Soft Tissue Rheumatic Lesions and HIV Infection in Zambians

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ABSTRACT. ***Objective.*** To explore the relationship between human immunodeficiency virus (HIV) infection and soft tissue rheumatic lesions in HIV-positive black Zambians.

Methods. We performed a prospective study of all patients over 18 years of age attending a rheumatic clinic in a teaching hospital. All patients underwent routine blood tests, and radiographs were performed when indicated. HIV status was determined by ELISA, and clinical staging was determined by World Health Organization criteria. Patients with isolated sacroiliac pain, enthesitis, or a soft tissue lesion were selected for analysis. For HIV-positive patients, only those in clinical stage 1 (asymptomatic or persistent generalized lymphadenopathy) were selected.

Results. Our study cohort comprised 120 patients (41 men, 79 women, age 23-70 yrs). Diagnosis and number (% HIV positive) were distributed as follows: sacroiliitis, 14 (100%); heel pain, 14 (100%); costochondritis, 3 (100%); polyenthesitis (≥ 4 sites), 20 (100%); carpal tunnel syndrome, 8 (63%); rotator cuff syndrome, 18 (30%); tendinitis, 8 (25%); sciatica/cervical spondylosis, 12 (16%); sacroiliac strain, 7 (0%); and de Quervain's tenosynovitis, 16 (0%). HIV seroprevalence was 54% overall, 74% in those under 45 years of age, and 17% in those over 45 years of age. Population prevalence of HIV in Lusaka is about 30% in the 30-40-year age range. Mean erythrocyte sedimentation rate (ESR) in 65 patients positive for HIV was 80 mm/h and in 55 patients negative for HIV, 18 mm/h. Within each subgroup the mean ESR was significantly higher in HIV-positive patients.

Conclusion. A young age and a raised ESR are both good indications of HIV infection in Zambian patients with soft tissue lesions. Enthesitis is a distinct HIV-related phenomenon, either an early form or a forme fruste of HIV-related spondyloarthropathy. (J Rheumatol 2006;33:2493–7)

Key Indexing Terms:
SOFT TISSUE LESIONS HIV ZAMBIA SPONDYLOARTHRITIS

The rheumatic manifestations of human immunodeficiency virus (HIV) infection are well documented[1]. We established the association of spondyloarthropathies (SpA) with HIV infection in Zambians and have observed patients with isolated enthesitis or sacroiliitis who are HIV positive[2]. However, the relationship with soft tissue lesions remains incompletely described. The emphasis nowadays is to make voluntary testing for HIV a routine part of medical care. Patients with sexually transmitted diseases or tuberculosis are routinely offered counseling for HIV testing. However distinguishing patients with a higher likelihood of HIV positivity remains a clinical challenge for health workers in areas with high HIV prevalence.

There is a need for simple clinical and laboratory algorithms to assist in the identification of patients with a high likelihood of HIV infection, particularly in the early stages of infection. Patients so identified could then be specifically targeted for further evaluation and HIV testing. We investigated 120 indigenous black Zambian patients with a spectrum of soft tissue lesions and analyzed the associations with concurrent HIV infection.

MATERIALS AND METHODS

Study participants. All patients older than 18 years who attended an outpatient rheumatic diseases clinic from January 1997 through December 1998 with isolated sacroiliac pain and tenderness, enthesitis, or a soft tissue lesion were studied prospectively. Patients who had attended reviews for at least 3 months were selected for analysis. Details of joint symptoms, heel pain, back pain and stiffness, mucosal and skin lesions, symptoms of acute anterior uveitis, conjunctivitis, urethritis, diarrhea, venereal exposure, and personal and family histories of arthritis were recorded. Demographic information (e.g., sex, age, occupation), history of trauma, and duration of symptoms were obtained. Special attention was paid to the affected part and also to joints, spine, entheses, sacroiliac joints, external genitalia, eyes, and buccal mucosa.

Laboratory testing. Full blood count, erythrocyte sedimentation rate (ESR), and renal and hepatic function tests, and a duplicate anonymous and unlinked test for HIV (ELISA) were carried out in all consenting patients. HIV infection was staged according to World Health Organization (WHO) clinical criteria[3]. Patients wishing to know their HIV status were offered pre-test counseling, and prognosis and options for treatment were given to those who tested positive. European Spondylarthropathy Study Group (ESSG) criteria were used to diagnose spondyloarthropathy in those who exhibited additional articular/extra articular features on followup[4].

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Evaluation of soft tissue lesions. The following specific diagnoses were confirmed: enthesitis: pain at an enthesial site accompanied by tenderness with or without swelling; plantar fasciitis: history of heel pain on start up after rest, especially overnight, with pain on palpation of the medial calcaneal tuberosity; Achilles insertional tendinitis: pain and swelling at the calcaneal insertion of the Achilles tendon; Achilles tendinitis: pain and tenderness in the tendon; lateral/medial epicondylitis at the elbow: resisted extension/flexion at the wrist; polyenthesitis: spontaneous pain and tenderness over at least 5 entheses with swelling in at least one or more sites; rotator cuff syndrome: pain despite a normal posterior/anterior radiograph of the shoulder; rotator cuff tendinitis: history of pain in the deltoid area and pain on resisted active movement (abduction, supraspinatus, external rotation infraspinatus, internal rotation suscapularis); bicipital tendinitis: anterior shoulder pain and pain on resisted active flexion or supination of the forearm; shoulder capsulitis: pain in the deltoid area and equal restriction of active and passive glenohumoral movement with a capsular pattern (external rotation greater than abduction greater than internal rotation); de Quervain's disease of the wrist: pain over the radial styloid, and tender swelling of the first extensor compartment and either pain produced by resisted extension of the thumb or positive Finkelstein's test; tenosynovitis of the wrist: pain on movement localized to the tendon sheaths in the wrist and reproduction of pain by resisted active movement; carpal tunnel syndrome: pain or paresthesiae or sensory loss in the distribution of the median nerve and either a positive Tinel's test, positive Phalen's test, nocturnal exacerbation of symptoms, or wasting of abductor policis brevis (nerve conduction testing was not available); sciatica/cervical spondylosis: lumbar/cervical pain in leg or shoulder/arm accompanied by signs of motor or sensory nerve root involvement due to nerve root compression in the lumbar or cervical spine; sacroiliac pain/tenderness: pain in the buttock with positive stress test (springing pelvis, knee/hip flexion, passive then adduction of thigh to contralateral iliac fossa). All patients with sacroiliac pain had a pelvic radiograph.

Inclusion/exclusion criteria. Patients were excluded if they had a history of (or were known to have had) arthritis or inflammatory myositis or a septic lesion. For HIV positive patients, only those with WHO clinical stage 1 (asymptomatic or persistent generalized lymphadenopathy) were included[3]. ESSG criteria were used to diagnose undifferentiated spondyloarthropathy (SpA).

Statistical analysis. The chi-squared test was used to explore differences between proportions; the imdependent samples t test was used to determine differences in means between 2 groups; and one-way ANOVA was used for differences in means of 3 or more groups. Differences were regarded as significant if the 2-tailed p value was < 0.05. Comparison groups comprised HIV positive versus HIV negative patients, and men versus women. Comparisons were made both within and between the various diagnostic groups. An ESR of > 30 mm/h was regarded as elevated, and age 45 years was the cutoff point between older and younger patients. Using these cutoff points, we calculated diagnostic sensitivities and specificities for HIV infection in association with age and elevated ESR.

RESULTS

Patients. One hundred and twenty patients (41 men, 79 women) were identified in the 2 years of study; mean followup duration: 9.4 months (range 3-18 mos); age range 23-75 years (78 under 45 years of age). Table 1 shows age, gender, HIV seroprevalence, and ESR. Table 2 shows ESR and age by diagnostic group and HIV status.

HIV seroprevalence. HIV seroprevalence for the whole group was 54.2%; 74.4% were positive among those under 45 years of age (n = 78); and 17% were positive among those over 45 years (n = 42). HIV prevalence in men was significantly higher than in women (p = 0.001). The higher proportion overall of HIV-positive men was partly explained by the absence of men with tenosynovitis and tendinitis, which are associated with low HIV seroprevalence. When the 24 patients with these lesions were excluded from analysis, the resultant HIV prevalence of 62% among women was not statistically significantly different from that of 70.7% among men. Furthermore, the occurrence of these lesions only in women implies gender-related and/or occupational exposure. This is highlighted by the fact that half of those with wrist tendinitis were nursing babies, which is a recognised risk factor for repetitive strain injury to the wrist in women.

Age and ESR. HIV-positive patients were significantly younger than their HIV-negative counterparts (p = 0.0005), but there was no statistically significant difference in mean age between men and women (p = 0.931). Comparison by gender and HIV status revealed no significant age differences between patients of the same HIV status. HIV-positive patients had a significantly higher mean ESR value than HIV-negative patients (p = 0.0001). This was true for the whole group as well as for both the within and between gender comparisons: HIV-positive men and women had a similar mean ESR value. HIV-negative women had a higher mean ESR than HIV-negative men, but the difference was not significant. HIV-positive patients with rotator cuff syndrome were significantly younger and had significantly higher ESR values than their HIV-negative counterparts (p = 0.05). Polyenthesitis patients (all HIV-positive) were similar in age and ESR values to HIV-positive patients with rotator cuff syndrome but were significantly younger and had significantly higher ESR values than HIV-negative patients with rotator cuff syndrome (p = 0.05). HIV-positive patients with carpal tunnel syndrome were younger (not significant) and had higher ESR values (significant: p = 0.001) than HIV-negative patients. They were, however, similar in age and ESR values (high) to HIV-positive patients with compression neuropathy due to sciatica/cervical spondylosis. HIV-negative patients with carpal tunnel syndrome were younger (p = 0.05) than the HIV-negative patients with sciatica/spondylosis and had similar (normal) ESR values.

Polyenthesitis. Twenty patients (8 men, 12 women) had polyenthesitis; all were HIV positive and had raised ESR (range 30-125 mm/h), and 19/20 were under 45 years. Two women 31 and 23 years old also had carpal tunnel syndrome at presentation; both had markedly elevated ESR at 104 and 114 mm/h, respectively. During followup, 2 other women (age 38 and 39 years with ESR of 116 and 73 mm/h at presentation, respectively) developed polyarthritis; the 39-year-old patient also developed acute anterior uveitis.

Rotator cuff syndrome. Eighteen patients were diagnosed with rotator cuff syndrome: 4/8 men and 2/10 women were HIV positive. HIV-positive patients all had elevated ESR (range 37-100 mm/h), significantly higher than the HIV-negative patients with rotator cuff syndrome (p = 0.001); they were also younger (p = 0.001). Of the 12 HIV-negative patients, only one 56-year-old woman had an elevated ESR at 40

Table 1. Age, gender, HIV seroprevalence and erythrocyte sedimentation rate (ESR) in the study cohort.

Variable	N	Age, Yrs, mean (SD)	HIV Prevalence, %	ESR, mm/h, mean (SD)
All patients	120	41.51 (13.57)	54.2	51.71 (36.96)
Men	41	41.66 (14.25)	70.7	60.12 (39.87)
Women	79	41.43 (13.29)	45.6	47.34 (34.82)
Positive	65	33.83 (8.16)	—	79.75 (17.10)
Negative	55	50.58 (13.11)	—	18.56 (8.61)
Positive men	29	35.03 (7.99)	—	79.70 (29.89)
Positive women	36	32.86 (8.29)	—	79.80 (25.06)
Negative men	12	57.67 (13.48)	—	12.80 (6.62)
Negative women	43	48.60 (12.45)	—	20.20 (8.45)

Table 2. ESR and age by diagnostic group and HIV status.

Diagnostic Group	HIV Status	N	Age, yrs mean (SD)	ESR, mean (SD)
Polyenthesitis	Pos	20	35.35 (5.29)	87.40 (29.46)
Rotator cuff syndrome	Pos	06	38.33 (1.33)	68.50 (23.52)
	Neg	12	59.75 (7.17)	21.83 (7.52)
Tendinitis	Pos	02	26.50 (2.12)	36.00 (16.97)
	Neg	06	43.33 (12.88)	18.50 (5.75)
Sciatica/cervical spondylosis	Neg	10	38.50 (6.36)	65.00 (21.21)
	Pos	2	64.40 (6.45)	14.80 (8.89)
Carpal tunnel syndrome	Pos	05	33.80 (13.14)	77.00 (29.48)
	Neg	03	43.67 (1.53)	16.00 (8.89)
Sacroiliac pain	Pos	14	26.69 (3.52)	86.92 (19.45)
	Neg	07	36.00 (8.86)	20.38 (12.95)
Tenosynovitis	Neg	16	46.40 (10.31)	19 (9.19)
Heel pain/periostitis	Pos	14	36.9 (7.45)	73.1 (23.92)

Pos: positive; Neg: negative.

mm/h. One of the 2 HIV-positive women (25-year-old with ESR of 90 mm/h at presentation) subsequently developed costochondritis and polyarthritis. All HIV-negative patients were over 45 years old (range 48-70 yr) and 4 of the 6 HIV-positive patients were less than 45 years old.

Wrist tendinitis. There were 8 women with wrist lesions (flexor carpi radialis and ulnaris insertional lesions). Three were middle-aged (53, 55, and 57 yrs). The rest were young women (age range 25-33 yrs) of whom 4 (including both HIV-positive patients) were nursing babies aged 3-7 months. In these 4 nursing women, symptoms started within 2-6 months of delivery. One HIV-positive patient subsequently developed polyenthesitis and then an oligoarthritis involving ankle and knee joints.

Carpal tunnel syndrome. Eight patients had carpal tunnel syndrome: 2/2 men and 3/6 women were HIV positive. All HIV-positive patients had an elevated ESR (range 45-114 mm/h), and all HIV-negative patients a normal ESR. Two HIV-positive patients (1 man, 1 woman) developed polyarthritis in the course of followup: the woman also developed polyenthesitis.

Sciatica/cervical spondylosis. Twelve patients (8 men, 4 women) were diagnosed with sciatica/cervical spondylosis: 4 patients with sciatica and 8 with cervical spondylosis; 2/8 men were HIV positive, both with sciatica due to lumbar disc prolapse; they were 34 and 43 years old and their ESR were 80 and 50 mm/h, respectively. They were the youngest in this diagnostic group. The remaining patients were middle-aged or elderly (range 57-75 yrs).

Tenosynovitis. Fifteen women had de Quervain's tenosynovitis and 1 woman had a trigger finger. All were HIV negative with a normal ESR. Nine were over 45 years of age.

Heel pain/periostitis. Thirteen patients had heel pain and tenderness (with or without localization to the calcaneal insertions of the Achilles tendon and/or plantar fascia), and one had clavicular shaft periostitis. Except for 2 women who were 49 and 54 years old, everyone in this group was under 45 years of age (range 26-39). All had ESR > 30 mm/h (range 30-115 mm/h). Four (2 men, 2 women) developed additional lesions in the course of followup as follows: one woman developed a knee monoarthritis and inflammatory low back pain; the other woman developed more enthesiopathic lesions in the mid-foot and elsewhere; one man developed clinical sacroiliitis; the other man developed a polyarthritis with polyenthesitis and sausage digits.

Sacroiliac pain/tenderness. Twenty-one patients had sacroiliac pain/tenderness. Three patients (2 men, 1 woman) reported

a history of injury, and in 4 women the problem arose in association with pregnancy/childbirth. Of the 7 in this "sacroiliac strain" subgroup, one pregnant woman had an ESR of 35 mm/h. The others had ESR values < 30 mm/h (range 5-28).

Fourteen patients (4 men, 10 women) developed spontaneous buttock pain with a positive clinical stress test for sacroiliitis, normal radiograph, and elevated ESR (range 34-110 mm/h). The majority (n = 11) of the patients with sacroiliitis were aged 20-30 years. The one patient negative for HIV was a 49-year-old woman with an ESR of 40 mm/h. Four HIV-positive patients subsequently developed polyarthritis and enthesitis; one patient each also developed dactylitis and anterior uveitis.

Costochondritis. Three patients were diagnosed with costochondritis: all had bilateral involvement mostly of the upper 1-5 costal cartilages. All had an elevated ESR and were HIV positive. A 40-year-old man developed additional lesions in the course of followup; these were a transient shoulder arthritis followed by an inflammatory myositis.

Sensitivity and specificity for HIV infection associated with age and ESR. Fifty-eight of the 65 HIV-positive patients were younger than 45 years whereas only 20 of the 55 HIV-negative patients were under 45 years, giving a sensitivity of 89.2%, specificity of 63.6%, and positive predictive value of 74.4%; 64 of the 65 HIV-positive patients, but only 6 of the 55 HIV-negative patients had an ESR > 30 mm/h, giving a sensitivity of 98.5%, specificity of 89.1%, and positive predictive value of 91.4%.

DISCUSSION

HIV infection has taken on the mantle of syphilis and systemic lupus erythematosus (SLE) as the great mimic. The recent rise in prevalence of spondyloarthropathies among HIV-infected sub-Saharan Africans, who lack genetic predisposition for these diseases, has drawn attention to HIV as a specific predisposing factor for some rheumatic diseases[2,5-7]. Non-specific musculoskeletal pain is common in the course of HIV infection. However, the link with specific soft tissue syndromes remains unclear. What is more, within the spectrum of soft tissue lesions, their natural history and distinguishing characteristics have not been described in sub-Saharan Africa, currently the epicenter of the world's HIV pandemic. Literature from the West consists of small series of patients known to be infected with HIV who are referred with rheumatic symptoms. The largest such series is that of 14 patients reported by Rowe, *et al*[8], the largest single group of whom had shoulder lesions. Since the majority of HIV infections occur in the young and energetic, it is to be expected that some soft tissue lesions will occur coincidentally with HIV infection. In the absence of defined clinical or laboratory indications, it is difficult to identify patients with a higher likelihood of HIV infection. This situation prevails in everyday clinical practice in regions with high HIV prevalence such as sub-Saharan Africa. This is particularly so in patients in the early stages of HIV infection when there is an absence of clinical signs. Our results show that whereas some forms of soft tissue lesions are clearly HIV-related, others do occur coincidentally. An elevated ESR generally has a sufficiently high positive predictive value for HIV infection to be used as a laboratory marker. However, ESR may be of greater clinical utility in patients with non-HIV related lesions, where the finding of an elevated ESR is a good indication for the likelihood of HIV infection.

In those patients with multiple tender entheses, we included only those who also had clinical swelling at one or more sites, thus protecting the integrity of our entry criteria and excluding patients with non-organic disease (e.g. regional pain syndromes, fibromyalgia). Our cohort of 120 patients comprised a heterogenous group linked only by a soft tissue rheumatic condition. As a group therefore, they form a basis against which any possible influence of HIV infection can be evaluated. Clinically, WHO stage 1 patients are indistinguishable from HIV-negative patients. Our inclusion criteria therefore ensured that comparison was restricted to clinically similar individuals.

The high association with HIV among patients with polyenthesitis, heel pain, chondritis, and inflammatory sacroiliitis (98% of 51) mirrors our previous report of patients with SpA[2]. This similarity is further highlighted by the fact that 11 (21.6%) of the 51 patients with these lesions developed additional features, with the majority evolving into undifferentiated SpA[4].

Enthesitis is well described as a systemic lesion in SpA and as a local lesion in sports injuries and occupational activities[9,10]. Isolated enthesitis has also been reported in some patients with undifferentiated SpA in the context of an HLA-B27-associated disorder[11]. None of the patients in the present series were tested for HLA-B27, but we have not identified any with this antigen in our previous studies or in our patients with SpA[2]. We previously reported 14 HIV-positive patients with isolated enthesitis, 4 of whom subsequently developed arthritis[2]. The 51 patients we report here confirm this lesion to be a distinct HIV-related phenomenon, which in some patients may either be an early form or a forme fruste of HIV-related SpA disease. The higher prevalence of HIV infection among younger patients is expected from general population prevalence patterns. However, the HIV seroprevalence of 74.4% among those aged below 45 years is significantly higher than the general population prevalence of about 30% for Lusaka[12]. HIV prevalences among patients with rotator cuff syndrome (6 of 18), tendinitis (2 of 8), and sciatica/spondylosis (2 of 12) are not different from expected general population estimates. However, in the within group analysis, a young age and an elevated ESR remain highly predictive of HIV infection.

In contrast, carpal tunnel syndrome (60% HIV positive) is clearly not a benign lesion in some younger patients.

The diagnostic classification criteria used in our study are certainly far from ideal. They are based on a syndromic

approach to the differential diagnosis of rheumatic problems, which creates the background for reclassification of patients over time. For example, in the tendinitis/enthesitis group, polyenthesitis (as noted above) is a distinct HIV-related entity. Most patients with tendinitis however, appear to have mechanically induced disease. It is noteworthy that the only HIV-positive patient with tendinitis with a high ESR at presentation subsequently developed polyarthritis and polyenthesitis. Similarly 2/6 HIV-positive patients with carpal tunnel syndrome (60% of whom were HIV positive) developed similar additional locomotor pathology. These are probably examples of patients seen early before the development of widespread disease. In this situation, a raised ESR is indicative of underlying HIV infection and progressive disease. Finally, pyogenic sacroiliitis is a recognized problem in patients with HIV[1,13]. In our evaluation of patients with sacroiliac pain, we carefully identified and excluded those who might have pyogenic sacroiliitis. Alternating buttock pain, absence of fever, other constitutional symptoms, and a symptomatic response to treatment with an antiinflammatory agent help identify patients for HIV screening. It is not surprising that the only patient to develop an extraarticular feature (uveitis) at followup came from this group.

Our observations indicate that certain lesions, in particular polyenthesitis, periostitis/heel pain, and costochondritis are in their own right strongly associated with HIV infection. Our study also clearly shows that a young age and an elevated ESR are both associated with sufficiently high positive predictive values to be used as diagnostic markers for early HIV infection among all patients with soft tissue lesions.

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