Tuberculous Posterior Sclero-Uveitis with Features of Vogt-Koyanagi-Harada Uveitis: An Unusual Case

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Conflict of interest: None declared

Patient: Male, 32

Final Diagnosis: Ocular tuberculosis (tuberculous posterior sclero-uveitis with features of Vogt-Koyanagi-Harada uveitis)

Symptoms: Pain and progressive visual impairment of his left eye

Medication: Systemic anti-tuberculosis treatment (6-month course)

Clinical Procedure: Thorough ophthalmological and systemic exploration

Specialty: Ophthalmology

Objective: Rare disease

Background: Ocular tuberculosis (TB) is a clinical entity that presents with a wide range of clinical manifestations. It is regarded as an extremely challenging condition from the point of view of diagnostic approach and calls for early diagnosis and prompt treatment, as it can potentially lead to blindness.

Case Report: This is a case report of a 32-year-old male from southern India who has been living and working in Greece over the last 10 years and presented with 2-week history of pain and progressive visual impairment of his left eye. He underwent a thorough clinical ophthalmological examination and imaging of the fundus, and the findings were consistent with uveitis. However, the manifestations of the inflammation were complicated as they included features that could be attributed mainly to Vogt-Koyanagi-Harada (VKH) disease and tuberculous serpiginous-like uveitis. Therefore, a systemic evaluation, together with specific laboratory and paraclinical investigations, were carried out to define the etiology of the inflammation and develop an optimal therapeutic plan. Taking into account specific findings from the chest imaging, a positive purified protein derivative (PPD) skin test, and sputum cultures positive for Mycobacterium tuberculosis (MTB), we set a diagnosis of posterior sclero-uveitis and started our patient on anti-tuberculosis treatment.

Conclusions: This case reveals an atypical manifestation of tuberculous sclero-uveitis imitating Vogt-Koyanagi-Harada disease together with a few characteristics of serpiginous-like tuberculous uveitis, emphasizing the fact that tuberculosis should always be included in the differential diagnosis of uveitis when there is no obvious underlying disease.

MeSH Keywords: Antibiotics, Antitubercular • Follow-Up Studies • Latent Tuberculosis • Mycobacterium Tuberculosis • Tuberculosis, Ocular • Uveitis, Posterior

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Background

Tuberculosis (TB) is a severe multi-systemic disease caused by *Mycobacterium tuberculosis* (MTB) and is currently regarded as the leading infectious cause of morbidity and mortality worldwide [1,2]. The majority of infections (more than 95%) are recorded in the developing world, especially in South Asia and Africa. The number of TB infections is increasing in both developing and developed countries, mainly due to 3 basic factors: global migration, human immunodeficiency virus (HIV), and multidrug-resistant tuberculosis [3–5]. Tuberculosis can cause multi-systemic granulomatous inflammation, primarily affecting the lungs in 80% of the patients, while in the other 20% it can affect other tissues, including the eyes. Ocular involvement is considered as a relatively uncommon extra-pulmonary manifestation and usually there is no correlation with clinical evidence of lung disease [6]. Ocular tuberculosis is a vision-threatening condition and is considered extremely challenging for ophthalmologists as it can present both as intraocular and extraocular disease, mimicking other clinical entities (especially various forms of uveitis) and complicating diagnosis and therapy [7]. In the vast majority of cases, it remains unclear whether the ocular inflammation occurs as a result of direct *Mycobacterium* infection or hypersensitivity reaction. The aim of this report is to describe a rare case of bilateral and asymmetrical tuberculous sclero-uveitis presenting as a Vogt-Koyanagi-Harada (VKH)-like/serpiginous-like TB uveitis, focusing on the broad range of clinical features and the significance of a thorough diagnostic and therapeutic approach. Additionally, we highlight how and why tuberculosis should be incorporated in the differential diagnosis of many ocular inflammations, as a possible etiologic factor.

Case Report

A 32-year-old man from southern India, who has been living and working in Greece over the past decade, presented with 2-week history of pain and progressive visual impairment of his left eye. Detailed medical history was free of hemoptysis, shortness of breath, long-standing cough, weight loss, and gastrointestinal or urinary symptoms. Our patient denied having fever or night sweats. Moreover, there were no symptoms to indicate connective tissue disorder. His past medical history was uneventful and no exposure to animals or recent traveling was recorded.

On examination, his Snellen visual acuity was 10/10 in the right eye and 1/10 in the left eye. Slit-lamp biomicroscopy of the anterior chamber revealed that there was no presence of flare and cells. The pupillary reflex and the eye movements were normal in both eyes. Fundoscopy of the affected eye showed mild vasculitis (phlebitis), optic disc swelling, and choroidal folds in close proximity to the optic disc and the macula. Moreover, at the periphery of the macula, there were some choroidal lesions that were causing curving of the vessels; this feature is usually observed in tuberculous serpiginous-like uveitis, which is described by tubercles (choroidal nodules) and choroidal tuberculomas (granulomas) [8,9]. In the right eye, the fundus examination did not reveal any pathological findings (Figure 1A, 1B). We decided to hospitalize the patient for a more thorough etiologic exploration and consultation with other clinics (Pulmonology, Internal Medicine, and Infectious Diseases service). Optical coherence tomography (OCT) of the left eye showed optic disc swelling, retinal folds, and macular exudative retinal detachment with cloudy fluid (Figure 1C, 1D), another finding that is regarded as typical of VKH disease [10,11]. The next step of our diagnostic approach was to carry out a fundus fluorescein angiography, which is a very important diagnostic tool because it allows evaluation of retinal and choroidal disorders. Our patient was unable to go on with an indocyanine angiography as he started feeling mild shortness of breath and dizziness immediately after the intravenous infusion of indocyanine, without any further complications, leading to the interruption of the procedure. The fluorescein angiography of the left eye in the early phases revealed optic disc diffuse hyperfluorescence with leakage, as well as delayed filling of the ophthalmoscopically observed perimacular choroidal lesions and initially pinpoint hyperfluorescent spots, clearly observed in the arteriovenous phase. At the same stage, no remarkable findings could be observed in the right fundus. In the latter stages of the angiography, asymmetrical pathological findings were detected in both eyes. The left eye angiography showed pinpoint areas of leakage in the subretinal space subsequent to the pinpoint spots of hyperfluorescence mentioned above. The fluorescein angiography findings (Figure 2) were indicative of Vogt-Koyanagi Harada disease [10,11]. To complete the imaging, we performed a B-mode ultrasound scan that showed the “T-sign” and a posterior juxtascleral fluid concentration, which are both pathognomonic echographic signs of posterior or scleritis (Figure 3).

Results of laboratory investigations, including full blood count and biochemistry assays, were unremarkable and no pathogens were detected in blood, sputum, and urine cultures. Results of further investigations were normal, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum rheumatoid factor (RF), angiotensin-converting enzyme (ACE), antinuclear antibodies, antineutrophil cytoplasmic antibodies (p and c), ELISA for human immunodeficiency virus (1 and 2), serology for syphilis (TPHA: Treponema pallidum hemagglutinin antigen, VDRL: Venereal Disease Research Laboratory), and viral hepatitis (B and C). However, because the chest X-ray revealed bilateral hilar lymphadenopathy (Figure 4A), we requested a chest CT scan to obtain a more detailed imaging of the lungs.
The CT scan illustrated multiple pulmonary infiltrates consistent with pulmonary tuberculosis (Figure 4B, 4C). Therefore, although our patient was vaccinated at childhood with BCG, we performed a tuberculin skin test, and the result was strongly positive (induration diameter: 25 mm). This result, together with positive sputum cultures for *Mycobacterium tuberculosis* and the radiologic findings, in combination with his migration from southern India, which is regarded as an endemic area for tuberculosis, led us to a diagnosis of tuberculous uveitis; specifically, the final diagnosis was tuberculous posterior sclerouveitis, mimicking mainly VKH disease, with some features of tuberculous serpiginous-like uveitis.

Subsequently, we immediately started our patient on systemic anti-tuberculosis treatment with isoniazid 300 mg/day, rifampicin 600 mg/day, ethambutol 15 mg/kg/day, and pyrazinamide 25 mg/kg/day. According to the standard 6-month course, the 4-drug regimen was administered for the first 2 months and after this interval, for the next 4 months only isoniazid and rifampicin were given. He was started on this particular regimen based on World Health Organization (WHO) guidelines for extrapulmonary tuberculosis [12].

Two months after the initiation of this medication, the patient’s clinical image improved significantly and his Snellen visual acuity improved to 9/10. Regular follow-up carried out every 2–3 months for the first 2 years after treatment indicated complete resolution with no recurrence of ocular tuberculosis or any other systemic manifestations of the disease (Figure 5).

**Discussion**

It is undisputed that ocular tuberculosis is a very complicated clinical issue due to the wide spectrum of clinical manifestations that it presents with. Various signs and symptoms have been recorded because it usually mimics other ophthalmic diseases [13–15]. It can be either primary (the eyes are the point of entry), which is quite rare, and it affects eyelids, cornea, conjunctiva and sclera, or secondary (occurring due to hematogenous transmission), which involves the uveal tract, retina, and optic nerve [16]. Ophthalmologists need to be aware of this mimicking behavior and should consider tuberculosis as a possible cause in any type of intraocular or extraocular inflammatory condition, unilateral or bilateral. TB is a possible
Figure 2. (A) Left eye: Early phases of the FA showing optic disc swelling and hyperfluorescent mass-like choroidal lesions. (B) Left eye: Early pinpoint spots in the arteriovenous phase of the FA (red arrows). (C) Right eye: Perimacular hyperfluorescent spots in the intermediate phases of the FA. (D) Left eye: More prominent hyperfluorescence of the choroidal lesions along with a cloudy macula (intermediate phases). (E) Right eye: Final phases of the FA showing increased hyperfluorescence of the spot lesions. (F) Left eye: Diffuse leakage (final phases) in the area of the pinpoint lesions observed earlier (red arrows).
cause of uveitis in up to 10% of cases, and this percentage is even higher in endemic areas [8]. In the past, tuberculosis was regarded as the most common cause of granulomatous uveitis, but over the course of time its prevalence has significantly changed. To be more specific, nowadays, we are able to recognize many inflammatory conditions, such as toxoplasmiasis or sarcoidosis, that were previously unknown and need to be taken into account in the differential diagnosis [17]. Uveitis can appear as anterior, posterior, intermediate, or panuveitis. The most common is posterior uveitis, with focal or multifocal lesions in the choroid, serpiginous-like choroiditis, 1 or more tubercles (choroidal nodules), choroidal tuberculomas (granulomas), subretinal abscess, neuroretinitis, and retinal vasculitis [8,9]. Because the most common presentation of ocular tuberculosis is in the uveal tract and manifests as a posterior uveitis [18], it is important to remember that Mycobacterium tuberculosis is an obligate aerobic bacterium usually detected in highly oxygenated tissues, such as the choroid, which has an extremely high oxygen tension and blood supply [19]. In anterior uveitis, it presents with granulomatous keratic precipitates and is often accompanied by iris granulomas or nodules and vitreitis. Intermediate uveitis is usually described with peripheral neovascularization, vitreous hemorrhage, and cystoid macular edema [17]. However, all these clinical findings may be indicative, but not pathognomonic for the disease. It is unclear whether ocular manifestations happen as a result of direct infection or due to a hypersensitivity reaction to mycobacteria. Most probably, direct hematogenous infection (dissemination from a distant site, such as the lungs) causes choroidal nodules and hypersensitivity response leads to vasculitis and choroiditis [20,21]. As expected, the diagnosis of ocular tuberculosis is often difficult, causing clinicians to be skeptical about the etiology of uveitis. Apart from the huge range of presentations, another obstacle is that direct histopathological samples cannot be obtained from choroid for biopsies, because this is impractical due to the invasiveness of the tissue. Consequently, in most reported cases, the diagnosis of tuberculous eye infection remains largely hypothetical and based on corroborative evidence [19]. It is estimated that approximately 60% of individuals with extrapulmonary tuberculosis do not have pulmonary disease. Therefore, ocular tuberculosis is commonly not correlated with clinical evidence from the respiratory system [6]. Moreover, in most cases with latent TB, chest X-rays show no pathological findings that could contribute to diagnosis [22]. However, even in non-endemic areas, a mycobacterial infection cannot be excluded by negative chest imaging. Diagnostic criteria for ocular tuberculosis from the available studies include: previous history of Koch’s contact, residence in or migration from endemic countries, ophthalmological findings, possible extraocular/systemic manifestations, radiological findings of active or latent TB, detection of Mycobacterium tuberculosis in non-ocular samples, positive tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) [QuantiFERON-TB Gold In-Tube (QFT; Celestis Inc. Carnegie, VIC, Australia) and ELISPOTPLUS (T-SPOT.TB, Oxford Immunotec, Oxford, UK)], exclusion of other possible etiologies, and response to anti-tuberculosis treatment (ATT) without any relapses of the disease [7,8]. A definitive diagnosis can be established after detecting Mycobacterium tuberculosis in ocular samples with polymerase chain reaction (PCR), culture...
growth, or demonstrating acid-fast bacilli on smears [23], but these tests do not have high sensitivity [7]. In general, PCR of aqueous and vitreous samples and interferon-gamma release assays (IGRAs) are preferred because they have higher specificity for TB [23].

Our patient presented with a unique combination of pathological findings, as the majority of them were imitating VKH disease, but there were also some findings that could be attributed to serpiginous-like tuberculous uveitis. Moreover, this particular presentation was accompanied by posterior scleritis, which has already been reported in ocular tuberculosis [24], but in our case contributed to a more complicated presentation of the disease. Serpiginous-like TB uveitis is considered to be a common presentation of tuberculous ocular infection, but there are no previous reports of VKH-like ocular disease. The VKH-like characteristics are more common those that define serpiginous-like disease. Therefore, our case can be described as a posterior VKH-like tuberculous sclero-uveitis.

We started our patient on a 6-month ATT regimen according to the WHO guidelines for extrapulmonary TB [12]. Recent reports describe anti-tuberculous drugs treatment periods that vary from 6 to 18 months, based on the patient's individualized approach [19,25]. We did not have a strong reason to include steroids in our treatment, although several studies reported a satisfying response to ATT when administered together with systemic steroids [18,26,27]. Currently, the administration of oral steroids in individuals with tuberculous ocular inflammation remains a controversial issue that needs further research. The use of steroids is recommended in other cases of extrapulmonary disease, such as TB pericarditis [28] and meningitis [29]. It is also important to emphasize that corticosteroids must not be given to patients with inflammation of the uveal

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**Figure 5.** Fundus of both eyes at 1 year after the end of the therapy. (A, B) Resolution of inflammatory signs in both eyes. (B) Absence of optic disc edema and remission of choroidal folds and mass-like choroidal lesions. (C) Total regression of the exudative macular detachment of the left eye. (D-G) Fluorescein angiography: absence of inflammatory signs. Hyperfluorescent areas in both eyes (in the intermediate phases) reflects the post-inflammatory lesions of the retinal pigment epithelium, since this hyperfluorescence decreases in the late phases.
tract before the aqueous and vitreous humors have been analyzed, as the etiology of uveitis might be unclear upon routine examination,

Our patient did not present with clear symptoms of active pulmonary disease. The vast majority of cases with ocular TB-related inflammation are associated with latent TB, which means that the patient is infected, but without having active disease [30–32]. It is estimated that almost one-third of the world’s population (approximately 2 billion individuals) has latent TB infection. People with latent TB infection do not present with symptoms of active disease and are not infectious, but it is thought that about 10% will eventually develop active TB. Immunosuppression, low socioeconomic status, and general decline are basic predisposing and triggering factors [33].

Regular follow-up is essential to monitor for recurrence of the inflammation and relevant complications that could affect vision. Inflammation can be either unilateral and asymmetric or bilateral; in bilateral inflammation, the first eye can become inflamed months or even years before the other [8].

Conclusions

Tuberculous uveitis is a very challenging clinical entity due to the complexity of the disease caused by its mimicking nature. Our case highlights that the atypical presentation of tuberculosis poses a difficult issue and should always be included in the differential diagnosis of uveitis with no known underlying cause. In cases in which it is not feasible to detect the etiologic factor, especially in endemic areas, the clinician should consider starting the patient on ATT treatment and monitoring their response, because in most individuals with ocular tuberculosis the diagnosis is mainly presumptive. Imaging plays a pivotal role both in the initial assessment and in follow-up. Despite the availability of sophisticated laboratory tests, thorough clinical examination and regular follow-up remain extremely important to achieve a better prognosis. In complicated cases, ophthalmologists need to consult with infectious diseases clinicians to develop an optimal therapeutic plan. Finally, we suggest that there is a pragmatic need for establishing specific diagnostic criteria for ocular tuberculosis, targeting accurate and early diagnosis to facilitate diagnosis and ensure a better outcome, since this is a treatable disease.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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