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Original Article

Types of Fundus Involvement in Intraocular Tuberculosis

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Abstract

OBJECTIVE: To evaluate the patients who were treated for intraocular tuberculosis retrospectively and present our findings and share our experience.

MATERIAL AND METHODS: This study was a descriptive, cross-sectional, retrospective study. Patients who were followed up with the diagnosis of intraocular tuberculosis in the Ophthalmology and Pulmonary Medicine Departments of Dokuz Eylul University Faculty of Medicine in the last 15 years and received anti-tuberculosis therapy were included.

RESULTS: A total of 16 eyes of 10 patients with a diagnosis of intraocular tuberculosis uveitis who were treated with anti-tuberculosis therapy were included in this study. The mean age was 48.1 [14.6] years (mean [standard deviation]). Four were [40%] male and 6 [60%] were female. Patients with tuberculosis uveitis had bilateral involvement (7 of 10 patients [70%]). Intraocular tuberculosis was presented in 7 eyes of 4 patients with serpiginous like choroiditis, 2 eyes of 2 patients with choroidal tuberculomas, 4 eyes of 2 patients with choroidal tubercles (miliary tuberculosis), and 3 eyes of 2 patients with intermediate uveitis. The mean duration from admission to treatment was 18.1 ± 17.4 days (range: 6-56 days). All patients in this study received a 4-drug regimen anti-tuberculosis therapy, Paradoxical reaction occurred in 30% of the patients. Eight patients had systemic steroid therapy and 4 had also topical steroid therapy. The mean length of follow-up was 14.7 months (standard deviation = 15.1, range: 6-48 months). Reactivation of intraocular tuberculosis was not observed in any patients.

CONCLUSION: High level of suspicion is a must for diagnosing intraocular tuberculosis. A complete ophthalmic examination can be performed in patients with suspected or proven tuberculosis. Early diagnosis and prompt treatment of intraocular tuberculosis can prevent serious complications and loss of vision.

KEYWORDS: Diagnosis, Intraocular Tuberculosis, Uveitis, Treatment
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INTRODUCTION

Tuberculosis (TB) still represents the leading infection globally; around 10.0 million people (range: 8.9-11 million) are infected with TB worldwide and its annual incidence is around 130 per 100 000 according to the latest report of the World Health Organization (WHO).[1] Turkey, is a member country of WHO, has a high TB incidence of 28 patients per 100 000 people.[2] However, the Tuberculosis Department of the Turkish Ministry of Health General Directorate of Public Health reported that the TB incidence in Turkey in 2018 was 14.1 per 100 000 people. Turkey is among the countries that have medium TB incidences.[3] Although pulmonary TB is the most common clinical type, TB infections can also be encountered in the extrapulmonary organs such as the pleura, lymph nodes and bones. Ocular TB is less frequently observed and its diagnosis and treatment are fraught with difficulties due to a wide variety of manifestations.[4,5] The estimated prevalence of intraocular TB ranges from 0.317% to 0.6% among the individuals with uveitis.[6,7] A few studies reported that the prevalence of intraocular TB ranges from 0.3% to 28.2% in uveitis patients who were from various countries.[8-10]

Uveitis can occur due to a broad spectrum of infectious and non-infectious causes. A comprehensive full systemic investigation and multimodal fundus imaging are often necessary to reach an accurate clinical conclusion and make the differential diagnosis in cases where the ocular findings are not specific enough. Intraocular TB is an uncommon extrapulmonary manifestation of TB and it presents with many forms of uveitis, including granulomatous anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis. Heterogeneous clinical manifestations of ocular TB and its subtle clinical features can create a challenge to form a diagnosis.[11] The collaborative ocular TB study (COTS) consensus group showed significantly higher hazard ratios of treatment failure associated with phenotypes of anterior uveitis, intermediate uveitis, and panuveitis compared to subtypes of tubercular choroiditis including serpiginous-like choroiditis, tuberculoma, and multifocal or unifocal choroiditis.

Early diagnosis and treatment of intraocular TB are very critical for achieving the optimal control of disease, and preventing or even slowing down the progression of the retinal damage and thereby lessening functional impairment. Intraocular TB should be handled and treated using a multidisciplinary approach. This case series aimed to evaluate a group of patients with intraocular TB and reflect the broad spectrum of disease presentation types.

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MATERIAL AND METHODS

A retrospective evaluation of patient data at the Department of Ophthalmology and Chest Diseases was performed. The medical files of all patients from January 2006 to January 2021 who received the diagnosis of intraocular TB and were treated with a 4-drug anti-tuberculosis therapy (ATT) were retrospectively reviewed. The study followed the tenets of the Declaration of Helsinki and received the approval of the institution's ethics committee (2021/20-04).

The diagnosis of presumed ocular TB disease was based on the proposed diagnostic criteria for ocular TB used in COTS-1.[12,13] The diagnostic criteria for TB uveitis used in COTS-1 are as follows, with patients having to satisfy both criteria 1 and 2, and at least 1 criterion from 3 or 4 (Table 1):

1. *Clinical signs that suggest TB uveitis includes the following:*
    a. Anterior uveitis (granulomatous or nongranulomatous), iris nodules, and ciliary body granuloma.
    b. Intermediate uveitis (granulomatous or nongranulomatous with exudates in the pars plana, with or without snowballs).
    c. Posterior and panuveitis, choroidal tubercle, choroidal granuloma, subretinal abscess, and serpiginous-like choroiditis.
    d. Retinitis, retinal vasculitis (RV), neuroretinitis, optic neuritis, endogenous endophthalmitis, panophthalmitis, and scleritis.
2. *Exclusion of other uveitic entities, where relevant, based on the clinical manifestations of the disease and regional epidemiologic findings.*
3. *Investigations documenting the mycobacteria or its genome:*
    a. Demonstration of acid-fast bacilli by microscopy or the culture of *Mycobacterium tuberculosis* from the ocular fluids.
    b. Positive polymerase chain reaction obtained from the ocular fluid for IS 6110 or other conserved sequences in mycobacterial genome.
    c. Evidence of confirmed active extrapulmonary TB histopathological examination or culture of a tissue sample from the affected tissue.
4. *Collaborative investigations:*
    a. PositiveMantoux test result (must be accompanied by the information regarding the antigen and amount of tuberculin injected, along with institutional practices in interpreting the test).
    b. Interferon γ release assay, such as QuantiFERON TB Gold (must be accompanied by the information regarding the institutional practices in interpreting the test).
    c. Evidence of healed or active TB on chest radiography (must be accompanied by information regarding the practices of the radiologists on the clinical features that are considered as evidence in this context).

When the suspicion of TB arose in any patient with uveitis, full systemic screening and laboratory blood tests (such as complete blood count, electrolytes, liver and kidney function tests, angiotensin-converting enzyme, antinuclear antibodies, infectious diseases like toxoplasma, brucella, syphilis, human immunodeficiency virus (HIV)) were performed to identify any possible cause of uveitis besides intraocular TB. Patients' files were reviewed for the symptoms, medical history, tuberculin skin test (TST), QuantiFERON-TB Gold, chest x-ray or chest computed tomography scan, sputum, or bronchial sampling results. A complete ophthalmological examination, includ- ing slit-lamp biomicroscopy and dilated indirect fundoscopy, was performed on all patients. At the follow-up visits, color fundus photography, fundus fluorescein angiography, optical coherence tomography, and visual field tests were performed, where deemed appropriate (Figures 1-3). The Standardization of Uveitis Nomenclature system was used to classify and grade the type of uveitis.[14] Patients with extraocular TB, ocular inflammation due to other causes (infectious and noninfectious) and those who did not attend the follow-up visits were excluded from the study.

The files of 12 patients were retrospectively evaluated. One patient with conjunctival TB and 1 patient with scleritis were excluded. Patients who fulfilled the diagnostic criteria and received a 4-drug regimen of anti-TB treatment with directly observed treatment strategy were only enrolled for this study if they fulfilled the following inclusion criteria: (1) availability of the patient's medical history together with the detailed ophthalmic examination, (2) sufficient laboratory investigations performed to exclude other causes, and (3) a minimum follow-up 6 months after the treatment. All patients had been examined by one of the uveitis and retina specialists (AOS and MK), and clinical parameters were recorded according to the diagnostic criteria for TB uveitis used in COTS-1. A chest physician (ESU) evaluated the patients for any signs of extrapulmonary and pulmonary TB.

Anti-tuberculosis therapy was defined as a multi-drug therapy consisting of a 4-drug regimen including isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, followed by 4 additional months of rifampicin and isoniazid, with a total therapy duration of at least 6 months, based on the clinical response. The treatment regimen in terms of the decision to

MAIN POINTS

- Diagnosis of ocular tuberculosis is more difficult due to its various presentations and requires experience.
- Tissue sampling or imaging in ocular tuberculosis (TB) is not possible in the differential diagnosis of TB.
- Tuberculosis should always be considered as a differential diagnosis in patients presenting with vague symptoms.
- To diagnose ocular TB, it is primarily to suspect the disease and evaluate the findings in line with this suspicion.
- In cases with ocular findings of chronic granulomatous inflammation, TB should be considered a differential diagnosis and investigated accordingly.
- Vision loss can be prevented by early diagnosis of ocular TB and correct treatment.
- The ocular examination should be considered in patients with suspected or proven TB.

Table 1. The Proposed Classification of Intraocular Tuberculosis (IOTB) (10)

Clinical Diagnostic Group	Case Definition Criteria
Confirmed IOTB (both 1 and 2)	1. At least 1 clinical sign suggestive of IOTB. 2. Microbiological confirmation of *Mycobacterium tuberculosis* from ocular fluids/tissues.
Probable IOTB (1, 2, and 3 together)	1. At least 1 clinical sign suggestive of IOTB (and other etiologies excluded). 2. Evidence of chest x-ray consistent with tuberculosis (TB) infection or clinical evidence of extraocular TB or microbiological confirmation from sputum or extraocular sites. 3. At least one of the following: a. Documented exposure to TB. b. Immunological evidence TB infection.
Possible IOTB (1, 2, and 3 together, or 1 and 4)	1. At least 1 clinical sign suggestive of IOTB (and other etiologies excluded). 2. Chest x-ray not consistent with TB infection and no clinical evidence of extraocular TB. 3. At least one of the following: a. Documented exposure to TB. b. Immunological evidence TB infection. 4. Evidence of chest x-ray consistent with TB infection or clinical evidence of extraocular TB but none of the characteristics given in 3.

initiate ATT or immunosuppression treatment, and the duration of the treatments were directed by the attending physicians in collaboration with the same Pulmonary Medicine specialist in accordance with the individual institutional protocols. The route of drug delivery for corticosteroids and use of corticosteroid-sparing immunosuppressive agents was determined by the ophthalmologist (uveitis specialist) on a case-by-case basis, with the consideration of clinical phenotypes, the severity of intraocular TB, patients' comorbidities, and treatment response. Patients continued their treatment with corticosteroids and other immunosuppressive therapies for uveitis during ATT. Ocular topical medications were also administered if deemed necessary, according to the anatomic location of the inflammation. Additional ocular therapies, including intraocular pressure-lowering medications, pars plana vitrectomy, argon laser photocoagulation over ischemic retina in association with neovascularization, and photodynamic therapy for the vascularized granuloma were performed when needed.

Demographic features and clinical findings including posterior segment manifestations, follow-up time, anatomic region of uveitis, treatment, response to treatment, duration of the treatment, several recurrences of inflammation, ocular complications, and complete ophthalmological examination, including best-corrected visual acuity (BCVA) at baseline and final visit, slit-lamp biomicroscopy and indirect ophthalmoscopy were taken into account. Recurrence of inflammation was described as any intraocular inflammation occurring in the same eye 6 or more months after the uveitis was treated.

Statistical Analysis

All statistical analyses were performed by using Statistical Package for the Social Sciences version 24.0 (IBM, Armonk, NY, USA). Values were recorded as n (%) and mean ± standard deviation (SD). Best-corrected visual acuity was recorded using Snellen charts and converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis, using conventional conversion tables. A P value <.05 was considered statistically significant.

RESULTS

A total of 16 eyes belonging to 10 patients with the diagnosis of intraocular TB uveitis who were treated with ATT were included in this study. The mean age was 48.1 [14.6] years (mean [SD]. Four patients were [40%] male and 6 of them were [60%] female. No contact of previous TB was present in the study group. Two patients were diagnosed with miliary TB, and 4 patients had radiological pulmonary findings compatible with the sequela of pulmonary TB. Furthermore,

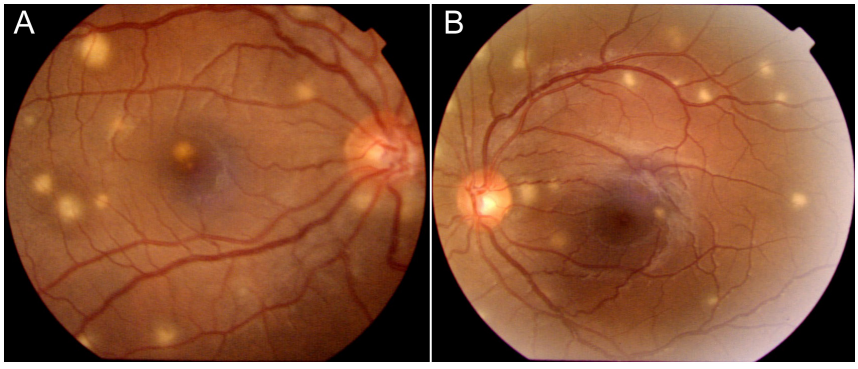

Figure 1. Fundus photograph of the right (A) and left (B) eyes of a 23-year-old male patient shows in the posterior fundus multiple tubercles (miliary choroidal lesions) (14).

Table 2. Pulmonary Features and Clinical Diagnostic Groups of Patients

Patient No.	Age	Ocular Findings	Pulmonary Findings	Exposure to TB	PPD	Quantiferon	Clinical Diagnostic Group (COTS-1)
1.	49	Miliary tuberculosis	Common micronodular densities	None	None	Positive	Probable IOTB
2.	23	Miliary tuberculosıs	Common micronodular densities	None	None	Positive	Probable IOTB
3.	29	Choroidal granuloma	No pulmonary radiological findings	None	21 mm	None	Possible IOTB
4.	43	Choroidal granuloma	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB
5.	57	Serpiginous-like choroiditis	No pulmonary radiological findings	None	None	Positive	Possible IOTB
6.	37	Serpiginous-like choroiditis	No pulmonary radiological findings	None	20 mm	None	Possible IOTB
7.	66	Serpiginous-like choroiditis	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB
8.	55	Serpiginous choroiditis	No pulmonary radiological findings	None	None	Positive	Possible IOTB
9.	60	Intermediate uveitis	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB
10.	62	Intermediate uveitis	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB

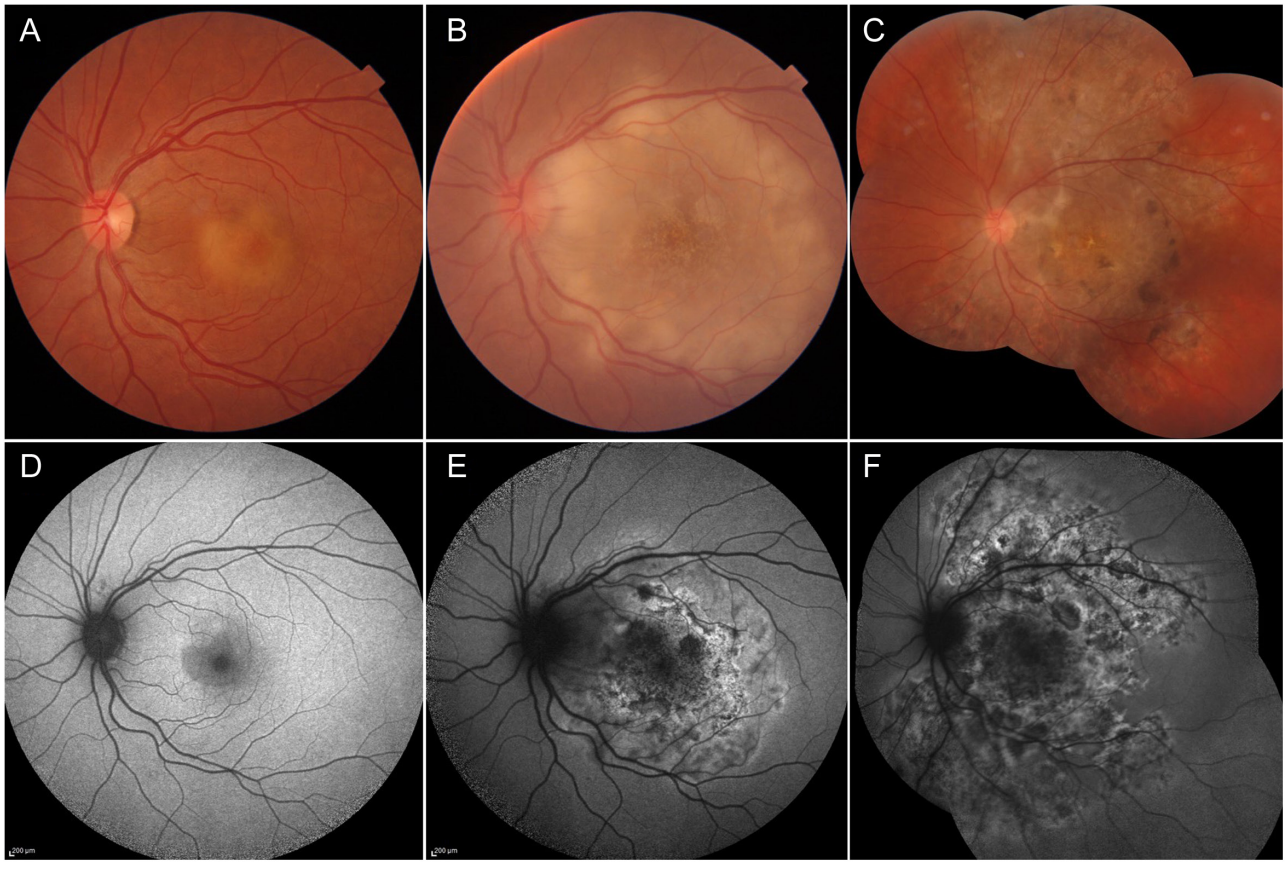

Figure 2. Fundus photograph (A-C; top line) and fundus autofluorescence (FAF; D-F; bottom line) of the left eye showing tubercular granuloma at the macular area. One month later, treatment delay due to the pandemic of COVID-19, tubercular granuloma exhibited an enlargement. (Please pay attention to the change seen in A-D to B-E). B and E images before the anti-tuberculosis therapy (ATT) (baseline), and tubercular granuloma FAF image (E) shows hyperautofluorescent lesion with surrounding blurred hypoautofluorescence ring in the patient (active choroidal granuloma). C and F images show inactive choroidal granuloma after 4-drug regimen of ATT.

Table 3. Demographics and Clinical Features of Patients with TB Uveitis

Patient No.	Age, years	Gender	Presentations of Uveitis	Visual Acuity		Time for Diagnosis (days)	Paradoxical Reaction	Systemic Steroid	Anterior Uveitis		Intermediate Uveitis	Panuveitis	Retinal vasculitis/ Serpiginous like choroiditis	Choroidal Granuloma	Retinal or vitreous hemorrhages	Neuroretinitis/ optic retinitis	Choroidal tubercules
				Baseline Right/Left (logMAR)	Final Right/Left (logMAR)				Granulomatous	Nongranulomatous							
1.	49	Male	Miliary tuberculosis	0.22/0.10	0.00/0.10	12	-	-	-	-	-	-	-	-	-	-	+
2.	23	Male	Miliary tuberculosis	0.00/0.00	0.00/0.00	14	-	-	-	-	-	-	-	-	-	-	+
3.	29	Female	Choroidal granuloma	1.30/-	1.00/-	23	-	+	-	-	-	-	-	+	+	-	-
4.	43	Female	Choroidal granuloma	0.40 /-	3.10 /-	22	+	+	-	+	-	+	+	+	-	-	-
5.	57	Female	Serpiginous-like choroiditis	-/ 0.05	-/ 0.40	32	-	+	-	-	-	-	+	-	-	-	-
6.	37	Female	Serpiginous-like choroiditis	0.00/0.00	0.00/0.00	29	+	+	-	-	-	-	+	-	-	-	-
7.	66	Female	Serpiginous-like choroiditis	0.10/0.90	0.00/0.22	24	+	+	-	+	-	+	+	-	-	-	-
8.	55	Male	Serpiginous-like choroiditis	0.10/0.10	0.15/0.15	26	-	+	-	-	-	-	+	-	-	-	-
9.	60	Male	Intermediate uveitis	0.22/0.40	0.10/0.10	25	-	+	-	+	+	-	-	-	-	-	-
10.	62	Female	Intermediate uveitis	0.40/-	0.05/-	31	-		-	+	+	-	-	-	-	-	-

the radiological findings of active TB were observed in only 20% of the patients. The QuantiFERON-TB Gold test of 8 patients was positive, and a positive TST (**>15 mm**) was seen in 2 patients where QuantiFERON-TB Gold test could not be obtained. Pulmonary features and clinical diagnostic groups of patients are summarized in Table 2**.**

Seven patients (70%) had bilateral involvement. The mean follow-up period was 14.7 months (SD = 15.1, range: 6-48 months). According to posterior segment manifestations, bilateral serpiginous-like choroiditis (4 out of 10 [40%]) was the most common type of fundus involvement. Two patients were presented with choroidal tuberculomas, 2 presented with multiple choroidal tubercles (miliary TB), and 2 presented with intermediate uveitis. Demographics and clinical features of the patients are described in Table 3.

No microbiologically-confirmed intraocular TB was noted in the present study. Thereby, 60% were classified as probable OTB, and 40% were as possible cases. The mean duration from admission to ATT was 23.8 ± 6.6 days (range: 12-32 days). The time between the onset of symptoms and the duration of diagnosis is shown in Table 3.

All patients received the 4-drug regimen ATT in this study. In most patients, no significant side effects were observed, except for minor side effects such as loss of appetite, nausea and vomiting. Hepatotoxicity due to pyrazinamide only developed in 1 patient, so the treatment was continued with moxifloxacin instead of pyrazinamide. Except for 1 patient, all patients completed the 6-month treatment without any problems. The patient with hepatotoxicity was treated for 9 months in a pyrazinamide-free regimen. Paradoxical reaction occurred in 30% of the patients. Corticosteroids were used to treat 8 patients (80%); a total of 4 eyes of 2 patients (25%) with topical and 8 patients (80%) with systemic corticosteroids. All patients taking corticosteroids experienced the resolution of intraocular inflammation. Reactivation of intraocular TB was not observed in any patients. Ocular complications that occurred following the diagnosis of uveitis were posterior subcapsular cataract in 2 eyes (12%), vascularized retinal granuloma in 1 eye (6%) and elevated intraocular pressure in 1 eye (6%).

Table 3 also shows the baseline and final BCVA. At the uveitis diagnosis, the mean BCVA was 0.27 ± 0.36 (1.3-0.0) logMAR units. During the follow-up, the mean visual acuity was 0.34 ± 0.78 (3.1-0.0) logMAR. During the follow-up, the BCVA was stabilized in 5 eyes (decrease and increase of less than 1 line), improved in 7 eyes (1 line), and decreased in 4 eyes (decrease of 1 line). Decreased visual acuity occurred due to the progression of serpiginous-like choroiditis towards the macula in 3 eyes and direct choroidal tuberculoma involving the macular area in 1 eye at presentation.

DISCUSSION

In the present study, serpiginous-like choroiditis was the most common presentation of fundus involvement in intraocular TB. Seven (70%) patients had bilateral involvement. The mean duration from admission to treatment was about 24 days. Three (30%) patients had a paradoxical response

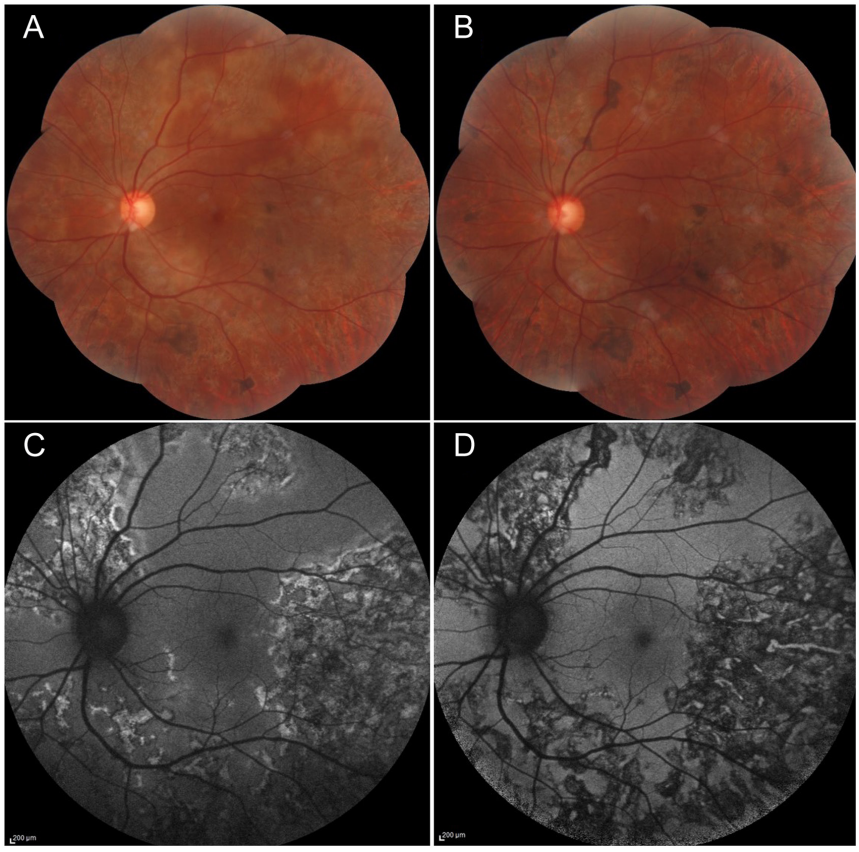

Figure 3. Color fundus photography (top line) and fundus autofluorescence (bottom line) in a 37-year-old woman with intraocular tuberculosis depicting the active serpiginous-like choroiditis prior to anti-tubercular therapy (A and C) and inactive serpiginous-like choroiditis after 4-drug anti-tubercular therapy plus systemic corticosteroids in the left eye (B and D).

to antituberculous therapy, and systemic corticosteroids were employed in these cases. All patients achieved remission, and no relapses had occurred until the follow-up.

A high degree of suspicion is warranted for diagnosing intraocular TB, which is often difficult to diagnose and treat. The diagnostic challenges include a variety of clinical presentations occur due to intraocular involvement, absence of related systemic findings in many patients and limitations of the currently available diagnostic tests and tools.[14] In many studies, the diagnosis of intraocular TB was evaluated on the basis of clinical features and systemic evaluation with the exclusion of other possible etiologies. Local tests such as the tissue culture test and polymerase chain analysis of the anterior or posterior fluids to support the diagnosis of intraocular TB were performed only in 6 of the 28 (21%) studies.[15] Moreover, the absence of pulmonary TB does not rule out the diagnosis of ocular TB. Gupta et al.[16] in a series with 386 patients, observed a relatively high positive predictive value for establishing the diagnosis of ocular TB and aimed to point out the ocular findings that might increase the accuracy of the diagnosis, especially in endemic areas for TB, even if bacilli could not be detected. They recommended to start ATT when one or more of the findings such as broad-based posterior synechia, serpiginous-like choroiditis, and RV with or without choroiditis who have positive TST results or QuantiFERON-TB Gold test results were present after ruling out the other possible causes for the uveitis. Delay in treatment may lead to permanent structural damage that can affect the long-term functional visual abilities. Hence, immediate diagnosis and treatment of intraocular TB are critical to achieve a better visual outcome. In this case series, 80% of the patients experienced a delay in the diagnosis, as a duration of over 21 days from the onset of symptoms was considered as a delay in diagnosis according to the WHO criteria in 1997, which might cause limited visual improvement. We concluded that the compliance of the patients, macular and/or optic disc involvement, and paradoxical reaction (therapy-induced Jarisch–Herxheimer reaction) could be factors affecting the treatment success and visual outcomes.

Clinical phenotypes of the disease are well-known and can be categorized as pulmonary and extrapulmonary manifestations. There has been an increase in the prevalence of extrapulmonary TB, most likely due to better reporting and improvements in diagnostic tools. Tuberculosis most commonly affects the lungs, but it may have various other extrapulmonary manifestations as well, including intraocular involvement. Ocular TB is an extrapulmonary mycobacterial infection with variable manifestations. Tuberculosis can have a variety of ocular manifestations, and consequently, may mimic several ocular inflammatory diseases. Making a diagnosis and establishing the specific therapeutic protocols generates a significant challenge. Ocular involvement occurs in approximately 1% to 2% of TB patients.[16] Most commonly, TB presents as posterior uveitis.[17,18] Intraocular TB usually occurs in apparently healthy individuals, it is rarely observed in patients with active pulmonary diseases. In this case series,

Table 4. All Case Reports on Intaraocular TB as of June 2021 in Turkey

S/N	Author(s) (Published year)	Study Design	Period of Study	Sample Size	Age Mean ± SD (range)	Gender Male (%)	No. of Patients Who Received ATT	No. of Drop outs /loss of Follow-ups	Phenotypes						Relevant History (Patients)		
									AU	IU	PU	Panuveitis	Retinitis/ Retinal vasculitis	Neuroretinitis/ Optic Neuropathy	Previous TB	Systemic TB	Contact History
1	Tunç et al (2003)	Case Report	2003	1	36	Female	1	-	-	-	MFC	-	-	-	-	+	+
2	Uysal et al (2007)	Case Report	2007	1	21	100	1	-	-	-	1	-	-	-	-	+	-
3	Kahraman et al (2009)	Retrospective Case Series	1997-2007	71	40.39 ± 16.45 (10-74)	60	1	-	-	-	-	-	1	-	-	+	-
4	Sızmaz et al (2010)	Retrospective	1996-2006	275	43.9 ± 17.3 (5-83)	42.5	17	-	8	-	2	7	-	-	-	4	-
5	Şen et al (2011)	Case Series	2011	2	25-45	50	2	-	-	-	2	-	-	-	-	2	-
6	Esgin et al (2013)	Case Report	2012	1	21	Female	1	-	-	-	1	-	-	-	-	+	-
7	Sungur et al (2015)	Case Report	2014	1	30	100	1	-	-	-	1	-	-	-	-	+	-
8	Özdal et al (2016)	Case Series	2010-2015	10	31.6 (6-46)	70	10	-	10	1	8	1	4	4	-	3	7
9	Metin et al (2015)	Case Report	2014	1	57	100	1	-	1	-	-	-	-	-	-	-	+
10	Esen et al (2016)	Case Report	2016	1	40	Female	1	-	-	-	1	-	-	-	-	+	-
11	Türker et al (2018)	Case Report	2017	1	20	Female	1	-	-	-	1	-	-	-	-	+	-
12	Oray et al (2017)	Retrospective	1995-2013	28	40.9 ± 12.6 (28-64)	64	17	-	-	-	17	-	-	-	-	-	17
13	Başarır et al (2017)	Case Report	2017	1	23	100	1	-	-	-	+	-	+	-	-	-	+
14	Özyurt et al (2019)	Case Report	2019	1	25	100	1	-	-	-	+	-	-	+	-	+	-

AU, anterior uveitis; IU, intermediate uveitis; PU, posterior uveitis; ATT, anti-tubercular therapy; MFC, multifocal choroiditis; SD, standard deviation; TB, tuberculosis; S/N, study number.

all patients were healthy except for visual symptoms. TB and HIV are often called as an intersecting epidemic. However, extra-pulmonary TB, which is more common among HIV-positive people than HIV-negative people, is difficult to detect through either sputum smear microscopy or chest x-rays. In the present study, HIV was not detected in any of the patients with intraocular TB.

Anterior and posterior uveitis, choroiditis, RV, optic disc nodules, solitary, or multiple choroidal nodules are common clinical findings of intraocular TB.[19-21] Anterior uveitis secondary to TB could be presented with unilateral or bilateral symptoms of conjunctival hyperemia, photophobia, and floaters. In patients with bilateral diseases, the disease is usually asymmetric. Anterior uveitis is characterized by large mutton-fat keratic precipitates, several or diffuse over the corneal endothelium.[22] Intermediate uveitis associated with TB particularly shows nonspecific clinical features. Patients generally present with a low-grade, smoldering chronic uveitis, vitreous snowball opacities, peripheral vascular sheathing, and peripheral retinochoroidal granuloma. The choroid is the most commonly affected site.[19] In this study, 18.75% of the eyes had intermediate uveitis, 18.75% had posterior uveitis, and 62.50% had panuveitis. As of June 2021, all published intraocular TB cases from Turkey are summarized in Table 4. The majority of the patients were published as case reports featuring a variety of the intraocular involvement.

To our best knowledge, this is the first manuscript reporting various clinical types of intraocular TB in Turkey. However, several drawbacks are present, such as its retrospective nature, and unstandardized clinical documentation and follow-up period. Additionally, the sample size was small, especially in the less common clinical phenotypes, and no TB-related anterior uveitis cases were evaluated.

CONCLUSION

The current study presents various ocular findings and discusses the difficulties faced in the diagnosis and treatment of intraocular TB. Outcomes of ATT was favorable in most of the patients with choroidal involvement, even in those with a delay in the initiation of therapy. It can be concluded that the compliance of the patients, macular and/or optic disc involvements and paradoxical reactions are factors affecting the treatment success and visual outcome. Intraocular TB still remains as a diagnostic and management problem for both ophthalmologists and pulmonologists. Ocular examinations can be considered in patients with suspected or proven TB. Early diagnosis and prompt treatment of ocular TB can prevent the severe complications and subsequent potential visual impairments. Tuberculosis should be considered in the differential diagnosis of cases especially with chronic intraocular granulomatous inflammation and those patients should be investigated accordingly.

Ethics Committee Approval: This study was approved by Ethics committee of Dokuz Eylül University, (Approval No: 2021/20-04).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2020*. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf. Accessed April 7, 2021.
2. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. *Tuberculosis Surveillance and Monitoring in Europe 2020-2018 Data*. Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/TB-Surveillance-report_24March2020.pdf
3. *Annual Tuberculosis Incidence Report of Tuberculosis Department of Turkish Ministry of Health General Directorate of Public Health*. Available at: https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz_db/dosya/Istatistikler/Yeni/2-Yllara_Gore_Toplam_TB_Olgu_Hz_ve_TB_Insidans_2005-2018.pdf
4. Sandgren A, Hollo V, van der Werf MJ. Extrapulmonary tuberculosis in the European Union and European Economic Area, 2002-2011. *Euro Surveill*. 2013;18(12). [CrossRef]
5. Albert DM, Raven ML. Ocular tuberculosis. *Microbiol Spectr*. 2016;4(6). [CrossRef]
6. Çakar Özdal MP, Yazici A, Tüfek M, Öztürk F. Epidemiology of uveitis in a referral hospital in Turkey. *Turk J Med Sci*. 2014;44(2):337-342. [CrossRef]
7. Çakar Özdal PT, Özateş S. Current approaches in diagnosis and treatment of ocular tuberculosis: A case series and literature review. *Retina Vitreus*. 2016;24(2):99-108.
8. Betzler BK, Gupta V, Agrawal R. Clinics of ocular tuberculosis: a review. *Clin Exp Ophthalmol*. 2021;49(2):146-160. [CrossRef]
9. Abdisamadov A, Tursunov O. Ocular tuberculosis epidemiology, clinic features and diagnosis: a brief review. *Tuberculosis (Edinb)*. 2020;124:101963. [CrossRef]
10. M A, El-Asrar A, Abouammoh M, Al-Mezaine HS. Tuberculous uveitis. *Middle East Afr J Ophthalmol*. 2009;16(4):188-201. [CrossRef]
11. Ang M, Vasconcelos-Santos DV, Sharma K, et al. Diagnosis of ocular tuberculosis. *Ocul Immunol Inflammm*. 2018;26(2):208-216. [CrossRef]
12. Agrawal R, Gunasekeran DV, Grant R, et al. Clinical features and outcomes of patients With tubercular uveitis treated with antitubercular therapy in the collaborative ocular tuberculosis study (COTS)-1. *JAMA Ophthalmol*. 2017;135(12):1318-1327. [CrossRef]
13. Agrawal R, Testi I, Mahajan S, et al. Collaborative ocular tuberculosis study consensus guidelines on the management of tubercular uveitis-report 1: guidelines for initiating antitubercular therapy in tubercular choroiditis. *Ophthalmology*. 2021;128(2):266-276. [CrossRef]
14. Trusko B, Thorne J, Jabs D, et al. The standardization of uveitis nomenclature (SUN) project. Development of a clinical

evidence base utilizing informatics tools and techniques. *Methods Inf Med*. 2013;52(3):259-65, S1, S1-6. [CrossRef]
15. Kee AR, Gonzalez-Lopez JJ, Al-Hity A, et al. Anti-tubercular therapy for intraocular tuberculosis: A systematic review and meta-analysis. *Surv Ophthalmol*. 2016;61(5):628-653. [CrossRef]
16. Gupta A, Bansal R, Gupta V, Sharma A, Bambery P. Ocular signs predictive of tubercular uveitis. *Am J Ophthalmol*. 2010;149(4):562-570. [CrossRef]
17. Saatci AO, Selver OB, Yaman A, Arikan G, Sayiner A, Akkoclu A. Photodynamic therapy as an adjunct to systemic treatment in a case with unilateral presumed vascularized choroidal tuberculous granuloma. *Int Ophthalmol*. 2009;29(4):293-296. [CrossRef]
18. Kocak N, Saatci AO, Cingil G, Cimrin A, Ucar ES. Miliary tuberculosis and bilateral multifocal choroidal involvement: place of indocyanine green angiography. *Bull Soc Belge Ophtalmol*. 2006;301(301):59-65
19. Gupta V, Gupta A, Rao NA. Intraocular tuberculosis--an update. *Surv Ophthalmol*. 2007;52(6):561-587. [CrossRef]
20. Gupta V, Gupta A, Arora S, Bambery P, Dogra MR, Agarwal A. Presumed tubercular serpiginouslike choroiditis: clinical presentations and management. *Ophthalmology*. 2003;110(9):1744-1749. [CrossRef]
21. Gupta V, Shoughy SS, Mahajan S, et al. Clinics of ocular tuberculosis. *Ocul Immunol Inflammm*. 2015;23(1):14-24. [CrossRef]
22. Tabbara KF. Ocular tuberculosis: anterior segment. *Int Ophthalmol Clin*. 2005;45(2):57-69. [CrossRef]