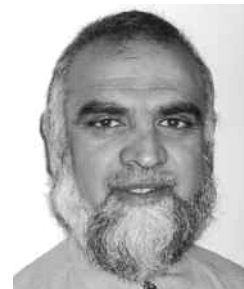


The Scourge of HIV Infection in Sub-Saharan Africa — A Rheumatological Perspective



Nowhere has the devastation from HIV/AIDS been more greatly felt than in sub-Saharan Africa. Of the estimated 33 million people globally who live with HIV/AIDS, 22.5 million or 5% of the adult population are from this region and 1.3 million people have succumbed to the infection in 2009¹. Much of the clinical and research efforts have been directed, and rightly so, at preventing the spread of the disease and treatment with highly active antiretroviral therapy (HAART). But like syphilis in previous times, HIV/AIDS has become the great mimic of the 21st century, and the burden from noninfectious systemic complications is substantial.

Since the first report of HIV-associated reactive arthritis almost a quarter of a century ago², a wide spectrum of HIV-related rheumatic syndromes have been reported³. Many of the syndromes have clinical features that overlap with those of the more classical rheumatic disorders. A striking example is diffuse infiltrative lymphocytosis syndrome masquerading as primary Sjögren's syndrome. The spondyloarthropathies (SpA), previously very rare in Africa, have emerged in the wake of the HIV pandemic, adding significantly to the diagnostic and therapeutic rheumatic burden⁴. Seemingly benign isolated soft-tissue lesions, such as Achilles tendonitis and epicondylitis, not infrequently herald the onset of a SpA. A range of autoantibodies, including antinuclear antibodies, antiphospholipid antibodies, anti-neutrophil cytoplasmic antibodies, and rheumatoid factor (RF) can occur in HIV/AIDS^{5,6}. Interpreting autoantibody tests can thus be challenging in an HIV-positive patient, although the antibodies are present mostly in low titers and are not associated with any clinical rheumatic disease.

Anti-citrullinated peptide antibodies (ACPA), especially antibodies to cyclic citrullinated peptide (anti-CCP), because of their presence in early disease and superior specificity to RF⁷, are an important component in the diagnosis of rheumatoid arthritis (RA). In this issue of *The Journal*, Du Toit, *et al* report on the prevalence of anti-CCP antibodies and RF in advanced HIV disease⁸. Nine of 60 (15%) asymptomatic patients were anti-CCP-positive, all in

low titers. Following highly active antiretroviral therapy, there was a significant decline of anti-CCP antibody titers, and only 2 (4%) of 49 patients tested positive at 6-month followup. Almost half the patients were also RF-positive at baseline, declining to 7% following HAART. Importantly, after a year of followup, no patient who tested positive for anti-CCP antibodies developed joint symptoms and only 1 of the RF-positive patients developed a self-limiting oligoarthritis.

The mechanism of autoantibody production in HIV/AIDS is poorly understood. Possible explanations are cross-reactivity between the virus and autoantigen³ and nonspecific polyclonal hypergammaglobulinemia due to B cell activation⁹. The authors conclude that although the anti-CCP antibodies can occur with advanced HIV disease, it has a better specificity for RA than RF. In real life, however, coinfection with tuberculosis (TB), which is a major cause of morbidity and the commonest cause of death in HIV/AIDS¹⁰, is a potential confounder. Anti-CCP antibodies have been detected in up to 37% of patients with TB¹¹.

As a next step, it would be worth exploring the fine specificities of ACPA in HIV/AIDS. A recent study in North American Indians has shown that the anti-Sa (citrullinated vimentin) antibody assay has better specificity for RA than the anti-CCP test¹². Another aspect that warrants further investigation is the clinical utility of the anti-CCP antibody test in HIV-associated inflammatory arthritis, particularly in reactive arthritis and psoriatic arthritis subtypes. There is mounting evidence of an increased prevalence of anti-CCP antibodies in idiopathic psoriatic arthritis and some early evidence that their presence is associated with more aggressive disease¹³.

In the broader rheumatology context, to the clinician working in HIV-endemic areas, the challenges go beyond distinguishing HIV-related rheumatic syndromes from more classical rheumatic disorders. Assessing disease activity in a patient with preexisting rheumatic disease who contracts HIV infection can be difficult. In a patient with systemic lupus erythematosus, proteinuria, leukopenia, and thrombo-

See Lack of specificity of anti-CCP antibodies in advanced HIV infection, *page 1055*

cytopenia can be explained equally on the basis of active lupus and HIV infection¹⁴. Moreover, HIV-associated immune complex glomerulonephritis can be indistinguishable histologically from lupus nephritis¹⁵. A nonspecific increase in erythrocyte sedimentation rate is common in advanced HIV infection and hence is a poor marker of active inflammation in a patient with RA who is HIV-positive¹⁶. The risk of severe infections with the use of immunosuppressive drugs, in an already immunocompromised host, is of serious concern. There is a pressing need for controlled trials to assess the safety of methotrexate in patients with HIV/AIDS, given the widespread use of the drug in the rheumatic diseases. As in HIV/AIDS, methotrexate use in RA is associated with increased risk of *Pneumocystis pneumonia*¹⁷ and B cell lymphomas¹⁸.

An emerging problem is that of HAART-related rheumatic complications, ranging from immune reactivation inflammatory syndromes, e.g., sarcoidosis, to bone disorders like osteoporosis and osteonecrosis (ON)³. As more patients receive HAART, the burden of ON from pain and physical disability is likely to put further strain on limited health resources in most of sub-Saharan Africa and where there is very limited access to arthroplasty surgery. Retrospective studies suggest that dyslipidemia, intravenous drug abuse, and protease inhibitors are risk factors for ON¹⁹, but these findings are not sufficiently robust to develop guidelines for screening of early preclinical disease which, in the case of hip ON, may be amenable to less costly core decompression surgery.

It is clear from this brief overview that many aspects of the interaction and potential impact of HIV/AIDS on diagnosis and management of rheumatic diseases require further research. While this may not appear to be one of the priorities for the industrialized world, it behooves the international rheumatology community to collaborate and support Africa in its efforts to find answers to these clinical conundrums²⁰. The benefits will be for all!

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REFERENCES

- UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. [Internet. Accessed March 28, 2011.] Available from: <http://www.unaids.org/globalreport/>
- Winchester R, Bernstein DH, Fischer HD, Enlow R, Solomon G. The co-occurrence of Reiter's syndrome and acquired immunodeficiency. *Ann Intern Med* 1987;106:19-26.
- Louthrenoo W. Rheumatic manifestations of human immunodeficiency virus infection. *Curr Opin Rheumatol* 2008;20:92-9.
- Njobvu P, McGill P. Human immunodeficiency virus related reactive arthritis in Zambia. *J Rheumatol* 2005;32:1299-304.
- Sene D, Piette JC, Cacoub P. Antiphospholipid antibodies, antiphospholipid syndrome and infections. *Autoimmun Rev* 2008;7:272-7.
- Bonnet F, Pineau JJ, Taupin JL, Feyler A, Bonarek M, de Witte S, et al. Prevalence of cryoglobulinemia and serological markers of autoimmunity in human immunodeficiency virus infected individuals: a cross-sectional study of 97 patients. *J Rheumatol* 2003;30:2005-10.
- Niewold TB, Harrison MJ, Paget SA. Anti-CCP antibody testing as a diagnostic and prognostic tool in rheumatoid arthritis. *QJM* 2007;100:193-201.
- du Toit R, Whitelaw D, Taljaard JJ, du Plessis L, Esser M. Lack of specificity of anti-cyclic citrullinated peptide antibodies in advanced HIV infection. *J Rheumatol* 2011;38:1055-60.
- Titanji K, Chiodi F, Bellocco R, Schepis D, Osorio L, Tassandin C, et al. Primary HIV-1 infection sets the stage for important B lymphocyte dysfunctions. *AIDS* 2005;19:1947-55.
- Straetmans M, Bierrenbach AL, Nagelkerke N, Glaziou P, van der Werf MJ. The effect of tuberculosis on mortality in HIV positive people: a meta-analysis. *PLoS One* 2010;5:e152415.
- Lima I, Santiago M. Antibodies against cyclic citrullinated peptides in infectious diseases — a systematic review. *Clin Rheumatol* 2010;29:1345-51.
- Ioan-Facsinay A, Willemze A, Robinson DB, Peschken CA, Markland J, van der Woude D, et al. Marked differences in fine specificity and isotype usage of the anti-citrullinated protein antibody in health and disease. *Arthritis Rheum* 2008;58:3000-8.
- Maejima H, Aki R, Watarai A, Shirai K, Hamada Y, Katsuoka K. Antibodies against cyclic citrullinated peptide in Japanese psoriatic arthritis patients. *J Dermatol* 2010;37:339-45.
- Gould T, Tikly M. Systemic lupus erythematosus in a patient with human immunodeficiency virus infection — challenges in diagnosis and management. *Clin Rheumatol* 2004;23:166-9.
- Haas M, Kaul S, Eustace JA. HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. *Kidney Int* 2005;67:1381-90.
- Ndakotsu MA, Salawu L, Durosinmi MA. Relation between erythrocyte sedimentation rate, clinical and immune status in HIV-infected patients. *Niger J Med* 2009;8:208-10.
- Mori S, Cho I, Ichiyasu H, Sugimoto M. Asymptomatic carriage of *Pneumocystis jiroveci* in elderly patients with rheumatoid arthritis in Japan: a possible association between colonization and development of *Pneumocystis jiroveci* pneumonia during low-dose MTX therapy. *Mod Rheumatol* 2008;18:240-6.
- Hoshida Y, Xu JX, Fujita S, Nakamichi I, Ikeda J, Tomita Y, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. *J Rheumatol* 2007;34:322-31.
- Matos MA, Alencar RW, Matos SS. Avascular necrosis of the femoral head in HIV infected patients. *Braz J Infect Dis* 2007; 11:31-4.
- Adebajo A, Gabriel SE. Addressing musculoskeletal health inequity in Africa. *Arthritis Care Res* 2010;62:439-41. *J Rheumatol* 2011;38:973-4; doi:10.3899/jrheum.110119