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Ocular Tuberculosis, Anti-Tuberculosis Prophylaxis, and Diseases Confused with Ocular Tuberculosis: Brief Report

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ABSTRACT

We present a case series of eight patients with ocular tuberculosis (OTB), latent tuberculosis (TB) or sarcoidosis, some of whom were receiving anti-tumor necrosis factor alpha (anti-TNF-α) therapy for various systemic diseases. Only one patient had a positive QuantiFERON®-TB test (QFT), and only one case showed a positive acid-resistant bacilli (ARB) test result. In a third case, brain imaging provided valuable assistance. Ocular tuberculosis should not be overlooked during clinical examination, as it remains a relevant diagnosis even in non-endemic regions. Over the last decade, the use of anti-TNF-α inhibitors for treating resistant uveitis has increased significantly. Consequently, it is essential to closely monitor patients for immunosuppression and remain vigilant about the risk of TB.

Keywords: Ocular tuberculosis, tumor necrosis factor-alpha inhibitors, uveitis.

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INTRODUCTION

Tuberculosis (TB) can affect the eye, referred to as ocular tuberculosis (OTB). The signs of OTB may present as various ocular changes, often mimicking other conditions, which can lead to misdiagnosis. The gold standard for OTB diagnosis is the direct demonstration of *Mycobacterium tuberculosis* (MTB) in tissues or fluids; however, obtaining positive results from ocular samples by culture or smear is difficult due to the low yield of MTB and the small size of the samples.[1–3] Therefore, the diagnosis of OTB is largely based on clinical suspicion and immunological tests.

Uveitis caused by OTB can occur in any part of the eye—including anterior, intermediate, posterior, or panuveitis—and may present as iris nodules, such as Koeppe and Busacca nodules,[4,5] keratic precipitates (KP),[6] choroidal tuberculoma, choroidal tubercles, multifocal choroiditis, and serpiginous-like choroiditis.[7,8]

Tumor necrosis factor-alpha (TNF-α) is a cytokine, a type of signaling molecule essential for immune system or inflammatory responses. When activated, immune cells, including macrophages, monocytes, and T lymphocytes, primarily produce TNF-alpha. Inhibitors of this cytokine are commonly used to treat various inflammatory diseases, such as uveitis.[9] Although anti-tumor necrosis factor-alpha (anti-TNF-α) treatment has benefits in inflammatory conditions, the risk

of TB remains a significant concern, particularly in endemic countries. Several case reports and observational studies have documented TB as an adverse drug reaction in patients receiving TNF inhibitors.[10,11]

The aim of this study is to provide a summary of diagnostic and therapeutic approaches for OTB through the presented cases and to emphasize the importance of using anti-TB prophylaxis for patients undergoing anti-TNF therapy.

MATERIALS AND METHODS

The study included eight cases with OTB or conditions resembling OTB. Each participant provided written informed consent to participate in the study. These patients were monitored at the Department of Ophthalmology, Uvea-Behçet Unit, Erciyes University Faculty of Medicine. The following data were recorded and evaluated: best corrected visual acuity (BCVA, logarithm of the minimum angle of resolution [logMAR]), intraocular pressures (IOP, mmHg), anterior segment findings, retinal and vitreous findings, fundus autofluorescence (FAF), fundus fluorescein angiography (FFA), and optical coherence tomography (OCT; Heidelberg Engineering, Heidelberg, Germany) findings, treatments, purified protein derivative (PPD) test, acid-resistant bacilli (ARB) test, QuantiFERON®-TB test (QFT), radioimaging results, and other findings.

RESULTS

This brief report includes the medical records of eight cases, summarized in Appendix 1.

Case 1

A 62-year-old male patient presented with grade 1+ (faint) cells in the anterior chamber and grade 1+ (minimal) vitritis on biomicroscopic examination in both eyes. A serpiginous-like lesion was observed in the retina of both eyes (Fig. 1a). Optical coherence tomography showed intraretinal edema in the right eye (Fig. 1b). Active OTB was considered as a preliminary diagnosis, and the QFT test returned positive. A consultation for pulmonary diseases was requested, but active pulmonary TB was ruled out. For latent TB, prophylaxis with 300 mg of isoniazid daily for nine months was planned. We initiated treatment with 48 mg oral prednol, following a weekly tapering schedule, and monitored its effects on a monthly basis. By the fourth month visit, the vitritis and macular edema in the right eye had regressed. The macula healed with atrophy after the resolution of the edema (Fig. 1c).

Case 2

An 18-year-old female patient, involved in animal husbandry, presented with complaints of pain, blurriness, and floaters in her right eye. Biomicroscopic examination revealed grade 2+ (moderate) positive cells in the anterior segment of the right eye. Fundus and biomicroscopic examination showed grade 1+ (minimal) vitritis in both eyes and hypopigmented lesions in the left eye. Fundus fluorescein angiography imaging revealed leakage in bilateral artery branches. Fundus autofluorescence imaging of the bilateral lesion showed a hyper-autofluorescent appearance around the lesion. Multifocal choroiditis was suspected, prompting further investigation. The patien"s biochemical and radiological tests returned normal results. The PPD skin test was anergic, and the QFT test was negative. Infectious markers were also negative. Based on these findings, a diagnosis of isolated bilateral multifocal choroiditis possibly due to TB was considered. Quadruple anti-tuberculosis therapy (ATT) with isoniazid, rifampicin, ethambutol, and pyrazinamide was initiated. At discharge, oral prednol was prescribed at 0.5 mg/kg daily. A fundoscopic examination one week after treatment showed bilateral hypopigmented lesions consistent with multifocal choroiditis. Minimal subretinal fluid had developed in the left eye, as shown in macular optical coherence tomography. Consequently, the patien"s oral prednol dose was increased from 32 mg daily to 64 mg, and a follow-up check was scheduled in four weeks. At the four-week follow-up, OCT imaging showed that subretinal edema had regressed. Fundus autofluorescence imaging showed significantly reduced photofluorescence around the lesions. The steroid dose was then reduced, and quadruple ATT treatment was continued. By the 10th week of treatment,

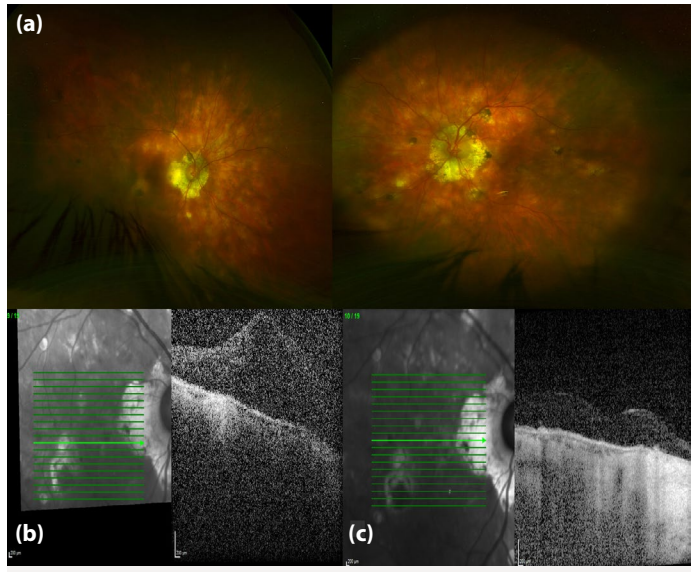

Figure 1. Serpiginous-like choroiditis in both eyes on the ultra-widefield fundus image **(a)**, intraretinal edema in the right eye on the macular optical coherence tomography (OCT) image (b), and macular atrophy following the resolution of macular edema in the same eye **(c)**.

vitritis had completely resolved. Isoniazid and rifampin were continued for six months, while ethambutol and pyrazinamide were discontinued after the second month. Significant improvement was observed in the retinal layers, and the subretinal fluid was completely resolved.

Case 3

A 3-year-old male patient with interferon-gamma deficiency is under follow-up care. He completed treatment for TB a year ago but is not currently receiving any treatment. The patient demonstrated light object tracking in both eyes. Fundus examination revealed a subretinal mass-like appearance in the superior temporal region of the right macula. Ocular tuberculoma was suspected. A pediatric chest diseases consultation was requested. Brain imaging showed a diffusion-limiting space-occupying lesion with pronounced flair hyperintense vasogenic edema around the left parietal lobe, located cortically and subcortically at the supraventricular level, measuring 2.5 cm at its widest point, suggestive of abscess/tuberculoma. The patient was referred to relevant departments for TB treatment. Following the observation of lymphadenopathy in the armpit, a skin biopsy indicated granulomatous folliculitis, and numerous bacilli were identified with the Ehrlich-Ziehl-Neelsen stain. Culture of a sample from axillary lymphadenopathy confirmed Mycobacterium tuberculosis. Quadruple anti-tuberculosis treatment with isoniazid (10 mg/kg), rifampicin (10 mg/kg), ethambutol (15 mg/kg), and pyrazinamide (20 mg/kg) was initiated by the pediatric department. Following these treatments, a reduction in the subretinal mass was observed, although complete regression was not achieved. The follow-up process is ongoing.

Case 4

A 55-year-old male patient is being followed up by the rheumatology department for rheumatoid arthritis and by the chest diseases department for pulmonary TB. The ARB test was positive, and Mycobacterium fortuitum was identified in the culture (Lowenstein-Jensen). The patient reported low vision in both eyes. Anterior segment examination revealed grade 3+ (marked) cells and posterior synechiae in the right eye, along with flare and extensive posterior synechiae in the left eye. Fundus examination showed grade 2+ (mild) vitritis in the right eye and grade 4+ (marked) vitritis with perivascular sheathing in the left eye. Clinical examination further revealed widespread capillaritis and periphlebitis in the left eye, while the right eye showed capillaritis and optic disc fluorescein leakage (Fig. 2a). On the same day, subconjunctival adrenaline and subtenon steroid injections were administered to the left eye. Clinical improvement was observed in the left eye after one day. The patient was

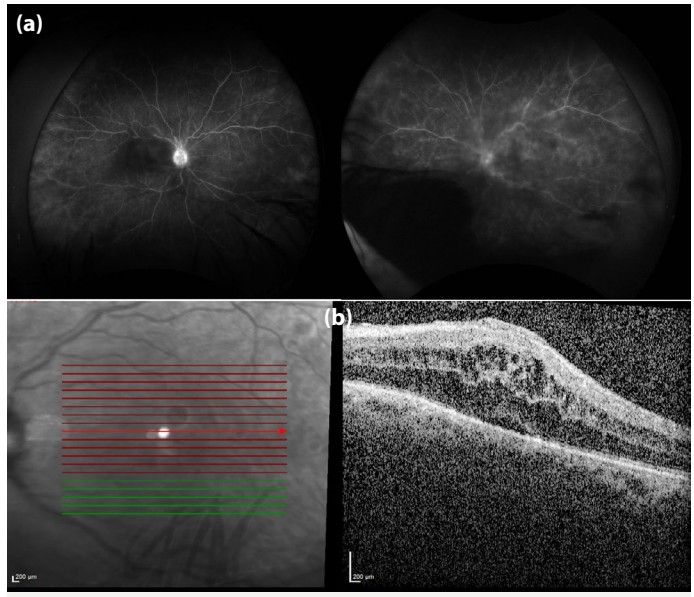

Figure 2. Widespread capillaritis and periphlebitis in the left eye, capillaritis and optic disc fluorescein leakage in the right eye on ultra-widefield fluorescein angiography **(a)**, and macular edema in the left eye **(b)**.

prescribed 40 mg of deltacortril, along with dexamethasone and cycloplegic eye drops. Due to the active TB infection, systemic anti-TNF-α treatment could not be initiated. Rituximab therapy was started, and the patient was referred to the rheumatology and chest diseases departments. The patient is under continued monitoring and has received intermittent intravitreal dexamethasone (Ozurdex®) implantation for left macular edema (Fig. 2b). Although there has been a reduction in macular edema, complete resolution has not yet been achieved.

Case 5

A 22-year-old male patient presented with complaints of low vision in both eyes. He had no known systemic diseases. Anterior segment examination revealed diffuse, dense, fine KPs on the cornea of both eyes, with grade 1+ (faint) cells in the anterior chamber. Posterior segment examination showed grade 4+ (marked) vitritis in both eyes. Two foci of retinitis were observed in the nasal area of the optic disc in the right eye, while no retinitis foci were noted in the left eye. Optical coherence tomography revealed subretinal fluid, predominantly in the right eye. Fundus fluorescein angiography showed bilateral frosted branch angiitis. Infectious markers were requested, but all results were negative. Behçe"s panuveitis was suspected, and a dermatology consultation was requested. The patient was diagnosed with Behce"s disease and started on treatment

with azathioprine 50 mg twice daily, oral prednol 48 mg daily, and adalimumab 40 mg subcutaneously every two weeks. Due to inadequate response, the adalimumab dose was increased to 40 mg weekly. When this treatment still failed to produce a sufficient response, weekly treatment with remicade 300 mg was initiated. Intermittent Ozurdex implantation was administered for uveitic macular edema. When the PPD test result reached 12 mm one year after starting anti-TNF-α therapy, isoniazid prophylaxis at 300 mg daily was planned for nine months. Following treatment with remicade and intravitreal Ozurdex, the posterior uveitis findings regressed. No lymphadenopathy or other signs of tuberculosis were found on computed tomography. Since the symptoms of active tuberculosis were not observed, the patient was classified as having latent tuberculosis, and anti-TB prophylaxis was initiated by the chest diseases department. The follow-up examination is ongoing and will continue to be closely monitored.

Case 6

A 16-year-old female patient with a history of epilepsy presented with complaints of floaters in her eyes. This was her second uveitis attack. Anterior segment examination revealed bilateral granulomatous KPs. Posterior segment examination showed pigmented cells in the vitreous from previous attacks and lesions in the peripheral retina. Fundus fluorescein angiography imaging revealed leakage areas in the peripheral retina, prompting a preliminary diagnosis of TB. A transbronchial biopsy from the right lung showed a high CD4/CD8 ratio, leading to a diagnosis of sarcoidosis based on clinical findings. The patient was started on oral prednol 48 mg daily and methotrexate 15 mg via subcutaneous injection. The treatment showed a positive response.

Case 7

A 39-year-old male patient presented with complaints of low vision in both eyes. He had no known systemic disease. Posterior examination revealed grade 4+ (marked) vitritis, and the retina could not be clearly visualized in either eye. Topical treatment was administered, and consultations with the chest and rheumatology departments were arranged for further investigation. The patien"s viral infectious markers were negative. At the follow-up visit in the second week, the fundus was more clearly visible, revealing findings consistent with hemiretinal vein occlusion in the left eye. The patien"s HLA-B*51 test was positive, suggesting secondary Behce"s vasculitis. Adalimumab treatment was initiated at 40 mg every two weeks. Isoniazid prophylaxis (300 mg daily) was also started due to a positive PPD test. When examined one year later, the leaks had completely resolved.

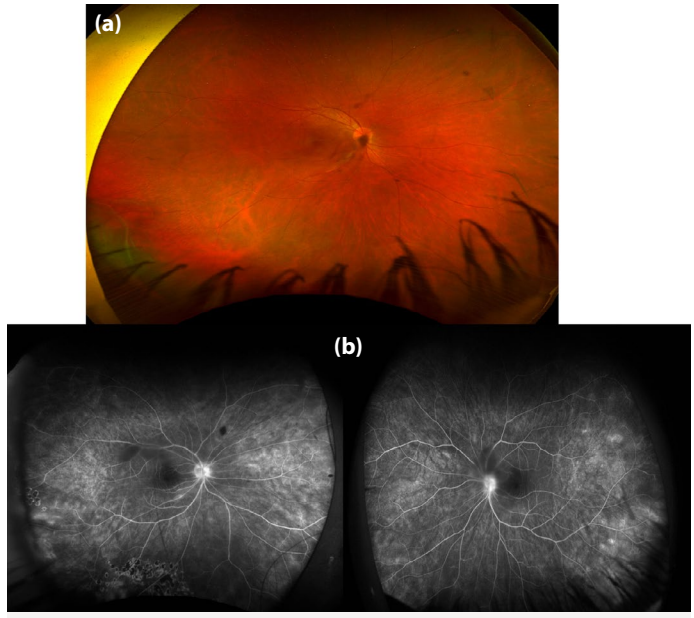

Figure 3. Schisis in the inferotemporal retinal area of the right eye on the ultra-widefield fundus image **(a)**, argon laser photocoagulation scars at the border of the schisis zone, and fluorescein leakage on the optic disc with widespread capillaritis in both eyes on ultra-widefield fluorescein angiography **(b)**.

Case 8

A 22-year-old female patient had been followed for uveitis for 10 years, with no etiology identified by rheumatology specialists. Her presenting complaint was floaters in both eyes. Posterior segment examination revealed grade 4+ (marked) vitritis in both eyes, with a snowbank inferiorly and a schisis in the inferotemporal retinal area of the right eye (Fig. 3a). Laser was applied around the schisis area due to the potential risk of retinal detachment. Optical coherence tomography showed subretinal fluid. There was fluorescein leakage on the optic disc and widespread capillaritis in both eyes (Fig. 3b). Viral markers were negative in the tests conducted to determine the etiology. The patien"s HLA-B*27 and QFT tests were positive, leading to a diagnosis of ankylosing spondylitis based on clinical findings. The patient was scheduled to begin oral prednol and Metoart 15 mg for pars planitis. Due to the positive QFT result, isoniazid prophylaxis at 300 mg daily was planned for nine months. During follow-up examinations, it was observed that the patient did not respond adequately to the treatment, and gastrointestinal complaints developed due to methotrexate. Consequently, adalimumab therapy was initiated at 40 mg weekly. Over approximately two years of close monitoring, the patient's clinical condition has significantly improved, and she continues to be followed without recurrence.

DISCUSSION

A precise international consensus on the therapeutic approach to OTB has yet to be established, largely due to the absence of standardized diagnostic criteria and gold-standard tests, which pose significant challenges in the diagnosis and treatment of this condition. Experience with OTB, including case reports and case series, can provide valuable guidance in its management. Although the cornerstone of OTB diagnosis is the direct demonstration of MTB in tissues or fluids, such evidence is difficult to obtain from ocular fluids or specimens. As a result, diagnosis often relies on clinical suspicion, immunological tests, corroborative tests, and radiological imaging. Of the first four cases we diagnosed as TB uveitis, only the first case had a positive QFT result, and only the fourth case tested positive for ARB. In our third case, brain imaging was instrumental in the diagnosis. None of the immunologic tests were positive across these cases, and diagnoses were predominantly based on ocular findings. During the diagnostic process, conditions that can cause granulomatous uveitis, particularly sarcoidosis, should be included in the differential diagnosis.[5] In our cases, sarcoidosis and TB were initially considered, and chest tomography ultimately led to a diagnosis of sarcoidosis by the chest diseases department. Accurate diagnosis of ocular TB and the initiation of anti-tuberculosis (anti-TB) therapy for a minimum of nine months, with or without anti-inflammatory therapy, is crucial to reducing relapses and improving visual acuity.[12] Additionally, uveitic macular edema may occur in some patients either before or despite treatment. Local treatment with an intravitreal dexamethasone implant may be a safe and effective option for managing macular edema secondary to tuberculous uveitis.[13,14]

Following the introduction of anti-TNF therapies, numerous reports have documented an increased incidence of TB infection, especially in the form of latent TB reactivation. Consequently, screening guidelines were established prior to initiating anti-TNF therapy. These guidelines recommend isoniazid prophylaxis for six to nine months or a combination of rifampicin and isoniazid for three months in cases of latent TB. Adherence to these recommendations has reduced the risk of TB in patients receiving anti-TNF therapy. In our last four cases, despite differing etiologies, anti-TNF treatment was continued due to positive PPD tests, with concurrent prophylactic treatment.

Ocular tuberculosis can mimic various diseases or types of uveitis, often leading to diagnostic confusion, as it can affect any structure of the eye. Ocular tuberculosis can present in diverse forms, including anterior, intermediate, posterior, or panuveitis, characterized by granulomatous involvement. However, in severe cases of non-granulomatous anterior uveitis, non-granulomatous causes should also be considered. Other ophthalmological findings may include eyelid granuloma, orbital or lacrimal gland granuloma, orbital abscess, phlyctenular keratoconjunctivitis, interstitial keratitis, retinitis, retinal vasculitis, scleritis, choroidal tubercles, choroidal tuberculoma, serpiginous-like choroiditis, subretinal abscess, optic neuropathy, neuroretinitis, and cranial nerve palsies. If these conditions are observed in patients with immunosuppressive conditions (such as Human Immunodeficiency Virus, HIV) or in those taking immunosuppressive medications (such as anti-TNF agents), OTB should be suspected. Furthermore, it is essential that patients undergoing immunosuppressive therapy be closely monitored and evaluated for latent tuberculosis to prevent the development of active tuberculosis. Consequently, patients with a positive PPD or QFT result should be considered for anti-TB prophylaxis.

This article has several limitations. Firstly, the sample size is small. Secondly, not all patients had OTB as a baseline condition. Thirdly, the age and treatment regimens of the patients were not homogeneous.

CONCLUSION

In conclusion, OTB should not be overlooked during clinical examination. Given the increasing frequency of anti-TNF use, it is essential to closely monitor patients for immunosuppression and to remain vigilant regarding the risk of TB.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Appendix 1. Symptoms, treatment, and signs of ocular tuberculosis in case series patients

Pt#	Sex (♂/♀) Age	Symptoms and pre-existing condition	BCVA (logMAR) and IOP (mmHg)	Anterior segment findings[a]	Retinal and vitreous findings[b]	FAF, FFA, and OCT findings	Treatments	PPD, ARB, and QTF Test	Radioimaging and other findings
1	♂ 62	•Senile macular degeneration	•1.3 logMAR in both eyes •IOPs within normal range in both eyes	• Grade 1+ (faint) anterior chamber cell in both eyes	•Serpiginous-like lesion in both eyes • Grade 1+ (minimal) vitritis in both eyes	•Intraretinal edema in the right eye	•Oral prednol 48 mg •Isoniazid 300 mg daily	•QTF test positive	–
2	♀ 18	•Pain, blurriness, and floaters in the right eye	•0 logMAR in both eyes •IOPs within normal range in both eyes	• Grade 2+ (moderate) anterior chamber cell in the right eye	• Grade 1+ (minimal) vitritis in both eyes •Bilateral multifocal choroiditis	•Minimal subretinal fluid in the left eye •Hyper-AF in the right eye •Leakage in bilateral artery branches	•Oral prednol 64 mg •Quadruple anti-TB treatment	•PPD test anergic •QTF negative	–
3	♂ 3	•Interferon-gamma deficiency and allogeneic bone marrow transplantation failure	–	• Normal anterior segment examination	–	•Subretinal mass in the superior temporal aspect of the right eye	•Quadruple anti-TB treatment	•*Mycobacterium tuberculosis* cultured	•Diffusion-limiting space-occupying lesion with marked flair hyperintense vasogenic edema in cranial MRI
4	♂ 55	•Rheumatoid arthritis and pulmonary tuberculosis	•1 logMAR in the right eye •1.3 logMAR in the left eye •IOPs within normal range in both eyes	• Grade 3+ (marked) anterior chamber cell in the right eye •Widespread posterior	• Grade 2+ (mild) vitritis in the right eye • Grade 4+ (marked) vitritis and perivascular sheathing in the	•Widespread capillaritis and periphlebitis in the left eye; capillaritis and optic disc fluorescein	•Deltacortril 40 mg •Rituximab •Ozurdex implantation in the left eye	•ARB test positive (*Mycobacterium fortuitum* cultured)	

Appendix 1 (cont). Symptoms, treatment, and signs of ocular tuberculosis in case series patients

Pt#	Sex (♂/♀) Age	Symptoms and pre-existing condition	BCVA (logMAR) and IOP (mmHg)	Anterior segment findings[a]	Retinal and vitreous findings[b]	FAF, FFA, and OCT findings	Treatments	PPD, ARB, and QTF Test	Radioimaging and other findings
				synechiae in the left eye	left eye	leakage in the right eye •Macular edema in the left eye			
5	♂ 22	•Methanol intoxication (1 year ago) •Use of methamphetamine, marijuana, and gabapentin	•2 logMAR (finger counting level) in both eyes •IOPs within normal limits	•Diffuse KPs in both eyes • Grade 1+ (faint) anterior chamber cell in both eyes	• Grade 4+ (marked) vitritis in both eyes	•Subretinal fluid in the left eye •Two retinitis foci in the nasal area of the optic disc (right eye) •Bilateral frosted branch angiitis	•Azathioprine 50 mg twice daily •Oral prednol 48 mg •Adalimumab 40 mg •Remicade 300 mg weekly •Ozurdex implantation •Isoniazid 300 mg daily	PPD test positive	–
6	♀ 16	•Floaters •Epilepsy •Previous uveitis attacks	• BCVA in both eyes and IOP within normal limits	•Bilateral granulomatous KPs	–	•Leakage in the peripheral retina	•Oral prednol 48 mg •Methotrexate 15 mg subcutaneous •Adalimumab 40 mg weekly		•High CD4/CD8 ratio
7	♂ 39	–	•0 logMAR in both eyes •IOPs within normal limits	• Grade 4+ (intense) anterior chamber cell in both eyes •Posterior synechiae in the left eye	Grade 4+ (marked) vitritis in both eyes	•Hemiretinal vein occlusion in the left eye	•Adalimumab 40 mg every two weeks •Isoniazid (prophylaxis, 300 mg daily)	•PPD test positive	•HLA-B*51 positive

Appendix 1 (cont). Symptoms, treatment, and signs of ocular tuberculosis in case series patients

Pt#	Sex (♂/♀) Age	Symptoms and pre-existing condition	BCVA (logMAR) and IOP (mmHg)	Anterior segment findings[a]	Retinal and vitreous findings[b]	FAF, FFA, and OCT findings	Treatments	PPD, ARB, and QTF Test	Radioimaging and other findings
8	♀ 22	•Floaters in both eyes •Uveitis for ten years	•0 logMAR in both eyes •IOPs within normal limits	•Band keratopathy in both eyes •Widespread posterior synechiae in both eyes	• Grade 4+ (marked) vitritis in both eyes •Snowbank and schisis in the temporal retina (right eye)	• Fluorescein leakage on the optic disc and widespread capillaritis in both eyes	•Isoniazid (prophylaxis, 300 mg daily)	•QTF test positive	•HLA-B*27 positive

AF: Autofluorescence; TB: Tuberculosis; PPD: Purified protein derivative; KP: Keratic precipitate; MRI: Magnetic resonance imaging; IOP: Intraocular pressure; logMAR: Logarithm of the minimum angle of resolution; ARB: Acid-resistant bacilli; FFA: Fundus fluorescein angiography; FAF: Fundus autofluorescence; OCT: Optical coherence tomography; BCVA: Best-corrected visual acuity; QTF: QuantiFERON®-TB Test; Pt: Patients; a: SUN grading scale was used for anterior chamber cell grading; b: NIH haze grading scale was used for vitritis grading.