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HIV Associated Arthritis: Case Report and Review of the Literature

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Abstract: HIV infection can be associated with different types of arthropathies which are often underdiagnosed. We present the case of a 52 year old HIV positive man on highly active antiretroviral therapy including indinavir who developed an acute painful oligoarthritis. We present this case on HIV associated arthritis and include a review on other HIV specific types of arthritis (acute symmetric arthritis and painful articular syndrome) which are assumed as entities exclusively apparent in HIV patients. The pathophysiology of arthritis in HIV infected patients is not yet completely understood but a direct role of the HIV on the initiation of synovitis is suspected in some of them. Additionally, there is evidence that antiretroviral drugs, in particular the protease inhibitor indinavir, can lead to arthritic complications as well.

Key words: HIV associated arthritis, HAART, indinavir, oligoarthritis

Introduction

Articular manifestations are a frequent but often underdiagnosed manifestation in patients infected with the human immunodeficiency virus (HIV). To date, only few valid studies are available. However, in those conducted in a prospective design with patients examined by rheumatalogists a conclusively high prevalence up to 70% was found (Berman et al. 1988, Medina-Rodriguez et al. 1993). Several apparently distinct forms of arthritis have been described in HIV patients including clinically well-defined reactive arthritis types such as Reiter´s syndrome. HIV associated arthritis, painful articular syndrome or acute symmetric arthritis seem to be HIV specific (Rynes et al. 1988, Munoz-Fernandez et al. 1991, Mody et al. 2003). The pathophysiology of HIV specific arthritis types is not fully understood but drugs of the highly active antiretroviral therapy (HAART), in particular indinavir, are supposed to cause arthritis or rheumatological complaints (Bouscaratet al. 1998, Zabraniecki et al. 1998, Leone et al. 1998, Pointud et al. 1998, Peyriere et al. 1999, Brooks et al. 2000, Grasland et al. 2000). In clinical practice, patients often present with overlapping features of several syndromes which do not fit into proper classification of either category. We present the case of a 52 year old HIV positive man who developed oligoarticular arthritis while being treated with indinavir and review both HIV specific arthritis types and arthritic pains reported during treatment with indinavir.

Case Report

A 52 year old HIV seropositive man with a history of cerebral toxoplasmosis and pneumocystis carinii pneumonia presented with an acute painful oligoarthritis of the lower limbs. Initially, the left upper ankle joint was painful, especially during physical activity. On clinical examination, mild oedema, tenderness and erythema of the upper left ankle joint could be detected. Within one week, identical symptoms occurred at the contralateral side. The pain deteriorated and was so interfering with walking that the patient was confined to a wheelchair in order to manage longer distances and could only walk few steps with crutches.

There were neither symptoms suggesting an antecedent bacterial or viral illness apart from HIV nor did a history of personal or family rheumatic disorders exist. The patient had already been treated by his general practitioner with diclofenac retard 100 mg daily for a week which had not altered his complaints. His regular medication comprised the antiviral substances stavudine (40 mg twice a day), lamivudine (150 mg twice a day), and indinavir (800 mg three times a day) for one year. Other medication included aciclovir and trimethoprim/sulfamethoxazole for the prophylaxis of opportunistic infections, valproic acid for epilepsy, and thyroxine.

The $CD4^+$ cell count was 81 cells/µl. The viral load was <50/ml. White cell blood count, serum ureate and c-reactive protein were normal, there was no increased body temperature. IgM-antibodies for Yersinia, Borrelia burgdorferi, Salmonella, Shigella, Chlamydia trachomatis, and Campylobacter jejuni as indicators of a reactive arthritis were negative. Furthermore, antinuclear antibodies, anti-DNS, HLA-B27, cryoglobulins, C3, C4, CH 100 were non-contributing. X-rays of the affected upper ankle joints showed effusions, but bone structures were completely intact. Ultrasound sonography of the abdomen excluded intraabdominal neoplasm. The acute pain was treated for 14 days with prednisolone 100 mg given intravenously and intense physical therapy. After ten days, the pain had already declined significantly, the prednisolone dosage was gradually decreased and completely removed after 6 weeks. Additionally, we changed the protease inhibitor indinavir to ritonavir.

The patient remained asymptomatic for a follow-up period of 12 months.

Discussion

The most common musculoskeletal manifestation seen during the course of HIV infection are arthralgias. Their prevalence varies from 4.5% to 46% (Munoz-Fernandez et al. 1991, Medina-Rodriguez et al. 1993). Typically, they are of moderate intensity affecting knees (51%), shoulders (29%) and elbows (26%) and have a relapsing or chronic course (Berman et al. 1988). In our patient, however, the pain was more severe and relatively acute.

Reiter´s syndrome which is defined as a seronegative, asymmetric arthropathy was the first reactive rheumatic disease to be described in association with HIV infection (Winchester et al. 1987, Davis et al. 1989). The arthritis was unusually severe with the early appearance of erosions and a relapsing time course. An intense enthesopathy most often of the feet as well as skin and mucous membrane involvement are commonly reported (Winchester et al. 1987, Reveille et al. 1989). Unlike in psoriatic arthritis and undifferentiated spondyloarthropathies, the HLA-B27 antigen appears to play a central role in the pathogenesis of Reiter´s syndrome and is present in approximately 70% to 80% of Caucasian patients (Reveille et al. 1989, Espinoza et al. 1992). Our patient had no signs of an adjacent enthesopathy and no other criteria defining Reiter's syndrome such as conjunctivitis or a genitourinary or enteric infection. For undifferentiated spondyloarthropathies as a further arthritic complaint, an increased association between HIV infection and undifferentiated spondyloarthropathies has been described (Buskila et al. 1990), but recent studies showed a prevalence of 0.27% making HIV-associated spondyloarthropathies as frequent as it is in HIV negative individuals (Berman et al. 1988).

In addition, HIV specific arthritis forms have been described. The painful articular syndrome is characterized by severe articular pain of short duration lasting from a few to 24 hours (Berman et al. 1988, Pouchot et al. 1992, Calabresse et al. 1991). None of the patients has objective synovitis, there are no signs of inflammation and the aetiology is still unclear. One hypothesis is that the painful episodes are ischaemic in nature and represent localized areas of a vascular necrosis (Gerster et al. 1991).

Rosenberg et al. (1989) described four patients with symmetric small joint arthritis of the hands, which they labeled acute symmetric polyarthritis (ASP). Although these patients had clinical criteria of rheumatoid arthritis such as periarticular osteoporosis and symmetric ulnar deviation, they had an atypical acute onset of their symptoms. Furthermore, two patients with ASP showed prominent new bone formation, a finding unusual for rheumatoid arthritis. Analysis of the synovial fluid revealed a level of p24 antigen that was tenfold higher than that of the serum, suggesting the possibility of a direct role of HIV in initiation of the synovitis. The bilateral occurrence of symptoms could have lead to the ASP diagnosis in our patient, however all other characteristics of a rheumatoid arthritis including rheumatoid factor were negative.

A distinct subacute oligoarthritis called HIV-associated arthritis characterized by extreme disability, primarily involving the knees and ankles was first described by Rynes et al. (1988). These observations were confirmed by Berman et al. (1999) who studied 270 HIV-positive patients and diagnosed HIV-associated arthritis in 7.8%. HIV-associated arthritis tends to be short lived with its peak intensity occurring in one to six weeks. Patients lack features of mucocutaneous involvement, and while radiographs may show a joint effusion, bone structures remain intact (Berman et al. 1999).

The response to treatment is rapid, especially to intraarticular steroids. Rheumatoid factor, antinuclear antibodies and HLA- B27 are negative. In some patients, HIV could be isolated from the synovial fluid and electron microscopy of the synovial fluid showed tubuloreticular inclusions suggesting a viral infection. Therefore, it has been speculated that HIV-associated arthritis is a direct consequence of HIV infection of the synovium. This is supported by animal studies of mammalian lentiviruses which are known to produce arthritis in sheep and goats (Crawford et al. 1980, Michaels et al. 1991). The characteristic signs and symptoms, the typical response to treatment and matching laboratory features suggest that the most likely diagnosis for our patient is HIV-associated arthritis.

Apart from these types of arthritis, it has to be taken into account that treatment with protease inhibitors, in particular indinavir, is associated with rheumatic disorders as well as other side effects such as renal calculi (Lerner et al. 1998), nail disorders (Bouscarat et al. 1998), and lipodystrophy. In a multicentre survey, Florence et al. (2002) concluded that non-specific joint pain was more often reported by patients on a treatment regimen with a protease inhibitor (indinavir, nelfinavir, ritonavir-saquinavir combination) than by patients with a non-protease inhibitor (35.5% vs 26.0%; $p = 0.01$). Most detailed information is available about indinavir with more than ten reported cases of frozen shoulder (Zabraniecki et al. 1998, Leone et al. 1998, Pointud et al. 1998, Peyriere et al. 1999). The time course from the onset of indinavir therapy and the beginning of symptoms of a frozen shoulder varies from two months to two years (Peyriere et al. 1999). Apart from frozen shoulders, temporomandibular dysfunction is another indinavir associated complaint (Florence et al. 2002). A case of an acute monoarthritis of the left knee resulting from a 6 week course of indinavir was reported by Brooks et al. (2000). As no bacterial, viral (apart from HIV infection), or fungal cause of arthritis could be demonstrated, intra-articular indinavir levels were measured. Although the intra-articular indinavir concentration of 1.36 µl/ml was within the serum range of 0.2-7.4 µg/ml, Brooks et al. (2000) assumed that indinavir crystals, analogous to ureate crystals, may occur in the synovial fluid because of the poor solubility of indinavir which varies inversely with pH. Although arthritic side effects of indinavir should be kept in mind, the clinical picture of oligoarthritis with an acute onset, a short duration, and rapid response to steroids sup-

Table 1. Synopsis of different types of arthropathy apparent in HIV infected patients. Typical features of the distribution, specific characteristics and therapies are presented. NSAID = nonsteroidal anti-inflammatory drugs.

type of arthropathy	distribution	pain characteristics	duration	specific characteristics	effective therapy
arthralgias	oligoarticular, large joints (knees, shoulders, elbows)	intermittent pain of moderate intensity; slow onset	self limiting course; lasting 4-6 weeks	frequently manifestation of acute HIV infection	NSAID effective
Reiter's syndrome	asymmetric, oligo-polyarticular; lower extremities	variable, often more severe than in HIV negative patients	relapsing or chronic course with intermittent exacerbations	urethritis, conjunctivitis, skin changes (keratoderma, frank psoriasis)	poor response to NSAID
undifferentiated spondyloarthropathy	low back pain, ankle and shoulder symptoms	variable	long term over weeks	enthesis, dactylitis, spondylitis,	steroids; NSAID less effective
HIV associated arthritis	variable pattern: mono-, oligo-, polyarticular, especially knees and ankles	extreme disability	short lived, 1 to 6 weeks duration; often self-limited	biopsy shows hypertrophy and hyperplasia of synoviocytes; positive culture for HIV virus	often self-limited, good response to intraarticular steroids
painful articular syndrome	predominantly knees, also elbow and shoulder	excruciating, leading to emergency admissions	2-24 hours	no objective synovitis	analgetics required
acute symmetric polyarthritis	symmetrical, small joints of the hand	acute onset, intermittent	relapsing time course	prominent new bone formation on X-ray	not reported

ports the diagnosis of HIV associated arthritis in our patient. Furthermore, the symptoms disappeared while still on indinavir.

In conclusion, different specific and unspecific arthropathies can be associated with HIV infection, a synopsis is given in Table 1. HIV infected patients with painful joints need a thoroughful work up including serological investigations and a complete history of medication. If no other reason can be found, specific HIV associated arthritis, painful articular syndrome, or acute symmetric polyarthritis must be considered.

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