

STEROID REFRACTORY EPISCLERITIS AS EARLY MANIFESTATION OF NEUROSYPHILIS

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Abstract

Since the incidence of syphilis is constantly rising in western countries during the last few years the awareness of atypical presentations of this treatable disease is warranted. Especially since early treatment results in complete elimination of *Treponema pallidum*, thus preventing disabilities and neurological deterioration as a consequence of late stage infection. We describe a case in which a patient with asymptomatic neurosyphilis presented with a history of longstanding episcleritis. The patient was first seen in an outpatient setting, where the resistance of ocular inflammation to steroid treatment led to the uncommon diagnosis. Prolonged antibiotic treatment resulted in a complete resolution of all clinical findings and a decrease of specific treponemal antibody titers. This case might serve as an example that with the recent increase in sexual transmitted diseases practitioners might be more often confronted with uncommon presentations of syphilis.

Key words: Episcleritis, Neurosyphilis, *Treponema pallidum*

CASE REPORT

In January 2003 a 62-year old man was referred to the outpatient clinic because of bilateral ocular redness that had been unchanged for eight months (Fig.1). The patient did not report any associated ocular pain or reduction in visual acuity. During the eight month period of ocular inflammation no constitutional symptoms, or episodes of fever, cough, swollen joints, headaches or neurological symptoms were observed. The medical history showed an insulin dependent diabetes mellitus type II and a presumed allergy against cat hair. Being a musician, travel abroad was a frequent occurrence.

After the diagnosis of bilateral episcleritis accompanied with a slight conjunctival injection was confirmed by ophthalmologic examination, topic and systemic steroids were administered for three months resulting in only a slight decrease of episcleritis and conjunctival inflammation. Apart from the bilateral episcleritis, a physical examination revealed very few scattered small reddish-brown maculae (4 mm in diameter) on both thighs (Fig. 2). Oral mucosal surfaces or genitales showed no apparent lesions. No enlarged lymph nodes were detectable. Pulmonary, cardiac, and abdominal examinations were normal. Except for an absence of

reflexes at the lower extremities no neurological symptoms were detected. Routine lab results showed a slight elevation in C-reactive protein (0.7 mg/dl), haptoglobin (305 mg/dl), quantitative anti-phospholipid-antibodies (11.37 U/ml), and HbA1c (11.6%). Hematologic parameters were normal, as were kidney and liver function tests.

The persistent ocular manifestations and the lack of responsiveness to steroid treatment invited a diagnosis of persistent infection or rheumatic disease. Additional immunological laboratory parameters (ANCA, ANA, rheumatoid factor, lupus anticoagulans activity) were all negative. Serologic testing revealed no actual responses to Bartonellae-, Chlamydiae-, or Borreliae-species or antibodies against HIV or hepatitis C virus. There were serologic markers of previous hepatitis B virus and varizella zoster infections. Remarkably, highly elevated serum titers could be found in the *Treponema pallidum* hemagglutination test TPPA (160.000, normal <80) and in the fluorescent treponemal-antibody absorption FTA (2560, normal <5). These results correlated with a slight elevation of VDRL titer (32, normal <2). Anti-Lues IgM was undetectable in IFT, ELISA or Western Blot.

Since there was serological evidence for persistent syphilis infection and apparent ocular symptoms, a spinal fluid examination for detection of CNS involvement was conducted. Cerebrospinal fluid (CSF) showed slight pleocytosis (78 cells/ μ l). Serologic testing of the CSF revealed increased treponemal specific titers: FTA IgG of 256 (normal <2), TPPA of 64000 (normal <2) and positive VDRL (4, normal <2). Since the index for intrathecal *Treponema pallidum* antibodies (ITPA) was dramatically increased (50.2, normal range 0.5 to 2.0) central nervous affection by a syphilis infection could be confirmed and the diagnosis of asymptomatic neurosyphilis with episcleritis was made.

Treatment consisted of Penicillin G iv. 4 x 5 Mio U/day for 14 days. After a few days the patient reported improvement of ocular symptoms and reduced episcleritis. Serologic testing three months later showed only modest reduction of lues specific titer (TPPA 40960) and continued elevated VDRL titer (32). Only residual episcleritis was detectable at that time. Since delayed reduction of titers was observed further antibiotic treatment with doxycycline was initiated until a few weeks later inflammation of the eyes was completely resolved.



Fig. 1. Painless ocular inflammation was the initial presenting symptom (A). Ophthalmologic examination confirmed the diagnosis of bilateral episcleritis accompanied with conjunctival injection (B).



Fig. 2. Clinical examination reveals a few scattered small reddish-brown maculae on both thighs.

DISCUSSION

Recent data regarding the incidence of sexual transmitted infectious diseases and in particular syphilis revealed increasing numbers of newly diagnosed cases each year. In the United States the introduction of effective antibiotic treatment and public health programs in the early 1940s initially led to a dramatic decrease of reported syphilis cases. Timely correlated with the AIDS epidemic the incidence further declined among homosexual men, while, in contrast, among heterosexual men increasing numbers could be

reported in the time period from 1985 to 1991. This brief increase was followed by an overall reduction of new infections, resulting in 2000 in the lowest rate of syphilis cases since reporting began [4]. Unfortunately, since 2000 a constant increase in the incidence of primary and secondary syphilis is again reported each year. In 2004 there was an 11.2% increase of reported cases (total 7980) compared to the previous year in the United States. The rate was 2.7 cases per 100.000 population [4].

In Germany a similar increase in newly diagnosed syphilis cases is reported since 2001. In 2004 in total

3345 cases (14% more than in 2003) were registered at the Robert Koch Institute. With the rate of 4.1 cases per 100.000 population in 2004 Germany has the highest incidence of reported syphilis infections in western Europe [9]. The observed overall increase of new cases in the U.S. and Europe are mainly caused by higher incidence rates among homo- and heterosexual men.

In our patient, high lues specific titers correlated with ocular symptoms and macular lesions of the skin. Latter are common cutaneous signs of secondary syphilis occurring after hematogenous dissemination of *T. pallidum* from the site of inoculation. The macular lesions are known to be small in diameter (3-10 mm) and involving the trunk and close extremities [5]. Interestingly, further signs like alopecia, condylomata lata, mucous patches or frequently observed constitutional symptoms of secondary syphilis as fever, weight loss, arthralgias and lymphadenopathy were absent in the presented case.

Among ocular manifestations of lues infection, anterior uveitis occurs in 5-10% of patients with secondary syphilis, especially in HIV infection [2]. Episcleritis/scleritis is a very rare symptom in lues, but cases of asymptomatic neurosyphilis with episcleritis have been described [5], although intraocular inflammation such as iritis is more common in this stage of the infectious disease [11].

In our case steroid refractory episcleritis was the only initial manifestation of secondary syphilis and of CNS infection, initiating further diagnosis and treatment for prevention of possible neurological consequences of late stage neurosyphilis. Since most cases of episcleritis are caused by non-infectious mainly rheumatoid-immunological diseases an initial treatment attempt with topical and systemic steroids in patients with this condition is suggested. Infective causes of episcleritis are rare and include streptococcal disease or infections with herpes or varicella viruses. Less likely tuberculosis, lues, influenza or mononucleosis can result in episcleritic inflammation [3].

Invasion of the cerebrospinal fluid is common even in early stages of untreated syphilis and results in abnormal CSF findings in 30-70% of patients with secondary syphilis [13]. The CNS involvement of patients with secondary syphilis is well defined and usually accompanied by signs of acute meningitis, increased CSF protein levels and lymphocytosis [9]. More specific examinations for the diagnosis of CSF involvement by *T. pallidum* are the VDRL, TPPA and FTA test [6]. The high sensitivity and specificity of the FTA test almost completely eliminates neurosyphilis as a possible diagnosis of abnormal CSF findings when a negative test result is obtained [7].

Despite the positive CSF findings confirming CNS involvement in our patient, there was no neurological deterioration: asymptomatic neurosyphilis with episcleritis was the correct diagnosis. The incidence of asymptomatic neurosyphilis ranges from 8-40% in untreated patients of secondary lues [8]. Although it is not known how many of untreated patients progress to symptomatic late neurosyphilis, persistence of CSF abnormalities over five years is highly predictive for the development of neurological symptoms [1]. There-

fore identification of asymptomatic cases with normal neurologic examinations and CSF abnormalities defines a population at risk for the development of symptomatic neurosyphilis [6], in which antibiotic treatment might prevent further disease progression.

Antibiotic treatment of syphilitic episcleritis is reported to improve ocular symptoms [14]. To ensure sufficient levels of antibiotics in the CSF, recommendations for treatment of established neurosyphilis include 12 to 24 Mio units/day of penicillin be given intravenously for up to 14 days [12]. Alternatively treatment with chloramphenicol, amoxicillin plus probenidicid, ceftriaxone or doxycycline (200 mg orally twice a day for up to three weeks) results in effective clearance of CSF infection [15].

Since elimination of microorganism is not a feasible marker for treatment response in syphilis, clinicians rely on the decline of lues specific serum titers as a surrogate marker for cure. Despite appropriate treatment, 15-25% of patients will not show a fourfold decline in titers over a 3 month period and are therefore at risk for treatment failure [10], though clinical proof for this assumption is not established. Our patient experienced only a modest reduction in VDRL and TPPA serum titers, thus antibiotic treatment was changed until total resolution of clinical findings was observed and VDRL declined to low, stable titers.

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