

Uveitis heralding previously unknown luetic and HIV infection. Syphilitic uveitis in an Italian referral center

Lucia Restivo, Alessandro Abbouda, Chiara Nardella, Alice Bruscolini,
Maria Pia Pirraglia and Paola Pivetti Pezzi

Dipartimento di Scienze Oftalmologiche, Servizio Speciale di Immunovirologia Oculare,
Sapienza Università di Roma, Rome, Italy

Abstract

Purpose. This study was conducted to determine the incidence of luetic uveitis in the last seven years at our uveitis center and to describe the characteristics and the role of uveitis in the diagnosis of syphilitic infection with or without unknown HIV infection.

Methods. We retrospectively reviewed syphilitic uveitis in patients observed at our center between 2004 and 2010. The diagnosis was based on the serological evidence for syphilis, uveitis, exclusion of other etiologies. All patients had HIV testing.

Results. We describe 14 new cases of luetic uveitis: 6 co-infected with previously unknown HIV-infection had panuveitis, while the most common presentation in HIV-negative patients was posterior uveitis.

Conclusions. Syphilis has been recognized as reemerging disease. The ocular inflammation can be the first symptom of syphilis. This study underlines the importance of a prompt and correct diagnosis of this ocular disease.

Key words

- HIV
- syphilis
- uveitis

INTRODUCTION

Syphilis has been recognized as a reemerging disease also in Italy, where in 2000 the cases of syphilis infection were 0.35 cases per 1000 person/year (p-y) while at the end of 2009 the number of cases were 1.08 cases per 1000 p-y, with a mean value of 0.92 cases per 1000 p-y in the decade from 2000 to 2009 [1]. Due to this reemergence, ocular syphilis, previously a rare manifestation of the infection, is increasingly observed [2-3]. Ocular manifestations of syphilis are heterogeneous and difficult to diagnose by clinical presentation. They can involve any structure of the eye from cornea to optic nerve [4]. Eye involvement can occur in all the stages of the disease. Uveitis is the most common ocular manifestation in syphilis disease and can develop in both the secondary and tertiary stage: iridocyclitis, chorioretinitis, vitritis, exudative retinal detachment, and perivasculitis have been described [5]. Patients with syphilis are frequently co-infected with human immunodeficiency virus [6]. The purpose of this study was to study the incidence of luetic uveitis in the last seven years at our uveitis center compared with the previous data collected in the same center between 1986-2003, and to describe the characteristics of uveitis and its role in the diagnosis of syphilitic infection with or without associated HIV infection.

MATERIALS AND METHODS

A retrospective analysis of the medical records of 2410 new patients examined at the Dipartimento Organi di Senso – Sapienza University of Rome, Italy, from January 2004 to December 2010 was carried out to identify patients with luetic eye disease. The diagnosis was based on the following criteria:

- 1) serological evidence for syphilis;
- 2) luetic eye disease;
- 3) exclusion of other etiologies, syndromes or association with other immunological or infectious diseases. During the first examination all patients were interviewed by the ophthalmologist in order to obtain the following data: demographic features (age, gender, profession), previous infections or immunological diseases with concomitant systemic findings, possible risk factors for sexually transmitted diseases (STD). All patients were submitted to these serological tests: reactive *Treponema pallidum* hemagglutination (TPHA) test combined with either a venereal disease research laboratory test (VDRL) or detection of fluorescent treponemal antibody-absorption test (FTA-ABS) IgM, or to automatable treponemal enzyme immunoassays (EIA). Other diseases with possible ocular manifestations such as tuberculosis or sarcoidosis were ruled out by clinical examination and specific laboratory tests in accordance

with the diagnostic protocol used in our center for uveitis patients. The incidence rate of new luetic infection was calculated as the number of new cases of disease during a period of follow up divided by the person-time-at-risk throughout the observation period in years. Multiplying the numerator and denominator by 1000, the incidence rate becomes number of new cases per 1000 person-years.

All patients with luetic infection had HIV testing with the enzyme-linked immunosorbent assay (ELISA) method with confirmation by Western blot analysis. Patients with a positive HIV test had also HIV-RNA status and CD4 count. We excluded all patients with other etiology of uveitis and negative serological evidence for the luetic disease. Fourteen patients fulfilled the diagnostic criteria displaying a syphilitic uveitis and were enrolled in this study and classified into one of the stages of syphilis [7, 8]. The lumbar puncture has been performed only in 7 patients with possible neurological involvement. The presence of a reactive cerebrospinal fluid (CSF) VDRL or TPHA test was used to define neurosyphilis [9]. Based on IUSG criteria, the luetic uveitis was classified in "anterior,

intermediate, posterior uveitis and panuveitis"; the onset should be defined as either "sudden" or "insidious" [10]. The complete ophthalmological examination led to these clinical features: uni/bilateral involvement, initial and final visual acuity, presence of inflammatory signs involving the anterior and/or posterior segment. We evaluated the course of inflammation, the number of relapses, the follow-up after local and systemic therapy, the incidence of complications and the visual prognosis. All patients underwent local therapy (mydriatics and steroids) and antiluetic systemic therapy with penicillin 24 MUI daily for 14 days. Two patients with allergy to penicillin were treated only after desensitization (Penicillin G 4MUI in 250 cc of physiological saline 6 times/day for 14 days and betamethasone phosphate 4 mg for twice daily). The mean follow-up was 29.4 ± 21.7 months (range, 6-72).

RESULTS

Luetic uveitis was diagnosed in 14 of 2410 cases with uveitis observed in our referral center in seven years (0.83 cases per 1000 p-y). The incidence of ocular syphilis shows a clear increase in comparison with the

Table 1

The demographics, serological and clinical features, the stage of disease of the fourteen patients with ocular syphilis

Patient	Age/Sex	Sex orientation	HIV-status	VDRL	FTA-ABS	TPHA	EIA	CSF-VDRL	Systemic signs	Stage of luetic disease
1	37/M	Heterosex	Neg	Pos	ND	Pos	Pos	ND	Neg	Secondary
2	46/M	Heterosex	Neg	Pos	ND	Pos	Pos	Pos	Neg	Tertiary
3	59/M	Heterosex	Neg	Pos	Pos	Pos	ND	ND	Neg	Secondary
4	47/M	Heterosex	Neg	Pos	Pos	Pos	ND	Pos	Rash palm of hands and sole of feet, genital ulcer	Tertiary
5	50/M	Heterosex	Neg	Pos	ND	Pos	ND	ND	Neg	Secondary
6	43/M	Heterosex	Neg	Pos	ND	Pos	Pos	Neg	Neg	Secondary
7	66/M	Heterosex	Neg	Pos	ND	Pos	ND	ND	Neg	Secondary
8	26/M	Heterosex	Neg	Pos	ND	Pos	Pos	ND	Neg	Secondary
9	39/M	Homosex	Pos	Pos	ND	Pos	Pos	ND	Retronuchal and laterocervical lymphadenopathy	Secondary
10	54/M	Homosex	Pos	Pos	ND	Pos	Pos	ND	Neg	Secondary
11	39/M	Heterosex	Pos	Pos	ND	Pos	Pos	Neg	Rash thorax and limbs	Secondary
12	50/F	Heterosex	Pos	Pos	ND	Pos	ND	Pos	Rash thorax and limbs	Tertiary
13	37/M	Heterosex	Pos	Pos	ND	Pos	Pos	Neg	Lymphadenopathy	Secondary
14	54/M	Heterosex	Pos	Pos	Pos	Pos	ND	Neg	Rash thorax, lymphadenopathy	Secondary

*ND = not determined; VDRL = venereal disease research laboratory test; FTA-ABS = fluorescent treponemal antibody-absorption test; EIA = enzyme immunoassays; TPHA = *Treponema pallidum* hemagglutination; CSF = cerebrospinal fluid.

Table 2

Luetic uveitis and complications in HIV-negative (8pt-12 eyes) and HIV-positive (6pt-9 eyes) patients. Complications (%)

	N. of patients	Intermediate uveitis (%)	Posterior uveitis (%)	Panuveitis (%)	Complications (%)			
					Cystoid macular edema	Epiretinal membrane	Ocular hypertension	Retinal detachment
HIV –	8	2 (14.3)	4 (28.6)	1 (7.1)	3 (37.5)	1(12.5)	1 (12.5)	0
HIV +	6	0	0	6 (42.9)	3 (50)	1 (16.7)	0	2 (33.3)
Total	14	2 (14.3)	4 (28.6)	7 (50)	6 (87.5)	2 (29.2)	1 (12.5)	2 (33.3)

previous epidemiological investigations performed in the same center (0.11 cases per 1000 p-y) [11, 12].

Out of fourteen patients affected by luetic uveitis one was female (7.1%) and 13 were males (92.9%); mean age at presentation of uveitis was 46.2 ± 10.4 (range 26-66 years); unilateral uveitis was observed in 7 patients (50%) and bilateral involvement in the other patients. The medical history revealed that 12 patients (85.7%) were heterosexual and 2 homosexual (14.3%). No patients was known to be positive for luetic infection before our first examination. The specific serological test revealed an unknown HIV-infection in 6 patients (42.8%).

In these patients, none of whom had AIDS, were determined the CD4 cell count and viral load (HIV-RNA) which respectively had a mean value of 418.73 ± 271.8 cells/mL (range 96-783 cells/mL) and of 145 087.6 ± 166 019.7 copies/ml (range 30.321- > 500 000). Of seven patients with available CSF studies, three were VDRL-positive and reactive: 2 HIV-negative patients and 1 HIV infected. *Table 1* shows the demographics, serological and clinical features of the fourteen patients. Four patients reported in the past history relevant cutaneous signs suggestive of luetic disease. They referred the presence of unidentified eritematous rash. Only one HIV-negative patient presented a rash of the palm of the hands and of the soles of the feet, and genital ulcer; while 3 HIV-positive patients referred the presence of thoracic rash and of the roots of the limbs. Three HIV-positive patients presented nonspecific lymphadenopathy (*Table 1*). All patients at the beginning of the ocular disease complained a reduction of visual acuity, visual fogging and ocular discomfort. Four out of 8 HIV-negative patients (50%) and 3 out of 6 HIV-positive patients (50%) had a bilateral ocular involvement. The onset of the ocular disease was “sudden” in 6 and “insidious” in 2 out of 8 HIV-negative patients, whereas out of 6 HIV coinfecting patients in 5 was “sudden” and in one “insidious”. As showed in *Table 2*, uveitis at the onset was anterior with acute exudative inflammation in 1 patient (7.1%), intermediate with snow balls and/or snow banks in 2 patients (14.3%), posterior with focal or diffuse chorioretinitis in 4 (28.6%) and diffuse uveitis in 7 (50%). In HIV-negative patient posterior uveitis was the most frequent form of ocular inflammation. Only 1 patient with posterior uveitis showed neuroretinitis with papillitis and widespread retinal edema (patient 5). All 6 HIV-positive patients presented panuveitis with

vitrinitis and diffuse or focal chorioretinal involvement; 1 patient presented bilateral diffuse chorioretinitis with papillitis in one eye and diffuse retinal vasculitis in the other one (patient 13). Furthermore 2 cases presented with hypopyon (patient 9-10). During the follow-up, two patients had a relapse: in the first HIV-negative patient was observed a recurrence of posterior uveitis, in the second HIV-positive patient a relapse of panuveitis, that resolved after systemic specific therapy. A follow-up visual acuity was available for all patients: an improvement was documented in 15 out of 21 eyes. The group of HIV positive patients had a worse initial visual acuity than HIV negative patients, but thanks to the early treatment, the final outcome is comparable to HIV negative patients (*Table 3*). The most frequent complications were unilateral cystoid macular edema, that developed in 6 patients (3 HIV-negative and 3 HIV-positive patients), traction retinal detachment in 2 HIV-positive patients, ocular hypertension in 1 HIV-negative patient and epiretinal membrane were observed in 1 HIV-negative and HIV-positive patient respectively (*Table 2*).

DISCUSSION

Actually many systemic infections, including syphilis, belong to the group of STD [13]. Worldwide, there are an estimated 12 million new syphilis cases every year, over 90% of which occur in developing countries [14]. Data collected by Italian National Institute of Health from 2000 to 2005, show an increase in Italy equal to 300% (from 351 cases in 2000 to 1403 cases in 2005) [1]. There are different but believable and complementary hypothesis about this recent epidemic trend of syphilis, in particular in the Western countries. For sure displacements (the so called “melting-pot”, journeys, migrations, in particular from areas with high incidence of syphilis) have an important role, but there are other behavioral factors (attention loss and underestimation of the risk, infrequent recourse to “safe-sex”, the introduction of antiretroviral therapy, the abuse of new recreative drugs). In step with this trend also the incidence of ocular syphilis is considerably increased, and luetic uveitis is the most frequent ocular manifestation of secondary or tertiary syphilis, as reported in many studies [4, 15]. Unlike of the other types of uveitis, luetic uveitis does not present pathognomonic signs and it can appear with aspecific ocular signs. This study, confirming the increase of luetic uveitis cases among the endogenous uveitis, describes 14 new cases of luetic

Table 3

Best corrected visual acuity in HIV-negative (8pt-12 eyes) and HIV-positive (6pt-9 eyes) patients

Patients	N. total eyes (%)	iVA			fVA		
		< 0	< 0.1	> 0.1	< 0	< 0.1	> 0.1
HIV-	12 (100)	1 (8.3)	1 (8.3)	10 (83.3)	1 (8.3)	1 (8.3)	10 (83.3)
HIV+	9 (100)	2 (22.2)	4 (44.5)	3 (33.3)	1 (11.1)	1 (11.1)	7 (77.8)

iVA = initial visual acuity; fVA = final visual acuity.

uveitis observed in the last seven years (0.83 cases per 1000 p-y), diagnosed in patients in good state of health and unsuspecting to be affected by any systemic disease. In the same center, the epidemiological investigations during the previous eighteen years (from 1986 to 2003) revealed an incidence of 0.11 cases per 1000 p-y. The ocular inflammation can be the first symptom of syphilis, and it's been helpful to detect previously unknown, asymptomatic HIV infection [16]. In literature many similar cases have been described but there is not a common opinion about the hypothesis that ocular syphilis can lead to initial HIV diagnosis [17]. Syphilis and HIV share the same risk factors in the matter of sexual transmission. Luetic infection probably increases the transmission and the susceptibility to HIV, because the chancre of primary syphilis serves as a fast way to infect for HIV [18]. Nevertheless in some cases HIV changes the clinical expression of syphilis, so there is a possible coexistence between the primary and the secondary state, otherwise in other cases there is a higher rate of symptomless primary syphilis and proportionately more HIV-positive patients present with secondary disease [19]. According to a recent review in HIV-negative patients we have revealed a prevalence of posterior form of uveitis and clinical pictures more heterogeneous than in HIV-positive patients. Furthermore some authors assert that the course of syphilis is more aggressive in HIV-positive patients [20]. In our study all HIV-positive patients had at onset signs of diffuse uveitis, while in HIV-negative patients only one case of panuveitis has been observed. Co-infected patients had also more complications than HIV-negative patients during the follow up. Tractional retinal detachment and cystoid macular edema had higher rate in the group of HIV positive patients (Table 2). Bilateral involvement has been reported in three patients of the six HIV-positive (50%) and in four patients of the eight HIV-negative patients (50%). One HIV-infected patient has presented papillitis in 1 eye and retinal vasculitis in the other one. Initial visual acuity had resulted worse in patients with co-infections, but thanks to a prompt diagnosis and the antiluetic specific penicillin therapy, final visual acuity was significantly improved in both the groups. No significant difference in the number of relapses has been observed in the two groups, in fact there was only one relapse in two different patients, the first HIV-positive and the second HIV-negative. These relapses have presented the same clinical picture of the first manifestation, but more serious in the patients with co-infection. Anyway this fact is indeed influenced by

a non homogeneous and too short follow-up; a longer monitoring is necessary to compare possible differences. Different studies investigated the effect of syphilis on the HIV viral load and on the CD4 count. These studies reveal that syphilis is able to induce a decrease of CD4 and a temporary improvement of HIV viral load [21, 22]. A recent systematic review of case series and case reports underlines the association between posterior uveitis and low CD4 counts (< 200 cells/ml) and the possibility to obtain negative non-treponemal tests in patients with ocular syphilis and HIV infection [23]. In our study the majority of patients had a good immunological status, so ocular syphilis seems to develop independently from immunosuppression caused by HIV, in according with Balba [6]. As the average of CD4 count was high (418.73 ± 271.8 cells/ μ l), it is possible to suppose that the HIV infection was recent, but is not possible to establish the temporary relationship between the two infections. Marra [24] suggests an high risk of neurosyphilis in HIV-positive patients with CD4 count < 350 cells/ml, but from data of this study is not possible to establish an high prevalence of neurosyphilis in patients co-infected, for the small number of patients who underwent lumbar puncture and their immunological status. The scientific debate about considering the ocular syphilis a type of neurosyphilis or not is still open [25].

CONCLUSIONS

This study underlines the possibility that the inflammation of uveal tract represents the beginning symptom of the luetic infection and of the eventual associated HIV infection; and the importance of a prompt and correct diagnosis of this ocular disease. A rapid diagnosis becomes a fundamental aspect of public health and an important instrument to control the diffusion of new epidemics. A prompt treatment prevents permanent disability and leads very often to a complete recovery. A wrong diagnosis or etiological classification leads to harmful therapies with worsening of uveitis and of the general state of health.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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