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HIV INFECTION AS A RISK FACTOR FOR SEPTIC ARTHRITIS

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SUMMARY

We prospectively studied the demographics, the clinical and diagnostic features, the HIV-1 serostatus and the therapeutic response for all new patients with septic arthritis (SA) admitted to the Department of Internal Medicine of the Centre Hospitalier de Kigali, Rwanda, over a 19 month period. SA was diagnosed in 24 patients (10 male, 14 female), of whom 19 (79%) were HIV-1 seropositive (HIVpos). Gonococcal arthritis was found in four patients, all HIVpos. Non-gonococcal bacterial arthritis was established in 16 patients, of whom 13 were HIVpos. Causative organisms involved in this group and the corresponding HIV-1 serostatus of the patients were: *Staphylococcus aureus*: 4; 2 HIVpos, 2 HIVneg; *Streptococcus pneumoniae*: 4; 4 HIVpos; *Salmonella* group B: 2; 2 HIVpos; *Streptococcus* group D: 1; 1 HIVpos; *Klebsiella pneumoniae*: 1; 1 HIVpos; undetermined: 4; 3 HIVpos, 1 HIVneg. Tuberculous arthritis was presumed in four patients, of whom two were HIVpos. HIV-1-associated SA had a classical acute presentation and an overall good prognosis. Compared to a control group consisting of hospitalized patients with malaria as the sole diagnosis, patients with SA were more likely to be infected with HIV-1 ($P = 0.005$, OR 6.3; 95% CI 1.7–22.2). Prevalence rate estimates of SA among HIVpos and HIVneg patients were 0.5 and 0.25%, respectively ($P = 0.38$). We conclude that HIV-1 infection appears as a risk factor for SA among patients hospitalized at the Centre Hospitalier de Kigali, but that SA cannot be used a a predictor for HIV-1 infection for hospitalized patients. SA occurs infrequently and may present at any stage of HIV-1 infection.

KEY WORDS: Septic arthritis, HIV-1 infection, Africa.

INFECTION with the human immunodeficiency virus type 1 (HIV-1) may be accompanied by a wide variety of rheumatological manifestations [1, 2]. However, few studies have focused on septic arthritis (SA).

In 1986, a nationwide seroepidemiological survey of HIV-1 infection conducted in Rwanda estimated the seroprevalence rate in the general population at 1.3% in rural areas and 17.8% in the cities. However, a peak prevalence of 30% was found among urban adults of the 26–40 yr age group [3].

In this study, we report the findings of a prospective cross-sectional study on SA at the Department of Internal Medicine of the Centre Hospitalier de Kigali (CHK), Rwanda. Particular attention is given to the demographic characteristics of the patients, the clinical and diagnostic features of SA, and its association with HIV-1 infection. An attempt is made to estimate the prevalence of SA among HIV-1-infected patients.

PATIENTS AND METHODS

The study was carried out from 1 September 1989 until 31 March 1990 and from 1 June 1990 until 31 May 1991.

All patients admitted to the Department of Internal Medicine of CHK with inflammatory joint disease were submitted to the following investigations if they consented. (1) Careful medical history and a full clinical evaluation with particular consideration of the Centers for Disease Control (CDC) staging system of HIV infection [4, 5] and the presence of the major and minor clinical signs of the World Health Organization Clinical Case Definition of AIDS (WHO/CCDA) [6]. (2) Screening for HIV-1 antibodies using an enzyme immunoassay (EIA; Vironostika, Organon Teknika, Boxtel, the Netherlands); positive tests with EIA were confirmed by the indirect immunofluorescence (Serofluor, Virion, Zurich, Switzerland) or the Western blot techniques (Biotech, Du Pont de Nemours, Wilmington, DE, USA). A Western blot test was considered positive if antibodies to at least one core protein (p17, p24, p55) and antibodies to at least one envelope protein (gp41, gp120, gp160) were present. All clinical investigators were blinded to the HIV-1 status of the patients. (3) In the case of joint effusion, examination of the synovial fluid including absolute and differential white cells counts, screening for microcrystals, determination of protein level, Gram and Ziehl–Neelsen stainings, and inoculation of a complete set of culture media for the isolation of common aerobic bacteria, mycobacteria and fungi, including Löwenstein and Sabouraud agar slants. (4) Radiographs of affected joints. (5) In patients with fever $\geqslant 38^{\circ}$C, at least one set of blood cultures for aerobic bacteria and fungi using brain–heart infusion and thioglycollate media as well as the

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TABLE I
Demographic, clinical and biological features, and outcome of 19 HIV-1-infected patients with septic arthritis

Patient number	Sex	Age	Involved joint	SF culture	Blood culture	WHO/CCDA	CDC stage	Associated diseases	Treatment outcome
Neisseria gonorrhoeae									
1	M	29	ankles right knee	−	−	−	II	conjunctivitis urethritis	ofloxacin 14 days cured
2	F	26	left knee intertarsals	+	−	−	II	conjunctivitis	norfloxacin 14 days cured
3	F	20	left ankle right proximal interphalangeal	+	−	−	II	tenosynovitis	ofloxacin 14 days cured
4	F	?	knees	−	−	−	III		ofloxacin 14 days cured
Staphylococcus aureus									
5	M	19	right knee	+	−	−	II	oesophageal candidiasis	RMP 40 days gentamicin 10 days cured
6	M	25	right knee	+	−	−	IVC1	pneumonia	oxacillin 40 days gentamicin 10 days sequelae
Streptococcus pneumoniae									
7	M	39	right knee left elbow right wrist left ankle	+	−	−	IVC1	pneumonia oesophageal candidiasis	ampicillin 40 days sequelae
8	F	35	left knee	+	−	−	IVC2	pneumonia pleural tuberculosis	ampicillin 40 days cured
9	F	23	right meta-tarsophalangeal	+	−	−	II	pneumonia	ampicillin 40 days cured
10	F	48	right knee	+	−	−	IVA	pneumonia	ampicillin 40 days arthrotomy cured
Streptococcus group D									
11	F	22	left sacroiliac	+	−	−	II	polyarthritis	gentamicin 6 days ampicillin 40 days cured
Salmonella group B									
12	M	25	elbows	+	+	+	IVC2	bacteraemia prostatitis	gentamicin 7 days norfloxacin 30 days cured
13	M	25	left sacroiliac	+	+	+	IVC2	bacteraemia	gentamicin 7 days norfloxacin 30 days cured
Klebsiella pneumoniae									
14	M	37	right knee	−	+	−	IVC1	oesophageal candidiasis pneumonia	gentamicin 7 days ceftriaxone 30 days cured
Undetermined									
15	F	37	right knee	−	−	−	III		gentamicin 10 days RMP 40 days cured
16	F	23	right sacroiliac	−	−	−	II		gentamicin 10 days oxacillin 40 days cured

TABLE I (*continued*)

Patient number	Sex	Age	Involved joint	SF culture	Blood culture	WHO/CCDA	CDC stage	Associated diseases	Treatment outcome
17	F	36	knees	−	−	+	IVA	pleuro-pneumonia	ampicillin 40 days cured
Mycobacterium tuberculosis									
18	M	41	right sacroiliac	−	−	+	IVC2	miliary tuberculosis	INH-RMP-EMB cured
19	F	23	left sacroiliac	−	−	+	IVC2	miliary tuberculosis	INH-streptom. EMB died

SF, synovial fluid; WHO/CCDA,World Health Organization clinical case definition for AIDS; CDC, Centers for Disease Control; INH, isoniazid; RMP, rifampicin; EMB, ethambutol; streptom., streptomycin.

centrifugation haemolysis system (Isolator, Du Pont de Nemours, Wilmington, DE, USA). (6) PPD tuberculin intradermal test with 5 TU (Institut Pasteur du Brabant, Brussels, Belgium).

Patients with a history suggestive of gonococcal arthritis were treated with norfloxacin 800 mg/day or ofloxacin 400 mg/day as a therapeutic test.

A diagnosis of pyogenic SA was established (1) when a pathogen was recovered from the synovial fluid or (2) when the culture of a purulent synovial fluid was negative but blood culture was positive or (3) when a dramatic improvement was achieved with antibiotics in a patient with purulent joint fluid.

A diagnosis of gonococcal arthritis was established on the basis of arthritis (1) when *Neisseria gonorrhoeae* was recovered from the synovial fluid or (2) when *N. gonorrhoeae* was recovered from the cervicovaginal exudate and a dramatic response to norfloxacin or ofloxacin was obtained within 72 h.

A diagnosis of probable tuberculous arthritis was considered in patients with joint involvement on X-ray together with a strong reactive PPD tuberculin intradermal test (diameter >15 mm) and a favourable response to a 2 month antituberculosis treatment.

From 1 July 1990 onwards, HIV-1 testing has been proposed to each patient admitted to the Department of Internal Medicine. The prevalence of SA among HIV-1-seropositive patients was estimated by dividing the number of HIV-1-seropositive patients with SA admitted to the Department of Internal Medicine between 1 July 1990 and 31 March 1991 by the total number of HIV-1-seropositive patients hospitalized in the department during the same period.

To investigate the degree of correlation between SA and HIV-1 infection, we used a control group consisting of patients with malaria as the sole diagnosis, a condition not known to be associated with HIV-1 infection. For each patient with SA, all malaria patients of the same age and sex hospitalized during the same study period were included as controls.

A matched analysis of the case–control data and the calculation of the odds ratio (OR) with 95% confidence intervals (CI) were carried out using a software package (Epi Info, Version 5, USD, Incorporated, Stone Mountain, GA, USA, 1990). Non-matched proportions were compared using the χ^2 test.

RESULTS

During the 19 month study period, SA was diagnosed in 24 patients (10 male and 14 female), of whom 19 (79%) (eight male and 11 female) were infected with HIV-1 (Table I).

All the patients with SA were heterosexual Rwandese. The median and mean age were 28 and 26 yr, respectively (range 18–48 yr).

Arthritis was the main reason for seeking medical care and was community acquired. Of the 19 HIV-1-seropositive patients with SA, five (26%) fulfilled the WHO/CCDA criteria, seven (37%) belonged to CDC stage II, two (11%) to stage III, two (11%) to stage IVA, three (16%) to stage IVC1 and five (26%) to CDC stage IVC2.

Demographic, clinical and biological features of SA and the response to treatment are detailed in Table I.

Gonococcal arthritis was diagnosed in four HIV-1-seropositive patients and was the first presenting manifestation of HIV-1 infection in three. Three patients belonged to CDC stage II and one to stage III. All patients were symptom free 24 h after the start of treatment.

Sixteen patients had non-gonococcal bacterial arthritis probably following haematogenous dissemination. Thirteen (81%) of them were HIV-1 seropositive. Of these, eight were classified as stage IV. All patients presented with at least one warm, swollen and painful joint which contained purulent synovial fluid. None of these patients had a previous history of arthritis, recent joint trauma or surgery. All except three had monoarthritis. Synovial fluid culture was positive in nine patients and a blood pathogen was isolated in three. *Streptococcus pneumoniae* was the most common pathogen recovered from HIV-1-seropositive patients (four), followed by *Staphylococcus aureus* (two), group B *Salmonella* (two), *Streptococcus* group D (one) and *Klebsiella pneumoniae* (one). Antibiotics given for 4–6 weeks cured all HIV-1-seropositive patients, but two retained sequelae. Three patients had no microorganism isolated from joint fluid or blood, but all responded favourably to antibiotics

TABLE II
Demographic, clinical and biological features, and outcome of five cases of HIV-1-negative septic arthritis

Patient number	Sex	Age	Involved joint	SF culture	Blood culture	WHO/CCDA	CDC stage	Associated diseases	Treatment outcome
Staphylococcus aureus									
1	M	18	elbows	+	+	−	NA	pneumonia	oxacillin 40 days gentamicin 10 days sequelae
2	M	18	left hip	+	+	−	NA	pneumonia endocarditis	oxacillin 40 days gentamicin 10 days sequelae
Undetermined									
3	F	26	left knee	−	−	−	NA		gentamicin 10 days RMP 40 days cured
Mycobacterium tuberculosis									
4	F	29	left sacroiliac	−	−	−	NA		INH-RMP-EMB cured
5	F	28	left sacroiliac	−	−	−	NA		INH-RMP-EMB cured

A diagnosis of tuberculous arthritis was presumed in four patients, of whom two, both HIV-1-seropositive, had concomitant miliary tuberculosis. One of these two patients died during hospitalization.

Between 1 July 1990 and 31 May 1991, 1850 HIV-1-seropositive and 1170 HIV-1-seronegative patients were admitted to the Department of Internal Medicine. Among the HIV-1-seropositive patients, SA was diagnosed in nine, while in the HIV-1-seronegative group three patients had SA. The estimated prevalences of SA among HIV-1-seropositive and HIV-1-seronegative patients hospitalized in the Department of Internal Medicine of CHK were thus 9/1850 (0.5%) and 3/1170 (0.25%), respectively ($P = 0.38$).

Among the 135 patients with malaria used as a control group, 67 (50%) were HIV-1 seropositive. Compared to this control group, patients with SA were significantly more likely to be infected with HIV-1 ($P = 0.005$; OR 6.3, 95% CI 1.7–22.2).

DISCUSSION

Although immune deficiency is the hallmark of HIV infection, SA has been reported in few HIV-positive patients. No previous prospective studies of the incidence and prevalence of septic arthritis in HIV-infected individuals are available, but several studies suggest that this combination is infrequent. In a longitudinal cohort study of 117 HIV-1-seropositive patients followed up over a mean period of 24.6 months, Calabrese *et al*. [7] reported one case of SA. Moreover, Solinger and Hess [8] did not find a single case among 1100 HIV-seropositive out-patients. Similarly, in 420 HIV-1-seropositive women followed up for 36–48 months in a longitudinal cohort study on the natural history of HIV-1 infection in Kigali, acute arthritis was diagnosed in only six subjects (S. Allen, personal communication), all having aseptic arthritis.

In a population with high HIV-1 seroprevalence, we found that the prevalences of SA among HIV-seropositive and -seronegative hospitalized patients are not statistically significantly different. However, compared to a control group, patients with SA were significantly more likely to be infected with HIV-1. We conclude that SA is strongly associated with HIV-1 infection, but that SA cannot be used as a predictor of HIV-1 infection for hospitalized patients in the Department of Internal Medicine where 80% of the patients are hospitalized for other infectious diseases.

Results of the use of the WHO/CCDA criteria and the CDC staging of HIV-1 infection in our HIV-1-seropositive patients suggest that SA may occur at an early as well as at an advanced stage of HIV-1 infection. Similar to patients without HIV infection, our patients with gonococcal arthritis had oligoarticular or polyarticular arthritis and were cured without sequelae. Our patients with non-gonococcal pyogenic SA had features characterized by haematogenous contamination of the joint, clinical evidence of infection (fever, acute arthritis, purulent joint fluid) and a favourable outcome. Two HIV-seropositive patients had tuberculous arthritis with classical presentation, but one of these died during hospitalization.

In Africa, before the AIDS epidemic, *N. gonorrhoeae* and *Staphylococcus aureus* were the more common causes of infectious arthritis [10].

A review of the literature showed that most cases of septic arthritis in HIV-positive patients are due to pyogenic bacteria other than *N. gonorrhoeae* and that the distribution varies across risk factor groups [9]. In

developing countries, the prevalent transmission of HIV via heterosexual contact explains the frequency of gonococcal arthritis, whereas the poor environmental conditions (crowding, defective hygiene) and the immune deficiency explain the risk factors for *Streptococcus pneumoniae* and *Salmonella typhi*. The higher rate of pneumococcal and *Salmonella* arthritis seen in our HIV-seropositive patients also accords with a previous study of bacteraemia in Africa [11].

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