Case Report/Series

Multimodal approach in the diagnosis and management of Eales disease: a case report

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ABSTRACT

Eales disease is a rare idiopathic occlusive retinal vasculitis with low prevalence in the general population. Its infrequent occurrence limits diagnostic and treatment guidelines, emphasizing the need for ongoing reports to establish effective protocols. This case report describes a patient presenting with symptoms of bilateral retinal vasculitis. Fundus examination revealed vitreous hemorrhage (VH) and peripheral retinal vasculitis. Laboratory and imaging tests were performed to exclude differential diagnoses, leading to Eales disease as the primary diagnosis. Pars plana vitrectomy, panretinal laser photocoagulation, intravitreal anti-vascular endothelial growth factor, and anti-tuberculosis therapy were administered. Long-term follow-up showed satisfactory outcomes. This report suggested Eales disease to be a diagnosis of consideration for ophthalmologists encountering male patients with recurrent VH. Clinical suspicion, including appropriate laboratory testing and imaging, is essential to developing a holistic approach to diagnosis and management, aiming to prevent progression and achieve optimal visual outcomes.

KEYWORDS periphlebitis, rare diseases, retinal vasculitis, vitreous hemorrhage

Eales disease, an inflammatory condition that damages retinal blood vessel walls in the fundus periphery (retinal periphlebitis), predominantly affects males between 20 and 40 years of age residing in tuberculosis (Tb)-endemic regions, notably India and Southeast Asian countries.[1–4] Eales disease occurs bilaterally in approximately 90% of cases, but its progression varies asymmetrically across stages, resulting in different visual impairments in each eye.[2,4] Given its infrequent occurrence, Eales disease etiology is poorly understood; however, it is mostly associated with Tb or tuberculin protein hypersensitivity.[5,6]

The theory that systemic disease involvement contributes to Eales disease leads to a diagnostic approach that excludes other diagnoses.[7] Patients frequently present with recurring blurred vision, photopsia, or floaters, indicating the presence of recurrent vitreous hemorrhage (VH), a hallmark sign of Eales disease.[3,4] These clinical signs stem from the three retinal abnormalities commonly seen in Eales disease, namely peripheral vasculitis, capillary ischemia, and neovascularization.[3] Therefore, diagnosis may require extensive blood work, systemic disease markers, sputum analysis, and non-ocular and ocular imaging modalities.

The optimal treatment strategy for Eales disease remains inconclusive, as laser photocoagulation, anti-vascular endothelial growth factor (VEGF) injection, vitreoretinal surgery, and other systemic therapies such as anti-tuberculosis treatment (ATT) are frequently mandated to alleviate and halt disease progression.[1,3] Therefore, multimodal treatment with a comprehensive and holistic approach is generally applied to Eales disease management. To better

understand the diagnostic and management strategies, we present a case of Eales disease and highlight the importance of a comprehensive diagnostic approach to identify rare idiopathic retinal vasculitis with an early and holistic multimodal treatment approach to achieve favorable long-term visual outcomes.

CASE REPORT

A 53-year-old man presented with blurred vision in his right eye and floaters in his left eye that had developed over the past 4 months. The initial best corrected visual acuity (BCVA) was hand movement in the right eye and 20/20 in the left eye. Intraocular pressure in both eyes was within normal limits. Fundus examination of the right eye revealed signs of VH, with no view of the retina. B-scan ultrasonography (USG) revealed vitreous hyperreflectivity and complete posterior vitreous detachment with a flat retina, suggesting a preretinal hemorrhage and VH (Figure 1a). Fundus examination of the left eye revealed peripheral retinal vasculitis, with a flame-shaped intraretinal hemorrhage in all four quadrants (Figure 1b).

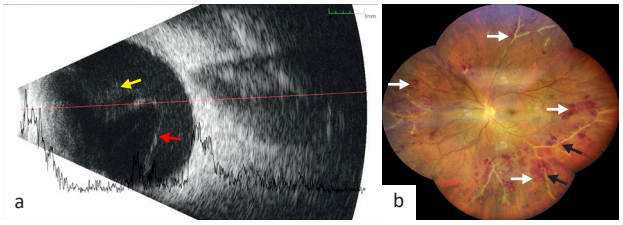

Figure 1. VA of hand movement in the right eye and 20/20 in the left eye. B-scan USG of the right eye (a) demonstrated total PVD (red arrow) without any retinal involvement and hyperreflective echoes (yellow arrow) in the vitreous cavity. A widefield fundus photograph of the left eye (b) showed peripheral vasculitis (black arrows) and flame-shaped intraretinal hemorrhages (white arrows) in all four retinal quadrants. PVD=posterior vitreous detachment; USG=ultrasonography; VA=visual acuity

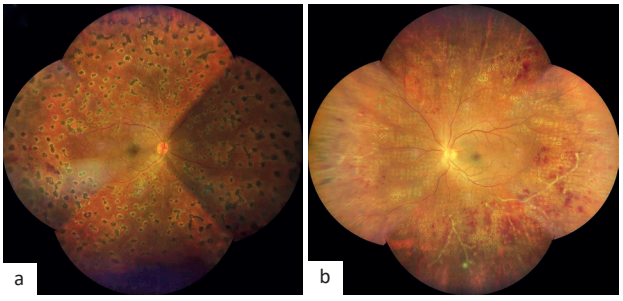

Figure 2. One month after primary interventions. Widefield fundus photographs of the right eye (a) and the left eye (b) show laser scars (shown by the black dots with the yellow borders). Best corrected visual acuity (BCVA) of the right eye was 20/40, and the left eye was 20/20

The patient was diagnosed with bilateral Eales disease and VH in the right eye. Pars plana vitrectomy (PPV) and endolaser photocoagulation were performed in the right eye, whereas panretinal photocoagulation laser treatment was performed in the left eye. One month after surgery, the right eye demonstrated clear vitreous and improved BCVA of 20/40 (Figure 2a), whereas the left eye vision remained at 20/20 (Figure 2b). He also consulted an internal medicine specialist and underwent a serum interferon-gamma release assay (IGRA), which showed positive results, thus prompting a 9-month course of ATT. The first 2 months consisted of a four-drug regimen: rifampicin (450 mg), isoniazid (300 mg), pyrazinamide (1,000 mg), and ethambutol (750 mg). This was followed by a continuation phase of rifampicin and isoniazid at the same dose for 7 months.

Due to the persistent complaint of blurred vision in the right eye, optical coherence tomography (OCT) was performed, revealing cystoid macular edema (CME) in the right eye (Figure 3a), whereas the left eye appeared normal (Figure 3b). Subsequently, 3-month doses of intravitreal bevacizumab injections were administered to the right eye. Intraretinal fluid remained in the right eye 4 months after the bevacizumab injection, although resolution was observed (Figure 3c). Furthermore, the left eye developed CME (Figure 3d); thus, 3-month intravitreal bevacizumab injections were administered to the left eye.

Four months after the last intravitreal bevacizumab injection in the left eye and completion of ATT, both eyes showed resolution of intraretinal fluid in the macula (Figure 3, e and f), with the left eye showing some epiretinal membranes. The patient developed a secondary cataract in the right eye (Figure 4). Consequently, phacoemulsification of the right eye with intraocular lens implantation was performed. At the last follow-up, 1 year after cataract surgery, vision remained 20/20 in both eyes.

DISCUSSION

Saxena and Kumar[3] developed a popular classification for Eales disease, as follows: stage 1, superficial retinal hemorrhages with inflammation

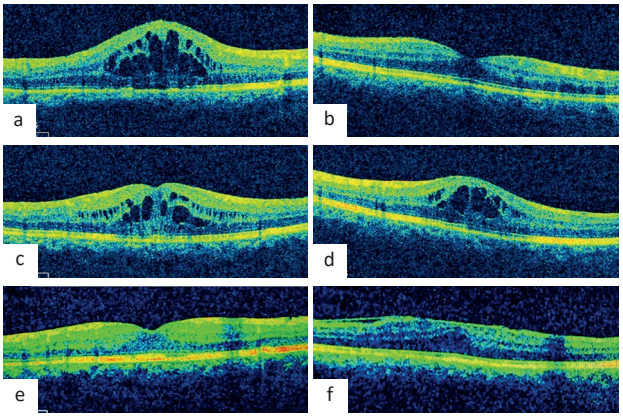

Figure 3. OCT images. A month after primary interventions (a and b), imaging depicts CME in the right eye (a) and normal macula condition in the left eye (b). Five months after primary interventions (c and d), imaging shows regression of macular edema post-bevacizumab injections in the right eye (C) and development of CME in the left eye (d). Nine months after primary interventions (e and f), imaging of the right eye (e) shows complete resolution, whereas the left eye (f) shows resolution of macular edema post-bevacizumab injections with an appearance of epiretinal membrane. The last BCVA of both eyes was 20/20. BCVA=best corrected visual acuity; CME=cystoid macular edema; OCT=optical coherence tomography

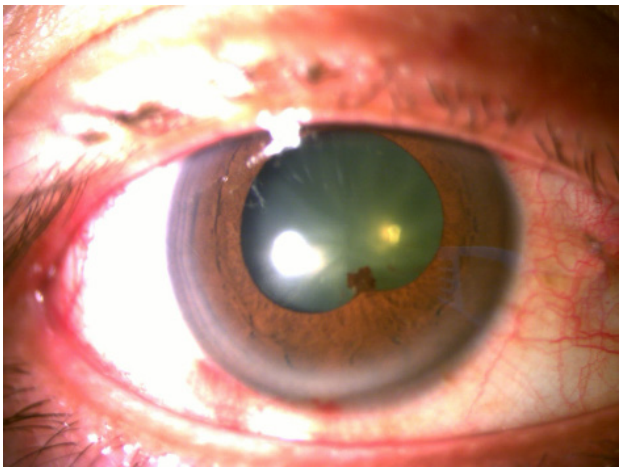

Figure 4. Cataract and posterior synechia were observed in the patient's right eye 1 year after the last treatment session. The patient underwent phacoemulsification and intraocular lens implantation

(periphlebitis) of small (1A) and large (1B) caliber vessels; stage 2A, capillary non-perfusion; stage 2B, neovascularization of disc/elsewhere; stage 3A, fibrovascular proliferation; stage 3B, VH; stage 4A, tractional/combined rhegmatogenous retinal detachment; stage 4B, neovascularization of the iris, neovascular glaucoma, complicated cataract, and optic atrophy. Most patients with Eales disease, including our patient, present to the hospital during stage 3B, when VH typically occurs.

A multifactorial etiology has been proposed for Eales disease. Several studies have proposed an association between Eales disease and Tb.[5,6] Patients with Eales disease may not carry viable organisms; however, in some cases, they are likely to carry non-viable organisms or *Mycobacterium tuberculosis* (MTB) DNA. The process of molecular mimicry between the retinal antigen and the MTB antigen eventually leads to ocular inflammatory changes.[5] However, the essential role of Tb in Eales disease remains unknown, as the disease has also been found in patients with Mantoux-negative results.[6] In this case, we report a patient with Eales disease with a positive IGRA result. This emphasizes the idea that countries with high rates of Tb infection, such as Indonesia, may need a comprehensive approach to assess idiopathic retinal vasculitis diseases and focus on Tb examinations, such as the polymerase chain reaction test, Mantoux test, IGRA, sputum smear, and consultation with a relevant specialist.

The presence of non-distinctive symptoms, which may be observed in other forms of retinal vasculitis with similar manifestations, establishes Eales disease as a per exclusionem diagnosis.[1,2,8] All retinal entities that manifest with similar peripheral retinal non-perfusion, such as branch retinal vein occlusion, proliferative diabetic retinopathy, Coats disease, and sickle cell disease, must be ruled out. Systemic diseases such as syphilis, sarcoidosis, toxoplasmosis, systemic lupus erythematosus, and Behçet's disease should also be excluded. Therefore, detailed clinical history, ocular and systemic examinations, and relevant diagnostic testing are required.[1,8] Owing to the frequent asymmetric presentation in both eyes, as shown in this case, thorough and careful evaluation is strongly recommended to identify peripheral signs in asymptomatic eyes.[2]

Because of the various signs, multiple imaging modalities are necessary to aid in the diagnosis of Eales disease, such as widefield fundus photography, B-scan USG, OCT or OCT angiography (OCTA), and fundus fluorescein angiography (FFA).[7,9] B-scan USG is particularly helpful in detecting VH, obscuring the view of the retina and retinal detachment. FFA and OCTA are useful in demonstrating active vasculitis, neovascularization, and non-perfusion areas of the retina, all of which help in tailoring treatment,

especially with the recent use of widefield angiography. A common complication of Eales disease is macular edema; thus, OCT is necessary as it is an excellent tool for the qualitative and quantitative analysis of edema within the macular region and other vitreoretinal abnormalities, such as traction or detachment.[2,10,11]

This case emphasizes the importance of a multimodal therapeutic approach in Eales disease management that depends on the clinical stage upon presentation. Patients without active peripheral vasculitis can be observed every 6–12 months. If VH occurs without a retinal tear, an assessment should be made 2–6 weeks after VH is found, aligning with the usual duration for a hemorrhage to resolve.[7] Steroids are the first-line treatment for patients in the inflammatory stage. Oral steroids are used in cases of bilateral vasculitis, whereas intraocular steroids are used for unilateral disease or as adjuvants, particularly when there is macular edema caused by inflammation.[4] However, the administration of steroids was halted before any infectious disease laboratory workup in previous studies on patients suspected of having Eales disease because its etiology is commonly associated with MTB infection. Because of the immunosuppressive properties of systemic steroids, which could potentially exacerbate the infection, steroid administration was delayed before laboratory results were obtained.[12] Our patient was also diagnosed with Eales disease at stage 3B (proliferative stage); thus, more aggressive treatment modalities were necessary to manage the disease, such as vitrectomy and laser treatments.

In cases of proliferative diseases and retinal ischemia, laser photocoagulation and anti-VEGF intravitreal injections are important therapeutic approaches.[4,7] VEGF upregulation after retinal ischemia results in neovascularization and fibrous proliferation, leading to retinal detachment or recurrent VH. Photocoagulation stops neovascularization, terminates vascular proliferation, and prevents occlusion progression, thus limiting the incidence of VH.[11] The use of laser ablation in areas with capillary non-perfusion is beneficial for visual outcomes.[4] Intravitreal injection of anti-VEGF has also been reported to prevent and regress neovascularization and decrease the need for PPV, compared with those receiving standard steroids and laser photocoagulation treatment alone.[13]

Moreover, recent studies have suggested that an anti-VEGF agent (aflibercept) can be used to treat recurrent macular edema due to Eales disease, primarily because of its ability to bind to all isoforms of VEGF-A, VEGF-B, and placental growth factor.[14,15] In this case, we administered bevacizumab injections to determine their effect on VH clearance and to treat CME by diminishing VEGF-mediated capillary hyperpermeability, and we obtained satisfactory results. The diverse functions of anti-VEGF agents have made them one of the primary medications for Eales disease.

PPV is frequently used in Eales disease with VH and retinal detachment as it has been suggested to improve visual prognosis.[1,7,16] Great visual outcomes can be attained with timely surgery if retinal detachment does not involve the macula and severe proliferative vitreoretinopathy does not develop.[13] Endolaser photocoagulation is mandatory during and/or after vitreous surgery, particularly in ischemic retinal areas, to minimize the occurrence of vascular sequelae and promote retinal attachment.[7,17]

The role of ATT in Eales disease remains unclear. However, in patients with active perivasculitis and a strong positive result for the Mantoux test or QuantiFERON Gold test, oral corticosteroids must be accompanied by empiric ATT to avoid reactivation of systemic disease.[7] Our case supports this theory as both eyes improved and remained stable after the completion of ATT treatment, proven by the resolution of CME and satisfactory vision at the last follow-up. The findings from this case and previous studies highlight the importance of systemic treatments, specifically ATT, for Eales disease outcomes.

Large studies are required to determine the role of systemic therapies in managing Eales disease. As our patient had MTB infection that was confirmed using IGRA, an infection-induced inflammatory process is likely to occur and cause a systemic increase in vascular permeability systemically.[18] Moreover, the upregulation of VEGF within the eyes may contribute further to capillary leakage through VEGF-mediated capillary permeability. These two processes may explain the development of complications, specifically CME, in Eales disease. Hence, using systemic therapy as monotherapy for Eales disease is not optimal, and a multimodal therapeutic approach comprising systemic and local treatments (e.g., ATT and anti-VEGF intravitreal injections) is preferable to prevent or mitigate complications of Eales disease.

Poor visual outcomes are associated with poor visual acuity, late presentation stages, and macular involvement.[4,9] Moreover, VH is the most common cause of vision loss, as was observed in our patient. Studies by Biswas et al[4] and Lee et al[19] as well as our case, prove that timely diagnosis and proper multimodal treatments may be crucial prognostic factors in acquiring good visual outcomes.

The limitation of this study is the lack of angiography imaging, either FFA or OCTA, owing to limited resources and the patient's preference related to his concern about the economic burden. Furthermore, despite a constant reminder of regular checkups, the patient was lost to follow-up a year after his last treatment; hence, later outcomes could not be acquired and reported. Nonetheless, the possibility of Eales disease should be considered in men with recurrent VHs. A thorough examination of both eyes must be performed because of the asymmetric bilateral presentation of Eales disease.

Comprehensive laboratory and imaging examinations should be performed to exclude non-ocular systemic diseases and other retinal vasculitis as well as to guide tailored treatment. A multimodal therapeutic approach involving steroids, laser photocoagulation, anti-VEGF therapy, and vitrectomy is frequently required to achieve good anatomical and functional visual outcomes. Moreover, a multidisciplinary approach involving other specialists for underlying systemic diseases, primarily Tb, should be mandated for patients with Eales disease.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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