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ORIGINAL PAPER

The spectrum of presumed tubercular uveitis in Tunisia, North Africa

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Abstract The purpose of this study was to analyze the spectrum of presumed tubercular uveitis in Tunisia, North Africa. We retrospectively reviewed the clinical records of 38 patients (65 eyes) diagnosed with presumed tubercular uveitis at two referral centers in Tunisia, between January 2009 and December 2011. Mean age at presentation was 42.7 years. Twenty-four patients were women (63.2 %) and 14 (36.8 %) were men. Twenty-three eyes (35.4 %) had posterior uveitis, 21 eyes (32.3 %) had intermediate uveitis, 13 eyes (20 %) had panuveitis, and 8 eyes (12.3 %) had anterior uveitis. Ocular findings included vitritis in 67.7 % of eyes, posterior synechiae in 47.7 %, multifocal non-serpiginoid choroiditis in 23.1 %, multifocal serpiginoid choroiditis in 21.5 %, periphlebitis in 21.5 %, and mutton-fat keratic precipitates in 20 %. Anti-tubercular treatment was prescribed in 33 patients (86.8 %) and was associated with systemic corticosteroids in 20 patients (52.6 %) and periocular injections of corticosteroids in four patients (10.5 %). After a mean follow-up of 14.2 months (range, 10–58), inflammation was controlled, with a significant improvement in visual acuity (VA) ($p = 0.028$). However, recurrences developed in two patients (5.3 %). Final VA was better than 20/40 in 27 eyes (41.5 %) and less than 20/200 in five eyes (7.7 %). In Tunisia, all anatomic types are possible in tuberculosis-associated uveitis, but posterior and intermediate uveitis are more frequent. Vitritis, posterior synechiae, multifocal serpiginoid or non-serpiginoid choroiditis, and periphlebitis are the most common manifestations.

Keywords Uveitis · Posterior uveitis · Retinal vasculitis · Tuberculosis · Tuberculin skin test · Interferon-gamma release tests

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Introduction

Tuberculosis is an infection caused by Mycobacterium tuberculosis (MT), mainly affecting lungs. Intraocular tuberculosis usually occurs in the absence of evident active systemic disease. Its diagnosis is often challenging because of the absence of confirmatory investigations. Presumption of tubercular uveitis is made on the basis of suggestive ocular features, evidence of latent or manifest tuberculosis, exclusion of other specific causes of uveitis, and positive response to anti-tubercular treatment (ATT) [1–4]. Misdiagnosis and

treatment with corticosteroids in the absence of ATT could be both sight and life-threatening [5, 6].

Data from previous studies in different geographic areas showed a large discrepancy in the proportion of tubercular uveitis which was found to range from 0.5 to 28.2 % of all causes of uveitis [7–10]. In Tunisia which is a tuberculosis endemic country, a previous study found that tubercular uveitis accounted for 1.1 % of all uveitis cases [11]. With advances in clinical diagnosis and laboratory testing, tuberculosis is increasingly being found to be associated with uveitis worldwide. Numerous studies on the pattern of tubercular uveitis in various geographic regions have been published, showing similarities and distinct differences in clinical characteristics, treatment modalities, and visual outcome [2, 3, 12–15]. However, data on the pattern of ocular tuberculosis in North Africa are lacking. The aim of this study was to characterize and analyze the spectrum of tubercular uveitis in two major referral centers in Tunisia.

Materials and methods

The clinical records of 38 patients (65 eyes) diagnosed with presumed tubercular uveitis at two referral centers in Tunisia, between January 2009 and December 2011, were retrospectively reviewed.

Tuberculosis was presumed to be the cause of uveitis when the following criteria were fulfilled:

1. Ocular findings consistent with intraocular tuberculosis
2. Exclusion of other possible infectious and noninfectious causes of uveitis
3. Strongly positive tuberculin skin-test (TST) result ($\geq$15 mm of induration/necrosis at 72 h) and/or positive QuantiFERON test and/or concomitant active extraocular tuberculosis
4. Good response to ATT when it was prescribed.

At presentation, all patients underwent a complete ophthalmic examination including measurement of best-corrected visual acuity (VA), tonometry, slit-lamp examination, and dilated fundus examination. Laser flare photometry was performed in 18 patients (47.4 %), fluorescein angiography in 34 patients (89.5 %), indocyanine green angiography in 14 patients (36.8 %), optical coherence tomography (OCT) in 34 patients (89.5 %), and ocular ultrasonography in four patients (10.5 %).

Table 1 Anatomic types of presumed tubercular uveitis

Anatomic type	Patients: *n* (percent)	Eyes: *n* (percent)
Anterior uveitis	5 (13.1)	8 (12.3)
Intermediate uveitis	11 (28.9)	21 (32.3)
Posterior uveitis	14 (36.8)	23 (35.4)
Panuveitis	8 (21.1)	13 (20)

Initial uveitis workup consisted of complete blood count, erythrocyte sedimentation rate, chest X-ray, TST (10 tuberculin units), and syphilis serology. QuantiFERON, only available since 2010, and search for acid-fast bacilli in sputum and urine were performed when the presentation or course of disease was suggestive of tuberculosis. When QuantiFERON was ordered after a TST was found positive, an interval of at least 1 month between the two tests was respected. All the patients were referred to the department of internal medicine for general examination.

The standard ATT protocol included isoniazid 300 mg/day, rifampin 600 mg/day, ethambutol 15 mg/kg/day, and pyrazinamide 25–30 mg/kg/day for the first 2 months. Thereafter, rifampin and isoniazid were administered for another 6–10 months. Systemic corticosteroids were given in cases of posterior uveitis, panuveitis, or intermediate uveitis associated with significant visual loss or macular edema. Periocular corticosteroid injection was used when systemic corticosteroid therapy was contraindicated and in patients with unilateral involvement. Topical steroids and mydriatics were used to control anterior chamber inflammation.

Student's *t* test was used to compare two proportions. One-way analysis of variance (ANOVA) was used to compare means for more than two groups. A *p* value less than 0.05 indicated statistical significance.

Results

Mean age at presentation was 42.7 years (range, 23–66). Twenty-four patients were female (63.2 %) and 14 (36.8 %) were male. At presentation, twenty-seven patients (71.1 %) had bilateral involvement of whom three had inactive uveitis in one eye. Eleven patients (28.9 %) had unilateral involvement. The

Table 2 Anterior and posterior segment findings at presentation

Ocular findings	N = 65	Percent
Keratic precipitates	27	41.5
Iris nodules	8	12.3
Vitritis	44	67.7
Snowballs	4	6.2
Multifocal non-serpiginoid choroiditis	15	23.5
Multifocal serpiginoid choroiditis	14	21.5
Periphlebitis	14	21.5

anatomic types of uveitis are shown in Table 1. The most frequent one was posterior uveitis (23 eyes, 35.4 %) followed by intermediate uveitis found in 21 eyes (32.3 %, of which 12 cases were associated with a significant inflammation of the anterior chamber), panuveitis in 13 eyes (20 %), and anterior uveitis in 8 eyes (12.3 %).

The ocular findings in eyes with presumed tubercular uveitis are described in Table 2. Mutton-fat keratic precipitates were noted in 13 eyes (20 %). The mean anterior chamber flare was 64.9 ph/ms (range, 2.6–771). Mean intraocular pressure was 13.66 mmHg (range, 9–25). A vitritis of variable severity was found in 44 eyes (67.7 %). Multifocal non-serpiginoid choroiditis was observed in 15 eyes (23.1 %), with a number of lesions ranging from 3 to more than 20, and a size varying from less than 1/8 optic disk diameter to one disk diameter. Choroidal lesions involved the peripheral retina in 10 cases (66.7 %) and both the peripheral retina and posterior pole in 5 eyes (33.3 %). The association of active and inactive lesions was seen in 8 eyes (53.3 %). Multifocal serpiginoid choroiditis was found in 14 eyes (21.5 %) (Figs. 1, 2). There were choroidal lesions noncontiguous to optic disk in 12 cases (85.7 %). The posterior pole and the periphery were both involved in 12 eyes (85.7 %). Periphlebitis was noted on fundus examination in 7 eyes (10.7 %) (Fig. 3). Fluorescein angiography disclosed subclinical periphlebitis in 7 eyes (10.7 %) and capillaritis in 13 eyes (20 %). Periphlebitis was segmental in type in 3 of 14 cases

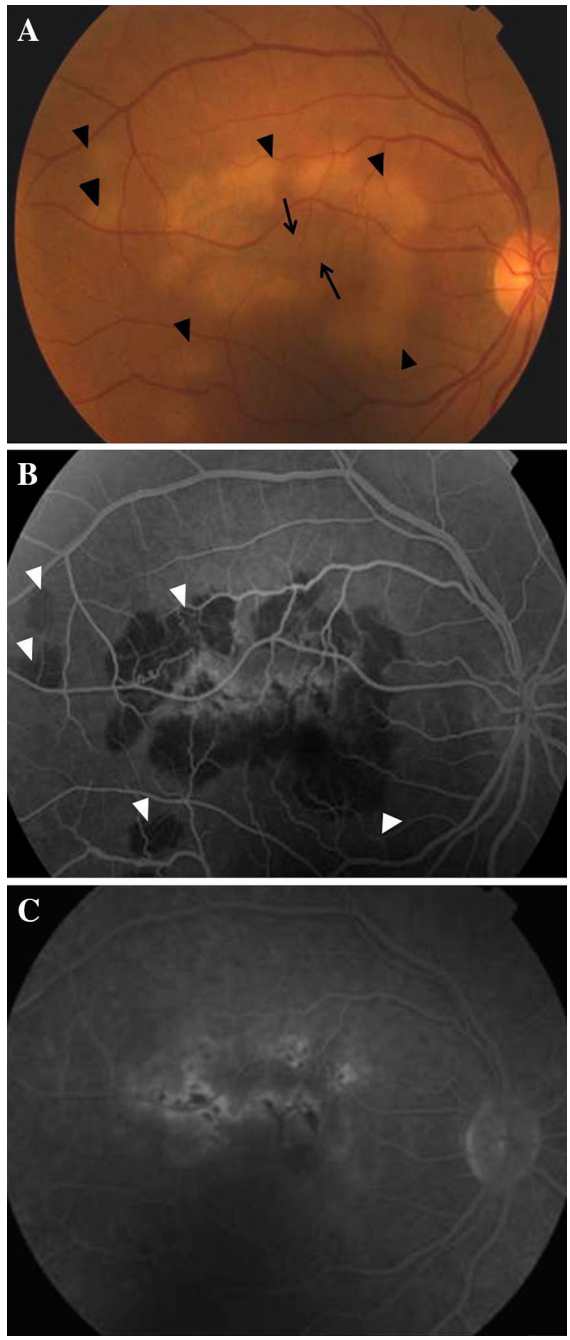

Fig. 1 Fundus photograph of the right eye of a patient with presumed ocular tuberculosis shows multifocal serpiginoid choroiditis with active (*arrowheads*) and inactive (*arrows*) lesions involving the posterior pole (**A**), Fluorescein angiography shows early *hypofluorescence* (**B**) and late staining of the active choroidal lesions (**C**)

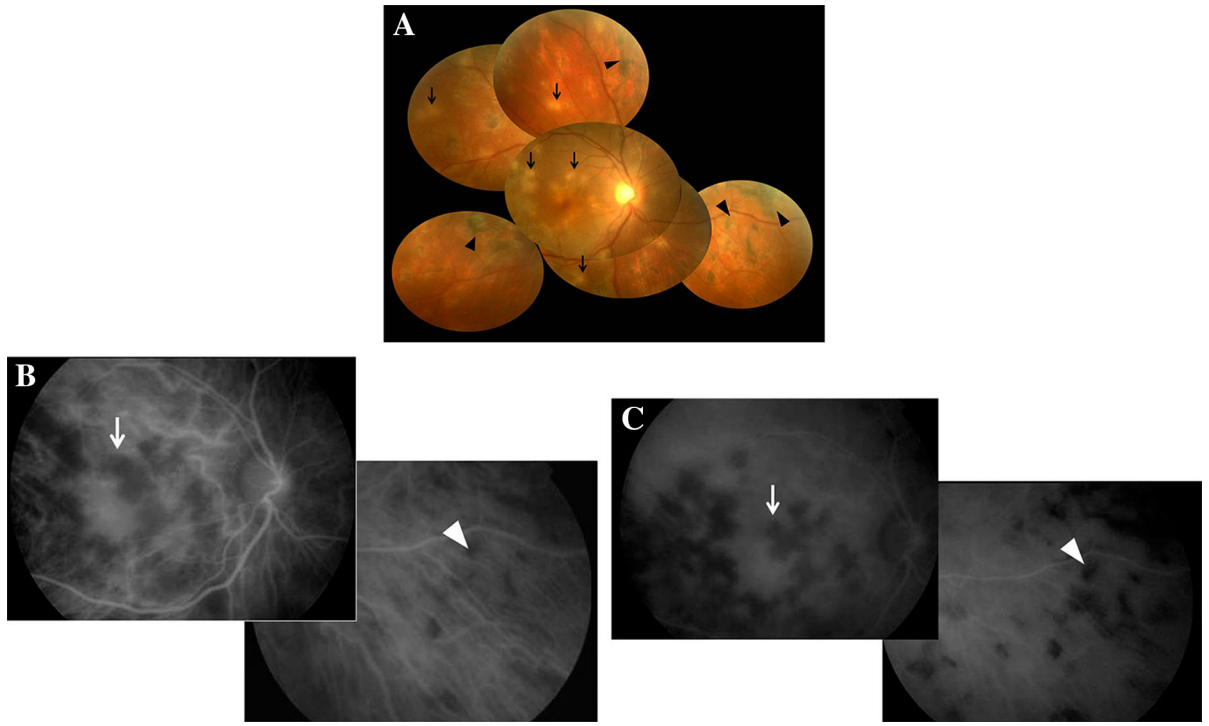

Fig. 2 Composite fundus photograph of the right eye of a patient with presumed ocular tuberculosis shows active (*arrows*) and healed (*arrowheads*) lesions of multifocal serpiginoid choroiditis (**A**), Indocyanine green angiogram shows *hypofluorescent areas* (**B** early phase, **C** late phase)

(21.4 %) and diffuse in 11 of 14 eyes (78.6 %). It was associated with multifocal choroiditis in 6 of 14 cases (42.8 %) (non-serpiginoid in 5 eyes and serpiginoid in one eye). Inactive foci of choroiditis underlying retinal vessels were found in 4 eyes (26.7 % of eyes with multifocal non-serpiginoid choroiditis and 6.1 % of all cases) (Fig. 4).

TST was strongly positive in 26 patients (68.6 %). An induration between 10 and 15 mm was noted in 7 patients (18.4 %) and an induration of less than 10 mm in 5 patients (13.2 %). QuantiFERON performed in 22 patients (57.9 %) was positive in 20 patients (90.9 %). The mean QuantiFERON value was 7.7 UI/ml (standard deviation 4.98).

Chest X-ray showed sequelae of pulmonary tuberculosis in 2 patients and mediastinal enlarged lymph node in one patient.

Three patients had a history of extraocular tuberculosis (7.9 %), the localization of which was nasal, pulmonary, and urogenital in one patient, each. Uveitis occurred 1–26 months after completion of ATT. There were two cases of active biopsy-proven extraocular tuberculosis infection (cutaneous lesion and tuberculous mediastinal lymphadenitis). Urine test allowed detection of acid-fast bacilli mycobacteria in one additional patient.

Eight patients had received systemic corticosteroids prior to referral before the diagnosis of tubercular uveitis was made. In 3 patients (5 eyes), uveitis worsened with development of new choroidal lesions. In the remaining 5 patients, ocular inflammation initially responded to corticosteroids but recurred later.

After diagnosis of presumed tubercular uveitis, ATT was prescribed in 33 patients (86.8 %). Four patients with mild anterior uveitis and one patient with intermediate uveitis and good VA were not given ATT. The mean duration of ATT was 6.8 months (range, 6–12). Transitory paradoxal progression of choroidal lesions was noted in 2 patients (3 eyes) with multifocal serpiginoid choroiditis after initiation of ATT (4.6 %).

In addition to ATT, 20 patients (52.6 %) received oral prednisone initiated with a dose of 1 mg/kg/day and then progressively tapered. The mean duration of

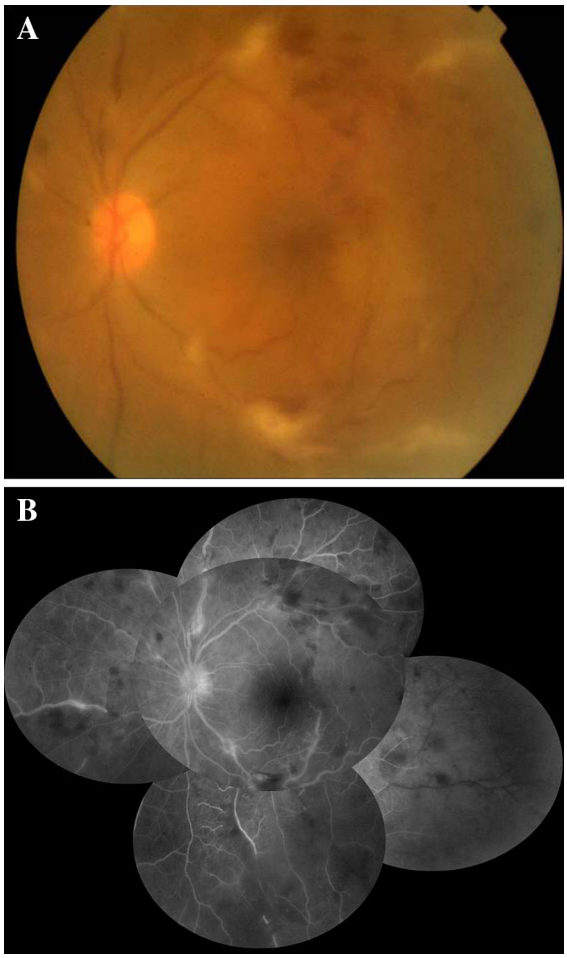

Fig. 3 Fundus photograph of the left eye of a patient with presumed ocular tuberculosis shows vitritis and perivascular infiltrates with superficial hemorrhages (**A**); composite fluorescein angiogram reveals segmental venous staining, blocking effect of retinal hemorrhages, peripheral retinal ischemia, and optic disk *hyperfluorescence* (**B**)

systemic corticosteroid therapy was 3.2 months (range, 1–9). Four patients (10.5 %) received a periocular injection of 40 mg of triamcinolone acetonide. The interval between initiation of ATT and systemic corticosteroids or periocular injections varied between 0 and 15 days.

Sectoral laser photocoagulation of peripheral extensive areas of retinal capillary non-perfusion was performed in 8 eyes (12.3 %).

Mean follow-up was 14.2 months (range, 10–58). Complications at presentation or during follow-up are summarized in Table 3. Posterior synechiae were noted in 31 eyes (47.7 %) (Fig. 5), papillitis in 17 eyes (26.2 %), macular edema in 13 eyes (20 %), and disk

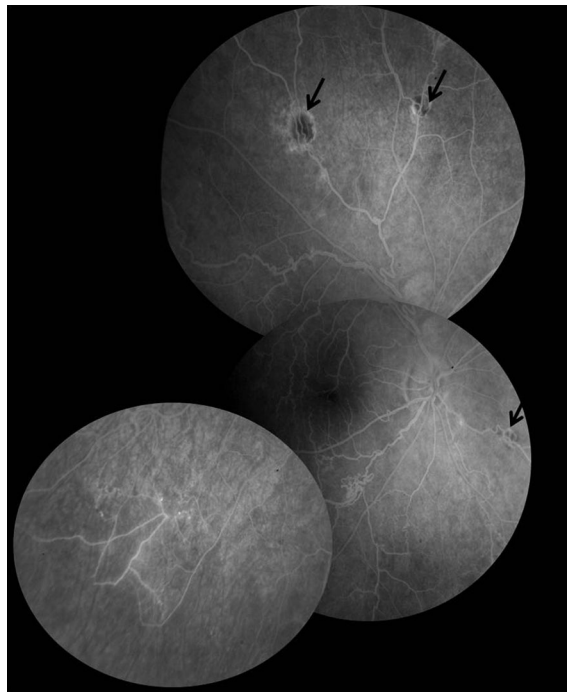

Fig. 4 Early-phase composite fluorescein angiogram of the right eye of a patient with presumed ocular tuberculosis shows inactive choroidal lesions (*arrows*) underlying retinal vessels, venous collaterals, and peripheral ischemic areas consistent with occlusive periphlebitis

Table 3 Ocular complications at presentation and during follow-up

Ocular complications	N = 65	Percent
Posterior synechiae	31	47.7
Papillitis	17	26.2
Macular edema	13	20
Serous retinal detachment	7	7.7
Epiretinal membrane	2	3.1
Peripheral retinal ischemia	8	12.3
Retinal neovascularization	2	3.1
Optic disk neovascularization	5	7.6
Tractional detachment	2	3.1

or preretinal neovascularization in seven eyes (10.7 %). Treatment resulted in resolution of inflammation and VA improvement. In fact, a statistically significative difference between LogMAR initial VA (0.63 with a standard deviation of 0.61) and LogMAR final VA (0.51 with a standard deviation of 0.63) was found in our patients ($p = 0.028$).

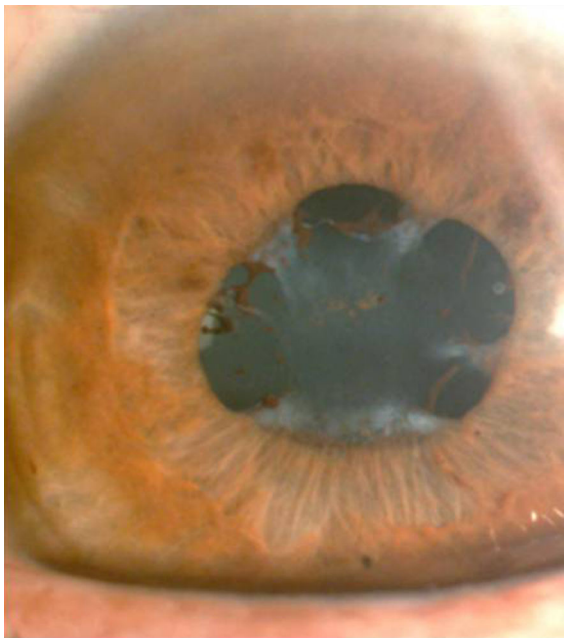

Fig. 5 Slit-lamp photograph shows broad-based posterior synechiae in a patient with chronic tubercular anterior uveitis

Recurrences occurred in two patients (four eyes) with anterior uveitis in one patient (two eyes) and intermediate uveitis in one patient (two eyes), 6 months and 1 year after the discontinuation of ATT, respectively. Only topical corticosteroids were given in these two patients.

Final VA was 20/40 or more in 27 eyes (41.5 %). It was <20/200 in five eyes (7.7 %) of five patients. Causes of visual impairment in these cases were macular scar in two eyes, disk neovascularization with tractional detachment in two eyes, and phtisis bulbi in one eye.

Discussion

Our study is the first to characterize and analyze the pattern of tubercular uveitis in referral centers from North Africa. Mean age of our patients is similar to the age of Saudi patients with tubercular uveitis [3] but is slightly higher than age of patients from other endemic areas, especially India [2]. In contrast to other reports, which found no sex difference or a male predominance [2, 3, 12], our patients were predominantly female (63.2 %).

Results of our study show that posterior uveitis is the most common anatomic type of tubercular uveitis, which is consistent with data from other geographic areas [2, 12, 13, 15]. However, the proportion of intermediate uveitis in our patients was noticeably high in comparison with other case series [2, 3, 12, 13, 15]. On the other hand, the low rate of isolated anterior uveitis in our patients (13.1 %) is similar to that reported in studies from United Kingdom but lower than that found in studies from India (up to 36 %) and the Netherlands (25 %) [1, 2, 15, 16].

Findings from our study, consistent with previous data, show that an array of clinical features frequently occurs in patients with tubercular uveitis including posterior synechiae, mutton-fat keratic precipitates, vitritis, multifocal non-serpiginoid or serpiginoid choroiditis, periphlebitis, and macular edema [1–4, 12–14]. Multifocal serpiginoid choroiditis, also called serpiginous-like choroiditis, was found to be a marker for tuberculosis in both endemic and non-endemic areas [1, 2, 14, 17–19]. It is characterized by irregular serpiginoid lesions of choroiditis with centrifugal extension, usually sparing the juxtapapillary area [17, 18]. Periphlebitis is a common expression of ocular tuberculosis. It is typically associated with mild vitritis and may result in peripheral retinal ischemia. Tuberculosis has been implicated in a subset of patients with occlusive retinal periphlebitis so-called Eales disease [20]. Foci of choroiditis under retinal vessels have been described as a typical feature of tubercular uveitis. This finding was noted in 6.1 % of our patients [1–3, 21]. Other uveitis manifestations are less specific for tuberculosis. Broad-based posterior synechiae have been reported to be a predictive sign of ocular tuberculosis [2], but we were unable to assess accurately the rate of this feature in our patients.

In addition to suggestive ocular features, evidence of exposure to MT further supports the diagnosis of tubercular uveitis. Patients may rarely present with concurrent systemic tuberculous disease [1, 2, 4, 12]. In our series, only three patients had a history of treated extraocular tuberculosis and two had active concomitant systemic tuberculosis. TST, available worldwide, is often helpful [3, 12, 21] but may be difficult to interpret. In fact, it is influenced by previous BCG vaccination, contact with other mycobacteria (risk of false positive test), and immunosuppression (risk of false negative test) [22]. TST is also usually negative in patients with disseminated tuberculosis [2]. Although TST has been performed in all our patients, it was strongly positive in only 26

patients (68.6 %), when a cut-off of 15 mm was considered. Interferon gamma Release Assays (IGRA) have shown better sensitivity and specificity than TST in detecting active or latent tuberculosis [23–25]. There is a cross-reactivity of these tests with only few other mycobacteria (risk of false positive test) [26]. On the other hand, an age of more than 55 years may be associated with a negative QuantiFERON result or an "equivocal" T-SPOT result (risk of false negative test) [27, 28]. QuantiFERON test was performed in 22 of our patients, with a positive result in 90.9 % of them.

Demonstration of acid-fast bacilli, culture of MT, or histopathologic evidence in ocular tissus or fluids are rarely possible. Specific conventional polymerase chain reaction (PCR) on aqueous humor may be helpful, but this test is found to have variable sensitivity rates in the literature [1, 2]. Multi-target PCR may yield higher positivity rates, with nevertheless the possibility of false positive results [29]. PCR technique was not available in our centers.

The majority of our patients received both ATT (86.8 %) and corticosteroids (63.1 %), either by systemic or periocular route, with a good overall outcome. These results are consistent with those of other series [3, 4, 12, 13, 30, 31]. The use of systemic corticosteroids alone may be associated with development of new ocular lesions or frequent recurrences [6, 14], and may also trigger systemic tuberculosis [5]. Therefore, ATT has a definite role in the treatment of tubercular uveitis, even when tuberculosis is latent. Recurrences of uveitis are significantly reduced when the patients receive ATT, as compared to those who do not [12]. ATT may help eradicating the load of MT in the eye or in other organs. Killing the sequestered bacteria probably mitigates immunologic hypersensitivity reactions involved in the pathogenesis of uveitis [12, 31, 32]. A duration of ATT of at least 9 months seems to give better results in terms of risk of recurrences. The need for a prolonged therapy may be explained by the slow multiplication of MT in the eye and the difficulty for drugs to reach them through blood-ocular barriers [31]. The ATT duration in our patients ranged between 6 and 12 months. Recurrences occurred in only two patients (5.2 %), after a mean follow-up of 14.2 months.

Prescription of ATT in mild anterior uveitis of presumed tubercular origin remains controversial because of the possible significant side effects of this treatment as compared to the potential visual benefit [12, 33]. We opted for topical steroid therapy alone in four patients with mild anterior uveitis. We did not note recurrences in these cases, but the follow-up was relatively short. Development of active uveitis in patients who already completed ATT regimen either for extraocular or ocular tuberculosis is a therapeutic challenge as poor compliance to ATT or drug resistance is difficult to rule out [4, 12, 33]. Three of our patients with a history of treated extraocular tuberculosis presented with uveitis 1–26 months after discontinuation of ATT. A second course of ATT was prescribed, after exclusion of other causes of uveitis. On the other hand, recurrences of ocular inflammation developed in two of our patients. They were mild and were treated with topical steroids alone.

Continuous progression of ocular inflammation after starting ATT has been described for different anatomic types of tubercular uveitis [34, 35], but especially in multifocal serpiginoid choroiditis [36], as was noted in three eyes (4.6 %) of two patients in the present series. This paradoxical worsening may be explained by the immune reaction to the release of bacterial antigens following ATT initiation and typically responds to increased corticosteroids or other immunosuppressants with continuation of ATT [36, 37].

In summary, tubercular uveitis has a predilection for young to middle-aged females in Tunisia. It may manifest with any anatomic type of uveitis but predominantly posterior and intermediate uveitis. The spectrum of ocular tuberculosis is wide, but the most common findings include vitritis, posterior synechiae, multifocal non-serpiginoid or serpiginoid choroiditis, and periphlebitis. IGRA results should be interpreted together with TST. The majority of our patients received a combination of ATT and corticosteroids which resulted in proper control of inflammation and significant improvement of VA. Visual impairment (VA $<$ 20/200) was rare at the end of follow-up. Our case series, although retrospective with a relatively limited number of patients, provides for the first time, data on ocular tuberculosis from North Africa. Intraocular tuberculosis remains a difficult diagnostic and therapeutic challenge. Further studies are required to better clarify treatment indications and management of recurrences.

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