

Osteoarticular infections in HIV-infected patients

23 cases among 1,515 HIV-infected patients

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Background The reported incidence of osteoarticular infections in HIV-infected patients has varied in the literature.

Patients and methods We determined the incidence and characteristics of osteoarticular infections reported in a database of 1,515 HIV-infected patients between 1983 and 2003.

Results 23 HIV-infected patients were identified with an osteoarticular infection, 11 of whom had a spondylodiscitis. 16 were intravenous drug abusers; this was identified as a risk factor for developing an osteoarticular infection. The most common agent was *Staphylococcus aureus*. 6 patients required surgical intervention and in a worst-case scenario more than one-fifth had recurrence of their infection.

Conclusion Development of an osteoarticular infection is a rare complication in this group of HIV-infected patients, but a remarkably high number of infections of the spine were seen.

Patients infected with the human immunodeficiency virus (HIV) are vulnerable to opportunistic infections because of their progressive immunosuppression. Multiple infections are often seen in this group of patients. Osteoarticular infections in HIV-infected patients have been reported with varying rates (Muñoz et al. 1991, Louthrenoo 1997, Ventura et al. 1997, Berman et al. 1988). The infections are incapacitating and are often difficult to treat. Knowledge of epidemiology, the agents responsible, course, and therapy of the infection is important for the orthopedic surgeon to ensure correct management.

Patients and methods

Since 1983, we have collected data on all HIV-positive patients seen in our hospital (Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands). The hospital is a secondary care unit for HIV-infected patients and provides an HIV treatment program based on national guidelines.

We conducted a retrospective analysis of 1,515 HIV-positive patients who were included in the database from January 1983 through November 2003 and who had an osteoarticular infection. The infections were diagnosed clinically, radiographically and/or microbiologically. Of the patients with an osteoarticular infection, we detailed personal characteristics, the type of infection, the joint and/or bone segments involved, the causative agent, risk factors for HIV and for developing an osteoarticular infection, CD4 count at the time of presentation, the use of antiretroviral therapy, pharmacological therapy, and outcome. For statistics, an unpaired t-test with Welch correction and a Chi-squared test were used.

Results

Of the 1,515 HIV-infected patients included in the database, 23 patients (1.5%), (15 males, 7 females, and 1 transsexual) were identified as having had an osteoarticular infection. 13 of them were followed prior to their infection and had attended our outpatient clinic for HIV patients. 8 patients were seen for the first time with an osteoarticular infection, and in 2 of the patients it was unclear whether they

had been followed before the osteoarticular infection was seen. 13 patients had had a positive test for HIV before their first visit to our clinic. Mean age was 35 (21–52) years. 12 patients died: 10 from causes not related to their osteoarticular infection and 2 from an unknown cause. 3 patients were lost to follow-up.

Types of infection and causative agents

6 patients presented with a septic arthritis and 4 patients had an aseptic arthritis. Septic spondylodiscitis was diagnosed in 10 patients and 1 patient was diagnosed as having an osteomyelitis. 1 other patient had a spondylodiscitis in combination with an osteomyelitis of both femoral condyles and proximal tibial heads. 1 patient developed an infection after total hip replacement (Table).

A causative agent was identified in 19 of the 23 patients. In 8 cases, *Staphylococcus aureus* was identified in blood cultures, punctures, or biopsies. 5 patients tested positive for mycobacterium species and 5 other patients were infected with streptococcus species. In 1 patient, a coli-group bacterium and *Enterobacter cloacae* was found. In 1 patient, no causative agent could be determined after aspiration of the affected joint. No aspiration was performed in 3 patients with clinical signs of arthritis.

Risk factors

Regarding risk factors for HIV, 16 patients were intravenous drug abusers, 3 were homosexual, 1 male patient was bisexual, and 1 patient originated from an HIV-endemic area. No risk factor was identified in 2 cases. The 16 patients identified as intravenous drug abusers (see below) did so during the months prior to their infection. All of them were on methadone treatment after that.

412 (27%) of the 1,515 HIV-infected patients were intravenous drug abusers, 16 of whom (4%) developed an osteoarticular infection. Of the remaining 1,103 patients who were not intravenous drug abusers, 7 (0.6%) developed an osteoarticular infection. Chi-squared test revealed IVD as being a risk factor for development of an osteoarticular infection in HIV-positive patients ($p < 0.001$).

The CD4 count was determined in 19 patients and averaged 284 (20–900). Of the 23 patients with osteoarticular infections, 5 were on highly active anti-retroviral therapy (HAART) at the time of

the osteoarticular infection. In 9 patients of the 11 who developed a spondylodiscitis, the CD4 count could be determined. The mean CD4 count in the 4 patients with a spondylodiscitis caused by mycobacterial species was $355/\text{mm}^3$. In the 5 patients with other species, the CD4 count was $352/\text{mm}^3$.

Regarding possible confounding factors, none of the patients had any preexisting disease such as diabetes, which might have predisposed them to development of osteoarticular infection.

Treatment

All of the 19 patients in whom a causative agent was determined received intravenous antibiotics or anti-tuberculostatics. In 12 patients, drug therapy was started on the day of diagnosis or on the day after. The mean time between diagnosis and start of therapy in the remaining 7 patients was 26 (7–40) days. The reason for this delay in starting therapy was unclear. The mean duration of antibiotic treatment was 106 (5–386) days. The 5 patients in whom a mycobacterium species was identified were treated for longer (mean 293 days) than the 14 patients in whom other species were found (mean 40 days). The mean duration of intravenous therapy could not be determined. Of the 4 patients for whom no causative agent was determined, 1 patient was treated with non-steroidal anti-inflammatory drugs (NSAID), 1 with acetaminophen, and the remaining 2 did not receive any drug treatment.

Interventions

6 patients required surgical intervention because of their osteoarticular infection. 1 patient (case 5) with osteomyelitis of a phalanx (hand) underwent a debridement. The patient died from an HIV-related cause (rampant CMV infection) 3 months after surgery.

In 1 patient (case 9), a total hip prosthesis was removed after several months of antibiotic therapy. No recurrent infection was seen; the patient died of an unknown cause 3 years after surgery. Another patient (case 14) developed a septic coxitis which resulted in femoral head resection. 3 months after the resection, the patient died of a drug overdose.

3 patients with a spondylodiscitis underwent surgical intervention. 1 patient with a spondylodiscitis at C4–C5 (case 7) underwent debridement of

Characteristics of the 23 HIV-infected patients with an osteoarticular infection

A	B	C	D	E	F	G	H	I	J	K	L
1	21	M	4	SD	C7/Th1	<i>Staphylococcus aureus</i>	Flucloxacillin	52	No	400	S
2	41	M	1	SD	L1/L2	<i>Mycobacterium xenopi</i>	Isoniazide, rifabutin, myambutol and pyrazinamide	386	No	250	S
3	41	M	2	SA	Elbow, knee	<i>Mycobacterium kansasii</i>	Rifampycin, myambutol and pyrazinamide	226	No	20	LF
4	27	M	3	SD	L2/L3	<i>Streptococcus sanguis</i>	Penicillin, feneticillin	38	No	ND	LF
5	26	F	3	OM	Phalanx	Coliform gram-negative group and <i>Enterobacter cloacae</i>	Penicillin, flucloxacillin, and gentamycin locally	33	Yes	50	D
6	39	M	1	OM/SD	Femur/tibia and T8/9	<i>Staphylococcus aureus</i>	Flucloxacillin	39	No	100	D
7	38	M	3	SD	C4/C5	<i>Staphylococcus aureus</i>	Flucloxacillin	45	Yes	40	D
8	31	M	3	SD	L5/S1	<i>Mycobacterium tuberculosis</i>	Isoniazide, rifampycine, myambutol, and pyrazinamide	271	No	370	D
9	33	F	3	IP	Hip prosthesis	<i>Streptococcus mitis</i>	Amoxycillin	83	Yes	590	D
10	31	T	–	SD	L4/5	<i>Mycobacterium tuberculosis</i>	Isoniazide, rifabutin, myambutol, and pyrazinamide	335	No	180	S
11	33	F	3	SA	Knee	<i>Streptococcus</i> group G	Penicillin	11	Yes	160	D
12	30	F	3	SD	C5/C6	<i>Streptococcus pyogenes</i>	Penicillin	43	No	ND	S
13	34	M	3	SA	Knee	<i>Streptococcus pyogenes</i> (HS group A)	Penicillin	5	No	220	R+D
14	30	M	3	SA	Hip	<i>Staphylococcus aureus</i>	Flucloxacillin, clindamycin, and gentamycin locally	94	Yes	40	D
15	45	F	3	SA	Knee	<i>Staphylococcus aureus</i>	Flucloxacillin	15	No	ND	LF
16	33	M	3	SD	L4/L5	<i>Staphylococcus aureus</i>	Fusidin, clindamycin	36	Yes	320	R+D
17	37	F	3	SA	Knee	<i>Staphylococcus aureus</i>	Flucloxacillin	15	No	220	D
18	52	M	1	AA	Ankle	Not determined	NSAIDs	56	No	690	S
19	29	F	3	AA	Ankles	Not determined	–	–	No	ND	D
20	48	M	–	AA	Phalanx	Not determined	Acetaminophen	–	No	60	S
21	44	M	3	AA	Knee	Not determined	–	–	No	170	D
22	47	M	3	SD	Th6	<i>Staphylococcus aureus</i>	Flucloxacillin	42	Yes	900	S
23	25	M	3	SD	Th11/TH12	<i>Mycobacterium tuberculosis</i>	Isoniazide, rifampycin, ethambutol, pyrazinamide	248	No	620	S
A Case						F Localization					
B Age (years)						G Agent					
C Sex						H Therapy					
M male						I Duration (days)					
F female						duration of drug therapy					
T transsexual						J Surgery					
D Risk factors						K CD4 count					
1 homosexual						ND not determined					
2 bisexual						L Outcome					
3 intravenous drug abuser						S successful treatment/free of infection					
4 HIV-endemic area.						R recurrent infection					
E Type						LF lost to follow-up					
SA septic arthritis						D deceased					
AA aseptic arthritis											
SD spondylodiscitis											
OM osteomyelitis											
IP infected prosthesis.											

the infected area and spondylodesis from C3 to C7 was performed. No recurrent infection was seen;

the patient died of an unknown cause almost 10 years after the osteoarticular infection.

8 months after debridement of a spondylodiscitis at L4–L5 (case 16), reinfection of the glenohumeral joint was seen with the same organism. The patient died of an unknown cause 10 years later. Because of neurological involvement, another patient with a spondylodiscitis (case 22) underwent acute debridement of Th6 and spondylodesis was performed. No recurrence of infection was seen and neurological recovery was complete.

Outcome

15 patients had full recovery after treatment of their osteoarticular infection, and no recurrence was seen at review or until they died. 3 patients were lost to follow-up. 2 patients (cases 13 and 16) had a relapse of their infection. 1 patient (case 13) was admitted to the hospital for intravenous treatment of a bacterial infection of the knee but left the hospital against medical advice. Several weeks later, the patient returned with an infection of the shoulder, involving the same agent (*Streptococcus pyogenes*). The other patient with a spondylodiscitis (case 16) had a recurrent infection of the shoulder several months after treatment.

The osteoarticular infection did not require any antimicrobial treatment in 3 patients; there was no recurrence until review or death ($n = 2$). In a worst-case scenario, one-fifth had recurrence of their infection.

Discussion

Of 1,515 HIV-infected patients, 23 (1.5%) were registered as having an osteoarticular infection in our hospital. Osteoarticular infection rates in HIV-infected patients have been widely variable in previous reports. In a study by Berman et al. (1988) evaluating 101 HIV-infected patients, none developed an osteoarticular infection. Another report (Ventura et al. 1997) described bacterial osteoarticular infections as being rare manifestations in HIV-infected patients, with 14 cases (0.3%) found among 4,023 patients. Other studies have shown a higher prevalence of osteoarticular infections (Louthrenoo 1997, Muñoz et al. 1998); it is stated in these reports that personal characteristics other than HIV infection may have played a role in the pathogenesis of these infections. IVD abuse has

been identified as a risk factor in the development of an osteoarticular infection (Vassilopoulos et al. 1997, Belzunegui et al. 1997), and we found the same. Osteoarticular infections are known complications of IVD abuse. However, it has been reported that HIV infection itself does not predispose an IVD-abusing individual to development of a spinal or osteoarticular infection (Muñoz et al. 1993, Ventura et al. 1997).

In our study the most common agent was *Staphylococcus aureus* (in 8 of 19 patients); this finding is supported by other reports (Muñoz et al. 1991, Vassilopoulos et al. 1997, Ventura et al. 1997). All patients undergoing antibiotic treatment were treated for 2 weeks or longer, with the exception of 1 non-compliant patient. The effect of HIV infection on the course of the infection remains unclear; no guidelines exist at the moment regarding the duration of intravenous antibiotic therapy in these patients. It is generally accepted, however, that antibiotic therapy should be continued for at least 4–5 weeks (Mader 1995). A factor that should be considered in achieving successful treatment is the compliance of the individual patient. Especially with a large number of IVD-abusers, as in our group, it is advisable to continue intravenous antibiotic treatment in a clinical setting as long as necessary.

The high number of patients with a spondylodiscitis in our group—11/23—is remarkable. Considering these spinal infections, Weinstein and Eismont (2005) demonstrated that the type of infection and the type of organism vary depending on the CD4 count, and that the CD4 count can be used as a predictor of the clinical course. This relationship could not be shown in our study. The mean CD4 count in mycobacterial-induced spondylodiscitis was no different from that in patients with spondylodiscitis caused by other agents. Of the 3 patients with a CD4 count of $< 200/\text{mm}^3$ (cases 6, 7, and 10), 1 had a surgical intervention but none had a recurrent infection. Of the 6 patients with a CD4 count of $> 200/\text{mm}^3$ (cases 1, 2, 8, 16, 22, and 23) 2 underwent surgical debridement and 1 patient suffered from recurrent infection. The latter group did not have a milder course of infection, but our group was not large enough to draw conclusions.

We conclude that an osteoarticular infection is a rare complication in HIV-infected patients.

Guidelines for treatment of these infections in HIV-infected patients are lacking, and a better understanding of the pathogenesis and effect of HIV infection on the course of the infection will be necessary for correct management. The contributory role of HIV infection alone—quite apart from IVD-abuse—remains unclear, but it has been suggested that HIV-infected patients are more susceptible to spinal infections (Weinstein and Eismont 2005).

Contributions of authors

VJFB: collection of data, main author. RMR: collection of data and review of HIV-related topics. BH: collection of data. WJW: final review of manuscript, review of matters relating to clinical orthopedics.

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