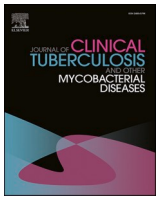
Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 34 (2024) 100413

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube



Clinical manifestation and long-term follow-up of presumed ocular tuberculosis in China

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ARTICLE INFO

Keywords:
Ocular tuberculosis
Optic neuropathy
Uveitis
Anti-tuberculous therapy

ABSTRACT

Background: This study aimed to report the clinical manifestations of presumed ocular tuberculosis (OTB) and the treatment response after anti-tuberculosis therapy (ATT) in a Chinese population.
Methods: Clinical data, including general characteristics, ocular lesions, visual acuity at baseline, and final follow-up of patients with presumed OTB from 2006 to 2022 in two eye clinics in China, were retrospectively analyzed.
Results: The study included 84 eyes of 52 patients. The following ocular manifestations were observed: anterior uveitis (4.8%), posterior uveitis (34.5%), panuveitis (11.9%), retinal vasculitis (40.5%) and optic neuropathy (8.3%). After ATT, the vision improved by varying degrees in 48 eyes (57.1%), remained stable in 34 eyes (40.5%) and decreased in 2 eyes (2.4%).
Conclusions: OTB is likely to be misdiagnosed as other infectious uveitis and optic neuropathy. Clinical features must be interpreted in conjunction with topical and general laboratory findings and in collaboration with other subspecialties to make a final diagnosis.

1. Background

Tuberculosis (TB) is a multisystem infectious disease caused by Mycobacterium tuberculosis (MTB) [1], which can also result in ocular diseases. Ocular tuberculosis (OTB) has a wide variety of clinical manifestations, including (but are not limited to) anterior uveitis, intermediate uveitis, retinal vasculitis, posterior uveitis, scleritis, and optic neuropathy [2–4]. However, the diagnosis of OTB is often delayed, as it is difficult to differentiate these clinical manifestations from other infectious and non-infectious conditions. A definitive diagnosis is possible only when TB bacilli can be observed or cultured from or when its DNA is amplified from the involved tissue. As this is difficult to achieve, TB is often presumed.

Here, we present the retrospective data of 52 (84 eyes) cases of presumed OTB from China. The aim of this study is to contribute our clinical experience and long-term management outcome on this poorly studied topic.

2. Methods

2.1. Study population and testing

This retrospective case series involved all patients who were diagnosed with presumed OTB at the First Affiliated Hospital of Army Medical University and Beijing Chaoyang Hospital from November 2006 to January 2022. The diagnostic criteria were as follows: 1) patients with clinical signs suggestive of OTB; 2) a positive result in at least one of the auxiliary examinations, including computed tomography (CT) chest scan, purified protein derivative (PPD) skin test, T cell spot (T-SPOT) test, or real-time polymerase chain reaction (PCR) in the aqueous humor for detecting MTB; 3) exclusion of other possible causes of uveitis. All patients were carefully examined by one specialist at each center. Best corrected visual acuity (BCVA), intraocular pressure (IOP), and ocular signs of the anterior and posterior segments were checked and recorded. The BCVA was measured using a decimal chart and converted into

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https://doi.org/10.1016/j.jctube.2023.100413

Available online 30 December 2023

logMAR. For VA of count fingers, hand movement, light perception and no light perception, value units of 2.0 logMAR, 2.3 logMAR, 2.7 logMAR and 3.0 logMAR were assigned respectively. The calculation of mean visual acuity was based on the involvement of data from the more severe eye in bilateral cases. Color fundus photography, fundus fluorescein angiography (FFA), B-scan ultrasonography, optical coherence tomography (OCT), fundus autofluorescence (FAF), visual field examination, visual evoked potential (VEP) test, optic nerve and brain magnetic resonance imaging (MRI) were performed according to the particular ocular condition of the patient. All patients underwent a CT chest scan, immunological investigation (PPD test and T-SPOT test), and aqueous PCR detection for MTB. According to the 2016 NICE guidelines [5], a skin induration measuring 5 mm or larger is considered a positive result irrespective of BCG vaccination status. Sputum culture test for MTB was performed according to the proposal of respiratory physician. For patients with bilateral ocular diseases, intraocular fluid sample was collected from unilateral eye with more severe inflammation. A targeted MTB real-time PCR kit (Z-RD-0060–2, Liferiver, Shanghai, China) was used according to the manufacturer's instructions. Different types of OTB were defined based on the Standardization of Uveitis Nomenclature (SUN) [6] and the Standardization of Nomenclature for Ocular Tuberculosis [7]. Optic neuropathy was diagnosed based on the examination results including visual loss, color vision loss, constriction of visual field and abnormal VEP test result. This study was approved by the institutional review board of the Institutional Review Board of the First Affiliated Hospital of Army Medical University (approval no. KY2020056) and was in accordance with the Declaration of Helsinki.

2.2. Therapeutic and follow-up regimen

A general practitioner consultation was sought for the evaluation of patient general condition. In patients with suspected pulmonary TB, a pulmonary biopsy was conducted when necessary to make a definitive pathology diagnosis. An appropriate anti-TB treatment was prescribed, including an initial joint anti-tuberculous therapy (ATT) (isonicotinic acid hydrazide (INH)) (5 mg/kg.d), rifampicin (RIF) (10 mg/kg.d), ethambutol (EMB) (15 mg/kg.d), and pyrazinamide (PZA) (15 mg/kg.d)), followed by a continuation phase consisting of INH plus RIF [8]. Aside from general medications, topical treatments, including glucocorticoid eye drops, periocular injection of triamcinolone acetonide (TA), vitreoretinal surgery, and retinal photocoagulation, were also applied to prevent and alleviate the ocular complications of OTB. No systemic steroid or immunosuppressant was used. All patients were followed up for at least six months. During these periods, general condition of the patient, BCVA, IOP, and ocular signs were checked at each follow-up visit. Ancillary imaging tests, such as color fundus photography, B-scan ultrasonography, and OCT, were performed as needed. All data were recorded, collected, and analyzed.

2.3. Statistical analysis

SPSS 26.0 statistical software was used to analyze the data. The Shapiro–Wilk test was used to evaluate the normality of data distribution. Non-normally distributed datawere expressed as median ± quartiles, while normally distributed data were expressed as the mean ± standard deviation.

3. Results

3.1. General characteristics of involved patients

Eighty-four eyes of 52 patients (40 males and 12 females) were included in this study group, with a mean age of 33.6 ± 12.2 years (range 12–64). Besides TB infection, no other severe systemic diseases, such as HIV, malignant tumor and diabetes mellitus, were diagnosed. All patients had received BCG vaccination. Only two patients presented with general symptoms, including one case with intermittent fever and chest pain, and another case with chronic cough. The main ocular symptom was impaired vision which could not be corrected by glasses (51 cases, 98.1 %), which was followed by eye floaters (15 cases, 28.8 %), red eye (8 cases, 15.4 %), and eye pain (5 cases, 9.6 %). The duration of ocular symptoms ranged from 1 weeks to 36 weeks, with a median time of 5 weeks. Besides ocular involvement, no other extrapulmonary TB lesion was identified. General characteristics all patients are shown in Table 1.

3.2. Results of auxiliary examinations

In regard to the auxiliary examinations, 34 cases (65.4 %) were found to have pulmonary changes by chest CT scan. Among them, sputum culture for MTB was also performed in 5 cases but none had a positive result. The positive rate of the PPD test was 61.5 % (32 cases). Thirty-seven cases (71.2 %) had a positive T-SPOT test. The PCR for MTB in the aqueous humor showed the lowest positive rate, at only 9.6 % (5 cases). Detailed examination results of all patients are also listed in Table 1. Among 34 patients who were found to have abnormal chest CT scan results, 2 patients received pulmonary biopsy examination and were found to have caseous necrotizing granulomatous (Fig. 1). The other patients refused to take this invasive examination.

3.3. Ocular manifestations and complications

The spectrum of ocular involvement could be classified as anterior uveitis (4 eyes in 3 cases), posterior uveitis (29 eyes in 18 cases), panuveitis (10 eyes in 6 cases), retinal vasculitis (34 eyes in 20 cases) and optic neuropathy (7 eyes in 5 cases). All patients with bilateral ocular involvement presented with similar clinical manifestations in two eyes. It is noteworthy that in two patients with complain of general symptoms, the ocular manifestations were both classified as panuveitis. According to the lesion involvement and the fundus manifestation, posterior uveitis could be subdivided into serpiginous-like choroiditis (SLC) (4 eyes in 2 cases), multifocal choroiditis (MC) (10 eyes in 5 case) and tuberculoma (15 eyes in 11 cases). Likewise, optic neuropathy could be subdivided

Table 1
General characteristics of the patients with presumed ocular tuberculosis.

Characteristics		Patients (n = 52)
Age (year), mean ± SD (range)		33.56 ± 12.18 (12–64)
Gender, n (%)		
Male		40 (76.9)
Female		12 (23.1)
Eyes, n (%)		
Unilateral		20 (38.5)
Bilateral		32 (61.5)
General symptoms, n (%)		
Intermittent fever		1 (1.9)
Chest pain		1 (1.9)
Chronic cough		1 (1.9)
Ocular symptoms, n (%)		
Impaired vision		51 (98.1)
Eye floaters		15 (28.8)
Red eye		8 (15.4)
Eye pain		5 (9.6)
Duration of symptoms (week), median (range)		5 (1–36)
Auxiliary examinations, n (%)		
Chest CT scan		34 (65.4)
PPD test	+	8 (15.4)
	++	11 (21.2)
	+++	13 (25)
T-SPOT test		37 (71.2)
Aqueous PCR for MTB		5 (9.6)

CT, computed tomography; PPD, purified protein derivative; T-SPOT, T cells spot; PCR, polymerase chain reaction; MTB, Mycobacterium tuberculosis; PPD test +, weakly positive result (5–10 mm); PPD test ++, moderately positive result (10–15 mm); PPD test +++, strongly positive result (>15 mm).

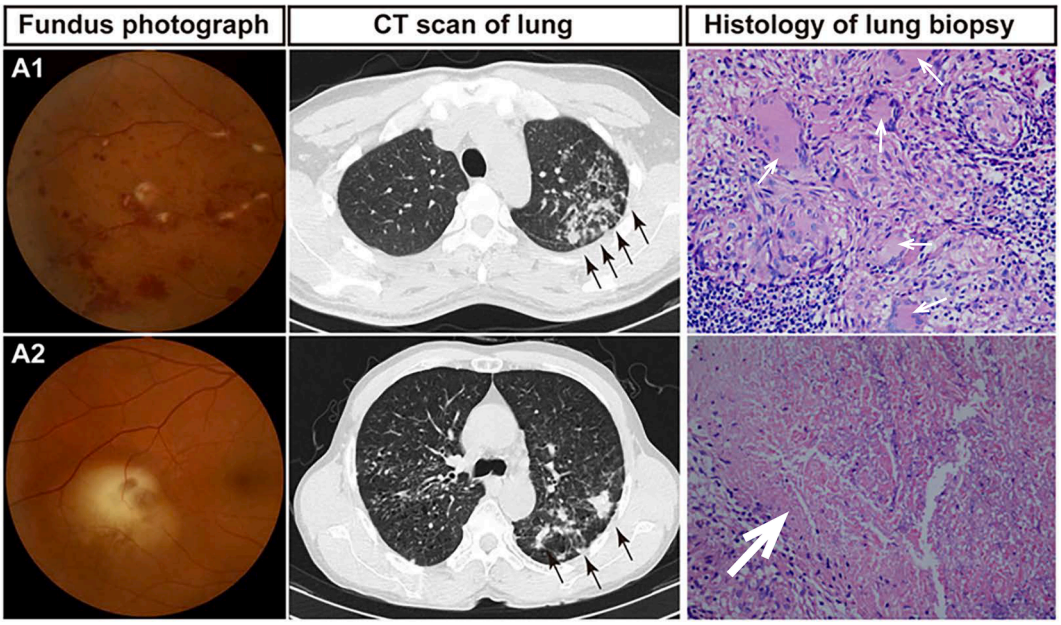

Fig. 1. Fundus, chest CT, and histology of patients receiving pulmonary biopsy examination. Fundus examination showed one patient with retinal vasculitis (A1) and another with posterior uveitis (A2). The black arrow shows pulmonary lesions in the chest CT scan. Hematoxylin and eosin stains of tissue from percutaneous pulmonary biopsy show caseous necrotizing granulomatous inflammation (white arrow) (400 × magnification).

into optic neuritis (4 eyes in 3 cases) and optic atrophy (3 eyes in 2 cases). The types of presumed OTB are listed in Table 2. Different types of ocular involvement had different ocular manifestations, which are shown in detail in Fig. 2. No extraocular lesion, including damage to the eyelids, cornea, sclera and conjunctiva, was found. Complications occurred in this cohort during the follow-up period are listed in Table 3.

3.4. General and topical treatments

All patients received an adequate and standard dose of ATT, except for one who refused any oral medication. Glucocorticoid eye drops were used in 14 eyes to taper inflammation in the anterior chamber. Thirteen eyes underwent vitreoretinal surgery due to tractional retinal detachment secondary to uveitis, and retinal photocoagulation was performed in 48 eyes for the treatment of non-perfusion areas or retinal neovascularization. Sixteen eyes with retinal vasculitis were given a periocular injection of TA (20 mg/0.05 mL) when they began anti-TB therapy.

3.5. Follow-up and visual prognosis

The mean follow-up time was 17.75 ± 10.23 months (range: 6–41). During this period, regression of intraocular inflammation was observed in all eyes except in one patient (2 eyes) who refused ATT. Scarring and regression of retinal lesions occurred in 16 and 13 eyes respectively. No topical or general recurrence was recorded. The mean logMAR BCVA was 1.37 ± 0.77 (0–3) at baseline and 1.07 ± 0.78 (0–3) in the final visit. Among different subtypes of OTB, the mean initial logMAR BCVA were 0.33 ± 0.06 in anterior uveitis, 1.46 ± 0.63 in posterior uveitis, 1.6 ± 0.77 in panuveitis, 1.22 ± 0.77 in retinal vasculitis and 2.26 ± 0.48 in optic neuropathy, respectively. The corresponding mean final logMAR BCVA were 0.11 ± 0.11, 0.99 ± 0.68, 0.99 ± 0.73, 1.09 ± 0.79 and 1.92 ± 0.8 respectively. Patients with optic neuropathy presented with the most severe visual impairment. At the last follow-up, 34/84 eyes (40.5 %) had stable visual acuity, and 48/84 eyes (57.1 %) had improved vision. One patient (2.4 %) who refused ATT had an aggravation of bilateral optic atrophy and a decrease in visual acuity of both eyes from count finger (CF) to hand movement (HM) at the end of the follow-up.

Table 2
Spectrum of ocular involvement.

Spectrum of ocular involvement, n (%)		Eyes (n = 84)
Anterior uveitis		4 (4.8)
Posterior uveitis	Serpiginous-like choroiditis	4 (4.8)
	Multifocal choroiditis	10 (11.9)
	Tuberculoma	15 (17.9)
Panuveitis		10 (11.9)
Retinal vasculitis		34 (40.5)
Optic neuropathy	Optic neuritis	4 (4.8)
	Optic atrophy	3 (3.6)

4. Discussion

With an increase in new TB cases every year, the incidence of OTB also increases [9]. However, the absolute number of Chinese patients with OTB may be underestimated due to the large population base in China and the historically low access to ophthalmologic care. Also, previous study showed that in Australia, only 2.47 % and 4.94 % of patients with OTB had concomitant active pulmonary tuberculosis and other extrapulmonary tuberculosis respectively [10], which was similar to the result of our study (only 2 patients presented with intermittent fever, chest pain and chronic cough, which might indicate the infection of MTB). This discordance between ocular signs and systemic clinical signs further added the difficulty of final diagnosis. Thus, to raise the awareness of ocular manifestations of presumed OTB is essential. The clinical type of patients in our series with presumed OTB is similar to that reported in other countries [10–12], which could be used as a reference in the future clinical interventions.

As shown in the Fig. 2, different clinical manifestations can be observed, depending on the different ocular involvements. Anterior uveitis may be granulomatous, and the surface of the iris may show multiple nodules, especially near the papillary border or the iris root. In the acute phase of OTB, anterior chamber inflammation such as KP, anterior chamber flare, posterior synechia associated with small grayish–yellow or reddish nodules near the iris root [13], and vitreous cells are common.

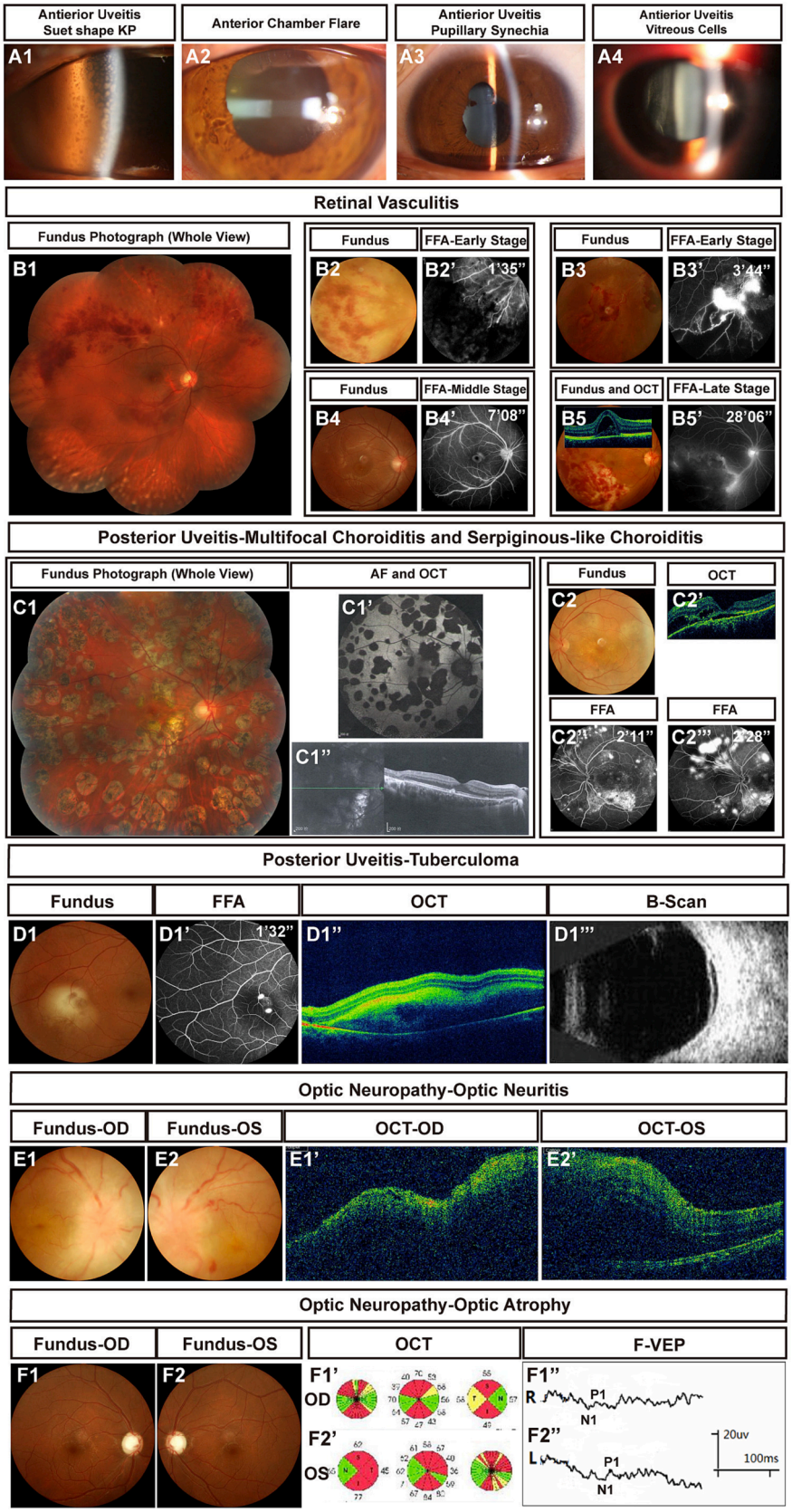

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Fig. 2. Clinical manifestations of different ocular involvements in presumed OTB. Fig. 2A showed keratic precipitates (A1), anterior chamber flare (A2), posterior synechia (A3), and vitreous cells floating in the vitreous body (A4) in anterior uveitis. Fig. 2B showed perivascular sheathing with exudates and retinal hemorrhage (B1) in retinal vasculitis. Retinal ischemia, retinal neovascularization, and macular edema secondary to retinal vasculitis were presented in fundus photography (B2, B3, B4, B5), OCT (B5), and FFA (B2′, B3′, B4′, B5′). Fig. 2C showed two different types of posterior uveitis. Multifocal choroiditis presented as choroidal lesions in fundus photography (C1), which were compatible with diffused hypo-autofluorescent lesions in FAF (C1′). OCT further indicated a destruction of the outer retinal structure (C1′′). In the case of serpiginous-like choroiditis (C2), retinal neovascularization could be seen through OCT (C2′) and FFA (C2′, C2′′). Fig. 2D showed another kind of posterior uveitis, tuberculoma, which presented as a large choroidal granuloma (D1). FFA showed a mass of hypo-fluorescence and several spots of hyper-fluorescence in the middle in the early stage (D1′). OCT showed adhesions between the retinal pigment epithelium (RPE)–choriocapillaris layer and the photoreceptor layer over the granuloma (D1′′). B-scan showed exudative retinal detachment (D1′′). Fig. 2E showed optic neuritis, which presented as papilla with an unclear boundary in fundus photography (E1, E2) and an elevated optic nerve in OCT (E1′, E2′). Fig. 2F showed optic atrophy with pale optic discs (F1, F2). The optic OCT showed a thinner retinal nerve fiber layer around the optic disc (F1′, F2′). Electrophysiological examination often showed a prolonged implicit time and reduced P2 wave amplitude (F1′′, F2′′).

Table 3
Complications of presumed ocular tuberculosis.

Complications	n (%)
Retinal ischemia	31 (36.9)
Retinal neovascularization	17 (20.2)
Macular edema	12 (14.3)
Tractional retinal detachment	13 (15.5)

In our cohort, the most common intraocular manifestation of the posterior segment involvement of TB is retinal vasculitis. The average and median ages of patients with retinal vasculitis were 31.6 and 27.5 years old, which further proved its predilection in young and healthy adults [14]. Retinal vasculitis in TB predominantly involves the veins and is seen as severe perivascular cuffing with infiltrates, usually accompanied by moderate vitritis, retinal ischemia, and neovascularization, secondary to vitreous hemorrhage [15]. As shown in Fig. 2B, FFA and OCT can help detect the range and degree of vascular signs of the disease and are useful in defining treatment.

According to the nomenclature of tubercular uveitis [7], tubercular choroiditis includes serpiginous-like choroiditis, multifocal choroiditis, tuberculoma, and focal choroiditis; the first three subtypes were seen in our study. As shown in Fig. 2C, the lesions of choroiditis may be solitary or multiple, with disruptions of the ellipsoid zone and some subretinal pigment epithelial lesions. A large tuberculoma can be located anywhere in the choroid: in the macula, the posterior pole, the equator, or in a juxtapapillary location.

In our cases, we found severe binocular visual impairment in patients with optic neuropathy. Consistent clinical signs, positive results of ocular or systemic investigations and exclusion of other possible causes of uveitis finally led to the conclusion of tubercular optic neuropathy [16]. However, the direct etiopathogenesis remained unclear. Optic neuropathy, including optic nodules, papillary edema, papillitis, optic neuritis, neuroretinitis, and optic chiasma arachnoiditis, could result from direct infection by mycobacterium and immune response to pathogens [16].

The diagnosis of OTB is often problematic due to the wide spectrum of possible presentations, and it is impractical to take a uveal biopsy for culture and direct histopathological examination to provide definitive proof of ocular infection [3,17]. Some studies have demonstrated that the detection of TB genes, such as MPB64, IS6110, and protein b, in ocular samples using the PCR technique enables the diagnosis of OTB without the need to detect positive acid-fast bacilli [18,19]. However, as PCR assays are expensive and require invasive sample procurement, this technique is not available in many regions. Most importantly, the previous research has proposed that some phenotypes of OTB, for example SLC, occur not only because of a direct invasion by TB bacilli but also because of an immunogenic reaction due to extraocular infective foci [20,21]. In this study, aqueous PCR for MTB was positive in only 5 cases (2 cases of tuberculoma, 2 cases of retinal vasculitis and 1 case of panuveitis), the low positive rate (9.6 %) further strengthened this contention. Thus, it is important to rely on non-ocular methods, such as chest CT, PPD test, and T-SPOT test, which may provide reliable results when used judiciously. In our study, 65.4 % of patients showed nodules, masses, or air-space consolidations in the chest CT scan; 61.5 % showed a positive reaction to the PPD test; and 71.2 % showed a positive T-SPOT test. Previous study showed that interferon gamma release assays such as the T Spot test are more reliable than PPD test [22], but negative results could not totally exclude TB infection. Certainly, only the necrotizing caseous granulomatous inflammation seen histologically from percutaneous transthoracic needle aspiration can give us the gold standard diagnosis of TB [23]. This clearly demonstrates that the non-ocular tests, including serological testing and radiological studies cannot be disregarded as an important way of evaluating presumed OTB patients [24].

Nowadays the treatment of OTB still faces much challenge. On one hand, only patients with a high pre-test probability and clinical suspicion of OTB would merit treatment. On the other hand, in patients with non-infectious uveitis whose PPD or T-SPOT test result is positive, the use of biologicals or immunosuppressants may trigger the activity of latent TB [25]. Also, there is no standard treatment regimen or length of therapy for OTB [3]. According to the recommendations of the American Thoracic Society, four drugs (isoniazid, RIF, EMB, and PZA) prescribed as ATT are used for pulmonary and extrapulmonary TB. In our study, we prescribed ATT together with periocular corticosteroids in patients with retinal vasculitis. The use of ATT in these patients presumably helped by killing intraocular microorganisms, thus eliminating the antigen load and the resulting inflammation due to hypersensitivity. The addition of periocular TA could have helped control the coexisting inflammatory reaction, limit damage to ocular tissues caused by delayed-type hypersensitivity, and reduce macular edema.

This study has several limitations. First, the retrospective design of this study added potential inclusion bias. Nevertheless, definite diagnostic criteria for presumed OTB could have reduced the differences among the involved individuals. Second, patients underwent examinations in different clinical centers, the heterogeneity of data limited the further analysis of correlation between auxiliary examinations and clinical presentations. Further studies are needed to establish a more standard approach for OTB diagnosis, treatment, and prophylaxis regimen.

5. Conclusion

In conclusion, OTB has a highly variable presentation and can involve any structure of the eye, producing various clinical manifestations. The diagnosis of OTB is often difficult to make, and clinical features must be interpreted in conjunction with laboratory findings and in collaboration with other subspecialties. The proper treatment of OTB and the determination of the need for ATT are critical and can lead to favorable outcomes.

Funding

This study was funded by the National Nature Science Foundation of China (81974138), National Basic Research Program of China (2018YFA0107301) and Scientific Research Program of Beijing

Municipal Commission of Education (KM202010025020).

7. Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the First Affiliated Hospital of Army Medical University (approval no. KY2020056). Study participants have given their full consent for publication.

CRediT authorship contribution statement

Jing Xie: Data curation, Methodology, Writing – original draft. **Ya Qu:** Data curation, Methodology, Writing – original draft. **Zhuyun Qian:** Data curation, Methodology, Writing – original draft, Writing – review & editing. **Xiaohong Meng:** Investigation, Supervision. **Jun Lin:** Investigation, Supervision. **Yong Liu:** Conceptualization, Funding acquisition, Writing – review & editing. **Zhengqin Yin:** Investigation, Supervision. **Yong Tao:** . **Shiying Li:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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