Algorithm of Choroiditis

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ABSTRACT

Choroiditis may present as focal or multifocal lesions, and could be due to infectious or noninfectious etiology. Focal choroidal lesions are commonly caused by toxoplasma infection, tuberculosis, sarcoidosis or serpiginous choroiditis. Multifocal choroiditis can be due to infective etiology, such as tuberculosis, or any autoimmune choroiditis, such as amnigous choroiditis or acute posterior multifocal placoid pigment epitheliopathy (APMPPE). Diffuse choroiditis may be correlated to panuveitis, such as Vogt-Koyanagi-Harada (VKH) syndrome or sympathetic ophthamlia. Other choroiditis may present as opportunistic infections in immunocompromised patients. Careful clinical examinations and tailored investigations would be helpful in making a prompt diagnosis of these different entities. Due to varied manifestations, diagnosis of choroiditis is challenging. This article will review the diagnostic approach of choroiditis based on clinical presentations, investigations and ancillary tests.

Keywords: Choroiditis, Central serous retinopathy, Ocular tuberculosis, Ocular sarcoidosis, Serpiginous choroiditis, Diffuse choroiditis.


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INTRODUCTION

The choroid is anatomically structured to react to any inflammatory or infective insult in either of the two ways: The focal or diffuse form of choroiditis regardless of the cause. The inflammation can involve the adjacent structures, such as retina and optic nerve. It is important to differentiate between a lesion that is predominantly retinitis vs one that is predominanantly choroiditis. Retinitis presents as a whitish patch with ill-defined border and associated retinal edema, while choroiditis presents as a yellowish patch with ill-defined margins over which retinal vessels can be seen. There are several described entities of choroiditis and these can be infective or noninfective in etiology. It is often a vision-threatening condition.

Choroiditis may present as focal or multifocal lesions. Any overlying vitreous inflammation can be helpful to differentiate infective and noninfective etiology, since infective etiology usually present with more severe vitritis. As a first step, conditions that can mimic choroiditis should be carefully exluded. Careful clinical examinations and tailored investigations would be helpful in making a prompt diagnosis of these different entities. Management should be planned immediately accordingly to restore vision and prevent further complications. Due to the wide spectrum of disease presentations, diagnosis of choroiditis is often challenging.

WHAT DISEASES SHOULD BE RULED OUT?

Diseases that can potentially be confused with choroiditis include multiple leak central serous retinopathy (CSR), age-related macular degeneration (ARMD), posterior scleritis and masquerade syndromes, such as intraocular lymphoma.

CSR can produce subretinal deposits, which can mimic an active patch of choroiditis. Careful slit-lamp examination invariably shows the absence of vitreous cells in CSR. The presence of subretinal fibrosis with secondary retinal detachment in healthy young patients, particularly in men, should alert the physician to look for multifocal CSR leaks. Fundus fluorescein angiogram can distinguish a multiple leak CSR from choroiditis, since it shows multiple leaks in the mid-arteriovenous phase and leakage in the late arteriovenous phases. The fundus fluorescein angiogram feature in diffuse choroiditis, such as Vogt-Koyanagi-Harada (VKH) syndrome reveal focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, large placoid areas of hyperfluorescence, pooling within the subretinal fluid and optic nerve staining.

Dry ARMD often produces a geographic atrophy, which may mimic healed choroiditis. However, such a scar is flat, round or oval. There are often other features of ARMD like drusen and retinal pigment epithelium atrophy. The fellow eye can also show features of ARMD. The wet type of ARMD can develop a CNVM. This condition can produce yellow or gray lesions with surrounding exudates and can mimic posterior uveitis. Careful evaluation can reveal the presence of hemorrhage. Such hemorrhages are quite uncommon in choroiditis. The absence of vitreous haze is again an important differentiating feature.

Intraocular lymphoma can mimic multifocal choroiditis. The classic fundus lesions consist of large, multifocal, yellow sub-RPE lesions. The lesions can be confluent or discrete. These lesions, along with vitritis, are considered to be pathognomonic of primary intraocular lymphoma. The sub-RPE lesions may regress spontaneously, leaving RPE atrophy and subretinal fibrosis. A leopard-spot appearance may be seen following resolution of the lesions. The diagnostic approach to patients with primary intraocular lymphoma includes complete neurological evaluation, magnetic resonance imaging (MRI) brain to rule out central...
nervous system lymphoma, cerebrospinal fluid cytology, and vitreous or chorioretinal or fine-needle aspiration biopsy. The definitive diagnosis of intraocular lymphoma, requires histologic analysis. This can be achieved by the confirmation of malignant cells in vitreous or retina. Vitreous biopsy remains the mainstay of diagnosis of primary intraocular lymphoma.9,10

Posterior scleritis is a rare type of scleritis that should be considered as one of the differential diagnosis of choroiditis. In posterior scleritis, pronounced ocular pain is generally regarded as the lead symptom of the disease. Pain is caused by destruction and stretching of the nerves passing through Tenon’s capsule and sclera. B-mode ultrasound examination and fundus fluorescein angiogram are the most helpful tools in the diagnosis of posterior scleritis. A characteristic feature in B-scan ultrasonography of posterior scleritis is T-sign, due to the fluid beneath the Tenon capsule.2,3,11

Once choroiditis is confirmed, we have to consider the various causes of the same. The algorithm below shows the diagnostic approach in choroiditis patient. The most common causes of choroiditis are mentioned (Fig. 1).

**OCULAR TOXOPLASMOSIS**

Ocular toxoplasmosis is a major cause of posterior uveitis worldwide. Ocular toxoplasmosis typically presents as unilateral focal retinitis at the border of a pre-existing pigmented retinochoroidal scar and an overlying vitritis. Over the recent years increasing numbers of atypical presentations have been described. Such atypical lesions are seen in elderly individuals and immunocompromised patients (Fig. 2).2,12

The diagnosis is based on clinical findings, but molecular biological diagnosis is necessary to confirm the diagnosis, mainly in atypical presentation. *Toxoplasma*-specific IgM can be detected in the serum, which may be indicative of a recently acquired infection. IgG will always be positive in patients with ocular toxoplasmosis, but it has low diagnostic value, because it is also positive in patients with prior infection. If the retinal lesions are typical for toxoplasmic retinochoroiditis, and samples of serum register positive for *Toxoplasma*-specific IgG and negative for *Toxoplasma*-specific IgM, and if the patient responds to appropriate anti-*Toxoplasma* therapy, most authorities will agree that the individual is suffering from a reactivated form of ocular toxoplasmosis. Interestingly, Bou et al (1999) found that among all patients with ocular toxoplasmosis, a positive aqueous humor polymerase chain reaction (PCR) was accompanied by positive PCR result with the blood sample. This result suggests that ocular toxoplasmosis should not be considered a local event. If there is clinical doubt about the diagnosis, paired samples of aqueous humor and serum should be collected and analyzed in parallel. The Goldmann-Witmer coefficient (GWC) is based on the comparisons of the levels of specific antibodies to total immunoglobulin in both aqueous humor and serum. The calculation of GWC is best done if old scars are present and/or if there is mild to severe anterior chamber reaction beyond 10 days of onset. Specific DNA can be detected in the intraocular fluids of patients with ocular toxoplasmosis using the PCR technique. PCR should be considered if the total size of lesion is large (>2 optic disk diameter) during the 10 days following symptom onset (Fig. 3).12-16

**OCULAR TUBERCULOSIS**

Tuberculosis is considered the most common cause of uveitis in developing countries. The ocular manifestations of tuberculosis may result from either active infection or an immunologic reaction to the organism. Disseminated choroiditis is the most common presentation. It may present as choroidal tubercles, deep, multiple, discrete, yellowish lesions between 0.5 and 3.0 mm in diameter located predominantly in the posterior pole; or tuberculomas, a single, focal, large, elevated choroidal mass that varies in size from 4 to 14 mm. Other less common presentations include multifocal choroiditis and a serpiginous-like choroiditis.1,2,17

Diagnosis of tuberculous uveitis encompasses suggestive clinical history and signs, exclusion of other known etiologies of uveitis, supportive investigations, such as positive Mantoux test and chest X-ray findings, response to empiric antituberculosis treatment and in some, evidence of *M. tuberculosis* or its DNA in ocular fluids/tissues.17,18

Immunological methods for the diagnosis of tuberculosis have been expanded with QuantiFERON TB gold
OCULAR SARCOIDOSIS

Sarcoidosis is a multisystem disease characterized by the formation of noncaseating granulomas in the affected tissue systems. The eye is involved in about 25 to 60% of the patients; in 10 to 20% of the patients, ocular involvement is the initial presenting sign, occurring before any other systemic manifestations. The clinical diagnosis of sarcoidosis is based on a combination of clinical and radiologic features and the presence of noncaseating (non-necrotizing) granulomas on tissue biopsy.20-22

It is universally accepted that the gold standard for the diagnosis of sarcoidosis is histopathological proof on biopsy tissue showing noncaseating granulomas, and exclusion of other diseases that produce granulomatous lesions, such as tuberculosis. However, biopsy of intraocular tissues is not performed due to its high risk for vision and is hardly accepted by uveitis patients.13 In patients with clinical suspicion of sarcoidosis but a normal chest X-ray, high-resolution computed tomography (HRCT) can be diagnostic.21,23

Ocular sarcoidosis is usually a chronic bilateral uveitis with insidious onset. The uveitis is characterized by granulomatous inflammatory reaction in the anterior segment (mutton-fat keratic precipitates, iris nodules, trabecular meshwork nodules and tent-shaped peripheral anterior synechiae); snowball and/or ‘string of pearls’ opacities in the vitreous; and in the posterior segment, nodular periphlebitis, multiple peripheral chorioretinal lesions, optic disk nodules and/or solitary choroidal nodules. Occasionally, especially in acute-onset sarcoidosis, atypical features, especially nongranulomatous anterior uveitis, may be seen.21,23

Laboratory investigations that support the diagnosis of ocular sarcoidosis are negative tuberculin test in a BCG examination. In contrast to Mantoux test, which may be relatively nonspecific, QuantiFERON TB gold can detect immune response to specific M. tuberculosis antigens, and thus are not influenced by BCG vaccination or by atypical mycobacterial infection. Moreover, QuantiFERON TB gold is a stronger indicator of exposure to M. tuberculosis than the Mantoux test. Recent studies indicate that QuantiFERON TB gold test is positive in serpiginous-like choroiditis compared to control.18,19

PCR has emerged as a powerful tool for rapid detection of the mycobacterial genome in clinical and research specimens. In addition to detecting M. tuberculosis DNA in active lesions, PCR may also disclose the presence of DNA from possibly dormant mycobacteria in normal tissues of latently infected individuals. PCR assays for M. tuberculosis indicate high specificity and sensitivity. Our study showed that in case of disseminated tuberculosis, PCR of anterior chamber tap is helpful (Fig. 4).1,19

Fig. 2: Fundus photograph showing focal toxoplasma choroiditis with overlying vitreous haze, ‘headlight in the fog’ appearance

Fig. 3: Diagnostic algorithm in suspected ocular toxoplasmosis12

Fig. 4: Diagnostic algorithm in suspected ocular tuberculosis18
vaccinated patient or having had a positive PPD (or Mantoux) skin test previously, elevated serum angiotensin converting enzyme (ACE) and/or elevated serum lysozyme, bilateral hilar lymphadenopathy (BHL) in chest X-ray, abnormal liver enzyme tests, and BHL in chest CT scan from patient with negative chest X-ray. ²¹,²³

**SERPIGINOUS CHOROIDITIS**

Serpiginous choroiditis, also known as geographic or helicoid choroidopathy, is a bilateral, chronic, recurrent, progressive disorder that primarily involves the choroid and choriocapillaris and that is characterized by the gray-white lesions that show centrifugal spread. These gray lesions turn pale in few weeks, while the active edge advances further and eventually results in the development of multiple jigsaw puzzle-shaped areas of chorioretinal atrophy. ¹,³,²⁴,²⁵

This disease is presumed to be autoimmune. Most cases of serpiginous choroiditis are not associated with systemic diseases. Recent studies reported that serpiginous-like choroiditis can be due to infectious entities, such as tuberculosis and toxoplasmosis. The exact mechanism remains unknown, but these ocular lesions probably represent the immune-mediated inflammatory response resulting in hypersensitivity reaction. ³,²⁵,²⁶

Classically, funduscopy reveals asymmetric bilateral disease with characteristic gray-white lesions at the level of the RPE projecting in a geographic manner from the optic nerve in the posterior fundus (Figs 5A to C).²⁴,²⁶

Far less commonly, macular or peripheral lesions may present without peripapillary involvement. Peripheral lesions may occur in isolated or multifocal pattern, termed as ‘ampiginous choroiditis’, or recently as ‘relentless placoid chorioretinitis’. Ampiginous choroiditis has a characteristic course and fundus appearance of serpiginous choroiditis that developed new small, isolated round white plaque-like lesions similar to those seen in acute posterior multifocal placoid pigment epimeliothiopathy (APMPPE). ¹,²⁷

The characteristic finding of APMPPE is multiple flat yellow-white (cream-colored) plaques at the level of the RPE. These vary in size and are clearly defined. The placoid lesions typically begin in the macula or posterior pole, with later-developing lesions noted more peripherally. The lesions do not extend beyond the equator. The bilateral lesions of APMPPE may appear similar to those of serpiginous choroidopathy. Acute lesions in both diseases may be yellowish and involve the choroid and retina at the level of the RPE, and RPE clumping can be seen late in the course of both diseases. Acute lesions of both APMPPE and serpiginous choroidopathy show early blockage of fluorescence and late hyperfluorescence in fundus fluorescein angiogram. Indocyanine green (ICG) angiogram reveals multiple hypofluorescent lesions in mid phases, that are usually more numerous than fluorescein angiogram finding. However, the acute lesions of APMPPE resolve within 2 weeks, and recurrence is uncommon (Figs 6A to D). ¹,²,²⁷,²⁸

Fundus fluorescein angiography helps to support the diagnosis. ICG angiography is the best test to evaluate the extent and activity of the disease and is helpful for the follow-up of patient with serpiginous choroiditis. Fundus angiogram shows blockage of the choroidal flush in the early phase of the study and staining of the active edge of the lesion in the later stage of the angiogram. ICG angiography reveals hypofluorescence throughout all phases for both acute and old lesions; it may reveal more extensive involvement than fundus fluorescein angiogram or clinical examination. Fundus autofluorescence imaging may be an exquisitely sensitive modality in detecting damage to the RPE and in monitoring the clinical course of patients with serpiginous choroiditis, with characteristic hypoautofluorescence corresponding closely to areas of regressed disease activity and hyperfluorescence highlighting areas of active disease. ²⁵,²⁶

**VKH SYNDROME**

VKH syndrome is a bilateral granulomatous panuveitis disorder involving not only the eye, but also extraocular
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VKH syndrome may be divided into four stages: A prodromal stage (about 1 or 2 weeks before the uveitis attack), a posterior uveitis stage (about 2 weeks after uveitis onset), an anterior uveal involvement stage (from 2 weeks to 2 months after the first uveitis attack) and a recurrent granulomatous anterior uveitis stage (2 months after uveitis onset).\(^7\)

The diagnosis of VKH syndrome is essentially clinical; exudative retinal detachment during the acute disease and sunset glow fundus during the chronic phase are highly specific to this entity. In patients presenting without extraocular changes, FFA, ICG angiography, OCT, FAF imaging, lumbar puncture and ultrasonography may be useful confirmatory tests. Either choroiditis or chorioretinitis was always the prominent finding within 2 weeks after uveitis onset.\(^2,7,8\)

Multifocal areas of pinpoint leakage followed by subretinal pooling on FFA, irregular hypofluorescence on ICGA, neuroepithelial detachment on OCT and retinal detachment on B-scan ultrasonography were frequently observed in patients with active choroiditis or chorioretinitis at presentation, whereas window defects on FFA, filling defects on ICGA and vitreous opacity on B-scan ultrasonography were common findings in patients with chronic uveitis.\(^7,8\)

SYMPATHETIC OPHTHALMIA

Sympathetic ophthalmia is a rare, bilateral, diffuse granulomatous, non-necrotizing panuveitis that may develop after either surgical or accidental trauma to one eye (the exciting eye), followed by a latent period and the appearance of uveitis in the uninjured fellow eye (the sympathizing eye). Ocular surgery, particularly vitreoretinal surgery, now has emerged as the main risk for the development of sympathetic ophthalmia.\(^2,29\)

Patients with sympathetic ophthalmia typically present with asymmetric bilateral panuveitis with more severe inflammation in the exciting eye than in the sympathizing eye, at least initially. Both eyes may show mutton-fat keratic precipitates, thickening of the iris, posterior synechiae

Figs 6A to D: (A) Fundus photograph showing a case of APMPPE, (B) fundus autofluorescence showing hyperautofluorescence suggestive of active lesion, (C) fundus fluorescein angiogram showing hypofluorescence of the lesions in the early stage, (D) fundus fluorescein angiogram showing hyperfluorescence in the late phase
intracellulare Toxoplasma gondii and disseminated terminal infection.1,2,30 which was not recognized clinically, was part of infectious multifocal choroiditis. In most cases, choroiditis multiple infectious agents may cause simultaneous, capsulatum thickening.2,4 B-scan ultrasonography frequently reveals choroidal visualized during the intermediate phase of the angiogram. reveals numerous hypofluorescent foci, which are best visualized during the intermediate phase of the angiogram. B-scan ultrasonography frequently reveals choroidal thickening.2,4

OPPORTUNISTIC INFECTIONS
The choroid is often site of opportunistic disseminated infection in immunocompromised individuals. Among acquired immune deficiency syndrome (AIDS) patients, pneumocystis choroiditis is the most common infection. The choroidal infection is classically bilateral and multifocal, slowly progressive, often not associated with visual loss, the multiple, yellowish, well-demarcated, choroidal lesions located in the posterior pole are not associated with vitritis, iritis or vasculitis. Cryptococcus choroiditis is uncommon. The lesions may be multifocal, solitary or confluent. Other uncommon causes of multifocal choroiditis in AIDS include lymphoma, Mycobacterium tuberculosis, Histoplasma capsulatum, Candida albicans, Aspergillus fumigatus, Toxoplasma gondii and Mycobacterium avium-intracellulare. Due to the profound immunosuppression, multiple infectious agents may cause simultaneous infectious multifocal choroiditis. In most cases, choroiditis which was not recognized clinically, was part of disseminated terminal infection.1,2,30

SUMMARY
Choroiditis may be due to many entities, either infective or noninfective in etiology and present as different clinical manifestations. There are some conditions that can mimic choroiditis and should be ruled out before diagnosing choroiditis. It is also important to differentiate predominantly retinitis and chorioretinitis. We should not presume the cause of choroiditis from its clinical manifestations only. Complete history and review of systems, detailed ophthalmic examinations, prompt ancillary tests and laboratory investigations should be done to confirm the diagnosis and starting prompt managements.

REFERENCES

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