Case Report

The rarity of gonococcal arthritis in association with HIV infection

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Abstract

Gonococcal urethritis is common with HIV, but gonococcal arthritis is rare. We report two HIV-positive patients with gonococcal arthritis and review previously published reports. A 27-year-old HIV-positive female presented with a pustular skin rash and acute oligoarthritis. *Neisseria gonorrhoeae* was cultured from the right elbow aspirate. The second patient, a 24-year-old HIV-positive female on zidovudine for one month, presented at 28 weeks gestation with acute oligoarthritis and peroneal tenosynovitis. *Neisseria gonorrhoeae* was cultured from the throat swab. Both patients responded to ceftriaxone. Gonococcal arthritis must be considered in HIV patients with acute arthritis.

Key words: *Neisseria gonorrhoeae*; arthritis; DGI; disseminated gonococcal infection; HIV; AIDS.

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Introduction

The spectrum of articular syndromes reported in association with HIV infection include reactive arthritis, psoriatic arthritis, undifferentiated spondyloarthropathies, non-specific arthralgia, HIV-associated arthritis, osteonecrosis, and septic arthritis. The widespread use of highly active anti-retroviral therapy (HAART) has resulted in a change in the spectrum of rheumatic manifestations, and articular syndromes are now seen less commonly, especially in Western populations [1,2]. HIV is associated with an increased risk of infections; although septic arthritis is well documented, it is uncommon. A review of HIV cohort studies shows a relatively low risk for septic arthritis [2]. Several studies of septic arthritis have shown that in HIV-positive patients, intravenous drug use was the most significant risk factor, and that the organisms involved were similar to septic arthritis in HIV-negative patients [3-5]. The organisms most commonly identified are *Staphylococcus aureus* and streptococcal species, which usually occur in patients with CD4 cell counts of > 200 cells/mm³. Opportunistic infections are more likely when the CD4 counts are < 200 cells/mm^3 [2].

The risk of transmission of HIV infection is increased in ulcerative and non-ulcerative sexually transmitted infections (STIs), with a two- to fivefold increase reported in most studies [6]. A twofold increase was reported with bacterial vaginosis, a 2.7- to 5-fold increase with chlamydia infection, a 2- to 5-fold increase with gonococcal urethritis, and a 2.3- to 8.6-fold increase was reported in syphilis [6,7]. There is a wide variation in the prevalence of gonococcal infection in patients with HIV infection, ranging from 1.7% and 2.7% in Zambia and Switzerland, respectively, to a higher prevalence of 12% and 19% in the USA and Jamaica, respectively [8]. The prevalence of gonococcal infection and HIV co-infection has been reported in about 5.4% of asymptomatic HIV-infected individuals in South Africa [9]. The effect of HIV on gonococcal infection is, however, less clear. It has been suggested that patients with HIV are immune compromised, and therefore more likely to develop disseminated gonococcal infection (DGI) [10].

According to the World Health Organization's 2011 report on the prevalence and incidence of sexually transmitted diseases (*Chlamydia trachomatis, Neisseria gonorrhoeae*, syphilis, and *Trichomonas vaginalis*), there were a total of 448 million new STIs in 2005, and *N. gonorrhoeae* accounted for about 88 million cases (19.6%) [11]. The 2012, UNAIDs report noted that at the end of 2011, there were a total of 34 million people living with HIV, and the majority of them were in developing countries in Africa [12]. Based on these statistics, one would expect many cases of HIV infection and gonococcal arthritis. However, in clinical

practice, although gonococcal urethritis is common in association with HIV infection, gonococcal arthritis is very uncommon. We report two patients with HIV infection and gonococcal arthritis and review the data on the previously reported cases of gonococcal arthritis and HIV infection.

We reviewed the records of two patients with HIV infection and gonococcal arthritis who were seen in the Department of Rheumatology at Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa. Their clinical data, results of laboratory tests, treatments, and outcomes were recorded. Ethics approval for the reporting of the patients was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. We conducted a PUBMED search to identify cases of HIV infection and gonococcal arthritis published in the English literature up to the end of August 2013 using the terms HIV or AIDS along with gonococcal arthritis, disseminated gonococcal infection, or septic arthritis.

Case Reports

Patient 1

A 27-year-old HIV-positive female presented with a one-week history of acute onset of severe joint pain and swelling involving the right elbow, right wrist, right knee, and left ankle. She worked as a machinist and was unable to walk for five days. HIV infection had been diagnosed eight months before presentation, and she was not on antiretroviral therapy. She recently completed a course of treatment for pulmonary tuberculosis. There was no history of pelvic discharge. On examination, she was apyrexial, and pustular lesions were noted on the right wrist and right knee. There was acute inflammation involving the right wrist, right knee, and left ankle. In addition, the swelling of the right elbow extended beyond the joint margin to involve the periarticular soft tissues. The white cell count was 7.14×10^9/L and C-reactive protein (CRP) was markedly elevated to 254 mg/L. The CD4 count was 86 cells/mm³ and the viral load was 46,778 copies/mL. The rheumatoid factor and anti-nuclear factor were negative, and the serum uric acid was normal. Plain radiographs of the affected joints were normal. A pharyngeal swab did not culture any organisms. *N. gonorrhoeae* was cultured from the right elbow joint aspirate. She was treated with intravenous ceftriaxone for 21 days, doxycycline and metronidazole. The repeat CRP decreased to 2 mg/L. There was complete resolution of her symptoms on discharge. She was started on antiretroviral therapy and was counseled about the importance of her partner being assessed and treated for sexually transmitted infections.

Patient 2

A 24–year-old pregnant female presented at 28 weeks gestation with a five-day history of pain and swelling involving the wrists and the right ankle. Rheumatic heart disease with mitral valve regurgitation was diagnosed at the age of 12 and mitral valve replacement was performed in 2011. She was on oral penicillin VK and warfarin therapy. Hypertension was diagnosed a year earlier and was well controlled on hydralazine. She was known to be HIV positive and was started on zidovudine for one month. On examination, she was apyrexial and did not have any skin lesions. There was active inflammation of both wrists and the right ankle with marked tenderness and limitation of movement. She also had right peroneal tenosynovitis. The white cell count was 16.2×10^9/L and the CRP was raised to 208 mg/L. The CD4 count was 680 cells/mm³ and the viral load was 2,236 copies/mL. The rheumatoid factor and anti-nuclear factor were negative. A joint aspirate was not performed, as the patient was on warfarin. The throat swab cultured *N. gonorrhoeae*, sensitive to ceftriaxone. She received intravenous ceftriaxone for 14 days and metronidazole. She improved on treatment. The repeat white cell count was 4.5×10^9/L and the CRP was 4 mg/L. She was counseled about the need for her partner to be assessed and treated for sexually transmitted infections.

Literature review

Based on the PUBMED search, we identified only 11 reports comprising 15 cases of gonococcal arthritis and HIV infection [3-5,10,13-19]. The demographic data, clinical features, laboratory findings, and outcome of these patients, together with our two patients, are summarized in Table 1. Some of the patients with gonococcal arthritis reported were part of a series of patients with septic arthritis. Thus, detailed clinical information about individual patients was not recorded in these reports (patients 5, 6, 8, 14, 15 in Table 1) [3-5,19]. An analysis of the previously reported patients showed that the median age was 28.5 years (range 20–47 years) in the 10 patients where age was recorded. There were 7 males and 5 females among the 12 patients about whom this information was available. The CD4 count was recorded in only 5 of the 15 patients, with a median CD4 count of 310 cells/mm^3 (range 114–380 cells/mm^3)

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Table 1. Manifestations of gonococcal arthritis in HIV+ patients in published reports

No	Author	Country	Age	Sex	Site of MSK infection	Skin lesions	Joint or blood culture	Mucosal swabs	Urethritis	CD4 cells /mm³	Treatment (days)	Response to treatment
1	Moyle *et al.*, 1990 [13]	UK	25	M	L shoulder, MTP L big toe, R 3rd MTP	Absent	R 3rd PIP +	U,P, Rec negative	Absent	114	IV benzylpenicillin (7) ampicillin (7) oral erythromycin (5)	Yes
2	Strongin *et al.*, 1991 [14]	USA	27	M	R Hip and L SC joint	Absent	R hip + BC negative	U, P, Rec negative	Absent		IV cephalosporin, amoxycillin (14)	Yes
3	Jacoby *et al.*, 1995 [10]	USA	35	F	Both wrists and ankles Tenosynovitis left hand and foot	Present	BC X 2 +	Not done		380	IV ceftriaxone (17)	
4	Louthrenoo *et al.*, 1995 [15]	Thailand	40	F	R elbow, L 2rd, 3rd MCP, MTP L big toe, both wrists, knees and ankles	Present	R knee, R wrist, L ankle +, Skin +	P+ Rec, C ,U negative	Absent	310	IV ceftriaxone (28)	Yes
5	Perez, 1999 [3]	Spain	28		R knee		R knee +					
6	Belzunegui *et al.*, 2000 [4]	Spain										
7	Tejeros *et al.*, 2003 [16]	Spain	37	M	R knee	Absent	R knee +		Absent	228	Ceftriaxone (14) cefuroxime (21)	Yes
8	Zalavras *et al.*, 2006 [5]	USA										
9	Saraux *et al.*, 2007 [17]	Rwanda	29	M	Ankles, R knee		Joint negative BC negative		Present		Ofloxacin (14)	Yes
10		Rwanda	26	F	L knee, intertarsals		L knee + BC negative		Absent		Norfloxacin (14)	Yes
11		Rwanda	20	F	L ankle, R PIP, tenosynovitis		L ankle + BC negative		Absent		Ofloxacin (14)	Yes
12		Rwanda		F	Knees		Joint negative BC negative	Cervico-vaginal +			Ofloxacin (14)	Yes
13	Yarav et al, 2009[18]	USA	47	M	Both shoulders	Absent	Both shoulders +	Negative	Absent	329	IV cefotaxime (7) oral doxycycline	Yes
14	Belkacem et al, 2013[19]	France		M	Arthritis (?site), tenosynovitis	Present			Absent			
15		France		M	Arthritis (?site) tenosynovitis	Present			Absent			
16	Current report	South Africa	27	F	R wrist, R elbow, R knee, L ankle	Present	R elbow +	P, U negative	Absent	86	IV ceftriaxone (21)	Yes
17		South Africa	24	F	Wrists R peroneal tenosynovitis	Absent	Not done	P +	Absent	680	IV ceftriaxone (14)	Yes

Blank spaces denote that this information was not reported in the publication; U: urethral, P: pharyngeal, Rec: rectal, C: cervical, L: left, R: right, MSK: musculoskeletal, MTP: metatarsophalangeal, PIP: proximal interphalangeal, SC: sternoclavicular, MCP: metacarpophalangeal, BC: blood culture

In the 10 patients where the treatment of the gonococcal arthritis was cited, all patients showed a response with improvement or resolution of symptoms. Six patients received therapy, which would also cover *C. trachomatis* infection, four patients received quinolones (patients 9, 10, 11, and 12), one received doxycycline (patient 13), and the remaining patient received erythromycin (patient 1), as shown in Table 1. Information about treatment of chlamydial infection was not reported in the remainder of the patients.

Discussion

Gonococcal arthritis occurs as a result of hematogenous spread of *N. gonorrhoeae*, resulting in DGI [20]. However, DGI is uncommon in patients with gonococcal urethritis and has been reported to occur in 0.5%–3% of patients [21]. In 1971, Barr *et al.* reported that 1.9% of their patients with gonorrhea developed DGI, which manifested as septic gonococcal dermatitis (in 3.0% of females and 0.7% of males) [22]. There are no recent estimates of the prevalence of DGI or gonococcal arthritis in patients with gonorrhea.

The risk of developing DGI is related to host, microbial, and immune factors [23]. Among the host factors, there is an increased risk in patients with systemic lupus erythematosus, congenital or acquired complement deficiency, or following a recent menstruation or pregnancy. DGI is three times more common in women, and most of the patients who develop DGI, both women and men, have asymptomatic mucosal infections [23]. In patients with HIV infection and gonococcal arthritis, there was an equal gender prevalence of seven males and seven females (including our two patients) in those whose gender was reported. These findings are different from the threefold increase in HIV-negative females with DGI. DGI is most common in the 15- to 35-year age group in HIV-negative patients, which is similar to the median age of 28.5 years in our review [20]. The results of CD4 counts were only available in seven patients (including our two patients), and we were unable to identify any association with DGI. The microbial factors associated with DGI depend on the virulence and growth factors of the organism. They include the outer membrane characteristics such as abundance of low molecular weight protein 1A (porin serotype 1A), a lack of protein II on the outer membrane, and the AHU auxotype which requires arginine, hypoxanthine, and uracil for growth [23]. Immune factors have also been implicated; viable *Neisseria gonorrhoeae* may not be required for the manifestations of DGI, as cultures of the blood, skin, and synovial fluid are frequently negative [23]. Urethritis was present in only 2 of the 13 patients with HIV infection and gonococcal arthritis in whom this information was reported (Table 1). Although HIV infection has been considered a risk factor by some authors, this is unlikely to be the case, as they have rarely been reported to occur together.

Two clinical forms of presentation have been reported in patients with DGI: the bacteraemic form, also referred to as the "dermatitis-arthritis syndrome," is characterized by the triad of skin lesions, tenosynovitis, and polyarthralgia; and the suppurative form, which usually presents as localized infectious arthritis with mono- or oligoarticular involvement [20,24]. These two forms are not clinically distinct and probably represent a continuum of the infection [21]. Our two patients had oligoarthritis, which usually occurs in the suppurative form of presentation. Patient 1 had the typical skin lesions, while patient 2 also had tenosynovitis; as these features are usually seen in the bacteraemic form, it is likely that our two patients had overlapping features of both forms of presentation. Skin lesions were present in 7 of the 11 patients with HIV and gonococcal arthritis, as shown in Table 1. The joint involvement in HIV-negative patients with the suppurative presentation is predominantly monoarticular compared to the oligoarticular involvement in 10 (58%) of the 17 patients with HIV infection (Table 1). Some of the other systemic manifestations of DGI such as meningitis, endocarditis, and osteomyelitis are much less common [20].

The diagnosis depends on a high index of suspicion. If urethritis is present, a Gram stain of the urethral exudate may show the presence of Gram-negative diplococci. Patients should also have blood cultures, culture of the synovial fluid, and swabs from the skin lesions and mucosal surfaces such as the urethra, cervix, pharynx, and rectum. *N. gonorrhoeae* is isolated from the synovial fluid in only about half the patients, from blood cultures in about one-third of patients, and rarely from the skin [23]. Endocervical swab cultures are positive in up to 90% of affected women, pharyngeal swabs in 50%–75%, urethral swabs in 20%, and rectal mucosa swabs in 15% of cases [25]. The use of nucleic acid amplification testing has helped to detect *N. gonorrhoeae* from skin and pharyngeal samples, and polymerase chain reaction (PCR) may lead to the detection of gonococcal DNA in the synovial cavity [23]. Table 1

shows that *N. gonorrhoeae* was isolated from joint fluid culture of 9 of the 11 patients who had joint aspirates, from 3 of the 7 patients who had mucosal swabs, and from blood culture in only 1 patient.

The majority of the patients with HIV and gonococcal arthritis in our review were treated with ceftriaxone or quinolones (Table 1). The response to treatment in our two patients was slow; they therefore received treatment with ceftriaxone for 14 and 21 days. Assessment and treatment of sex partners of patients for STIs is mandatory, as they usually have an asymptomatic infection.

In conclusion, although gonococcal urethritis is common in patients with HIV infection, DGI is rare; we were only able to identify 15 previously reported cases apart from our two patients. There are many possible causes of acute arthritis in HIV-positive patients, and gonococcal arthritis must be included in the differential diagnosis. When DGI is suspected, it is essential to obtain samples from mucosal sites, as blood, synovial fluid, and skin cultures are often negative. It is of paramount importance for the sex partner(s) of the patient to be evaluated and treated for STIs to prevent re-infection. In HIV-positive patients with gonococcal arthritis, an oligoarticular presentation was more common and there was no significant gender difference compared to HIV-negative patients.

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Disclosures

Rasha Maharaj is a member of the AbbVie advisory board (South Africa). Girish M. Mody is a member of the Vimovo advisory board for Astra Zeneca (South Africa).

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