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Rheumatologic manifestations of HIV-1 and HTLV-I infections

ABSTRACT

HIV infection is the new "great mimic." Although its more common signs and symptoms are well known, HIV infection sometimes presents with rheumatologic manifestations, as does human T-cell lymphotropic virus type I (HTLV-I), the causative agent of adult T-cell leukemia. This review briefly describes these manifestations and presents a logical clinical approach to their diagnosis and treatment.

KEY POINTS

Suspect an underlying HIV infection in high-risk patients in several situations: the acute onset of symmetric polyarthritis (especially in young men); a sudden clinical exacerbation of psoriasis or psoriatic arthritis; parotid gland enlargement in the absence of antinuclear antibodies; septic arthritis; and various vasculitides.

Nonspecific joint pain is the most common rheumatic manifestation of HIV infection, occurring in 12% to 45% of HIV-infected patients.

Up to 33% of HIV-infected patients with psoriasis develop arthritis, compared with 5% to 10% of HIV-negative patients.

Arthritis can develop in patients infected with human T-cell lymphotropic virus type I (HTLV-I), both with and without adult T-cell leukemia.

MOST PHYSICIANS are well aware of the usual clinical signs of AIDS, such as opportunistic infections and Kaposi's sarcoma. However, HIV disease is protean in its clinical manifestations, and generalists and specialists alike must therefore be aware of its alternative presentations.

Among the many clinical manifestations of HIV infection are a variety of rheumatic diseases. While relatively uncommon, they may occur early in the course of the infection. Thus, they may be vital to recognize, especially now that we have potent antiretroviral drugs to treat AIDS.

This review briefly focuses on the various rheumatic complications of HIV-1 and another human retrovirus, human T-cell lymphotropic virus type I (HTLV-I). It also outlines a practical approach to diagnosis and treatment.

RHEUMATOLOGIC MANIFESTATIONS OF HIV INFECTION

Acquired immunodeficiency syndrome (AIDS), first recognized in 1981, has become common. Nearly 1 million Americans are now infected with HIV, the causative agent of AIDS. Most of them are men, and a disproportionate number are members of minority populations. Among African American men, the prevalence of HIV infection is estimated to be close to 2%.¹

Rheumatologic manifestations of HIV infection are rare.² Their incidence varied significantly in different studies, depending on the population, risk factors for the infection, stage of the disease, and treatment of the underlying disease.

The most common rheumatic syndromes of HIV infection are listed in **TABLE 1**.

Arthralgia

Nonspecific joint pain is the most common rheumatic manifestation of HIV infection, occurring in 12% to 45% of HIV-infected patients.³ The pain is usually mild, intermittent, and polyarticular, and tends to occur later in the course of HIV infection. The differential diagnosis should always include serious underlying conditions such as infections (bacterial, mycobacterial, viral, opportunistic), drug reactions, HIV neuropathy and myelopathy, and various myopathies.

Painful articular syndrome

In one study,⁴ 10% of patients with HIV infection experienced a syndrome of severe joint pain lasting less than 48 hours, affecting mainly the knees, shoulders, and elbows. There is no clinical or laboratory evidence of an inflammatory process. The pain usually responds to analgesics, but some patients need to be admitted to the hospital for effective pain management with narcotic analgesics.

Idiopathic or HIV-associated arthritis

Some patients present with oligoarthritis or polyarthritis affecting large weight-bearing joints such as the knees and ankles.⁵ Analysis of synovial fluid shows a mild inflammatory process, but serologic tests are negative for rheumatoid factor, HLA-B27, antinuclear antibodies, and antibodies against extractable nuclear antigens. Further, the patients lack the typical clinical features of other seronegative inflammatory arthropathies such as Reiter's syndrome or psoriatic arthritis. The etiology of this arthropathy remains unclear, although a direct role for HIV has been proposed.

Key point. *The acute onset of symmetric polyarthritis, especially in young men, should always raise the possibility of an underlying HIV infection.*

This arthropathy lasts approximately 1 month on the average,⁴ but occasionally lasts up to 6 months. Nonsteroidal anti-inflammatory drugs (NSAIDs) usually can control the inflammatory process. Antiretroviral drugs have led to improvement in a few cases.⁶

Reiter's syndrome

Reiter's syndrome was the first rheumatic syndrome described in association with HIV

TABLE 1

Rheumatologic manifestations of HIV-1 infection

Articular syndromes

- Arthralgias
- Painful articular syndrome
- Idiopathic or HIV-associated arthritis
- Reiter's syndrome
- Psoriatic arthritis
- Undifferentiated spondyloarthropathy
- Avascular necrosis

Musculoskeletal infections

- Septic arthritis
- Osteomyelitis
- Pyomyositis
- Septic bursitis

Connective tissue diseases

- Sjögren's-like syndrome or diffuse infiltrative lymphocytosis syndrome
- Myopathy (inflammatory or noninflammatory)
- Vasculitis

infection (in 1987).⁷ Whether HIV-infected patients have a higher incidence of Reiter's syndrome than in the general public is controversial^{8,9}; the incidence ranged from 0.1% to 9.9% in different studies.¹⁰

Clinically, patients can present with the classic triad of oligoarticular arthritis, urethritis, and conjunctivitis, or with an incomplete form. The disease is mild and self-limiting in some patients, but severe and disabling in others. Most patients (70%–80%) are HLA-B27-positive.⁷

Key point. *Axial involvement and radiographic evidence of sacroiliitis are extremely rare in HIV-infected patients with Reiter's syndrome or psoriatic arthritis.*

Mild cases are treated with NSAIDs, whereas cyclosporine,¹¹ etretinate,¹² and sulfasalazine^{7,11,13,14} have been reported to be beneficial in more severe cases. Earlier reports suggested that immunosuppressive agents such as methotrexate or azathioprine might promote the development of opportunistic infections and Kaposi's sarcomas.⁷ Although no controlled studies have yet examined this issue, immunosuppressive agents might be used in carefully selected patients with close

Suspect HIV if a young man suddenly develops symmetric polyarthritis

follow-up and aggressive prophylaxis against opportunistic infections.

Psoriatic arthritis

HIV-infected patients can develop a range of psoriatic skin manifestations, from mild seborrheic dermatitis to severe psoriasis vulgaris and pustular psoriasis.¹⁵ Although initial reports suggested that HIV-infected patients have an increased prevalence of psoriasis, recent studies have not.¹⁶ Nevertheless, up to 33% of HIV-infected patients with psoriasis develop arthritis, compared with 5% to 10% of HIV-negative patients.¹⁷

Psoriatic arthritis resembles the arthritis of Reiter's syndrome. In both diseases most patients have the HLA-B27 antigen, and spinal involvement is rare. These observations led Reveille et al¹⁷ to speculate that HIV-associated psoriasis and Reiter's syndrome constitute a disease continuum.

In some patients, the psoriasis and psoriatic arthritis become fulminant, usually as their immune deficiency progresses and opportunistic infections develop.¹⁵

Key point. A sudden clinical exacerbation of psoriasis or psoriatic arthritis in a patient at high risk should always raise the suspicion of an underlying HIV infection.

NSAIDs are the first line of treatment. In more severe cases, oral retinoids (etretinate),¹¹ and gold¹⁸ have been used, with variable success. Although initial reports suggested that methotrexate treatment increases the risk of opportunistic infections,^{7,19} recent reports of three patients with severe psoriatic arthritis treated with methotrexate, pentamidine (for *Pneumocystis carinii* pneumonia prophylaxis), and antiretroviral drugs revealed a safer profile.^{20,21}

Musculoskeletal infections

Surprisingly few HIV-infected patients develop musculoskeletal infections, but these can include septic arthritis, osteomyelitis, pyomyositis, and septic bursitis.²²

Septic arthritis occurs mainly in young patients, with or without a history of intravenous drug abuse. In a recent retrospective study and review of published cases,²² intravenous drug abuse was identified as a risk factor in 29% of the cases. The infection can

occur during all stages of HIV infection: the median observed CD4 count was 200 cells/ μ L, which indicates advanced disease.

Septic arthritis usually affects one joint only, although 20% of cases are polyarticular. The most common organisms are *Staphylococcus aureus* (29%), atypical *Mycobacteria* (15%), and *Streptococcus* (11%). However, opportunistic pathogens such as *Sporothrix schenckii*, *Helicobacter*, and *Nocardia* have been reported in a number of cases, highlighting the need for an aggressive diagnostic search in some patients.²²

The diagnosis is usually established by culturing the synovial fluid and blood. Treatment with antibiotics or incision and drainage or both leads to full recovery in 90% of cases.

Key point. The diagnostic workup of young patients at risk for HIV infection presenting with septic arthritis should always include HIV testing.

Osteomyelitis occurs mostly in the advanced stages of HIV infection and is most commonly due to *Mycobacteria* (atypical species and *M tuberculosis*) and *Staphylococcus aureus*.²² Fever and localized bone pain are common on presentation. Most cases require an aggressive diagnostic approach, including bone biopsy. Despite antibiotic treatment or drainage or both, the rate of mortality due to complications of bone infections remains high: approximately 20%.

Pyomyositis is an infection of the striated muscles. It was formerly seen only in tropical climates; however, reported cases have increased since the onset of the HIV epidemic. Patients typically present with fever and localized muscle pain (occasionally after a local minor injury). For unknown reasons, the disease affects men almost exclusively.²²

Computed tomography or magnetic resonance imaging of the affected muscle provides the diagnosis, but aspiration of the muscle is required to identify the responsible organism. *Staphylococcus aureus* is the most commonly isolated agent (67%), followed by *Salmonella* (12%) and *Streptococcus* species (6%).²² With appropriate antibiotic treatment, 90% of patients recover fully, although recurrences at different muscle sites have been reported.

Rule out drug reactions and infections in HIV patients with vasculitis

Rheumatologic manifestations of HTLV-I infection

H TLV-I AND HTLV-II were discovered before HIV, in the early 1980s. While all three are human retroviruses, HTLV-I and HTLV-II are only distantly related to HIV. They are, however, similar to HIV in that they are sexually transmitted and are associated with a variety of clinical syndromes, including a number of rheumatic diseases.

HTLV-I infection is much rarer than HIV. In the United States, seroprevalence rates of HTLV-I among volunteer blood donors range between 0.016% and 0.025%,²⁹ and the infection is most common among intravenous drug abusers, particularly in the Southeast and Northeast. It is far more common in southern Japan and the northern Caribbean.

HTLV-I causes adult T-cell leukemia and HTLV-I-associated myelopathy (also known as tropical paraparesis).³⁰ However, it can also be associated with a variety of rheumatic disorders, including a rheumatoid arthritis-like disease, a Sjögren's-like syndrome, and several other inflammatory disorders such as uveitis, vasculitis, polymyositis, and pneumonitis (TABLE 2).^{31,32}

HTLV-I-associated arthritis

Arthritis can develop in HTLV-I-infected patients, both with and without adult T-cell leukemia.³¹

Patients with adult T-cell leukemia can develop an erosive polyarthritis involving the wrists, ankles, proximal interphalangeal joints, and knees.³¹ Typically, the patients are rheumatoid factor-negative. The prognosis depends on the type of underlying adult T-cell leukemia, ranging from an

TABLE 2

Rheumatologic manifestations of HTLV-I infection

Symmetric erosive polyarthritis (rheumatoid arthritis-like)
Sjögren's-like syndrome
Uveitis
Polymyositis
Vasculitis

acute form with a poor prognosis to a chronic smoldering form with a better overall prognosis.

In patients without adult T-cell leukemia, HTLV-I-associated arthritis is indistinguishable from classic rheumatoid arthritis: like rheumatoid arthritis, it is symmetric, polyarticular, and characterized by synovial proliferation.³² Most patients are rheumatoid factor-positive and have an elevated erythrocyte sedimentation rate and C-reactive protein levels. Usual treatment consists of NSAIDs, corticosteroids, and slow-acting antirheumatic medications.³¹ Recently, intravenous interferon produced encouraging results.³³

Although most reported cases occurred in Japan, cases are beginning to be seen in this country. At this point clinicians should be aware of these associations and consider screening all persons with poorly defined rheumatic disorders or unexplained myelopathy who have a history of intravenous drug abuse or travel to an endemic region.

Diffuse infiltrative lymphocytosis syndrome (Sjögren's-like syndrome)

This distinctive clinical syndrome consists of bilateral parotid enlargement, xerostomia, and multiple extraglandular manifestations including interstitial pneumonitis, lymphocytic hepatitis, lymphocytic nephritis, and lymphocytic vasculitis.²³ Typically the affected organs are heavily infiltrated by CD8-bearing lymphocytes.

Although 20% to 25% of HIV patients experience sicca symptoms, only 1% to 2% of outpatients with HIV infection are identified with this syndrome.²⁴ This syndrome differs

from classic Sjögren's syndrome in several ways: antinuclear antibodies and anti-Ro/La antibodies are absent, most patients are men, extraglandular manifestations are prominent, and a high prevalence have the HLA-DR5 or DR6 antigens.²³

Key point. *Parotid gland enlargement in the absence of antinuclear antibodies should raise the suspicion of HIV infection with diffuse infiltrative lymphocytosis syndrome.*

The differential diagnosis should include Sjögren's syndrome, hepatitis C infection, HTLV-I infection, and lymphoma.

Therapy for isolated salivary gland

involvement includes antiretroviral drugs and local therapeutic measures (dental care, antibiotics), whereas extraglandular involvement may necessitate glucocorticoids or other immunosuppressive agents or both.

Vasculitis

A number of vasculitic syndromes have been described in HIV patients,²⁵ including:

- Systemic necrotizing vasculitides (polyarteritis, Churg-Strauss syndrome, and overlapping forms)
- Hypersensitivity vasculitides (Henoch-Schönlein purpura, hypersensitivity)
- Granulomatous angiitis (lymphomatoid granulomatosis)
- Primary angiitis of the central nervous system
- Vasculitis associated with diffuse infiltrative lymphocytosis syndrome.

Drug hypersensitivity reactions and various infections (due to cytomegalovirus, hepatitis C virus, hepatitis B virus, and varicella zoster virus) should always be ruled out during the initial evaluation of patients with vasculitis. In patients with life-threatening complications, treatment with steroids or immunosuppressives or both is indicated, although controlled studies assessing the efficacy of such therapy are lacking.²⁵

Key point. *Although the role of HIV in the pathogenesis of various vasculitides is unclear, it appears prudent to include HIV testing in the initial evaluation of vasculitis in selected patients, particularly those at risk for sexually transmitted or blood-borne diseases.*

Myopathy

Many different muscle diseases have been described in HIV patients.¹⁰ These include myalgias, polymyositis, dermatomyositis, zidovudine (AZT) myopathy, nemaline rod myopathy, pyomyositis, and wasting myopathy.

Polymyositis and dermatomyositis have been reported in HIV patients in several cases.²⁶ Their clinical presentation and course resemble the classic form, although they predominantly occur in the proximal lower extremities. Muscle biopsy shows extensive infiltration by CD8-positive cells. Treatment with prednisone (0.5 mg/kg) usually induces remission and clinical improvement.

AZT myopathy. AZT was the first antiretroviral agent used for treating HIV infection. Dalakas et al²⁷ reported a myopathy related to AZT treatment, manifesting with proximal weakness and exhibiting characteristic mitochondrial abnormalities on muscle biopsy ("ragged red fibers"). Creatine kinase (CK) levels are usually elevated. Discontinuing AZT leads to clinical improvement and a gradual decrease in CK levels in a few weeks.

Wasting myopathy. Some HIV patients develop a wasting syndrome characterized by progressive weight loss and a noninflammatory myopathy.²⁸ Although CK levels are usually elevated, muscle biopsy does not show evidence of an inflammatory process. In a small series, three of five patients improved after prednisone therapy.²⁸

Key point. *Muscle biopsy is frequently required to diagnose myopathy in HIV patients.*

CLINICAL APPROACH

HIV infection should be viewed as the great mimic of disease, just as syphilis and systemic lupus erythematosus were viewed in years past. Therefore, all clinicians must consider HIV infection in their differential diagnoses, and test for HIV antibodies in all patients at risk. Recent advances in antiretroviral therapy have reduced morbidity and mortality considerably, making early diagnosis more important than ever. If we test for HIV only in patients with classic presentations of HIV disease such as opportunistic infections and Kaposi's sarcoma, we will overlook many cases of HIV infection.

Risk factors for HIV infection

Keep HIV infection in mind when performing the history and physical examination. Merely being sexually active places a person at risk. Intravenous drug abuse is also a major risk behavior, as are a history of a blood transfusion before 1985 and occupational exposure to blood or blood products. Other risk factors include:

- Men having sex with other men
- Multiple partners, either heterosexual or homosexual
- Passive anal sex
- A history of sexually transmitted diseases

**Think of HIV
as the new
"great mimic"**



- A history of minor opportunistic infections such as oral *Candida* or dermatomal zoster
- Unexplained laboratory abnormalities such as cytopenias, especially thrombocytopenia
- Unexplained constitutional symptoms such as prolonged fever, fatigue, and weight loss.

The clinician must start with a candid and nonjudgmental assessment of risk and then test for HIV-1 antibody if there is suspicion. If the HIV-1 antibody test is positive, the patient needs detailed counseling about the significance of the test in terms of his or her current medical problem and the need for

comprehensive care of the underlying HIV infection. While not all clinicians will undertake the primary care of the underlying HIV disease, it is imperative that every clinician know where to refer such patients.

A similar model should be used for HTLV-I testing. While the suspicion for HTLV-I infection at the present time is confined largely to those with intravenous drug use or extensive travel history to endemic areas, testing should be considered for persons at risk with poorly defined rheumatic disorders, unexplained myelopathy, or peripheral T-cell malignancies. Once diagnosed, patients with HTLV-I infection should be referred to a specialist with expertise in this infection and its complications.

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