Osteoarticular bacterial infections are rare in HIV-infected patients

14 cases found among 4,023 HIV-infected patients

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Among 4,023 HIV-infected patients admitted to a large Italian university hospital in the period 1985–1996, 14 had concomitant HIV and bacterial osteoarticular infections. *Staphylococcus aureus* infections were commonest and were diagnosed in 8 patients. Intravenous drug addiction was the only risk factor significantly associated with the development of osteoarticular infection ($p = 0.04$). In contrast, no statistical correlations were found with age, sex, absolute number of circulating T-CD4+ lymphocytes, neutrophils and stage of HIV infection. In conclusion, osteoarticular infections are uncommon in HIV-infected patients and are more directly related to parenteral drug abuse than to HIV.

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Bacterial and fungal infections are increasingly found in patients with HIV infection (Currier and Feinberg 1995, Tumbarello et al.1995, 1996), but skeletal infections appear to be rare. To date, only a few cases of osteoarticular infections (OI) have been reported concomitantly with HIV infection (Berman et al. 1991, Edelstein and McCabe 1991, Vail and Urbaniak 1991, Sabbagh et al. 1992, Edelstein et al. 1993, Marce et al. 1993). A review of the presence of osteoarticular involvement in 556 HIV-infected patients identified only 20 patients (4%) with skeletal infections—i.e., 17 with septic arthritis and 3 with osteomyelitis. *Staphylococcus aureus* and *Candida albicans* were the commonest pathogens (Munoz et al. 1991b). *Mycobacterium tuberculosis* was the causative agent in 1 case of cervical vertebral osteomyelitis. We have extensively discussed this unusual clinical condition in a previous report (Ventura et al. 1996) and therefore it is not considered in this study.

We conducted a retrospective analysis of all HIV-infected patients admitted to our university hospital, identifying all patients in whom a diagnosis of OI had been made and evaluated risk factors related to OI.

Patients and methods

All 4,023 patients with HIV infection admitted to the Department of Infectious Diseases, Catholic University, Rome from 1985 to 1996 were studied. Anti-HIV antibody was identified by enzyme-linked immunoadsorbent assay (ELISA) and confirmed by Western blot. Patients with HIV infection were classified according to the Center for Disease Control CDC classification (1992). Peripheral T-CD4+ lymphocytes were determined by flow cytometry analysis. OI were diagnosed clinically, radiographically and microbiologically. To identify the risk factors associated with the development of OI, a case-control study was performed. Each patient suffering from OI (case; group A), was matched for age and sex with 2 HIV-infected patients (n 28; group B) who had the following characteristics: (a) admitted to the same ward during the same period, (b) with the same stage of HIV infection and (c) absence of OI. To analyze the clinical presentation and the outcome of OI better, each case was also compared to a randomly selected control patient with OI, but without HIV infection (n 14; group C).

The following parameters were reviewed for groups A and B: risk factors for HIV infection, white blood cell count/mm^3 (WBC), neutrophil count/mm^3 (PMN) and T-CD4+ absolute lymphocyte number/mm^3. In patients with OI (groups A and C), we also analyzed: clinical presentation, involved joint and/or bone segments, radiographic findings, etiologic agents isolated from blood and/or from purulent discharge, drug treatment and clinical outcome. The out-

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Table 1. Clinical and epidemiological findings in patients with HIV disease and osteoarticular bacterial infections

Case	Age	Sex	Risk factor	Type/ Localization	Etiology	Positive sample	T CD4+ mm^3	Therapy	Outcome (months)
1	41	F	IVDA	SA Shoulder	Not determinated	None	340	Cephalotin + gentamicin –> ofloxacin	A (6)
2	25	F	IVDA	SA Knee	Escherichia coli	B, SF	263	Ceftriaxone + amikacin	A (4)
3	30	M	IVDA	OM Femoral head	Enterococcus faecalis + Acinetobacter anitratus	Pus	8	Vancomycin + imipenem	B (7)
4	35	M	IVDA+D	OM Ileum	Salmonella typhi murium	B	45	Ciprofloxacin –> cotrimoxazole	D (1)
5	26	M	IVDA	OM Femur	Not determinated	None	50	pefloxacin	A (2)
6	29	M	IVDA+NS	OM Frontal bone	Staphylococcus aureus	B, pus	45	Cephalotin + gentamicin	A (3)
7	40	F	IVDA	OM Fibula	Pseudomonas aeruginosa	B, pus	206	Ceftazidime + gentamicin	B (7)
8	37	M	IVDA	OM Tibia	Staphylococcus aureus + Corynebacterium striatum	B, pus	81	Ciprofloxacin + netilmicin + erythromycin Curettage+external fixator	B (24)
9	38	M	IVDA	OM Femur	Staphylococcus aureus + Staphylococcus haemolyticus	Pus	286	Ciprofloxacin + erythromycin	C (26)
10	39	M	IVDA	Sacroileitis	Staphylococcus aureus	B, pus	412	Ceftazidime + gentamicin –> pefloxacin	A (5)
11	28	M	IVDA	Sacroileitis	Staphylococcus aureus	B, pus	441	Cephalotin + netilmicin –> vancomycin	A (3)
12	27	M	IVDA	Sacroileitis	Staphylococcus aureus	B	67	cephalotin + gentamicin –> vancomycin	C (9)
13	39	M	–	SD L2–L3	Staphylococcus aureus	B, pus	180	clindamycin + gentamicin	A (2)
14	30	F	IVDA	SD L3–L4	Staphylococcus aureus	B	288	clindamycin+ amikacin	A (6)

Risk factors: IVDA intravenous drug abuse, D Diabetes, NS neurosurgery procedures.
Type: SA Septic arthritis, OM osteomyelitis, SD Spondylodiscitis.
Positive sample: B Blood, SF Synovial fluid.
Therapy: –> switched to.
Outcome: A negative cultures, negative radiographic and/or scintigraphic findings, absence of pain and swelling, complete functional recovery of the involved skeletal site,
B negative cultures, negative scintigraphy, negative radiographic findings regarding activity of the infection, but positive findings regarding anatomical sequelae (i.e., pseudoarthrosis, kyphosis, osteoarthritis), presence of pain and swelling, each degree of functional impairment of the involved site,
C chronic course with persistent positive cultures, radiological progression of the lesion, presence of pain and swelling, discharging fistula, etc. (In these patients, long-term oral therapy with ciprofloxacin was instituted);
D death of the patient.

come was evaluated according to the following categories:

A) negative cultures, negative radiological and/or scintigraphic findings, absence of pain and swelling, complete functional recovery of the involved site;

B) negative cultures, negative scintigraphy, negative radiological findings regarding activity of the infection, but positive regarding presence of anatomical sequelae (i.e., pseudoarthrosis, kyphosis, arthrosis), presence of pain, swelling and functional impairment of the involved site;

C) chronic course with persistent positive cultures, radiological progression of the lesion, presence of pain and swelling, discharging fistula, etc. (In these patients long-term oral therapy with ciprofloxacin was instituted);

D) death because of the infection.

Statistics

Quantitative variables were tested for normal distribution and compared by means of the Student's two-tailed t-test. Differences in group proportions were assessed by use of the χ^2-test or, for small numbers, Fisher's exact test. 95% test-based confidence intervals (CI) were used to determine the statistical significance of the odds ratio (OR). Alpha was set at 0.05 and all tests of statistical significance were two-tailed.

Results

Among the 4,023 HIV-infected patients we identified 14 patients (10 men) (0.3%) with OI. Their mean age was 33 (25–41) years. 9 patients were in the C3 category, while 5 were in the B3 category, according to CDC criteria. 2 patients had septic arthritis (cases 1 and 2), 7 had osteomyelitis (cases 3–9), 3 had sacroileitis (cases 10–12) and 2 had spondylodiscitis (cases 13 and 14). We found no significant variation in the incidence of OI during the study (1985–1996).

13 patients were intravenous drug abusers, whereas 1 admitted having high-risk heterosexual contacts. All patients presented with fever (> 38 °C), localized pain and swelling with functional impairment.

Table 2. Radiographic findings of patients with osteoarticular bacterial infections

No.	Radiography	CT/MRI	Scintigraphy
1	Joint space narrowing	ND	hot spots
2	Nil	ND	hot spots
3	Nil	ND	hot spots
4	Nil	focal osteopenia and soft tissue mass	hot spots
5	Nil	ND	hot spots
6	Lytic lesion	ND	ND
7	Periosteal thickening	ND	hot spots
8	Lytic lesion	ND	ND
9	Focal osteopenia	ND	ND
10	Periosteal thickening	soft tissue mass and sequestra	hot spots
11	Periosteal thickening	soft tissue mass	hot spots
12	Focal osteopenia	soft tissue mass and erosion of articular surface	hot spots
13	Nil	disk narrowing and soft tissue mass L2-L3	hot spots
14	Lytic lesion	epidural and paravertebral collection and vertebral destruction L3-L4	hot spots

ND not done, Nil normal, CT scan-computed tomography, MRI magnetic resonance imaging

Laboratory tests indicated a mean peripheral lymphocyte count of 1010/mm^3, with an absolute T-CD4+ lymphocyte count of 193/mm^3 (8–441). The mean level of circulating PMN was 5025/mm^3 (620–11760).

The 2 cases of septic arthritis were monoarticular; 1 in the knee and the other in the shoulder. *Escherichia coli* was isolated from blood and synovial fluid in case 2, while the cultures were negative in case 1. Antibiotic treatment for 4–6 weeks was successful in both patients.

Osteomyelitis was located in the femoral head in case 3, in the femoral shaft in cases 5 and 9, in the fibula (case 7), tibia (case 8), ileum (case 4) and frontal bone (case 6). In 4 patients with osteomyelitis, a previous trauma and/or a local surgical procedure was reported. *Staphylococcus aureus* was isolated from blood and surgical specimens in case 6. *Staphylococcus aureus* was isolated in association with other microorganisms, i.e., *Staphylococcus haemolyticus* in case 9 and *Corynebacterium striatum* in case 8. *Salmonella typhimurium* was detected in case 4 and *Pseudomonas aeruginosa* in case 7, whereas *Acinetobacter anitratus* and *Enterococcus faecalis* were found in case 3. Blood cultures were constantly negative in case 5. Cases 3, 5, 6–9 responded favorably to antibiotic therapy, in case 8 also required surgery (curettage and external fixator), while 1 patient with bacteremia due to *Salmonella typhi-murium* died of septic shock (case 4, Table 1).

Staphylococcus aureus was isolated in 3 patients with sacroileitis (cases 10–12) and in 2 patients with spondylodiscitis (cases 13 and 14) and none of the isolated strains was methicillin-resistant. Antibiotic therapy for 4–6 weeks was effective in these cases as well. In 2 patients, 1 with sacroileitis (case 11) and 1 with osteomyelitis of the femural diaphysis (case 9), it was necessary to continue the antibiotic therapy for 3 months, with oral ciprofloxacin after the initial 6 weeks of intravenous therapy before clinical resolution.

In 8 cases, the skeletal radiographic findings were abnormal, in the other 6 cases they were normal. Scintigraphy with ^{99m}Tc-MDP was done in 11 cases and indicated infection in all. CT, performed in 4 patients, indicated the presence of bone lysis and soft tissue inflammation in all. MRI, performed in only 1 case, detected spondylodiscitis.

Regarding the predisposing factors, patients were intravenous drug abusers, none had any preexisting disease of the musculoskeletal system which might have predisposed to the development of OI. 1 patient underwent a brain biopsy (case 6) and developed frontal bone osteomyelitis and case 4 had diabetes.

On univariate analysis, only intravenous drug abuse was significantly associated with the development of OI ($p = 0.04$; OR =10; 95%IC =1.03–66, group A vs. group B). On the other hand, CDC classification, number of circulating T-CD4+ cells and PMN cells were not significantly associated with the development of OI. Comparing group A and C, no statistically significant differences were observed as regards the clinical presentation and outcome of OI.

Discussion

During 11 years, we identified 14 patients with OI among 4,023 consecutive HIV-infected patients. Interestingly, the risk of developing OI was, in our series, related neither to HIV infection "per se" nor to the degree of immunodeficiency, but to intravenous drug abuse.

Although previous reports (Chandrasekar and Narula 1986, Lopez-Longo et al. 1987, Munoz et al. 1991a) have indicated as characteristics of the OI observed in i.v. drug abusers, the male prevalence, the younger age and the preferential localization at the fibrocartilaginous joints, our study confirmed only the first two aspects. Bone scintigraphy was of value, especially in the early phase of the infection, since it was positive in all patients who had a clinical presentation suggestive of infection. The clinical findings

are essential for detection of real bone involvement, since HIV-infected subjects without osteoarticular symptoms may have increased radionuclide uptake due to bone marrow hypercellularity of no clinical significance (Rubies-Prat et al. 1996). In our series, CT and MRI of the spine were also useful for the definition of vertebral involvement and the detection of soft-tissue collection (Gold et al. 1991, Torda et al. 1995). CT-scan also had a role in monitoring the response to therapy (Magid and Fishman 1992, Torda et al. 1995).

In our study and in previous reports (Munoz et al. 1991a, b, Hughes et al. 1992, Sabbagh et al 1992), *S. aureus* was the most frequently isolated pathogen, whereas a polymicrobial infection was more rarely documented and no fungal infection was observed. Concerning drug treatment, therapeutic strategies depend both on gram-stain results and the patient's risk factors. In particular, if clusters of a gram-positive organism (suggestive of staphylococci) were seen on gram stain, a combination of a first-generation cephalosporin (e.g., cephalothin) and gentamicin was used. When the gram stain was negative or a gram-negative organism was suspected, a combination of a third-generation cephalosporin (ceftriaxone, ceftazidime) and an aminoglycoside (gentamicin, netilmicin, amikacin) was given. In selected patients with osteomyelitis, we used intravenous therapy with quinolones (ciprofloxacin) with good results. Vancomycin was prescribed to selected patients with documented *S. aureus* infection unresponsive to conventional antibiotic therapy, despite the fact that the isolated strains were "in vitro" methicillin-susceptible. The recommended duration of intravenous therapy for OI in HIV-infected patients is not yet well defined; however, it is generally accepted that antibiotic therapy should be continued for at least 4–5 weeks (Mader and Calhoun 1995). The switch to oral therapy is controversial and it must always follow an adequate parenteral therapy. Although we have only a limited experience of 2 patients, one can suggest, in accordance with previous reports (Mader and Calhoun 1995), that oral antibiotics should be administered to selected patients with a chronic course for several months, depending on clinical, radiographic findings and patient's compliance.

On the basis of our 10 years' experience, we conclude that osteoarticular infections are rare complications of HIV infection and that do not differ clinically from those observed in HIV seronegative patients. The role of drug addiction as a risk factor for HIV infection, may favor the development of osteoarticular infections in intravenous drug abusers, independently of HIV-induced immunodeficiency.

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References

Berman A, Reboredo G, Spindler A, Lasala M E, Lopez H, Espinoza L R. Rheumatic manifestation in population at risk for HIV infection: the added effect of HIV. J Rheumatol 1991; 18 (10): 1564-7.

Center for Disease Control (1992) revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992; N° RR-17: 1-19.

Chandrasekar P H, Narula A P. Bone and joint infections in intravenous drug abusers. Rev Infect Dis 1986; 8 (6): 904-11.

Currier J S, Feinberg J. Bacterial infection in HIV disease. AIDS Clin Rev 1995. 96; 131-52.

Edelstein H, McCabe R. Candida albicans septic arthritis and osteomyelitis of the sternoclavicular joint in patients with human immunodeficiency virus infection. J Rheumatol 1991; 18 (1): 110-1.

Edelstein H, Chirurgi V A, Hybarger C P. Osteomyelitis of the jaw in patients with human immunodeficiency virus. South Med J 1993; 86 (11): 1215-8.

Gold R H, Hawkins R A, Katz R D. Bacterial osteomyelitis: findings on plain radiography, CT, MR and scintigraphy . AJR Am J Roentgenol 1991; 157 (2): 365-70.

Hughes R A, Rowe I F, Shanson D, Keat A C S. Septic bone, joint and muscle lesions associated with human immunodeficiency virus infection. Br J Rheumatol 1992; 31 (6): 381-8.

Lopez-Longo F J, Menard H A, Carreno L, Cosin J, Ballesteros R, Montegaudo I. Primary septic arthritis in heroin users: early diagnosis by radiologic imaging and geographic variations in the causative agents. J Rheumatol 1987; 14 (5): 991-4.

Mader J T, Calhoun J. Osteomyelitis. In: Principles and Practice of Infectious Diseases. (Eds. Mandell G L, Douglas R G, Bennett J E). Churchill Livingstone, New York 1995: 922-30.

Magid D, Fishman E K. Musculoskeletal infections in patients with AIDS: CT findings. AVR Am J Roentgenol 1992; 158 (3): 603-7.

Marce S, Antoine J F, Schaeverbeke T, Vernhes J P, Bannwarth B, Dehais J. Enterobacter cloacae vertebral infection in a heroin addict with HIV infection. Ann Rheum Dis 1993; 52 (9): 695.

Munoz Fernandez S, Quiralte J, Del Arco A, Balsa A, Cardenal A, Pena J M, Vasquez J J, Gijon Banos J. Osteoarticular infection associated with the human immunodeficiency virus infection. Clin Exp Rheumatol 1991a; 9 (5): 489-93.

Munoz Fernandez S, Cardenal A, Balsa A, Quiralte J, Del Arco A, Pena J M, Barbado F J, Vazquez J, Gijon J. Rheumatic manifestation in 556 patients with human immunodeficiency virus infection. Semin Arthritis Rheum 1991b; 21 (1): 30-9.

Rubies-Prat J, Coll J, del Rio L, Soriano J C, Marinoso M L, Serrano S. Increased radionuclide uptake on bone scintiscan: a common but not clinically significant finding for human immunodeficiency virus type 1-infected patients free of osteoarticular symptoms. Clin Infect Dis 1996; 23, 170-2.

Sabbagh M, Meyer O, De-Bandt M, Salamon-Ceron D, Perrone C, Rosebaum W, Tremoliere F, Kahn M F. Bone manifestations associated with acquired immunodeficiency syndrome (AIDS). Ann Med Interne Paris 1992; 143 (1): 50-6.

Torda A J, Gottlieb T, Bradbury R. Pyogenic vertebral osteomyelitis: analysis of 20 cases and review. Clin Infect Dis 1995; 20 (2): 320-8.

Tumbarello M, Tacconelli E, Caponera S, Cauda R, Ortona L. The impact of bacteremia on HIV infection. Nine years' experience in a large Italian university hospital. Infect 1995; 31 (2): 123-31.

Tumbarello M, Tacconelli E, Lucia M B, Cauda R, Ortona L. Predictors of Staphylococcus aureus pneumonia associated with human immunodeficiency virus infection. Resp Med 1996; 90: 531-7.

Vail T P, Urbaniak J R. Hematogenous patellar osteomyelitis associated with human immunodeficiency virus. Orthop Rev 1991; 20 (9): 788-90.

Ventura G, Cauda R, Paliotta V F, Colosimo C, Lucia M B. Pott's disease of the cervico-occipital junction in an AIDS patient. Tuber Lung Dis 1996; 77, 188-90.