Int Ophthalmol (2019) 39:317–333
https://doi.org/10.1007/s10792-017-0815-9

ORIGINAL PAPER

Presumed tuberculous uveitis in a university-based tertiary referral center in Saudi Arabia

Awad Al-Qarni · Marwan A. Abouammoh · Abdullah N. Almousa · Ahmed Mousa · Ahmed M. Abu El-Asrar

Received: 31 May 2017 / Accepted: 15 December 2017 / Published online: 9 January 2018

Abstract

Purpose To describe clinical characteristics and outcomes of treatment in patients with presumed tuberculous uveitis (PTU).

Methods All patients diagnosed with PTU between January 1996 and March 2013 were reviewed. The diagnosis was made when clinical findings were consistent with possible intraocular tuberculosis, strongly positive purified protein derivative (PPD) skin test result, and response to anti-tuberculous therapy with no other cause of uveitis as suggested by history, symptoms, or ancillary testing.

Results Ninety patients (141 eyes) were identified. There were 43 males (47.3%) and 47 females (52.7%). Mean age was 48.2 ± 14.4 years. Mean duration of symptoms prior to presentation was 6.7 ± 8.3 months. Ten eyes (7.1%) had anterior uveitis, 18 eyes (12.8%) had intermediate uveitis, 34 eyes (24.1%) had posterior uveitis, and 79 eyes (56%) had panuveitis. Macular edema was present in 33.3% of the eyes at presentation. All patients received anti-tuberculous therapy and systemic corticosteroids. Mean follow-up after completion of therapy was 36 ± 2.5 months. Only 2 eyes developed recurrent inflammation after treatment completion. At last follow-up, all eyes showed resolution of inflammation, associated with significant improvement in visual acuity. There was a significant positive correlation between initial and final VA. Eyes that had macular edema at presentation showed a significant reduction in central macular thickness at final follow-up.

Conclusions There is delay in presentation of patients with PTU. The most common anatomic diagnosis was panuveitis. Treatment with anti-tuberculous therapy combined with systemic corticosteroids resulted in resolution of inflammation and macular edema with significant improvement in visual acuity.

Keywords Uveitis · Tuberculosis · Macular edema · Visual acuity

Awad Al-Qarni and Marwan A. Abouammoh have contributed equally to this work.

A. Al-Qarni · M. A. Abouammoh · A. N. Almousa · A. Mousa · A. M. Abu El-Asrar (✉)
Department of Ophthalmology, College of Medicine, King Saud University, Old Airport Road, P. O. Box 245, Riyadh 11411, Saudi Arabia
e-mail: abuasrar@ksu.edu.sa; abuelasrar@yahoo.com

A. Al-Qarni
King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia

A. M. Abu El-Asrar
Dr. Nasser Al-Rashid Research Chair in Ophthalmology, King Saud University, Riyadh, Saudi Arabia

Introduction

Tuberculosis (TB) is of a growing concern because of its high prevalence in endemic nations and recent resurgence in developed nations. The World Health Organization (WHO) reported that one-third of the world's population is latently infected, with an incidence of > 9 million active TB cases yearly [1–3]. The reported proportion of uveitis cases attributable to TB also varies geographically (Table 1). In Saudi Arabia, tuberculous uveitis is the most common cause for admission among uveitis patients [4], and it is the second most common uveitic entity [5]. Its prevalence varies in reported series from 2 to 28% [4–31].

Obtaining biopsy specimens from intraocular tissues for making a confirmatory histopathologic diagnosis is difficult and potentially morbid. In addition, due to difficulty in obtaining microbiologic evidence, in nearly all reported cases, the diagnosis of tuberculous uveitis is usually presumptive. In most studies, the diagnostic criteria for presumed tuberculous uveitis were: (1) Ocular findings consistent with possible intraocular TB with no other cause of uveitis suggested by history of symptoms or ancillary testing. (2) Strongly positive tuberculin skin test results (15 mm or more area of induration/necrosis). (3) Response to anti-tuberculous therapy with the absence of recurrences [32–40]. The absence of clinically

Table 1 Frequency of tuberculous uveitis in the most recent reported series from different countries

Author	Year	Total no. of patients	No. of tuberculosis patients (%)	Country
Amin et al. [6]	2016	414	20 (4.4)	Egypt
Nguyen et al. [7]	2016	212	19 (9)	Vietnam
Kianersi et al. [8]	2015	2016	4 (0.2)	Iran
Al Dhahri et al. [5]	2014	642	114 (17.8)	Saudi Arabia
Vos et al. [9]	2013	585	66 (11.3)	Netherland
Llorenç Bellés et al. [10]	2012	416	25 (6)	Spain
Ducommun et al. [11]	2012	654	12 (1.8)	Switzerland
Sanghvi et al. [12]	2011	2368	45 (1.9)	UK
Al-Mezaine et al. [4]	2010	351	99 (28.2)	Saudi Arabia
Kazokoglu et al. [13]	2008	761	3 (0.3)	Turkey
Pathanapitoon et al. [14]	2008	200	3 (2.2)	Thailand
Khairallah et al. [15]	2007	472	5 (1.1)	Tunisia
Rathinam et al. [16]	2007	8759	488 (5.6)	India
Yang et al. [17]	2005	1752	13 (0.7)	China
Sengun et al. [18]	2005	300	4 (1.3)	Turkey
Soheilian et al. [19]	2004	544	8 (1.5)	Iran
Singh et al. [20]	2004	1233	125 (10.1)	India
Wakabayashi et al. [21]	2003	189	13 (6.9)	Japan
Islam and Tabbara [22]	2002	200	21 (10.5)	Saudi Arabia
Mercanti et al. [23]	2001	655	46 (7.02)	Italy
Kaimbo Wa Kimbo et al. [24]	1998	336	20 (6)	Congo
Kotake et al. [25]	1997	551	1 (0.2)	Japan
Merrill et al. [26]	1997	385	2 (0.5)	USA
Rodriguez et al. [27]	1996	1273	8 (0.6)	USA
Thean et al. [28]	1996	712	2 (0.28)	UK
Smit et al. [29]	1993	750	20 (2.7)	Netherland
Weiner and Ben Ezra [30]	1991	400	3 (0.7)	Israel
Palmares et al. [31	1990	450	10 (2.2)	Portugal

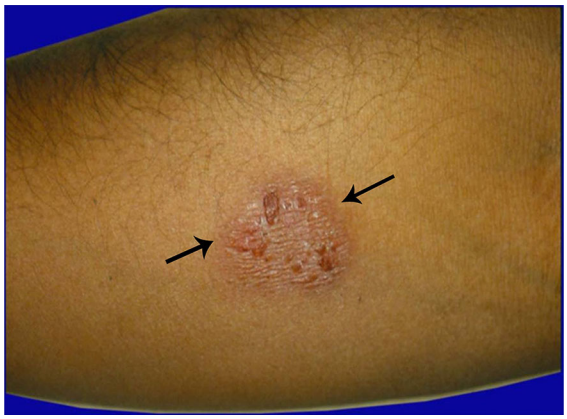


Fig. 1 A patient with presumed tuberculous uveitis with strongly positive tuberculin skin test (arrows)

evident pulmonary TB does not rule out the possibility of ocular TB, as about 60% of patients with extrapulmonary TB have no evidence of pulmonary TB [41].

Ocular TB is treated as other forms of extrapulmonary TB with the first-line combination regimen comprising isoniazid, rifampicin, pyrazinamide, and ethambutol for a total of 6–12 months [42–44]. Ocular tuberculosis is a great mimicker of many uveitis entities. Of the various intraocular manifestations, the most common clinical presentation appears to be posterior uveitis, followed by anterior uveitis, panuveitis, and intermediate uveitis. In addition, it can present as endophthalmitis and panophthalmitis [45].

To the best of our knowledge, only one report described a small series of presumed tuberculous uveitis patients from Saudi Arabia.[35] The aim of this study is to describe the pattern of clinical manifestations, complications, response to treatment, and recurrences after discontinuation of treatment for presumed tuberculous uveitis in a university-based tertiary referral center in Riyadh, Saudi Arabia.

Methods

The medical records of all patients who had the diagnosis of presumed tuberculous uveitis (PTU) seen in the Uveitis Clinic of King Abdulaziz University Hospital, Riyadh, Saudi Arabia, from January 1996 till March 2013 were retrospectively reviewed after obtaining approval of the institutional review board. Diagnosis of PTU disease was based on ocular findings consistent with possible intraocular TB with no other cause of uveitis suggested by history, clinical findings, or ancillary testing, strongly positive tuberculin skin test results (15 mm or more area of induration/necrosis), and response to anti-tuberculous therapy (ATT) with the absence of recurrences after completion of treatment. Patients were diagnosed, treated, and followed up by the same physician (A.M.A). Systemic evaluation for all patients was carried out by an internist.

All patients underwent a complete ocular examination as well as systemic examination. The baseline investigations for every patient included: complete blood count, urea and electrolytes, erythrocyte sedimentation rate, Syphilis serology, urine analysis, purified protein derivative (PPD) skin test of 5 tuberculin units injected intradermally and evaluated after 48 and 72 h (Fig. 1), and chest CT scan. Ancillary tests such as ultrasonography, ultrasound biomicroscopy, fundus fluorescein angiography, indocyanine green angiography, and optical coherence tomography (OCT) and specific laboratory test were performed when it was indicated. All patients with PTU received standard treatment with anti-tuberculous medication for 9 months starting with four drugs in the first 2 months (isoniazid 300 mg daily, rifampicin 450 mg daily, pyrazinamide 30 mg daily, and ethambutol 15 mg/kg daily), followed by a continuation phase with isoniazid and rifampicin only. Systemic corticosteroids (1 mg/kg) and pyridoxine were started along with anti-tuberculous medication to all patients. The follow-up was every 2 weeks for 8 weeks and then every 1–2 months as required to monitor response to therapy.

Charts were reviewed for demographic data including age, sex, and nationality, presenting symptoms, duration of symptoms, laterality, history of contact with TB patient prior to presentation, and history of old or current TB infection in other body organs. Ocular examination findings at the first visit were collected which included best-corrected visual acuity (BCVA), intraocular pressure (IOP), keratic precipitate, anterior chamber reaction according to the SUN classification [46], anterior chamber flare, iris nodules, posterior synechiae, lens status, rubeosis iridis, vitritis, snowballs, retinal vasculitis, optic disk hyperemia or swelling, tractional retinal detachment, ischemia and neovascularization, choroiditis (focal, multifocal, or serpiginous-like), and macular edema. Treatment

Table 2 Initial visual acuity in different anatomical groups

Initial visual acuity	Panuveitis ($n = 79$) No. (%)	Intermediate ($n = 18$) No. (%)	Posterior ($n = 34$) No. (%)	Anterior ($n = 10$) No. (%)	Total ($n = 141$) No. (%)
$\geq$ 20/40	23 (29.1)	6 (33.3)	17 (50.0)	2 (20.0)	48 (34.0)
20/50–20/100	31 (39.2)	3 (16.7)	6 (17.6)	6 (60.0)	46 (32.6)
20/125–20/200	10 (12.7)	4 (22.2)	2 (5.9)	1 (10.0)	17 (12.1)
< 20/200	15 (19.0)	5 (27.8)	9 (26.5)	1 (10.0)	30 (21.3)

duration of anti-tuberculosis and steroid medications was collected separately, and laser or surgical intervention was documented. Laser photocoagulation was applied to ischemic areas of the retina after the inflammation has resolved. Argon laser at 0.2-s duration and 400-microns spot size was used. Laser power was titrated until white blanching of the retina is seen. Laser spacing was half to one burn diameter in between. At the last follow-up, ocular examination, duration of follow-up, macular edema status, and any complications or recurrences after treatment were documented.

Statistical methods

Data were collected and entered using Microsoft Access 2007® database. Data management and cleaning were then conducted where missing and incomplete data were reviewed and corrected. Data analysis was then conducted using SPSS® version 19.0 (*IBM Inc.*, Chicago, Illinois) and *StatsDirect*® statistical software, version 2.7.2 (*StatsDirect* Ltd., Cheshire, UK). Chi-square test was utilized to detect the association between categorical variables, where Fisher's exact test was used whenever appropriate. Student's T test was used to investigate the significance in difference between pre- and post-intervention indices in case of continuous variables. Stepwise logistic regression analysis was conducted to identify the variables that influenced the attainment of visual acuity of $\geq$ 20/40 at last follow-up and the development of any complication of cataract or glaucoma or subretinal neovascular membranes during follow-up. $P < 0.05$ was considered statistically significant.

Results

A total of 90 patients (141 eyes) were identified. Age ranged from 18 years to 80 years with a mean of 48.2 ($\pm$ 14.4) years. Forty-three were males (47.3%). Right eye was involved in 16 patients (17.8%), left eye was

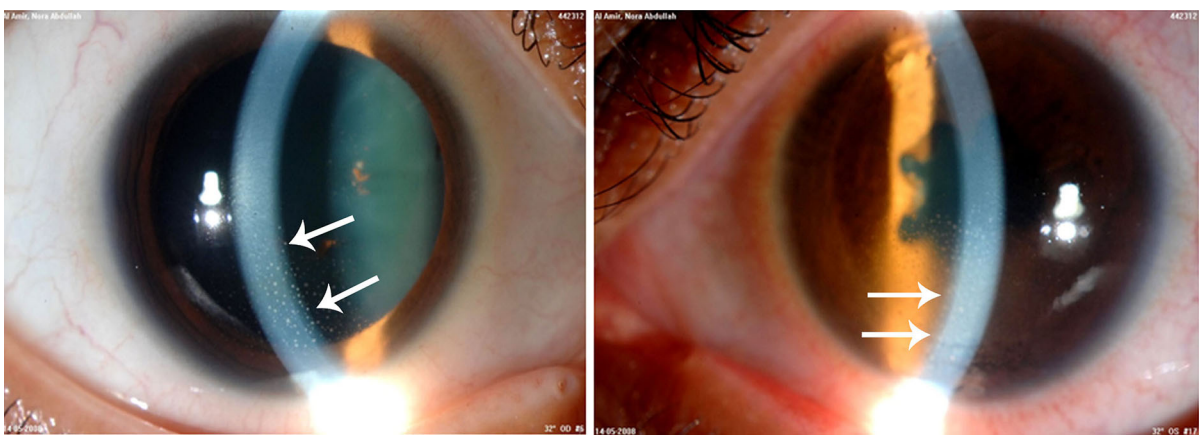


Fig. 2 Slit-lamp biomicroscopy of a patient with presumed intraocular tuberculosis shows mutton-fat keratic precipitates (arrows) and posterior synechiae

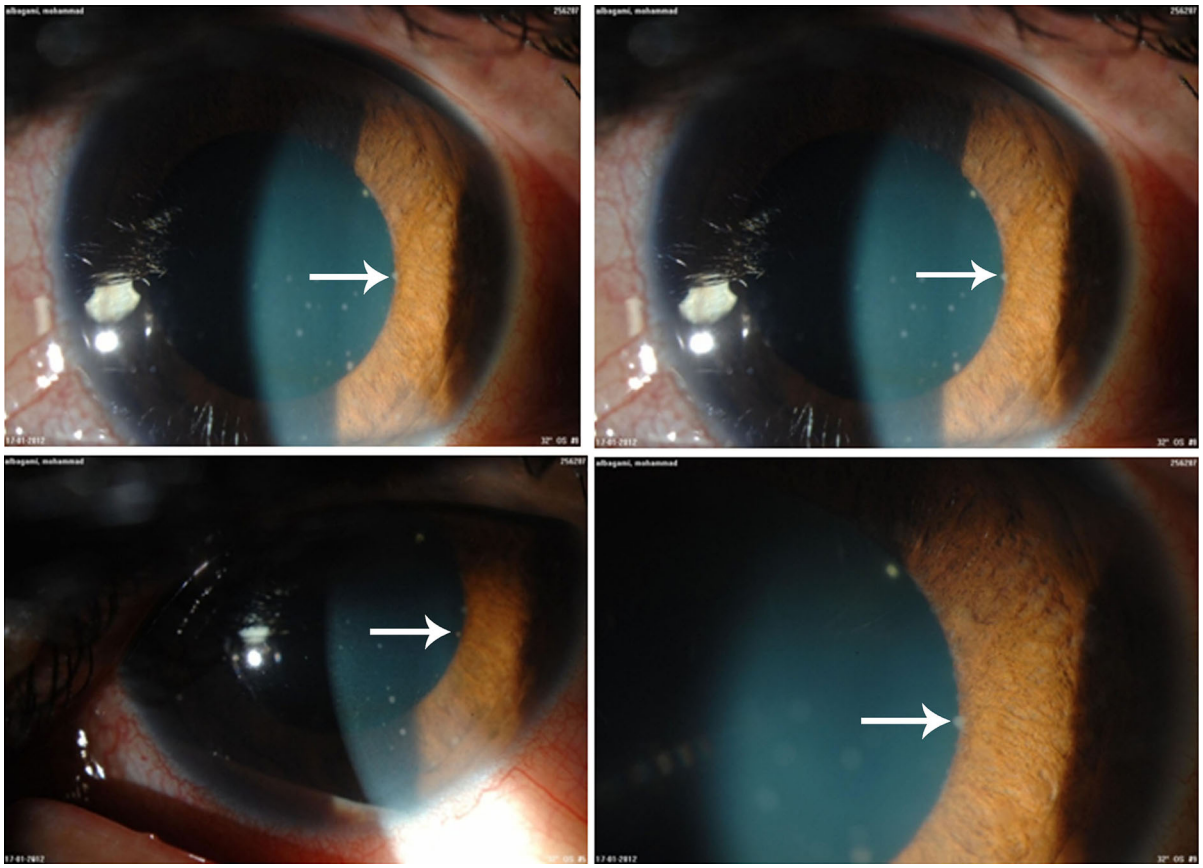


Fig. 3 Slit-lamp biomicroscopy of a patient showing multiple iris nodules at the pupillary border (arrows) and on midiris

the presenting eye in 23 patients (25.6%), and both eyes were involved in 51 patients (56.6%). The mean duration of symptoms for the whole group was 6.7 ± 8.3 months (range 0.03–36 months).

The main presenting symptom was decreased vision in 88 patients (97.8%). Other symptoms were pain in 6 patients (6.7%), floaters in 6 patients (6.7%), redness in 4 patients (4.4%), and photophobia in 2 patients (2.2%). Review of past medical history showed history of contact with active pulmonary TB in 16 patients (17.8%), history of pulmonary TB in 1 patient (1.1%), history of TB in other parts of body in 1 patient (1.1%), and history of anti-TB treatment in 2 patients (2.2%). Chest X-ray/CT chest showed findings suggestive of old pulmonary TB in 23 patients (25.6%). Based on the Standardization of Uveitis Nomenclature (SUN),[46] the presenting features were anterior uveitis in 10 eyes (7.1%), intermediate uveitis in 18 eyes (12.8%), posterior uveitis in 34 eyes (24.1%), and panuveitis in 79 eyes (56%). The initial BCVA in each group was collected and analyzed as shown in Table 2.

The clinical characteristics at presentation were as follows: 58 eyes (41.1%) had mutton-fat keratic precipitates (Fig. 2), 15 eyes (10.6%) had anterior chamber reaction > 2+, 9 eyes (6.4%) had hypopyon, 12 eyes (8.5%) had iris nodules (Fig. 3), 33 eyes (23.4%) had posterior synechiae (Fig. 2), 5 eyes (3.5%) had rubeosis iridis, 83 eyes (65.1%) had vitritis, 18 eyes (12.7%) had large snowballs (Fig. 4), 28 eyes (19.9%) had retinal vasculitis (Fig. 5), 26 eyes (18.4%) had optic disk hyperemia, 5 eyes (3.5%) had tractional retinal detachment, and 17 eyes (12.1%) had retinal neovascularization (Fig. 6). Choroiditis was found in 19 eyes (13.5%). Among eyes with choroiditis, focal choroiditis was in 3 eyes (15.8%) (Fig. 7), multifocal choroiditis in 14 eyes (73.7%) (Fig. 8), and serpiginous-like choroiditis in 2 eyes (10.5%) (Fig. 9).

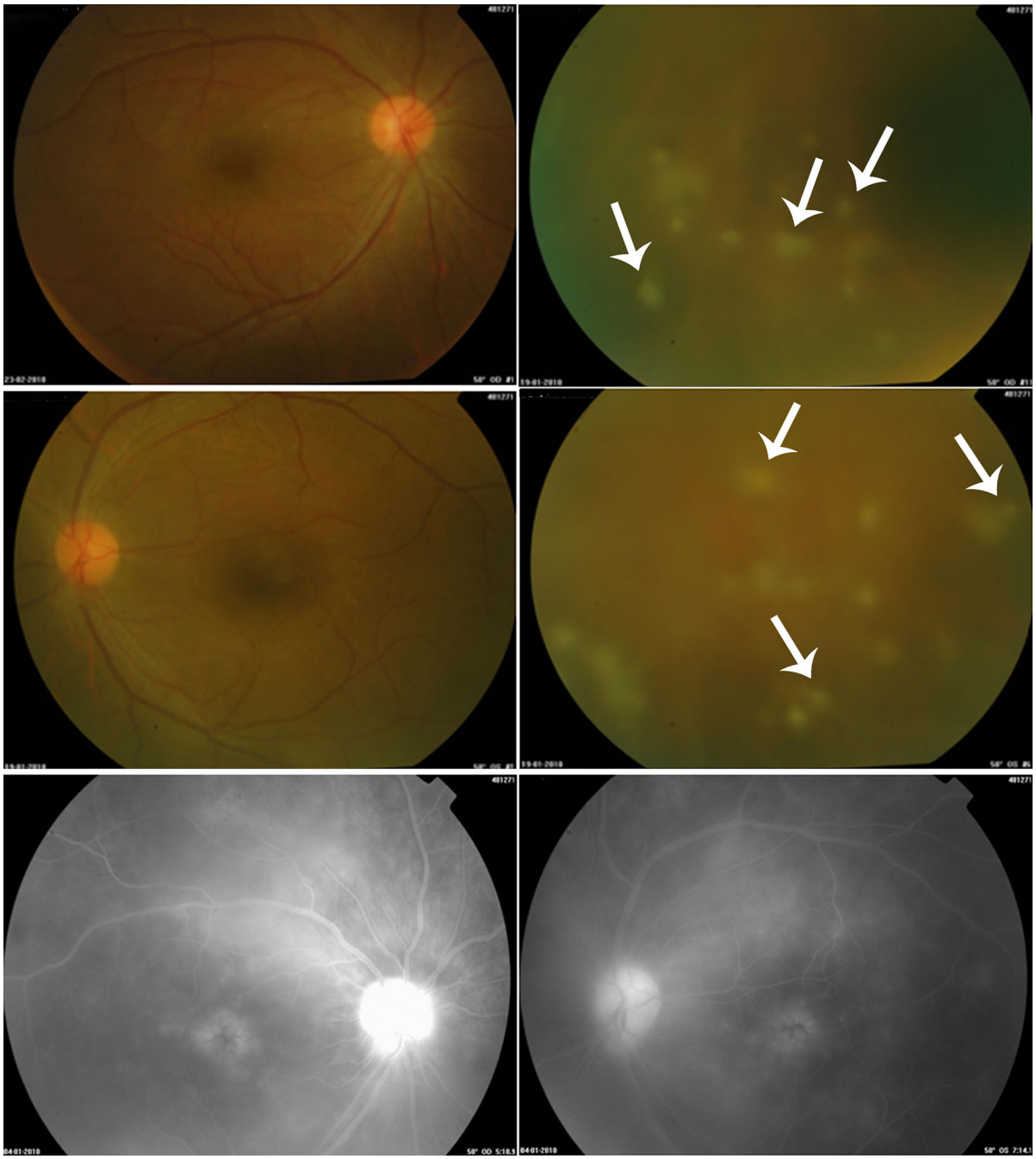


Fig. 4 Fundus photographs of a patient showing large snowballs in a patient with intermediate uveitis (arrows). Fluorescein angiography shows leakage in a typical wheel-spoke pattern suggestive of cystoid macular edema

Macular edema was present in 47 out of 141 eyes (33.3%). The largest percentage (61.1%) was within the intermediate uveitis group (11 out of 18 eyes). Macular edema was present in 34.2% of the panuveitis group (27 out of 79 eyes) and in 26.5% of the posterior uveitis group (9 out of 34 eyes). The mean central macular thickness was 438.6 (± 132.6) microns in eyes with macular edema at initial presentation. In the

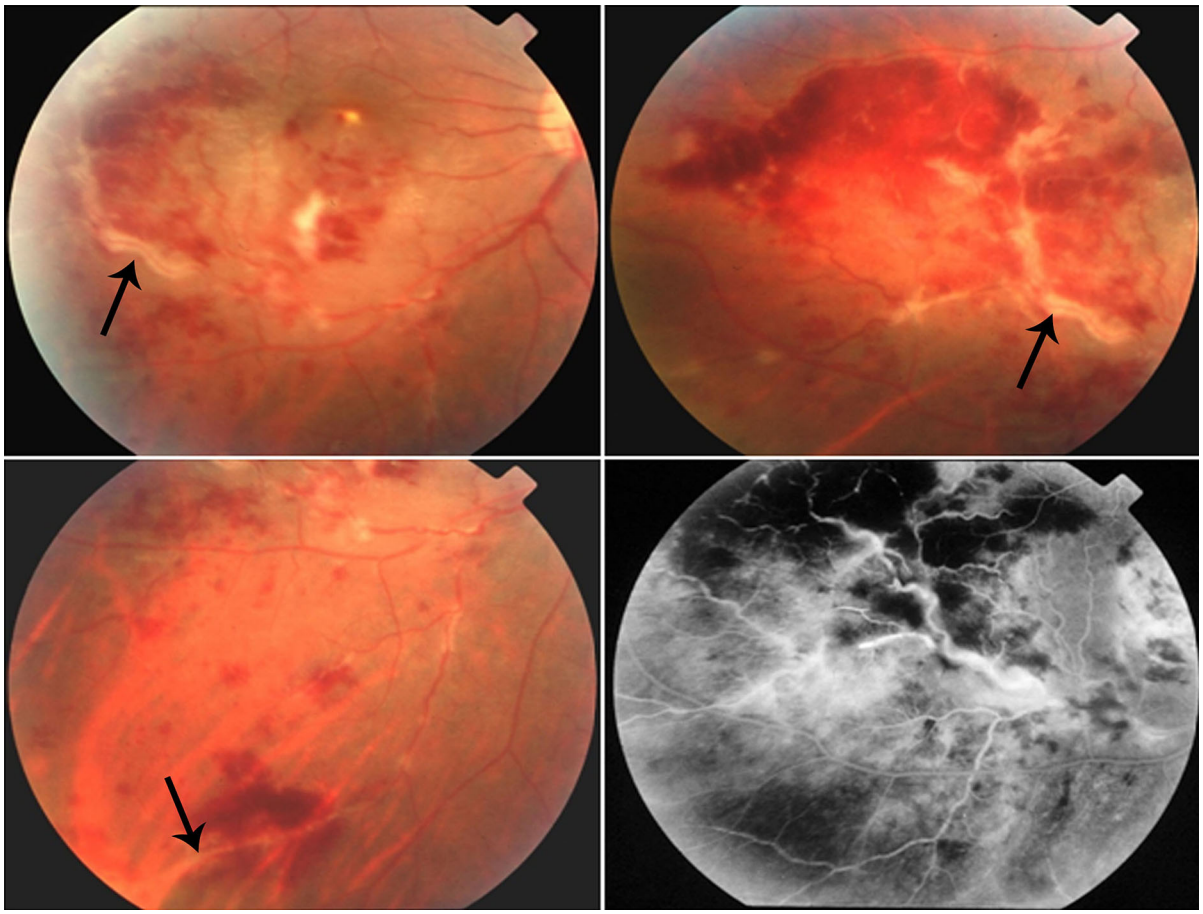
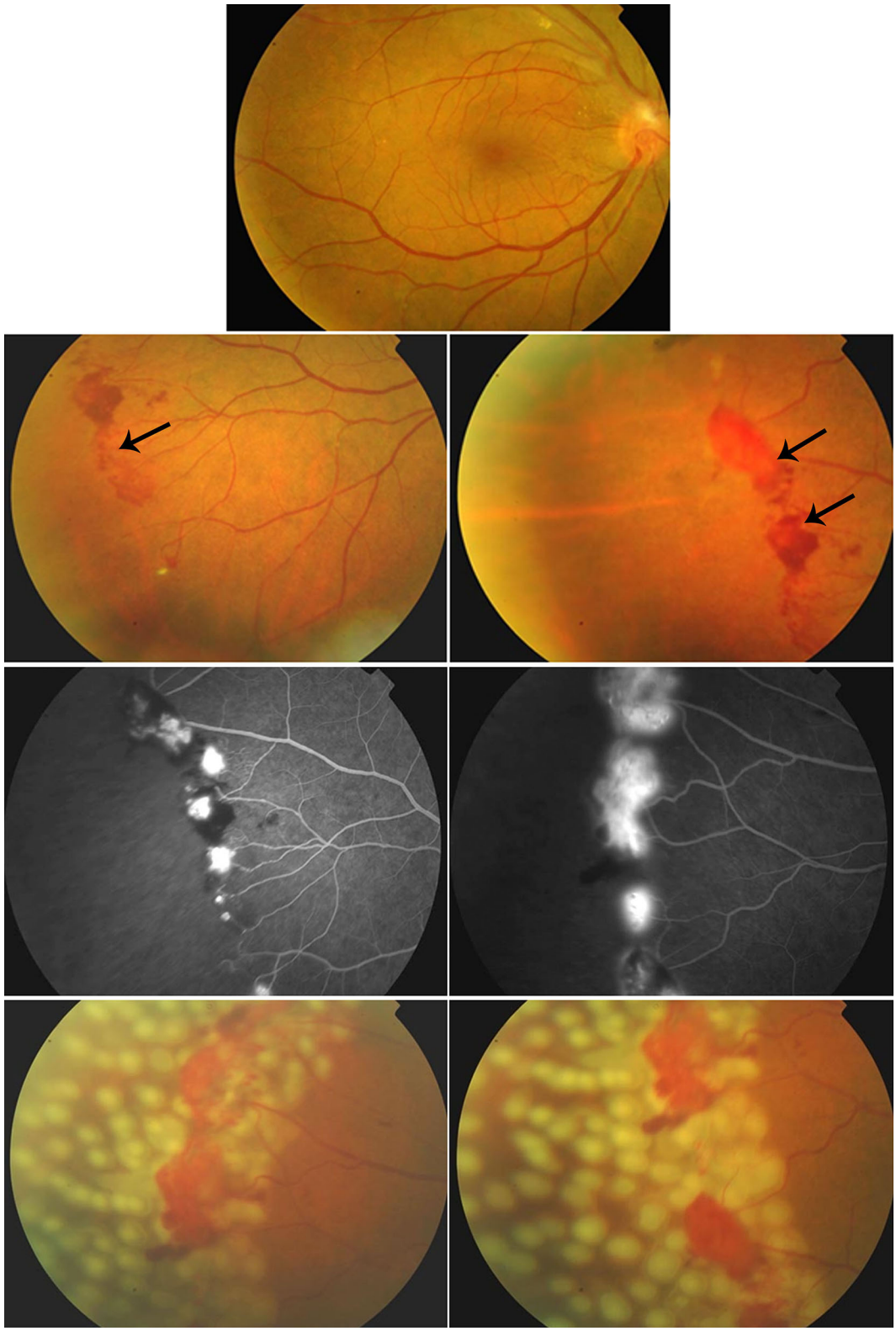


Fig. 5 Left/right eye of a patient showing perivenous sheathing (arrows) and intraretinal hemorrhages in a patient with retinal vasculitis. Fluorescein angiography shows leakage from the retinal veins and retinal non-perfusion

whole study group, the mean PPD size was 24.4 ± 10 mm of induration (range 15–80 mm).

All patients received ATT for 9 months. The mean duration of systemic corticosteroid treatment in the whole group was 4.2 ± 1.3 months (range 2–8 months). All patients having retinal vasculitis with retinal ischemia (18 eyes) received scatter laser photocoagulation. Six eyes presented with vitreous hemorrhage and needed early pars plana vitrectomy with endolaser. The log MAR visual acuity has significantly improved from a mean preoperative value of 0.82 (± 0.76) [Snellen equivalent 20/125] to a mean value of 0.65 (± 0.68) [Snellen equivalent 20/80] at the last follow-up visit assessment ($P = 0.008$). In patients with macular edema, treatment resulted in significant reduction in central macular thickness ($P < 0.001$) associated with significant improvement in BCVA ($P = 0.003$). The total number of eyes with complications was 39 eyes (27.7%). Table 3 shows the distribution of various complications among different groups.

Univariate analysis was performed to investigate the factors predicting final visual acuity of 20/40 or better. The following factors were investigated: age, visual acuity at presentation, glaucoma at presentation, presence of keratic precipitates, anterior chamber reaction, presence of hypopyon, iris nodules, posterior synechiae, rubeosis iridis, lens status, vitritis, retinal vasculitis, optic nerve hyperemia and swelling, tractional retinal detachment, retinal neovascularization, choroiditis, and macular edema. Our analysis demonstrated the presence of a significant positive association between final visual acuity of ≥ 20/40 and clinical findings at presentation, including initial



◀**Fig. 6** Left/right eye of a patient showing midperipheral retinal neovascularization (*right*) (arrows). Fluorescein angiography shows leakage from these neovessels (*middle*). Laser treatment was applied to ischemic retina (*left*)

visual acuity of ≥ 20/40 ($P < 0.001$), and clear lens ($P = 0.001$). Multivariate analysis further confirmed our findings by demonstrating a significant positive association between final visual acuity of ≥ 20/40 and initial visual acuity of ≥ 20/40 [odds ratio = 12.5; 95% confidence internal (CI) = 1.5–45.1], and clear lens at presentation [odds ratio = 2.1; 95% CI = 2.8–58.7]. Among the 48 eyes that presented with visual acuity of ≥ 20/40, 39 eyes (81.3%) achieved a final visual acuity of ≥ 20/40. In comparison, among the remaining 93 eyes that had < 20/40 at presentation, only 41 eyes (44.1%) achieved ≥ 20/40 ($P < 0.001$) (Table 4). Development of glaucoma was significantly associated with visual acuity of < 20/40 ($P < 0.007$).

The mean duration of the interval between discontinuation of treatment and last follow-up of the whole group was 36(± 2.5) months (range from 12 to 144 months). Only two patients (2.2%) had recurrence after discontinuation of treatment. The first patient presented with intermediate uveitis and had a 9-month course of ATT and 4 months of corticosteroids therapy. Four months after completion of treatment, the patient presented with a similar clinical picture and had a repeated full workup. Another course of ATT for 9 months was administered to the patient. We followed up the patient for 4 years with no recurrence. We questioned the compliance of this patient during the course of ATT. The second patient presented with panuveitis and had a 9-month course of ATT and 4-month course of systemic corticosteroid therapy. Ten months after cessation of treatment, the patient presented with a picture similar to his initial presentation and had a repeated full battery of investigations and workup. ATT was reinstituted along with systemic corticosteroids, and the patient was still under treatment at the time of data collection.

Discussion

Tuberculous uveitis is a major cause of uveitis in Saudi Arabia [4, 5, 22]. In this series, a presumption of tuberculous uveitis was made on the basis of the presence of characteristic ocular lesions in the context of evidence of previous exposure to *M. tuberculosis.* The specificity of the tuberculin skin test for *M. tuberculosis* increases with larger skin reactions and with a history of exposure to an active case of tuberculosis. An induration greater than 15 mm is unlikely to be because of previous Bacilli Calmette–Guerin (BCG) vaccination [47].

The mean duration of symptoms in the whole group was 6.7 months. Cimino et al. [37] reported a mean diagnostic delay of 5.7 ± 4 years (Table 5) [12, 37, 48–54]. This relatively long delay in the

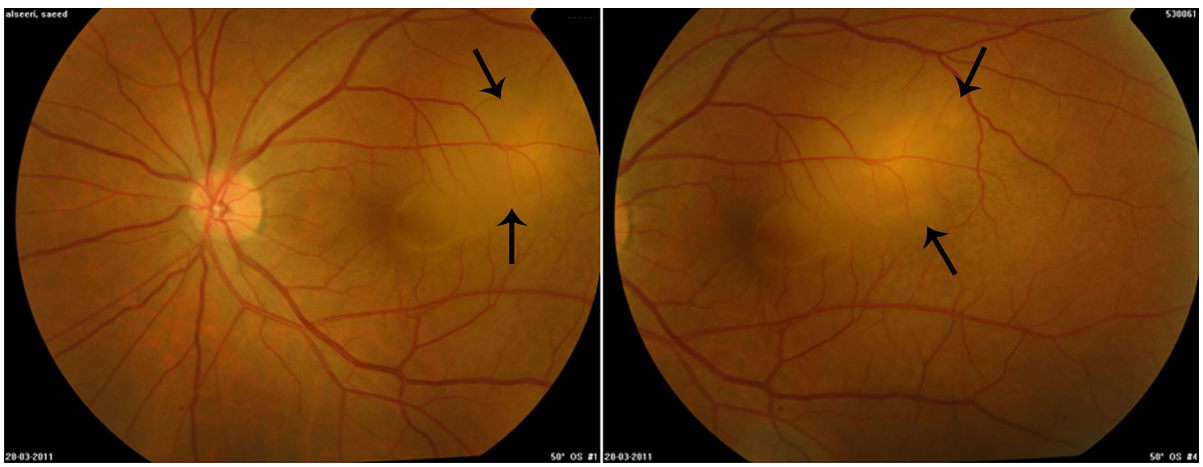


Fig. 7 Fundus photographs of the left/right eye of a patient showing subretinal amelanotic choroidal mass (arrows) with exudative retinal detachment

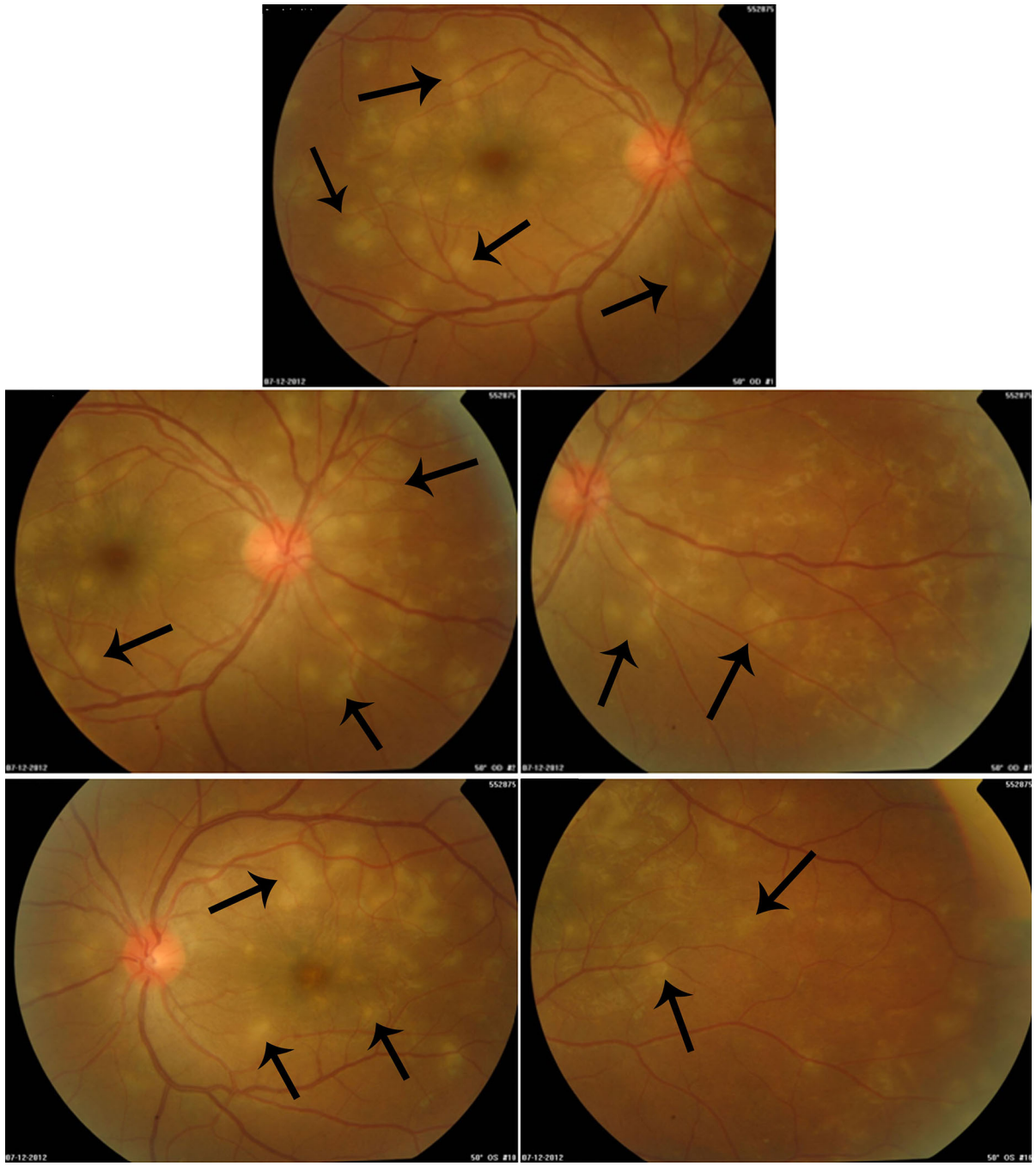


Fig. 8 Fundus photographs of the left/right eye of a patient showing multifocal choroiditis (arrows)

diagnosis is probably due to lack of suspicion as tuberculous uveitis is a great mimicker. In addition, the difficulty in isolating the organism using commonly available diagnostic tests may play a role in the diagnostic delay. In the present study, the most common anatomic diagnosis was panuveitis (56%), followed by posterior uveitis (24.1%). This was similar to what has been reported in previous studies

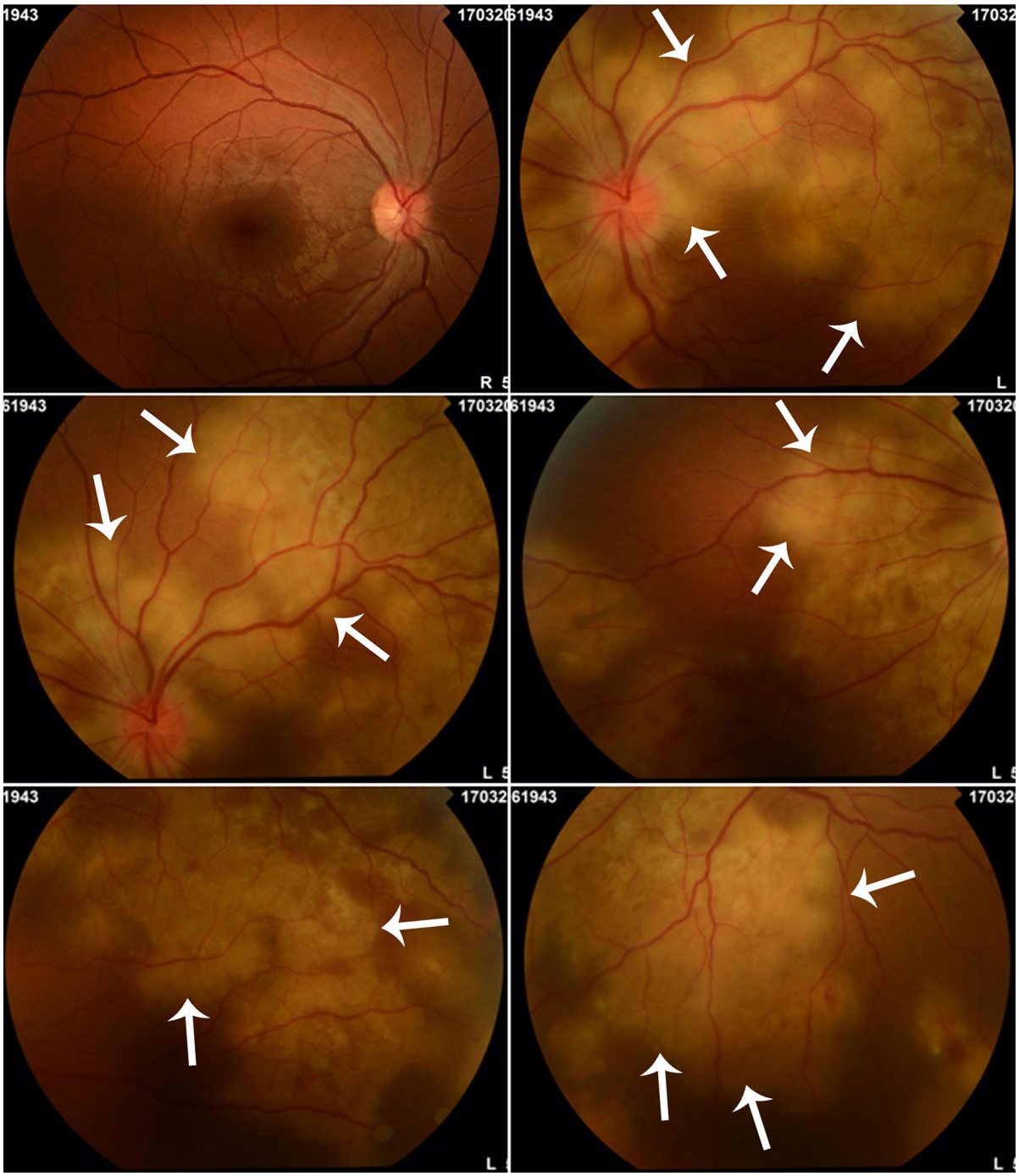


Fig. 9 Fundus photographs of the left/right eye of a patient showing widespread serpiginous-like choroiditis, which extended from the peripapillary region to midperipheral retina

Table 3 Distribution of various complications among different groups

Category Variable	Panuveitis No. (%)	Intermediate No. (%)	Posterior No. (%)	Total No. (%)
Complications				
Cataract	9 (10.1)	7 (38.9)	4 (11.8)	20 (14.2)
Glaucoma	8 (9.0)	1 (5.6)	2 (5.9)	11 (7.8)
CNVM	0 (0.0)	0 (0.0)	4(11.8)	4 (2.8)
Hypotony	4 (4.5)	0 (0.0)	0 (0.0)	4 (2.8)
Total No. (%)	21 (26.6)	8 (44.4)	10 (25.6)	39(27.7)

CNVM choroidal neovascular membrane

Table 4 Relationship between initial visual acuity and final visual acuity

Visual acuity at last follow-up	Visual acuity at presentation				Total eyes
	< 20/200	20/125–20/200	20/50–20/100	≥ 20/40	
≥ 20/40	6	5	30	39	80 (56.7%)
20/50–20/100	9	8	12	8	37 (26.2%)
20/125–20/200	2	3	2	0	7 (5.0%)
< 20/200	13	1	2	1	17 (12.1%)
Total eyes	30 (21.3%)	17 (12.1%)	46 (32.6%)	48 (34%)	141 (100%)

with panuveitis as the most common presentation of PTU [12, 35, 55]. However, posterior uveitis was the most common presentation of PTU in few other studies [45, 48].

Retinal vasculitis was present in 28 eyes. Neovascularization at the disk or elsewhere in the retina was present in 14 eyes, while traction retinal detachment and vitreous hemorrhage were found in 4 eyes. Several studies demonstrated that retinal periphlebitis is a common manifestation of PTU [32, 34, 56, 57]. Such cases were also managed with ATT and systemic corticosteroids. In addition, retinal photocoagulation to the ischemic areas and early vitrectomy if necessary were performed and resulted in anatomic and functional improvement [58]. We believe that any patient who presents with occlusive retinal periphlebitis associated with a strongly positive PPD test should be managed as a case of presumed tuberculous retinal vasculitis. Those cases with negative medical workup, including PPD, can be termed as idiopathic occlusive vasculitis.

Choroid is a preferable place for *M. tuberculosis* [59]. In our study, choroiditis was present in 19 eyes. In a previous study from India, multifocal choroiditis was a common presentation among patients with PTU [57]. Clinical features that may help to clinically distinguish tuberculous serpiginous-like choroidopathy from serpiginous choroidopathy include the country of origin of the patient (i.e., patients from areas where TB is endemic), significant vitritis, and the presence of multifocal lesions in posterior pole and periphery [60]. Several case reports of tumor-like mass (choroidal tuberculoma) emphasize the need to consider TB in the differential diagnosis of such clinical presentation [61–64].

Macular edema is a major cause of vision loss in uveitis [65]. In our study, macular edema was present in one-third of the eyes. The largest rate within each group was in the intermediate uveitis group (61.1%), followed by panuveitis (34.2%), and posterior uveitis (26.5%). Macular edema improved clinically after treatment with ATT and systemic corticosteroid therapy. Variable rates of macular edema in tuberculous uveitis have been reported ranging from 8.9% by Sanghvi et al. [12] in a group of 45 patients to 42.5% by Al-Mezaine et al. in a group of 52 patients [35].

Table 5 Demographics and clinical findings of presumed intraocular tuberculosis in previous series

	Cimino et al.	Sanghvi et al.	Manousaridis et al.	Llorenc et al.	Mao et al.	Basu et al.	La Dista Nora et al.	Khochtali et al.	Gunasekeran et al.	Current study
Year	2009	2011	2013	2013	2014	2014	2014	2015	2017	2017
Number of patients	37	27	21	33	46	40	77	38	354	90
Number of eyes	NA	48	36	58	66	61	128	65	643	141
Average age	55 (median)	36.1	46	45.6	45.7	34.4	46	42.7	48.5	48.2
Male	40.50%	41%	71%	57.60%	58.70%	67.5%	57.10%	36.80%	0.534	47.30%
Delay in diagnosis (mean)	68.4 months	NA	NA	NA	NA	12 months	NA	NA	NA	6.7 months
Anatomic classification										
Anterior uveitis	1(2.7%) Patient	6(12.5%) Eyes	4(11%) Eyes	6(18.2%) Patients	NA	5(12.4%) Eyes	27(21%) Eyes	8(12.3%) Eyes	NA	10(7.1%) Eyes
Intermediate uveitis	None	7(14.6%) Eyes	None	9(27.3%) Patients	NA	3(7.5%) Eyes	17(13.3%) Eyes	21(32.3%) Eyes	NA	18(12.8%) Eyes
Posterior uveitis	8(21.6%) Patients	16(33.3%) Eyes	29(80.5%) Eyes	11(33.3%) Patients	NA	37(56%) Eyes	48(37.5%) Eyes	23(35.4%) Eyes	NA	34(24.1%) Eyes
Panuveitis	28(75.7%) patients	19(39.6%) Eyes	3(8.3%) Eyes	7(21.2%) patients	NA	15 (37.5%) eyes	30(23.4%) eyes	13(20%) eyes	NA	79(56%) eyes
Choroiditis	NA	8 (16.8%) Eyes	9 (23.5%) Eyes	14 (18.3%) Eyes	16 (35%) Eyes	6 (9%) Eyes	18 (14%) Eyes	29 (45%) Eyes	87 (25%) Patients	19 (14%) Eyes
Vasculitis	NA	2(4.2%) Eyes	22(61%) Eyes	27(46.6%) Eyes	25(54%) Patients	31(47%) Eyes	58(45%) Eyes	14(21.5%) Eyes	125(35.3%) Patients	28(19.9%) Eyes
Complications										
CME	NA	4(14.8%) Patients	5(13.9%) Eyes	13(22.4%) Eyes	NA	5(7.5%) Eyes	34(45%) Patients	13(20%) Eyes	107(30.5%) Patients	47(33.3%) Eyes
Cataract	NA	3(11.1%) Patients	NA	23(39.6%) Eyes	NA	10(15%) Eyes	12(16%) Patients	None	71(20.1%) Patients	20(14.2%) Eyes
CNVM	NA	NA	2(5.5%) Eyes	10(17.2%) Eyes	NA	NA	8(10%) Patients	None	6(1.7%) Patients	4(2.8%) Eyes
Glaucoma	NA	NA	NA	14(24.1%) Eyes	NA	2(3%) Eyes	18(24%) Patients	None	99(28.1%) Patients	11(7.8%) Eyes

Table 5 continued

	Cimino et al.	Sanghvi et al.	Manousaridis et al.	Llorenc et al.	Mao et al.	Basu et al.	La Dista Nora et al.	Khochtali et al.	Gunasekeran et al.	Current study
Recurrence*	3(8.1%) Patients	3(11.1%) Patients and wrong diagnosis in 7(25.9%) Patients	None	NA	None	None	2(6.3%) Patients	2(5.3%) Patients	None	2(2.2%) Patients

NA not available

*Of those who completed full course of anti-TB medications

Similarly, Gupta et al. reported a high rate of cystoid macular edema (CME) (53%) in patients with TB-related intermediate uveitis [45].

The mean PPD skin test size in the whole group was 24.4 (± 10) mm. Similar findings were reported by Babu et al. who found that 96.1% of the patients had a strongly positive Mantoux test with induration of ≥ 21 mm in their series of 51 patients with PTU [66]. Similar findings were also reported by Ang et al. [67].

The treatment of ocular inflammation associated with tuberculosis should be directed against both the infection and the inflammatory reaction [68]. In the current study, all the patients were treated with ATT and systemic corticosteroids. All eyes showed resolution of inflammation with only 2 patients having recurrences after completion of the treatment. In addition, there was a significant improvement in visual acuity. Treating PTU with systemic corticosteroids alone may, in some cases, lead to the development of miliary tuberculosis even in the absence of active systemic disease at the time of presentation [32, 44]. In addition, several studies demonstrated that treating PTU patients with systemic corticosteroid alone resulted in having continued recurrent episodes of active inflammation or showed worsening, and inflammation was controlled only by concomitant treatment with ATT [38, 56, 66, 69–71]. Although the inflammation can be controlled initially by the use of systemic corticosteroid alone, elimination of recurrences in patients treated with anti-tuberculous drugs strongly favors the use of specific therapy in patients with presumed tuberculous uveitis [38, 56, 66, 69–71]. In addition to systemic corticosteroids, dexamethasone intravitreal implants were reported to be safe and effective as an adjunct anti-inflammatory therapy to ATT [72, 73].

ATT in these patients could help by killing the intraocular microorganisms, thus resulting in reduced antigen load and resultant inflammation. The reduced antigen load would reduce the hypersensitivity reactions also, which probably results in eliminating the recurrences in these patients [56]. Recently, it has been demonstrated that there is a selective distribution of *M. tuberculosis* in the retinal pigment epithelium of the enucleated eye of a case of panuveitis [74]. Such findings suggest preferential location of *M. tuberculosis* in the retinal pigment epithelium in eyes with panuveitis resulting from tuberculosis and also that recurrences in tuberculous choroiditis could result from reactivation of sequestered organisms in the

retinal pigment epithelium. Prevention of such recurrences requires a longer course of treatment with systemic anti-mycobacterial agents, preferably for at least 6–9 months. Paradoxical intraocular reactions after starting the treatment such as worsening of the inflammation or existing lesions, or appearance of new lesions have been described [45, 57]. None of our patients had such a reaction to ATT.

In the current study, 80 eyes (56.7%) had visual acuity of $\geq$ 20/40 at the last follow-up. The initial presenting visual acuity was a significant predictor for the final visual acuity. Thus, eyes that had good visual acuity at presentation were more likely to have good final visual acuity. Initial visual acuity was also shown to be significantly associated with final visual acuity in previous studies [4]. This highlights the importance of early diagnosis and prompt intervention. Our analysis also demonstrated that development of glaucoma was a significant predictor of a worse visual outcome.

In conclusion, patients with presumed tuberculous uveitis usually have a delayed presentation. Thus, it is important to have a high index of suspicion of the diagnosis in patients with unexplained chronic uveitis. Panuveitis is the most common anatomic diagnosis of tuberculous uveitis. It is a readily treatable disease, and the consequences of delay in either ocular or systemic diagnosis can be very serious. Macular edema can occur in up to one-third of the patients. Treatment with ATT combined with systemic corticosteroids induced resolution of inflammation with very low incidence of recurrence and is associated with a significant improvement in visual acuity.

Acknowledgements The authors thank Ms. Connie Unisa-Marfil for secretarial assistance. This work was supported by King Saud University through Vice Deanship of Research Chair (Dr. Nasser Al-Rashid Research Chair in Ophthalmology [AMA]), Riyadh, Saudi Arabia.

Compliance with ethical standards

Conflict of interest The authors declare that they do not have any conflict of interest on the content of manuscript and study undertaken.

References

1. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC (1999) Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 282:677–686
2. World Health Organisation. Tuberculosis Fact Sheet 2015. World Health Organization; 2016. http://www.who.int/mediacentre/factsheets/fs104/en/. Accessed 21 November 2016
3. Centers for Disease Control (USA). Tuberculosis—Data and Statistics 2015. http://www.cdc.gov/tb/statistics/default.htm. Accessed 21 November 2017
4. Al-Mezaine HS, Kangave D, Abu El-Asrar AM (2010) Patterns of Uveitis in patients admitted to a university hospital in Riyadh, Saudi Arabia. Ocul Immunol Inflamm 18:424–431
5. Al Dhahri H, Al Rubaie K, Hemachandran S et al (2015) Patterns of uveitis in a university-based tertiary referral center in Riyadh, Saudi Arabia. Ocul Immunol Inflamm 23:311–319
6. Amin RM, Goweida M, Bedda A, Kamel A, Radwan A (2016) Clinical patterns and causes of intraocular inflammation in a uveitis patient cohort from Egypt. Ocul Immunol Inflamm. https://doi.org/10.1080/09273948.2016.1236972
7. Nguyen M, Siak J, Chee SP, Diem VQ (2016) The spectrum of uveitis in Southern vietnam. Ocul Immunol Inflamm. https://doi.org/10.1080/09273948.2016.1231826
8. Kianersi F, Mohammadi Z, Ghanbari H, Ghoreyshi SM, Karimzadeh H, Soheilian M (2015) Clinical patterns of uveitis in an iranian tertiary eye-care center. Ocul Immunol Inflamm 23:278–282
9. Vos AG, Wassenberg MWM, de Hoog J, Oosterheert JJ (2013) Diagnosis and treatment of tuberculous uveitis in a low endemic setting. Int J Infect Dis 17:e993–e999
10. Llorenç Bellés V, Adán Civera A, Espinosa Garriga G et al (2012) Uveitis diagnosis characterization at a referral centre in the area of Barcelona, Spain. Med Clin (Barc) 138:277–282
11. Ducommun M-A, Eperon S, Khonkarly MB, Cavassini M, Guex-Crosier Y (2012) Long-term close follow-up of chorioretinal lesions in presumed ocular tuberculosis. Eur J Ophthalmol 22:195–202
12. Sanghvi C, Bell C, Woodhead M, Hardy C, Jones N (2011) Presumed tuberculous uveitis: diagnosis, management, and outcome. Eye 25:475–480. https://doi.org/10.1038/eye.2010.235
13. Kazokoglu H, Onal S, Tugal-Tutkun I et al (2008) Demographic and clinical features of uveitis in tertiary centers in Turkey. Ophthalmic Epidemiol 15:285–293
14. Pathanapitoon K, Kunavisarut P, Ausayakhun S, Sirirungsi W, Rothova A (2008) Uveitis in a tertiary ophthalmology centre in Thailand. Br J Ophthalmol 92:474–478
15. Khairallah M, Ben Yahia S, Ladjimi A et al (2007) Pattern of uveitis in a referral centre in Tunisia, North Africa. Eye 21:33–39
16. Rathinam SR, Namperumalsamy P (2007) Global variation and pattern changes in epidemiology of uveitis. Indian J Ophthalmol 55:173–183
17. Yang P, Zhang Z, Zhou H et al (2005) Clinical patterns and characteristics of uveitis in a tertiary center for uveitis in China. Curr Eye Res 30:943–948

18. Sengün A, Karadağ R, Karakurt A, Saricaoğlu MS, Abdik O, Hasiripi H (2005) Causes of uveitis in a referral hospital in Ankara, Turkey. Ocul Immunol Inflamm 13:45–50
19. Soheilian M, Heidari K, Yazdani S, Shahsavari M, Ahmadieh H, Dehghan M (2004) Patterns of uveitis in a tertiary eye care center in Iran. Ocul Immunol Inflamm 12:297–310
20. Singh R, Gupta V, Gupta A (2004) Pattern of uveitis in a referral eye clinic in north India. Indian J Ophthalmol 52:121–125
21. Wakabayashi T, Morimura Y, Miyamoto Y, Okada AA (2003) Changing patterns of intraocular inflammatory disease in Japan. Ocul Immunol Inflamm 11:277–286
22. Islam SMM, Tabbara KF (2002) Causes of uveitis at the eye center in Saudi Arabia: a retrospective review. Ophthalmic Epidemiol 9:239–249
23. Mercanti A, Parolini B, Bonora A, Lequaglie Q, Tomazzoli L (2001) Epidemiology of endogenous uveitis in northeastern Italy. Analysis of 655 new cases. Acta Ophthalmol Scand 79:64–68
24. Kaimbo Wa Kimbo D, Bifuko A, Dernouchamps JP, Missotten L (1998) Chronic uveitis in Kinshasa (D R Congo). Bull Soc Belge Ophtalmol 270:95–100
25. Kotake S, Furudate N, Sasamoto Y, Yoshikawa K, Goda C, Matsuda H (1997) Characteristics of endogenous uveitis in Hokkaido, Japan. Graefes Arch Clin Exp Ophthalmol 235:5–9
26. Merrill PT, Kim J, Cox TA, Betor CC, McCallum RM, Jaffe GJ (1997) Uveitis in the southeastern United States. Curr Eye Res 16:865–874
27. Rodriguez A, Calonge M, Pedroza-Seres M, et al (1996) Referral patterns of uveitis in a tertiary eye care center. Arch Ophthalmol (Chicago, Ill 1960) 114:593–599
28. Thean LH, Thompson J, Rosenthal AR (1996) A uveitis register at the Leicester royal Infirmary. Ophthalmic Epidemiol 3:151–158
29. Smit RL, Baarsma GS (1995) Epidemiology of uveitis. Curr Opin Ophthalmol 6:57–61
30. Weiner A, BenEzra D (1991) Clinical patterns and associated conditions in chronic uveitis. Am J Ophthalmol 112:151–158
31. Palmares J, Coutinho MF, Castro-Correia J (1990) Uveitis in northern Portugal. Curr Eye Res 9(Suppl):31–34
32. Rosen PH, Spalton DJ, Graham EM (1990) Intraocular tuberculosis. Eye 4:486–492
33. Sheu SJ, Shyu JS, Chen LM, Chen YY, Chirn SC, Wang JS (2001) Ocular manifestations of tuberculosis. Ophthalmology 108:1580–1585
34. Sakai J, Matsuzawa S, Usui M, Yano I (2001) New diagnostic approach for ocular tuberculosis by ELISA using the cord factor as antigen. Br J Ophthalmol 85:130–133
35. Al-Mezaine HS, Al-Muammar A, Kangave D, Abu El-Asrar AM (2008) Clinical and optical coherence tomographic findings and outcome of treatment in patients with presumed tuberculous uveitis. Int Ophthalmol 28:413–423
36. Sarvananthan N, Wiselka M, Bibby K (1998) Intraocular tuberculosis without detectable systemic infection. Arch Ophthalmol (Chicago, III 1960) 116:1386–1388
37. Cimino L, Herbort CP, Aldigeri R, Salvarani C, Boiardi L (2009) Tuberculous uveitis, a resurgent and underdiagnosed disease. Int Ophthalmol 29:67–74
38. Morimura Y, Okada AA, Kawahara S et al (2002) Tuberculin skin testing in uveitis patients and treatment of presumed intraocular tuberculosis in Japan. Ophthalmology 109:851–857
39. Wolfensberger TJ, Piguet B, Herbort CP (1999) Indocyanine green angiographic features in tuberculous chorioretinitis. Am J Ophthalmol 127:350–353
40. Abu El-asrar A, Abouammoh M, Al-mezaine HS (2009) Tuberculous uveitis. Middle East Afr J Ophthalmol 16:188–201
41. Alvarez S, McCabe WR (1984) Extrapulmonary tuberculosis revisited: a review of experience at Boston City and other hospitals. Med 63:25–55
42. Schlaegel TF, Weber JC (1969) Double-blind therapeutic trial of isoniazid in 344 patients with uveitis. Br J Ophthalmol 53:425–427
43. Woods AC, Wood R, Senterfit LB (1958) Studies in experimental ocular tuberculosis. XVIII. The effect of cortisone combined with specific antibacterial therapy on experimental ocular tuberculosis in the immune-allergic rabbit. AMA Arch Ophthalmol 59:559–578
44. Hamade IH, Tabbara KF (2010) Complications of presumed ocular tuberculosis. Acta Ophthalmol 88:905–909
45. Gupta V, Gupta A, Rao NA (2007) Intraocular Tuberculosis—An Update. Surv Ophthalmol 52:561–587
46. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 140(3):509–516
47. Rowland K, Guthmann R, Jamieson B, Malloy D (2006) Clinical inquiries. How should we manage a patient with a positive PPD and prior BCG vaccination? J Fam Pract 55:718–720
48. Manousaridis K, Ong E, Stenton C, Gupta R, Browning AC, Pandit R (2013) Clinical presentation, treatment, and outcomes in presumed intraocular tuberculosis: experience from Newcastle upon Tyne, UK. Eye (Lond) 27:480–486. https://doi.org/10.1038/eye.2013.11
49. Llorenç V, González-Martin J, Keller J et al (2013) Indirect supportive evidence for diagnosis of tuberculosis-related uveitis: from the tuberculin skin test to the new interferon gamma release assays. Acta Ophthalmol 91:99–107. https://doi.org/10.1111/j.1755-3768.2012.02564.x
50. Mao Y, Peng XY, You QS, Wang H, Zhao M, Jonas JB (2014) Tuberculous uveitis in China. Acta Ophthalmol 92:393–397. https://doi.org/10.1111/aos.12351
51. Basu S, Monira S, Modi RR et al (2014) Degree, duration, and causes of visual impairment in eyes affected with ocular tuberculosis. J Ophthalmic Inflamm Infect 4:3. https://doi.org/10.1186/1869-5760-4-3
52. La Distia Nora R, Van Velthoven MEJ, Ten Dam-Van Loon NH et al (2014) Clinical manifestations of patients with intraocular inflammation and positive QuantiFERON-TB gold in-tube test in a country nonendemic for tuberculosis. Am J Ophthalmol 157:754–761
53. Khochtali S, Gargouri S, Abroug N et al (2015) The spectrum of presumed tubercular uveitis in Tunisia, North Africa. Int Ophthalmol 35:663–671
54. Gunasekeran DV, Gupta B, Cardoso J, Pavesio CE, Agrawal R (2017) Visual morbidity and ocular complications in

presumed intraocular tuberculosis: an analysis of 354 cases from a non-endemic population. Ocul Immunol Inflamm. https://doi.org/10.1080/09273948.2017.1296580
55. Gineys R, Bodaghi B, Carcelain G et al (2011) QuantiFERON-TB gold cut-off value: implications for the management of tuberculosis-related ocular inflammation. Am J Ophthalmol 152(433–440):e1
56. Gupta V, Arora S, Gupta A, Ram J, Bambery P, Sehgal S (1998) Management of presumed intraocular tuberculosis: possible role of the polymerase chain reaction. Acta Ophthalmol Scand 76:679–682
57. Bansal R, Gupta A, Gupta V, Dogra MR, Sharma A, Bambery P (2012) Tubercular serpiginous-like choroiditis presenting as multifocal serpiginoid choroiditis. Ophthalmology 119:2334–2342
58. El-Asrar AMA, Al-Kharashi SA (2002) Full panretinal photocoagulation and early vitrectomy improve prognosis of retinal vasculitis associated with tuberculoprotein hypersensitivity (Eales' disease). Br J Ophthalmol 86:1248–1251
59. Helm CJ, Holland GN (1993) Ocular tuberculosis. Surv Ophthalmol 38:229–256
60. Vasconcelos-Santos DV, Rao PK, Davies JB, Sohn EH, Rao NA (2010) Clinical features of tuberculous serpiginouslike choroiditis in contrast to classic serpiginous choroiditis. Arch Ophthalmol 128:853–858
61. Massaro D, Katz S, Sachs M (1964) Choroidal tubercles. a clue to hematogenous tuberculosis. Ann Intern Med 60:231–241
62. Cangemi FE, Friedman AH, Josephberg R (1980) Tuberculoma of the choroid. Ophthalmology 87:252–258
63. Mansour AM, Haymond R (1990) Choroidal tuberculomas without evidence of extraocular tuberculosis. Graefes Arch Clin Exp Ophthalmol 228:382–383
64. Alaraj AM, Al-Dhibi H, Al-Mezaine HS, Abu El-Asrar AM (2013) Solitary presumed choroidal tuberculomas masquerading as choroidal tumors. Saudi Med J 34:86–90
65. Lardenoye CWTA, van Kooij B, Rothova A (2006) Impact of Macular Edema on Visual Acuity in Uveitis. Ophthalmology 113:1446–1449
66. Babu K, Satish V, Prakash O, Subbakrishna DK, Murthy KR (2009) Role of the mantoux test and treatment with antitubercular therapy in a South Indian patient population of presumed intraocular tuberculosis. Ocul Immunol Inflamm 17:307–311
67. Ang M, Wong WL, Li X, Chee S-P (2013) Interferon γ release assay for the diagnosis of uveitis associated with tuberculosis: a Bayesian evaluation in the absence of a gold standard. Br J Ophthalmol 97:1062–1067
68. Bodaghi B, LeHoang P (2000) Ocular tuberculosis. Curr Opin Ophthalmol 11:443–448
69. Gupta V, Gupta A, Arora S, Bambery P, Dogra MR, Agarwal A (2003) Presumed tubercular serpiginouslike choroiditis: clinical presentations and management. Ophthalmology 110:1744–1749
70. Gupta A, Gupta V, Arora S, Dogra MR, Bambery P (2001) PCR-positive tubercular retinal vasculitis: clinical characteristics and management. Retina 21:435–444
71. Bansal R, Gupta A, Gupta V, Dogra MR, Bambery P, Arora SK (2008) Role of anti-tubercular therapy in uveitis with latent/manifest tuberculosis. Am J Ophthalmol 146(772–779):e2
72. Agarwal A, Handa S, Aggarwal K, Sharma M, Singh R, Sharma A, Agrawal R, Sharma K, Gupta V (2017) The role of dexamethasone implant in the management of tubercular uveitis. Ocul Immunol Inflamm. https://doi.org/10.1080/09273948.2017.1400074. [Epub ahead of print]
73. Jain L, Panda KG, Basu S (2017) Clinical outcomes of adjunctive sustained-release intravitreal dexamethasone implants in tuberculosis-associated multifocal serpigenoid choroiditis. Ocul Immunol Inflamm. https://doi.org/10.1080/09273948.2017.1383446. [Epub ahead of print]
74. Rao NA, Saraswathy S, Smith RE et al (2006) Tuberculous uveitis: distribution of Mycobacterium tuberculosis in the Retinal Pigment Epithelium. Arch Ophthalmol 124:1777