CASE REPORTS

Arthritis in a human T lymphotropic virus type I (HTLV-I) carrier

Shinji Ijichi, Takemasa Matsuda, Ikuro Maruyama, Tomomaro Izumihara, Kazuhisa Kojima, Tatsuru Niimura, Yoshikazu Maruyama, Shunro Sonoda, Aichi Yoshida, Mitsuhiro Osame

Abstract

The case is described of a 57 year old woman with polyarthritis fulfilling the 1987 revised criteria of the American Rheumatism Association for rheumatoid arthritis, accompanied by clinical carrier state infection of HTLV-I. Anti-HTLV-I IgM antibodies were detected by western blot analysis in her synovial fluid and serum. Atypical lymphocytes with nuclear convolutions were found in synovial fluid and synovial tissue obtained from the affected knee joint, suggesting in situ activation of HTLV-I infected lymphocytes in the affected synovial compartment. The HTLV-I antigens were detected (1.2%) in short term cultured synovial fluid lymphocytes, by indirect immunofluorescence. These findings supported the possibility that HTLV-I has a role in triggering or modifying inflammation in the synovial compartment.

Infectious agents probably have a major role in triggering autoimmune diseases.¹ In particular, viruses that infect lymphocytes persistently, including human retroviruses, are attractive candidate pathogens for autoimmune diseases.

Human T lymphotropic virus type I (HTLV-I), well known for its connection with adult T cell leukaemia/lymphoma² and HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP),^{3,4} is a retrovirus that shares a relative tropism for CD4 positive T lymphocytes.⁵ This retrovirus has also been implicated in chronic arthritis, not only as a rare manifestation of adult T cell leukaemia/lymphoma⁶⁻⁸ but also associated with carrier state infection.^{9,10} One of the interests of this manifestation is the clinical similarity to rheumatoid arthritis, and it may be a model for the immunopathological mechanism of virus associated autoimmune diseases.

We describe a patient with arthritis associated with HTLV-I infection and provide the results of some immunological and virological studies.

Case report

The patient, a 57 year old Japanese woman, presented with an 18 year history of painful swelling of both knees, shoulder stiffness, low back pain, general fatigue, and chronic cough. Uncustomary exercise caused aggravation of these symptoms and was occasionally accompanied by fever and asthma-like symptoms. Constipation started when she was 51, and she had had two episodes of dysuria. Her brother

died at 66 of adult T cell leukaemia. She had no history of blood transfusion. Prednisolone 5 mg daily (orally) was effective but had been discontinued before admission.

Physical examination on admission showed that the patient had rheumatoid arthritis, according to the 1987 revised criteria of the American Rheumatism Association (ARA)¹¹; she presented with morning stiffness and painful swelling of three joints (right wrist and both knees). According to the ARA classification by the tree method the RA subset was 2, because the radiographic change typical of RA was not shown. There was no evidence of lymphadenopathy or hepatosplenomegaly. A neurological examination showed brisk lower leg reflexes and decreased vibration sense in both feet. A chest x ray disclosed patchy reticular opacities in the right lung field with pleural thickening. Cervical magnetic resonance imaging showed mild stenosis of the spinal canal.

Normal results were obtained for the following tests: complete blood count, urine analysis, renal and liver functions, serum creatine kinase, serum calcium, and serum C3 and C4. Atypical lymphocytes with nuclear convolutions were detected in peripheral blood as a minor component (<0.01%). The sedimentation rate was 74 mm in 1 hour. The protein profile disclosed an increase in the gammaglobulin fraction (18.5 g/l). Serological tests showed C reactive protein 48 mg/l (normal <8), IgG 21.13 g/l (normal 8.8-19.0), IgA 4.77 g/l (normal 0.8-3.8), IgM 2.96 g/l (normal 0.5-3.0), IgE 19 IU/ml (normal <250), rheumatoid factor (RAFA) titre 1/2560, and antinuclear antibody titre 1/80 with a diffuse and speckled pattern. Anti-DNA antibody (radioimmunoassay) value was 6.4 U/ml (normal <10.0). Antibodies to extractable nuclear antigens were positive and antibodies to RNP, Sm, SS-A, SS-B, and Scl-70 antigens were negative. The *Treponema pallidum* haemagglutination test was positive without detectable IgM antibodies to *Treponema pallidum* by fluorescent treponemal antibody absorption test. HLA-DR typing showed the presence of the DR4 antigen. The tuberculin skin reaction was indefinite ($\pm$; erythema of 9 $\times$ 6 mm).

An analysis of synovial fluid obtained by arthrocentesis of the knee showed 10.1 $\times$ 10⁹ leucocytes/l (52% neutrophils, 23% normal lymphocytes), including 16% of adult T cell leukaemia-like atypical lymphocytes (fig 1). No crystals were detected in the synovial fluid. Her cerebrospinal fluid contained 360 mg/l protein, 2.6 mmol/l glucose, and 8.7 $\times$ 10⁶/l white cells (97% lymphocytes).

Center of Rheumatic Diseases, Kagoshima Red Cross Hospital, Kagoshima, Japan
S Ijichi
T Matsuda
T Izumihara
K Kojima
T Niimura

Third Department of Internal Medicine, Faculty of Medicine, Kagoshima University, Kagoshima, Japan
S Ijichi
I Maruyama
Y Maruyama
M Osame

Department of Virology, Faculty of Medicine, Kagoshima University, Kagoshima, Japan
S Sonoda

First Department of Pathology, Faculty of Medicine, Kagoshima University, Kagoshima, Japan
A Yoshida

Correspondence to:
Dr Takemasa Matsuda,
The Center of Rheumatic Diseases, Kagoshima Red Cross Hospital,
2545 Hirakawa-cho,
Kagoshima 891-01,
Japan.

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Figure 1 Arrows denote atypical lymphocytes with nuclear indentations in the synovial fluid. (May-Giemsa stain.)

Figure 2 Western blot analysis in the serum and synovial fluid samples from the patient. Lanes 1, 3, 5, and 7 show the results for anti-HTLV-I IgG antibodies, and lanes 2, 4, 6, and 8 show that for anti-HTLV-I IgM antibodies. Lanes 1 and 2 are negative controls, lanes 3 and 4 are positive controls. The sample of lanes 5 and 6 is the serum, and that of lanes 7 and 8 is the synovial fluid of the patient.

The antibody titre to HTLV-I by particle agglutination method was 1/2048 in serum, 1/512 in synovial fluid, and 1/32 in cerebrospinal fluid. Western blot analysis confirmed the presence of IgG and IgM antibodies to HTLV-I antigens in serum and synovial fluid (fig 2), and the absence of antibodies to HIV (human immunodeficiency virus) in serum. Table 1 shows the results of antibody tests for some viruses which have been previously described in association with polyarthritis.¹²

Arthroscopy showed synovial proliferation with superficial fibrillation of the cartilage. The synovial villi were thickened, hyperaemic, and

Table 1 Results of serum antibody tests for viruses which had been previously described in association with polyarthritis

Virus antibody tests	Method	Result
Anti-HTLV-I	PA*	1/2048
Anti-HTLV-I IgG	WB*	+
Anti-HTLV-I IgM	WB	+
Anti-HIV (HTLV-III)	WB	-
Anti-HBs antigen (HBs* antigen)	RIA*	-
Anti-rubella virus IgG	RIA	-
Anti-rubella virus IgM	EIA*	1/3200
Anti-mumps virus IgG	EIA	<1/100
Anti-mumps virus IgM	EIA	1/400
Anti-adenovirus type 7	EIA	<1/100
Anti-varicella-zoster virus IgG	NT*	<1/4
Anti-varicella-zoster virus IgM	IFA*	1/80
Anti-herpes simplex type 1 IgG	IFA	<1/10
Anti-herpes simplex type 1 IgM	IFA	1/80
Anti-EBV*-capsid antigen IgG	IFA	<1/10
Anti-EBV*-capsid antigen IgA	IFA	1/1280
Anti-EBV*-capsid antigen IgM	IFA	1/10
Anti-EBV-early antigen IgG	IFA	<1/10
Anti-EBV-early antigen IgA	IFA	1/160
Anti-EBV-early antigen IgM	IFA	<1/10
Anti-EBV-nuclear antigen	IFA	<1/10
Anti-cytomegalovirus IgG	IFA	1/10
Anti-cytomegalovirus IgM	IFA	1/40
Anti-Coxsackie viruses B1-B6	IFA	<1/10
Anti-ECHO virus type 6	CF*	<1/4
Anti-ECHO virus type 9	NT	1/8
Anti-parvovirus B19 IgG	EIA	1/4
Anti-parvovirus B19 IgM	EIA	Trace positive

*PA=particle agglutination; WB=western blot analysis; HBs=hepatitis B surface; RIA=radioimmunoassay; EIA=enzyme immunoassay; NT=neutralisation test; IFA=indirect fluorescent antibody test; EBV=Epstein-Barr virus; CF=complement fixation test.

Figure 3 Photomicrograph of a histological section of knee synovium, showing perivascular infiltration of lymphocytes and plasma cells, mild hyperplasia of the lining cells, and increased small vessels. Arrows show high endothelial venule-like vessels. (Haematoxylin and eosin.)

focally necrotic. Some free-floating debris and a detached cartilage nodule (5×8 mm) were detected. Microscopic study indicated that this cartilage nodule was a synovial osteochondroma without the deposition of calcium pyrophosphate dihydrate crystals.

Table 2 Phenotypic characterisation of peripheral blood lymphocytes, synovial fluid lymphocytes, and cultured synovial fluid lymphocytes

Lymphocytes	HTLV-I antigens* (%)	Lymphocyte subpopulations (%)†							
		CD5	CD4	CD8	HLA-DR	DR ⁺ CD4	DR ⁺ CD8	CD29 ⁺ CD4	CD45RA ⁺ CD4
Peripheral blood	0.0	58.8	23.6	21.8	32.6	1.5	1.9	16.0	7.3
Synovial fluid	0.0	89.8	28.9	59.5	71.3	16.3	44.2	27.9	0.5
Cultured synovial fluid‡	1.2		17.4	66.8	65.7	12.2	42.7	12.2	0.4

*HTLV-I antigens were detected on acetone fixed cytopreparation by an indirect immunofluorescence staining technique using a monoclonal antibody to HTLV-I antigens (GIN-14).¹² More than 500 lymphocytes were counted by fluorescence microscopy.
†Dual immunofluorescence staining techniques were performed using FACStar (Becton Dickinson, Mountain View, CA). All monoclonal antibodies were obtained from Coulter Immunology, Hialeah, FL.
‡Synovial fluid lymphocytes (1.5×10^6) were incubated in 1 ml of RPMI-1640 medium supplemented with 10% heat inactivated, normal human serum, 35 U/l recombinant interleukin-2 (Takeda Chemical Industries), 1 µg/ml phytohaemagglutinin-P, and antibiotics for 10 days. The medium was changed four times during the culture.

Figure 4 Photomicrograph of a histological section of knee synovium, showing infiltration of mononuclear cells including atypical lymphocytes with nuclear indentations (arrows) (Haematoxylin and eosin.)

A synovial biopsy specimen was obtained under direct vision with an arthroscope. Synovial specimens displayed perivascular infiltration of lymphocytes and plasma cells, mild hyperplasia of the lining cells, and increased small vessels (fig 3). Several small vessels in the lesions were lined by plump endothelial cells and were surrounded by a thick perivascular sheath (high endothelial venule-like vessels). About 10% of the scattered mononuclear cells in the lesions were atypical lymphocytes with nuclear indentations (fig 4).

Peripheral blood and synovial fluid mononuclear cells were isolated by Ficoll-Hypaque separation from samples treated with heparin. The expression of intracytoplasmic HTLV-I antigens and T cell surface antigens in peripheral blood lymphocytes, synovial fluid lymphocytes, and cultured synovial fluid lymphocytes was determined (table 2). We could not detect HTLV-I antigens in natural peripheral and synovial fluid lymphocytes, but 1.2% of cultured synovial fluid lymphocytes had HTLV-I antigens. Each T cell subset of the peripheral blood lymphocyte population was normal. An increase in the number of cells bearing CD8 and the helper inducer phenotype (CD29⁺CD4) was found in synovial fluid; HLA-DR⁺CD4 and HLA-DR⁺CD8 subsets were also increased.

Discussion

For the following reasons we conclude that the

polyarthritis of this patient is associated with HTLV-I carrier state infection. (1) She had rheumatoid arthritis subset 2 (ARA classification tree) accompanied by clinical carrier state infection of HTLV-I. (2) A serological analysis of antibodies to the viruses which had been previously described in association with polyarthritis¹³ showed that HTLV-I was the only virus with IgM antibodies to it that we could detect in the serum of this patient. (3) The presence of atypical lymphocytes with nuclear convolutions, which suggests the presence of HTLV-I infected lymphocytes,¹⁴ was confirmed in the synovial fluid (16%) and synovial tissue (about 10% of infiltrated cells) obtained from this patient. Such atypical lymphocytes were also detected in her peripheral blood as a minor component (<0.01%). These results suggested in situ activation of HTLV-I infected lymphocytes in the affected synovial compartment. (4) The HTLV-I antigens were detected (1.2%) in short term cultured synovial fluid lymphocytes in this patient by indirect immunofluorescence.

The particularly interesting feature of the arthritis in this case is not only its manifestation of HTLV-I carrier state infection, but also its analogy with rheumatoid arthritis, for which a viral cause has long been sought. Interestingly, a phenotypic analysis of T cell subpopulations in synovial fluid of this patient showed that the CD8 and the CD29⁺CD4 subsets (helper inducer phenotype) were increased in synovial fluid in comparison with peripheral blood; HLA-DR⁺CD4 and HLA-DR⁺CD8 subsets also were increased in synovial fluid. These increases have previously been described in patients with rheumatoid arthritis.¹⁵⁻¹⁷ The distinctive feature of this case, differentiating it from RA, was the presence of atypical lymphocytes with convoluted nuclei in the synovial compartment, suggesting that HTLV-I infection may trigger or modify the autoimmune reactions. It remains to be determined, however, whether these lymphocytes play a primary part in the pathogenesis of this proliferative synovitis or represent only an epiphenomenon, resulting from activation of a passenger virus in an immunoproliferative disease of entirely different pathogenesis.

Several disorders show HTLV-I associated lymphocytosis in the lesions, including HAM/TSP,^{3,4} bronchopneumonopathy,¹⁸ and polyarthritis.^{9,10} Recent reports of encephalopathy¹⁹⁻²¹ in patients with HAM/TSP increase the interest in the distribution of HTLV-I

associated lesions, because the distribution is the same as that of caprine arthritis-encephalitis virus associated lesions.²² This caprine virus is a retrovirus whose clinical features include arthritis, pneumonia, meningoencephalitis, and paralysis. Although our patient had had mild myelopathy, her HAM/TSP cannot be confirmed because of the abnormality of her cervical magnetic resonance imaging results.

We have suggested that migration of proliferative lymphocytes associated with HTLV-I from blood to the central nervous system plays a part in lesion growth in HAM/TSP.²³⁻²⁴ The synovial specimens obtained from our patient showed that several small vessels in the lesions were lined by plump endothelial cells (high endothelial venule-like vessels), as previously described in rheumatoid synovium.²⁵⁻²⁸ It is suggested that high endothelial venule-like structures in autoimmune lesions mediate the lymphocyte trafficking into inflamed tissues.²⁹ Analysis of the interaction between HTLV-I infected lymphocytes and endothelium may clarify the pathogenesis of HTLV-I associated disorders.

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