Clinical features of infectious uveitis in a Tunisian population

Manifestations cliniques des uvéites infectieuses dans une population tunisienne

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Résumé

Introduction : Les uvéites infectieuses (UI), une des principales causes d'inflammation oculaire en Tunisie, ont diverses étiologies et présentations cliniques.

But : Rapporter les causes et les caractéristiques cliniques des UI dans une population tunisienne.

Méthodes : Etude observationnelle rétrospective incluant les patients atteints d'UI référés à notre service entre Février 2019 et Janvier 2022. Un examen ophtalmologique et des examens complémentaires appropriés ont été effectués.

Résultats : Quatre-vingts yeux de 63 patients ont été inclus (37 femmes et 26 hommes). L'âge moyen des patients était de 45 ans. L'UI était unilatérale dans 43 cas, bilatérale dans 17, et unilatérale alternante dans trois cas. La panuvéite était prévalente (35 % des cas), suivie de l'uvéite postérieure (31 %), antérieure (18 yeux), intermédiaire (6 yeux) puis antérieure et intermédiaire (3 yeux). Les uvéites non granulomateuses (55%) prédominaient sur les uvéites granulomateuses (45%). Les étiologies étaient dominées par les bactéries (29 patients ; 46%), principalement la tuberculose (23 patients), suivies par les virus (19 patients), notamment Herpès simplex. Un cas d'infection fongique et 14 cas d'infections parasitaires, particulièrement la toxoplasmose, ont été trouvés. Le délai diagnostique initial moyen était de 16 mois. Les complications étaient essentiellement les vasculites occlusives (19 yeux), la cataracte (17 yeux), l'œdème maculaire cystoïde (17 yeux) et l'œdème papillaire (15 yeux).

Conclusion : Cette étude a présenté les caractéristiques cliniques et les étiologies des UI dans notre service. La tuberculose reste une des étiologies les plus fréquentes en Tunisie. Une étude nationale multicentrique permettrait une évaluation plus précise.

Mots-clés : uvéite infectieuse, tuberculose, herpes viridae, toxoplasmose, panuvéite

Abstract

Background: Infectious uveitis (IU), one of the main causes of ocular inflammation in Tunisia, has various etiologies and clinical presentations.

Aim: To report the causes and clinical features of IU in a Tunisian population.

Methods: Patients with IU referred to our department from February 2019 to January 2022 were included in a retrospective observational study. Ophthalmic examination and appropriate ancillary tests were performed.

Results: Eighty eyes of 63 patients were included (37 female and 26 male). The mean age was 45 years. IU was unilateral in 43 cases, bilateral in 17, and unilateral alternating in three cases. Panuveitis was the most common anatomic location (35% of cases) followed by posterior (31%), anterior (18 eyes), intermediate (6 eyes) and anterior and intermediate uveitis (3 eyes). Non granulomatous uveitis (55%) occurred more frequently than granulomatous uveitis (45%). Etiologies were dominated by bacterial infections (29 patients; 46%), mainly tuberculosis (23 patients), followed by viruses (19 patients), mainly Herpes simplex virus. Fungal infection was found in one patient, while parasites accounted for 14 cases, mostly toxoplasmosis. Mean initial diagnostic delay was 16 months. The most common complications included occlusive retinal vasculitis (19 eyes), cataract (17 eyes), cystoid macular edema (17 eyes) and papilledema (15 eyes).

Conclusion: This study highlighted the causes and clinical features of IU in our setting. Tuberculosis remains one of its most frequent etiologies in Tunisia. However, a larger multicenter national study would allow a more precise evaluation.

Keywords: infectious uveitis, tuberculosis, herpesviruses, toxoplasmosis, panuveitis

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INTRODUCTION

Infectious uveitis (IU) is due to several causes. They include bacterial, viral, parasitic and fungal etiologies. The epidemiology varies significantly according to the cause and geographic location. IU alone accounts for 30 to 50% of all uveitis in developing countries (1), whereas it represents 20% of all uveitis in the developed world (2). Numerous studies about IU in various geographic regions have been published, showing similarities but also differences in epidemiologic profiles and etiologies (3-5).

In Tunisia, a previous study describing the pattern of uveitis found that IU represent 29% of all uveitis, with the most common etiologies being herpes viruses and toxoplasmosis (6). Other studies about IU have focused on a specific infectious etiology (7-10).

Accurate diagnosis and appropriate management are the key to preserve patients' vision. Any delay could lead to the worsening of the visual prognosis. It is important to distinguish IU from non-infectious uveitis, because the treatment of the latter, based on corticosteroids and immunosuppressants could be detrimental in IU.

The purpose of our study was to analyze causes of IU and their clinical features.

METHODS

Study design and settings

Case series study of all patients with IU referred to the ophthalmology department of Habib Thameur University Hospital, Tunis, between February 2019 and January 2022. Sixty-three consecutive patients were included

Clinical examination and laboratory analyses

All patients had a comprehensive ocular and systemic medical history, and a complete ophthalmic examination including: best-corrected Snellen visual acuity, slit-lamp examination, applanation tonometry and dilated funduscopy.

The anatomic location (anterior, intermediate, posterior, panuveitis) and the course of the disease (acute, chronic, recurrent) were determined based on the Standardization of Uveitis Nomenclature (SUN) Working Group criteria (11). Patients were classified as having nongranulomatous uveitis if they exhibited none or small keratic precipitates with absence of iris nodules and/or choroidal granulomas, and granulomatous uveitis if large mutton-fat keratic precipitates, iris nodules and/or optic disc and choroidal granulomas were seen. The unilateral, bilateral, or unilateral alternating character of the IU was also recorded.

The etiological diagnosis was based on a combination of clinical and laboratory findings. Based on the anatomic classification, all patients underwent a standard diagnostic protocol including: complete blood count, erythrocyte sedimentation rate, C-reactive protein test, treponema pallidum hemagglutination testing (syphilis), Human Immunodeficiency Virus (HIV) serology, Mantoux tuberculin test (MTT), interferon gamma release test (QuantiFERON-TB) when available, and chest imaging (X-ray and/or Computed tomography: CT-scan). Patients with diagnostic leads provided by the history and general or ophthalmic examination, underwent further ancillary testing including serologies for Rickettsia conorii, Coxiella burnetti, Bartonella henselae, toxoplasmosis, toxocariasis and measles. Conjunctival biopsy with histopathological examination was performed in the presence of conjunctival nodules. In doubtful cases, anterior chamber paracentesis (ACP) with fluid sampling for microscopy, cytology, culture (bacteria and fungi), and qualitative detection of pathogen DNA (herpesviruses and toxoplasmosis) by polymerase chain reaction (PCR) were performed.

B-scan ocular ultrasound was performed when funduscopy was impossible. The diagnosis of cystoid macular edema (CME) was based on clinical examination and optical coherence tomography. Fluorescein angiography was undertaken in patients with suspicion of posterior segment involvement.

Data analysis

Basic descriptive statistics (mean, median, confidence interval [CI] and standard deviation [SD]) were computed for all variables using SPSS software (version 25.0). Correlation between the anatomic location of IU and diagnostic delay was studied. Results were considered significant when the p value was ≤ 0.05.

RESULTS

Eighty eyes of 63 patients were included. The clinical and demographic characteristics are shown in Table 1. The mean age at onset was 45 years (range 12–68 years). In all, 26 patients (41%) were between the ages of 50 and 70 years. There was a slight female predominance with 37 female and 26 male patients (female to male ratio was 1.4 :1).

IU was unilateral in 43 patients (68%), bilateral in 17 patients and unilateral alternating in three patients. Bilateral disease was seen in 13 of 23 patients with tuberculosis, two of two patients with rickettsial multifocal retinitis, one patient with syphilis and one patient with coxiella burnetti

multifocal retinitis. Unilateral disease was seen in all patients with herpetic (13 eyes) or toxoplasma (10 eyes) IU. Unilateral alternating disease was found in 2 of 23 patients with tuberculosis and one patient with measles.

IU were mostly acute (35 patients; 55%), 15 patients had recurrent IU and 13 patients had chronic IU. Nongranulomatous uveitis (55%) occurred more frequently than granulomatous uveitis (45%).

Panuveitis was the most common anatomic location (28 eyes; 35%). Twenty-five eyes (31%) were diagnosed with posterior uveitis, 18 eyes with anterior uveitis, 6 eyes with intermediate uveitis and 3 eyes with anterior and intermediate uveitis.

Etiologies are shown in Table 2. The most common cause, regardless of the anatomic location, was bacterial infection (29 patients; 46%), followed by viral (19 patients), parasitic (14 patients) and fungal (1 patient) infections.

A mean diagnostic delay of 16 months (range 2- 36 months) was noted. Ocular tuberculosis (OT) had the longest delay, with six patients having more than 2 years of delay.

Among bacterial IU (46 eyes; 57%), tuberculosis was the leading cause. It accounted for 78% of bacterial uveitis (36 eyes of 23 patients) with a female predominance (14 female and 9 male patients) and a mean age at presentation of 44 years. Panuveitis was the most common form in OT (15/36 eyes), followed by posterior uveitis (8/36 eyes) (Figure 1).

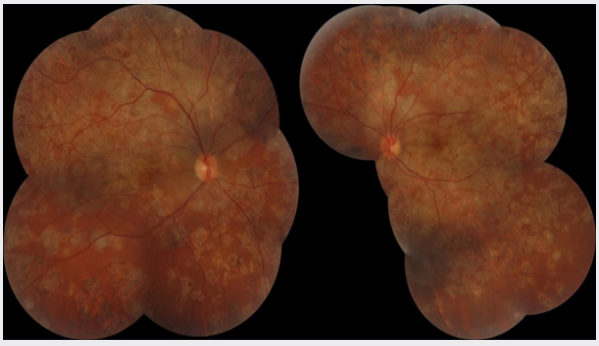

Figure 1. Color fundus photography showing bilateral serpiginous-like choroidopathy in patient with presumed ocular tuberculosis with a positive QuantiFERON-TB test

The diagnosis of OT was based on clinical and paraclinical arguments. Typical clinical features included: granulomatous anterior uveitis (21 eyes), intermediate uveitis with snowballs (10 eyes), multifocal choroiditis (7 eyes), and serpiginous-like choroidopathy (1 eye). Paraclinical tests comprised positive MTT (21/23 patients) and positive QuantiFERON-TB (10/10 patients). Histopathological examination of a conjunctival nodule made the diagnosis in one patient, by showing an epithelioid cell granuloma with caseating necrosis. Chest imaging showed some signs suggestive of tuberculosis: multiple pulmonary nodules in 5 cases, mediastinal lymph nodes' enlargement in 1 case, parenchymal and pleural calcifications in 1 case each.

Rickettsiosis was the second most frequent bacterial infection (four eyes of two patients), followed by coxiella burnetti, syphilis (two eyes of one patient each) and cat scratch disease (two eyes of two patients). All of these etiologies were confirmed by positive serologies.

In IU of parasitic origin (14 eyes), toxoplasmosis was the most prevalent (10 eyes) followed by toxocariasis (four eyes). Both toxoplasmosis and toxocariasis occurred more in female patients, with a mean age of 33 and 17 years respectively. The diagnosis of toxoplasmosis was clinical in eight patients and supported by a positive serology and a positive aqueous humor (AH) PCR for toxoplasma gondii in one patient each. The diagnosis of toxocariasis was based on clinical and anamnestic criteria in three patients, and supported by a positive serology in one patient. The diagnosis of unilateral fungal IU was confirmed by a positive AH culture for candida albicans, in one patient.

In the viral uveitis group (19 patients), Herpes simplex virus (HSV) was the most common virus (10 eyes), followed by Varicella zoster virus (VZV) (5 eyes) and Cytomegalovirus (CMV) (2 eyes). For HSV, the diagnosis was clinical in most patients, and based on a positive AH PCR for HSV in four patients. For CMV, the diagnosis was clinical in both patients and supported by a positive AH PCR for CMV in one of them.

Other diagnoses included anterior uveitis secondary to measles and HIV retinal vasculitis (one patient each), both confirmed by positive serologies.

We identified two types of VZV infection. The first type was an infection with exclusive ocular involvement (unilateral granulomatous panuveitis). The diagnosis was confirmed by the presence of VZV DNA in AH (three patients). The second type associated ocular involvement (unilateral granulomatous anterior uveitis) with ipsilateral herpes zoster ophthalmicus, so the diagnosis was clinical (two patients).

The most common etiologies of anterior uveitis were HSV (10 of 18 eyes) and tuberculosis (5 of 18 eyes). Other anterior uveitis included one case of measles and two cases of VZV. Fourteen of 25 posterior uveitis' cases were due to bacterial infection

including 10 eyes with tuberculosis and two eyes each with coxiella burnetti and bartonella henselae infections (Figure 2). Other posterior uveitis included toxoplasmosis (6 of 25 eyes), toxocariasis (2 of 25 eyes), HIV retinal vasculitis (1 of 25 eyes) and CMV necrotizing retinitis (2 of 25 eyes). Of the two CMV retinitis, one patient was undergoing immunosuppressive treatment with mycophenolate mofetil for a dermatopolymyositis and the second one was HIV positive. The two patients were diagnosed with an indolent and a fulminant form of necrotizing retinitis respectively. The most common etiology of panuveitis was bacterial infection (19 of 28 eyes) comprising 13 eyes with tuberculosis, 4 eyes with rickettsiosis and 2 eyes with syphilis. Other panuveitis included toxoplasmosis (4 of 28 eyes), toxocariasis (2 of 28 eyes) and VZV (3 of 28 eyes). Cases with anterior and intermediate IU (three eyes) were all due to tuberculosis.

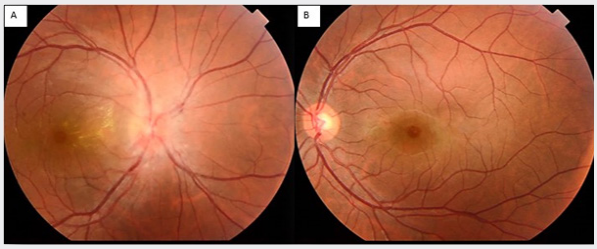

Figure 2. A: Color fundus photograph of the right eye showing papilledema with macular exudates corresponding to a neuroretinitis in a Bartonella henselae infection, B: Left eye normal fundus photography.

Eleven patients had an ACP. Polymerase chain reaction yielded an etiologic diagnosis in nine cases: four tested positive for HSV, three for VZV, one for CMV and one for toxoplasmosis. The culture of AH sampling confirmed the presence of Candida albicans in one patient.

The most common complications encountered in our series, were occlusive retinal vasculitis predominantly vein occlusions (19 eyes) (Figures 3,4), cataract (17 eyes), CME (17 eyes) and papilledema (15 eyes). Other less frequent complications comprised retinal detachment (two eyes) and choroidal neovascularization (one eye).

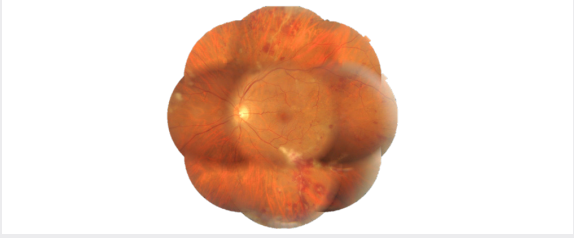

Figure 3. Color fundus photography showing peripheral severe retinal vasculitis (vein) in a 43-year-old-male with presumed ocular tuberculosis and positive QuantiFERON-TB test.

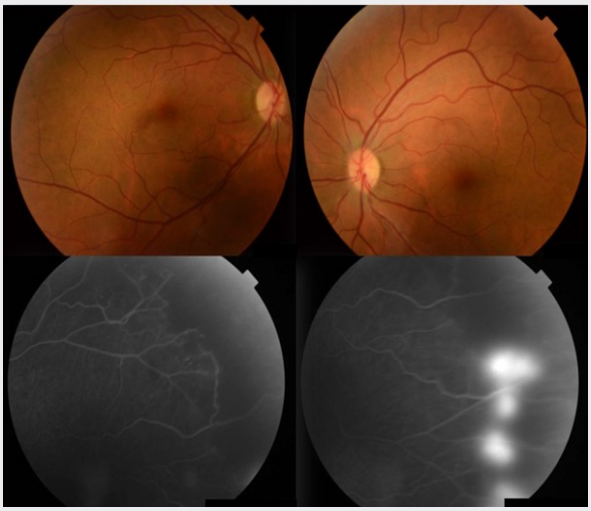

Figure 4. A, B: Color fundus photography: no abnormalities in the posterior pole in a 56-year-old female with a positive QuantiFERON-TB test. C, D: Fluorescein angiography showing an area of peripheral retinal non perfusion with temporal “sea fan” retinal neovascularization (Pseudo-Eales vasculitis).

Table 1. General characteristics of the patients and distribution according to different classification criteria

	No (%)
Mean Age	**45 years (12-68 years)**
Sex	
Female	37 (59)
Male	26 (41)
Ocular involvement	
Unilateral	43 patients (68)
Bilateral	17 patients
Unilateral alternating	3 patients
Anatomical location	
Panuveitis	28 eyes (35)
Posterior	25 eyes (31)
Anterior	18 eyes
Intermediate	6 eyes
Anterior and intermediate	3 eyes
Type of inflammation	
Granulomatous	36 eyes (45)
Non-granulomatous	44 eyes (55)
Chronological course	
Acute	35 patients (55)
Recurrent	15 patients
Chronic	13 patients

Table 2. Etiologies of infectious uveitis

Type of infection	No of patients
Bacteria	29
Tuberculosis	23
Rickettsiosis	2
Bartonella henselae (Cat scratch disease)	2
Treponema pallidum (Syphilis)	1
Coxiella burnetti	1
Viruses	19
Herpes simplex virus	10
Varicella zoster virus	5
Cytomegalovirus	2
Measles	1
HIV	1
Parasites	14
Toxoplasmosis	10
Toxocariasis	4
Fungi	1
Candida albicans	

DISCUSSION

The mean age at presentation in our study, regardless of the etiology, was 45 years with a slight female predominance (female to male ratio was 1.4 :1). This result was similar to prior studies about IU in the United States (5,12). Findings from our study, consistent with those from an Iranian report, showed that age at onset of IU widely varied with the etiology, and appeared to be younger in parasitic infections. In our study, the mean age of patients with toxocariasis was 17 years, similar to their study (19 years) and it was 33 years for toxoplasmosis, older than that found in their study (23 years) (13).

IU was mostly unilateral in our population (68%), which is comparable to what has been showed by Tsirouki et al with infectious conditions being one of the most common causes of unilateral uveitis in the developing world (1).

In our series, panuveitis was the most frequent anatomic location, accounting for 35% of eyes, followed by posterior uveitis in 31%, anterior and intermediate uveitis. Tsirouki et al found that IU in developing countries more commonly manifests as posterior uveitis and panuveitis (1). In pediatric IU, the posterior form was the most common (40.3%), followed by anterior uveitis (36.8%), panuveitis (15.7%) and intermediate uveitis (7%) (4). However, most of these surveys, including our study, reporting panuveitis and posterior uveitis as more frequent than anterior uveitis, come from tertiary care centers, and this might have led to referral bias. In contrast, anterior uveitis is more commonly reported in general practice (1,14).

Our study showed that OT (36 eyes), HSV (17 eyes), and toxoplasmosis (10 eyes) were the most common etiologies. Causes of IU exhibit a significant differentiation between the developed and developing countries (1). The most common infections in developing countries include: toxoplasmosis (6,13), tuberculosis (15-17) and HSV (6,14); which is consistent with our results. Causes of IU in developed countries were dominated by herpetic uveitis (5,12,18) and toxoplasmosis (5,12).

In our series, the most common etiology of anterior uveitis was HSV (10 of 18 eyes), which is similar to what has been found in a previous study in Tunisia (6), as well as in Virginia (12) and Spain (18).

In our study, rickettsiosis was the second most frequent bacterial infection manifesting as an acute multifocal retinitis (4 eyes of 2 patients). Khairallah et al showed that posterior segment involvement is common rickettsial IU and is often asymptomatic. A careful dilated funduscopy, complemented by fluorescein angiography in selected cases are recommended in patients with fever and/or skin rash, living or returning from endemic areas, especially during spring or summer (8).

The etiological diagnosis of IU was based on a constellation of clinical and laboratory findings, including ACP, performed in 11 patients. Toxoplasmosis was mostly diagnosed based on clinical features, but the detection of toxoplasma DNA in AH by PCR confirmed the diagnosis in one of ten patients. Diagnosis of herpetic uveitis was also based in the majority of cases on typical clinical features such as: unilateral IU; granulomatous anterior uveitis and associated keratitis. Atypical cases benefited from AH analysis which confirmed the diagnosis in 8 of 17 patients.

In our study, the diagnostic delay ranged from 2 to 36 months with a significant correlation between diagnostic delay and posterior uveitis (p=0.013). Ocular tuberculosis had the longest diagnostic delay. These results were consistent with other studies, with a diagnostic delay for OT ranging from 6.7 months in Saudi Arabia to 11 months in the United Kingdom (19, 20).

The identification of the causative agent in IU is challenging. Atypical or doubtful cases require additional testing to establish an accurate diagnosis. Remarkable advancements in molecular and immunological technologies have been made, and the diagnosis of IU has been greatly improved

by the use of PCR on AH samples (21). Another diagnostic tool, represented by multiplex PCR, has been evaluated by Nakano et al in a multicenter study in Japan. They concluded that it was equivalent to conventional PCR. However, both techniques have detection limits. The diagnosis must be made carefully based on patients' symptoms, clinical findings, laboratory tests, and patients' responses to treatment (22).

The most common complications in our series were occlusive retinal vasculitis (19 eyes), followed by cataract (17 eyes), CME (17 eyes) and papilledema (15 eyes). These results were comparable to has been reported in the literature, whether it concerned all cases of uveitis (6) or specifically IU (12).

Our study is the first population-based study of IU in Tunisia. Previous studies have either focused on all uveitis (6), or exclusively on specific etiologies (7-10). Our study was subject to limitations including its retrospective and monocentric nature, and the limited sample size. A number of infectious etiologies was absent, such as bacterial infections (leprosy, brucellosis, Lyme disease, leptospirosis, Whipple's disease) and other emerging viral infections, bacterial endophthalmitis and parasitic infections. Another limitation is that our study was conducted in a tertiary care center, which is not representative of the general population, but rather reflects a select subset with more difficult or severe cases, leading to a referral bias (14).

CONCLUSION

Our population-based data provided an estimate of the IU main causes and clinical features in a Tunisian population. Depending on the anatomic location of the uveitis, numerous etiologies may be encountered but the differential diagnosis should particularly focus on tuberculosis, herpetic uveitis and toxoplasmosis. A future large-scale, prospective and multicenter national study would allow a more precise evaluation of the epidemiological and clinical profile of IU in Tunisia. This will help in the establishment of standardized management protocols adapted to our particular context, thus decreasing the incidence of this vision-threatening disease.

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