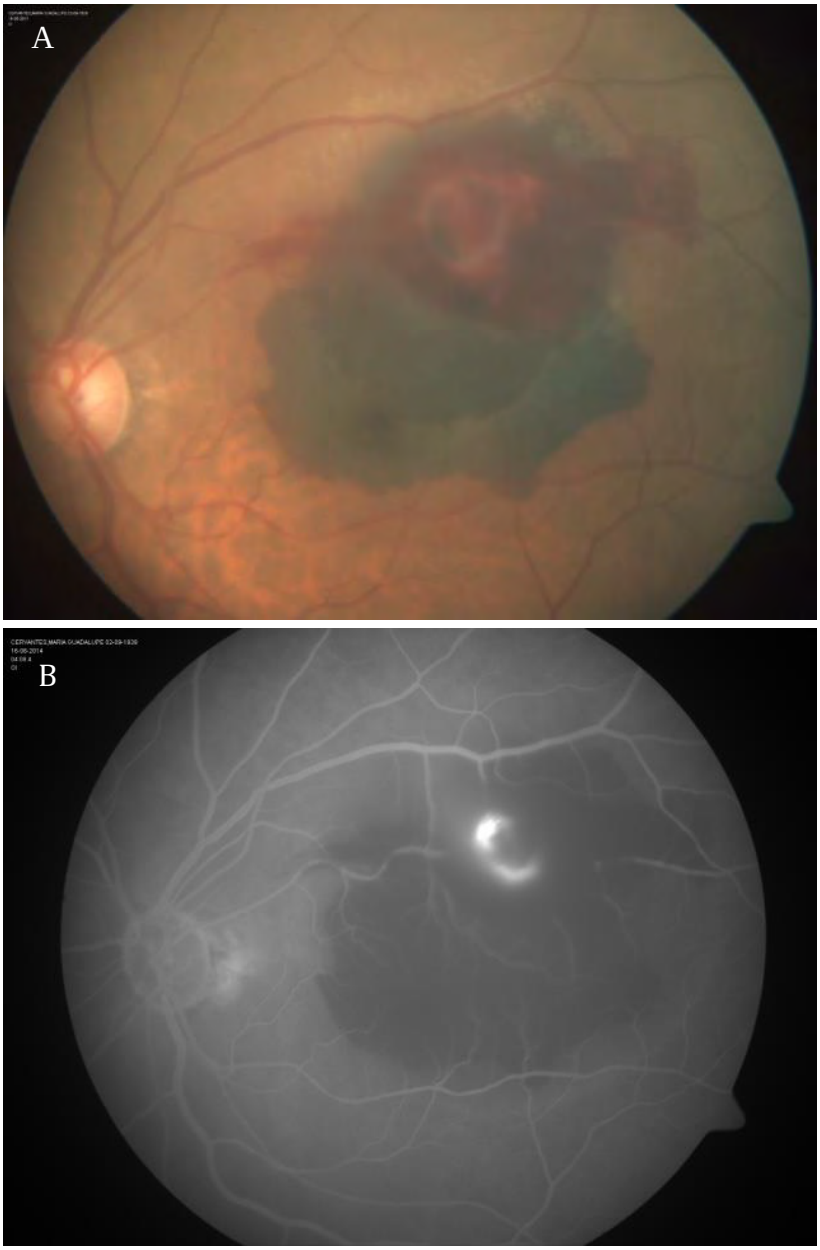


Fig. (1). A 74-year-old female patient complains of floaters and photopsia in her left eye from 8 days ago. Diagnosis of systemic arterial hypertension was made 20 years before. Visual acuity was 20/100, intraocular pressure 16 mmHg, fundus examination revealed subretinal and intraretinal hemorrhage (**A**) and fluorescein angiography showed a hyperfluorescent lesion in the superior temporal arterial vessel in the second branch (**B**). No treatment was performed and visual acuity was recovered to 20/60 three months later.

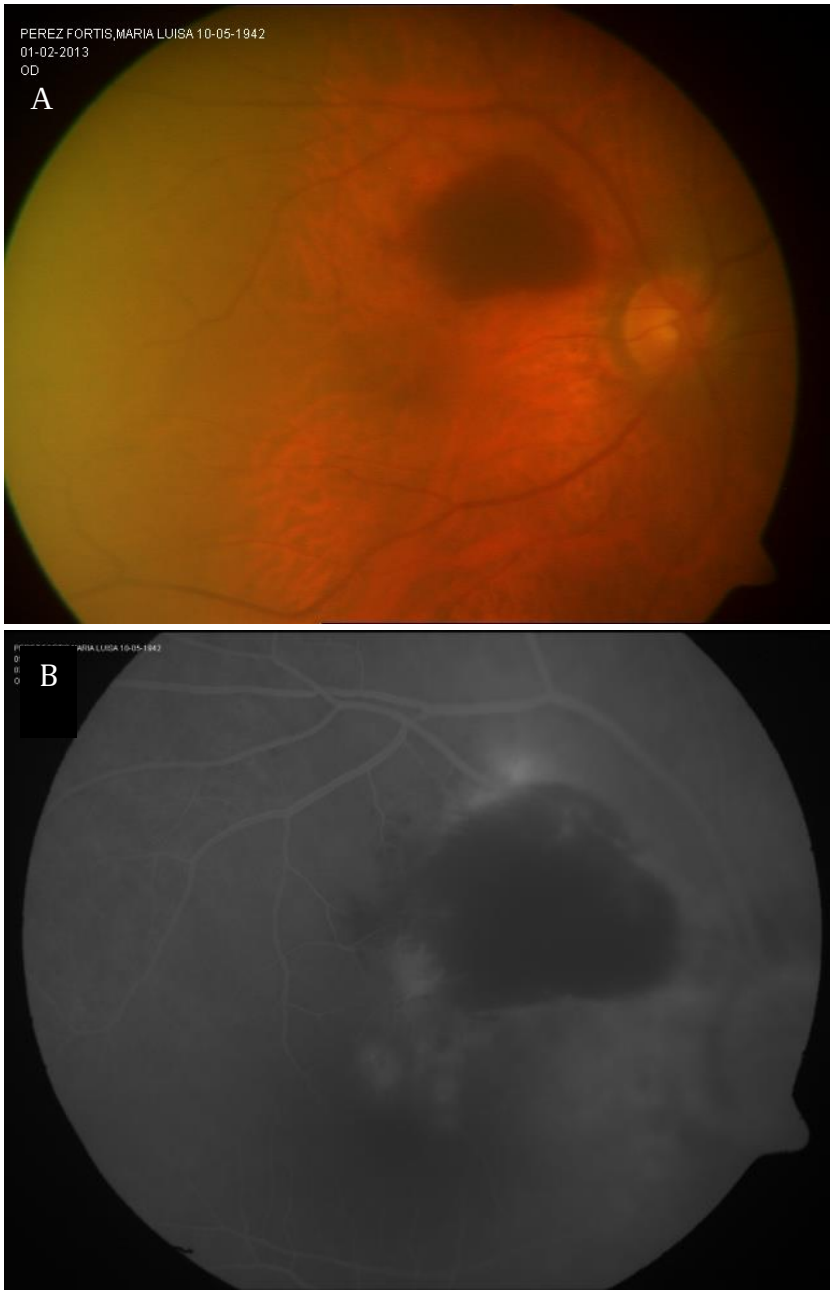


Fig. (2). 70-year-old female with floaters, visual acuity 20/100, intraocular pressure 12 mmHg. Fundus examination revealed a intraretinal hemorrhage on the superior temporal artery (**A**) with increased hyperfluorescence on the same spot (**B**). No treatment was performed and final visual acuity was 20/40.

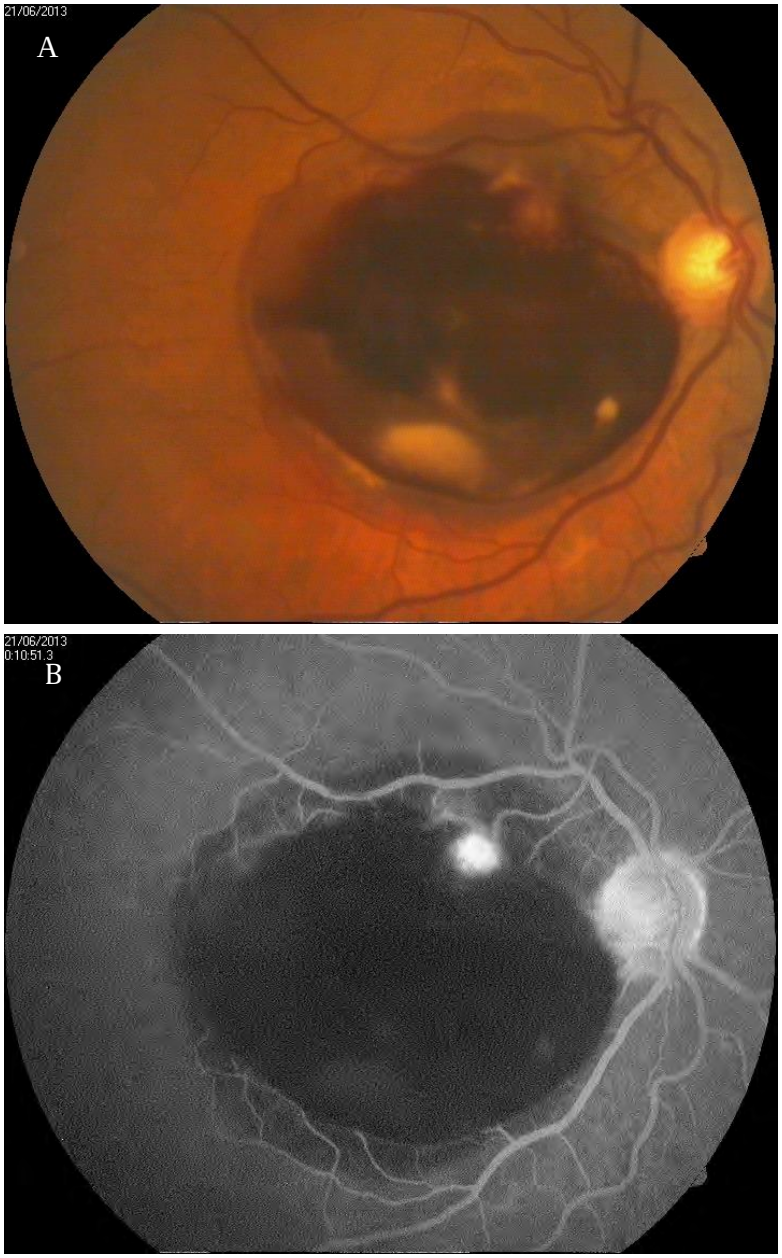


Fig. (3). A 77-year-old female with decreased visual acuity from one week before. Visual acuity was counting fingers, intraocular pressure 18 mmHg, in fundus examination a subretinal and subhyaloid hemorrhage was found (**A**). Fluorescein angiography revealed a hyperfluorescent spot that increased in intensity with time (**B**). Laser hyaloidotomy was performed and the final visual acuity was 20/800.

Optical Coherence Tomography (OCT) can contribute to achieve a correct diagnosis. Typical findings include an abnormal saccular dilatation in the internal layers that characteristically elevates the internal limiting membrane and ganglion cell layer, modifying the normal architecture of the adjacent retina. The layers beneath the macroaneurysm are hyporreflective due to a masking effect (Fig. **4**).

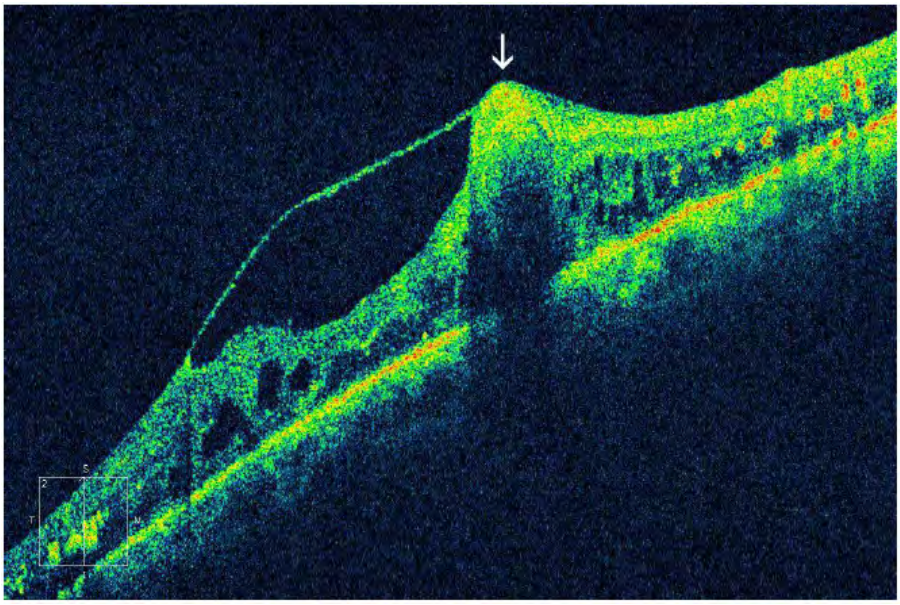


Fig. (4). OCT image showing a saccular dilatation (arrow) that elevates the retina, with a posterior shadow. Intraretinal fluid and hyper-reflective foci due to hard exudates may also be observed.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes any cause of hemorrhage and exudates, such as diabetic retinopathy, venous occlusions, radiation retinopathy, Coats´ disease, retinal telangiectasis, age-related macular degeneration, retinal capillary angioma, cavernous hemangioma, malignant melanoma.

MANAGEMENT

There is no established consensus regarding the timing to treat the patient or the ideal treatment for this lesion but it is generally accepted to treat when there is exudation involving the fovea with decreased visual acuity [7, 8]. Laser photocoagulation is the most common treatment, and it can be applied directly or

surrounding the macroaneurysm and using threshold or subthreshold laser [9, 10]. Parodi *et al.* found the same obliteration of the lesion and visual recovery using threshold *vs* subthreshold laser but complications including scar growth, choroidal neovascularization, subretinal fibrosis, arterial branch occlusion, epiretinal membranes, increased exudation and retinal traction were avoided using subthreshold laser. They used a diode infrared laser (810 nm) for the subthreshold patients and a krypton laser (647 nm) for the threshold group. The selective damage to the retinal pigment epithelial cells may lead to a better balance of angiogenic factors and cytokine release [7, 9].

Another alternative is the use of antiangiogenic therapy. In 37 eyes, Pichi *et al.* proved that 3 intravitreal injections with bevacizumab (0.05ml/1.25mg) in patients with complicated macroaneurysms affecting the fovea, are safe and effective to improve visual acuity from 20/80 to 20/25 and central macular thickness from 520.38 +/- 191.05 to 214.84 +/- 26.86 microns [10].

Pars plana vitrectomy is recommended when persistent vitreous hemorrhage or preretinal hemorrhage is present. It is also justified when the etiology of the hemorrhage is undefined.

There is poor visual prognosis when subretinal hemorrhage exists because of photoreceptor deterioration and controversy exists whether to treat with pneumatic displacement *versus* observation.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Ryan SJ. Retina. Fourth edition 2006. Section 5. Retinal Vascular Diseases. Chapter 81. Acquired Retinal Macroaneurysm. Mosby: Philadelplia 2006; pp. 1475-1478.

[2] Panton RW, Goldberg MF, Farber MD. Retinal arterial macroaneurysms: risk factors and natural history. Br J Ophthalmol 1990; 74(10): 595-600.
[http://dx.doi.org/10.1136/bjo.74.10.595] [PMID: 2285682]

[3] Goldenberg D, Soiberman U, Loewenstein A, Goldstein M. Heidelberg spectral-domain optical coherence tomographic findings in retinal artery macroaneurysm. Retina 2012; 32(5): 990-5. [http://dx.doi.org/10.1097/IAE.0b013e318229b233] [PMID: 22127222]

[4] Abdel-Khalek MN, Richardson J. Retinal macroaneurysm: natural history and guidelines for treatment. Br J Ophthalmol 1986; 70(1): 2-11. [http://dx.doi.org/10.1136/bjo.70.1.2] [PMID: 3947596]

[5] Townsend-Pico WA, Meyers SM, Lewis H. Indocyanine green angiography in the diagnosis of retinal arterial macroaneurysms associated with submacular and preretinal hemorrhages: a case series. Am J Ophthalmol 2000; 129(1): 33-7. [http://dx.doi.org/10.1016/S0002-9394(99)00337-2] [PMID: 10653410]

[6] Moradian S, Soheilian M. Periretinal hemorrhage due to retinal arterial macroaneurysm: The role of ICG angiography in solving a diagnostic dilemma. J Ophthalmic Vis Res 2009; 4(2): 125-6. [PMID: 23264858]

[7] Battaglia Parodi M, Iacono P, Pierro L, Papayannis A, Kontadakis S, Bandello FM. Subthreshold laser treatment *versus* threshold laser treatment for symptomatic retinal arterial macroaneurysm. Invest Ophthalmol Vis Sci 2012; 53(4): 1783-6. [http://dx.doi.org/10.1167/iovs.11-8772] [PMID: 22395893]

[8] McCabe CM, Flynn HW Jr, McLean WC, *et al.* Nonsurgical management of macular hemorrhage secondary to retinal artery macroaneurysms. Arch Ophthalmol 2000; 118(6): 780-5. [http://dx.doi.org/10.1001/archopht.118.6.780] [PMID: 10865314]

[9] Parodi MB, Iacono P, Ravalico G, Bandello F. Subthreshold laser treatment for retinal arterial macroaneurysm. Br J Ophthalmol 2011; 95(4): 534-8. [http://dx.doi.org/10.1136/bjo.2009.175547] [PMID: 20956278]

[10] Pichi F, Morara M, *et al.* Intravitreal bevacizumab for macular complications from retinal arterial macroaneurysms. Am J Ophthalmol 2013; 129(1): 33-7.

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 10

Macular Telangiectasia

Yogin Patel[1] and **Michael D. Ober**[1,2,*]

[1] *Department of Ophthalmology, Henry Ford Health System, Detroit, MI, USA*

[2] *Retina Consultants of Michigan, Southfield, MI, USA*

Macular telangiectasia (MacTel) was best classified and described by Gass and Blodi as a form of idiopathic juxtafoveolar retinal telangiectasis [1] and is also commonly referred to as idiopathic perifoveal telangiectasia. This is a group of disorders which affects the vasculature of the posterior pole. Numerous classification schemes have been designed to categorize it, most notably, that of Gass and Blodi [1] and an update by Yannuzzi *et al.* [2]. Two major subclassifications are of greatest importance; MacTel type 1 refers to a unilateral presentation with prominent microaneurysms that is often grouped within the spectrum of Coats disease. MacTel type 2 is more often referred to simply as MacTel, and represents an acquired bilateral retinal vascular disorder. For the purposes of this review, we will focus on MacTel type 2.

Different studies quote very different numbers for the prevalence of this condition ranging from as high as 0.1% in the Beaver Dam Eye Study to 0.0045 to 0.022% in the Melbourne collaborative cohort study [3, 4]. The age at onset is usually in the late 40s to early 60s. There may be a slight female predominance depending on the study population quoted.

ESSENTIALS OF DIAGNOSIS

Patients will often present with a pericentral scotoma or metamorphopsia. Visual acuity rarely progresses to legal blindness but visual dysfunction is common. The clinical presentation begins with subtle changes noted in the posterior pole.

* **Corresponding author Michael D. Ober:** Retina Consultants of Michigan, 29201 Telegraph Road, Suite 606, Southfield, MI 48034, USA; Tel: (248) 356-8610; Fax: (248) 356-6473; E-mail: obermike@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

Lesions most often begin just temporal to the fovea (Figs. **1A, B**). They may then further evolve to include the larger perifoveal region. The initial presenting change is often a loss of transparency in the retina temporal to the fovea. With time the lesion may evolve to include dilation of capillaries and will likewise spread from their temporal perifoveal origin. Histological studies have demonstrated that the dilated capillaries are mostly located in the deeper retinal layers [1]. Although, Yannuzzi and others have observed the involvement of both the superficial and deep plexus [2]. Later changes include dilated venules, which are often associated with the abnormal capillaries. These vessels tend to increase in diameter as they approach the fovea, in contrast to normal vessels. In addition, these vessels often take characteristic right angle turns, which represent diving of the vessel toward the deeper retinal layers. Associated changes in the RPE include crystalline deposits (Figs. **3A, B**), pigment migration, and hyperplasia following these venules [2]. Over the time, secondary atrophy of the pigment epithelium and neurosensory retina may develop. Some eyes may accumulate vitelliform material under the central macula. Lamellar thinning of the inner retina within the fovea is common and manifests with the development of inner lamellar cystic changes (Fig. **4**). On occasion the atrophic changes may progress to a full thickness macular hole.

Neovascularization is another common later stage development usually preceded by the appearance of the right angle venules and pigmentary changes. As with any neovascularization, it may be associated with hard exudate, edema, and hemorrhage. The neovascularization stems from retinal vessels, but may be indistinguishable from choroidal neovascularization with chorioretinal anastomosis from other etiologies. Late changes may include the formation of a disciform scar.

Multimodal imaging is critical in the diagnosis of MacTel. One of the earliest signs of the disease, even before clinical changes appear, is the loss of the hypofluorescent center in fundus autofluorescence photos which later progress to more pronounced hypoautofluorescence corresponding to RPE atrophy with adjacent granular hyperautofluorescence (Figs. **5A, B**). This has been postulated as a direct result of the depletion in macular pigment [5]. Fluorescein angiography (FA) findings are often diagnostic and include the characteristic telangiectatic

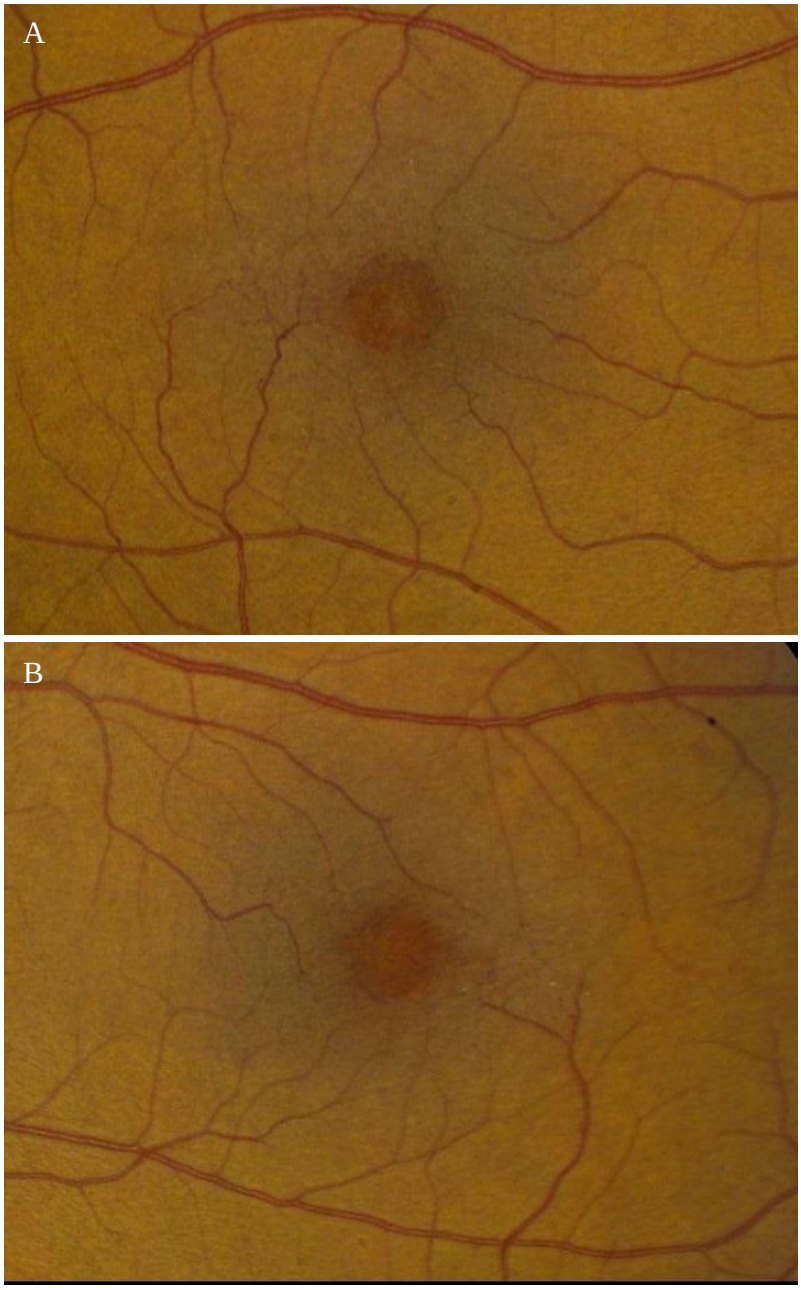


Fig. (1). (**A** and **B**) Color fundus photographs demonstrating the subtle loss of retinal transparency and right angle vessels most notable temporal to both foveae. Retinal pigment epithelial hyperplasia can be seen surrounding the right angle vessels (not shown here). Vessels temporal to the fovea are noted to be of irregular caliber and telangiectatic (Photo Credit: Colin Griffin).

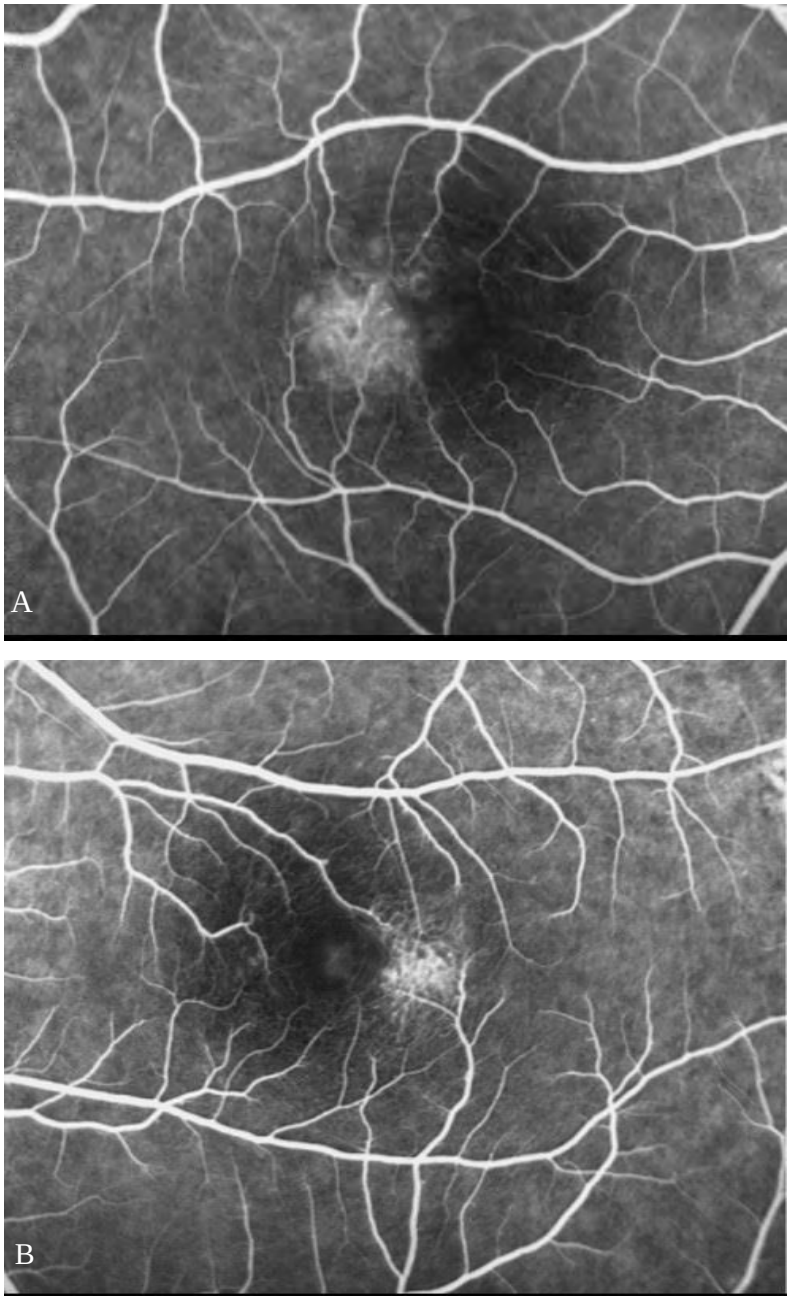


Fig. (2). (**A** and **B**) Venous phase fluorescein angiogram showing characteristic dilatation and leakage of telangiectatic vessels most notably temporal to the foveae (Photo Credit: Colin Griffin).

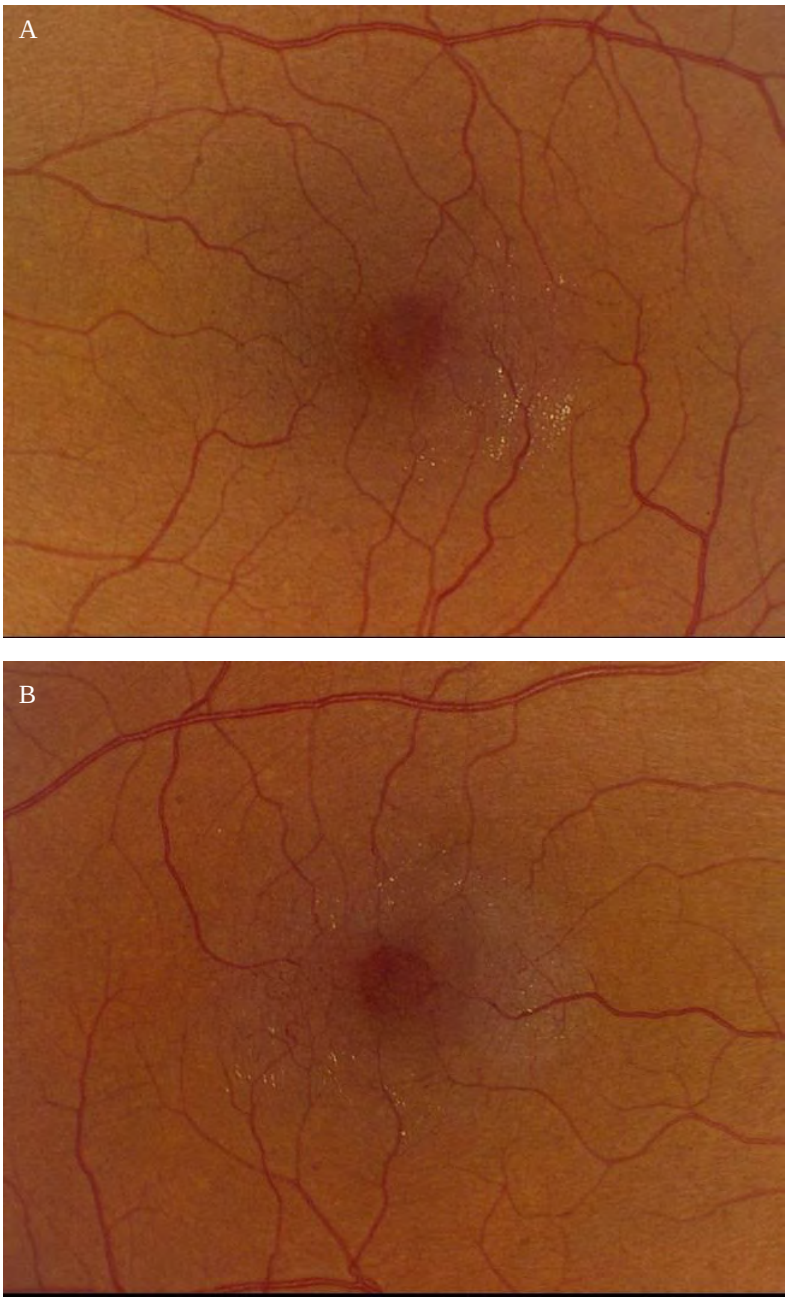


Fig. (3). (**A** and **B**) Color fundus photographs demonstrating loss of retinal transparency, right angle vessels, and crystalline dots at the vitreoretinal interface (Photo Credit:Matthew Lawrence, CRA)

capillaries temporal to the fovea that leak in later frames (Figs. **2A, B**). In the absence of neovascularization, corresponding optical coherence tomography (OCT) does not include retinal thickening, subretinal fluid, or pronounced cystic changes in the region of FA leakage, but rather distortion of the foveal pit with the temporal side becoming larger and thinner [5]. As the disease progresses there is often disruption of the normal photoreceptor inner segment and outer segment layer. This is followed by the formation of atrophic lamellar holes, which do not demonstrate corresponding leakage on FA.

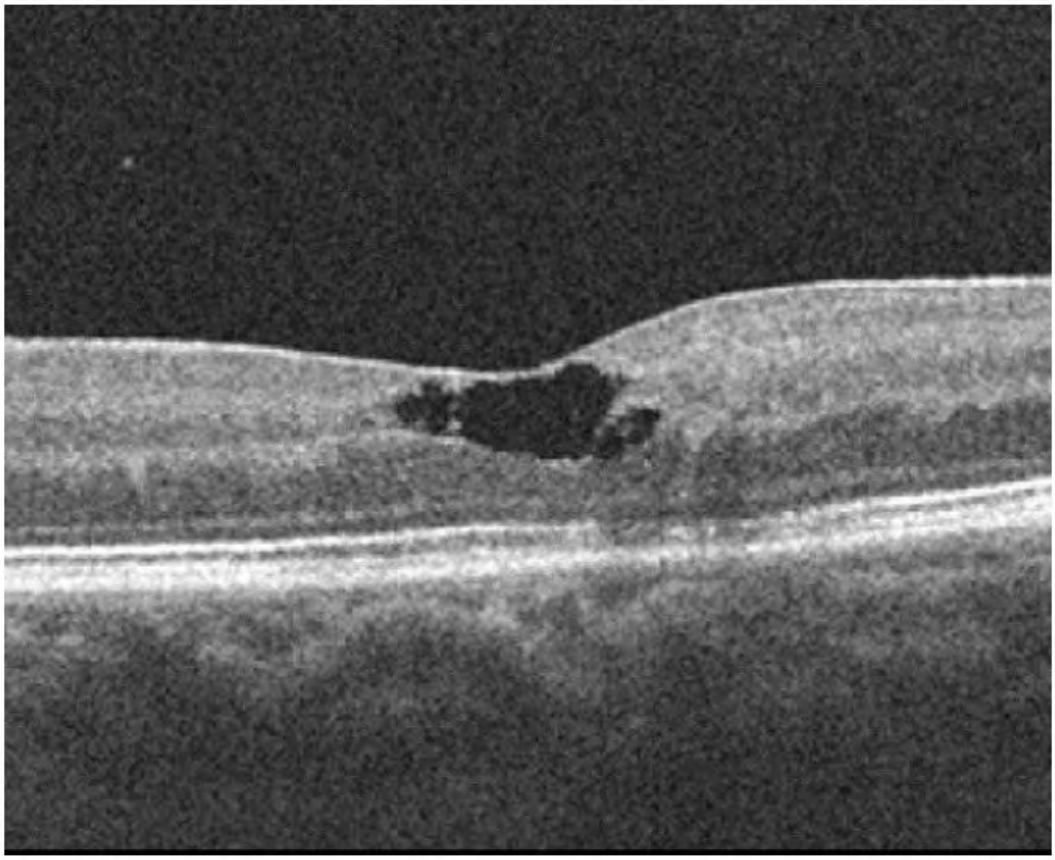


Fig. (4). Outer retinal cavity formation from photoreceptor disruption. Some abnormality in retinal pigment migration (Photo Credit: Patricia Streasick, CRA).

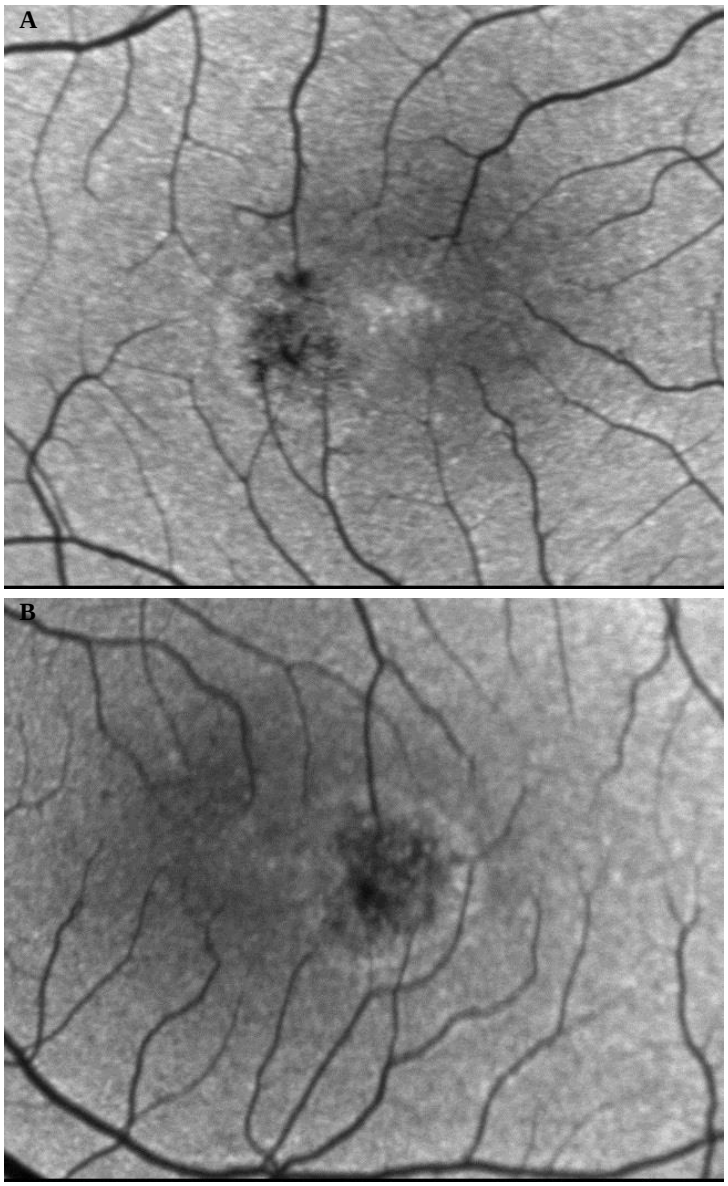


Fig. (5). (**A** and **B**) Fundus autofluorescence showing moderate increase and decrease in autofluorescence (Photo Credit: Courtney McClenahay).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes a variety of vascular anomalies of the retina. Branch retinal vein occlusions may result in abnormal collateral vessels

formation, but emanate from an abnormal arterial-venous crossing point and are most frequently unilateral or at least highly asymmetric. Radiation can cause similar telangiectatic vascular changes, but requires relevant history and often presents with cotton-wool spots and pre-retinal neovascularization. Neovascular AMD may present with similar appearing neovascularization including chorioretinal anastomosis, but occurs in the presence of drusen, pigment, and atrophy without the abnormal retinal capillary vascular telangiectatic changes. Late stage neovascular scar formation from MacTel may be indistinguishable from that of other etiologies, but often age and the fellow eye examination is revealing.

MANAGEMENT

As of yet, there are no accepted methods of treatment for the disorder when it presents without neovascularization. Laser photocoagulation and PDT appear to be of no benefit [6]. Anti-vascular endothelial growth factor (VEGF) treatment has led to debatable anatomic improvement but no visual gain [7, 8]. Intravitreal steroids have likewise demonstrated no positive effect on disease course [9]. Anti-VEGF has shown positive results when treating early stages of neovascularization [10]. Surgical intervention has met with poor outcomes in limited numbers of patients [11]. The macular holes in MacTel have also had limited success with surgical correction, mainly thought to be the result of the atrophic rather than transactional nature of formation [12]. Future efforts are currently focused on a randomized trial utilizing a ciliary neurotrophic factor emitting implant, but no data was yet available at the time of writing [13].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Gass JD, Blodi BA. Idiopathic juxtafoveolar retinal telangiectasis. Update of classification and follow-up study. Ophthalmology 1993; 100(10): 1536-46.

[http://dx.doi.org/10.1016/S0161-6420(93)31447-8] [PMID: 8414413]

[2] Yannuzzi LA, Bardal AM, Freund KB, Chen KJ, Eandi CM, Blodi B. Idiopathic macular telangiectasia. Arch Ophthalmol 2006; 124(4): 450-60.
[http://dx.doi.org/10.1001/archopht.124.4.450] [PMID: 16606869]

[3] Klein R, Blodi BA, Meuer SM, Myers CE, Chew EY, Klein BE. The prevalence of macular telangiectasia type 2 in the Beaver Dam eye study. Am J Ophthalmol 2010; 150(1): 55-62.e2.
[http://dx.doi.org/10.1016/j.ajo.2010.02.013] [PMID: 20609708]

[4] Aung KZ, Wickremasinghe SS, Makeyeva G, Robman L, Guymer RH. The prevalence estimates of macular telangiectasia type 2: the Melbourne Collaborative Cohort Study. Retina 2010; 30(3): 473-8.
[http://dx.doi.org/10.1097/IAE.0b013e3181bd2c71] [PMID: 19952995]

[5] Gillies MC, Zhu M, Chew E, *et al.* Familial asymptomatic macular telangiectasia type 2. Ophthalmology 2009; 116(12): 2422-9.
[http://dx.doi.org/10.1016/j.ophtha.2009.05.010] [PMID: 19815294]

[6] De Lahitte GD, Cohen SY, Gaudric A. Lack of apparent short-term benefit of photodynamic therapy in bilateral, acquired, parafoveal telangiectasis without subretinal neovascularization. Am J Ophthalmol 2004; 138(5): 892-4.
[http://dx.doi.org/10.1016/j.ajo.2004.06.010] [PMID: 15531343]

[7] Gamulescu MA, Walter A, Sachs H, Helbig H. Bevacizumab in the treatment of idiopathic macular telangiectasia. Graefes Arch Clin Exp Ophthalmol 2008; 246(8): 1189-93.
[http://dx.doi.org/10.1007/s00417-008-0795-6] [PMID: 18386039]

[8] Charbel Issa P, Finger RP, Kruse K, Baumüller S, Scholl HP, Holz FG. Monthly ranibizumab for nonproliferative macular telangiectasia type 2: a 12-month prospective study. Am J Ophthalmol 2011; 151(5): 876-886.e1.
[http://dx.doi.org/10.1016/j.ajo.2010.11.019] [PMID: 21334595]

[9] Wu L, Evans T, Arévalo JF, *et al.* Long-term effect of intravitreal triamcinolone in the nonproliferative stage of type II idiopathic parafoveal telangiectasia. Retina 2008; 28(2): 314-9.
[http://dx.doi.org/10.1097/IAE.0b013e31814cf03e] [PMID: 18301037]

[10] Kovach JL, Rosenfeld PJ. Bevacizumab (avastin) therapy for idiopathic macular telangiectasia type II. Retina 2009; 29(1): 27-32.
[http://dx.doi.org/10.1097/IAE.0b013e31818ba9de] [PMID: 18936721]

[11] Berger AS, McCuen BW II, Brown GC, Brownlow RL Jr. Surgical removal of subfoveal neovascularization in idiopathic juxtafoveolar retinal telangiectasis. Retina 1997; 17(2): 94-8.
[http://dx.doi.org/10.1097/00006982-199703000-00002] [PMID: 9143035]

[12] Gregori N, Flynn HW Jr. Surgery for full-thickness macular hole in patients with idiopathic macular telangiectasia type 2. Ophthalmic Surg Lasers Imaging 2010; 41 Online: 1-4.
[PMID: 21158375]

[13] Chew EY, Clemons TE, Peto T, *et al.* Ciliary neurotrophic factor for macular telangiectasia type 2: Results from a phase 1 safety trial. Am J Ophthalmol 2014. pii: S0002-9394(14)00819-8.

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 11

Sickle Cell Retinopathy

Luke B. Lindsell and **Aziz A. Khanifar***

Retina Group of Washington, Washington DC, USA

ESSENTIALS OF DIAGNOSIS

Sickle cell disease is an autosomal recessive condition comprising several different forms of mutated hemoglobin. Patients who are homozygous for the hemoglobin S gene (HbS) have the most severe form of sickle cell anemia. Other genotypes of clinical importance to ophthalmologists include HbSC disease (double heterozygote for HbS and HbC), HbS/b-thal (double heterozygote for HbS and beta-thalassemia), and sickle cell trait (one normal Hb allele and one HbS allele). In general, patients with the more severe genotype of sickle cell disease have less severe ophthalmic manifestations. For example, HbSS has the most critical systemic complications, the ocular manifestations are less severe compared to HbSC disease which has a more moderate systemic course. Although sickle cell trait is relatively asymptomatic, under hypoxic conditions both systemic and ophthalmic consequences can occur [1].

Relative hypoxia causes mutated hemoglobin to polymerize, ultimately altering the morphology of the red blood cell (RBC) to the characteristic sickle shape. These abnormal RBCs occlude terminal arterioles, leading to ischemia and possible tissue infarction [2]. Sickle cell retinopathy is one end-organ manifestation of the disease. Similar to diabetic eye disease, both non-proliferative and proliferative forms occur, and the proliferative disease is associated with more significant visual morbidity [3].

* **Corresponding author Aziz A. Khanifar:** Retina Group of Washington, Washington DC, USA; Tel: (301) 495-2357, Fax: (301) 495-2359; E-mail: azizkhanifar@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

Non-proliferative sickle cell retinopathy is characterized by several possible findings:

1. Vascular tortuosity – more common in HbSS disease (Fig. **1**).
2. Salmon patch hemorrhages – located between the internal limiting membrane (ILM) and retinal surface ("blowout" of occluded arteriole) [4] (Fig. **2**).
3. Intraretinal hemorrhages (Fig. **1**).
4. Iridescent spots – small schisis cavity in area of resolved intraretinal hemorrhage. Hemosiderin-laden macrophages appear as glistening spots [4] (Fig. **3**).
5. Black sunburst – flat areas of hyperpigmentation resulting from intraretinal hemorrhage infiltrating the subretinal space and damaging the retinal pigment epithelium (RPE) (Fig. **4**).

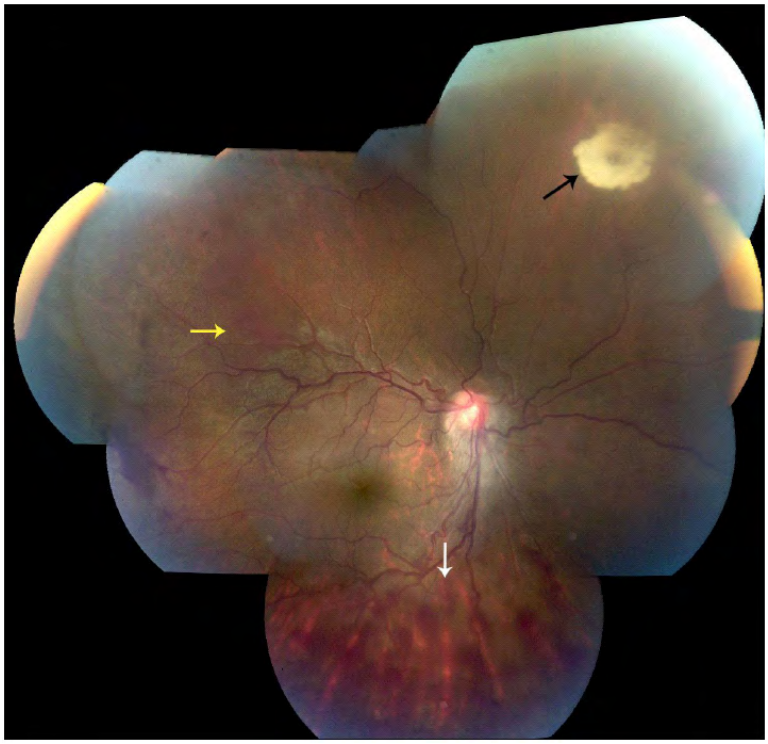


Fig. (1). Color photo montage. Resolving intraretinal hemorrhage that will become a sunburst or possibly iridescent spots (black arrow). Faint resolving salmon patch hemorrhage (yellow arrow). Vitreous hemorrhage (white arrow). Vascular tortuosity is also evident.

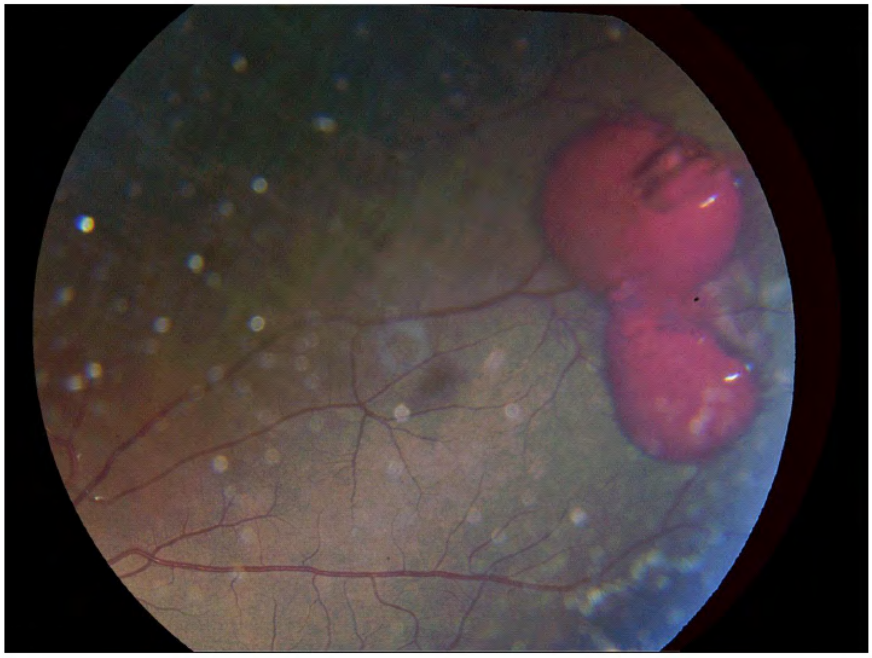


Fig. (2). Color photo. Large peripheral salmon patch.

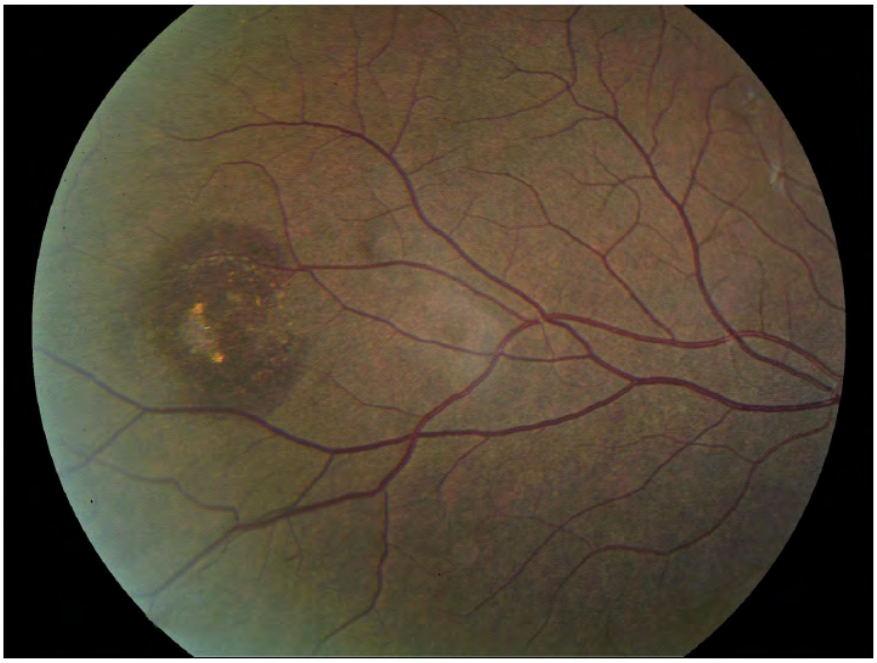


Fig. (3). Color photo. Iridescent spots.

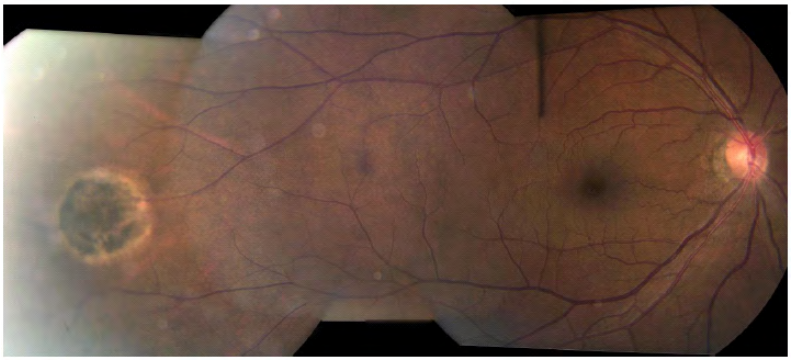


Fig. (4). Color photo. Sunburst.

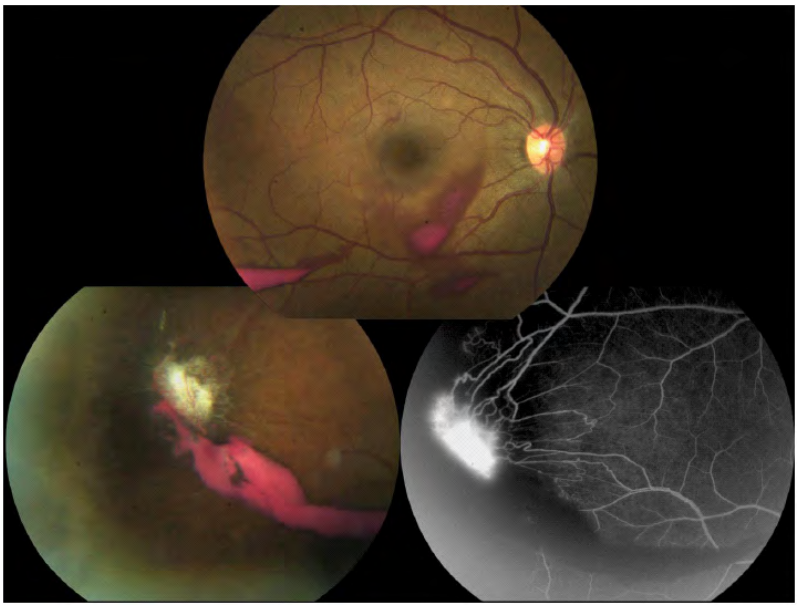


Fig. (5). Multiple imaging modalities. **Top**: Color photo. Central vitreous hemorrhage. **Bottom left**: Color photo. Same eye with the peripheral fibrotic sea fan which was the source of the vitreous hemorrhage. Bottom right: Fluorescein angiogram. Irregular peripheral vasculature.

Proliferative sickle cell retinopathy (PSR) causes visual loss primarily with vitreous hemorrhage (Fig. **5**) and retinal detachment (tractional or tractional-rhegmatogenous). Fortunately, however, the incidence of proliferative disease is low [5]. The hallmark of the disease is neovascularization which initially appears as tufts at the interface between vascular and avascular retina. This typically occurs in the temporal quadrant. These tufts can progress to a characteristic “sea

fan" configuration (Figs. **5**-**7**). Fibroglial tissue can proliferate over the surface of the sea fan and scaffold into the vitreous to potentially initiate a tractional retinal detachment. Wide field fluorescein angiography (FA) is essential in evaluating the extent of peripheral non-perfusion [6, 7] (Fig. **8**).

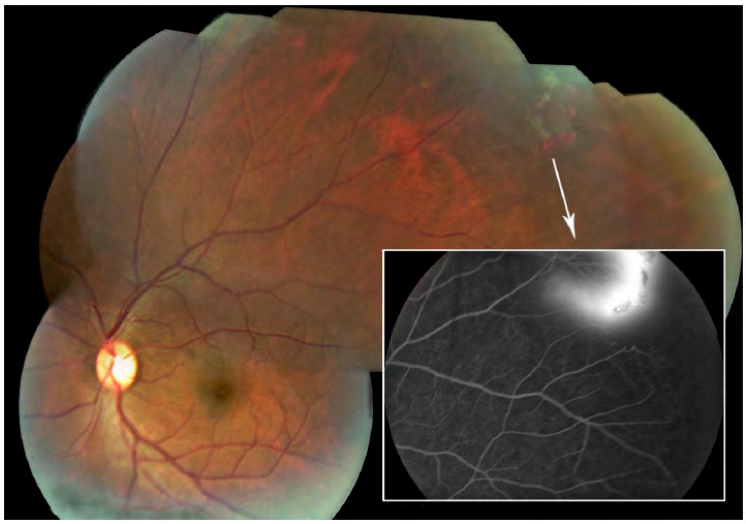


Fig. (6). Multiple imaging modalities. Color photo montage: Peripheral sea fan with hemorrhages at avascular retinal border. Inset fluorescein angiogram: Leakage associated with sea fan.

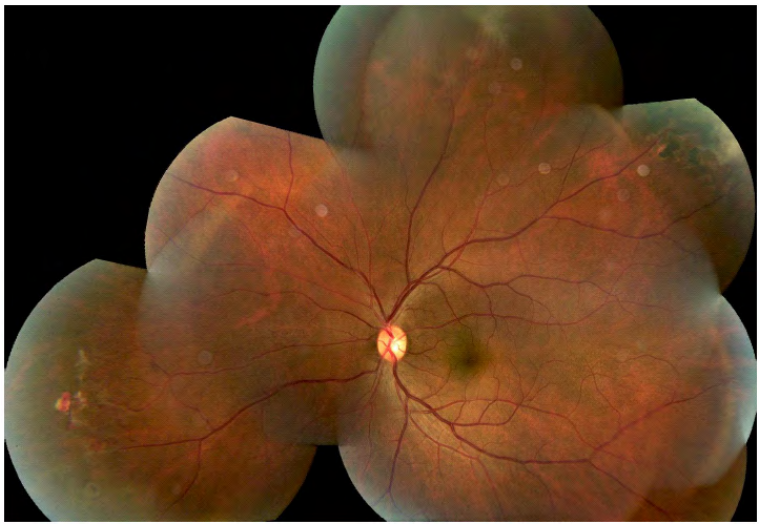


Fig. (7). Color photo montage. Same patient from Fig. (**9**), three years after superotemporal scatter laser photocoagulation. Note regression of the sea fan superotemporally and presence of a newer sea fan nasally.

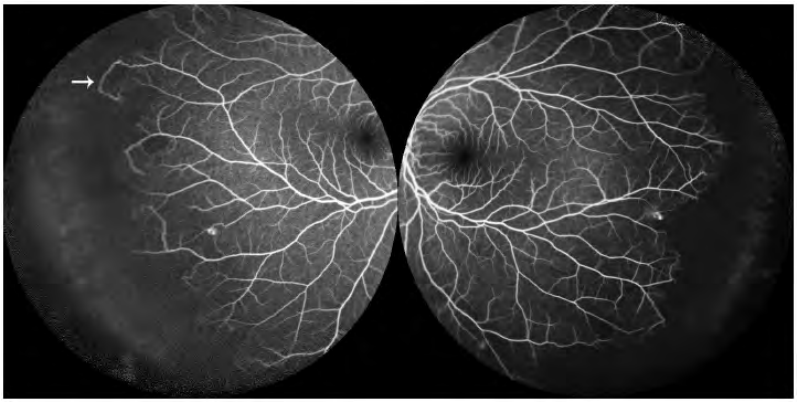


Fig. (8). Fluorescein angiogram. Peripheral non-perfusion in both eyes. An area of arterio-venous anastomosis in the right eye (white arrow).

Other retinal findings of importance in sickle cell disease:

1. Angioid streaks – rare finding, usually no significant visual sequelae unless subfoveal choroidal neovascularization occurs.
2. Maculopathy – an enlarged foveal avascular zone, with no impact on visual acuity, may be demonstrated with FA [8] (Fig. **9**). Spectral domain optical coherence tomography (SDOCT) can detect 3 different findings: a) enlarged foveal depression with central thinning [9], b) temporal macular thinning [9] (Fig. **10**), and c) inner retinal atrophy as a consequence of focal infarction [10].

DIFFERENTIAL DIAGNOSIS

1. Proliferative diabetic retinopathy 2. Retinal vein occlusion 3. Familial exudative vitreoretinopathy 4. Retinopathy of prematurity 5. Radiation retinopathy 6. Ocular ischemic syndrome 7. Sarcoidosis 8. Talc retinopathy	9. Eales disease 10. Other collagen vascular diseases (eg lupus, rheumatoid arthritis) 11. Acute retinal necrosis 12. Behçet's disease 13. Pars planitis

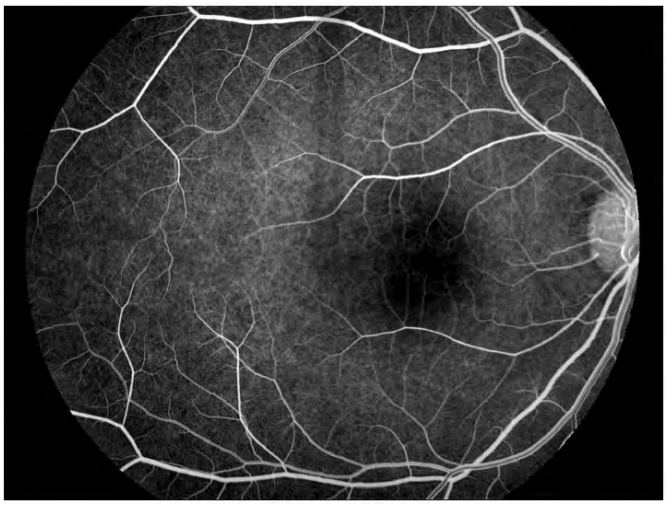


Fig. (9). Fluorescein angiogram. Enlarged foveal avascular zone.

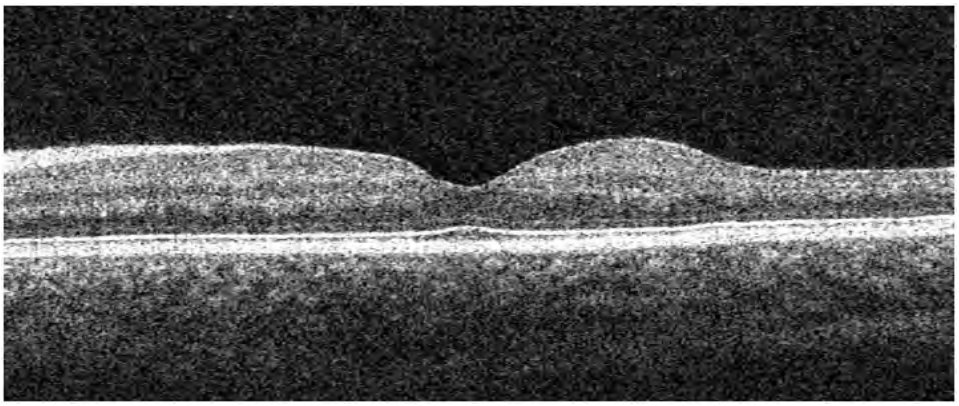


Fig. (10). Optical coherence tomogram. Neurosensory retinal thinning in the temporal macula of the left eye. The temporal macula is a watershed region, and relative ischemia in this region can produce this finding which usually has no visual consequence.

MANAGEMENT

The non-proliferative form of the disease requires serial observation. Vitreous hemorrhage is the most common proliferative manifestation requiring intervention although a majority of these will clear spontaneously. Sea fans will frequently spontaneously regress, and small peripheral lesions without vitreous hemorrhage can be observed [5, 8]. Scatter photocoagulation is the preferred method for managing large areas of neovascularization or any neovascularization with concurrent vitreous hemorrhage [8]. Case reports have shown success with

intravitreal anti-vascular endothelial growth factor for sea fan regression [11]. Small gauge pars plana vitrectomy surgery is indicated for patients with non-clearing vitreous hemorrhages and tractional retinal detachments. Intraoperatively, segmentation and localized photocoagulation are recommended [12]. Care should be taken to minimize intraocular pressure elevation.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Jackson H, Bentley CR, Hingorani M, Atkinson P, Aclimandos WA, Thompson GM. Sickle retinopathy in patients with sickle trait. Eye (Lond) 1995; 9(Pt 5): 589-93. [http://dx.doi.org/10.1038/eye.1995.145] [PMID: 8543078]

[2] Lim JI. Ophthalmic manifestations of sickle cell disease: update of the latest findings. Curr Opin Ophthalmol 2012; 23(6): 533-6. [http://dx.doi.org/10.1097/ICU.0b013e328358b921] [PMID: 23047170]

[3] Elagouz M, Jyothi S, Gupta B, Sivaprasad S. Sickle cell disease and the eye: old and new concepts. Surv Ophthalmol 2010; 55(4): 359-77. [http://dx.doi.org/10.1016/j.survophthal.2009.11.004] [PMID: 20452638]

[4] Gagliano DA, Goldberg MF. The evolution of salmon-patch hemorrhages in sickle cell retinopathy. Arch Ophthalmol 1989; 107(12): 1814-5. [http://dx.doi.org/10.1001/archopht.1989.01070020896034] [PMID: 2597073]

[5] Downes SM, Hambleton IR, Chuang EL, Lois N, Serjeant GR, Bird AC. Incidence and natural history of proliferative sickle cell retinopathy: observations from a cohort study. Ophthalmology 2005; 112(11): 1869-75. [http://dx.doi.org/10.1016/j.ophtha.2005.05.026] [PMID: 16171867]

[6] Patel M, Kiss S. Ultra-wide-field fluorescein angiography in retinal disease. Curr Opin Ophthalmol 2014; 25(3): 213-20. [http://dx.doi.org/10.1097/ICU.0000000000000042] [PMID: 24614144]

[7] Cho M, Kiss S. Detection and monitoring of sickle cell retinopathy using ultra wide-field color photography and fluorescein angiography. Retina 2011; 31(4): 738-47. [http://dx.doi.org/10.1097/IAE.0b013e3181f049ec] [PMID: 21836403]

[8] Bonanomi MT, Lavezzo MM. Sickle cell retinopathy: diagnosis and treatment. Arq Bras Oftalmol 2013; 76(5): 320-7. [http://dx.doi.org/10.1590/S0004-27492013000500016] [PMID: 24232951]

[9] Chow CC, Genead MA, Anastasakis A, Chau FY, Fishman GA, Lim JI. Structural and functional correlation in sickle cell retinopathy using spectral-domain optical coherence tomography and scanning laser ophthalmoscope microperimetry. American Journal of Ophthalmology 2011; 152(4): 704-11 e2.
[http://dx.doi.org/10.1016/j.ajo.2011.03.035]

[10] Witkin AJ, Rogers AH, Ko TH, Fujimoto JG, Schuman JS, Duker JS. Optical coherence tomography demonstration of macular infarction in sickle cell retinopathy. Arch Ophthalmol 2006; 124(5): 746-7.
[http://dx.doi.org/10.1001/archopht.124.5.746] [PMID: 16682603]

[11] Siqueira RC, Costa RA, Scott IU, Cintra LP, Jorge R. Intravitreal bevacizumab (Avastin) injection associated with regression of retinal neovascularization caused by sickle cell retinopathy. Acta Ophthalmol Scand 2006; 84(6): 834-5.
[http://dx.doi.org/10.1111/j.1600-0420.2006.00779.x] [PMID: 17083555]

[12] Williamson TH, Rajput R, Laidlaw DA, Mokete B. Vitreoretinal management of the complications of sickle cell retinopathy by observation or pars plana vitrectomy. Eye (Lond) 2009; 23(6): 1314-20.
[http://dx.doi.org/10.1038/eye.2008.296] [PMID: 18836414]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 12

Radiation Retinopathy

Veronica Kon Graversen*

University of North Carolina at Chapel Hill, NC, USA

Radiation retinopathy (RR) is the result of ultra-structural impairment of the vascular endothelial cells and pericytes of the retina and choroid after exposure to ionizing radiation [1]. Several factors influence the development of retinopathy, including the type of radiation received (external-beam irradiation *versus* local radioactive plaque therapy), total dosage and fraction size schemes used, concomitant systemic vascular diseases, simultaneous chemotherapy, and pregnancy [2, 3]. These factors determine the interval to onset and severity of the disease. The dose required to produce retinopathy is variable, but it is generally accepted that exposure to 30-35 Gray leads to visual changes [3]. The median time interval to onset of retinopathy is 27 months but may range from few months to several years [4].

ESSENTIALS OF DIAGNOSIS

Photoreceptors are relatively preserved and resistant to the radiation effects. Therefore, the degree of visual loss depends on the severity of the occlusive vasculopathy and its sequelae.

Clinical Features: The earliest signs include capillary dilation and microaneurysm formation. Later in the course of the disease, a nonproliferative phase may develop. This phase is exudative. Hard exudates, intraretinal (superficial or deeper) and preretinal hemorrhages, telangiectasia, cotton wool spots and macular edema are frequently seen (Figs. **1** and **2**).

* **Corresponding author Veronica Kon Graversen:** Ophthalmology Department, University of North Carolina at Chapel Hill, NC, USA; Tel: (919)518-6361; Email: veronicakonjara@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

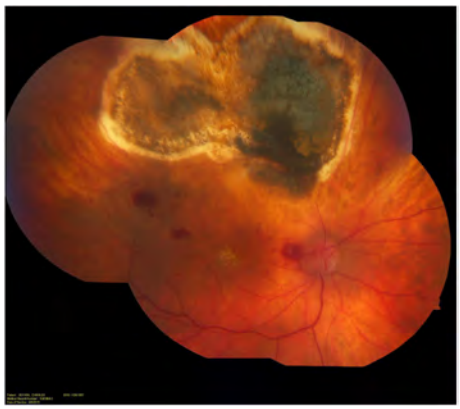


Fig. (1). Fundus photograph of a patient treated with ophthalmic plaque radiation for choroidal melanoma. The patient developed non-proliferative radiation retinopathy, showing retinal hemorrhages, hard exudates and telangiectasia.

Extensive retinal ischemia may lead to vascular occlusions, retinal neovascularization (Fig. **2**), vitreous hemorrhage, retinal detachment, and, in some cases, neovascular glaucoma. These late changes are recognized as the proliferative phase of the disease [1, 3].

Rarely, choroidal neovascular membranes (CNV), chorioretinal anastomosis and intravitreal polypoidal neovascularization have been reported [5 - 7].

Imaging. The diagnosis is mainly clinical; however, retinal diagnostic imaging provides valuable tools monitoring the progression of the disease and treatment response.

Optical coherence tomography: Ensures early recognition of macular changes. More severe and chronic cases may reveal outer retinal disruption [8].

Fluorescein angiography: Initial findings include varying degrees of capillary closure and dilation of microvasculature (Fig. **2**). The most affected areas are the peripapillary region and the macula [9].

Indocyanine green angiography: Detects areas of choriocapillaris perfusion defects [10].

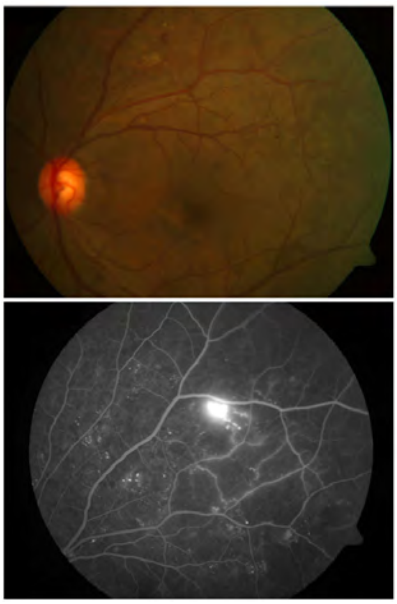


Fig. (2). Fundus photograph shows microaneurysms, hard exudates and and retinal hemorrhages. Fluorescein angiography reveals microaneurysms, capillary closure and retinal neovascularization.

DIFFERENTIAL DIAGNOSIS

1. Diabetic retinopathy.
2. Retinal vascular occlusions.
3. Occlusive retinopathy.
4. Retinal telangiectasia.
5. Human immunodeficiency virus retinopathy.
6. Hypertensive retinopathy.

MANAGEMENT

There are no specific treatment guidelines for radiation retinopathy. Macular ischemia is usually irreversible and is the most feared complication that results in blindness. Focal laser treatment can be applied to areas of macular edema [11]. In recent years, intravitreal or periocular steroids and anti-vascular endothelial growth factor (VEGF) therapies have been successfully used to treat center-involving macular edema [11 - 13]. Bevacizumab has been the most studied anti-VEGF in cases of radiation retinopathy. Nevertheless, similar outcomes have been reported with other anti-VEGF agents. Refractory cases may benefit from

combination therapy with intravitreal triamcinolone and anti-VEGF agents [14]. Anti-VEGF agents have also been combined with micropulse laser with promising results [15].

Argon laser panretinal photocoagulation is the standard therapy for areas of capillary nonperfusion with associated neovascularization. An approach similar to the one published in the ETDRS is applied [11]. Photodynamic therapy has been proposed for the treatment of severe cases of macular edema or CNV. Hyperbaric oxygen therapy remains controversial [11, 12]. One case report proposed oral pentoxifylline as a potential therapy to improve visual acuity [16].

Non-clearing vitreous hemorrhage or retinal detachment is treated with standard vitrectomy techniques [1].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Spielberg L, de Potter P, Leys A. Radiation retinopathy. In: Ryan SJ. Retina. 5th Ed. vol 2. St Luis. Mosby 2012; pp. 1083-90.

[2] Kumar B, Palimar P. Accelerated radiation retinopathy in diabetes and pregnancy. Eye (Lond) 2000; 14(Pt 1): 107-8.
[http://dx.doi.org/10.1038/eye.2000.28] [PMID: 10755117]

[3] Jeganathan VS, Wirth A, MacManus MP. Ocular risks from orbital and periorbital radiation therapy: a critical review. Int J Radiat Oncol Biol Phys 2011; 79(3): 650-9.
[http://dx.doi.org/10.1016/j.ijrobp.2010.09.056] [PMID: 21281895]

[4] Kaushik M, Pulido JS, Schild SE, Stafford S. Risk of radiation retinopathy in patients with orbital and ocular lymphoma. Int J Radiat Oncol Biol Phys 2012; 84(5): 1145-50.
[http://dx.doi.org/10.1016/j.ijrobp.2011.12.097] [PMID: 22592046]

[5] Berker N, Aslan O, Batman C, Elgin U, Ozkan SS. Choroidal neovascular membrane in radiation retinopathy. Clin Experiment Ophthalmol 2006; 34(6): 625-6.
[http://dx.doi.org/10.1111/j.1442-9071.2006.01292.x] [PMID: 16925720]

[6] Mendrinos E, Pilly B, Baglivo E, Donati G, Safran AB, Pournaras CJ. Chorioretinal anastomosis as a rare complication of radiation retinopathy. Acta Ophthalmol 2009; 87(4): 473-5.

[http://dx.doi.org/10.1111/j.1755-3768.2008.01280.x] [PMID: 18652579]

[7] Pang CE, Freund KB. Intravitreal polypoidal choroidal vasculopathy in radiation retinopathy. Ophthalmic Surg Lasers Imaging Retina 2014; 45(6): 585-8.
[http://dx.doi.org/10.3928/23258160-20141008-04] [PMID: 25347829]

[8] Raman R, Pal SS, Krishnan T, Laxmi G, Radke N, Sharma T. High-resolution optical coherence tomography correlates in ischemic radiation retinopathy. Cutan Ocul Toxicol 2010; 29(1): 57-61.
[http://dx.doi.org/10.3109/15569520903331674] [PMID: 19874210]

[9] Amoaku WM, Archer DB. Fluorescein angiographic features, natural course and treatment of radiation retinopathy. Eye (Lond) 1990; 4(Pt 5): 657-67.
[http://dx.doi.org/10.1038/eye.1990.93] [PMID: 2282939]

[10] Takahashi K, Kishi S, Muraoka K, Tanaka T, Shimizu K. Radiation choroidopathy with remodeling of the choroidal venous system. Am J Ophthalmol 1998; 125(3): 367-73.
[http://dx.doi.org/10.1016/S0002-9394(99)80148-2] [PMID: 9512155]

[11] Reichstein D. Current treatments and preventive strategies for radiation retinopathy. Curr Opin Ophthalmol 2015; 26(3): 157-66.
[http://dx.doi.org/10.1097/ICU.0000000000000141] [PMID: 25730680]

[12] Giuliari GP, Sadaka A, Hinkle DM, Simpson ER. Current treatments for radiation retinopathy. Acta Oncol 2011; 50(1): 6-13.
[http://dx.doi.org/10.3109/0284186X.2010.500299] [PMID: 20722590]

[13] Finger PT, Chin K. Anti-vascular endothelial growth factor bevacizumab (avastin) for radiation retinopathy. Arch Ophthalmol 2007; 125(6): 751-6.
[http://dx.doi.org/10.1001/archopht.125.6.751] [PMID: 17562985]

[14] Shah NV, Houston SK, Markoe A, Murray TG. Combination therapy with triamcinolone acetonide and bevacizumab for the treatment of severe radiation maculopathy in patients with posterior uveal melanoma. Clin Ophthalmol 2013; 7: 1877-82.
[PMID: 24092966]

[15] Murray T. Micropulse laser therapy for the treatment of radiation retinopathy. Retina today 2013; 71-2.

[16] Gupta P, Meisenberg B, Amin P, Pomeranz HD. Radiation retinopathy: the role of pentoxifylline. Retina 2001; 21(5): 545-7.
[http://dx.doi.org/10.1097/00006982-200110000-00026] [PMID: 11642393]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 13

Ocular Ischemic Syndrome

Eleonora Lavaque*

Retina Department, Hospital Oftalmológico Santa Lucia, Buenos Aires, Argentina

Retina Department, Instituto Médico de Ojos, Buenos Aires, Argentina

Ocular ischemic syndrome (OIS) is caused by ocular hypoperfusion. Carotid stenosis superior to 70% or complete occlusion due to atherosclerosis is the common cause of this rare condition. In 80% of the cases, OIS is found unilaterally, on the same side of the carotid stenosis [1, 2]. Occasional causes of OIS secondary to ophthalmic artery obstruction include Takayasu disease or giant cell arteritis [3].

Described risk factors are: age between 50-80 years, male gender 2:1, and vascular diseases such as arterial hypertension (75%), diabetes (56%), coronary diseases, vascular stroke and hemodialysis [3 - 5].

ESSENTIALS OF DIAGNOSIS

Ninety percent of the patients present with a history of slowly progressive visual loss in the affected eye. Dull ischemic pain develops gradually and is relieved when the patient lies down [4, 5].

Anterior segment ischemic signs include iris or angle neovascularization, iridocyclitis with flare and cells in 20% of cases, cataract, iris atrophy, sluggish pupillary reaction to light [1]. Other less common signs of OIS are dilatation of conjunctival and episcleral vessels, corneal edema, and bullous keratopathy [4, 6].

Posterior segment signs are more frequent than anterior segment signs [4]. Posterior segment ischemic signs include narrow retinal arteries, perifoveal telangi-

* **Corresponding author Eleonora Lavaque:** Retina Department, Hospital Oftalmológico Santa Lucia, Buenos Aires, Argentina; Tel: 00-9-54-56458302; Fax: 00-54-11-48124494; E-mail: eblavaque@hotmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

ectasia, dilated retinal veins, mid-peripheral retinal hemorrhages and micro-aneurysms. Neovascularization in the optic disc or retina and its complications (fibrovascular proliferation, cotton-wool spots, vitreous hemorrhage) may be present but are not frequent (Figs. **1-3**) [3, 4].

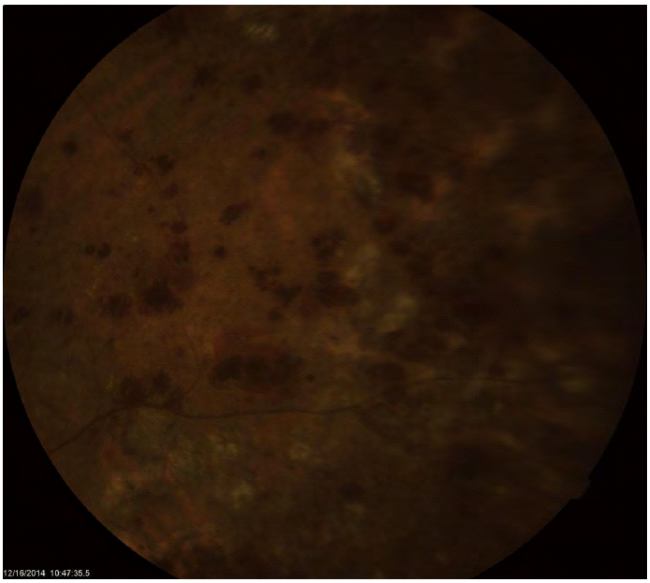


Fig. (1). Fundus photograph shows round circumscribed hemorrhages at the classical midperipherical location.

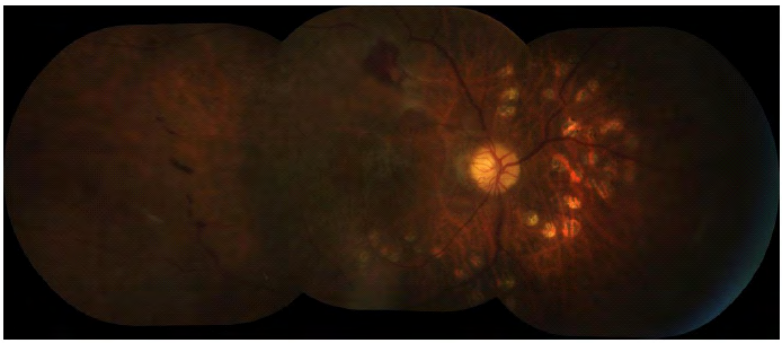


Fig. (2). 70-year-old Caucasian male patient. Medical background: diabetes, hypertension, coronary bypass, acute ischemic cerebral stroke, recent left carotid surgery, endarterectomy 2 months before, and indication for future right carotid endarterectomy because of 79% stenosis. Best-corrected visual acuity was 20/40 in the right eye, and hand motion in the left eye. Positive biomicroscopy: rubeosis iridis, hyphema in left eye. Intraocular pressure 15/60 mm hg. Fundus photograph of the right eye: preretinal hyaloid fibrosis, preretinal hemorrhage at an arteriovenous crossing. Ocular fundus findings in left eye: vitreous hemorrhage.

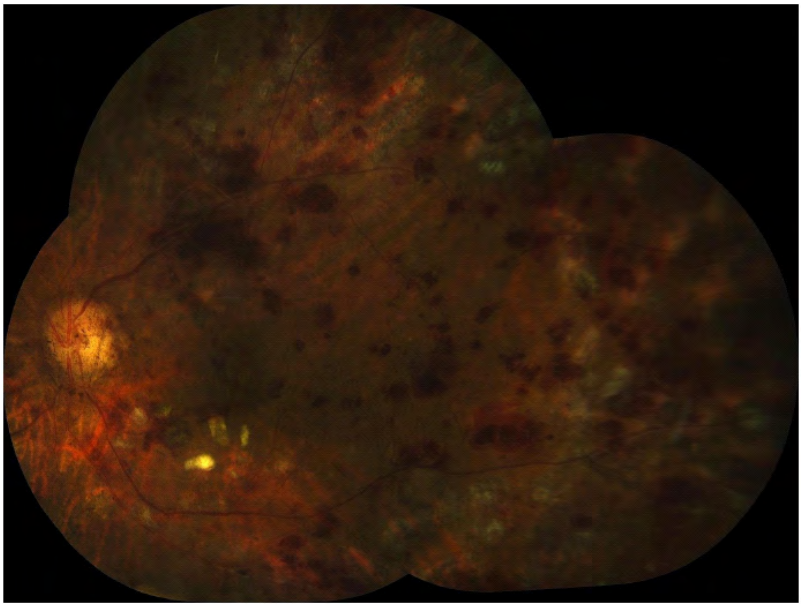


Fig. (3). Left eye of the same patient as Fig. (**2**), after vitrectomy and endophotocoagulation. Round hemorrhages and photocoagulation scars are present. After vitrectomy, visual acuity improved to 20/100, intraocular pressure improved to 26 mmHg with topical treatment.

A cherry-red spot, characteristic of macular ischemia, is seen in 12% of eyes, due to IOP exceeding the perfusion pressure or to a result of embolic occlusion of the central retinal artery [1, 4].

Eighty percent (80%) of OIS present with very characteristic retinal hemorrhages: they are round, located in the external retinal layers, and at the mid-periphery (Fig. **1**) [2, 3].

Intraocular pressure is usually normal or low. Although anterior segment neovascularization is frequent, elevated intraocular pressure is less common than expected due to flow restriction to the ciliary body. Normal-tension glaucoma can be present in eyes with normal ocular tension due to hypoperfusion to the optic disc [1, 2, 4].

In fluorescein angiography, 60% presents prolonged arm-to-choroid and arm-to-retina circulation time (Fig. **4**). The normal retinal filling time is approximately 5 seconds, but in the affected eye it may be 1 minute or longer [4].

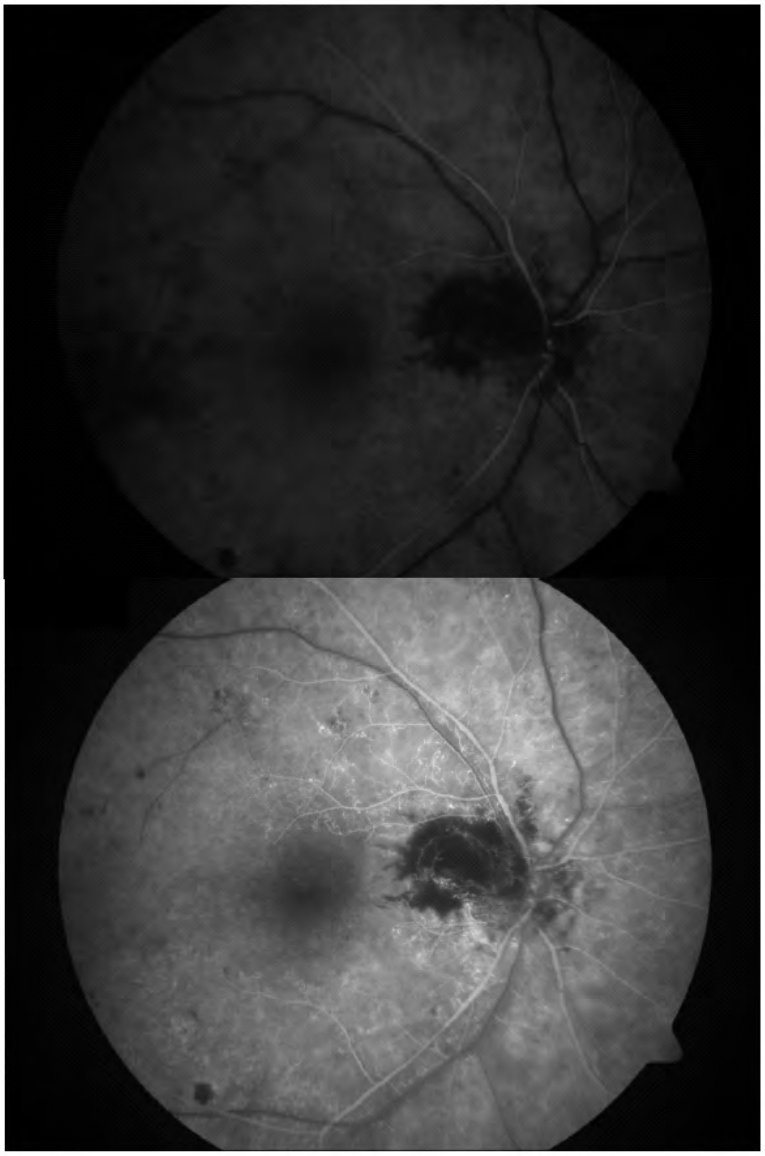


Fig. (4). Fluorescein angiogram of an ocular ischemic syndrome. Top: Image 47 seconds after dye injection, showing only arterial filling. Bottom: Image 1:05 minutes after dye injection, showing delayed vein filling, and significant capillary nonperfusion (Images courtesy of Gerardo Garcia-Aguirre).

The majority of eyes affected with OIS show staining of the retinal vessels at a late phase. Endothelial cell damage and increased permeability due to chronic ischemia are responsible for this sign [2]. Macular edema and hyperfluorescence

of the optic disc are less common signs [4]. The unilateral nature of all these signs should alert the physician of the presence of an OIS.

Due to the frequent association with carotid artery stenosis, patients with OIS must undergo Doppler ultrasound of the carotid arteries to measure the degree of obstruction, which is usually significant. If carotid Doppler ultrasound yields no relevant result, Doppler ultrasound of retrobulbar vessels should be performed. Ocular plethysmography and invasive techniques such as carotid arteriography are usually performed only previous to carotid surgery [4, 7, 8].

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis is made with retinal vascular diseases such as diabetic retinopathy or retinal vein occlusion. In OIS, intraretinal hemorrhages are less numerous than in diabetic retinopathy, they are round and mostly located in the mid-periphery (Fig. **1**). The presence of hard exudates and fibrovascular proliferation also suggests diabetic retinopathy. Absence of delayed choroidal and arterial filling time in a fluorescein angiogram also points to diabetic retinopathy or vein occlusion [4, 8]. Diabetic retinopathy may coexist with OIS, so marked asymmetry of retinopathy in a diabetic patient should raise the suspicion of OIS [3].

MANAGEMENT

Treatment is directed towards reducing retinal and anterior segment ischemia. Panretinal photocoagulation is indicated in patients with iris and posterior segment neovascularization to prevent neovascular glaucoma or intraocular hemorrhages (Fig. **3**). However, it is effective in only 35% of eyes since choroidal ischemia, which is unaffected by laser photocoagulation, plays an important role in developing neovascularization [3, 4, 6].

Since the most frequent etiology is significant carotid artery obstruction, carotid artery endarterectomy (CEA) is the surgical method of choice, and has proven to be effective for the treatment of OIS [9].

Mortality rate for OIS is as high as 40% within 5 years of onset. Patients with ocular ischemic syndrome should be referred for consultation to the neurologist,

vascular surgeon and cardiologist [5].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Brown GC, Magargal LE. The ocular ischemic syndrome. Clinical, fluorescein angiographic and carotid angiographic features. Int Ophthalmol 1988; 11(4): 239-51.
[http://dx.doi.org/10.1007/BF00131023] [PMID: 3182177]

[2] Sharma S, Brown GC. In: The Ocular Ischemic Syndrome. Ryan SJ, Hinton DR, Schachat AP, *et al.*, editors. Elsevier; 2006. pp. 1491-502.

[3] Mendrinos E, Machinis TG, Pournaras CJ. Ocular ischemic syndrome. Surv Ophthalmol 2010; 55(1): 2-34.
[http://dx.doi.org/10.1016/j.survophthal.2009.02.024] [PMID: 19833366]

[4] Zemba M, Avram CI, Ochinciuc U, Stamate AC, Camburu RL. Ocular ischemic syndrome--a case report. Oftalmologia 2013; 57(2): 17-22.
[PMID: 24386788]

[5] Sivalingam A, Brown GC, Magargal LE. The ocular ischemic syndrome. III. Visual prognosis and the effect of treatment. Int Ophthalmol 1991; 15(1): 15-20.
[http://dx.doi.org/10.1007/BF00150974] [PMID: 2010264]

[6] Kerty E, Eide N. Chronic ocular ischaemia. Acta Ophthalmol (Copenh) 1989; 67(4): 386-92.
[http://dx.doi.org/10.1111/j.1755-3768.1989.tb01620.x] [PMID: 2678884]

[7] Chen CS, Miller NR. Ocular ischemic syndrome: review of clinical presentations, etiology, investigation, and management. Compr Ophthalmol Update 2007; 8(1): 17-28.
[PMID: 17394756]

[8] Hashimoto M, Ohtsuka K, Ohtsuka H, Nakagawa T. Normal-tension glaucoma with reversed ophthalmic artery flow. Am J Ophthalmol 2000; 130(5): 670-2.
[http://dx.doi.org/10.1016/S0002-9394(00)00588-2] [PMID: 11078851]

[9] Dzierwa K, Pieniazek P, Musialek P, *et al.* Treatment strategies in severe symptomatic carotid and coronary artery disease. Med Sci Monit 2011; 17(8): RA191-7.
[http://dx.doi.org/10.12659/MSM.881896] [PMID: 21804476]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 14

Dry Age-Related Macular Degeneration

Ana Domínguez Yates and **Virgil Alfaro***

Retina Consultants of Charleston, Charleston, South Carolina, USA

Age related macular degeneration (AMD) is a progressive and chronic disorder, characterized by the onset of degenerative changes in the macular area in people of 50 years of age or older [1]. Besides age, other risk factors are white race [2], smoking [3, 4] and female gender [5, 6]. Advanced AMD, is the leading cause of severe central vision loss in this age group, and geographic atrophy (GA) is responsible for 25% of cases. The Pathophysiologic mechanism still remains unclear but it is well known that the Retinal Pigment Epithelium (RPE) plays a key role [7]. Environmental and genetics factors can alter any given patient's susceptibility to the disease [8].

ESSENTIALS OF DIAGNOSIS

The changes in AMD involve the outer retina, RPE, Bruch's membrane and choriocapillaris [9]. Drusen are the hallmark features of AMD. They become visible on biomicroscopic fundus examination when their diameter exceeds 25 μm. They can be classified [10] by size as small (< 0-63 μm diameter), medium (64-124 μm diameter) or large (> 0-125 μm diameter) (Fig. **1**).

According to their appearance they can be classified as hard or soft. Hard or crystalline drusen (Fig. **2**) appear as small, round yellow-white spots with sharp borders. They correspond to accumulation or entrapment of hyaline material, lipids and mucopolysaccharides underneath RPE [11, 12]. Large areas of small hard drusen increase the risk of soft drusen and RPE atrophy at a relatively young age [13, 14]. Soft drusen are pale yellow-white spots, more than 63 μm in diame-

* **Corresponding author Virgil Alfaro:** Retina Consultants of Charleston, 3531 Mary Ader Ave # D, Charleston, SC 29414, Estados Unidos, USA; Tel: +1 843-763-4466; E-mail: virgil.alfaro@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

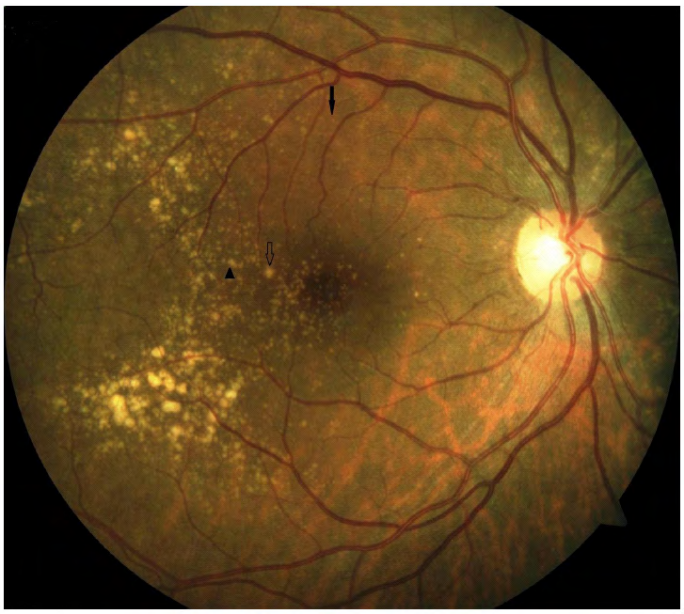


Fig. (1). 60-year-old patient with Dry AMD and visual acuity of 20/20 in both eyes. Small drusen (filled arrow); medium drusen, with a diameter equal or greater than one half of a large drusen (arrowhead); and large drusen, diameter greater than or equal to a large vein at the disc margin (unfilled arrow).

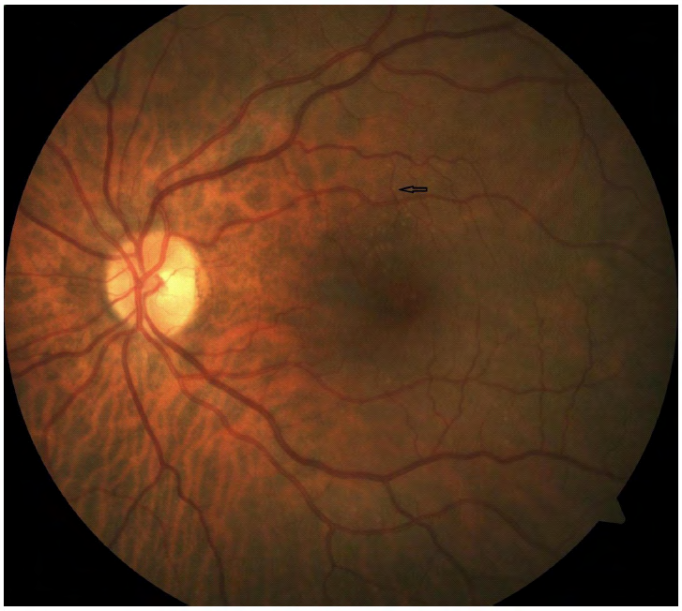


Fig. (2). Some small drusen in the superior macula in a 61-year-old patient. Hard drusen appear bright with sharp and very well defined borders (unfilled arrow).

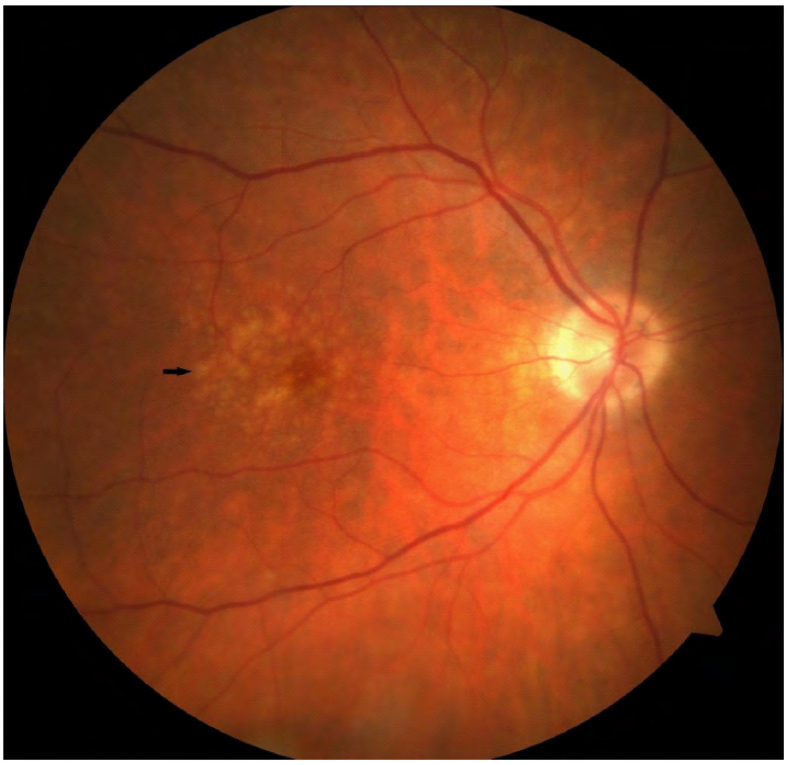


Fig. (3). Soft drusen in a 77-year-old patient. Big and pale yellow–white lesions ill-defined margins (arrow).

ter, with ill-defined boundaries, are preferentially located within the fovea (Fig. **3**). They are a result of RPE dysfunction and derive from basal linear deposits, between the RPE and the Bruch's membrane [11, 12]. Most of the molecular constituents of drusen reflex their complex pathogenesis: protein (immune response modulator; immunoglobulin and complement components; inflammation molecules), cellular components (RPE blebs, lipofuscin, and melanin, as well as choroidal dendritic cell), glycoconjugates, neutral lipids and zinc [15].

On Fluorescein angiography (FA), hard drusen appear as a bright early hyperfluorescence secondary to a window defects (Fig. **4 a-c**). On the other hand, soft drusen appear as progressively hyperfluorescent spots that persist in late phases due to staining (Figs. **5 a-d** and **6 a-c**).

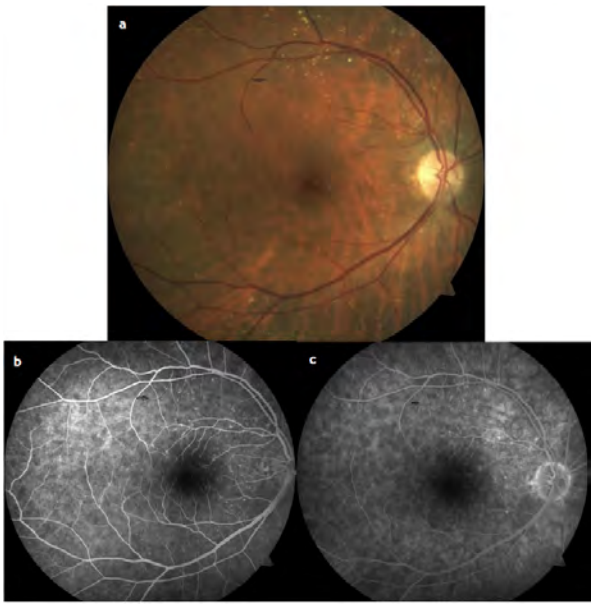


Fig. (4). a) Small hard (unfilled arrow) and medium drusen around and between the temporal arcades, right eye. **b**) Early hyperfluorescence due to transmission defect, secondary to attenuation or hypopigmentation of the RPE cells overlying the drusen. **c**) Fluorescence fades in late frames.

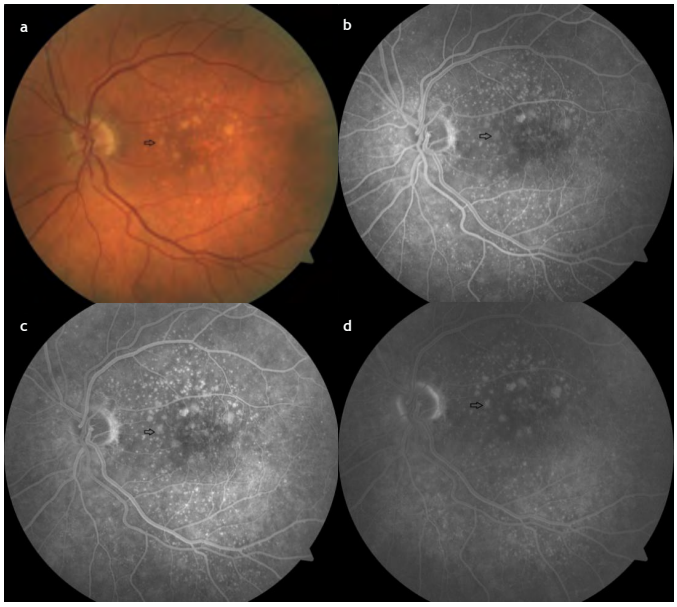


Fig. (5). a) Soft drusen (unfilled arrow) and RPE defects in a left eye. **b**) and **c**) Fluorescein angiogram showing progressive increase in intensity through arteriovenous phase; **d**) hyperfluorescence persists in late stages due to staining.

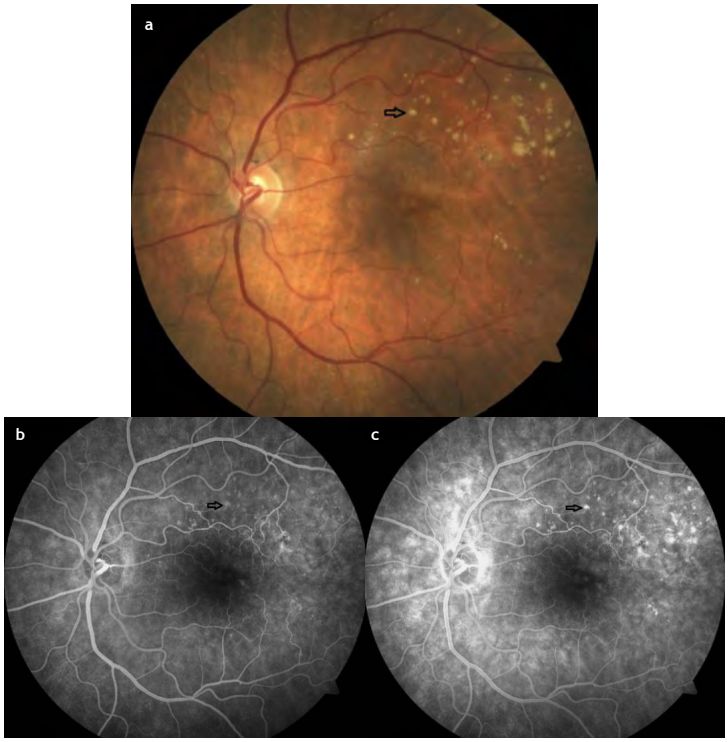


Fig. (6). Soft drusen (unfilled arrow): Funds photographs: **a**) funds photographs; (**b**) early and (**c**) late FA frames.

Optical Coherence Tomography (OCT) shows soft drusen as well-defined convex accumulations of homogenous moderately reflective material, underneath the highly reflective RPE layer (Fig. **7 a, b**) (Figs. **8** and **9**) or like multiple excrescences in succession giving a "sawtooth" configuration (Figs. **7c**, **10** and **11**). The RPE appears to be clearly defined. Hard drusen are discrete nodules with moderately and highly reflective material, producing RPE disruptions. In either case, the hyperreflective junction between the inner and outer photo-receptors segments is elevated, with overlying compression of the outer retinal layers [16].

Drusen may evolve rapidly and are prone to coalesce and become confluent, separating the RPE basement membrane from the rest of Bruch´s membrane over long distances, forming a so-called drusenoid pigment epithelial detachment (DPED). These lesions are often located in the central macula, appearing as a pale yellow or white shallow elevation of the RPE (Figs. **12 a** and **13 a**) [17]. On FA,

they appear as a progressive hyperfluorescence secondary to dye pooling and faint stain in the late frames (Figs. **12 b-d** and **13 b-d**). OCT shows areas of elevation of the RPE, with medium to high homogeneous internal reflectivity. Bruch´s membrane is seen as a thin moderately reflective line underneath it (Figs. **12 e**, **13 e** and **14**) [18].

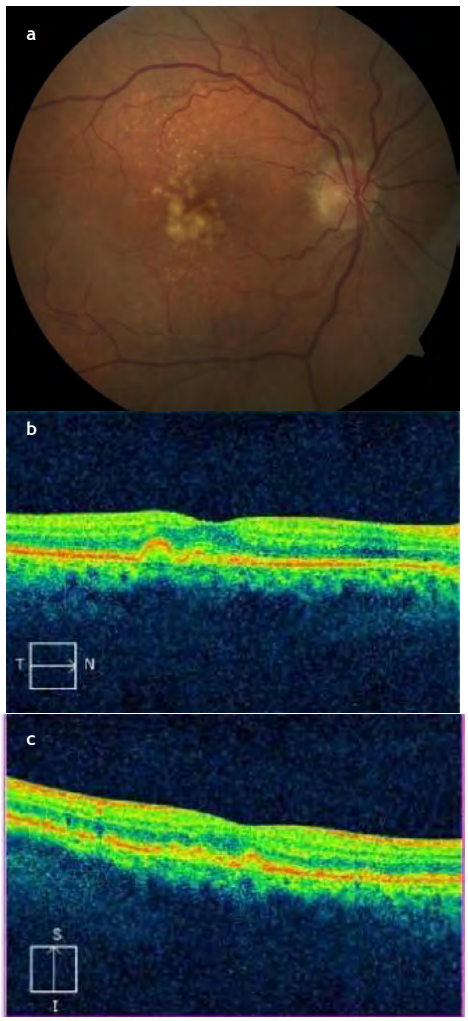


Fig. (7). a) Fundus color photograph of soft drusen at the perifoveal area; **b**) OCT showing elevation of the highly reflective RPE layer with homogeneous moderately reflective material below it; **c**) “sawtooth” pattern.

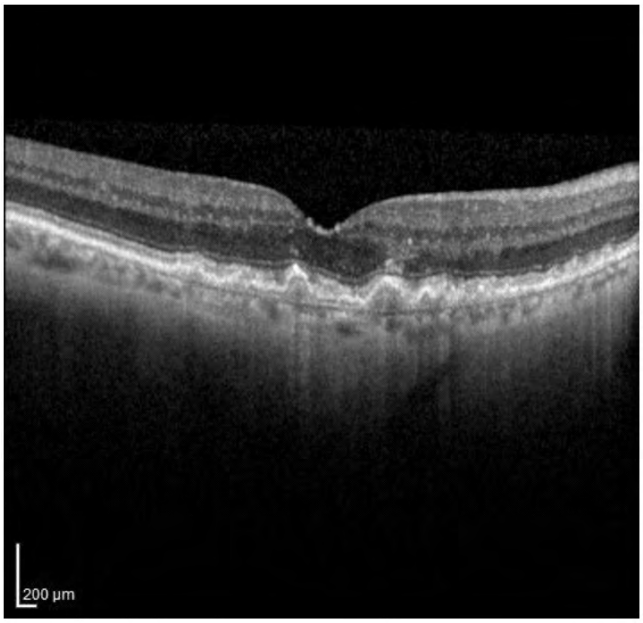


Fig. (8). Soft drusen with moderately reflective material and elevation of the ellipsoid layer.

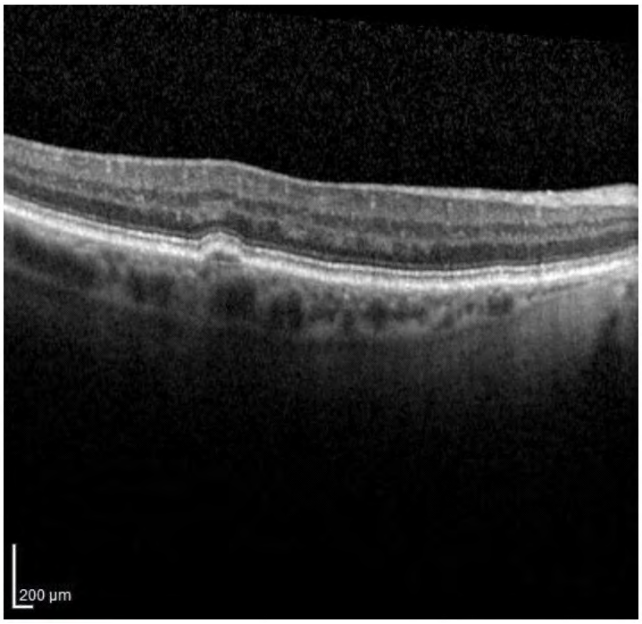


Fig. (9). Soft drusen underneath a clearly defined RPE layer.

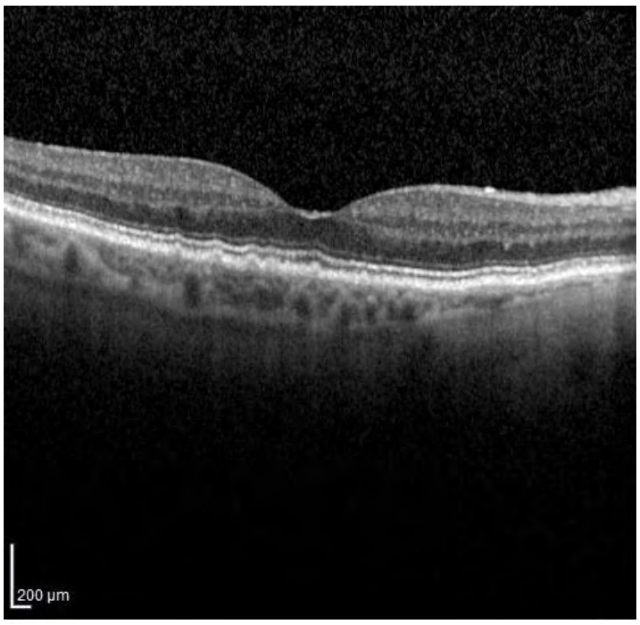


Fig. (10). Multiple excrescences in succession given a “sawtooth” of the RPE.

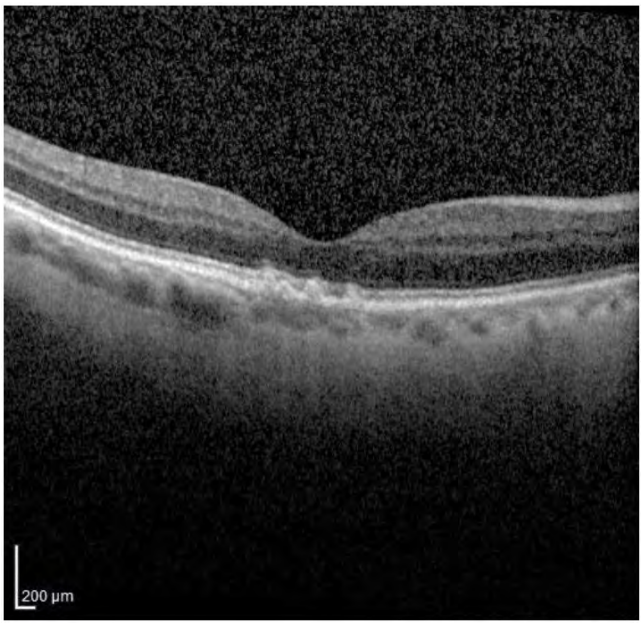


Fig. (11). Multiple excrescences in succession given a saw toothed of the RPE.

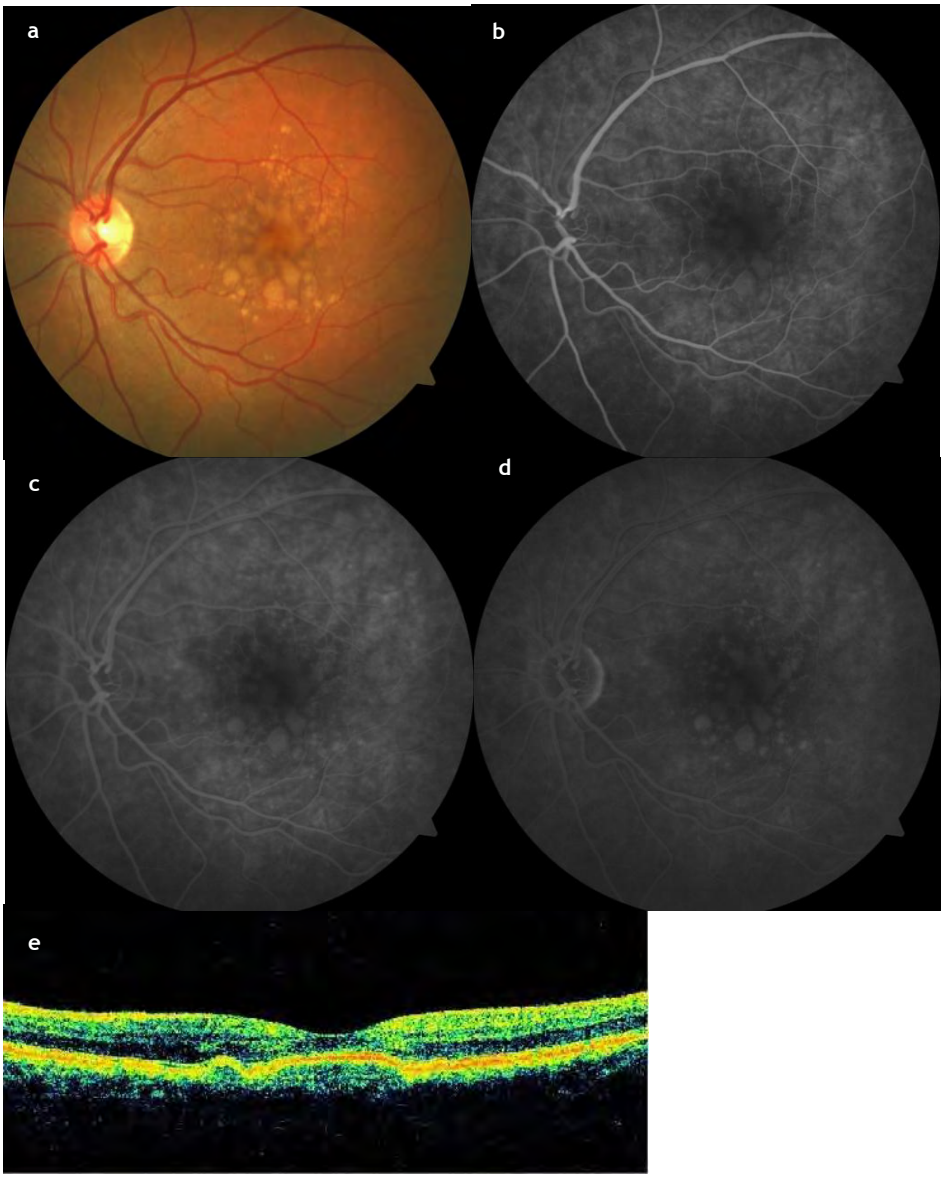


Fig. (12). a) Fundus Photograph of confluent large drusen conforming a drusenoid PED **b**) and **c**) progressive hyperfluorescence throughout angiogram and **d**) faint stain in late phases; **e**) OCT RPE elevation. The Bruch´membrane is clearly seen as a thin hyperreflective line behind it.

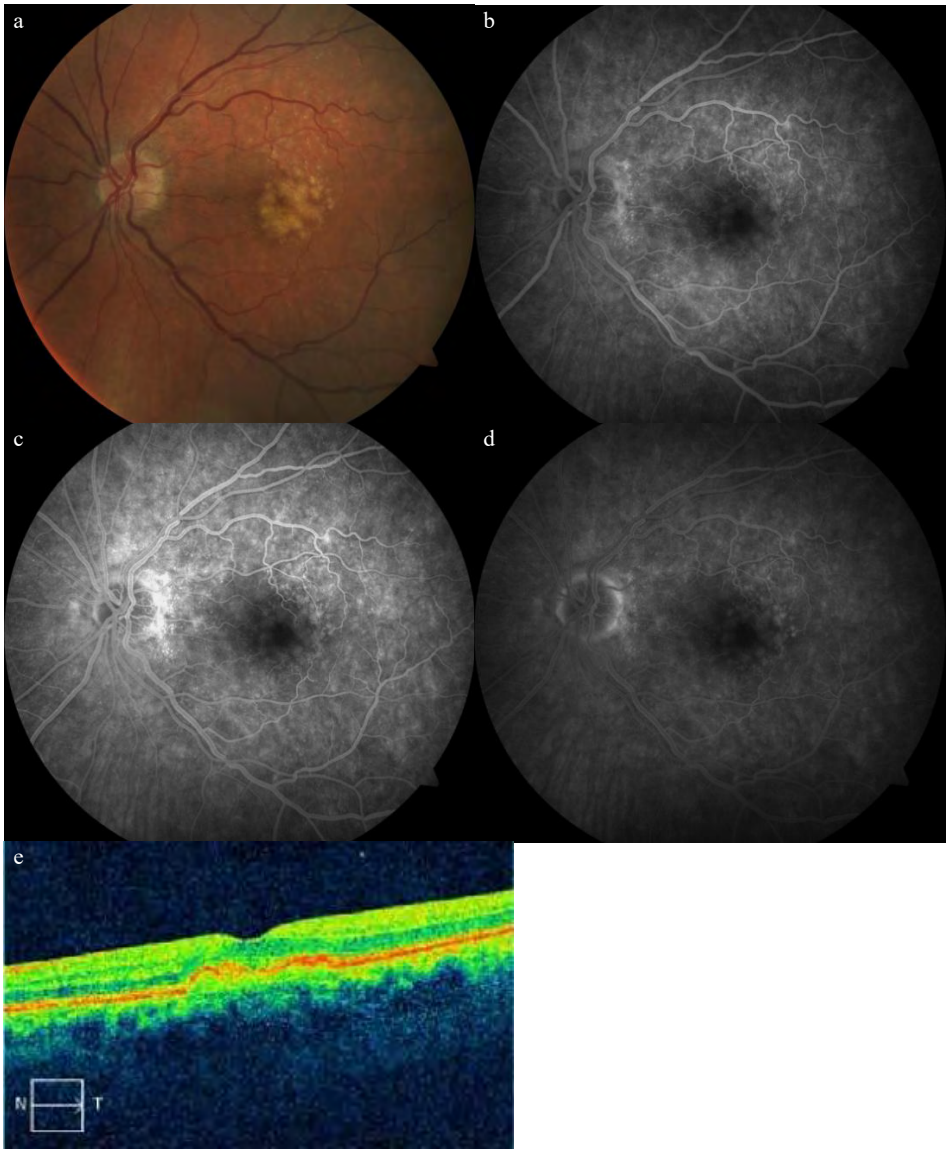


Fig. (13). a) Color photo of drusenoid pigment epithelium detachment **b**), **c**) and **d**) early and late phases of FA with fluorescein pooling into the space. The margins appear to be well-defined during the frames; **e**) OCT shows homogenous reflectivity underneath the RPE layer elevation.

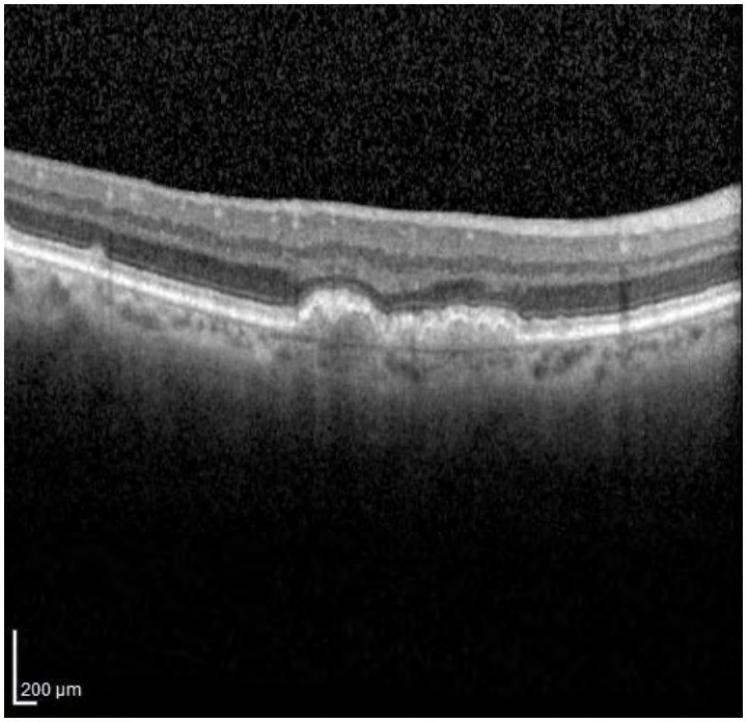


Fig. (14). OCT showing confluent soft drusen (DPED) in the inferior macula.

Depigmentation is an area of RPE atrophy, less weel defined, less regular in shape, and less severe than Atrofia geográfica. Clumps of gray or black pigment may be observed in or beneath the retina. FA shows mottled early hyperfluorescence that fades later in the study and hypofluorescence by blockage respectively (Fig. **15 a-d**) [19]. OCT shows clumping of hyperreflective material at the level of the RPE. Hyperreflective particles in the inner retinal layers indicate RPE migration [16].

Drusen evolve dynamically overtime, and can fade and disappear. This spontaneous regression is coupled with hyper and hypopigmentation changes and calcified drusen (chalky-white or shiny drusen) (Fig. **16**) [20]. More frequently, drusen are able to evolve and progress, and over time increase in volume, height and area. The presence of large, confluent and extensive soft drusen and RPE abnormalities are associated with increased risk of progression to advanced AMD and central visual loss [8, 21, 22]. Furthermore, the presence of DPEDs possesses

an additional high risk of developing geographic atrophy [17].

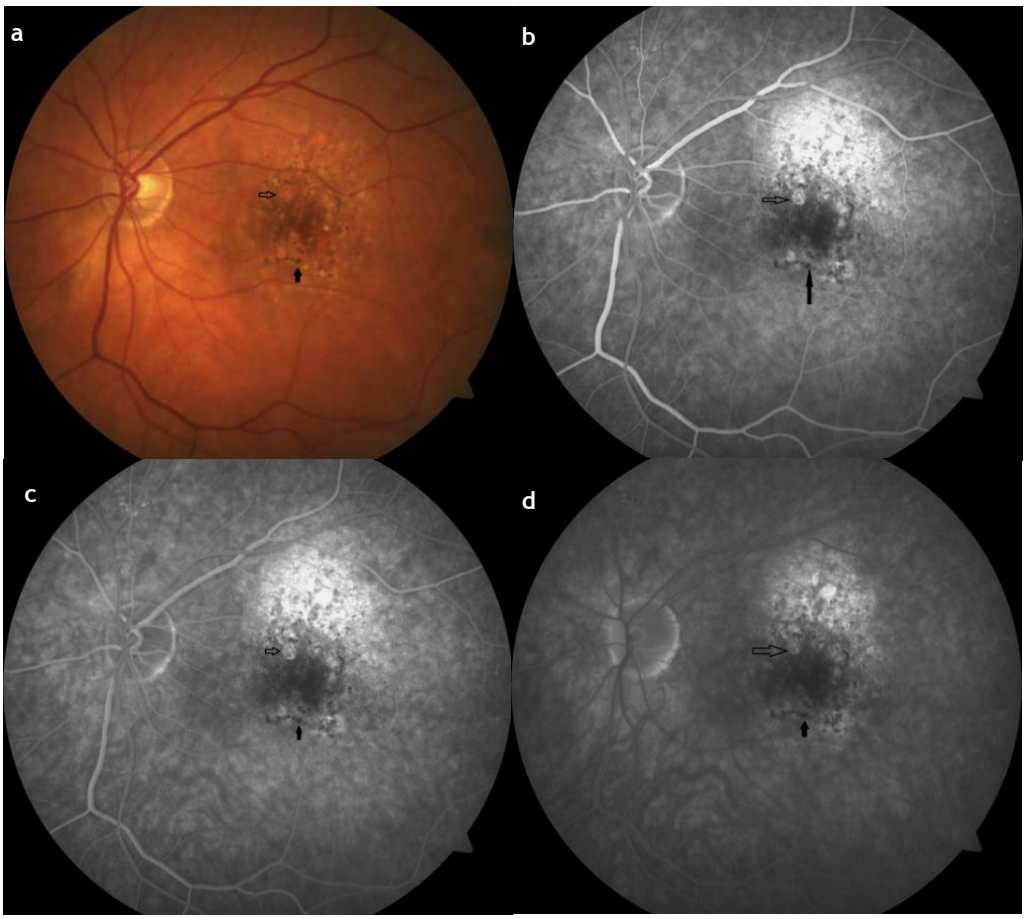


Fig. (15). a) Drusen and hyper (fill arrow) and hypopigmentation (unfilled arrow) of the RPE in the center of the macula area; **b**) and **c**) FA: low signal intensity due to fluorescein blocking at areas of pigment clumping (fill arrow) and mottled hyperfluorescence secondary to loss of RPE cells (unfilled arrow) during arteriovenous frames; **d**) the window defect fades in the late phase (unfilled arrow) but keeps the same shape and size.

Most authors use the Age-Related Eye Disease Study severity scale to grade AMD [23]. It is subdivided in mild, when only a few drusen are present (Fig. **17**), moderate, when several drusen are present (Fig. **18**), and advanced, when neovascular disease and/or geographic atrophy (GA) involving the center of the macula are present.

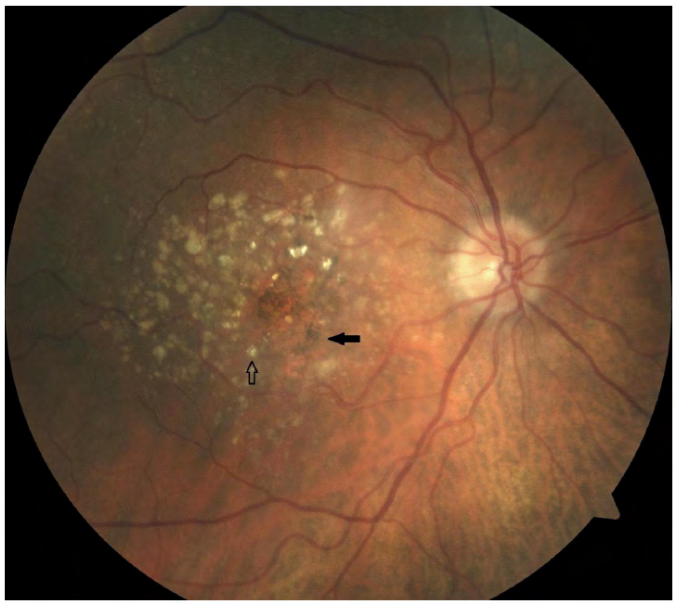


Fig. (16). Soft drusen, calcified shiny drusen (unfilled arrow) and hyper and hypopigmentation changes (fill arrow).

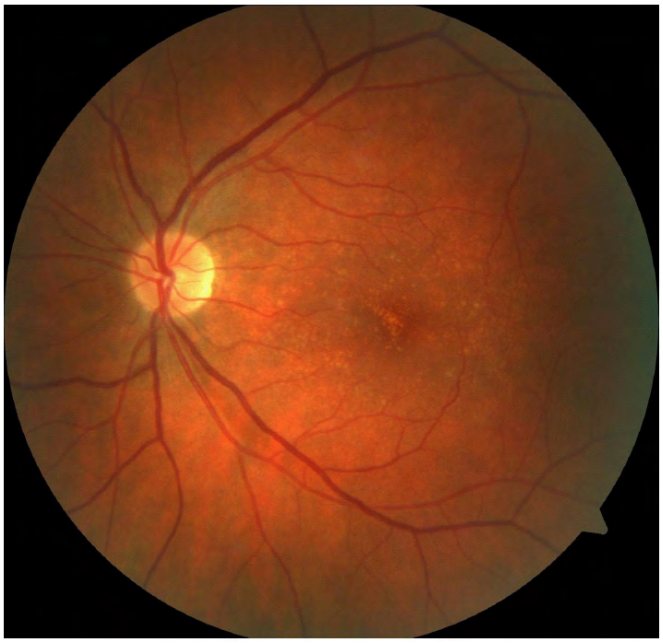


Fig. (17). Mild AMD with extensive small drusen or at least one intermediate size drusen and / or abnormalities in one or eyes.

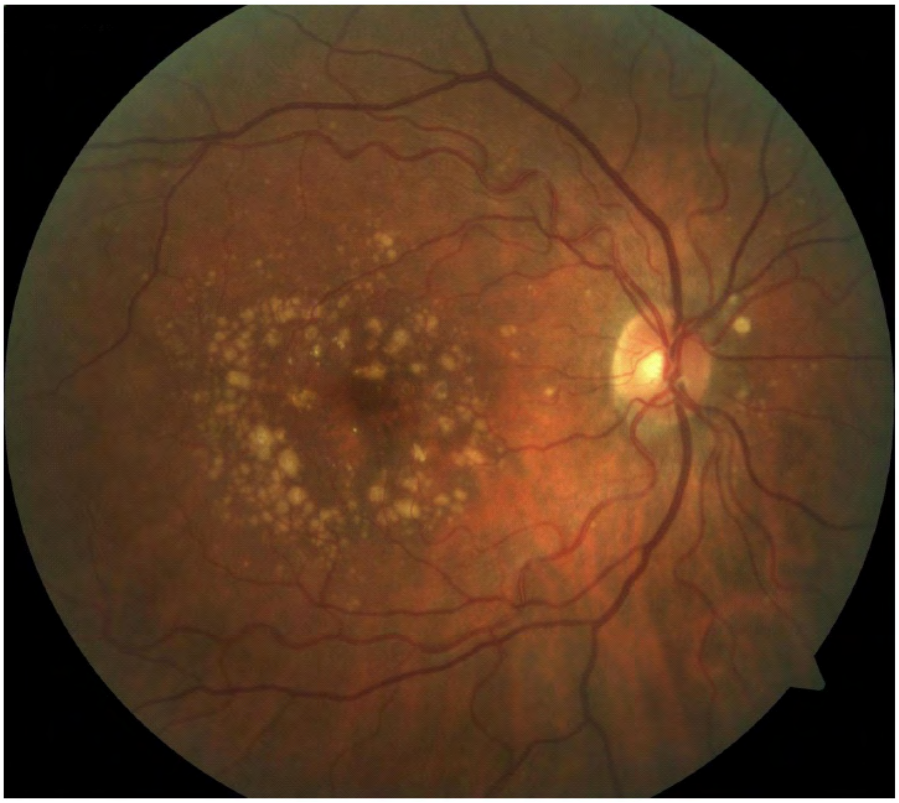


Fig. (18). Moderate AMD with extensive intermediate drusen, at least 1 large drusen and /or GA not involving the center of the macula, either in one or both eyes.

GA is usually a round or oval sharply demarcated patch of partial or complete RPE loss, with associated atrophy of the overlying retina and underlying choriocapillaris, typically with exposure of large choroidal blood vessels and relative color change to the surrounding RPE (Figs. **19-21**) [24]. It may involve the central macula (Fig. **22**) or spare it (Fig. **23**). GA tends to spare the foveal center until the later stages of the disease (Fig. **24**). In FA, GA appears as a well-defined hyperfluorescent area at late phases, due to staining of the deep choroid and sclera (Fig. **25 a-e**). OCT shows retinal thinning with attenuation of the outer retina, hyporeflectivity of the RPE, and loss of the layered structure of the retina, with prominent choroidal deep vessels (Figs. **26-28**) [18].

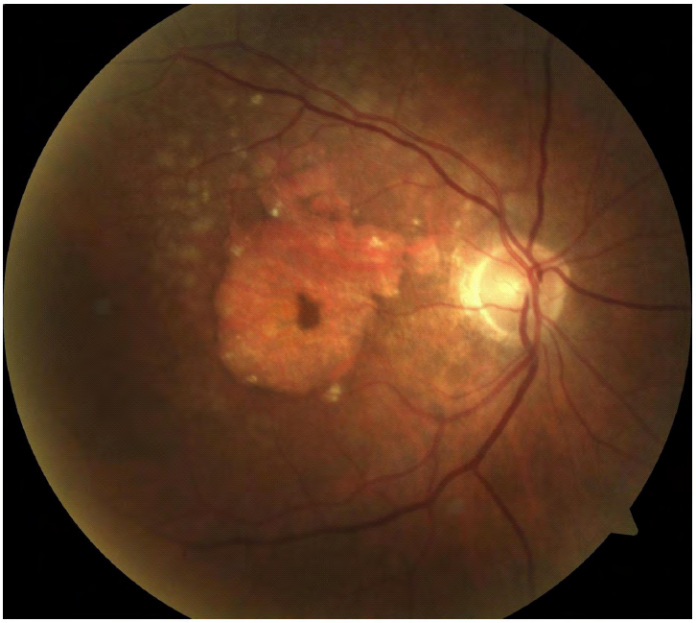


Fig. (19). Large GA with atrophy of the choriocapillaris and exposure of the underlying choroidal vessels. RPE alteration in the center of the lesion and surrounding the border.

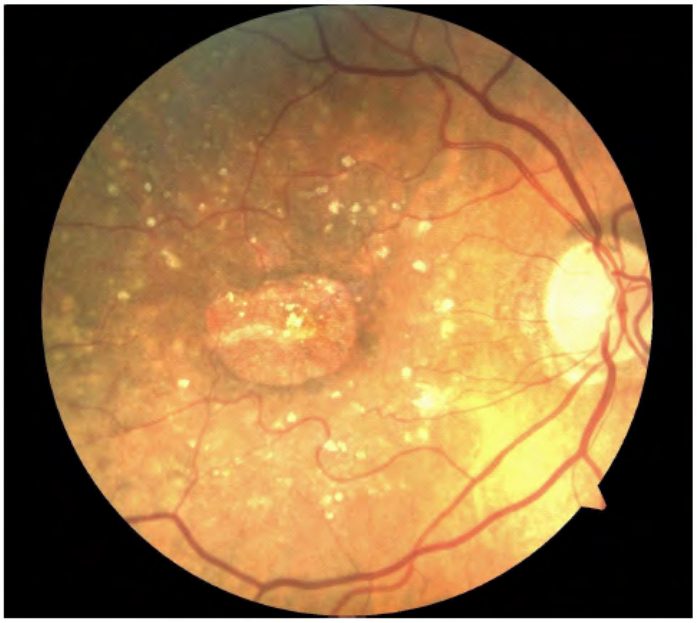


Fig. (20). Intermediate GA.

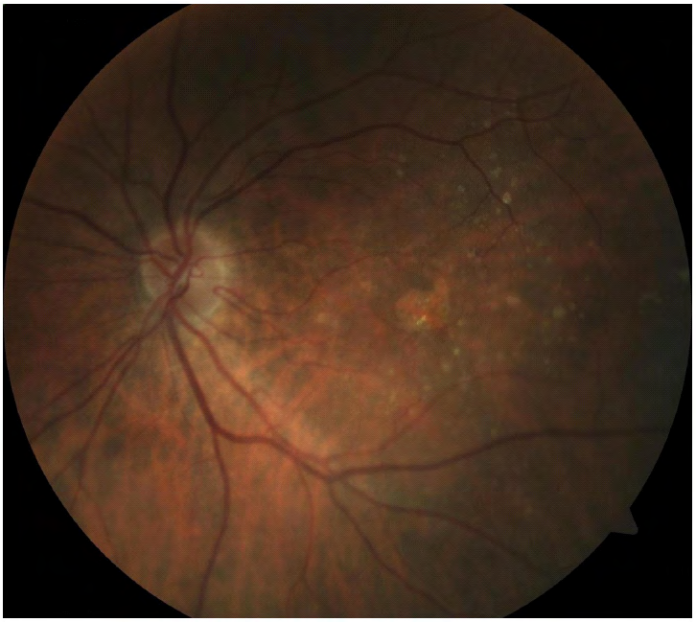


Fig. (21). Small GA.

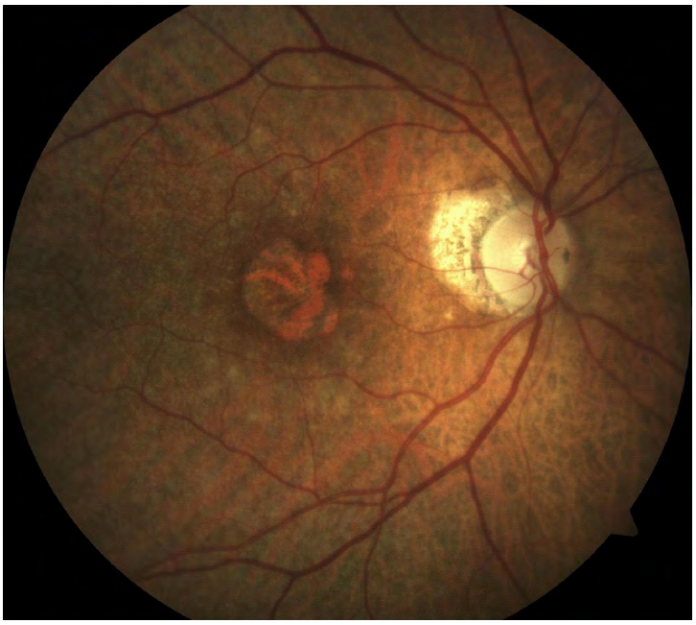


Fig. (22). Round patch of central GA involving the center point of the macula, sharply demarcated, with large choroidal blood vessels in the back in a patient with advanced AMD.

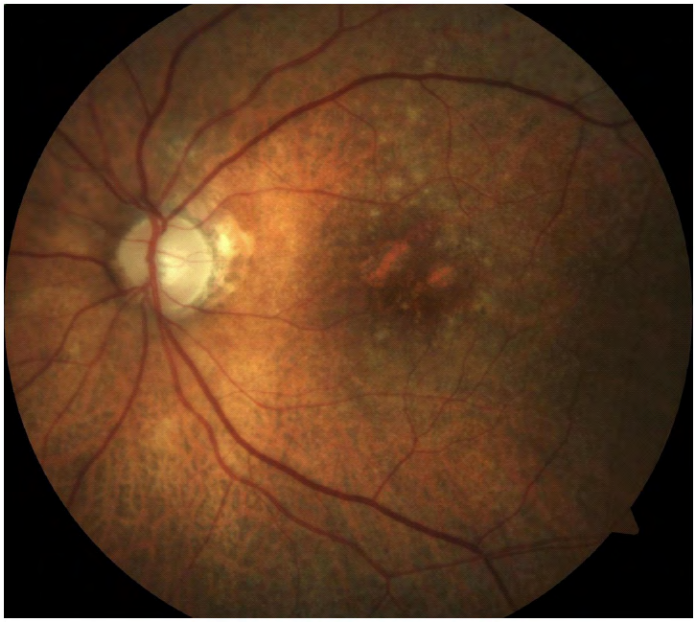


Fig. (23). Drusen, RPE changes and non-central GA in a 95-year-old patient.

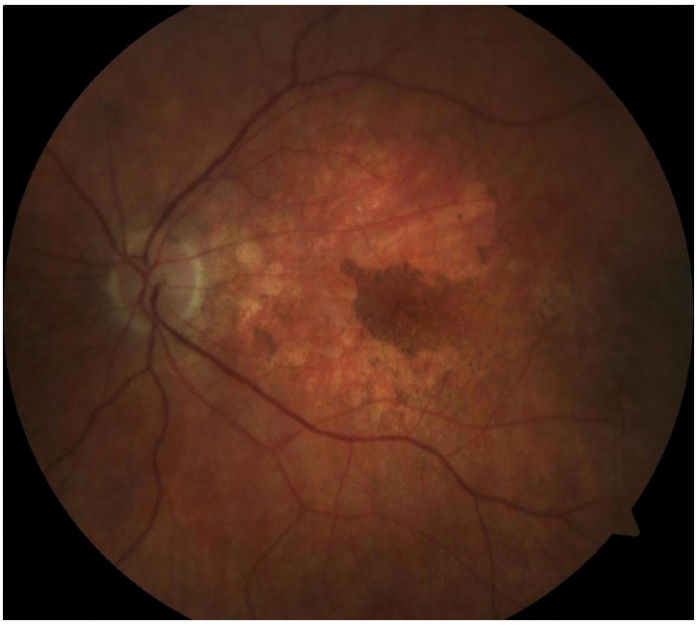


Fig. (24). Large GA sparing the central fovea until late stages.

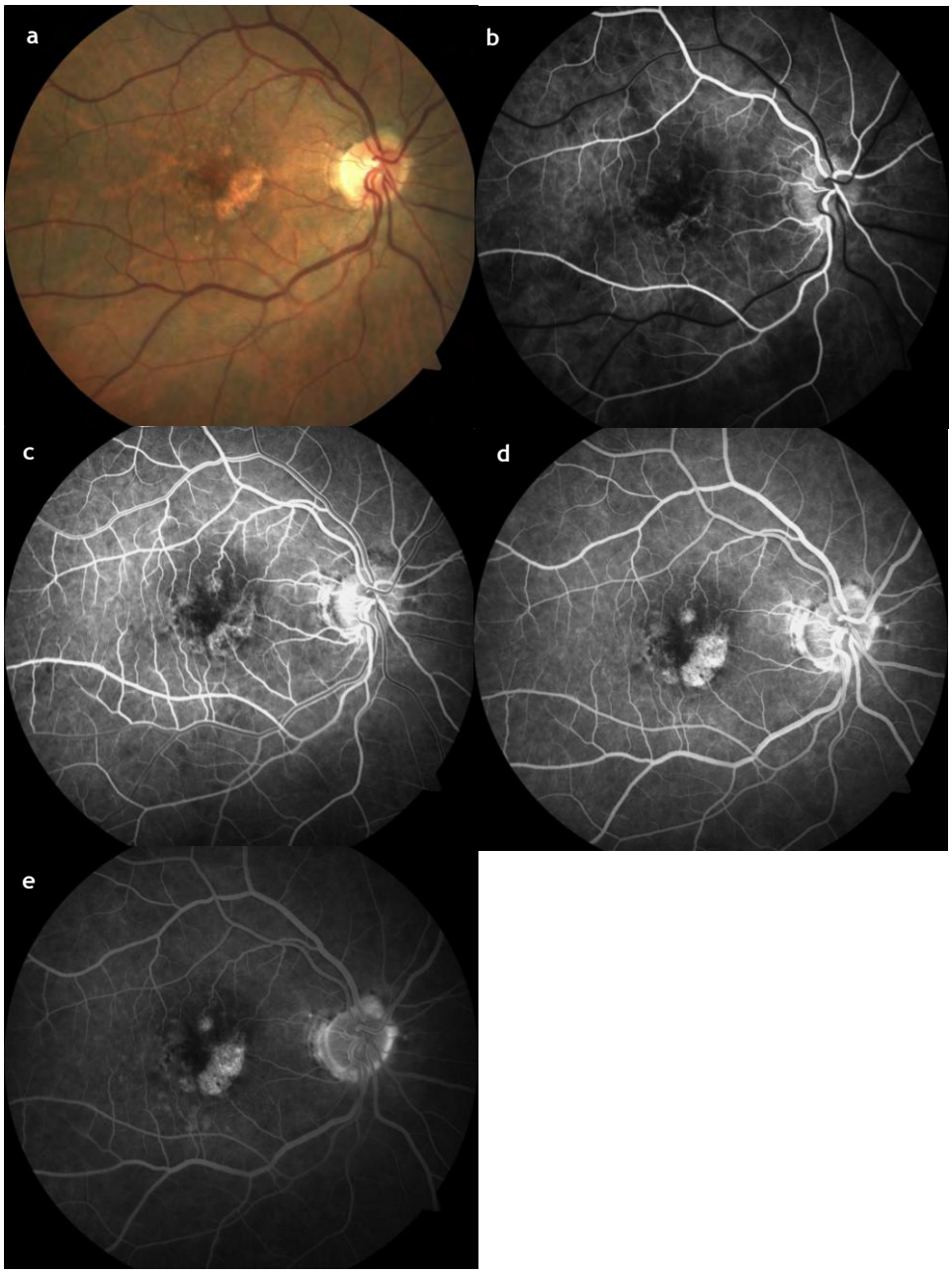


Fig. (25). a) 71-year-old patient with non-central GA; **b**) **c**) **d**) progressive well-defined hyperfluorescence of the atrophic area. Hyperfluorescence increases in late phases; **e**) late phase shows intense hyperfluorescence because of staining of the underlying choroid and sclera.

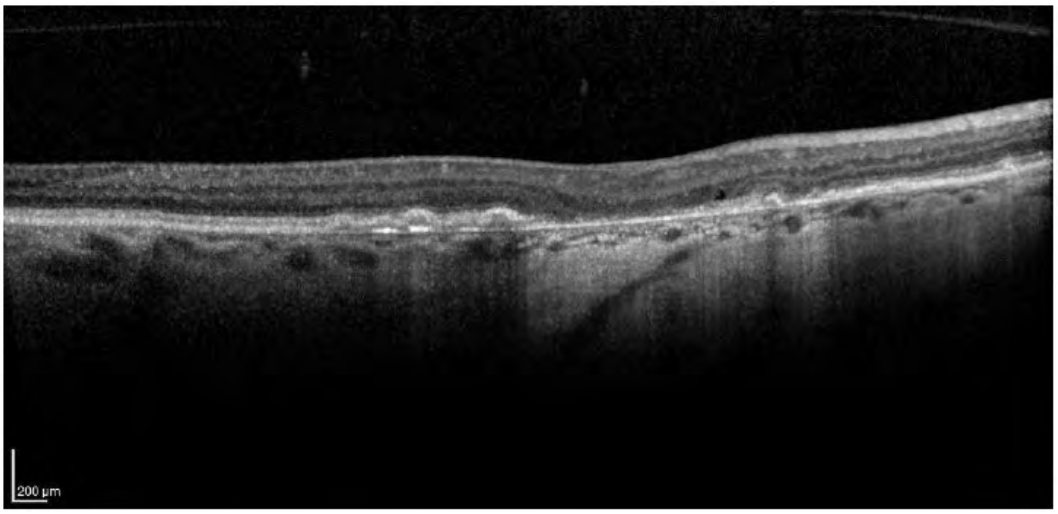


Fig. (26). Central GA, with outer retinal thinning (loss of the external limiting membrane -ELM- and inner /outer segment junction) and atrophy of RPE cells, Bruch´s membrane, and choriocapillaris. Highly reflective signal from the choroid vessels in the atrophic area.

Accumulation of lipofuscin (LF) granules in RPE cells increases in AMD [25]. Normally, Funds autofluorescence (FAF) is able to visualize lipofuscin yielding a distinctive pattern (Fig. **29**). Variations in the FAF signal reflect modifications in the density of LF. In early AMD, FAF is able to show more widespread abnormalities than funds examination and FA. Some hard and soft drusen may present a ring pattern. Confluent drusen have a mildly increased signal (Fig. **30**). FAF is useful to identify a drusenoid PED (mild, diffuse increased signal corresponding exactly with the detached area) or an RPE tear. Pigment clumping are focal changes with an increased FAF signal and RPE atrophy appears as decreased autofluorescence patch. The borders of an area of GA (junctional zone) can have five different patterns in FAF, that can predict the rate of progression: no change, indicating slow progression; focal (Fig. **31**), indicating slow progression; banded (Fig. **32**), indicating rapid progression; patchy, indicating slow progression, or diffuse (Fig. **33**), indicating rapid progression [26].

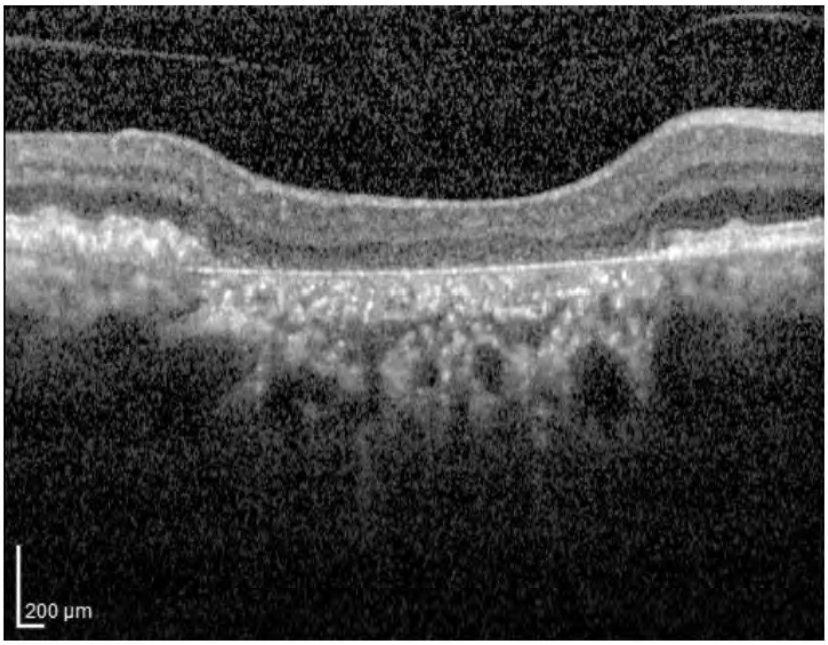


Fig. (27). Central GA with loss of the layered structure of the retina.

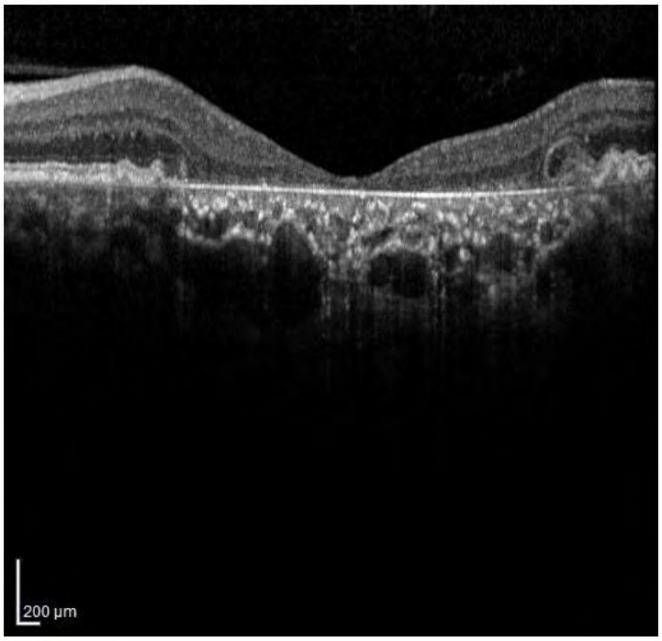


Fig. (28). Important retinal thinning due to GA in a patient with advanced AMD.

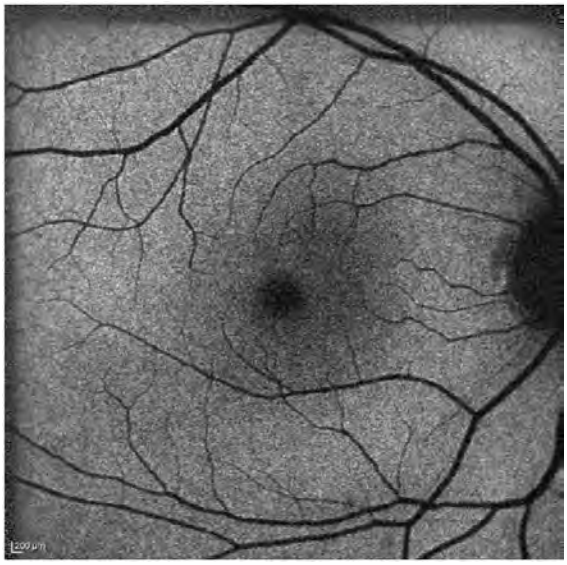


Fig. (29). Topographic distribution of FAF in a normal right eye. There is a homogeneous background with very low intensity on the optic disc (no autofluorescent material) and retina vessels (absorption by blood compounds). A gradual decrease in signal in the inner macula toward the fovea (absorption by luteal pigment).

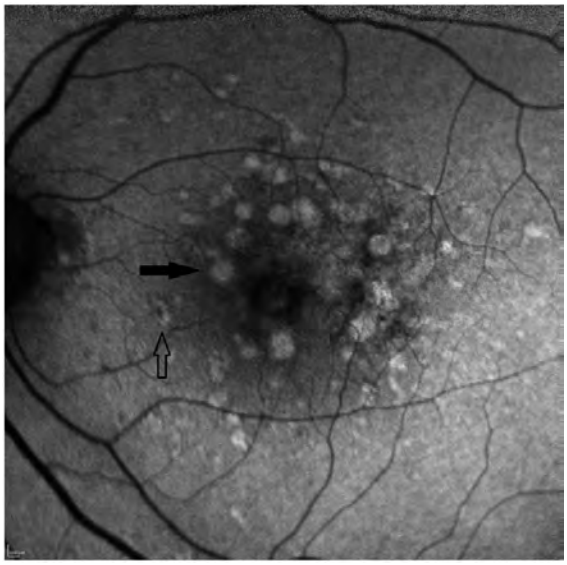


Fig. (30). FAF of a patient with moderate AMD. Drusen in a ring pattern (unfilled arrow) with decreased FAF intensities in the center, within or below the range of the normal background signal, surrounded by an annulus of increased FAF (may correspond to pigment clumping in fundus photos). Large and confluent soft drusen (arrow) have an increased signal.

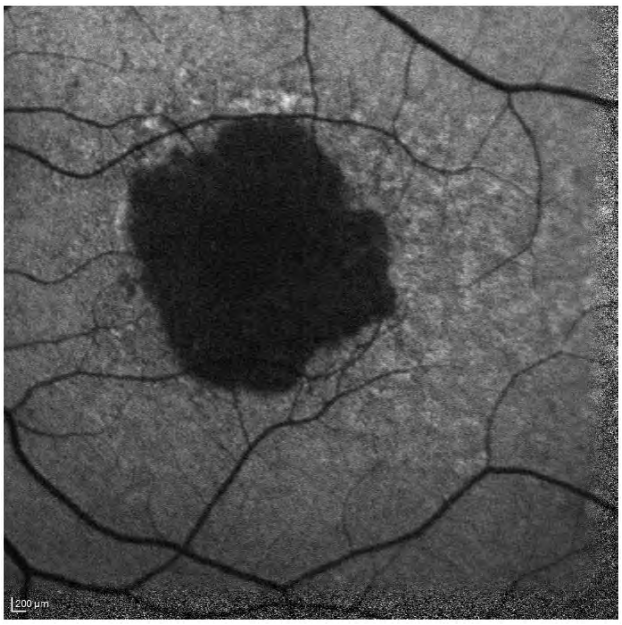


Fig. (31). GA is seen as an area of strong reduction in FAF signal secondary to RPE cell death. Focal pattern in a left eye: individual hyperautoflorescence spots around the GA margin, not in continuous pattern.

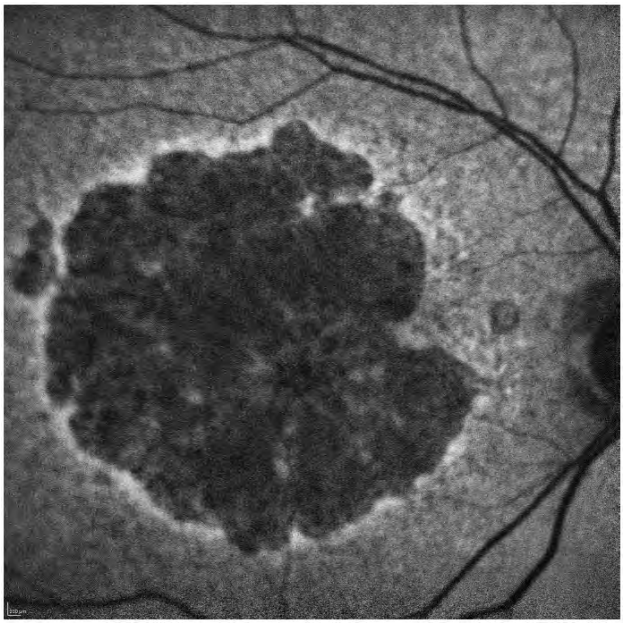


Fig. (32). Banded pattern: continuous hyperautofluorescence around the junction area between the normal retina and the atrophy. It is related to rapid progression.

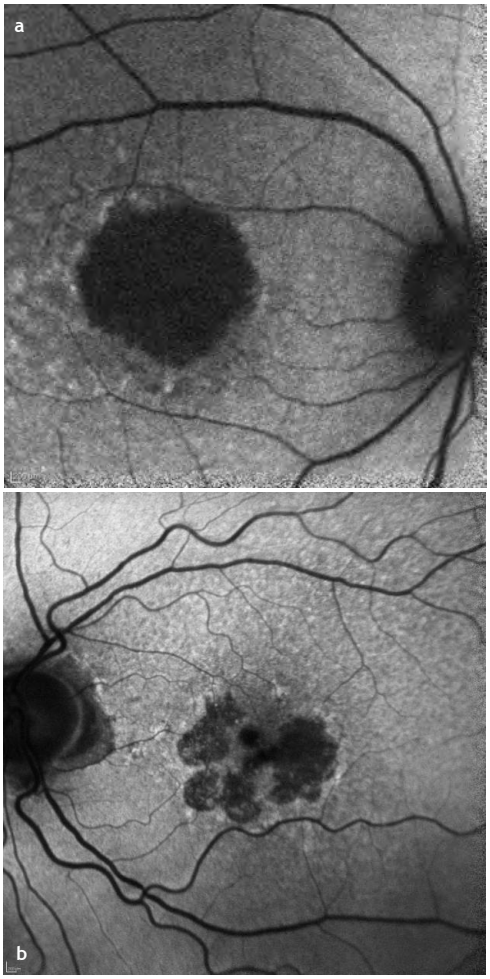


Fig. (33). Diffuse pattern: increased FAF intensity at the junctional zone and some spots elsewhere. It is associated with rapid progression of the atrophy; **a**) right eye and **b**) left eye of two different patients.

DIFFERENTIAL DIAGNOSIS

Sequelae of central serous chorioretinopathy may mimick dry AMD (Fig. **34**) [27]. Pattern dystrophy is a group of macular dystrophies with deposition of yellow or gray pigment at the RPE. They typically appear in younger patients and have a characteristic pattern in FA (Fig. **35**) [28, 29]. Adult-onset foveomacular vitelliform dystrophy may also resemble dry AMD (Fig. **36**), and can be confused with DPED (Fig. **37 a, b**) or with a solely large subfoveal drusen. In FA, the vitelliform material blocks the background fluorescence early and stains in late

frames. OCT shows a highly reflective material (Fig. **36 b,c**) [30, 31]. Other differential diagnoses include chloroquine toxicity (Fig. **38 a-d**) [32 - 34], cuticular basal laminar drusen (Fig. **39 a-h**) [35], central areolar choroidal [36], and dominant drusen [37].

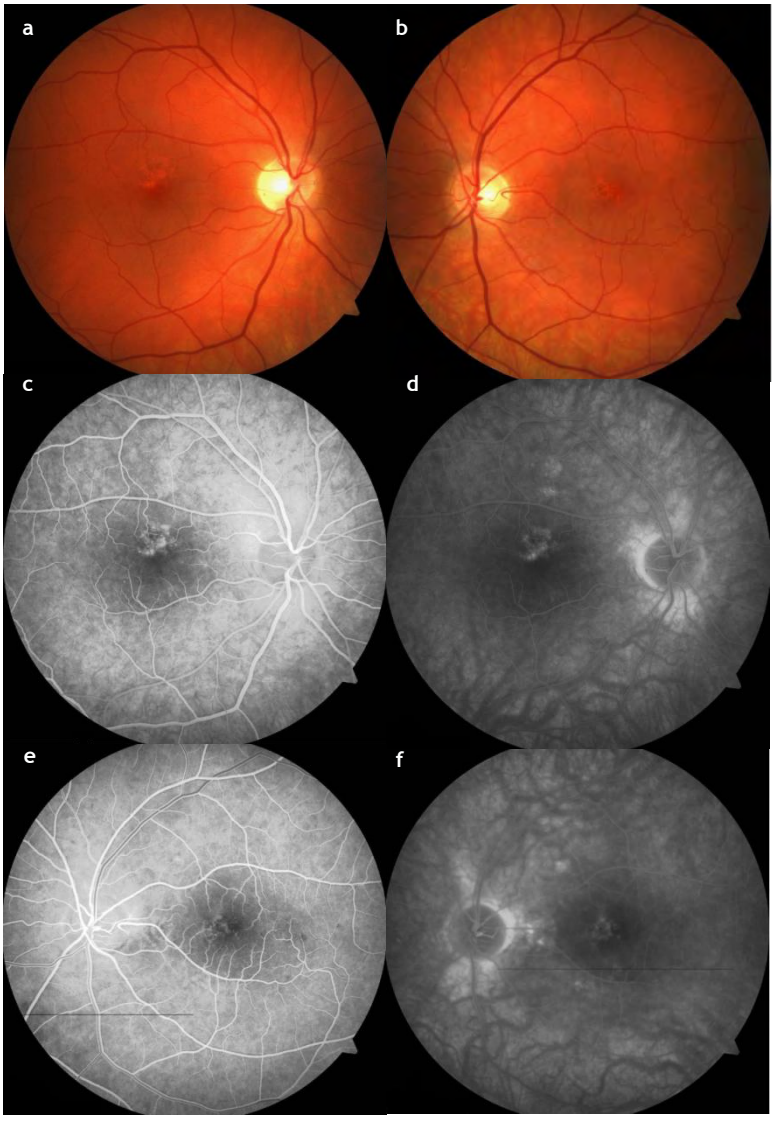


Fig. (34). 49-year-old man, visual acuity 20/20 in both eyes and history of previous CSC; **a**) **b**) fundus photos of RPE defects in both eyes. Early and late FA frames showing blockage and transmission defect in the right eye (**c**) (**d**) and the left eye (**e**) (**f**).

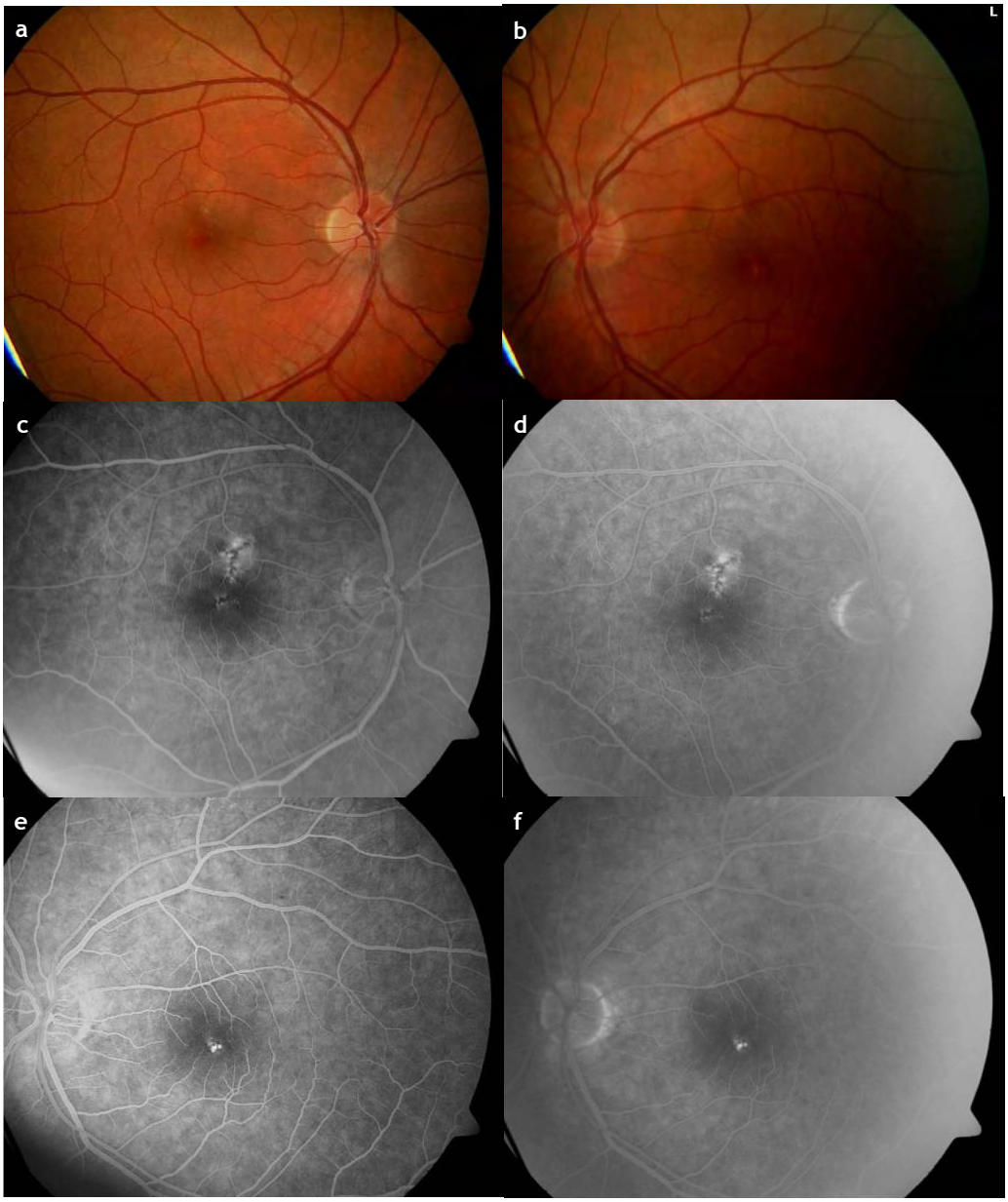


Fig. (35). 43-year-old woman with asymmetric Butterfly Dystrophy. Visual acuity remains 20/20 in both eyes. Fundus photos of right (**a**) and left eye (**b**). FA in early and late phases in the right eye (**c**), (**d**) and left eye; (**e**) and (**f**), showing the typical feature with a hypofluorescence center surrounded by a hyperfluorescent rim.

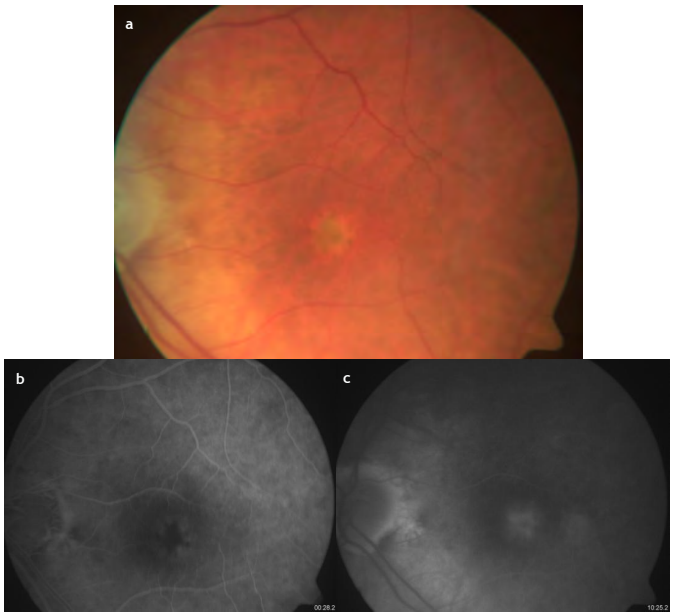


Fig. (36). a) Fundus photo of a left eye with Adult- onset foveomacular vitelliform dystrophy. Early FA **b**) with central hypofluorescence due to blockage. Late frame shows **c**) hyperfluorescence due to deposit stains.

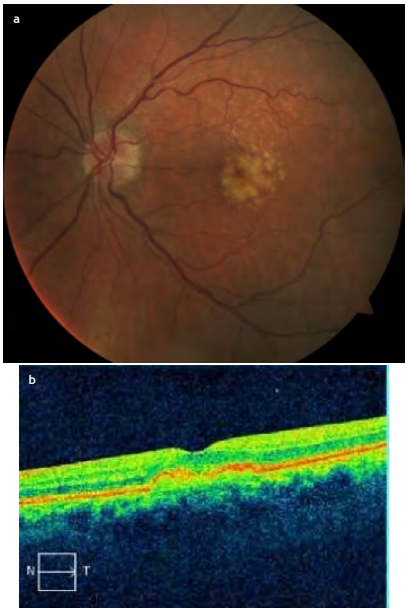


Fig. (37). a) Confluent large soft drusen in the left eye of a 71-year-old patient, imitating a round central yellow vitelliform spot; **b**) OCT showing a DPED.

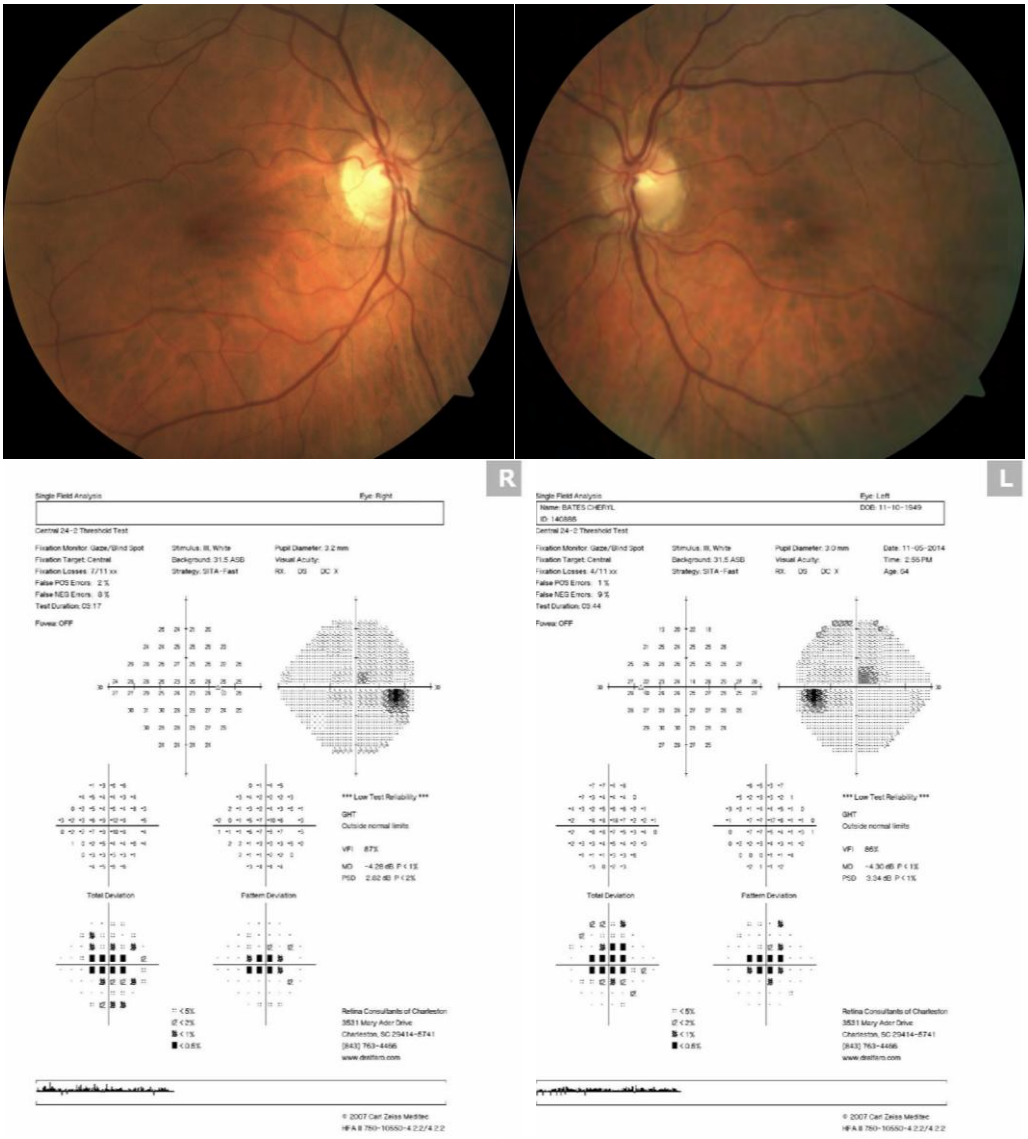


Fig. (38). 65-year-old female patient, with a history of hydroxychloroquine treatment and eye toxicity; **a**) funds photograph of the right eye, showing no abnormalities; **b**) fundus photograph of the left eye, showing pigment changes; **c**) and **d**) visual fields with central scotoma in both eyes.

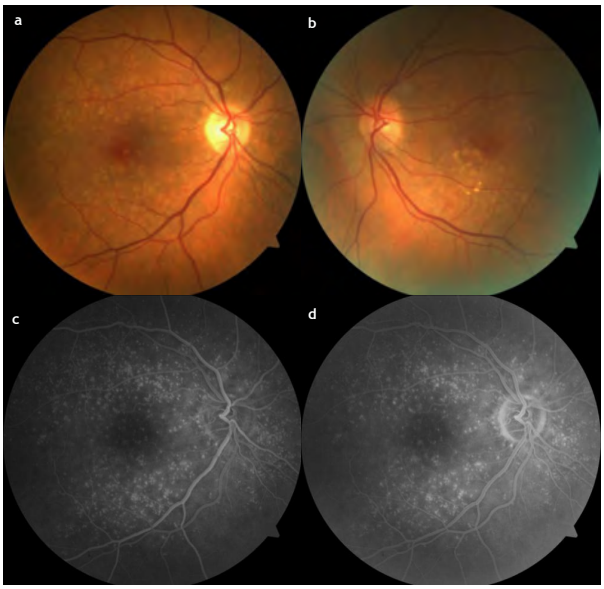


Fig. (39). a) and **b**) Right and left eyes of a patient with Basal Laminar Drusen. In the color photos there are some drusen and defects in the RPE in the posterior pole in both eyes. Right eye FA (**c**) and (**d**). In FA the small, round and widely spread drusen are more evident, forming a "stars in the sky" pattern presenting early hyperfluorescence.

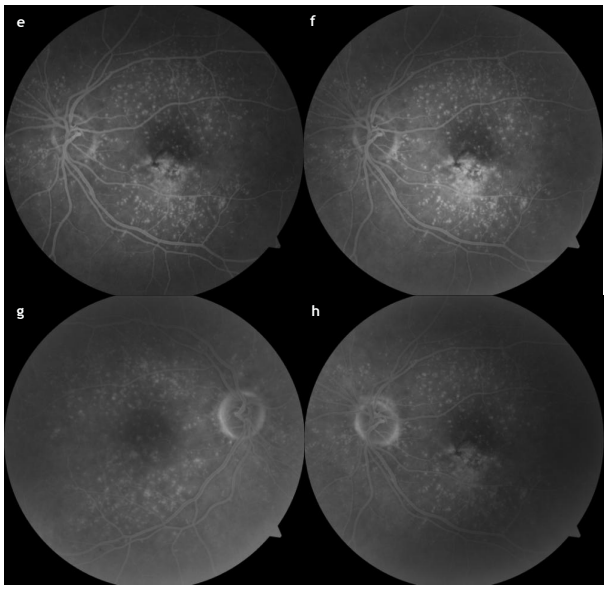


Fig. (39). Left eye FA (**e**) and (**f**). At late phases in the right (**g**) and left eye (**h**), the hyperfluorescence fades.

MANAGEMENT

There is no adequate therapy for GA in advanced AMD. The AREDS Study was designed to assess whether active treatment with antioxidants and/or zinc could reduce the risk of developing advanced AMD or visual acuity loss. The largest risk reduction was observed in patients with confluent soft drusen or patients with contralateral advanced AMD. Treatment options for prevention and progress of GA are limited [38].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bird AC, Bressler NM, Bressler SB, *et al.* An international classification and grading system for age-related maculopathy and age-related macular degeneration. Surv Ophthalmol 1995; 39(5): 367-74. [http://dx.doi.org/10.1016/S0039-6257(05)80092-X] [PMID: 7604360]

[2] Friedman DS, Katz J, Bressler NM, Rahmani B, Tielsch JM. Racial differences in the prevalence of age-related macular degeneration: the Baltimore Eye Survey. Ophthalmology 1999; 106(6): 1049-55. [http://dx.doi.org/10.1016/S0161-6420(99)90267-1]

[3] Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. Eye (Lond) 2005; 19(9): 935-44. [http://dx.doi.org/10.1038/sj.eye.6701978] [PMID: 16151432]

[4] Klein R, Lee KE, Gangnon RE, Klein BE. Relation of smoking, drinking, and physical activity to changes in vision over a 20-year period: the Beaver Dam Eye Study. Ophthalmology 2014; 121(6): 1220-8. [http://dx.doi.org/10.1016/j.ophtha.2014.01.003] [PMID: 24594095]

[5] Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992; 99(6): 933-43. [http://dx.doi.org/10.1016/S0161-6420(92)31871-8] [PMID: 1630784]

[6] Friedman DS, O'Colmain BJ, Muñoz B, *et al.* Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004; 122(4): 564-72. [http://dx.doi.org/10.1001/archopht.122.4.564] [PMID: 15078675]

[7] de Jong PT, de Jong MD. Age-related macular degeneration. N Engl J Med 2006; 355(14): 1474-85. [http://dx.doi.org/10.1056/NEJMra062326] [PMID: 17021323]

[8] Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 2004; 122(4): 598-614.
[http://dx.doi.org/10.1001/archopht.122.4.598] [PMID: 15078679]

[9] Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. JAMA Ophthalmol 2014; 132(3): 338-45.
[http://dx.doi.org/10.1001/jamaophthalmol.2013.5799] [PMID: 24626824]

[10] Ferris FL, Davis MD, Clemons TE, *et al.* A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. Arch Ophthalmol 2005; 123(11): 1570-4.
[http://dx.doi.org/10.1001/archopht.123.11.1570] [PMID: 16286620]

[11] Sarks SH, Arnold JJ, Killingsworth MC, Sarks JP. Early drusen formation in the normal and aging eye and their relation to age related maculopathy: a clinicopathological study. Br J Ophthalmol 1999; 83(3): 358-68.
[http://dx.doi.org/10.1136/bjo.83.3.358] [PMID: 10365048]

[12] Kliffen M, van der Schaft TL, Mooy CM, de Jong PT. Morphologic changes in age-related maculopathy. Microsc Res Tech 1997; 36(2): 106-22.
[http://dx.doi.org/10.1002/(SICI)1097-0029(19970115)36:2<106::AID-JEMT4>3.0.CO;2-N] [PMID: 9015257]

[13] Vingerling JR, Dielemans I, Hofman A, *et al.* The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology 1995; 102(2): 205-10.
[http://dx.doi.org/10.1016/S0161-6420(95)31034-2] [PMID: 7862408]

[14] Sarks SH. Drusen patterns predisposing to geographic atrophy of the retinal pigment epithelium. Aust J Ophthalmol 1982; 10(2): 91-7.
[http://dx.doi.org/10.1111/j.1442-9071.1982.tb00366.x] [PMID: 7103872]

[15] Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in Drusen formation and age related macular degeneration. Exp Eye Res 2001; 73(6): 887-96.
[http://dx.doi.org/10.1006/exer.2001.1094] [PMID: 11846519]

[16] Pieroni CG, Witkin AJ, Ko TH, *et al.* Ultrahigh resolution optical coherence tomography in non-exudative age related macular degeneration. Br J Ophthalmol 2006; 90(2): 191-7.
[http://dx.doi.org/10.1136/bjo.2005.076612] [PMID: 16424532]

[17] Cukras C, Agrón E, Klein ML, *et al.* Natural history of drusenoid pigment epithelial detachment in age-related macular degeneration: Age-Related Eye Disease Study Report No. 28. Ophthalmology 2010; 117(3): 489-99.
[http://dx.doi.org/10.1016/j.ophtha.2009.12.002] [PMID: 20079925]

[18] Forte R, Querques G, Querques L, Massamba N, Le Tien V, Souied EH. Multimodal imaging of dry age-related macular degeneration. Acta Ophthalmol 2012; 90(4): e281-7.
[http://dx.doi.org/10.1111/j.1755-3768.2011.02331.x] [PMID: 22269083]

[19] The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. Am J Ophthalmol 2001; 132(5): 668-81.

[http://dx.doi.org/10.1016/S0002-9394(01)01218-1] [PMID: 11704028]

[20] Toy BC, Krishnadev N, Indaram M, *et al.* Drusen regression is associated with local changes in fundus autofluorescence in intermediate age-related macular degeneration. Am J Ophthalmol 2013; 156(3): 532-42.e1.
[http://dx.doi.org/10.1016/j.ajo.2013.04.031] [PMID: 23830564]

[21] Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. Am J Ophthalmol 2004; 137(3): 486-95.
[http://dx.doi.org/10.1016/j.ajo.2003.11.069] [PMID: 15013873]

[22] Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 1997; 104(1): 7-21.

[23] The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. Control Clin Trials 1999; 20(6): 573-600.
[http://dx.doi.org/10.1016/S0197-2456(99)00031-8] [PMID: 10588299]

[24] Brar M, Kozak I, Cheng L, *et al.* Correlation between spectral-domain optical coherence tomography and fundus autofluorescence at the margins of geographic atrophy. Am J Ophthalmol 2009; 148(3): 439-44.
[http://dx.doi.org/10.1016/j.ajo.2009.04.022] [PMID: 19541290]

[25] Bearelly S, Khanifar AA, Lederer DE, *et al.* Use of fundus autofluorescence images to predict geographic atrophy progression. Retina 2011; 31(1): 81-6.
[http://dx.doi.org/10.1097/IAE.0b013e3181e0958b] [PMID: 20890245]

[26] Schmitz-Valckenberg S, Fleckenstein M, Scholl HP, Holz FG. Fundus autofluorescence and progression of age-related macular degeneration. Surv Ophthalmol 2009; 54(1): 96-117.
[http://dx.doi.org/10.1016/j.survophthal.2008.10.004] [PMID: 19171212]

[27] de Jong EK, Breukink MB, Schellevis RL, *et al.* Chronic central serous chorioretinopathy is associated with genetic variants implicated in age- relate macular degeneration. Ophthalmology 2015; 22(3): 562-70.

[28] Esteves F, Dolz-Marco R, Hernández-Martínez P, Díaz-Llopis M, Gallego-Pinazo R. Pattern dystrophy of the macula in a case of steinert disease. Case Rep Ophthalmol 2013; 4(3): 129-33.
[http://dx.doi.org/10.1159/000355385] [PMID: 24163680]

[29] Hsieh RC, Fine BS, Lyons JS. Patterned dystrophies of the retinal pigment epithelium. Arch Ophthalmol 1977; 95(3): 429-35.
[http://dx.doi.org/10.1001/archopht.1977.04450030071006] [PMID: 843272]

[30] Seddon JM, Afshari MA, Sharma S, *et al.* Assessment of mutations in the Best macular dystrophy (VMD2) gene in patients with adult-onset foveomacular vitelliform dystrophy, age-related maculopathy, and bull's-eye maculopathy. Ophthalmology 2001; 108(11): 2060-7.
[http://dx.doi.org/10.1016/S0161-6420(01)00777-1] [PMID: 11713080]

[31] Lim JI, Enger C, Fine SL. Foveomacular dystrophy. Am J Ophthalmol 1994; 117(1): 1-6.
[http://dx.doi.org/10.1016/S0002-9394(14)73007-7] [PMID: 8291575]

[32] Michaelides M, Stover NB, Francis PJ, Weleber RG. Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of

therapy. Arch Ophthalmol 2011; 129(1): 30-9.
[http://dx.doi.org/10.1001/archophthalmol.2010.321] [PMID: 21220626]

[33] Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011; 118(2): 415-22.
[http://dx.doi.org/10.1016/j.ophtha.2010.11.017] [PMID: 21292109]

[34] Stelton CR, Connors DB, Walia SS, Walia HS. Hydrochloroquine retinopathy: characteristic presentation with review of screening. Clin Rheumatol 2013; 32(6): 895-8.
[http://dx.doi.org/10.1007/s10067-013-2226-2] [PMID: 23515601]

[35] van de Ven JP, Boon CJ, Smailhodzic D, *et al.* Short-term changes of Basal laminar drusen on spectral-domain optical coherence tomography. Am J Ophthalmol 2012; 53(14): 2099.
[http://dx.doi.org/10.1016/j.ajo.2012.03.012]

[36] Boon CJ, Klevering BJ, Cremers FP, *et al.* Central areolar choroidal dystrophy. Ophthalmology 2009; 116(4): 771-82.
[http://dx.doi.org/10.1016/j.ophtha.2008.12.019] [PMID: 19243827]

[37] Deutman AF, Jansen LM. Dominantly inherited drusen of Bruch's membrane. Br J Ophthalmol 1970; 54(6): 373-82.
[http://dx.doi.org/10.1136/bjo.54.6.373] [PMID: 5448127]

[38] A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001; 119(10): 1417-36.
[http://dx.doi.org/10.1001/archopht.119.10.1417] [PMID: 11594942]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 15

Wet Age-Related Macular Degeneration

Gerardo García-Aguirre[*, 1,2]

[1] *Retina Department, Asociaciós para Evitar la Ceguera en Mexico, Mexico City, Mexico*

[2] *Ophthalmology, Escuela de Medicina - Tec de Monterrey, Mexico City, Mexico*

Age-related macular degeneration (AMD) is one of the leading causes of legal blindness in patients over 60 years, especially in developed countries [1]. The prevalence of the disease varies according to ethnicity [2], and is more common in smokers [3, 4] and in women [5, 6]. The disease is classified in two stages, known as dry AMD (which is discussed in another chapter) which is characterized by the presence of drusen in the posterior pole, and wet AMD, in which the patient develops neovascularization that stems from the choroid, penetrates Bruch's membrane, and by leakage of fluid, hemorrhage and scarring, affecting the center of the macula.

ESSENTIALS OF DIAGNOSIS

When a choroidal neovascularization (CNV) develops, patients may complain of metamorphopsia and a central or paracentral relative scotoma.

Clinical examination usually reveals drusen, and the presence of intraretinal or subretinal fluid that causes thickening of the retina. Hemorrhage and hard exudates may also be observed (Figs. **1-6**).

[*] **Corresponding author Gerardo García Aguirre:** Retina Department, Asociaciós para Evitar la Ceguera en Mexico, Vicente García Torres 46, San Lucas Coyoacan, Mexico City 04030, Mexico; Tel: +52 (55) 10841400; E-mail: jerry_gar_md@yahoo.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

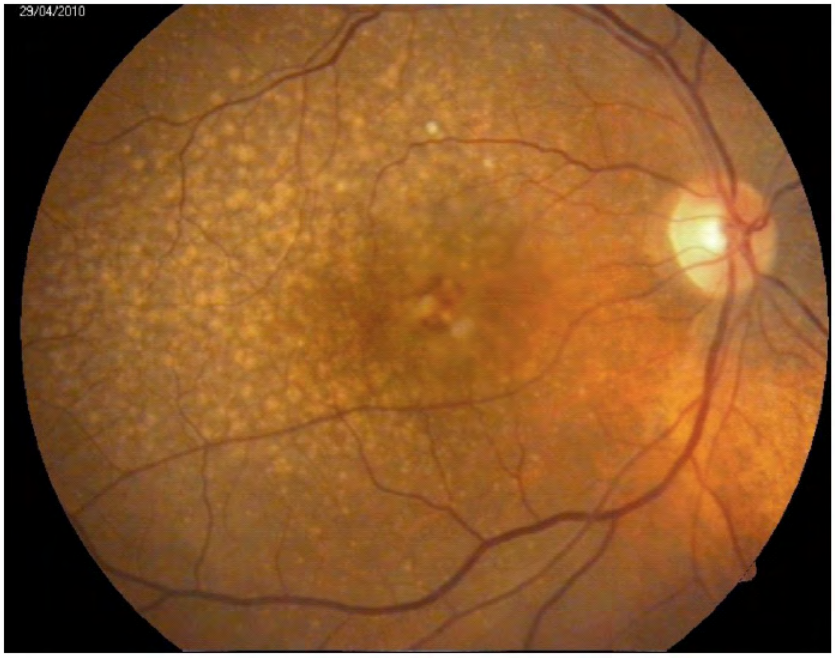


Fig. (1). Fundus photograph of the right eye with subfoveal CNV showing multiple soft and hard drusen in the macular area. A small subretinal hemorrhage may be observed nasal to the fovea.

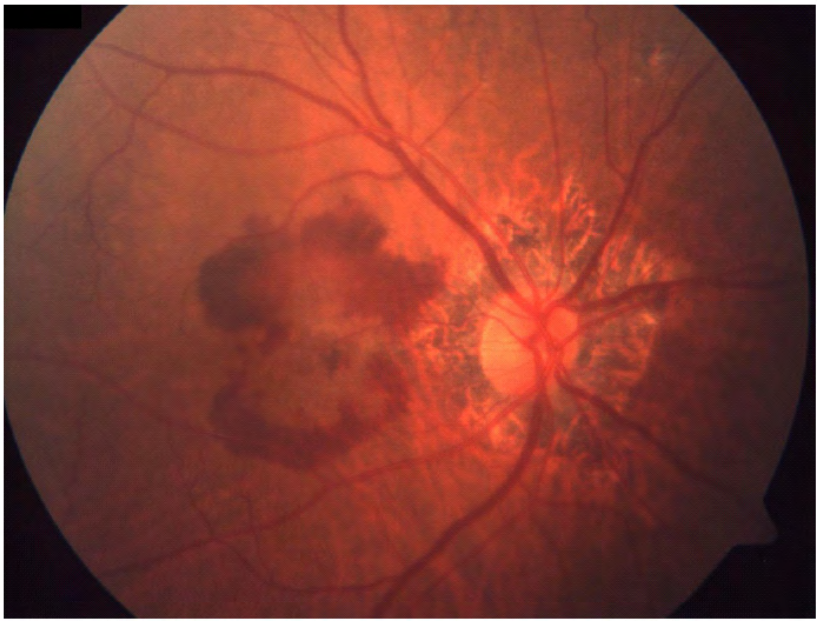


Fig. (2). Fundus photograph of the right eye with a subfoveal CNV and large submacular hemorrhage.

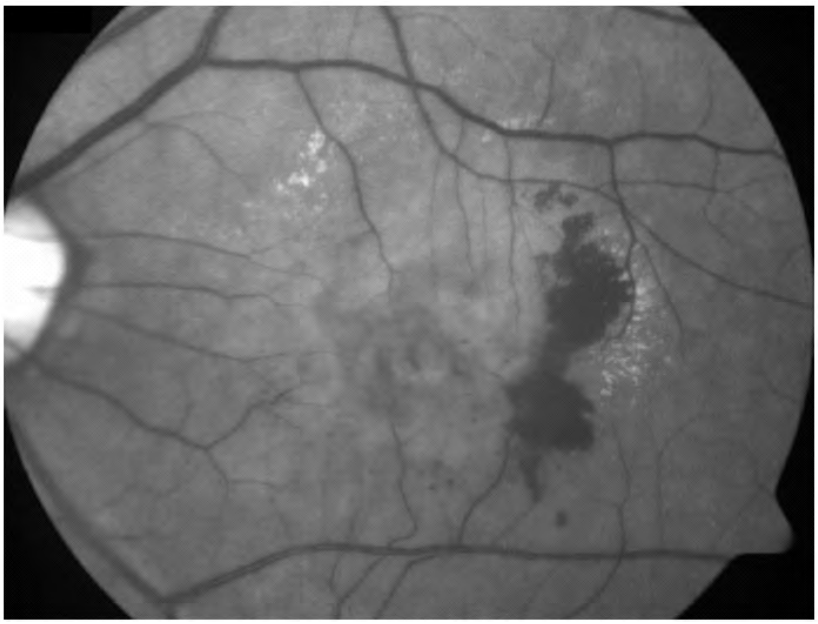


Fig. (3). Red-free fundus photograph of the left eye, showing a subfoveal CNV surrounded by hard exudates and submacular hemorrhage.

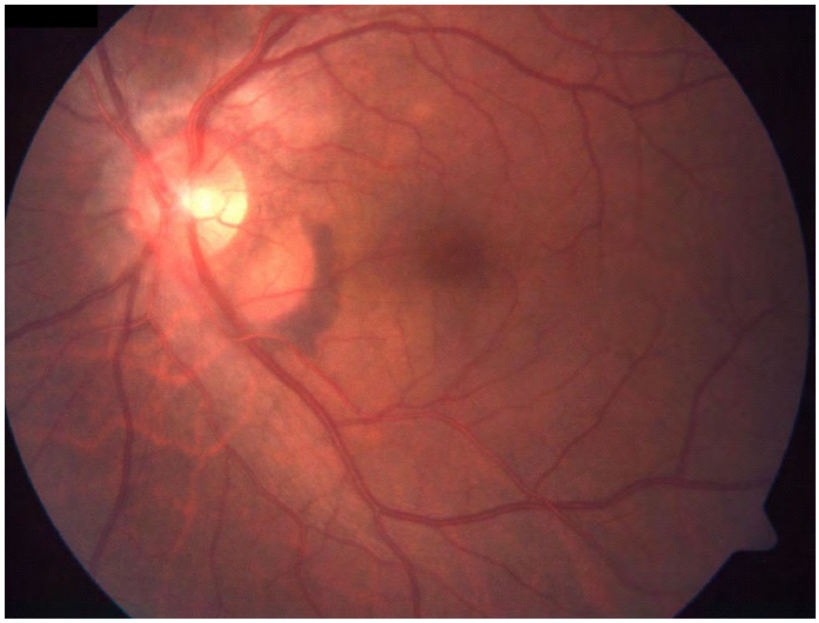


Fig. (4). Fundus photograph of the left eye displaying an extrafoveal CNV, just adjacent to the inferotemporal border of the optic nerve, with associated subretinal hemorrhage.

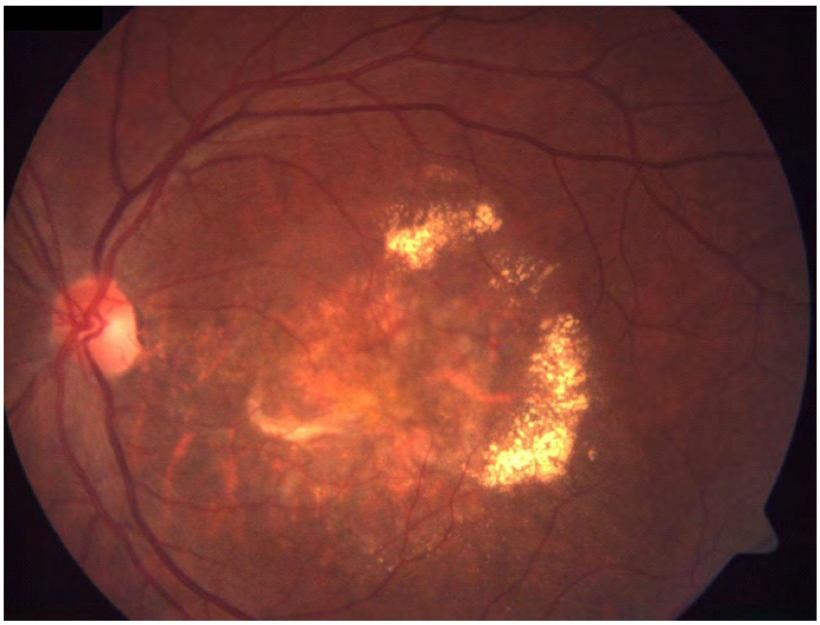


Fig. (5). Fundus photograph of the left eye, showing a subfoveal CNV with abundant hard exudates and some subretinal fibrosis.

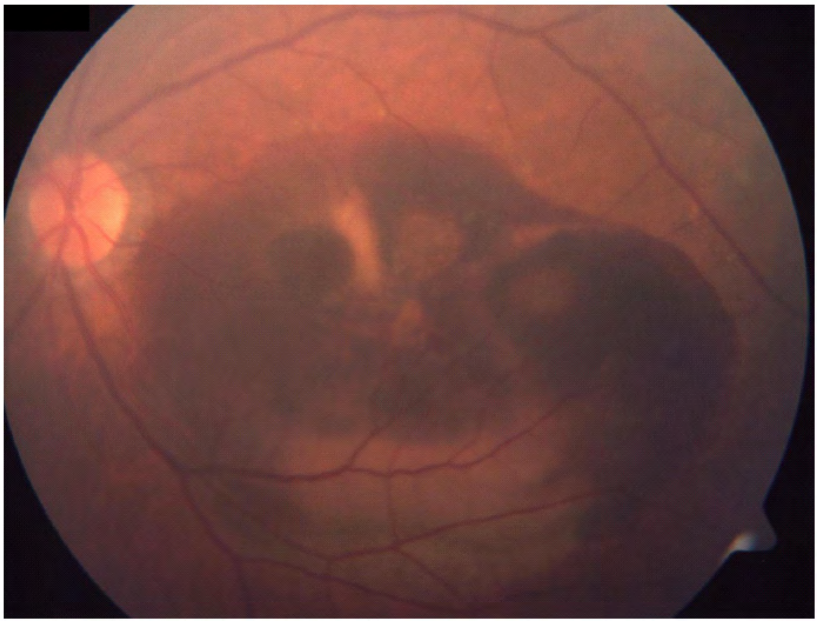


Fig. (6). Fundus photograph of the left eye showing a massive submacular hemorrhage secondary to CNV.

Fluorescein angiography (FA) is very useful, showing an area of early hyperfluorescence that increases in intensity and size as the study progresses due to leakage of fluorescein. Accumulation of dye secondary to a pigment epithelium detachment (PED) may also be observed (Figs. **7**-**15**).

Optic coherence tomography (OCT) of the macula is an invaluable adjuvant in the diagnosis and follow-up of patients with CNV secondary to AMD. Different abnormalities may be observed in any given case, including intraretinal fluid, subretinal fluid, PED, and/or a hyper-reflective subretinal lesion. Hard exudates and hemorrhages are also observed as hyper-reflective foci (Figs. **16**-**19**)

Indocyanine green angiography (ICGa) is also useful in some cases, especially when suspecting a CNV with an arteriolar component (Figs. **20**, **21**).

If the CNV has not been treated and has been present for several months, subretinal fibrosis begins to appear, which usually grows into a large disciform scar that may occupy the entire macular area. The presence of fibrotic tissue has a very bad visual prognosis (Figs. **22**-**25**).

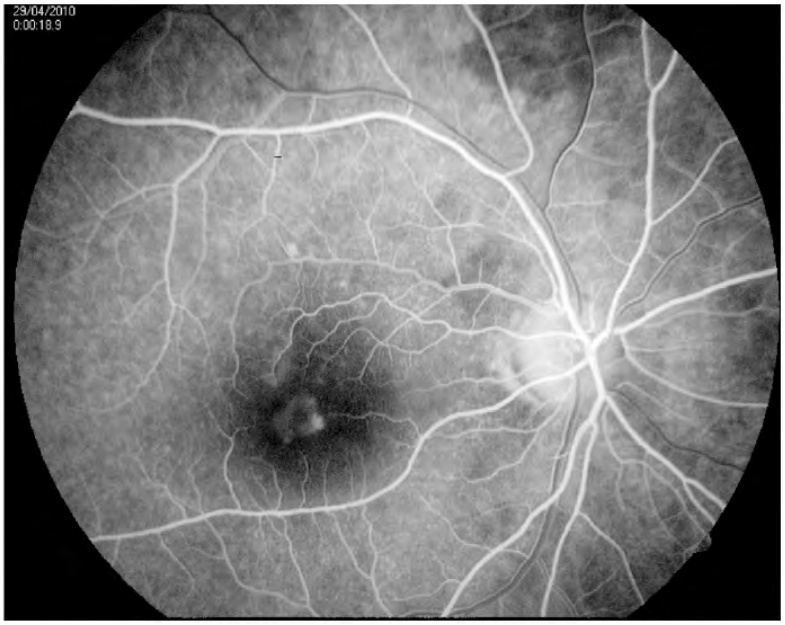


Fig. (7). Early fluorescein angiogram of the same eye as Fig. (**1**), showing hyperfluorescence in the subfoveal area.

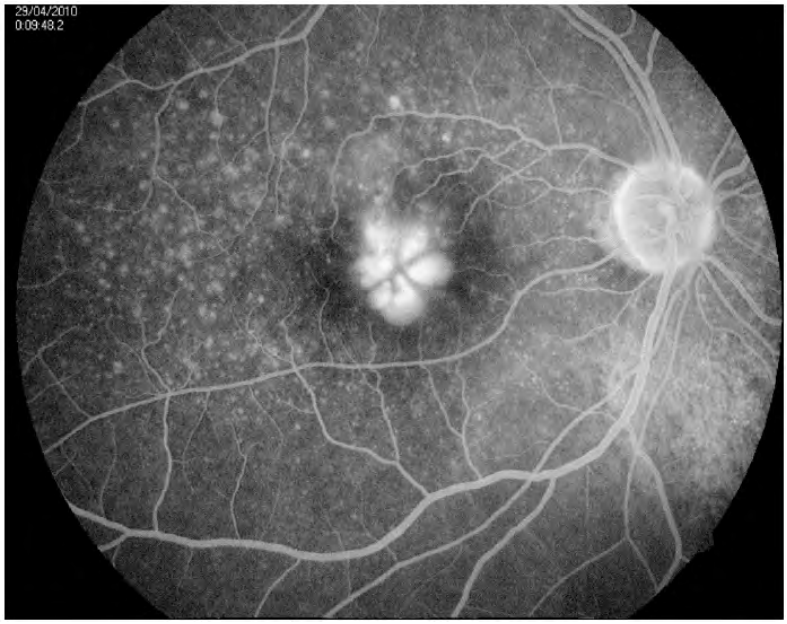


Fig. (8). Late fluorescein angiogram of the same eye as in Fig. (**7**), showing increase of hyperfluorescence in the foveal area. Hyperfluorescence secondary to drusen is also observed throughout the macula.

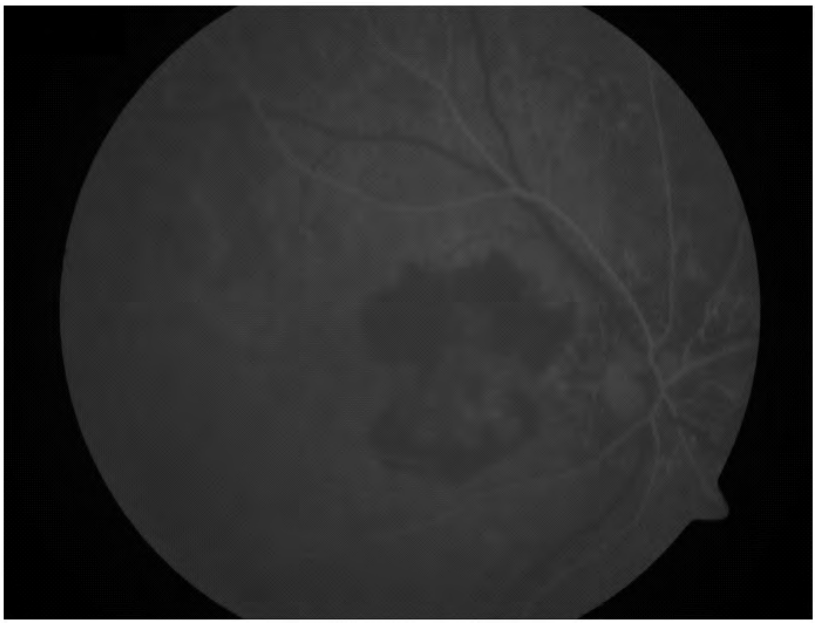


Fig. (9). Early fluorescein angiogram of the same eye as in Fig. (**2**), showing mild hyperfluorescence in the center of the macula and blockage secondary to hemorrhage.

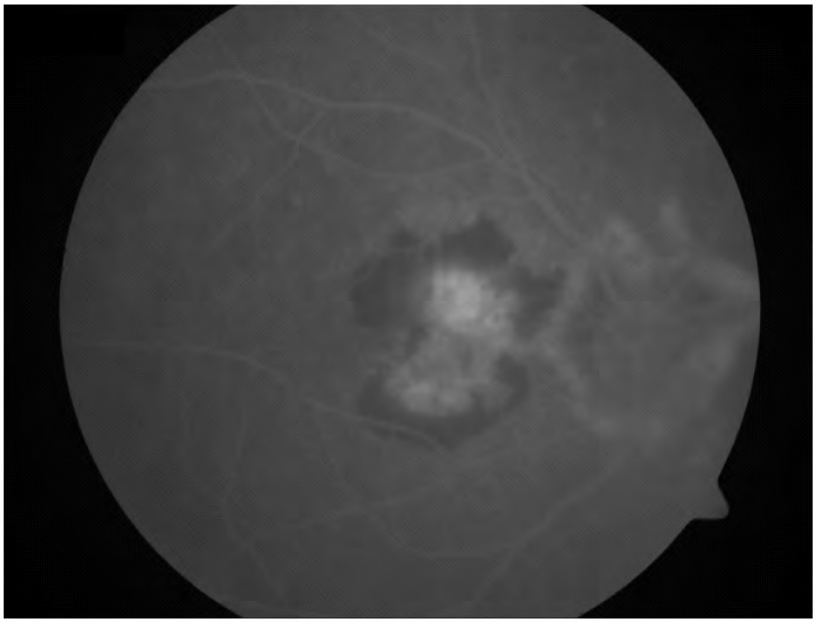


Fig. (10). Late fluorescein angiogram of the same eye as in Fig. (**9**), showing leakage of fluorescein secondary to CNV, surrounded by blockage secondary to hemorrhage.

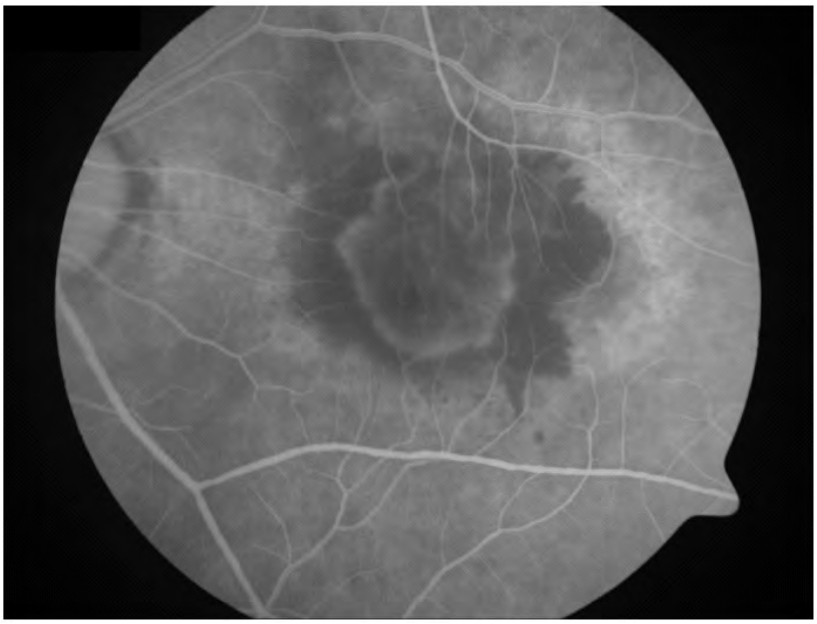


Fig. (11). Fluorescein angiogram of the same eye as in Fig. (**3**), showing a large area of hyperfluorescence that involves the center of the macula, surrounded by blockage secondary to subretinal hemorrhage.

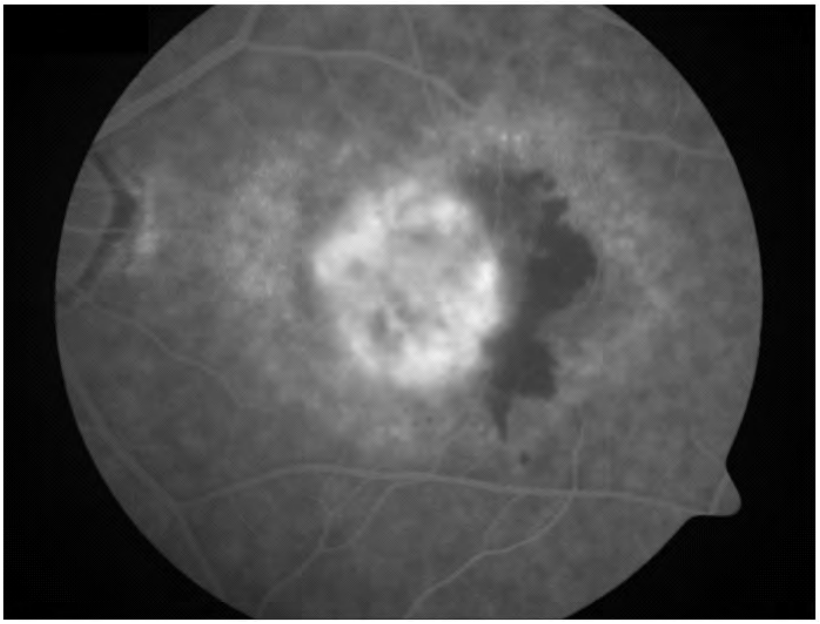


Fig. (12). Late fluorescein angiogram of the same eye as in Fig. (**11**), showing leakage of fluorescein secondary to a large subfoveal CNV.

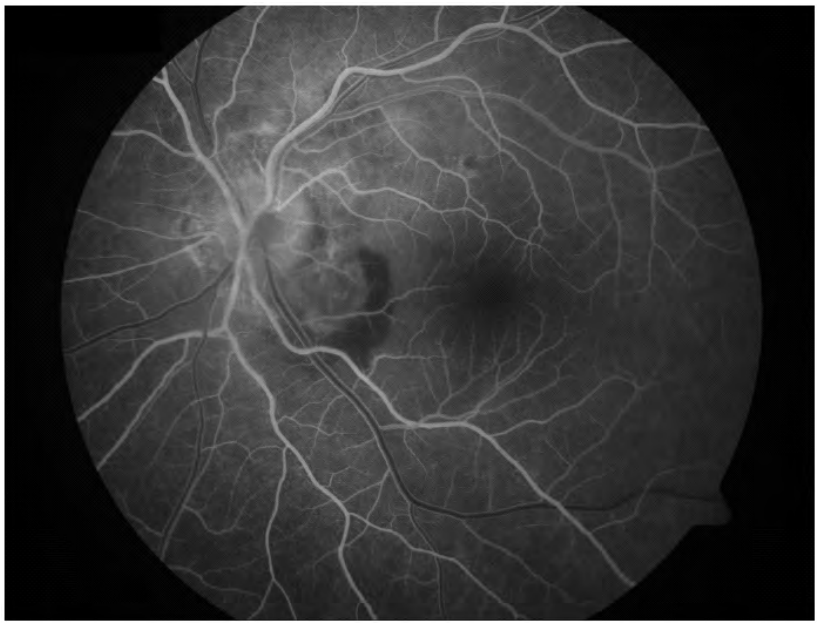


Fig. (13). Early fluorescein angiogram of the same eye as in Fig. (**4**), showing hyperfluorescence surrounding the optic disc.

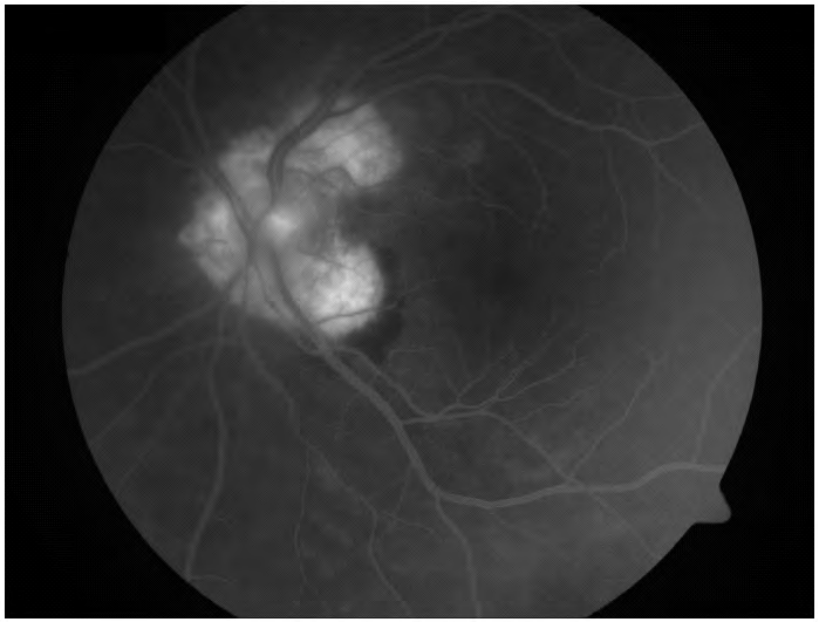


Fig. (14). Late fluorescein angiogram of the same eye as in Fig. (**13**), showing leakage of fluorescein surrounding the optic nerve.

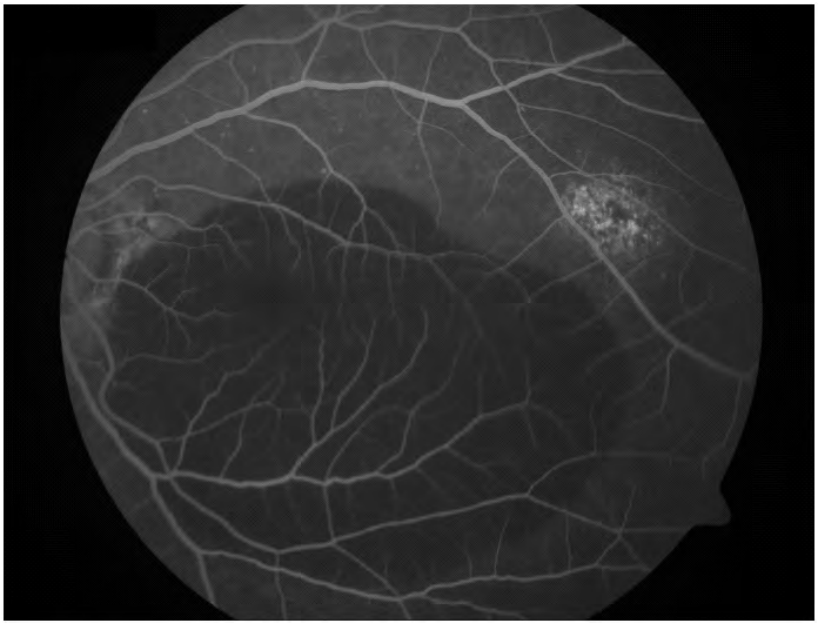


Fig. (15). Fluorescein angiogram of the same eye as in Fig. (**6**), showing a large area of blockage secondary to massive subretinal hemorrhage.

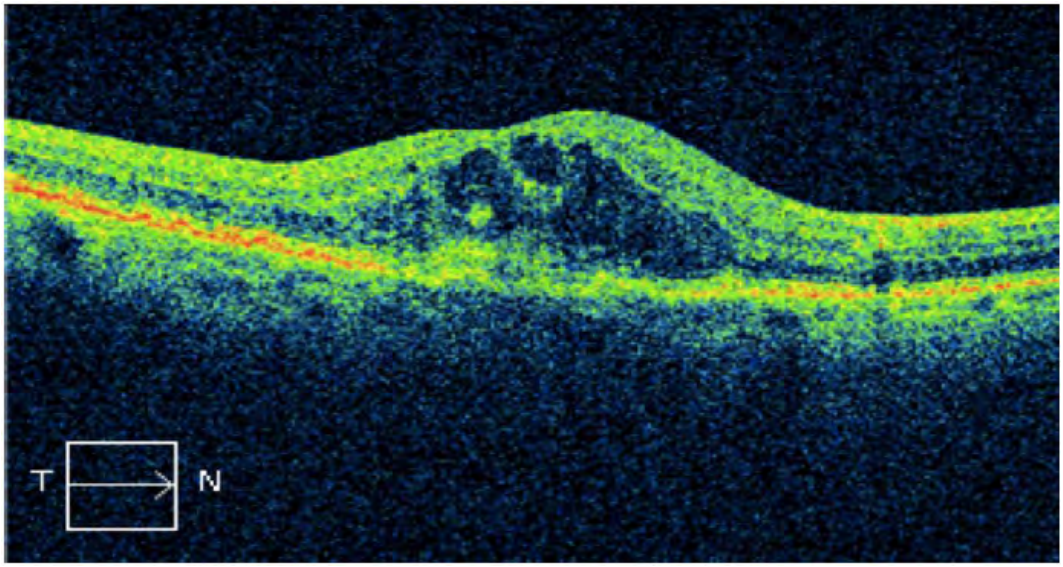


Fig. (16). OCT of the macula showing increased retinal thickness, accumulation of intraretinal fluid and the presence of a subfoveal hyper-reflective lesion corresponding to a CNV.

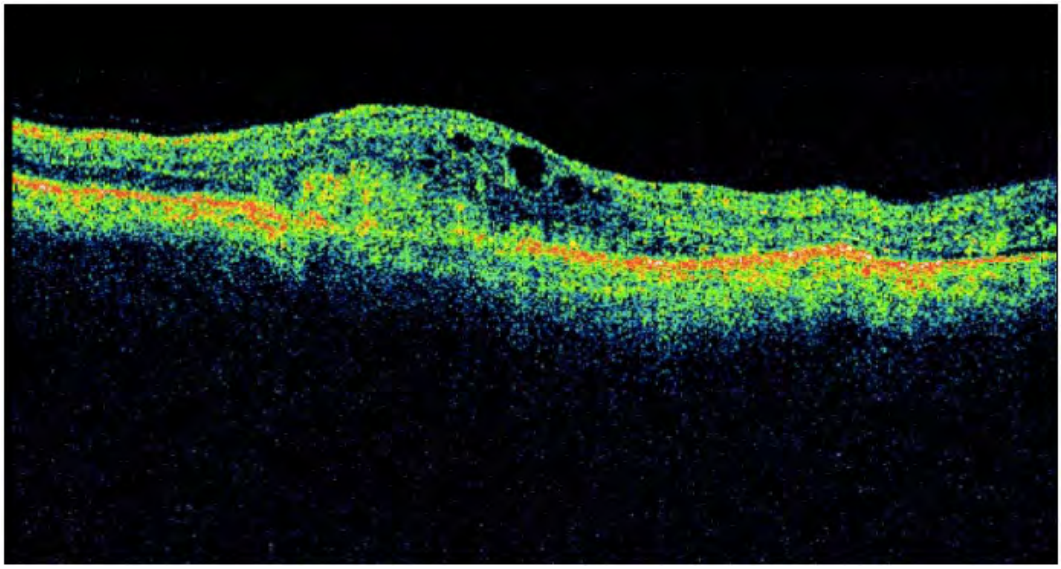


Fig. (17). OCT of the macula showing increased retinal thickness, accumulation of intraretinal fluid and the presence of an extrafoveal hyper-reflective lesion corresponding to a CNV.

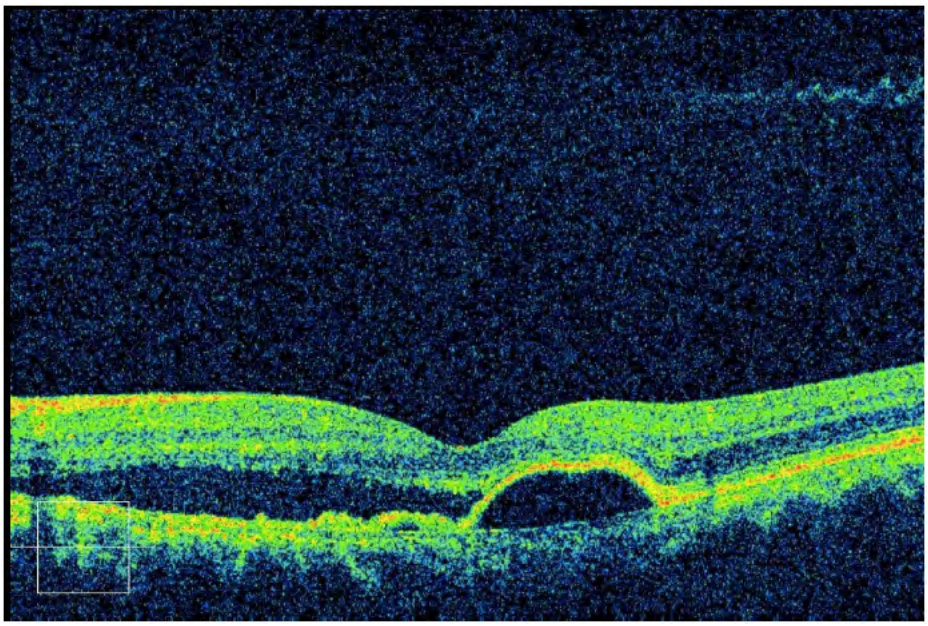


Fig. (18). OCT of the macula showing accumulation of subretinal fluid and the presence of a pigment epithelial detachment.

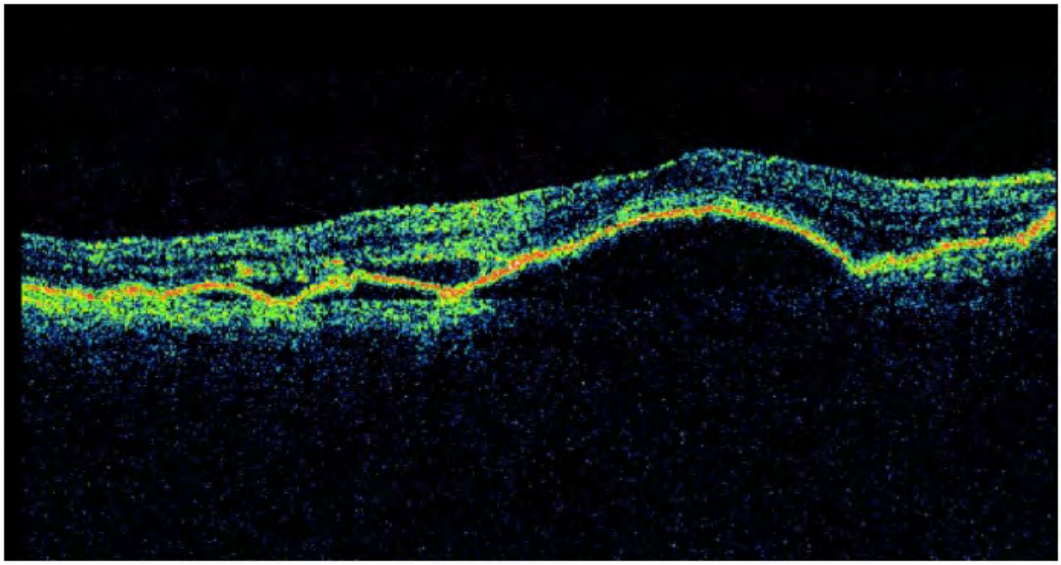


Fig. (19). OCT of the macula showing accumulation of subretinal fluid and the presence of several pigment epithelial detachments.

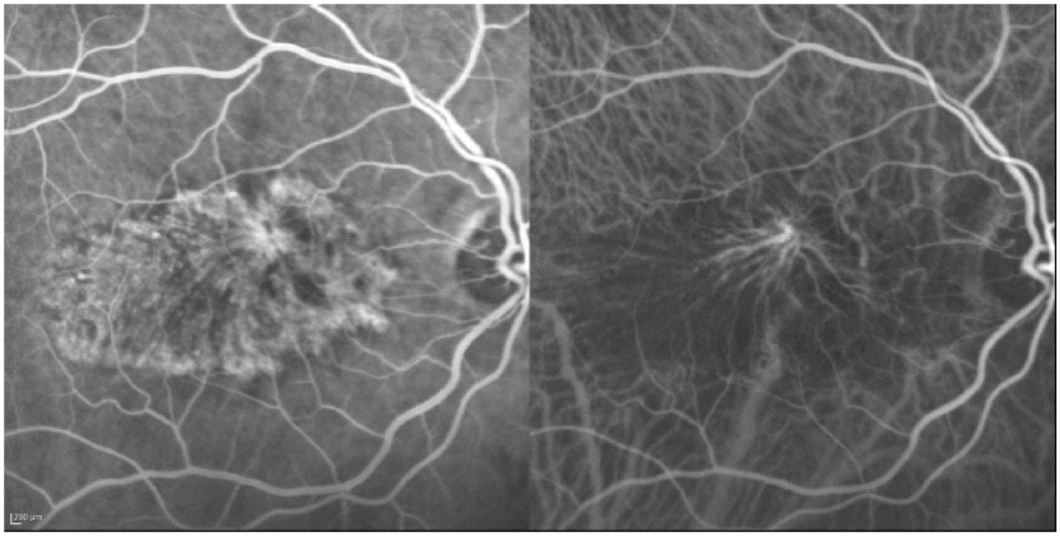


Fig. (20). Combined fluorescein-indocyanine green angiography. The image on the left corresponds to fluorescein angiography, showing diffuse hyperfluorescence in the macular area. The image on the right corresponds to indocyanine green angiography, showing thick vessels where the neovascularization originates. These are called arteriolized CNVs.

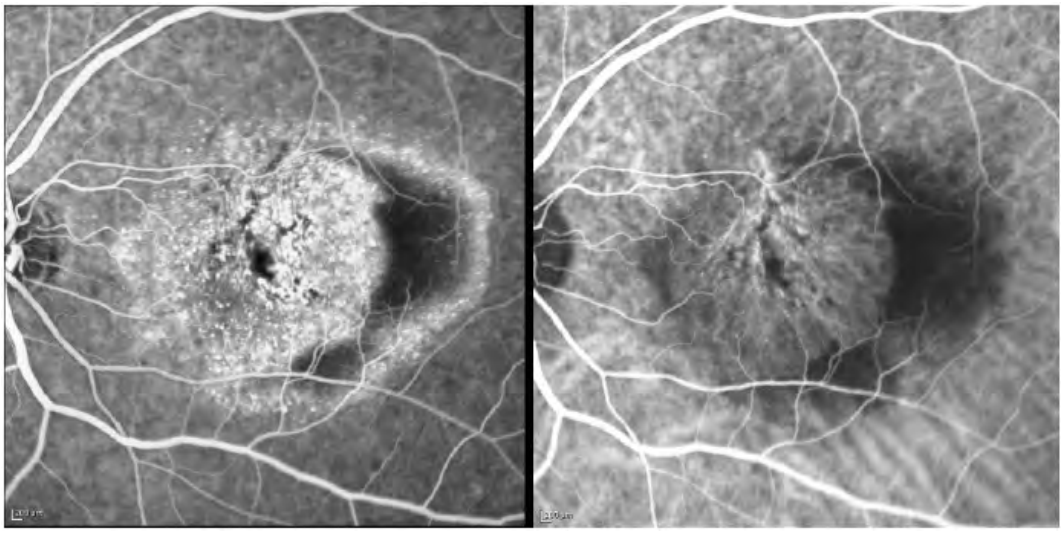


Fig. (21). Combined fluorescein-indocyanine green angiography. The image on the left corresponds to fluorescein angiography, showing diffuse hyperfluorescence in the macular area. The image on the right corresponds to indocyanine green angiography, showing thick vessels where the neovascularization originates. These are called arteriolized CNVs.

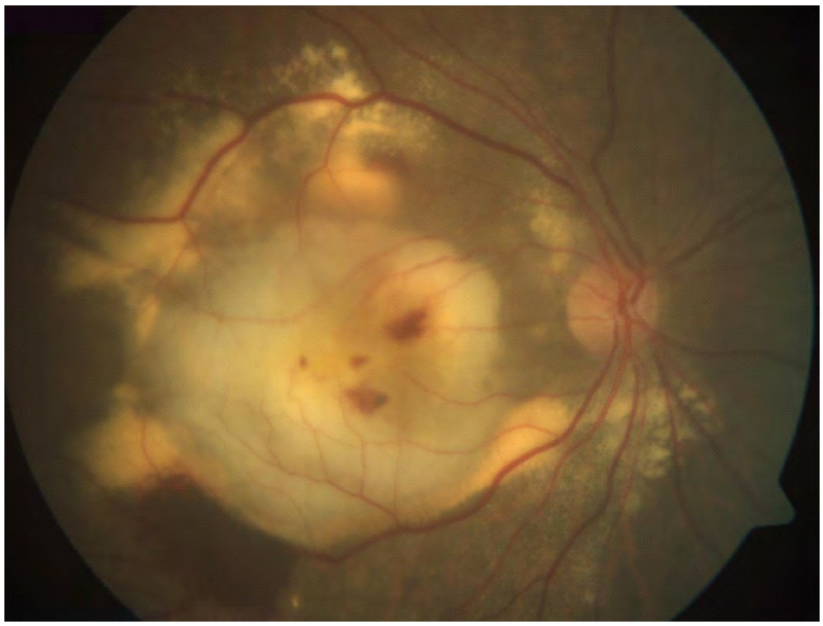


Fig. (22). Fundus photograph of the right eye showing a large area of subretinal fibrosis. Hard exudates, intraretinal and subretinal hemorrhage can also be observed.

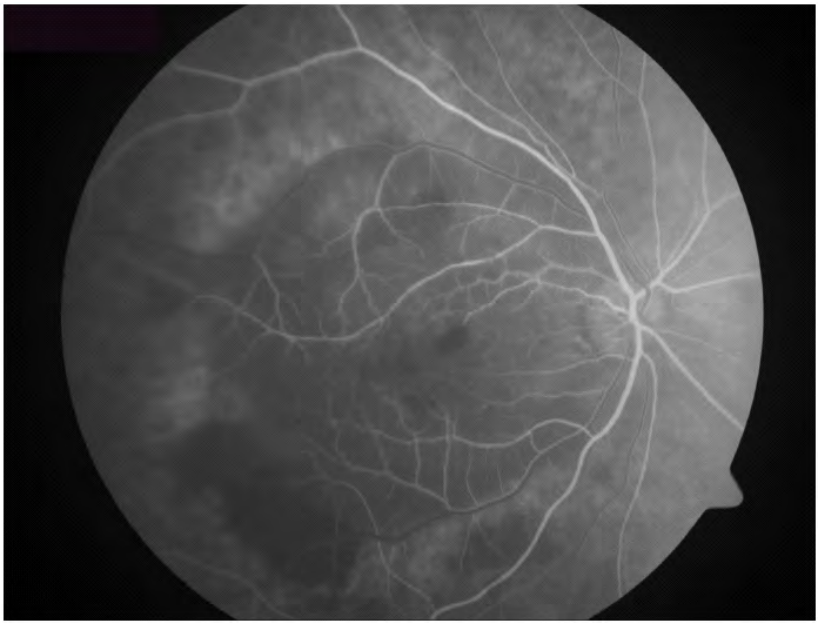


Fig. (23). Early fluorescein angiogram of the same eye as in Fig. (**22**) showing mild diffuse hyperfluorescence in the macular area.

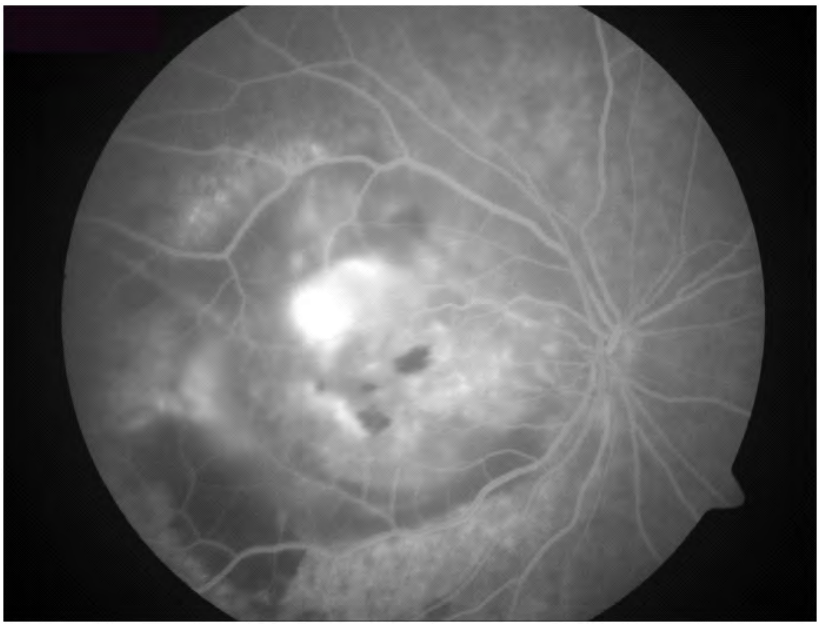


Fig. (24). Late fluorescein angiogram of the same eye as in Fig. (**23**), showing an area of intense fluorescein leakage, and some blockage secondary to hemorrhage.

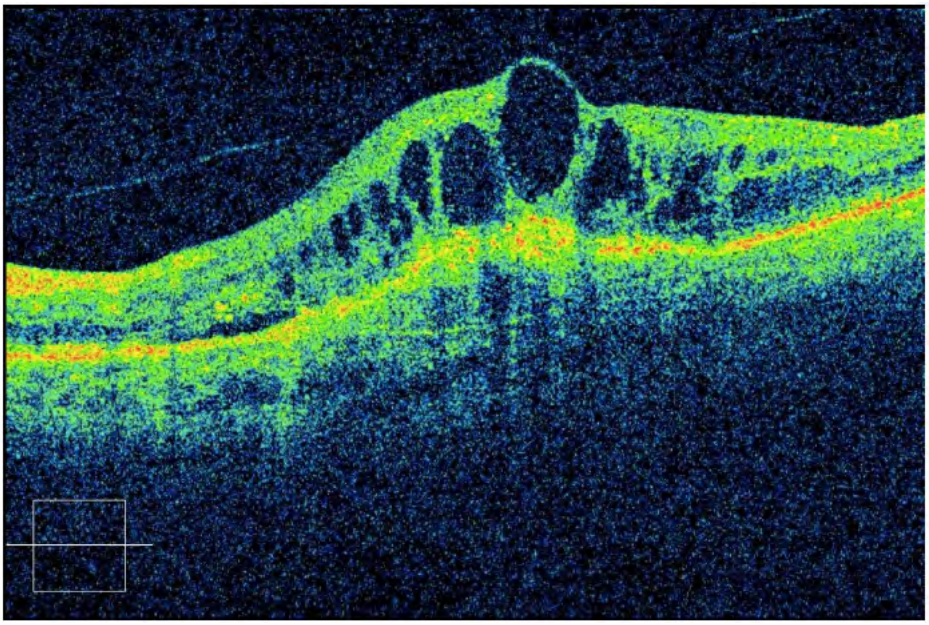


Fig. (25). OCT of a case of disciform scar, showing large quantities of intraretinal fluid, distortion of the retinal layers, and presence of a large subretinal hyper-reflective lesion corresponding to subretinal fibrosis.

DIFFERENTIAL DIAGNOSIS

When putting together the age of the patient, the clinical appearance, the presence of AMD in the contralateral eye, and the findings in FA and OCT, the diagnosis is usually straightforward. An entity that shares some of the features observed in wet AMD is central serous chorioretinopathy (CSC). It presents as subretinal fluid associated to a PED. It usually affects younger patients but may be present at any age. The presence of drusen in the same or the other eye might facilitate the differential diagnosis. Also, CSC lacks hemorrhage or hard exudates, which are relatively common in CNV.

Differential diagnosis should also be made with other causes of CNV, such as high myopia, presumed ocular histoplasmosis syndrome or idiopathic.

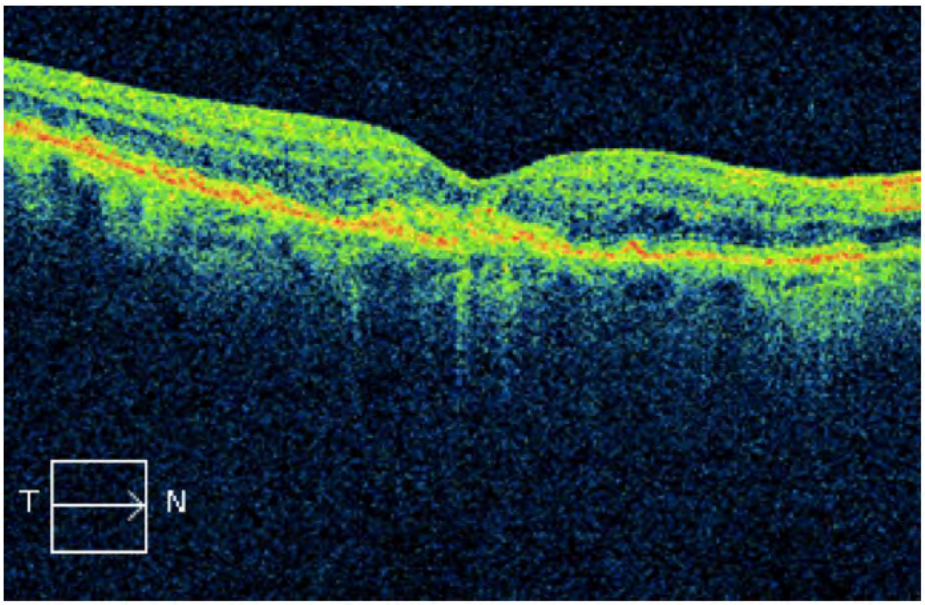


Fig. (26). OCT of the same eye as in Fig. (**16**) after intravitreal anti-VEGF therapy, showing decreased retinal thickness, recovery of foveal contour and improvement of intraretinal fluid. Some hyper-reflective tissue is still observed in the subfoveal area.

MANAGEMENT

The gold standard for the management of CNV secondary to AMD is the injection of intravitreal anti-VEGF agents. Available agents are aflibercept [7],

bevacizumab [8, 9] and ranibizumab [8 - 10], which are injected on a monthly basis until intraretinal and/or subretinal fluid disappears. Injection of these agents usually results in the arrest of disease progression and improved visual acuity (Figs. **26**-**28**).

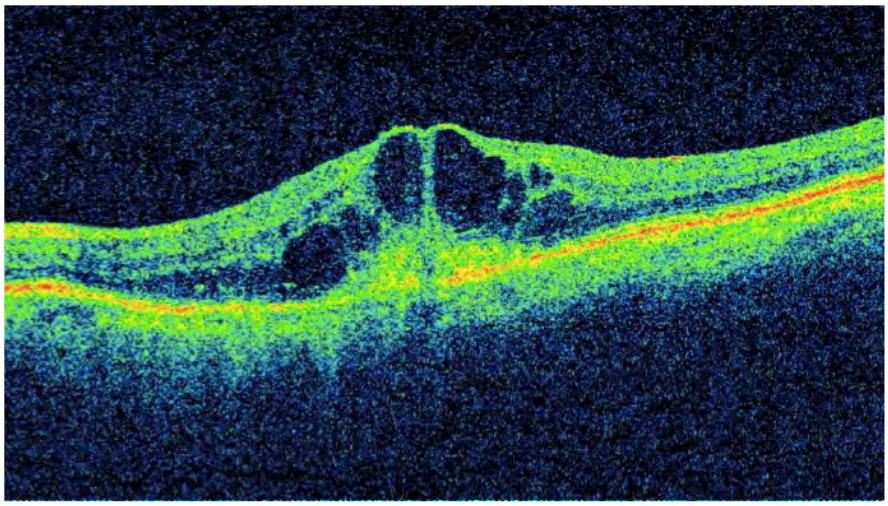


Fig. (27). OCT showing loss of foveal depression, increased retinal thickness, presence of intraretinal fluid, and the presence of a hyper-reflective lesion under the fovea.

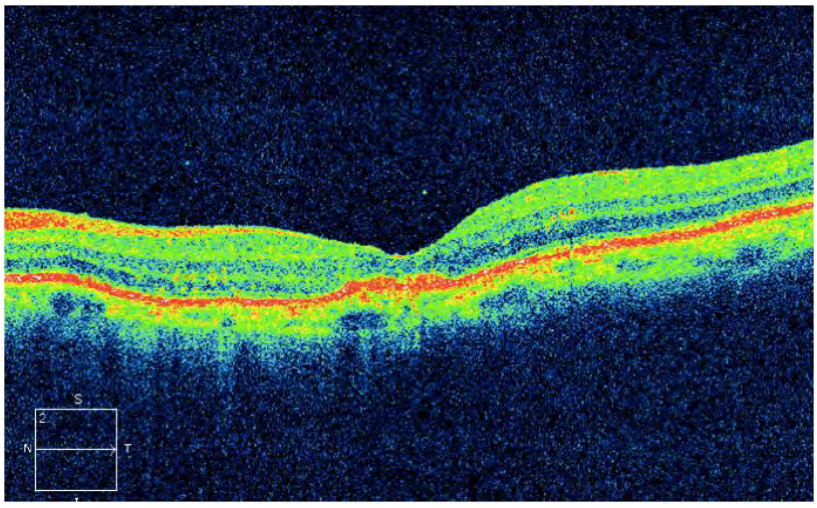


Fig. (28). OCT of the same eye as in Fig. (**27**) after intravitreal anti-VEGF therapy, showing decreased retinal thickness, recovery of foveal contour and improvement of intraretinal fluid. Some hyper-reflective tissue is still observed in the subfoveal area. The retina in the foveal area is thinner than normal.

Other treatments include laser photocoagulation, which is reserved for cases in which the CNV is located outside the macula [11], and photodynamic therapy with verteporfin, which is sometimes used as an adjuvant to anti-VEGF therapy in non-responder cases [12].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bird AC, Bressler NM, Bressler SB, *et al.* An international classification and grading system for age-related maculopathy and age-related macular degeneration. Surv Ophthalmol 1995; 39(5): 367-74. [http://dx.doi.org/10.1016/S0039-6257(05)80092-X] [PMID: 7604360]

[2] Friedman DS, Katz J, Bressler NM, Rahmani B, Tielsch JM. Racial differences in the prevalence of age-related macular degeneration: the Baltimore Eye Survey. Ophthalmology 1999; 106(6): 1049-55. [http://dx.doi.org/10.1016/S0161-6420(99)90267-1] [PMID: 10366070]

[3] Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. Eye (Lond) 2005; 19(9): 935-44. [http://dx.doi.org/10.1038/sj.eye.6701978] [PMID: 16151432]

[4] Klein R, Lee KE, Gangnon RE, Klein BE. Relation of smoking, drinking, and physical activity to changes in vision over a 20-year period: the Beaver Dam Eye Study. Ophthalmology 2014; 121: 1220-8. [http://dx.doi.org/10.1016/j.ophtha.2014.01.003] [PMID: 24594095]

[5] Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992; 99: 933-43.

[6] Friedman DS, O'Colmain BJ, Muñoz B, *et al.* Eye diseases prevalence research group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004; 122: 564-72.

[7] Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, *et al.* Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014; 121(1): 193-201. [http://dx.doi.org/10.1016/j.ophtha.2013.08.011] [PMID: 24084500]

[8] Martin DF, Maguire MG, Fine SL, *et al.* Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012; 119(7): 1388-98. [http://dx.doi.org/10.1016/j.ophtha.2012.03.053] [PMID: 22555112]

[9] Chakravarthy U, Harding SP, Rogers CA, *et al.* Ranibizumab *versus* bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology

2012; 119(7): 1399-411.
[http://dx.doi.org/10.1016/j.ophtha.2012.04.015] [PMID: 22578446]

[10] Rosenfeld PJ, Brown DM, Heier JS, *et al.* Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006; 355(14): 1419-31.
[http://dx.doi.org/10.1056/NEJMoa054481] [PMID: 17021318]

[11] Ladas ID, Chatziralli IP, Kotsolis AI, *et al.* Intravitreal ranibizumab *versus* thermal laser photocoagulation in the treatment of extrafoveal classic choroidal neovascularization secondary to age-related macular degeneration. Ophthalmologica 2012; 228(2): 93-101.
[http://dx.doi.org/10.1159/000337347] [PMID: 22571933]

[12] Tozer K, Roller AB, Chong LP, *et al.* Combination therapy for neovascular age-related macular degeneration refractory to anti-vascular endothelial growth factor agents. Ophthalmology 2013; 120(10): 2029-34.
[http://dx.doi.org/10.1016/j.ophtha.2013.03.016] [PMID: 23714319]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 16

Polypoidal Choroidal Vasculopathy

Jans Fromow Guerra*

Retina Department, Asociación para Evitar la Ceguera en México, IAP, México City, México

ESSENTIALS OF DIAGNOSIS

Polypoidal choroidal vasculopathy (PCV) is a retinal disorder involving the choroidal vasculature characterized by the presence of aneurysmal polypoidal dilations that commonly arise from a network of branching choroidal vessels, that was described in 1982 by Lawrence Yanuzzi. PCV usually shows a broad spectrum of manifestations both clinically and epidemiologically. For this reason, it has been widely debated whether to consider it a subtype of neovascular age-related macular degeneration (AMD) or a separate clinical entity. Some of the characteristics of PCV are shared by AMD but some others are radically different.

Epidemiology Essentials of PCV

- PCV predominantly occurs at a mean age of 68.4 years with a range of 21-93 years [1 - 3].
- PCV is more prevalent in non-Caucasians, such as Asians and African-Americans where it has been reported to be responsible up to 23-54.7% of wet AMD cases in these populations [4]. However, in Caucasians the prevalence of this disease has been reported in about 8-13% [5].
- PCV is more prevalent in females than in males in Caucasian (female 52% to 65%) populations and the opposite in Asians (men 63% to 78%) [2].

* **Corresponding author Jans Fromow Guerra:** Retina Department, Asociación para Evitar la Ceguera en México, IAP, Vicente García Torres, 46. San Lucas Coyoacán, México DF. México 04030; Tel: +52.55.10841400; Fax: +52.55.10841404; E-mail: fromow@me.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

Clinical Essentials of PCV

- Localization: PCV can present in different regions: peripapillary, macular or extramacular. Prevalence of each one of these presentations varies according to different ethnic groups [6]. Different reports state that unilateral disease can be found in up to 79.4% to 91.8% of cases [6 - 8].
- Clinical appearance: Clinical examination will reveal orange-reddish colored vascular dilatations often associated to pigment epithelial detachments (PED), subretinal hemorrhage, hard exudates and drusen (Fig. **1**).

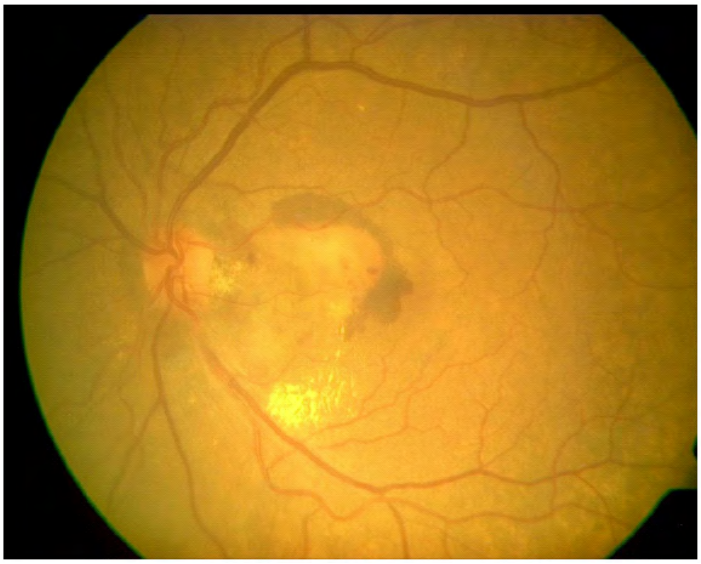


Fig. (1). Clinical appearance of peripapillary PCV.

- Angiographic & OCT Analysis (Figs. **2**-**6**): Indocyanine green angiography (ICGA) should be considered as the gold standard in PCV diagnosis since findings in FA can be easily mistaken for wet AMD especially in elderly patients with drusen and bilateral disease [8, 9]. ICGA will often reveal single or multiple polyps appearing as vascular aneurysmal dilatations arising from inner choroidal vessels often seen as a neovascular plaque or a so-called “branching vascular networks” (BVN). These findings are usually seen within the first 6 minutes after the injection of ICG [10]. However, PCV lesions may not be easily seen due to minor or extensive hemorrhage. A classification of PCV has been developed regarding the presence or absence of BVN determined by ICGA:

Type I PCV or "Polypoidal CNV" with an apparent BVN and type 2 PCV or "Typical PCV" with no or faint BVN. These 2 different PCV subtypes have distinct clinical course, treatment response and genetic background [11 - 13]. OCT shows important diagnostic characteristics (Figs. **2**, **3** and **6**). In most cases a sharp elevated PED is observed, that may be associated to a flat, shallower PED. Polypoidal lesions are usually attached to the back surface of the elevated PED. In type I PCV the flat shallower PED is associated with the BVN giving a "double layer sign" [14].

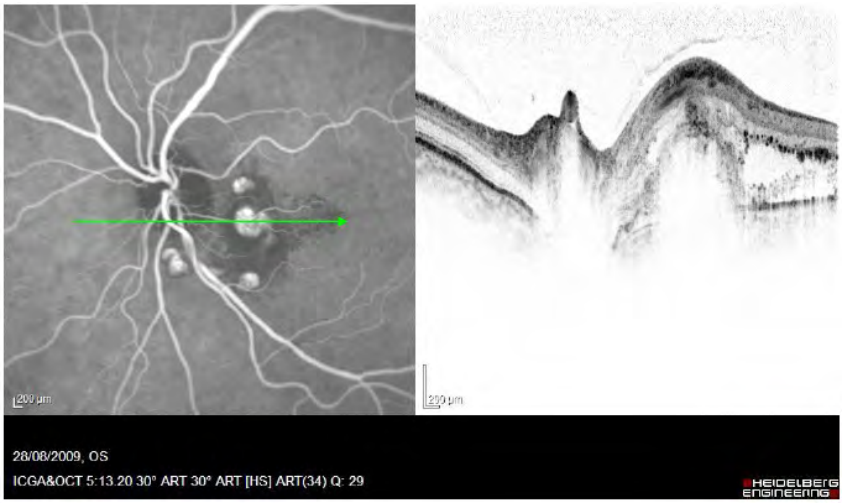


Fig. (2). ICGA and OCT appearance of peripapillary PCV of the same patient as Fig. (**1**).

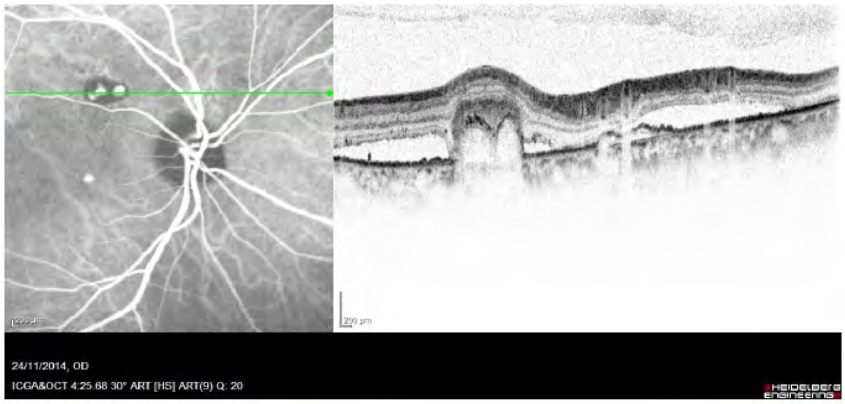


Fig. (3). Left: ICG-Macular Type 2 PCV with no or faint branching vascular network. Right. OCT image where an associated PED can be clearly observed.

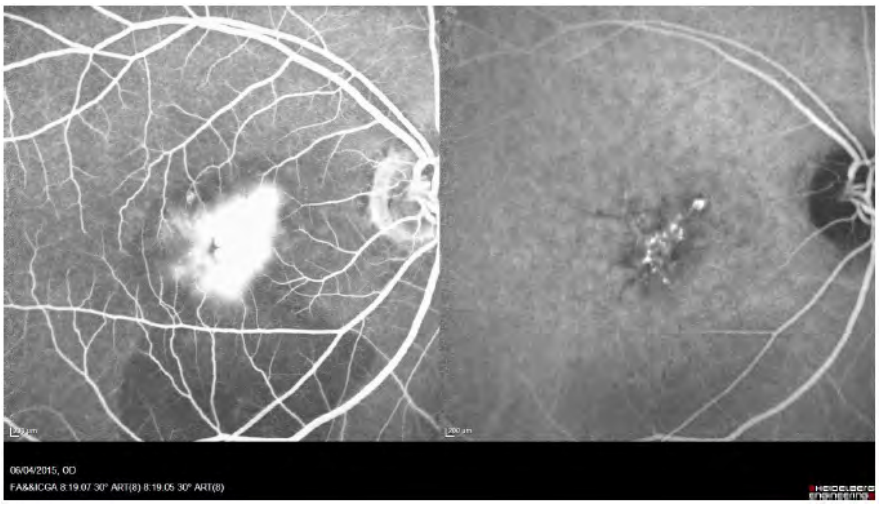


Fig. (4). Left: Fluorescein Angiogram, Right: ICG-Angiogram. This comparison clearly shows the advantage of ICGA in the diagnosis of PCV, that clearly delineates the lesions, which cannot be distinguished in FA. Macular Type 1 PCV with apparent branching vascular network from which the polyps arise.

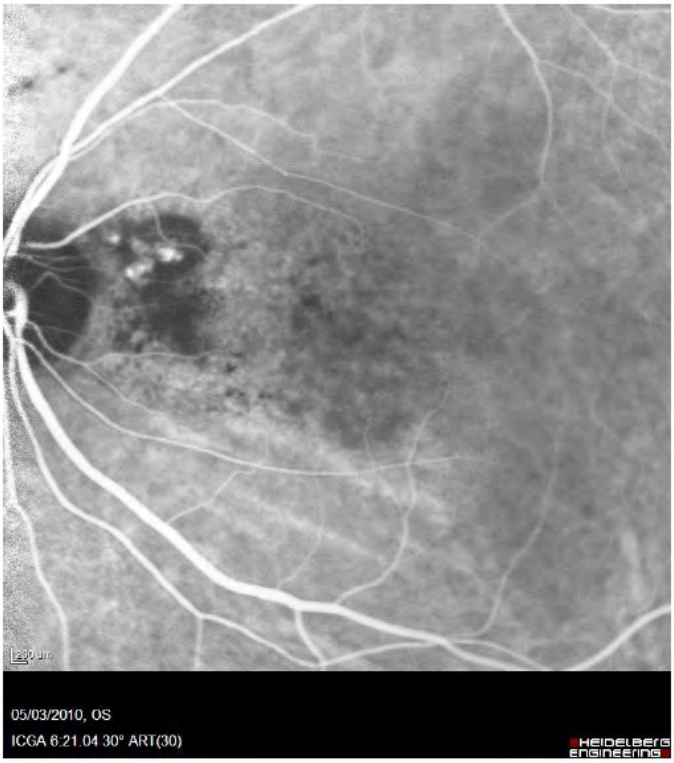


Fig. (5). ICGA of peripapillary Type 2 PCV with no apparent BVN.

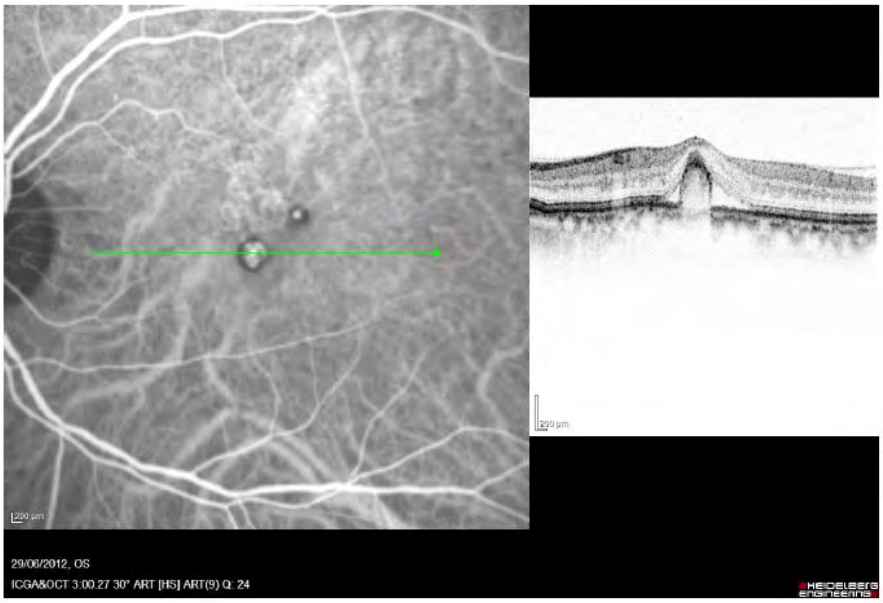


Fig. (6). Left: ICGA. Macular Type 1 PCV with apparent branching vascular network from which the polyps arise. Right: OCT showing a polyp PED.

DIFFERENTIAL DIAGNOSIS

There are two main clinical entities that should be considered first in the differential diagnosis of PCV: "Regular" wet AMD, especially if there is a chronic neovascular process with insufficient anti-VEGF treatment response, and central serous chorioretinopathy (CSC), which in fact shares similar characteristics including increased choroidal thickness. Furthermore, CSC has been regarded as a risk factor for PCV [14, 15].

MANAGEMENT

There are several trials that show the efficacy of Anti-VEGF treatment for PCV. Also, since 2002 the efficacy of Photodynamic Therapy with verteporfin for this entity has been proven, and some others promote a combination approach [8, 16, 17]. To give scientific solution to this question, a multicenter, double-masked trial known as EVEREST compared these three treatment regimens. The six-month results revealed that PDT plus ranibizumab therapy and PDT monotherapy were both superior to ranibizumab monotherapy in achieving complete polyp

regression (77.8 percent and 71.4 percent *vs.* 28.6 percent, respectively; $p < 0.01$) [18]. Ongoing studies are evaluating other Anti-VEGF options such as aflibercept.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bessho H, Honda S, Imai H, Negi A. Natural course and funduscopic findings of polypoidal choroidal vasculopathy in a Japanese population over 1 year of follow-up. Retina 2011; 31(8): 1598-602. [http://dx.doi.org/10.1097/IAE.0b013e31820d3f28] [PMID: 21478804]

[2] Imamura Y, Engelbert M, Iida T, Freund KB, Yannuzzi LA. Polypoidal choroidal vasculopathy: a review. Surv Ophthalmol 2010; 55(6): 501-15. [http://dx.doi.org/10.1016/j.survophthal.2010.03.004] [PMID: 20850857]

[3] Al-Rashaed S. Idiopathic polypoidal choroidal vasculopathy in a young man: case report and literature review. Middle East Afr J Ophthalmol 2008; 15(2): 90-3. [http://dx.doi.org/10.4103/0974-9233.52000] [PMID: 21346845]

[4] Sho K, Takahashi K, Yamada H, *et al.* Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. Arch Ophthalmol 2003; 121(10): 1392-6. [http://dx.doi.org/10.1001/archopht.121.10.1392] [PMID: 14557174]

[5] Ciardella AP, Donsoff IM, Huang SJ, Costa DL, Yannuzzi LA. Polypoidal choroidal vasculopathy. Surv Ophthalmol 2004; 49(1): 25-37. [http://dx.doi.org/10.1016/j.survophthal.2003.10.007] [PMID: 14711438]

[6] Hou J, Tao Y, Li XX, Zhao MW. Clinical characteristics of polypoidal choroidal vasculopathy in Chinese patients. Graefe's archive for clinical and experimental ophthalmology. Albrecht Von Graefes Arch Klin Exp Ophthalmol 2011; 249(7): 975-9. [http://dx.doi.org/10.1007/s00417-010-1575-7]

[7] Chang YC, Wu WC. Polypoidal choroidal vasculopathy in Taiwanese patients. Ophthalmic Surg Lasers Imaging 2009; 40(6): 576-81. [http://dx.doi.org/10.3928/15428877-20091030-07] [PMID: 19928723]

[8] Cho M, Barbazetto IA, Freund KB. Refractory neovascular age-related macular degeneration secondary to polypoidal choroidal vasculopathy. Am J Ophthalmol 2009; 148(1): 70-8 e1. [http://dx.doi.org/10.1016/j.ajo.2009.02.012]

[9] Stangos AN, Gandhi JS, Nair-Sahni J, Heimann H, Pournaras CJ, Harding SP. Polypoidal choroidal vasculopathy masquerading as neovascular age-related macular degeneration refractory to ranibizumab. Am J Ophthalmol 2010; 150(5): 666-73.

[http://dx.doi.org/10.1016/j.ajo.2010.05.035] [PMID: 20719300]

[10] Koh AH, Chen LJ, Chen SJ, *et al.* Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. Retina 2013; 33(4): 686-716.
[http://dx.doi.org/10.1097/IAE.0b013e3182852446] [PMID: 23455233]

[11] Kawamura A, Yuzawa M, Mori R, Haruyama M, Tanaka K. Indocyanine green angiographic and optical coherence tomographic findings support classification of polypoidal choroidal vasculopathy into two types. Acta Ophthalmol 2013; 91(6): e474-81.
[http://dx.doi.org/10.1111/aos.12110] [PMID: 23848133]

[12] Tanaka K, Nakayama T, Mori R, *et al.* Associations of complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) genotypes with subtypes of polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci 2011; 52(10): 7441-4.
[http://dx.doi.org/10.1167/iovs.11-7546] [PMID: 21896867]

[13] Miki A, Honda S, Kondo N, Negi A. The association of age-related maculopathy susceptibility 2 (ARMS2) and complement factor H (CFH) variants with two angiographic subtypes of polypoidal choroidal vasculopathy. Ophthalmic Genet 2013; 34(3): 146-50.
[http://dx.doi.org/10.3109/13816810.2012.749288] [PMID: 23289808]

[14] Yang LH, Jonas JB, Wei WB. Optical coherence tomographic enhanced depth imaging of polypoidal choroidal vasculopathy. Retina 2013; 33(8): 1584-9.
[http://dx.doi.org/10.1097/IAE.0b013e318285cbb3] [PMID: 23584691]

[15] Kim SW, Oh J, Kwon SS, Yoo J, Huh K. Comparison of choroidal thickness among patients with healthy eyes, early age-related maculopathy, neovascular age-related macular degeneration, central serous chorioretinopathy, and polypoidal choroidal vasculopathy. Retina 2011; 31(9): 1904-11.
[http://dx.doi.org/10.1097/IAE.0b013e31821801c5] [PMID: 21878855]

[16] Shima C, Gomi F, Sawa M, Sakaguchi H, Tsujikawa M, Tano Y. One-year results of combined photodynamic therapy and intravitreal bevacizumab injection for retinal pigment epithelial detachment secondary to age-related macular degeneration. Graefe's archive for clinical and experimental ophthalmology =. Albrecht Von Graefes Arch Klin Exp Ophthalmol 2009; 247(7): 899-906.
[http://dx.doi.org/10.1007/s00417-009-1067-9]

[17] Song JH, Byeon SH, Lee SC, Koh HJ, Kwon OW. Short-term safety and efficacy of a single intravitreal bevacizumab injection for the management of polypoidal choroidal vasculopathy. Ophthalmologica 2009; 223(2): 85-92.
[http://dx.doi.org/10.1159/000175312] [PMID: 19023226]

[18] Koh A, Lee WK, Chen LJ, *et al.* EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone *versus* ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. Retina 2012; 32(8): 1453-64.
[http://dx.doi.org/10.1097/IAE.0b013e31824f91e8] [PMID: 22426346]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 17

Retinal Angiomatous Proliferation (RAP)

Maximiliano Gordon[1,2,*] and **Guillermo Gordon**[†]

[1] *Centro de la Visión Gordon-Manavella, Rosario, Santa Fe, Argentina*

[2] *Retina Department, Ophthalmology Service, Hospital Provincial del Centenario, Rosario, Santa Fe, Argentina*

Retinal Angiomatous Proliferation (RAP), or type 3 neovascularization, is a different form of exudative age-related macular degeneration (AMD) [1]. Its main characteristic is an abnormal anastomosis between the choroidal and the retinal vessels. The pathogenesis of this entity remains controversial [2 - 4]. Yannuzzi *et al.* believe that the neovascular process originates within the neurosensory retina. In contrast, Gass proposed that the process begins with choroidal neovascularization (CNV) [1].

Gass' classification scheme is based on neovascularization relationship to the retinal pigment epithelium (RPE). Type 1 neovascularization describes new blood vessels growing under the RPE, while in Type 2 neovascularization these proliferate over the RPE. Freund has proposed modifying Gass' original classification by adding Type 3 neovascularization, which refers to a type of neovascularization with preference for the retina [1].

ESSENTIALS OF DIAGNOSIS

Symptoms are similar to those of AMD. However, patients with RAP tend to be older. The classical findings include retinal and preretinal hemorrhages, and pigment epithelial detachments, as well as small and multiple intraretinal blood [5].

[*] **Corresponding author Maximiliano Gordon:** Centro de la Visión Gordon - Manavella, Montevideo 763, CP 2000, Rosario - Santa Fe, Argentina; Tel/Fax: +54(341)4400239/4244850; E-mail: maximilianogordon19@gmail.com

[†] Died

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

RAP classification distinguishes three vasogenic stages based on the nature and progression of the neovascularization process. Stage I involves capillary proliferation within the retina originating from the deep retinal plexus (intraretinal neovascularization [IRN]). Stage II is determined by IRN extending into the subretinal space (subretinal neovascularization [SRN]). Stage III describes progression to CNV, that can be clearly determined clinically or angiographically. This stage is sometimes characterized by a vascularized pigment epithelial detachment and retinal choroidal anastomosis (RCA) [6]. Stage-I RAP lesions manifest with intraretinal neovascularization with telangiectatic retinal capillaries and small angiomatous structures perfused by the retinal circulation. Stage-II RAP lesions extend beyond the photoreceptor layer into the subretinal space resulting in subretinal neovascularization. A serous PED is often seen. In stage-III RAP, it is presumed that an RCA is formed. Patients that are not treated for stage-III RAP lesions can develop large fibrotic scars [7]. In these cases, fluorescein angiography revealed poorly defined staining that simulates occult CNV (Figs. **1** and **3**).

Indocyanine green angiography (Fig. **3**) often helps make an accurate diagnosis. It revealed a focal area of hyperfluorescence corresponding to the neovascularization ("hot spot"). OCT may reveal intraretinal hyperreflectivity, corresponding to angiomatous proliferation associated with intraretinal or subretinal fluid (Figs. **2** and **4**) and/or RPE detachment [6]. Dilated fundus exam showed hemorrhages and lipid exudates in an area of occult CNV on the basis of fluorescein angiography and indocyanine green angiography (ICG) revealed the presence of a hot spot. These findings led to the diagnosis of RAP [6, 7].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should include other forms of CNV with ICG hot spots (occult CNV) and polypoidal choroidal vasculopathy (PCV). This latter disease presents with normally larger retinal hemorrhages and round reddish-orange macular lesions in the eye fundus. OCT is also a helpful tool in differentiating RAP, PCV, and occult membranes. In PCV, polyps appear in OCT as abrupt neurosensory detachment. Other differential diagnosis is macular telangiectasia.

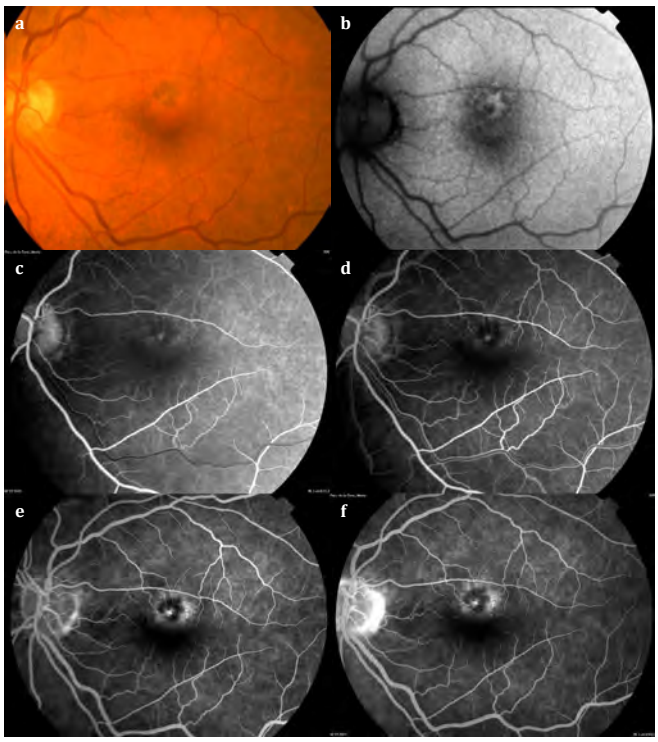


Fig. (1). A 73-year-old woman with retinal angiomatous proliferation. Fundus photograph and autofluorescence revealing perifoveal lesion (**a** and **b**). Fluorescein angiogram showing hyperfluorescence with diffuse leakage of dye (**c-f**) (Courtesy of Alejandro Lavaque, Argentina).

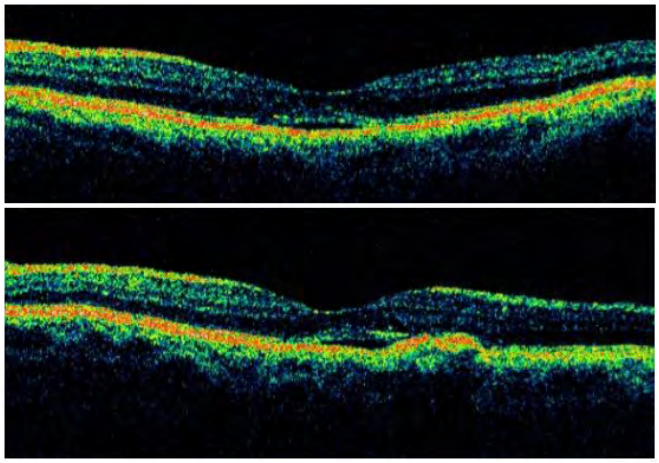


Fig. (2). OCT of the same patient shown in Fig. (**1**). OCT scans showing subretinal fluid and hyperreflective subretinal lesion (Courtesy of Alejandro Lavaque, Argentina).

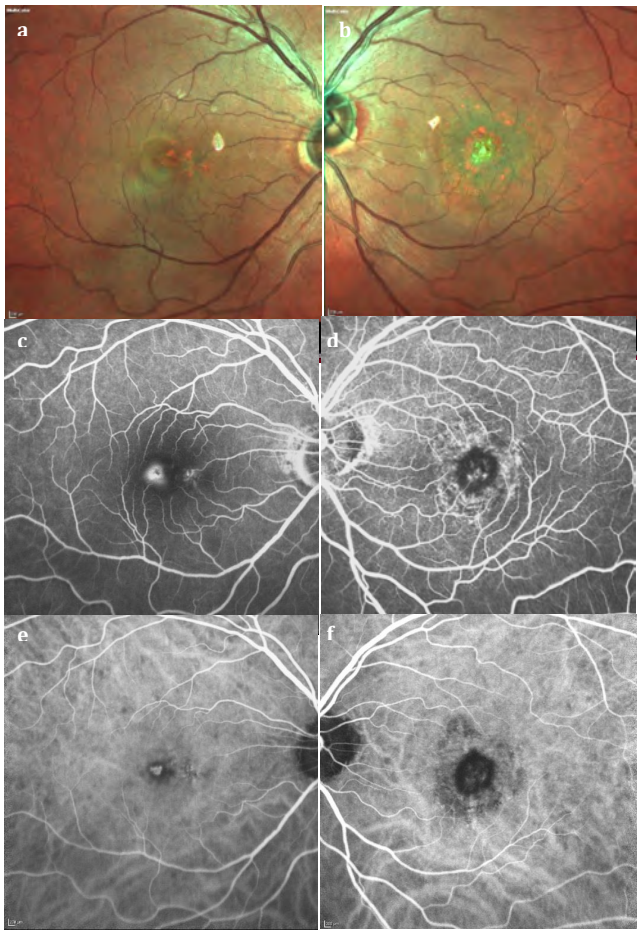


Fig. (3). Fundus photograph (**a-b**), fluorescein angiography (**c-d**) and ICG (**e-f**) of patient with retinal angiomatous proliferation (Courtesy of Gerardo Garcia Aguirre, Mexico).

The main differences are telangiectasias not associated with serous PED, a healthier RPE and less frequent choroidal neovascularization associated with parafoveal telangiectasias [8, 9].

MANAGEMENT

Some treatment options for RAP lesions have been thermal laser photocoagulation, surgical ablation, PDT, intravitreal triamcinolone, intravitreal antiangiogenic drugs and combined treatments.

Fig. (4). OCT of the same patient shown in Fig. (**3**). OCT scans showing intraretinal fluid and hyperreflective subretinal lesion. (Courtesy of Gerardo Garcia Aguirre).

Apparently, traditional thermal laser photocoagulation is an effective treatment for some stage-I and early stage-II RAP lesions outside the fovea. However, when RAP exists in association with a PED, the effectiveness of most treatments is deeply affected.

According to short-term results reported on non-randomized studies, RAP lesions treated with photodynamic therapy (PDT) and intravitreal triamcinolone acetate (IVTA) [10 - 12] revealed apparently better VA outcomes and/or a reduced number of treatment sessions in comparison with PDT alone. However, there was also a high frequency of recurrence [13, 14]. Krebs I. *et al.* [15] found minimal differences between the PDT monotherapy group and the combined PDT and IVTA group regarding progress of distance VA, retinal thickness and lesion size, and he concluded that new therapeutic strategies might be necessary to address RAP lesions, probably including therapy with antiangiogenic drugs. As is the case

with classic and occult lesions, intravitreal injection of antiangiogenic agents seems to be more effective in the treatment of RAP lesions than PDT alone.

Short-term experience with intravitreal injection of anti-vascular endothelial growth factor (VEGF) in RAP has only been reported in some uncontrolled studies [16, 17], which showed favorable outcomes; however, frequent intravitreal injections are expected [18 - 21].

Another treatment option consists of surgical excision of the feeder artery and vein by means of diathermy technique, if appropriate, for stage-II RAP lesions with or without serous PED [22]. Future treatments include a combined therapeutic approach to the management of RAP lesions.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Scott AW, Bressler SB. Retinal angiomatous proliferation or retinal anastomosis to the lesion. Eye (Lond) 2010; 24(3): 491-6.
[http://dx.doi.org/10.1038/eye.2009.311] [PMID: 20019765]

[2] Hartnett ME, Weiter JJ, Garsd A, Jalkh AE. Classification of retinal pigment epithelial detachments associated with drusen. Graefes Arch Clin Exp Ophthalmol 1992; 230(1): 11-9.
[http://dx.doi.org/10.1007/BF00166756] [PMID: 1547961]

[3] Kuhn D, Meunier I, Soubrane G, Coscas G. Imaging of chorioretinal anastomoses in vascularized retinal pigment epithelium detachments. Arch Ophthalmol 1995; 113(11): 1392-8.
[http://dx.doi.org/10.1001/archopht.1995.01100110052025] [PMID: 7487600]

[4] Schneider U, Gelisken F, Kreissig I. Retinal choroidal anastomosis in classic choroidal neovascularization demonstrated by indocyanine green angiography. Acta Ophthalmol Scand 1995; 73(5): 450-2.
[http://dx.doi.org/10.1111/j.1600-0420.1995.tb00307.x] [PMID: 8751127]

[5] Yannuzzi LA. Retinal angiomatous proliferation in AMD. Review of Ophthalmol. 2003.

[6] Yannuzzi LA, Negrão S, Iida T, *et al.* Retinal angiomatous proliferation in age-related macular degeneration. Retina 2001; 21(5): 416-34.
[http://dx.doi.org/10.1097/00006982-200110000-00003] [PMID: 11642370]

[7] Koreen L, Hollar MW, Cousins SW. Where Do PCV and RAP Fit in the Spectrum of AMD CNV Subtypes? Determining lesion morphology provides for better diagnosis and treatment. Retinal Physician, Issue: October 2010.

[8] Gass JD, Oyakawa RT. Idiopathic juxtafoveolar retinal telangiectasis. Arch Ophthalmol 1982; 100(5): 769-80.
[http://dx.doi.org/10.1001/archopht.1982.01030030773010] [PMID: 7082207]

[9] Coscas G. Chorioretinal anastomoses 1994. Springer 2009.
[http://dx.doi.org/10.1007/978-3-642-01467-3_11]

[10] Sutter FK, Kurz-Levin MM, Fleischhauer J, Bösch MM, Barthelmes D, Helbig H. Macular atrophy after combined intravitreal triamcinolone acetonide (IVTA) and photodynamic therapy (PDT) for retinal angiomatous proliferation (RAP). Klin Monatsbl Augenheilkd 2006; 223(5): 376-8.
[http://dx.doi.org/10.1055/s-2006-926564] [PMID: 16705508]

[11] Mantel I, Ambresin A, Zografos L. Retinal angiomatous proliferation treated with a combination of intravitreal triamcinolone acetonide and photodynamic therapy with verteporfin. Eur J Ophthalmol 2006; 16(5): 705-10.
[PMID: 17061221]

[12] van de Moere A, Kak R, Sandhu SS, Talks SJ. Anatomical and visual outcome of retinal angiomatous proliferation treated with photodynamic therapy and intravitreal triamcinolone. Am J Ophthalmol 2007; 143(4): 701-4.
[http://dx.doi.org/10.1016/j.ajo.2006.10.045] [PMID: 17386286]

[13] Reche-Frutos J, Calvo-Gonzalez C, Donate-Lopez J, *et al.* Retinal angiomatous proliferation reactivation 6 months after high-dose intravitreal acetonide triamcinolone and photodynamic therapy. Eur J Ophthalmol 2007; 17(6): 979-82.
[PMID: 18050128]

[14] Montero JA, Ruiz-Moreno JM, Sanabria MR, Fernandez-Munoz M. Efficacy of intravitreal and periocular triamcinolone associated with photodynamic therapy for treatment of retinal angiomatous proliferation. Br J Ophthalmol 2009; 93(2): 166-70.
[http://dx.doi.org/10.1136/bjo.2008.141903] [PMID: 18971240]

[15] Krebs I, Krepler K, Stolba U, Goll A, Binder S. Retinal angiomatous proliferation: combined therapy of intravitreal triamcinolone acetonide and PDT *versus* PDT alone. Graefes Arch Clin Exp Ophthalmol 2008; 246(2): 237-43.
[http://dx.doi.org/10.1007/s00417-007-0651-0] [PMID: 17674018]

[16] Saito M, Shiragami C, Shiraga F, Nagayama D, Iida T. Combined intravitreal bevacizumab and photodynamic therapy for retinal angiomatous proliferation. Am J Ophthalmol 2008; 146: 935–941. retinal angiomatous proliferation. Graefes Arch Clin Exp Ophthalmol 2007; 245: 1597-602.
[PMID: 17437123]

[17] Lo Giudice G, Gismondi M, De Belvis V, Cian R, Tavolato M, Galan A. Single-session photodynamic therapy combined with intravitreal bevacizumab for retinal angiomatous proliferation. Retina 2009; 29(7): 949-55.
[http://dx.doi.org/10.1097/IAE.0b013e3181af106d] [PMID: 19584653]

[18] Meyerle CB, Freund KB, Iturralde D, *et al.* Intravitreal bevacizumab (Avastin) for retinal angiomatous proliferation. Retina 2007; 27(4): 451-7.
[http://dx.doi.org/10.1097/IAE.0b013e318030ea80] [PMID: 17420697]

[19] Ghazi NG, Knape RM, Kirk TQ, Tiedeman JS, Conway BP. Intravitreal bevacizumab (avastin) treatment of retinal angiomatous proliferation. Retina 2008; 28(5): 689-95.
[http://dx.doi.org/10.1097/IAE.0b013e318162d982] [PMID: 18463511]

[20] Joeres S, Heussen FM, Treziak T, Bopp S, Joussen AM. Bevacizumab (Avastin) treatment in patients with retinal angiomatous proliferation. Graefes Arch Clin Exp Ophthalmol 2007; 245(11): 1597-602.
[http://dx.doi.org/10.1007/s00417-007-0580-y] [PMID: 17437123]

[21] Gharbiya M, Allievi F, Recupero V, Martini D, Mazzeo L, Gabrieli CB. Intravitreal bevacizumab as primary treatment for retinal angiomatous proliferation: twelve-month results. Retina 2009; 29(6): 740-9.
[http://dx.doi.org/10.1097/IAE.0b013e3181a0be1d] [PMID: 19516116]

[22] Borrillo JL, Sivalingam A, Martidis A, Federman JL. Surgical ablation of retinal angiomatous proliferation. Arch Ophthalmol 2003; 121(4): 558-61.
[http://dx.doi.org/10.1001/archopht.121.4.558] [PMID: 12695253]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 18

Choroidal Neovascular Membrane in Degenerative Myopia

Federico Furno Sola[1,2,*]

[1] *Ophthalmology Service, Sanatorio Mapaci, Rosario, Santa Fe, Argentina*

[2] *Grupo Laser Visión, Rosario, Santa Fe, Argentina*

ESSENTIALS OF DIAGNOSIS

Myopia is a common condition in many countries, particularly in East Asia, affecting approximately 40% of Chinese adults older than 40 years. The prevalence of myopia in developed countries is reported to be between 11% and 36%. The overall prevalence of pathologic myopia is approximately 1% to 4% in the general adult population although there is a wide geographical variation. The associated prevalence of visual impairment due to pathologic myopia is estimated to be 0.1% to 1.4%. The definition of pathologic myopia is not standardized, but is historically classified in clinical trial literature as a myopic refractive error greater than -6 diopters, or an axial length >26 mm, associated to degenerative changes involving the sclera, choroid and retina. Choroidal neovascularization secondary to pathological myopia is a common vision-threatening complication and often affects adults of working age, and develops in approximately 5% to 10% of patients with pathological myopia. The overall prevalence of choroidal neovascularization secondary to pathological myopia is therefore estimated to be approximately 0.04% to 0.05% in the general population [1, 2].

The chorioretinal lesions are viewed as a consequence of excessive axial elongation. It is believed that progressive distension of the posterior pole stretches the retina, choroid and sclera, as evidenced by the straightening of the temporal

* **Corresponding author Federico Furno Sola:** Grupo Laser Visión, Mariano Moreno 1397, Rosario – Santa Fe, Argentina; Tel: +54 (0341) 4472122; Email: furnosola@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

retinal vessels, the appearance of peripapillary atrophy, and the thinning of the retina and choroid. Various changes may occur in the fundus of a patient with myopia, related to the presence of myopic conus, staphylomas, retinal pigment epithelium and choroid disturbances and atrophic areas (Figs. **1**-**3**). Lacquer cracks are linear or stellate; the lines are fine, irregular in caliber, yellowish-white, horizontally oriented, single and/or multiple. Lacquer cracks are ruptures of Bruch´s elastic lamina and carry a guarded visual prognosis because of their association with focal degenerative lesions and subretinal neovascularization along their course [1, 2].

It is generally accepted that the pigmented lesion described by Fuchs and the hemorrhagic lesion reported by Foerster represent different stages of the process of the development of CNV in myopia (Fig. **2**). Neovascularization has been identified to precede the development of Fuchs spots. The growth of choroidal new vessels induces a sudden painless reduction in vision usually associated with metamorphopsia. Biomicroscopically, it is observed as a light-gray, round or elliptic macular lesion (Fig. **3**). The lesion is usually discrete in size and located next to the fovea [1, 2].

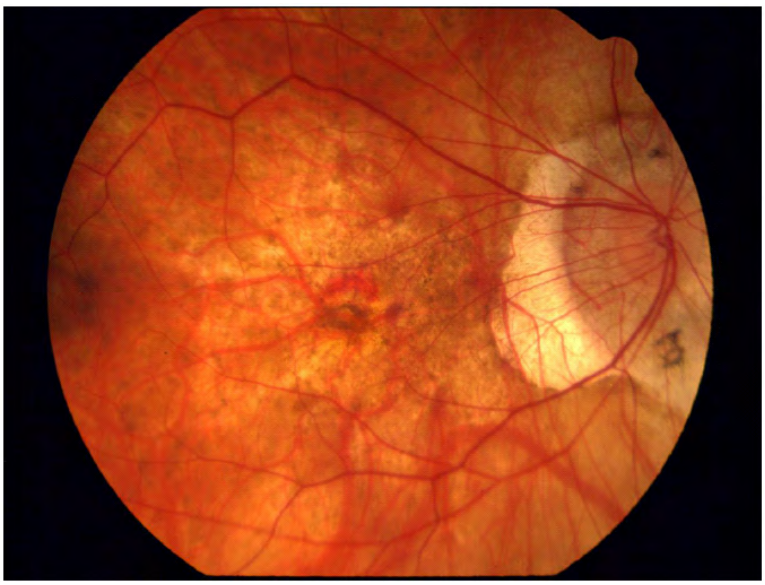


Fig. (1). Numerous areas of pigment epithelium atrophy and choriocapillaris extend to the macular region. A circular myopic crescent is visible.

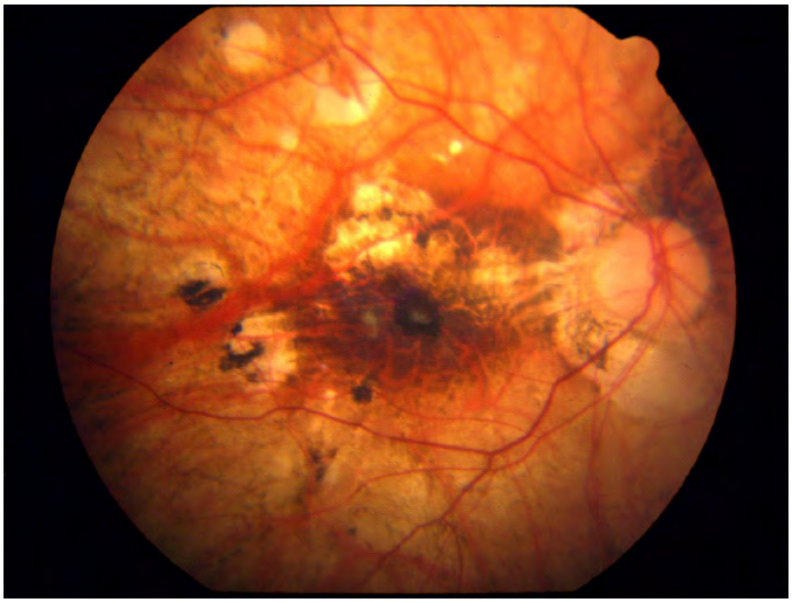


Fig. (2). Numerous areas of pigment epithelium and choriocapillaris atrophy extend into the macular region. A circular myopic crescent is visible. Hemorrhage occupies the center of the fovea.

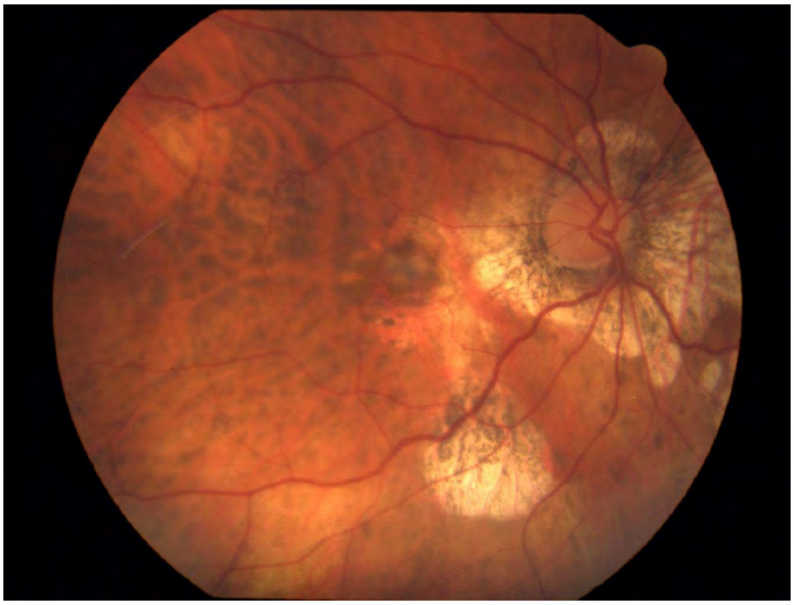


Fig. (3). Numerous areas of atrophy of the pigment epithelium and choriocapillaris extend to the macular region. A circular myopic crescent is visible. Choroidal new vessels with neovascular lesion and macular edema.

Fluorescein angiography usually shows a lesion that is hyperfluorescent early in the study (Fig. **4**). Later in the study, the hyperfluorescent area grows, although leakage does not increase significantly (Fig. **5**). ICG angiography may detect a focal hyperfluorescent area that fades with dye washout. On OCT, the CNV extends above the RPE (Figs. **6** and **7**), and generally lacks a significant amount of subretinal or intraretinal fluid [1, 2].

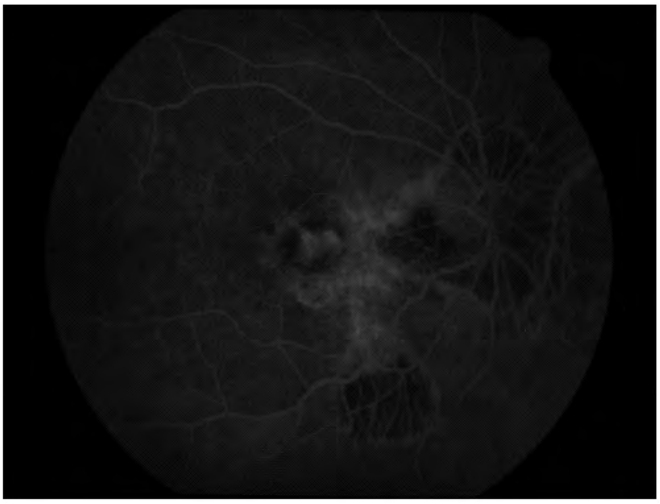


Fig. (4). Mid phase of fluorescein angiography shows a hyperfluorescent zone located at the foveal avascular zone.

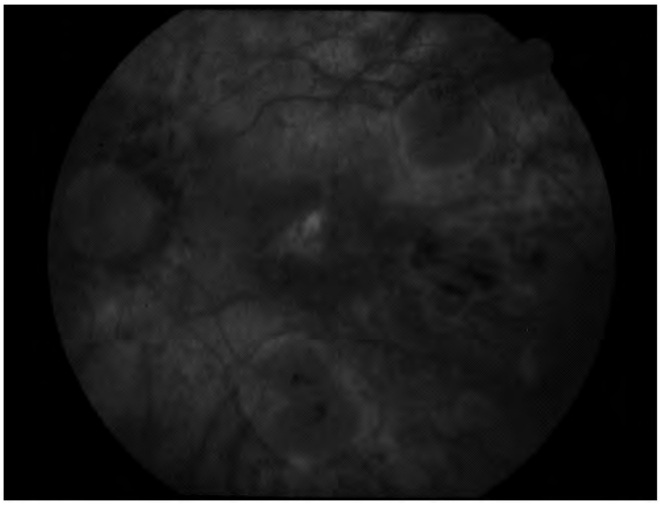


Fig. (5). Late frame of fluorescein angiography, showing dye leakage.

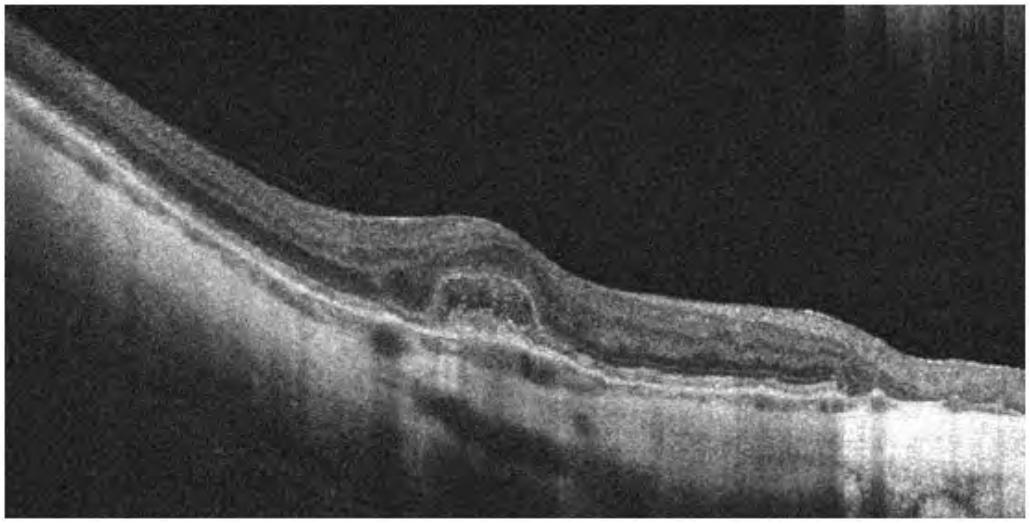


Fig. (6). Optical coherence tomography, showing hyperreflective subretinal material with macular edema.

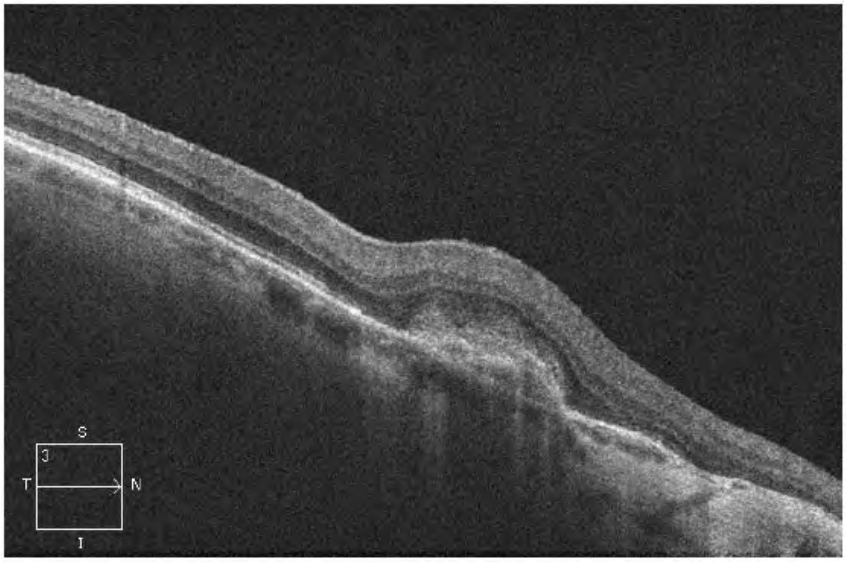


Fig. (7). Optical coherence tomography showing hyperreflective subretinal material.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of myopic CNV should include other causes of CNV such as age-related macular degeneration, idiopathic, angioid streaks, trauma, tumors, multifocal choroiditis and presumed ocular histoplasmosis syndrome. The refractive error and the presence of findings compatible with high myopia such as

a posterior staphyloma or the rectification of the temporal arcades should make the diagnosis relatively straightforward.

MANAGEMENT

The visual prognosis in cases of choroidal new vessels in degenerative myopia remains controversial. Laser photocoagulation and photodynamic therapy has fallen by the wayside with the advent of anti-VEGF therapies. The RADIANCE study is the first controlled trial in patients with myopic CNV to demonstrate that intravitreal ranibizumab treatment was superior compared with photodynamic therapy. During the RADIANCE study different dose regimens were assessed, which showed rapid and similar improvements in mean BCVA from baseline up to month 3 that were sustained with continued individualized ranibizumab treatment up to month 12 [1, 2].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Wolf S, Balciuniene VJ, Laganovska G, *et al.* RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology 2014; 121(3): 682-92.e2. [http://dx.doi.org/10.1016/j.ophtha.2013.10.023] [PMID: 24326106]

[2] Ryan SJ, Hincon DR, Schachat AP, Wikinson CP (Eds). Retina. 4th ed. Philadelphia: Elsevier 2006; Vol. 2.

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 19

Angioid Streaks

Michael Larsen[1,*], Mette K.G. Andersen[1], Naresh Mandava[2] and **Richard Hwang[3]**

[1] *Department of Ophthalmology, Glostrup Hospital and Faculty of Health Sciences, University of Copenhagen, Kobenhave Denmark*

[2] *Department of Ophthalmology, University of Colorado School of Medicine, Aurora, CO, USA*

[3] *Vitreoreitnal Disease and Surgery, Department of Ophthalmology, University of Colorado School of Medicine, Aurora, CO, USA*

Angioid streaks is the term used for a characteristic type of posterior segment lesion consisting of irregular and sometimes branching lines with a red or brownish appearance that extend from the rim of the optic disc to the periphery of the fundus (Figs. **1-4**, **8A, B**, **9A, B**) [1]. They were originally described by Doyne in 1889 [2]. The streaks are caused by breaks in the Bruch's membrane – retinal pigment epithelium (RPE) complex [1].

Angioid streaks can be seen in the presence of various extraocular conditions, most commonly pseudoxanthoma elasticum, a connective tissue disorder caused by defects in the *ABCC6* gene [3]. It gives rise to lax and dimpled skin, mainly on the flexor side of the neck, elbows and knees (Fig. **6**). The inheritance is mostly autosomal recessive, but autosomal dominant patterns can also be seen. The precise physiological function of ABCC6 is unknown, but it can be seen to be involved in transporting intracellular elements to the extracellular space. Defects in the ABCC6 protein lead to the accumulation of mineralized and fragmented

* **Corresponding author Michael Larsen:** Department of Ophthalmology, Glostrup Hospital and Faculty of Health Sciences, University of Copenhagen, Kobenhave, Denmark; Email: MICLAR01@regionh.dk

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

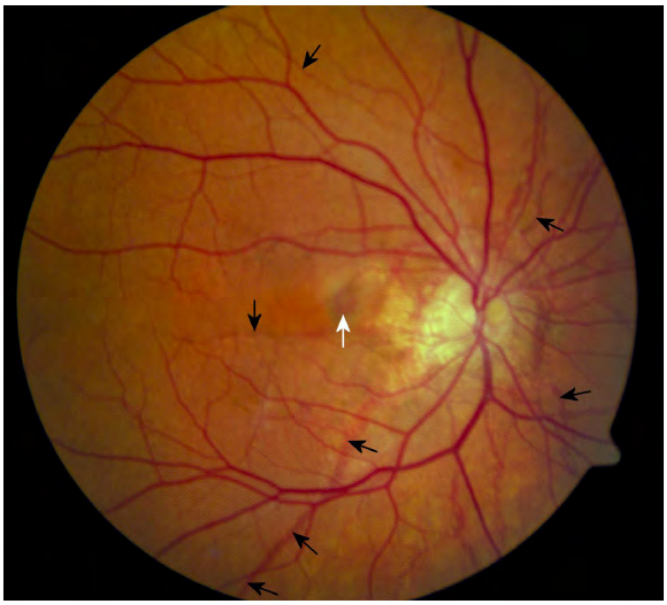


Fig. (1). Angioid streaks (black arrows) of the classic red type that resemble large choroidal blood vessels. The streaks are found behind the retinal blood vessels at the level of the retinal pigment epithelium. Red streaks stain early and prominently on fluorescein angiograms. Subfoveal choroidal neovascularization is also seen in this case (white arrow).

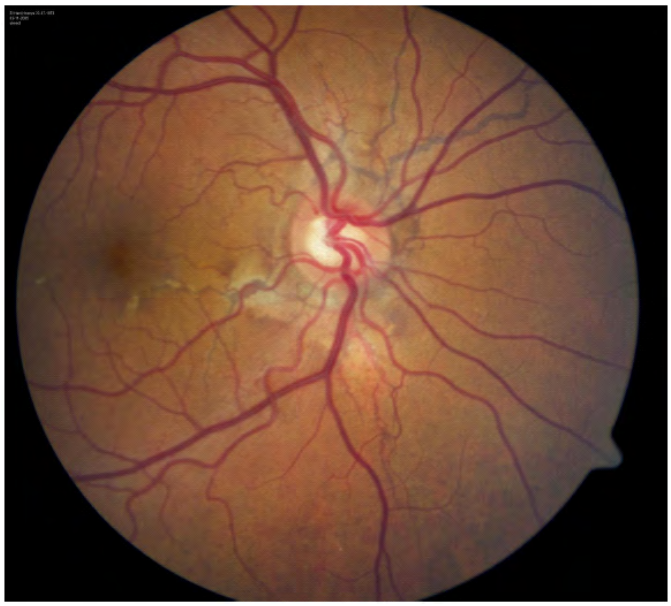


Fig. (2). Brownish and greyish pigmented angioid streaks temporal and superior of the optic disc in a patient with pseudoxanthoma elasticum. Note also subfoveal hemorrhage and choroidal neovascularization.

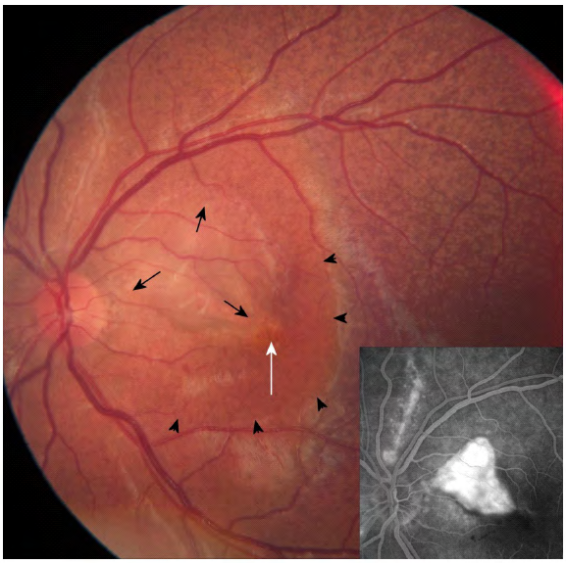


Fig. (3). Parafoveal classic subretinal neovascularization of choroidal origin (black arrows) in a patient with angioid steaks, one of which can be seen superior to the optic nerve head. Fluorescein angiography (lower right) shows prominent leakage, which explains the serous detachment of the neurosensory retina (black arrowheads). The upper right part of the color fundus photograph shows the spotted orange peel (peau d'orange) appearance of the diffuse outer retinal degeneration.

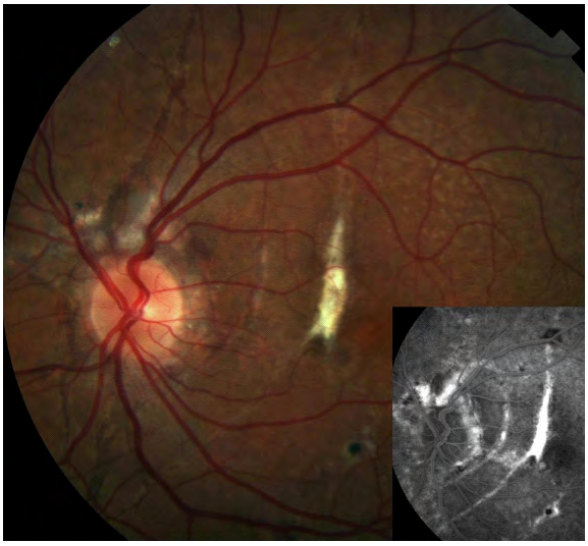


Fig. (4). Angioid streaks, a mixture of brownish streaks, pale atrophic areas, mainly around the margin of the optic disc, curved streaks concentric with the disc that are reminiscent of traumatic choroidal rupture lines and a small active choroidal neovascularization of approximately 250 μm diameter at the inferonasal margin of the fovea, emanating from the inferior tip of the large pale defect of the retinal pigment epithelium.

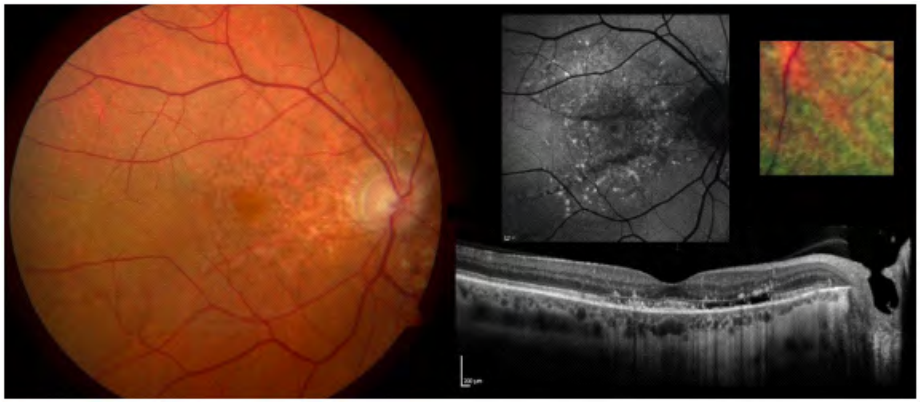


Fig. (5). Angioid streaks and diffuse degeneration of the outer retina in a man aged 42 with pseudoxanthoma elasticum. A peau d'orange pattern is seen most prominently in the temporal fundus. It is highlighted in a color-stretched section shown in the upper right of the montage. Fundus autofluorescence is absent corresponding to the streaks and elevated in the scattered dots that are spread over the rest of the macula. Optical coherence tomography shows varying degrees of photoreceptor outer segment atrophy and pigment epithelium attenuation in the central macula.

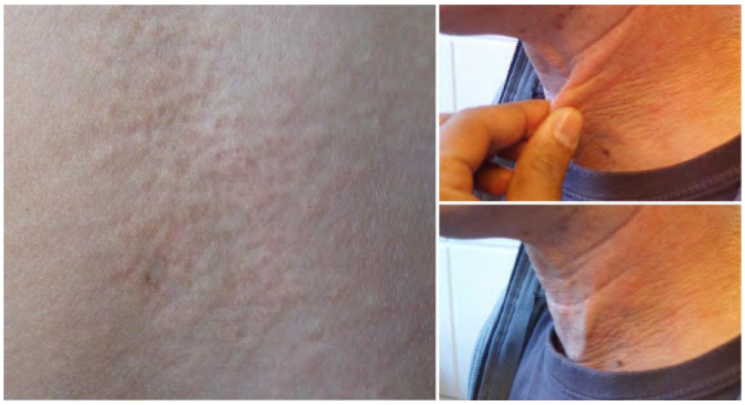


Fig. (6). Hyperkeratotic papules and rugged skin surface in an 18-year-old woman with pseudoxanthoma elasticum (left) and loose skin that remains elevated after having been pinched on the neck of a 45-year-old man (right) with the same condition.

elastic fibers in the connective tissue of the skin, vessel walls, and Bruch's membrane with consequent weakening of these tissues. Angioid streaks have also been reported in Paget's disease, hemolytic conditions such as hereditary spherocytosis, sickle cell disease and thalassemia and in Ehlers-Danlos syndrome (type 6), Marfans syndrome, senile elastosis, acromegaly, retinitis pigmentosa, lead poisoning, and Bassen-Kornzweig syndrome.

Sporadic observations suggest that minor blunt trauma to the eye can lead to the formation or expansion of angioid streaks and induction of choroidal neovascularization (CNV). The same mechanism is suspected to be the cause of subretinal hemorrhage in the absence of CNV. Patients with angioid streaks are therefore advised to avoid contact sports and to wear protective goggles when engaging in activities where eye trauma may occur.

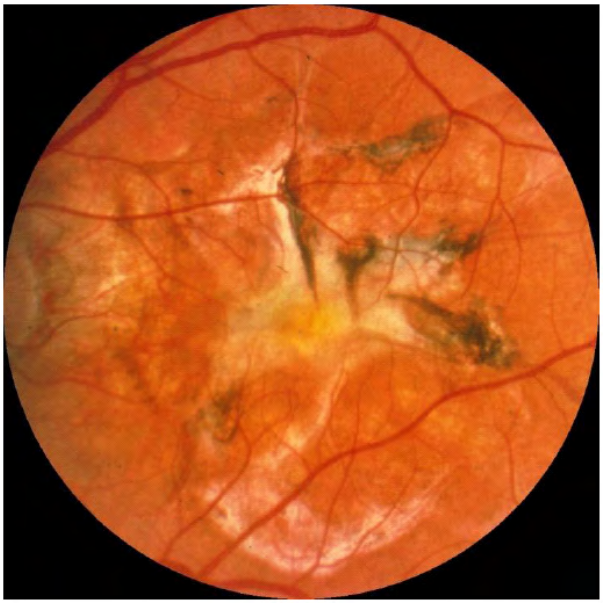


Fig. (7). Fibrotic end-stage submacular choroidal neovascularization in an eye with angioid streaks, two of which are crossing the rim of the image at 12 o'clock and 1 o'clock, respectively.

ESSENTIALS OF DIAGNOSIS

Clinical diagnosis can usually be made with fundoscopy. Angioid streaks typically appear as bilateral narrow jagged lines beneath the retina with an interconnecting pattern radiating out from the peripapillary region (Figs. **1-4**, **8A, B**, **9A, B**). They are evident a few millimeters from the optic disc and have a thickness of 50-500 μm [4 - 6]. The streaks develop and spread very slowly over decades, presumably as a result of mechanical stress in a thickened, calcified and fragile Bruch's membrane. The streaks are often bright red and can be mistaken for large fundus vessels, hence the term angioid (Greek, having the appearance of a blood vessel). Pale atrophic streaks can also be seen as hyperpigmentation along

the borders of the streaks. Angioid streaks are associated with a high risk of invasion of the subretinal space by CNV arising from the streaks. Smaller localized defects in Bruch's membrane can also give rise to pink patches in the peripheral fundus called salmon spots. Multiple small semiconfluent yellow dots are seen in many cases, mostly temporal of the fovea, a characteristic that has been likened to the skin of an orange and therefore is called *peau d'orange* (Figs. **3**, **5**, **8A, B**, **9B**). Autofluorescence fundus photography shows absence of autofluorescence corresponding to the streaks and hyperfluorescence in areas with *peau d'orange* elements (Figs. **5**, **9H-J**).

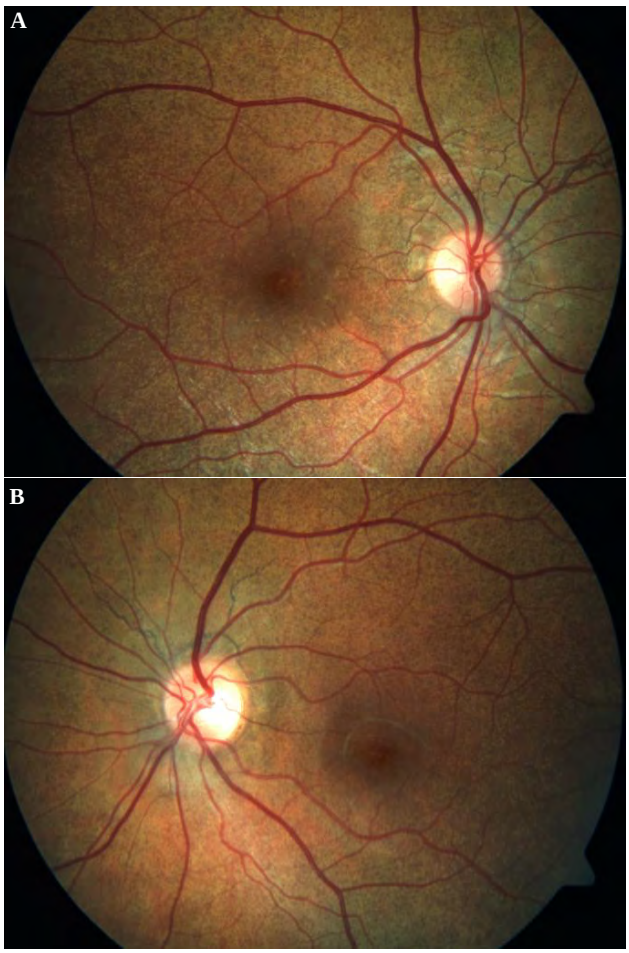


Fig. (8). A 24-year-old female with biopsy-proven pseudoxanthoma elasticum, with angioid streaks emanating from the peripapillary region with a peau d' orange pigmentary pattern of the peripheral retina in the right (**A**) and left (**B**) eyes.

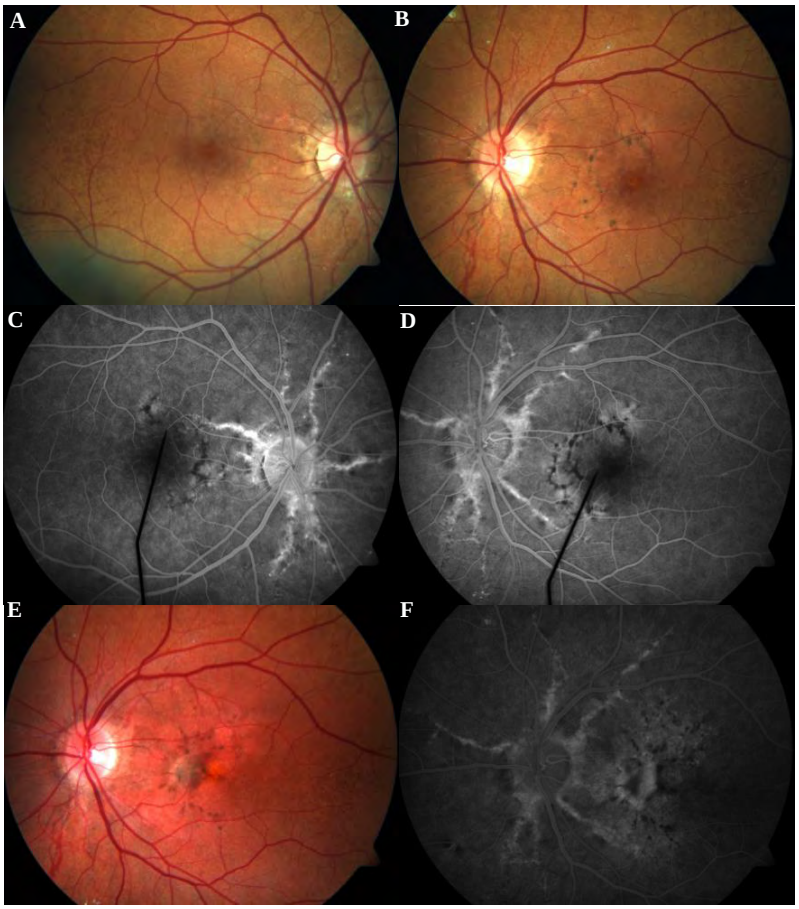


Fig. (9). A 36-year-old female with skin biopsy proven pseudoxanthoma elasticum, with angioid streaks in the right (**A**) and left (**B**) eyes. Note the retinal pigment epithelial changes in the left macula and the peau d' orange changes in the left temporal macula. Fluorescein angiogram of the right (**C**) and left (**D**) eyes defines the angioid streaks well and shows no evidence of leakage. One year after diagnosis, the patient developed subfoveal hemorrhage and subretinal fluid in the left eye (**E**). Fluorescein angiogram demonstrated leakage from an active choroidal neovascularization (CNV) (**F**). Her left eye was treated with two bevacizumab injections without improvement.

During fluorescein angiography, angioid streaks can have a "window defect" due to RPE atrophy adjacent to them (Figs. **9C, D**). Angioid streaks may show up as irregular hyperfluoresence during early phases and varied degrees of staining in late phases (Figs. **10B, C, E**). Leakage is evident when CNV is present (Figs. **9F**, **10C**). Angiography can help aid in diagnosis when the clinical appearance on ophthalmoscopy is unclear [6, 7].

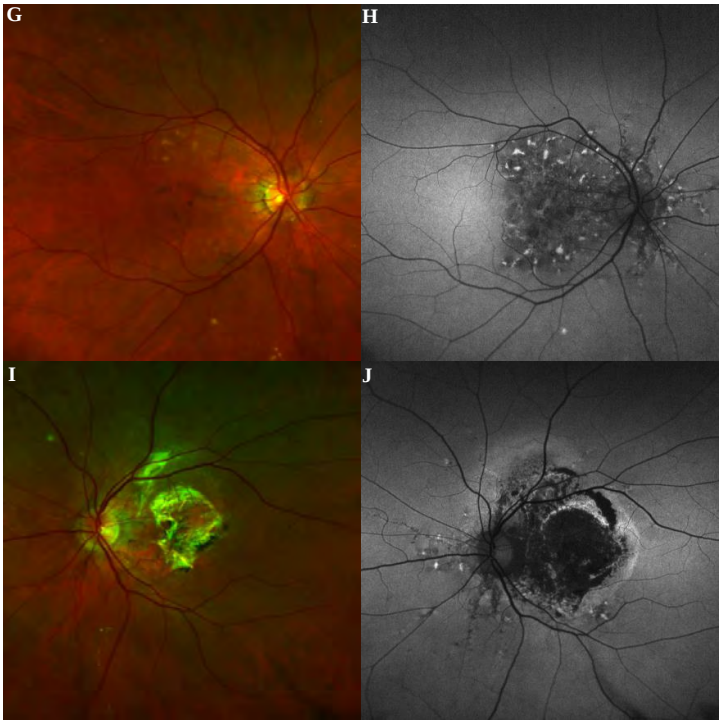


Fig. (9). Four years later, she developed CNV in the right eye, and has been treated with scheduled bevacizumab in the right eye. Vision remained stable one year after initiating scheduled bevacizumab treatment. Her right eye shows RPE atrophy and mild cystoid macular edema without hemorrhage (**G**) and her left eye shows a disciform scar (**I**). Fundus autofluorescence clearly defines the areas of RPE atrophy in both eyes (**H,J**).

When neither fundoscopy nor fluorescein angiography can confirm the diagnosis, indocyanine green angiography (ICG) can be a useful tool. Angioid streaks show up as well defined late phase hyperfluoresence and in some cases are only detectable by ICG angiography [8].

CNV with foveal involvement is the primary cause of symptomatic visual dysfunction in eyes with angioid streaks (Figs. **2**-**4**, **9E, F**). Neovascularization arises from streaks that approach or reach the fovea and must be considered a constant threat that increases with the proximity of the streak to the fovea. Neovascularization is believed to be promoted by the underlying defect in Bruch's membrane. The lesion is commonly a classic (type 2) choroidal neovascularization. Fibrotic involution of streaks after intravitreal VEGF-inhibition therapy

indicates that angioid streaks are composed of vascular tissue that bridges the gap left by the rupture in Bruch's membrane [9]. Fibrotic involution is also the natural end-stage of the spontaneous course of CNV development (Figs. **7**, **9I**, **10A, D, F, G**).

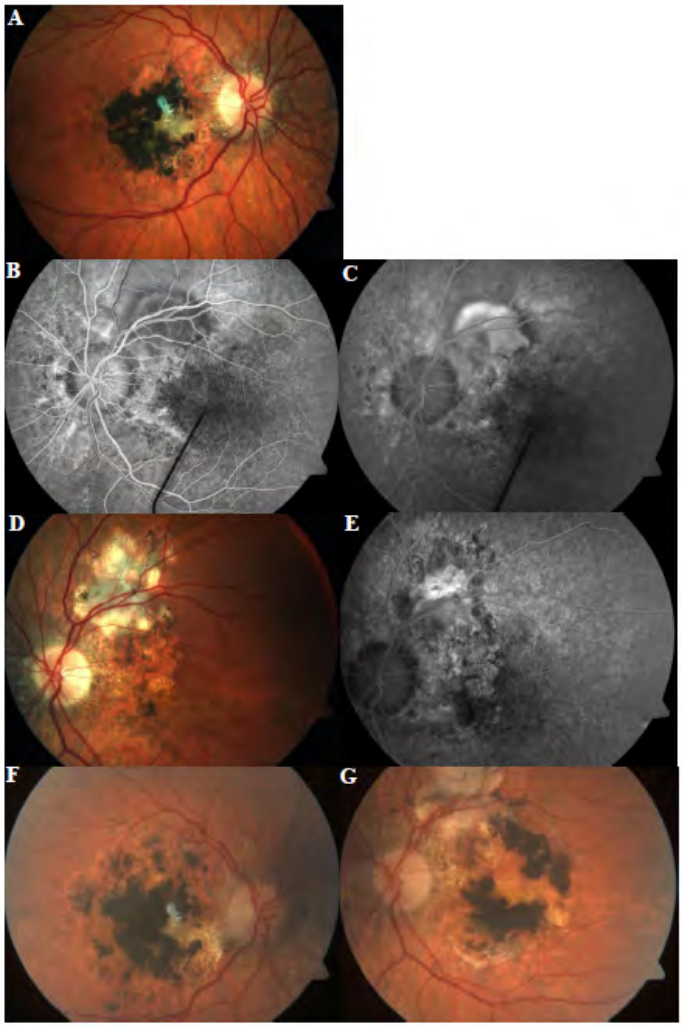


Fig. (10). A 54 year-old male with angioid streaks, with a disciform scar and crystalline bodies in the right eye (**A**). Fluorescein angiography of left eye shows early hyperfluoresence (**B**) with late leakage (**C**) consistent with a choroidal neovascular membrane along the superior arcade. The CNV was treated with laser and was inactive the following month. Six months after laser, there is a subretinal scar underneath the superior arcade (**D**) in the left eye and fluorescein angiography shows late staining but no active leakage (**E**). Eight years later, he developed additional scarring in the right (**F**) and left (**G**) eyes.

DIFFERENTIAL DIAGNOSIS

The occasional observation of curvilinear RPE defects that are concentric with the optic disc in eyes with angioid streaks suggests that these eyes are prone to traumatic choroidal rupture (Fig. **4**). Consequently, patients with lesions typical of traumatic choroidal rupture should be examined for angioid streaks and systemic conditions related to angioid streaks. Angioid streaks should be suspected in cases that may at first glance appear to be age-related macular degeneration with CNV, idiopathic peripapillary degeneration, peripapillary choroidal neovascularization, or lacquer-cracks in myopic degeneration.

MANAGEMENT

Patients with angioid streaks are usually asymptomatic and can be monitored. Because of the brittleness of Bruch's membrane, patients should be warned of the potential risk of choroidal rupture from mild trauma. Symptoms arise if the lesions extend to the foveola, resulting in metamorphopsia, scotomas, and decreased vision. Complications such as traumatic Bruch's membrane rupture or macular CNV can also dramatically impact vision. Untreated CNV has poor prognosis because of the possible development of a disciform scar (Fig. **9G-J**, **10A**). Historically, several treatments have been evaluated including laser photocoagulation, transpupillary thermotherapy, photodynamic therapy, subretinal CNV extraction, and macular translocation therapy. Most treatments, when effective, were only able to achieve short term stabilization or a delay of disease progression, with recurrence being the rule [5]. While certain treatments may be considered in select cases, treatment with anti-VEGF agents has proven to be the most effective. Most studies, which have a limited number of patients and use either bevacizumab [10 - 12] or ranibizumab, have found stabilization or improvement of best corrected visual acuity (BCVA) in a majority of patients after treatment [13 - 18]. Treatment in earlier disease stages appears to result in increased BCVA more frequently than treatment in advanced stages, where only stabilization is achieved [12]. Frequent follow up is still required given the high rate of recurrence and currently there is no data to support any one particular treatment regimen *e.g.* fixed interval *vs* pro re nata (PRN). Several studies have investigated combined treatments such as PDT and anti-VEGF [5, 16 - 18] with

encouraging results but further studies will be required to determine whether combination therapy offers significant advantages over single therapy treatment.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Charbel Issa P, Finger RP, Holz FG, Scholl HP. Multimodal imaging including spectral domain OCT and confocal near infrared reflectance for characterization of outer retinal pathology in pseudoxanthoma elasticum. Invest Ophthalmol Vis Sci 2009; 50(12): 5913-8. [http://dx.doi.org/10.1167/iovs.09-3541] [PMID: 19553619]

[2] Doyne R. Choroidal and retinal changes the result of blows on the eyes. Trans Ophthalmol Soc U K 1889; 9: 128.

[3] Bergen AA, Plomp AS, Hu X, de Jong PT, Gorgels TG. ABCC6 and pseudoxanthoma elasticum. Pflugers Arch 2007; 453(5): 685-91. [http://dx.doi.org/10.1007/s00424-005-0039-0] [PMID: 16604369]

[4] Agarwal A, Ed. Gass`atlas of macular diseases. 5th ed., Edinburgh, UK: Elsevier Saunders 2012.

[5] Gliem M, Finger RP, Fimmers R, Brinkmann CK, Holz FG, Charbel Issa P. Treatment of choroidal neovascularization due to angioid streaks: a comprehensive review. Retina 2013; 33(7): 1300-14. [http://dx.doi.org/10.1097/IAE.0b013e3182914d2b] [PMID: 23719398]

[6] Georgalas I, Papaconstantinou D, Koutsandrea C, *et al.* Angioid streaks, clinical course, complications, and current therapeutic management. Ther Clin Risk Manag 2009; 5(1): 81-9. [PMID: 19436620]

[7] Smith JL, Gass JD, Justice J Jr. Fluorescein fundus photography of angioid streaks. Br J Ophthalmol 1964; 48: 517-21. [http://dx.doi.org/10.1136/bjo.48.10.517] [PMID: 14221775]

[8] Dithmar S, Holz FG. Fluorescein angiography in ophthalmology. Springer Science & Business Media 2008.

[9] Bloch SB, Larsen M. Fibrosis of extramacular angioid streaks following ranibizumab treatment of subfoveal choroidal neovascularization. Acta Ophthalmol 2011; 89(1): e102-4. [http://dx.doi.org/10.1111/j.1755-3768.2009.01813.x] [PMID: 20222906]

[10] Neri P, Salvolini S, Mariotti C, Mercanti L, Celani S, Giovannini A. Long-term control of choroidal neovascularisation secondary to angioid streaks treated with intravitreal bevacizumab (Avastin). Br J Ophthalmol 2009; 93(2): 155-8. [http://dx.doi.org/10.1136/bjo.2008.145896] [PMID: 18971232]

[11] Sawa M, Gomi F, Tsujikawa M, Sakaguchi H, Tano Y. Long-term results of intravitreal bevacizumab injection for choroidal neovascularization secondary to angioid streaks. Am J Ophthalmol 2009; 148(4): 584-590.e2.
[http://dx.doi.org/10.1016/j.ajo.2009.04.026] [PMID: 19541288]

[12] Finger RP, Charbel Issa P, Schmitz-Valckenberg S, Holz FG, Scholl HN. Long-term effectiveness of intravitreal bevacizumab for choroidal neovascularization secondary to angioid streaks in pseudoxanthoma elasticum. Retina 2011; 31(7): 1268-78.
[http://dx.doi.org/10.1097/IAE.0b013e318207d1dc] [PMID: 21386758]

[13] Vadalà M, Pece A, Cipolla S, *et al.* Angioid streak-related choroidal neovascularization treated by intravitreal ranibizumab. Retina 2010; 30(6): 903-7.
[http://dx.doi.org/10.1097/IAE.0b013e3181cafc75] [PMID: 20531143]

[14] Myung JS, Bhatnagar P, Spaide RF, *et al.* Long-term outcomes of intravitreal antivascular endothelial growth factor therapy for the management of choroidal neovascularization in pseudoxanthoma elasticum. Retina 2010; 30(5): 748-55.
[http://dx.doi.org/10.1097/IAE.0b013e3181c596b1] [PMID: 19996818]

[15] El Matri L, Kort F, Bouraoui R, Karim B, Chebil A, Chaker N. Intravitreal bevacizumab for the treatment of choroidal neovascularization secondary to angioid streaks: one year of follow-up. Acta Ophthalmol 2011; 89(7): 641-6.
[http://dx.doi.org/10.1111/j.1755-3768.2009.01836.x] [PMID: 21155980]

[16] Artunay O, Yuzbasioglu E, Rasier R, Sengul A, Senel A, Bahcecioglu H. Combination treatment with intravitreal injection of ranibizumab and reduced fluence photodynamic therapy for choroidal neovascularization secondary to angioid streaks: preliminary clinical results of 12-month follow-up. Retina 2011; 31(7): 1279-86.
[http://dx.doi.org/10.1097/IAE.0b013e318205b228] [PMID: 21394063]

[17] Donati MC, Virgili G, Bini A, *et al.* Intravitreal bevacizumab (Avastin) for choroidal neovascularization in angioid streaks: a case series. Ophthalmologica 2009; 223(1): 24-7.
[http://dx.doi.org/10.1159/000161879] [PMID: 18849633]

[18] Prabhu VV, Morris RJ, Shah PK, Narendran V. Combination treatment of low fluence photodynamic therapy and intravitreal ranibizumab for choroidal neovascular membrane secondary to angioid streaks in Paget's disease - 12 month results. Indian J Ophthalmol 2011; 59(4): 306-8.
[http://dx.doi.org/10.4103/0301-4738.82000] [PMID: 21666317]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 20

Presumed Ocular Histoplasmosis Syndrome

Manuel Garza-León[1,*], Luz Elena Concha del Río[2] and **Miguel Pedroza Seres[3]**

[1] *Department of Medical Sciences, Division of Health Sciences, Universidad de Monterrey, Monterrey, Nuevo León, México*

[2] *Uveitis Department, Asociación para Evitar la Ceguera en México. I.A.P, Mexico*

[3] *Uveitis and Ocular Inmunology Department, Instituto de Oftalmología Conde de Valenciana, México, DF. Clínica de Retina, Guadalajara, J., Mexico*

Presumed ocular histoplasmosis syndrome (POHS) is an inflammatory eye disease that has been reported to be associated with systemic fungal infection by *Histoplasma capsulatum* [1]. It is restricted mainly to endemic countries and is mainly seen in the midwest of the United States and where *Histoplasma capsulatum* is endemic [2], although there have been reports of a similar disease from countries that are nonendemic zones for the microorganism [3].

ESSENTIALS OF DIAGNOSIS

POHS is a posterior uveitis, predominantly diagnosed clinically by the observation of characteristic fundus lesions in one or both eyes. The ocular triad of POHS consists in the presence of multiple atrophic choroidal spots (known as *histo spots*) (Fig. **1**), peripapillary atrophy (PPA) and maculopathy (Figs. **2**-**5**). Macular lesions are secondary to choroidal neovascularization (CNV) or atrophy and most of the time display a disciform pattern (Figs. **4**, **6**). Also, one of the key manifestations of POHS is the absence of inflammation in the vitreous. The disease occurs predominately in young adults and linear streaks are described in 5-16% of cases [3, 4]. Initially the disease occurs in one eye, being able to affect the second eye in 9-22% of cases [5, 6].

* **Corresponding author Manuel Garza-León:** Department of Medical Sciences, Division of Health Sciences, Universidad de Monterrey, Monterrey, Nuevo León, México; Tel: +52 8188824208; Fax: +52 81888242'8; E-mail: manuel@drgarza.mx

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

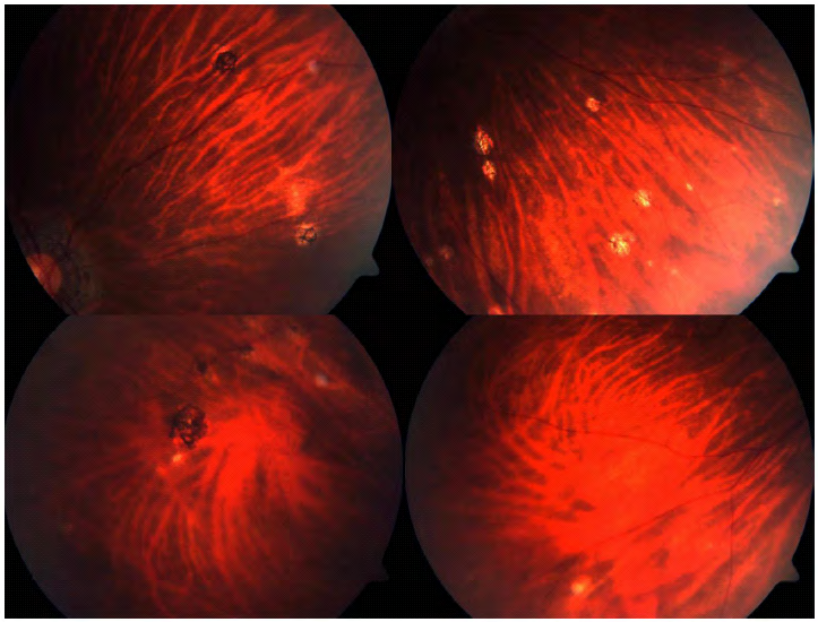


Fig. (1). Fundus photographs of a 62-year-old female. Visual acuity was 20/30 in the right eye and 20/25 in the left eye. The anterior segment had no inflammation, there were no vitreous cells. Several chorioretinal scars were observed in the posterior pole and periphery.

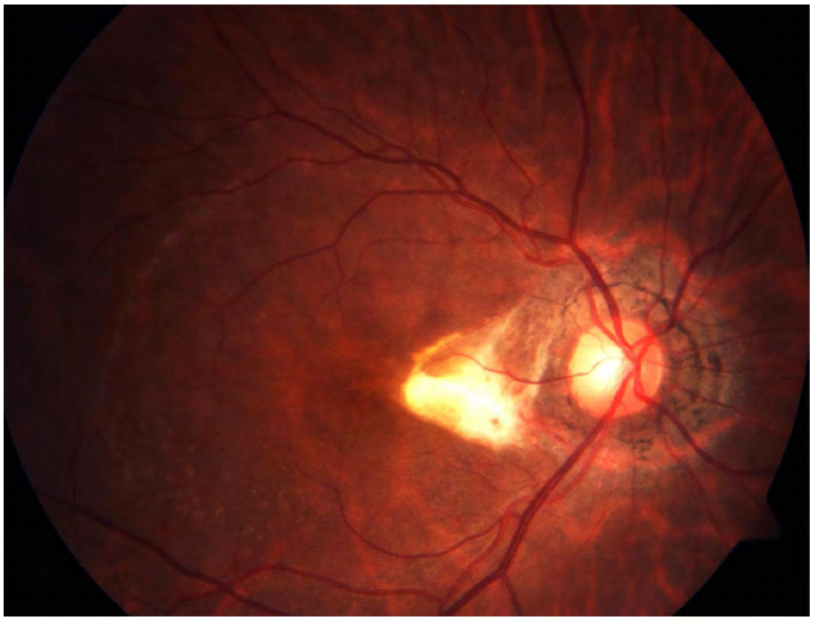


Fig. (2). Fundus photograph of the same patient as Fig. (**1**).

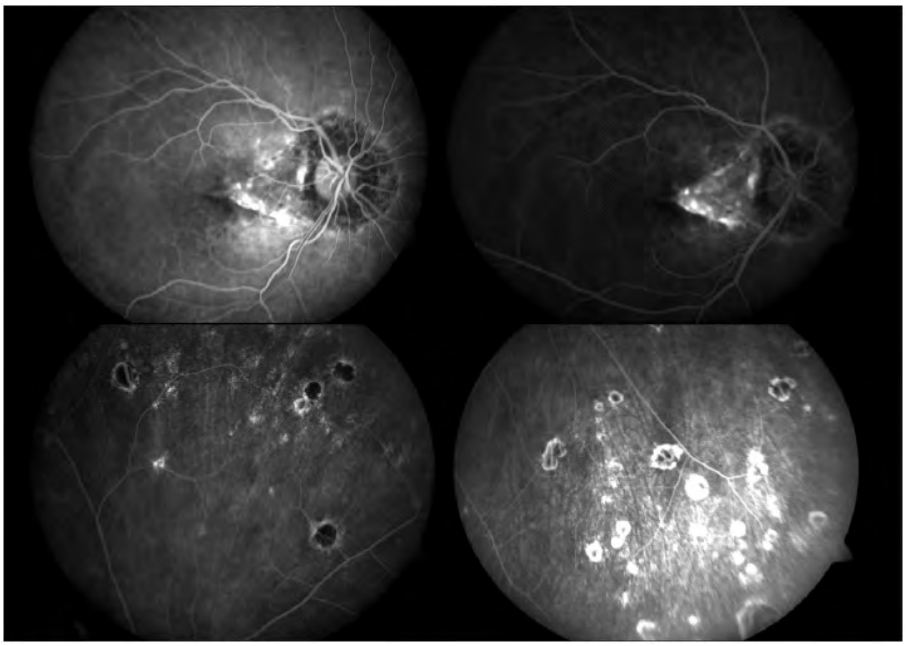


Fig. (3). Fluorescein angiogram of the same patient as Figs. (**1** and **2**). Dye accumulation due to a fibrous scar is observed adjacent to the optic nerve. Several histo spots may be observed in the periphery.

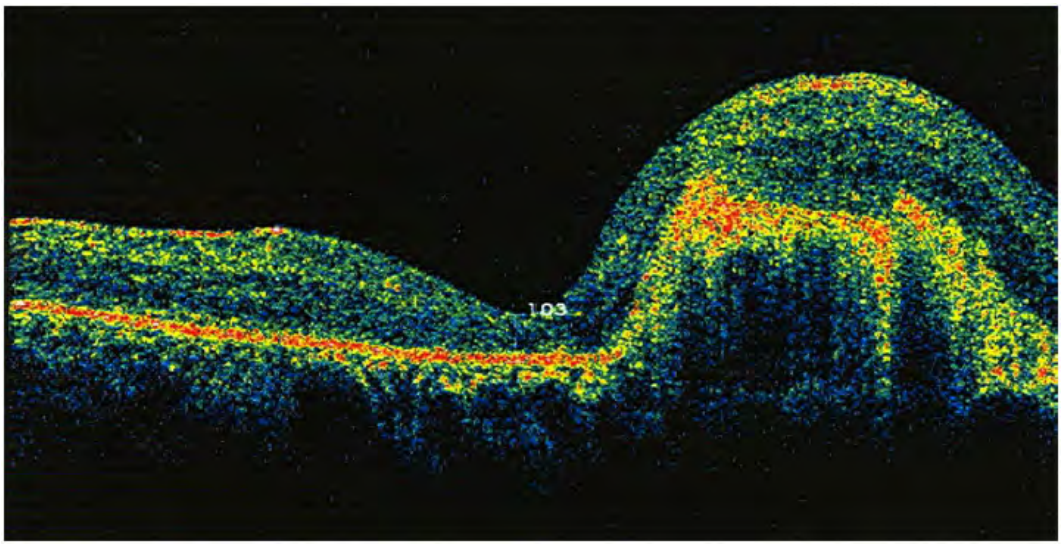


Fig. (4). OCT of the macula of the same eye as Figs. (**1-3**). A large area of subretinal fibrosis is observed.

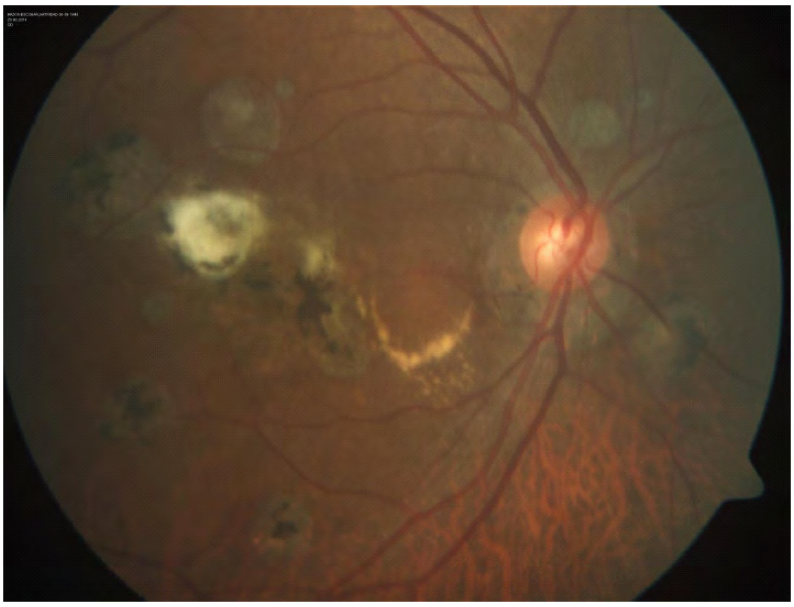


Fig. (5). Color fundus photograph of the posterior pole of a right eye displaying all the components of the triad: circumferential, pigmented peripapillary atrophy with a subretinal choroidal neovascularization superotemporal to the fovea, and chorioretinal scars.

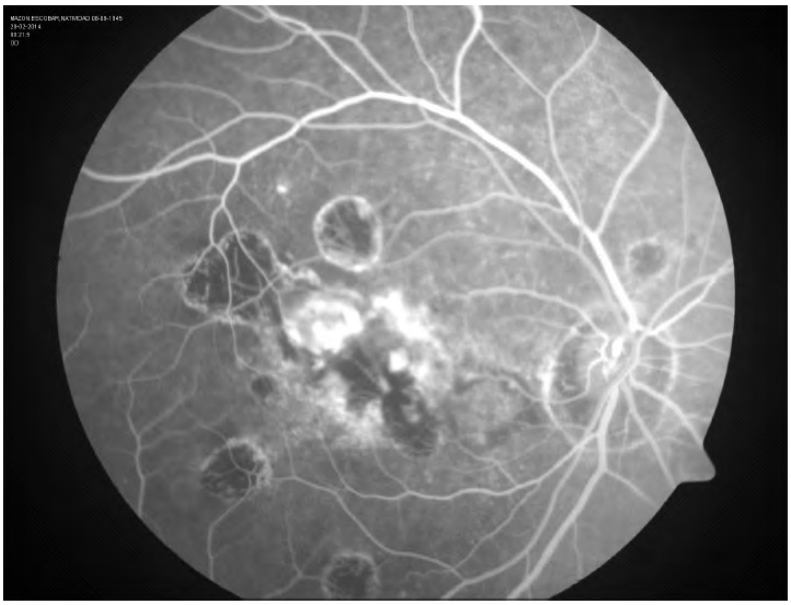


Fig. (6). Fluorescein angiogram of the same eye as Fig. (**5**), showing zones of atrophy of the RPE and choriocapillaris, and leakage secondary to CNV.

Patients may describe metamorphopsia, reduced vision, or paracentral scotomas from possible active CNV. Those with PPA and extrafoveal chorioretinal scars do not manifest visual symptoms. The characteristic ocular presentation was associated with infection with *H. capsulatum* through epidemiological studies. However, only rarely has the *H. capsulatum* antigen and organism been identified in an eye with POHS. Diagnosis by histoplasmin skin testing (Fig. **7**) has been abandoned since it was suggested that there was a possibility of flare-up of maculopathy when performing the test [7].

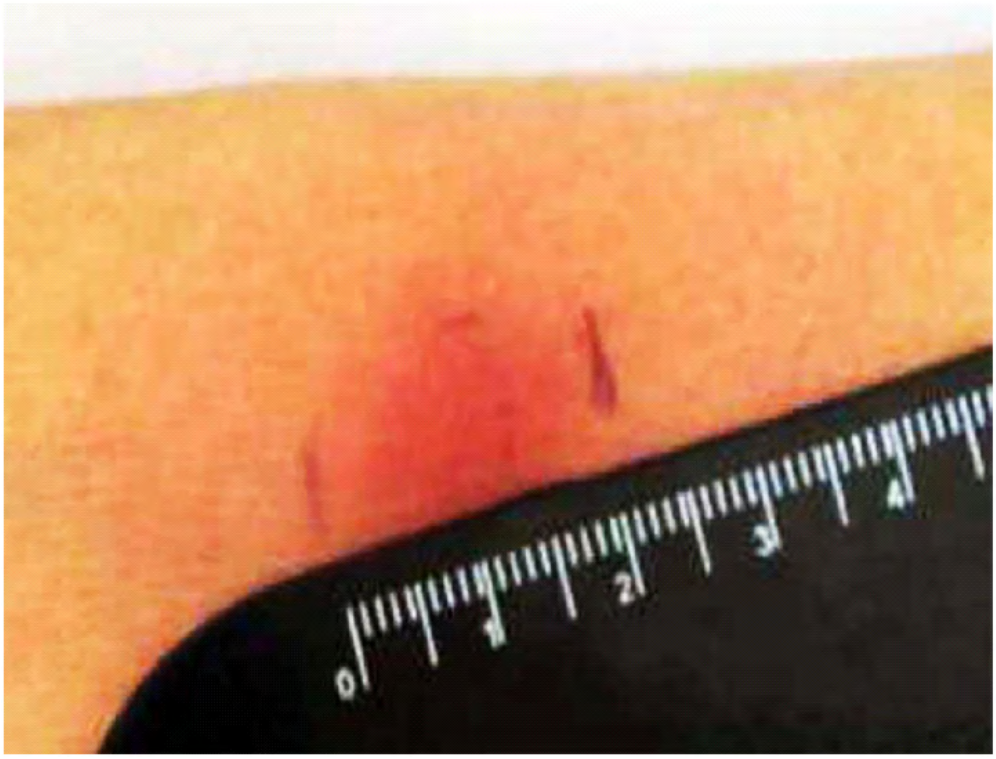


Fig. (7). Histoplasmin skin testing.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes multifocal choroiditis and panuveitis (MFC), which belong to the group of conditions called “white dot syndromes” and may mimic lesions of POHS. A disease similar to MFC but without the vitritis seen in the active phase is called punctate inner choroidopathy (PIC) [8]. POHS should

also be differentiated from multiple evanescent white-dot syndrome (MEWDS), acute posterior multifocal placoid pigment epitheliopathy and birdshot retino-choroidopathy.

Other causes of CNV, like idiopathic CNV, choroidal rupture with CNV, myopic CNV, and exudative age-related macular degeneration (AMD) are also included in the differential diagnosis of POHS. Other infectious conditions such as ocular inflammation secondary to tuberculosis, syphilis, toxoplasmosis, and sarcoidosis produce granulomatous fundus lesions that may resemble those of POHS. But these conditions are usually related to other signs of inflammation in any part of the eye, such as keratic precipitates, anterior uveitis, vitreous cells, and cotton balls in the vitreous. As mentioned earlier, the absence of these inflammatory signs and very importantly the presence of a clear vitreous help diagnoses POHS.

MANAGEMENT

Due to the absence of inflammation, treatment of patients with POHS is indicated only when there is evidence of CNV. In up to 60% of patients who don't receive treatment for CNV, visual acuity result is 20/200 or worse, and almost three quarters of these patients experience reduced visual acuity after initial diagnosis [9].

Visual prognosis for patients with subfoveal CNV secondary to POHS is poor. Photodynamic therapy [10], submacular surgery [11], systemic, periocular and intravitreal steroids [12, 13], and radiation [14] were proposed as therapy options, but intravitreal anti-vascular endothelial growth factor therapy [15, 16] is the treatment of choice nowadays.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Woods AC, Wahlen HE. The probable role of benign histoplasmosis in the etiology of granulomatous uveitis. Trans Am Ophthalmol Soc 1959; 57: 318-43.
[PMID: 16693576]

[2] Asbury T. The status of presumed ocular histoplasmosis: including a report of a survey. Trans Am Ophthalmol Soc 1966; 64: 371-400.
[PMID: 5964934]

[3] Suttorp-Schulten MS, Bollemeijer JG, Bos PJ, Rothova A. Presumed ocular histoplasmosis in The Netherlands--an area without histoplasmosis. Br J Ophthalmol 1997; 81(1): 7-11.
[http://dx.doi.org/10.1136/bjo.81.1.7] [PMID: 9135400]

[4] Fountain JA, Schlaegel TF Jr. Linear streaks of the equator in the presumed ocular histoplasmosis syndrome. Arch Ophthalmol 1981; 99(2): 246-8.
[http://dx.doi.org/10.1001/archopht.1981.03930010248004] [PMID: 7469859]

[5] Five-year follow-up of fellow eyes of individuals with ocular histoplasmosis and unilateral extrafoveal or juxtafoveal choroidal neovascularization. Arch Ophthalmol 1996; 114(6): 677-88.
[http://dx.doi.org/10.1001/archopht.1996.01100130669006] [PMID: 8639078]

[6] Lewis ML, Schiffman JC. Long-term follow-up of the second eye in ocular histoplasmosis. Int Ophthalmol Clin 1983; 23(“): 125-35.
[http://dx.doi.org/10.1097/00004397-198302320-00013]

[7] Krause AC, Hopkins WG. Ocular manifestation of histoplasmosis. Am J Ophthalmol 1951; 34(4): 564-6.
[http://dx.doi.org/10.1016/0002-9394(51)90300-5] [PMID: 14819184]

[8] Leung TG, Moradi A, Liu D, *et al.* Clinical features and incidence rate of ocular complications in punctate inner choroidopathy. Retina 2014; 34(8): 1666-74.
[http://dx.doi.org/10.1097/IAE.0000000000000125] [PMID: 24743642]

[9] Olk RJ, Burgess DB, McCormick PA. Subfoveal and juxtafoveal subretinal neovascularization in the presumed ocular histoplasmosis syndrome. Visual prognosis. Ophthalmology 1984; 91(12): 1592-602.
[http://dx.doi.org/10.1016/S0161-6420(84)34113-6] [PMID: 6084225]

[10] Rosenfeld PJ, Saperstein DA, Bressler NM, *et al.* Verteporfin in Ocular Histoplasmosis Study Group. Photodynamic therapy with verteporfin in ocular histoplasmosis: uncontrolled, open-label 2-year study. Ophthalmology 2004; 111(9): 1725-33.
[http://dx.doi.org/10.1016/j.ophtha.2004.02.014] [PMID: 15350329]

[11] Berger AS, Conway M, Del Priore LV, Walker RS. POllack JS, Kaplan HJ. Submacular surgery for subfoveal choroidal neovascular membranes in patients with presumed ocular histoplasmosis. Arch Ophthalmol 1997; 115(8): 991-6.
[http://dx.doi.org/10.1001/archopht.1997.01100160161004] [PMID: 9258220]

[12] Martidis A, Miller DG, Ciulla TA, Danis RP, Moorthy RS. Corticosteroids as an antiangiogenic agent for histoplasmosis-related subfoveal choroidal neovascularization J Ocul Pharmacol Ther 1999; 15(5): 425-8.
[http://dx.doi.org/10.1089/jop.1999.15.425]

[13] Rechtman E, Allen VD, Danis RP, Pratt LM, Harris A, Speicher MA. Intravitreal triamcinolone for choroidal neovascularization in ocular histoplasmosis syndrome. Am J Ophthalmol 2003; 136(4): 739-41.
[http://dx.doi.org/10.1016/S0002-9394(03)00389-1] [PMID: 14516819]

[14] Liem SE, Armbruster FC. Proton-beam irradiation of subfoveal choroidal neovascular membranes in presumed ocular histoplasmosis syndrome: a case report. J Am Optom Assoc 1998; 69(8): 493-9.
[PMID: 9747044]

[15] Ramaiya KJ, Blinder KJ, Ciulla T, Cooper B, Shah GK. Ranibizumab *versus* photodynamic therapy for presumed ocular histoplasmosis syndrome. Ophthalmic Surg Lasers Imaging Retina 2013; 44(1): 17-21.
[http://dx.doi.org/10.3928/23258160-20121221-07] [PMID: 23410808]

[16] Cionni DA, Lewis SA, Petersen MR, *et al.* Analysis of outcomes for intravitreal bevacizumab in the treatment of choroidal neovascularization secondary to ocular histoplasmosis. Ophthalmology 2012; 119(2): 327-32.
[http://dx.doi.org/10.1016/j.ophtha.2011.08.032] [PMID: 22133795]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 21

Epiretinal Membrane

Aristides J. Mendoza[1,2,*]

[1] *Retina Department, Centro Oftalmológico de Valencia (CEOVAL), Valencia, Venezuela*

[2] *Retina Department, OftalmoSalud, Arequipa, Peru*

The epiretinal membrane (ERM) represents the growth of avascular fibrotic tissue on the surface of the retina in the macular area, which causes loss of vision and distortion of images when it contracts [1].

ERMs can be caused by a variety of eye problems. They are classified as idiopathic when not linked to any other eye disease and usually appear after a posterior vitreous detachment as a result of the formation of retinal tears that release inflammatory cells and pigment epithelial cells deposited at the posterior pole. Secondary ERMs are associated with retinal detachment, intraocular inflammation, trauma and vascular diseases of the retina [2]. There are two types of ERMs that have different clinical presentations: simple and contractile. Simple ERMs are membranes with cellophane-like films on the internal limiting membrane (ILM) with little or no visual symptoms. In general, they are composed mainly of glial cells. On the contrary, tractional ERMs are thicker with contractile properties that cause wrinkling of the retina and are usually accompanied by decreased vision and metamorphopsia. They are composed of glial cells and contractile cells [3], and are also known as "macular puckers" (Fig. **1**).

Epiretinal membranes cause macular structural changes such as retinal folds, vascular leakage, macular thickening, cystoid macular edema, pseudohole formation, foveal ectopia, and foveal detachment by tractional forces on the retinal surface [4].

[*] **Corresponding author Aristides J. Mendoza:** Retina Department, OftalmoSalud, Arequipa, Av Mariscal Benavides No 307, Urb Selva Alegre, Arequipa, Peru; Tel: +51(054)287373; E-mail ampcff@hotmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

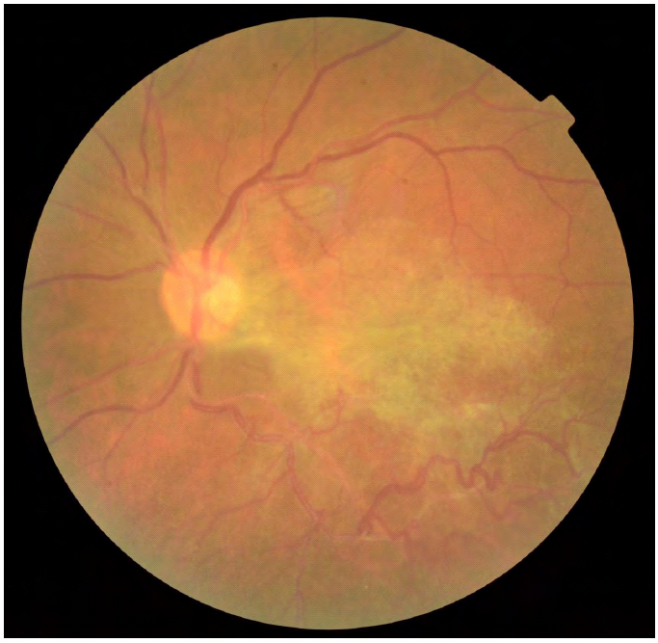


Fig. (1). Macular pucker secondary to BRVO (Courtesy of Mitzy E. Torres Soriano).

ESSENTIALS OF DIAGNOSIS

Epiretinal membranes typically affect otherwise healthy elderly individuals and are unilateral in approximately 90% of cases. Visual symptoms and decreased visual acuity will depend on the degree of distortion caused in the traction retinal membrane, which can generate a micro detachment of the posterior pole, as well as the presence or absence of macular or perimacular edema. Usually, thin epiretinal membranes don't cause many symptoms. However, in advanced cases, there is a reduction in vision, micropsia, metamorphopsia, Amsler grid distortion and, occasionally, monocular diplopia. Spontaneous separation of an epiretinal macular membrane, although uncommon, can occur [5, 6].

Slit lamp ophthalmoscopy: brightness or abnormal reflectivity in the macular region suggests the presence of an ERM (Fig. **2a**). More advanced ERMs can become opaque and thick, and may obscure underlying retinal features (Fig. **1**). ERMs cause changes in the retinal architecture with loss of foveal contour as a result of contraction.

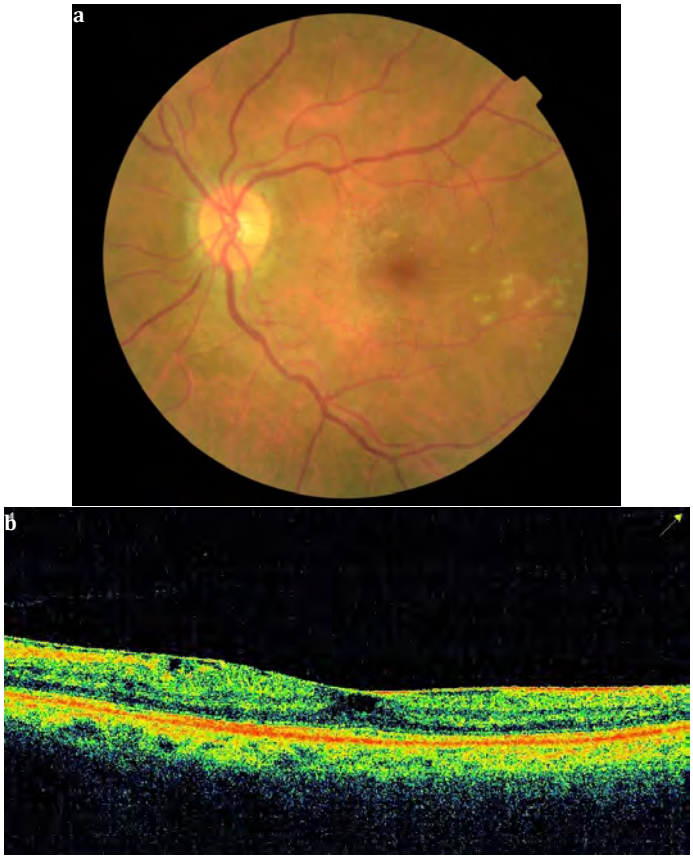


Fig. (2). (**a**) Fundus photograph that shows the typical clinical appearance of an ERM. The membrane adherent to the surface of the retina contracts and the retinal surface appears wrinkled. (**b**) OCT scan confirms ERM (Courtesy of Mitzy E. Torres Soriano).

In addition to visual acuity testing, the most common clinical tests involve fluorescein angiography and optic coherence tomography (OCT). Fluorescein angiography is moderately helpful, since it can show retinal vascular tortuosity, straightening, and leakage, as well as cystoid macular edema. OCT is the diagnostic method of choice, typically demonstrating a hyperreflective line in the surface of the retina that may be associated to retinal folding, increased macular thickness, cystoid macular edema, traction macular retinal detachment, and both lamellar or macular hole formation (Figs. **2b**, **3-6**). Amsler grid testing may help quantifying metamorphopsia in eyes with macular distortion [7]. Abnormal macular function has been shown using the electroretinogram [8, 9].

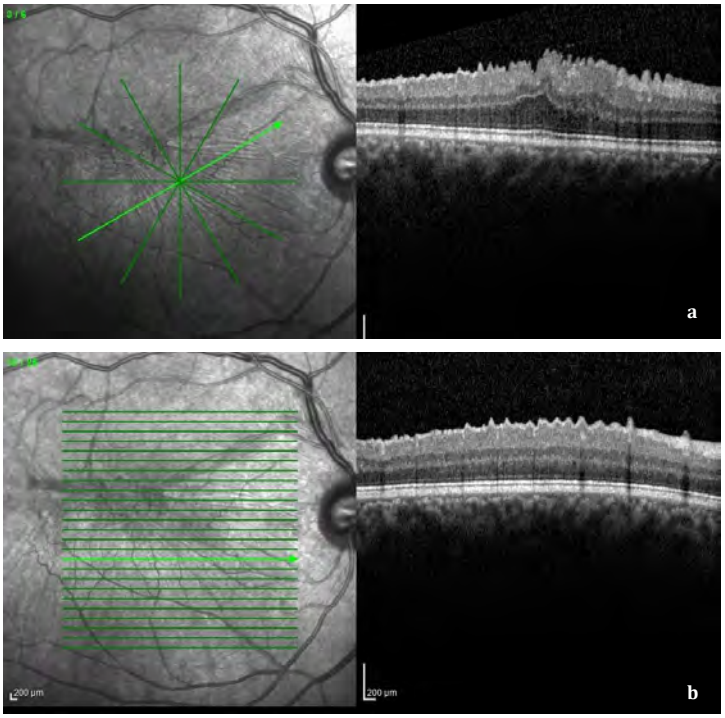


Fig. (3). (**a**) and (**b**) OCT of epiretinal membrane showing marked corrugation of the retinal surface, loss of foveal depression and diffuse retinal thickening with intraretinal fluid in multiple layers (Courtesy of Centro de la Visión Gordon-Manavella, Rosario-Argentina).

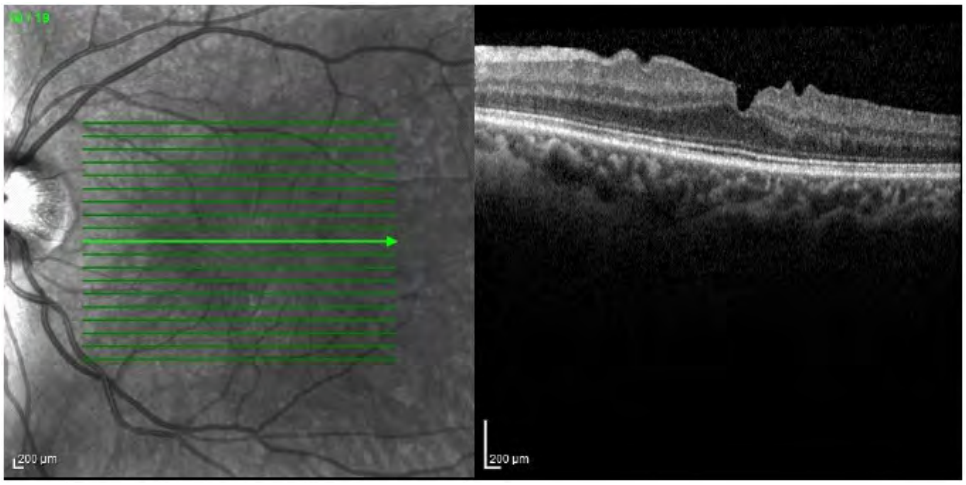


Fig. (4). Spectral domain optical coherence tomography image showing epiretinal membrane with retinal folds, and macular thickening (Courtesy of Centro de la Visión Gordon-Manavella, Rosario-Argentina).

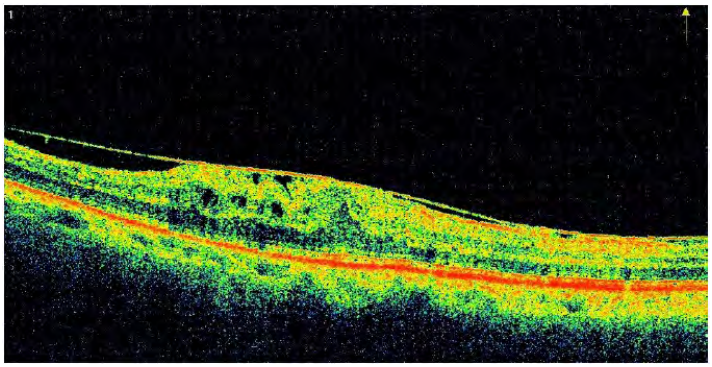


Fig. (5). OCT demonstrates ERM and intraretinal fluid (Courtesy of Mitzy E. Torres Soriano).

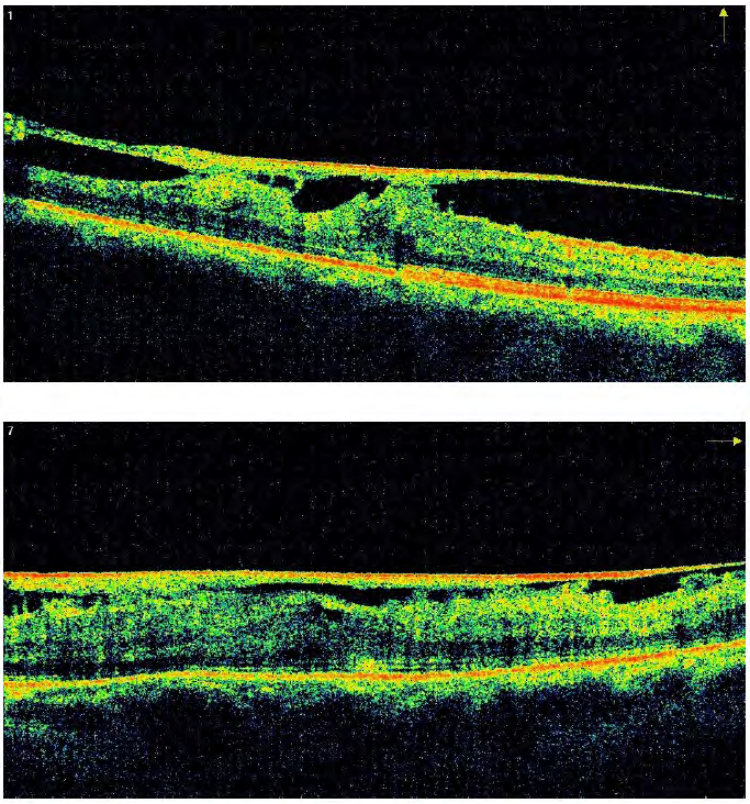


Fig. (6). OCT scan of the same lesion shown in Fig. (**5**), demonstrating a thickened ERM with severe distortion of the retina (Courtesy of Mitzy E. Torres Soriano).

DIFFERENTIAL DIAGNOSIS

The clinical appearance of an ERM is fairly distinctive. However, macular hole,

parafoveal telangiectasia, vitreomacular traction syndrome, subfoveal neovascular membrane and macular edema must also be considered. It is a very common pathology, and therefore may coexist with any of the diagnoses mentioned above.

MANAGEMENT

Most of patients with ERM have symptoms that are mild and either nonprogressive or slowly progressive, and treatment is rarely indicated. In a few cases, the membrane may spontaneously release, with a marked decrease in symptomatology and improvement in visual acuity (VA). For patients with significant symptoms and substantially reduced VA (usually 20/60 or less), pars plana vitrectomy (20, 23 or 25 gauge) with epiretinal membrane peeling can diminish the severity of symptoms and improve VA in 75% of cases or more. There is no difference in visual outcome between eyes operated with 23 gauge and 25 gauge [10]. ERM recurrence is observed in approximately 10% of cases after surgery [11]. The reasons for recurrence are the incomplete removal of the ERM and the presence of residual ILM after ERM peeling. To enhance the visualization of these transparent or semi-transparent structures and to overcome ERM recurrence, various staining methods have been used, including indocyanine green (ICG), trypan blue (TB), triamcinolone acetonide (TA), and brilliant blue G (BBG) [12].

The best candidates for surgery are those who have had membranes for a relatively short time, because the potential for visual recovery decreases as the duration of preoperative symptoms increases. Integrity of the retinal layers seen by OCT may be used to predict a good visual outcome [13].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bu SC, Kuijer R, Li XR, Hooymans JM, Los LI. Idiopathic epiretinal membrane. Retina 2014; 34(12):

2317-35.
[http://dx.doi.org/10.1097/IAE.0000000000000349] [PMID: 25360790]

[2] Joshi M, Agrawal S, Christoforidis JB. Inflammatory mechanisms of idiopathic epiretinal membrane formation. Mediators Inflamm 2013; 2013: 192582.
[http://dx.doi.org/10.1155/2013/192582]

[3] Kampik A, Green WR, Michels RG, Nase PK. Ultrastructural features of progressive idiopathic epiretinal membrane removed by vitreous surgery. Am J Ophthalmol 1980; 90(6): 797-809.
[http://dx.doi.org/10.1016/S0002-9394(14)75195-5] [PMID: 7446667]

[4] Massin P, Allouch C, Haouchine B, *et al.* Optical coherence tomography of idiopathic macular epiretinal membranes before and after surgery. Am J Ophthalmol 2000; 130(6): 732-9.
[http://dx.doi.org/10.1016/S0002-9394(00)00574-2] [PMID: 11124291]

[5] Sumers KD, Jampol LM, Goldberg MF, Huamonte FU. Spontaneous separation of epiretinal membranes. Arch Ophthalmol 1980; 98(2): 318-20.
[http://dx.doi.org/10.1001/archopht.1980.01020030314015] [PMID: 7352883]

[6] Scudder MJ, Eifrhg DE. Spontaneous surface wrinkling retinopathy. Ann Ophthalmol 1982; 94: 44.
[PMID: 1137279]

[7] Bouwens MD, Van Meurs JC. Sine Amsler Charts: a new method for the follow-up of metamorphopsia in patients undergoing macular pucker surgery. Graefes Arch Clin Exp Ophthalmol 2003; 241(2): 89-93.
[http://dx.doi.org/10.1007/s00417-002-0613-5] [PMID: 12605261]

[8] Tanikawa A, Horiguchi M, Kondo M, Suzuki S, Terasaki H, Miyake Y. Abnormal focal macular electroretinograms in eyes with idiopathic epimacular membrane. Am J Ophthalmol 1999; 127(5): 559-64.
[http://dx.doi.org/10.1016/S0002-9394(98)00447-4] [PMID: 10334349]

[9] Moschos M, Apostolopoulos M, Ladas J, *et al.* Assessment of macular function by multifocal electroretinogram before and after epimacular membrane surgery. Retina 2001; 21(6): 590-5.
[http://dx.doi.org/10.1097/00006982-200112000-00005] [PMID: 11756881]

[10] Kovacević D, Antić IV, Valković A. Comparison of 23 gauge and 25 gauge PPV in the treatment of epiretinal membranes and macular holes. Coll Antropol 2014; 38(4): 1213-6.
[PMID: 25842761]

[11] Grewing R, Mester U. Results of surgery for epiretinal membranes and their recurrences. Br J Ophthalmol 1996; 80(4): 323-6.
[http://dx.doi.org/10.1136/bjo.80.4.323] [PMID: 8703883]

[12] Kwok AKh, Lai TY, Yuen KS. Epiretinal membrane surgery with or without internal limiting membrane peeling. Clin Experiment Ophthalmol 2005; 33(4): 379-85.
[http://dx.doi.org/10.1111/j.1442-9071.2005.01015.x] [PMID: 16033350]

[13] Inoue M, Morita S, Watanabe Y, *et al.* Preoperative inner segment/outer segment junction in spectral-domain optical coherence tomography as a prognostic factor in epiretinal membrane surgery. Retina 2011; 31(7): 1366-72.
[http://dx.doi.org/10.1097/IAE.0b013e318203c156] [PMID: 21233786]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 22

Idiophatic Macular Hole

Luis M. Suarez-Tata[1,*], Moravia B. Suarez-Tata[1] and **Reinaldo García[1]**

[1] *Retina & Vitreous Service, Clínica Oftalmológica El Viñedo, Valencia, Venezuela*

Idiopathic macular hole (MH) is an acquired full thickness defect of the retina in the central macula. Macular holes were first described by Knapp in 1869 [1]. They typically occur in the sixth to eighth decade of life with a 3:1 predominance in women. The incidence of bilaterally is 5% to 10%. Tangential vitreoretinal traction (TVT) is the presumed cause of the MH.

ESSENTIALS OF DIAGNOSIS

Visual acuity, depending on the stage and severity of the MH, may be near normal or severely reduced to less than 20/400. Amsler grid will often reveal a central scotoma or metamorphopsia.

Slit-lamp biomicroscopic examination usually shows a round retinal defect that involves the fovea. Several diagnostic maneuvers may be used to find out if the lesion observed in examination is indeed a full-thickness defect (*vs.* a macular *pseudo* hole). If a tall, narrow beam is focused on the lesion, the patient may perceive a break or dent in the beam (the so-called "Watzke-Allen test). This also may be tested using the aiming beam of a retinal laser photocoagulator.

The gold-standard diagnostic tool is optic coherence tomography (OCT), due to the fact that it is non-invasive, has a very high resolution, allows careful evaluation of retinal structures and the vitreomacular interface.

[*] **Corresponding author Luis M. Suarez Tata:** Clínica Oftalmológica El Viñedo, Valencia, Venezuela; Tel/Fax: +58 (412) 3474188; E-mail: luismiguelsuarez@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

It also enables quantitative information such as minimum hole diameter, base diameter and retinal edge thickness [2].

Fluorescein angiography may also be used but has fallen into disuse, since findings are vague (a window defect corresponding to loss of xanthophyll pigment), and compared to OCT has very little sensitivity and specificity.

Classification

Gass described different stages of development of MH (Table **1**) [3, 4]. Nowadays, with OCT and the identification of vitreomacular traction and its relationship with MH, the International Vitreomacular Traction Study Group has proposed a new classification based on OCT findings and the status of the vitreomacular interface (Tables **2**-**4**) [5].

Table 1. Stage of development of idiopathic macular hole.

Normal	Layer of vitreous cortex lying on internal limiting membrane of retina (Figs. **1** and **2**)
Stage 1A:	Early contraction of outer part of vitreous cortex with foveolar detachment (Fig. **3**)
Stage 1B:	Occult hole. Dehiscense of the retinal photoreceptor layer at the umbo with centrifugal retraction of the retinal receptors. Further vitreous contraction and condensation of the prefoveal vitreous cortex with foveal detachment (Figs. **3**-**5**)
Stage 2:	Small perifoveal dehiscense. Small (< 400 μm) (Figs. **6** and **7**)
Stage 3:	Larger central full-thickness hole usually accompanied by a rim of retina elevation (>400 μm) (Figs. **8** and **9**). The posterior cortical vitreous remains attached. There may be a small operculum overlying the macular hole.
Stage 4:	Macular hole has an associated complete posterior vitreous detachment. These holes are usually large (> 400 μm) (Figs. **10**-**13**)

Based on Gass JD [3, 4].

DIFFERENTIAL DIAGNOSIS

There are several diseases that may resemble MH clinically but have distinct appearances on OCT. Macular pseudohole is an epiretinal membrane that spares the center of the fovea, causing its borders to elevate, clinically resembling a MH. The Watzke-Allen test is negative, and on OCT, the outer retinal layers are spared (Figs. **12**-**14**). Lamellar macular hole is also usually associated to an epiretinal membrane, and on OCT shows an irregular foveal contour with schisis of the

retinal layers in the parafovea, and a preserved photoreceptor layer (Figs. **14-19**). Vitreomacular traction syndrome has also to be considered, and actually is believed to play an important role in the pathophysiology of MH. Other differential diagnoses include macular telangiectasia and solar retinopathy [6, 7].

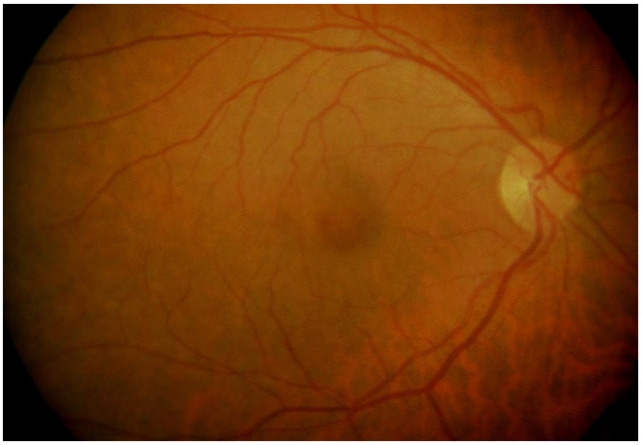


Fig. (1). Fundus photograph showing a normal macula.

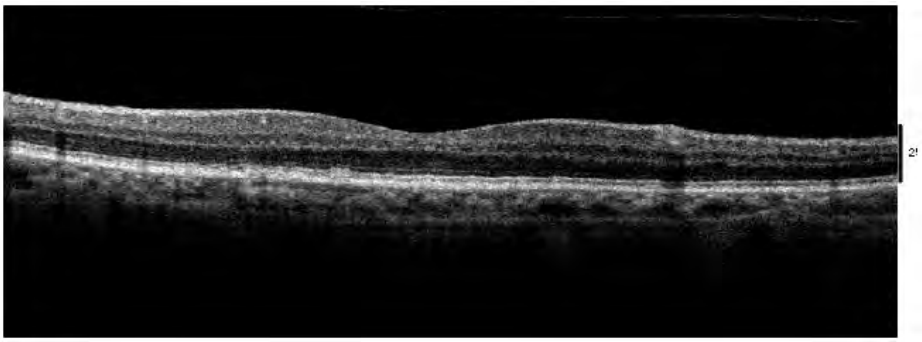


Fig. (2). Optical coherence tomography (OCT) image of a normal macula.

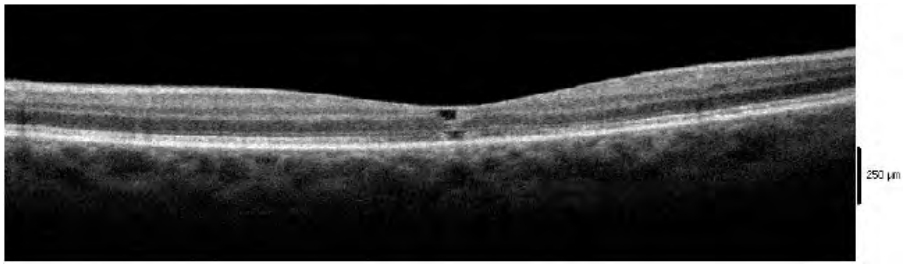


Fig. (3). OCT image of a macular hole stage 1-A, showing hyporeflective spaces in the inner and outer retina.

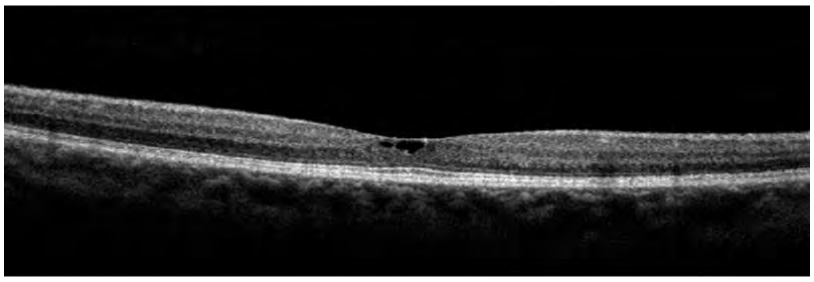


Fig. (4). OCT image of a macular hole stage 1-B, showing hyporeflective space in the inner retina.

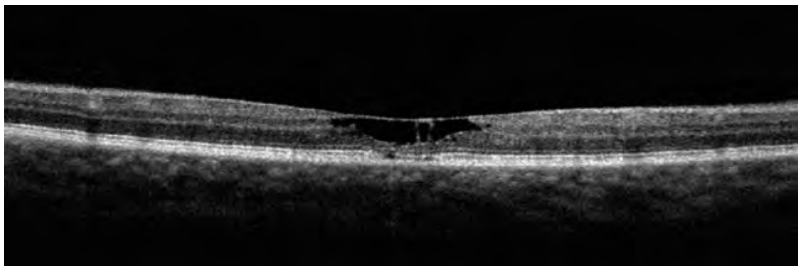


Fig. (5). OCT image of a macular hole stage 1-A, showing extensive hyporeflective spaces in the inner retina.

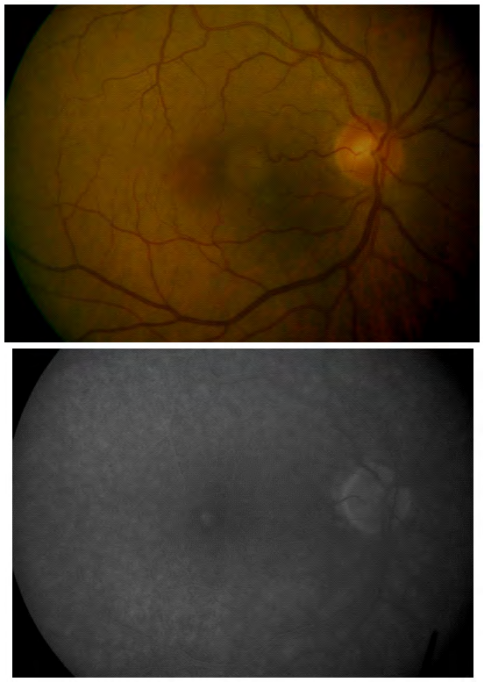


Fig. (6). A 74-year-old patient with a reduction of visual acuity to 20/70. Idiopathic macular hole stage 2. Appears as a small round defect in the fovea. Fluorescein angiogram shows an area of window defect.

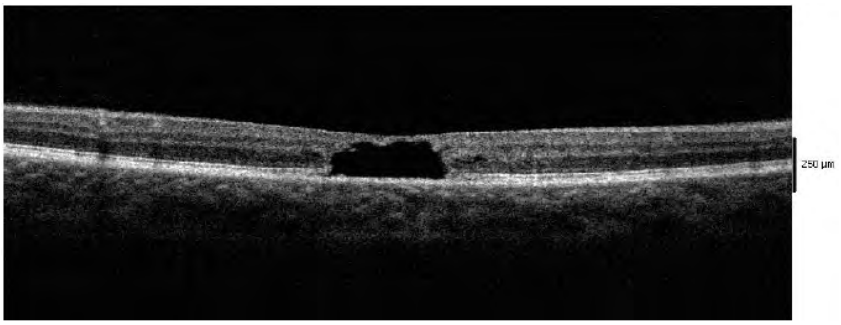


Fig. (7). OCT image of a macular hole stage 2, showing extensive defect in the outer retina.

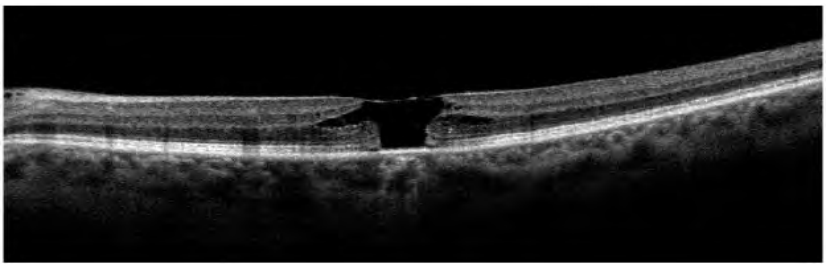


Fig. (8). OCT image of a stage 3 macular hole with extensive separation of the outer layers.

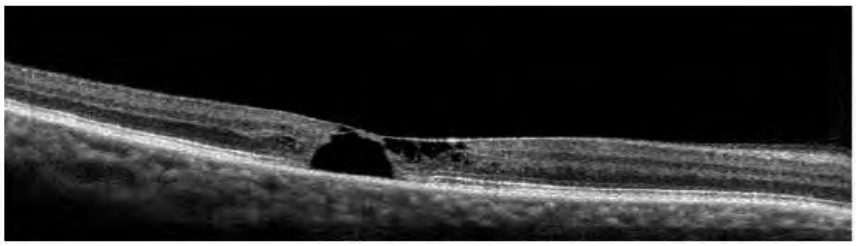


Fig. (9). OCT image of a stage 3 macular hole, showing separation of the inner and outer retinal layers.

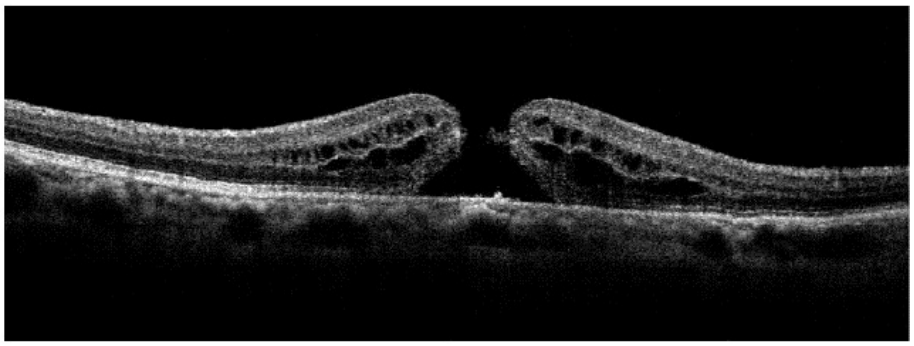


Fig. (10). OCT image of a full thickness macular hole with elevated borders, cystoid macular degeneration and irregular retinal pigment epithelium.

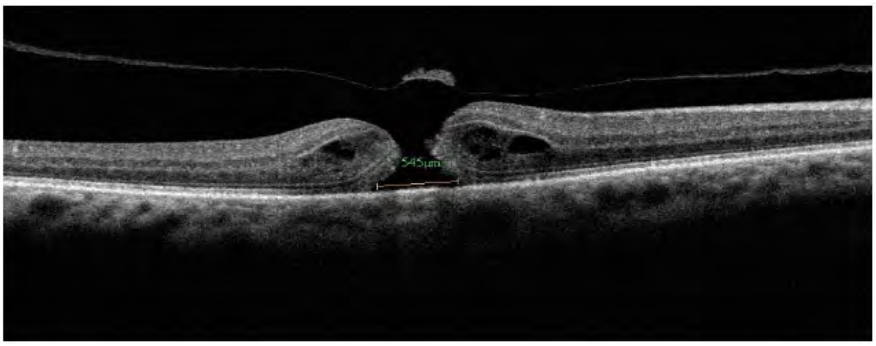


Fig. (11). OCT image of a full thickness macular hole with a pseudo-operculum.

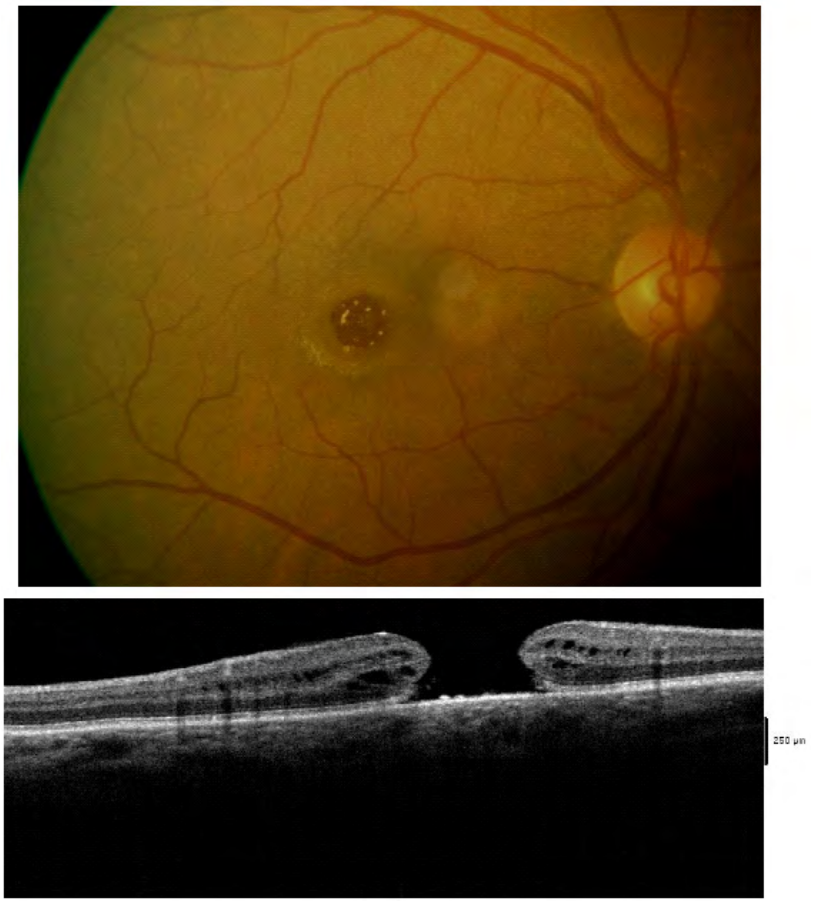


Fig. (12). Fundus photograph (top) and OCT (bottom) of a chronic macular hole. The photograph shows a large hole with pigment changes at its bottom. OCT shows a large hole with somewhat flat borders and irregular retinal pigment epithelium.

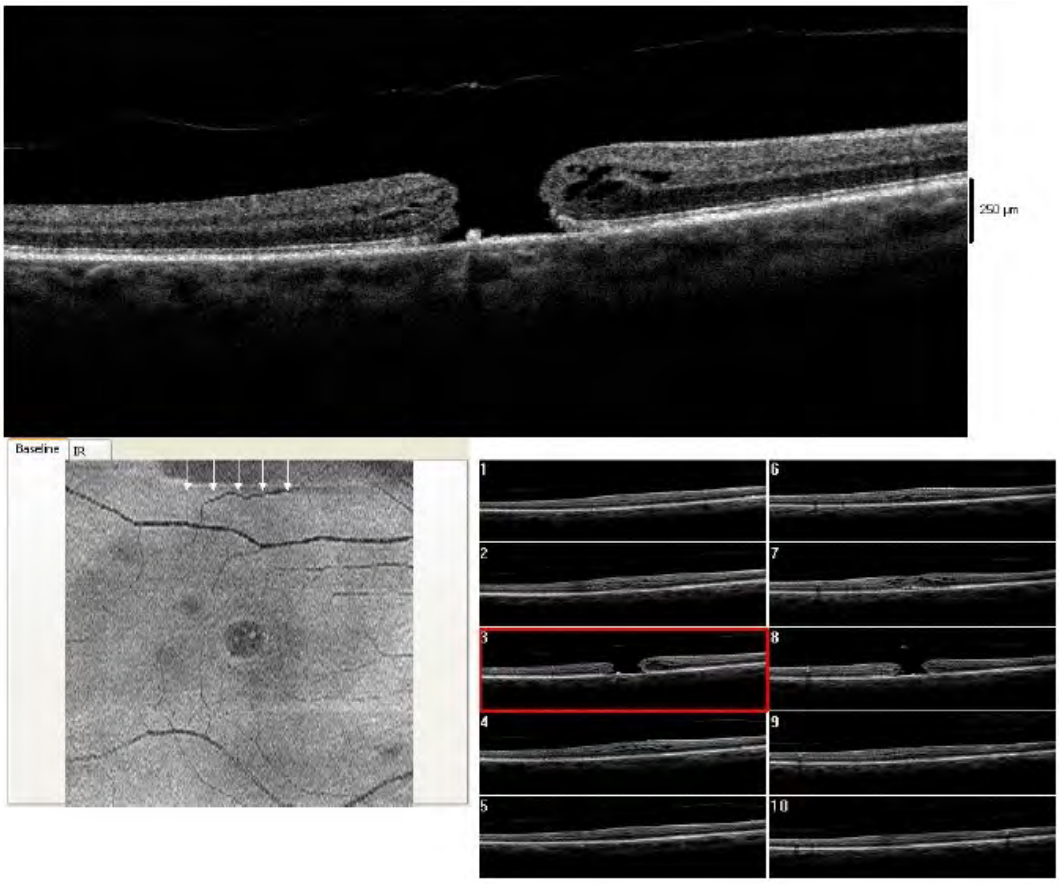


Fig. (13). Full thickness macular hole with small dots at the level of the retinal pigment epithelium.

Table 2. Correlation between commonly used clinical macular hole stages and the international vitreomacular traction study (IVTS) classification system [5].

Full-Thickness Macular Hole Stages in Common Use Classification System	International Vitreomacular Traction Study
Stage 0	Vitreomacular adhesion (VMA)
Stage 1: Impending macular hole (Impending or Occult Hole)	Vitreomacular traction (VMT)
Stage 2: Small hole	Small or medium FTMH with VMT
Stage 3: Large hole	Medium or large FTMH with VMT
Stage 4: FTMH with PVD	Small, Medium, or large FTMH without VMT

Abbreviations: FTMH full thickness macular hole; PVD posterior vitreous detachment.
Based on International Vitreomacular Traction Study Classification.

Table 3. IVTS classification system for vitreomacular adhesion, traction, and macular hole [5].

Classification	Subclassification
Vitreomacular adhesion (VMA)	Size: focal (≤1500 μm) or broad (>1500 μm) Isolated or concurrent
Vitreomacular traccion (VMT)	Size: focal (≤1500 μm) or broad (>1500 μm) Isolated or concurrent
Full-thickness macular hole	Size: small (≤250 μm), medium (>250- ≤400 μm), or large (>400 μm) Status of vitreous: with or without VMT Cause: primary or secondary

Based on International Vitreomacular Traction Study Classification.

Table 4. IVTS classification system for macular hole [5].

Full-thickness macular hole (FTMH)
Full-thickness foveal lesion that interrupts all macular layers from the ILM to the RPE
Classification
By Size
(horizontally measured linear width across hole at narrowest point, not ILM)
Small (≤250 μm)
Medium (>250 μm and ≤400 μm)
Large (>400 μm)
By presence or absence of VMT
By Cause
Primary (initiated by VMT)
Secondary (directly due to associated disease or trauma known to cause macular hole in the absence of prior VMT)
Based on International Vitreomacular Traction Study Classification.

Based on International Vitreomacular Traction Study Classification.

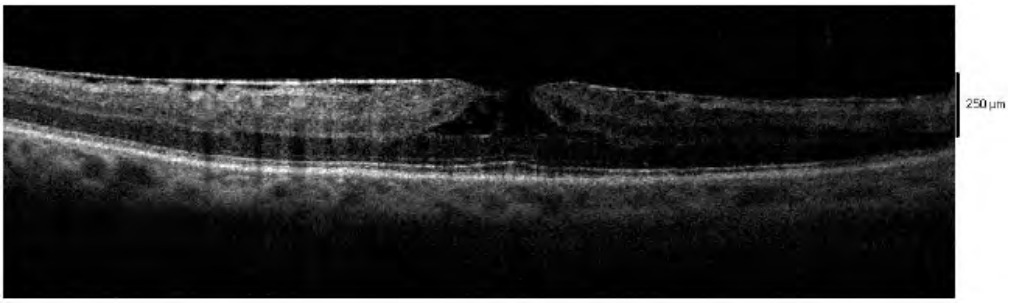


Fig. (14). Macular pseudohole with epiretinal membrane, but no full thickness interruption of all retinal layers.

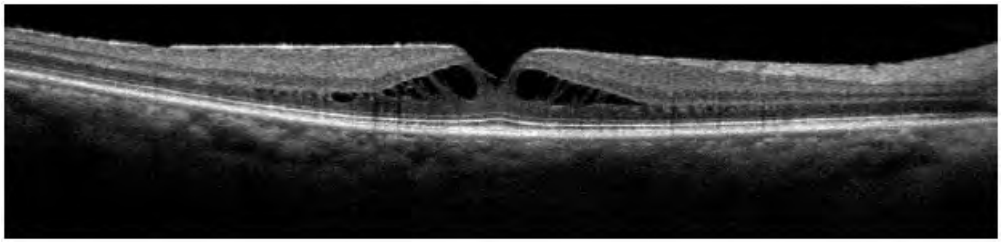


Fig. (15). OCT image of a macular pseudohole with epiretinal membrane with cystoid macular edema.

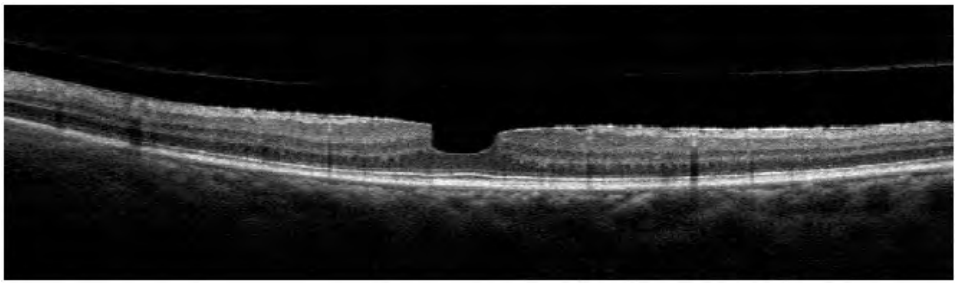


Fig. (16). OCT image of a macular pseudohole with epiretinal membrane that causes an irregular foveal contour.

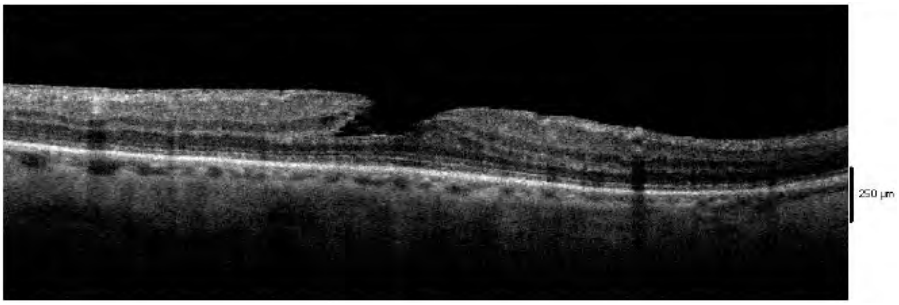


Fig. (17). OCT image of an epiretinal membrane causing a lamellar macular hole.

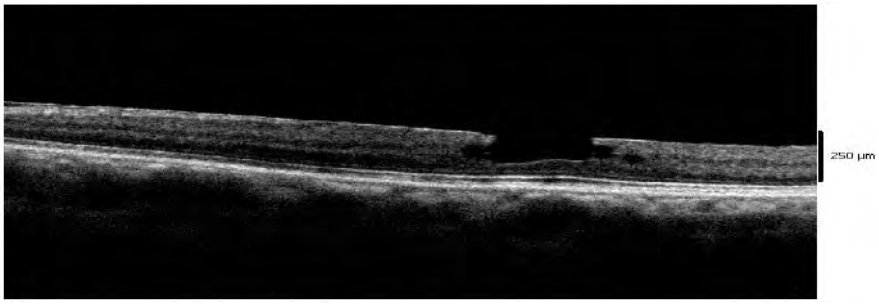


Fig. (18). OCT image showing another case of epiretinal membrane causing a lamellar macular hole. The foveal contour is irregular and there is some separation of the inner retinal layers.

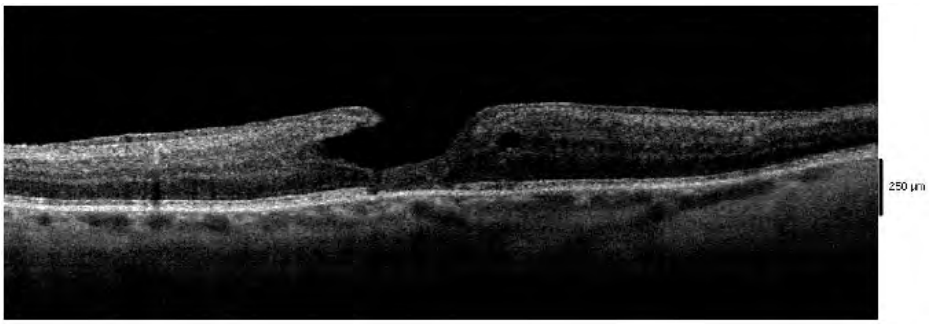
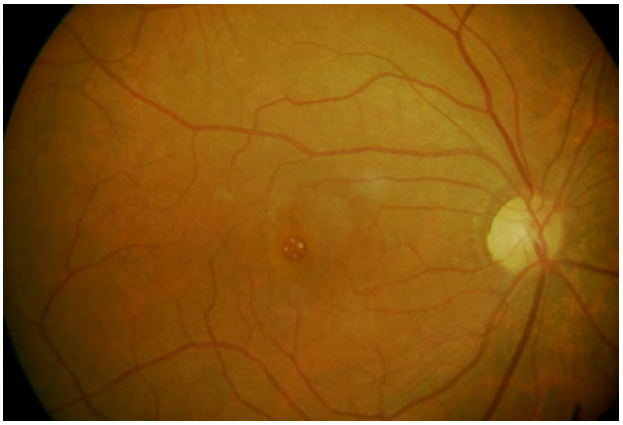
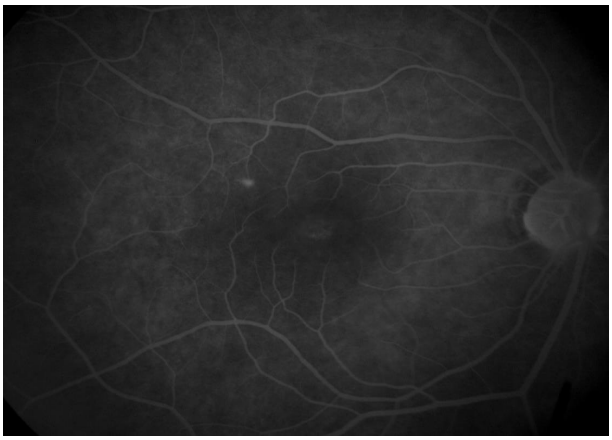


Fig. (19). OCT image showing another case of epiretinal membrane causing a lamellar macular hole. There is some fibrous epiretinal proliferation seen as a very thick epiretinal membrane that covers the entire macular surface.

Pre- and postoperative

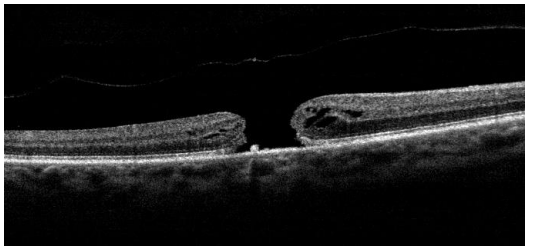


A

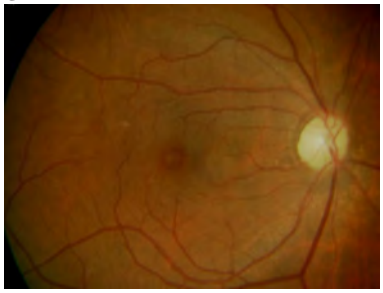


B

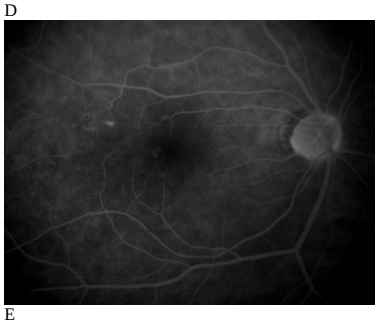
Fig. 20 contd.....



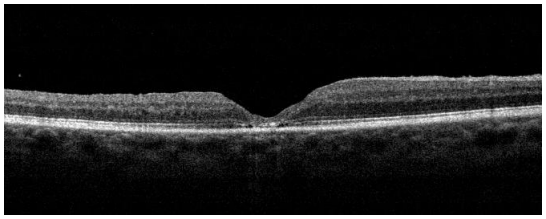
C



D



E



F

Fig. (20). A. Fundus photograph of the right eye of a 65 year old female patient showing the pre-operative appearance of a stage 4 macular hole (yellow dots in the center of the hole at the level of the retinal pigment epithelium).Visual acuity was 20/200.

B. Fluorescein angiogram showing a window defect in the fovea.

C. OCT image showing a full thickness macular hole.

D.E.F. Fundus photograph, angiogram and OCT of the same eye three months after vitrectomy and ILM removal. Three months post-operative appearance of full thickness macular hole, now closed and vision improved to20/50.

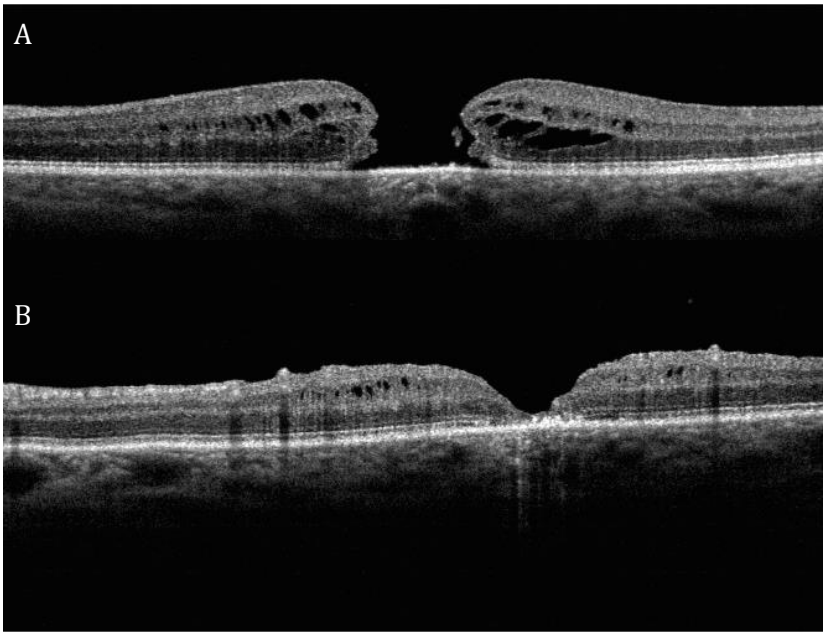


Fig. (21). A. Preoperative OCT image of a full-thickness macular hole. **B**. Postoperative appearance of the same eye.

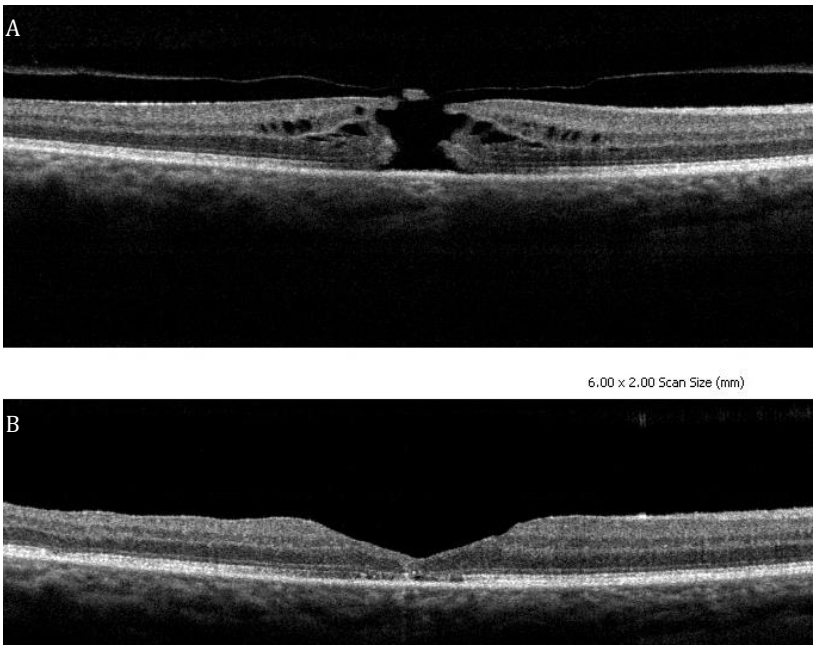


Fig. (22). A. OCT image showing a full thickness macular hole with pseudo-operculum. **B**. Postoperative OCT image showing some defects in the outer retinal layers.

MANAGEMENT

The standard surgery for the repair of MH was described by Kelly and Wendel [8] in 1991 and involves a standard three-port pars plana vitrectomy, posterior hyaloid separation, stripping of epiretinal/internal limiting membranes (ILM) and gas tamponade. A total air-fluid gas exchange is performed, followed by an air-gas exchange using a non-expansile concentration of gas (C_2F_6, C_3F_8 or SF_6). Although closure of the hole is the rule, the fovea rarely recovers its normal contour (Figs. **20-22**)

Controversial issues in macular hole surgery today involve peeling and staining the ILM. The most common dyes are Indocyanine green (ICG) [9, 10], Trypan blue [11], triamcinolone acetonide [12, 13], and Brilliant blue G (BBG) [14]. Staining improves the visibility and the ease of stripping the ILM, but studies suggest that it may also cause retinal damage.

Different instruments have been used to grasp the ILM creating a surgical plane. These instruments include the micro-barbed micro-vitreoretinal blade or the diamond-dusted silicone cannula. After lifting an edge of the membrane, it is stripped with fine end-gripping tissue forceps.

The success rate for macular hole surgery approaches 80% to 90% with closure of the macular hole and improvement in visual acuity. However, the most important predictors of visual outcomes are its size and the time of duration [15].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Knapp. Ueber isolitre Zerreissungen der Aderhaut in Folge von Traumen auf dem Augapfel. Arch Augenheilk 1869; 1: 6-29.

[2] Desai VN, Hee MR, Puliafito CA. Optical coherence tomography of macular holes. In: Madreperla SA, McCuen BW, Eds. Macular hole. Boston, Mass: Botterworth-Heinemann 1999; pp. 37-47.

[3] Gass JD. Idiopathic senile macular hole. Its early stages and pathogenesis. Arch Ophthalmol 1988; 106(5): 629-39.
[http://dx.doi.org/10.1001/archopht.1988.01060130683026] [PMID: 3358729]

[4] Gass JD. Reappraisal of biomicroscopic classification of stages of development of a macular hole. Am J Ophthalmol 1995; 119(6): 752-9.
[http://dx.doi.org/10.1016/S0002-9394(14)72781-3] [PMID: 7785690]

[5] Duker JS, Kaiser PK, Binder S, *et al.* The international vitreomacular traction study group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology 2013; 120(12): 2611-9.
[http://dx.doi.org/10.1016/j.ophtha.2013.07.042] [PMID: 24053995]

[6] Yun C, Oh J, Hwang SY, Togloom A, Kim SW, Huh K. Morphologic characteristics of chronic macular hole on optical coherence tomography. Retina 2012; 32(10): 2077-84.
[http://dx.doi.org/10.1097/IAE.0b013e31825620ba] [PMID: 22617832]

[7] Smiddy WE, Gass JD. Masquerades of macular holes. Ophthalmic Surg 1995; 26(1): 16-24.
[PMID: 7746619]

[8] Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. Arch Ophthalmol 1991; 109(5): 654-9.
[http://dx.doi.org/10.1001/archopht.1991.01080050068031] [PMID: 2025167]

[9] Da Mata AP, Burk SE, Riemann CD, *et al.* Indocyanine green-assisted peeling of the retinal internal limiting membrane during vitrectomy surgery for macular hole repair. Ophthalmology 2001; 108(7): 1187-92.
[http://dx.doi.org/10.1016/S0161-6420(01)00593-0] [PMID: 11425673]

[10] Haritoglou C, Gandorfer A, Gass CA, Schaumberger M, Ulbig MW, Kampik A. Indocyanine green-assisted peeling of the internal limiting membrane in macular hole surgery affects visual outcome: a clinicopathologic correlation. Am J Ophthalmol 2002; 134(6): 836-41.
[http://dx.doi.org/10.1016/S0002-9394(02)01816-0] [PMID: 12470751]

[11] Vote BJ, Russell MK, Joondeph BC. Trypan blue-assisted vitrectomy. Retina 2004; 24(5): 736-8.
[http://dx.doi.org/10.1097/00006982-200410000-00008] [PMID: 15492627]

[12] Kimura H, Kuroda S, Nagata M. Triamcinolone acetonide-assisted peeling of the internal limiting membrane. Am J Ophthalmol 2004; 137(1): 172-3.
[http://dx.doi.org/10.1016/S0002-9394(03)00782-7] [PMID: 14700661]

[13] Takasu I, Shiraga F, Otsuki H. Triamcinolone acetonide-assisted internal limiting membrane peeling in macular hole surgery. Retina 2004; 24(4): 620-2.
[http://dx.doi.org/10.1097/00006982-200408000-00021] [PMID: 15300089]

[14] Enaida H, Hisatomi T, Hata Y, *et al.* Brilliant blue G selectively stains the internal limiting membrane/brilliant blue G-assisted membrane peeling. Retina 2006; 26(6): 631-6.
[PMID: 16829804]

[15] Kusuhara S, Negi A. Predicting visual outcome following surgery for idiopathic macular holes. Ophthalmologica 2014; 231(3): 125-32.
[http://dx.doi.org/10.1159/000355492] [PMID: 24296852]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 23

Macular Pseudo-hole

Jose A. Roca[1,*], Hugo Luglio[2] and **Daniela Roca[1]**

[1] *Ophthalmology Department, Clínica Ricardo Palma, Lima-Peru, Peru*

[2] *Macula D&T, Lima-Peru, Peru*

ESSENTIALS OF DIAGNOSIS

The term "macular pseudo-hole" (MPH) was coined by Allen and Gass in 1976 [1] to describe any foveal lesion that has a biomicroscopic appearance of a full-thickness macular hole (FTMH), but is not. It is usually formed by a centrifugal contraction of an epiretinal tissue (epiretinal membrane) that surrounds but does not cover the foveolar area, making the borders have a more vertical appearance [2].

The patient usually has no complaints, and the visual acuity is normal or nearly normal, ranging from 20/15 to 20/100 (median 20/25) [3]. Because of the good surgical results of true macular holes, it is important to differentiate between a true macular hole and a macular pseudo-hole. The appearance of a true macular hole is different, usually very round, with a halo of marginal detachment surrounding the hole, tiny yellow deposits in its base (within the hole), a translucent operculum in front of some holes, and a zone of hyperfluorescence corresponding to the size of the hole during the early stages of angiography. These characteristics are not seen in a macular pseudo-hole.

Biomicroscopy of a patient with a macular pseudo-hole usually reveals crinkling of the inner retinal surface surrounding the hole in the epiretinal membrane and a punched-out appearance in the area of the hole (Fig. **1**) [4]. As the slit beam is

Correspondence: **Corresponding author Jose A. Roca:** Ophthalmology Department, Clínica Ricardo Palma, Torre B, piso 10, San Isidro, Lima-Peru; Tel: +51 (1) 2242224; E-mail: jaroca62@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

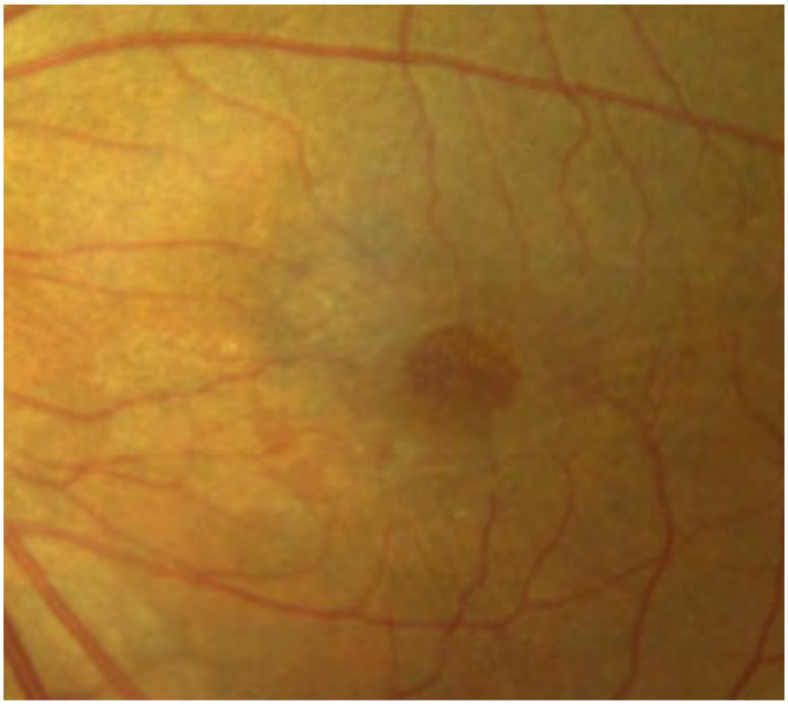


Fig. (1). Fundus photograph of the left eye, showing a macular pseudohole with an epiretinal membrane.

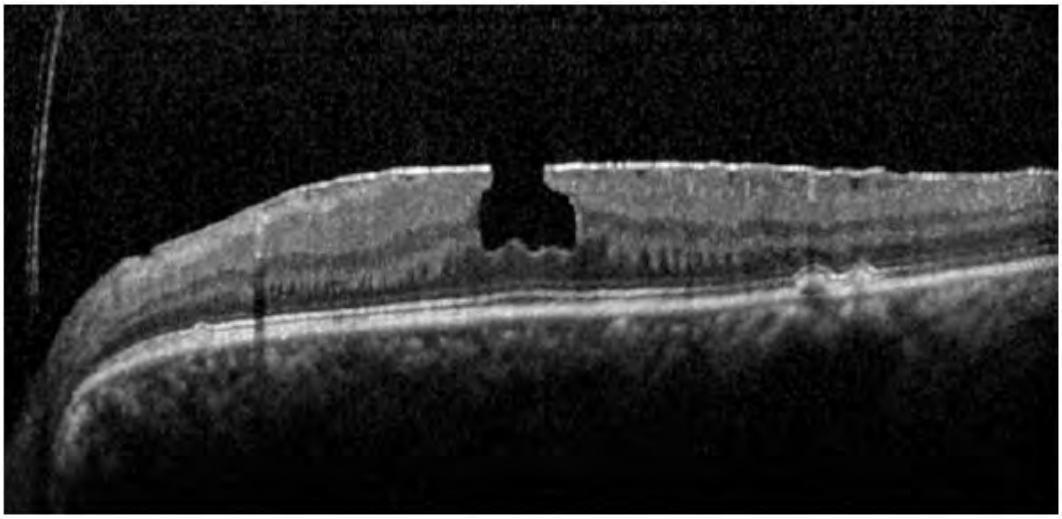


Fig. (2). OCT of the same patient of Fig. (**1**), showing a macular pseudo-hole with an epiretinal membrane with a U form fovea and preserved outer retinal layers.

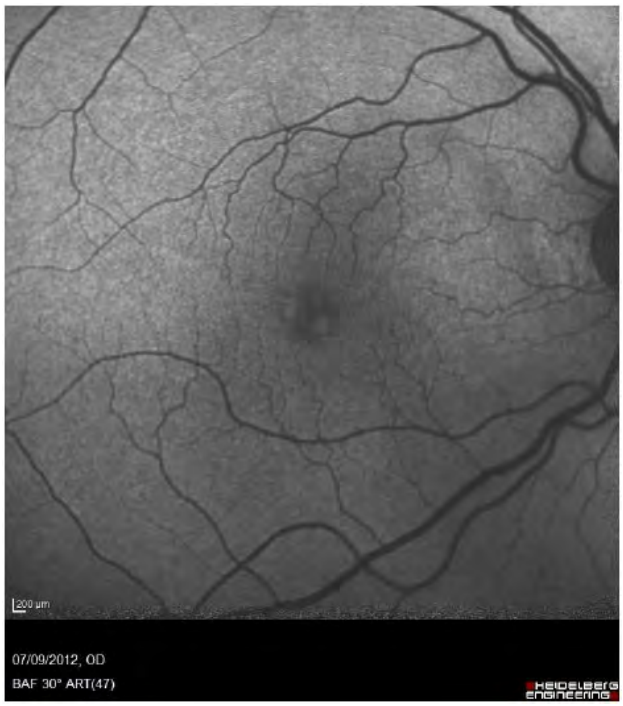


Fig. (3). Autofluorescence of a macular pseudo-hole.

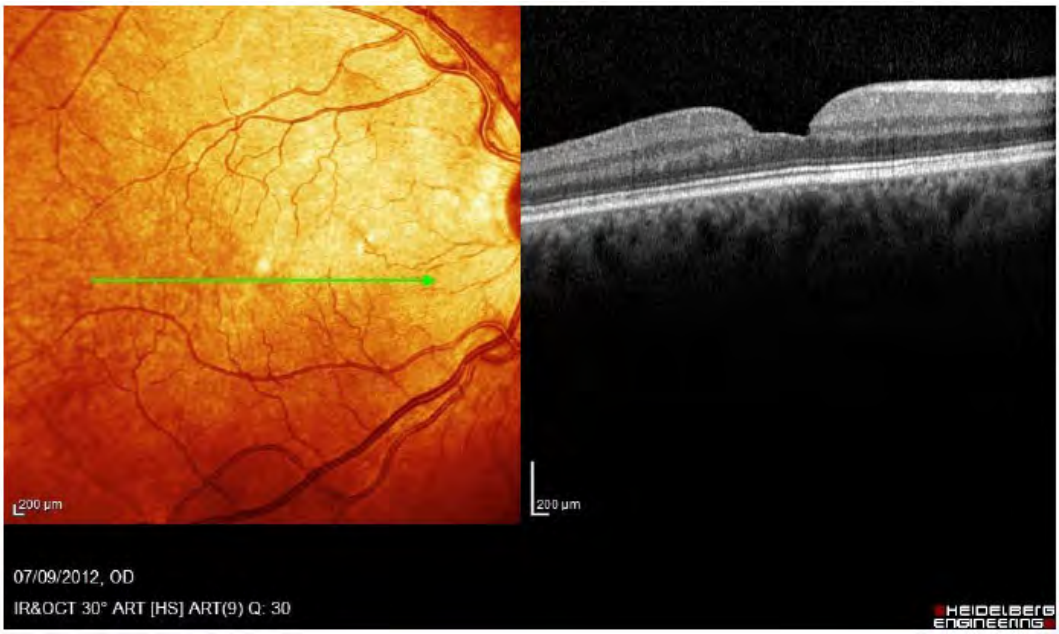


Fig. (4). OCT image of a macular pseudohole showing slight distortion of the foveal contour.

moved across the pseudo-hole, there is usually a light reflex that is evidence of retinal tissue in the base; the Watzke-Allen sign is negative (positive in FTMH). The Amsler grid test usually is not decisive in the diagnosis because some patients who have macular pseudo-holes present scotomas. Fluorescein angiography is generally normal but may show a very faint zone of hyperfluorescence corresponding with the pseudo-hole. This zone of hyperfluorescence is typically much less prominent than the finely granular area of hyperfluorescence seen with a full-thickness hole [3]. The presence of the semitransparent perifoveolar epiretinal membrane probably causes the foveolar area to appear faintly hyperfluorescent in contrast to the perifoveolar area. Autofluorescence imaging demonstrates bright fluorescence of macular holes with appearance similar to that obtained by fluorescein angiography. In contrast, macular pseuodoholes show no such autofluorescence (Fig. **3**) [5]. Scanning laser ophthalmoscope (SLO) microperimetry examination shows no deep scotomas (patients with FTMH have deep scotomas); this exam has 100% sensitivity and specificity for the differential diagnosis with FTMH [6]. Optical coherent tomography (OCT) examination makes the diagnosis of macular pseudo-holes much easier; the OCT characteristics of a macular pseudo-holes are: thickening of the macula contracted by an ERM, the U or V shape of the fovea, and no loss of retinal tissue at the umbo of the fovea (retention of photoreceptors) (Figs. **2** and **4**) [7 - 9]. Using high-resolution OCT, Witkin *et al.* also described cases combining foveal thickening due to ERM contraction, with stretching of the foveal edge resulting in the thinning of the foveal floor. These cases may in fact represent a type of macular pseudohole induced by both centripetal and centrifugal contraction of the ERM between several eccentric epicenters [10].

Fish *et al.* reported that the diagnosis by the initial examining physician was correct in only 43% of eyes with macular pseudo-holes [11].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should be made with a stage 1-A impending hole (foveolar yellow lesion), solitary drusen, small RPE detachment, small atrophy of the RPE, choroidal neovascularization, a small focal area of central serous chorioretinopathy, foveolar detachment with epiretinal membrane, focal retinal atrophy

associated with bilateral idiopathic juxtafoveolar retinal telangiectasis, pattern dystrophy, cystoid macular edema, and solar maculopathy [12].

MANAGEMENT

Visual prognosis in these patients is usually good. In a few patients, the additional contraction of an eccentrically located perifoveal epiretinal membrane may distort the foveal area. Pars plana vitrectomy to peel the epiretinal membrane may be indicated in patients with worsening vision. In few of them, the epiretinal membrane may peel free from the inner retinal surface. Most patients with MPH will not experience much visual changes.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Allen AW Jr, Gass JD. Contraction of a perifoveal epiretinal membrane simulating a macular hole. Am J Ophthalmol 1976; 82(5): 684-91.
[http://dx.doi.org/10.1016/0002-9394(76)90002-7] [PMID: 998690]

[2] Gaudric A, Tadayoni R. Macular hole. Ophthalmology 2015.
[http://dx.doi.org/10.1016/B978-1-4557-0737-9.00117-X]

[3] Tsujikawa M, Ohji M, Fujikado T, Saito Y, Motokura M, Ishimoto I. Differentiating full thickness macular holes from impending macular holes and macular pseudoholes. Tano Br J Ophthalmol 1997; 81: 117-22.
[http://dx.doi.org/10.1136/bjo.81.2.117] [PMID: 9059244]

[4] Gass JD. Stereoscopic atlas of macular diseases: diagnosis and treatment. 3rd ed. St Louis: CV Mosby 1987; pp. 684-93.

[5] Ciardella AP, Lee GC, Langton K, Sparrow J, Chang S. Autofluorescence as a novel approach to diagnosing macular holes. Am J Ophthalmol 2004; 137(5): 956-9.
[http://dx.doi.org/10.1016/j.ajo.2003.11.040] [PMID: 15126174]

[6] Tsujikawa M, Ohji M, Fujikado T, *et al.* Differentiating full thickness macular holes from impending macular holes and macular pseudoholes. Br J Ophthalmol 1997; 81(2): 117-22.
[http://dx.doi.org/10.1136/bjo.81.2.117] [PMID: 9059244]

[7] Haouchine B, Massin P, Tadayoni R, Erginay A, Gaudric A. Diagnosis of macular pseudoholes and

lamellar macular holes by optical coherence tomography. Am J Ophthalmol 2004; 138(5): 732-9. [http://dx.doi.org/10.1016/j.ajo.2004.06.088] [PMID: 15531306]

[8] Chen JC, Lee LR. Clinical spectrum of lamellar macular defects including pseudoholes and pseudocysts defined by optical coherence tomography. Br J Ophthalmol 2008; 92(10): 1342-6. [http://dx.doi.org/10.1136/bjo.2007.133041] [PMID: 18684752]

[9] Martinez J, Smiddy WE, Kim J, Gass JD. Differentiating macular holes from macular pseudoholes. Am J Ophthalmol 1994; 117(6): 762-7. [http://dx.doi.org/10.1016/S0002-9394(14)70319-8] [PMID: 8198160]

[10] Witkin AJ, Ko TH, Fujimoto JG, *et al.* Redefining lamellar holes and the vitreomacular interface: an ultrahigh-resolution optical coherence tomography study. Ophthalmology 2006; 113(3): 388-97. [http://dx.doi.org/10.1016/j.ophtha.2005.10.047] [PMID: 16513456]

[11] Fish RH, Anand R, Izbrand DJ. Macular pseudoholes. Clinical features and accuracy of diagnosis. Ophthalmology 1992; 99(11): 1665-70. [http://dx.doi.org/10.1016/S0161-6420(92)31747-6] [PMID: 1454341]

[12] Smiddy WE, Gass JD. Masquerades of macular holes. Ophthalmic Surg 1995; 26(1): 16-24. [PMID: 7746619]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 24

Vitreomacular Traction

Mitzy E. Torres Soriano[1,2,3,*] and **Maximiliano Gordon**[2,3]

[1] *Unidad Oftalmológica "Dr. Torres López", Centro Médico Cagua, Cagua, Venezuela*

[2] *Retina Department, Ophthalmology Service, Hospital Provincial del Centenario, Rosario, Santa Fe, Argentina*

[3] *Centro de la Visión Gordon-Manavella, Rosario, Argentina*

Vitreomacular Traction Syndrome (VMT) occurs as a result of incomplete posterior vitreous detachment, resulting in persistent vitreous traction on the posterior retina [1].

The prevalence of VMT syndrome is 22.5 per 100,000 population. The annual incidence is 0.6 per 100,000 population. The prevalence and incidence of VMT associated with diabetic retinopathy, diabetic macular edema, age-related macular degeneration, and other macular diseases (concurrent VMT) are much higher [2].

ESSENTIALS OF DIAGNOSIS

Patients may be asymptomatic or present the following symptoms: decreased visual acuity, metamorphopsia, photopsia, and micropsia [1]. Symptoms usually progress gradually [3].

Optical coherence tomography (OCT) allows visualization of the vitreomacular interface and confirms vitreomacular adhesion or traction. Intraretinal cystic changes and foveal detachment can be seen.

Recently, OCT-based anatomic definitions and classifications have been proposed by the International Vitreomacular Traction Study (IVTS) Group to define these entities (Table **1**) [4].

* **Corresponding author Mitzy E. Torres Soriano:** Centro de la Visión Gordon - Manavella, Montevideo 763, CP 2000, Rosario - Santa Fe, Argentina; Tel: +54 (0341) 4400239; E-mail: mitzytorres@yahoo.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

Table 1. IVTS classification system for vitreomacular adhesion and vitreomacular traction.

Vitreomacular Adhesion (VMA): Evidence of perifoveal vitreous cortex detachment from the retinal surface. Macular attachment of the vitreous cortex within a 3-mm radius of the fovea. No detectable change in foveal contour or underlying retinal tissues.	**Classification** ***By size of attachment area:*** Focal <1500 µm (Fig. **1**) Broad >1500 µm, parallel to RPE and may include areas of dehiscence ***(By presence of concurrent retinal conditions:)*** Isolated Concurrent
Vitreomacular Traction (VMT): Evidence of perifoveal vitreous cortex detachment from the retinal surface. Macular attachment of the vitreous cortex within a 3-mm radius of the fovea Association of attachment with distortion of the foveal surface, intraretinal structural changes, and/or elevation of the fovea above the RPE, but no full-thickness interruption of all retinal layers.	**Classification** ***By size of attachment area:*** Focal <1500 µm (Figs. **2**, **3** and **5**) Broad >1500 µm, parallel to RPE and may include areas of dehiscence (Fig. **4**) ***By presence of concurrent retinal conditions:*** Isolated Concurrent

Based on International Vitreomacular Traction Study Classification.

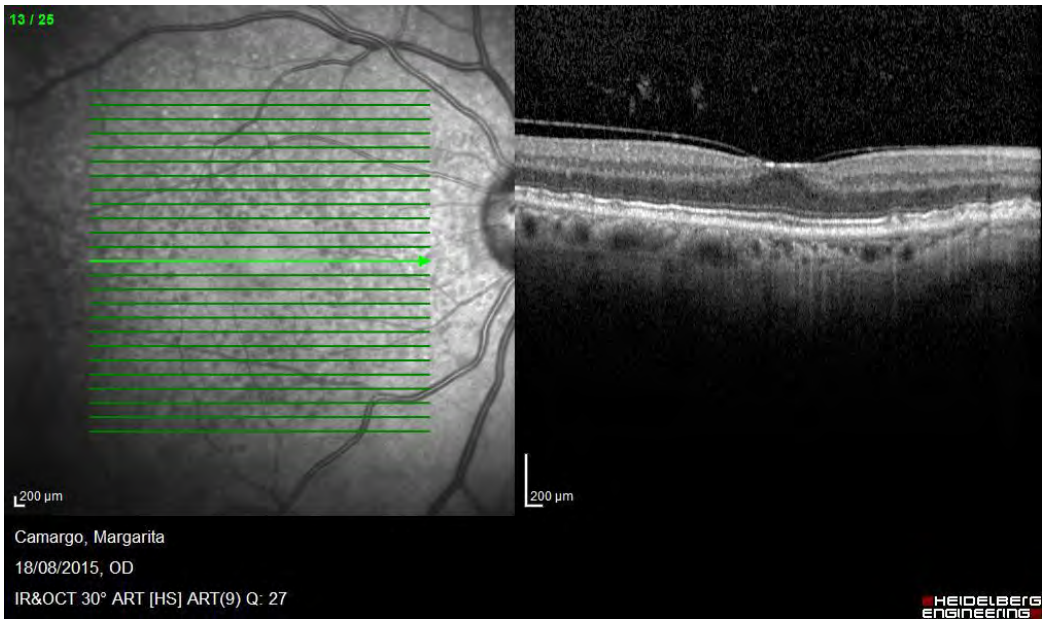


Fig. (1). Focal vitreomacular adhesion: partial vitreous detachment.

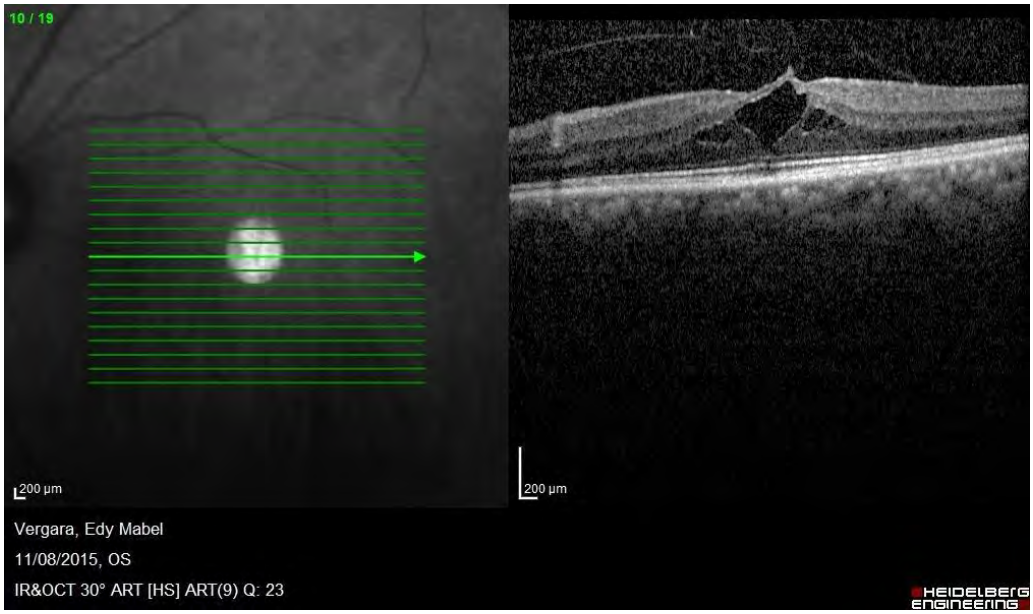


Fig. (2). Focal vitreomacular traction causing distortion of the foveal contour and separation of retinal layers.

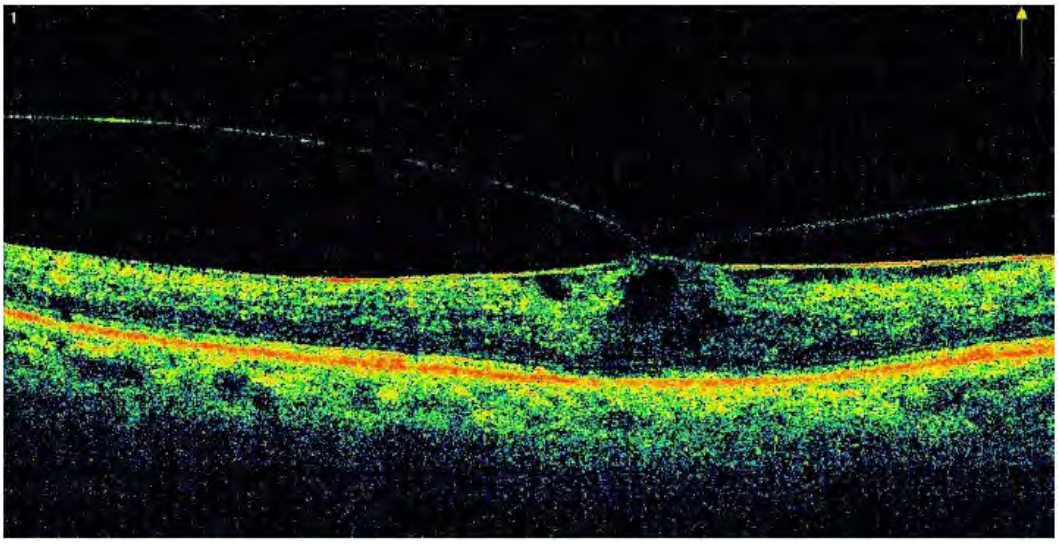


Fig. (3). Focal vitreomacular traction in V pattern, epiretinal membrane and significant distortion of the retinal architecture.

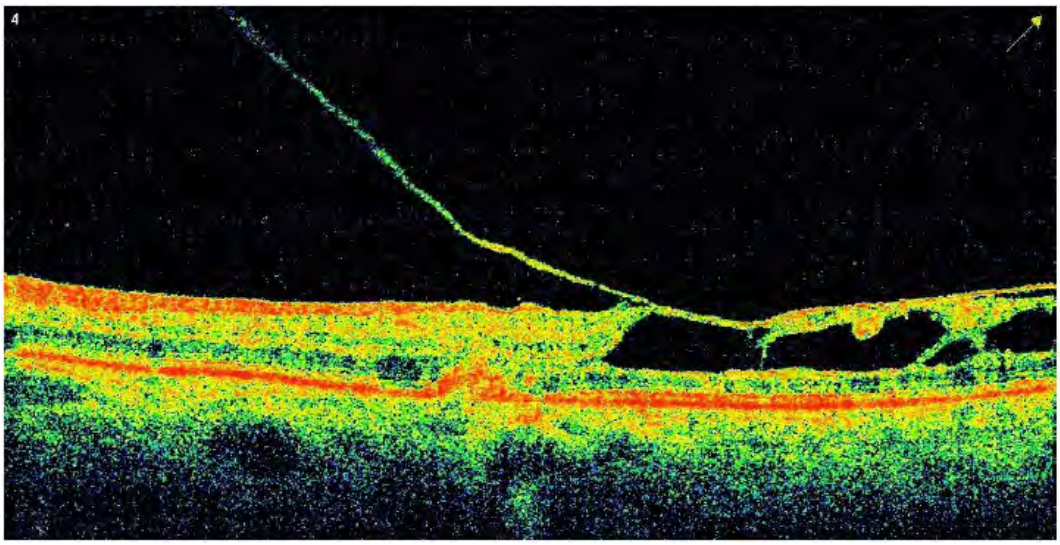


Fig. (4). Spectral domain OCT scan reveals a broad vitreomacular traction and severe distortion of retinal layers.

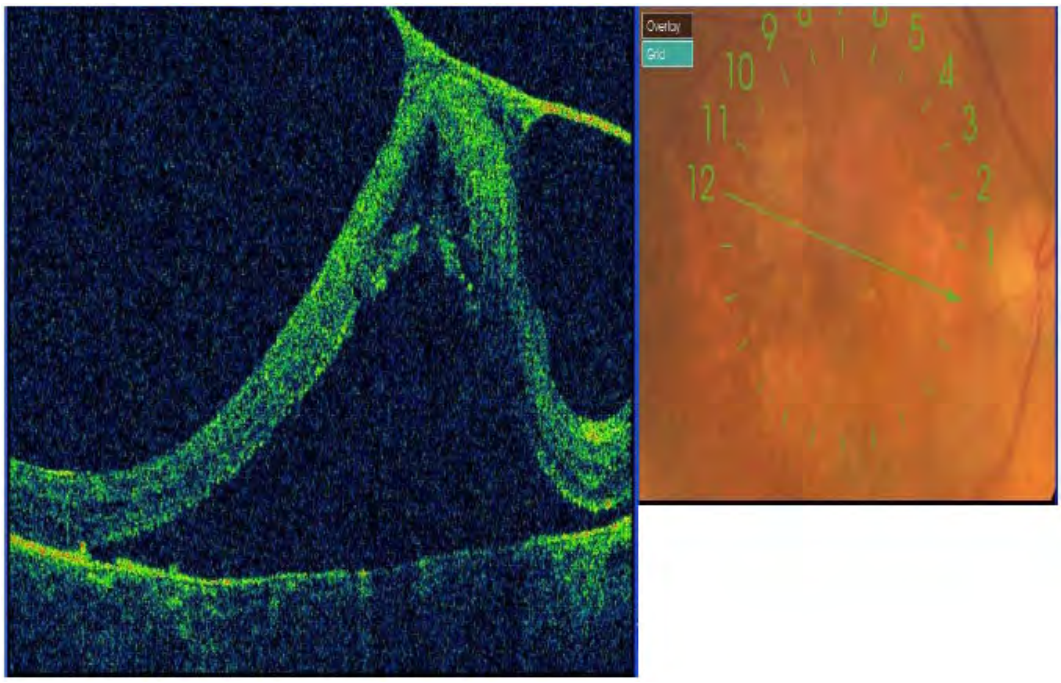


Fig. (5). OCT image showing severe vitreomacular traction causing foveal detachment (Courtesy of Francys Torres MD, Maracay, Venezuela).

Fluorescein angiography can reveal retinal capillary leakage in the macula due to cystoid macular edema (CME). An associated foveal retinal detachment may be noted as fluorescein pooling [3, 5].

B-scan ultrasound reveals partial posterior vitreous detachment which is seen as a thin, smooth, continuous membrane with focal attachment to the retinal surface [3, 6].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis can include [3]: early full thickness macular hole, pseudophakic CME, other causes of CME (uveitis, diabetic macular edema, exudative age related macular degeneration, macular telangiectasia) and ERM, which could be present as concurrent macular disease (Fig. **3**).

MANAGEMENT

Asymptomatic VMA patients are not candidates for surgical therapy [8]. VMA usually resolves spontaneously as part of the normal process of PVD, although it may progress to VMT. Periodic monitoring with OCT every 3 months is necessary. Even in cases that progress to a VMT syndrome, observation still remains an option, given the possibility of spontaneous resolution (11%) of VMT (Fig. **6**) [7, 9].

(a)

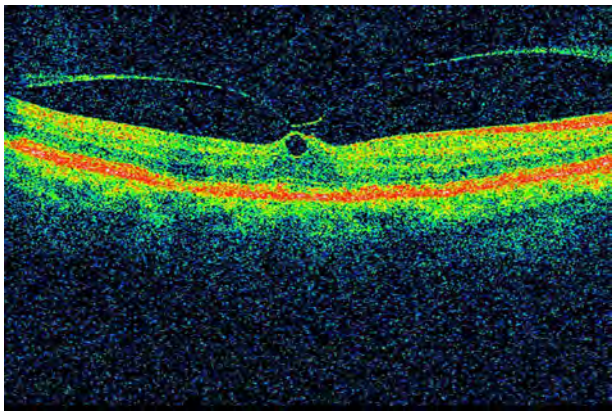


Fig. 6 contd.....

(b)

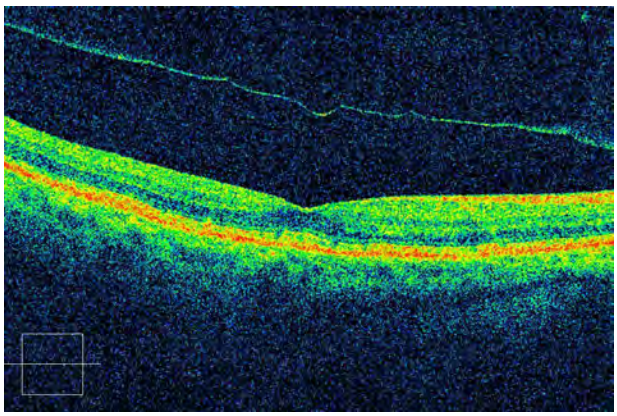


Fig. (6). (**a**) Vitreomacular traction causing distortion of the foveal contour. (**b**) Spontaneous resolution of vitreomacular traction after 4 months.

Posterior vitrectomy combined with stripping of the posterior hyaloid and ILM peeling would be the surgical treatment of choice [10, 11].

The medical therapy of VMT consists of pharmacologic vitreolysis. Jetrea® (ocriplasmin) was approved for the treatment of patients with symptomatic VMA [12 - 14]. Vitrectomy may still be required in patients failing ocriplasmin therapy and also in about 20% of the patients successfully treated with ocriplasmin [15, 16].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Hikichi T, Yoshida A, Trempe CL. Course of vitreomacular traction syndrome. Am J Ophthalmol 1995; 119(1): 55-61. [http://dx.doi.org/10.1016/S0002-9394(14)73813-9] [PMID: 7825690]

[2] Jackson TL, Nicod E, Simpson A, Angelis A, Grimaccia F, Kanavos P. Symptomatic vitreomacular adhesion. Retina 2013; 33(8): 1503-11. [http://dx.doi.org/10.1097/IAE.0b013e31829232fd] [PMID: 23714857]

[3] Bottós J, Elizalde J, Arevalo JF, Rodrigues EB, Maia M. Vitreomacular traction syndrome. J Ophthalmic Vis Res 2012; 7(2): 148-61.
[PMID: 23275824]

[4] Duker JS, Kaiser PK, Binder S, *et al.* The international vitreomacular traction study group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology 2013; 120(12): 2611-9.
[http://dx.doi.org/10.1016/j.ophtha.2013.07.042] [PMID: 24053995]

[5] Hermann D, Schubert MD, Binder S, de Smet MD, Gaudric A. Retina and vitreous diseases of the vitreous and the vitreoretinal interface. Basic Clin Sci Course (BCSC). 2013; pp. 302-4.

[6] Johnson MW. Tractional cystoid macular edema: a subtle variant of the vitreomacular traction syndrome. Am J Ophthalmol 2005; 140(2): 184-92.
[http://dx.doi.org/10.1016/j.ajo.2005.01.033] [PMID: 16086944]

[7] García-Layana A, García-Arumí J, Ruiz-Moreno JM, Arias-Barquet L, Cabrera-López F, Figueroa MS. A review of current management of vitromacular traction & macular hole. J Ophthalmol 2015; 2015: 809640.

[8] Stalmans P, Duker JS, Kaiser PK, *et al.* Oct-based interpretation of the vitreomacular interface and indications for pharmacologic vitreolysis. Retina 2013; 33(10): 2003-11.
[http://dx.doi.org/10.1097/IAE.0b013e3182993ef8] [PMID: 23881226]

[9] Hikichi T, Yoshida A, Trempe CL. Course of vitreomacular traction syndrome. Am J Ophthalmol 1995; 119(1): 55-61.
[http://dx.doi.org/10.1016/S0002-9394(14)73813-9] [PMID: 7825690]

[10] Yamada N, Kishi S. Tomographic features and surgical outcomes of vitreomacular traction syndrome. Am J Ophthalmol 2005; 139(1): 112-7.
[http://dx.doi.org/10.1016/j.ajo.2004.08.055] [PMID: 15652835]

[11] Witkin AJ, Patron ME, Castro LC, *et al.* Anatomic and visual outcomes of vitrectomy for vitreomacular traction syndrome. Ophthalmic Surg Lasers Imaging 2010; 41(4): 425-31.
[http://dx.doi.org/10.3928/15428877-20100525-07] [PMID: 20608611]

[12] FDA approves Jetrea for symptomatic vitreomacular adhesion in the eyes. 2012. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm324369.htm.

[13] European Medicines Agency. European Medicines Agency - Human Medicines - Jetrea. 2013; 1(January). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002381/WC500137451.pdf

[14] Stalmans P, Benz MS, Gandorfer A, *et al.* Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med 2012; 367(7): 606-15.
[http://dx.doi.org/10.1056/NEJMoa1110823] [PMID: 22894573]

[15] US Food and Drug Administration Center for Drug Evaluation and Research. Medical review(s). 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125422Orig1s000MedR.pdf

[16] Syed YY, Dhillon S. Ocriplasmin: a review of its use in patients with symptomatic vitreomacular adhesion. Drugs 2013; 73(14): 1617-25.
[http://dx.doi.org/10.1007/s40265-013-0124-1] [PMID: 24062204]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 25

Pseudophakic Cystoid Macular Edema

Andrés Bastien*

Universidad de Buenos Aires-Universidad del Salvador, Retina and Vitreous, Argentina

ESSENTIALS OF DIAGNOSIS

Pseudophakic cystoid macular edema (CME) was first described in 1953 by A. Ray Irvine, Jr., in patients with unexplained visual loss following intracapsular cataract surgery [1]. The cause of the visual loss was identified by Gass and Norton as marked macular edema with a classic perifoveal petalloid pattern of staining and late leakage from the optic nerve on intravenous fluorescein angiography (Figs. **1 - 3**) (FA) [2]. The incidence of angiographic CME has decreased with the transition from intracapsular cataract extraction (60%) to extracapsular cataract surgery (20%) and with small-incision phacoemulsification [3, 4]; 20-30% of patients undergoing phacoemulsification have CME on FA [5, 6] and optical coherence tomography (OCT) (Figs. **4** and **5**) suggests that it may be found in up to 40% of patients [7]. The majority of patients do not experience visual changes [6, 8]. The incidence is lower with current surgical techniques (0.1% to 2.35%) [9, 10].

Most patients with CME have spontaneous resolution of the edema within 3-4 months [11] One year after surgery, a small minority of patients (<1%) in the absence of treatment may still have decreased visual acuity from CME [12].

Pathogenesis

Various factors and many presumed mechanisms may be involved in the pathogenesis of CME, including the release of mediators of inflammation such as

* **Corresponding author Andrés Bastien:** Universidad de Buenos Aires-Universidad del Salvador, Retina and Vitreous, Argentina; Tel/Fax: 00541148114482; E-mail: andresbastien@aol.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

prostaglandins, light toxicity, and mechanical irritation [13 - 15]. Inflammatory mediators disrupt the blood-aqueous barrier (BAB) and blood-retinal barrier (BRB), leading to increased vascular permeability resulting in macular edema. Breakdown of the BAB and BRB may be associated with diabetes, glaucoma, and uveitis [16]. Surgical complication of the anterior segment may lead to the release of arachidonic acid from cell membranes, with production of either leukotrienes *via* the lipooxygenase pathway or prostaglandins *via* the cyclooxygenase pathway [13, 14]. These inflammatory biomarkers result in increased retinal vessel permeability and the development of edema. Contraction of the posterior hyaloid as a result of inflammation may lead to mechanical traction onto the perifoveal retinal capillaries and result in CME [15].

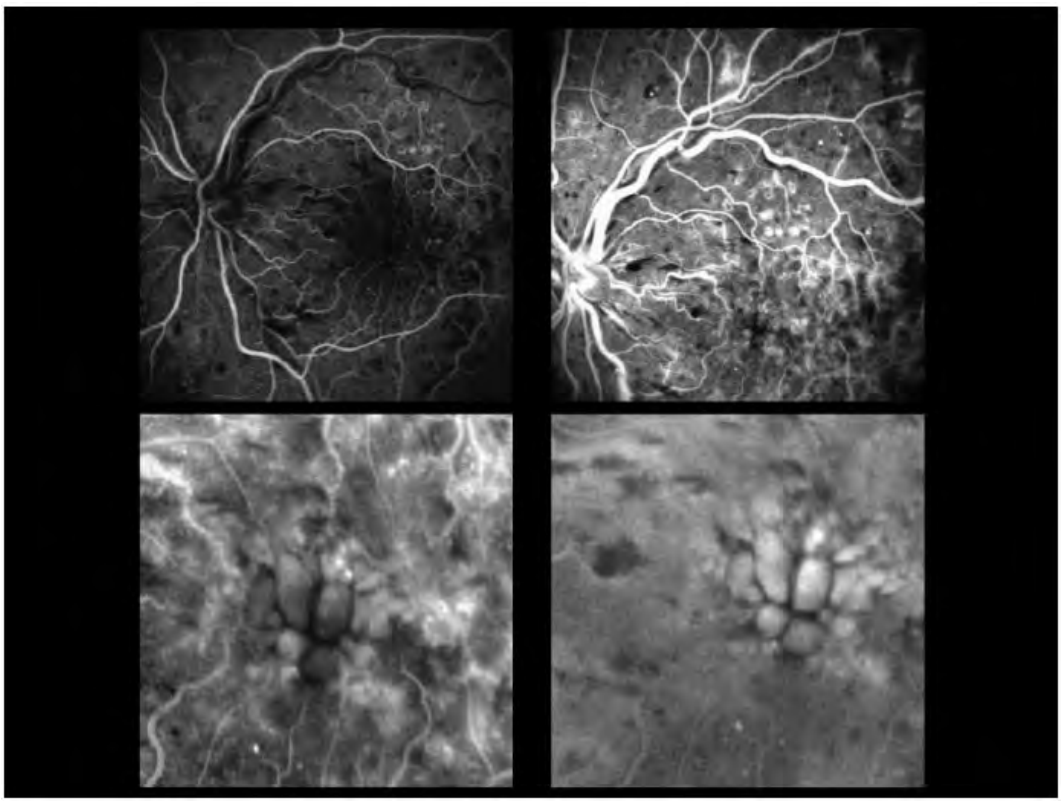


Fig. (1). Fluorescein angiography. Perifoveal petalloid staining.

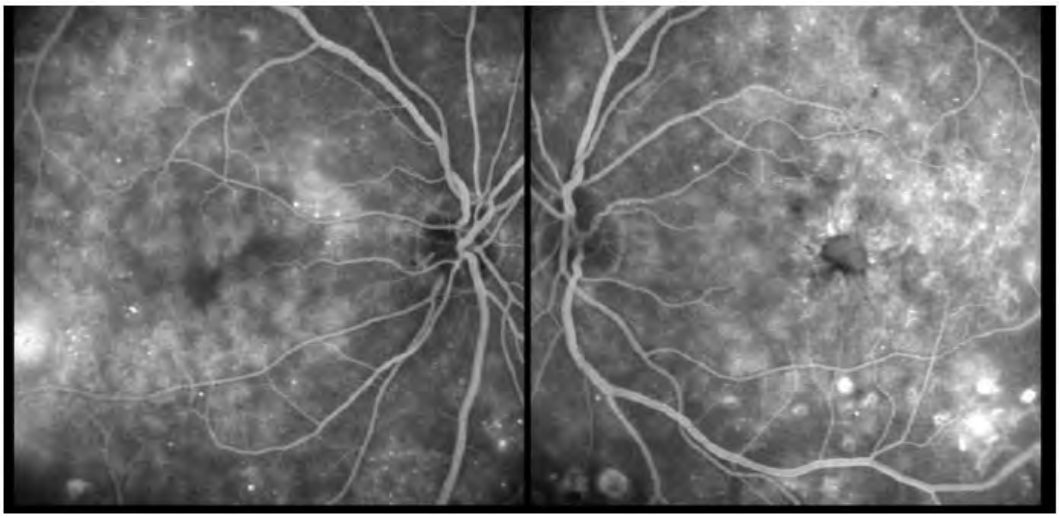


Fig. (2). Fluorescein angiography. Perifoveal petalloid staining.

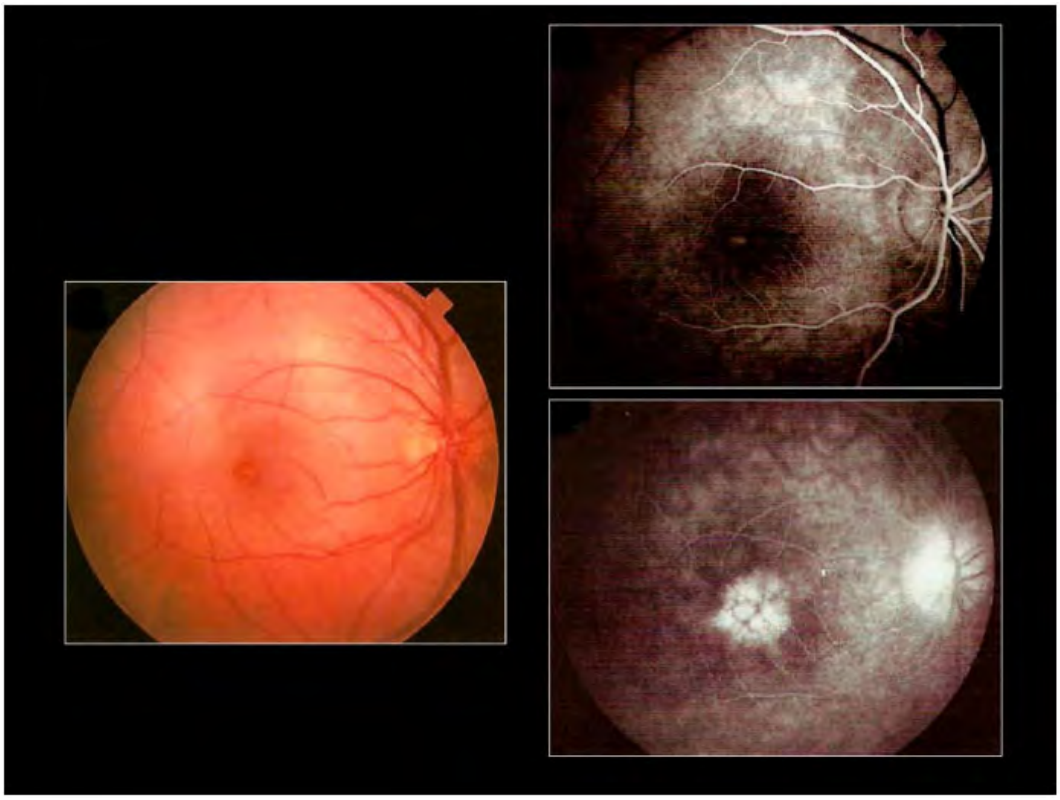


Fig. (3). Fluorescein angiography with macular late leakage.

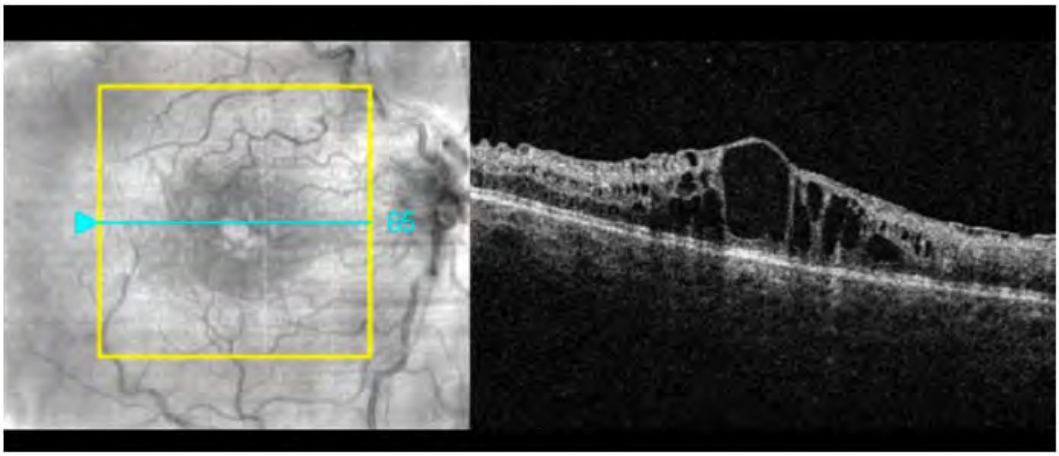


Fig. (4). OCT. Macular thickening. Cystic spaces in outer plexiform layer.

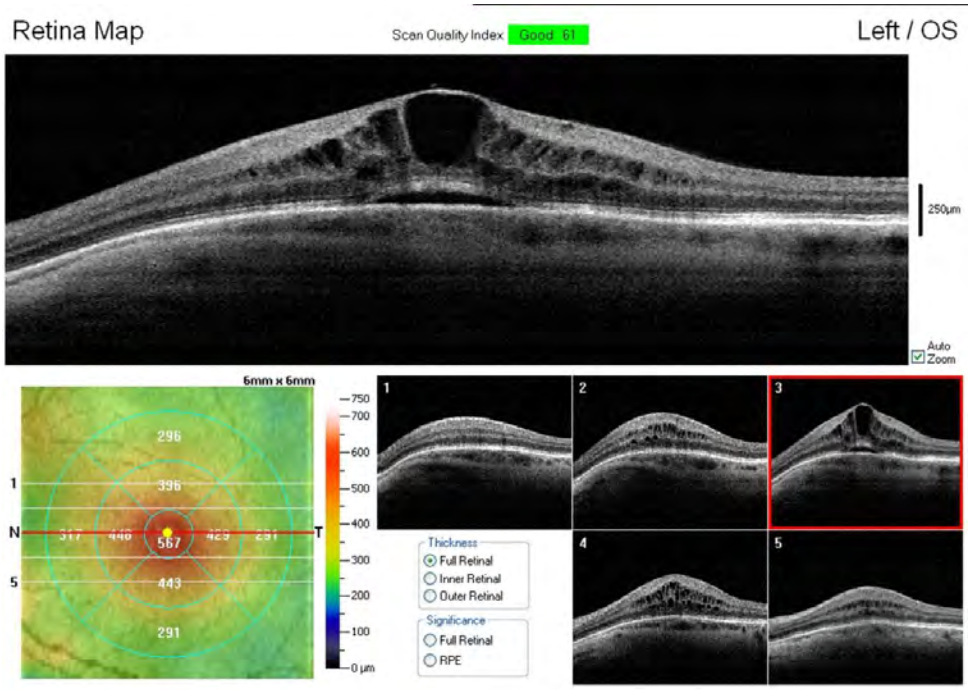


Fig. (5). OCT. Macular thickening. Cystic spaces in outer plexiform layer and subfoveal fluid.

Incidence and Risk Factors

The most frequent appearance of CME occurs at 6 weeks after surgery. Incidence increases in patients with high-risk characteristics including diabetes mellitus,

hypertension, history of central retinal vein occlusion, history of uveitis, epiretinal membrane, or following complicated cataract surgery (Fig. **6**) [3, 9]. A recent large retrospective study showed no increased incidence of clinical CME in glaucoma patients undergoing uncomplicated cataract extraction [17]. Although that study found no relationship between the use of prostaglandin analogs for the treatment of glaucoma and the development of CME, other studies have found that prostaglandins, synthesized by the uvea and lens epithelial cells, may be one of the inflammatory mediators associated with CME [18].

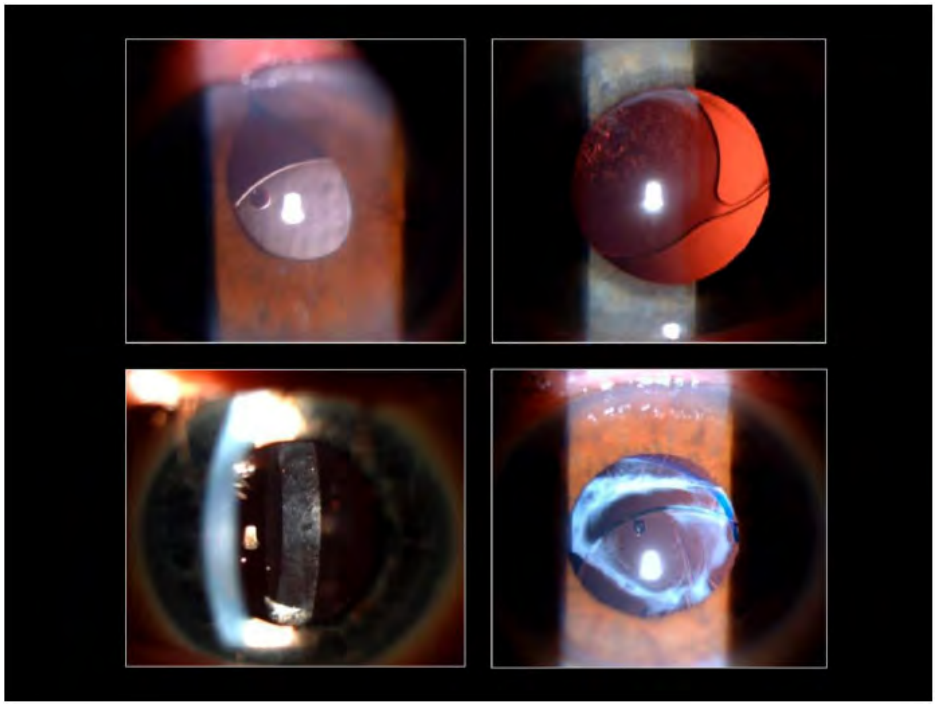


Fig. (6). Complicated anterior segment surgeries. Subluxated IOLS, anterior vitreous.

DIFFERENTIAL DIAGNOSIS

Metabolic disorders: Diabetes, Retinitis pigmentosa, Inherited CME (autosomal-dominant).

Ischemia: Vein occlusion, Diabetic retinopathy, Hypertensive retinopathy, Vasculitis, Collagenosis (Fig. **7**).

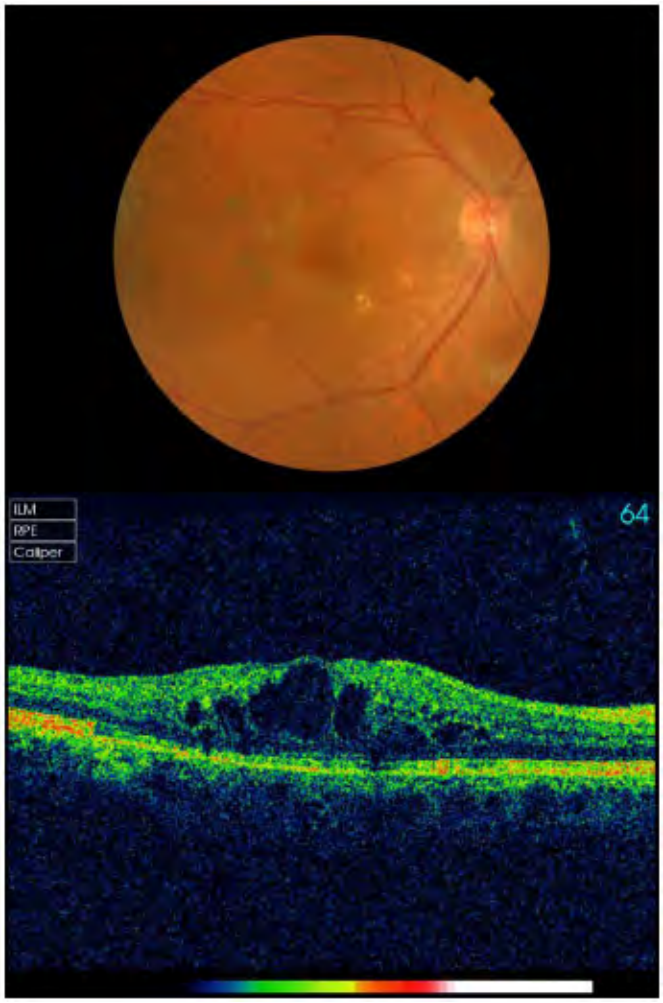


Fig. (7). Cystoid macular edema in telangiectasias.

Hydrostatic forces: Retinal vascular occlusions, Venous occlusion, Arterial hypertension, Low Intraocular Pression (Fig. **8**).

Mechanical forces: Vitreo macular traction (Fig. **9**) [21].

Inflammation: Intermediate uveitis, Diabetic Macular Edema, Choroidal inflammatory diseases (Vogt-Koyanagi Harada, Birdshot).

Pharmacotoxic effects: Latanoprost, Betaxolol [19].

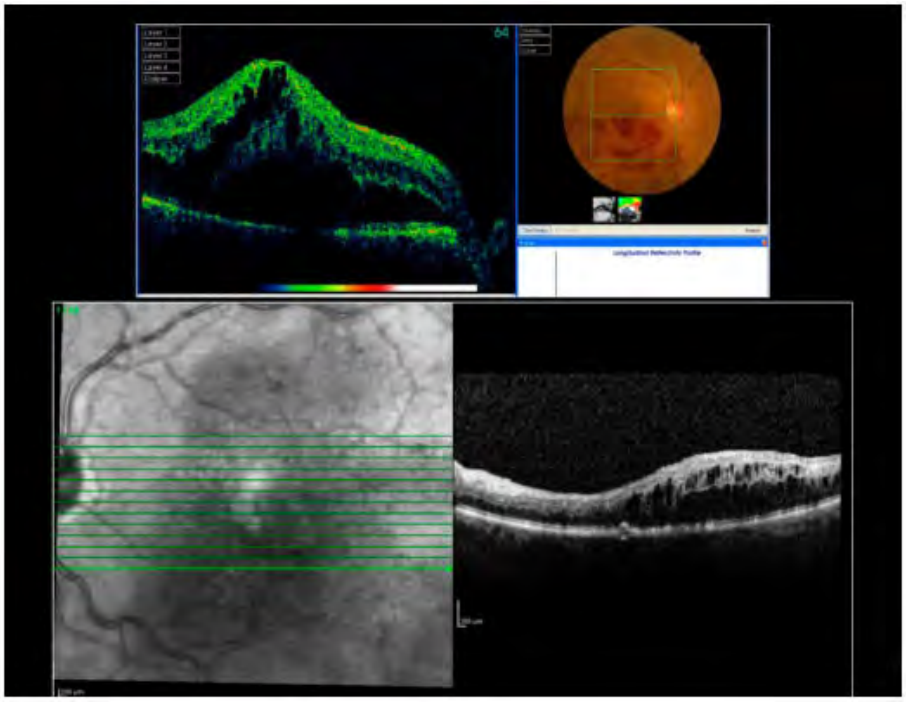


Fig. (8). Differential diagnosis: cystoid macular edema in retinal vein occlusion.

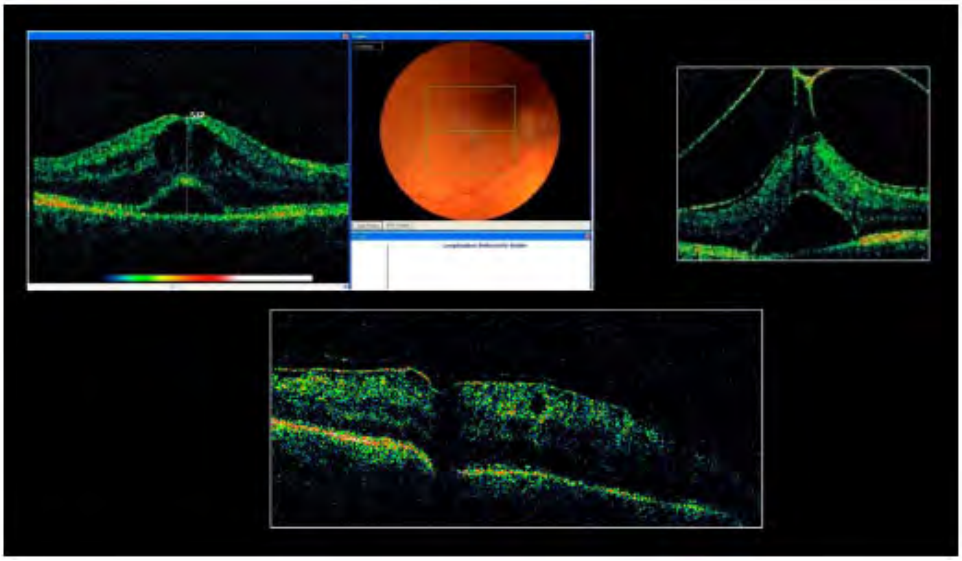
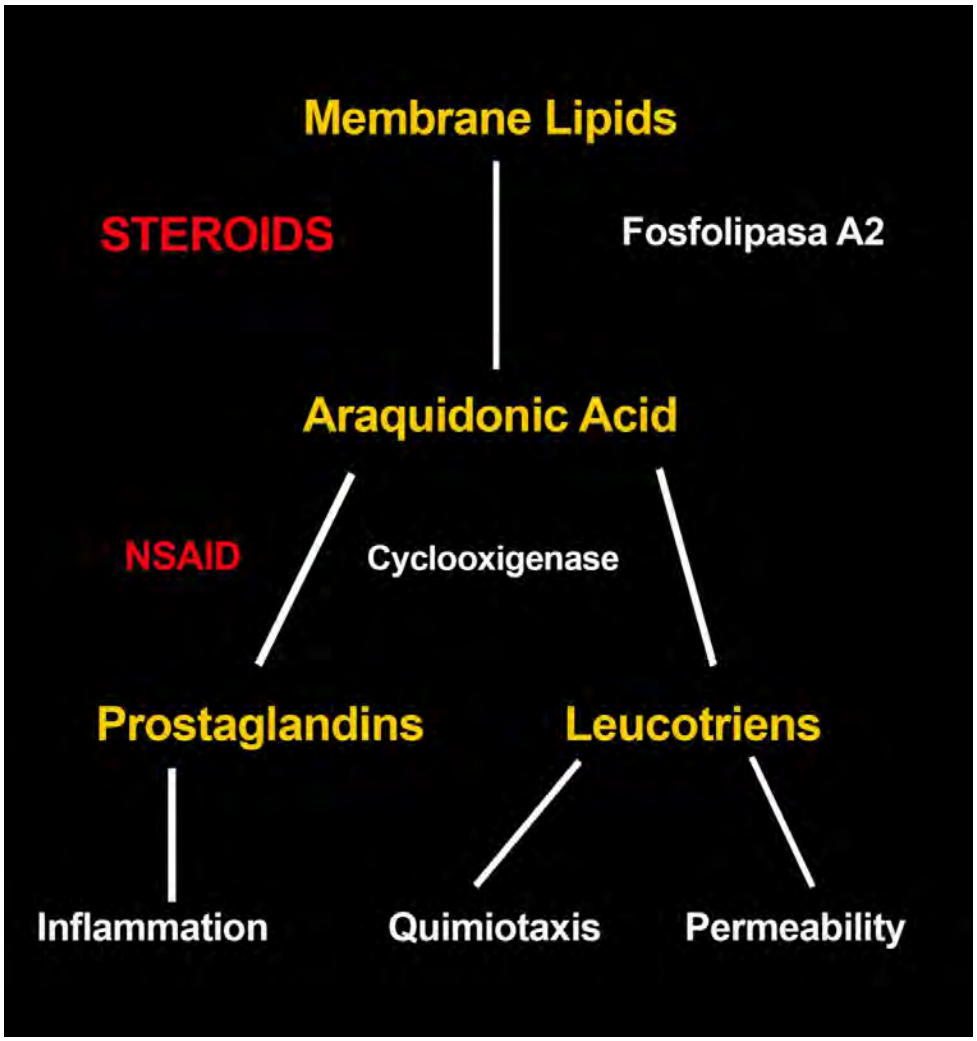


Fig. (9). Macular edema associated with vitreo macular traction, epiretinal membrane and central serous retinopathy.



Graphic 1. Mechanism of action for Steroids and NSAID in CME.

MANAGEMENT

CME is diagnosed by decreased visual acuity, by FA with the classic appearance of perifoveal petalloid staining with or without late leakage from the optic disk, or by OCT. Characteristics of CME on OCT include macular thickening and cystic spaces in the outer plexiform layer, occasionally with subfoveal fluid [16, 20]. (Figs. **10 - 13**).

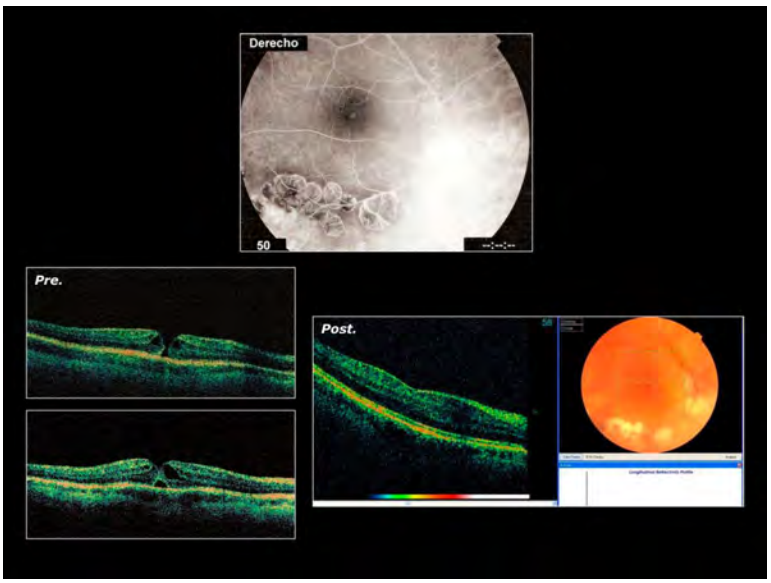


Fig. (10). Degenerative myopic patients. History of bilateral retinal detachment surgery. Cataract surgery and pseudophakic macular edema. Treatment with topical non-steroidal anti-inflammatory drugs plus topical steroids for 3 months. Edema resolution.

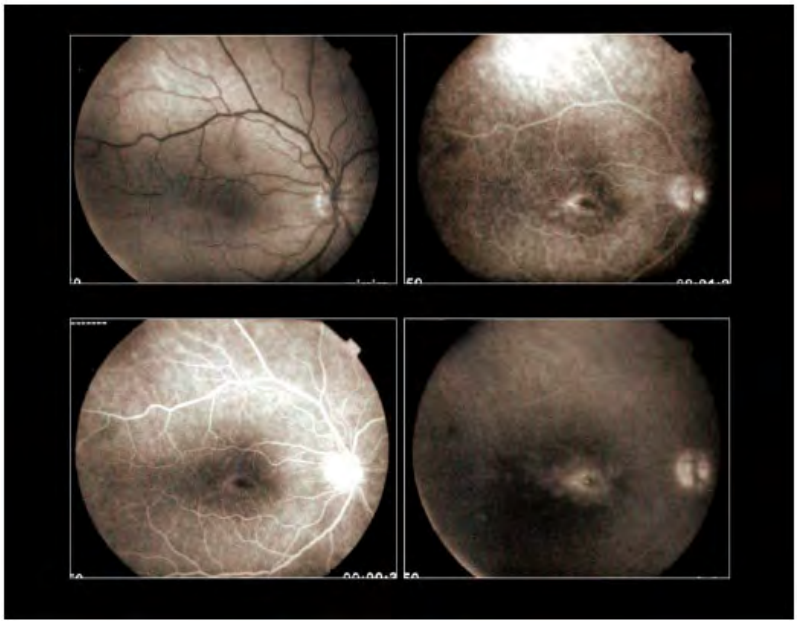


Fig. (11-A). Pseudophakic patients with chronic edema.

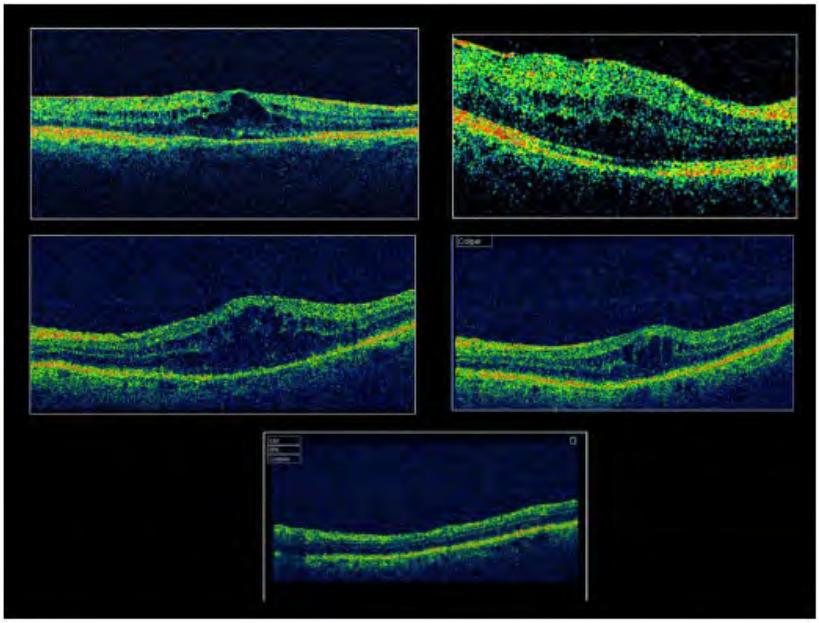


Fig. (11-B). OCT with cystoid edema and the evolution during 6 months treated with topical steroids plus topical non-steroidal anti-inflammatory drugs. Edema resolution.

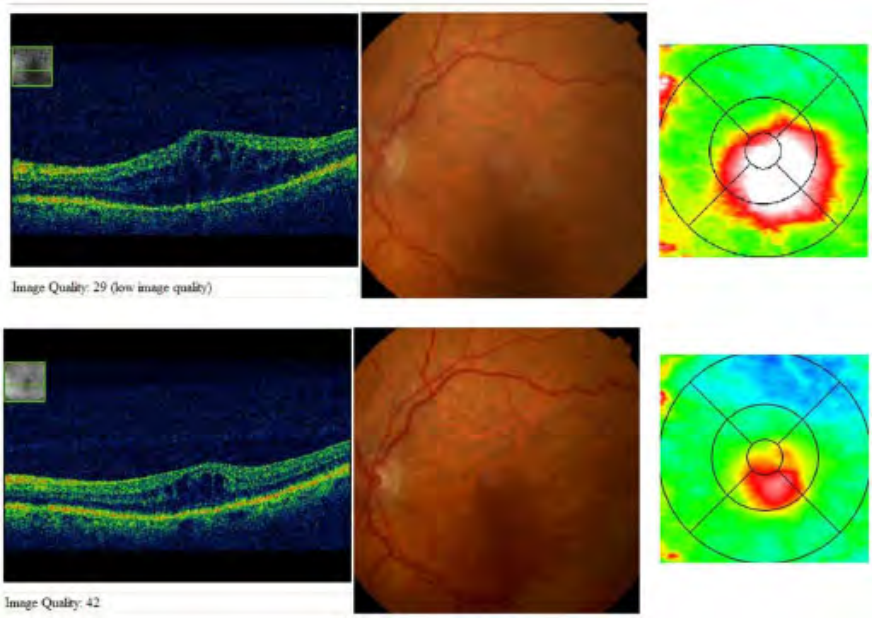


Fig. (12). Pseudophakic macular edema in complicated cataract surgery, with vitreous loss. Resolution after 8 months of topical combination of steroids and non-steroids.

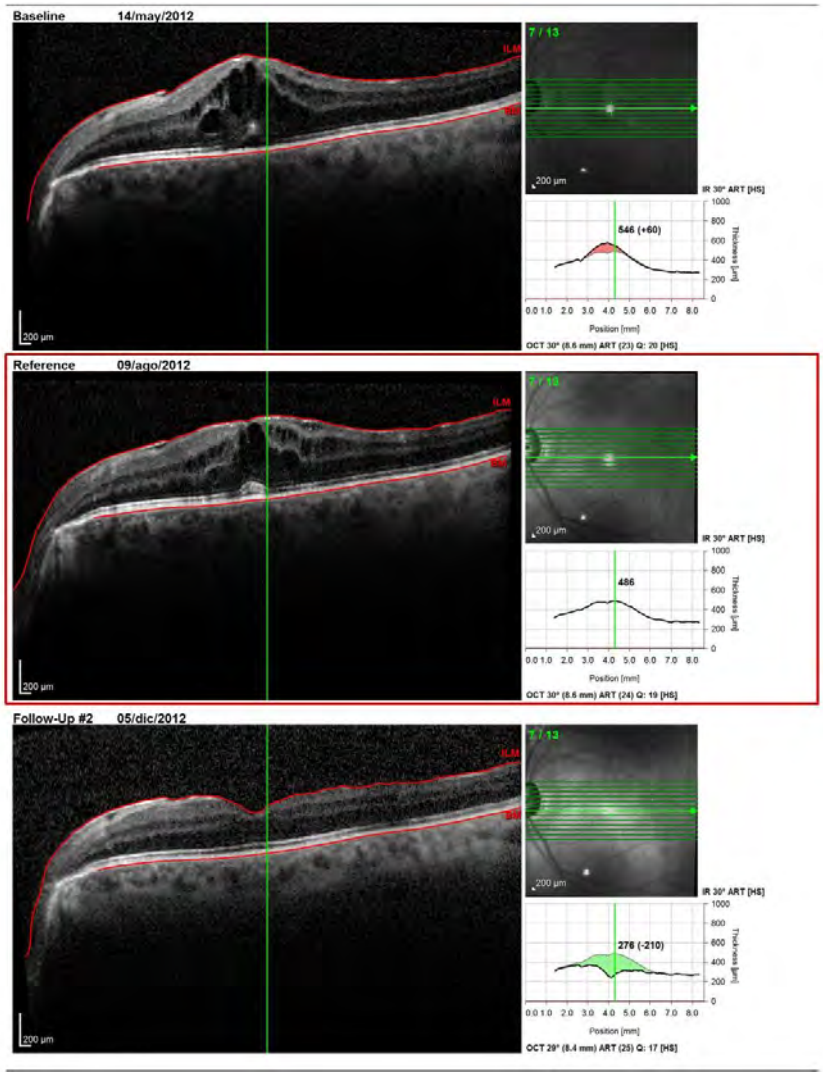


Fig. (13). Pseudophakic macular edema. Resolution after 7 months of treatment with topical combination of steroids and non-steroids.

Corticosteroids (Graphic 1) [13, 22 - 31].

- Topical
- Intravitreal injection
- Subtenon

Nonsteroidal anti-inflammatory drugs (Graphic 1) [32 - 39].

• Topical.

Anti-vascular endothelial growth factor [40 - 48].

Surgical: pars plana vitrectomy [49 - 53].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol 1953; 36(5): 599-619.
[http://dx.doi.org/10.1016/0002-9394(53)90302-X] [PMID: 13040458]

[2] Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. Arch Ophthalmol 1966; 76(5): 646-61.
[http://dx.doi.org/10.1001/archopht.1966.03850010648005] [PMID: 5955948]

[3] Flach AJ. The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. Trans Am Ophthalmol Soc 1998; 96: 557-634.
[PMID: 10360304]

[4] Stark WJ Jr, Maumenee AE, Fagadau W, *et al.* Cystoid macular edema in pseudophakia. Surv Ophthalmol 1984; 28 (Suppl.): 442-51.
[http://dx.doi.org/10.1016/0039-6257(84)90226-1] [PMID: 6463847]

[5] Gulkilik G, Kocabora S, Taskapili M, Engin G. Cystoid macular edema after phacoemulsification: risk factors and effect on visual acuity. Can J Ophthalmol 2006; 41(6): 699-703.
[http://dx.doi.org/10.3129/i06-062] [PMID: 17224950]

[6] Ursell PG, Spalton DJ, Whitcup SM, Nussenblatt RB. Cystoid macular edema after phacoemulsification: relationship to blood-aqueous barrier damage and visual acuity. J Cataract Refract Surg 1999; 25(11): 1492-7.
[http://dx.doi.org/10.1016/S0886-3350(99)00196-0] [PMID: 10569164]

[7] Lobo CL, Faria PM, Soares MA, Bernardes RC, Cunha-Vaz JG. Macular alterations after small-incision cataract surgery. J Cataract Refract Surg 2004; 30(4): 752-60.
[http://dx.doi.org/10.1016/S0886-3350(03)00582-0] [PMID: 15093635]

[8] Cagini C, Fiore T, Iaccheri B, Piccinelli F, Ricci MA, Fruttini D. Macular thickness measured by

optical coherence tomography in a healthy population before and after uncomplicated cataract phacoemulsification surgery. Curr Eye Res 2009; 34(12): 1036-41.
[http://dx.doi.org/10.3109/02713680903288937] [PMID: 19958122]

[9] Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg 2007; 33(9): 1550-8.
[http://dx.doi.org/10.1016/j.jcrs.2007.05.013] [PMID: 17720069]

[10] Loewenstein A, Zur D. Postsurgical cystoid macular edema. Dev Ophthalmol 2010; 47: 148-59.
[http://dx.doi.org/10.1159/000320078] [PMID: 20703048]

[11] Bradford JD, Wilkinson CP, Bradford RH Jr. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. Retina 1988; 8(3): 161-4.
[http://dx.doi.org/10.1097/00006982-198808030-00001] [PMID: 3231908]

[12] Shelsta HN, Jampol LM. Pharmacologic therapy of pseudophakic cystoid macular edema: 2010 update. Retina 2011; 31(1): 4-12.
[http://dx.doi.org/10.1097/IAE.0b013e3181fd9740] [PMID: 21187730]

[13] Conway MD, Canakis C, Livir-Rallatos C, Peyman GA. Intravitreal triamcinolone acetonide for refractory chronic pseudophakic cystoid macular edema. J Cataract Refract Surg 2003; 29(1): 27-33.
[http://dx.doi.org/10.1016/S0886-3350(02)01441-4] [PMID: 12551663]

[14] Hudes GR, Li WY, Rockey JH, White P. Prostacyclin is the major prostaglandin synthesized by bovine retinal capillary pericytes in culture. Invest Ophthalmol Vis Sci 1988; 29(10): 1511-6.
[PMID: 3049428]

[15] Schubert HD. Cystoid macular edema: the apparent role of mechanical factors. Prog Clin Biol Res 1989; 312: 277-91.
[PMID: 2678144]

[16] Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol 2012; 23: 26-32.

[17] Law SK, Kim E, Yu F, Caprioli J. Clinical cystoid macular edema after cataract surgery in glaucoma patients. J Glaucoma 2010; 19(2): 100-4.
[PMID: 20160577]

[18] Miyake K, Sugiyama S, Norimatsu I, Ozawa T. Prevention of cystoid macular edema after lens extraction by topical indomethacin (III) radioimmunoassay measurement of prostaglandins in the aqueous during and after lens extraction procedures. Albrecht Von Graefes Arch Klin Exp Ophthalmol 1978; 209(2): 83-8.
[http://dx.doi.org/10.1007/BF00407841] [PMID: 311170]

[19] Miyake K, Ota I, Maekubo K, Ichihashi S, Miyake S. Latanoprost accelerates disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema in early postoperative pseudophakias. Arch Ophthalmol 1999; 117(1): 34-40.
[http://dx.doi.org/10.1001/archopht.117.1.34] [PMID: 9930158]

[20] Kim SJ, Belair ML, Bressler NM, *et al.* A method of reporting macular edema after cataract surgery using optical coherence tomography. Retina 2008; 28(6): 870-6.
[http://dx.doi.org/10.1097/IAE.0b013e318169d04e] [PMID: 18536605]

[21] Martinez MR, Ophir A. Pseudophakic cystoid macular edema associated with extrafoveal vitreoretinal traction. Open Ophthalmol J 2011; 5: 35-41.
[http://dx.doi.org/10.2174/1874364101105010035] [PMID: 21643426]

[22] Benhamou N, Massin P, Haouchine B, Audren F, Tadayoni R, Gaudric A. Intravitreal triamcinolone for refractory pseudophakic macular edema. Am J Ophthalmol 2003; 135(2): 246-9.
[http://dx.doi.org/10.1016/S0002-9394(02)01938-4] [PMID: 12566041]

[23] Boscia F, Furino C, Dammacco R, Ferreri P, Sborgia L, Sborgia C. Intravitreal triamcinolone acetonide in refractory pseudophakic cystoid macular edema: functional and anatomic results. Eur J Ophthalmol 2005; 15(1): 89-95.
[PMID: 15751245]

[24] Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. Ophthalmic Res 2006; 38(4): 218-45.
[http://dx.doi.org/10.1159/000093796] [PMID: 16763379]

[25] Jonas JB, Kreissig I, Degenring RF. Intravitreal triamcinolone acetonide for pseudophakic cystoid macular edema. Am J Ophthalmol 2003; 136(2): 384-6.
[http://dx.doi.org/10.1016/S0002-9394(03)00230-7] [PMID: 12888077]

[26] Wittpenn JR, Silverstein S, Heier J, Kenyon KR, Hunkeler JD, Earl M. A randomized, masked comparison of topical ketorolac 0.4% plus steroid *vs* steroid alone in low-risk cataract surgery patients. Am J Ophthalmol 2008; 146(4): 554-60.
[http://dx.doi.org/10.1016/j.ajo.2008.04.036] [PMID: 18599019]

[27] Khurana RN, Palmer JD, Porco TC, Wieland MR. Dexamethasone intravitreal implant for pseudophakic cystoid macular edema in patients with diabetes. Ophthalmic Surg Lasers Imaging Retina 2015; 46(1): 56-61.
[http://dx.doi.org/10.3928/23258160-20150101-09] [PMID: 25559510]

[28] Fenicia V, Balestrieri M, Perdicchi A, MauriziEnrici M, DelleFave M, Recupero SM. Intravitreal injection of dexamethasone implant and ranibizumab in cystoid macular edema in the course of irvine-gass syndrome. Case Rep Ophthalmol 2014; 5(2): 243-8.
[PMID: 25232337]

[29] Sacchi M, Villani E, Gilardoni F, Nucci P. Efficacy of intravitreal dexamethasone implant for prostaglandin-induced refractory pseudophakic cystoid macular edema: case report and review of the literature. Clin Ophthalmol 2014; 8: 1253-7.
[http://dx.doi.org/10.2147/OPTH.S63829] [PMID: 25061272]

[30] Kessel L, Tendal B, Jørgensen KJ, *et al.* Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. Ophthalmology 2014; 121(10): 1915-24.
[http://dx.doi.org/10.1016/j.ophtha.2014.04.035] [PMID: 24935281]

[31] Brynskov T, Laugesen CS, Halborg J, Kemp H, Sørensen TL. Longstanding refractory pseudophakic cystoid macular edema resolved using intravitreal 0.7 mg dexamethasone implants. Clin Ophthalmol 2013; 7: 1171-4.
[http://dx.doi.org/10.2147/OPTH.S46399] [PMID: 23818753]

[32] Asano S, Miyake K, Ota I, *et al.* Reducing angiographic cystoid macular edema and blood-aqueous barrier disruption after small-incision phacoemulsification and foldable intraocular lens implantation: multicenter prospective randomized comparison of topical diclofenac 0.1% and betamethasone 0.1%. J Cataract Refract Surg 2008; 34(1): 57-63.
[http://dx.doi.org/10.1016/j.jcrs.2007.08.030] [PMID: 18165082]

[33] Burnett J, Tessler H, Isenberg S, Tso MO. Double-masked trial of fenoprofen sodium: treatment of chronic aphakic cystoid macular edema. Ophthalmic Surg 1983; 14(2): 150-2.
[PMID: 6341914]

[34] Flach AJ, Dolan BJ, Irvine AR. Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. Am J Ophthalmol 1987; 103(4): 479-86.
[http://dx.doi.org/10.1016/S0002-9394(14)74268-0] [PMID: 3551617]

[35] Flach AJ, Jampol LM, Weinberg D, *et al.* Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. Am J Ophthalmol 1991; 112(5): 514-9.
[http://dx.doi.org/10.1016/S0002-9394(14)76851-5] [PMID: 1951587]

[36] Gamache DA, Graff G, Brady MT, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: I. Assessment of anti-inflammatory efficacy. Inflammation 2000; 24(4): 357-70.
[http://dx.doi.org/10.1023/A:1007049015148] [PMID: 10850857]

[37] Hariprasad SM, Akduman L, Clever JA, Ober M, Recchia FM, Mieler WF. Treatment of cystoid macular edema with the new-generation NSAID nepafenac 0.1%. Clin Ophthalmol 2009; 3: 147-54.
[http://dx.doi.org/10.2147/OPTH.S4684] [PMID: 19668559]

[38] Miyake K, Nishimura K, Harino S, *et al.* The effect of topical diclofenac on choroidal blood flow in early postoperative pseudophakias with regard to cystoid macular edema formation. Invest Ophthalmol Vis Sci 2007; 48(12): 5647-52.
[http://dx.doi.org/10.1167/iovs.07-0262] [PMID: 18055815]

[39] Warren KA, Fox JE. Topical nepafenac as an alternate treatment for cystoid macular edema in steroid responsive patients. Retina 2008; 28(10): 1427-34.
[http://dx.doi.org/10.1097/IAE.0b013e31817e7ead] [PMID: 18664937]

[40] Aiello LP, Avery RL, Arrigg PG, *et al.* Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994; 331: 1480-7.

[41] Andreoli CM, Miller JW. Anti-vascular endothelial growth factor therapy for ocular neovascular disease. Curr Opin Ophthalmol 2007; 18(6): 502-8.
[http://dx.doi.org/10.1097/ICU.0b013e3282f0ca54] [PMID: 18163003]

[42] Arevalo JF, Garcia-Amaris RA, Roca JA, *et al.* Primary intravitreal bevacizumab for the management of pseudophakic cystoid macular edema: pilot study of the Pan-American Collaborative Retina Study Group. J Cataract Refract Surg 2007; 33(12): 2098-105.
[http://dx.doi.org/10.1016/j.jcrs.2007.07.046] [PMID: 18053911]

[43] Arevalo JF, Maia M, Garcia-Amaris RA, *et al.* Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. Ophthalmology

2009; 116(8): 1481-1487, 1487.e1.
[http://dx.doi.org/10.1016/j.ophtha.2009.04.006] [PMID: 19545901]

[44] Barone A, Prascina F, Russo V, *et al.* Successful treatment of pseudophakic cystoid macular edema with intravitreal bevacizumab. J Cataract Refract Surg 2008; 34(7): 1210-2.
[http://dx.doi.org/10.1016/j.jcrs.2008.02.037] [PMID: 18571091]

[45] Barone A, Russo V, Prascina F, Delle Noci N. Short-term safety and efficacy of intravitreal bevacizumab for pseudophakic cystoid macular edema. Retina 2009; 29(1): 33-7.
[http://dx.doi.org/10.1097/IAE.0b013e31818a1fbc] [PMID: 18854783]

[46] Demirel S, Batioğlu F, Özmert E. Intravitreal ranibizumab for the treatment of cystoid macular edema in Irvine-Gass syndrome. J Ocul Pharmacol Ther 2012; 28(6): 636-9.
[PMID: 22731243]

[47] Díaz-Llopis M, Amselem L, Cervera E, García-Delpech S, Torralba C, Montero J. Intravitreal injection of bevacizumab for pseudophakic cystoid macular edema resistant to steroids. Arch Soc Esp Oftalmol 2007; 82(7): 447-50.
[PMID: 17647121]

[48] Ghasemi Falavarjani K, Parvaresh MM, Modarres M, Hashemi M, Samiy N. Intravitreal bevacizumab for pseudophakic cystoid macular edema; a systematic review. J Ophthalmic Vis Res 2012; 7(3): 235-9.
[PMID: 23264866]

[49] Fung WE. Vitrectomy for chronic aphakic cystoid macular edema. Results of a national, collaborative, prospective, randomized investigation. Ophthalmology 1985; 92(8): 1102-11.
[http://dx.doi.org/10.1016/S0161-6420(85)33917-9] [PMID: 3876532]

[50] Harbour JW, Smiddy WE, Rubsamen PE, Murray TG, Davis JL, Flynn HW Jr. Pars plana vitrectomy for chronic pseudophakic cystoid macular edema. Am J Ophthalmol 1995; 120(3): 302-7.
[http://dx.doi.org/10.1016/S0002-9394(14)72159-2] [PMID: 7661201]

[51] Patel A, de Bustros S, Michels RG. Pars plana vitrectomy for aphakic cystoid macular edema. Retina 1985; 5(1): 11-5.
[http://dx.doi.org/10.1097/00006982-198500510-00003] [PMID: 4001583]

[52] Pendergast SD, Margherio RR, Williams GA, Cox MS Jr. Vitrectomy for chronic pseudophakic cystoid macular edema. Am J Ophthalmol 1999; 128(3): 317-23.
[http://dx.doi.org/10.1016/S0002-9394(99)00158-0] [PMID: 10511026]

[53] Peyman GA, Canakis C, Livir-Rallatos C, Conway MD. The effect of internal limiting membrane peeling on chronic recalcitrant pseudophakic cystoid macular edema: a report of two cases. Am J Ophthalmol 2002; 133(4): 571-2.
[http://dx.doi.org/10.1016/S0002-9394(01)01402-7] [PMID: 11931800]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

CHAPTER 26

Central Serous Chorioretinopathy

Daniel D. Kim[1], Paul Baciu[1] and **Michael D. Ober[1,2,*]**

[1] *Department of Ophthalmology, Henry Ford Health Systems, Detroit, MI, USA*

[2] *Retina Consultants of Michigan, Southfield, MI, USA*

ESSENTIALS OF DIAGNOSIS

Central serous chorioretinopathy (CSC) is an idiopathic disorder characterized by serous detachment of the neurosensory retina. It has an incidence of roughly 6/100,000 individuals [1 - 3]. Affected patients are usually young to middle age adults (ages 25-45), male (5-10:1 male:female ratio), and of "Type A" personality [4 - 6]. The symptoms present unilaterally (60-90% of the time) and patients often complain of blurred central vision and metamorphopsia with a hyperopic shift [1 - 3, 5, 7]. A history of recent psychosocial stressors, or steroid use is often present. Disorders causing elevated levels of catecholamines are known to predispose. Furthermore, pregnancy, phosphodiesterase inhibitors, and illicit drug use have also less commonly been associated with onset of symptoms [2, 3, 6, 8].

Despite decades of study, the precise etiology and pathophysiology remain elusive. Much has been learned, however, through multimodal imaging studies that often yield pathognomonic findings (Fig. **1**). Fluorescein angiography (FA) in acute cases reveals a focal leak at the level of the retinal pigment epithelium (RPE) appearing as an expanding hyperfluorescent dot (30% have more than one) sometimes elevating into a smokestack appearance in 10-20% (Figs. **2** and **3**). Ultimately, the subretinal fluid pocket can extend inferiorly due to gravity creating descending atrophic tracts, which are best seen with fundus autofluorescence (FAF) [2, 3, 6, 8]. Chronic cases reveal multiple leaks in close

* **Corresponding author Michael D. Ober:** Retina Consultants of Michigan, 29201 Telegraph Road, Suite 606, Southfield, MI 48034, USA; Tel: (248) 356-6473; Fax: (248) 356-6473; E-mail: obermike@gmail.com

Mitzy E. Torres Soriano, Gerardo García Aguirre, Maximiliano Gordon & Veronica Kon Graversen (Eds.)
© 2016 The Author(s). Published by Bentham Science Publishers

proximity with mottled hyper and hypofluorescence of the RPE corresponding to "sick RPE syndrome" [9, 10]. Indocyanine green angiography (ICGA) demonstrates hyperfluorescence in mid-frames (not present early or late) often described as choroidal hyperpermeability (Fig. **4**) [2, 3, 6, 8, 11, 12].

As OCT technology has improved, it has become critical for diagnosis. Findings include subretinal fluid, RPE detachments, and retinal atrophy. Less common features include cystoid macular edema or cystoid macular degeneration, which is differentiated by lack of corresponding FA leakage and poor visual potential [2, 5, 8]. While relatively new, visualization of the choroid using enhanced-depth imaging shows marked thickening of the choroid in CSC (Fig. **5**), most prominent in zones of choroidal permeability with active angiographic leakage [8, 13].

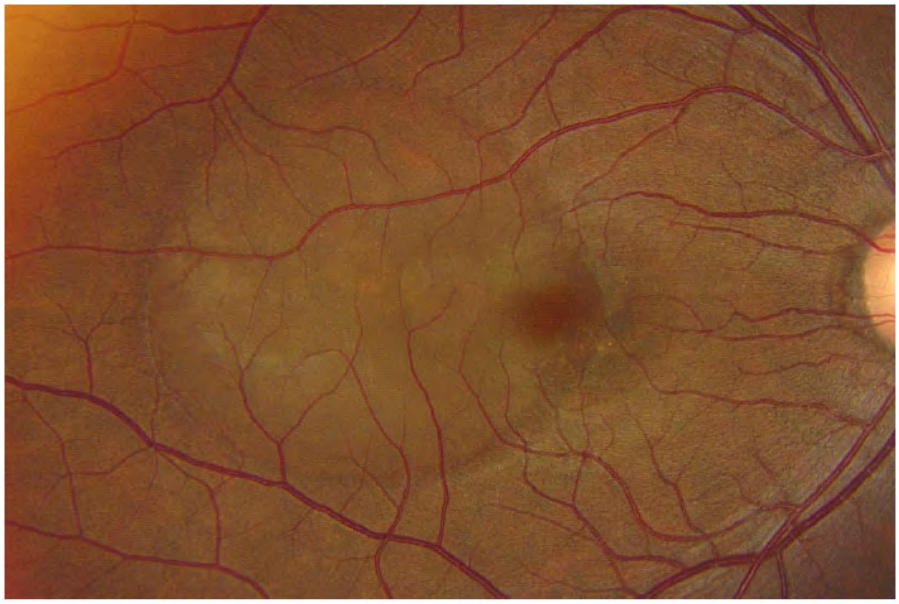


Fig. (1). CSC Fundus photo showing subretinal fluid causing serous retinal detachment (Photo Credit: Henry Ford Ophthalmic Photography).

Fundus autofluorescence is being used more frequently to image patients with CSC. Over time, a neurosensory detachment leads to an accumulation of lipofuscin from shed photoreceptor outer segments yielding patches of speckled hyperautofluorescence that can become more prominent when subretinal fluid first resolves. Over time, these areas become hypoautofluorescent as noted around

old leaks and chronic descending atrophic tracts [2, 8, 14]. Other diagnostic modalities include multifocal ERG, which shows broad retinal functional disturbances, and abnormal visual field testing, especially on microperimetry, indicating that central visual acuity underestimates the amount of visual impairment [8, 15].

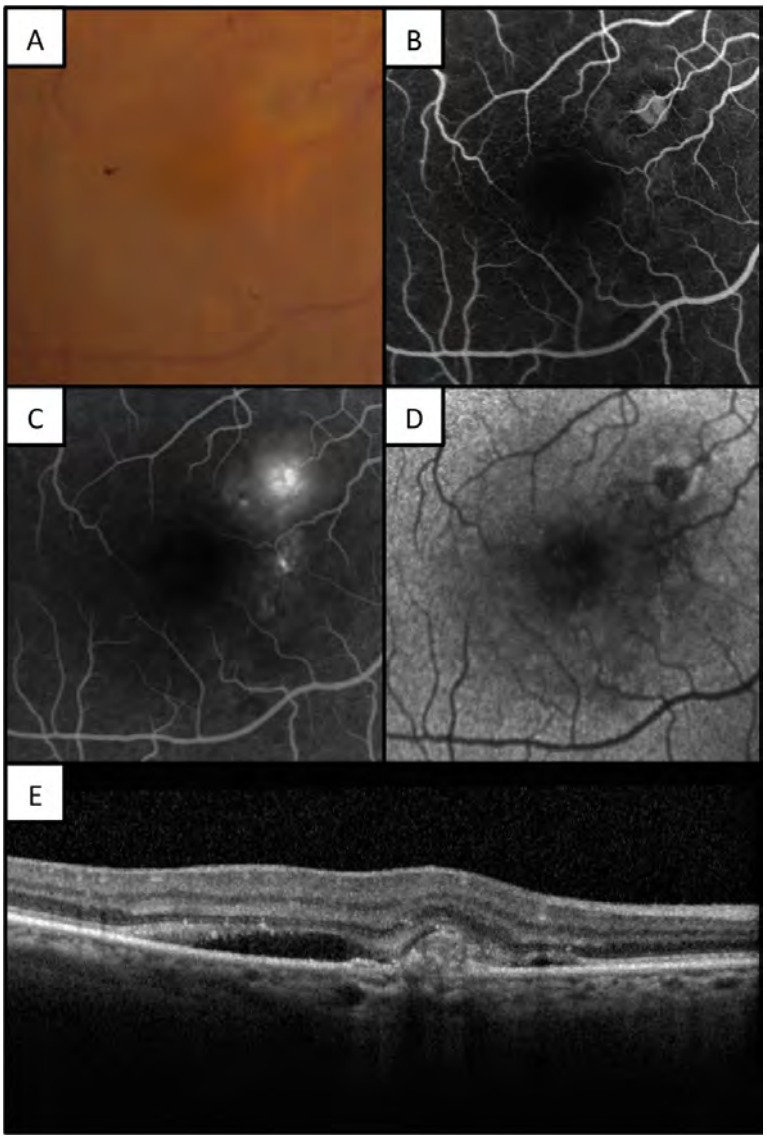


Fig. (2). RPE blowout as imaged by fundus photography (**A**), early (**B**) and late (**C**) fluorescein angiography, autofluorescence (**D**) and OCT (**E**) (Photo Credit: Lorrene Santiego).

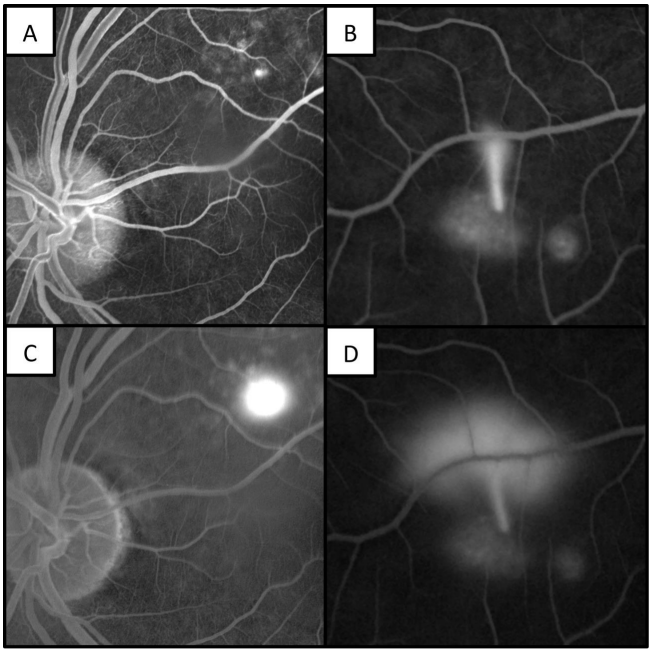


Fig. (3). Classic fluorescein angiography findings. Expansile dot, early (**A**) and late phase (**C**). Smokestack, mid (**B**) and late phase (**D**) (Photo Credit: A & C – Courtney McClenahan, B & D – Henry Ford Ophthalmic Photography).

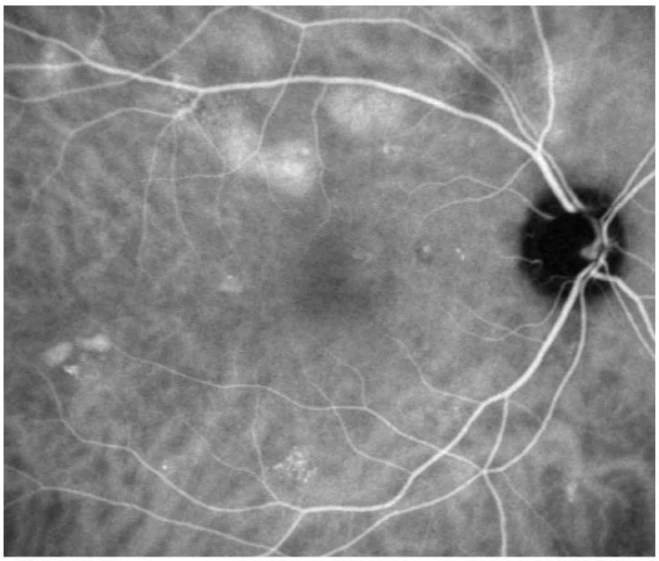


Fig. (4). Mid-phase hyperpermeability on ICGA (Photo Credit: Courtney McClenahay).

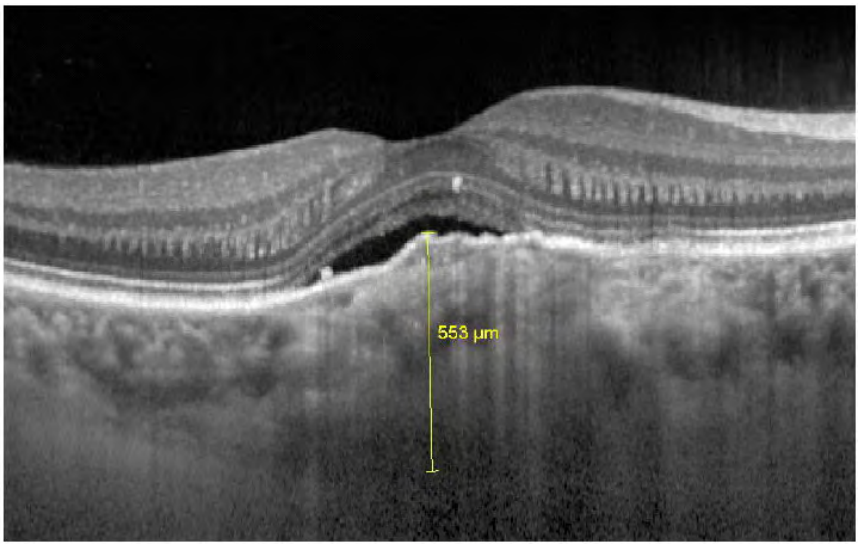


Fig. (5). Enhanced Depth OCT imaging showing choroidal thickening and subretinal fluid (Photo Credit: Logan Jabouri).

DIFFERENTIAL DIAGNOSIS

Polypoidal choroidal vasculopathy is well known to masquerade as CSC in the active phase while pattern dystrophy may mimic the late pigmentary changes [16]. Severe variants of CSC are known to occur with multiple large RPE detachments, dependent exudative retinal detachment and RPE tears all of which can simulate severe inflammatory disorders such as Vogt-Koyanagi-Harada syndrome or posterior uveitis. The most common item on the differential, however is age related macular degeneration with occult choroidal neovascularization, especially in patients older than 50 years old [2, 3]

MANAGEMENT

Patients who fit a “typical” patient profile for CSC, generally require no further work-up, but testing for elevated systemic catecholamine levels or sleep apnea should be considered in the appropriate patient context [2, 3]. CSC is generally treated conservatively as it most often consists of self-limited episodes that resolve over weeks to months. However, chronic CSC can lead to permanent visual impairment [4, 17, 18].

Improving underlying conditions such as eliminating or reducing corticosteroid use and stress reduction are first line treatments. Most patients are observed without any further intervention for the first few months, but timing of potential treatment is individual. Many factors can trigger the need for additional treatment including failure of spontaneous resolution, monocular status, specific vocational needs (*i.e.* pilot or commercial drivers license), recurrent disease, need for ongoing or increased corticosteroid use, *etc*.

Verteporfin based photodynamic therapy (PDT) (QLT, Vancouver, CA) has orphan drug designation for the treatment of CSC and is the current mainstay of therapy. PDT leads to coagulation of the choroid. The subsequent reperfusion typically yields a reduction in choroidal thickness, elimination of choroidal hyperpeability on ICGA and focal leak on FA as well as resolution of subretinal fluid (Fig. **6**). The vast majority of patients treated with PDT have resolution of fluid and improvement in vision [2 - 4, 8, 10 - 12, 17].

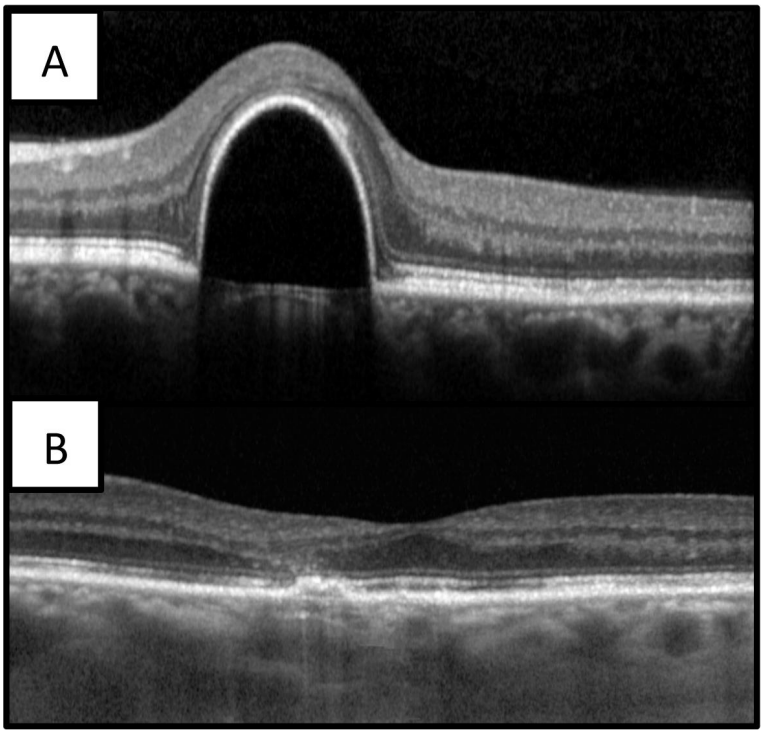


Fig. (6). OCT imaging of PED before (**A**) and after (**B**) PDT. (Photo Credit: Courney McClenahay).

Thermal laser photocoagulation will also successfully treat CSC, but is only indicated for extrafoveal leaks due to the laser induced scotoma and propensity for secondary choroidal neovascularization [2, 8]. Furthermore, it does not address the underlying choroidal hyperpermeability and thus may, in theory, carry a greater risk of recurrence in the first year. Micropulse diode laser is currently being investigated as a safer alternative to thermal laser photocoagulation [2, 8].

Anti-VEGF agents continue to be investigated with several studies showing promise; however the self-limiting nature of CSC is a confounding factor in measuring outcomes. In the authors' opinion, anti-VEGF does not significantly alter natural history based upon detailed examination patients showing no change in choroidal thickness or choroidal hyperpermeability following treatment (unpublished data) [2, 3, 8, 11, 17]. Numerous systemic medications have also been investigated with studies looking at anti-glucocorticoid (mifepristone), anti-mineralocorticoid (eplerenone, finesteride), ketoconazole, rifampin, *H pylori* eradication, and high dose anti-oxidants but thus far, evidence has been inconclusive [1, 6, 7, 19 - 21].

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, Behar-Cohen F. Mineralocorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy: a pilot study. Retina 2013; 33(10): 2096-102.
[http://dx.doi.org/10.1097/IAE.0b013e318297a07a] [PMID: 23719402]

[2] Fine HF, Ober MD, Hariprasad SM. Current concepts in managing central serous chorioretinopathy. Ophthalmic Surg Lasers Imaging Retina 2014; 45(1): 9-13.
[http://dx.doi.org/10.3928/23258160-20131220-01] [PMID: 24392907]

[3] Liew G, Quin G, Gillies M, Fraser-Bell S. Central serous chorioretinopathy: a review of epidemiology and pathophysiology. Clin Experiment Ophthalmol 2013; 41(2): 201-14.
[http://dx.doi.org/10.1111/j.1442-9071.2012.02848.x] [PMID: 22788735]

[4] Chan WM, Lai TY, Lai RY, Liu DT, Lam DS. Half-dose verteporfin photodynamic therapy for acute

central serous chorioretinopathy: one-year results of a randomized controlled trial. Ophthalmology 2008; 115(10): 1756-65.
[http://dx.doi.org/10.1016/j.ophtha.2008.04.014] [PMID: 18538401]

[5] Plateroti AM, Witmer MT, Kiss S, D'Amico DJ. Characteristics of intraretinal deposits in acute central serous chorioretinopathy. Clin Ophthalmol 2014; 8: 673-6.
[http://dx.doi.org/10.2147/OPTH.S48894] [PMID: 24729682]

[6] Ratanasukon M, Bhurayanontachai P, Jirarattanasopa P. High-dose antioxidants for central serous chorioretinopathy; the randomized placebo-controlled study. BMC Ophthalmol 2012; 12: 20.
[http://dx.doi.org/10.1186/1471-2415-12-20] [PMID: 22800086]

[7] Mateo-Montoya A, Mauget-Faÿse M. Helicobacter pylori as a risk factor for central serous chorioretinopathy: Literature review. World J Gastrointest Pathophysiol 2014; 5(3): 355-8.
[PMID: 25133035]

[8] Quin G, Liew G, Ho IV, Gillies M, Fraser-Bell S. Diagnosis and interventions for central serous chorioretinopathy: review and update. Clin Experiment Ophthalmol 2013; 41(2): 187-200.
[http://dx.doi.org/10.1111/j.1442-9071.2012.02847.x] [PMID: 22788713]

[9] Polak BC, Baarsma GS, Snyers B. Diffuse retinal pigment epitheliopathy complicating systemic corticosteroid treatment. Br J Ophthalmol 1995; 79(10): 922-5.
[http://dx.doi.org/10.1136/bjo.79.10.922] [PMID: 7488581]

[10] Mathew CS. Central serous chorioretinopathy. Kerala J Ophthalmol 2012; XXIV(1): 11-8.

[11] Bae SH, Heo J, Kim C, *et al.* Low-fluence photodynamic therapy *versus* ranibizumab for chronic central serous chorioretinopathy: one-year results of a randomized trial. Ophthalmology 2014; 121(2): 558-65.
[http://dx.doi.org/10.1016/j.ophtha.2013.09.024] [PMID: 24268858]

[12] Yannuzzi LA, Slakter JS, Gross NE, *et al.* Indocyanine green angiography-guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: a pilot study. Retina 2003; 23(3): 288-98.
[http://dx.doi.org/10.1097/00006982-200306000-00002] [PMID: 12824827]

[13] Jirarattanasopa P, Ooto S, Tsujikawa A, *et al.* Assessment of macular choroidal thickness by optical coherence tomography and angiographic changes in central serous chorioretinopathy. Ophthalmology 2012; 119(8): 1666-78.
[http://dx.doi.org/10.1016/j.ophtha.2012.02.021] [PMID: 22521082]

[14] von Rückmann A, Fitzke FW, Fan J, Halfyard A, Bird AC. Abnormalities of fundus autofluorescence in central serous retinopathy. Am J Ophthalmol 2002; 133(6): 780-6.
[http://dx.doi.org/10.1016/S0002-9394(02)01428-9] [PMID: 12036669]

[15] Kim SW, Oh J, Huh K. Correlations among various functional and morphological tests in resolved central serous chorioretinopathy. Br J Ophthalmol 2012; 96(3): 350-5.
[http://dx.doi.org/10.1136/bjo.2011.204503] [PMID: 21617156]

[16] Yannuzzi LA, Freund KB, Goldbaum M, *et al.* Polypoidal choroidal vasculopathy masquerading as central serous chorioretinopathy. Ophthalmology 2000; 107(4): 767-77.
[http://dx.doi.org/10.1016/S0161-6420(99)00173-6] [PMID: 10768341]

[17] Chung YR, Seo EJ, Lew HM, Lee KH. Lack of positive effect of intravitreal bevacizumab in central serous chorioretinopathy: meta-analysis and review. Eye (Lond) 2013; 27(12): 1339-46. [http://dx.doi.org/10.1038/eye.2013.236] [PMID: 24202051]

[18] Forooghian F, Meleth AD, Cukras C, Chew EY, Wong WT, Meyerle CB. Finasteride for chronic central serous chorioretinopathy. Retina 2011; 31(4): 766-71. [http://dx.doi.org/10.1097/IAE.0b013e3181f04a35] [PMID: 21273946]

[19] Meyerle CB, Freund KB, Bhatnagar P, Shah V, Yannuzzi LA. Ketoconazole in the treatment of chronic idiopathic central serous chorioretinopathy. Retina 2007; 27(7): 943-6. [http://dx.doi.org/10.1097/IAE.0b013e318050ca69] [PMID: 17891021]

[20] Nielsen JS, Jampol LM. Oral mifepristone for chronic central serous chorioretinopathy. Retina 2011; 31(9): 1928-36. [http://dx.doi.org/10.1097/IAE.0b013e31821c3ef6] [PMID: 21878843]

[21] Steinle NC, Gupta N, Yuan A, Singh RP. Oral rifampin utilisation for the treatment of chronic multifocal central serous retinopathy. Br J Ophthalmol 2012; 96(1): 10-3. [http://dx.doi.org/10.1136/bjophthalmol-2011-300183] [PMID: 22053102]

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

SUBJECT INDEX

© 2016 The Author(s). Published by Bentham Science Publishers

E

F

G

H

I

L

M

N

O

P

R

S

T

V

W

© 2016 The Author(s). Published by Bentham Science Publisher. This is an open access chapter published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

Mitzy E. Torres Soriano

Dr. Mitzy E. Torres Soriano graduated with honors in medicine at the University of Carabobo, Maracay, Venezuela in 2001. Then in 2003 she began her postgraduate studies in Ophthalmology in Hospital Miguel Pérez Carreño (Caracas, Venezuela) where she also served as Chief Resident, and completed them in 2005. From 2006 to 2008, she did a fellowship in Retina and Vitreous in Asociación para evitar la Ceguera. Hospital Dr. Luis Sánchez Bulnes, in Mexico. She dedicates her clinical practice to the medical and surgical treatment of retinal and vitreous diseases.

She has taken many courses and attended numerous congresses on ophthalmology, and has also written various articles and book chapters. She provides review services to several science international journals about ophthalmology and contributes in retinal clinical research.

Gerardo García-Aguirre

Dr. Gerardo García-Aguirre graduated magna cum laude, obtaining his medical degree at the School of Medicine, Tecnológico de Monterrey, in Monterrey, Mexico in 2002, and his residency in Ophthalmology and Retina fellowship at Asociación para Evitar la Ceguera en México, in Mexico City. In 2008 he became an attending physician at the same hospital. He is author or coauthor of over 30 papers, 15 book chapters and one book in the field of ophthalmology.

Maximiliano Gordon

Dr. Maximiliano Gordon graduated in medicine from Universidad Nacional de Rosario, Rosario, Argentina, in 1999. He did an ophthalmology residency at Centro de la Vision, located in Rosario, between 2000 and 2002, and a fellowship in Retina and Vitreous at the Asociación para Evitar la Ceguera, at Hospital Luis Sanchez Bulnes, located in Mexico City, Mexico, between 2006 and 2008.

With more than 10 years of experience in clinical and surgical management of diseases of the retina and vitreous, he currently works as a retina specialist in Centro de la Vision Gordon-Manavella and as instructor in the residency program of the Retina department of Hospital Provincial del Centenario, in Rosario.

Veronica Kon Graversen

Dr. Veronica Kon Graversen attended Catholic University of Santiago de Guayaquil, School of Medicine where she graduated Summa Cum Laude. She was then accepted into one of the most prestigious ophthalmology training programs in Latin America at the Ophthalmology Institute Conde de Valenciana in Mexico city. She then completed a two-year Retina and Vitreous surgical fellowship at the Association to Prevent Blindness in Mexico (APEC), Luis Sanchez Bulnes Hospital, under the preceptorship of Hugo Quiroz Mercado.

Dr. Kon Graversen completed a second ophthalmology residency program at the University of North Carolina at Chapel Hill, where she also served as Chief Resident. She is eligible to be board certified in Ophthalmology. She has published numerous articles in peer-reviewed journals and has lectured at multiple international meetings. She recently moved to Denmark with her husband and is affiliated with Glostrup Hospital.