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TUMOURS AND INFECTIONS

Reactivation of chronic haematogenous osteomyelitis in HIV-infected patients

Siyo Z[1], Marais LC[2]

[1] MBChB, FC Orth SA; Department of Orthopaedics, School of Clinical Medicine, University of KwaZulu-Natal, Pietermaritzburg, South Africa
[2] MBChB, FC Orth SA, MMed Ortho, PhD; Department of Orthopaedics, School of Clinical Medicine, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Corresponding author: Dr Z Siyo, Department of Orthopaedic Surgery, School of Clinical Medicine, University of KwaZulu-Natal, Grey's Hospital, Pietermaritzburg, 3200, South Africa; email: zukosiyo@gmail.com

Abstract

Background: The aim of the study is to determine the prevalence of HIV infection among adult patients with reactivation of haematogenous chronic osteomyelitis.

Methods: A retrospective analysis of prospectively collected data from 143 adult patients with chronic osteomyelitis.

Results: A total of 143 patients were included in the study group, with a mean age of 38 years (range 14–78 years). Twenty-two per cent (n=31) of patients were diagnosed with reactivation of chronic haematogenous osteomyelitis, while 78% of patients had contiguous chronic osteomyelitis (29% [n=42] post-operative and 49% [n=70] post-traumatic, respectively). Forty (28%) patients were found to be HIV positive with a mean CD4 count of 414 cells/mm³ (range 13–1 034 cells/mm³). Twenty-four (60%) of patients with HIV were on antiretroviral therapy at time of diagnosis. The prevalence of HIV infection among patients with contiguous (post-operative or post-traumatic) infections was 32%, in comparison to 13% in the group with reactivation of chronic haematogenous infections (p=0.04; OR 3.2; 95% CI 1.0–9.8).

Conclusion: The prevalence of HIV infection among patients with reactivation of chronic haematogenous osteomyelitis appeared to be lower than that seen in patients with chronic osteomyelitis from other causes and lower than that seen in the general population in South Africa.

Level of evidence: Level 4

Key words: haematogenous, osteomyelitis, HIV, AIDS

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Introduction

The total number of people living with human immunodeficiency virus (HIV) in South Africa is currently estimated at approximately 7.06 million. In the age group 15–49 years, the national prevalence is estimated at 16.8%.[1] The prevalence in KwaZulu-Natal, the second largest province in South Africa with a population of approximately 11.1 million people, is currently estimated at 21.5%.[2] HIV infection results in a combination of immune suppression and chronic inflammation through the mechanisms of immune exhaustion with effector T-cell dysfunction and immune senescence with premature aging of the immune system.[3] The resulting neutrophil, monocyte and B-lymphocyte abnormalities lead to a decreased capacity for bacterial phagocytosis and an increased rate of bacterial infections. Methicillin-resistant *Staphylococcus aureus* infection is, for example, 6–18 times more common in HIV patients than in the general population.[4] HIV co-infection is presumed to be among the major contributing factors to the pathogenesis of bone infection.

Chronic osteomyelitis can be defined as a biofilm-based infection where the majority of pathogens are sessile-based and are resiliently attached to the nidus of infection.[5] In the case of chronic haematogenous osteomyelitis, the nidus of infection is typically a sequestrum that is formed following acute osteomyelitis in childhood. The appropriate treatment of acute haematogenous osteomyelitis has resulted in a drastic decrease in the incidence of chronic osteomyelitis of haematogenous origin in the developed world; however, it remains fairly common in the developing world.[6] Owing to the unique characteristics of the causative organisms, reactivation of chronic osteomyelitis may occur as much as 65 years following the initial infection.[7,8] These characteristics include the internalisation of bacteria by osteoblasts which is mediated by the sigma B regulon in the case of *Staphylococcus aureus*.[9] The exact cause of the reactivation of infection has, however, not been clearly defined but it is believed to be associated with a decrease in local or systemic immune protection. Jellis reported a possible increase in haematogenous osteomyelitis in patients with HIV infection. This was however only a comment and further data on the topic was not provided.[10] To the best of our knowledge, there is currently no data on the reactivation of chronic haematogenous osteomyelitis in HIV patients.

The aim of the study is to determine the prevalence of HIV infection among adult patients with reactivation of haematogenous chronic osteomyelitis.

Materials and methods

A retrospective descriptive study was performed on prospectively collected data from consecutive patients seen at a tertiary-level tumour and sepsis unit with chronic osteomyelitis. All adult patients over the age of 14 years assessed from January 2011 to December 2014 were included in the study. Patients excluded from the study were those with atypical infections including fungal, parasitic and tuberculosis, acute post-operative infection, periprosthetic joint infection or hand sepsis.

Following ethical approval from the relevant biomedical ethics review board, data were collected with respect to patient age, cause of osteomyelitis (haematogenous or contiguous), physiological host stage and anatomic nature of the disease according to the Cierny and Mader classification system, HIV status, CD4 count and the presence of antiretroviral therapy.

For the purposes of this study chronic osteomyelitis was defined as an infection involving bone, with a duration of at least ten days, where the causative organisms were thought to have persisted either intracellularly or in interactive biofilm-based colonies. Haematogenous chronic osteomyelitis was defined as the reactivation of chronic osteomyelitis resulting from a previous episode of acute osteomyelitis of haematogenous origin. Contiguous chronic osteomyelitis was defined as chronic osteomyelitis resulting from a prior open fracture (post-traumatic) or operative intervention (post-operative).

All patients were screened for HIV infection. Following clinical, radiological and biochemical evaluation, patients were classified according to a modified version of the original Cierny and Mader classification system *(Table I).*[11] In terms of the physiological status of the host, the Cierny and Mader classification system was modified in order to provide a more pragmatic and objective definition of a C host. A patient was classified as a C host if one major or more than two minor risk factors were present *(Table II).* In order to remove any ambiguity during classification of the anatomical nature of the disease, this was performed prior to, rather than following, the debridement.

Statistical analysis was performed using Stata 13.0 (StataCorp. College Station, Texas). Continuous variables were reported as mean (± SD) or median (with interquartile range) and categorical variables as numbers and percentages, unless otherwise stated. Categorical data were compared using the Fisher's exact test or the chi-square test. All tests were two-sided, and the level of significance was set at $p<0.05$.

Table I: Modified version of the original Cierny and Mader classification system that served to guide treatment strategy selection[11]

Classification	Characteristic
Physiological	
Type A host	No risk factors
Type B host	Fewer than three minor risk factors
Type C host	One major and/or three or more minor risk factors
Pathoanatomy	
I – Medullary	No cortical sequestration
II – Cortical	Direct contiguous involvement of cortex only
III – Combined (stable)	Both cortex and medullary regions involved
IV – Combined (unstable)	As for III plus unstable prior to debridement
Nidus	
Sequestrum	Cortical sequestrum present
Implant	Biofilm-based infection in presence of implant
No identifiable nidus	Minimal necrosis osteomyelitis
Impairment	
Minimal	Patient able to perform ADL (activities of daily living)
Severe	Unable to perform ADL

Table II: Risk factors used to stratify the physiological status of the host[11]

Major risk factors	Minor systemic risk factors	Minor local risk factors
CD4 count <350 cells/mm³	HIV infection	Poor soft tissues requiring flap
Albumin <30 g/L	Anaemia	Chronic venous insufficiency
HbA1C ≥8%	Smoking	Peripheral vascular disease
Cellulitis or abscess	Diabetes mellitus	Previous radiation therapy
Malignancy at site of infection	Rheumatoid arthritis	Surgery will result in instability
Pathological fracture	Chronic lung disease	Adjacent joint stiff/arthritic
	Chronic cardiac failure	Heterotopic ossification
	Paraplegia/quadriplegia	Failed reconstruction elsewhere
	Drug or substance abuse	Foot involvement
	Chronic corticosteroid use	Pelvic involvement
	Active tuberculosis	Adjacent joint involved
	Ischaemic heart disease	Segmental resection of ≥6 cm required to achieve cure
	Cerebrovascular disease	
	Compliance and motivation	
	Age >65 years	
	Common variable immune deficiency	

Results

A total of 149 patients met the inclusion criteria. Four patients with early post-operative infection and two patients with fungal osteomyelitis were excluded, leaving a total of 143 patients in the study group. The mean age of patients was 38 years (range 14–78; standard deviation [SD] 15.5 years). Twenty-eight per cent (n=40) of patients were found to be HIV positive with a mean CD4 count of 414 cells/mm³ (range 13–1 034; SD 132 cells/mm³). Sixty per cent (n=24) of patients with HIV were on antiretroviral therapy at time of diagnosis.

Twenty-two per cent (n=31) of patients were diagnosed with reactivation of chronic haematogenous osteomyelitis, while 78% of patients had contiguous chronic osteomyelitis (29% [n=42] post-operative and 49% [n=70] post-traumatic, respectively). The location of the infection was the tibia in 52% of cases (n=75), femur in 27% (n=39), humerus, pelvis or foot in 5% (n=7), fibula or radius/ulna in 3% (n=5) and clavicle in 1% of cases. Overall, 15% (n=21) of patients were classified as A hosts, 41% (n=59) were B hosts and 44% (n=63) C hosts. Of the B hosts, nine patients were HIV-positive with a mean CD4 of 627 cells/mm³. Thirty-one (49%) of C hosts were HIV-positive, mean CD4 352 cells/mm³.

The prevalence of HIV infection among patients with contiguous (post-operative or post-traumatic) infections was 32%, in comparison to 13% in the group with reactivation of chronic haematogenous infections (p=0.04; OR 3.2; 95% CI 1.0–9.8) *(Table III).* In addition, there was a significant difference between the two groups in terms of the site of infection, the physiological stage of the host and the anatomic nature of the disease *(Table III).* Two of the four HIV patients in the haematogenous group (mean CD4 487 cells/mm³) were on antiretroviral medication compared to 12 of the 28 patients in the contiguous group (mean CD4 405 cells/mm³).

Discussion

Considerable controversy remains regarding the association of HIV infection and the development of bone infections. In the 1990s, Jellis and Hoekman independently reported an infection rate of operatively treated fractures of 24% and 33% in symptomatic HIV patients.[10,12] In contrast, a study by Harrison *et al*., in 2002, showed that the risk of post-operative infection is dependent on wound contamination. HIV status was not found to be a risk factor for wound infection following operative management of closed fractures.[13] The study reinforced earlier findings that asymptomatic HIV-positive patients with high energy open injuries were prone to infection compared to HIV negative.[14] In contrast to this, Howard *et al*. showed that HIV does not necessarily increase early infection in open fractures.[15] These findings were echoed by Niewoudt *et al*., who noted that HIV did not appear to be associated with an increased risk of deep infection or non-union in grade III open tibia fractures treated with circular external fixation.[16] The influence of CD4 count on the development of infection also remains unclear. Guild *et al*., showed an increased infection rate in patients with a CD4 count below 300.[17] All of the above-mentioned studies, however, focused on contiguous (post-operative or post-traumatic) infections. Limited data is available on the impact of HIV on haematogenous osteomyelitis.

Lavy and co-workers noted a three-fold increase in the number of septic cases treated in Malawi and speculated that this may, at least in part, have been the result of an increased seroprevalence of HIV.[18] While osteomyelitis was mentioned in this report, haematogenous osteomyelitis was not specifically looked at. In 1996 Jellis reported an increase in the incidence of adult long-bone haematogenous osteomyelitis in patients with HIV and further stated that it was a common orthopaedic presentation of adults with advanced HIV disease.[10]

The aim of this study was to determine the prevalence of HIV infection among adult patients presenting with chronic haematogenous osteomyelitis in an attempt to investigate the possible association between HIV infection and adult chronic osteomyelitis. Intuitively, it seems reasonable to expect that an immune-compromising disease like HIV/AIDS might cause an increase in the incidence of reactivation of quiescent adult osteomyelitis, especially in patients with very low CD4 counts.

Somewhat surprisingly we found a lower prevalence of HIV infection among adult patients presenting with chronic haematogenous osteomyelitis in comparison to adult osteomyelitis from other causes (13% vs 32%, p=0.04). The prevalence of HIV infection in the contiguous group of patients was comparable to that seen in the general population of the region where the study was performed; however, in the haematogenous group it was considerably lower. In addition, the HIV-positive patient who did present with haematogenous osteomyelitis did not have

Table III: Comparative statistics of patients with reactivation of chronic haematogenous osteomyelitis and contiguous osteomyelitis

	Haematogenous chronic osteomyelitis (n=31)	Contiguous chronic osteomyelitis (n=112)	p-value
Site			**0.01**[iii]
Tibia	12 (39%)[i]	63 (56%)	
Femur	15 (48%)	24 (21%)	
Humerus	-	7 (6%)	
Other	4 (13%)	18 (16%)	
Host staging[12]			**<0.01**[iii]
A-host	13 (42%)	8 (7%)	
B-host	10 (32%)	49 (44%)	
C-host	8 (26%)	55 (49%)	
Anatomic classification[12]			**<0.01**[iii]
Type 1	-	3 (3%)	
Type 2	-	2 (2%)	
Type 3	26 (84%)	44 (39%)	
Type 4	5 (16%)	63 (56%)	
HIV status			**0.04**[iv]
Positive	4 (13%)	36 (32%)	
Negative	27 (87%)	76 (68%)	
CD4 count [vi]	**487 (360–646)**[ii]	**405 (13–1 034)**	**0.47**[v]

(i) n (%); (ii) mean (range); (iii) chi-square test; (iv) Fisher's exact test (v) t-test; (vi) CD4 count of HIV-positive patients in each group

exceptionally low CD4 counts. While this study by no means provides the definitive answer, it appears that HIV infection may not necessarily be associated with the reactivation of quiescent haematogenous osteomyelitis in adults, as was initially thought.

This study has several shortcomings. Due to the retrospective nature of the study it was not possible to determine how many patients with haematogenous osteomyelitis remained asymptomatic. Thus, we were unable to compare the true prevalence of reactivation in HIV-positive and -negative patients. A long-term prospective follow-up of patients with haematogenous osteomyelitis will be required for this purpose. A further limitation is the small sample size, especially in the haematogenous group. The question therefore remains unanswered and further research in the field is warranted.

Conclusion

The prevalence of HIV infection among patients with reactivation of chronic haematogenous osteomyelitis appeared to be lower than that seen in patients with chronic osteomyelitis from other causes, and lower than that seen in the general population in South Africa. This appears to be in contradiction to previous reports stating that HIV infection may be associated with adult chronic haematogenous osteomyelitis.

Ethics statement

Prior to commencement of the study ethical approval was obtained from the following ethical review boards:

1. KwaZulu-Natal Department of Health (KZ_2016RP44_836)
2. Biomedical Research Ethics Committee (BREC 204/16)

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.
Informed written consent was not obtained from all patients included in the study.

Declarations

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

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Author contributions

ZS: Literature review conceptualisation, design, data collection and analysis, manuscript.
LCM: Conceptualisation, design, data collection and analysis, manuscript.

ORCID

Siyo Z http://orcid.org/0000-0002-8420-9244
Marais LC http://orcid.org/0000-0002-1120-8419

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