Inflammatory joint disease and human immunodeficiency virus infection

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Abstract

Nine men positive for antibody to human immunodeficiency virus (HIV) who developed peripheral, non-erosive arthritis were followed up. The clinical features were compatible with reactive arthritis but were atypical in several respects: the joint symptoms were generally severe, persistent, and unresponsive to non-steroidal anti-inflammatory drugs. The onset of arthritis was associated with various infections, none of which are known to be associated with the development of reactive arthritis. HLA typing was performed for three patients, all of whom were positive for HLA-B27. HIV was isolated from the synovial fluid of one patient. No patient had AIDS before developing arthritis, but four progressed to having AIDS after a mean of 7.5 months, and two died. Arthritis resolved in only one patient.

The possibility of HIV infection should be considered in all patients with conditions suggesting reactive arthritis. Synovitis in patients with severe immunodeficiency has important pathogenetic implications.

Introduction

Bacterial and viral infections are major causes of acute inflammatory arthritis and probably play a considerable part in the development of some important forms of chronic arthritis. Sexually transmitted infections are well recognised as causing both septic and aseptic arthritis. Aseptic arthritis, which is especially prevalent in young men, has been referred to as sexually acquired reactive arthritis,¹ and a clear genetic predisposition associated with the HLA-B27 antigen is well recognised.² Recent work has elucidated the pathogenesis of sexually acquired reactive arthritis,³ but substantial gaps in our knowledge remain; in many patients no causal organism has been identified.

Human immunodeficiency virus (HIV) has profound and well documented effects on the response of the immune system to infections with other organisms.⁴ The development of inflammatory arthritis in patients with HIV infection raises issues that may be practically important in the management of such patients and theoretically important in providing insight into the pathogenetic

mechanisms of arthritis. We report on nine patients in whom aseptic arthritis with some distinctive clinical features occurred in association with HIV infection.

Patients and methods

We studied nine homosexual men positive for HIV antibody. All presented with acute peripheral arthritis, five to rheumatology departments at three London hospitals and four to the Praed Street sexually transmitted diseases clinic, between October 1985 and November 1986. Clinical histories were taken and full clinical examinations performed, with particular emphasis on rheumatic signs and symptoms and possible infection. Standard radiographs were taken of affected joints. Disease associated with HIV infection was classified according to the classification suggested by the Communicable Diseases Centre,⁵ and progression to AIDS was assumed if a patient developed one of the opportunistic infections or malignancies that form the Communicable Diseases Centre's criteria for AIDS.⁶

A full blood count, including a differential white cell count and when possible an analysis of T cell subsets, was performed for all patients. Blood was tested for erythrocyte sedimentation rate, C reactive protein, liver enzymes, bilirubin, rheumatoid factor, antinuclear factors, and evidence of syphilis (*Treponema pallidum* haemagglutination and Venereal Disease Research Laboratory tests). Three patients were HLA typed for antigens at the A and B loci. Antibodies to HIV were detected with a competitive enzyme linked immunosorbent assay (ELISA) and confirmed with a non-competitive ELISA (Abbott).

Effusions were aspirated from all the patients. Two patients underwent arthroscopy and synovial biopsy under local anaesthesia by procedures described previously.³ Samples of synovial fluid were examined by routine bacteriological procedures and additionally for opportunist pathogens related to HIV such as atypical mycobacteria and cytomegalovirus. Samples from five patients were cultured for HIV. The fluid was cultured with normal peripheral blood lymphocytes stimulated by phytohaemagglutinin in a ratio of synovial cells to lymphocytes of 1:3. A second culture was established with Hut 78 cells. Growth of the virus was indicated by a characteristic cytopathic effect and by a positive reaction in immunofluorescence and reverse transcriptase assays.

Stools were examined by routine bacteriological procedures. Urethral swabs were tested for *Chlamydia trachomatis* (Microtrak technique⁷), as was a synovial biopsy specimen from one patient (case 1). Serum samples were examined for IgG antibody to *C trachomatis* by microimmunofluorescence.⁸

Results

CLINICAL FINDINGS

Reiter's syndrome, ankylosing spondylitis, sacroiliac and wrist pain, psoriasis, and iritis had each occurred in one patient. Before developing arthritis none of the patients had had AIDS. Seven did not have any symptoms of AIDS (Communicable Diseases Centre group 2), and two had a history of weight loss, chronic diarrhoea, and minor problems related to HIV infection (group 4A).

At presentation eight of the patients were acutely unwell. Coincident with the development of arthritis (table) three had developed oral candidiasis, shingles, or genital herpes or a combination of these (group 4C2). In one of these patients and in two others persistent generalised lymphadenopathy (group 3) had developed. Acute urethritis or acute diarrhoea, or both, occurred in three patients, though no pathogens were isolated. The three other patients had no clinical evidence of acute infection associated with the onset of arthritis.

One patient had a long history of psoriasis. In four patients a psoriatic rash had developed de novo at the onset of arthritis. In one patient this rash was on the soles of the feet and was impossible to distinguish clinically or

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histologically from keratoderma blennorrhagica. Conjunctivitis developed in two patients and anterior uveitis in one.

The peripheral arthritis was oligoarticular (one to five joints) in six patients and polyarticular (more than five joints) in three, affecting a mean of four joints. It affected the knee in eight patients, metatarsophalangeal joints in five, small joints of the hands in five, and ankles, wrists, and shoulders in four. Radiographs of peripheral joints were normal in six patients, but two showed loss of periarticular bone density, and in one case the metatarsophalangeal joints, which had been normal on presentation, showed evidence of fusion. A bone scan showed hot spots in the right ankle and left metatarsophalangeal joints of one patient.

Clinical features developing for first time in homosexual men positive for antibody to HIV in association with arthritis

	Case No								
	1	2	3*	4	5*	6	7	8*	9
Oral candidiasis	+	+	+	-	-	-	-	-	-
Shingles	-	-	+	-	-	-	-	-	-
Perianal herpes simplex	+	-	-	-	-	-	-	-	-
Lymphadenopathy	-	-	+	+	-	-	-	-	+
Urethritis	-	-	-	-	-	-	+	+	+
Acute diarrhoea	-	-	-	-	-	-	-	+	+
Psoriasis	+	†	+	-	+	-	-	+	-
Keratoderma blennorrhagica	+	-	-	-	-	-	-	-	-
Conjunctivitis	-	+	-	-	-	-	+	-	-
Uveitis	-	-	-	-	-	-	-	+	-

*HLA typing done: patient positive for HLA-B27.

†Deterioration of pre-existing psoriasis.

Four patients had symptoms typical or highly suggestive of spondylitis, though none developed abnormalities visible in radiographs or bone scans. Two others had transient spinal stiffness and pain. Five of these patients had severe pain and limitation of the neck. One patient developed plantar fasciitis.

PATHOLOGICAL FINDINGS

Concentrations of C reactive protein or the erythrocyte sedimentation rate were raised in all patients. C reactive protein was raised in four (range 48-115 mg/l, mean 82) and erythrocyte sedimentation rate in five (range 37-120 mm in the first hour, mean 89). A normochromic anaemia occurred in six patients (mean haemoglobin concentration 105 g/l). All patients yielded negative results on testing for rheumatoid factor and antinuclear antibody. The three patients who were HLA typed were positive for HLA-B27.

Serum IgG antibody to *C trachomatis* was assayed in eight patients at presentation. The only one who had a titre of 1/>16 was the patient with a history of Reiter's syndrome. Synovium and synovial fluid were examined for chlamydial antigen but none was detected. On histological examination the synovium from two patients showed non-specific changes of synovitis and skin biopsy specimens from three patients showed typical changes of psoriasis.

HIV was shown in the synovial fluid of one patient by its cytopathic effect, immunofluorescence, and reverse transcriptase activity. Synovial fluid from two other patients produced a typical cytopathic effect but negative results on immunofluorescence and reverse transcriptase assays, although particles resembling retrovirus were seen in one sample on electron microscopy.

PROGRESSION OF DISEASE AND ITS MANAGEMENT

Only one patient recovered completely from his arthritis; he was ill for seven months. All other patients had intermittent episodes of synovitis. Four patients experienced severe deterioration in mobility associated with severe pain and stiffness of the joints, although deformities of the joints and changes visible on radiography were minimal. HIV infection in these four patients worsened simultaneously, progressing to AIDS after a mean of 30 weeks, and two patients died. One of the other two patients developed peripheral neuropathy and retrobulbar neuritis.

All patients were treated with non-steroidal anti-inflammatory agents, but their symptoms generally responded poorly, especially in those with spondylitis or advanced HIV infection. Methotrexate was used in one patient but was associated with the development of fevers, malaise, and tender lymphadenopathy. Psoriasis was controlled with topical treatment

and etretinate. Parenteral and intra-articular steroids and ultraviolet light treatment were avoided owing to their potentially immunosuppressive effects.

Discussion

Reactive arthritis is to be expected in a proportion of men exposed to infections of the genital tract. Winchester *et al* reported the concurrence of Reiter's syndrome and AIDS⁹; psoriasis has also been linked with HIV infection.¹⁰ The patients whom we describe, however, were comparatively well before onset of arthritis, and their clinical features were atypical of reactive arthritis.¹¹ These observations have important implications for both management of patients and the underlying pathogenetic mechanisms of inflammatory arthritis.

Striking features of these patients included the degree of systemic illness associated with the onset of arthritis, unusually severe symptoms of the peripheral joints and spine that resisted treatment with non-steroidal anti-inflammatory drugs, the occurrence of arthritis in arm and leg joints, the low incidence of enthesopathy, and a tendency for symptoms to persist. No infection known to precipitate reactive arthritis was identified in any patient. Probably, however, arthritis in these patients is precipitated in some way by infection. One potentially arthritogenic agent could be HIV itself. A virus that, like HIV, is a retrovirus has been isolated from the synovium of goats with caprine arthritis-encephalitis syndrome, a form of chronic arthritis; when the isolated virus is inoculated into kids of goats free from specific pathogen arthritic lesions similar to those of the spontaneous disease are produced.¹² The finding of HIV in joint material may, however, simply reflect widespread dissemination of the virus throughout the body. Other infectious agents including other viruses, fungal and bacterial pathogens, and commensal micro-organisms rendered pathogenic by immunodeficiency may take part in the development of arthritis in subjects positive for HIV. At present an infectious cause of this arthritis is merely speculative, but the possibility that synovitis and other lesions result from interaction between micro-organisms in immunodeficient subjects requires investigation. Although deteriorating HIV infection seems to precipitate or exacerbate arthritis, possibly the emergence of arthritis may adversely affect the immune system and therefore promote replication of HIV and the progression to AIDS.

The development of arthritis in patients severely deficient in T lymphocytes bearing CD4 molecules suggests that these helper/inducer cells may not be important in the pathogenesis of arthritis in such patients. Conversely, the relative or absolute increase in T lymphocytes bearing CD8 molecules seen in some patients might indicate that these suppressor/cytotoxic cells are important in the development of arthritis. We did not measure immune complexes in our patients as they may be present in subjects who are positive for HIV antibody but do not have symptoms of disease¹³ and their presence would therefore not help to elucidate pathogenetic mechanisms of arthritis in our patients. Rheumatoid factor and antinuclear antibodies, however, were consistently absent.

Treatment of arthritis in patients positive for HIV antibody is difficult as there is evidence that immunosuppressive drugs such as methotrexate and azathioprine may increase the risk of progression to AIDS.⁹ Non-steroidal anti-inflammatory agents, however, often do not adequately control symptoms. Sulphasalazine might be useful and has yet to be evaluated. The role of drugs that act against HIV, such as azidothymidine, is currently being evaluated.

Whether the arthritis that we have described should be regarded as reactive, psoriatic, or a distinct entity is not clear. Potentially misleading labels should probably be avoided so that further investigations can proceed without prejudice. The documentation of immunological defects in patients with HIV infection may help clarify the interplay of genetic, environmental, and immunological factors in the development of inflammatory lesions triggered by infection.

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Influence of C4 null genes on infection with human immunodeficiency virus

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Abstract

The hypothesis that complement is important in the host response to human immunodeficiency virus (HIV) was tested. Complement C4 and Bf allotypes were determined in 26 patients who fulfilled the diagnostic criteria for persistent generalised lymphadenopathy due to HIV, 72 homosexuals who were negative for antibody to HIV, and 185 control subjects drawn from the local population. HLA-A, B, and DR were also typed and the phenotypes examined for the presence of supratypes and C4BQ0. Eleven patients (42%) had C4B null alleles compared with only 13 (18%) homosexuals who were negative for antibody and 28 (15%) controls. From estimates of gene frequencies the difference between the patients with lymphadenopathy and the controls was significant after conservative correction. In the patients only a minority (six) of the C4B null alleles were contained within ancestral haplotypes. Together with the fact that C4 null alleles result in partial deficiency of C4, this finding suggests that products of complement genes are important in infection with HIV or its consequences, or both. A role is proposed for complement and Fc receptors.

Introduction

The serological response to human immunodeficiency virus (HIV) varies substantially among subjects. Several studies have shown that lower titres of antibody to HIV are associated with a higher concentration of virus and a more severe outcome,^{1,2} but whether the titre falls as a consequence of failing immune function or whether some patients have an inherently defective response and therefore a more rapid course is unclear. Our work suggests that infection of the follicular dendritic cell and the consequent destruction of the germinal centre is an important factor in the failure of

specific immune responses, including synthesis of antibody to HIV.² We therefore postulated that infection of the follicular dendritic cell may depend on antibody, complement, and receptors for the Fc moiety of antibody and complement and proposed that genes controlling the components of complement may be important in determining susceptibility to infection with HIV. Accordingly, we undertook allotyping for the class III genes (C4 and Bf) within the major histocompatibility complex as well as those in class I (HLA-A, B, and C) and class II (HLA-DR and DQ).

Patients and methods

We compared two groups of homosexual subjects attending the immunology clinic at this hospital. All were white residents of Western Australia. They were tested for antibodies to HIV by commercial enzyme immunoassays (Abbott or Genetic Systems) and were typed for HLA-A, B, C, DR, and DQ with a standard microcytotoxicity assay. The fourth component of complement (C4) and the factor B (Bf) component of the alternate pathway were typed by methods described previously.³ In the method for C4 the bands are assessed by densitometry and null alleles can be assigned with confidence. Null alleles at the C4B locus were assigned if fewer than two alleles had been identified and the densitometric ratio of C4A to C4B was ≥ 1.5 .

One of the groups studied comprised 26 patients positive for antibody to HIV who fulfilled the standard criteria for persistent generalised lymphadenopathy; the other comprised 72 subjects who did not have symptoms, who were negative for antibody, but who considered themselves at risk of infection with HIV. The frequencies of the alleles in the two groups were compared with those in a control population of 185 white subjects drawn at random from the town of Busselton. The frequencies of alleles and phenotypes were analysed by the χ^2 test or Fisher's exact test. Probability values were multiplied by the number of complement alleles detected in these populations (20).

Serum C4 concentrations were determined by automated rate nephelometry (Beckman ICS) and the results compared by Student's *t* test.

Results

The patients who were negative for HIV antibody and the controls did not differ significantly in the frequency of any alleles, including C4. The figure shows, however, that 11 patients (42%) who were positive for antibody to HIV and had persistent generalised lymphadenopathy had C4B null alleles (C4BQ0), compared with 13 (18%) of the homosexuals who did not have antibodies (data not shown) and 28 (15%) of the controls. In the patients the increased frequency of C4BQ0 corresponded to a decrease in other C4B alleles ($p < 0.005$); no such changes were found in alleles at the C4A locus. As five of the 26 patients who had antibodies to HIV were homozygous for C4B null alleles we estimated gene frequencies by direct counting; they were

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