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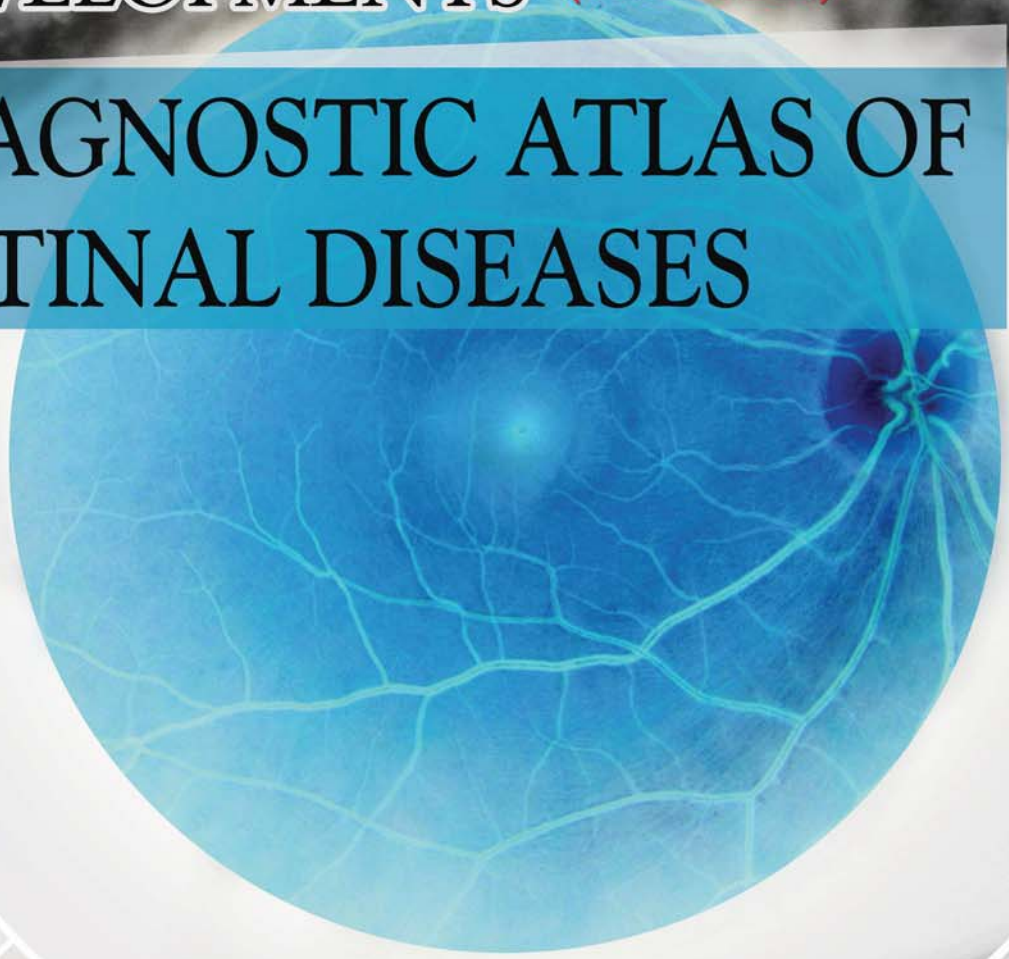
DIAGNOSTIC ATLAS OF RETINAL DISEASES



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Mitzy E. Torres Soriano
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Bentham Books

Ophthalmology: Current and Future Developments

(Volume 3)

(Diagnostic Atlas of Retinal Diseases)

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Ophthalmology: Current and Future Developments

Volume # 3

Diagnostic Atlas of Retinal Diseases

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PREFACE

We are honored to contribute to the information and education of ophthalmology stu-dents 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 chap-ter 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 pos-sible 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 real-ize 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.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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CHAPTER 1

Ocular Toxoplasmosis

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Ocular toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii*. Infections may be acquired congenitally or through the ingestion of infected raw meat, contaminated vegetables or water. A significant proportion of the world population (approximately the third) is infected by *T. gondii* which is responsible for the majority of infectious uveitis cases, which in some countries might be up to 50%. It is the main cause of infectious posterior in immunocompetent individuals, and the second most common in patients with HIV/AIDS [1 - 3].

ESSENTIALS OF DIAGNOSIS

Clinical presentation in immunocompetent individuals varies according to the age of the patient and the size, location and severity of the retinochoroidal lesions. Symptoms usually include floaters and decreased visual acuity, which may be secondary to vitreous inflammation or to macular involvement. In immuno-compromised patients, the presentation may vary [4].

The disease may result from congenitally acquired toxoplasmosis or newly acquired infection. Toxoplasmosis usually affects a single eye, causing one or more lesions. Sometimes, lesions in different stages may be observed in the same eye (Fig. **1**) [4 - 6].

Typical active lesions appear as yellowish or whitish areas of retinal inflammation (Fig. **2**), with adjacent choroiditis, vasculitis, papillitis (Fig. **3**), hemorrhage and vitritis. The primary infection occurs in the retina, but other structures such as the choroid, vitreous or anterior chamber may be involved. After the active phase, there is atrophy of the retina and the choroid that leaves a well-circumscribed round punched-out scar (Fig. **4**). There is pigment clumping and chorioretinal atrophy that allows the visualization of underlying sclera.

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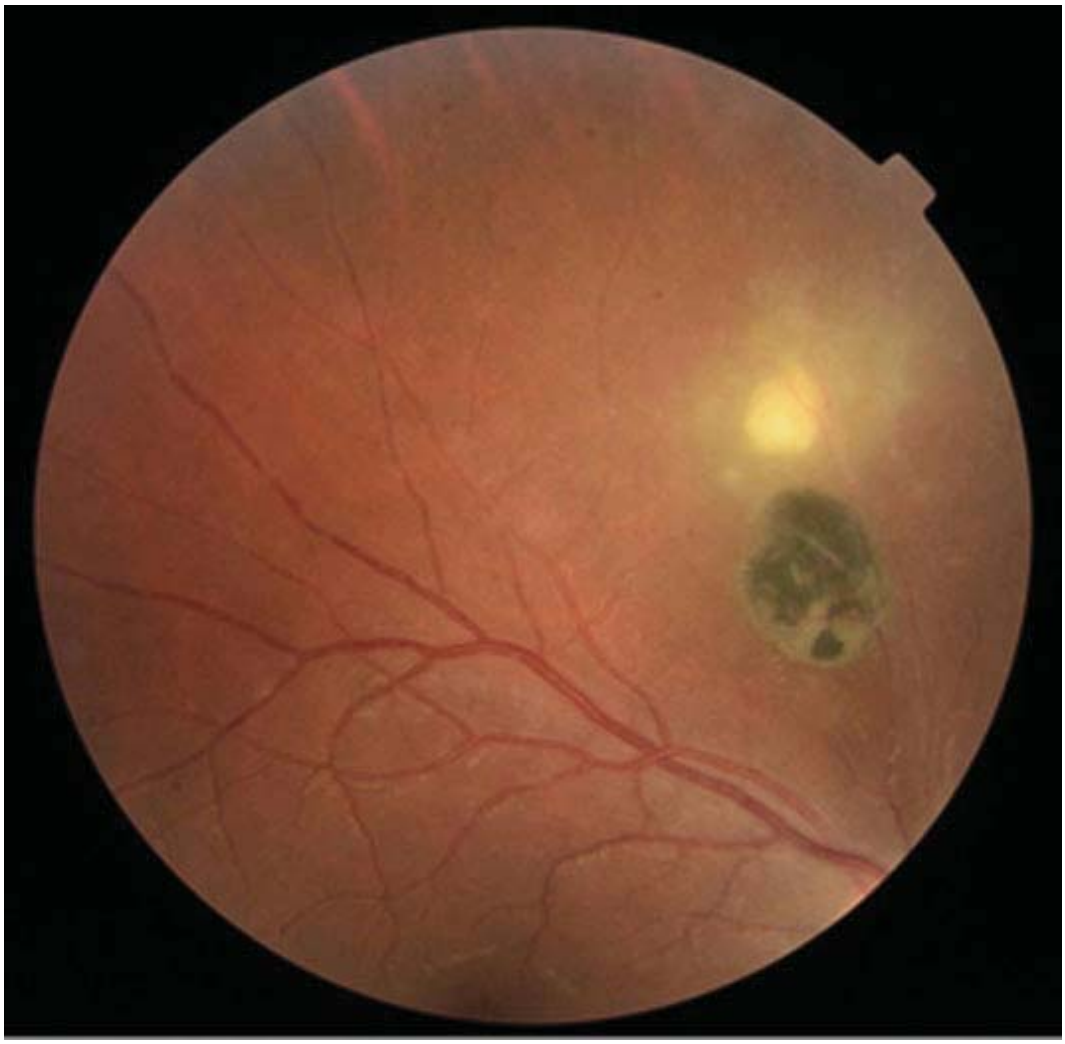

Fig. (1). The acute lesion is seen often contiguous to an old pigmented scar (Image courtesy of Naty C. Torres Soriano MD, Venezuela).

Toxoplasmosis may present atypically, causing punctate outer retinal toxoplasmosis, retinal vasculitis, retinal vascular occlusions, rhegmatogenous or serous retinal detachments, unilateral pigmentary retinopathy, neuroretinitis and additional forms of optic neuropathy, peripheral retinal necrosis and scleritis. Ocular complications, seen more frequently in children, include choroidal neovascularization, cataract, glaucoma, optic nerve atrophy and retinal detachment [4 - 6].

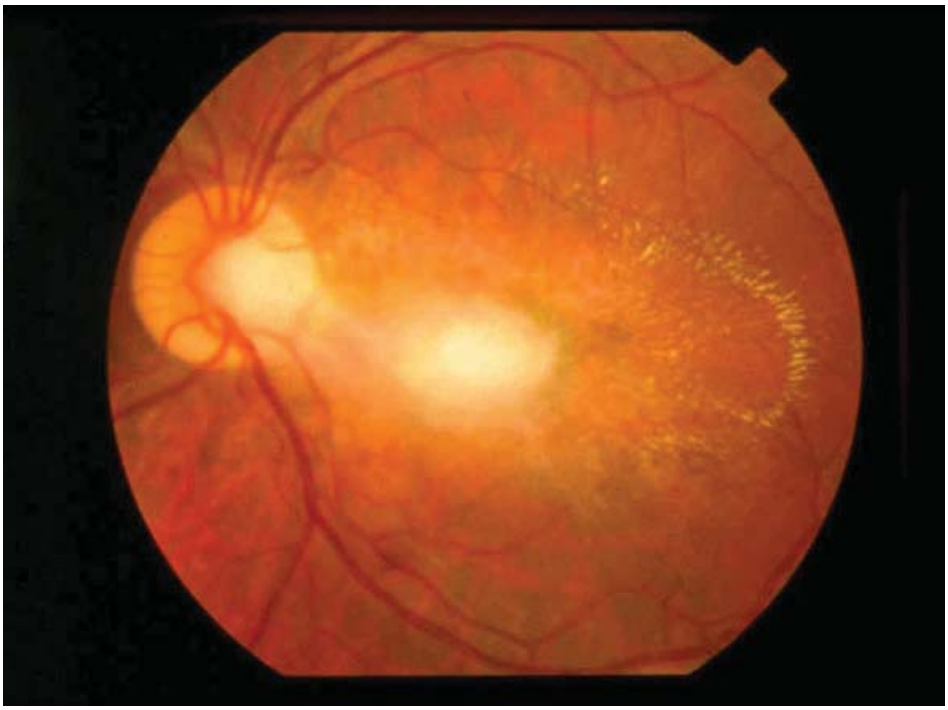

Fig. (2). Acute toxoplasmosis presents grayish inflammatory infiltrate within retinal and subretinal tissue.

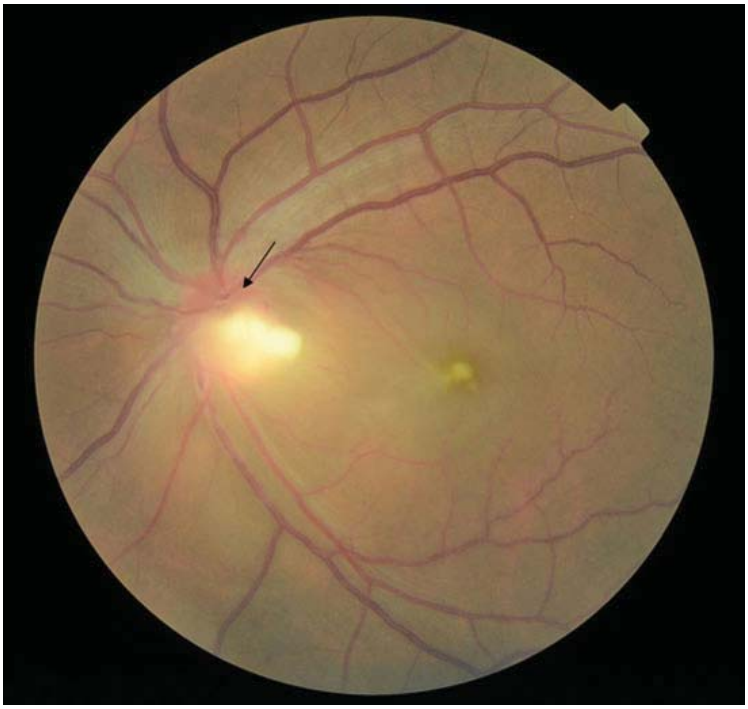

Fig. (3). The arrow allows observation of optic disc inflammation (Courtesy of Mitzy E. Torres Soriano, MD).

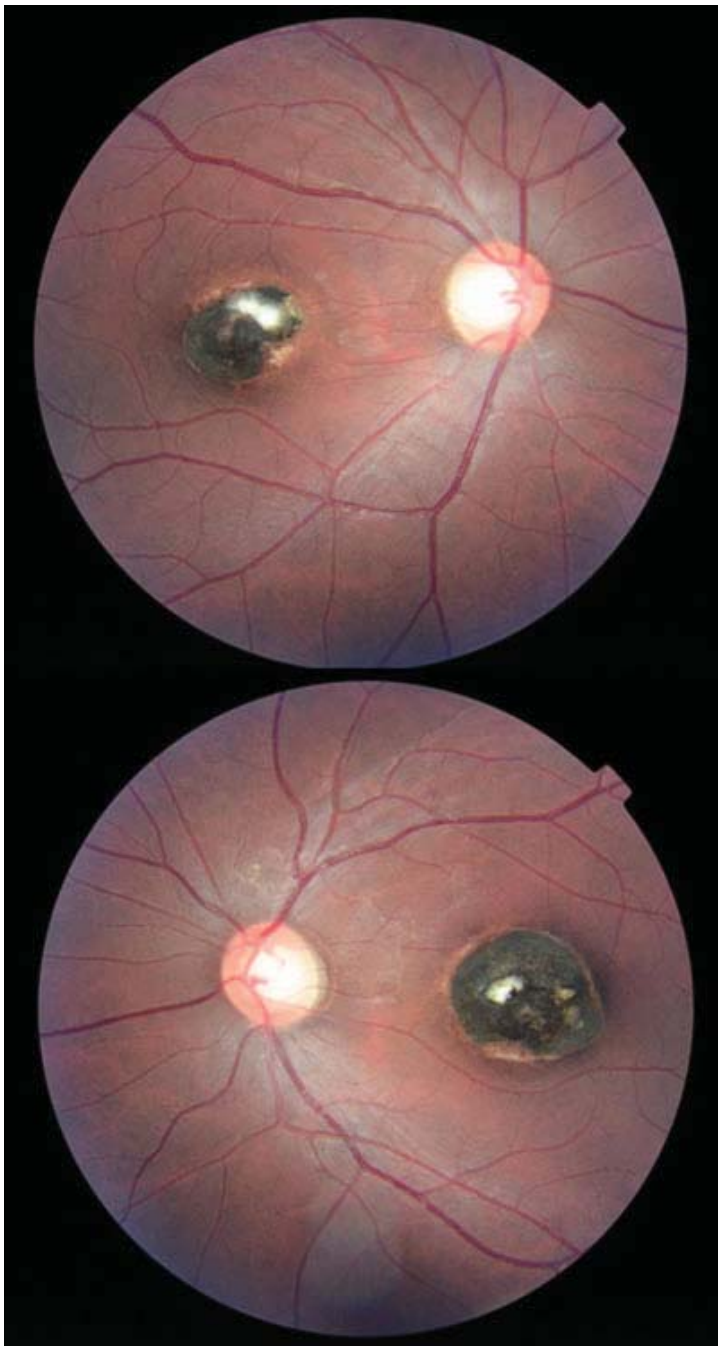

Fig. (4). Macular scar secondary to congenital ocular toxoplasmosis (Courtesy of Manuel Torres López MD, Venezuela).

The diagnosis of ocular toxoplasmosis is usually clinical, since presentation is usually typical [7]. There is no reliable diagnostic test to identify toxoplasmic

uveitis. Positivity of anti-*T gondii* IgG antibodies does not confirm the toxoplasmic etiology, but a negative IgG generally discards the possibility. Positivity of these antibodies usually persist for many years after the primary infection. Other diagnostic tool is looking for the presence of *T. gondii* DNA in the vitreous using polymerase chain reaction, which is especially useful in eyes with atypical presentation [4].

DIFFERENTIAL DIAGNOSIS

Diseases that cause focal retinitis should be considered in the differential diagnosis, such as CMV, herpes simplex virus, herpes zoster virus, fungal retinitis (candidiasis, blastomycosis), septic retinitis, ocular toxocariasis, sarcoidosis, syphilis and tuberculosis. Punctate outer retinal toxoplasmosis should be differentiated from the white dot syndromes [4].

MANAGEMENT

Although ocular toxoplasmosis is usually self-limited, treatment should be initiated as soon as the diagnosis is made in order to avoid scarring, which is the usual cause of long-term visual impairment [8]. The treatment of choice is the combination of systemic antimicrobial drugs and corticosteroids. Antimicrobial agents used most frequently include trimethoprim and sulfamethoxazole, sulfadiazine and pyrimethamine or clindamycin and sulfadiazine [4, 9]. Oral prednisolone (1 mg/kg daily) is started at the third day of treatment and tapered over two to six weeks [7, 10, 11]. Intravitreal clindamycin injection and possibly steroids may be indicated for patients that have contraindication for systemic therapy specific for toxoplasmosis [12]. Treatment with spiramycin should be initiated immediately after diagnosis of recently acquired maternal infection [4].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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CHAPTER 2

Ocular Tuberculosis

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Tuberculosis (TB) is a clinical disease caused by infection with *Mycobacterium tuberculosis* and is characterized pathologically by granuloma formation [1]. TB may affect the eye by direct invasion of the tubercle bacillus following hematogenous dissemination, or *via* a hypersensitivity reaction to the bacillus located elsewhere in the body [2].

Ocular TB is not common; since the 1980's, it is considered as an etiology of uveitis from 0-4%.

Ocular TB may not be associated with clinical evidence of pulmonary TB; up to 60% of patients with extrapulmonary TB may not have been diagnosed with pulmonary TB [3, 4].

ESSENTIALS OF DIAGNOSIS

Extraocular TB can appear on the external eye as a lid abscess or manifest as chronic blepharitis or atypical chalazia. It can present as a mucopurulent conjunctivitis with regional lymphadenopathy. It can also present as a phlyctenule (an inflammatory nodule at the junction of the cornea and sclera), infectious keratitis, interstitial keratitis, or as an infectious scleritis. Rarely, the orbital disease can also occur [4] (Fig. **1**). All of these presentations are rare and are easy to diagnose as material can be obtained for culture and biopsy [2 - 7].

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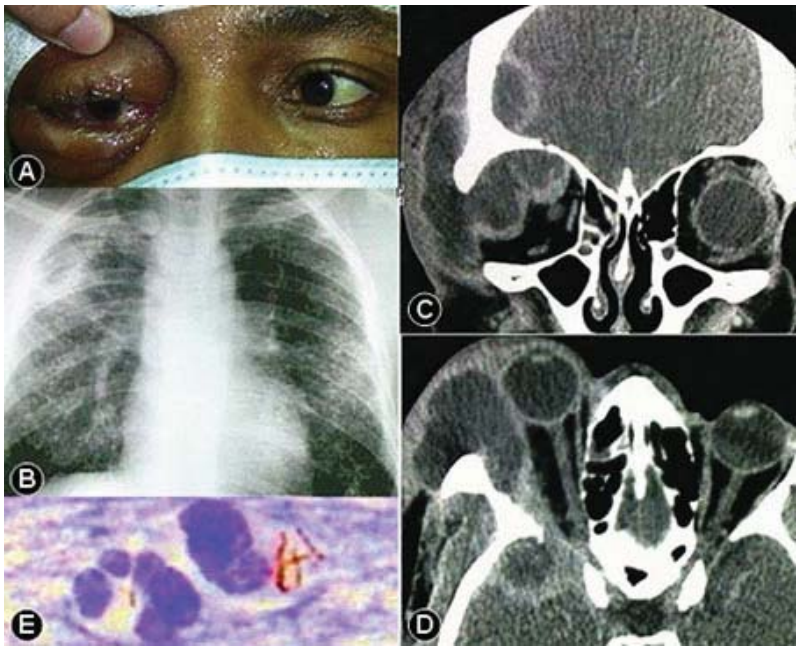

Fig. (1). (Garcia *et al.*). **A**) Right orbital syndrome "frozen orbit" with proptosis and mucopurulent conjunctivitis by direct invasion of the tubercle bacillus following haematogenous dissemination. **B**) Miliary tuberculosis is uncommon but carries a poor prognosis. It represents haematogeneous dissemination of an uncontrolled tuberculous infection. Miliary deposits appear as 1-3 mm diameter nodules, which are uniform in size and uniformly distributed. **C**-**D**) Computed tomographic scan of the head, showing a lesion in the superolateral part of the right orbit with extension into the orbital fissure and soft tissues without bony erosion. **E**) Histopathology showing chronic granulomatous inflammation with giant cells and caseation necrosis. (H&E).

Intraocular TB often involves delicate structures that are difficult or impossible to biopsy or culture. It may present as unilateral or bilateral granulomatous iritis or iridocyclitis with mutton-fat keratic precipitates and/or granulomatous nodules of the iris (Koeppe or Busacca nodules). Broad-based posterior synechiae and hypopyon may be observed. Intermediate uveitis can also occur. More commonly, intraocular TB presents with involvement of the posterior part of the eye. Vitritis, retinitis and/or choroiditis, and retinal vasculitis would be the presenting clinical scenario. Choroidal lesions including granulomas are probably the most common findings in confirmed cases of ocular TB and can be an early sign of disseminated disease [3, 4]. Choroidal tubercles are solitary, or few in number, yellowish lesions typically elevated centrally with poorly defined borders, and commonly situated in posterior pole (Figs. **2** and **8**). Inflammatory cells and subretinal fluid may be present (Fig. **3**). Tubercles can be solitary or miliary. Multifocal lesions predominantly present in choroid are also common (Figs. **4** and **5**) and sometimes can simulate "Serpiginous-like choroiditis" with two distinct patterns (Fig. **6**): one with multifocal discrete choroidal lesions that are initially noncontiguous and later

progress to form diffuse lesions with an active edge resembling serpiginous choroiditis, and a solitary, diffuse plaque-like lesion with an amoeboid extension [7]. The retina involvement alone is rare.

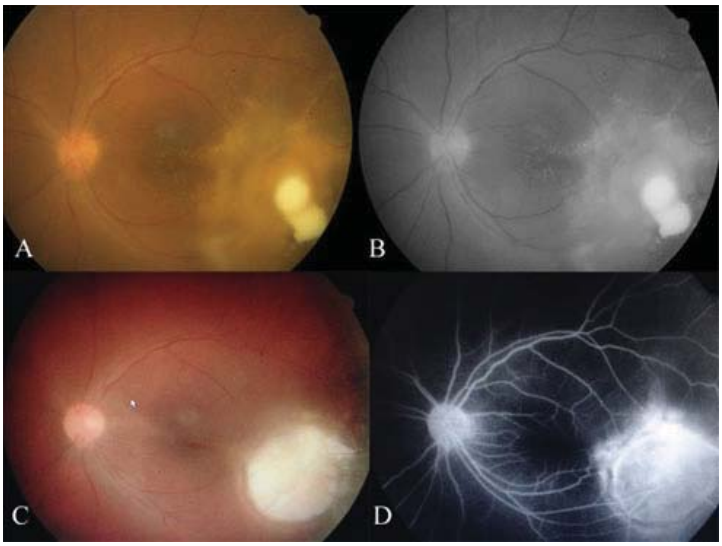

Fig. (2). (Garcia *et al.*). Choroidal tuberculoma. **A**-**B**) Left eye color (**A**) and red free (**B**) fundus photograph showing a yellowish-white choroidal mass elevated centrally with poorly defined borders and commonly situated in posterior pole. Inflammatory cells (vitritis), subretinal fluid and a macular star are present. **C**) Same lesion one month after treatment showing no inflammatory cells, consolidation, and no subretinal fluid. **D**) Fluorescein angiogram reveals late homogeneous hyperfluorescence with well-defined borders.

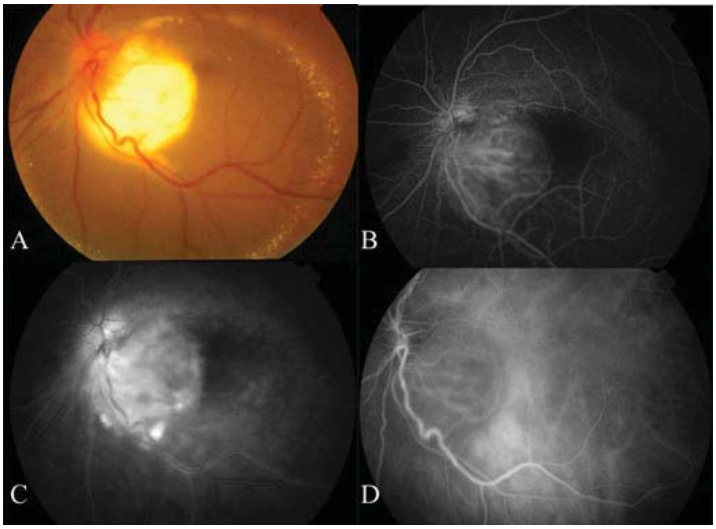

Fig. (3). (Garcia *et al.*). Choroidal tuberculoma. **A**) Left eye fundus photograph showing a yellowish-white peripapillary choroidal mass with exudative retinal detachment. **B**-**C**) Fluorescein angiogram (FA) reveals early mottled hyperfluorescence and late moderate hyperfluorescence. **D**) Indocyanine green angiography (ICG-V) shows hypofluorescence in the late phase. (Courtesy of J. Fernando Arevalo and Sulaiman Al-Sulaiman).

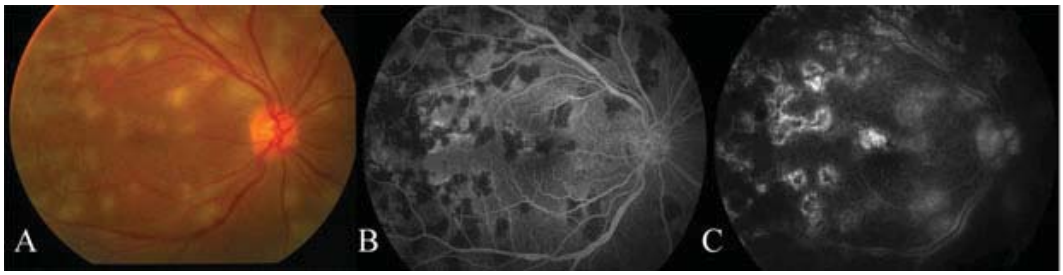

Fig. (4). (Garcia *et al.*). Presumed tuberculous multifocal choroiditis (MFC). **A**) Right eye fundus photograph of a 26-year-old male with a strongly positive tuberculin skin test (TST). It shows multiple yellowish choroidal infiltrates of varying sizes. **B**) Early phase fluorescein angiogram (FA) showing hypofluorescence of these lesions. **C**) Late phase FA depicting late hyperfluorescence. (Courtesy of J. Fernando Arevalo and Sulaiman Al-Sulaiman).

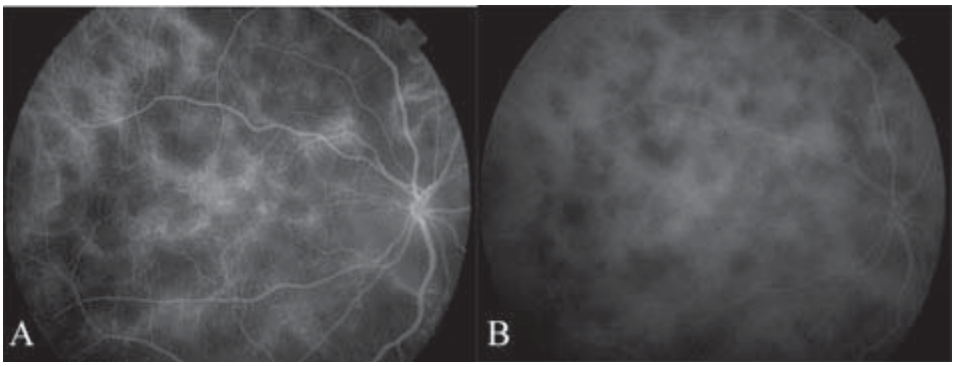

Fig. (5). (Garcia *et al.*). **A**-**B**) Indocyanine green angiography (ICG-V) of another patient with presumed tuberculous multifocal choroiditis showing hypofluorescence throughout all phases. (Courtesy of J. Fernando Arevalo and Sulaiman Al-Sulaiman).

The retina is often involved in setting of choroidal TB as retinochoroiditis. Exudative retinal hemorrhagic periphlebitis in a patient with uveitis is highly suggestive of tubercular etiology. The optic nerve may be swollen mimicking an ischemic optic neuropathy. It can also present as an optic neuritis or papillitis [2 - 7] (Fig. **7**).

Choroidal tubercles are hypofluorescent in fluorescein angiography (FA), but become hyperfluorescent in late phase (Figs. **2D**, **3 B-D**, **4 B-C**, **5**, **6 B-C**, **9**). OCT scans through the area of suspected granuloma revealed an elevation of the choroid with an area of localized contact between the choriocapillaris-retinal pigment epithelium complex and the overlying neurosensory retina ("contact sign") despite the presence of subretinal fluid around the lesion (Fig. **10**) [8].

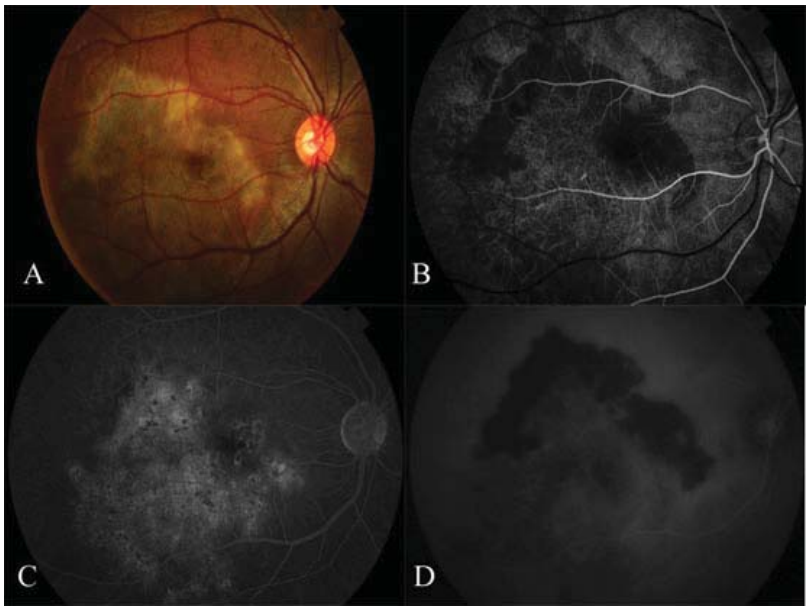

Fig. (6). (Garcia *et al.*). Serpiginous-like choroiditis **A**) Right eye fundus photograph of a 28-year-old male with a family history of miliary tuberculosis and a positive tuberculin skin test (TST) showing a serpiginous-like choroiditis. Note the yellowish active edge with amoeboid spread and central atrophy along with some hyperpigmentation. **B**-**C**) Fluorescein angiogram (FA) showing early hypofluorescence and late hyperfluorescence. **D**) Late phase indocyanine green angiography (ICG-V) showing persistent hypofluorescence of the active edge. (Courtesy of J. Fernando Arevalo and Sulaiman Al-Sulaiman).

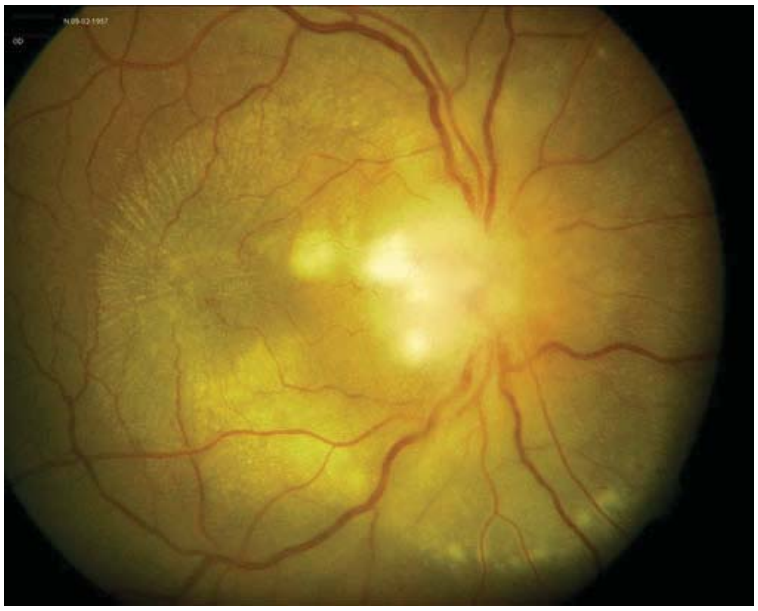

Fig. (7). (Garcia *et al.*). Right eye color fundus photograph of a presumed tuberculous neuroretinitis showing a yellowish-white mass elevated centrally with poorly defined borders over the optic nerve. Inflammatory cells (vitritis), subretinal fluid and a macular star are present.

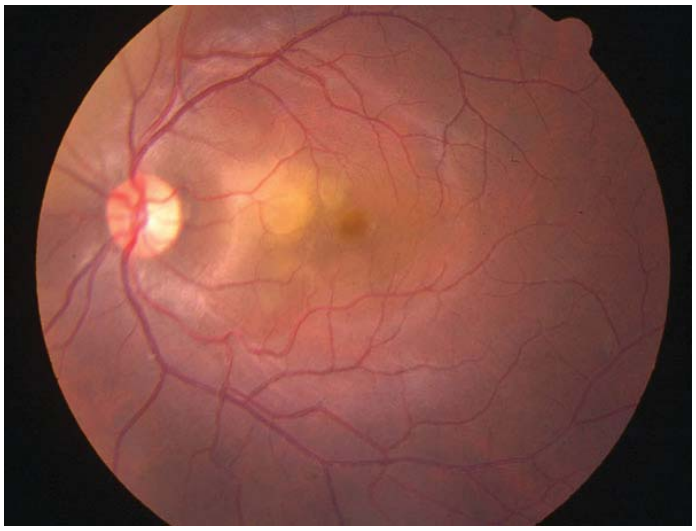

Fig. (8). Fundus photograph showing a granuloma next to the fovea with subretinal fluid.

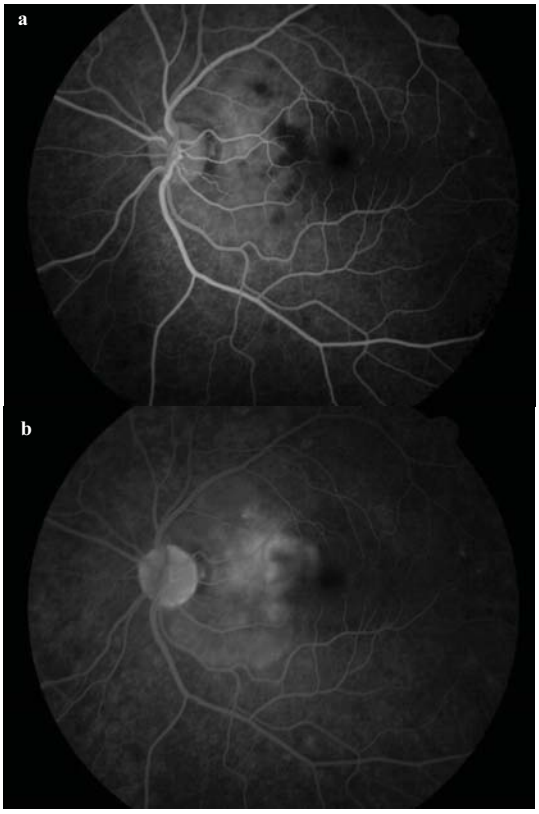

Fig. (9). FA of the same eye as Fig. (**8**). (**A**) FA demonstrates central hypofluorescence with a ring of leaking surrounding the granuloma, choroidal tubercles are hypofluorescent in fluorescein angiography in early stages. (**B**) FA demonstrates choroidal tubercles are hyperfluorescent in fluorescein angiography in late stages.

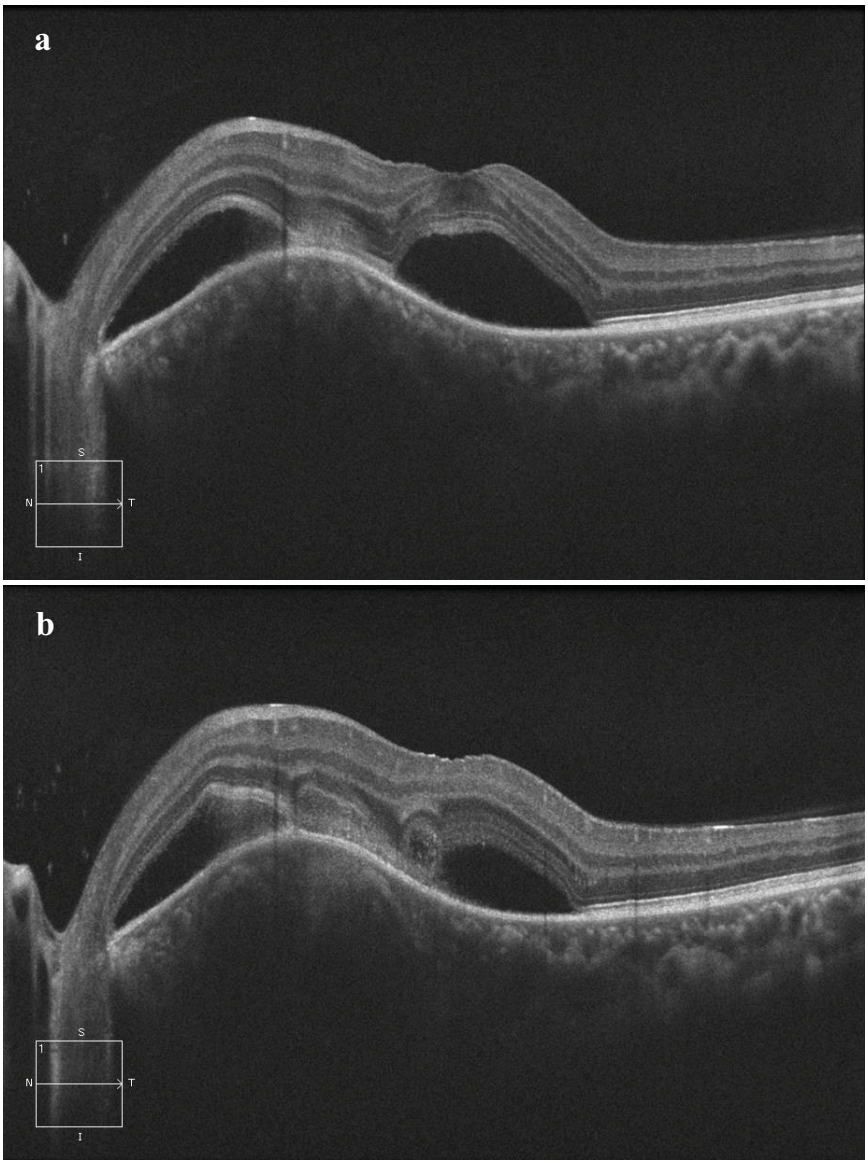

Fig. (10). OCT scan of the same lesion shown in Fig. (**9**), which shows attachment of the retinal pigment epithelial-choriocapillaris layer and the neurosensory retina over the granuloma ("contact" sign), inflammatory retinal infiltrate in the deeper retinal layers and subretinal fluid.

The "definitive" diagnosis of TB is established by isolation of M tuberculosis bacilli from ocular tissues. However, because this is difficult to achieve, the diagnosis of ocular TB is often "presumed" in the presence of suggestive ocular findings in combination with any of the following: systemic findings consistent with TB infection; positive interferon-γ release assay (Quantiferon Gold), which

is not affected by prior BCG vaccination; or positive tuberculin skin test (TST) >15 mm or >10 mm for those living in high-incidence areas, or high-risk congregates settings (*e.g.*, health care workers), or >5 mm in persons with HIV infection. However, vaccination with BCG poses a potential source of cross-reactions and TST false-positive results. In addition, clinical response to anti-TB treatment (ATT) further supports a presumed diagnosis of ocular TB. Finally, polymerase chain reaction (PCR) is a powerful tool for rapidly detecting mycobacterial genome from small sample of ocular fluid with minimal risk of cross-contamination, but it can still lead to false-negatives from ocular fluid samples [2, 5]. Patients diagnosed with active TB should also be tested for HIV due to high incidence of co-infection.

DIFFERENTIAL DIAGNOSIS

Granulomatous uveitis is common in sarcoidosis, syphilis, herpes simplex, varicella zoster, leprosy, Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. Choroidal granulomas or chorioretinitis are common in syphilis, sarcoidosis, cryptococcosis, serpiginous, toxoplasmosis, and fungal lesions [2, 5].

MANAGEMENT

Ocular TB is treated as other forms of extrapulmonary TB with the first-line combination regimen comprising isoniazid, rifampin, pyrazinamide, and ethambutol for a total of 6–12 months. During the first 2 months, known as the intensive phase of treatment, all 4 drugs are given, followed by 4–10 months of 2 drugs (usually isoniazid and rifampin). Optimal dosing of oral steroids is unclear but in hypersensitivity uveitis systemic prednisone it was used at 1 mg/kg without appreciable harm. Reduced dosing may be appropriate in patients with presumed active ocular infection. Special consideration should be given to patients recently started on highly active antiretroviral therapy (HAART) for HIV infection, as there have been several cases of immune reconstitution inflammatory syndrome (IRIS) presenting as a paradoxical flare of ocular TB [9 - 11].

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 3

Cytomegalovirus Retinitis

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Cytomegalovirus (CMV) is a double-stranded DNA virus, member of the herpesvirus family, which can be acquired through placental transfer, breast feeding, sexual contact, blood transfusions and organ or bone marrow transplants [1]. It is estimated that at least 50% of the world population is seropositive to the virus, occurring at a higher rate in lower socioeconomic groups, developing countries, and homosexual men [1, 2]. However, CMV infection mainly manifests in immunocompromised patients, including those with AIDS, inherited immunodeficiency states, malignancies, and patients under systemic immunosuppressive chemotherapy after transplantation, constituting a major cause of morbidity and mortality in this population. Clinical manifestations may include retinitis, hepatitis, colitis, pneumonitis and encephalitis. In patients with AIDS, CMV retinitis usually occurs when the CD4 T-cell count is below 50 cells/mm^3 [2, 3]. Although the incidence of the infection has dramatically decreased since the use of HAART (highly active antiretroviral therapy), it remains the most common opportunistic ocular infection in this group of patients. There are rare cases of CMV retinitis reported in immunocompetent patients [4].

ESSENTIALS OF DIAGNOSIS

The symptoms are related to the localization of the retinal lesions; small lesions in the periphery can be asymptomatic. At presentation, the most common symptoms are decreased visual acuity, floaters, photopsias, ocular pain and scotomas [1]. The anterior segment manifestations are usually mild, with fine keratic precipitates and anterior chamber cells. Vitreous cells can be present. Papillitis is rare, but may also occur [1, 2].

CMV retinal lesions can be unilateral or bilateral. The retinitis is characterized by granular whitening areas with irregular borders due to retinal necrosis and edema,

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usually accompanied by hemorrhages. Small satellite lesions are characteristic [2]. Vascular sheathing with appearance of "frosted branch" can also be observed [1, 5] (Figs. **1**-**4**).

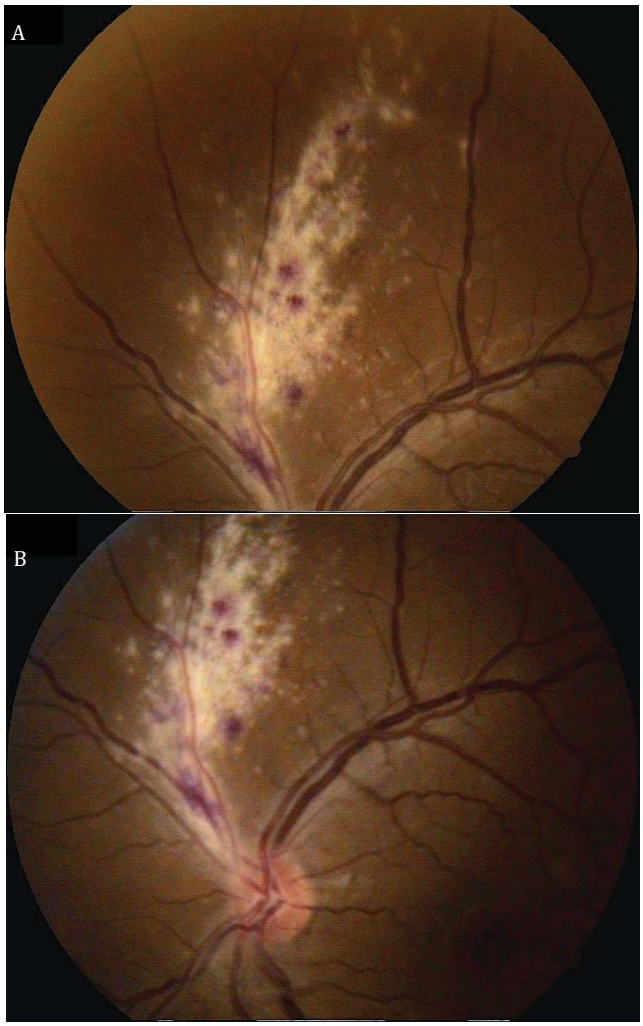

Fig. (1). Fundus photographs of the left eye of a 25-year-old male patient with AIDS and active CMV retinitis. Images **(A)** and **(B)** show involvement of the superonasal arcade with the presence of retinal whitening and hemorrhages.

The localization of the lesions is divided into three zones: zone 1 -- the area within one disc diameter (1500 μm) of the optic disc margin or two disc diameters (3000 μm) of the fovea; zone 2 -- extends from zone 1 to the equator; zone 3 -- the remaining retina to the ora serrata [1, 2, 6]. Progression was defined as an extension of the lesion border of 750 μm or the appearance of a new lesion, at least ¼ of the disc area in size, separated from the previous lesion by 750 μm [1].

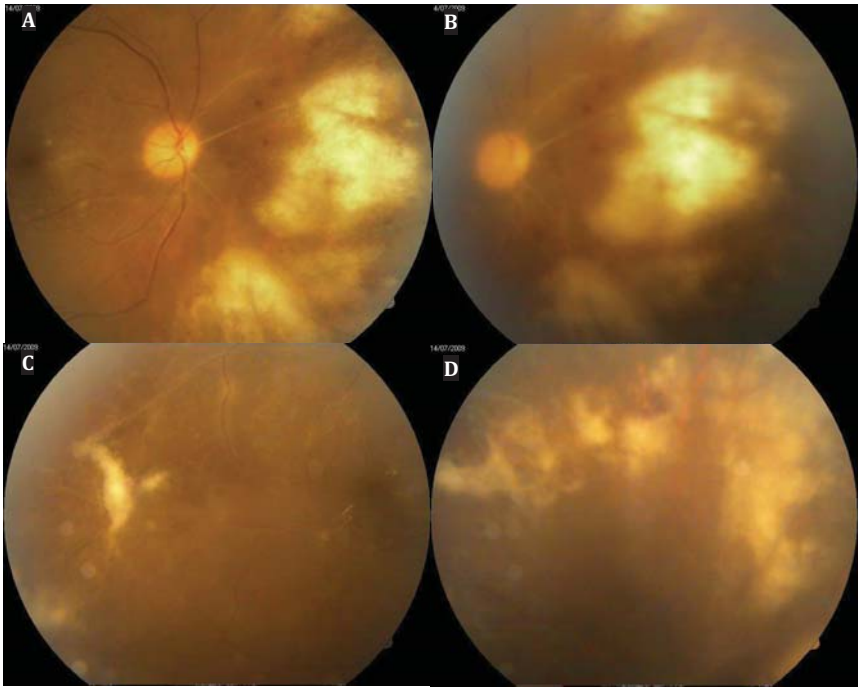

Fig. (2). Acute CMV retinitis OD, with retinal whitening, hemorrhages and perivascular sheathing in a 35-year-old male patient with AIDS. Fundus photographs show plaques of CMV retinitis involving nasal **(A)** and **(B)** temporal **(C)** and superior **(D)** areas.

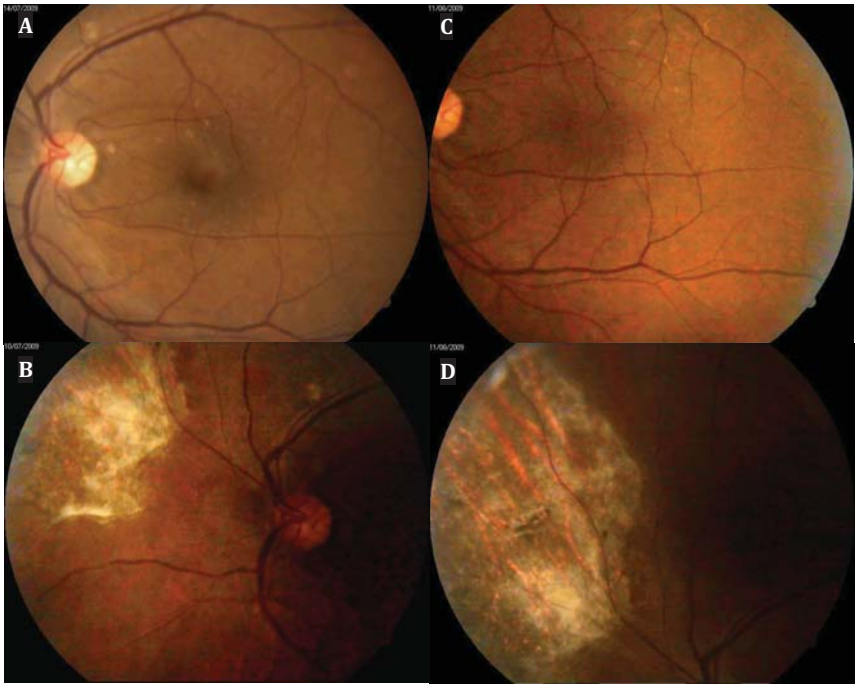

Fig. (3). The same patient of Fig. (**2**), showing improvement one month after treatment with valganciclovir.

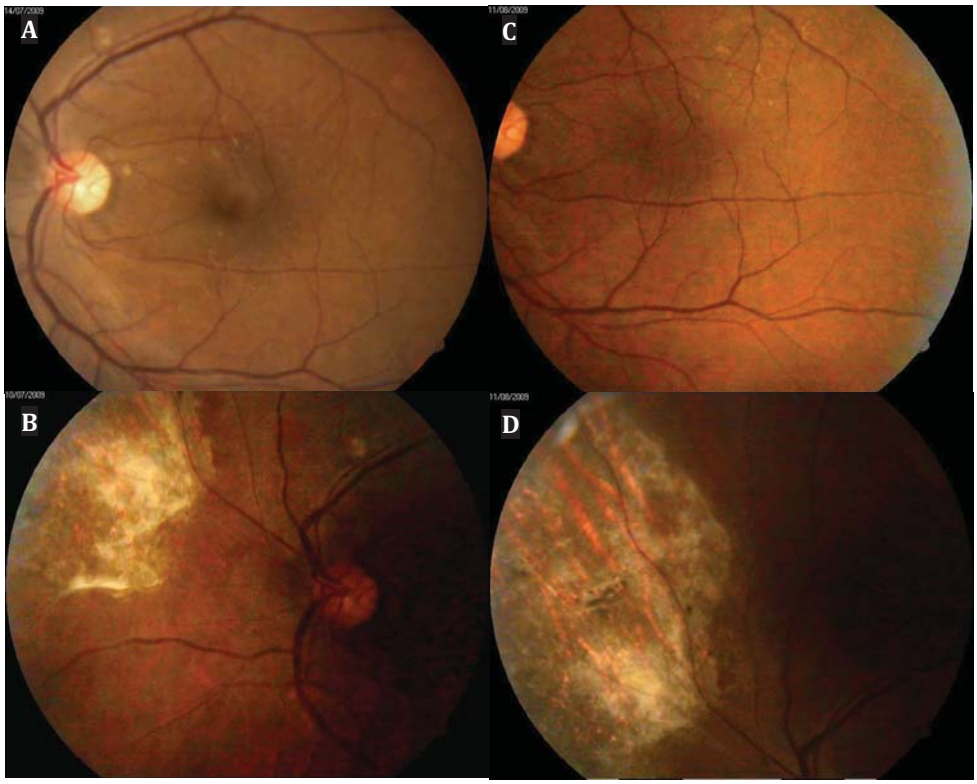

Fig. (4). Left eye of the same patient as Fig. (**2**). **(A)** and **(B)** in acute phase with granular appearance secondary to disrupted pigment epithelium. **(C)** and **(D)** show appearance one month after treatment with valganciclovir.

Rhegmatogenous retinal detachment is the most common complication of CMV retinitis (it occurs in 50% of patients after the first year of diagnosis), and is related to the extent and localization of retinal necrosis, being more frequent if the necrosis areas are in zone 3 [7].

DIFFERENTIAL DIAGNOSIS

The initial small CMV lesions can simulate the cotton-wool spots present in HIV-retinopathy. Toxoplasmic retinochoroiditis differs from CMV by the presence of a chorioretinal scar and severe vitritis. Other causes of retinochoroiditis, like syphilis and tuberculosis, should be discarded [1, 2]. Necrotizing herpetic retinopathies are also considered in the differential diagnosis; however, unlike CMV retinitis, these show rapid progression. In contrast to CMV retinitis, acute retinal necrosis (ARN) occurs in immunocompetent patients and presents severe vitritis. Progressive outer retinal necrosis manifests in immunocompromised patients as multiple areas of necrosis, most of them at the periphery [1].

MANAGEMENT

The medical therapy includes ganciclovir, a synthetic nucleoside analog of deoxyguanosine, that acts by inhibition of viral DNA synthesis [1, 2]. Intravenous administration of ganciclovir shows better results than other delivery routes. The oral administration is an effective alternative during the maintenance phase [8]. The main adverse effect of ganciclovir is myelosuppression. Intravitreal ganciclovir is an alternative of treatment, which avoids the effect of bone marrow suppression [3, 9]. Ganciclovir intravitreal implant is more effective at reducing the risk of progression of CMV retinitis than intravenous administration; however, it is no longer commercially available. Furthermore, intravenous therapy decreases the risk of extraocular manifestations due to CMV [10].

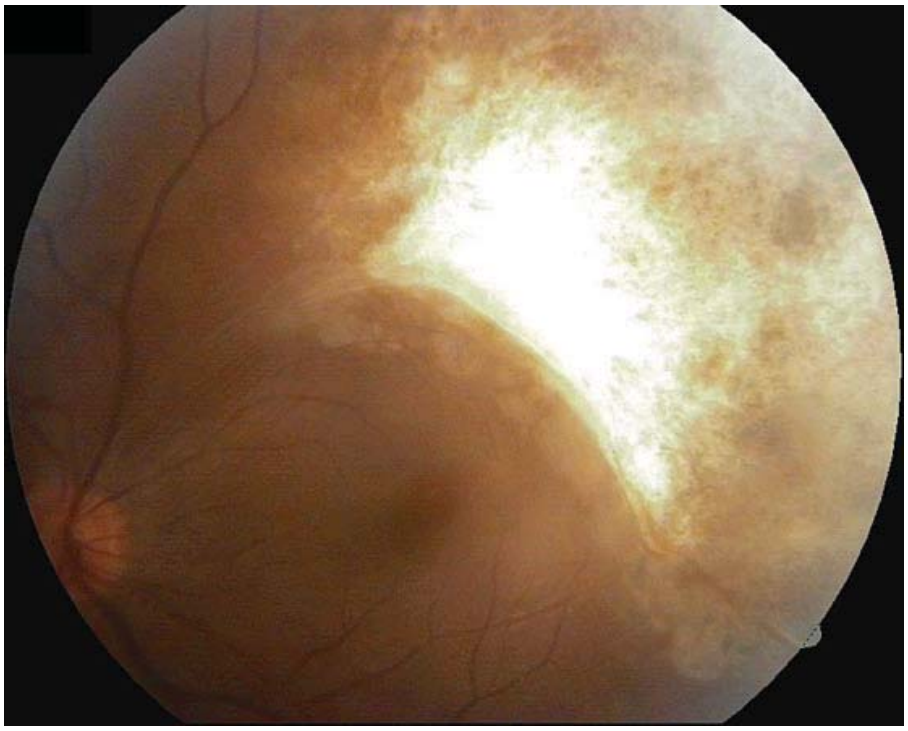

Fig. (5). Fundus photograph of the left eye of a 39-year-old male patient with AIDS and a history of CMV retinitis. The image shows preretinal fibrosis involving the superotemporal arcade, and chorioretinal scars due to laser photocoagulation.

Foscarnet is a pyrophosphate analog that inhibits CMV DNA polymerase. The route of administration is intravenous or intravitreal. Previous studies demonstrated that the survival rate in patients with AIDS treated with foscarnet is higher than in patients treated with ganciclovir [11]. Adverse effects of foscarnet include nephrotoxicity, hypocalcemia, anemia and gastrointestinal disorders [2, 3].

Cidofovir, a nucleotide analog of cytosine, must be administered intravenously together with oral probenecid to minimize nephrotoxicity. Cidofovir can cause immune recovery uveitis and hypotony. Valganciclovir is a prodrug of ganciclovir that has a great oral bioavailability, and is indicated in induction and maintenance treatment of CMV [1, 3]. In cases of zone 1 disease threatening the posterior pole and macula, intravitreal injection of agents is warranted.

Argon laser coagulation is recommended as prophylaxis for atrophic lesions (Fig. **5**). Surgical management, in cases of rhegmatogenous retinal detachment, is pars plana vitrectomy with silicone oil tamponade [1, 2, 7].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 4

Necrotizing Herpetic Retinopathies

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'Necrotizing herpetic retinopathies' (NHR) is a term recently proposed because of the wide variety of clinical manifestations of herpetic retinal infections. The severity, location and progression are determined by patient's immune status and virus-related factors [1].

Two forms of retinal necrosis have been described: a fulminant, acute retinal necrosis (ARN) (Figs. **1** and **2**), characterized by a rapidly progressive inflammation and necrosis *of the peripheral retina* that leads to retinal detachment (RD); and another one characterized by multifocal, discrete, white, outer retinal lesions that progress rapidly to confluence. The latter is mainly found in immunocompromised patients and was previously known as progressive outer retinal necrosis (PORN) (Fig. **3**).

NHR is caused by reactivation of a previous infection or by a primary infection from the vaccine strain virus. Case reports have described viral retinitis following the administration of intravitreal steroids and in patients with coexisting medical immune-altering comorbidities. Varicella-zoster virus (VZV) and herpes simplex virus (HSV) have been identified as the causative infectious agents in most cases, and, in fewer cases, cytomegalovirus (CMV) or Epstein-Barr virus (EBV).

The Herpes virus involved in the infection correlates with the patient's age. VZV and HSV-1 affect frequently middle aged patients (median age, 57 and 47 years, respectively), while HSV-2 has a bimodal distribution with peaks in the third and sixth decades. It has been reported that younger age, history of neonatal herpes, preexisting chorioretinal scar, and triggering events, such as trauma or systemic corticosteroids, are more commonly associated with HSV-2 reactivation [2]. There is an increased risk of VZV for patients who use azathioprine and/or steroids, and it is more frequent among new users [3].

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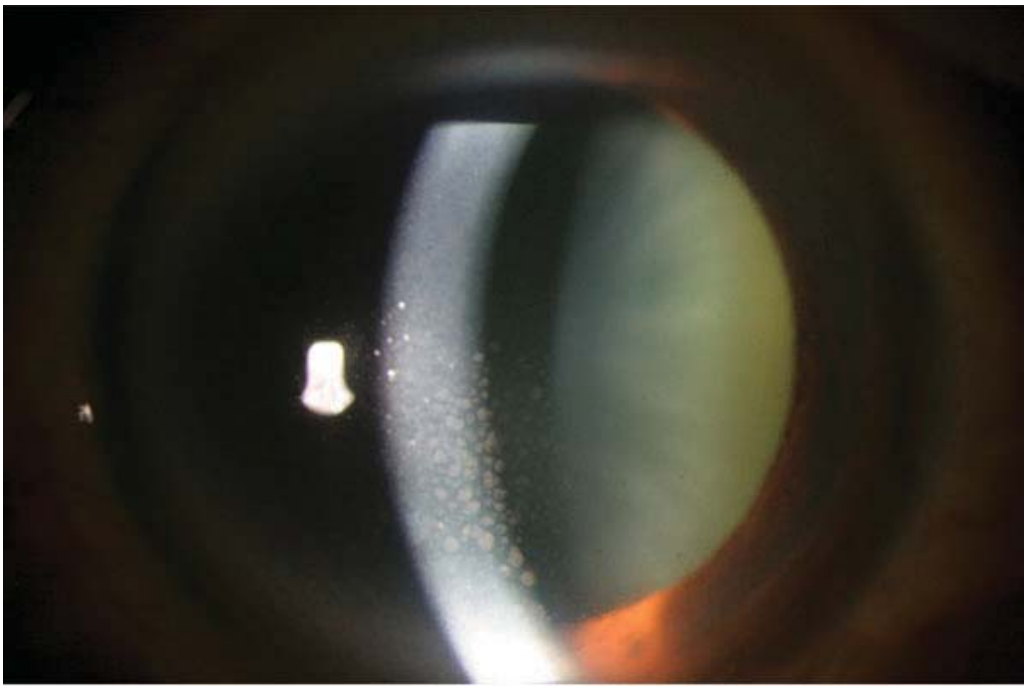

Fig. (1). Anterior segment of a patient with ARN. Multiple granulomatous keratic precipitates.

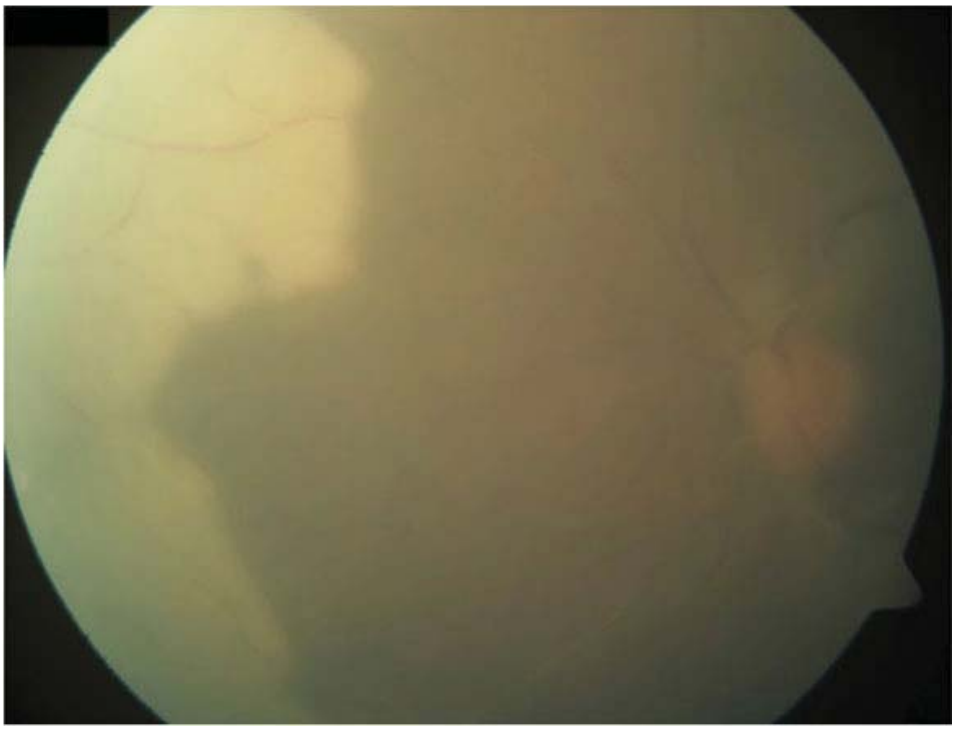

Fig. (2). ARN characterized by peripheral confluent white patches associated with vitritis, disc swelling and vascular sheathing.

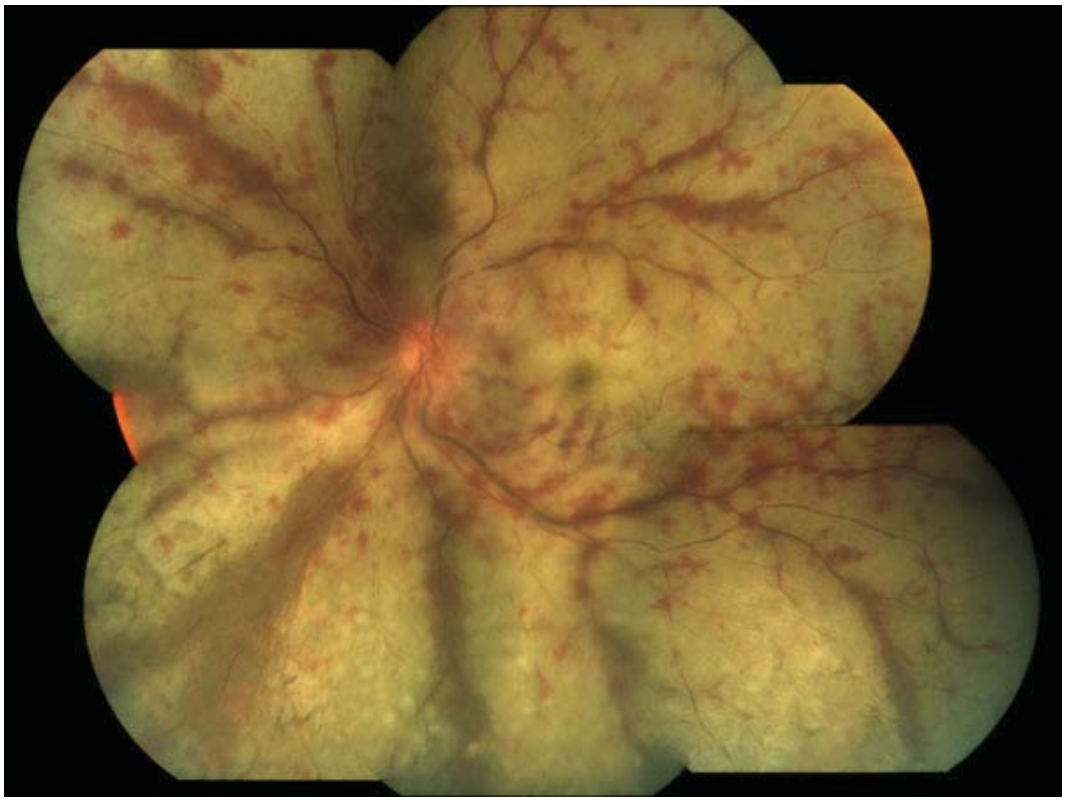

Fig. (3). Fundus picture showing the classical "cracked mud appearance" in progressive outer retinal necrosis.

ACUTE RETINAL NECROSIS: ESSENTIALS OF DIAGNOSIS

ARN is characterized by progressive unilateral intraretinal inflammation and necrosis. Clinical diagnosis is based on criteria published by the American Uveitis Society, which include anterior uveitis, vitritis, retinal necrosis beginning in the peripheral retina, and occlusive vasculitis involving the retina and the choroid. Other features that may be observed include optic neuropathy or atrophy, scleritis, and pain [4]. Newer criteria have been added: hyperemia of the optic disc and elevated intraocular pressure. They include clinical course and virologic testing for the diagnosis [5].

Other types of herpetic uveitis with posterior involvement include: 1) multifocal posterior necrotizing retinitis (MPNR), which runs a more aggressive course, macular involvement is *observed in* 50% of cases at presentation, with poorer visual prognosis and a higher rate of RD [6]; 2) slow-type ARN; 3) only vasculitis/papillitis; and 4) panuveitis with lack of necrotic lesions and no obvious vasculitis or papillitis [7].

Diagnosis of NHR is usually clinical. In atypical presentations, laboratory testing of aqueous or vitreous specimens may help; some clinicians use it as a routine test, to determine the precise etiologic agent and avoid treatment resistance. Two techniques can be used: polymerase chain reaction (PCR) analysis and intraocular antibody testing. PCR is a sensitive and specific method [8]; however it can yield false-positive results, especially for VZV. Intraocular IgA testing for herpes virus in ARN syndrome has been performed sporadically and not systematically [9].

Fluorescein angiography (FA) shows retinal vessel occlusion and dye extravasation in cases where there is mild anterior chamber and vitreous reaction. ICG can detect retinal vasculitis and the extent of choroidal inflammation [10].

MANAGEMENT

Treatment must be immediate and appropriate for a favorable visual outcome and prevention of fellow eye involvement, which is the case in 10% of patients despite systemic antiviral treatment [11], and has been associated with CNS involvement in the immunocompromised host [12].

Intravenous acyclovir 10-15 mg/kg divided TID or oral valacyclovir 1,000-2,000 mg TID or oral famciclovir for 10 days followed by 1,000 mg of oral valacyclovir TID or acyclovir 400 mg q4h for 6–14 weeks. The ideal duration of treatment is unknown and its purpose is resolution of inflammation/infection and protection of fellow eye [13]. Adverse effects include renal dysfunction, gastrointestinal irritation and, rarely, nervous system toxicity [14].

Intravenous (IV) antiviral therapy is recommended when there is an associated systemic herpetic virus infection, if patient is HIV+, when there are problems with treatment compliance, if retinal necrosis is close to the macular area, is widely extended or VA is poor. In immunosuppressed patients or in cases of encephalitis or disseminated dermatitis, IV treatment and monitoring for neurological or dermatological complications is suggested. Long-term immunosuppressive therapy is potentially linked to the lack of response to acyclovir in patients with autoimmune diseases [15].

If retinitis threatens or involves the optic nerve or macula, or if there is presence of occlusive vasculitis or serous detachment involving the posterior pole, an intravitreal injection with ganciclovir sodium (2 mg/0.05 ml) or foscarnet (1.2 mg/0.05 ml) can be used two to three times a week [12].

Systemic corticosteroids are used in cases of severe inflammation at an initial dose of 0.5-1 mg/kg/day of prednisone, at least 24 hours after the antiviral

therapy. If the patient has anterior chamber inflammation, topical steroids, cycloplegic and pressure-lowering drops, if ocular hypertension coexists, are added [12].

Resolution of ARN begins approximately 3 weeks after initiation of treatment. In untreated patients, inflammation decreases 1 to 3 months after symptoms begun.

Laser photocoagulation applied posterior to active retinitis has been recommended to prevent RD, but no prospective studies have proven it successful [14].

RD rate after ARN ranges from 20-50% [16]. In patients receiving oral valacyclovir, RD rate is 30% [13]. Retinal detachments combine rhegmatogenous and tractional components. Surgical treatment is focused on both. Some surgeons recommend three-port pars plana vitrectomy, lensectomy, air-fluid exchange, endophotocoagulation, and gas or silicone oil tamponade to improve the rate of retinal reattachment from 22% to 88%-100% [14].

PROGRESSIVE OUTER RETINAL NECROSIS: ESSENTIALS OF DIAGNOSIS

PORN is a devastating disease, first described in patients with HIV. It is characterized by multifocal retinitis with discrete granular borders beginning in the periphery with involvement of the posterior pole in 30% of cases, without vitritis or occlusive vasculitis and extremely rapid progression (Fig. **3**) [17, 18]. Within 4 weeks, 61% of cases become bilateral and two thirds of the patients progress to no light perception. It has a poor prognosis as well as poor response to antiviral treatment related the immunodeficient state.

MANAGEMENT

Treatment includes induction at high doses of systemic antiviral double therapy (valganciclovir for 3 weeks and IV foscarnet for 2 weeks) to protect the other eye and the CNS, followed by maintenance antiviral therapy (oral valganciclovir and IV foscarnet) until healing is achieved [19]. Intravitreal ganciclovir or foscarnet injections improve visual prognosis. Regimen includes 3 times a week for 2 weeks, followed by once or twice a week until the retinitis is stabilized.

The use of HAART probably influences the prognosis as it does with CMV retinitis.

About 70% of eyes develop rhegmatogenous RD within a median time of 30 to 90 days after presentation [20, 21]. It happens during the active necrotic phase or in

the inactive phase secondary to epiretinal membranes and vitreoretinal gliosis [17].

DIFFERENTIAL DIAGNOSIS

Necrotising retinitis may be caused by other non-viral infectious agents such as *Toxoplasma gondii* or *Treponema pallidum,* Behcet's disease, intraocular lymphoma, sarcoidosis or aspergillosis. Toxoplasmosis patients have dense yellow-white lesions with better-defined borders, occasionally with small satellite lesions or a scar. They mostly have more intense inflammation, with less retinal hemorrhages, and vasculitis is more prominent adjacent to areas of necrosis. The peripheral retina is usually less involved. Serum titers or PCR analysis can aid in diagnosis.

Syphilis is a bilateral disease with multiple manifestations ranging from retinitis, vasculitis, papillitis to only vitritis. VDRL and FTA-ABS laboratories are a must.

Sarcoidosis is a bilateral disease with granulomatous manifestations in anterior segment, snowballs/string of pearls vitreous opacities, multiple small, round, white or whitish-yellow, chorioretinal peripheral lesions (active and atrophic), with peri-pherebitis and optic disc or choroidal granuloma.

Lymphoma patients present with a chronic uveitis, mild anterior segment inflammation, marked vitreous haze and creamy retinal, subretinal and/or intra-retinal lesions with feathery or distinct borders, single or multiple confluent lesions.

In Behcet's disease, ocular findings include vitritis and retinal perivasculitis mostly of veins. Retinitis presents with scattered superficial yellow-white solitary or multiple infiltrates of the inner retina with indistinct margins.

Aspergillus endophthalmitis is a very rare disease seen in immunodeficient patients with anterior chamber inflammation and a retinal yellowish white mass [22].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

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CHAPTER 5

Ocular Syphilis

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Syphilis is a chronic sexually transmitted disease caused by the spirochete *Treponema Pallidum.* Based on its progression, it can be classified as early (primary, secondary and early latent) syphilis, late syphilis and neurosyphilis. Any organ may be affected, including skin, blood vessels, heart, bone, nervous system and the eye [1 - 7].

ESSENTIALS OF DIAGNOSIS

Ocular involvement may occur in any stage of infection and may present in a variety of ways, with panuveitis being the most common manifestation (25% to 54%) [4]. Anterior uveitis has a prevalence of 8%-38% and posterior uveitis varies from 18% to 37% (Figs. **1**-**3**). Optic nerve involvement has been reported in 20% to 38% of cases [3, 8 - 13]. More than half of the cases are bilateral, and visual acuity may range between counting fingers to 20/20. Apart from panuveitis, patients may present with retinal vasculitis (Fig. **4**), macular edema (Figs. **5**-**7**), punctate retinitis (Figs. **8** and **9**) and, in advanced stages, pigmentary retinopathy will develop (Fig. **10**). Gass *et al.* [2] named the distinctive posterior uveitis involvement as "Acute syphilitic posterior placoid chorioretinitis". It is characterized by the presence of one or more placoid, yellowish outer retinal lesions typically in the macula (Fig. **11**) [11]. Since the optic nerve and retina are considered to be extensions of the CNS, ocular syphilis is regarded as a variant of neurosyphilis; thus, every patient with syphilitic uveitis should undergo lumbar puncture and CSF analysis for the detection of neurological involvement [14].

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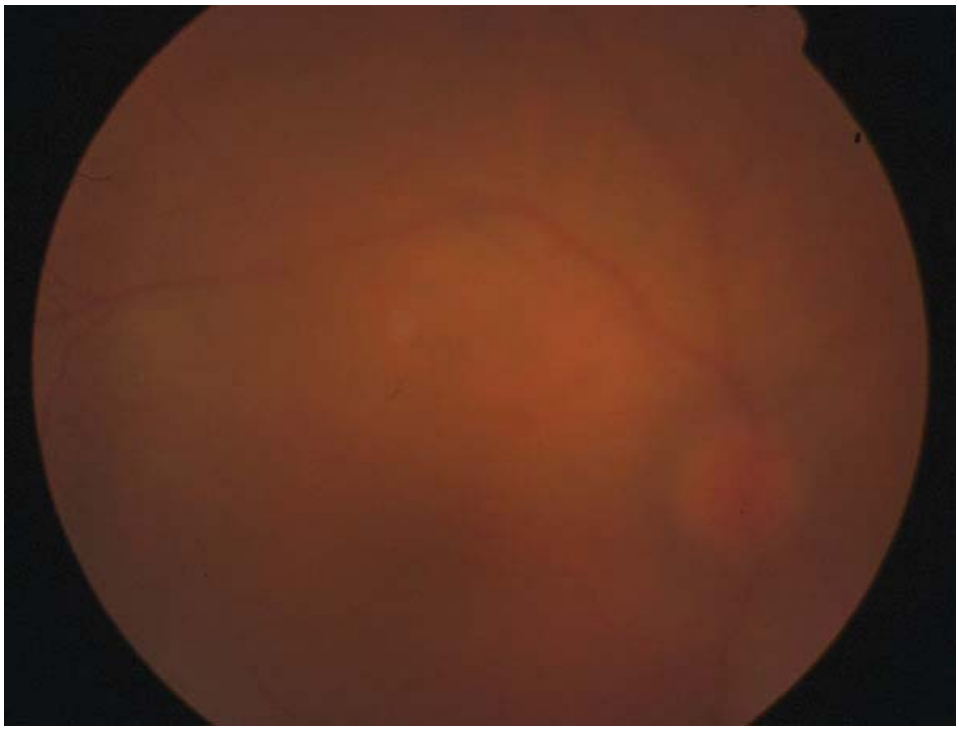

Fig. (1). Syphilitic panuveitis. Vitreous and optic nerve inflammation.

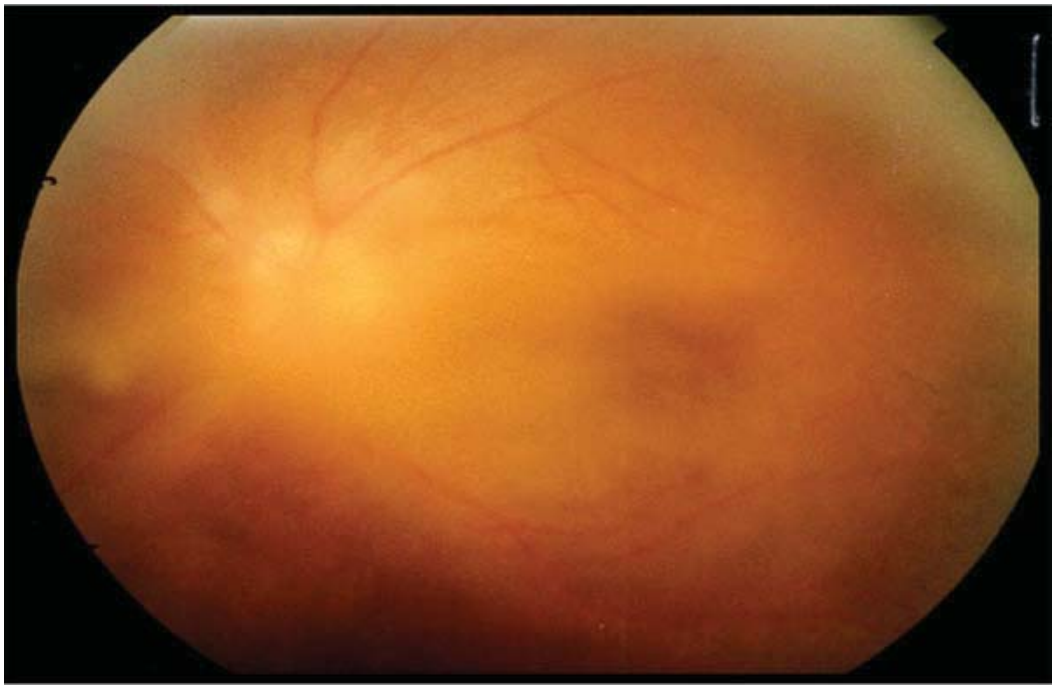

Fig. (2). Ocular syphilis: Severe vitreous inflammation with areas of retinitis.

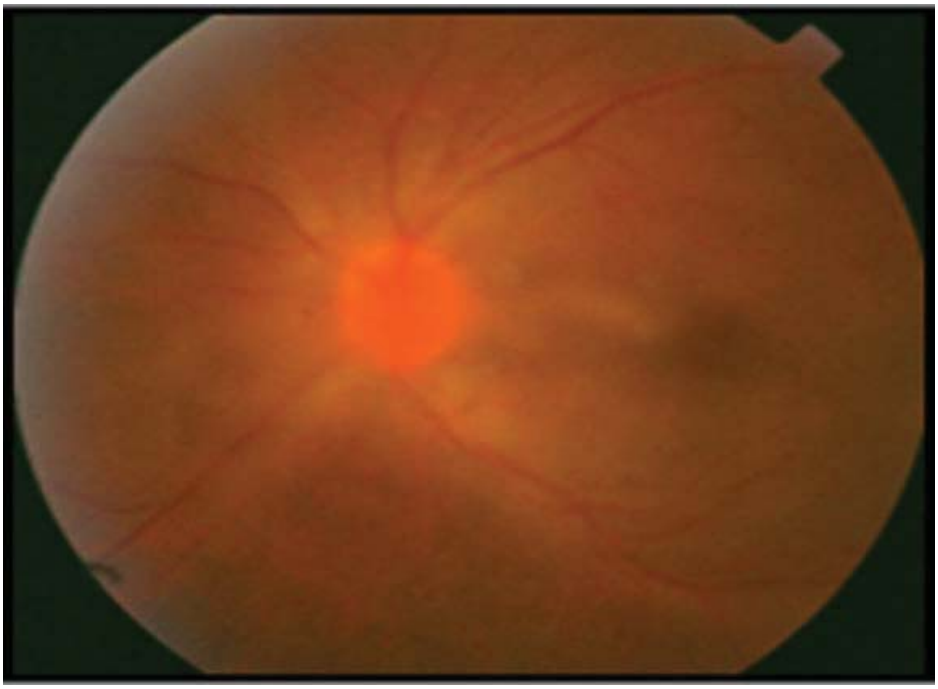

Fig. (3). Ocular syphilis after Penicillin treatment: Improvement of vitreous and retinal inflammation.

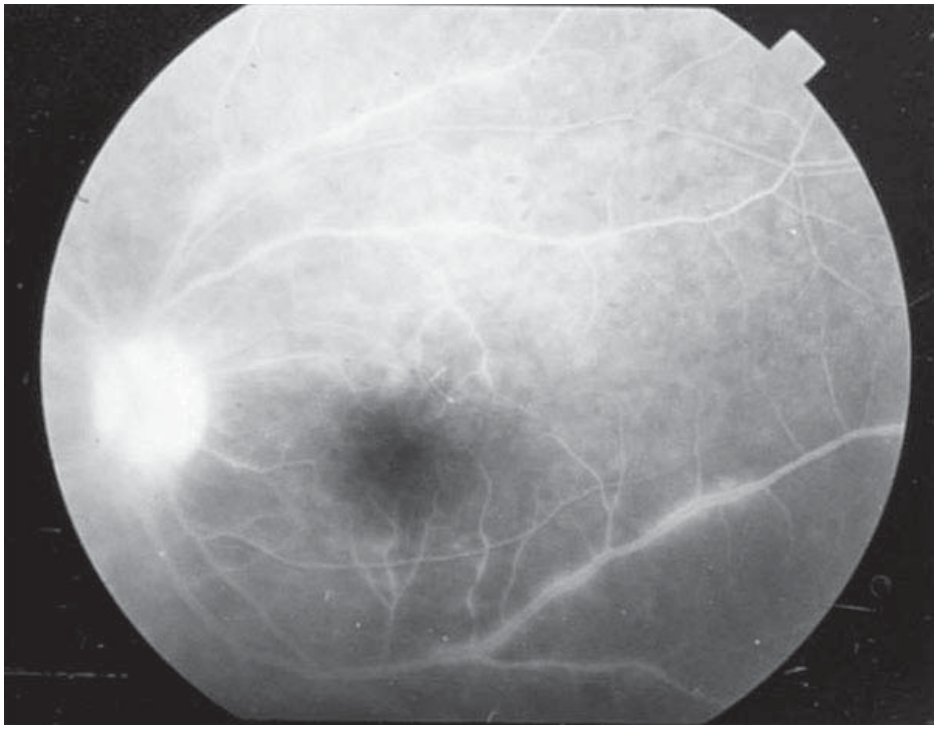

Fig. (4). Syphilitic vasculitis. Retinal angiography shows venular staining.

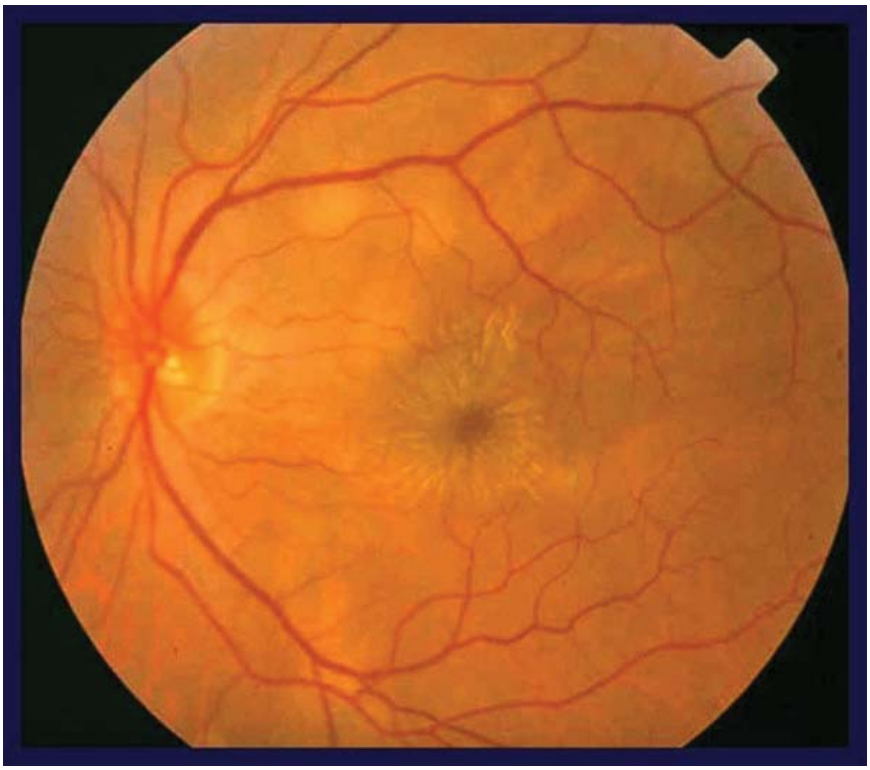

Fig. (5). Syphilitic retinitis with macular star.

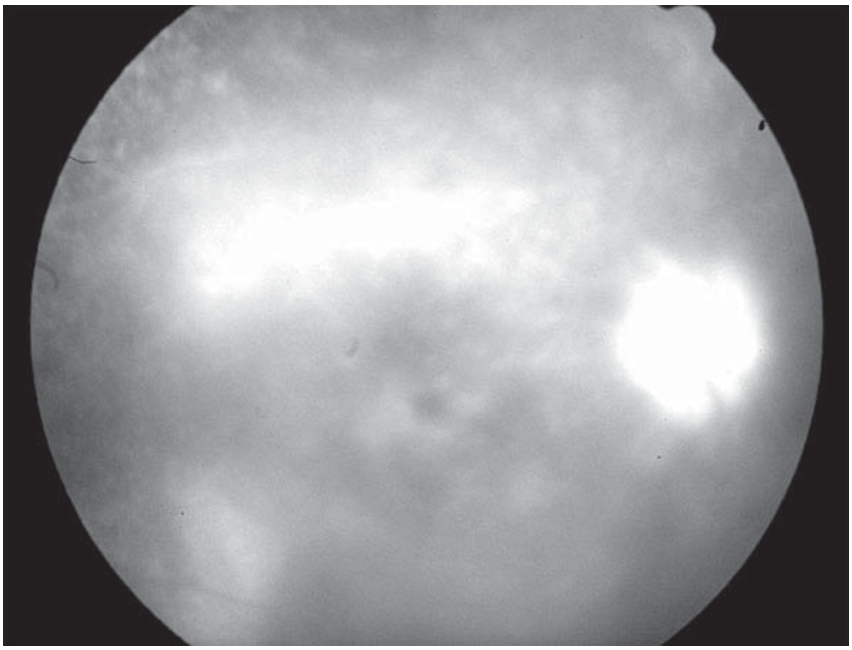

Fig. (6). Syphilitic optical neuritis, retinitis and cystic macular edema. Right-eye retinal angiography.

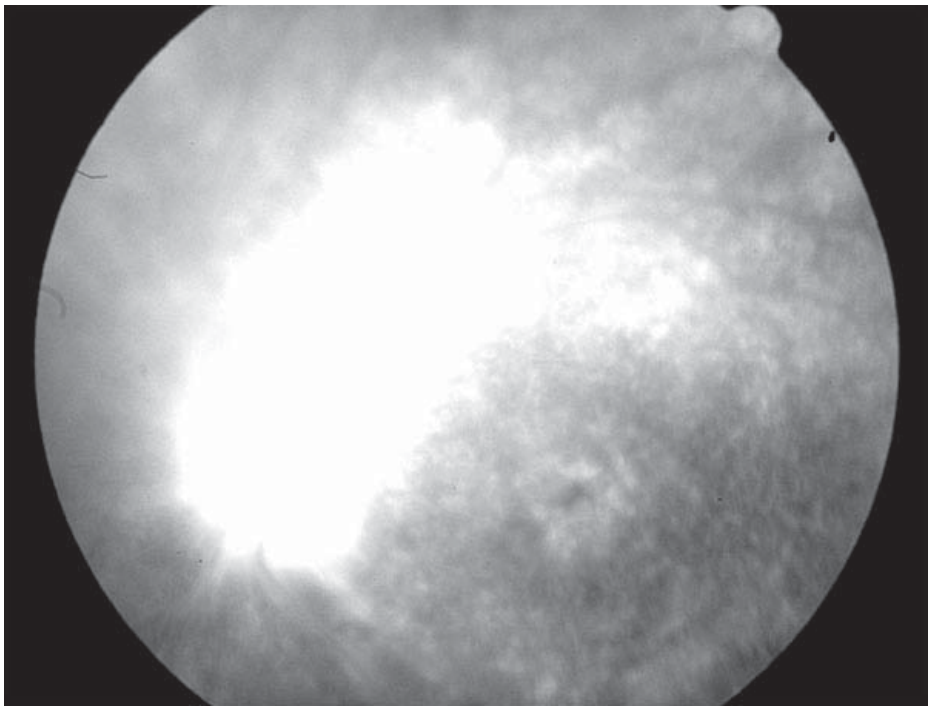

Fig. (7). Syphilitic optical neuritis, retinitis and cystic macular edema. Left eye retinal angiography.

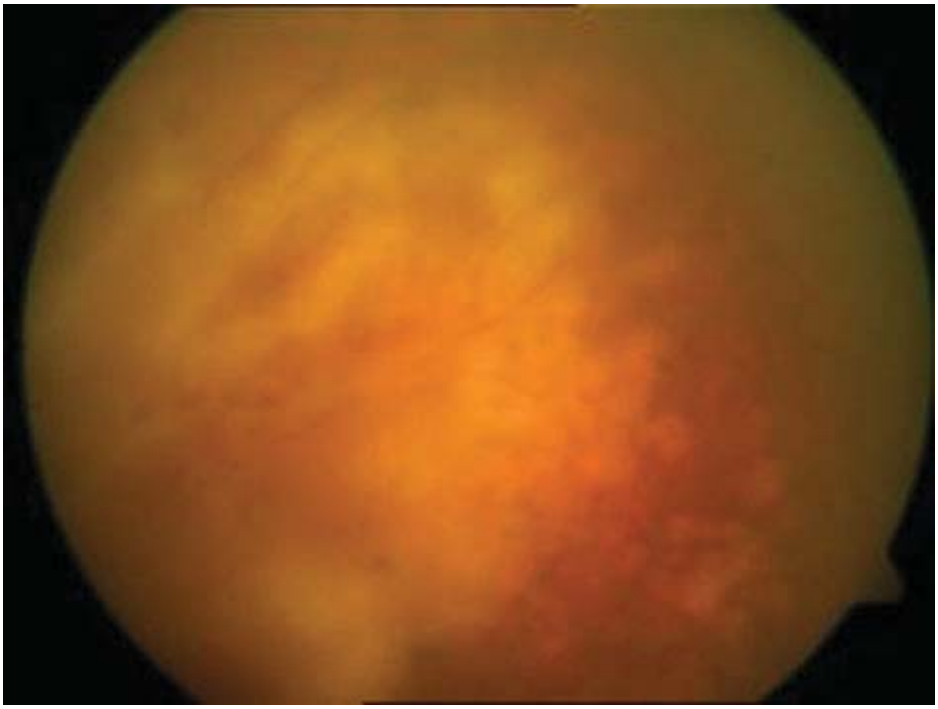

Fig. (8). Syphilitic retinitis mimicking acute retinal necrosis.

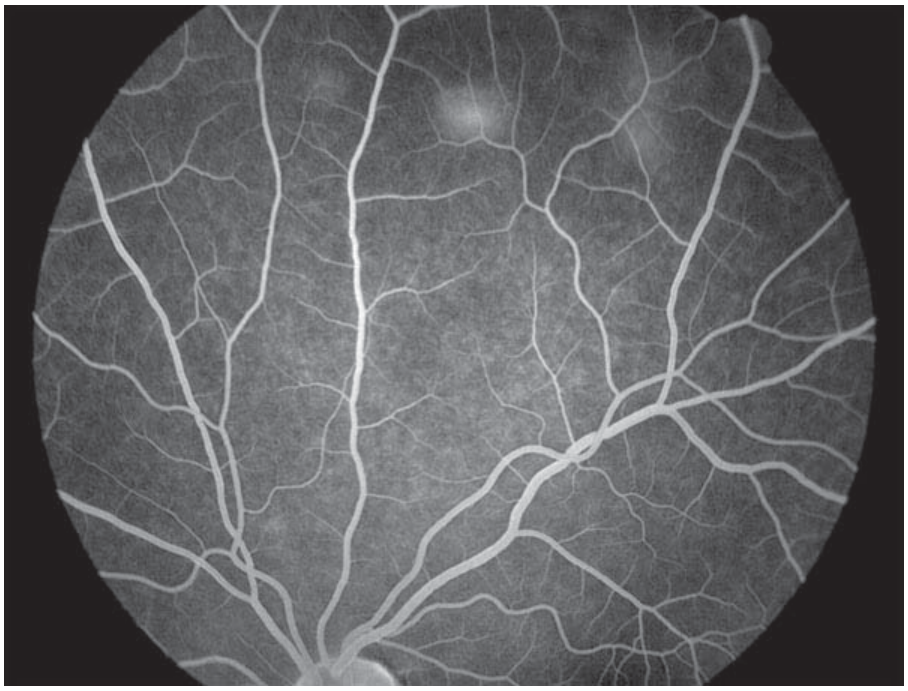

Fig. (9). Syphilitic multifocal retinitis. Retinal angiography shows hyperfluorescent lesions.

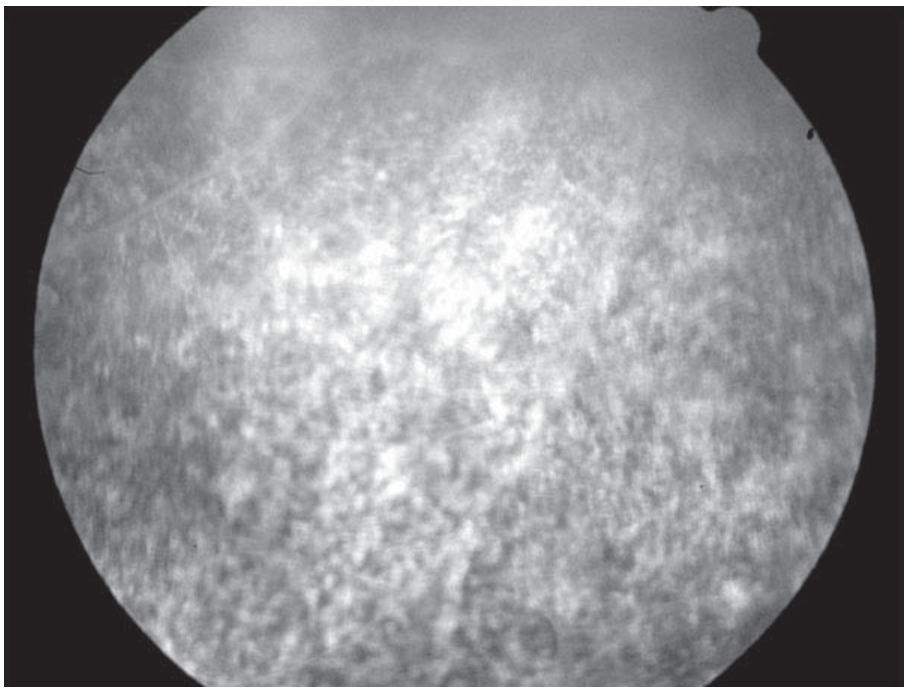

Fig. (10). Ocular syphilis. Late pigmentary changes. Retinal angiography with patches of hyperfluorescence and hypofluorescence.

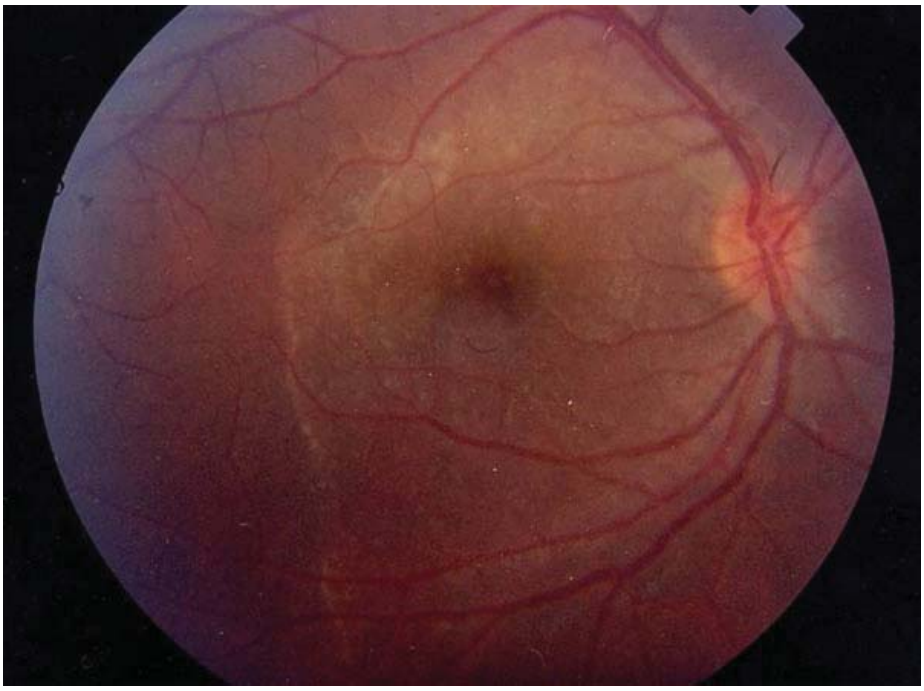

Fig. (11). Right eye syphilitic macular retinitis: Pinpoint coalescent areas of retinitis with subretinal fluid.

Up to 43.8% of patients may have mucocutaneous manifestations of secondary syphilis (Figs. **12** and **13**) [10].

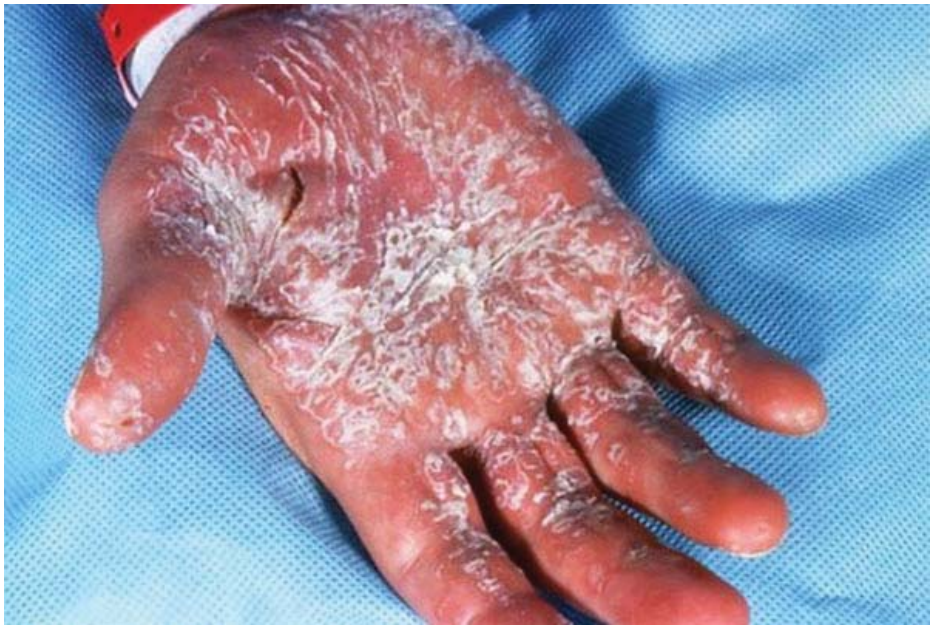

Fig. (12). Secondary syphilis rash. Typical palm dermatosis with scale of lesions.

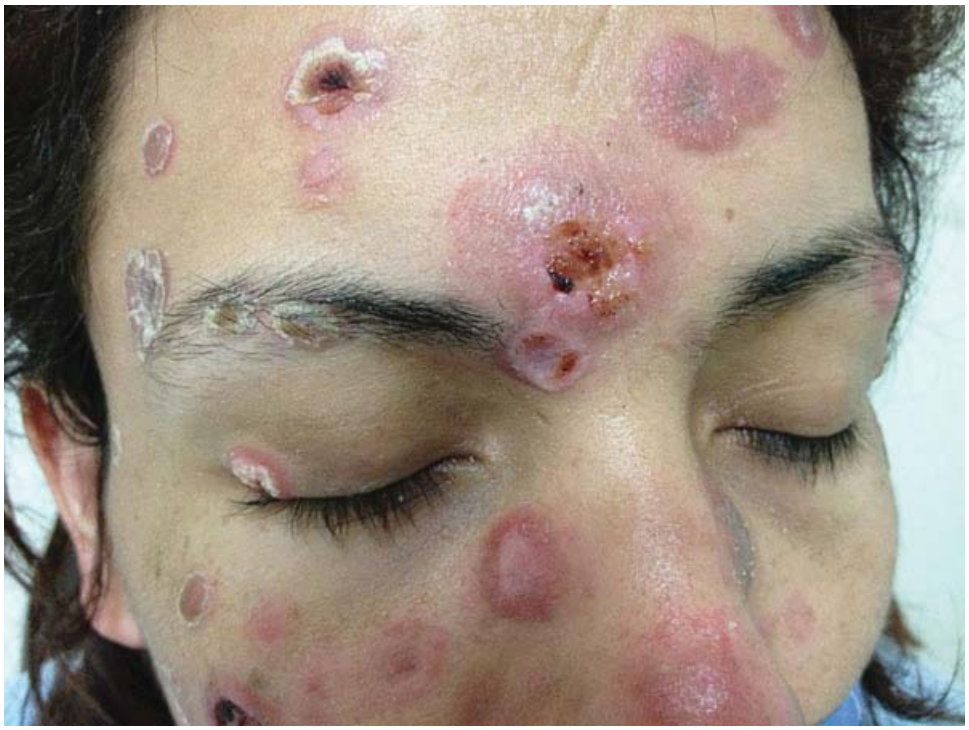

Fig. (13). Secondary syphilis rash. Disseminated chancroid lesions.

Fluorescein Angiograpy (FA) shows a distinctive pattern during the early phases, consisting of faint hyperfluorescence with scattered spots of hypofluorescence also known as leopard spotting (Fig **10**). At the late phases, FA shows progressive hyperfluorescence [14]. Optical Coherence Tomography (OCT) in patients with acute syphilitic posterior placoid chorioretinitis shows characteristic outer retinal abnormalities, including disruption of the ellipsoid layer, nodular thickening of the Retinal Pigmentary Epithelium (RPE) with loss of the interdigitation zone, and, in some cases, loss of the external limiting membrane, accumulation of subretinal fluid, and punctate hyper-reflectivity in the choroid [15].

Appropriate laboratory studies can aid in confirming the diagnosis. The gold standard consists in direct visualization of the organism *via* dark-field microscopy with immunofluorescent staining [1, 3, 6, 10, 16]. In addition, serologic tests can be used. The reagin tests (VDRL, RPR) are used in screening for early syphilis infection. The treponemal tests (FTA-ABS, MHA-TP) can be used to confirm the diagnosis and guide management. The nontreponemal tests titers can be useful to monitor therapeutic response [16]. Persons testing positive for syphilis should also be tested for HIV [8 - 13].

DIFFERENTIAL DIAGNOSIS

Intraocular syphilis differential diagnosis may include a wide range of ocular inflammatory diseases such as Vogt-Koyanagi-Harada syndrome, primary intraocular lymphoma [17], herpetic retinal necrosis, *etc*. Syphilis is known as the 'great masquerader' because it may mimic different diseases [6]; therefore, syphilis should be always considered in the differential diagnosis of ocular inflammation.

MANAGEMENT

The Centers for Disease Control and Prevention (CDC) [18] recommends high-dose IV penicillin G 18 to 24 million units per day for 10 to 14 days. For HIV-positive patients, they also recommend an additional treatment of intramuscular benzathine penicillin at a dose of 2.4 million units weekly for 3 weeks. In case of severe penicillin allergy, one can consider ceftriaxone, oral doxycycline, or azithromycin. The Jarisch-Herxheimer reaction (JHR) can occur in up to a third of neurosyphilis patients following penicillin therapy [16]. The reaction usually includes fever, sweating, and temporary worsening of disease symptoms. Some authors suggest the use of steroids prior to antibiotics in cases of severe neurosyphilis to prevent JHR [16].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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[PMID: 21160459]

CHAPTER 6

HIV-Related Retinal Microangiopathy

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HIV affects the human retina in a distinct way by developing ischemic microangiopathy that may be observed as cotton-wool spots, microvascular abnormalities more evident at the retinal periphery, intraretinal hemorrhages and, rarely, arterial plaques [1]. It is asymptomatic in most of the patients.

ESSENTIALS OF DIAGNOSIS

The main clinical sign of this pathology is the presence of cotton-wool spots, which appear as fluffy white patches on the retina, usually along the major vascular arcades (Figs. **1**-**4**). This is the earliest and most consistent finding in HIV microangiopathy, occurring approximately 50–60% of patients with advanced disease [2], and is directly affected by CD4+ count: 45% of patients with CD4+ less than 50 cells/μL will present microangiopathy [3] and it has been also related to HIV viral load [4].

These lesions are the result of nerve fiber damage and accumulation of axoplasmic material within the nerve fiber layer [3]. According to histopathological findings, vascular abnormalities include pericyte necrosis, endothelial cell swelling and thickened basement membranes [5]. Hypotheses for the cause of cellular damage include immunoglobulin deposition, endothelial cell infection by HIV and hyperviscosity secondary to increased red cell aggregation, fibrinogen and increased polymorphonuclear leukocyte rigidity [6 - 10].

The clinical importance of microangiopathy is that it is a marker for patients with severely compromised immune system and high risk of vision-threatening opportunistic infections.

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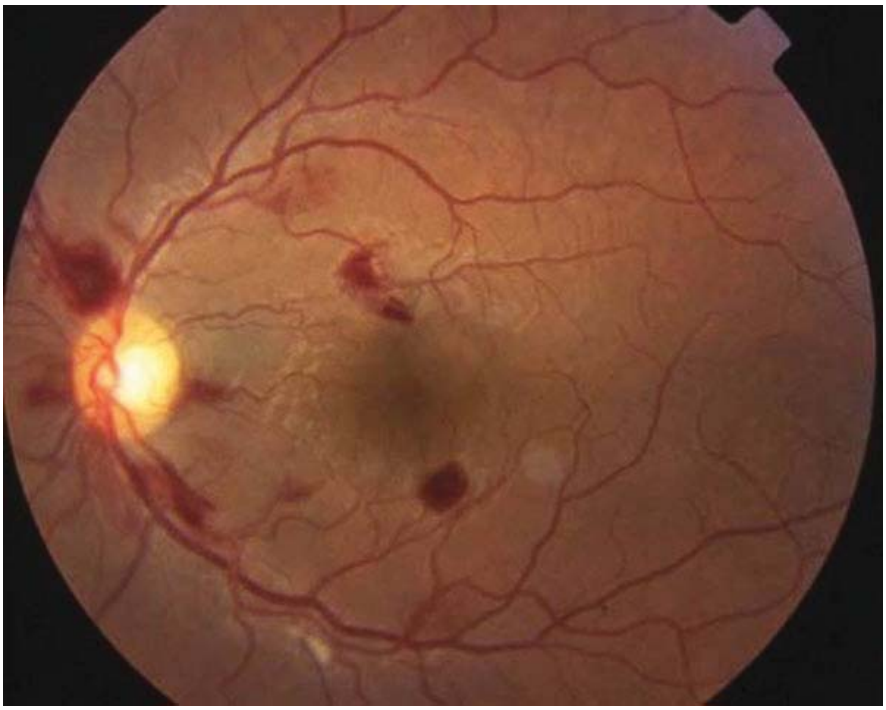

Fig. (1). HIV-related retinal microangiopathy: Intraretinal microhemorrhages and one cotton-wool spot.

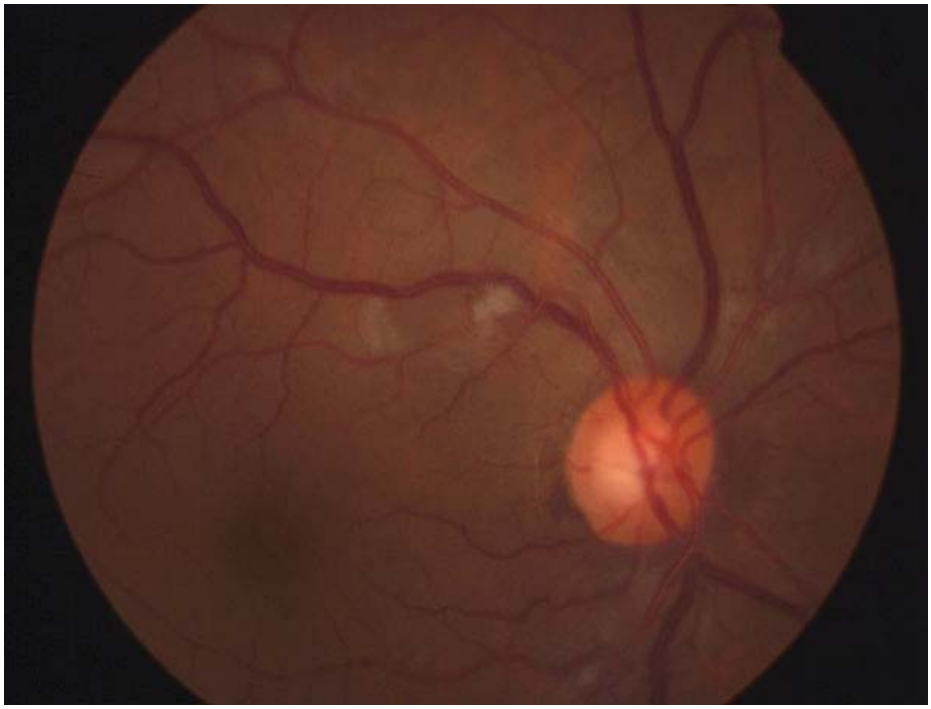

Fig. (2). HIV-related retinal microangiopathy. Right eye.

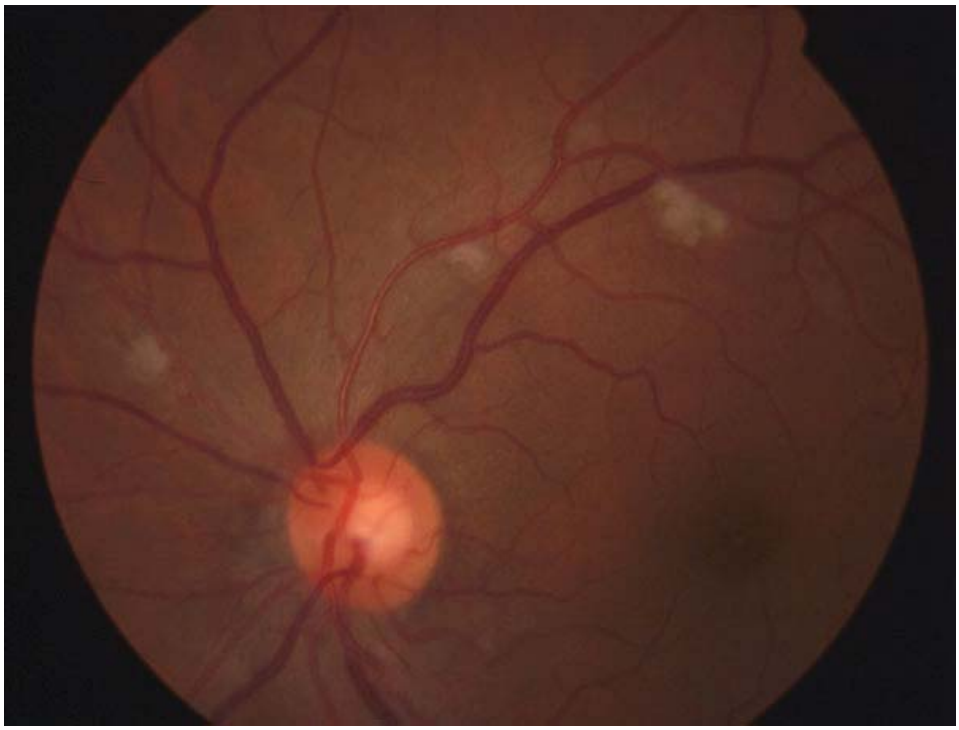

Fig. (3). HIV-related retinal microangiopathy. Left eye.

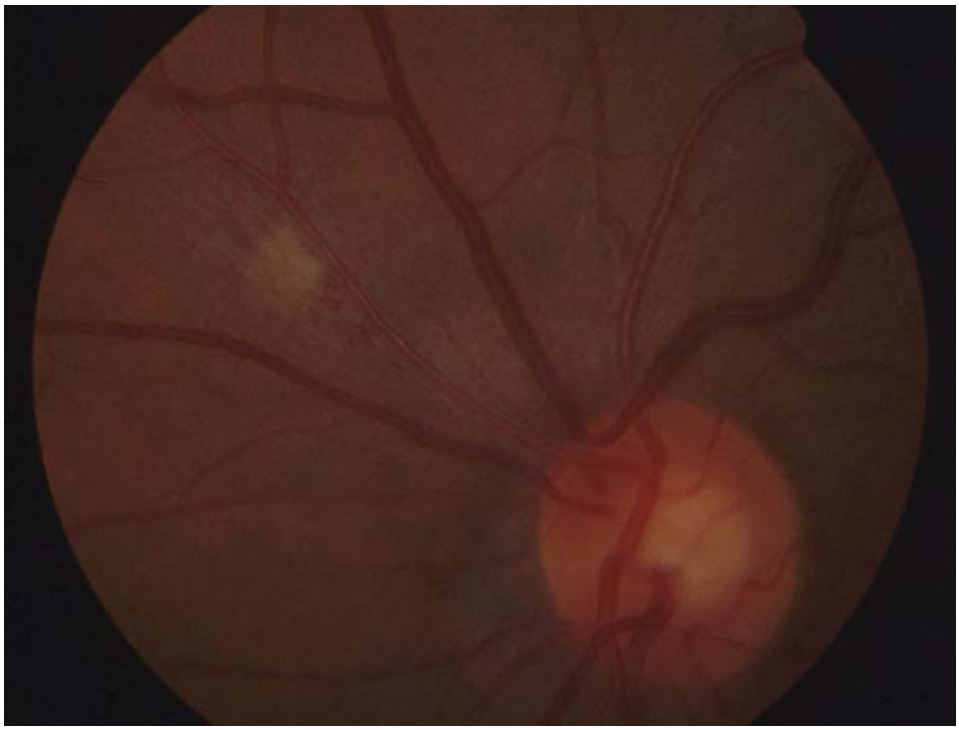

Fig. (4). Close-up of the same eye as Fig. (**3**). HIV-related cotton-wool spot with small retinal hemorrhages.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes diabetic retinopathy, hematologic disorders, systemic lupus erytematosus, antiphospholipid syndrome, hypertension, radiation retinopathy, interferon-associated retinopathy, Susac syndrome, among many other hemodynamic disturbances and inflammatory conditions.

MANAGEMENT

There is no specific treatment. Cotton-wool spots usually disappear within several weeks related to CD4 count improvement.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 7

Neuroretinitis

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Neuroretinitis is a term that describes a clinical picture in the posterior pole comprising edema of the optic nerve head and the presence of hard exudates in the macula arranged in a stellate pattern usually called a "macular star".[1]. It may be caused by different etiologies, although the most common cause is *Bartonella* Sp. infection (Cat-scratch disease) [2, 3].

ESSENTIALS OF DIAGNOSIS

Patients with neuroretinitis usually complain of unilateral painless decrease of visual acuity, although they may be asymptomatic.

Diagnosis is based on clinical manifestations readily apparent in ophthalmologic examination. The borders of the optic disc may appear blurred, elevated and/or hyperemic, and the macula may appear thickened, with the presence of hard exudates arranged in a macular star pattern (Figs. **1**-**5**). Hard exudates may not be visible if the patient is examined very early in the disease, and become apparent after approximately two weeks of onset [1, 4]. After treatment is initiated, hard exudates may increase (because of fluid absorption and lipid deposition) before disappearing. Rarely, if the disease causes multiple recurrences, the optic disc may become pale [1, 4, 7].

Fluorescein angiography shows papillary hyperfluorescence. Peripapillary vessels may also show hyperfluorescence secondary to vascular incompetence [1]. Optical coherence tomography may show intra or subretinal fluid, and the presence of hyper-reflective foci corresponding to hard exudates [5]. Auto-fluorescence may also highlight exudates in the macular region [6].

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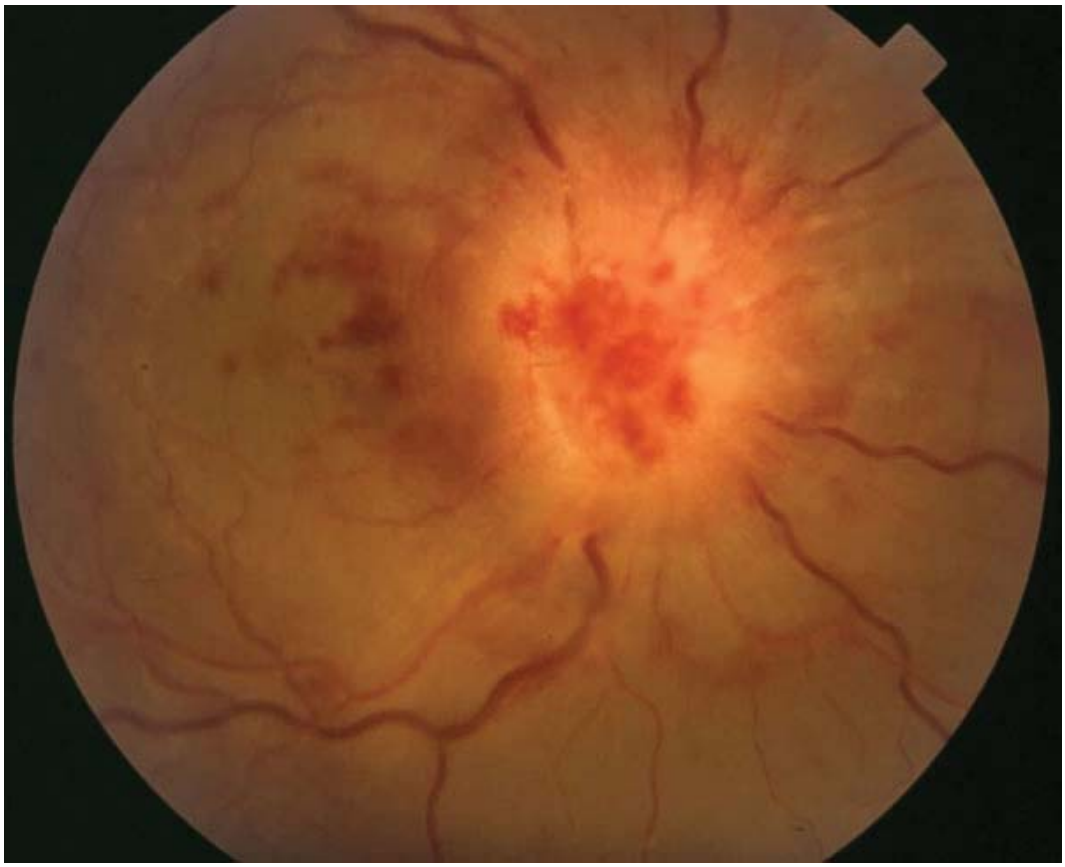

Fig. (1). Patient with papillitis and juxtapapillary choroidal involvement.

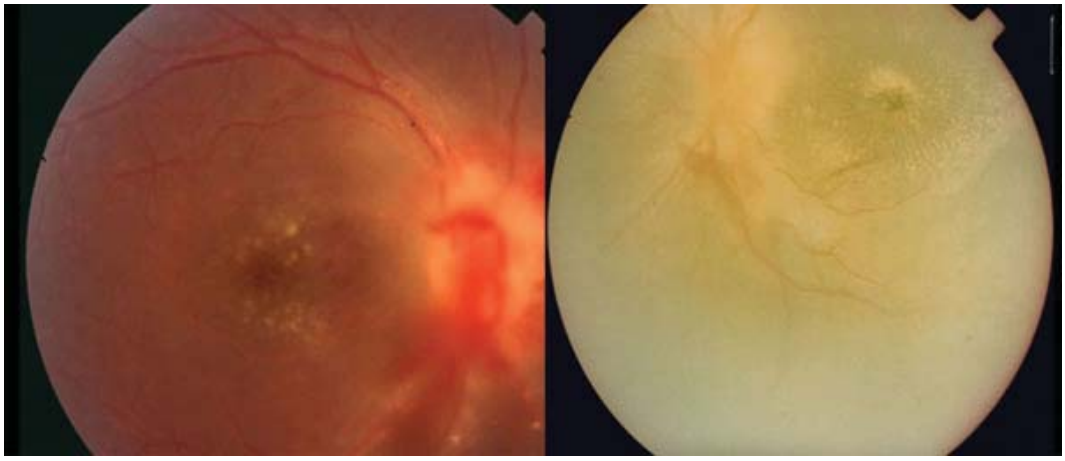

Fig. (2). Papillitis and peripapillary nerve fiber layer hemorrhages. There is a variable degree of lipid staining into the macula.

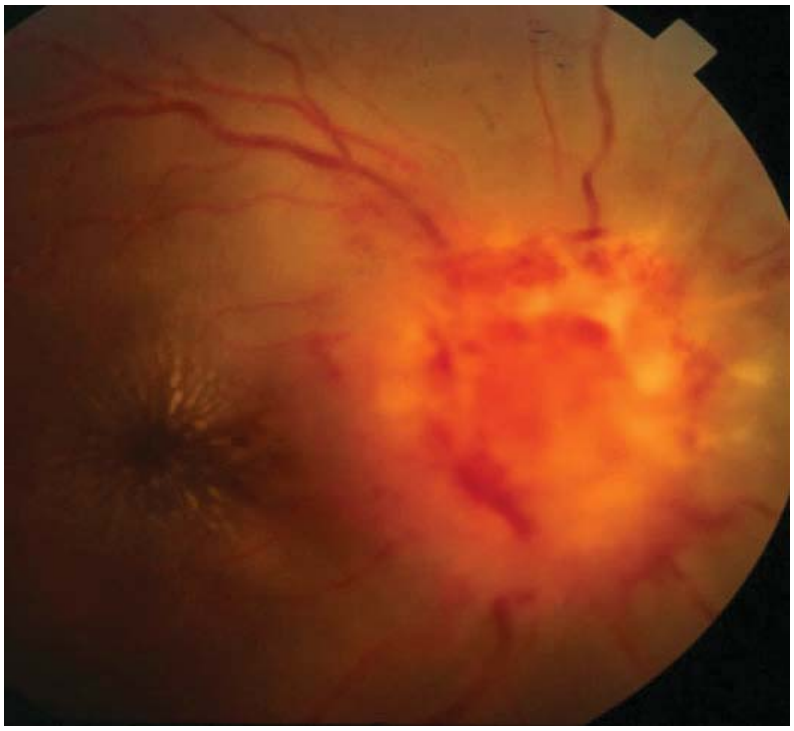

Fig. (3). Infiltrated nerve, prominent vessels and macular star in a patient with toxoplasmosis.

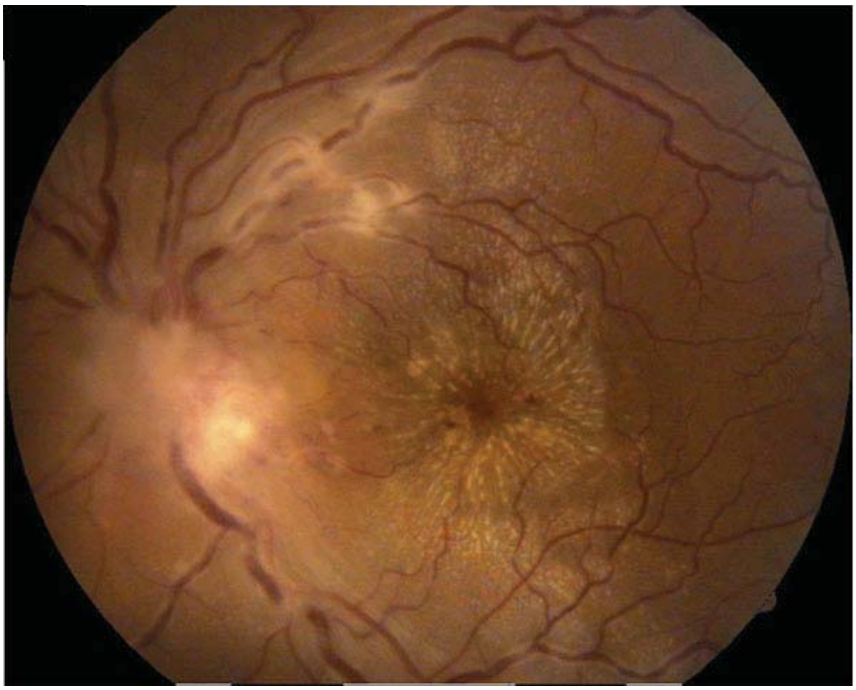

Fig. (4). Fundus photograph of patient with neuroretinitis demonstrates optic disc edema, vasculitis and macular star figure (Courtesy of Ophthalmology Department, Hospital Central de Maracay, Venezuela).

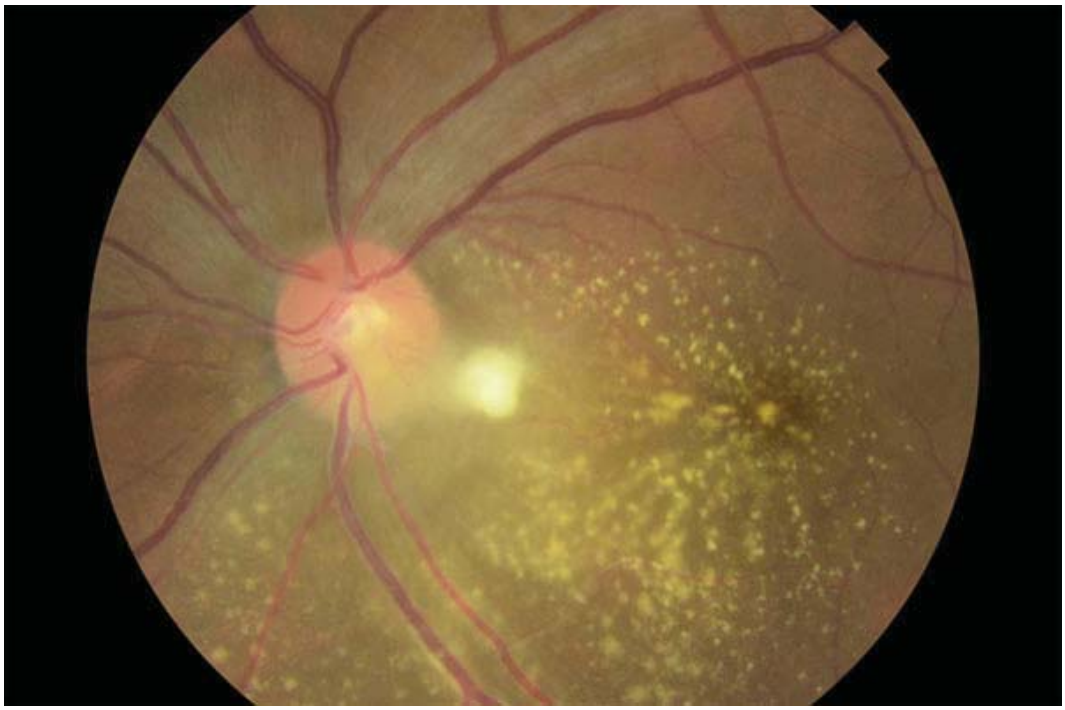

Fig. (5). Fundus photograph of patient with juxtapapillary focus of active chorioretinitis and macular star. The patient was seropositive for *Leptospira* Sp. (Courtesy of Mitzy E. Torres Soriano, MD).

DIFFERENTIAL DIAGNOSIS

Since the most frequent cause (two thirds of cases) of neuroretinitis is *Bartonella* Sp. infection (cat-scratch disease), diagnostic workup should always include titers of anti-*Bartonella* antibodies. Other tests that should be included are VDRL, FTA-ABS and PPD. If anti-*Bartonella* antibodies are negative, other infectious causes should be sought, such as Lyme disease, herpes simplex virus, toxoplasmosis, or leptospirosis.

Other diseases that may cause a clinical picture similar to neuroretinits are hypertensive retinopathy, diabetic retinopathy, papilledema, and ischemic optic neuropathy [1, 4, 8].

MANAGEMENT

Treatment of neuroretinitis should be implemented according to the cause. In case of Cat-scratch disease, which is the most common cause, systemic broad spectrum antibiotics should be initiated. Systemic steroids may be started two or three days after antibiotics, to hasten recovery. Most patients achieve complete resolution of the disease, with a very good visual recovery [1 - 4, 6]. However, a minority of

patients may suffer from repeated episodes of neuroretinitis. The etiology of this recurrent idiopathic neurorretinitis is not yet known, but eyes may develop optic atrophy in time due to the recurrent episodes of inflammation [7 - 9].

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 8

Endophthalmitis

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ESSENTIALS OF DIAGNOSIS

Endophthalmitis (E): Severe intraocular inflammation associated with lid swelling, pain (absent in 26% of cases), anterior chamber with cells or hypopyon, vitritis and blurring or loss of vision, without involving the sclera and the extraocular orbital structure. "Panophthalmitis" involves outer layers (Figs. **1c** and **6**). Cases with an infectious etiology are the most devastating ones and carry guarded prognosis.

Classification (Table **1**)

Table 1. Endophthalmitis Classification.

Exogenous Endophthalmitis (EE)	• Postoperative Endophthalmitis * Acute. * Chronic. • Post-traumatic Endophthalmitis (Fig. **16**) • Associated with infectious keratitis.
Endogenous Endophthalmitis (Ee) (Figs. **1**, **21**-**23**, **27**, **28**)	• Focal (anterior and posterior). • Diffuse (anterior and posterior).

- ***Postoperative Endophthalmitis (PE):***

E. is a potentially blinding complication with irreversible tissue damage after ocular surgery [1] (Figs. **2**-**5**, **7**-**14**, **26**, **29**). Most of the cases arise from cataract surgeries [2]. Early diagnosis and prompt treatment are therefore essential.

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Commensal organisms found in the normal ocular flora are the most common cause. A mandatory step to reduce bacteria in the wound area is to apply povidone-iodine 5-10% to the cornea, conjunctival sac and periocular skin for a minimum of 3 minutes prior to surgery.

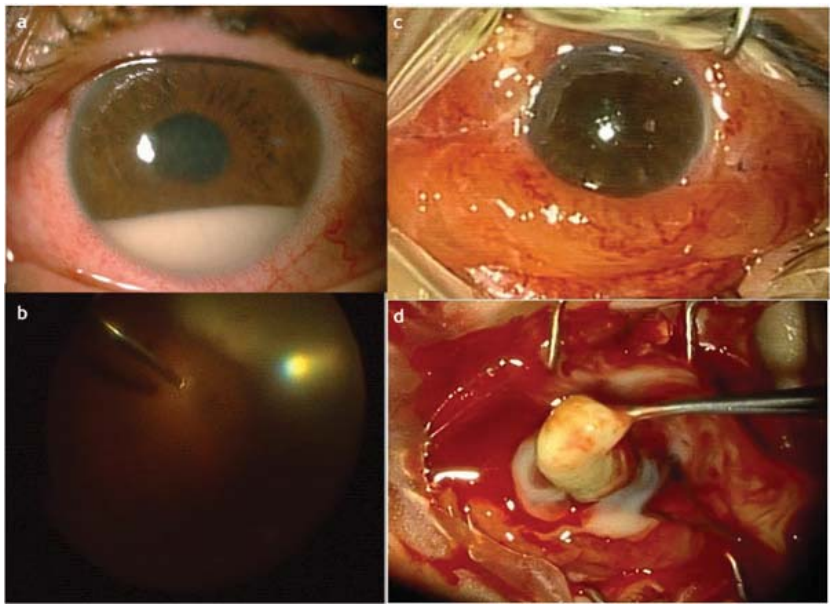

Fig. (1). *Klebsiella spp.* Endogenous Endophthalmitis. 50-year-old woman. Diabetes. *Klebsiella spp.* hepatic abscess. **a**) Hypopyon and corneal haze. **b**) Identification of subretinal abscess during vitrectomy. **c**) Progression into panophthalmitis. **d**) Evisceration.

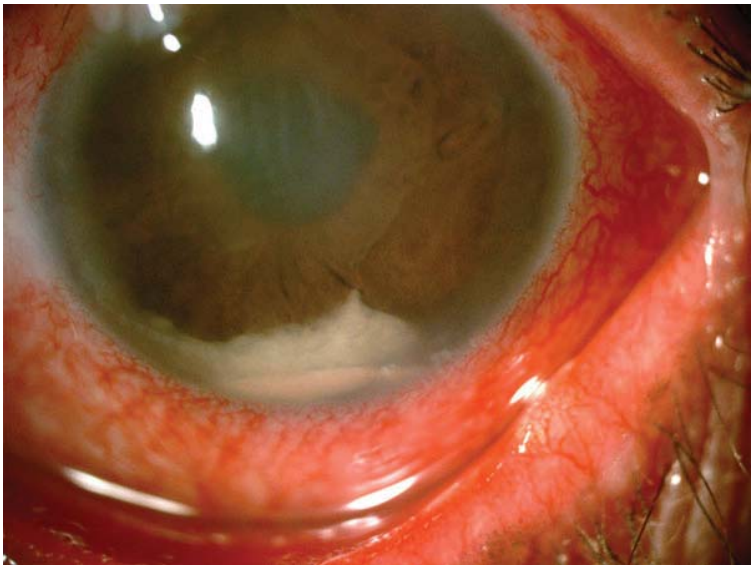

Fig. (2). Postoperative Endophthalmitis: Hypopyon associated with fibrin clot. Hazy cornea, pupillary membrane. Gram-positive Coccus.

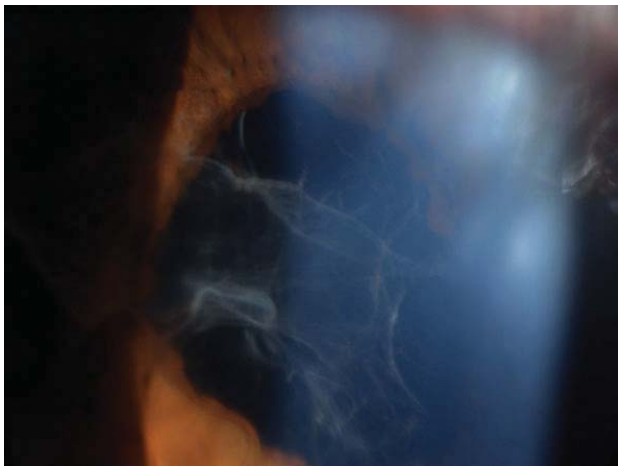

Fig. (3). Exogenous Endophthalmitis. Anterior chamber fibrin.

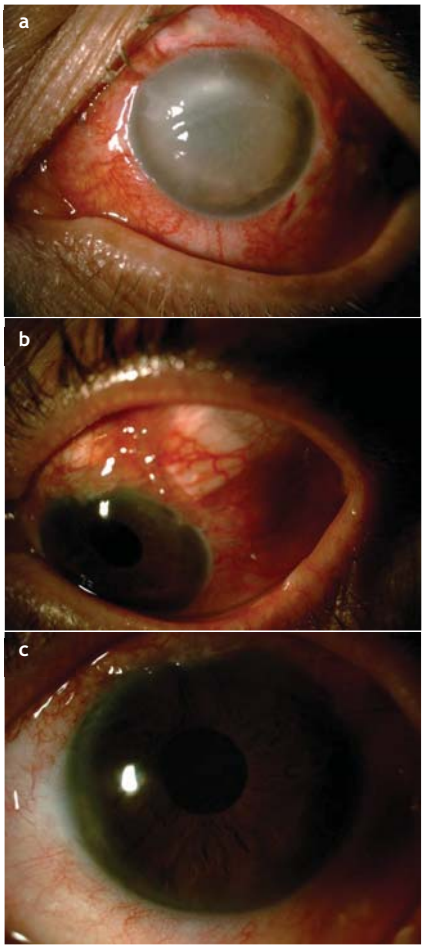

Fig. (4). a) Late bleb-associated endophthalmitis. Not culture proven. Treated with intravitreal medication and vitrectomy. **b**) Scleral patch over trabeculectomy site. **c**) Good progress.

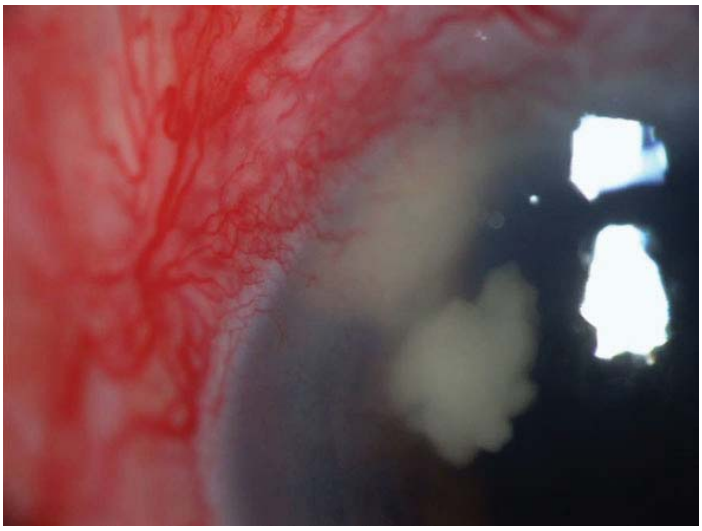

Fig. (5). Corneal wound abscess after phacoemulsification.

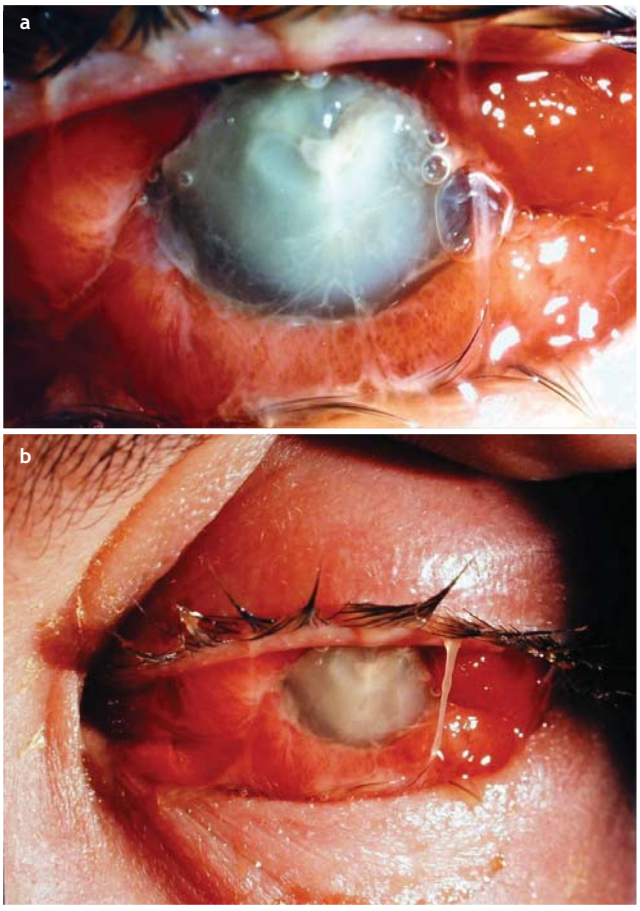

Fig. (6). a) and **b**) Panophthalmitis.

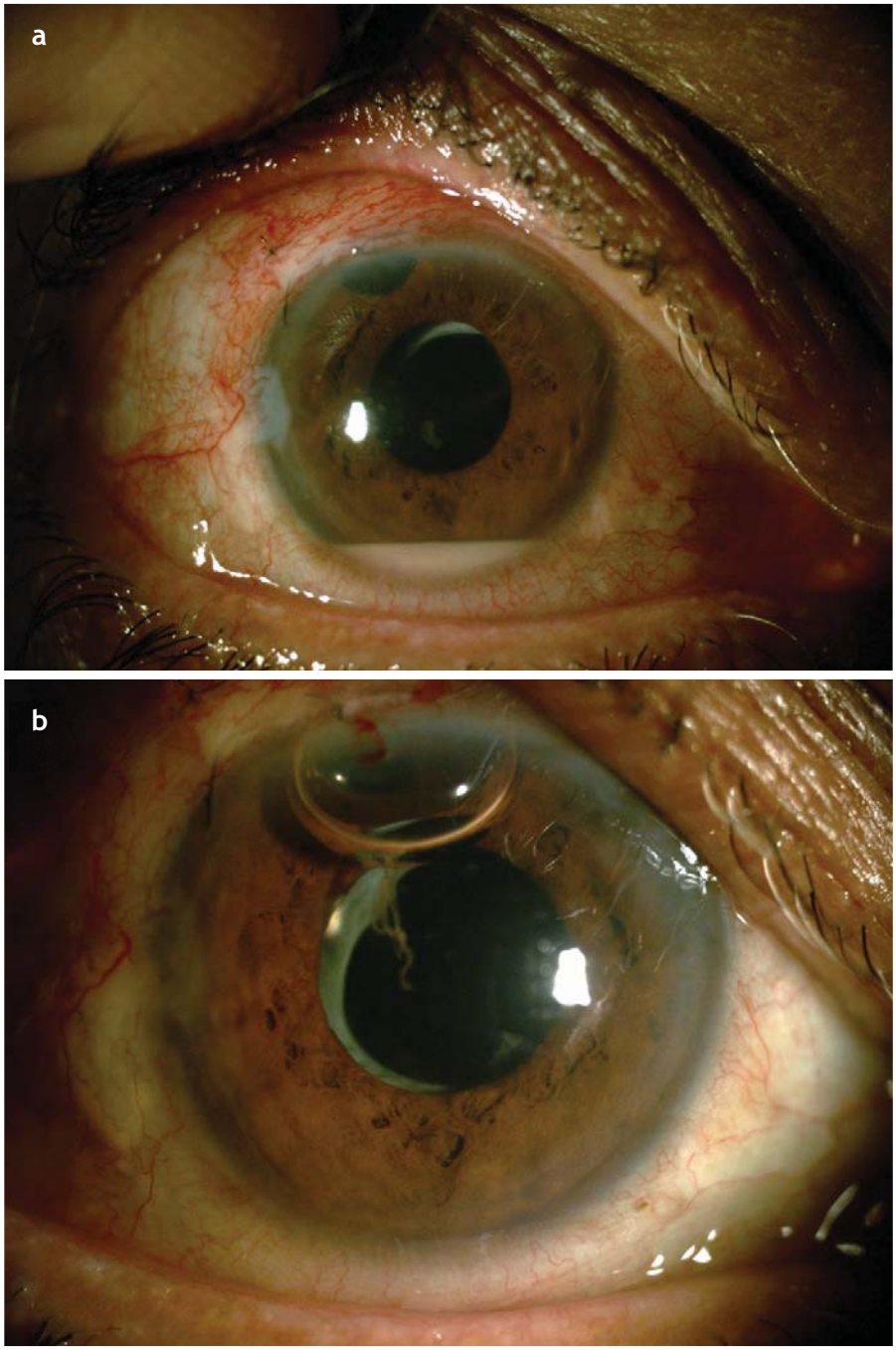

Fig. (7). Acute-onset postoperative endophthalmitis. **a**) Hypopyon. **b**) After injection treatment and anterior chamber irrigation.

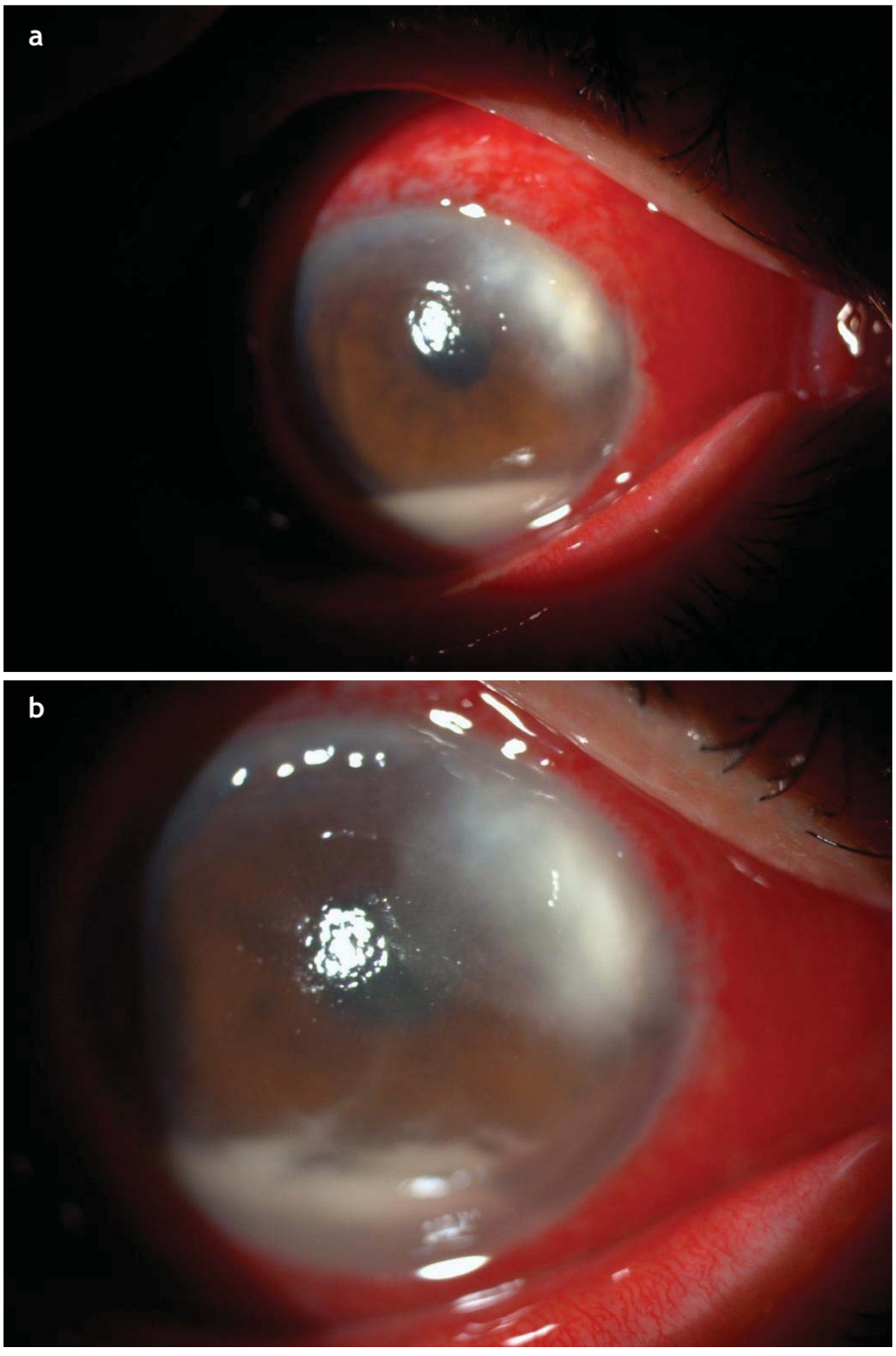

Fig. (8). Acute-onset postoperative endophthalmitis. **a**) Hypopyon and corneal wound abscess. **b**) Negative progress. Bacterial source.

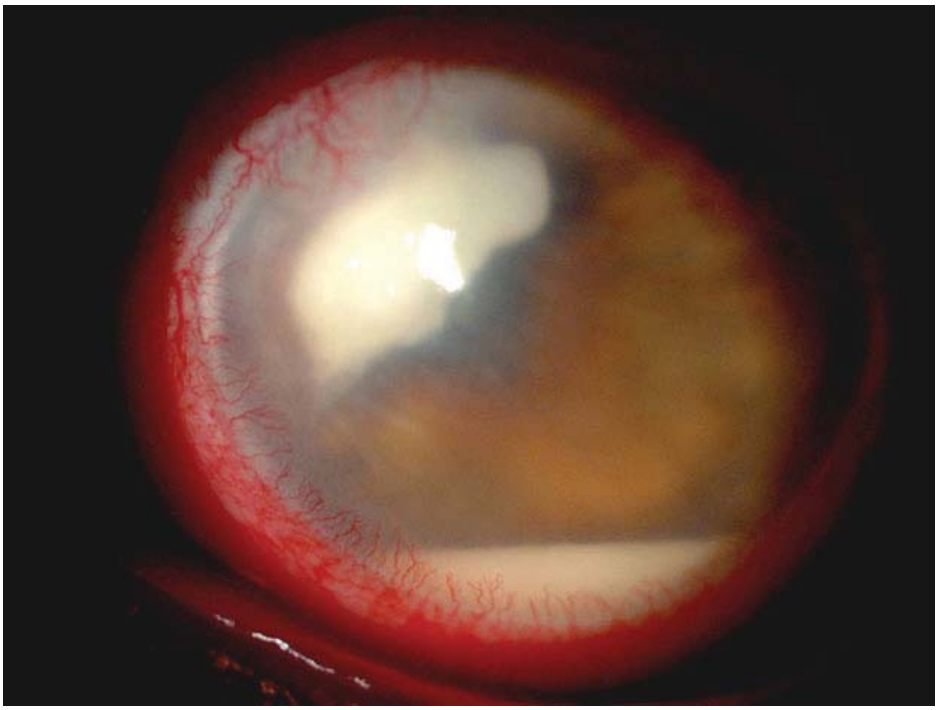

Fig. (9). Exogenous fungal postoperative endophthalmitis. One month after phacoemulsification.

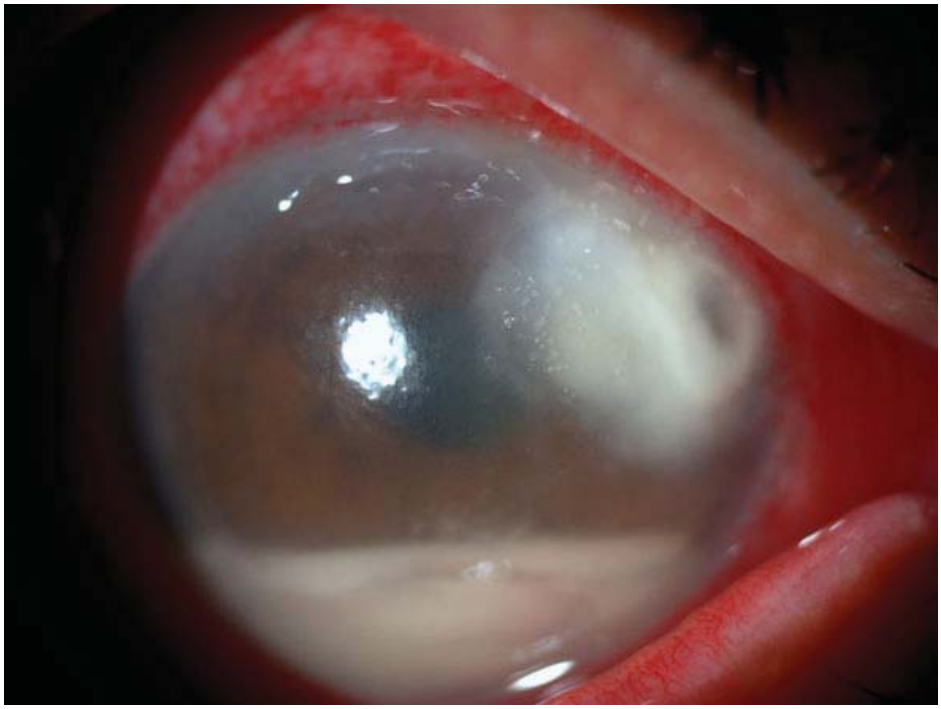

Fig. (10). Postoperative bacterial endophthalmitis. Source of infection: phacoemulsification incision. One week after surgery.

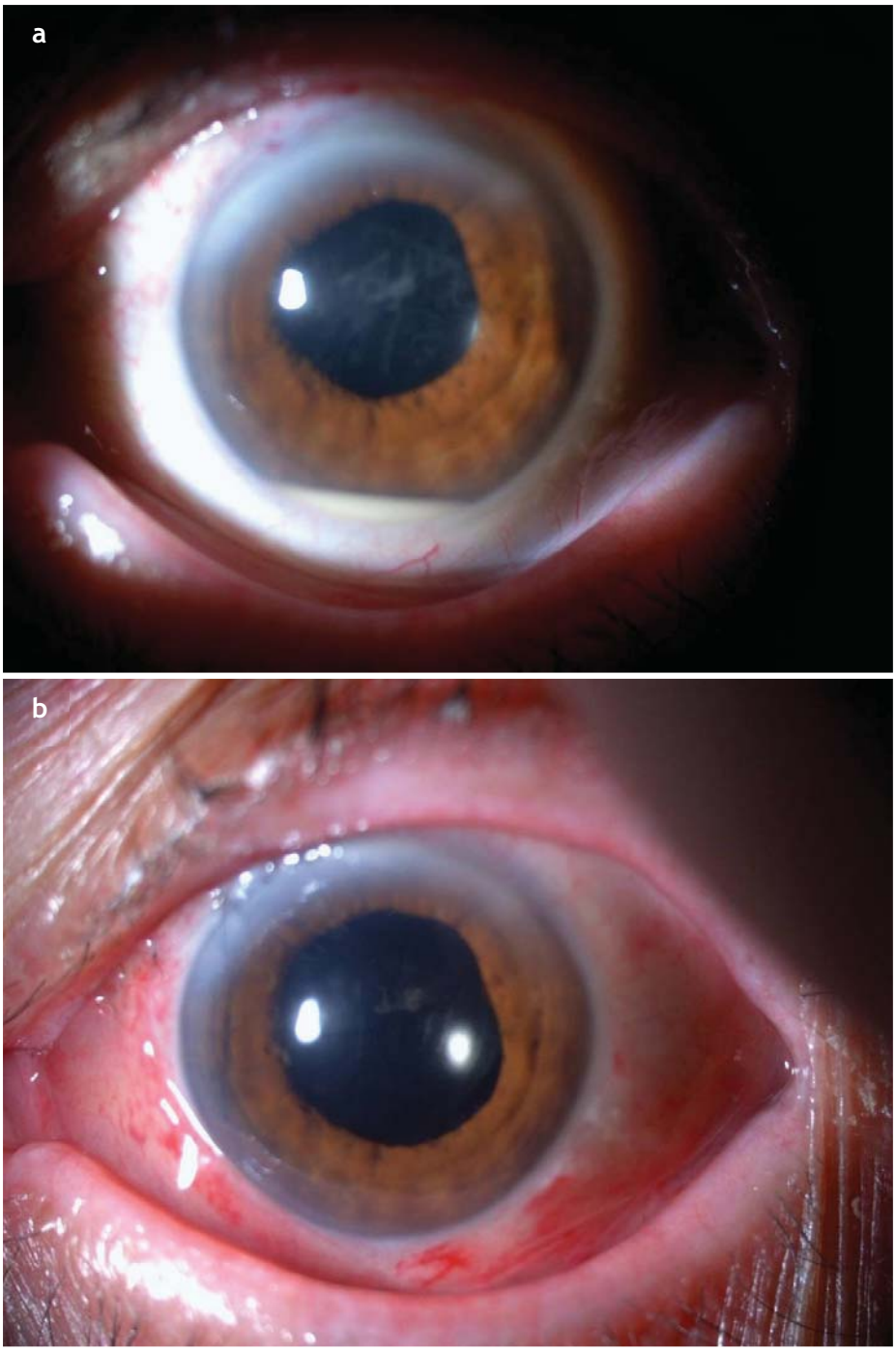

Fig. (11). a) Acute endophthtalmitis after phacoemulsification. Germ: *St. epidermidis*. **b**) 48 hours post intravitreal treatment.

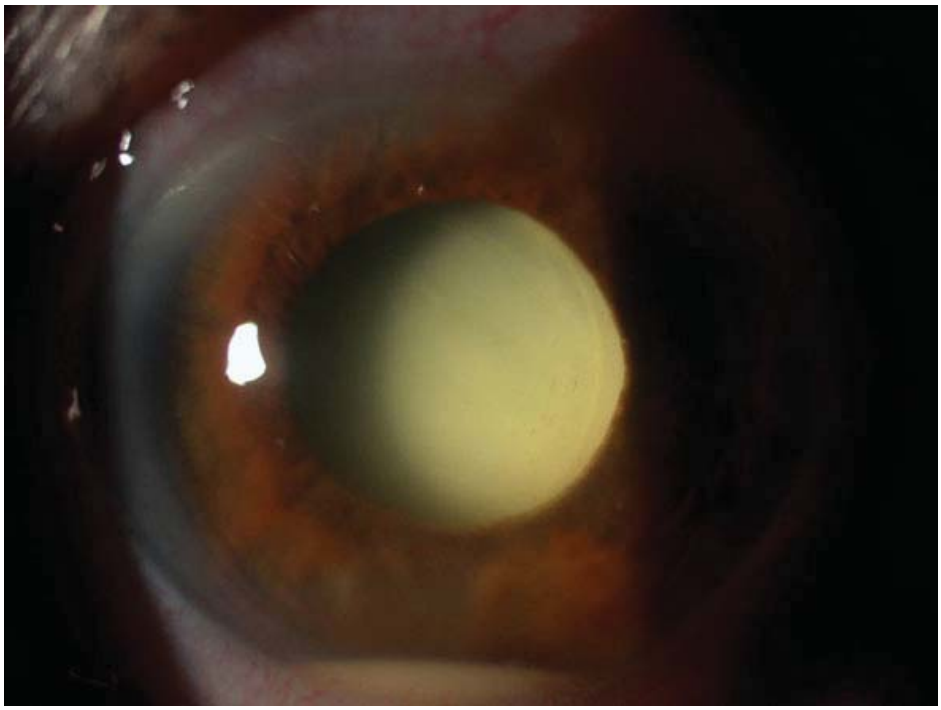

Fig. (12). Acute-onset postoperative endophthalmitis after cataract extraction. *St. epidermidis.*

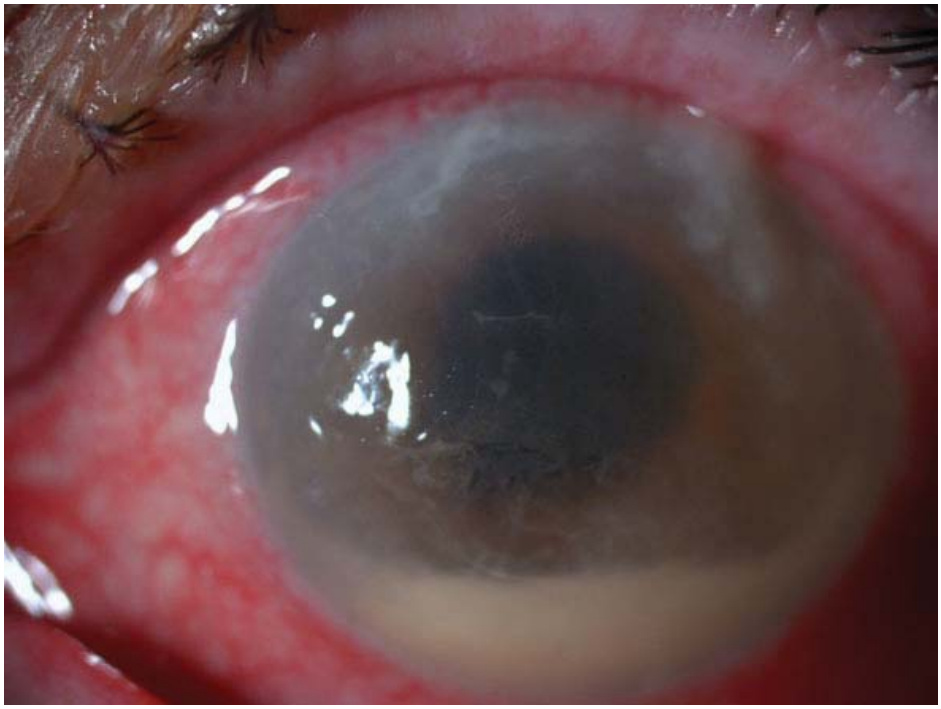

Fig. (13). Acute postoperative endophthalmitis after phacoemulsification. *Pseudomona aeruginosa.*

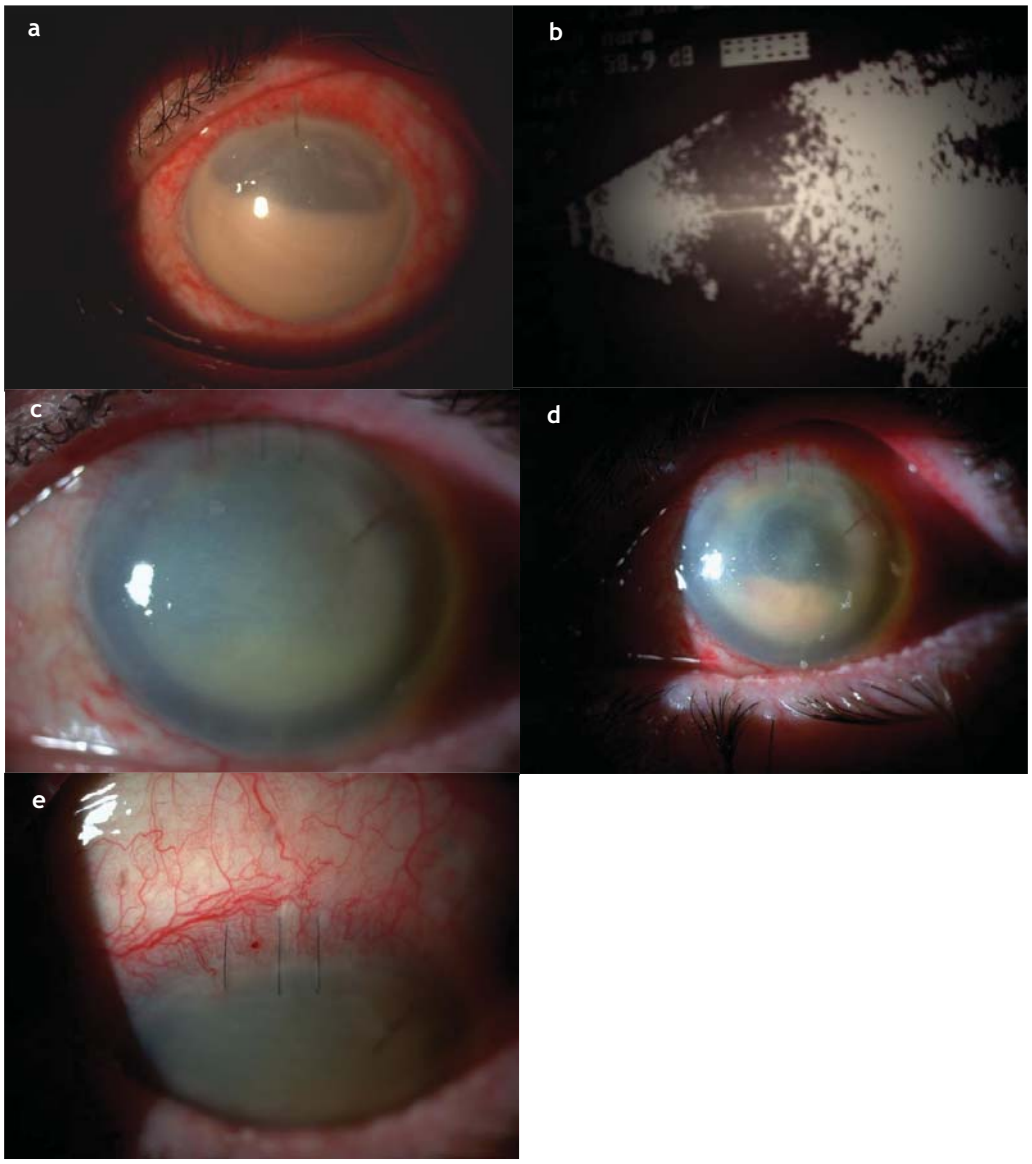

Fig. (14). a) Postoperative endophthalmitis 6 month after cataract surgery. **b**) Ocular ultrasound: vitritis. **c**) Good outcome. **d**) and **e**) Post amphotericin B treatment.

E. hyperacute: Fulminant cases occur within the first 24 hours. Very low incidence (1/14,000). Mainly caused by Gram-negative bacteria. Unfavorable prognosis even with accurate treatment. *i.e. Pseudomona aeruginosa* (Fig. **15**), *Streptococcus viridans.*

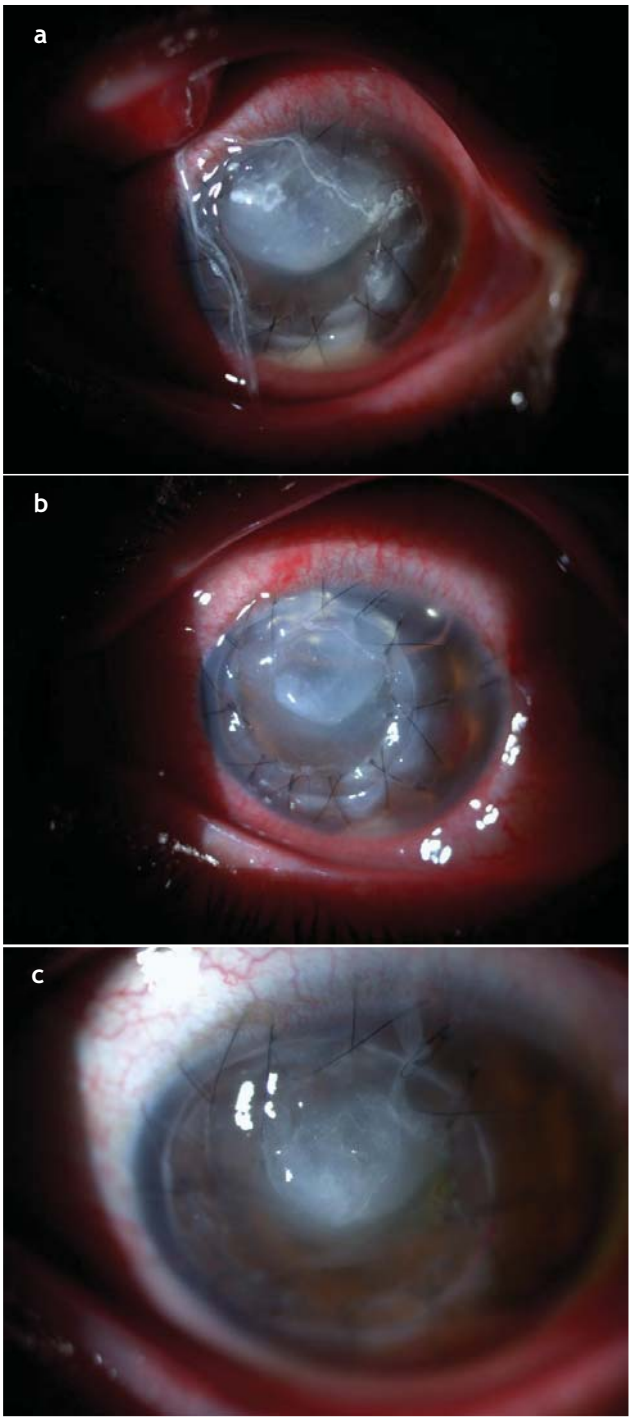

Fig. (15). a) *Pseudomonas aeruginosa* postoperative endophthalmitis following keratoplasty. **b**) Treated with intravitreal and intrastromal injections of ceftazidime and anterior chamber irrigation. **c**) Good infectious outcome but retinal detachment occurs.

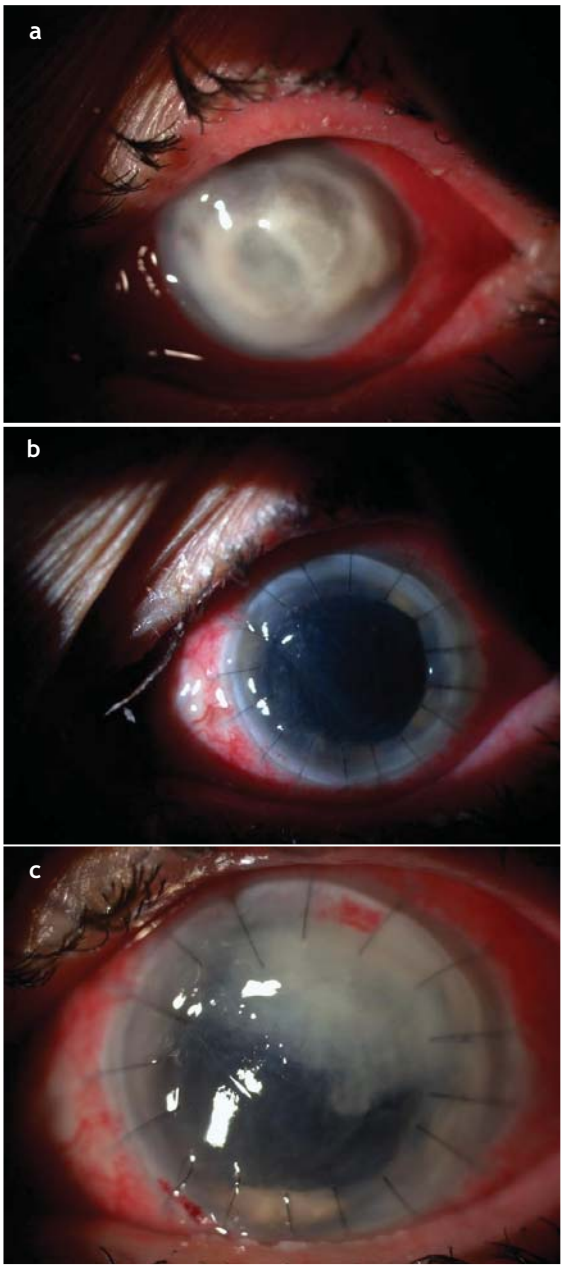

Fig. (16). a) *Fusarium spp.* post-traumatic endophthalmitis. **b**) 48 hours after keratoplasty. **c**) Poor outcome. Treatment: evisceration.

E. Acute: The most frequent cases occur within the 1st and 5th day after surgery. Incidence: 1/1,000 [3]. Mainly caused by Gram-positive bacteria. Prognosis depends on germ virulence, host defenses and treatment accuracy. *i.e. Staphylococcus epidermidis* and *S. aureus* [4].

E. Chronic: It occurs more than 6 weeks after surgery (Figs. **17**-**20**). Granulomatous uveitis associated with hypopyon or white-appearing plaque on the posterior lens capsule, which may enlarge over time. Most commonly cultured organisms include *Propionibacterium acnes* (Figs. **18** and **19**) [5] and *coagulase-negative staphylococci (CNS)*. Favorable prognosis.

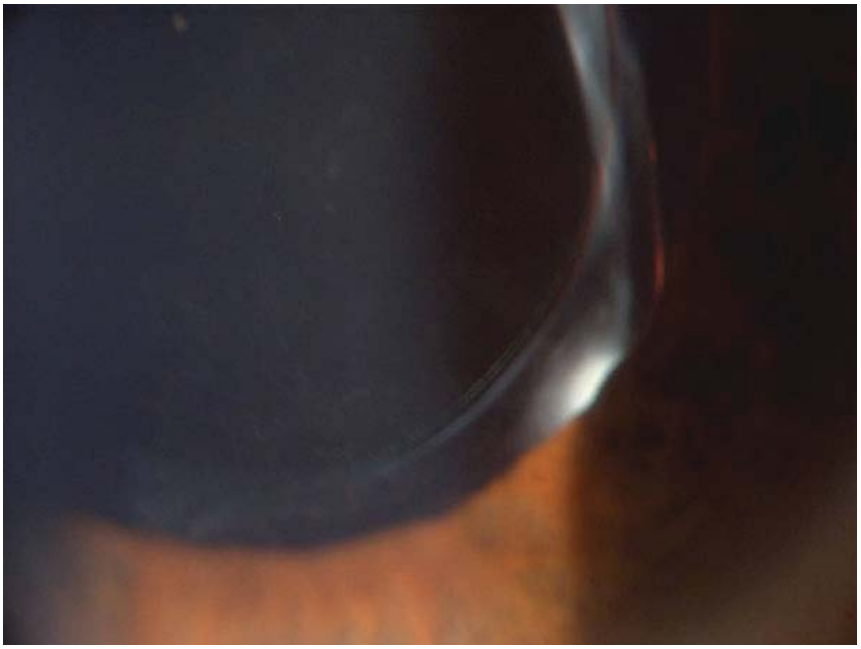

Fig. (17). *P. acnes w*hite-appearing plaque on intraocular lens haptic.

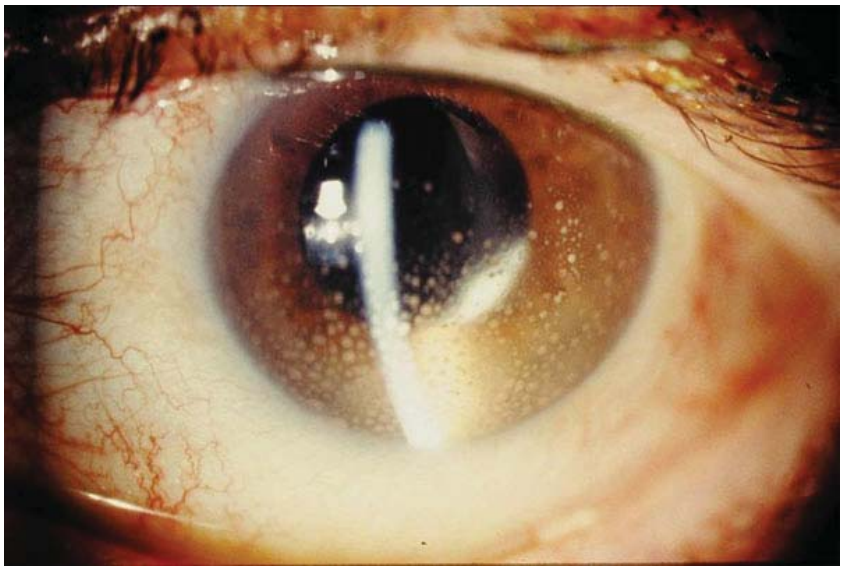

Fig. (18). Delayed-onset endophthalmitis. Chronic *P. acnes* uveitis.

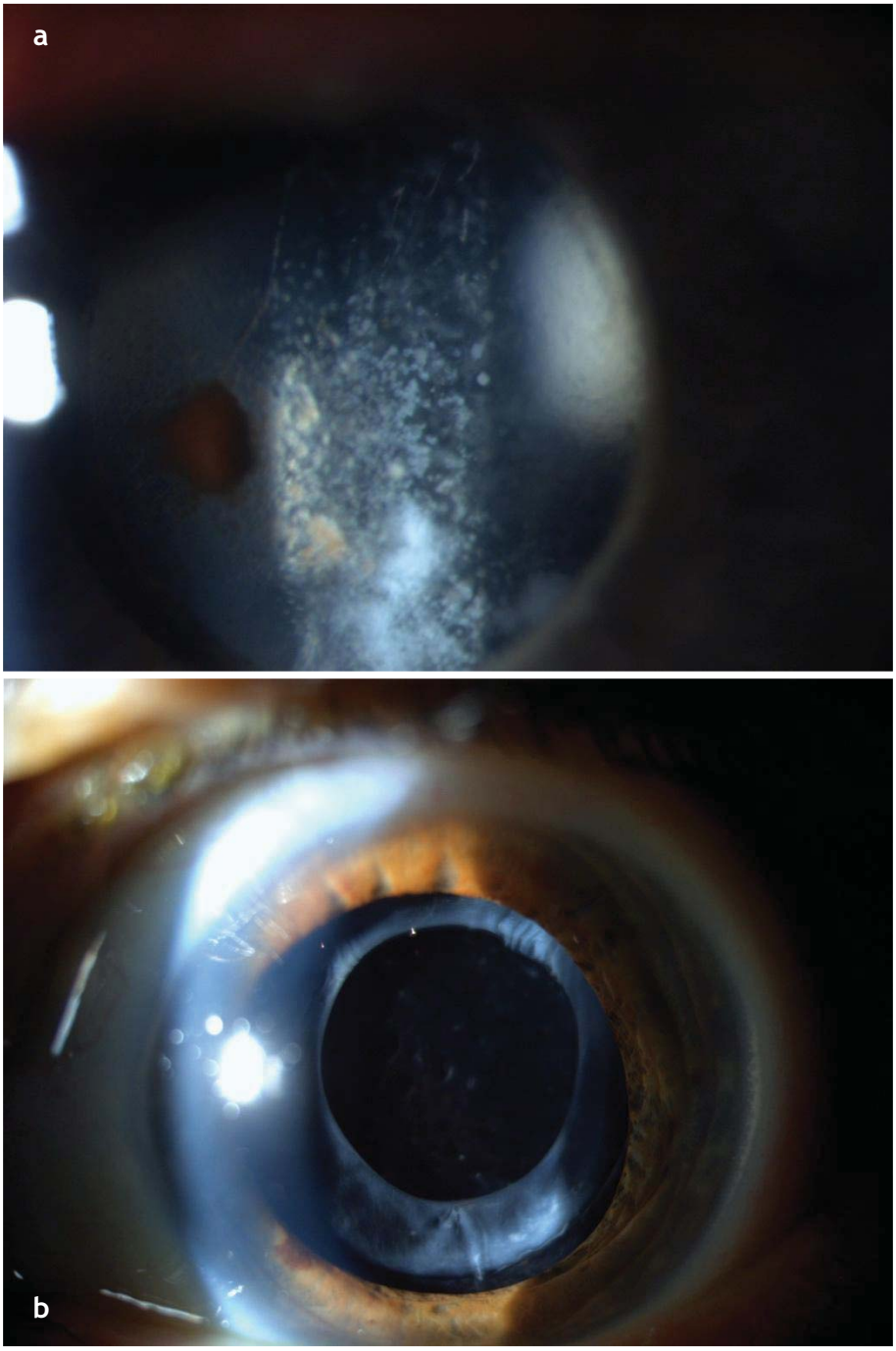

Fig. (19). a) *P. acnes w*hite-appearing plaque on the posterior lens capsule. **b**) After vancomycin treatment.

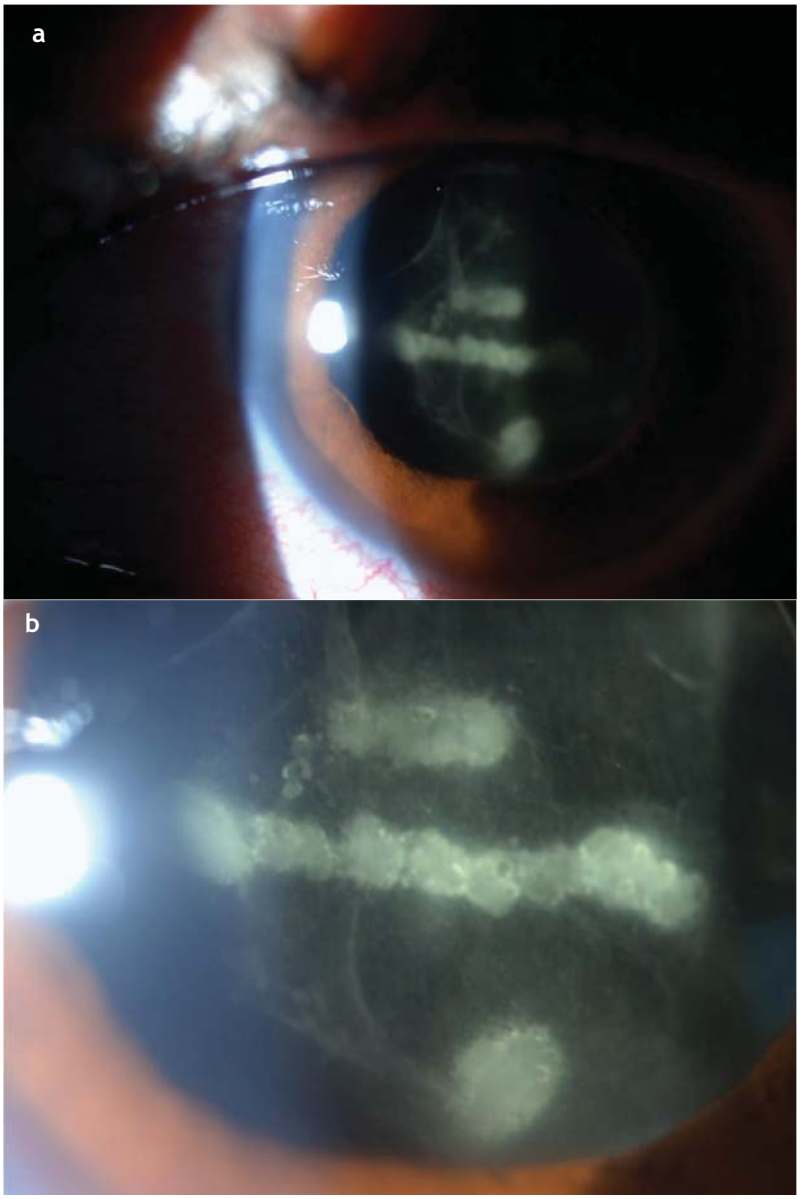

Fig. (20). a) Chronic endophthalmitis. Gram-positive Coccus. **b**) Close-up image.

E. associated with infectious keratitis:

Primarily associated to surgical wound abscess or severe infectious keratitis. Cases may be acute with bacterial source and chronic with fungal source. In comparison to other types of E. diagnosis, tests should be done by corneal wound scraping (as in the case of infectious keratitis) instead of anterior chamber tap and vitreous biopsy.

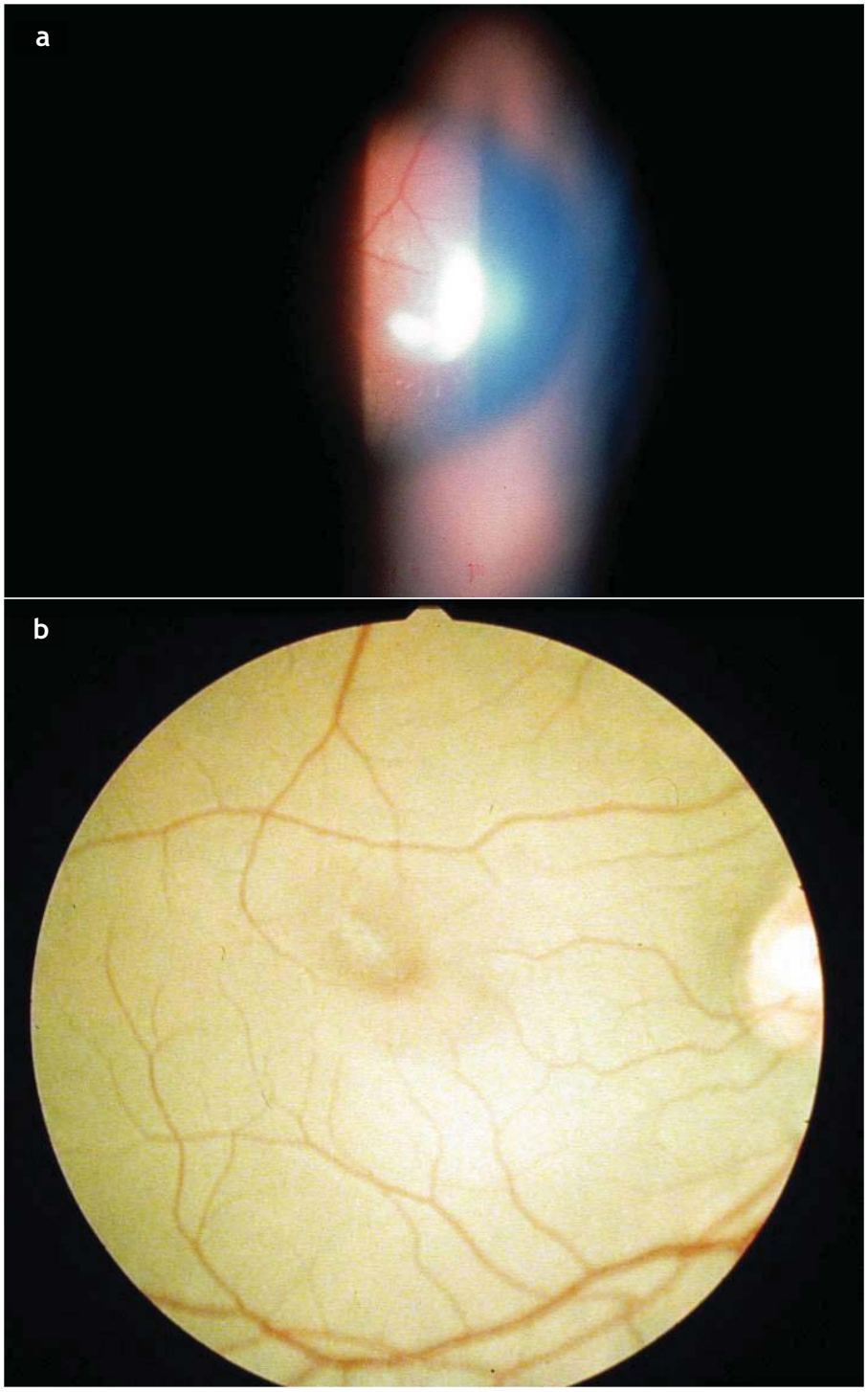

Fig. (21). a) *Candida albicans* endogenous endophthalmitis after gynecological procedure. **b**) Treated with systemic fluconazole.

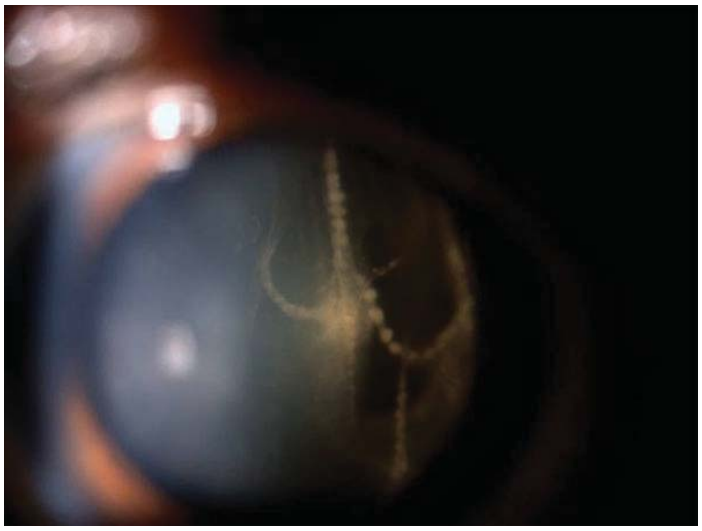

Fig. (22). Endogenous endophthalmitis. Candida fluffy balls in the vitreous.

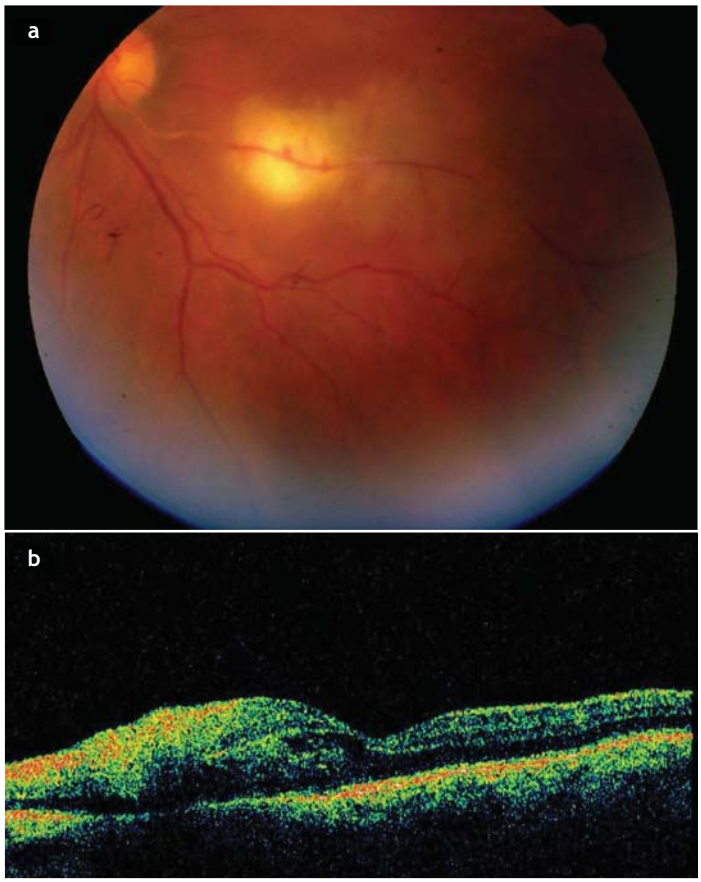

Fig. (23). a) Focal mycotic chorioretinitis. **b**) OCT of the chorioretinal lesion.

DIFFERENTIAL DIAGNOSIS (Table **2**).

Table 2. Differential diagnosis.

E. Acute (<6 week)	E. Chronic (>6 week)
• Toxic Anterior Segment Syndrome (TASS) (Figs. **24**, **25**). • Surgical Trauma inflammation. • Phacogenic uveitis. • Sympathetic uveitis. • Other inflammatory uveitis.	• Chronic iridocyclitis (intraocular lens material, detritus, mechanical trauma, intraocular lens off-center). • Postoperative phacoanaphylactic uveitis. • Masquerade syndrome. • Other uveitis.

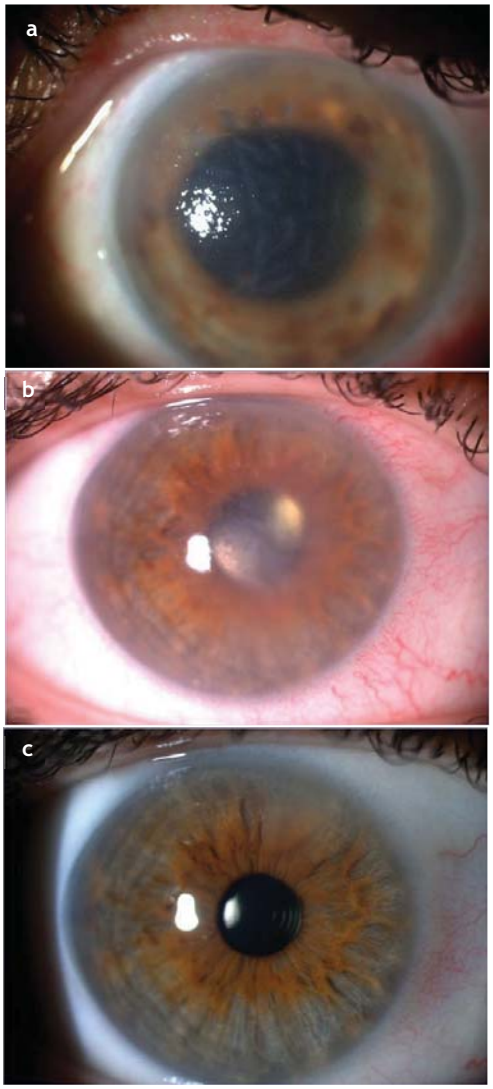

Fig. (24). Toxic Anterior Segment Syndrome (TASS). **a**) 24 hours, **b**) 48 hours, **c**) 1 month after surgery.

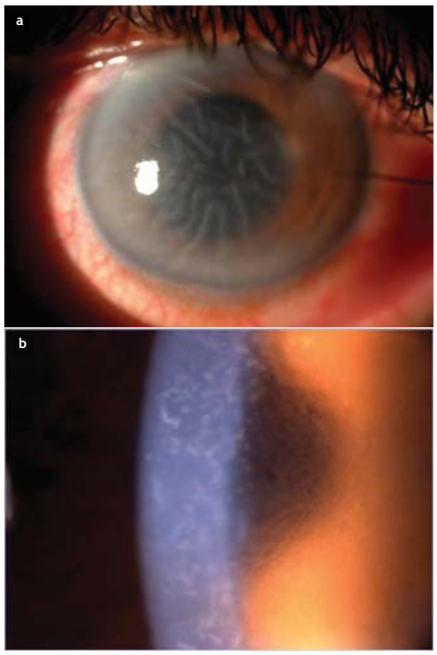

Fig. (25). Toxic Anterior Segment Syndrome (TASS). **a**) 24 hours **b**) 48 hours.

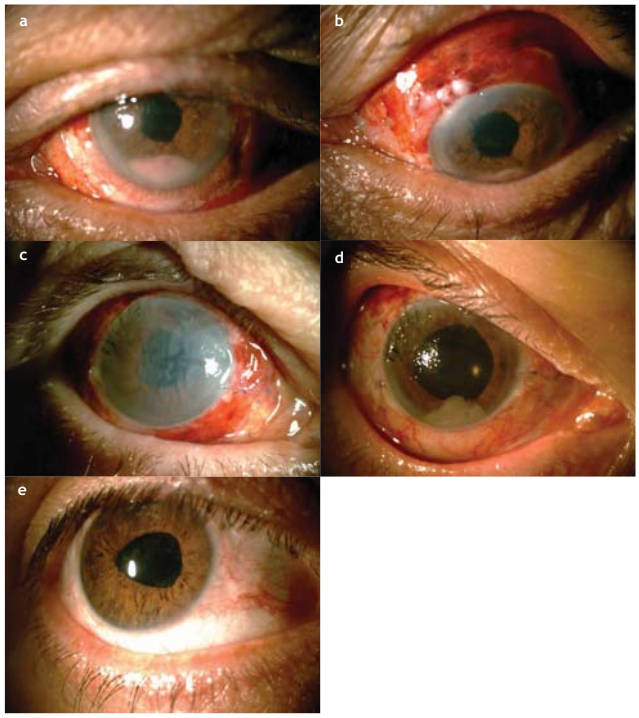

Fig. (26). Acute-onset postoperative endophthalmitis. **a**) and **b**) Fibrin clot (note corneal wound). **c**) Corneal wound abscess. **d**) 48 hours after surgical treatment. **e**) 4 months later. Germ: *St. epidermidis*.

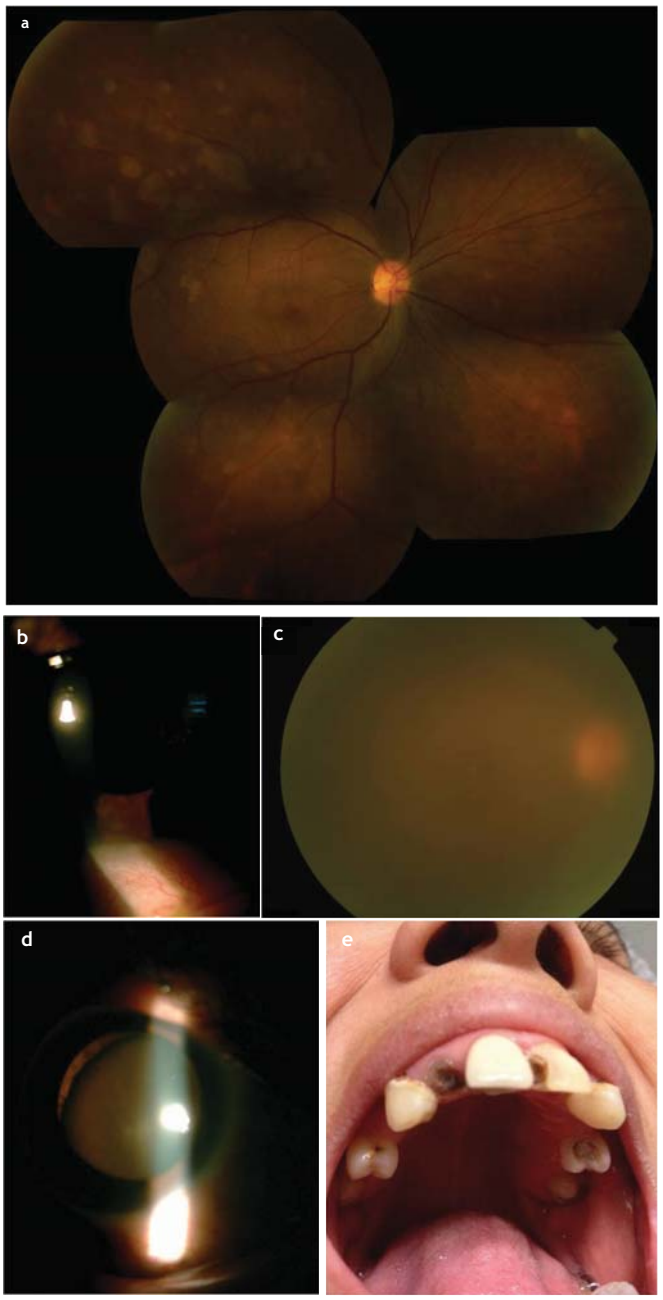

Fig. (27). Endogenous endophthalmitis. **a**) Multifocal chorioretinitis. **b**) Diffuse evolution: hypopyon. **c**) Diffuse evolution: vitreitis. **d**) Subluxated lens after resolution of case with intravitreal and systemic treatment. Germ: *St. aureus*.**e**) Most likely: odontogenic source.

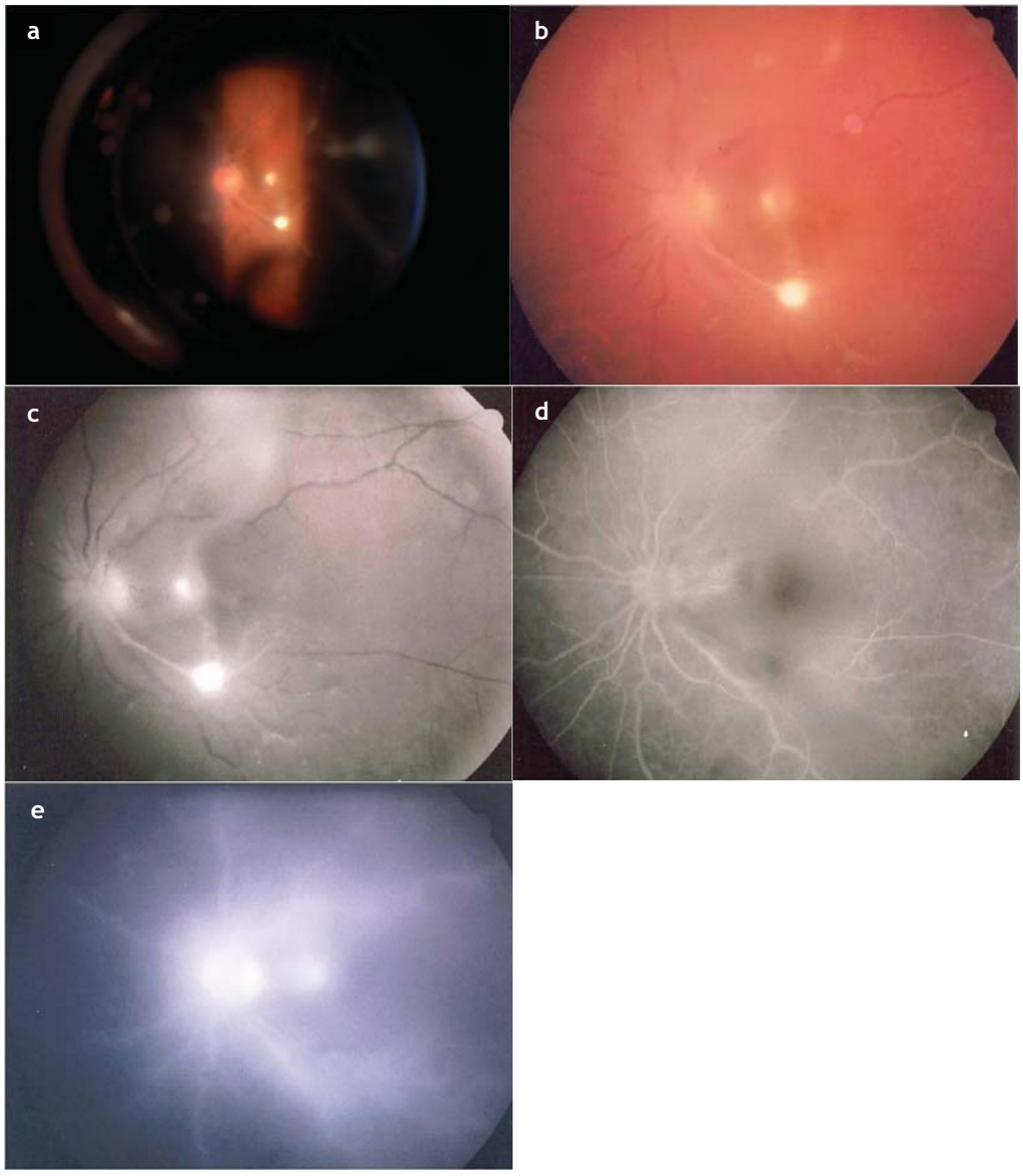

Fig. (28). a and **b**) Endogenous endophthalmitis. Candida fluffy balls in the vitreous. Also, you can see Candida chorioretinitis, which typically presents as a small, creamy white, circumscribed chorioretinal lesion with overlying vitreous inflammation. **c**, **d**, **e**) Angiogram.

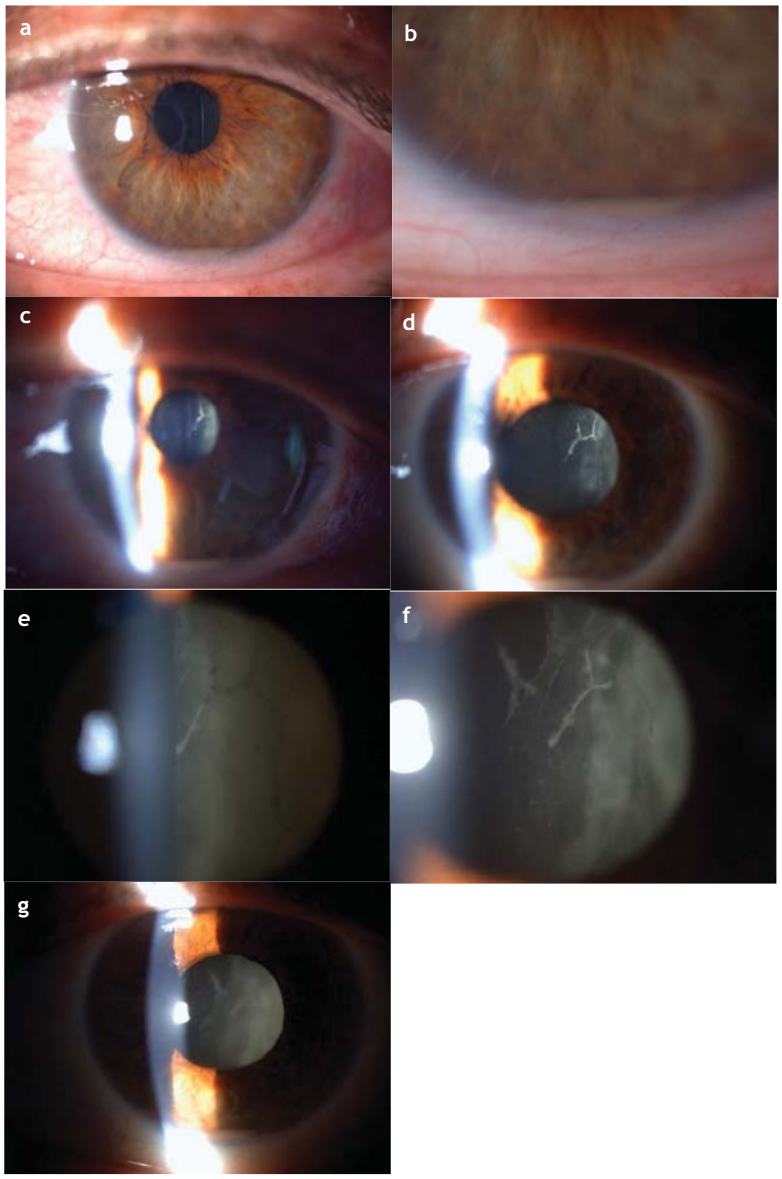

Fig. (29). a, **b**, **c**, **d**, **e**, **f**, **g**) Postoperative endophthalmitis: Hypopyon and vitritis.

MANAGEMENT

Early diagnosis and prompt treatment are essential. Symptoms and signs are characteristic. Ocular ultrasound is useful in eyes with opaque media. Anterior chamber tap and vitreous biopsy should be done for culture. Identification of the microorganism is obtained in 60-70% from aqueous humor and in 20-30% from vitreous material [6]. The treatment options include:

1. Antimicrobial therapy (intravitreal Table **3**, topical and systemic therapy).
2. Anti-inflammatory therapy (intravitreal, topical and systemic therapy).
3. Supportive therapy (cycloplegic, antihypertensive drugs).
4. Surgical therapy: Vitrectomy.

The Endophthalmitis Vitrectomy Study (EVS) recommends [4]:

Table 3. Intravitreal injections. Common intravitreal medications.

Amikacin	0.4 mg/0.1 ml
Ampicillin	0.5 mg/0.1 ml
Cefazolin	2-2.5 mg/0.1 ml
Ceftazidime	2.25 mg/0.1 ml
Vancomycin	1 mg/0.1 ml
Amphotericin B	5-10 mcg/0.1 ml
Dexamethasone	0.4 mg/0.1 ml

Fig. (30). Pars plana vitrectomy to obtain vitreous sample.

Initial vision: Hand Motion (HM) or better: Vitreous tap (Fig. **30**) and Intravitreal therapy.

Initial vision: Light Perception (LP): Pars plana vitrectomy plus intravitreal therapy.

Poor prognosis factors: Initial vision less than HM, absent red reflex, delay treatment, reoperations, diabetes and fungal etiology.

Special Considerations:

* Chronic E: Partial or Total capsulectomy and removal of the intraocular lens may be considered [5].

* Post-traumatic Endophthalmitis: Reports indicate that penetrating trauma (PT) accounts for 13-25% of all E cases (Fig. **16**). Incidence after PT varies from 2.8 to 22% [7]. An increased risk has been associated with intraocular foreign bodies (IOFB), delayed timing of primary repair (more than 24 hours) and rural setting [8]. *S. epidermidis* is the most commonly isolated organism and *B. cereus comes in second place* [9]. Treatment includes early vitrectomy, debridement of necrotic tissue and removal of any IOFB. Intravitreal, systemic (vancomycin and an aminoglycoside or a third-generation cephalosporin are indicated; consider clindamycin until *Bacillus* species can be ruled out) and topical antibiotic therapy is recommended (Table **4**: Systemic Drugs).

Table 4. Systemic drugs.

Urban Trauma: • Ceftazidime 1 g every 6-8 h • Vancomycin 500 mg every 6 h • Methylpredisolon 1 mg/kg/24 h	*Rural Trauma:* • Amikacin 15 mg/kg/24 h • Vancomycin 500 mg /6 h • Clindamycin 600 mg/6 h • Methylpredisolon 1 mg/kg/24 h
Suspect fungal origin: Amphotericin B 0.5 mg/kg/day IV. Voriconazole 200 mg PO q12 h.	

* Endogenous Endophthalmitis (Ee): Ee is caused by hematogenous spread of infectious organisms from distant sites of the body. Very low frequency (Incidence 2-8%) [10, 11]. Risk factors: Immunosuppression (diabetes, leukemia, lymphoma, asplenia, hypogammaglobulinemia, bone marrow transplant, systemic lupus, chronic alcoholism, steroid use and prematurity), intravenous antibiotic and intravenous drug abuse. Sources: endocarditis is the most common source in bacterial cases (Figs. **1**, **27**) and intravenous catheters and intravenous hyperalimentation, in cases of fungal infection [12]. *Candida* spp. is the most

frequent source of Ee (Figs. **21**, **22**, **23**, **28**) [1]. *Focal anterior and posterior* endophthalmitis present white-appearing localized lesions in the iris, ciliary body and choroids. Anterior diffuse E includes anterior segment inflammation, chemosis, hypopyon, fibrin clot but with mild or moderate vitreous inflammation. Posterior diffuse E involves severe vitreous inflammation which does not allow the visualization of the retina. The treatment of focal cases is based on oral therapy while diffuse cases are managed similarly to PE (oral fluconazole is indicated. Intravenous or intravitreal amphotericin B may be considered).

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 9

Acute Posterior Multifocal Placoid Pigment Epitheliopathy

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First described in 1968 by Don Gass, MD [1], Acute Posterior Multifocal Placoid Pigment Epitheliophaty (APMPPE) is a bilateral but asymmetrical condition affecting young people between the second and fourth decades of life without sex predilection.

This is an idiopathic condition, but a viral prodrome has been associated in about one third of patients.

ESSENTIALS OF DIAGNOSIS

To arrive at a diagnosis of APMPPE, both clinical and ophthalmoscopic features are important. Patients complain of blurred vision, photopsias and scotomas in one eye; the second eye may not be involved until several days or weeks after the first one. Several reports exist about the potential central nervous system (CNS) vasculitis changes associated with APMPPE [2, 3].

Ophthalmoscopic features include multiple, flat, deep yellow-white plaques located at the posterior pole (Fig. **1**). Lesions appear to be at the level of retinal pigment epithelium (RPE), but controversy exists about whether APMPPE is a primary disease of RPE or a consequence of vasculitis affecting choroidal vessels [4, 5]. A few weeks after the improvement of fundus appearance, plaques begin to heal, leaving RPE mottling and atrophy (Fig. **2**).

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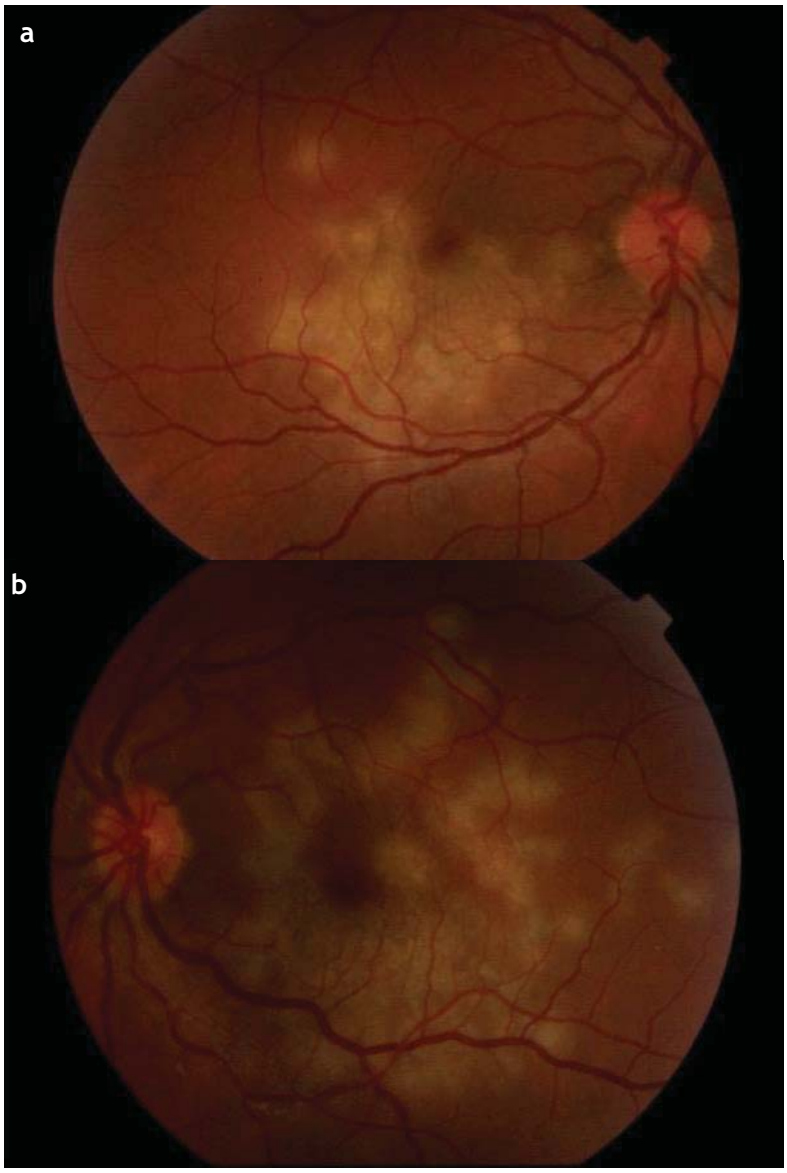

Fig. (1). (a) and **(b)** Color fundus photographs showing multiple, deep yellow-white lesions in a case of APMPPE in a young woman with bilateral involvement (Courtesy of Maximiliano Gordon, MD).

Others forms of compromise include serous retinal detachment, retinal vasculitis, papillitis and vitreous haze [6 - 9].

Ancillary tests include fluorescein angiography (FA), indocyanine green angiography (ICGA), visual field perimetry and optical coherence tomography (OCT).

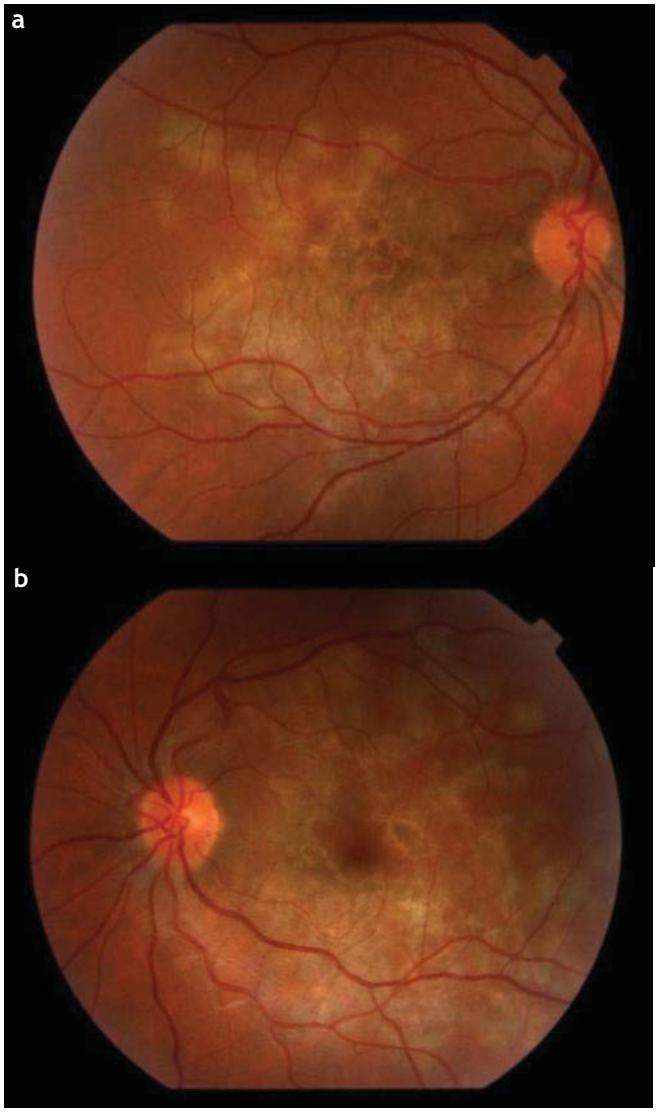

Fig. (2). (a) and **(b)** Color fundus photographs of the same patient after treatment with corticosteroids because of macular involvement and severe visual loss. Observe RPE mottling and atrophy (Courtesy of Maximiliano Gordon MD).

FA shows the characteristic pattern with early blocking hypofluorescence in the acute phase followed by staining and pooling in the late frames. Late state is characterized by hyperfluorescence without leakage (Fig. **3**), a consequence of windows defect [8]. Hypofluorescence, in both intermediate and late frames [6], is observed in ICGA.

Static perimetry shows objectively the scotoma referred by patients.

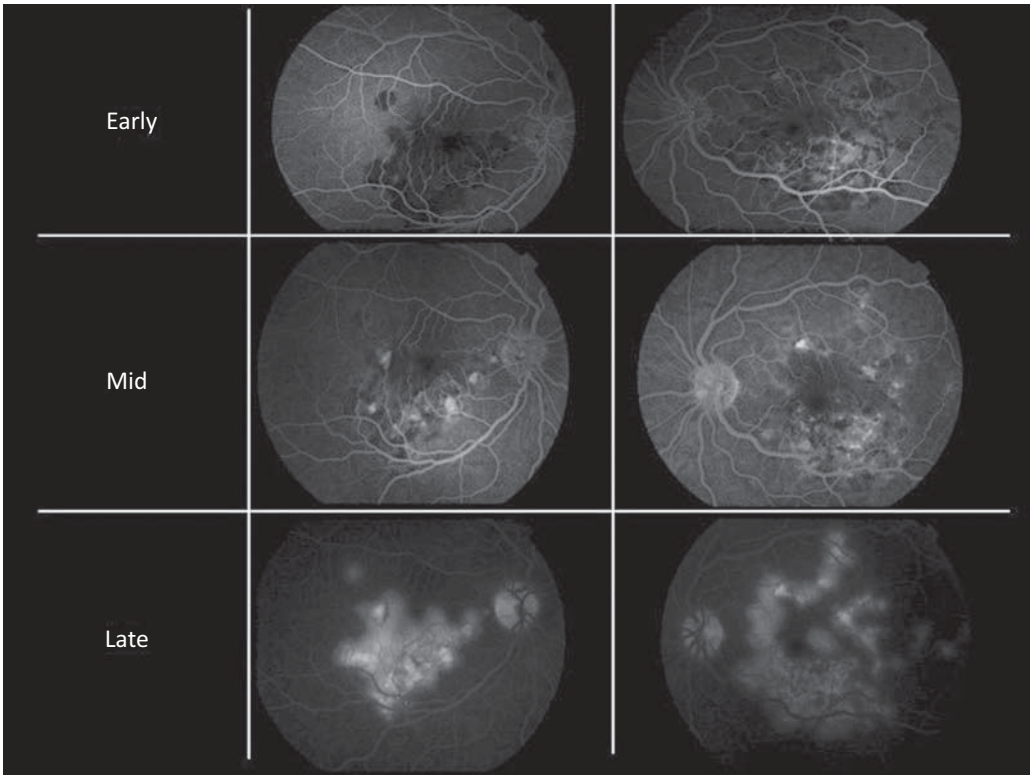

Fig. (3). Fluorescein angiography (FA) of the same patient. Early frames show a blocking hypofluorescence with staining and pooling in mid frames. Late state is characterized by hyperfluorescence without leakage (Courtesy of Maximiliano Gordon, MD).

OCT demonstrates a nodular hyper-reflectivity at the level of photoreceptors and RPE (Fig. **4**) consequence of inflammatory cells besides intracellular cystoid edema [10]; OCT is also useful for evidencing subretinal fluid [11].

A prospective observational case series study proposes an OCT classification including four stages for APMPPE, describing an early stage with a dome-shaped elevation of photoreceptors layer (stage 1) to two distinct layers of photoreceptors and RPE in the resolution phase (stage 4) [12].

DIFFERENTIAL DIAGNOSIS

Differential diagnoses include white dot syndromes; granulomatous disorders, like sarcoidosis [13], tuberculosis and syphilis; VKH syndrome, especially when APMPPE presents bilaterally with lesions in the macula; and subretinal fluid is important for a careful consideration of clinical course and treatment response to arrive at the diagnosis [14].

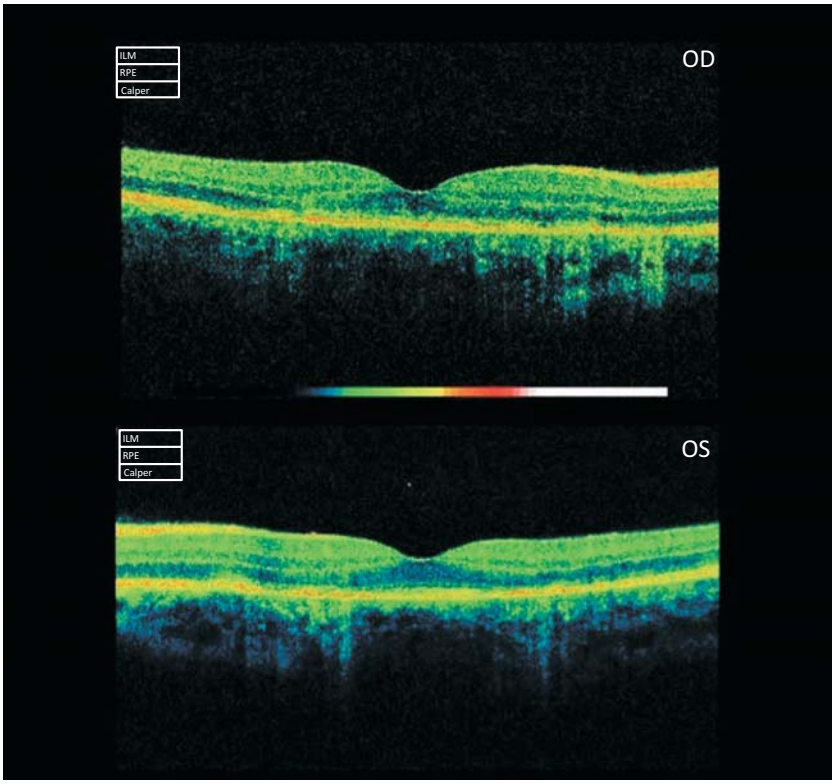

Fig. (4). OCT images showing alterations in outer layers of retina, a nodular hyper-reflectivity at the level of the RPE (Courtesy of Maximiliano Gordon, MD).

MANAGEMENT

The disease has a good prognosis, and visual acuity generally improves after a few weeks. No treatment is required except in some cases with macular involvement where corticosteroids may be indicated to prompt visual recovery. In some cases of central nervous system involvement, corticosteroids are an option.

There is a case report where the use of immunosuppressive therapy is necessary to prevent neurological complications in one patient with recurring meningoencephalitis in sinusitis-associated APMPPE [2].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 10

Multiple Evanescent White Dot Syndrome

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ESSENTIALS OF DIAGNOSIS

Multiple evanescent white dot syndrome (MEWS) is a rare, predominantly unilateral posterior uveitis [1, 2]. It is characterized by the presence of multiple, small, white or yellowish white dots located at the level of the outer retina, RPE, and inner choroid. The lesions may range in size from 100 μm to a half disc diameter and may concentrate around the optic disc and along the vascular arcades extending to mid-periphery (Figs. **1** and **3**). Each lesion is composed of many smaller dots which can be appreciated at high magnification by slit lamp biomicroscopy [3]. Macular examination reveals the presence of tiny white or orange specks, which confer the fine granular aspect of the fovea, considered to be pathognomonic of this syndrome [4, 5]. Optic disc inflammation, along with vitreous cells, can accompany the deep retinochoroidal lesions. In infrequent occasions, a mild anterior segment inflammation is observed [6]. Sometimes a relative afferent pupillary defect is noted [3].

Symptoms include the development of vision loss of sudden onset, visual field defects, floaters, photopsias and dyschromatopsia [2].

Approximately one third of the cases are preceded by a flu-like illness [3]. Women are more frequently affected than men [1]. In spite of the fact that initially MEWDS was thought to be an acute, monophasic, self-limited, unilateral disease with a quick resolution of the alterations, the disorder may have bilateral involvement, relapse, be complicated by choroidal neovascularization, or develop chorioretinal scars [2, 3]. Occasionally, it has been reported to be associated to acute multifocal choroiditis and panuveitis [7], acute zonal occult outer retinopathy [8], acute idiopathic blind spot enlargement syndrome [9] or acute macular neuroretinopathy [10].

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Visual field tests usually show a blind spot enlargement, associated to paracentral, temporal, or scattered scotomas, which may not be correlated with ophthalmologic findings [2, 3, 11].

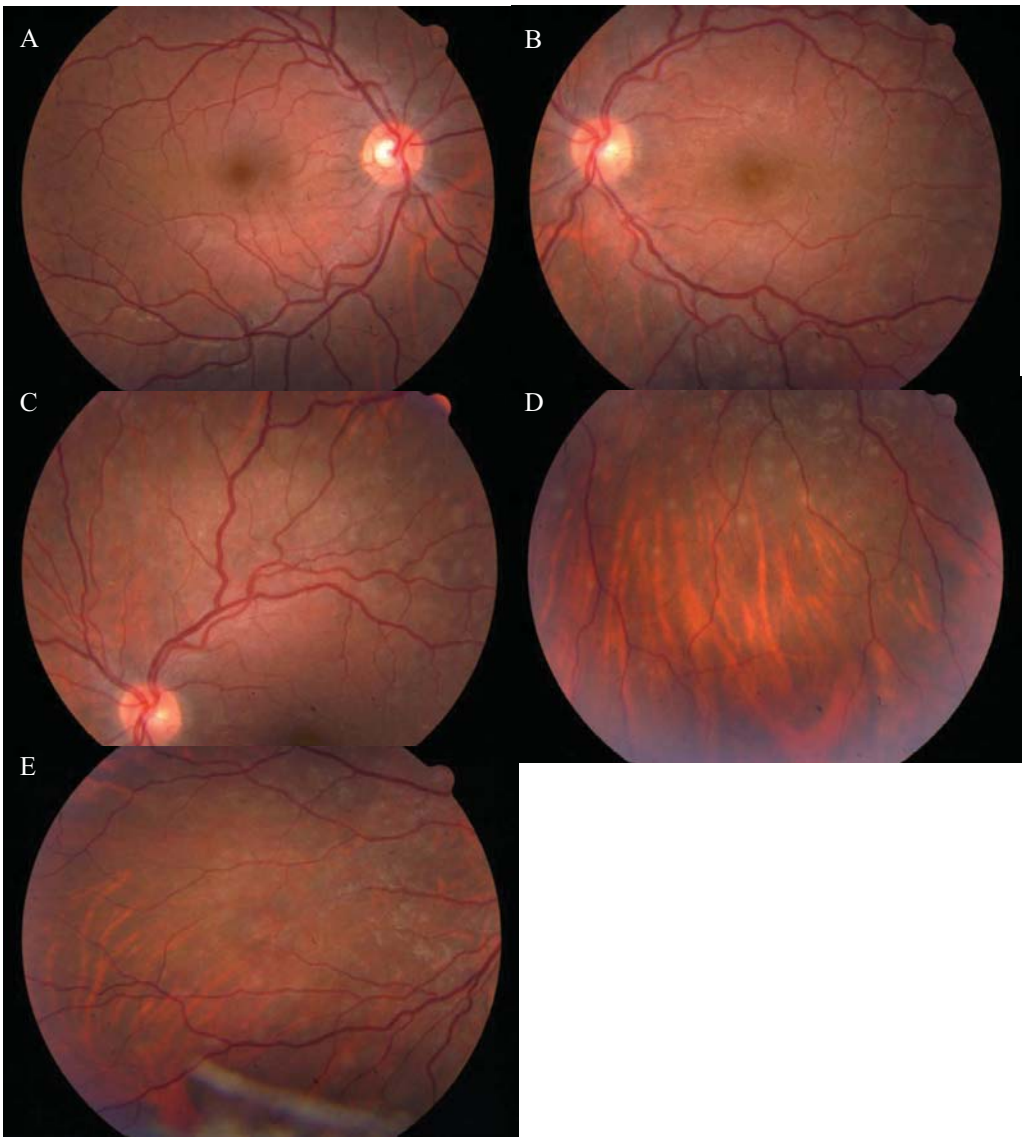

Fig. (1). 24-year-old male patient. Multiple evanescent white dot syndrome was diagnosed in his left eye. **(A)** Right eye is unaffected. **(B)** Macular granularity along with subtle undefined multiple white dots at posterior pole can be observed. **(C)** Temporal, **(D)** inferior, and **(E)** nasal periphery are also involved with the typical lesions.

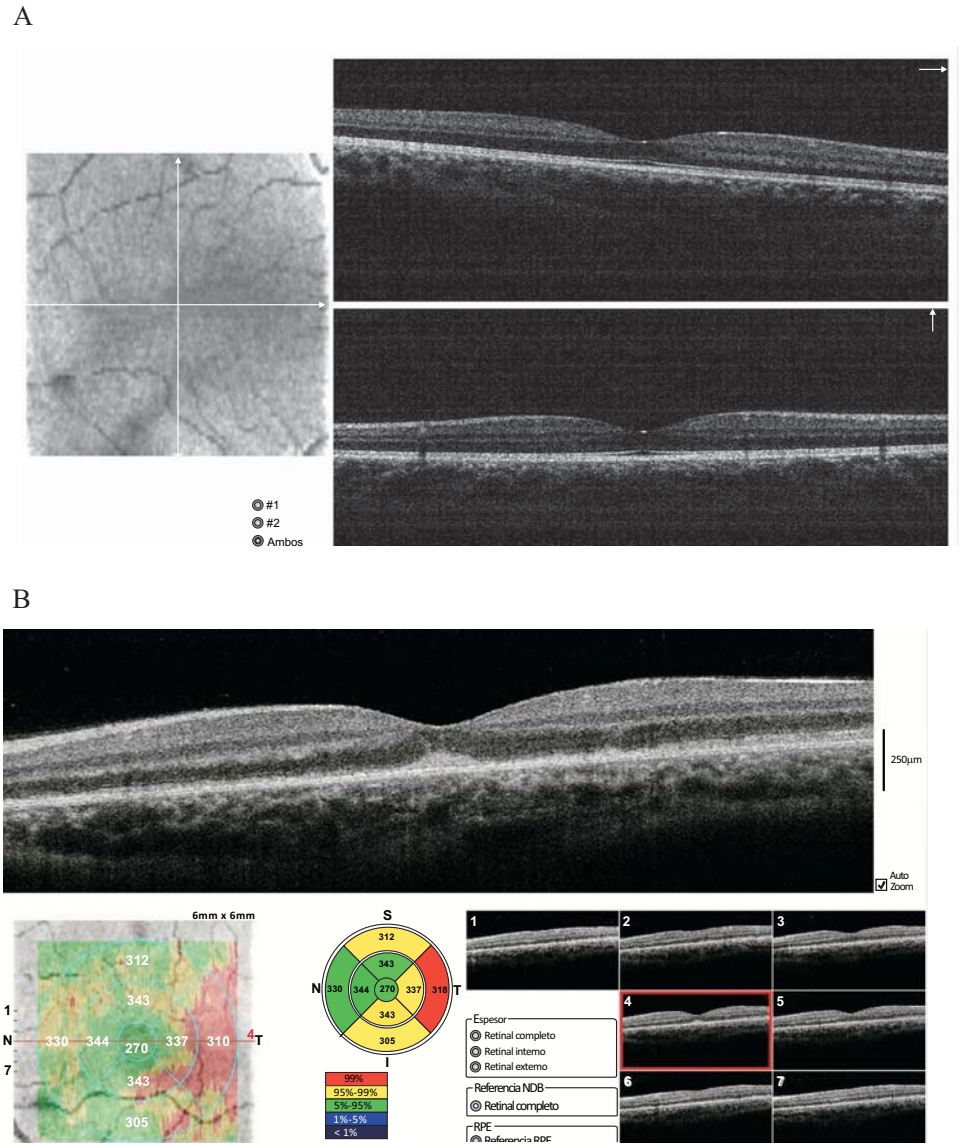

Fig. (2). Spectral-domain optical coherence tomography of the same patient from Fig. (**1**). **(A)** Right eye is unremarkable. **(B)** At left eye, outer layers are disrupted, and a dome-shaped pattern can be observed at the fovea.

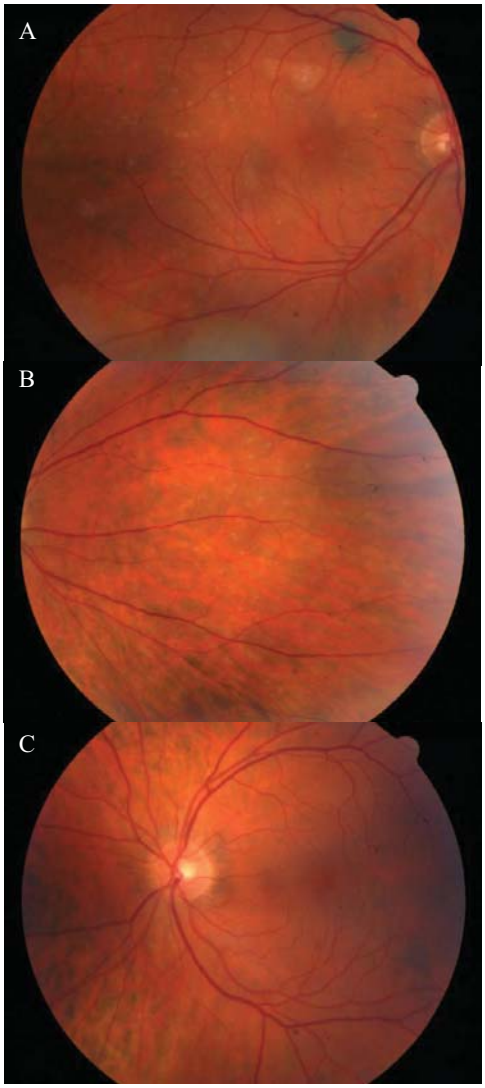

Fig. (3). 42-year-old male patient. Multiple evanescent dot syndrome was diagnosed in his right eye. **(A)** Macular granularity can be noted, along with multiple subtle white dots –some of them confluent– at posterior pole. **(B)** The same lesions are observed peripherally. **(C)** Left eye is unaffected.

Classically, fluorescein angiography (FA) reveals early hyperfluorescent spots in a wreath-like hyperfluorescence pattern, which correspond to the white dots in the acute phase, with late staining of the retinal pigment epithelium (Fig. **4**) [12]. However, Dell'Omo *et al.* demonstrated the presence of early hypofluorescent lesions combined with the previously described hyperfluorescent lesions in some patients. Late leakage from the optic disc may also be seen. These manifestations in the angiogram change during the course of the disease, implying the resolution

or persistence of the lesions at retinal or choroidal layers [12]. Dell'Omo *et al.* described in the same work cited above, the correlation between indocyanine green angiography (ICGA) and FA in patients with this ailment. They found that early hypofluorescent lesions in FA correspond to early hypofluorescent lesions in ICGA [12]. This may be attributed to inflammatory lesions located at the level of the outer retina and RPE with concomitant variable involvement of the underlying choriocapillaris. In addition, they showed that early hyperfluorescent lesions in FA correspond to intermediate hypofluorescent lesions in ICGA [12].

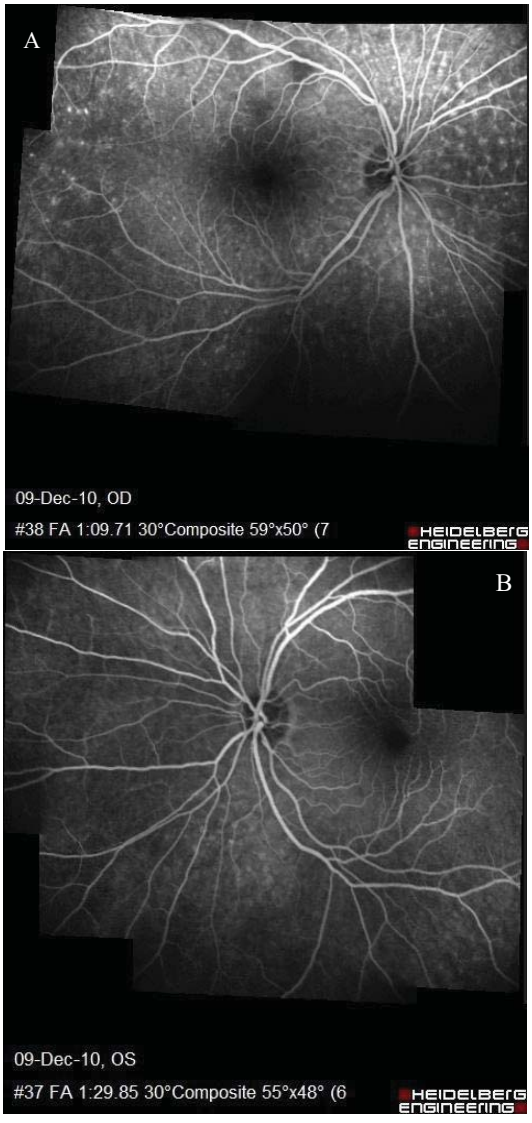

Fig. (4). Fluorescein angiography of the same patient from Fig. (**3**). **(A)** Note the multifocal hyperfluorescent lesions in a wreath-like pattern in the right eye. **(B)** Left eye is unremarkable.

Fundus autofluorescence reveals hyperautofluorescent images which correspond to the white dots. Hypoautofluorescent pinpoint areas surrounding the disc and in the macula are also observed. During the course of the disease, hypoautofluorescent lesions disappear, while hyperautofluorescent lesions may decrease in number, retract centripetally, develop into hypoautofluorescent areas, or disappear without becoming hypoautofluorescent lesions [13].

Findings at the OCT consist of a multifocal or diffuse attenuation and disruption of the hyper-reflective band of the photoreceptor IS/OS junction layer. White dot lesions correspond to hyper-reflective dome-shaped images at the subretinal space (Figs. **2** and **5**) [11, 14].

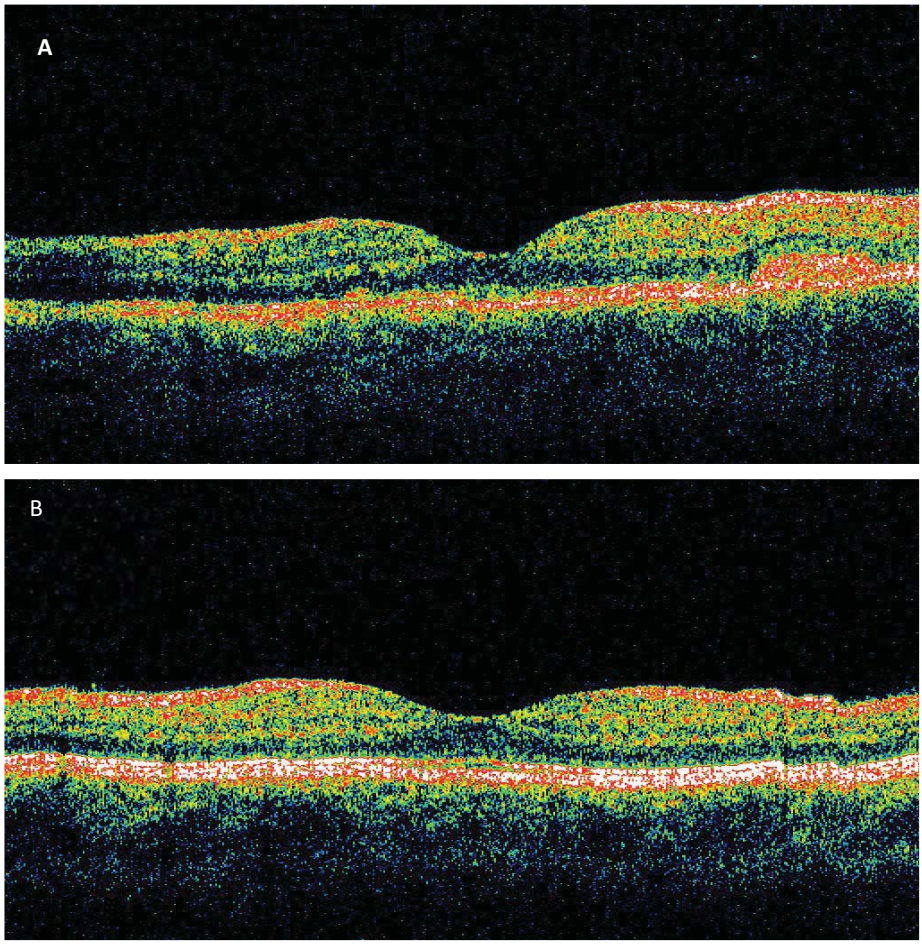

Fig. (5). Time-domain optical coherence tomography of the same patient from Fig. (**3**). **(A)** The IS/OS junction layer is disrupted and a dome-shaped image at the subretinal space can be observed in the affected eye. **(B)** The unaffected eye shows a continuous hyper-reflective IS/OS junction layer.

Full field and multifocal electroretinography show abnormal patterns during the course of the ailment [11].

DIFFERENTIAL DIAGNOSIS

White dot syndromes consist of a group of diseases whose main feature is the presence of deep whitish-yellow lesions, located at the level of the photoreceptors, RPE, and choroid [2]. MEWDS, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), serpiginous choroiditis, multifocal choroiditis with panuveitis (MCP), birdshot chorioretinopathy (BSC), and diffuse unilateral subacute neuroretinitis (DUSN) are included in this group. Other diseases, such as Vogt Koyanagi Harada (VKH) disease, sympathetic ophthalmia (SO), sarcoidosis, Behçet disease, syphilis, tuberculosis, toxoplasmosis, presumed ocular histoplasmosis syndrome (PHOS), and primary vitreoretinal lymphoma (PVRL) are also studied as part of the differential diagnosis of white dot syndromes [2]. The presence of significant anterior chamber inflammation, keratic precipitates, and posterior synechia rules out the diagnosis of MEWDS. They are usually found in VKH syndrome, SO, sarcoidosis, syphilis, and tuberculosis. Lesions are self-limited in MEWDS, while they are persistent in serpiginous choroiditis, MCP, BSC, DUSN, VKH disease, SO, sarcoidosis, Behçet disease, syphilis, tuberculosis, toxoplasmosis, and PHOS. Vitritis may be significant in PVRL, sarcoidosis, syphilis, toxoplasmosis, and tuberculosis, while it is mild in MEWDS.

MANAGEMENT

MEWDS is a self-limited disease which resolves without the need of treatment. Occasionally, recurrences may be observed [15 - 18].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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[PMID: 17846954]

CHAPTER 11

Multifocal Choroiditis

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ESSENTIALS OF DIAGNOSIS

There has been much discussion over the years regarding whether multifocal choroiditis (MFC) and punctate inner choroidopathy (PIC) represent different names for the same disease entity [1]. However, there are clearly differences between MFC with panuveitis and PIC [2, 3]. This chapter will deal only with the forms of MFC with associated intraocular inflammation, rather than PIC/MFC without inflammation.

Multifocal choroiditis (MFC) is a chronic inflammatory condition that is typically bilateral, and more commonly seen in women. The age range is broad, but it most commonly affects young to middle-aged myopic females [2 - 4]. The most common presenting complaints are decreased visual acuity, floaters, and photopsias. On exam most patients will present with vitreous cells, and approximately 50% will have anterior chamber cells. Fundoscopic findings consist of multiple yellow to grey lesions, 50 to 1,000 microns in size, at the level of the retinal pigment epithelium (RPE) and inner choroid layer [3, 5]. The lesions may be distributed anywhere in the fundus from the peripapillary region, within the arcades, and into the periphery. Active lesions maybe associated with indistinct borders and subretinal fluid. Some patients present with disc edema, cystoid macular edema (CME); and in 25 to 39% of patients, macular and peripapillary choroidal neovascularization may develop [2, 3]. Inactive lesions appear as clearly defined, punched-out scars with variable pigmentation (Figs. **1a**, **1b** and **1c**).

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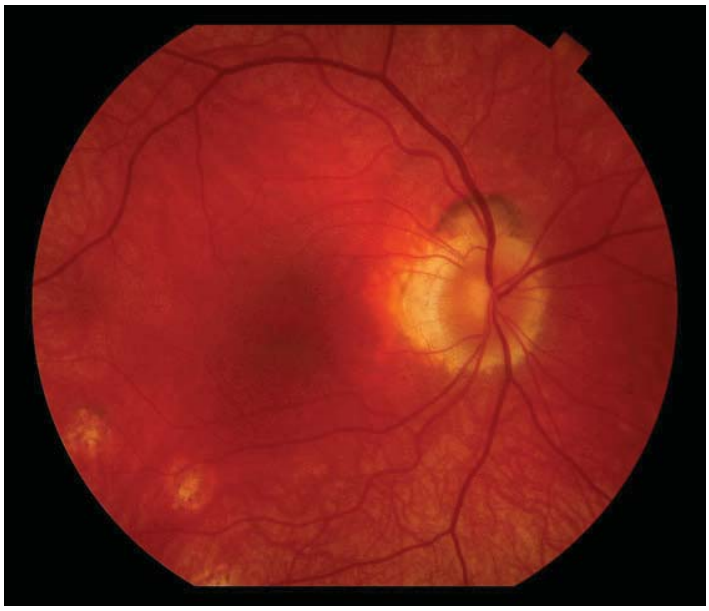

Fig. (1). 25-year-old woman with chronic granulomatous iridocyclitis and multifocal choroiditis. She presented 3 years earlier with granulomatous KP OU, AC cells, vitreous cell, haze and multifocal choroidal lesions as well as subretinal neovascular membranes OU. The uveitis has recently been well controlled on systemic immunomodulatory therapy, with no new lesions or subretinal neovascular membranes. Fig. (**1a**). Color fundus photo -- Posterior pole (Right eye). There is no vitreous haze. There is mild disc hyperemia. There are inactive atrophic choroidal lesions, and a white ring of subretinal fibrosis around the disc, with two old peripapillary subretinal neovascular membranes.

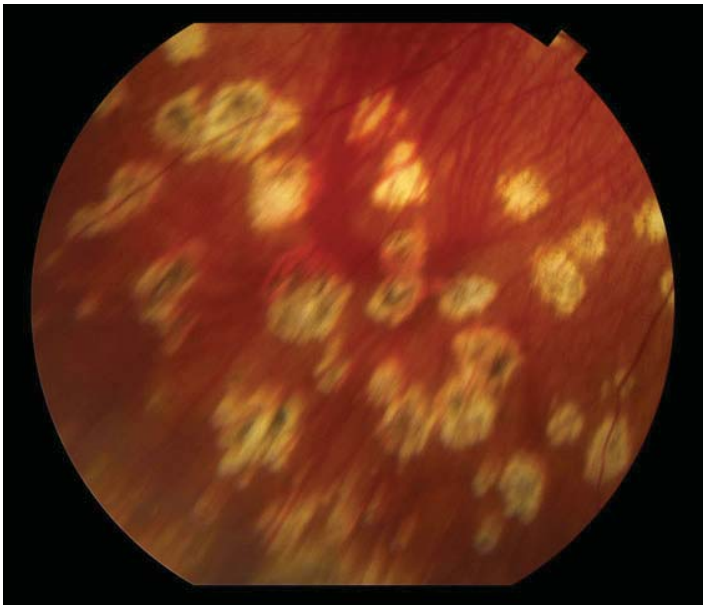

Fig. (1b). Color fundus photo -- Periphery (Right eye). Inactive atrophic lesions with distinct borders and variable pigmentation.

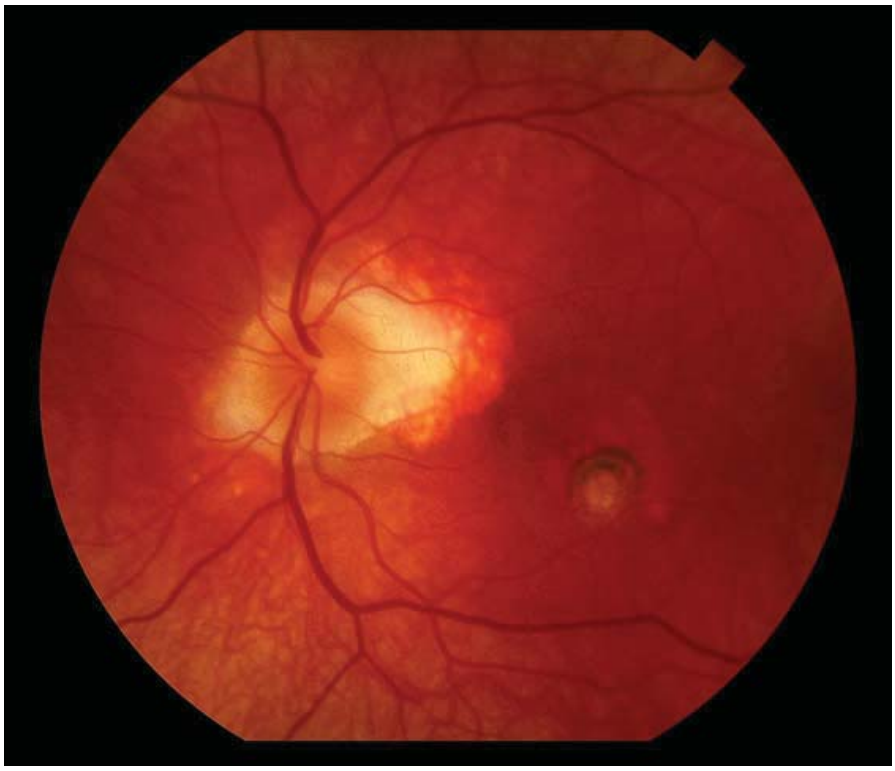

Fig. (1c). Color fundus photo -- Posterior pole (Left eye). There is no vitreous haze. There is mild disc edema and hyperemia. There is an atrophic lesion inferior to the fovea with an adjacent scar of a subretinal neovascular membrane. There are extensive peripapillary scarring and evidence of a peripapillary neovascular membrane.

Active lesions show conical sub-RPE material, underlying choroidal hyper-reflectivity, and overlying vitreous cells on SD-OCT imaging [1, 2]. Choroidal hyper-reflectivity is thought to result from changes in both photoreceptors overlying the sub-RPE deposits and from disturbance in RPE itself [2]. In the inactive phase, depending on permanent photoreceptor and RPE damage, there maybe variable reconstitution of the normal outer retinal layers, reduction of choroidal hyper-reflectivity, persistent RPE elevation, or small punched out scars with absence of RPE [1, 2] (Figs. **1d**, **1e** and **1f**).

On fluorescein angiography (FA), active lesions show early hypofluorescence with late staining and leakage. Inactive scars demonstrate window defects with early hyperfluorescence, well defined borders, and late fading [1, 4]. Indocyanine angiography (ICG) demonstrates hypofluorescent round spots, 200 to 500 microns in size, in the posterior pole. On fundus autofluorescence (FAF), the RPE elevations are seen as round areas of minimal hyperautoflorescence or absent autofluorescence in areas of RPE dehiscence [1].

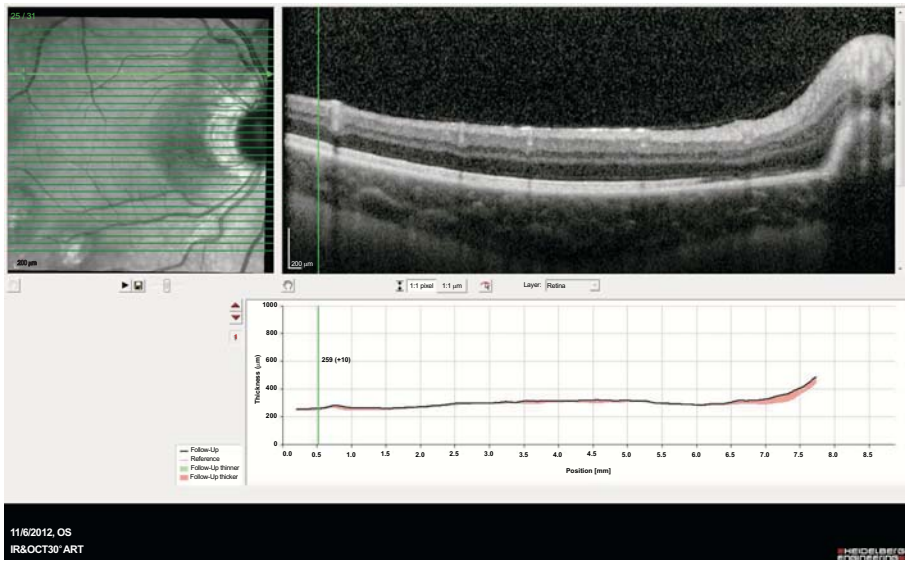

Fig. (1d). Inactive peripapillary CNV (Right eye). Infrared (IR) fundus photograph of the right eye of the above patient showing inactive atrophic choroidal lesions, peripapillary white ring of subretinal fibrosis, and temporal darker placoid area. Horizontal OCT scan (green arrow) shows hyper-reflective RPE elevation with disruption of outer retinal layers and RPE, and increased reflectivity and thickening of the inner retinal layers consistent with the inactive peripapillary net. Focal disruption of ellipsoid zone (EZ), and intact RPE and ELM are noted temporal to the RPE elevation. Mild increase in choroidal hyper-reflectivity in the area underlying EZ loss along with increased choroidal thickness are noted.

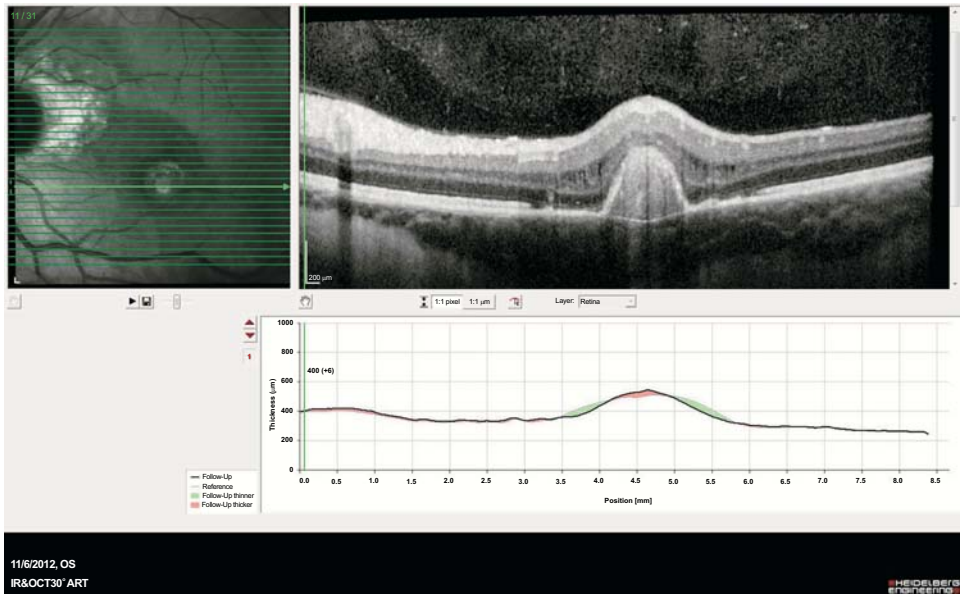

Fig. (1e). Inactive CNV (Left eye). IR fundus image of the same patient as above showing extensive peripapillary scarring and adjacent atrophic lesion in the macula. Horizontal OCT scan (green arrow) shows focal RPE elevation. There is loss of EZ overlying and adjacent to these areas. Overlying inner retinal layers show thickening with trivial intra-retinal cystic spaces. There is no subretinal fluid.

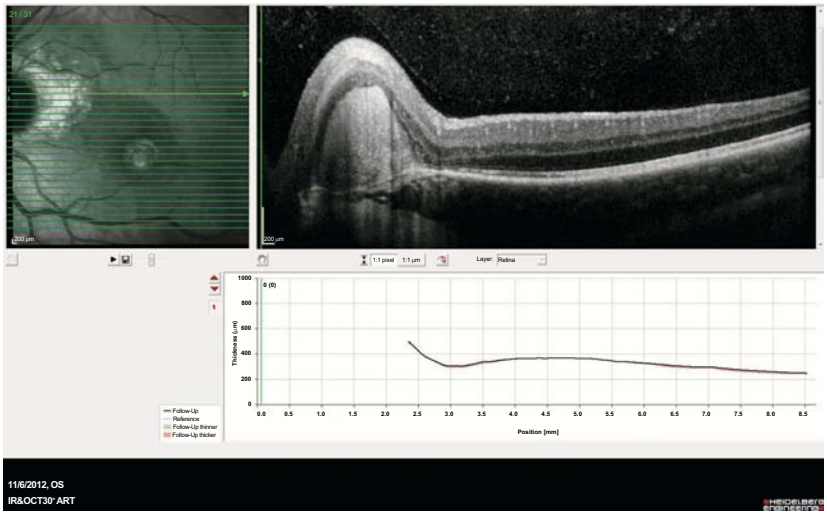

Fig. (1f). Inactive peripapillary CNV. IR fundus photo of the left eye of the same patient as above showing extensive peripapillary scaring and adjacent atrophic lesion. The horizontal OCT scan (green arrow) shows hyper-reflective sub-RPE elevation with underlying and adjacent hyper-reflectivity involving the inner choroidal layer, consistent with the inactive net in Fig. (**1c**) Temporal areas of loss of EZ and interdigitation zone are seen.

In eyes with MFC associated with active inflammation, histopathological examination of choroidal neovascular membrane shows infiltration of CD-20 positive B lymphocytes, which maybe modified by steroid therapy and clinical stage of the disease [3]. Patients with MFC may have normal, moderately reduced, or severely reduced ERGs.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is extensive so one must keep an open mind to both inflammatory and infectious conditions with similar clinical presentation.

- Presumed ocular histoplasmosis (no intraocular inflammation)
- Punctate inner choroidopathy (no intraocular inflammation)
- Tuberculosis
- Sarcoidosis
- Syphilis
- Sympathetic Ophthalmia
- Birdshot retinopathy
- AMPEE
- PIOL
- Other uncommon infectious diseases (West Nile, pneumocystis, Lyme, *etc.*)

MANAGEMENT

Detailed history and astute observations will help guide the workup, given the extensive differential diagnosis. Workup should include FTA-ABS or other specific treponemal test to rule out syphilis, PPD or QuantiFERON gold to exclude TB. ACE, lysozyme and chest imaging may be helpful to diagnose sarcoidosis. HLA-A29 testing may be indicated if there is concern of atypical birdshot choroidopathy.

Treatment is based upon visual acuity, severity of inflammation, presence of CME and choroidal neovascular membrane (CNVM) formation. Corticosteroid therapy is typically instituted as first line treatment. Oral prednisone maybe started at moderately high dose (1 mg/kg) and tapered with clinical reduction in inflammation. Long-term oral steroids use is not desirable, given significant side effects. Peri- or intra-ocular steroids may be very helpful in controlling inflammation, keeping in mind the risks of cataract and glaucoma.

In corticosteroid-refractory cases, or cases in which corticosteroids cannot be tapered to acceptable levels (5 mg oral prednisone daily or equivalent by 6 months), other immunomodulatory agents may be used. Commonly used agents include the antimetabolites methotrexate, mycophenolate, and azathioprine. If these are insufficient to control inflammation, biological agents such as the TNF inhibitors may be considered. CNV is treated as other forms of CNV, typically with anti-VEGF agents, although local steroid therapy is particularly helpful in inflammatory CNV [2, 4].

MFC is a chronic disease with variable long-term visual prognosis that is largely dependent upon the presence or absence of CME and CNVM.

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 12

Punctate Inner Choroidopathy

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ESSENTIALS OF DIAGNOSIS

Punctate inner choroidopathy (PIC) typically affects young myopic females, with a mean age of onset of 26 years (range 16 to 40 years) [1]. Clinically, patients present with blurred vision, central or paracentral scotomas, enlargement of the blind spot, or photopsias. On exam there is no clinically apparent intraocular inflammation [1, 2]. Fundoscopic findings consist of yellow lesions with indistinct borders that measure 100 to 300 microns in size, typically located in the posterior pole or the mid periphery. These PIC lesions occur at the level of the inner choroid and retinal pigment epithelium (RPE). Active lesions may be associated with small amounts of subretinal fluid and serous retinal detachment. Occasionally, the optic nerve is hyperemic, but cystoid macular edema (CME) does not occur. The acute lesions may resolve after a few weeks, leaving atrophic spots with a punched out appearance and variable pigmentation [2, 3] (Figs. **1** and **2**). In many patients, such resolution leads to improvement of visual symptoms but in about 25% of eyes more severe visual loss subsequently occurs, primarily due to development of choroidal neovascularization (CNV).

Active lesions in PIC demonstrate early mild hyperfluorescence with late leakage on fluorescein angiography. With disease progression, damage to the RPE occurs and window defects are seen. Leakage of fluorescein into the subretinal space may be observed in patients with a serous retinal detachment [2, 4]. The small, multiple subretinal lesions demonstrate hypofluorescence in the early, middle, and late phases of the ICG [2, 4]. ERG may be normal or show mild asymmetry of b-wave amplitude. SD-OCT may show RPE elevation with hyper-reflective sub-RPE signals, obscuration and displacement of photoreceptors and disruption of Bruch's membrane. Over time with resolution of RPE elevations, the photoreceptor layer may become visible again. Some patients may show no RPE

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elevation, but localized disruption of the outer retinal layers and RPE, with sparing of the choroid and Bruch's membrane [4] (Figs. **3a** and **3b**).

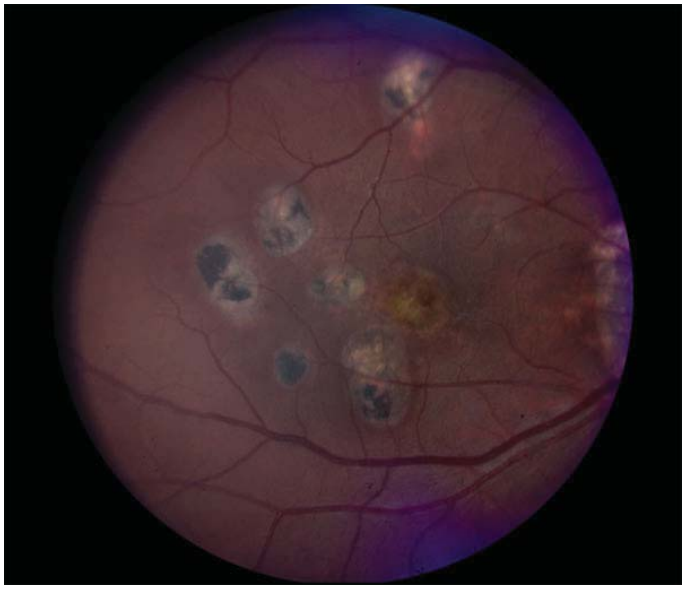

Fig. (1). Atrophic lesions in the macula of the right eye of a patient with MFC without inflammation/PIC. This patient developed multiple CNVM over time in both eyes, with no evidence of intraocular inflammation at any point. This is the type of presentation which is typically referred to as PIC, but may also be considered MFC without inflammation.

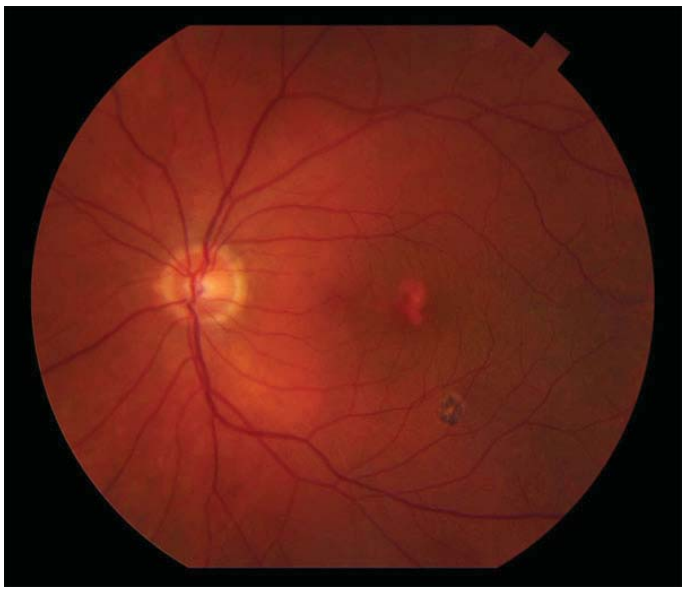

Fig. (2). Atrophic lesions in the macula of the left eye of a 39-year-old male with PIC. The patient had multiple bilateral atrophic spots in both fundi and developed multiple CNVM over time in both eyes, with no evidence of intraocular inflammation.

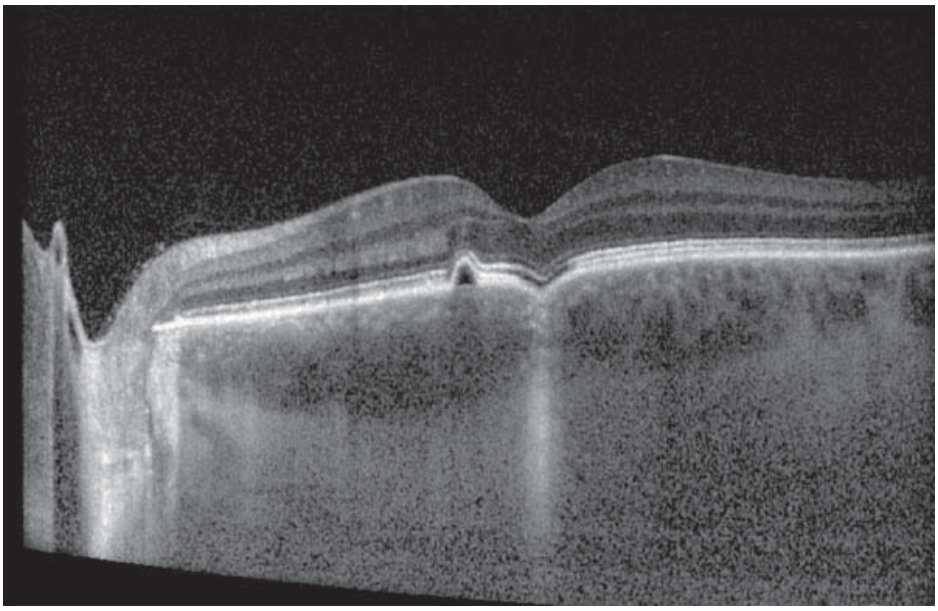

Fig. (3a). SD-OCT of the left eye of the patient in Fig. (**2**). Nasal to the fovea, a focal elevation of the RPE is seen with corresponding disruption of the overlying inner segment- outer segment layer (Ellipsoid layer, EZ). Adjacent OPL shows moderate reflectivity. No edema of surrounding retina is seen. Temporal to this hump, underlying the foveal contour, a V-shaped hernia of the OPL, ILM and disrupted EZ, into the inner choroidal layer is seen.

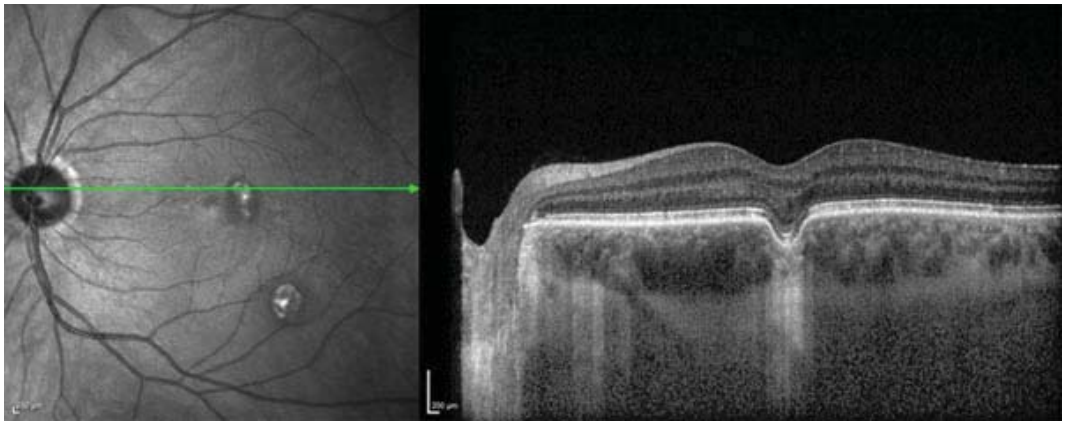

Fig. (3b). IR image of the left macula of the patient in Fig. (**2**), showing atrophic macular lesions in PIC. The SD-OCT scan of the sectioned lesion (green arrow) shows sub foveal V- shaped incarcerated hernia of the OPL and inner retina into the choroid. Loss of outer retina and RPE is seen in the V shaped depression.

DIFFERENTIAL DIAGNOSIS

Ocular histoplasmosis syndrome (OHS) lesions may appear identical to PIC lesions, however OHS lesions are typically also present in the periphery, which is spared in PIC. Neither condition is associated with vitritis. Some authorities believe PIC to be a variant of MFC as these two different entities share many

similar characteristics and clinical signs. Multifocal choroiditis without inflammation and PIC may represent the same entity. However, multifocal choroiditis with panuveitis is distinct from PIC, as there is evidence of intraocular inflammation, and CME is frequent (see Chapter 11 on multifocal choroiditis).

MANAGEMENT

Treatment is typically not offered for PIC, unless there is development of CNV. There is no data yet on the efficacy of immunosuppressive therapy in preventing recurrent PIC lesions and recurrent CNV, although immunosuppressive therapy may be offered in cases with frequent recurrences. PIC-associated CNV membranes are treated the same way as CNV secondary to other causes.

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 13

Birdshot Retinochoroidopathy

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ESSENTIALS OF DIAGNOSIS

Birdshot retinochoroidopathy is a relatively rare autoimmune chronic posterior uveitis, which always has bilateral involvement [1]. Its progression is slow, but it can lead to a severe retinal dysfunction in spite of the fact that visual acuity may not be significantly altered [2, 3]. It is mainly characterized by the presence of multifocal, hypopigmented choroidal lesions with indistinct borders [1 - 5] (Figs. **1a**-**d**, **2a**-**d**, **3a**-**b**, **4**). The latter have a spectrum of presentation, typically oval or round spots, but can be irregular in shape, or they can present a linear configuration. They are usually found around the optic disc, and frequently located in the inferior and nasal periphery [5]. However, they can be seen sometimes in other locations [1]. Anterior segment inflammation is mild or absent. There is no synechia formation. Vitritis is mild or moderate, although it is present in all cases. Retinal vasculitis is frequently observed, mostly as phlebitis [1, 4, 5]. Optic disc edema is also seen [1] (Figs. **1c**-**d**, **3c-d**).

Related symptoms reported, besides visual acuity impairment, include the presence of blurred vision, floaters, color vision deficiency, poor contrast sensitivity, nyctalopia, glare, photopsia, photophobia, fluctuating vision, decreased peripheral vision, metamorphopsia, and loss of depth perception [1 - 4, 6].

The most frequent complication is macular edema, which is the most common cause of decreased visual acuity in patients with this ailment [7, 8]. Other complications described include optic atrophy [7, 9], epiretinal membrane [10], choroidal neovascular membrane [7, 9], and retinal neovascularization [7].

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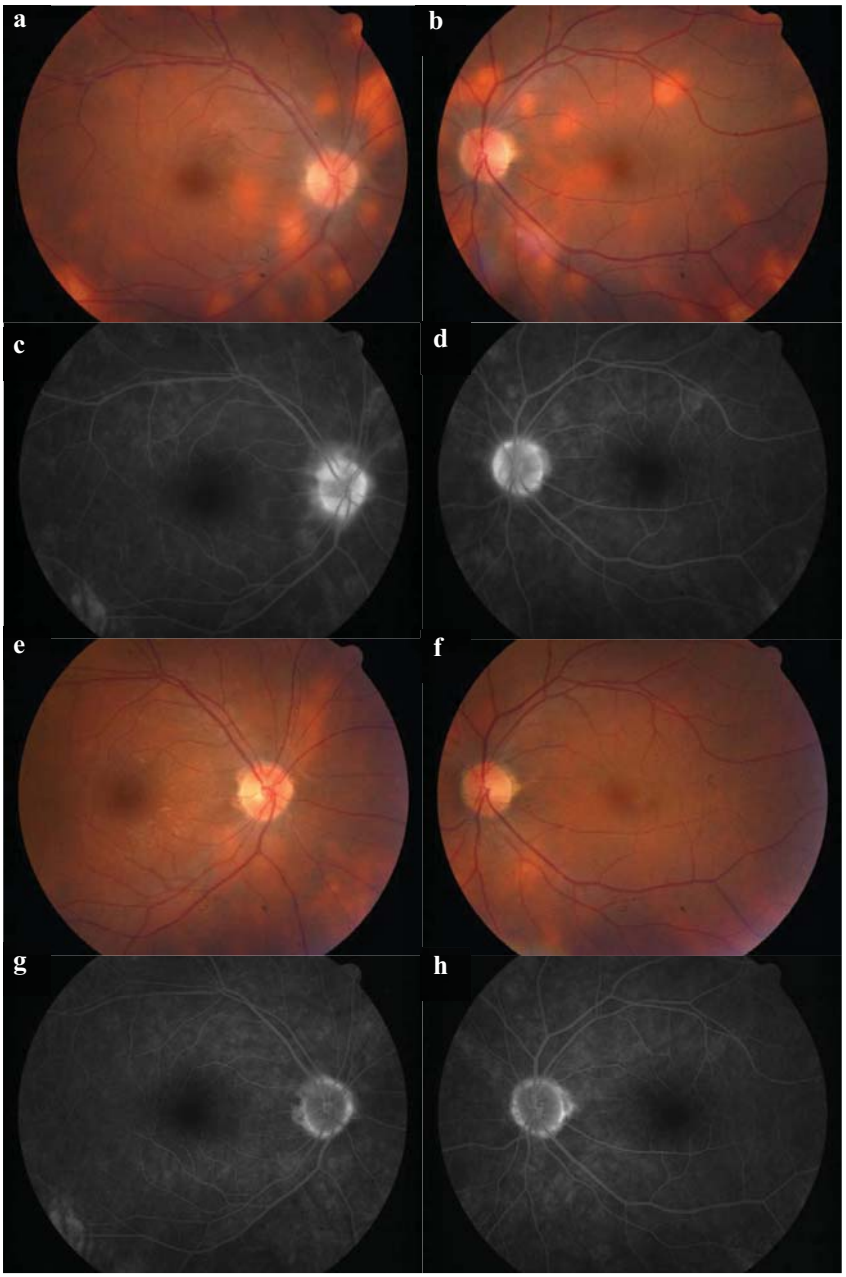

Fig. (1). 37-year–old female patient who complained about mild blurred vision in both eyes. Typical birdshot spots can be seen in both eyes at posterior pole (**a** and **b**) and periphery. Fluorescein angiography revealed the presence of hyperfluorescence of the optic disc in both eyes, without correlation between choroidal lesions and the angiographic features (**c** and **d**). She was treated with oral cyclosporine for 5 years, and her birdshot spots gradually disappeared (**e** and **f**). It can be noted that the hyperfluorescence of the optic disc in both eyes also disappeared due to the treatment (**g** and **h**).

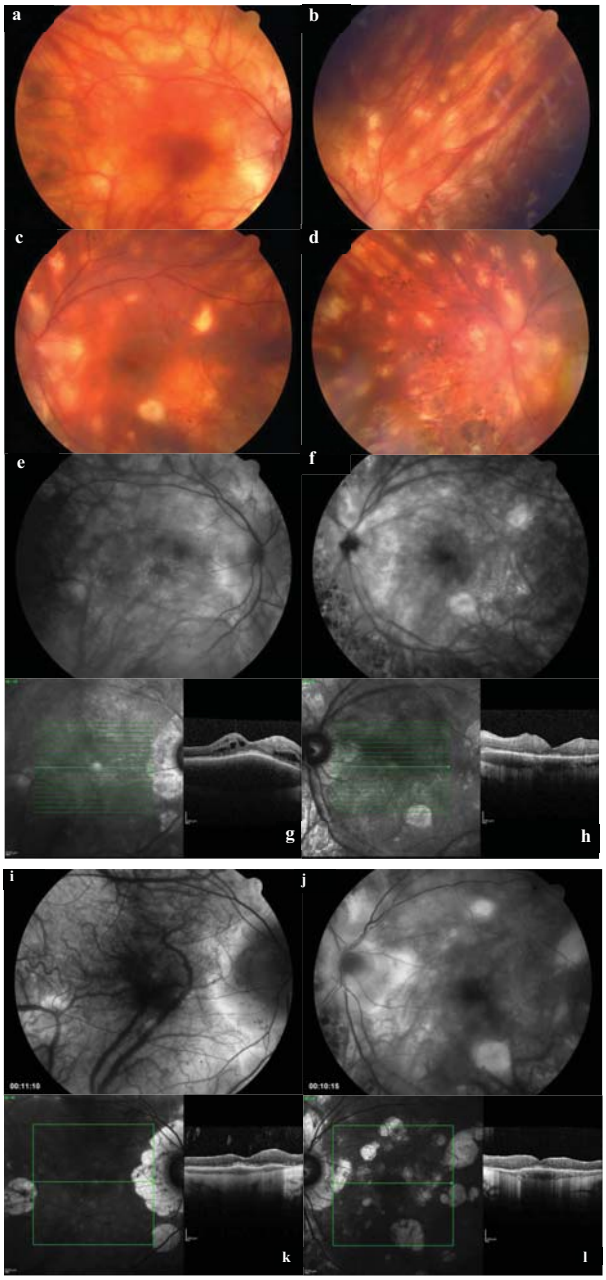

Fig. (2). 48-year–old male patient who had been diagnosed with birdshot retinochoroidopathy 7 years ago. Choroidal lesions at posterior pole and periphery are more discrete, and some of them are mildly pigmented (**a**, **b**, **c** and **d**). Fluorescein angiography and OCT revealed the presence of macular edema in both eyes (**e**, **f**, **g**, and **h**). After one year of treatment with cyclosporine and periocular corticosteroids, macular edema was adequately controlled in both eyes, as it can be observed in fluorescein angiography and OCT (**i**, **j**, **k**, and **l**).

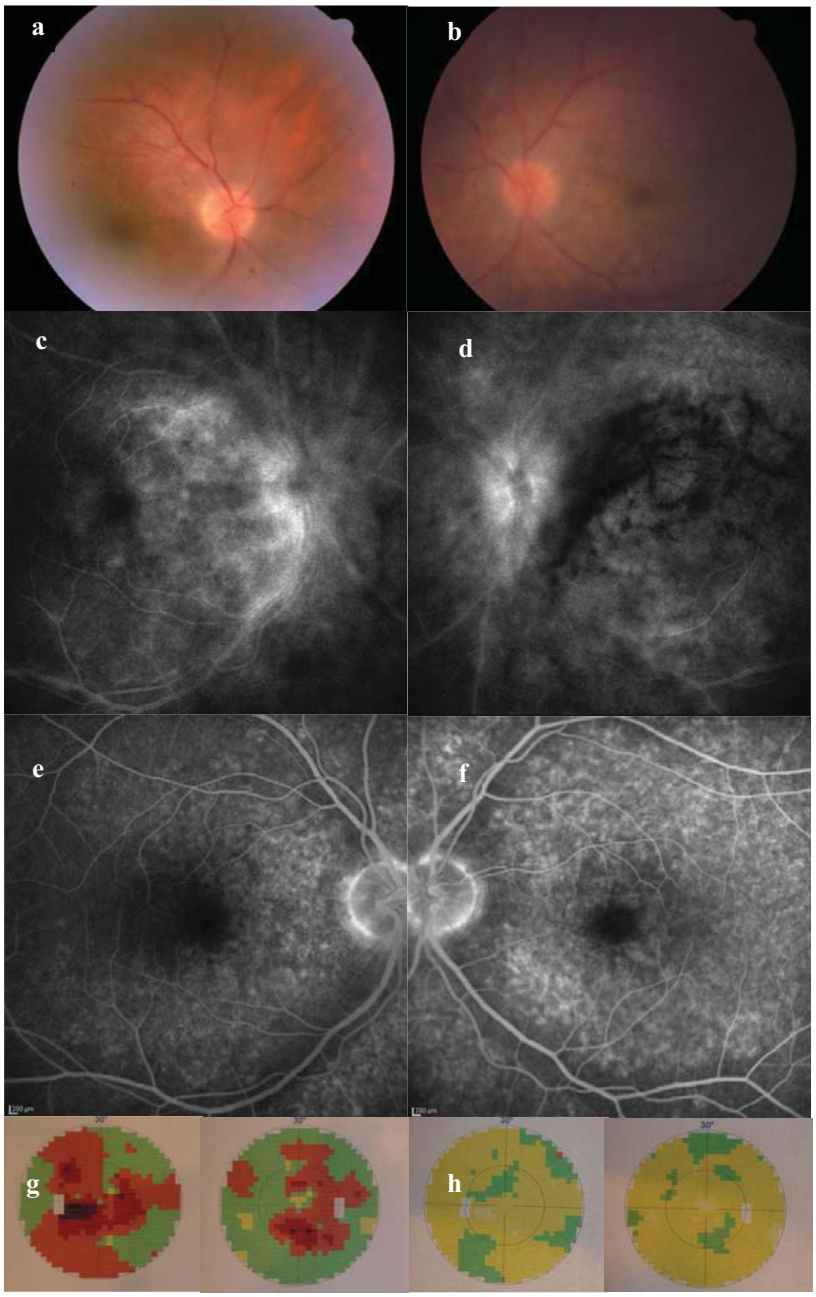

Fig. (3). 38-year-old male patient who had been diagnosed with birdshot retinochoroidopathy 2 years ago. Papillitis, retinal vasculitis, and a 2+ vitreous haze was observed in both eyes (**a** and **b**). Fluorescein angiography shows an intense hyperfluorescence of the optic disc, vascular leakage, and posterior pole edema (**c** and **d**). He was treated with high-dose oral meprednisone, cyclosporine, and mycophenolate mofetil with a favorable outcome in both eyes, as it can be appreciated in the fluorescein angiography taken 2 years later (**e** and **f**). During the follow-up with automated perimetry, a correlation with the clinical improvement of the intraocular inflammation was noted (**g** and **h**).

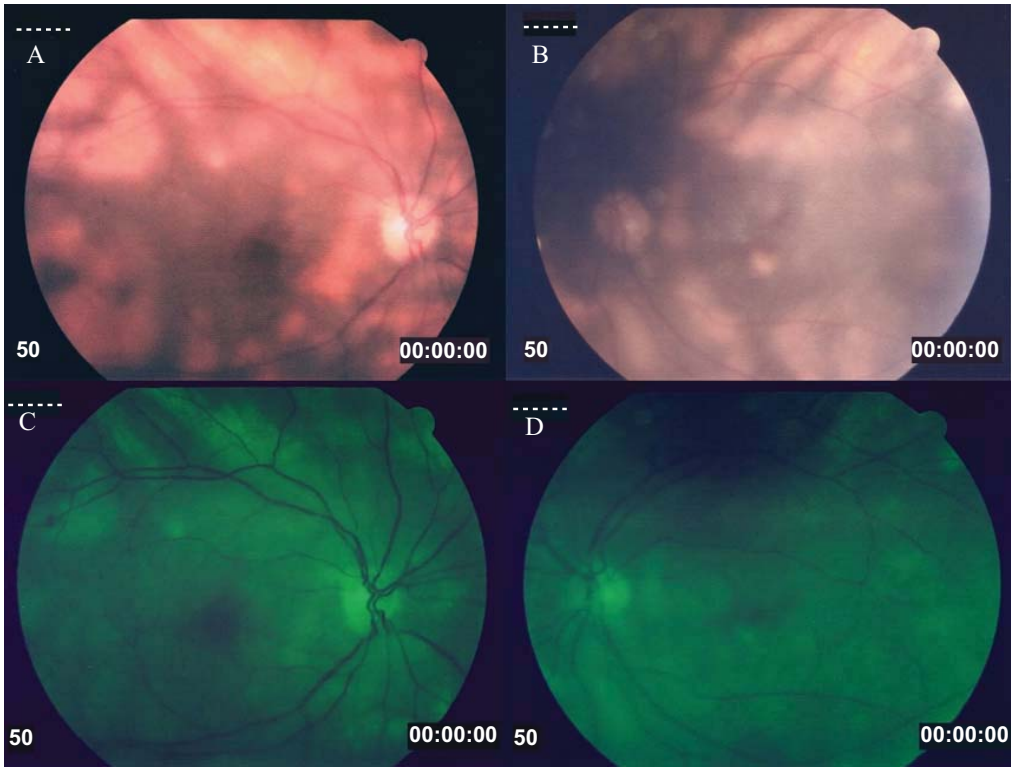

Fig. (4). Birdshot retinochoroidopathy in the right (**A**) and left (**B**) eyes in a 49-year-old woman with a three-month history of blurred vision. Color fundus photographs (**A** and **B**) show hypopigmented patches involving the macula and mid-periphery. Red-free photos of both eyes (**C** and **D**). (Courtesy of Juan Manuel Jimenez Sierra, Mexico).

The ability of fluorescein angiography to detect birdshot spots varies (Figs. **1c**-**d**, **2e**-**f**, **3c**-**d** and **5**) [1, 3, 11]. However, it is mainly useful to assess macular edema, retinal vasculopathy and optic disc inflammation [1, 6, 11]. Macular edema and vitreoretinal interface pathology assessments are carried out best by optical coherence tomography (Fig. **2g**-**h**). Gradual thinning of the outer retina, with a loss of the highly reflective photoreceptor band, is another feature found by this study [12]. Electroretinography usually shows an impairment of cone and rod function (Fig. **6**), which is demonstrated by abnormal scotopic rod b-wave amplitudes and cone b-wave implicit times [13]. Automated perimetry assessment may be useful for monitoring the response to treatment [14, 15] (Fig. **3g**-**h**), despite the fact there is a lack of consistency between the wide range of visual field defects found during the course of the disease [2].

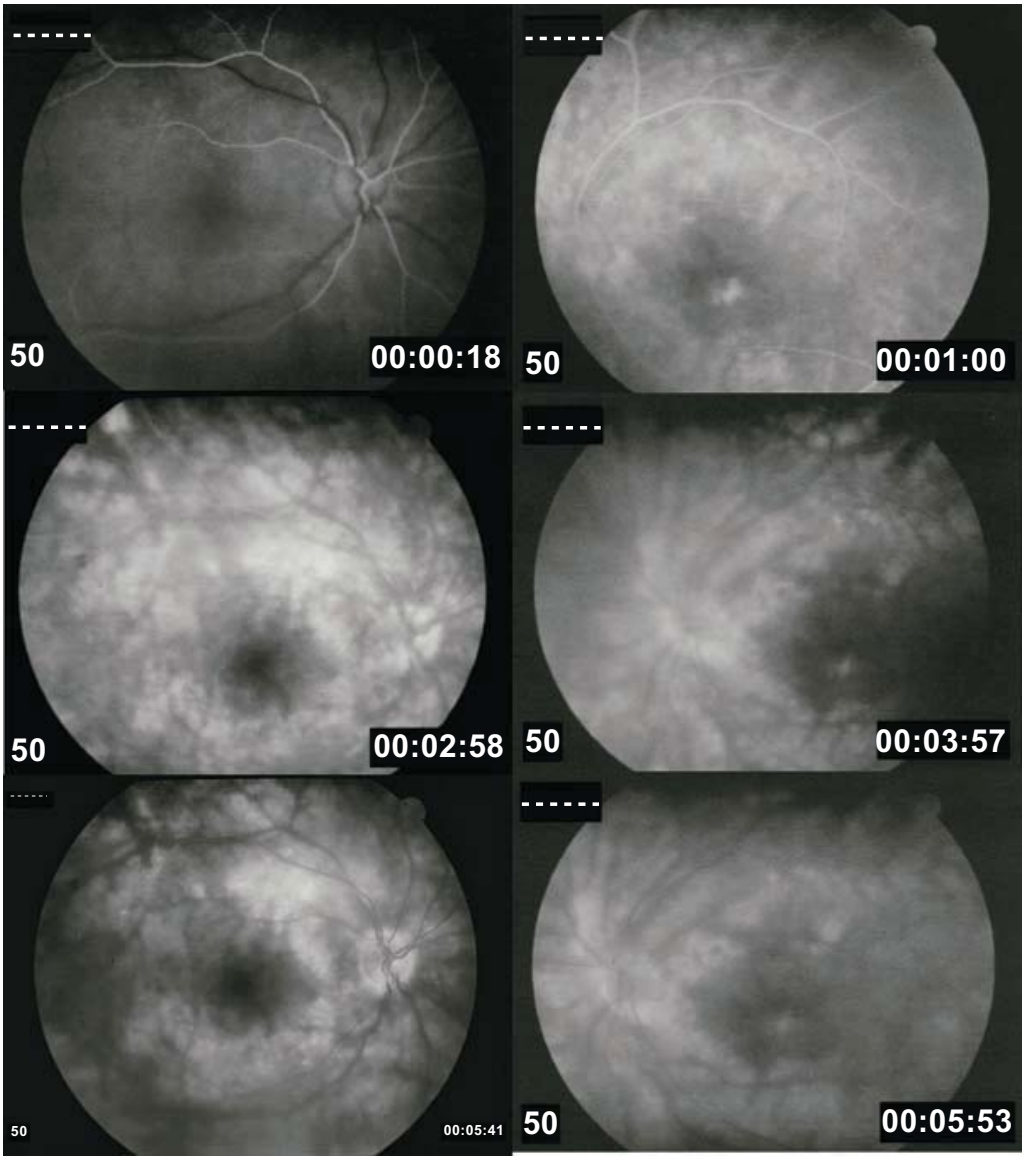

Fig. (5). Fluorescein angiography reveals mild hyperfluorescence of the hypopigmented lesions and disc staining of right eye in the late phases of the angiogram. (Courtesy of Juan Manuel Jimenez Sierra, Mexico).

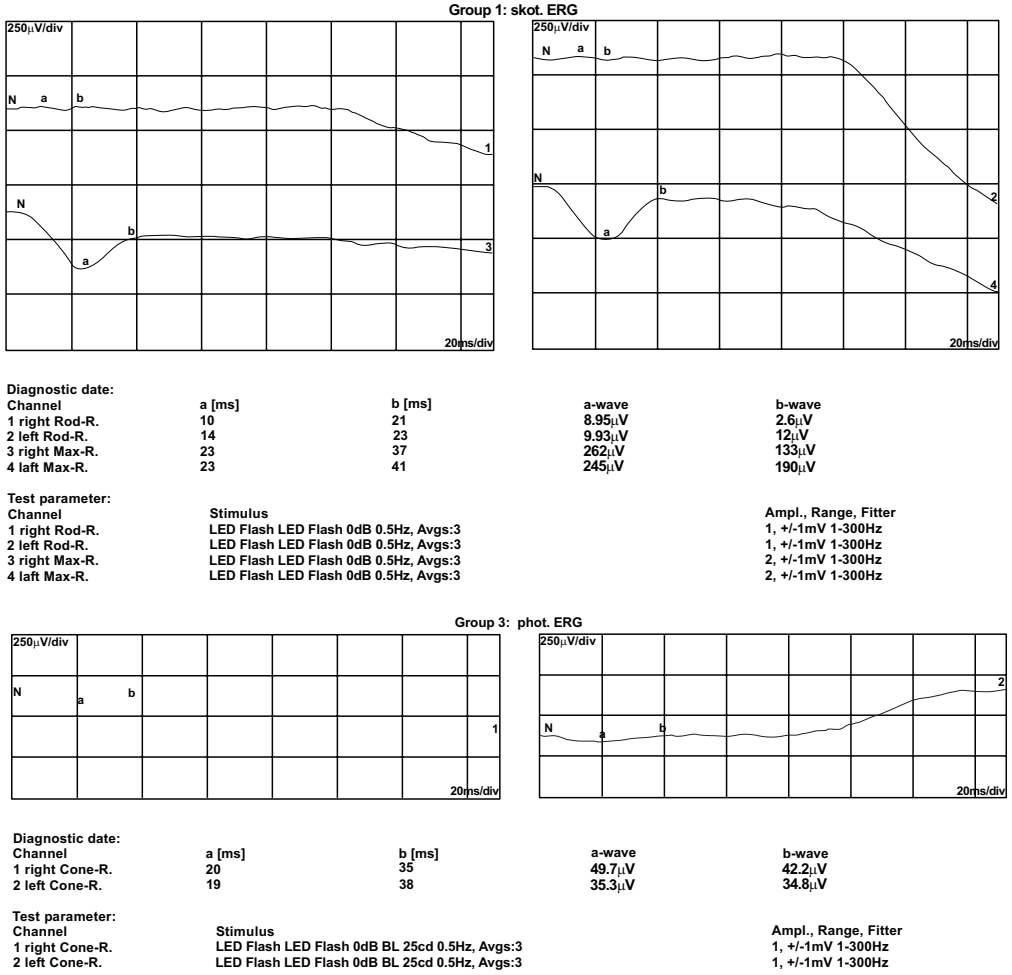

Fig. (6). The ERG reveals bilateral severely depressed rod and cone function. (Courtesy of Juan Manuel Jimenez Sierra, Mexico).

DIFFERENTIAL DIAGNOSIS

Multifocal deep lesions can occur in several entities, including Vogt Koyanagi Harada (VKH) syndrome, sympathetic ophthalmia, sarcoidosis, multifocal choroiditis and panuveitis (MCP), syphilis, tuberculosis, primary vitreoretinal lymphoma, posterior scleritis, acute posterior multifocal placoid pigmentary epitheliopathy (APMPPE) and multiple evanescent white dot syndrome (MEWDS) [5]. Significant anterior chamber inflammation, keratic precipitates, and posterior synechia, signs that rule out the diagnosis of birdshot retinochoroidopathy, are usually present in VKH syndrome, sympathetic ophthalmia, sarcoidosis, syphilis, and tuberculosis [5]. Systemic involvement can be observed in VKH syndrome, sarcoidosis, posterior scleritis, syphilis,

tuberculosis and primary vitreoretinal lymphoma. Birdshot retinochoroidopathy has no significant associated systemic involvement [5]. The presence of the multifocal deep lesions in APMPPE and MEWDS are self-limited and of short duration, while in birdshot retinochoroidopathy, they are persistent [4]. In patients with MCP, multifocal chorioretinal scars with pigmented borders of 50 to 100 microns in diameter are seen within the periphery and posterior pole. Active lesions are of a yellow-white color and involve the choroid and outer retina. These distinctive lesions are quite different from the subtle choroidal lesions of birdshot retinochoroidopathy [4].

MANAGEMENT

As a non-infectious uveitis, corticosteroids are the main treatment to control active intraocular inflammation in birdshot retinochoroidopathy [16]. Since this disease has a chronic course with progressive visual function impairment, immunosuppressive therapy is introduced early to avoid this deleterious progression [8] (Figs. **1e**-**h**, **2i**-**l**, **3e**-**h**). Importantly, the use of immunosuppressive therapy helps to reduce side-effects from prolonged use of higher doses of corticosteroids. Steroid-sparing drugs which were used to treat this entity include cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, and chlorambucil [10, 17 - 19] (Fig. **3e**-**f**). Biological agents were also reported to be used in the management of refractory cases of birdshot retinochoroidopathy. Among them, adalimumab [20, 21], infliximab [22], daclizumab [23] and tocilizumab [24] seem to have promising results in controlling active inflammation and macular edema.

Besides systemic corticosteroids, local therapy is useful for controlling active inflammation (Fig. **2i**-**l**). Both periocular [25] and intravitreal triamcinolone acetonide [26 - 28] were successfully employed in this setting, the latter being more effective. However, ocular hypertension and cataract development are frequent complications of their use, and it is necessary to repeat them. Retisert, a nonbiodegradable fluocinolone acetonide intravitreal implant, has been proven to be effective in controlling ocular inflammation of birdshot chorioretinopathy [29]. More information on the effectiveness of other intraocular treatment options, such as the ozurdex implant [30] and intravitreal sirolimus [31], is still to be reported.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 14

Serpiginous Choroiditis

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Serpiginous choroiditis (SC) is an acute and chronic inflammatory disease which is usually bilateral but may also be asymmetric. Its etiology is unknown. This rare, recurrent and multifocal disorder affects the inner choroid, the retinal pigment epithelium (RPE), and, secondarily, the retina. The average onset interval between the two eyes is about 5 years [3]. The disease is most often seen in otherwise healthy young to middle-aged individuals, and reports indicate that men have a higher prevalence than women [1, 4]. As per most uveitis epidemiological reports, SC constitutes less than 5% of cases of posterior uveitis [2, 6], except for one report from India, which found that 19% of their posterior uveitis cases correspond to SC [2, 5].

ESSENTIALS OF DIAGNOSIS

Patients present with painless, unilateral paracentral scotoma, metamorphopsia, or decreased vision. It typically extends from the peripapillary region, characterized by patches of gray-white inflammation in the retina and choroid, and spreads centrifugally, over a period of months or years, by means of recurrent episodes of patchy choroiditis in a serpiginous distribution outward from the optic disc to involve the macula and peripheral fundus [1, 2] (Fig. **1A** and **1B**). Far less commonly, macular (macular serpiginous choroiditis) or peripheral lesions in isolation, or in a multifocal pattern (atypical or ampiginous choroiditis), are observed [2, 6]. Acute lesions appear gray-white, or yellow, and involve the choriocapillaris and RPE [2]. Approximately one third of the patients present vitreous cellular inflammation during the active phase of the disease [1]. Over a period of weeks, the acute gray-white lesions, which may appear identical to those of the acute stage of acute posterior multifocal placoid pigment epitheliopathy (APMPPE), with or without treatment, are partially replaced by mottling and depigmentation of the RPE (Fig. **1E**); the grayish-white appearance in the boundaries of the active lesion often remains for a month or longer [1]. Over a

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period of months, varying degrees of atrophy of the underlying choroid develop within the discrete zone of previous activity [2, 7]. Chorioretinal atrophy, subretinal fibrosis, and extensive areas of pigment clumping in the RPE may be described in chronic cases [1, 2, 7] (Fig. **3A** and **3B**). In about two thirds of patients with SC, one or both eyes present scarring in the initial stage [1, 2]. At intervals, varying from weeks to years, the patients are subject to recurring episodes of activity that involve a different area of the fundus each time, usually a contiguous one [1, 2].

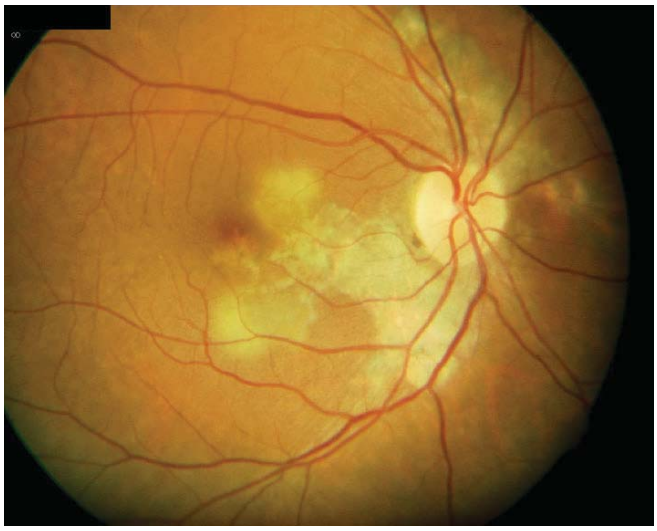


Fig. (1A). This 48-year-old woman had a history of paracentral scotoma in her right eye. Note the inactive scar in her right eye, and the yellow-white active lesions at the nasal border of the fovea.

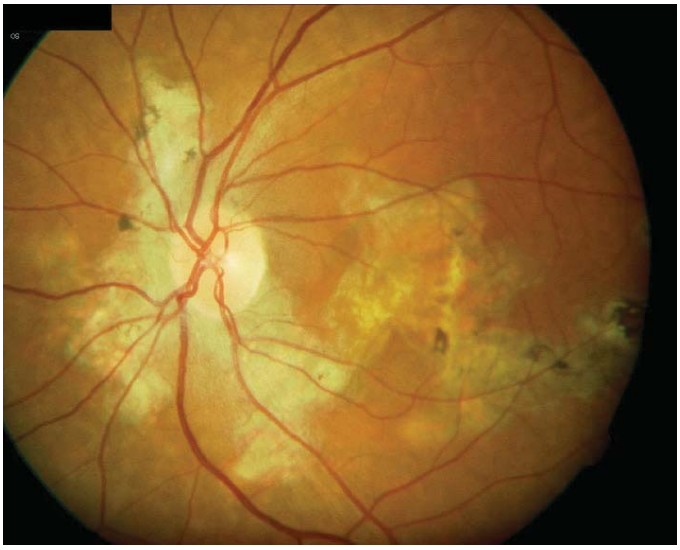


Fig. (1B). Left eye shows the characteristic serpiginous extension of the inactive process from the disc.

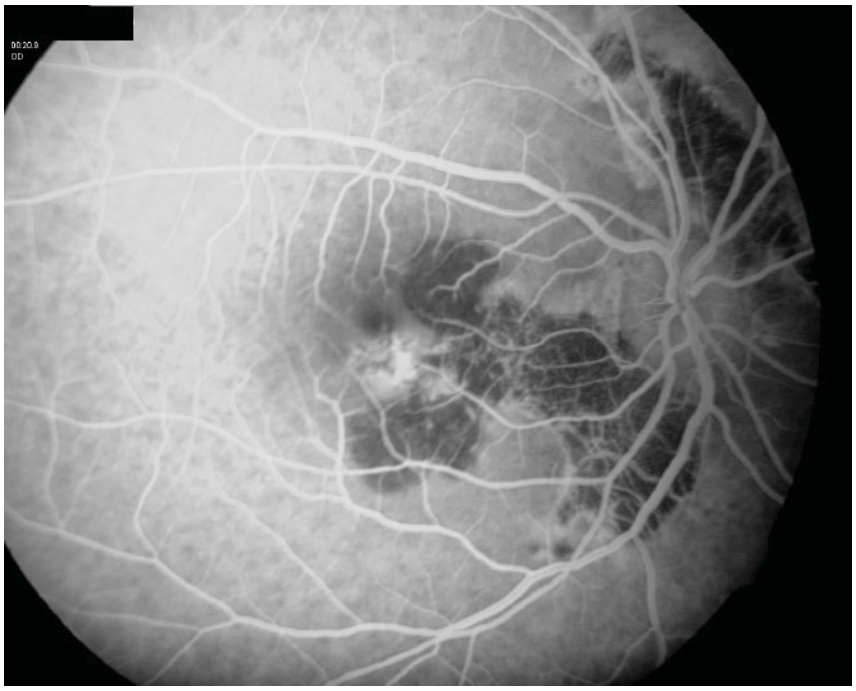


Fig. (1C). The fluorescein shows that the active lesions seen in Fig. (**1A**) appear nonfluorescent.

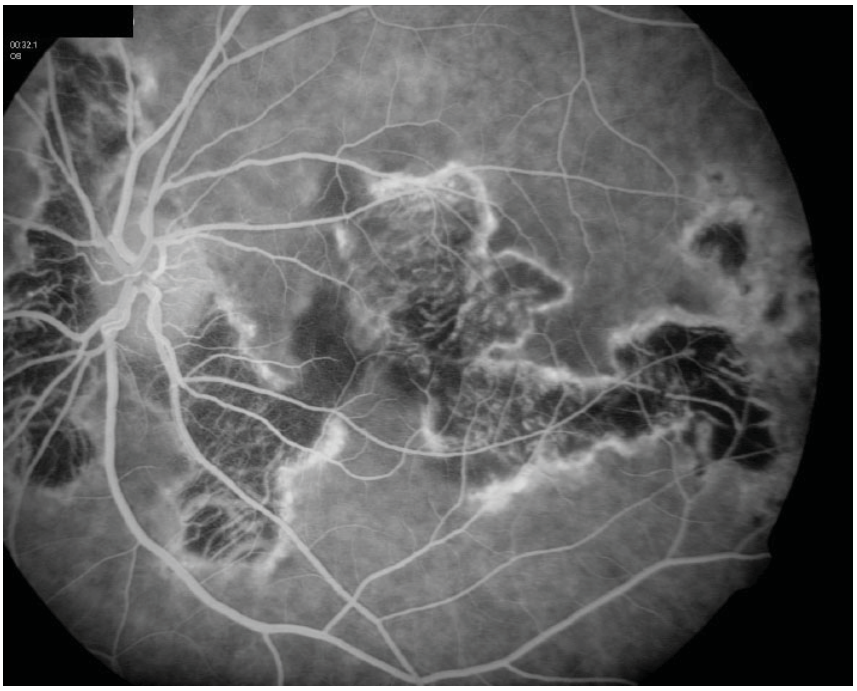


Fig. (1D). Left eye: Failure of the atrophic areas to fluoresce. As fluorescein diffuses from the neighboring choriocapillaris, the atrophic areas show progressive staining from the margin centrally.

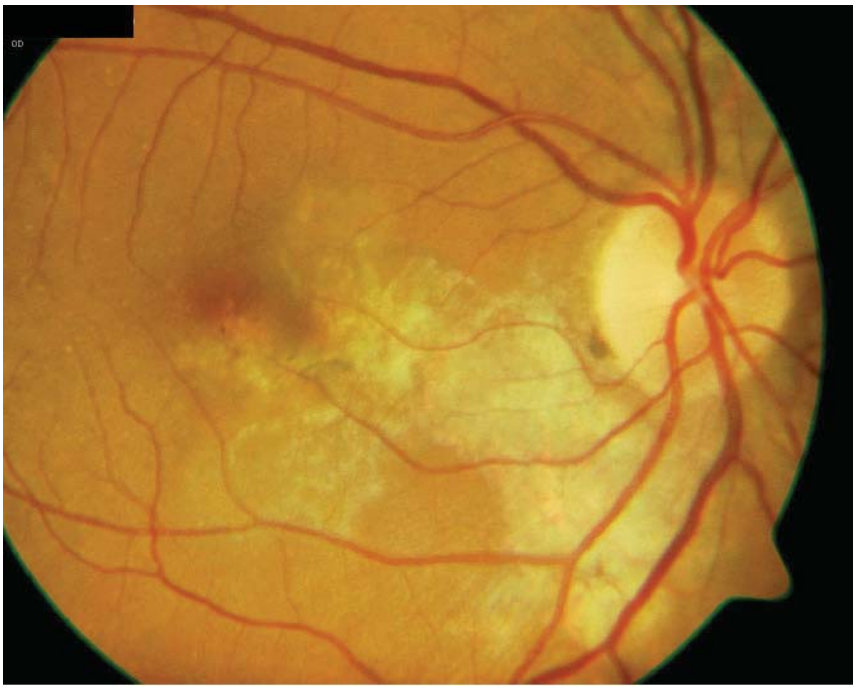


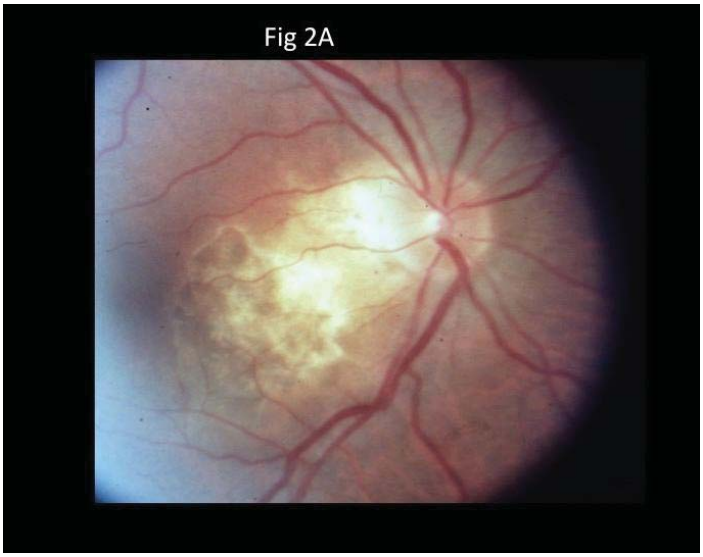
Fig. (1E). Right eye shows that the acute lesions, after a few weeks, have been replaced by mottling and depigmentation of the RPE.

In most cases, the macular area is involved [8], but the disease usually spares the fovea, thus leaving visual acuity unaffected [1]. Choroidal neovascularization may develop at the edge of an old area of chorioretinal atrophy in 13-35% of the patients [2] (Fig. **2A** and **2B**).

The diagnosis of SC is made mainly on clinical findings. Fluorescein angiography: During the early phase, the acute gray-white lesions appear non-fluorescent, and later, they show evidence of staining that usually begins at the margin of the lesion and spreads centrally [1]. In the late angiogram, hyperfluorescence could also be seen in the active areas. The atrophic lesions show progressive staining from the margin centrally [1, 7] (Fig. **1C** and **1D**). ICG angiography shows dark areas which correspond to the visible chorioretinal lesions, and reduced hypofluorescent areas in the late phase as compared to the early phase [2].

Fundus autofluorescence is said to be useful to identify RPE damage in acute episodes of SC. The lesion was followed by hyperautofluorescence 2 to 5 days afterwards, confirming the boundaries of RPE damage [6].

According to the optical coherent tomography (OCT), reflectance of the photoreceptor layer showed an increase in the areas of hyperautofluorescence in the early stage. During the scarring phase of the disease, autofluorescence decreased progressively [6].



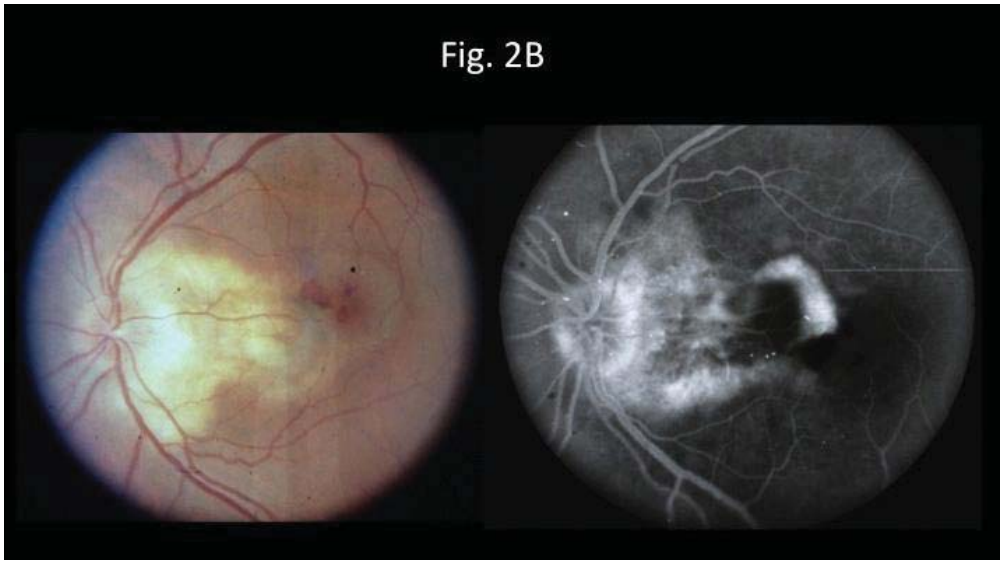


Fig. (2). A (right eye) and 2B (left eye). This 41-year-old woman had a history of long-lasting poor visual acuity in her right eye, and recent loss of central vision in her left eye. Both eyes show characteristic late changes of Serpiginous choroiditis. The left eye shows a subfoveal choroidal neovascular membrane highlighted during the fluorescein angiogram.

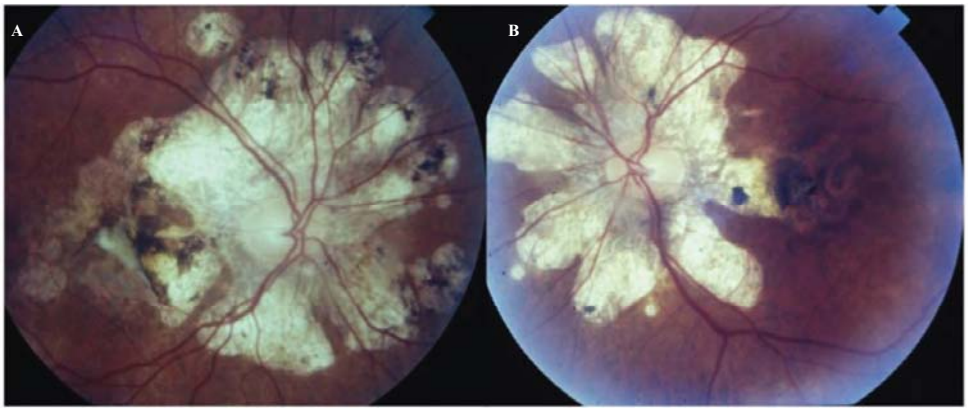


Fig. (3A and 3B). Fundus photograph showing inactive advanced serpiginous choroiditis in both eyes, with peripapillary chorioretinal atrophy extending into the macula beneath fovea, with scarring tissue left by a choroidal neovascular membrane.

DIFFERENTIAL DIAGNOSIS

Serpiginous choroiditis may simulate any of the diseases causing peripapillary chorioretinal scarring and neovascularization, and any posterior uveitis with a serpentine-like pattern [1]. The bilateral lesions of APMPPE may appear similar to those of SC [8]; this latter condition does not seem, however, to be progressive and the ultimate scars are more superficial than in SC.

According to limited histopathological studies, pathogenesis is still not clear, but the condition seems to be related to an organ-specific autoimmune inflammatory process [5].

MANAGEMENT

In general, the active lesions resolve spontaneously over the course of a few months [1, 2, 6]. Taking into consideration published material and recommendations from uveitis experts, it can be concluded that an early combined treatment of systemic corticosteroids and immunosuppressive agents can successfully preserve central vision [6, 8]. Conventional dosage of intravitreal ranibizumab or bevacizumab has been proven to provide good results for choroidal neovascularization secondary to SC [5, 9]. The best course of treatment for SC remains open to discussion due to the absence of prospective randomized trials [6, 10].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 15

Diffuse Subretinal Fibrosis Syndrome

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Diffuse subretinal fibrosis syndrome (also known as subretinal fibrosis and uveitis syndrome) is a rare entity that occurs primarily in young female patients. It is characterized by permanent visual loss due to multifocal choroiditis and progressive areas of subretinal fibrosis. In 1984, Palestine and associates described three young women with vitreous inflammation, multifocal progressive fibrotic subretinal lesions, cystoid macular edema, electroretinogram and electro-oculogram changes [1]. In 1996, Gass and colleagues described the clinical and histopathological findings in four eyes of three elderly patients with multifocal choroiditis and massive subretinal fibrosis [2].

ESSENTIALS OF DIAGNOSIS

Usually the presentation is bilateral, but asymmetrical. In most of the patients, the initial symptoms are unilateral visual loss, floaters, metamorphopsias and photopsia [3]. The clinical findings consist in numerous small yellow choroidal lesions in the posterior pole which may extend out to the mid peripheral retina. Within days or weeks, turbid subretinal fluid begins to accumulate around the lesions causing a retinal detachment [3, 4]. The choroidal lesions coalesce creating areas of subretinal fibrosis (Figs. **1** and **2**). Mild to moderate anterior chamber reaction and/or vitreous cells are typically present. In some cases there may be cystoid macular edema or choroidal neovascularization. The manifestations in the second eye can be observed in the following months. Recurrent episodes of inflammation can occur [4, 5].

The underlying cause of the disease remains unknown; however, histopathologic examination shows that immune mechanism may play a role in the pathogenesis of the disease, suggested by the presence of local antibodies against the retinal pigment epithelium [6]. Gass *et al.* [2] showed degeneration of the outer retina and retinal pigment epithelium, fibrous tissue proliferation between the retina and

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Bruch's membrane, and granulomatous inflammation.

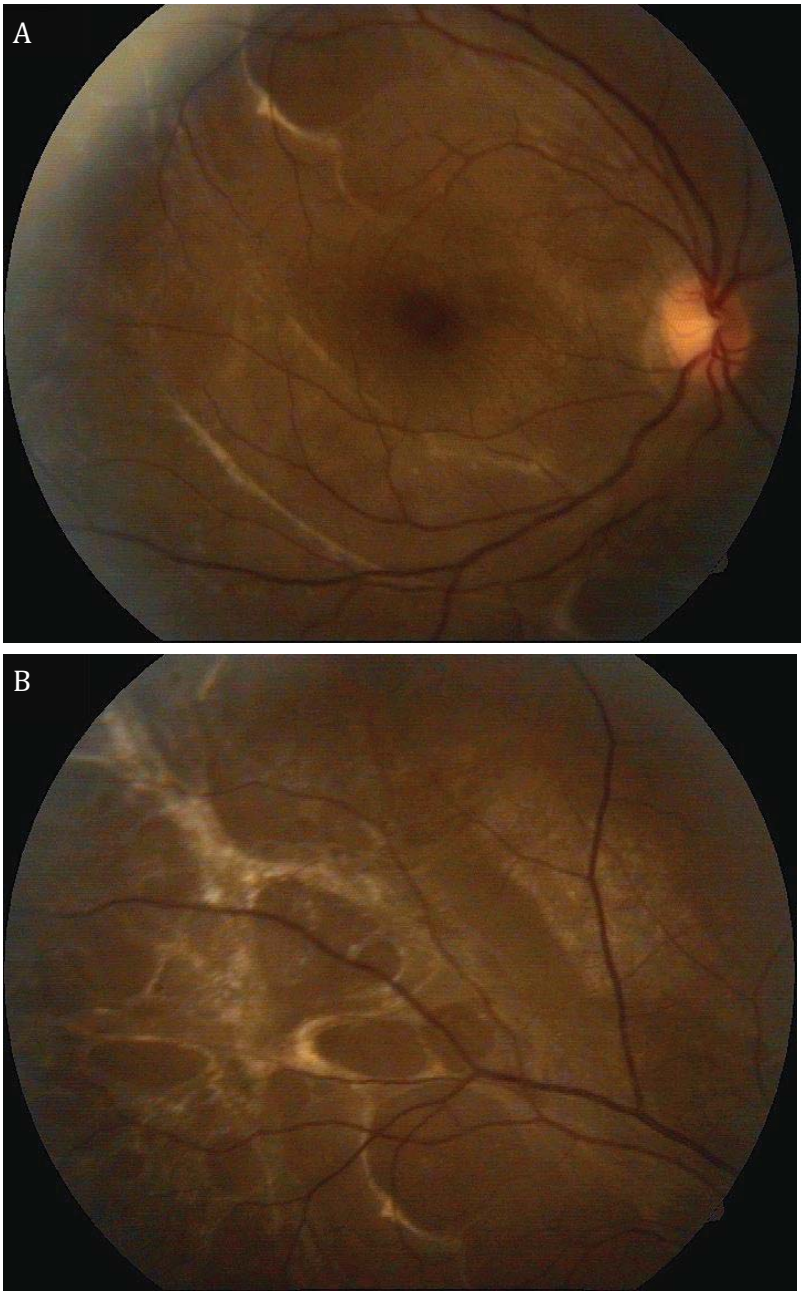

Fig. (1). Fundus photographs of the right eye of a 22-year-old female patient. Image **a** shows lines of subretinal fibrosis in the macular area. Image **b** shows the superior temporal quadrant with marked subretinal fibrotic tissue.

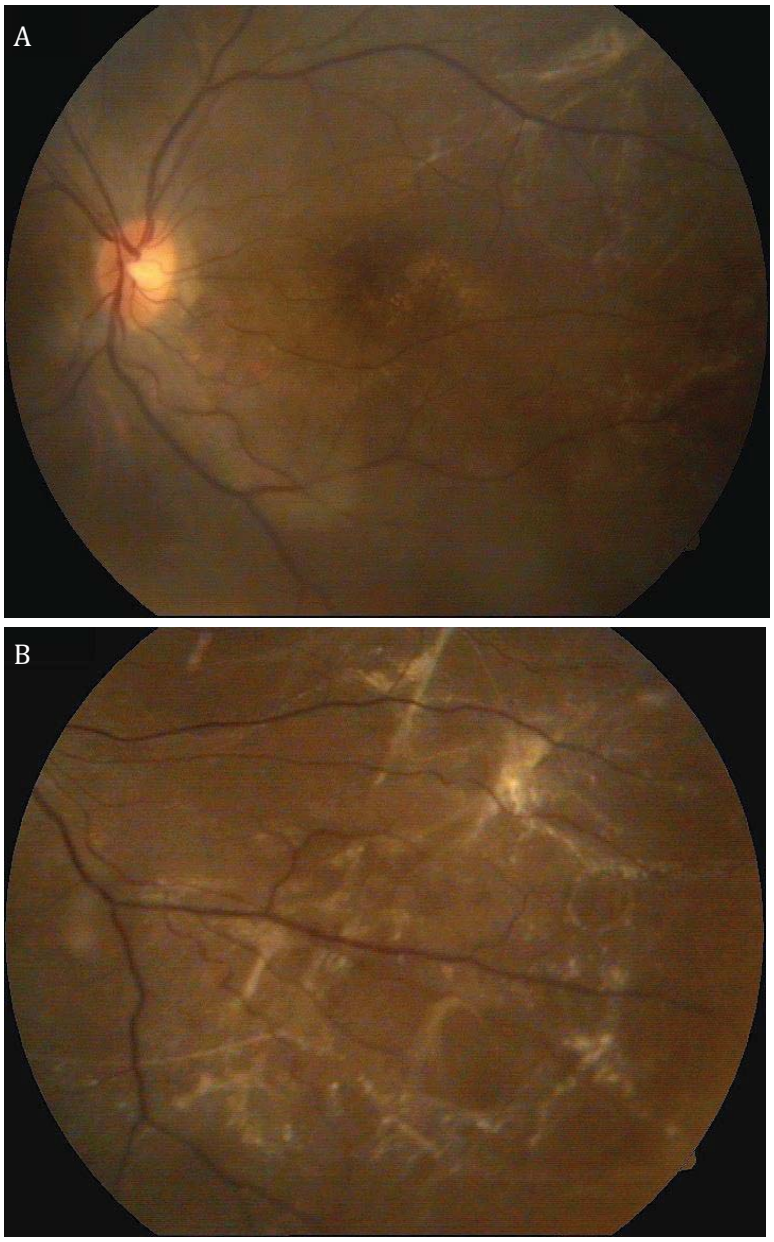

Fig. (2). Fundus photographs of the left eye of a 22-year-old female patient (same patient as Fig. (**1**)). Images **a** and **b** show marked subretinal fibrotic tissue in the macular area and in the temporal mid-periphery, respectively.

During the active phase, fluorescein angiography shows early hypofluorescence followed by late leakage in choroidal lesions. Leakage could be due to inflammation or the presence of choroidal neovascularization. The areas of subretinal fibrosis show late staining [3] (Fig. **3**).

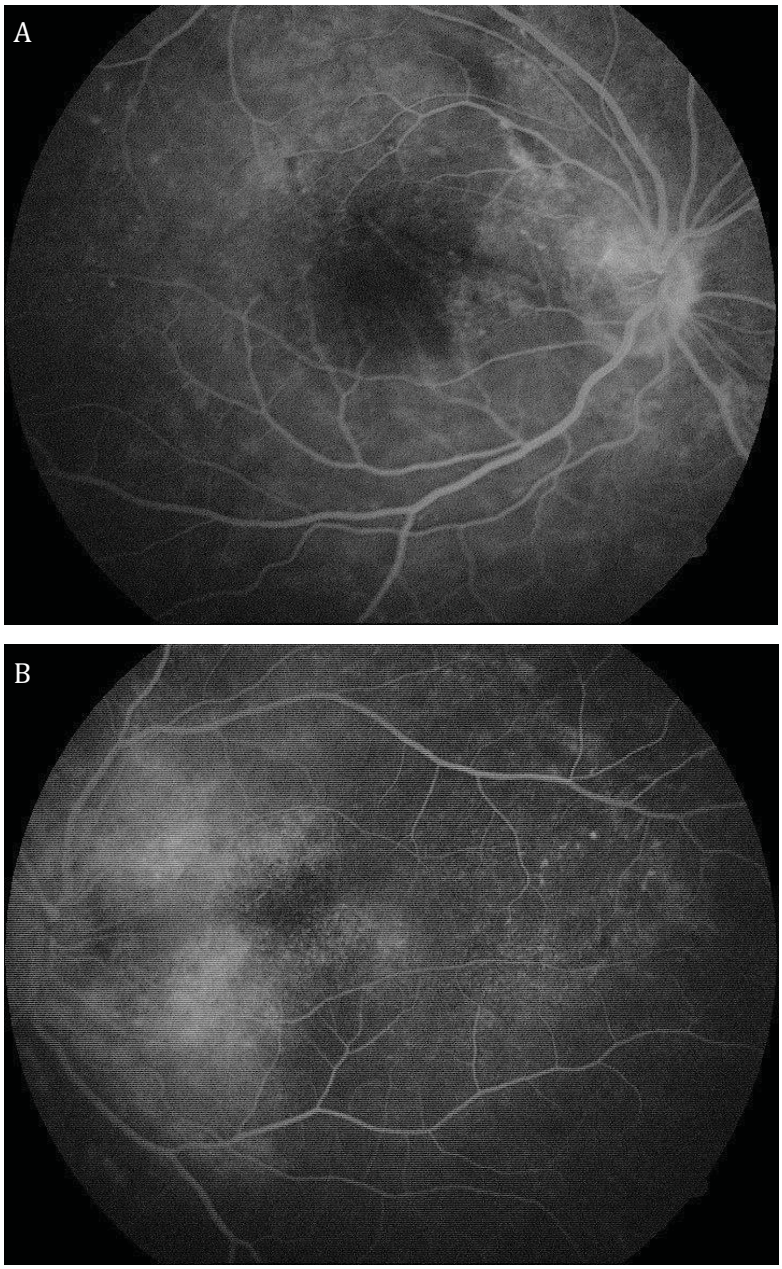

Fig. (3). Late phase fluorescein angiogram of the right (**a**) and left (**b**) eye of a 22-year-old female patient (same patient as Figs. (**1**) and (**2**)) showing hyperfluorescence in the areas of subretinal fibrosis and dot-shaped lesions corresponding to atrophy.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes white dot syndromes, birdshot retino-choroidopathy, tuberculosis, toxoplasmosis, pathologic myopia, sympathetic

ophthalmia. There are other causes of subretinal fibrosis, such as ocular histoplasmosis syndrome, syphilis, serpiginous choroiditis, central serous chorioretinopathy and chronic rhegmatogenous retinal detachment.

MANAGEMENT

The use of systemic steroids has improved anatomic and visual outcomes [4]. In most severe cases, the treatment with immunosuppressive agents like cyclosporine and azathioprine has been described. The use of infliximab has been reported in one patient with diffuse subretinal fibrosis syndrome and spondyloarthropathy with good visual results [5]. Ranibizumab has also been used in a patient with macular edema with no anatomic or functional improvement [7].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 16

Diffuse Unilateral Subacute Neuroretinitis

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Diffuse Unilateral Subacute Neuroretinitis mainly affects children and young adults. Brazil, Latin America, southeastern and mid-western United States are endemic areas. There are also case reports from South Africa, China, and India [1-3].

In 1983, Gass defined the disease as a syndrome caused by a retinal nematode, though the etiological agent has remained uncertain. At least two agents have been described and classified according to the size of the larva and the endemic area of the disease: *Ancylostoma caninum*, the smaller agent, measuring about 400-1000 micrometers, most likely in the third larval stage is the most prevalent in Latin America and southern United States; *Baylisascaris procyonis*, between 1,500 and 2,000 micrometers, prevails in northern and midwestern United States and usually infests the raccoon and opossum. Other hypothesized causes of the disease have been *Toxocara canis* and a trematode, *Alaria mesocercaria*, coming from contaminated frog meat [4].

ESSENTIALS OF DIAGNOSIS

In its initial stage, the disease is characterized by vision loss, usually unilateral, vitritis, papillitis, retinal vasculitis, and grayish-white evanescent lesions in the outer retina (Fig. **1**). In the late stage, it shows progression of vision loss, optic atrophy, narrowing vascular and diffuse changes in the retinal pigment epithelium (Fig. **2**), which may occur months or years after disease onset. The patho-physiology of the syndrome is related to two effects: a local toxic effect in the outer retina caused by products released by the worm, and also by a diffuse toxic reaction affecting both the outer and inner retina. This first effect would be related to the gray-white lesions and the second, to the loss of visual function and

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alterations diagnosed on electroretinography, loss of retinal ganglion cells, and vascular narrowing.

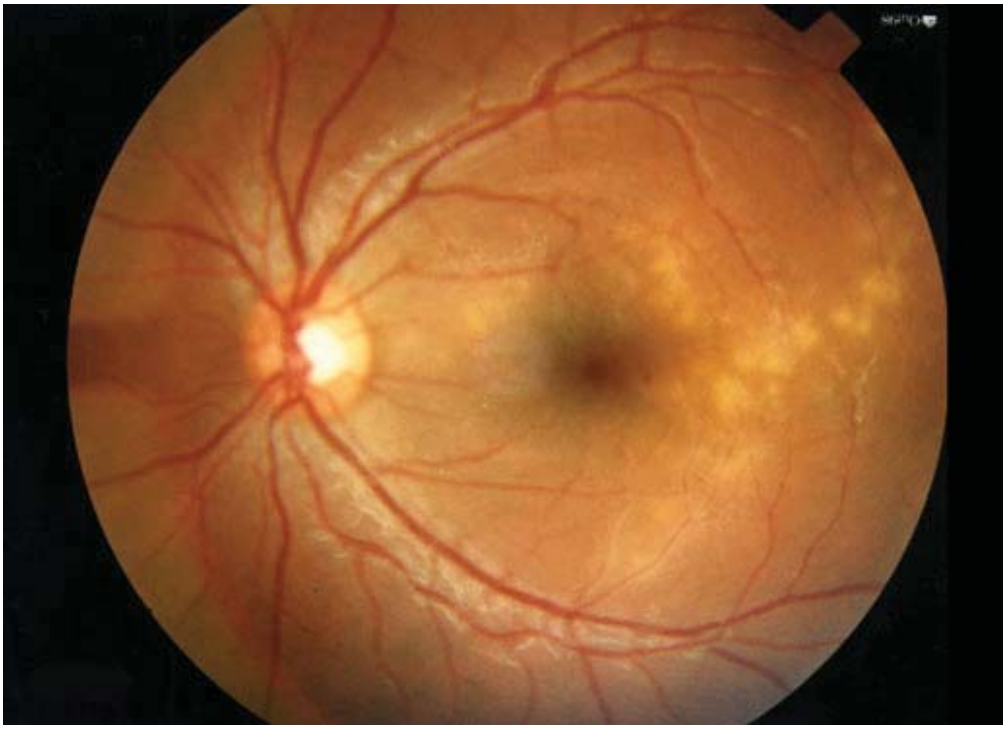

Fig. (1). Example of a case in the acute phase with active retinal lesions.

With the evolution of the disease, involvement of the retinal pigment epithelium as well as vascular narrowing increases. Some cases may progress to choroidal neovascularization and subretinal fibrosis [1 - 5].

The diagnosis is made by identification of a mobile larva in the retina, a pathognomonic finding in fundus examination. The nematode usually appears in the shape of an "S", due to its motion, where it moves by coiling and uncoiling. The most likely place to find it is close to the retinal areas with the greatest amount of white lesions. The agent is usually identified in less than 50% of cases because of the nematode's characteristic retinal location, which may be confused with reflexes of the retina itself, and the difficulty in examining some patients, especially children. Increased vitreous cellularity is found in all patients, but the amount is associated with the stage of disease. Relative afferent pupillary defect (Marcus Gunn pupil) is also found in virtually all cases. Some patients may have ciliary injection, cellular reaction in the anterior chamber, flare, keratic precipitates, and hypopyon. Atypical presentations have been described, with

serous retinal detachment or areas of hemorrhage and retinal exudation [6, 7]. In fluorescein angiography, the early stages of the disease usually show hyperfluorescence by contrast extravasation from the capillaries in the optic nerve and early hypofluorescence in gray-white lesions, which, in the later stages of the examination, acquire a slight coloration. There may be a large leak of perivenous contrast in the early stages of the disease, as well as some evidence of change in the retinal pigment epithelium. With the evolution of the disease and the progressive loss of pigmentation in the retinal pigment epithelium, the angiographic manifestations appear as increased choroidal fluorescence by transmission. The electroretinogram shows changes in almost all patients, with the B-wave being more affected than the A-wave, usually with subnormal findings or even rarely an extinct electroretinogram. Optical coherence tomography (OCT) identifies the diffuse atrophy of the nerve fiber layer and focal edema in the area affected by the parasite. From retinal fundus images, it is postulated that the causative agent of the disease is located in the subretinal space, but through OCT, the worm has been described in additional topographies such as the intraretinal or even premacular space [2, 5 - 10].

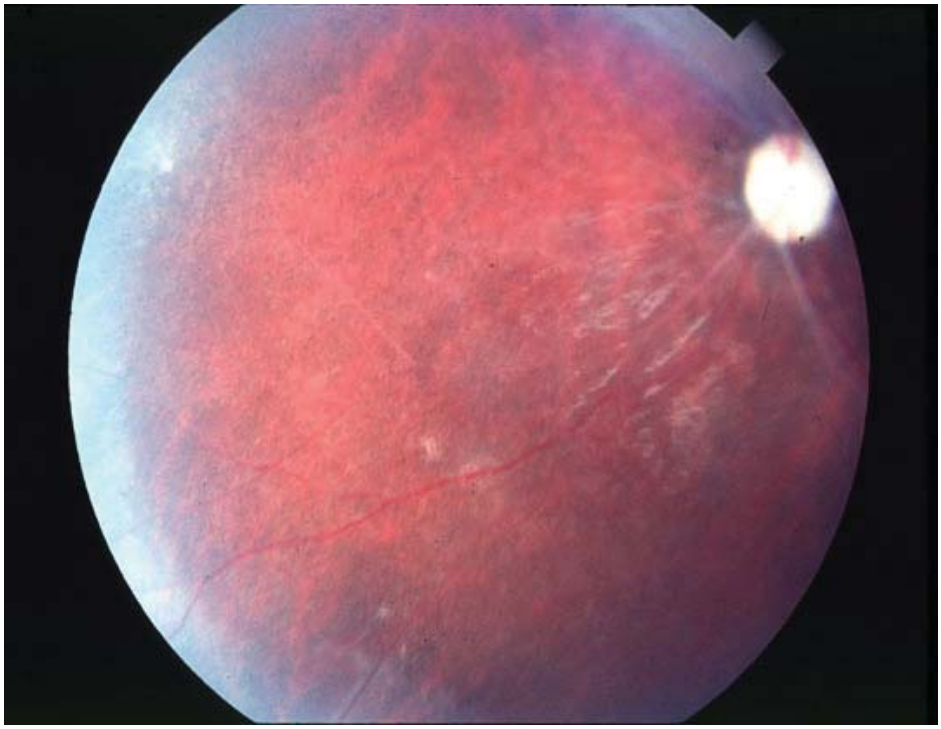

Fig. (2). Example of a case in the chronic phase, with vascular narrowing, degeneration of the RPE and optic nerve pallor.

DIFFERENTIAL DIAGNOSIS

Initial Stage: Placoid epitheliopathy, white dot syndrome, multifocal choroiditis due to toxoplasmosis, serpiginous choroiditis, toxoplasmosis in form of retinitis punctata, Behcet's disease, pseudo-presumed ocular histoplasmosis syndrome, sarcoidosis, and retinal abscess, among others. Late Stage: Unilateral retinitis pigmentosa, traumatic chorioretinopathy, and presumed ocular histoplasmosis syndrome.

MANAGEMENT

Treatment consists of correct identification of the retinal location of the worm and its destruction by laser photocoagulation. In cases involving small worms, the treatment tends to be quick, but in those cases where the worm is large and thus moves faster, especially in contact with the laser, technical difficulty increases. It is important to document the topographical position before the treatment to ensure that the worm is completely destroyed. In cases where the clinical features strongly suggest the disease but there is a difficulty in finding the mobile larva, or in order to assist in the laser treatment, systemic treatment with oral albendazole at a dose of 400 mg daily for 30 days can be used. There are reports that the use of thiabendazole and ivermectin cannot eliminate the larvae, where it is necessary to complement treatment with laser photocoagulation [3, 9, 11 - 14].

Prognosis: The prognosis depends on the stage at which treatment is performed. Photocoagulation gives good results if carried out in the early stage of the disease. In the late stage, with significant impairment in visual acuity, treatment may halt the progression of the disease but does not restore vision in most cases. OCT helps in evaluating the efficacy of treatment by assessing the loss of the nerve fiber layer.

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 17

Vogt Koyanagi Harada Disease

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ESSENTIALS OF DIAGNOSIS

Vogt Koyanagi Harada Disease (VKH) is an acute bilateral, granulomatous panuveitis that presents typically with an exudative retinal detachment and variable association with extraocular manifestations. It is common in pigmented populations, and certain ethnic groups have a genetic predisposition to develop it. Most authors have reported that it more frequently affects female patients (ratio 2-3:1), age range 4-73 years. Typically three different stages have been described: prodromal, acute uveitic, and convalescent [1].

The prodromal stage is characterized by symptoms similar to those of aseptic meningitis, like neck stiffness and headache; in addition, sensitivity of the hair and skin can be observed. Less frequently, focal neurologic signs have been reported. Deafness and tinnitus may also be present.

In the acute uveitic stage the patient may refer bilateral redness, photophobia, and blurred vision; in some patients a delay of 2 to 4 days between the first and the second eye can be found. In the early stage, the characteristic lesion is a diffuse choroiditis that may be observed clinically as subretinal fluid or serous retinal detachment (Fig. **1**). Other clinical findings are anterior uveitis, optic disc hyperemia, and mild vitreous haze.

The convalescent stage is characterized by depigmentation; alopecia, poliosis and vitiligo may also be observed (Fig. **6**). Vitiligo can be found in the head, eyelids, and trunk, particularly on the sacrum (Fig. **5**). A sunset-glow fundus appearance is frequently observed (Fig. **2**). Multiple depigmented, small, round areas of chorioretinal atrophy can be found in the mid-periphery (Fig. **3**).

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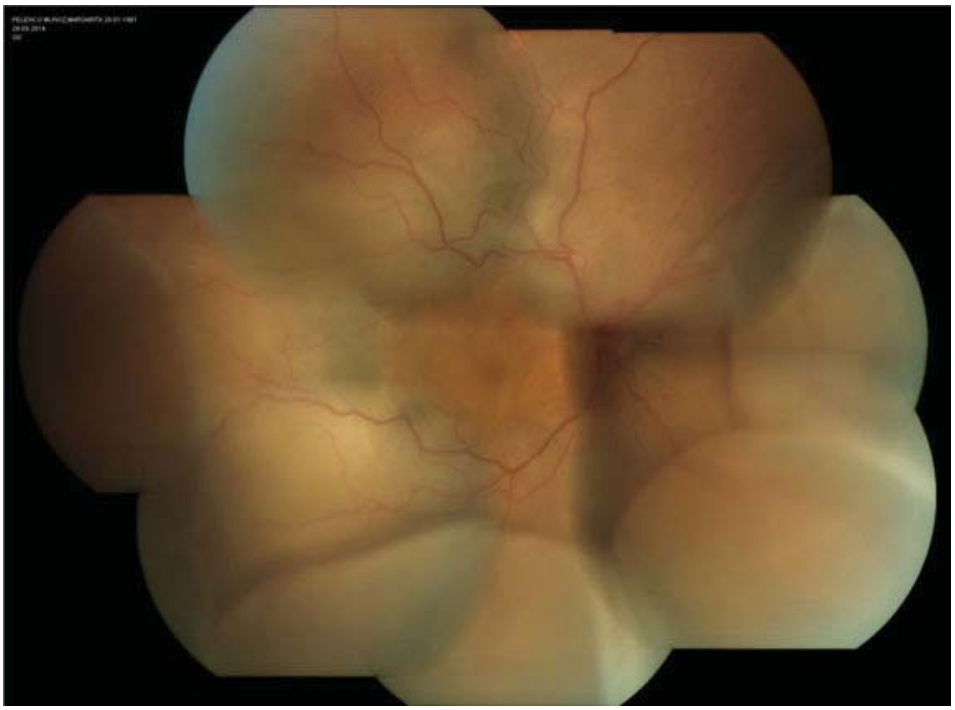

Fig. (1). Bullous serous retinal detachment. Acute uveitic stage.

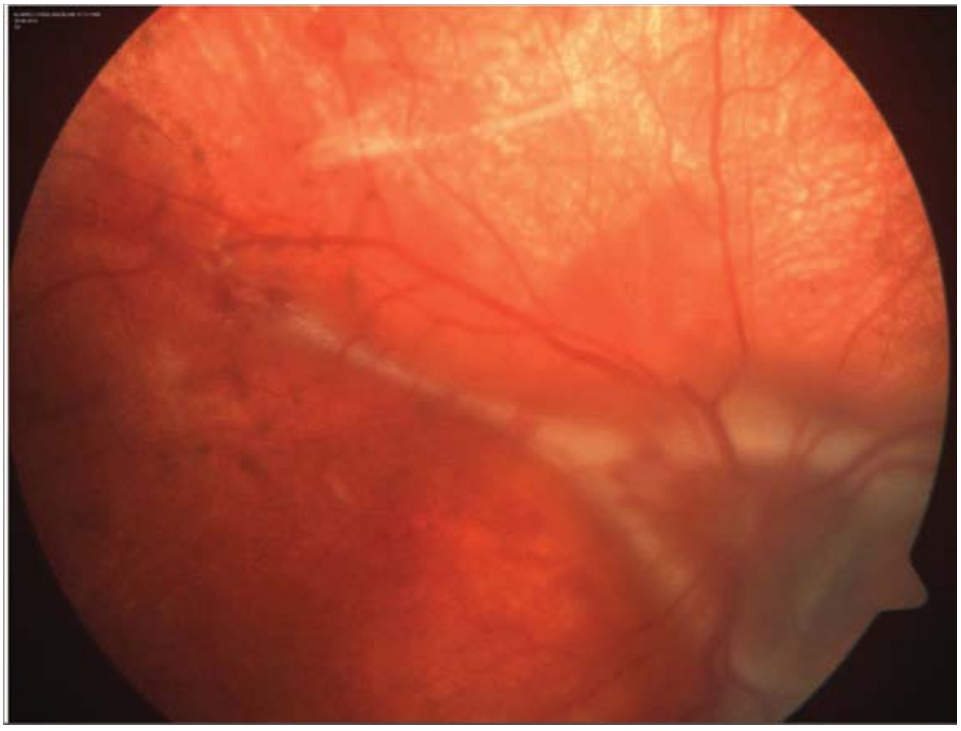

Fig. (2). "Sunset glow fundus", subretinal and peri-papillary fibrosis. Convalescent stage.

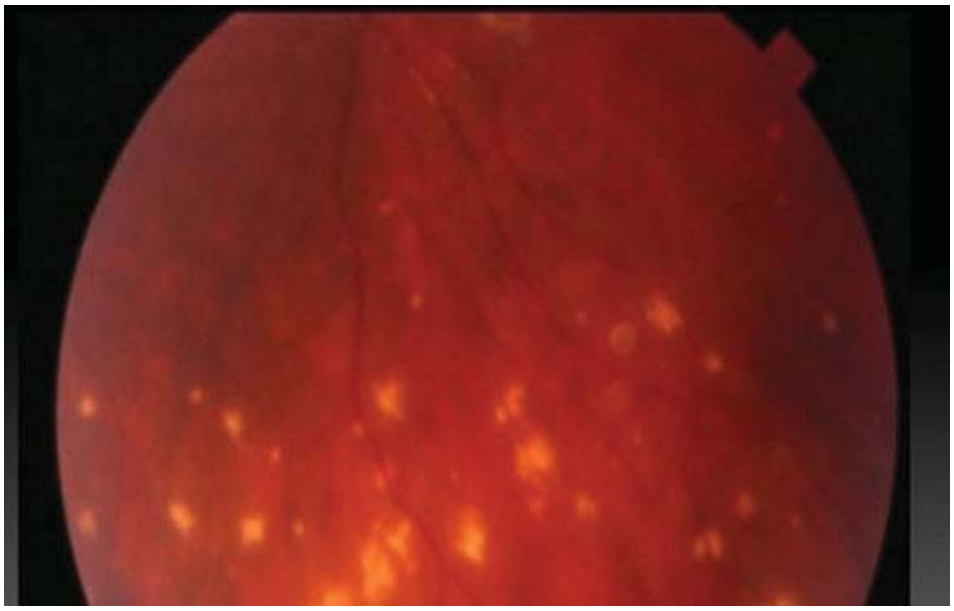

Fig. (3). Nummular lesions. Convalescent stage.

Some patients, particularly the undertreated ones, may go into the chronic–recurrent phase (Fig. **4**), which is characterized by a smoldering panuveitis with a recurrent anterior granulomatous uveitis and focal choroiditis.

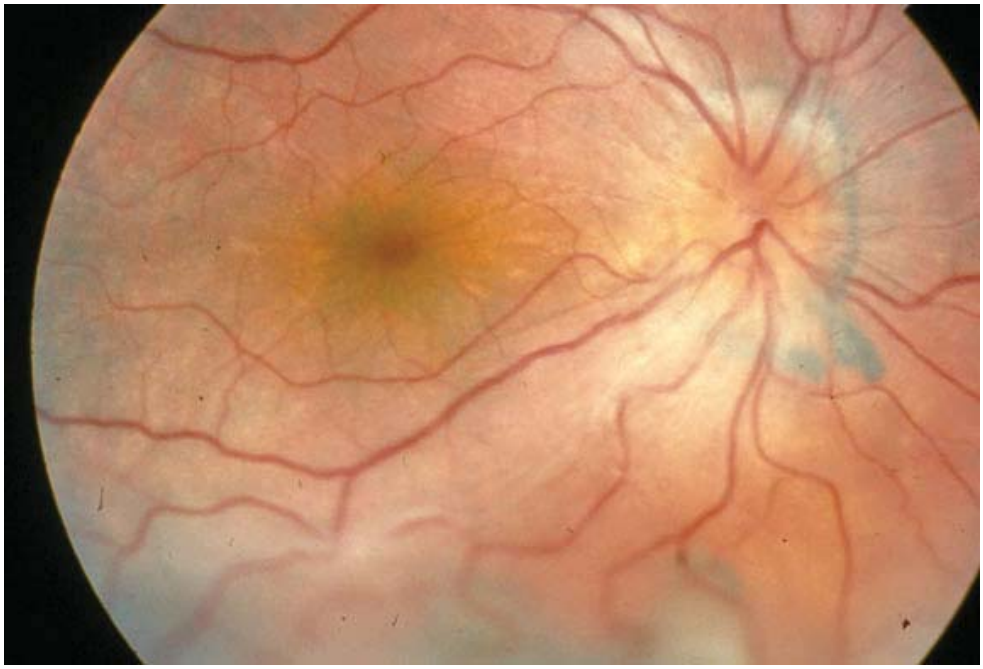

Fig. (4). Pigment migration and serous retinal detachment. Chronic stage.

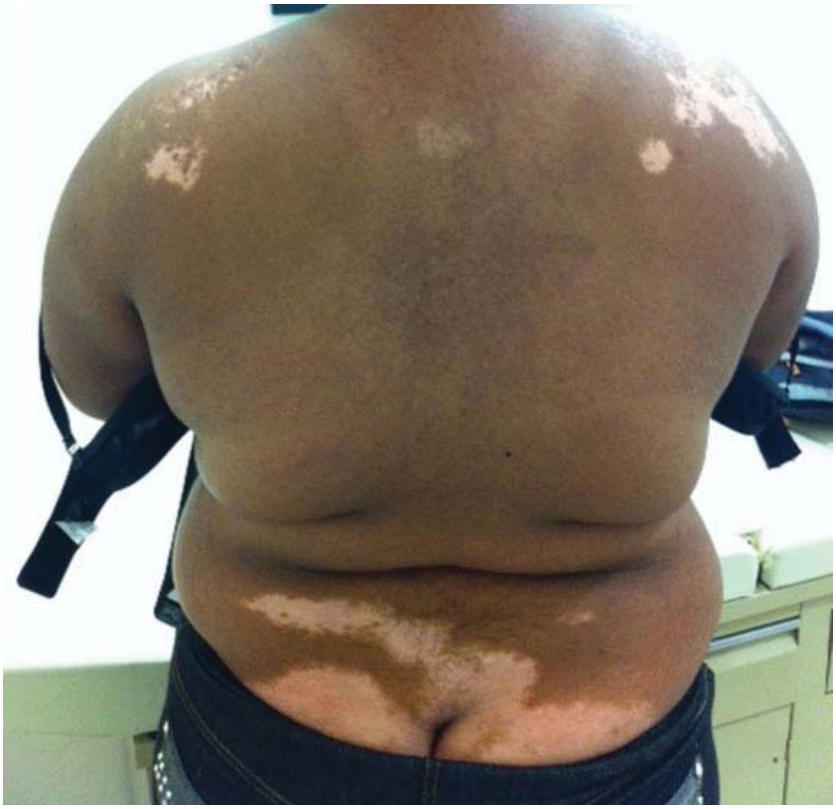

Fig. (5). Vitiligo. Convalescent stage.

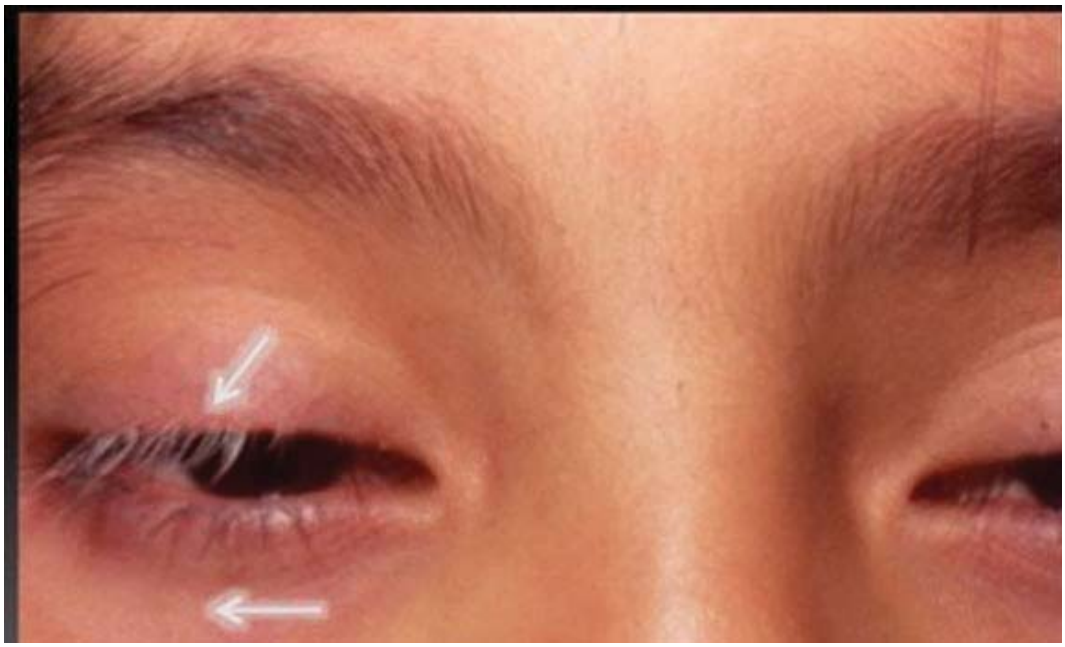

Fig. (6). Poliosis and vitiligo. Convalescent stage.

DIFFERENTIAL DIAGNOSIS

Sympathetic Ophthalmia: There is a history of ocular trauma.

Uveal Effusion Syndrome: Lacks intraocular inflammation and may involve both eyes although not simultaneously.

Posterior Scleritis: This is often bilateral. It frequently affects women. Pain is a frequent complaint. Exudative macular detachment and choroidal folds can be seen. Ultrasound can help in the differential.

Sarcoidosis, serous retinal detachment is unusual. Classic retinal vasculitis is not seen in VKH.

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE): There is a viral prodrome followed by a bilateral sudden loss of vision. Multiple white-yellow flat or placoid lesions are located at the RPE level; no bullous serous retinal detachments or anterior segment inflammation is seen.

Primary intraocular B-cell lymphoma presents as a chronic uveitis; it may be associated with nervous system manifestations. In the posterior pole, raised, lobulated, multifocal yellowish, subretinal lesions can be found. Patients tend to be older than in VKH [2].

MANAGEMENT

The mainstay of therapy in acute VKH is intravenous methylprednisolone (1 g/day for 3 days), followed by oral administration of high-dose corticosteroids (1 mg/kg/day) with gradual tapering according to clinical response. Some authors suggest 1-2 doses of periocular depot corticosteroids in the first weeks. It has been reported that high–dose oral corticosteroids (1-2 mg/day) may be as effective as intravenous therapy. Treatment is usually required for at least 6-9 months [3].

In chronic-recurrent cases further treatment with immunosuppressive agents may be required [3]. Nowadays there is a tendency to start immunosuppressive therapy early in the course of the disease to avoid recurrences. Recently, the use of anti-TNF therapy in refractory cases of VKH or in case of intolerance to conventional therapy has been suggested [4].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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[http://dx.doi.org/10.3109/09273948.2013.775312] [PMID: 23617262]

CHAPTER 18

Pars Planitis

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Pars planitis is a type of intermediate uveitis of unknown etiology that tends to affect children and young adults. The term "intermediate uveitis" indicates that the main site of inflammation resides in the pars plana, peripheral retina and the vitreous base [1, 2].

ESSENTIALS OF DIAGNOSIS

Pars planitis mainly affects patients in the first and second decades of life. It may be completely asymptomatic, since external signs of inflammation are rare, and manifest late in the course of the disease when there is strabismus or lack of a red reflex.

The main manifestations of this disease occur in the vitreous, where inflammatory cells are observed. These cells tend to coalesce and form white roundish opacities that float in the anterior vitreous, called "snowballs" because of their characteristic appearance (Figs. **1** and **2**). Snowballs may also merge into whitish plaques that lie over the retina called "snow banks", which are more frequently (but not always) found inferiorly [3]. Snow banks may eventually undergo fibrotic transformation, originating a cyclitic membrane, which is usually pretty adherent to the inferior peripheral retina, pars plana and posterior capsule.

Pars planitis may also affect the anterior segment. Cells, flare and posterior synechiae may be present. Band keratopathy and autoimmune epitheliopathy may also be observed in more advanced and chronic cases [1 - 5].

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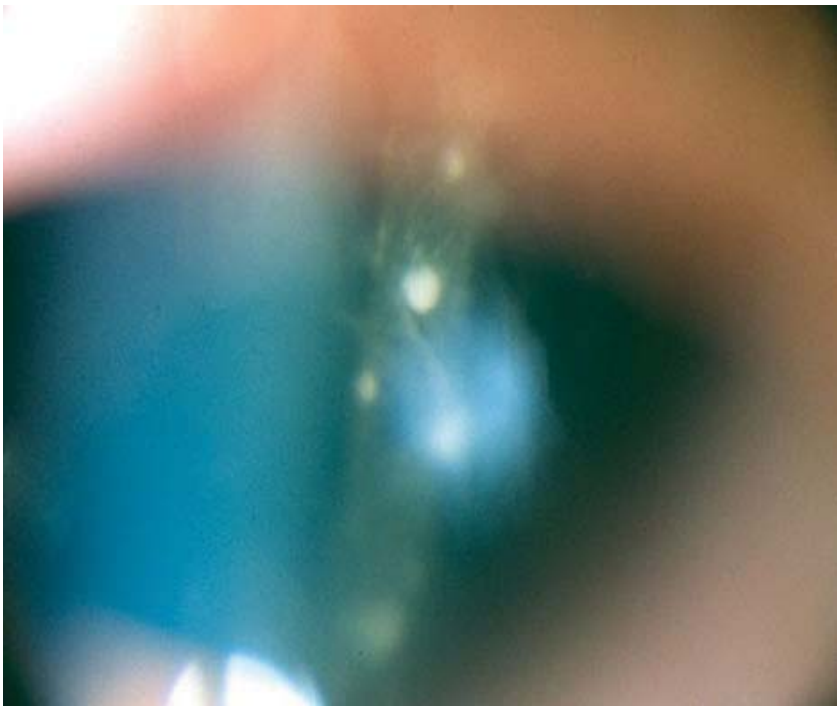

Fig. (1). Snowballs: floating, globular and yellow-white conglomerates of inflammatory cells in the anterior vitreous.

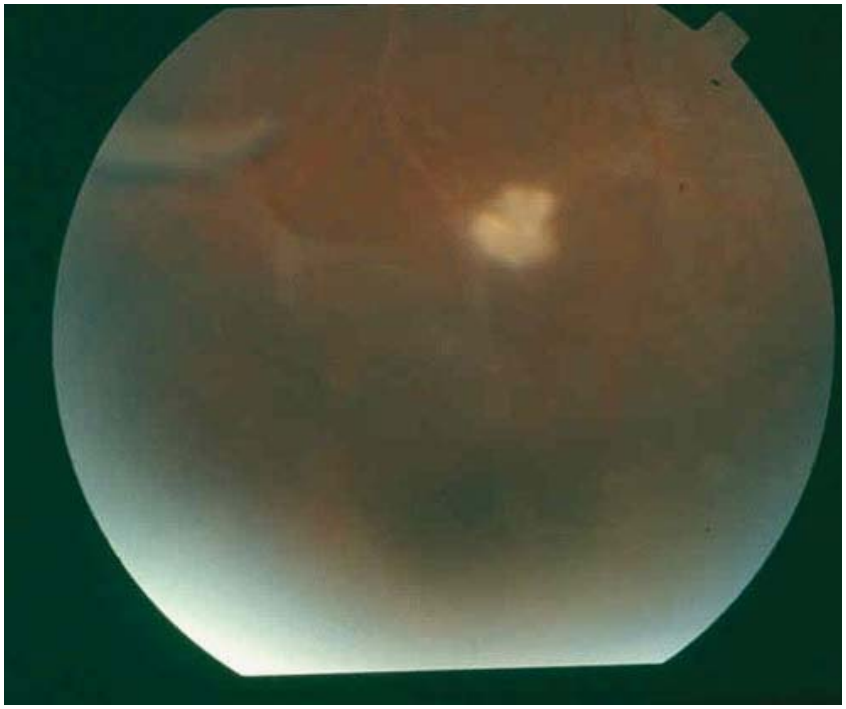

Fig. (2). Snowball located in the inferior vitreous cavity.

Fluorescein angiography is a very useful diagnostic tool for this disease. Perivascular hyperfluorescence in a "fern" pattern is very characteristic of pars planitis (Fig. **3**). Optic disc hyperfluorescence and cystoid macular edema may also be present [1, 6]. Cystoid macular edema, observed in 44% to 63% of eyes, is the main cause of visual loss in these patients, and can readily be diagnosed using fluorescein angiography (Fig. **4**) and optical coherence tomography (Fig. **4**) [1, 3, 6].

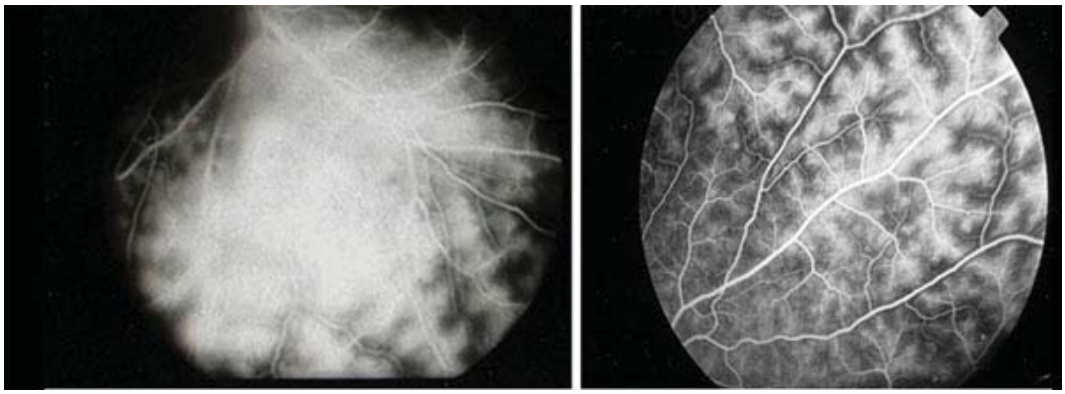

Fig. (3). Retinal fluorescein angiography showing retinal vasculitis in a characteristic "fern" pattern.

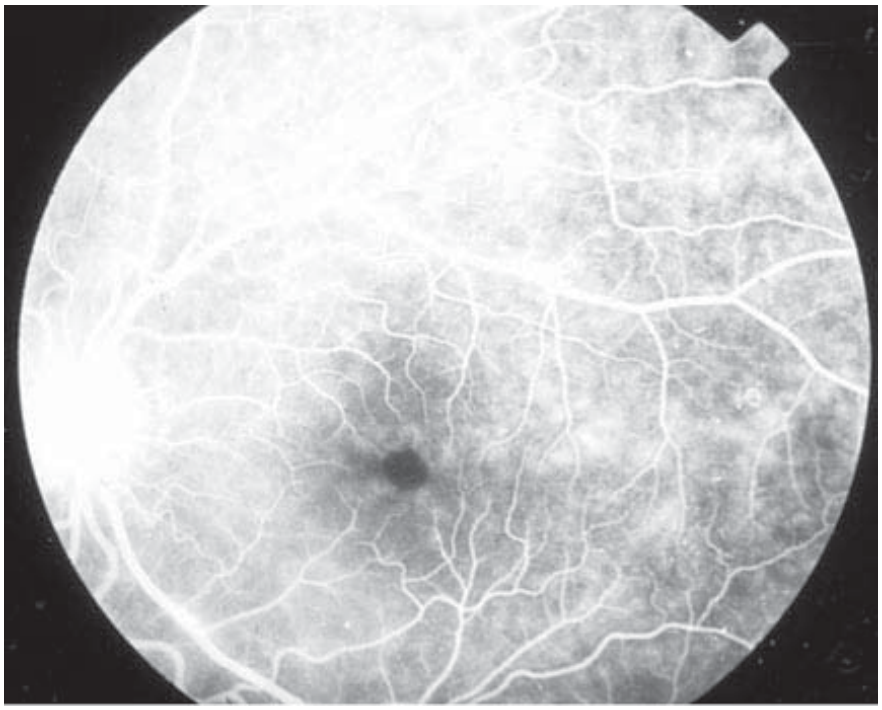

Fig. (4). Retinal fluorescein angiography showing perifoveal hyperfluorescence compatible with cystoid macular edema, hyperfluorescence of the optic disc and perivascular hyperfluorescence due to vasculitis.

DIFFERENTIAL DIAGNOSIS

In our population, pars planitis is a relatively common of uveitis in children, and therefore a case with a very typical picture is diagnosed basically on clinical grounds. The diagnostic workup for a young patient with intermediate uveitis with a less typical clinical picture should include tests to rule out infectious diseases such as tuberculosis, syphilis, toxocariasis, toxoplasmosis, Lyme disease or cat scratch disease. Other non-infectious diseases such as primary intraocular lymphoma, sarcoidosis or multiple sclerosis should also be included in the differential, although they rarely affect patients at such a young age [7].

MANAGEMENT

Treatment should be initiated in patients with active disease, especially if there is cystoid macular edema, if visual acuity is 20/40 or worse, or if visual acuity decreases two lines from a previous measurement. The first line of therapy consists of periocular corticosteroid injection (betamethasone or triamcinolone). Injection is repeated every 4-8 weeks according to treatment response. In unresponsive eyes, systemic corticosteroids may be added. In our experience, deflazacort is preferable to prednisone because it causes less undesirable side effects. When corticosteroid therapy fails to control inflammation adequately, immunosuppressive drugs such as methotrexate, cyclosporine, azathioprine, mycophenolate mofetil or cyclophosphamide may be initiated, with adequate attention paid to potential side effects [8 - 11]. If treatment is initiated in a timely fashion, a good proportion of patients preserve adequate visual function.

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 19

Sarcoidosis

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Sarcoidosis is a multisystem disease of unknown etiology, characterized by a chronic inflammatory process leading to formation of noncaseating granulomas [1]. Ocular sarcoidosis can precede systemic involvement in 9% of the cases [2], and 10-90% of patients will have ocular compromise during the course of the disease [3]. The most common ophthalmological manifestation is uveitis [4].

ESSENTIALS OF DIAGNOSIS

Clinical features: A wide range of pathology including anterior, intermediate, posterior uveitis or panuveitis can be seen. Posterior uveitis occurs in 20-25% of patients. The clinical presentation is usually bilateral and insidious, with mild to severe inflammation. Iridocyclitis with mutton-fat keratic precipitates, iris nodules and posterior or peripheral synechiae are commonly described. Snowball-like opacities described as "string of pearls" are observed in inferior periphery. Optic nerve edema or infiltration have been reported in few cases. Retinal periphlebitis is the hallmark of sarcoidosis, producing the so-called "candle-wax drippings" [5]. This appearance is secondary to dense aggregates of mononuclear cells (Fig. **1**). Periphlebitis is usually nonocclusive. However, cases of severe vasculitis with vascular occlusions and retinal ischemia have been reported. These findings may lead to peripheral retinal neovascularization, vitreous hemorrhage and rarely, retinal detachment [6]. Punch-out peripheral chorioretinal lesions can also be seen (Fig. **2**). Cystoid macular edema may occur in the setting of chronic inflammatory changes. Choroidal neovascular membranes (CNV), posterior scleritis and sarcoid granulomas of the choroid are less frequent complications [7, 8].

Imaging: Retinal diagnostic imaging is helpful in challenging cases. Optical coherence tomography is useful to monitor macular changes, and fluorescein angiography will detect early complications. Segmental staining of the venous wall is a classic finding (Fig. **3**).

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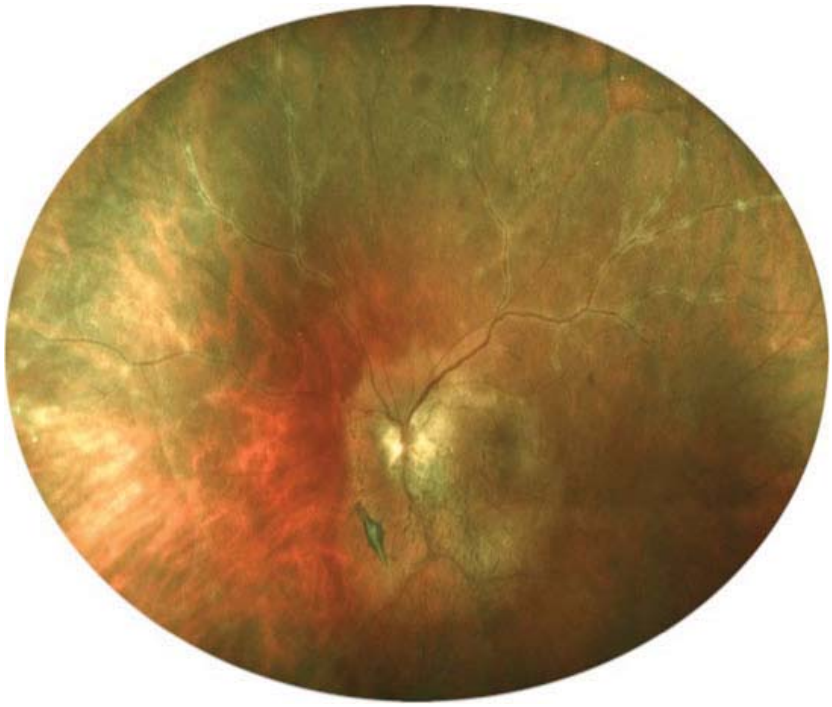

Fig. (1). Disc edema and periphlebitis on presentation.

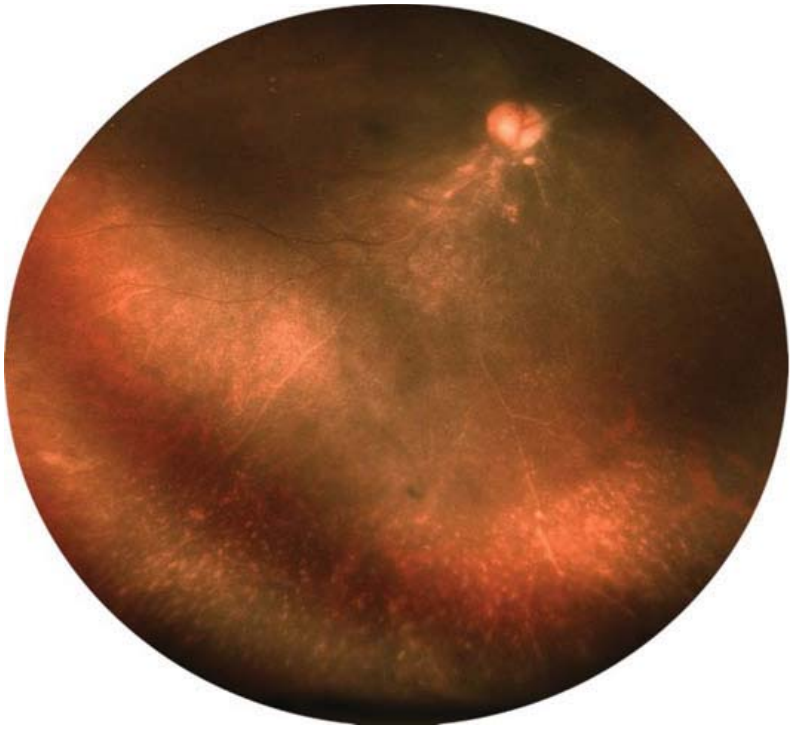

Fig. (2). Peripheral hypopigmented chorioretinal lesions in a case of sarcoid.

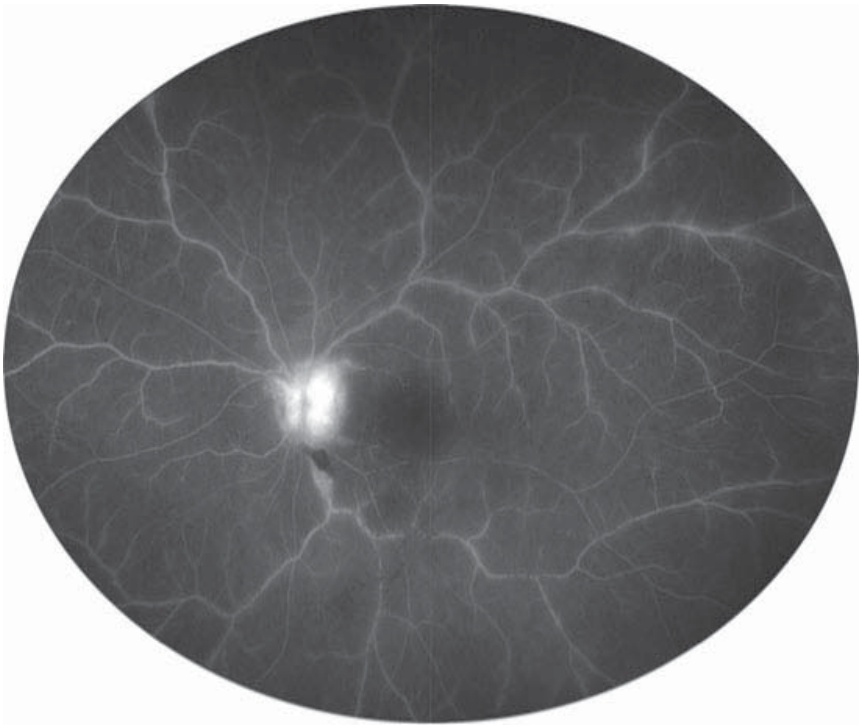

Fig. (3). Fluorescein angiogram showing segmental staining of venous wall and hyperfluorescence of the disc.

Other tests: **Angiotensin converting enzyme** levels can be elevated in 60-90% of patients with sarcoidosis, but a normal result doesn't exclude the diagnosis. **Lysozyme** levels are likely to increase in patients with active disease. **Chest radiograph** may show hilar adenopathy. If significant clinical suspicion with negative test results, a CT scan of the chest and/or gallium scan can be requested; however, definite diagnosis requires a biopsy showing noncaseating granulomas.

DIFFERENTIAL DIAGNOSIS (*POSTERIOR UVEITIS)*

1. Toxoplasmosis
2. Toxocariasis
3. Vogt-Koyanagi-Harada syndrome
4. Intraocular lymphoma
5. Behcet's disease
6. Whipple's disease
7. Birdshot retinochoroidopathy
8. HIV paraviral syndrome
9. Eales disease
10. Multiple sclerosis

MANAGEMENT

Ocular involvement in sarcoid warrants aggressive therapy. The mainstay of treatment are steroids [9]. Anterior uveitis is treated with topical prednisolone and cycloplegic agents. These medications are tapered within few weeks. Non-resolving inflammation, intermediate or posterior uveitis require periocular or systemic steroids. Treatment should be maintained for few weeks and then slowly tapered over the course of 6-12 months. Refractory cases may respond to immunosuppressive therapy. Methotrexate is the most commonly used agent [10]. Azathioprine, Mycophenolate Mofetil or cyclosporine have also been described successfully. Laser pan retinal photocoagulation is the standard approach in cases of proliferative retinopathy. Non-clearing vitreous hemorrhage is treated with standard pars plana vitrectomy [11].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 20

Retinoblastoma

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Retinoblastoma is the most frequent malignant intraocular tumor in childhood, and one of the most frequent malignant tumors overall at this age. Around 8000 new cases occur annually worldwide [1], and most of them in the first 8 years of life. The importance of early diagnosis lies in the fact that it is almost always fatal without a timely treatment.

ESSENTIALS OF DIAGNOSIS

Although leukocoria is the classic symptom, when leukocoria is observed the tumor is usually in a late stage. Ideally, diagnosis must be made when the tumor is small, which needs a dilated fundoscopy performed by a trained ophthalmologist. Retinoblastomas usually appear as whitish tumors that may grow towards the vitreous cavity (endophytic) or to the subretinal space (exophytic), or may seed into the vitreous. Rare presentations include seeding of the anterior chamber and an endophthalmitis-like picture [2 - 4].

B-scan ultrasound shows a hyper-reflective mass, with foci of higher hyper-reflectivity corresponding to calcification, and orbital shadowing behind the mass. Computed tomography shows an intraocular tumor with calcifications.

The severity of the disease is divided in different stages according to the International Classification of Retinoblastoma [5]:

1. Group A (Fig. **1**): Small tumors (≤3 mm), confined to the retina, >3 mm from the fovea, >1.5 mm of the optic disc.
2. Group B (Fig. **2**): Larger tumors (>3 mm) confined to the retina, in any location, with clear subretinal fluid ≤ 6 mm from the tumor margin.

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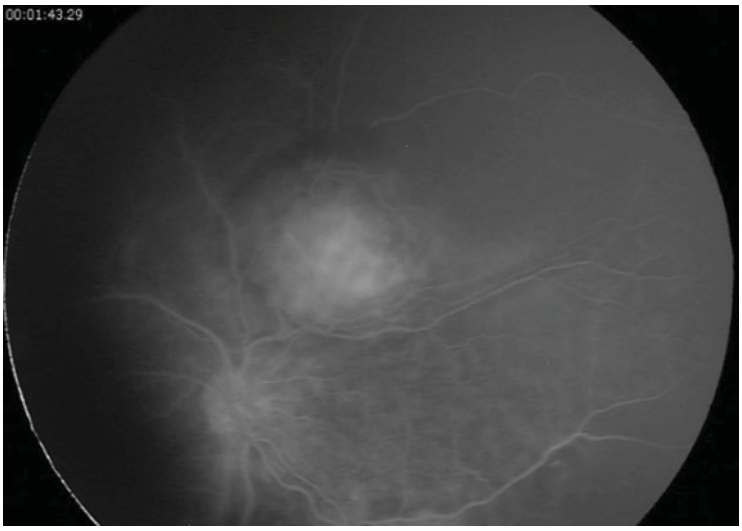

Fig. (1). Fluorescein angiogram showing a hyperfluorescent mass superonasal to the optic disc classified as Group A.

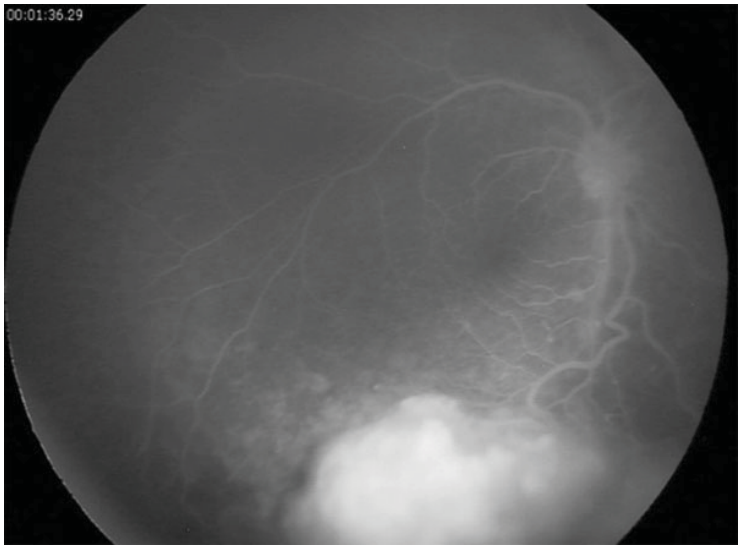

Fig. (2). Fluorescein angiogram showing a large (>3 mm) hyperfluorescent mass in the inferior retina, classified as Group B retinoblastoma.

3. Group C (Fig. **3**): Localized vitreous and/or subretinal seeding (<6 mm in total from tumor margin). If there is more than 1 site of subretinal/vitreous seeding, then the total of these sites must be <6 mm.
4. Group D (Fig. **4**): Diffuse vitreous and/or subretinal seeding (>6 mm in total from tumor margin). If there is more than 1 site of subretinal/vitreous seeding, then the total of these sites must be ≥6 mm. Subretinal fluid >6 mm from tumor margin.

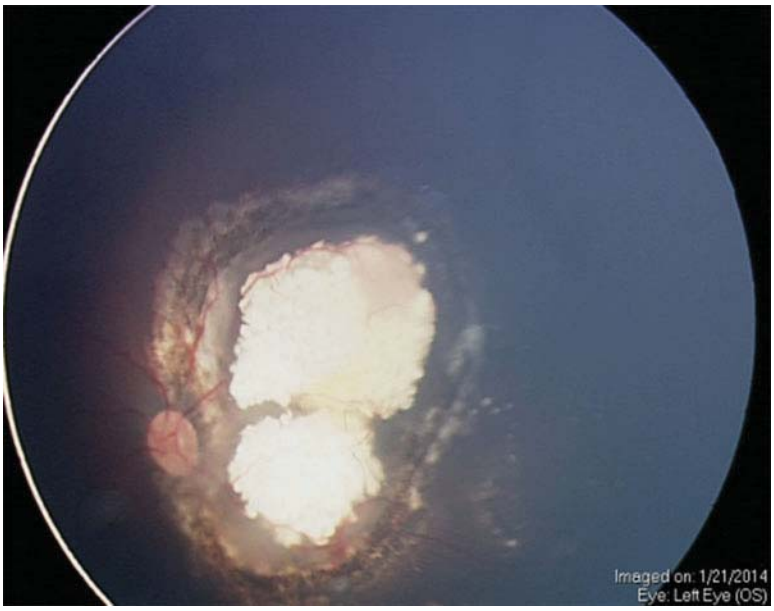

Fig. (3). Fundus photograph showing two whitish subretinal tumors in the posterior pole, classified as Group C retinoblastoma.

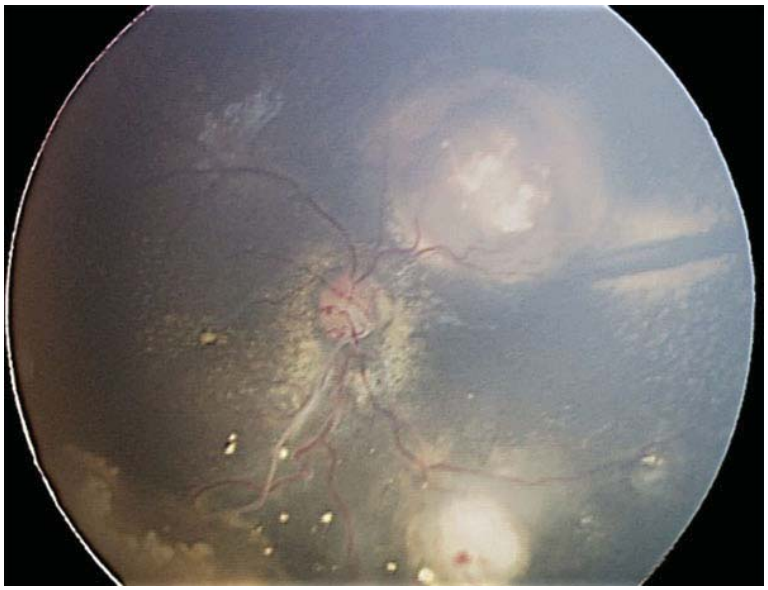

Fig. (4). Fundus photograph showing multiple exophytic and endophytic tumors, with subretinal and vitreous seeding, classified as Group D retinoblastoma.

5. Group E (Figs. **5** & **6**): No visual potential; or presence of any 1 or more of the following: Tumor in the anterior segment, tumor in or on the ciliary body, neovascular glaucoma, vitreous hemorrhage obscuring the tumor or significant hyphema, phthisical or pre-phthisical eye, or orbital cellulitis-like presentation.

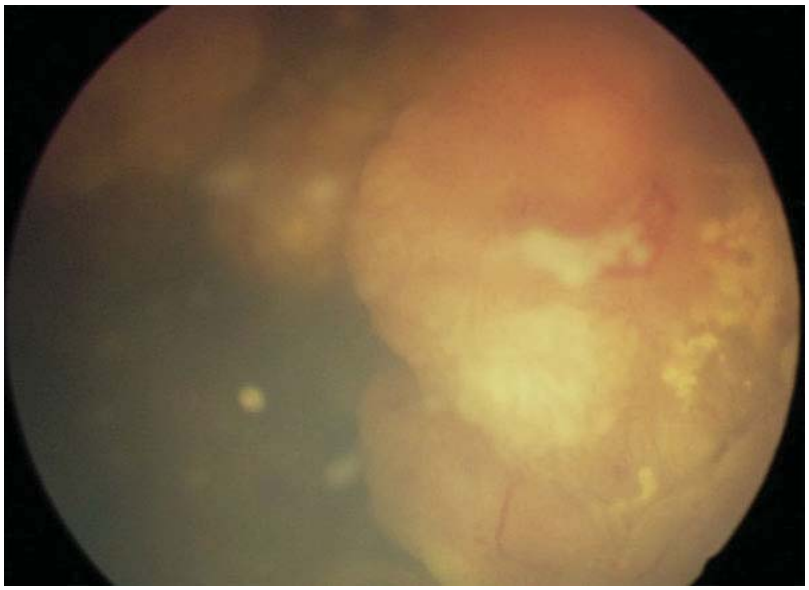

Fig. (5). Fundus photograph showing a whitish mass occupying a significant part of the vitreous cavity, with vitreous seeding and hemorrhage.

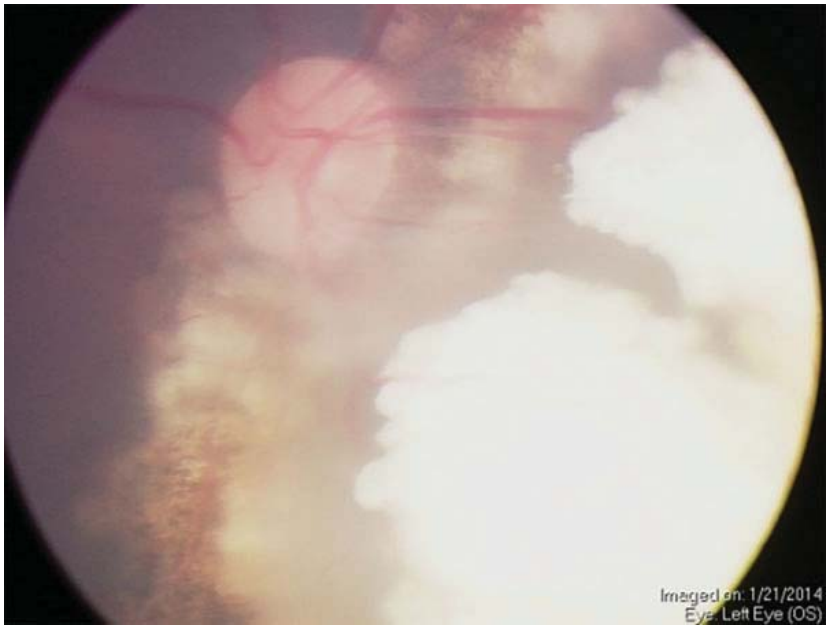

Fig. (6). Fundus photograph showing an endo and exophytic whitish tumor, occupying a significant part of the vitreous cavity.

Retinoblastoma is caused by mutations in the RB1 gene. About two thirds of cases are unilateral and one third bilateral. Ninety-five percent of cases are sporadic, while 5% are familiar [6, 7].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should be made with other causes of leukocoria, such as Coats' disease, familial exudative vitreoretinopathy, persistent fetal vasculature, congenital cataract, advanced retinopathy of prematurity, Norrie disease or chorioretinal coloboma. In most occasions, the clinical picture along with a B-scan ultrasound are sufficient to make the diagnosis [8, 9].

MANAGEMENT

The key step for successful treatment is a timely diagnosis, since advanced tumors are more difficult to treat [10 - 19]. Treatment is tailored according to disease stage according to the International Classification of Retinoblastoma, and if the disease is unilateral or bilateral. Smaller tumors are usually treated with systemic chemotherapy first, and laser thermotherapy immediately afterwards (Figs. **7**-**9**). An alternative to systemic chemotherapy is intra-arterial chemotherapy delivered *via* an endovascular catheter to the ophthalmic artery. More severe disease usually requires enucleation.

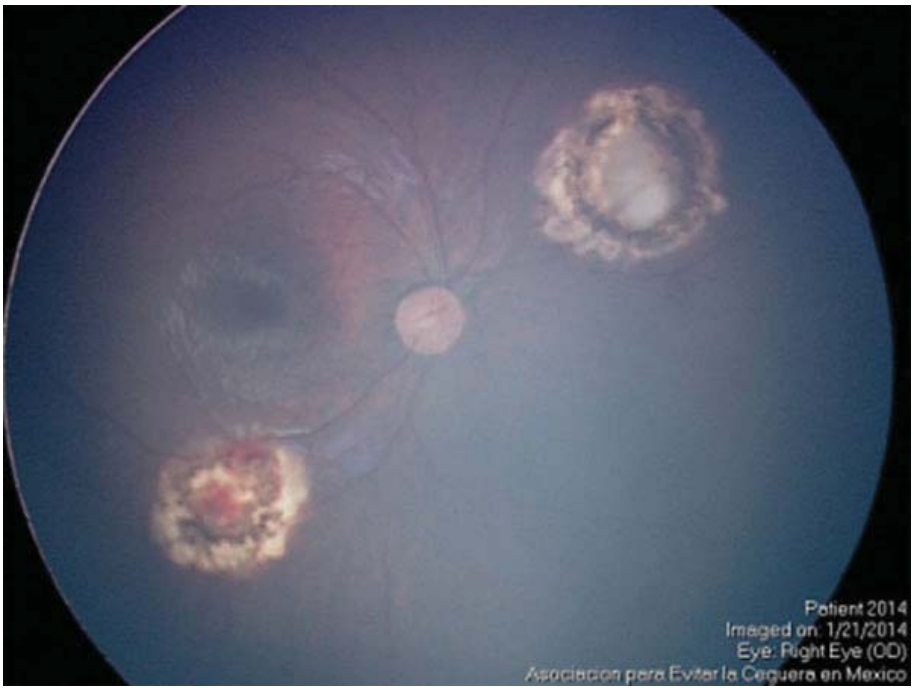

Fig. (7). Fundus photograph showing two small retinoblastomas immediately after chemotherapy and laser thermotherapy.

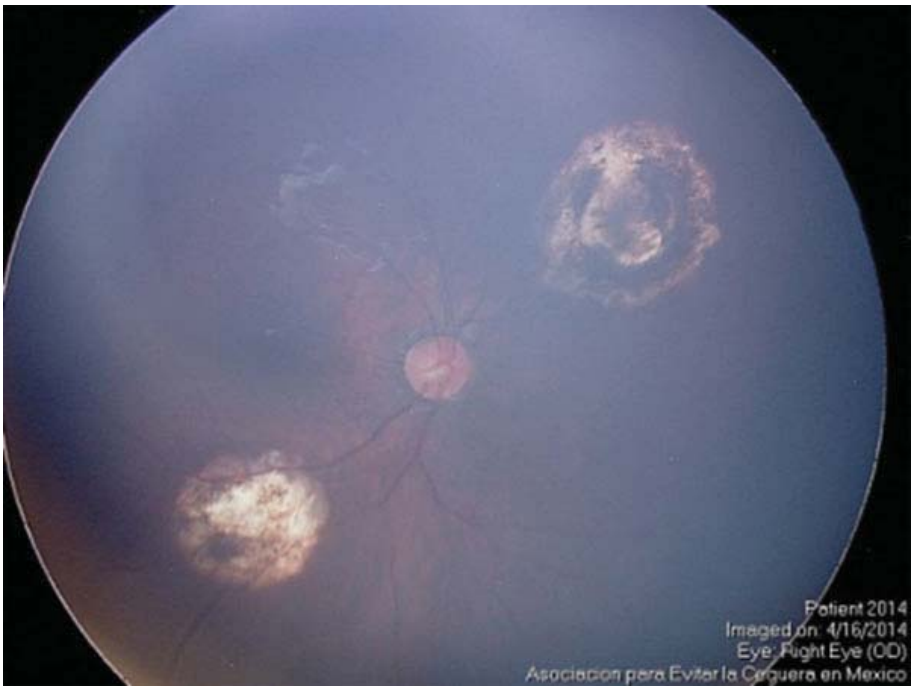

Fig. (8). Same eye as Fig. (**7**), three months after treatment. Significant tumor reduction and chorioretinal scars are apparent.

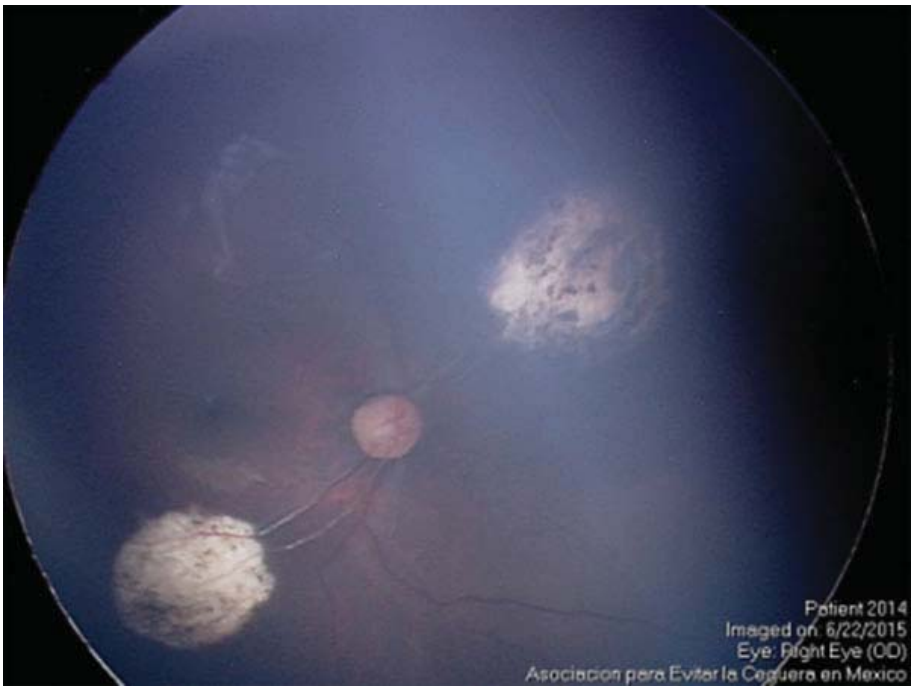

Fig. (9). Same eye as Figs. (**7** and **8**), 1 year after treatment. Disappearance of tumors is noted, without signs of recurrence.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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CHAPTER 21

Cavernous Hemangioma of the Retina

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Cavernous hemangioma of the retina is a rare congenital vascular hamartoma with a very particular appearance, which was described as early as 1937 [1]. It may be an isolated finding, or it may be associated with one or more intracranial cavernous hemangiomas, as well as with angiomatous hamartomas of the skin [1]. If the tumor does not affect the macula, patients are usually asymptomatic, unless vitreous hemorrhage or macular fibrosis develop.

ESSENTIALS OF DIAGNOSIS

Clinical examination reveals a group of blood-filled saccules within the inner retinal layers or on the surface of the optic disc [1, 3]. The appearance is usually described as a "cluster of grapes" (Fig. **1**), that may be located anywhere in the retina, but usually follows the course of a retinal vein. It may be associated to an epiretinal membrane or a vitreous hemorrhage [3].

Fluorescein angiography shows delayed filling of the saccules, due to the low-flow status of this tumor [3]. Fluorescence blockage may be observed if there is hemorrhage present (Fig. **2**).

DIFFERENTIAL DIAGNOSIS

Since the clinical appearance of the tumor is quite peculiar, differential diagnosis does not pose a significant challenge most of the times.

The main differential diagnosis is with a capillary hemangioma of the retina, which differs from a cavernous hemangioma in that the former has prominent feeder vessels that may be easily observed clinically and with fluorescein angiogram.

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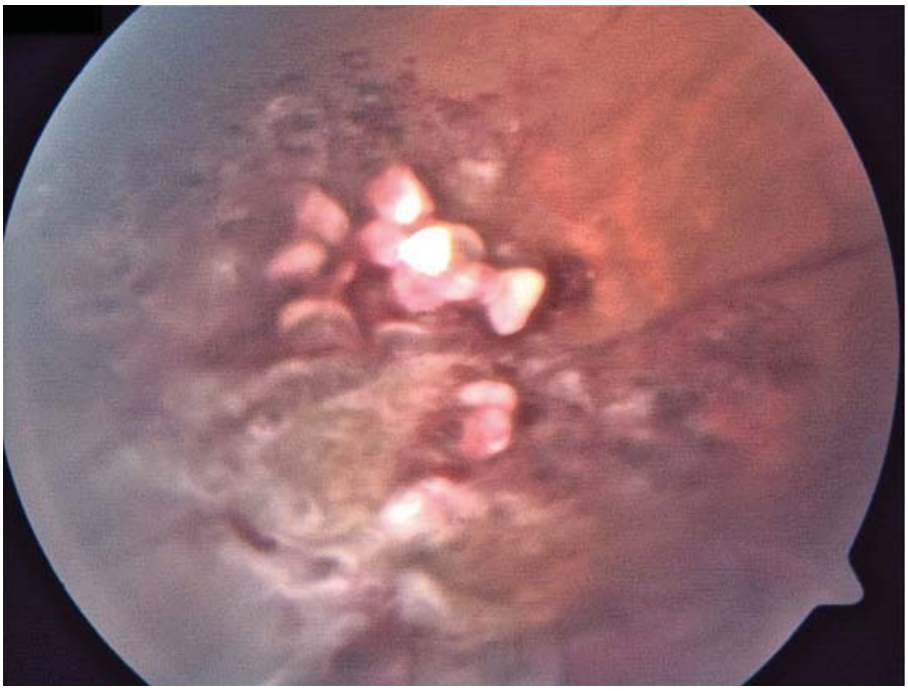

Fig. (1). Cavernous hemangioma of the retina with characteristic “cluster-of-grapes” appearance.

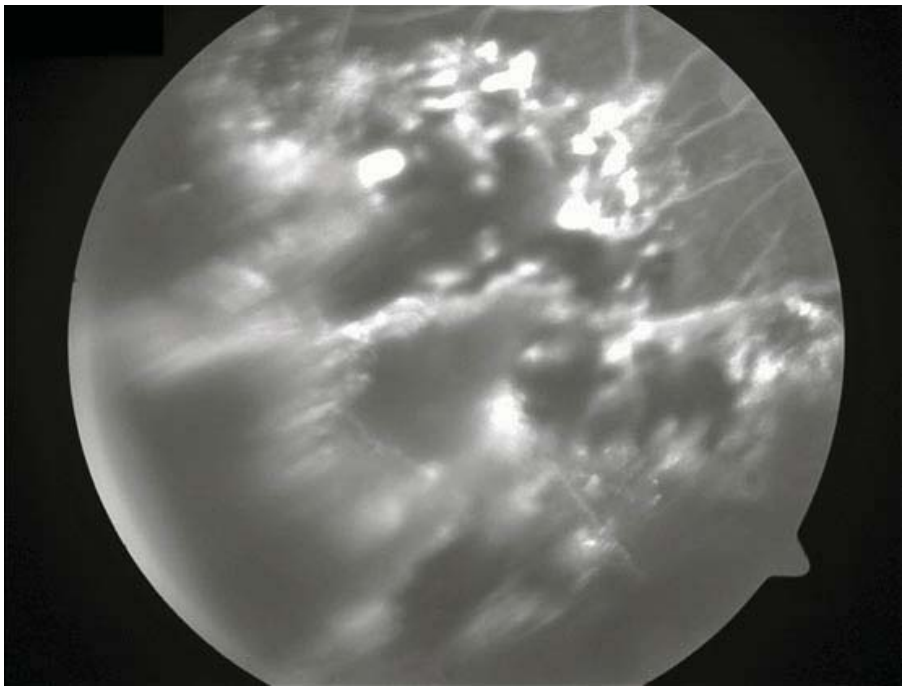

Fig. (2). Fluorescein angiography shows hyperfluorescent saccular caps and blocked fluorescence due to retinal hemorrhages.

MANAGEMENT

In most instances, treatment for a cavernous hemangioma of the retina is not necessary because the lesion is outside of the macula. These tumors, however, can develop an epiretinal membrane or vitreous hemorrhage that may require vitrectomy [1, 4]. If the tumor involves the macula and visual acuity is decreased, photocoagulation [2, 3] or intravenous infliximab [1, 5] have been advocated.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 22

Von Hippel-Lindau Disease

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Von Hippel-Lindau disease (VHL) is an autosomal dominant systemic syndrome that results from a mutation in the *VHL* gene on chromosome 3 (3p25-26) [1, 3]. *VHL* mutations have been associated to the development of different tumors. The most frequent are hemangioblastomas of the retina and central nervous system, clear-cell renal carcinoma and pheochromocytomas, pancreatic islet cell tumors and endolymphatic sac tumors [2, 4 - 6]. All of these tumors may occur sporadically, so a clinical diagnosis of VHL disease in a patient without a positive family history requires the presence of two tumors. Approximately 20% of VHL disease patients result from a *de novo* mutation and do not have a family history [2, 7]. Vascular tumors of the retina and choroid are a major source of long-term visual disability [8]. Capillary hemangioma of the retina (RCH) associated with VHL appears in the second and third decades of life with a median of 17.6 years, there is no sex or racial predisposition, but it is more common in whites [1].

The estimated incidence of VHL is 1/36000 [1, 11]. VHL disease is suggested to account for approximately a third of patients with a CNS hemangioblastoma [2, 9, 10]. Retinal hemangioblastoma is seen in more than 60% of patients with VHL disease [3].

ESSENTIALS OF DIAGNOSIS

The hallmark lesion of VHL disease is the RCH, which can occur as a peripheral lesion in 90.4% of cases (Figs. **1**-**6**, **8**-**10**) and a juxtapapillary tumor in 9.6% of the cases (Figs. **7** and **12**) [11]. Half of the patients with retinal hemangioblastoma have bilateral involvement [3].

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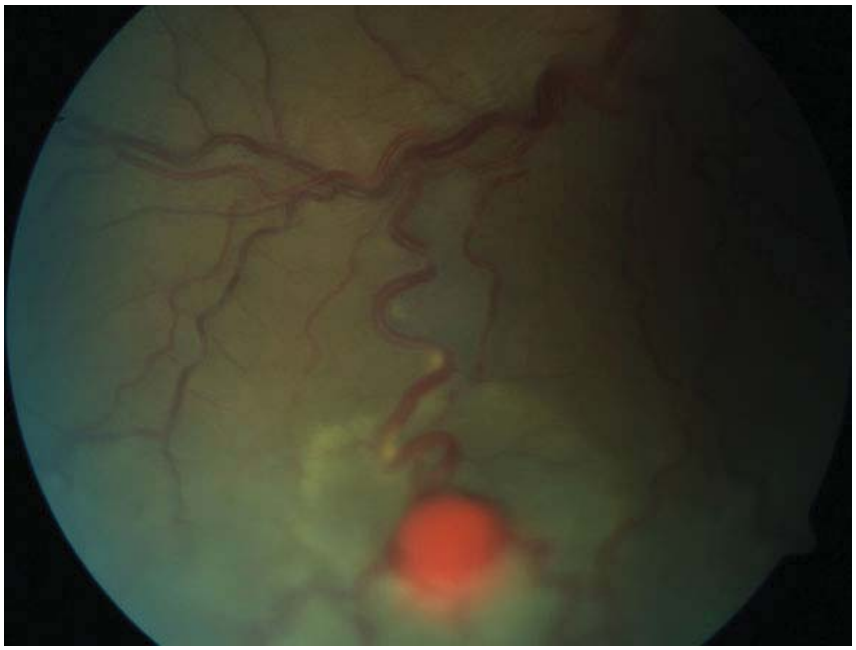

Fig. (1). Small peripheral angioma with characteristic feeder and draining vessels and the presence of subretinal fluid.

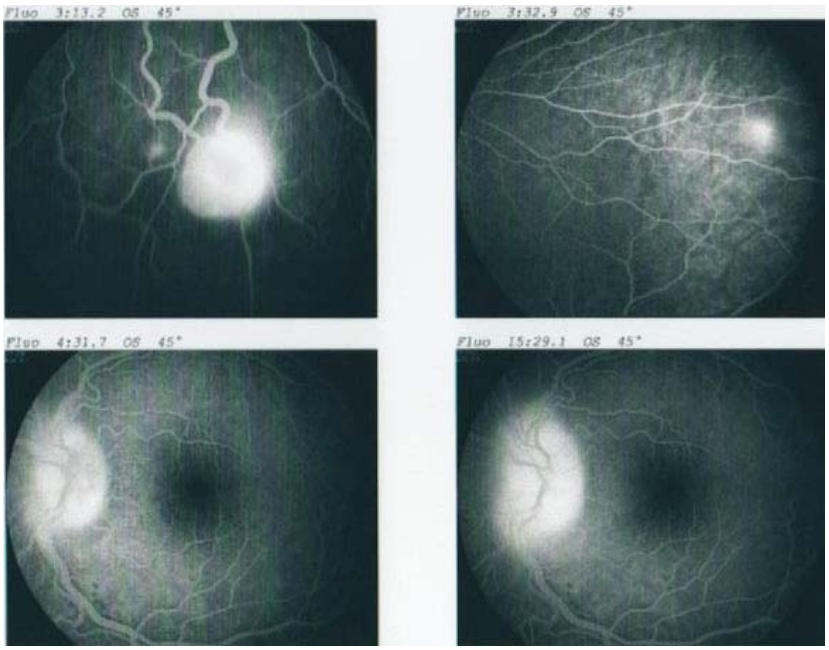

Fig. (2). Fluorescein angiogram at 3 minutes and late-phases with hyperfluorescence and leakage of the tumor. In this angiogram we can see 2 different-sized angiomas as well as optic nerve hyperfluorescence secondary to papilledema.

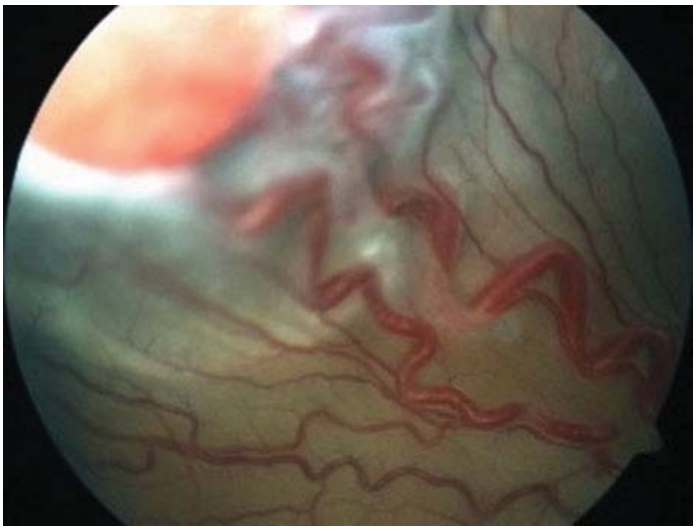

Fig. (3). Large peripheral angioma with prominent feeder vessels and serous retinal detachment, located supero temporal.

Fig. (4). Composed color photograph of the right eye of a patient with VHL where we can see 2 different-sized angiomas with serous retinal detachment, feeder and draining vessels as well as early macular edema and papilledema.

Clinically, the tumor appears as a red or grayish mass located most commonly in the superotemporal mid-peripheral retina [1]. These tumors are often endophytic and are classically associated with a dilated tortuous feeding artery and a draining vein that shows tortuosity or focal telangiectasias (Figs. **1**, **3**-**6**). Alternatively, RCH may be exophytic and arise from the outer retinal layers. Exophytic tumors are not usually associated with arteriovenous shunting. They tend to develop in the juxtapapillary region and are frequently misdiagnosed as papilledema (Fig. **7**) [12].

Histologically, retinal hemangioblastoma appears as a network of thin vascular capillary-like channels lined by endothelial cells and pericytes. These vascular channels are separated by foamy VHL-associated tumor cells, also known as stromal cells [3].

The main ocular complications of retinal hemangioblastoma are retinal exudation (25%) due to incompetent capillary vessels, and tractional retinal detachment (9%). Retinal or vitreous hemorrhages are rare and only occur in fewer than 3% of cases; anterior segment complications such as cataract and neovascular glaucoma are also rare and have been found to occur during the end-stage of the disease. Two percent of eyes with RCH also show neovascularization in the iris [3].

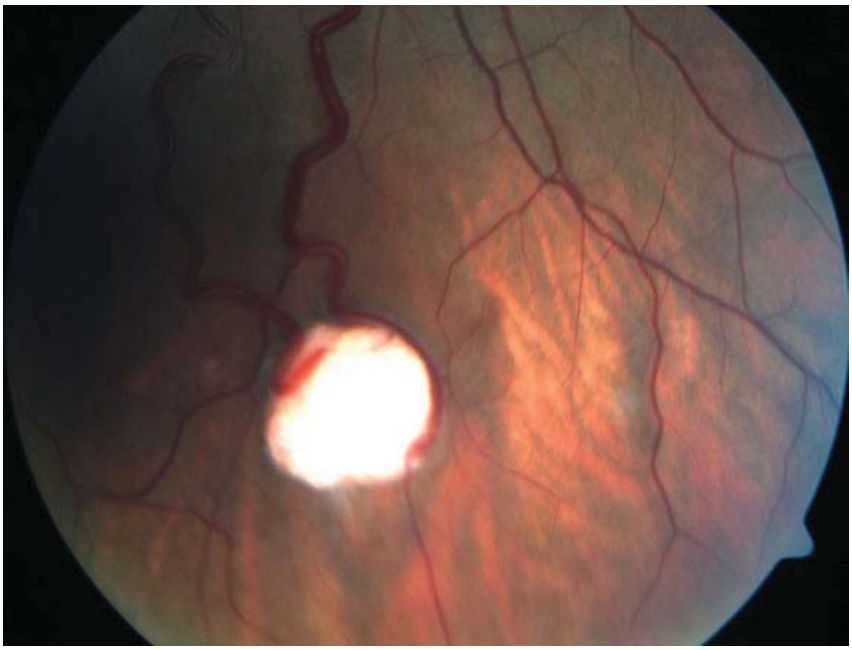

Fig. (5). Inferior tumor (angiomatous lesion) associated with VHL disease. This lesion may be whitish, pinkish or gray.

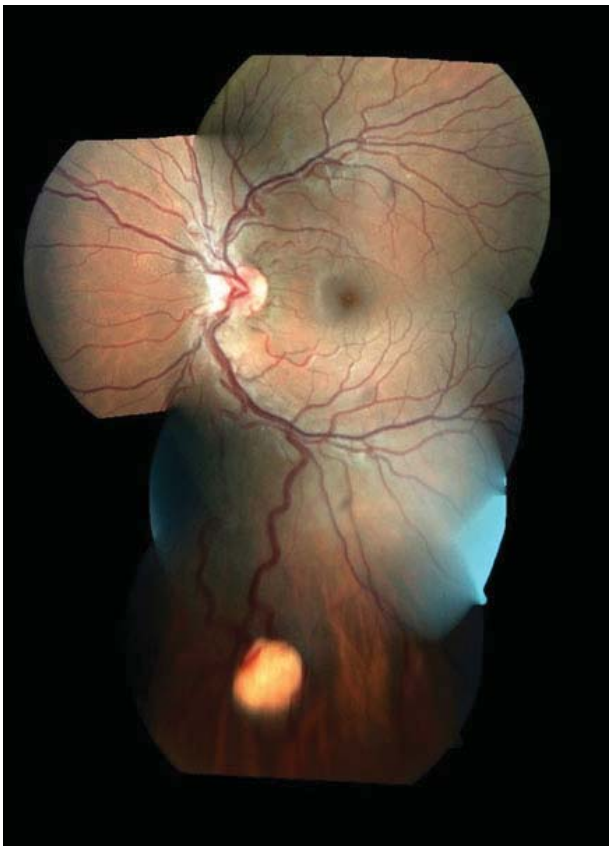

Fig. (6). Peripheral angioma in the left eye of a patient with VHL. The angioma has no subretinal fluid and has been stable for more than 6 years without treatment.

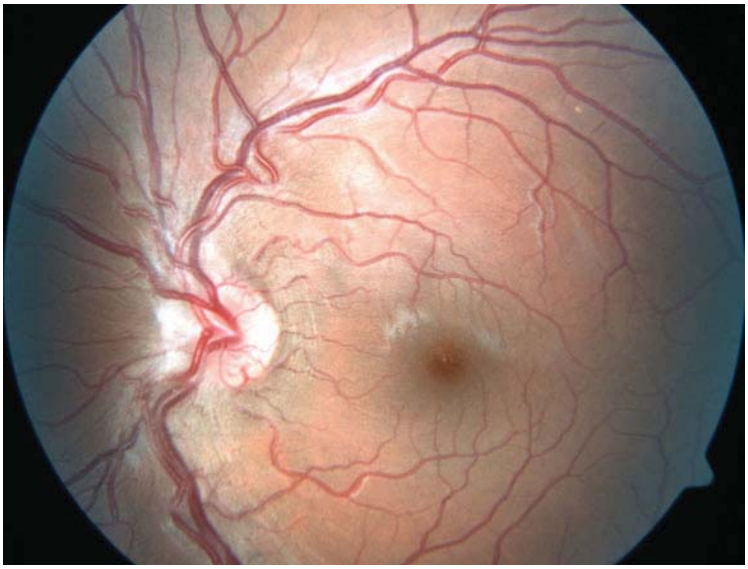

Fig. (7). Small optic disc angioma which has mild macular edema. This is an endophytic tumor.

Fluorescein angiography (FA) is a valuable tool in characterizing the vascular nature of RCH and in distinguishing it from some simulating entities (Figs. **2** and **9**) [12].

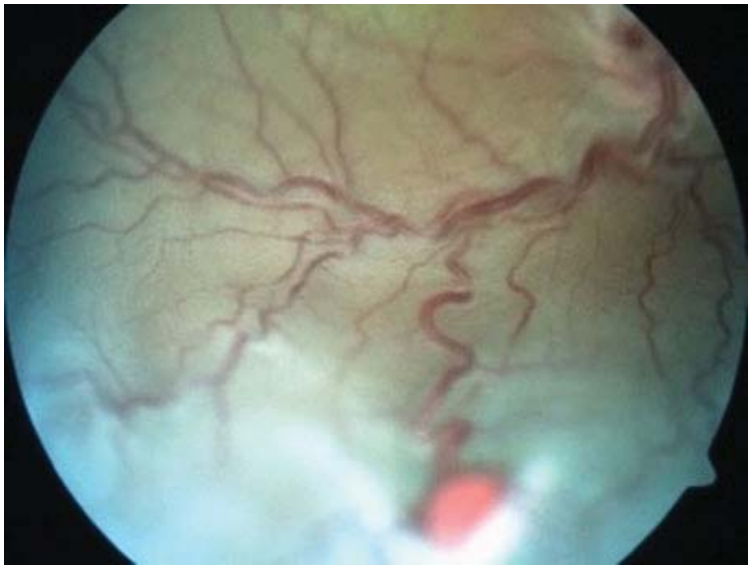

Fig. (8). Serous and tractional retinal detachment due to retinal angioma in VHL disease.

Fig. (9). Late-phase fluorescein angiogram with diffuse leakage of the tumor and very subtle pooling in the subretinal space. As well multiple angiomas may be demonstrated by fluorescein angiography as in this case where we can see a very small angioma near the larger one.

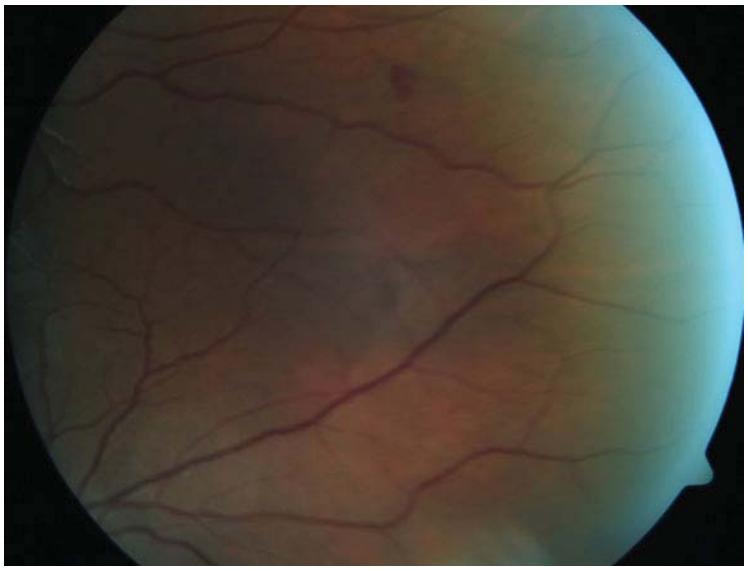

Fig. (10). Small retinal angioma in the equator of a patient with VHL disease.

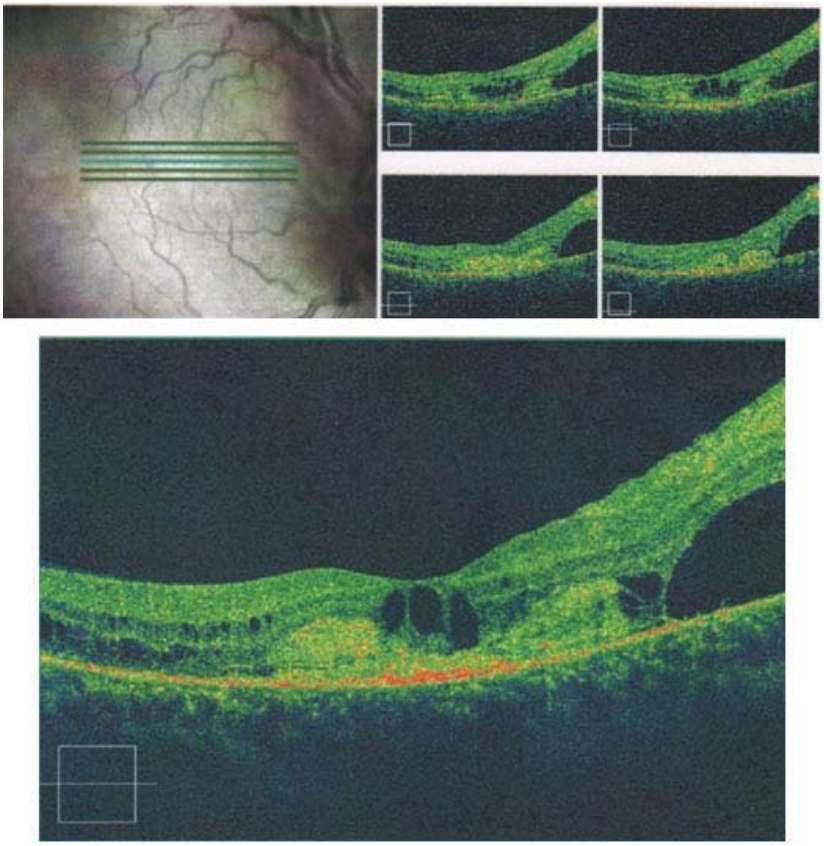

Fig. (11). OCT scan demonstrating large intraretinal cystic cavities, subretinal fluid and cystoid macular edema.

Spectral-domain optical coherence tomography (OCT) shows retinoschisis around the retinal tumor and also around the feeder and draining vessels. Retinoschisis is observed under the internal limiting membrane and in the inner and outer retinal layers (Figs. **11** and **12**) [13]. The detached retina adjacent to the tumor appears to have focal loss of the outer retinal layers, and usually shows extensive disruption of the photoreceptor layer, possibly secondary to traction from growth of the adjacent tumor [12].

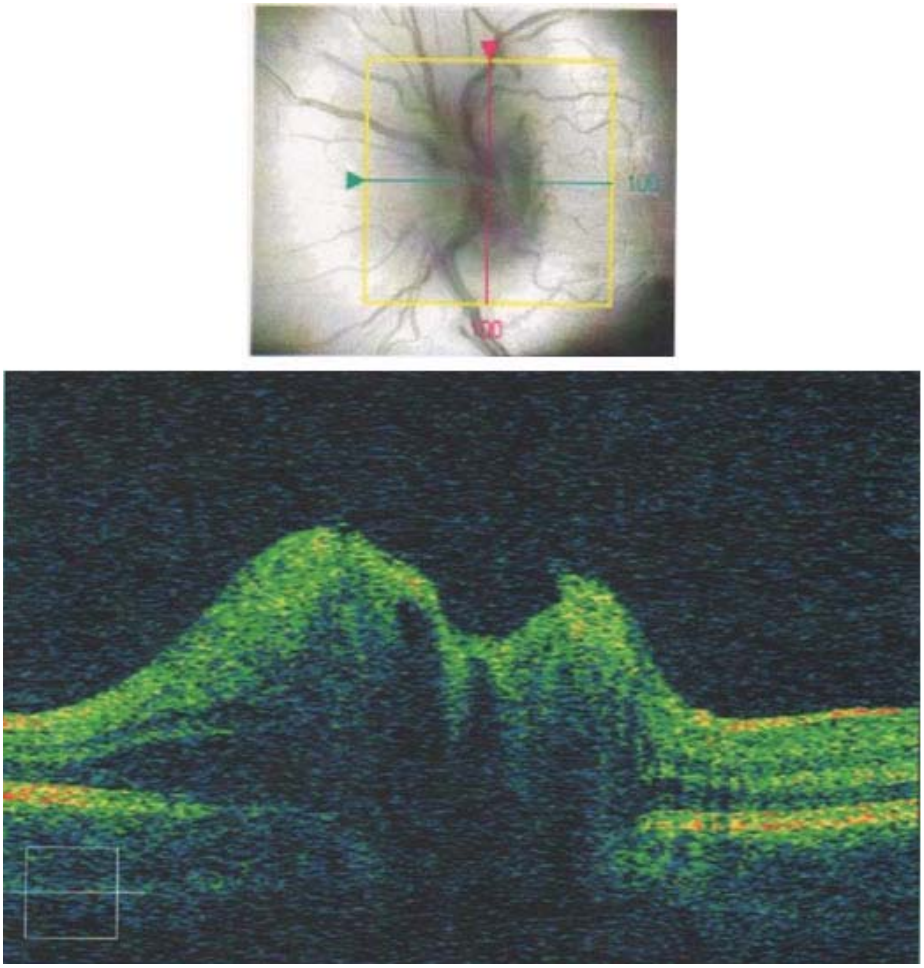

Fig. (12). OCT of optic disc swelling secondary to intracranial hypertension due to brain hemangiomas in VHL disease.

When the tumor is exophytic, it is observed in the outer layers of the retina. The tumor usually protrudes into the subretinal space and shows marked shadowing due to its high flow and vascularity. Associated cystoid macular edema and subretinal fluid is described [12].

In summary, photoreceptor loss, cystoid macular edema, pre-retinal traction and disorganization of the adjacent retina have been described [12].

DIFFERENTIAL DIAGNOSIS

The presence of multiple retinal angiomas strongly suggests VHL disease [14]. The presence of exudate, fibroglial proliferation, vitreous hemorrhage or folds of retinal detachment may generate confusion. The differential diagnosis includes vascular disorders such as acquired vasoproliferative retinal tumors, Coats disease, retinal arterial macroaneurysm, diabetic retinopathy, racemose hemangioma, retinal cavernous hemangioma, sickle cell retinopathy and FEVR. Also, inflammatory conditions such as nematode endophthalmitis and toxoplasmosis should be considered. Tumors such as retinoblastoma, retinal astrocytoma and malignant melanoma may also mimic this disease [1]. OCT helps differentiate it from other simulating entities, such as choroidal neovascular membranes or tumors of the retinal pigment epithelium or choroid [12].

MANAGEMENT

VHL disease is a complex multisystem disorder, and therefore requires multi-disciplinary management in order to prevent avoidable morbidity and mortality.

Kim *et al.* described the different treatments for RCH. Small tumors (54.8%; <0.5 mm in size) are usually treated with laser photocoagulation. Moderate-sized RCH (24.7%; 0.5-3.0 mm in size) are treated with transpupillary thermotherapy, and large RCH (20.5%; >3.0 mm in size) are treated with a combination of transpupillary thermotherapy and cryotherapy [11]. In this study 90% of small RCH regressed, whereas only 67% of large RCH regressed. Peripheral RCH showed better response to treatment than juxtapapillary [11]. Transpupillary thermotherapy could be an effective method for tumor regression in moderate-to-large-sized RCH showing a resolution rate of 70% [11].

Thermal photocoagulation is the treatment of choice for small peripheral angiomas while Photodynamic therapy (PDT) may be preferred for larger RCH [15, 16]. Addition of intravitreal anti-VEGF drugs may be beneficial [15].

Vitreoretinal surgery should be confined to advanced stages with tractional detachment or when no other treatment option is available [15]. External drainage with scleral buckling, relaxing retinectomy and gas tamponade are some of the options for management [16 - 18].

Other surgical techniques have also been described, including the use of chandelier illumination to enable bimanual manipulation of tissue, endolaser around the tumor, endoresection of lesions and endodiathermy to cauterize the tumor feeder vessels, as well as the use of long-acting gas tamponade [19].

The treatment of juxtapapillary angiomas is still a therapeutic dilemma. As one of the major mechanisms of disease is poor regulation of VEGF production, using an anti-VEGF agent could in theory be helpful [20 - 23].

Treatment of massive lesions is more problematic and recurrence often follows treatment.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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CHAPTER 23

Astrocytoma Tuberous Sclerosis

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Tuberous sclerosis complex (TSC), also known as Bourneville's disease, was first identified in 1880, after the autopsy of a 15-year-old teenager who suffered from lifelong epilepsy [1]. It is described as an autosomal-dominant, neurocutaneous disease that has a great number of manifestations, involving many organ systems, but most frequently the brain, skin, kidney, heart, and eyes. In 80-90% of the cases, it is diagnosed before the age of 10, even in stages of intrauterine development [2, 3]. The incidence is estimated at 1:6,000-10,000 live births [4, 5]. TSC is caused by a mutation in either of two tumor suppressor genes: TSC1 on chromosome 19q34 or TSC2 on chromosome 16p13 [6, 7]. Both genes act cooperatively to regulate cellular growth and differentiation [8]. Mutations of these genes result in the formation of hamartomas.

ESSENTIALS OF DIAGNOSIS

TSC diagnosis may not be easy because some signs and symptoms vary from one individual to another. However, during the first TSC consensus conference in 1998, the diagnostic criteria were divided into major features and minor features. Major features are facial angiofibromas, periungual fibromas, three or more hypomelanotic macules, Shagreen patch (connective tissue nevus), cortical tuber, subependymal nodules, subependymal giant cell astrocytomas, multiple retinal nodular hamartomas, cardiac rhabdomyoma (multiple or single), lymphangioleiomyomatosis, and renal angiomyolipoma. Minor features include the following: multiple, randomly-distributed pits in dental enamel (more than 14), hamartomatous rectal polyps, bone cysts, cerebral white matter migration lines, gingival fibromas, non-renal hamartoma, retinal achromic patch, "confetti" skin lesions, and multiple renal cysts [9]. In 2012, during the second TSC consensus conference, the existing criteria were revised and some minor changes were made.

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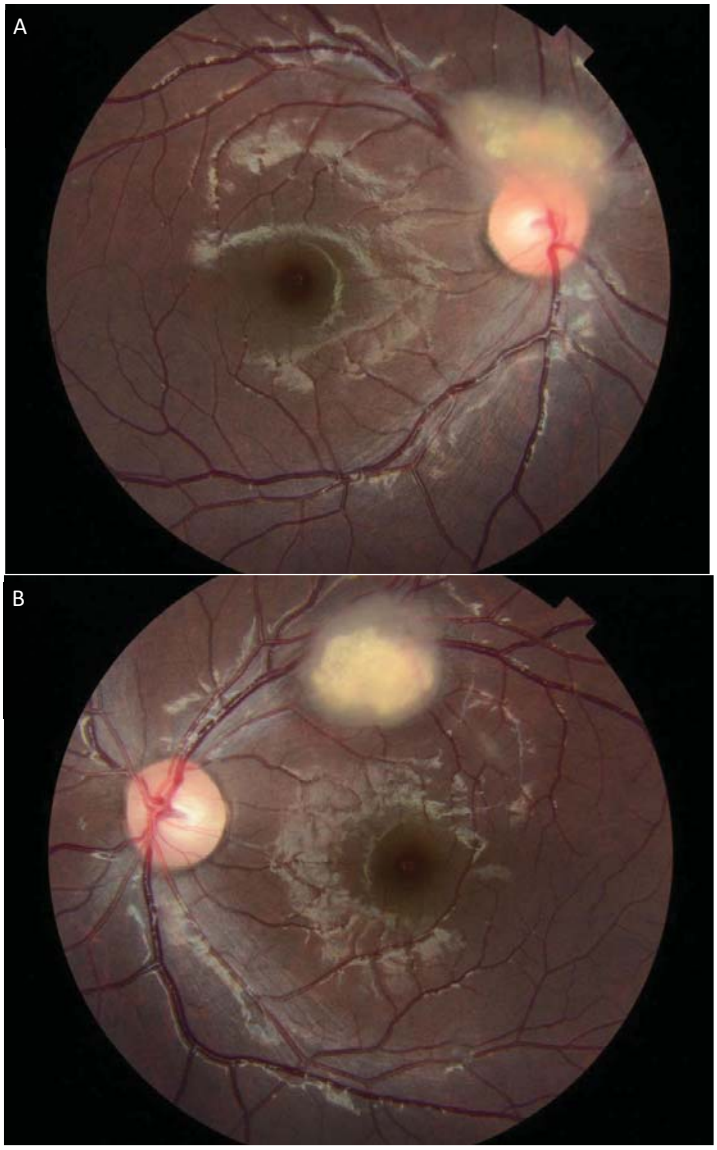

Fig. (1). Color fundus photographs of 9 year-old male patient with Tuberous Sclerosis showed solid grey-yellowish lesions with a jelly-like translucent appearance on top and accumulation of circular opacities in the inside, spread in the center of the tumor, having the appearance of fish eggs, located at the superior periphery of the optic nerve in the right eye (**A**) and at the level of the superior temporal vascular arcade in the left eye (**B**).

A strong emphasis was placed on the importance of genetic testing, which was included in the major criteria and was made a definite criterion for diagnosis, irrespective of the clinical presentation [10]. It was also established that the combination of two major features or the combination of one major feature with

two minor features are sufficient to make a definite diagnosis. Patients with TSC have demonstrated numerous eye findings, which may affect the orbit and eye adnexa, as well as the intraocular structures of the eye, including the anterior and posterior segments, and in some cases, may result in secondary glaucoma. The retina is the eye layer most frequently affected. According to different studies, retinal astrocytic hamartoma or retinal astrocytoma is present in 25-53% of TSC patients [11, 12]. It can occur as a calcified or non-calcified lesion. Calcified astrocytic hamartoma is a multinodular, elevated, ovoid, or circular "mulberry-like" lesion usually located at the posterior pole near the optic nerve, with a yellowish color due to calcification (Fig. **1**). The non-calcified variant appears as a flat or slightly elevated grey-yellow lesion, generally found on the peripheral retina. It is a benign tumor composed of a proliferation of well-differentiated astrocytes. Astrocytoma can be congenital or can become apparent some time after birth. Although it is usually a stable lesion, there have been cases that showed progressive growth [13, 14].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should always consider retinoblastoma, as well as choroidal melanoma.

MANAGEMENT

Treatment for these tumors is not necessary except if visual acuity is compromised because of macular edema or intraretinal hemorrhages. In those cases, the use of a combined bevacizumab and triamcinolone acetonide intravitreal injection has shown good results [15].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 24

Retinal Vasoproliferative Tumor

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Retinal vasoproliferative tumor (RVPT, also known as peripheral vascular tumor, pseudoangiomatous proliferation of the retina or reactive retinal astrocytic tumor) is a relatively uncommon vascular disease of the retina, characterized by the presence of a solid retinal lesion located in the periphery (Fig. **1**), which can be an isolated finding (76%) or secondary to a pre-existing ocular inflammatory or vascular disease, such as intermediate uveitis, retinitis pigmentosa or Coats' disease [1, 2]. This entity is more common in males, and typically occurs in the 3rd and 4th decades of life. It is usually asymptomatic, until there is a vitreous hemorrhage, or the macula becomes affected [3].

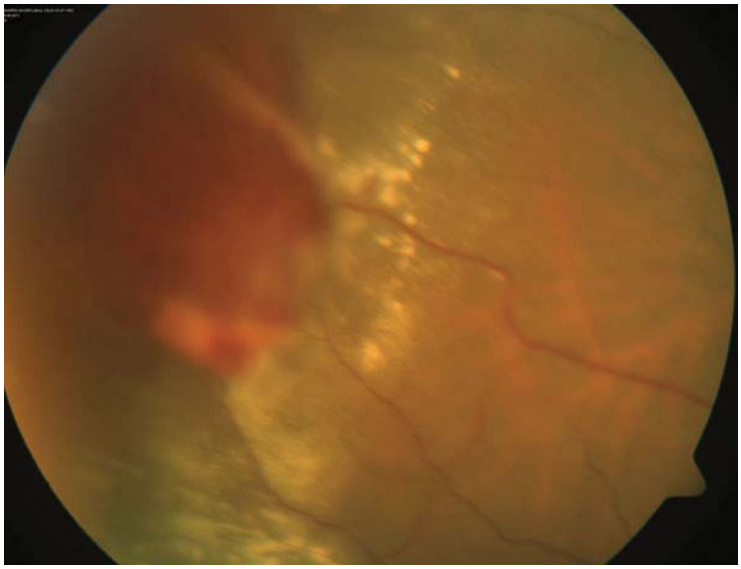

Fig. (1). Fundus photograph of the superotemporal retinal periphery on the right eye of a 17 year-old male, showing a tumor surrounded by hard exudates, with intra and preretinal hemorrhage.

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ESSENTIALS OF DIAGNOSIS

Clinical examination reveals a peripheral orange or pinkish retinal mass (Fig. **2**) that is generally located in the inferotemporal quadrant (Fig. **3**), usually with concomitant intra or preretinal hemorrhage (Figs. **4**-**6**). Hard exudates and a serous retinal detachment may be observed surrounding the lesion in 80% and 50% of cases, respectively. The macula may be affected by an epiretinal membrane (25%) (Fig. **7**) or cystoid macular edema (14%). Vitreous hemorrhage is present in 18% [1].

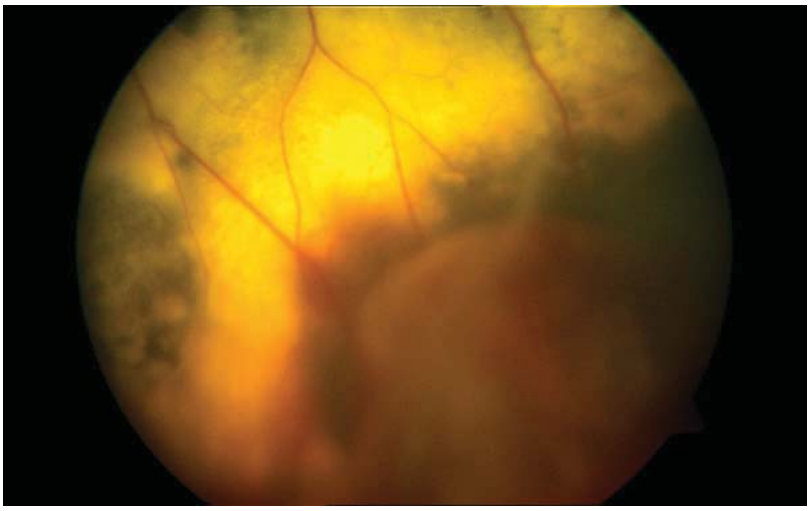

Fig. (2). Fundus photograph of the inferotemporal retinal periphery on the left eye of a 35 year-old male, showing a tumor surrounded by hard exudates and a shallow retinal detachment, and with some preretinal hemorrhage.

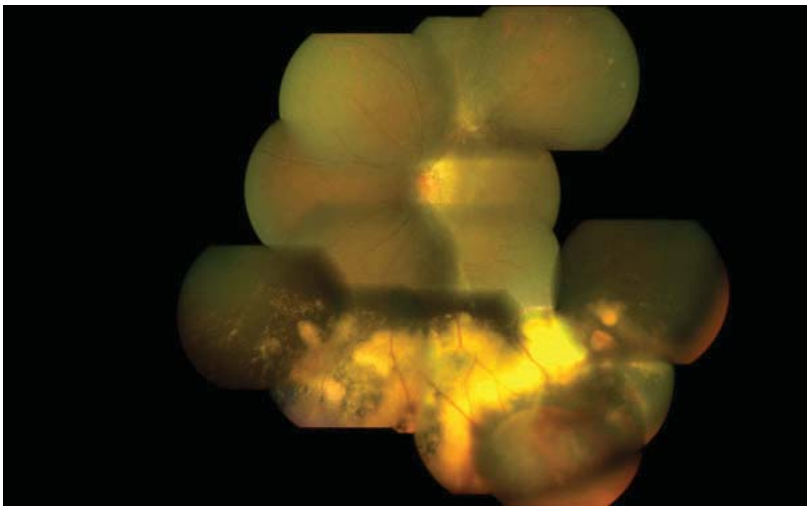

Fig. (3). Composite photograph of the same eye described in Fig. (**2**).

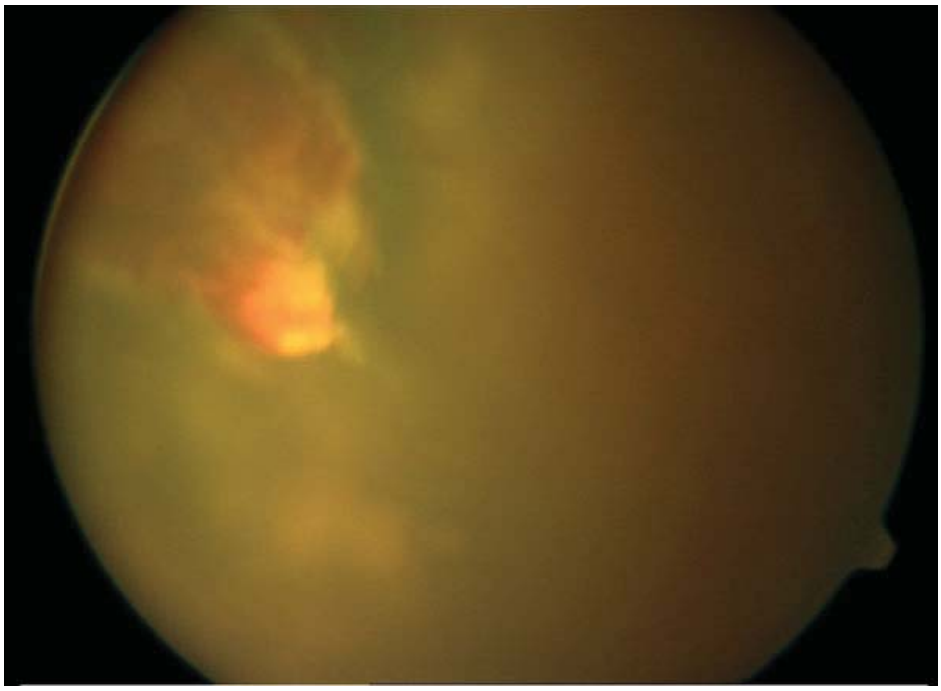

Fig. (4). Fundus photograph of the superotemporal retinal periphery on the right eye of a 25 year-old male, showing a tumor with preretinal and vitreous hemorrhage.

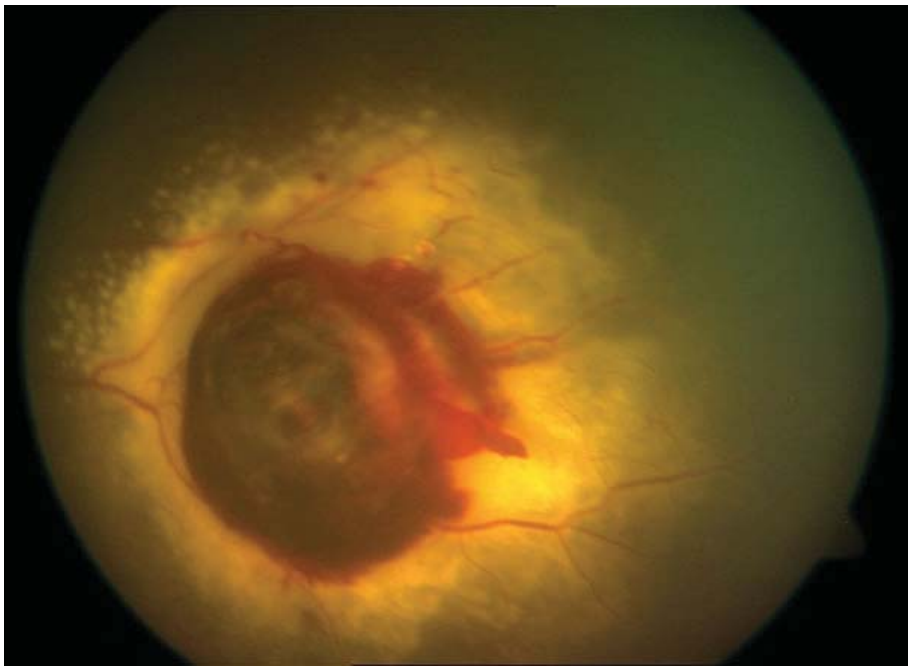

Fig. (5). Fundus photograph of the left eye of a 29 year-old male, showing a tumor with preretinal hemorrhage surrounded by hard exudates.

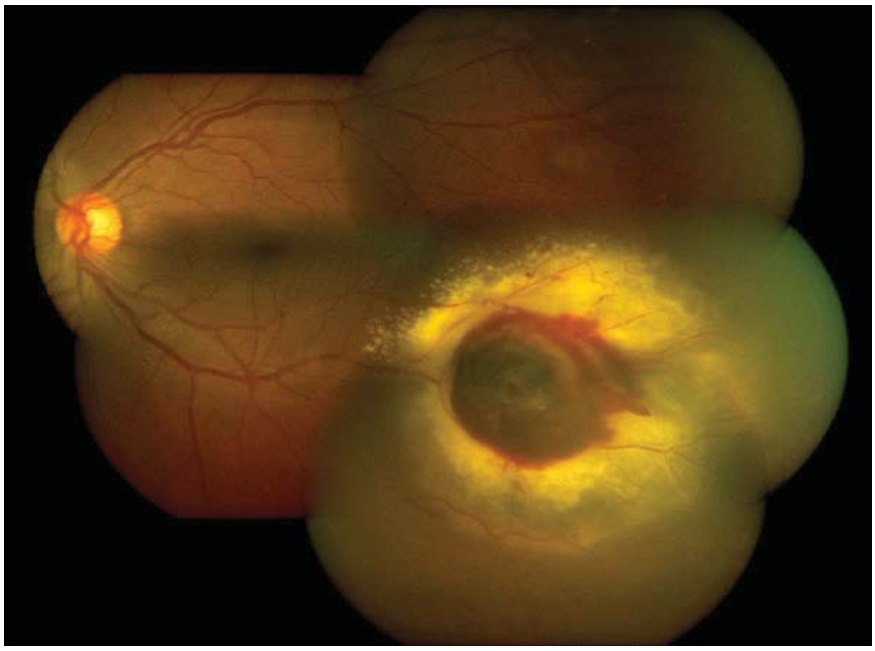

Fig. (6). Composite photograph of the same eye described in Fig. (**5**).

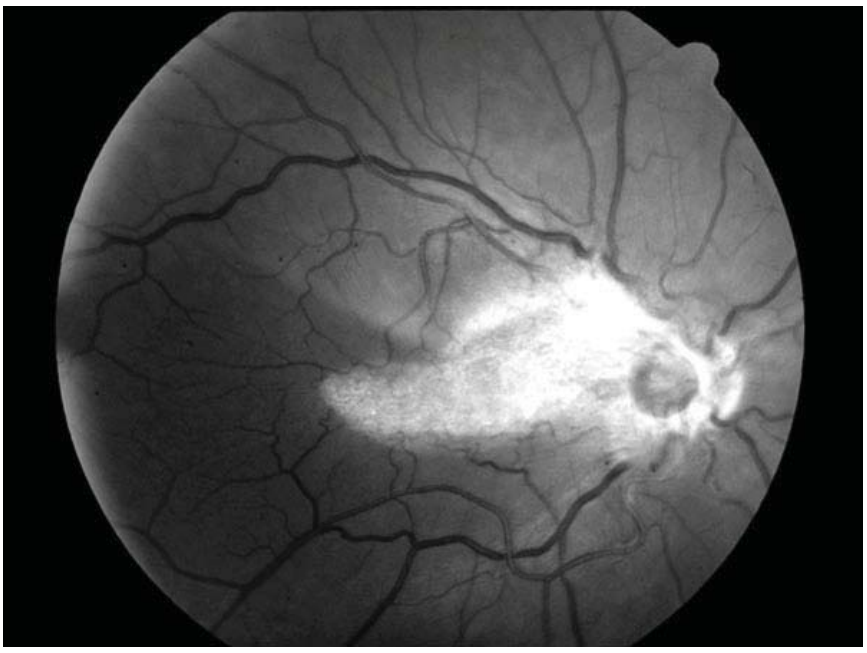

Fig. (7). Red-free photograph of posterior pole of the same eye described in Fig. (**1**), showing an epiretinal membrane.

Fluorescein angiography shows diffuse patchy hyperfluorescence in the tumor that may be obscured by intra or preretinal hemorrhage (Fig. **8**). Perilesional

vascular leakage secondary to vascular incompetence is also observed. Capillary closure may be present, usually anterior to the tumor (Figs. **9** and **10**). Epiretinal membranes might be vascularized (Fig. **11**) [4].

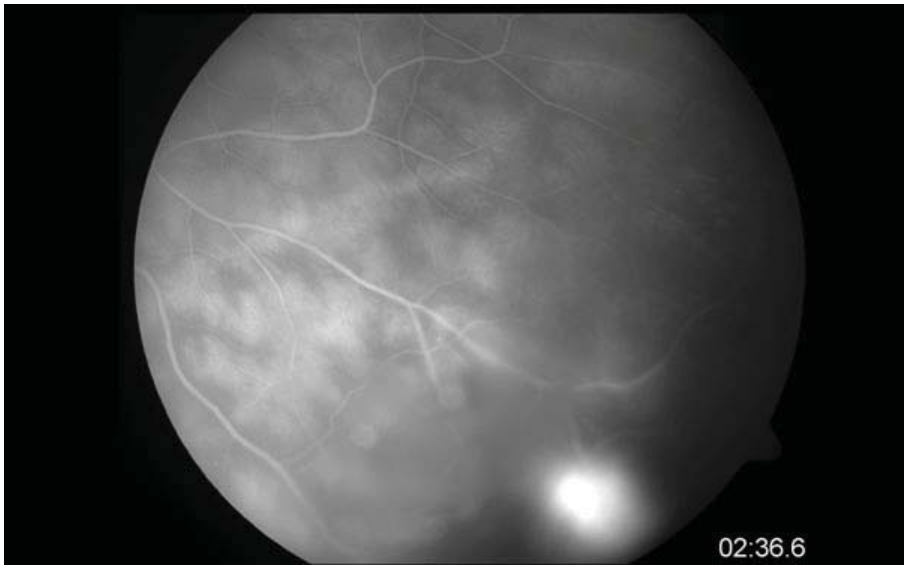

Fig. (8). Fluorescein angiogram of the eye described in Figs. (**2** and **3**), showing diffuse perivascular hyperfluorescence.

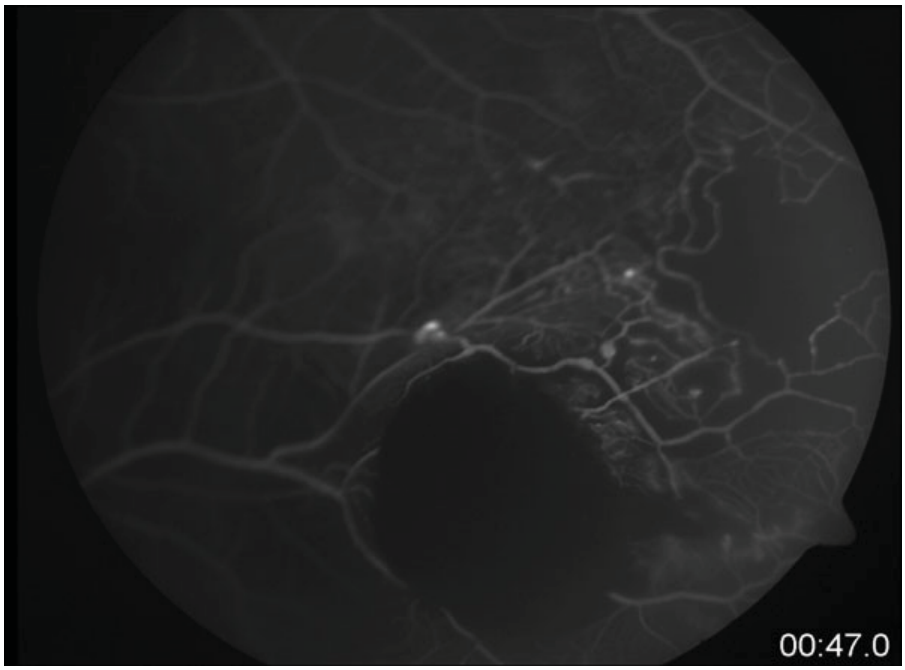

Fig. (9). Fluorescein angiogram of the eye described in Figs. (**5** and **6**), showing hypofluorescence secondary to preretinal hemorrhage, as well as dilated vessels and capillary closure.

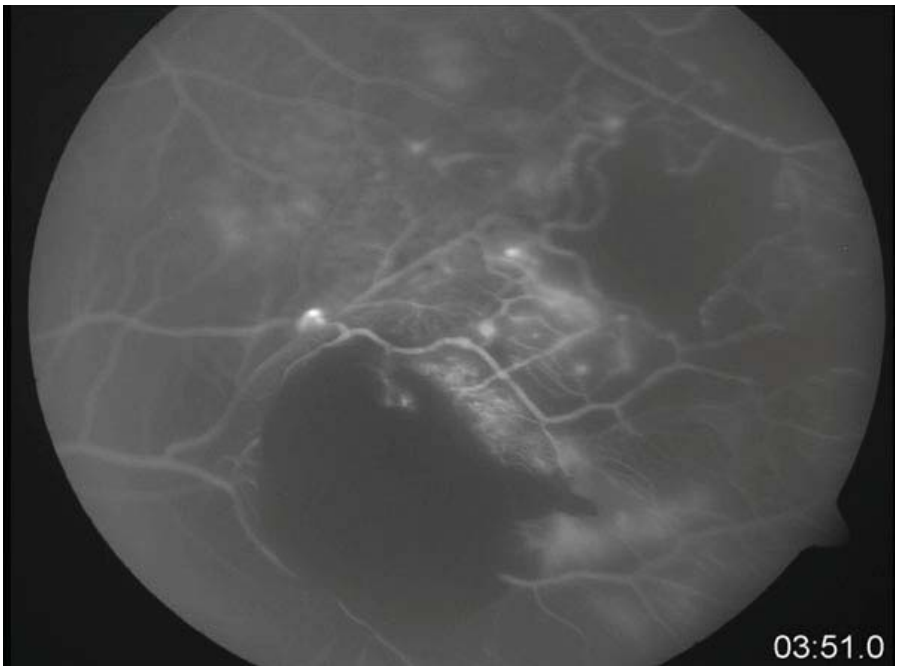

Fig. (10). Fluorescein angiogram of the eye described in Figs. (**5** and **6**), showing late perivascular hyperfluorescence.

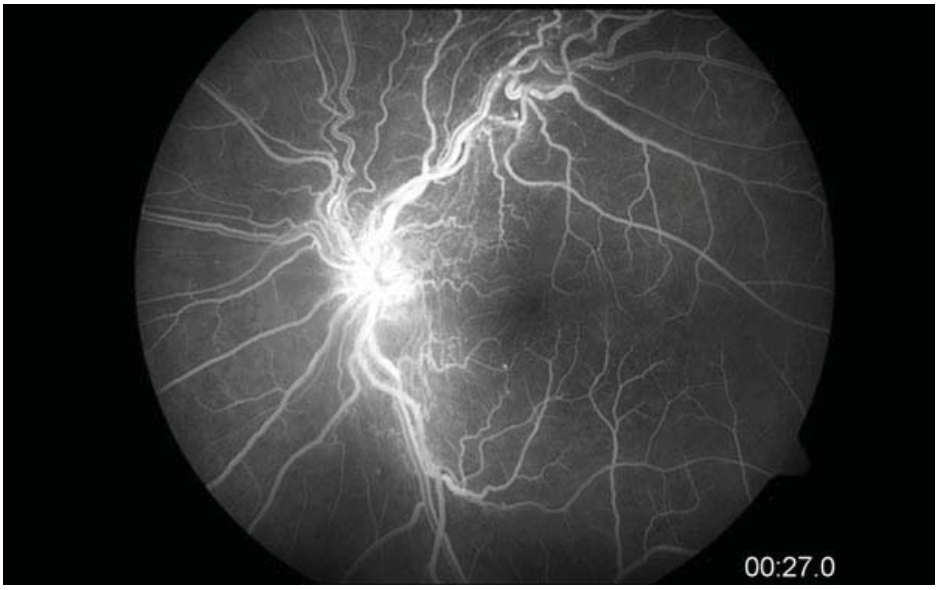

Fig. (11). Fluorescein angiogram of the eye described in Figs. (**2**, **3** and **8**), showing vascularization of the epiretinal membrane.

Optical coherence tomography (OCT) is useful when an epiretinal membrane (Fig. **12**) or cystoid macular edema is present.

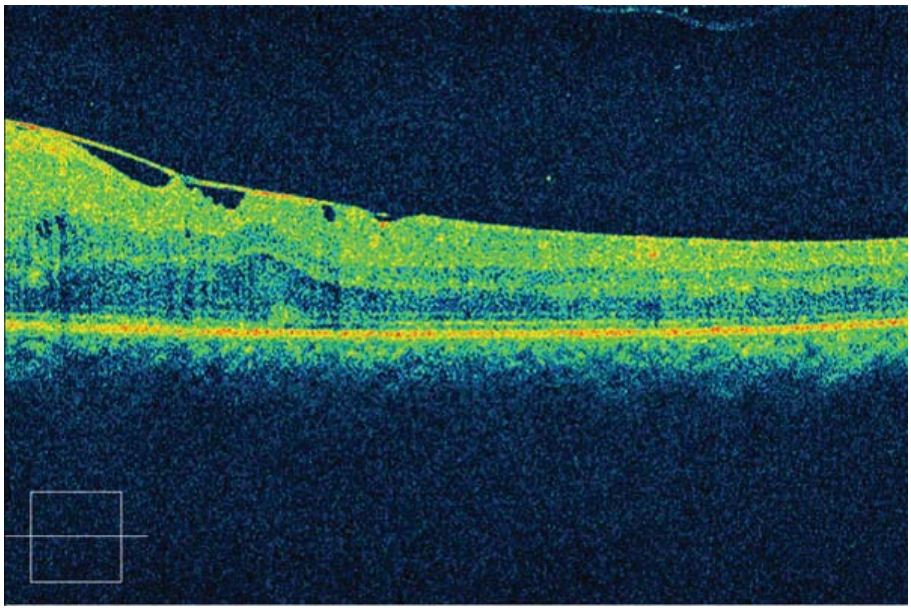

Fig. (12). Optical coherence tomography image of the eye described in Figs. (**2**, **3**, **8** and **11**), showing an epiretinal membrane.

B-scan ultrasound and ultrabiomicroscopy are very useful in this disease, in order to differentiate this tumor (entirely dependent on the retina) from choroidal lesions (Figs. **13**-**15**).

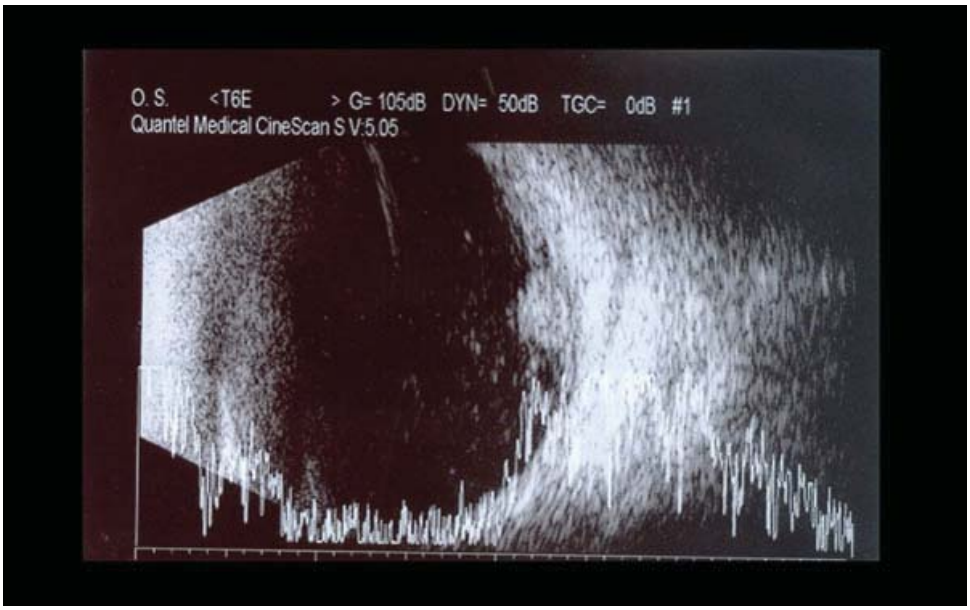

Fig. (13). B-Scan ultrasound of the eye described in Figs. (**2**, **3**, **8**, **11** and **12**), showing a tumor surrounded by scarce subretinal fluid.

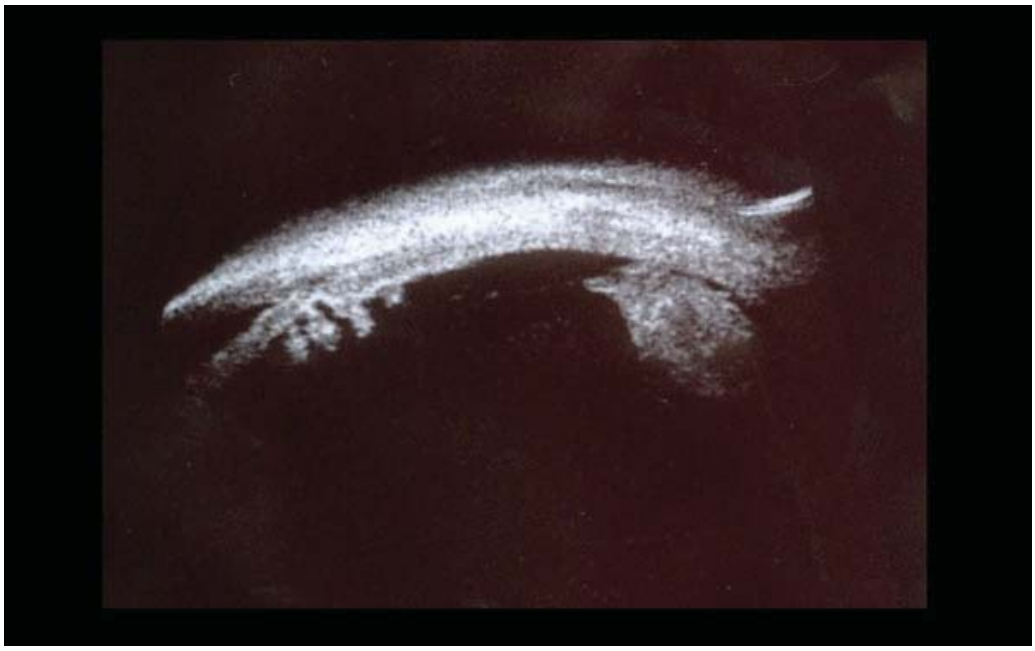

Fig. (14). Ultrabiomicroscopy of the eye described in Figs. (**2**, **3**, **8**, **11**, **12** and **13**), showing a tumor in the far periphery, that is clearly originated on the retina and not the choroid, with surrounding subretinal fluid.

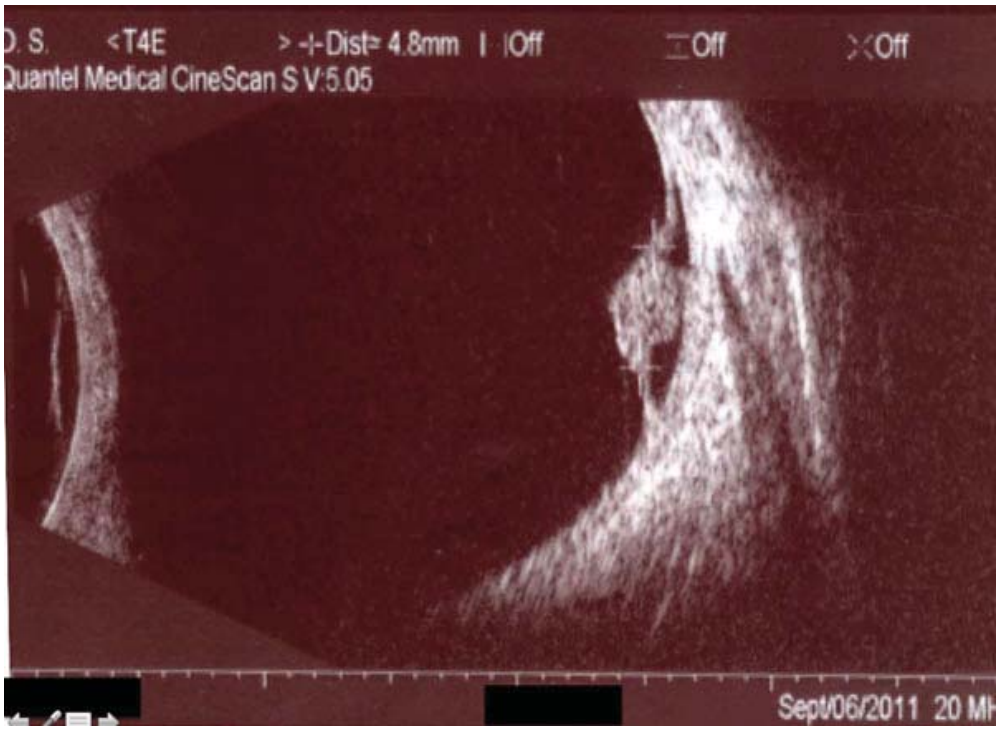

Fig. (15). B-Scan ultrasound of the eye described in Figs. (**5** and **6**), showing a tumor that originates in the retina, surrounded by subretinal fluid.

DIFFERENTIAL DIAGNOSIS

This disease must be differentiated from capillary hemangioma (associated to Von Hippel-Lindau disease or not), amelanotic choroidal melanoma, peripheral exudative hemorrhagic chorioretinopathy and Coats' disease [3].

The main difference between RVPT and a capillary hemangioma is the presence of prominent feeder vessels in the latter, which are really evident on clinical examination and fluorescein angiography. Capillary hemangiomas are also more likely to be multiple and bilateral.

The key to differentiate RVPT from an amelanotic choroidal melanoma is the appearance in B-scan ultrasounds, which in the former shows a mass entirely dependent on the retina, while in the latter the mass originates from the choroid.

In contrast to RVPT, peripheral exudative hemorrhagic chorioretinopathy usually occurs in patients above the age of 60 years, and is characterized by large subretinal exudation and hemorrhage, which sometimes may be confused with a tumor, but no real tumor is seen.

Coats' disease also displays telangiectatic retinal vessels, subretinal exudation and serous retinal detachment, but no tumor is present.

MANAGEMENT

Treatment of RPVT depends on whether there is macular involvement or vitreous hemorrhage.

In eyes where there is no significant epiretinal membrane, cystoid macular edema or vitreous hemorrhage, treatment is directed only to the tumor. There are several treatment modalities that have been described, including cryotherapy, laser photocoagulation [1], photodynamic therapy [5], plaque brachytherapy [6], and intravitreal anti-VEGF agents [7], with very favorable success rate. When performing laser photocoagulation (the treatment of choice for many), the suggested parameters are a large spot (≥500 μm), with long duration (≥300 msec), and low power (100-150 mW), in order to penetrate deeper into the lesion. Frequently, several sessions are required in order to treat the full lesion (Fig. **16**).

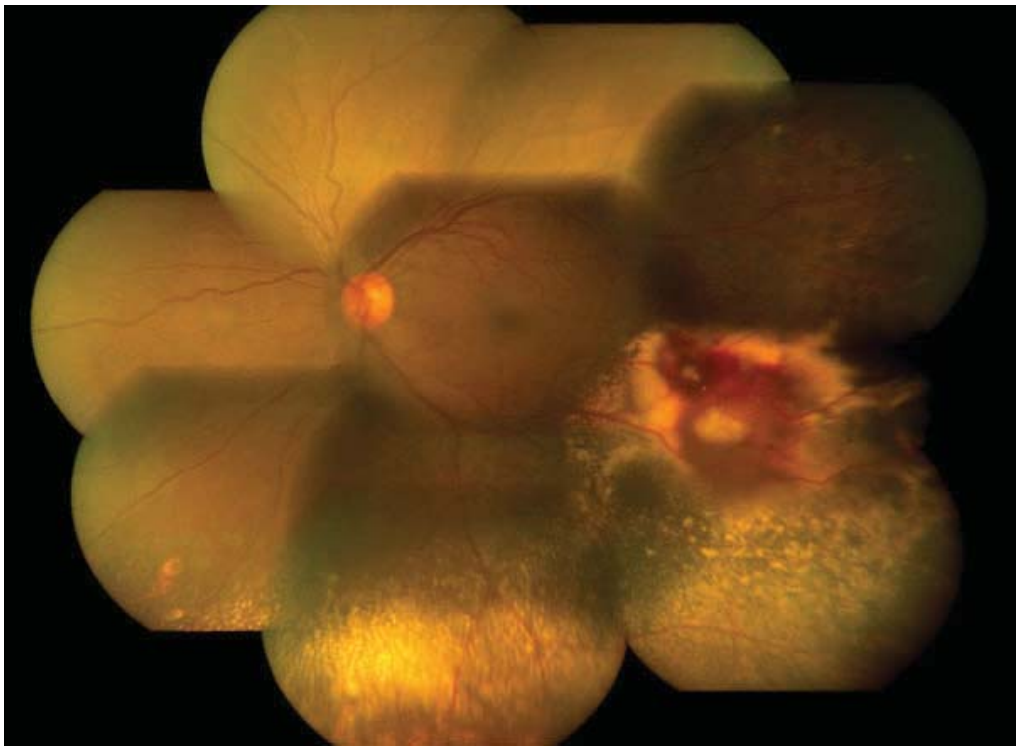

Fig. (16). Composite fundus photograph of the eye described in Fig. (**6**), after treatment with laser photocoagulation, showing marked decrease in lesion size.

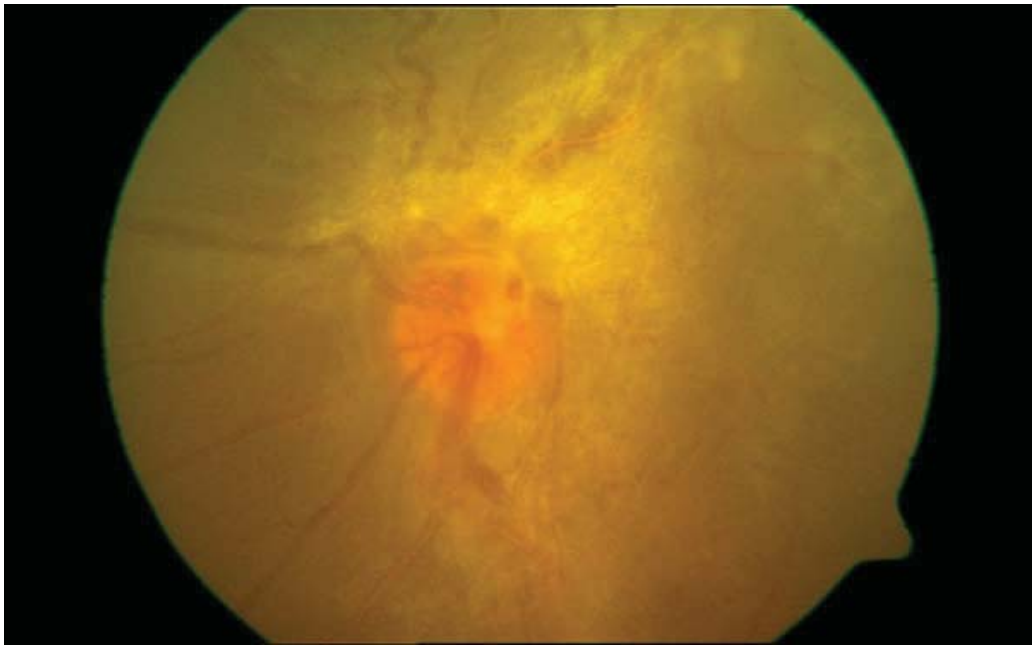

Fig. (17). Fundus photograph of the eye described in Fig. (**3**), showing an epiretinal membrane. Fluorescein angiogram (Fig. **11**) shows that the membrane is vascularized.

In cases where there is significant cystoid macular edema, the tumor should be treated as described above, in addition to topical non-steroidal or steroidal anti-inflammatory medications. Periocular or intraocular steroids or intravitreal anti-VEGF medications should be attempted in case of persistent cystoid macular edema. Care should be taken when administering anti-VEGF agents to patients with a vascularized epiretinal membrane, since contraction of the membrane after intravitreal injection may occur (Figs. **17** and **18**).

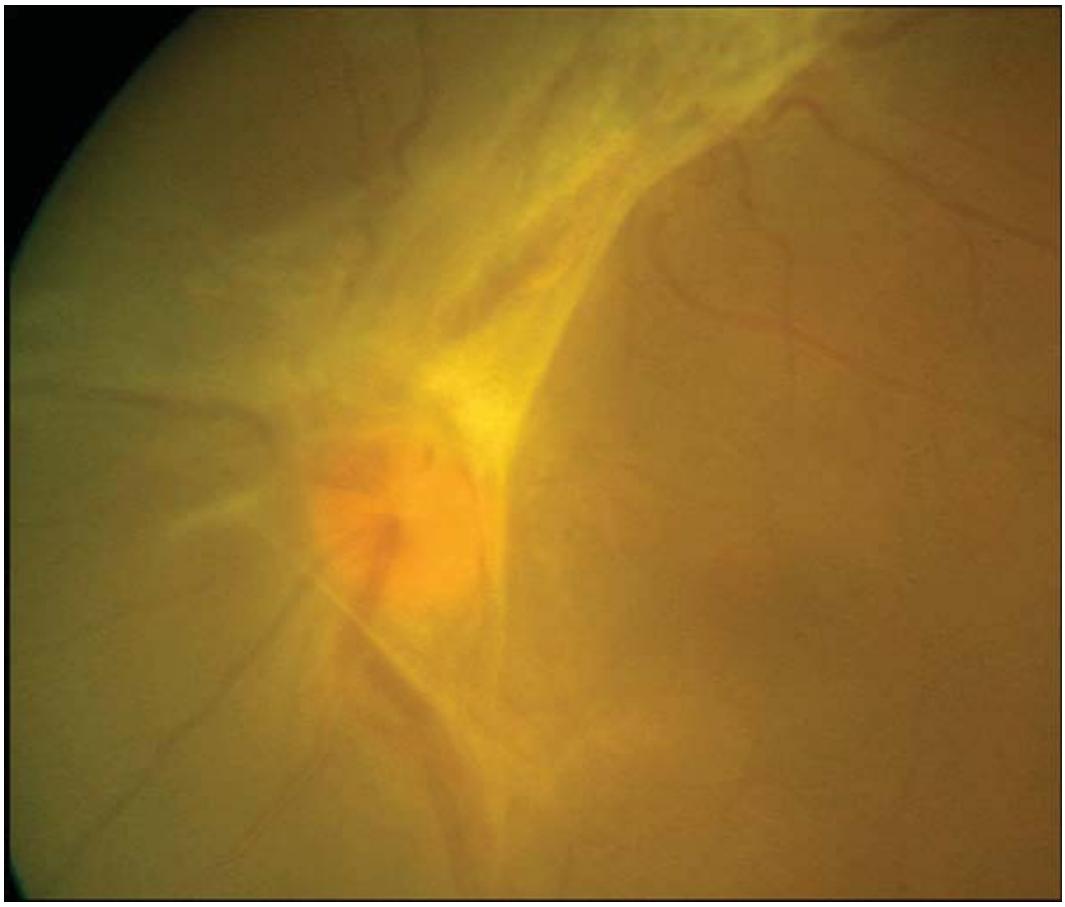

Fig. (18). One week after intravitreal injection of 1.25 mg of bevacizumab, significant contraction of the membrane can be observed.

In cases where there is an epiretinal membrane and/or persistent vitreous hemorrhage that account for significant decrease of visual acuity, the treatment of choice is pars-plana vitrectomy with removal of the epiretinal membrane (Fig. **19**) and endophotocoagulation of the tumor.

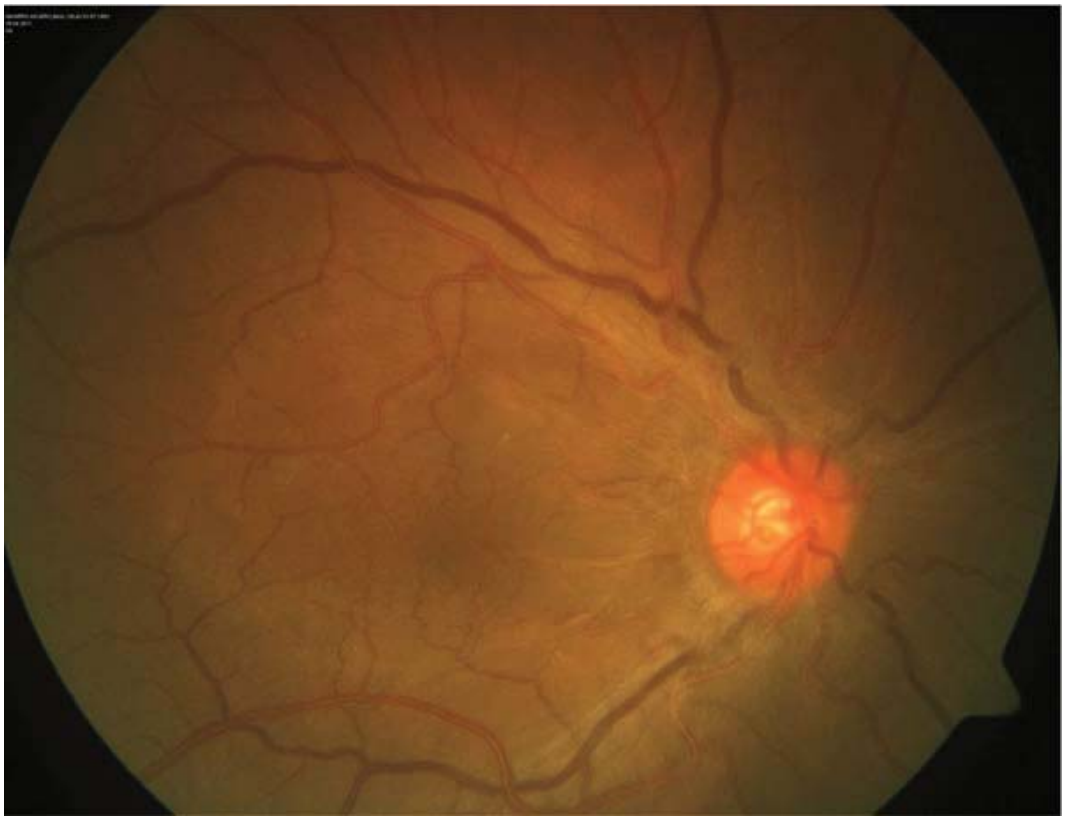

Fig. (19). Fundus photograph of the eye described in Fig. (**7**), after pars plana vitrectomy and removal of the epiretinal membrane. There is some persistent vascular tortuosity.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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[http://dx.doi.org/10.1038/sj.eye.6702782] [PMID: 17347676]

CHAPTER 25

Melanocytoma

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[2] *Hospital General "Dr. Manuel Gea González", Mexico City, Mexico*

Melanocytoma is a variant of a melanocytic nevus, which usually appears in the optic disc (although it may appear anywhere in the uveal tract), characterized by a very dark color and composed by heavily pigmented round to oval cells with small, round, uniform nuclei [1].

ESSENTIALS OF DIAGNOSIS

Melanocytomas appear as a very dark mass, usually near the optic disc, although they may be observed in any component of the uveal tract. Most of them are asymptomatic, but some visual loss is expected in one fourth of the cases, usually related to the presence of intra or subretinal fluid secondary to exudation [2]. More severe visual loss may occur in case of an associated retinal vein occlusion, tumor necrosis, malignant transformation or choroidal neovascularization (Fig. **3**) [1 - 6].

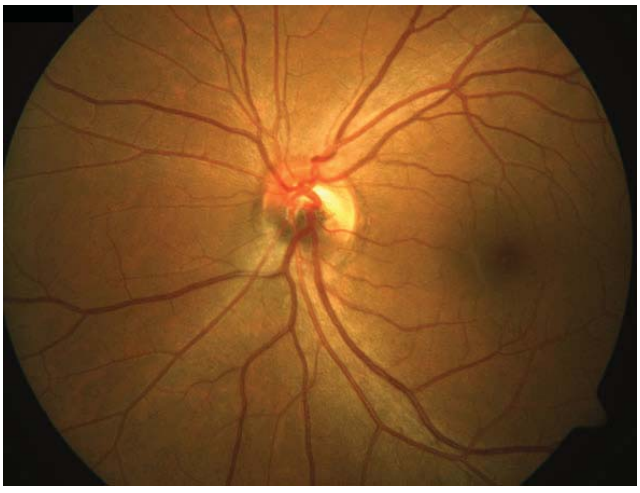

Fig. (1). Fundus photograph showing an intensely pigmented lesion on the inferior aspect of the optic nerve.

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The diagnosis of melanocytoma is usually reached with fundoscopic examination, where a very darkly pigmented mass is observed over or near the optic disc (Figs. **1**-**3**). Rarely, melanocytomas may appear elsewhere, making the diagnostic process harder (Fig. **4**). Since the tumor usually involves different layers of the retina, it may obscure some features such as vessels or the border of the optic disc.

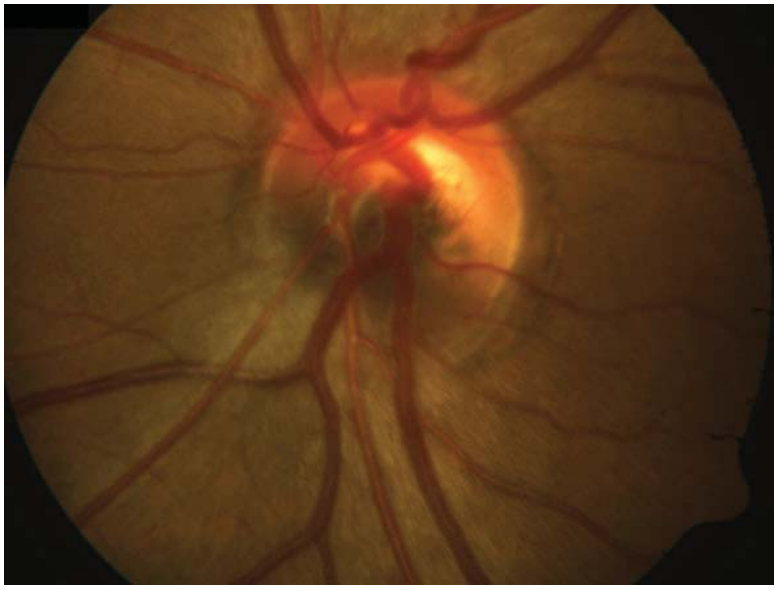

Fig. (2). Close-up of the same lesion shown in Fig. (**1**).

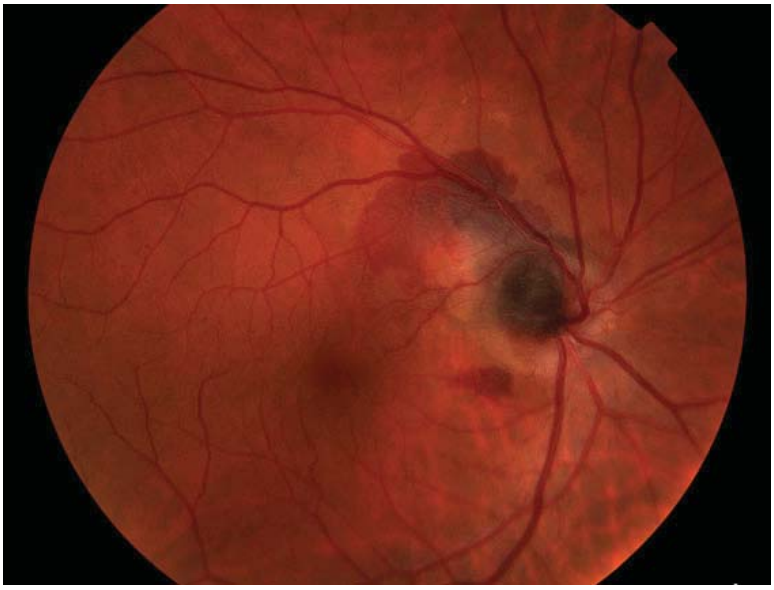

Fig. (3). Fundus photograph showing optic disc melanocytoma associated with subretinal hemorrhage due to CNV.

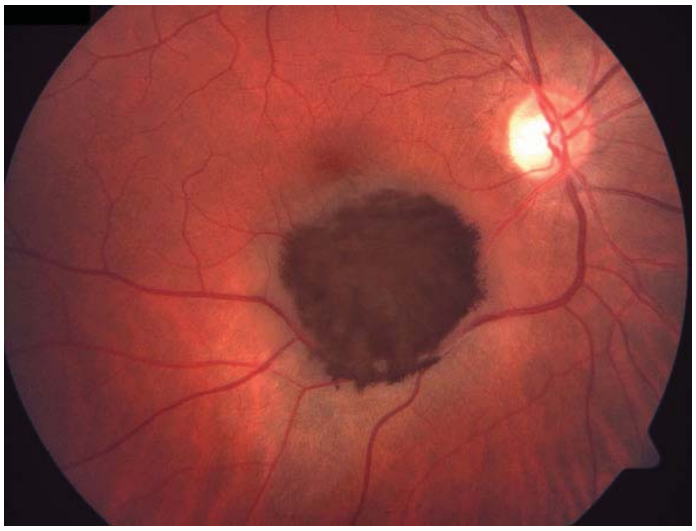

Fig. (4). Fundus photograph showing a dark pigmented lesion that appears to have subretinal, intraretinal and epiretinal components.

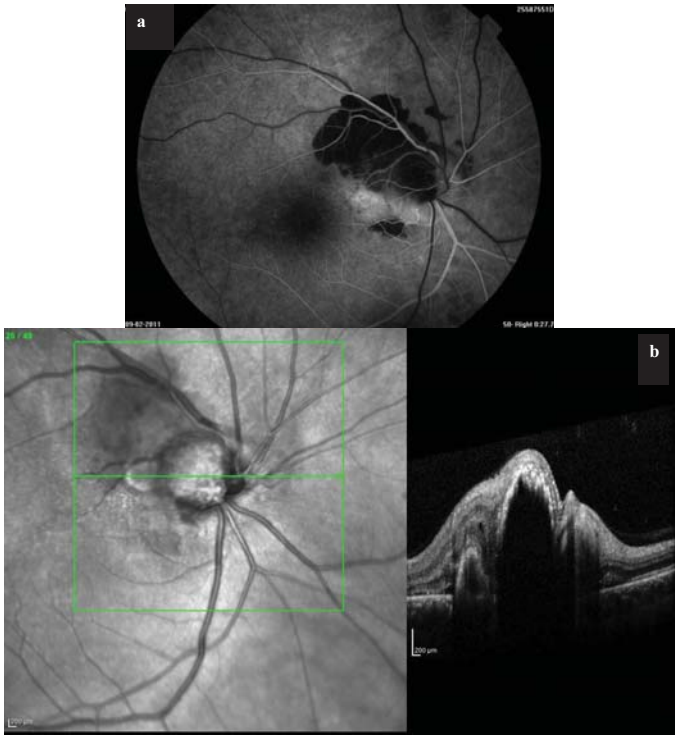

Fig. (5). FA and OCT of the same patient of Fig. (**3**). (**a**) Fluorescein angiogram shows an area of hypofluorescence that results from subretinal hemorrhage and optic disc melanocytoma, as well as a peripapillary focus of hyperfluorescence (CNV) in early arteriovenous phase. (**b**) Spectral domain OCT of the lesion shows hyper-reflectivity at its anterior tumor surface and dense posterior shadowing with an optically empty appearance.

Fluorescein angiogram shows an area of hypofluorescence secondary to blockage of the normal choroidal, retinal and/or optic nerve fluorescence (Fig. **5a**). Optical coherence tomography of the lesion shows an elevated mass with a very hyper-reflective internal surface that obscures the underlying tissue (Figs. **5b** and **6**), which may be accompanied by intra or subretinal fluid (Fig. **7**). Ultrasonography may be useful to document the presence and growth of a mass (Fig. **8**), although it is hard to differentiate a melanocytoma from other elevated lesions of the optic disc by these means.

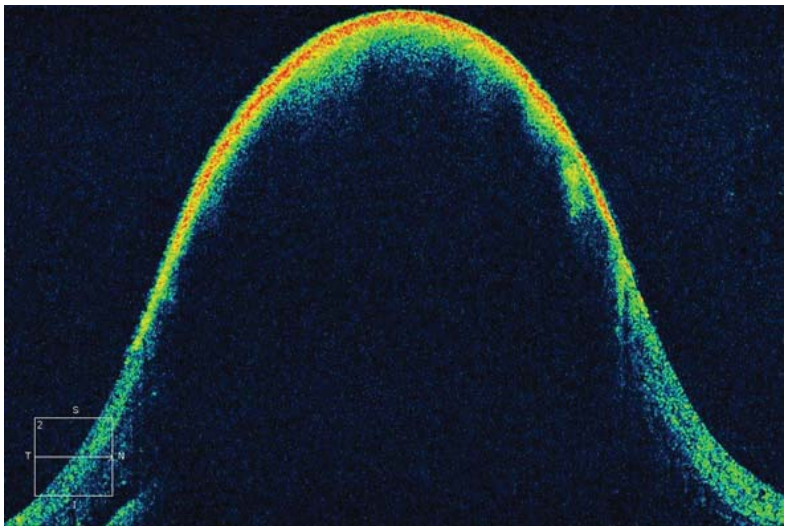

Fig. (6). OCT of the lesion shown in Fig. (**4**), showing elevation of the retina, as well as a very hyper-reflective internal surface which obscures the underlying tissue.

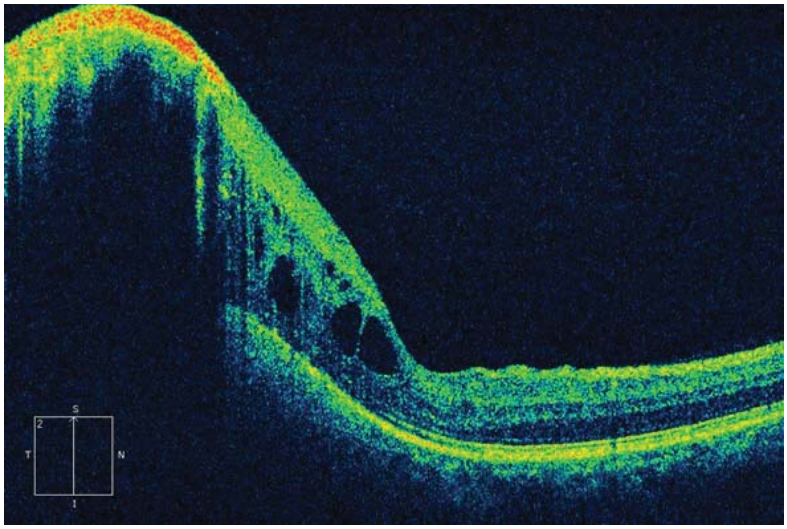

Fig. (7). OCT of the macula of the same lesion shown in Figs. (**4** and **6**), which shows the presence of intraretinal fluid.

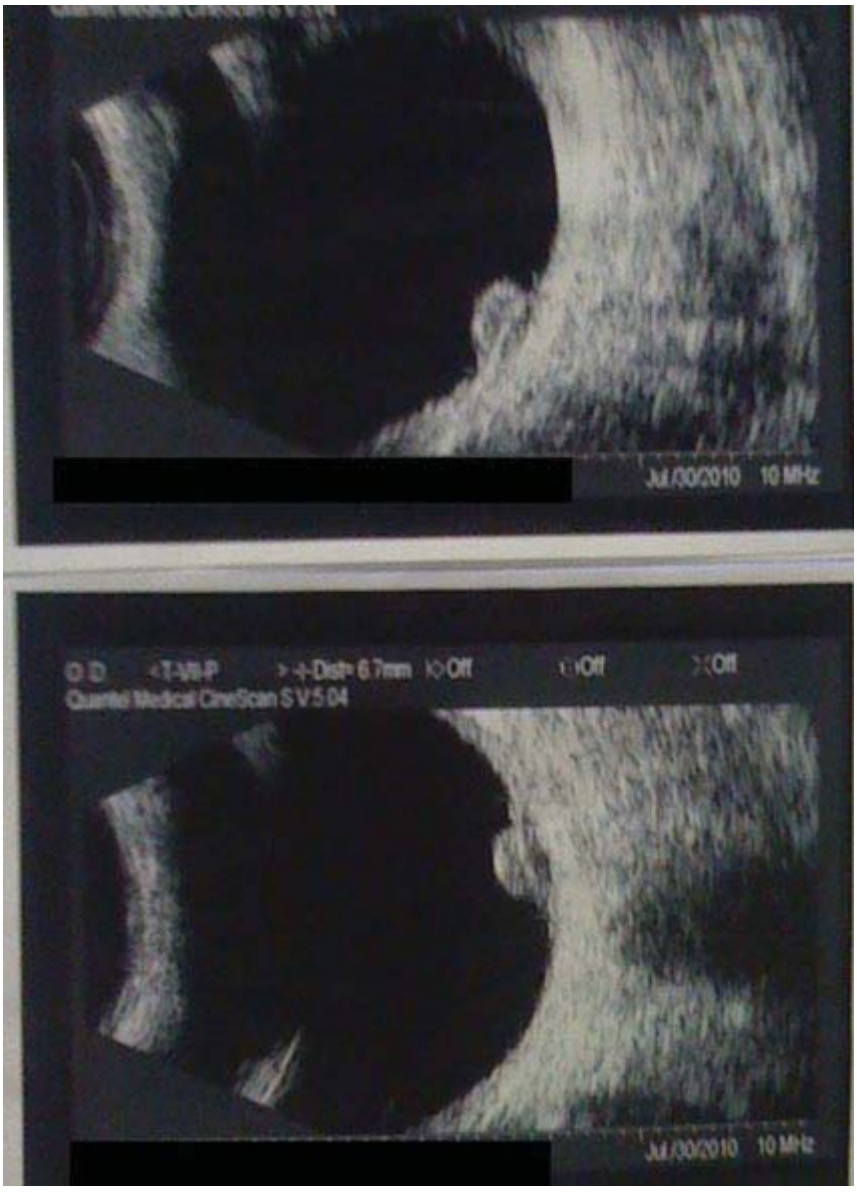

Fig. (8). B-scan ultrasound showing a tumor in the posterior pole, which apparently has an epiretinal and a subretinal component.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis must be made with choroidal melanoma. There are several characteristics that may point to melanocytoma, such as the intense pigmentation, the fact that melanocytoma affects several layers of the retina but melanomas stem from the choroid, and that melanomas rarely, if ever, involve the optic disc. Other diagnoses that need to be considered include pigmented lesions

such as choroidal nevi or congenital hypertrophy of the retinal pigment epithelium. A combined hamartoma of the retina and retinal pigment epithelium may also present as pigmented tissue over the retina, near the optic disc, that spans several layers of the retina. This hamartoma, however, lacks the intense pigmentation of a melanocytoma, and usually causes folds of the internal retinal surface.

MANAGEMENT

Melanocytomas are lesions with good prognosis. Since most tumors are asymptomatic, annual examination of the fundus is indicated to detect malignant transformation. Cases with intraretinal of subretinal fluid, or choroidal neovascularization may be treated with intravitreal anti-VEGF agents [6, 7].

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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[http://dx.doi.org/10.2147/OPTH.S80152] [PMID: 25834382]

CHAPTER 26

Congenital Hypertrophy of the Retinal Pigment Epithelium

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Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a hamartoma of the retinal pigment epithelium (RPE) [1], first described by Reese and Jones in the 1950s [2, 3], but its congenital nature was not described until 1974 by Buettner *et al*. [4].

ESSENTIALS OF DIAGNOSIS

It is characterized by a flat, well-demarcated, darkly pigmented lesion, typically located at the midperiphery of the retina [2, 5, 6]. It has two different clinical manifestations: a solitary congenital form whose etiology is still not well understood, but it is believed to be the result of a local process occurring during retina development [7]; and the lesions occurring as part of the Familial Adenomatous Polyposis (FAP) clinical spectrum, in which a truncating mutation between codons 463 and 1387 in the APC gene induces the additional formation of intestinal polyps, osteomas, skin tumors, supernumerary teeth and desmoid tumor (Gardner's syndrome) [2, 7, 8].

Solitary CHRPE, also named "benign melanoma of the RPE" or "hypertrophy with hyperpigmentation of the RPE" [6], is usually discovered coincidentally during a fundus examination [6]. It can present as single (Figs. **1**, **4**, **5**) or multiple (Figs. **2** and **3**) hyperpigmented lesions, which can be surrounded by a marginal halo and depigmented lacunae within the lesions (Figs. **4** and **5**) [5, 6]. The prevalence in normal population ranges between 1.2 and 4.4% [9 - 11]. The coloration and shape of the lesions are variable and can range from gray to black and from round to oval respectively [9]. There is no predilection for gender, although some studies have found a slightly higher incidence in females [6], and

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the most frequent localization seems to be the inferonasal quadrant [5]. The size of the lesion varies widely and can range from 3 to 11 mm, and the median distance to the fovea and optic nerve head is approximately 12 mm [5].

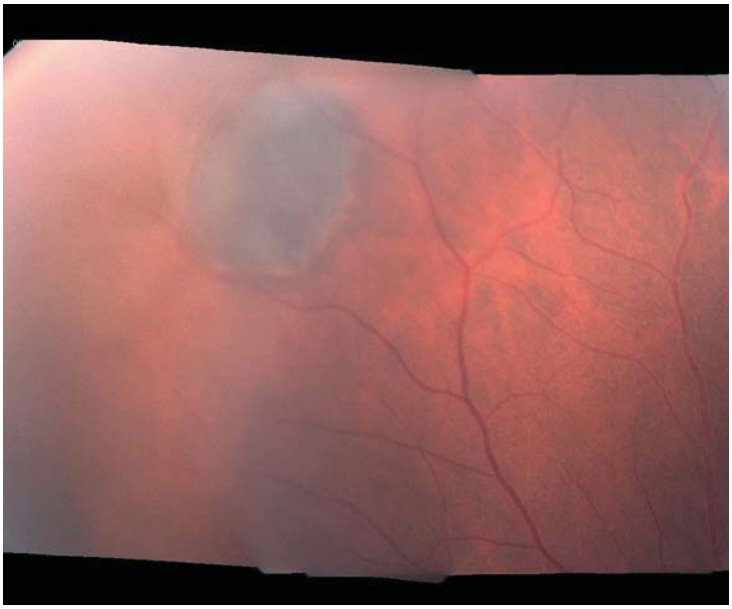

Fig. (1). Peripheral fundus photograph showing an intensely pigmented lesion with well-demarcated borders and a hypopigmented halo around it.

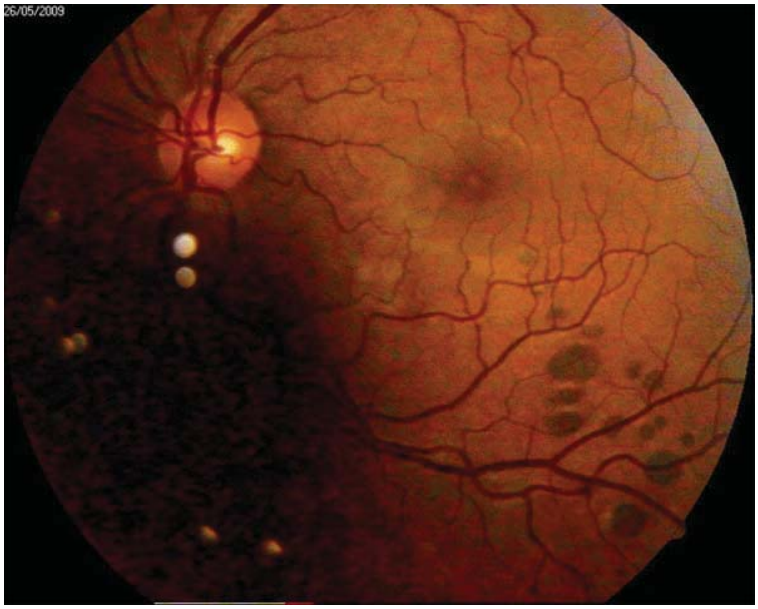

Fig. (2). Congenital grouped pigmentation of the retina (bear tracks) (Courtesy of Mitzy E. Torres Soriano MD).

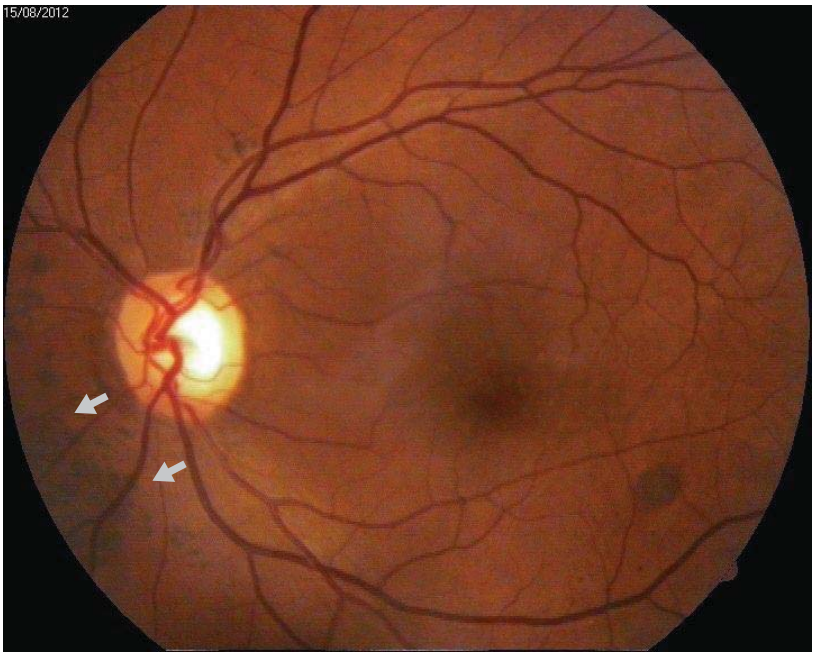

Fig. (3). Grouped congenital hypertrophy of the retinal pigment epithelium (Grey arrows) (Courtesy of Mitzy E. Torres Soriano MD).

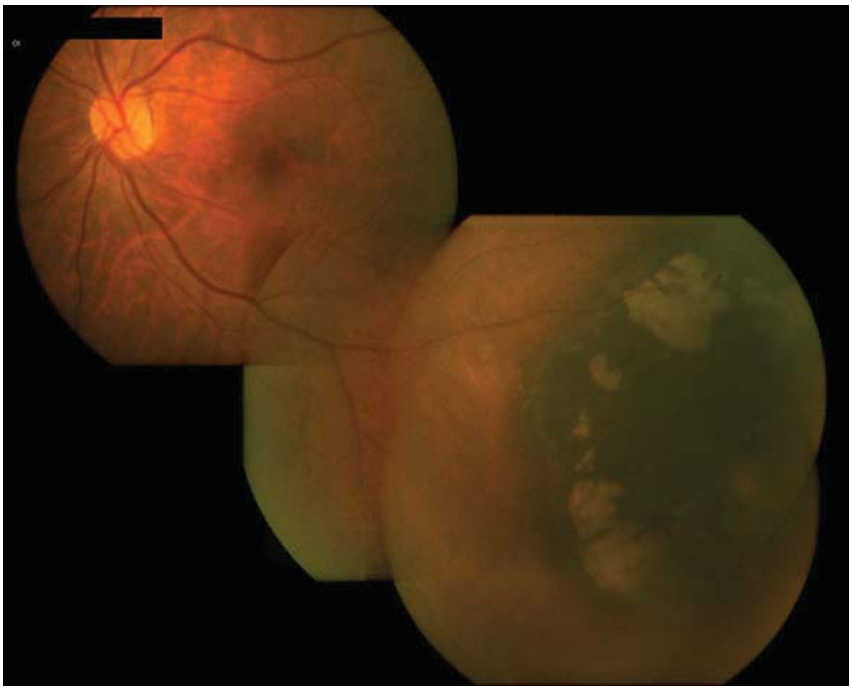

Fig. (4). Image showing a pigmented lesion in the inferotemporal periphery, with well-demarcated borders and hypopigmented lacunae within the lesion.

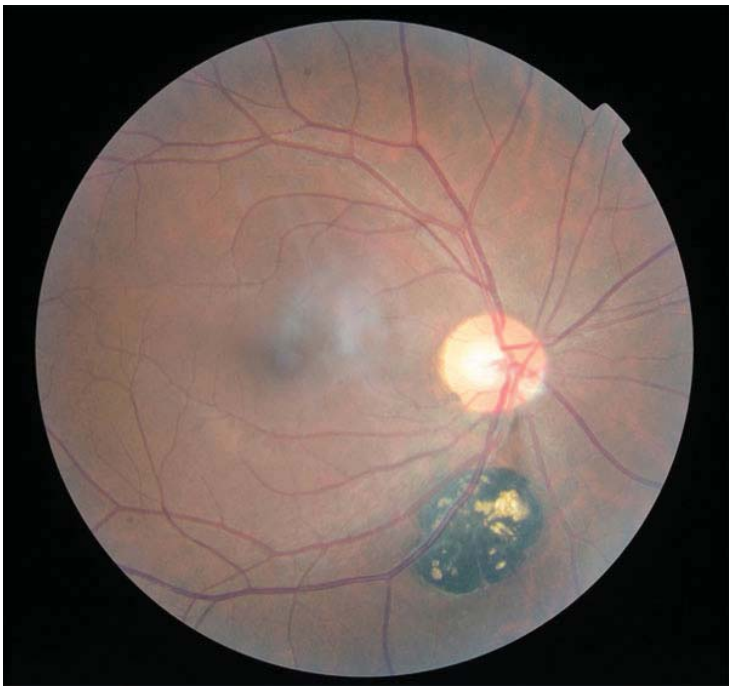

Fig. (5). Congenital hypertrophy of the retinal pigment epithelium with depigmented lacunae (Courtesy of Manuel Torres López MD).

Although it is normally considered a stable, asymptomatic and benign lesion, recent studies have documented flat enlargement of the lesions in up to 80% of the patients after three years of photographic follow-up, with a median rate of enlargement of up to 10 μm/month (2 μm/mm lesion base/month) [6]. Furthermore, the depigmented lacunae also show slow enlargement over time in 40% of cases [6]. Risk of malignancy of CHRPE is very low and extremely rare. However, there are some reports in which classic CHRPE lesions spawn elevated nodules that develop its own retinal blood supply and that turn out to be epithelioma or malignant epitheliomas after histopathological analysis (previously wrongly labeled as adenomas and adenocarcinomas) [12, 13]. A relative visual field defect coinciding with the anatomical location of the lesion has been described and can evolve from a relative scotoma in children to an absolute scotoma in adults [6, 14]. Vision loss may also occur in those nodular forms of CHRPE, mainly due to remote macular edema [6, 15].

On fundus photographs, CHRPE appears as a well-demarcated, dark lesion. Pigmentation may be heterogeneous within lesion and can be associated to other minor findings like white without pressure, vascular sheathing and depigmented linear RPE streaks (Figs. **1**, **4**, **5**). Multiple areas of grouped congenital hyper-

trophy of the retinal pigment epithelium (CHRPE) are commonly called "bear tracks" (Figs. **2** and **3**) [6, 16]. Fluorescein angiography shows an early blockage of the choroidal flush [16]; Optical coherence tomography (OCT) shows thinning of the neurosensory retina overlaying the CHRPE [14]. It also shows a disorganization of the internal retinal architecture, the photoreceptor layer is markedly attenuated while the RPE emits a higher and thicker signal (enhanced reflectivity), which in turn preclude the observation of the underlying choroidal vessels. The retinal tissue surrounding the CHRPE has normal characteristics by OCT [14].

The histopathology of CHRPE, first described by Kurz and Zimmerman [6], will correlate with the level of pigmentation. Highly pigmented areas of the lesion will show hypertrophic RPE cells with loss of nuclear basal polarity, variable number of rounded intact melanosomes and little or no lipofuscin, over an otherwise normal Bruch's membrane [17]. Depigmented lacunae show thin RPE cells, with cytoplasmic vacuoles and very few small melanosomes over a thick Bruch's membrane. Photoreceptors overlying the hypertrophic RPE usually show marked degeneration while the choroid remains normal [14, 17].

DIFFERENTIAL DIAGNOSIS

The relevance of correctly diagnosing CHRPE lies in the ability of the clinician to rule out other pigmented lesions with similar features, like choroidal nevus or choroidal melanoma [6]. Furthermore, CHRPE-like bilateral and multifocal lesions may be associated with FAP and Gardner´s Syndrome in which the prevalence is around 90% [18]. Those lesions resemble classic solitary CHRPE; the main differences are the pisciform configuration (fishtail-shaped hypo-pigmented change at one or both ends of an oval, round or bean shaped lesion); and multiplicity of scattered lesions in both eyes [10, 18, 19].

Primary tumors of the RPE, contrary to CHRPE, usually develop feeder vessels, yellow lipoproteinaceous deposits, subretinal exudation and sometimes intraocular inflammation, vitreous traction, posterior synechiae and cataract [12]. Fluorescein angiography accentuates the feeder vessels and mild hyperfluorescence of the tumor [12]. Ultrasonography will show an elevated mass (derby hat-shaped mass) with medium to high internal reflectivity [12].

MANAGEMENT

Normally, CHRPE do not require any treatment besides follow-up with fundus photographs [6, 12]. There is no consensus about the best course of treatment in

case of documented flat enlargement of the lesions which threatens the fovea, in case of nodular transformation or suspected malignant epithelioma. External radiation, plaque brachytherapy, external surgical removal and local photocoagulation are some of the treatment modalities that have been suggested.

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 27

Combined Hamartoma of Retina and Retinal Pigment Epithelium

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ESSENTIALS OF DIAGNOSIS

In 1973, Gass reported a series of 7 patients with an unusual lesion of the retinal pigment epithelium (RPE) and retina simulating either choroidal melanoma or retinoblastoma. He used the term "combined hamartoma of retina and RPE" (CHRRPE) to define it [1]. It is a benign tumor, but it can cause significant visual loss [2]. It is typically found in young children, often with symptoms of strabismus or reduced visual acuity [1].

It is usually a solitary, unilateral lesion located at the optic disc or posterior pole and typically appears slightly elevated, having various amounts of pigmentation, retinal vascular tortuosity, and epiretinal membrane (ERM) [2] (Figs. **1** and **2**).

Different complications may occur that produce decreased visual acuity, particularly with macular tumors, including epiretinal membrane (ERM), macular exudation, macular edema, retinal detachment, vitreous hemorrhage, choroidal neovascularization, foveal or optic disc dragging [1 - 3].

Fluorescein angiography shows hypofluorescence of choroid background in the arterial phase. Retinal vascular is tortuous and telangiectatic. Dye leakage from vessels within the lesion in late phases [2] (Fig. **3**). OCT can reveal elevated lesion with high reflectivity of the inner retina, hypo-reflective shadowing of the underlying tissue and epiretinal membrane [2] (Fig. **4**). B-scan ultrasound can demonstrate slightly elevated solid mass involving the disc and adjacent retina or the macular area.

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Fig. (1). Color fundus photograph: Peripapillary hyperpigmented lesion with exudation in posterior pole.

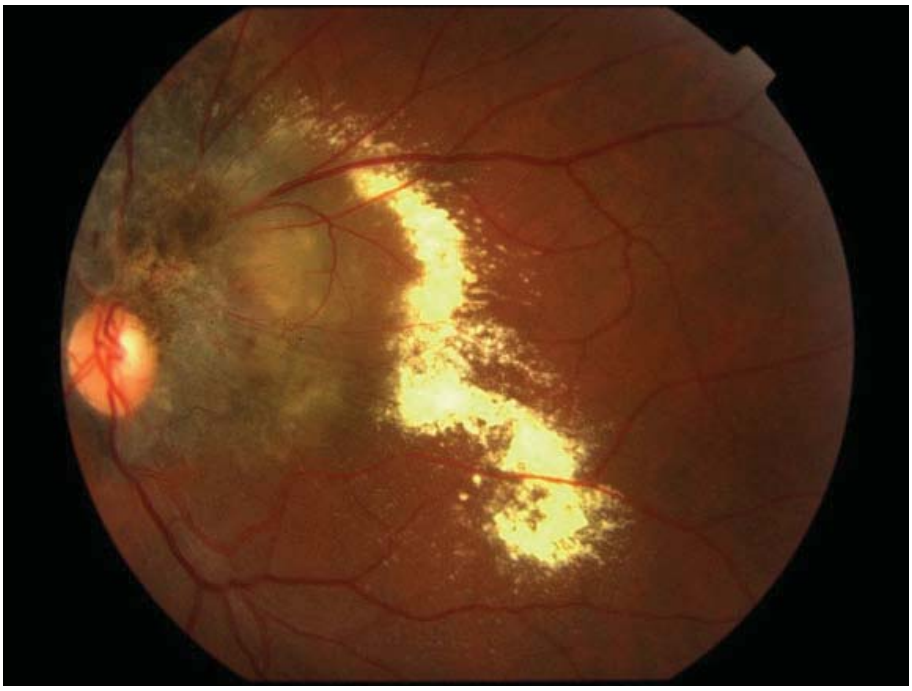

Fig. (2). Color fundus photograph: Exudation in the posterior pole.

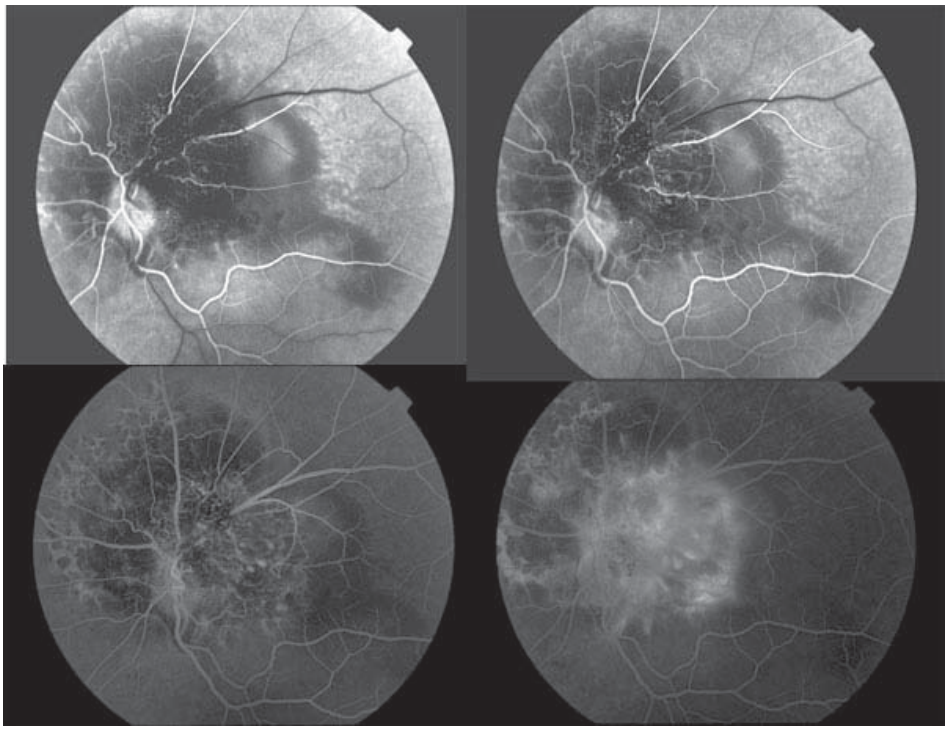

Fig. (3). Fluorescein angiography: Hypofluorescence because of blockage in the early phases, and hyperfluorescence in late phases because of exudation.

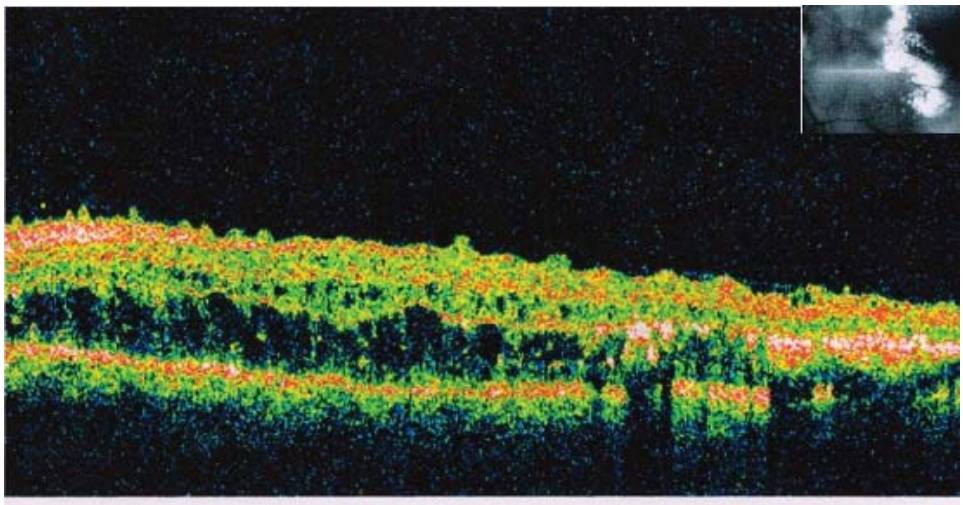

Fig. (4). Epiretinal membrane with contraction of de macular surface and disorganization of the neuroretinal tissue is observed. Intra and subretinal fluid is present.

DIFFERENTIAL DIAGNOSIS

Choroidal melanoma, choroidal nevus, retinoblastoma, toxocariasis, astrocytoma, hemangioma [1].

Sometimes it may be extremely difficult to distinguish between ERM and CHRRPE, but hyperpigmentation may rarely present in ERM [2].

MANAGEMENT

Depends on the type of complications.

Vitrectomy: In retinal detachment, vitreous hemorrhage, and ERM.

ERM: The use of vitrectomy in the management of CHRRPE remains controversial [2 - 4]. It is not recommended in the case of longstanding visual loss or if marked cystoid macular edema is present [2].

In cases of CNV secondary to CHRRPE, sub-macular surgery was reported [3]. And the use of intravitreal injections of anti-VEGF agents has not been found in the literature.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 28

Choroidal Nevi

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ESSENTIALS OF DIAGNOSIS

Choroidal nevi are benign melanocytic tumors of the ocular fundus. They are reported in 6.5% of the general white population [1]. Despite their benign nature and their low potential for causing visual symptoms [2], choroidal nevi have been the subject of interest among ophthalmologists mainly because of their clinical resemblance and potential malignant transformation to choroidal melanoma. Although the true malignant potential of choroidal nevi is not known, these lesions have long been suspected of being precursors of choroidal melanoma [3, 4]. However, most of the interest in choroidal nevi lies in the difficulties associated with differentiating them from small choroidal melanomas leading to delayed or unnecessary treatment with potentially life-threatening consequences or visually damaging complications, respectively [5, 6].

Clinically, choroidal nevi are asymptomatic, and appear as flat melanocytic choroidal lesion; drusen can be present in the surface. They remain unchanged over time (Figs. **1**-**5**).

Optical coherence tomography demonstrated the choroidal mass with overlying drusen and without subretinal fluid (Figs. **4** and **6**).

In ultrasonography, a thickness of ≥2 mm and a largest base diameter of ≥7 mm were most predictive of conversion to melanoma [7].

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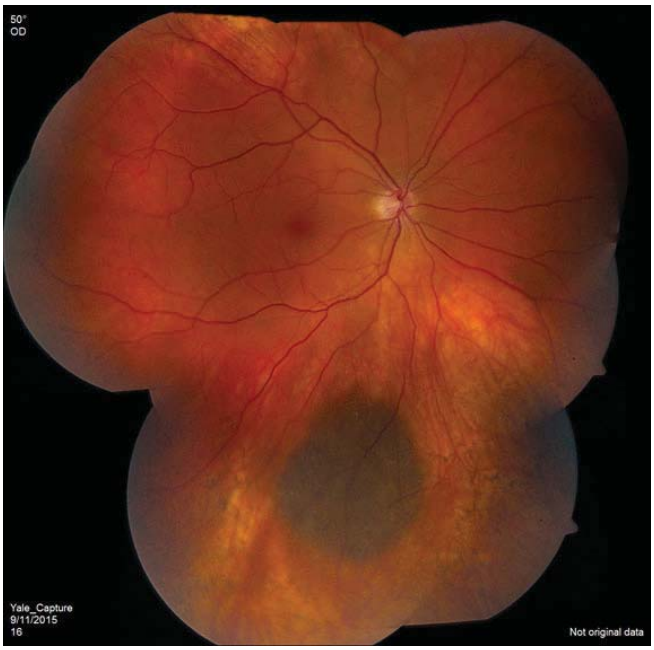

Fig. (1). 59-year-old female with a choroidal melanocytic lesion followed for a year with no signs of growth, subretinal fluid or lipofuscin deposits. Note the overlying drusen and surrounded retinal pigment epithelium changes. The lesion was less than 2 mm thick.

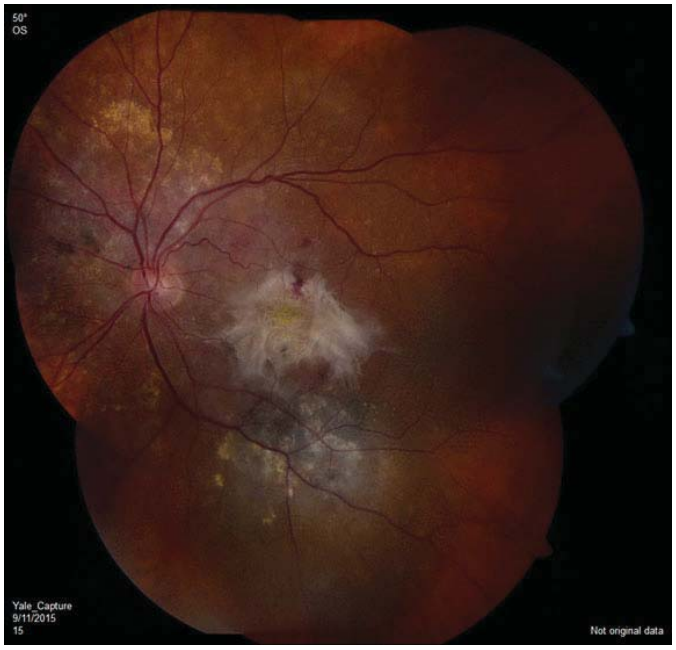

Fig. (2). 88-year-old female with age-related macular degeneration, retinal drusen and a small pigmented melanocytic lesion involving the inferior arcade. Retinal drusen and retinal pigment epithelium hyperplasia are noted over the lesion. Tumor thickness was 2.2 mm. The lesion has been stable with no documented change in 3 years.

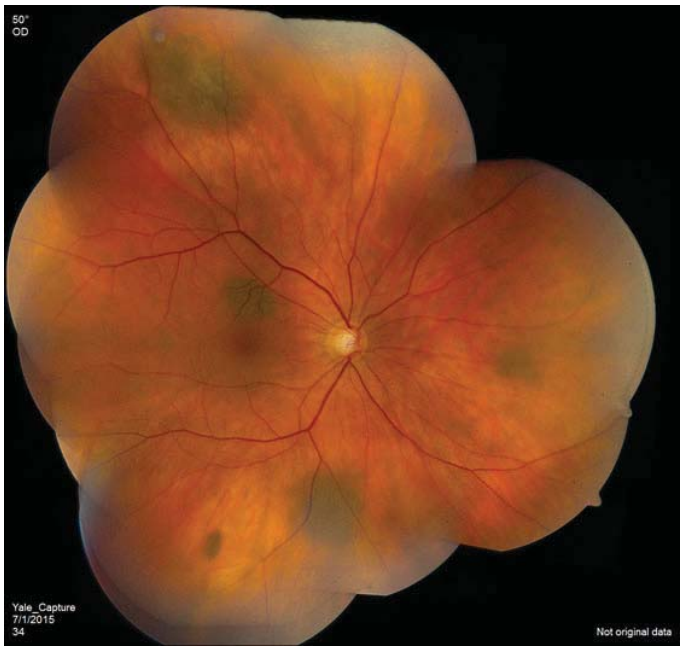

Fig. (3-A). Right eye of a 76-year-old patient with bilateral multiple pigmented choroidal lesions followed for 8 years with no documented change. No history of cutaneous melanoma or any other cancer was present (differential diagnosis includes metastatic cutaneous melanoma and bilateral diffuse uveal proliferation – BDUMP)

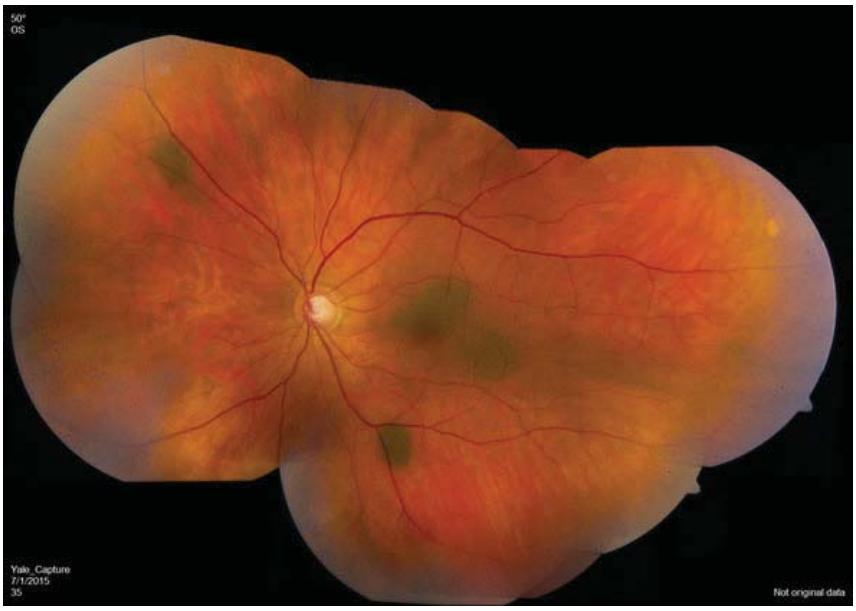

Fig. (3-B). Left eye of a 76-year-old patient with bilateral multiple pigmented choroidal lesions followed for 8 years with no documented change. No history of cutaneous melanoma or any other cancer was present (differential diagnosis includes metastatic cutaneous melanoma and bilateral diffuse uveal proliferation – BDUMP)

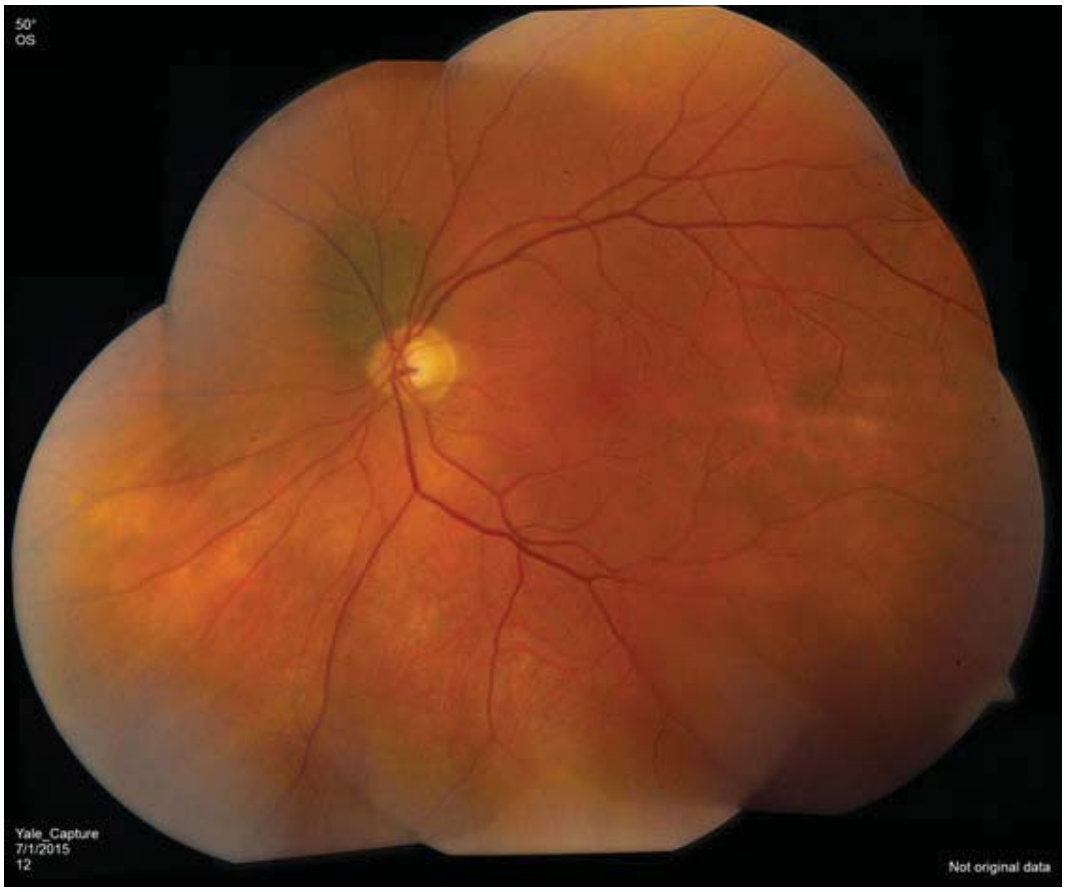

Fig. (4). 79-year-old male followed for 4 years for this 3 x 3 x 1.3 mm choroidal melanocytic lesion adjacent to the optic disc. Below is the optical coherence tomography over the lesion, showing the choroidal mass without subretinal fluid.

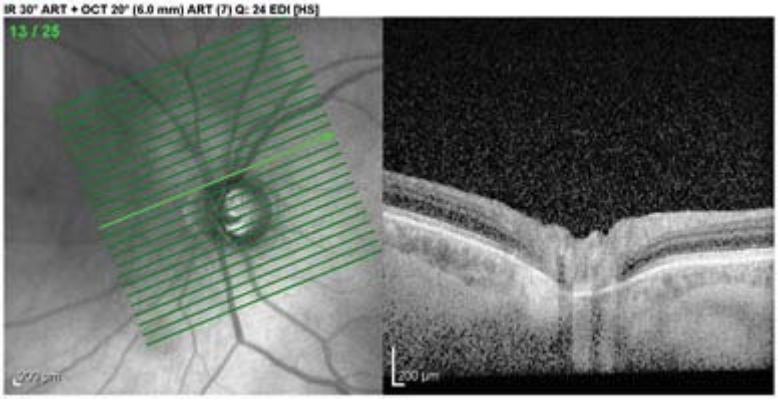

Fig. 5 contd.....

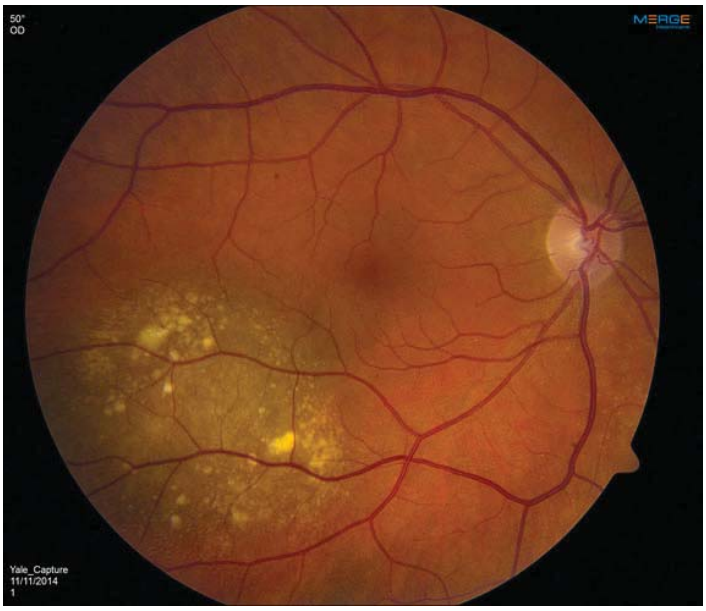

Fig. (5). 53-year-old patient with a choroidal melanocytic lesion with overlying drusen. No subretinal fluid or orange pigmentation was present. This lesion has been stable for 2 years.

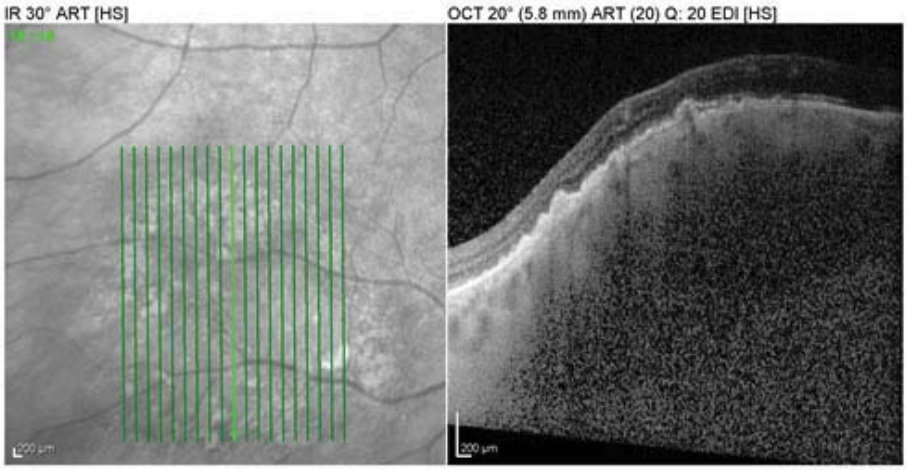

Fig. (6). Optical coherence tomography of the same patient of Fig. (**5**) showing the choroidal mass with overlying drusen and retinal thinning.

DIFFERENTIAL DIAGNOSIS

The conditions that simulate choroidal nevi include choroidal melanoma, congenital hypertrophy of the retinal pigment epithelium (RPE), peripheral exudative hemorrhagic chorioretinopathy, hemorrhagic RPE detachment, choroidal hemangioma, age-related macular degeneration, RPE hyperplasia, and others [8].

But the most important differential diagnosis is choroidal melanoma. Choroidal nevi rarely transform into melanomas, although most choroidal melanomas are thought to arise from pre-existing nevi. The annual rate of malignant transformation of a choroidal nevus was estimated to be one in 8845 [7].

In an analysis of 2514 choroidal nevi, factors predictive of growth into melanoma included greater thickness (more than 2 mm), subretinal fluid, symptoms, orange pigment, margin near disc (rule: To Find Small Ocular Melanoma), and two new features: ultrasonographic hollowness and absence of halo [4]. Choroidal melanocytic tumors that display no factors have 3% chance for growth in five years, and most likely represent choroidal nevi. Tumors that display one factor have 38% chance to grow and those with two or more factors have more than 50% chance. The presence of documented growth in these small tumors increased three times the risk for metastatic disease compared with a tumor without growth [7].

Enlargement of small choroidal melanocytic lesions, in the absence of other risk factors, is not invariably a sign of malignancy. Enlargement of choroidal nevi is a slow process occurring over a mean follow-up of 15 years. This has to be contrasted with growth of small melanomas that occurs faster and is therefore detectable over a shorter period of time: when small tumors start to grow, they generally grow rapidly [4].

MANAGEMENT

No treatment is needed, but it is necessary to follow up periodically to rule out factors predictive of growth into melanoma, clinical and ultrasonographic exam (Fig. **7**) [7].

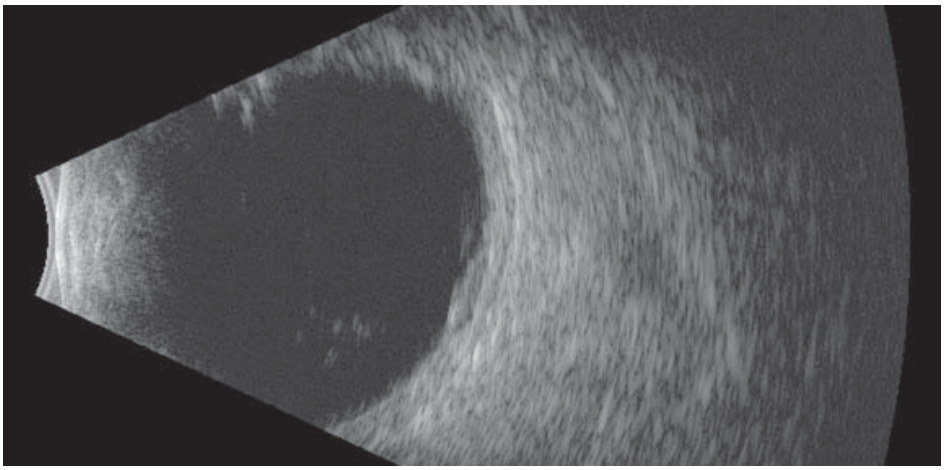

Fig. (7). B-scan ultrasound of the same image as before showing a 2 mm choroidal mass.

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 29

Choroidal Melanoma

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Choroidal melanoma is the most common primary malignant intraocular tumor and the second most common type of primary malignant melanoma in adults, affecting approximately 5–11 individuals per million per year. Uveal melanoma at all ages is more common in men. The mean age at presentation is 60 years [1,2].

Two important risk factors for the development of uveal melanoma are a preexisting choroidal nevus and the presence of congenital ocular or oculodermal melanocytosis [2].

Uveal melanomas arise from melanocytes within the uveal tract [1]. Four cell types are recognized in choroidal and other uveal melanomas: spindle A, spindle B, epithelioid and mixed. The epithelioid cell type is usually the most aggressive, conveying a worse prognosis.

ESSENTIALS OF DIAGNOSIS

Choroidal melanoma appears as a pigmented (55%) (Figs. **1** and **2**), nonpigmented (15%) (Figs. **3** and **4**), or mixed pigmented (30%), elevated, oval-shaped mass [3, 4]. It may assume different configurations: dome-shaped (75%), mushroom-shaped (19%), or flat/diffuse (6%). It is often associated with subretinal fluid, orange pigment, and occasional subretinal or vitreous hemorrhage (Fig. **5**) [3].

Choroidal melanomas may be asymptomatic for prolonged periods of time, and may be found incidentally during ophthalmoscopy. When symptomatic, they may cause photopsia, floaters, visual field loss, or visual acuity loss [2, 3].

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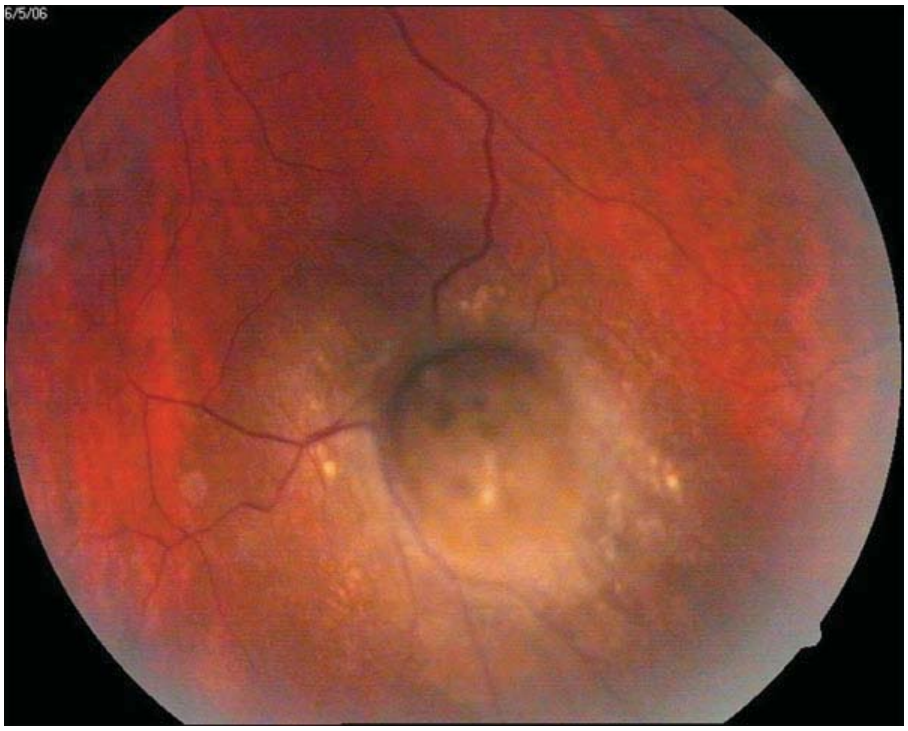

Fig. (1). Peripheral fundus photograph showing a pigmented subretinal mass surrounded by defects in the retinal pigment epithelium.

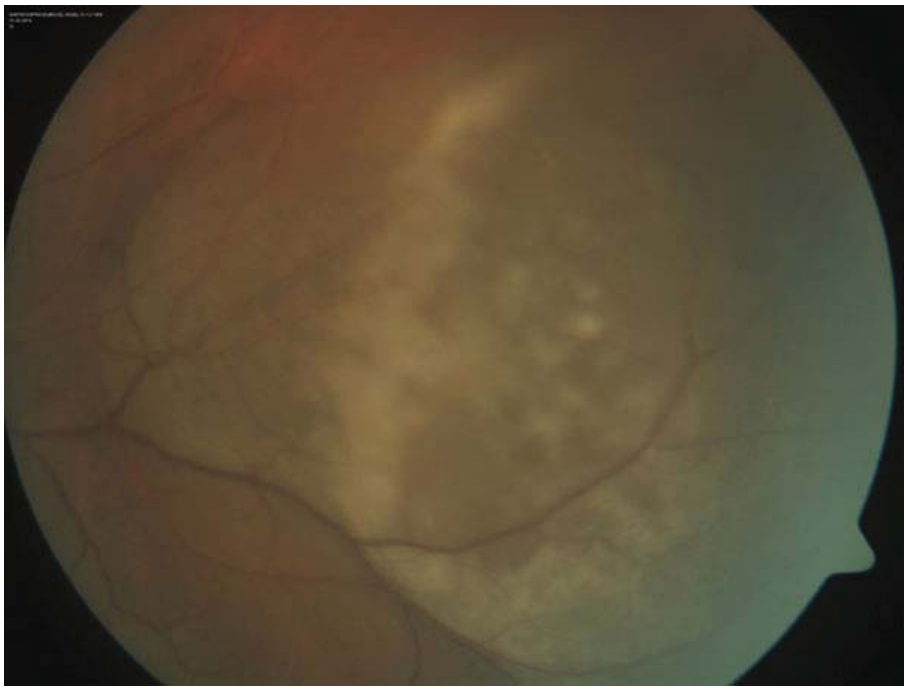

Fig. (2). Peripheral fundus photograph showing a large pigmented subretinal mass.

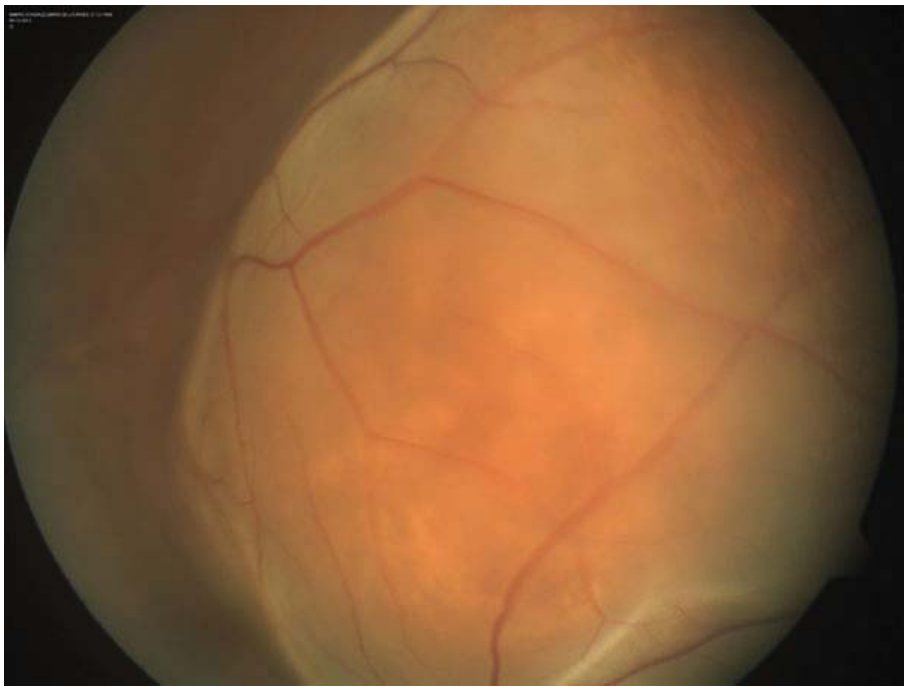

Fig. (3). Peripheral fundus photograph showing a large nonpigmented subretinal mass with surrounding subretinal fluid.

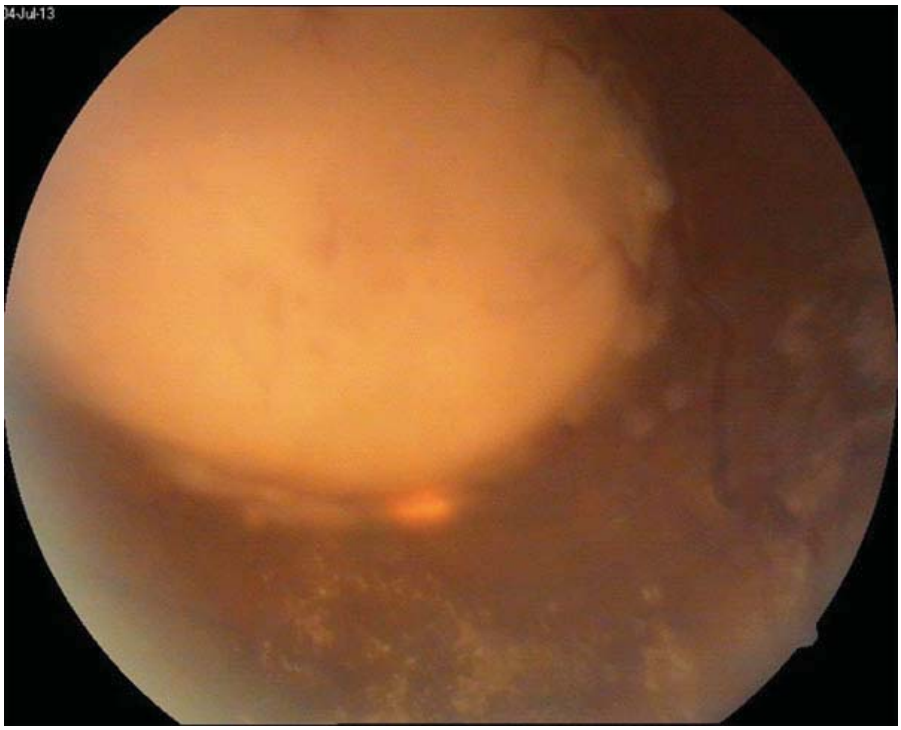

Fig. (4). Peripheral fundus photograph showing a large nonpigmented subretinal mass.

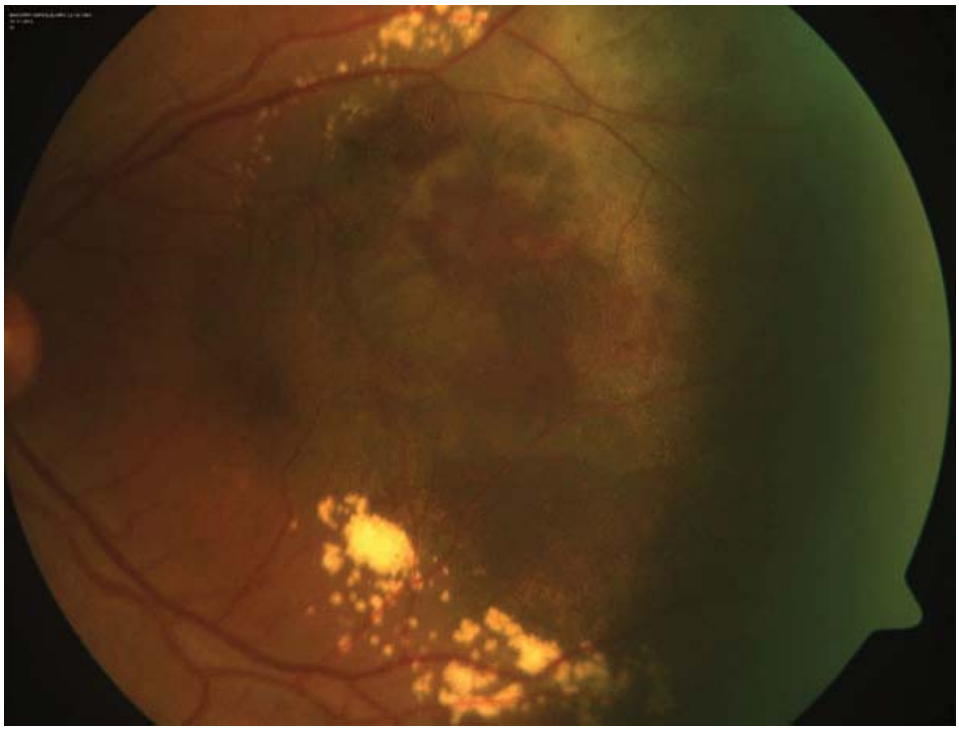

Fig. (5). Fundus photograph showing a very large pigmented subretinal mass with subretinal hemorrhage and surrounded by hard exudates.

Choroidal melanomas are classified into three categories based on the tumor thickness measured by ultrasonography: small (1-2.5 mm apical height, 5-16 mm basal diameter), medium (2.5–10 mm apical height and <16 mm longest basal diameter), and large (apical height >2 mm and >16 mm longest basal diameter or >10 mm apical height, regardless of basal or >8 mm apical height if <2 mm from the disc) [5].

Diagnosis of choroidal melanoma is based on clinical examination and ancillary testing that includes ultrasonography, fluorescein angiography, indocyanine green angiography, enhanced depth imaging optical coherence tomography, auto-fluorescence and fine needle aspiration biopsy [6].

Standardized A-scan ultrasound of the eye is useful for tumors thicker than 2-3 mm. It shows an initial prominent spike, with low-to-medium internal reflectivity. Standardized ultrasound has a diagnostic accuracy of more than 95% (Fig. **6**). B-scan ultrasound is used to establish the diagnosis, evaluate possible extraocular extension, estimate tumor size, show choroidal excavation and orbital shadowing; a collar-stud configuration is pathognomonic [7].

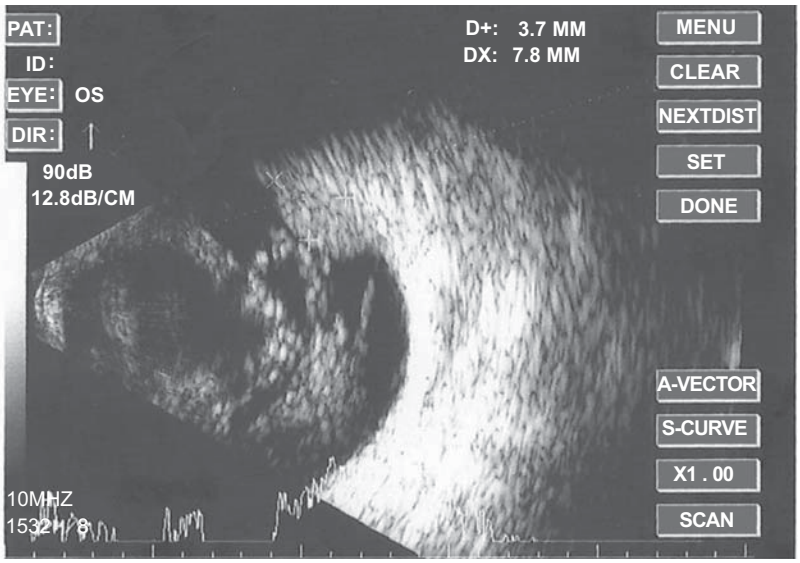

Fig. (6). B-scan ultrasound showing a choroidal mass.

Fluorescein angiography (Figs. **7** and **8**) shows changes ranging from normal to hypofluorescence secondary to blockage of background. Some choroidal melanomas demonstrate intrinsic vascularization with a "double circulation pattern", that refers to simultaneous fluorescence of retinal and choroidal circulation within the tumor. This pattern is infrequent, but when found it is very suggestive of choroidal melanoma [8].

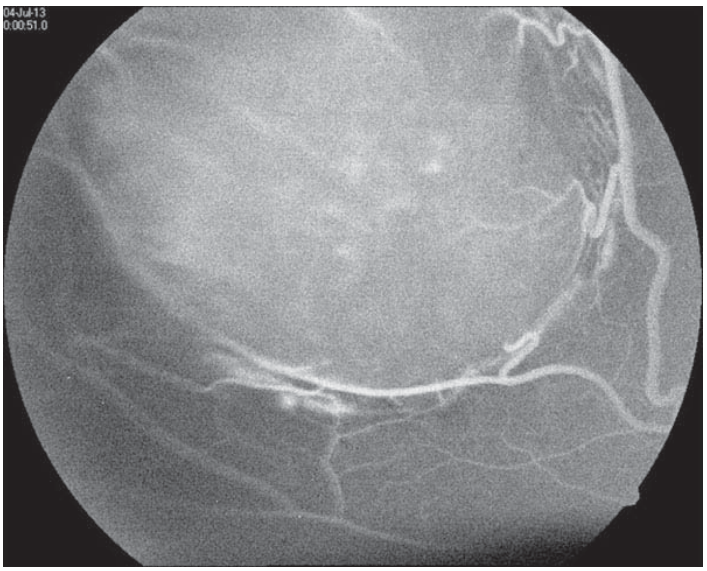

Fig. (7). Fluorescein angiogram of the same case as Fig. (**1**), showing blockage of choroidal fluorescence by the tumor, and surrounding retinal pigment epithelium defects.

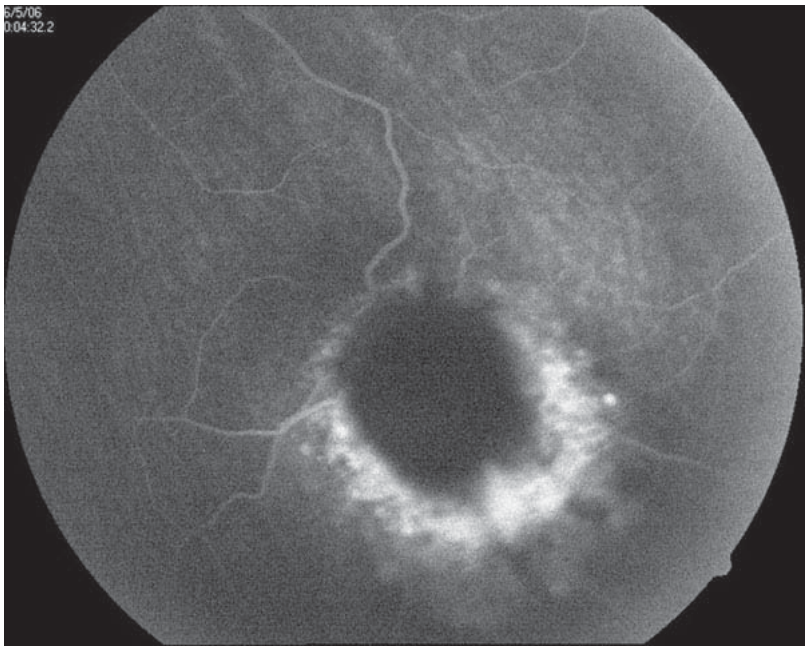

Fig. (8). Fluorescein angiogram of the same case as Fig. (**4**) showing mild hyperfluorescence of the tumor.

DIFFERENTIAL DIAGNOSIS

Choroidal nevus, peripheral exudative hemorrhagic chorioretinopathy, congenital hypertrophy of the RPE, choroidal hemangioma, choroidal metastasis, uveal effusion and retinal detachment are all differential diagnoses [2].

MANAGEMENT

The management of choroidal melanoma depends on tumor size, location, associated features, status of the contralateral eye, systemic status, and patient preference [3]. The first step in treatment of uveal melanoma is to assess metastatic disease; systemic monitoring with physical examination, liver function tests, chest tomography, PET scan and brain imaging using MRI are needed. After systemic evaluation, the tumor may be treated based on the following recommendations:

- Small tumors usually respond to transpupillary thermotherapy, photodynamic therapy, proton beam radiation or iodine radiotherapy plaque.
- Medium tumors are treated with iodine radiotherapy plaque, proton beam radiation therapy or enucleation.
- Large tumors need an extensive evaluation for metastatic disease and usually require enucleation [3].

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 30

Choroidal Metastasis

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Metastatic lesions are the most common malignancy of the eye, with the choroid as the most common location for ocular metastases. Choroidal metastases have been recorded in up to 12% of patients with solid tumors during necropsy [1]. Breast and lung cancers are most likely to metastasize to the choroid, but metastases have been reported with thyroid carcinomas, skin melanomas, gastrointestinal tumors, and pelvic cancers. There is a high rate of concurrent extra-ocular metastases in patients with choroidal lesions (37 to 86%), but up to 32% have no other metastatic lesions when ocular involvement is diagnosed [2].

ESSENTIALS OF DIAGNOSIS

Clinical features: Symptoms include decreased visual acuity, scotoma, metamorphopsia, photopsia, floaters, and pain [2 - 4]. Patients may also be asymptomatic. The lesions are bilateral in 36 to 56% of patients at diagnosis [2]. The lesions appear as yellow subretinal masses in 94% of patients, and 73% are associated with subretinal fluid (Fig. **1A**) [3, 5]. The lesions are single in most cases but may be multiple, and most are posterior to the equator [5]. Posterior uveitis, anterior uveitis, and conjunctival hyperemia have also been reported in association with choroidal lesions.

Imaging: On autofluorescence, the lesions appear hypoautofluorescent with overlying hyperautofluorescence corresponding to lipofuscin and subretinal fluid [6]. Ultrasonography shows medium to high internal reflectivity with A-scan and the height-to-base ratio is significantly lower than in melanomas [5, 7]. On fluorescein angiography, the lesions typically are hypofluorescent during the arterial and early venous phase, becoming hyperfluorescent in the late venous phase (later than in the case of choroidal hemangioma or melanoma) (Fig. **1B**). They also often contain dilated retinal capillaries with pinpoint leakage at the

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border [4, 6, 8]. Optical coherence tomography may reveal a pattern of hyperintense irregular spots in the context of the photoreceptor layer and in the retinal pigment epithelium, subretinal fluid (Fig. **1C**), and marked irregularity of the retinal pigment epithelium with thickening and gross undulation [9]. With MRI, a metastatic lesion may appear as a well-demarcated mass that is isointense on T1 and hypointense on T2 [10]. Fine needle aspiration biopsy can be used for diagnosis in the case of unidentified primary tumor [4].

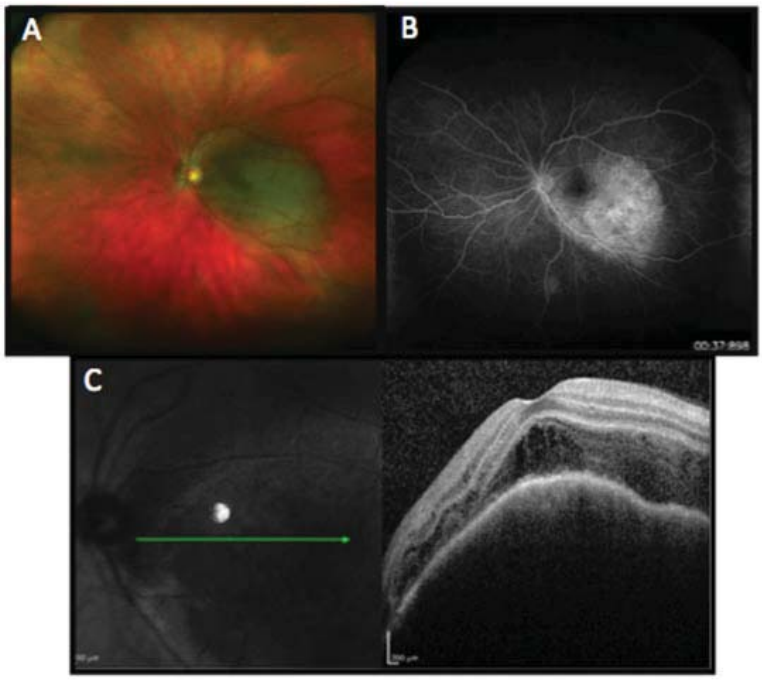

Fig. (1). A 60-year-old female with a history of stage IV non-small cell lung adenocarcinoma treated with chemotherapy was referred for evaluation of a macular lesion noted on an examination for blurred vision of the left eye. Right eye visual acuity and examination was normal. Panel A shows a large yellow choroidal mass in the macula of the left eye on wide-angle fundus photography. Fluorescein angiography showed diffuse hyperfluorescence throughout the lesion with punctate hyperfluorescence on the margins (panel B). Macula OCT through the lesion revealed subretinal fluid (panel C). The patient was referred for external beam radiation therapy.

DIFFERENTIAL DIAGNOSIS

1. Choroidal nevus
2. Amelanotic melanoma
3. Lymphoma
4. Choroidal hemangioma
5. Choroidal osteoma
6. Granuloma
7. Posterior scleritis

MANAGEMENT

Therapy should be determined on an individual case basis based on the status of the systemic malignancy and location of the choroidal lesions. External beam radiotherapy is the most common treatment and has reasonable success, with regression in 53-93% of patients [3, 4, 11, 12]. Other reported treatments include gamma knife radiosurgery (GKR), proton beam radiotherapy, plaque brachytherapy, transpupillary thermotherapy, photodynamic therapy, and intravitreal injections of antiangiogenic agents. Successful results with gamma knife radiosurgery have been reported in 2 trials, with the larger study (57 patients) demonstrating a 63% response rate at 7 months [13, 14]. Proton beam radiotherapy was used in a trial composed of 63 patients, with 84% demonstrating regression [15]. Plaque brachytherapy was investigated in a study of 36 patients, and 94% of patients had regression lasting at least 11 months [16]. Transpupillary thermotherapy was employed in the study of 59 eyes with regression or inhibition of growth in 71% [17]. The use of anti-VEGF injections has been described in multiple case reports, and pooled analysis of 20 patients showed that intravitreal bevacizumab combined with systemic chemotherapy resulted in regression in 77% of patients [18]. Systemic treatments are often needed in addition to local therapy, especially in the case of bilateral, multifocal metastases [3, 4].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 31

Leukemic Retinopathy

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Leukemias are a group of malignant neoplastic disorders of white blood cells, characterized by a diffuse replacement of the bone marrow by neoplastic cells [1]. In these patients, retinopathy is a common finding that has been described in up to 50% of patients at the time of diagnosis [2]. In some cases, ocular findings can be the initial manifestation of the disease [3]. They present themselves more frequently in the acute forms than in the chronic forms, and it can be seen like a primary infiltrate in 3% of the patients and as secondary complications in 39% [4]. Retinal manifestations can occur in about 90% of patients with acute leukemia [5].

ESSENTIALS OF DIAGNOSIS

Ophthalmic manifestations can be classified in two main categories: primary or direct leukemic infiltration and secondary or indirect infiltration.

Direct infiltration can show three patterns: anterior segment manifestations, orbital manifestations and neuro-ophthalmologic signs [1]. Secondary manifestations are the result of the associated hematologic abnormalities such as anemia, thrombocytopenia, hyperviscosity and immunosuppression [6]. These manifestations can be observed as retinal or vitreous hemorrhages, infections and vascular occlusions [1].

Frequently, ocular manifestations are asymptomatic [7]. Symptoms, when present, include decreased visual acuity, vitreous infiltration with leukemic cells and sudden unilateral vision loss [3].

Early retinal manifestations are vascular dilatation and tortuosity, retinal hemorrhages that may be dot-shaped or flame-shaped and frequently have a white

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center (Roth's spots) [1]. Roth's spots are an unspecific sign caused by rupture of the retinal capillaries with cluster of leukemic cells, platelets, septic emboli or fibrin material in the center [8].

The hemorrhages and infiltrates can be present in all retinal layers, but especially in internal layers with focal destruction (Figs. **1**-**4**) [5]. Leukemic large infiltrates can cause serous retinal detachments. Small infiltrates tend to be perivascular. Subretinal infiltration is referred to as subretinal hypopyon. Cotton-wool spots are thought to be secondary to ischemia, hyperviscosity or leukemic infiltration [1].

Peripheral retinal microaneurysms and retinal neovascularization may be seen [1]. The neovascularization is more common in chronic myelogenous leukemia [2]. Cases of central vein occlusion secondary to hyperviscosity associated to leukocytosis have been reported [4]. Serous retinal detachments are rare. They are associated with lymphoblastic invasion to choroid vasculature causing retinal pigment epithelium dysfunction that produces subretinal ischemia and accumulation of fluid [5]. The internal limiting membrane acts as a barrier against infiltration, but leukemic cells may infiltrate vitreous, possibly *via* the optic nerve head [1]. When the optic nerve is involved, it could be by direct infiltration or secondary to intracranial hypertension [1].

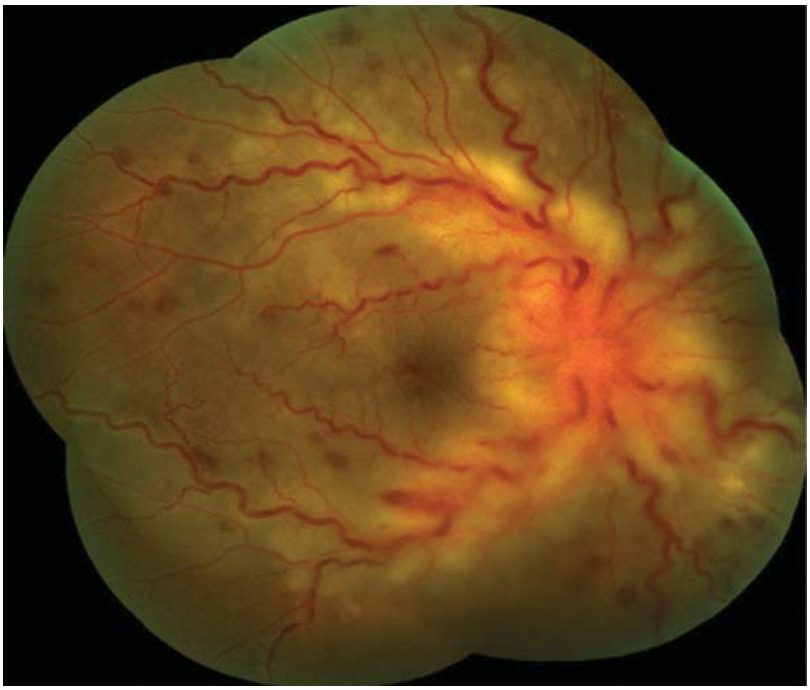

Fig. (1). Fundus photograph of a patient with diagnosis of Acute Myelocytic Leukemia, showing disc edema, vascular tortuosity, perivascular infiltration and dot-shaped hemorrhages.

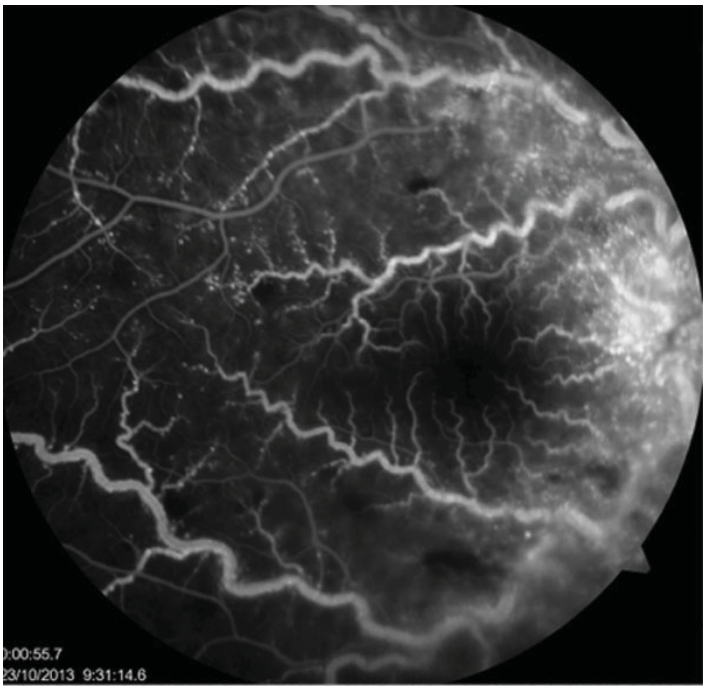

Fig. (2). Early phase of a fluorescein angiogram of the same fundus as Fig. (**1**), showing vascular tortuosity, multiple microaneurysms and vascular hyperfluorescence.

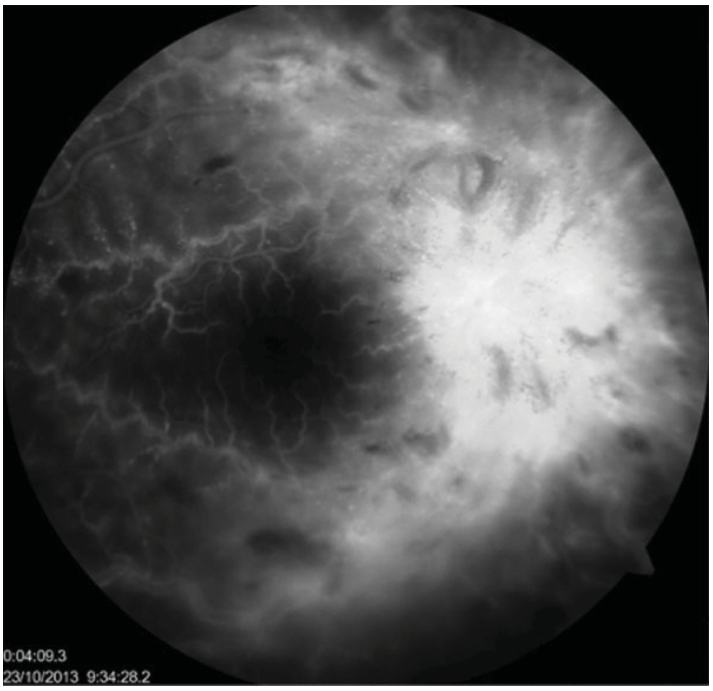

Fig. (3). Late phase of a fluorescein angiogram of the same fundus as Fig. (**1**), showing leakage, especially in the vessels of the posterior pole.

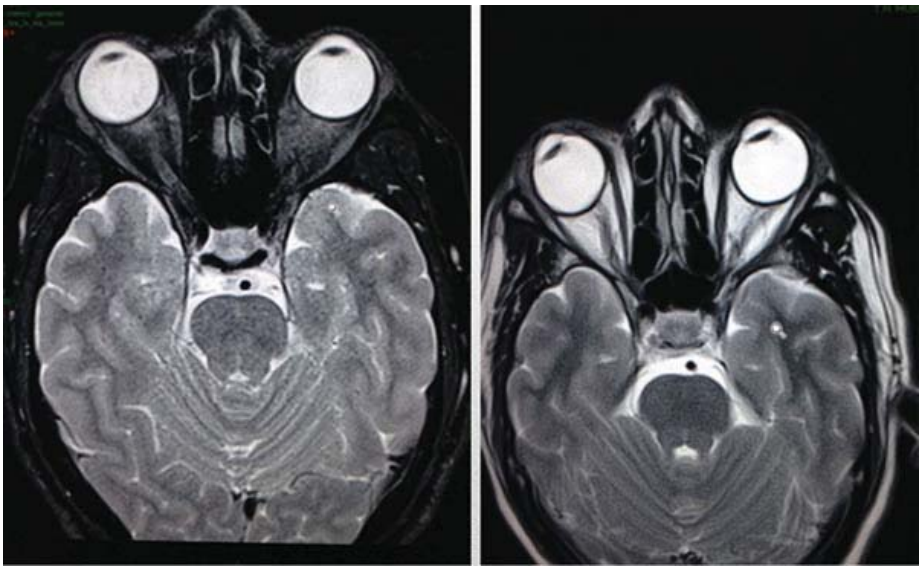

Fig. (4). Magnetic resonance imaging of the same patient as Fig. (**1**), showing retrobulbar infiltration.

Ocular complications occur when the disease is active, but rarely present when the patient is experimenting remission [9].

DIFFERENTIAL DIAGNOSIS

Roth's spots, dot-shaped or flame-shaped hemorrhages may also be observed in cases of severe anemia, thrombocytopenia or hyperviscosity [1]. Other diseases with these characteristics are diabetic retinopathy, septic chorioretinitis, sickle cell retinopathy and collagenopathies. When there is choroidal infiltration, differential diagnoses include Harada syndrome, central serous chorioretinopathy, uveal effusion syndrome, choroidal hemangioma and metastases [10].

MANAGEMENT

Intraocular leukemic manifestations are treated generally with systemic chemotherapy, or, if response is incomplete, ocular radiation in doses higher than 10Gy (Fig. **5**) [10]. Some authors state that radiotherapy in higher doses (more than 30 Gy) is necessary to avoid relapses [9].

There have been reports of serous retinal detachments in remission phase treated with radiation and intravenous steroids [9].

The life expectancy of patients with leukemic disease and ocular manifestations is worse than in patients that do not have ocular involvement. Ocular leukemic infiltration is associated with low survival rate [3].

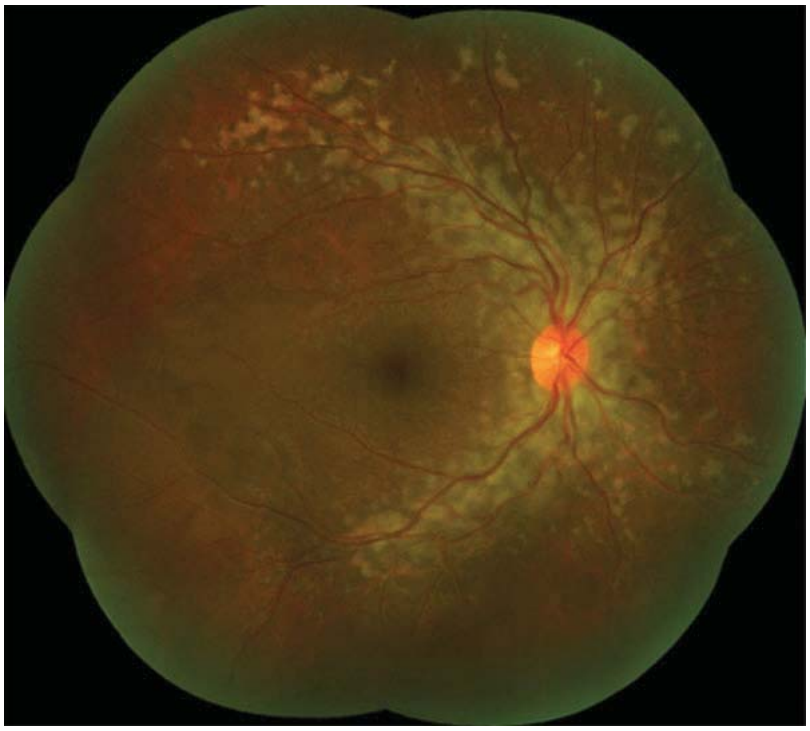

Fig. (5). Fundus photograph of the same patient as Fig. (**1**), after radiotherapy, with significant improvement of vascular tortuosity, disc edema, hemorrhages and infiltrates.

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 32

Primary Intraocular Lymphoma

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ESSENTIALS OF DIAGNOSIS

Primary intraocular lymphoma (PIOL), also known as primary vitreoretinal lymphoma, a subset of primary central nervous system lymphoma (PCNSL), is a rare non-Hodgkin's lymphoma that involves the retina and vitreous. The majority of PIOL is diffuse large B-lymphoma, although rare T-cell variants have been described [1].

In the US, it is estimated that there are 300-380 new cases of PIOL annually [1]. Approximately 80% of PIOL patients eventually develop PCNSL and approximately 20% of PCNSL patients present with PIOL [1]. Clinically, PIOL typically presents in older patients, with median age of 60 years [1].

Patients may present with blurred vision and/or floaters, but visual acuity is typically better preserved than would be expected for the degree of inflammation. Anterior segment signs are frequently absent, although cells in the anterior chamber and keratic precipitates may be seen. Rare cases may present with infiltration of the iris or angle, or with a pseudohypopyon. Fundoscopic exam reveals vitritis in the majority of cases. The vitreous cells may form clumps, sheets or strands, with mild to moderate haze [1]. White to orange infiltrates may be seen deep to the retina or RPE (Fig. **1**), often imparting a characteristic "leopard skin" appearance (Fig. **2**). Isolated subretinal lesions with associated exudative retinal detachment may also be seen. Cystoid macular edema is typically absent, in contrast to uveitis cases of similar cellularity. Optic nerve infiltration may occur.

Symptoms of CNS involvement may include behavioral changes, cognitive disorders, hemiparesis and/or ataxia. A strong indicator of CNS involvement is new-onset seizures [2].

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Fig. (1). Fundus photograph of a 53-year-old Caucasian male with PIOL. Note the large subretinal mass as well as numerous smaller lesions.

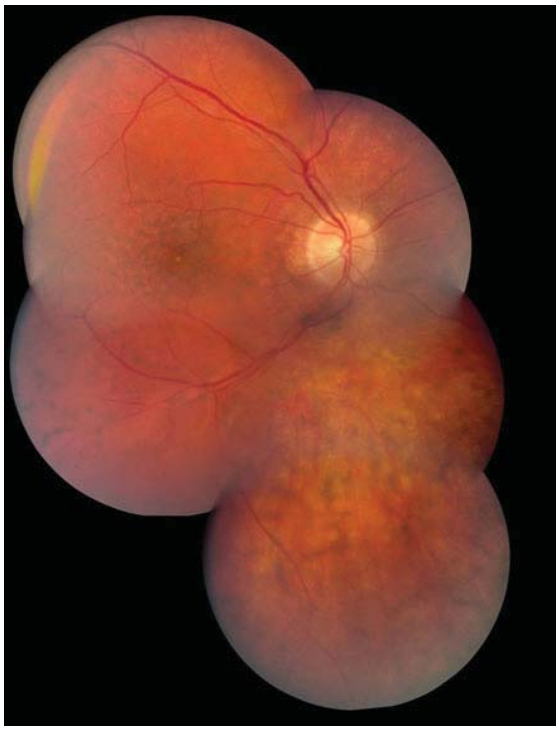

Fig. (2). Note the classic "leopard-like" appearance of the pigmentary changes in this patient with PIOL.

Fundus autofluorescence (FAF) may reveal a granular pattern, with hyperautofluorescent spots ranging from 50 to 250 microns alternating with adjacent hypoautofluorescent spots [3, 4]. Fluorescein angiography (FA) may demonstrate hypofluorescent round spots which correlate with the hyperautofluorescent spots on FAF [3]. Indocyanine green angiography typically shows small hypofluorescent lesions in the early phase, becoming less apparent in the late phases [2]. OCT findings include nodular hyper-reflective spots under the RPE, separation of Bruch's membrane from the RPE, disruption of the ellipsoid zone, hyper-reflective bands above the RPE and hyper-reflective signals in the retina [3, 4].

Ultrasonography can be used in cases of limited fundus view secondary to dense vitritis. Abnormal ultrasonographic findings are nonspecific and may include vitreous debris and retinal detachment.

Because PCIOL is closely related to PCNSL, it is imperative to evaluate the CNS. MRI with contrast is more sensitive than CT for detecting lymphomatous lesions in the CNS [5], but both have limited ocular value. Cerebrospinal fluid (CSF) evaluation is recommended despite a low yield for lymphoma cells in the CSF.

Diagnosis is typically made based on vitrectomy, although multiple biopsies may be required to arrive at a diagnosis [6]. It is recommended that for antibody determination, cytological evaluation and PCR an undiluted pure vitreous specimen be obtained by cutting and manually aspirating the specimen into a 3 cc syringe. For flow cytometry and cultures, diluted vitreous samples may be obtained after turning on the infusion and cutting the vitreous and aspirating into a 20 cc syringe. Diluted vitreous wash in the machine cassette may also be submitted for cytology [6, 7]. Communication with the cytologist/pathologist is recommended before obtaining the specimen. Occasionally, the vitreous does not have enough cellularity to make a diagnosis, and retinal biopsy may be required [6, 7].

Ocular cytological and histological exam reveals large lymphocytes, with large irregular nuclei, prominent nucleoli and scanty basophilic cytoplasm. Vitreous specimens may also contain reactive T-lymphocytes, necrotic cells and debris that may confound the identification of malignant cells. Biochemical and PCR analysis of vitrectomy specimens may assist in differentiating PIOL from chronic uveitis. IL-10 is elevated in the presence of malignant B lymphocytes, whereas IL-6 and IL-12 are elevated in inflammatory states. PIOL specimens may thus exhibit a high IL-10: IL-6 ratio (>1) [1, 2]. Immunohistochemistry or flow cytometry demonstrate monoclonality, either B-cell (kappa or lambda light chain)

or T-cell type of the lymphoma cells. Molecular analysis may also demonstrate IgH gene rearrangement [1, 3].

DIFFERENTIAL DIAGNOSIS

As it is a "masquerade syndrome", the differential diagnosis is wide and includes infectious and non-infectious uveitis, white dot syndromes and other neoplasms.

- Multifocal choroiditis
- Tuberculosis
- Sarcoidosis
- Syphilis
- Sympathetic Ophthalmia
- Birdshot retinopathy
- APMPPE
- Pneumocystis choroiditis
- Metastatic cancers
- Amelanotic melanoma

MANAGEMENT

A high index of suspicion is of utmost importance in the diagnosis and management of PIOL. Bilateral ocular involvement is typically treated as though there is CNS involvement, even if it cannot be found on imaging or CSF studies. The International PCNSL Collaborative group recommends systemic treatment if disease involves the CNS, and local treatment if disease is limited to the eye only [1]. Close monitoring by the ophthalmologist and neuro-oncologist is crucial.

For unilateral PIOL, intravitreal methotrexate (MTX), intravitreal rituximab or external beam ocular radiation have been suggested; and for bilateral PIOL, systemic chemotherapy in addition to intravitreal medications is recommended. For patients with coexisting PIOL and PCNSL, a high-dose MTX based systemic therapy, possibly with systemic rituximab, and local ocular therapy has been proposed. Whole brain radiotherapy in conjunction with ocular radiotherapy is typically reserved for patients who fail chemotherapy or are too debilitated for other therapies [1, 2].

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 33

Idiopathic Uveal Effusion

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Idiopathic uveal effusion (IUE) is an extremely uncommon disease, characterized by abnormal accumulation of serous fluid in the cilio-choroidal space, usually associated with non-rhegmatogenous retinal detachment, with no obvious cause such as trauma, surgery or inflammation. The disease shows middle-aged male preponderance but has been also described in females and in ages 20 to 80. The relapsing-remitting courses often lead to severe visual loss, secondary to chronic submacular fluid with RPE changes [1,2].

There are several hypotheses in the pathogenesis of IUE. Pathologic studies showed in most of the cases an abnormally thick sclera, with irregular distribution of collagen fibers and deposition of proteoglycans, suggesting some form of ocular mucopolysaccharidosis. In these cases of scleral thickening, the main hypothesis is vortex vein compression or reduced scleral permeability. In patients with normal sclera, chronic hypotony or increased choroidal permeability of unknown etiology has been suggested as possible causes of the fluid accumulation [3 - 6].

ESSENTIALS OF DIAGNOSIS

Patients consult for fluctuating vision or superior visual field defect, due to the exudative retinal detachment.

At the exam, these eyes, frequently nanophthalmic, show a normal cornea, shallow anterior chamber, and dilated episcleral veins as well as blood in the Schlemm's canal. The latter two are probably signs of vascular congestion. There is no evidence of inflammatory signs.

Fundoscopy varies from a slight, anterior peripheral cilio-choroidal elevation to an annular choroidal detachment with bullous retinal detachment with shifting

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fluid and secondary RPE changes (Fig. **1**). The ora serrata is usually easily visualized without indentation (Fig. **2**) due to the peripheral effusion. The vitreous is clear. In patients with resolved retinal detachment, a patchy subretinal pigmentation has been described as leopard spots or pseudoretinitis pigmentosa.

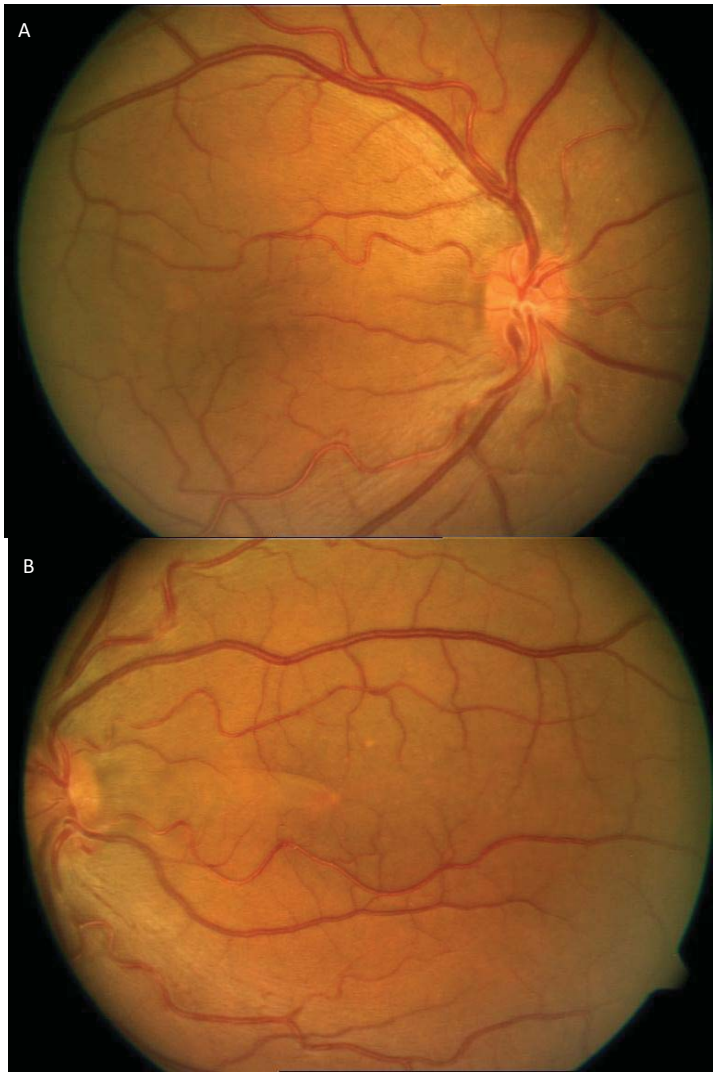

Fig. (1). A and **B**. 31-year-old male, presented with decreased visual acuity (0.3 in both eyes), nanophthalmia and high hyperopia (+17.00 D). Fundus photographs show bilateral serous retinal detachment, with shifting subretinal fluid and secondary RPE changes. (Courtesy of Mitzy E. Torres Soriano MD).

B-scan, UBM, and fluorescein angiography (Fig. **3**) are useful tools in reaching an appropriate diagnosis, especially with choroidal tumors, and also to assess the scleral and choroidal thickening.

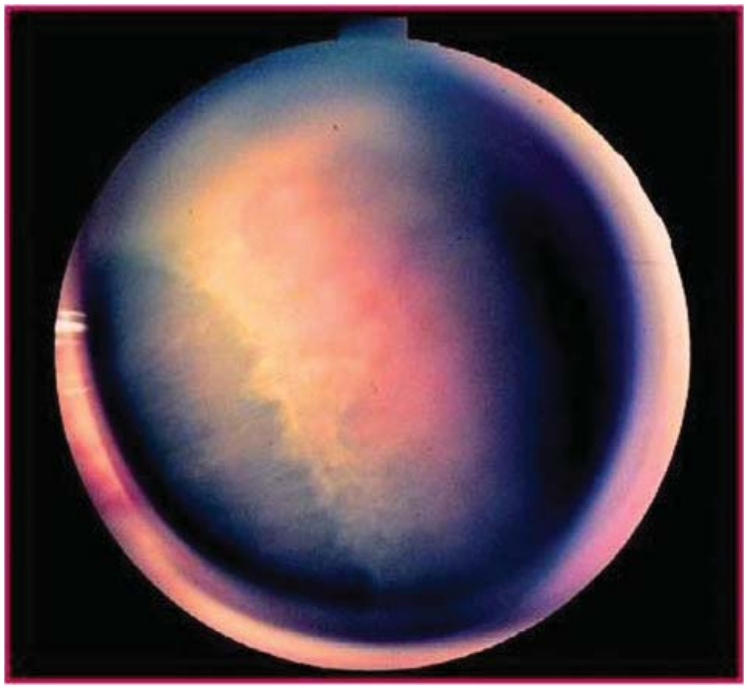

Fig. (2). Annular peripheral choroidal detachment: Pars plana is visible directly through pupil.

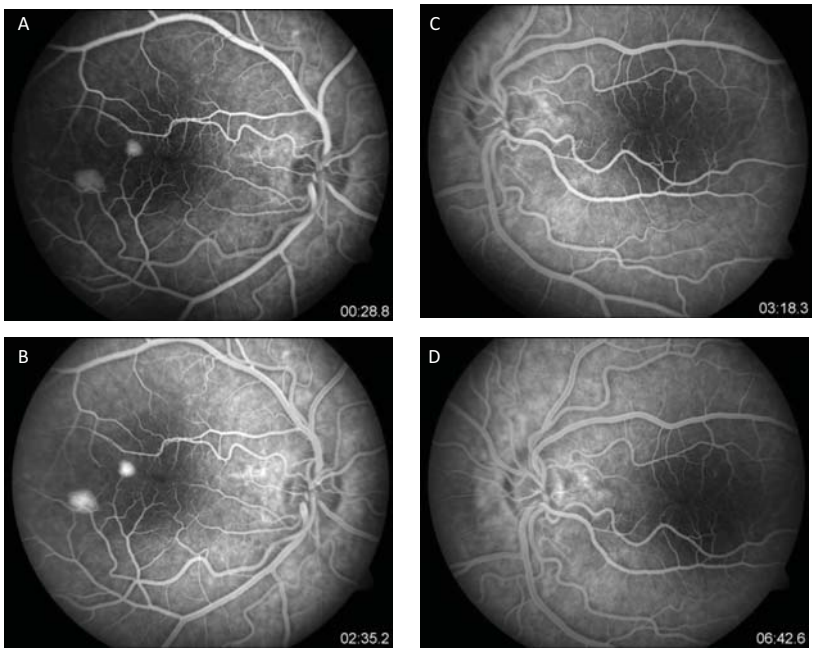

Fig. (3). The same patient of Figs. (**1** and **2**). **A** and **B** (Right eye): FA shows two hyperfluorescent points. **A**, **B**, **C** and **D**: FA revealed mild RPE changes and vascular congestion in both eyes. (Courtesy of Mitzy E. Torres Soriano MD).

ICG shows diffuse granular choroidal hyperfluorescence in the early phase, which increases and persists in the late phase [7].

OCT shows significant choroidal thickening with low reflective areas, which could represent dilated choroidal vessels or an enlargement of the suprachoroidal space [8].

DIFFERENTIAL DIAGNOSIS

Should be made with annular choroidal melanoma; Vogt-Koyanagi-Harada; CCS in the chronic form; posterior scleritis; choroidal tumors (hemangioma, metastasis, osteoma); lymphoma; reactive lymphoid hyperplasia; rhegmatogenous retinal detachment; and choroidal hematoma.

MANAGEMENT

Systemic treatment with steroids and NSAID have been described with poor results.

Brockhurst described the vortex vein decompression through scleral resection as a difficult technique with great risk of extensive hemorrhages [9]. Gass developed preequatorial scleral windows, a more effective and simple procedure (Figs. **4** & **5**) [10]. Uyama treated patients with a subscleral sclerectomy under a scleral flap of two-thirds' thickness, also with success, even though additional procedures were required in one-third of the cases [11].

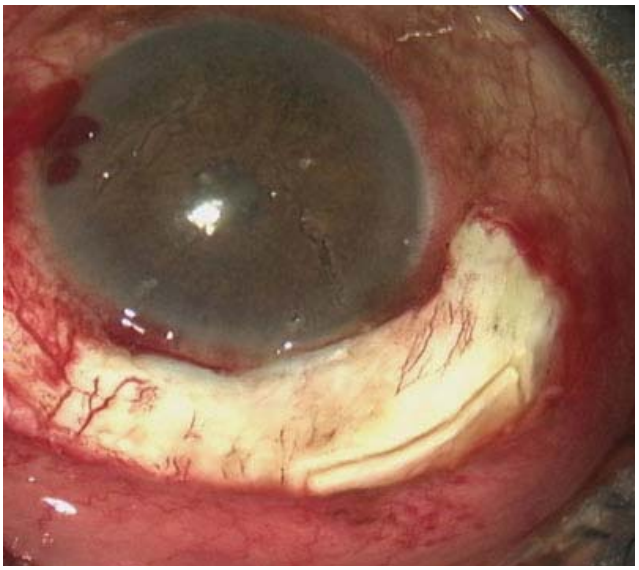

Fig. (4). Wide peripheral pars plana sclerotomy.

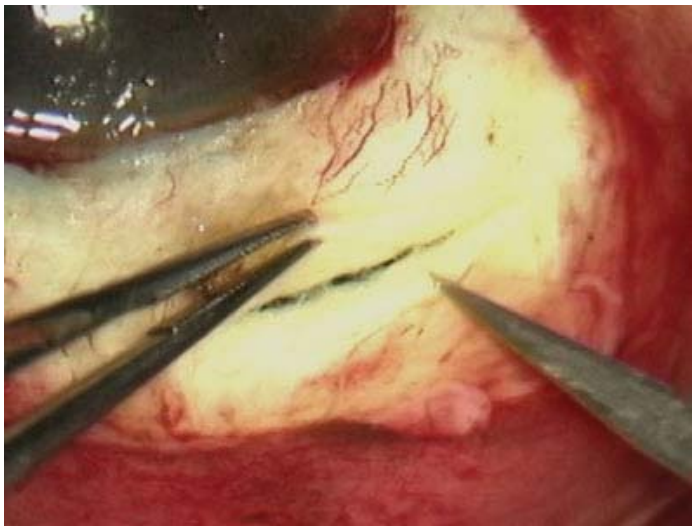

Fig. (5). Sclerotomy attaining suprachoroidal space.

Other cases of wide pars plana linear sclerotomies [12], scleral windows with mitomycin [13], scleral resection with vitrectomy and endodrainage [14], scleral puncture with diathermy [15], and full thickness sclerotomy have also been described, with good results.

Sclerotomy leads to anatomic improvement in 96% of treated eyes with one (83%) or two procedures [16]. Final VA improves by two or more lines in 56% of eyes, remains stable in 35%, and worsens in 9%.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 34

Hypotony Maculopathy

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ESSENTIALS OF DIAGNOSIS

Hypotension, defined as intraocular pressure (IOP) of less than 6.5 mm Hg, provokes scleral shrinking and inward bowing of the posterior pole, creating the characteristic aspect of this syndrome: hypotony, decreased visual acuity, disc swelling in early stages, vascular tortuosity (Fig. **1**), chorioretinal folds (Fig. **2**), mild cystoid macular edema, and hyperopic shift in refraction [1, 2].

Hypotony occurs under several conditions that unbalance the aqueous humor production/outflow ratio. Outflow may be excessive, as in over filtering blebs (the most common cause of the syndrome), wound leaks, and cyclodialysis cleft.

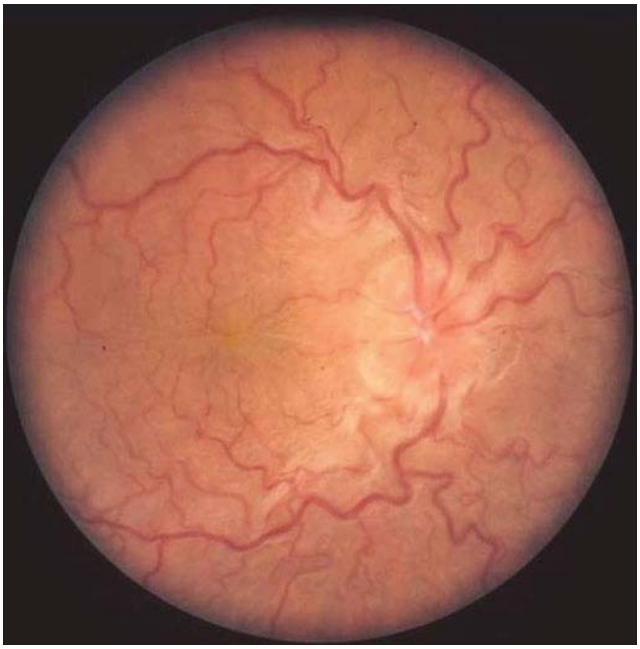

Fig. (1). Vascular tortuosity and disc swelling in the acute phase of hypotensive syndrome.

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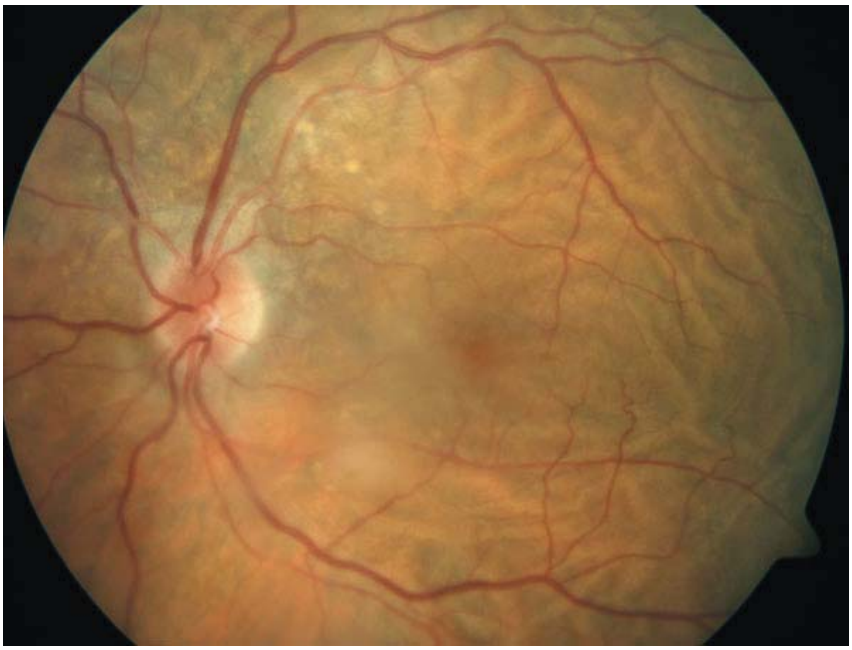

Fig. (2). Chorioretinal folds. Traumatic hypotension. (IOP 2 mm Hg. VA 20/200).

Aqueous production can be significantly reduced due to ciliary body malfunction, as in tractional cyclitic membranes or ciliary body hypoperfusion in vascular occlusive diseases, diabetic coma or uremia.

Persistent hypotension results in chorioretinal changes and poor vision. Usually, the medical history of previous surgery or trauma and the clinical aspect lead to the diagnosis. However, sometimes auxiliary imaging could be useful, especially in mild cases. These are the most frequent ancillary tests:

Fluorescein Angiography: Shows capillary disc leakage in the acute phase and enhances the aspect of the choroidal folds, with alternating hypo- and hyper-fluorescent bands (Fig. **3**), due to the folding of the RPE. This is useful to differentiate from pure retinal folds that do not alter background fluorescence [2].

Optical Coherence Tomography: Can help to detect subtle folds, difficult to see in ophthalmoscopy, as well as mild macular edema. Also serves to monitor the outcome of treatment [3].

Ultrabiomiocroscopy: Useful for the evaluation of the position and integrity of the ciliary body, revealing traction or atrophy, as well as the presence and extent of cyclodyalisis clefts [4, 5] (Fig. **4**).

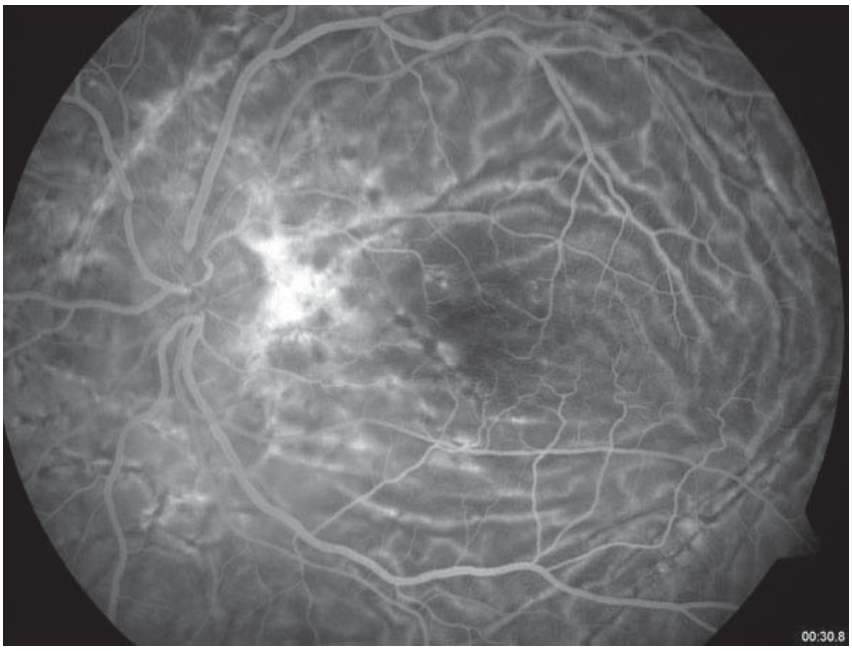

Fig. (3). Hypo- and hyperfluorescent bands.

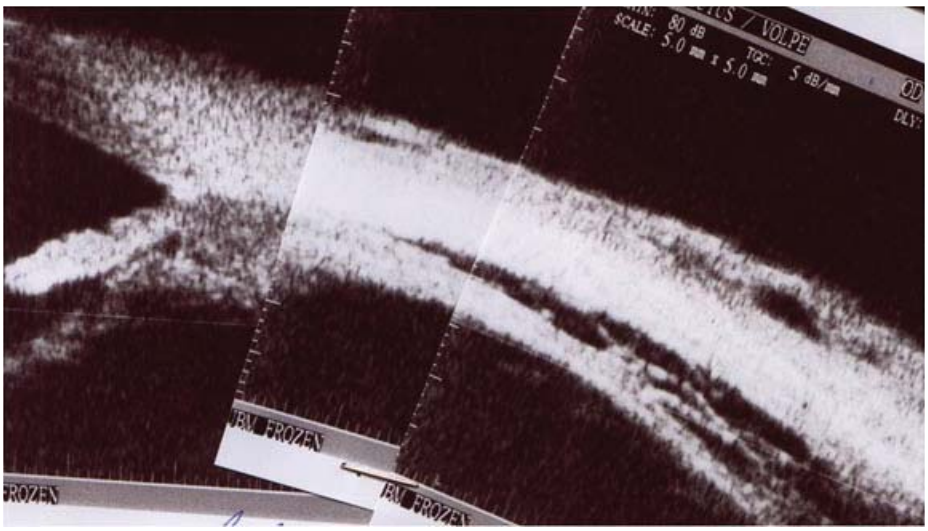

Fig. (4). Cyclodialisis cleft.

DIFFERENTIAL DIAGNOSIS

In the acute phase, all causes of papilledema should be considered, but most frequently the diagnosis must be done with other causes of chorioretinal folds: idiopathic folds, usually bilateral and with good visual acuity; choroidal tumors, particularly melanoma and metastasis; retrobulbar mass; scleritis; shallow retinal detachment; and choroidal neovascularization or scarring.

MANAGEMENT

The aim of the treatment is normalization of the IOP, which may reverse the inward scleral bowing and restore vision.

Leakage from a filtrating bleb is the most common cause of hypotony. Conservative management with aqueous suppressants reducing flow, bandage contact lenses, collagen sheets, cyanoacrylate glue and peribleb autologous blood are non invasive procedures that may help to seal the leak (*i.e.* laser to induce inflammation, aminoglycosides to promote wound healing or quick taper of topical steroids) [1]. More frequently, surgery is required.

Transconjunctival flap sutures [6, 7], bleb revision with resuturing of the scleral flap [8, 9], and placing a donor scleral patch [10] are techniques highly successful in increasing IOP, with success rates varying from 80% to 94%. However, 50% of these eyes will require antiglaucoma medication and 8% may need new filtering procedures [8].

In ocular trauma, the resolution of the cyclodialysis cleft has been attempted and anecdotally reported with transscleral scarring, lens implantation with haptic compressing the dialysis, and encircling anterior scleral buckling (Figs. **5**-**7**) [1].

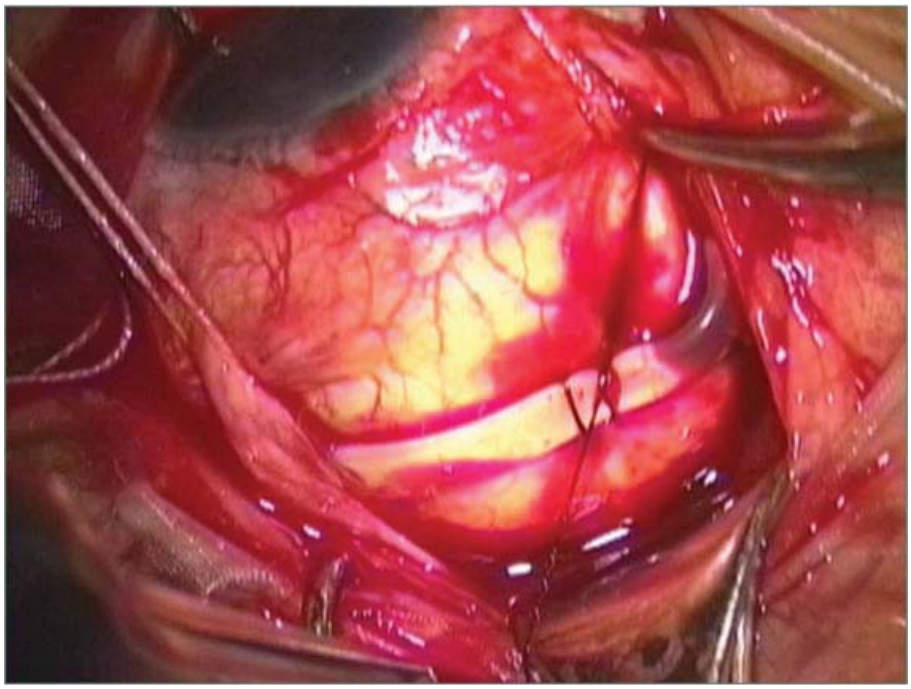

Fig. (5). Preequatorial (9 mm from the limbus) encircling band.

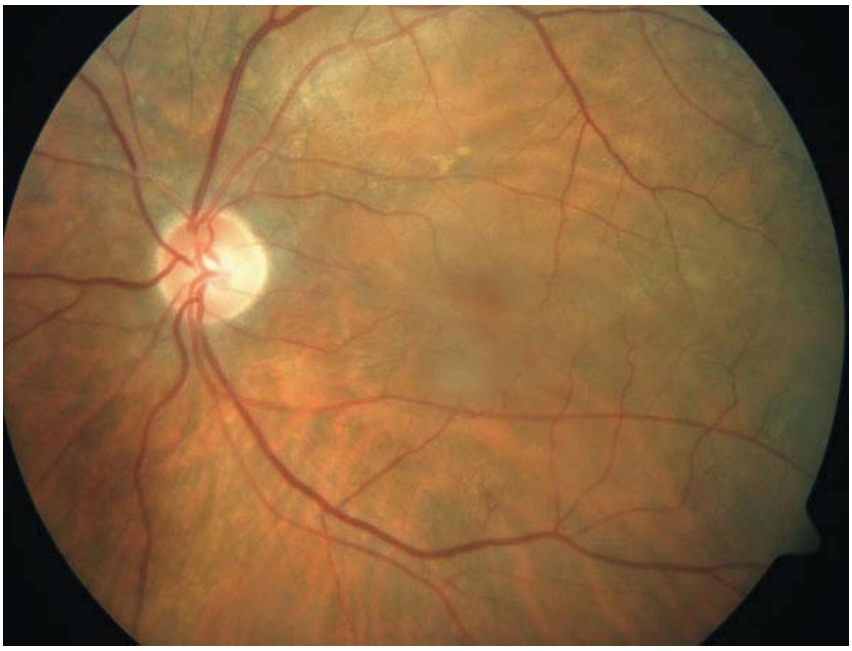

Fig. (6). Postoperative aspect of posterior pole of the same patient of Fig. (**2**): VA 20/25, IOP 10 mmHg (2 months post surgery).

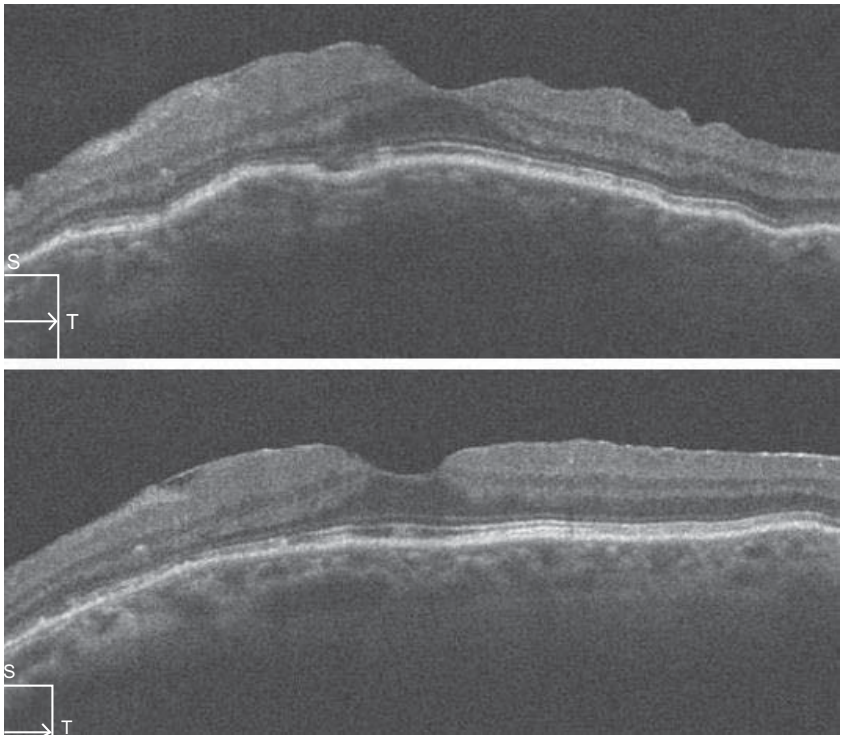

Fig. (7). Pre and postop OCT = amelioration of chorioretinal folds.

The most commonly used procedure is direct suture of the ciliary body to the scleral spur (direct surgical cyclopexy) (Fig. **8**) [11, 12]. Even though many cases will need more than one procedure, the final success rate is satisfactory [13]. Good results have been also reported with vitreoretinal procedures with silicone oil tamponade [14].

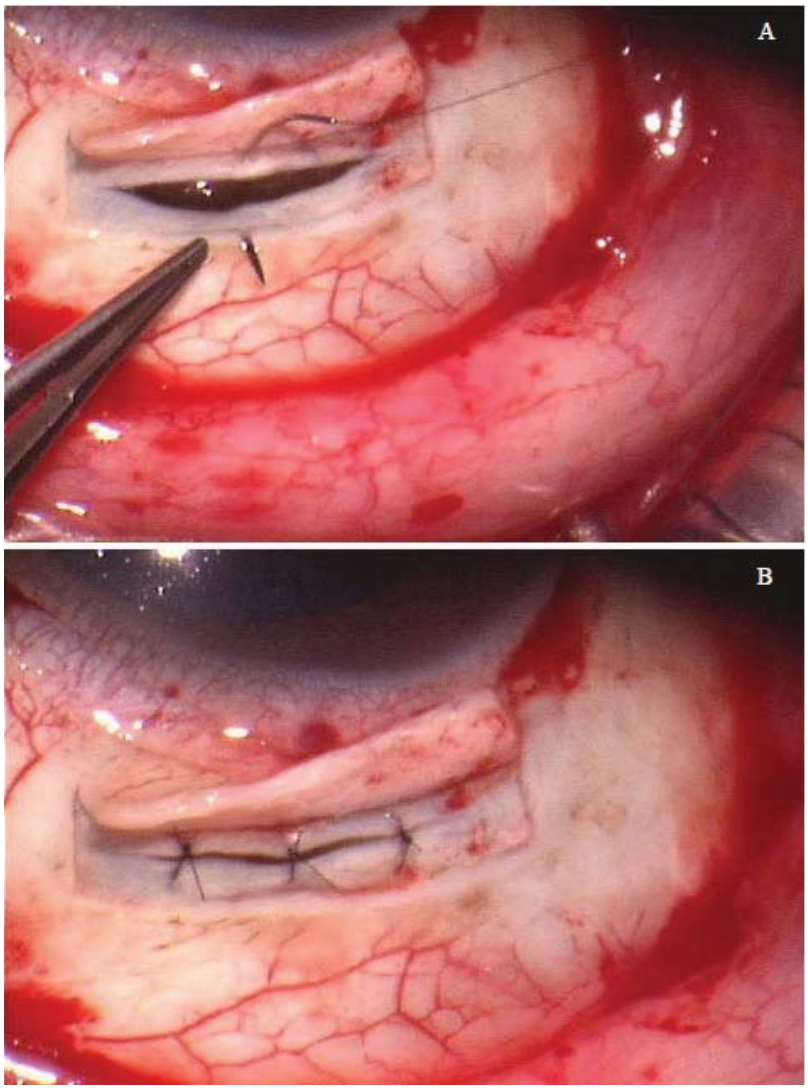

Fig. (8). (**a** and **b**) Direct cyclopexy under scleral flap (Courtesy Emilio Dodds MD. Consultores Oftalmológicos. Buenos Aires, Argentina).

Tractional compromise of the ciliary body must also be treated with vitreoretinal techniques, with careful and complete peeling of the ciliary processes [15].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 35

Pregnancy-associated Retinal Diseases

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HYPERTENSION: PRE-ECLAMPSIA AND ECLAMPSIA

Ocular changes occur in 30-50% of patients with eclampsia and in 20-25% of patients with pre-eclampsia, and they consist in visual disturbances such as scotoma, diplopia, loss of visual acuity. These may be signs of alert for seizures in patients with pre-eclampsia. The effects of eclampsia and pre-eclampsia occur at the level of the retina, the choroid and the optic nerve.

Retinopathy in Toxemia: The changes correspond to those of hypertensive retinopathy: arteriolar spasms in 40-100% of patients with pre-eclampsia [1] (which are reversible in the postpartum period); diffuse narrowing (also reversible); and also hemorrhages, soft exudates, diffuse macular edema and papilledema may occur more frequently in women with chronic hypertension diagnosed before pregnancy [2]. These would indicate placental insufficiency, since the severity of retinal changes correlates with higher perinatal mortality rates. Therefore, induction of labor is recommended in cases of severe retinopathy. Inducing labor at the right time not only can improve the chances of survival for a baby born prematurely, but also can improve the outcome of systemic changes in the mother.

Localized Choroidal Infarction and Infarction of the RPE: Elschnig spots are one of the most common changes in toxemia. Choroidal insufficiency is a frequent ocular complication in patients with pre-eclampsia and eclampsia. Clinically, it presents as serous retinal detachments or yellow lesions at the level of the RPE [3, 4].

Retinal Detachment in Toxemia: It is a serous, exudative detachment that is

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usually bilateral and bullous. When the macula is not involved, it can be asymptomatic [3, 4]. It presents in 10% of patients with eclampsia and in 1-2% of patients with pre-eclampsia. It is not associated to fetal risk and it usually resolves after delivery. Macular RPE changes or optic atrophy only occur exceptionally or in rare cases, and lead to permanent loss of visual acuity.

Cases of temporary cortical visual impairment, serous bilateral retinal detachment [5] which resolves after 48 hours, unilateral vitreous hemorrhage and reversible blindness associated with cerebral venous sinus thrombosis and central retinal vein thrombosis have been identified in association with Hellp syndrome (hemolysis, elevated liver enzymes and low platelet count) in women with severe pre-eclampsia or eclampsia presenting on the 3rd trimester of pregnancy or in the postpartum period.

DIABETIC RETINOPATHY

Keeping glycemia and glycated hemoglobin (HbA1c) levels under control before conception and during pregnancy can reduce the risk of miscarriage [6, 7], birth defects and perinatal morbidity. Also, the status of retinopathy in diabetic women should be assessed and determined before conception. This is particularly important in the case of patients with severe nonproliferative or proliferative retinopathy, since laser photocoagulation can reduce progression during pregnancy [8]. Laser treatment of diabetic macular edema before pregnancy may be recommended, although the effects of pregnancy on macular edema have not been appropriately studied yet.

Progression of diabetic retinopathy in pregnant women depends mainly on the duration of diabetes and the severity of retinopathy at the beginning of pregnancy [8 - 11]. The baseline severity of retinopathy at the beginning of pregnancy is the main risk factor for the progression of the disease, according to the *Diabetes in Early Pregnancy Study (DIEP)*. Women with a HbA1c level of more than 6 standard deviations (SD) above the control mean are at higher risk of progression of retinopathy in comparison to patients with a HbA1c baseline level within 2 SD of the control mean.

CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy (CSCR) is caused by localized RPE dysfunction resulting in the accumulation of subretinal fluid (Figs. **1** and **2**). It is more frequent in men between 20 and 50 years old. Pregnant women are more likely to develop CSCR.

In general, pregnant women with diabetic macular edema should not receive treatment during pregnancy since there is a high rate of spontaneous regression postpartum. Possible exceptions may include cases in which the fovea is threatened by fluid or severe progressive macular edema presents at the beginning of pregnancy [12].

CSCR associated to pregnancy may present at any stage in normal pregnancy, although it is more frequent in the third trimester, and it usually resolves in the postpartum period, leaving some subtle mottling of the RPE. It may recur in a future pregnancy. It has been associated to hormonal or hemodynamic changes, reduced osmotic pressure and hypercoagulable states [13].

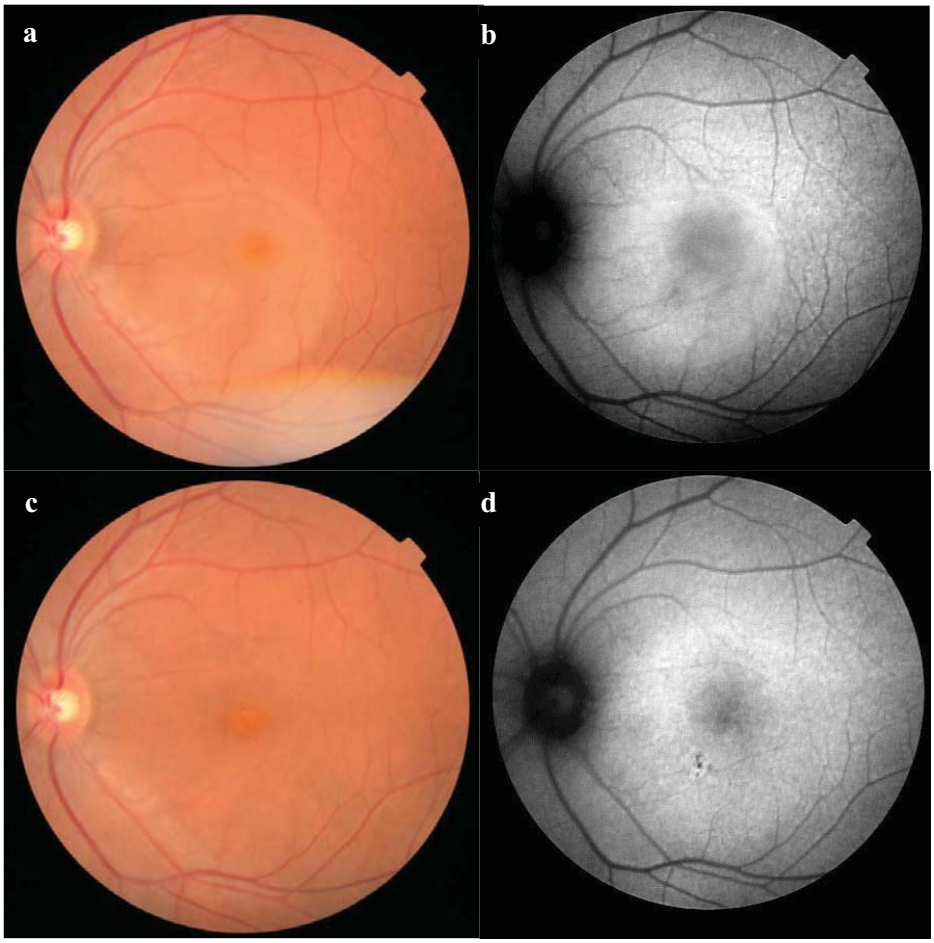

Fig. (1). **a** and **b**) Fundus photograph and autofluorescence image showing typical central serous chorioretinopathy in left eye in sixth month of first pregnancy. **c** and **d**) Fundus photograph and autofluorescence after complete resolution. (Courtesy of Manuel Torres MD, Cagua, Venezuela).

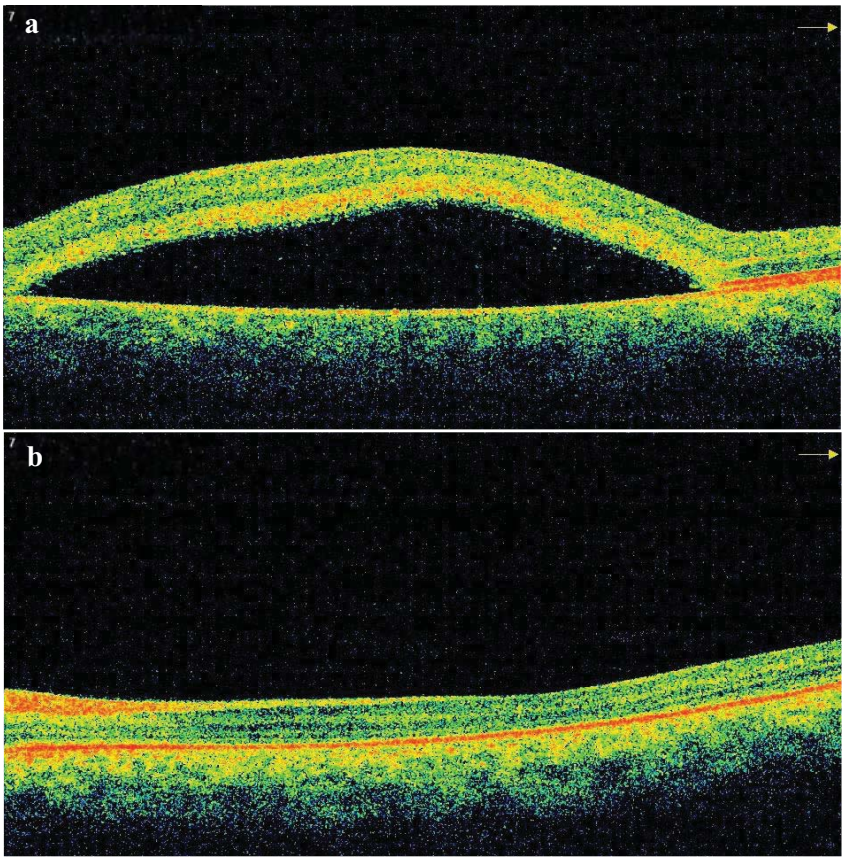

Fig. (2). a) OCT shows area of detachment as hyporeflectivity between neurosensory retina and RPE of the same patient of Fig. (**1**). **b**) Shows retinal atrophy after spontaneous resolution of CSC with poor final visual acuity. (Courtesy of Manuel Torres MD, Cagua, Venezuela).

PRERETINAL OR RETROHYALOID HEMORRHAGES

These can develop spontaneously during normal pregnancies or may be induced by Valsalva maneuvers (vomiting, coughing, labor strain), and usually have a positive prognosis.

UVEAL MELANOMA

Generalized hyperpigmentation and pregnancy are closely related, probably because of hormonal reasons. Many cases of choroidal melanoma during pregnancy, as well as a high rate of growth of melanomas in patients diagnosed before conception, have been reported [14]. On the other hand, it is a known fact that pregnancy does not increase the risk of metastasis in women with melanoma diagnosed before conception, and no data were reported about cases of metastasis to the fetus.

CHANGES IN BLOOD COAGULATION

Disseminated intravascular coagulation (DIC): It develops during pregnancy in cases of premature rupture of membranes, complicated miscarriage, stillbirth and severe pre-eclampsia. It mainly affects the posterior submacular and peripapillary choroid with trombotic occlusion of the choriocapillaris in those regions, resulting in changes of the RPE and serous retinal detachment in the macular and peripapillary regions [15]. If DIC resolves, the patient usually recovers vision and only mild RPE changes remain [15, 16].

Thrombotic thrombocytopenic purpura: It may develop in women who are pregnant for the first time. In 8% of cases, it includes visual changes due to thrombus formation in the choriocapillaris and secondary RPE ischemia. Clinically, symptoms are usually bilateral and consist of retinal serous detachments, yellow spots at the level of the RPE and localized arteriolar narrowing. After-effects include pigmentary changes of the RPE and Elschnig spots. In most cases, patients recover baseline vision after several weeks [17, 18].

OTHER CAUSES FOR BLINDNESS OR SEVERE LOSS OF VISION

During pregnancy, concentration and activity of clotting factors increase. The risk of stroke in pregnant women is 13 times higher compared to the risk in nonpregnant women. Retinal or choroidal vascular occlusions may also be indicators of this greater risk of vaso-occlusive disease [19].

CONFLICT OF INTEREST

The authors confirm that the authors have no conflict of interest to declare for this publication.

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Declared none.

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SUBJECT INDEX

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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.