

Osteoarticular mycobacterial infections in patients with the human immunodeficiency virus

J. Belzunegui, M. Santisteban¹,
M. Gorordo¹, E. Barastay,
C. Rodríguez-Escalera,
L. Lopez-Dominguez,
C. Gonzalez, M. Figueroa

Rheumatology Unit, Hospital Donostia
(San Sebastian) and Hospital Basurto¹,
Bilbao, Spain.

Please address correspondence to:
Dr J. Belzunegui, Rheumatology Unit,
Hospital Donostia, P.Dr. Beguiristain s/n,
20014 San Sebastian, Spain.

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ABSTRACT

Objective. Data about the characteristics of patients with the human immunodeficiency virus (HIV) and concomitant mycobacterial skeletal infection are scarce. Thus, our aim was to describe this condition in a cohort of 11 patients.

Methods. A review of the records of 11 HIV-positive individuals with microbiological confirmation of mycobacterial osteoarticular infection was conducted. The studied data included: age, sex, risk factor for the HIV, days between the onset of symptoms and diagnosis, evidence of previous tuberculosis, location of the infection, isolated organism, diagnostic method, laboratory data (erythrocyte sedimentation rate, haemoglobin, leukocyte count), number of CD4⁺ lymphocytes, anti-retroviral therapy, treatment and outcome.

Results. Eight patients were men and 3 were women. The median age was 34.2 years (range 20-46 years). Previous tuberculosis was present in 5 cases. Mean days between the onset of symptoms and diagnosis was 124 (range 20-365 days). Infections involved the knee (4 cases), spine (3 cases), hip (2 cases), elbow (1 case) and tibia (1 case). ESR was frequently elevated. The CD4 count ranged from 0.03 to 0.779 x 10⁹/l (mean 0.245 x 10⁹/l). *M. tuberculosis* was the responsible organism in 9 cases, *Mycobacterium tuberculosis* plus *Staphylococcus aureus* in one case and *M. Kansasii* in one case. Patients received specific treatments with good results. Surgery was necessary in 4 cases. No deaths occurred. Four patients were anti-retroviral naïve at the moment the diagnosis was made. The remainder 8 were on zidovudine therapy.

Conclusion. The immunologic status of patients with HIV and concomitant mycobacterial skeletal infections is quite variable. The outcome of this condition seems to be good.

Introduction

Tuberculosis (TB) is the most deadly infectious disease in the world. In recent decades one of the main reasons for its resurgence is the worldwide spread of the human immunodeficiency virus (HIV). The risk of TB is more than 25-30 times higher among HIV-

infected persons than among HIV-seronegative controls. This virus increases the risk of reactivation of latent foci of infection and the progression of a primary tuberculous infection to a more atypical and disseminated extra-pulmonary manifestations (1). On the other hand, a variety of atypical mycobacteria have been described as a cause of skeletal infection in this population (2). The aim of our study was to show the characteristics of patients with the HIV suffering from a concomitant osteoarticular infection caused by *Mycobacterium tuberculosis* or atypical mycobacteria, on which there are few studies in the literature.

Methods

A retrospective study was carried out. Among more than 6,000 outpatients who attended the Donostia Hospital and Basurto Hospital (Basque Country, northern Spain) in the period 1981-2002, 11 were admitted because of a skeletal mycobacterial infection confirmed by microbiological methods. We conducted a study showing their clinical, immunologic and laboratory data, treatment and outcome. Analysed items included: age; sex; risk factors for HIV; evidence of previous TB; findings of chest radiographs, Mantoux test and urine cultures; days between the onset of symptoms and diagnosis; location of the infection; isolated organism; laboratory data, including the erythrocyte sedimentation rate (ESR), haemoglobin and leukocyte count; number of CD4 positive lymphocytes; treatment; outcome 6 months after the end of treatment; and anti-retroviral therapy. Diagnosis of skeletal infection was made on the basis of a positive culture on Löwenstein medium of samples obtained from the affected site. HIV positivity was diagnosed in the 11 cases by enzyme-linked immunoabsorbent assay and Western blot.

Results

Table I shows some of the clinical and immunologic data for the patients. Eight were men and 3 were women. The principle risk factor for HIV was intravenous drug addiction in all cases. The median age was 34.2 years (range

20-46 years). The knee (4 cases) was the most commonly involved site, followed by the spine (3 cases), hip (2 cases) elbow (1 case) and tibia (1 case). Nine infections were caused by *Mycobacterium tuberculosis*, one by *Mycobacterium tuberculosis* + *Staphylococcus aureus* and one by *Mycobacterium kansasii*. The mean number of days from the onset of symptoms to diagnosis was 124 (range 30-365). A history of previous TB was present in 5 cases (3 pulmonary, 1 intestinal, 1 lymphonodular). Chest radiograph was performed in 10 patients: only in 2 of them was apical fibrosis observed. Five individuals were tuberculin tested with positive results in all of them. Urine samples were cultured in 4 cases with negative results. The mean ESR was 52 mm/h, (range 15-115 mm/h), haemoglobin count 112 g/l (range 85-140 g/l) and leukocyte count $5.4 \times 10^9/l$ (range $2.1 - 11 \times 10^9/l$). The median number of CD4 positive lymphocytes was $0.245 \times 10^9/l$. Five patients had <0.2 CD4+ lymphocytes $\times 10^9/l$. One subject with infection caused by *Mycobacterium kansasii* showed the lowest number ($0.03 \times 10^9/l$).

He received isoniazid, rifampin and ethambutol for 14 months. The remainder were treated with a standard regimen of isoniazid and rifampin for 10-14 months along with pyrazinamid or ethambutol for the first 2 months. Because of hepatic toxicity the treatment was changed in 3 cases: isoniazid was stopped in 2 cases and rifampin in one case. A new regimen of rifampin plus pirazinamide plus ethambutol in the first two and isoniazid plus pirazinamide plus ethambutol in the remainder was carried out for 18 months with good tolerance. In two cases with spine involvement and subsequent neurologic deficit, surgery with anterior spinal debridement was necessary. Arthroto-my with drainage was performed in another two. Moderate sequelae (pain and/or limitation of motion) 6 months after the end of treatment was found in 4 cases. At that moment all patients were still alive. Only 8 patients were on zidovudine therapy when the diagnosis of skeletal mycobacterial infection was made. The remaining 3 were anti-retro-

Table I. Clinical and immunologic data on the 11 patients.

Case	Age (yrs.)	Sex	Delay in diagnosis (days)	Previous TB	Location	No. of CD4 lymphocytes ($10^9/l$)	Need for surgery
1	38	M	120		Spine	0.182	Yes
2	30	M	90	Yes	Spine	0.033	Yes
3	33	M	75		Hip	0.270	Yes
4	36	M	30		Hip	0.289	
5	28	M	90	Yes	Tibia	0.126	
6	38	F	90	Yes	Spine	0.232	
7	37	F	270		Elbow	0.779	
8	33	F	60		Knee	0.240	
9	20	M	120		Knee	0.350	
10*	46	M	365	Yes	Knee	0.170	Yes
11**	38	M	60	Yes	Knee	0.030	

* *Mycobacterium tuberculosis* + *Staphylococcus aureus*; ** *Mycobacterium kansasii*.

viral naive and initiated therapy after admission. No patients were on triple anti-retroviral therapy.

Discussion

TB is the most common life-threatening HIV-related infection worldwide. In our country in 1995 40% of illnesses leading to a diagnosis of acquired immunodeficiency syndrome were caused by *Mycobacterium tuberculosis* (3). Bone and joint mycobacterial infections are rare and they represent 4-14% of all skeletal infections (4-9) in subjects with HIV. Figure 1 shows an algorithm for the diagnosis and treatment of skeletal TB in this population. In our cohort the age, sex ratio, location and delay in diagnosis were similar to those showed in other reports. A previous history of TB was seen in 45% of our cases. It could be explained by the fact that HIV-induced CD4+ T-lymphocyte depletion leads to a defective immunologic response to *Mycobacterium tuberculosis* and subsequently to a high risk of reactivation of latent foci of TB. Thus, if skeletal infection is suspected in an HIV population, a meticulous routine investigation into aspects of this disease (previous TB, findings of chest radiographs, factors favouring the contact with or the dissemination of *M. tuberculosis*) should be mandatory. Because tuberculosis is endemic in our country and 30% of the general population and more than 40% of the HIV-infected drug user population in Spain

are PPD-positive, this skin test does not seem to be a good marker of active infection (10).

Atypical mycobacteria have been widely described in the literature as a cause of skeletal infection in patients with the HIV. However, all reports involved an isolated or small number of cases. *Mycobacterium xenopi*, *M. kansasii*, *M. avium intracelulare*, *M. terrae* and *M. haemophilum* have all been described in the literature as causative agents of skeletal infection in patients with HIV. Hirsch *et al.* (2) reviewed the characteristics of 31 individuals with this type of infection and found all of them to be severely immunocompromised. Despite the fact that *Mycobacterium avium intracelulare* is the most common type of infection described in patients with non-skeletal infection, *M. kansasii*, as in our series, seems to be the most frequently isolated organism in patients with osteoarticular involvement.

In our cohort, one culture of synovial fluid yielded *Mycobacterium tuberculosis* plus *Staphylococcus aureus*. Polymicrobial septic arthritis is a very rare condition. It has been described in two patients with HIV (2), atypical mycobacteria (*Mycobacterium avium intracelulare*+*Mycobacterium kansasii*) being the isolated causative agents in both cases. We have not encountered in the literature infectious arthritis caused simultaneously by *M. tuberculosis* plus Gram positive or negative bacteria in HIV-positive patients.

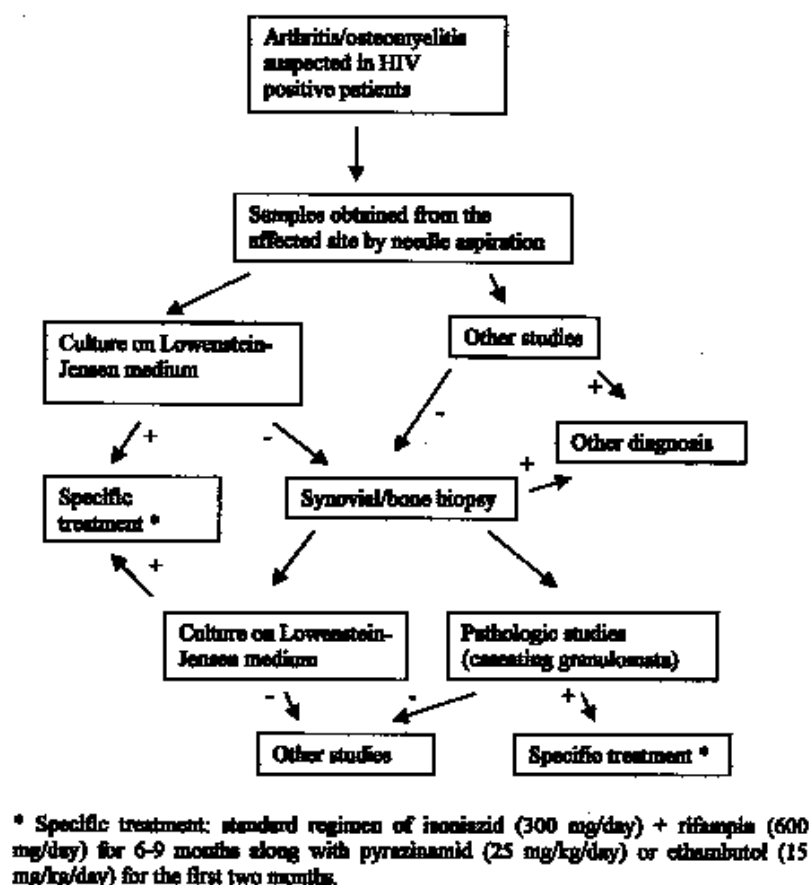


Fig. 1. Algorithm for the diagnosis of skeletal tuberculosis in HIV-infected individuals.

The CD4⁺ lymphocyte counts in HIV-infected subjects with non-skeletal TB are generally in the range of 0.15 – 0.35 x 10⁹/l. Little data is available regarding the immunologic status of patients with HIV and concomitant mycobacterial osteoarticular infection. As in our cases, and as expected, all reported individuals with infections caused by atypical mycobacteria (2) were severely immunocompromised (median number of CD4⁺ lymphocytes 0.05 x 10⁹/l). In a report of 16 HIV-positive subjects with Pott's disease (11) the median number of CD4⁺ lymphocytes was 0.496 x 10⁹/l (±0.253). In our series the degree of immunosuppression was quite variable and only 5 patients had <0.2 CD4⁺ lymphocytes x 10⁹/l. This suggests that, besides the lymphocyte depletion caused by the virus, the endemic character of TB in Spain and environmental factors such as intravenous drug addiction could play a role in the development of the tuberculous disease.

Outcome of this type of infection seems to be good, not being influenced by the presence of the HIV, and patients are usually successfully treated with a regimen of specific anti-tuberculous drugs. Govender *et al.* (11) and Leibert *et al.* (12) studied 42 patients (16 HIV positive and 26 HIV negative) and 26 patients (7 HIV positive and 19 HIV negative) with spinal tuberculosis respectively. They did not find differences in clinical outcome between the two subgroups. The Centers for Disease Control and Prevention, the American Thoracic Society (1) and the British Thoracic Society (13) do not recommend longer treatment for HIV-infected patients with tuberculosis than for HIV-negative patients with this disease, although the clinical and bacteriologic response to treatment should be followed closely. The duration of the treatment should be individualized according to the presence/absence of multi-drug resistant strains and the need for changes in treatment due to

drug-related toxicity, which is very frequent in our country because of the high prevalence of chronic viral hepatic disease seen in intravenous drug addicts, the main risk factor in HIV-positive Spanish population.

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