Arthritis and angioimmunoblastic lymphadenopathy

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SUMMARY We report 2 contrasting cases of a seronegative polyarthritis associated with angioimmunoblastic lymphadenopathy (AILD). Both cases were nonerosive, with symmetrical involvement of the elbows, wrists, knees, and ankles. In one the arthritis appeared concurrently with the main systemic manifestations of AILD. The second presented with polyarthritis 18 months before the onset of AILD. This patient received azathioprine for 11 months before developing AILD, which raises the possibility of this drug being the causative agent.

Angioimmunoblastic lymphadenopathy (AILD) is a recently described lymphoproliferative disorder of unknown aetiology and pathogenesis.^{1–3} The typical clinical features are lymphadenopathy, hepatosplenomegaly, rash, and hypergammaglobulinaemia. Both arthralgia and arthritis have also been described in 18 cases^{4–13} and appear to be less common but definite clinical features.

In most of the reported cases rheumatic features have not been well described. In some cases arthralgia alone has been mentioned,^{4,9,11} but in 11 cases arthritis has been a feature.^{4–13} Five cases have been documented as being seronegative^{4,7–9,13} and 3 as being seropositive.^{4,6,10} Two of the seropositive patients appeared to have had coexistent rheumatoid arthritis. In one case¹² with bilateral carpal tunnel syndrome and polyarthropathy, synovial histology was obtained which showed a mononuclear infiltrate.

We describe 2 contrasting cases. In the first case the arthritis appeared with the main systemic manifestations of AILD, while in the second case the arthritis preceded the onset of AILD by 18 months.

Case reports

CASE 1

A 50-year-old Caucasian woman presented in August 1980 with a one-week history of fever, sore throat, swollen glands, and an itchy rash over her arms and trunk, which later spread to involve her palms, lower legs, feet, and face.

Her symptoms continued, and in early September she was admitted to hospital following the onset of a

polyarthritis involving her knees, ankles, elbows, and wrists. Examination revealed hepatosplenomegaly, generalised lymphadenopathy, and a maculopapular rash. There was active synovitis of the metacarpophalangeal, wrist, knee, and ankle joints. She ran an intermittent fever of up to 38.5°C.

Haemoglobin was 13.1 g/dl, leucocytes $9.3 \times 10^9/l$ (71% neutrophils, 12% lymphocytes, and 9% eosinophils). ESR 58 mm/h. Electrolytes, urea, and liver function tests were normal. Serum albumin was 35 g/l and globulin 40 g/l. Protein electrophoresis showed a diffuse increase in gammaglobulin. Latex test for rheumatoid factor and antinuclear antibody test (ANA) were negative. C3 was normal. Chest and joint x-rays were normal except for mild degenerative changes in the right knee. Aspiration of the left knee revealed clear, straw coloured fluid with a moderate number of leucocytes, of which 88% were polymorphonuclear. Culture was sterile and no crystals were seen.

Lymph node biopsy from the right groin showed the features of angioimmunoblastic lymphadenopathy (Fig. 1). The normal lymph node architecture was almost entirely replaced by a proliferation of small blood vessels and a polymorphic infiltrate, including immunoblasts, plasma cells, and eosinophils with frequent mitotic figures.

In early October she was transferred to the oncology unit at St Bartholomew's Hospital. Examination at that time revealed ankle oedema and crackles in the left lower zone of the chest. Computed tomography showed mediastinal and abdominal para-aortic lymphadenopathy. There was diffuse lung shadowing with small bilateral pleural effusions and hepatosplenomegaly.

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Fig. 1 Lymph node showing proliferation of small blood vessels and a polymorphic infiltrate including immunoblasts, plasma cells, and eosinophils. (H and E, $\times 200$).

A regimen of mustine, vinblastine, procarbazine, and prednisolone at 6-week intervals was begun. After 6 cycles she went into clinical remission, with regression of her lymphadenopathy, hepatosplenomegaly, and arthritis, and this has been maintained to date (August 1982).

CASE 2

A 73-year-old woman presented in December 1977 with a 3-month history of pain and stiffness affecting her wrists, shoulders, hips, and ankles. Examination revealed active synovitis of her shoulders, elbows, wrists, left knee, and both ankles. ESR was 129 mm/h and haemoglobin was 9.1 g/dl. The latex test for rheumatoid factor and ANA test were both negative. X-rays showed no erosions.

She made little improvement on either aspirin or naproxen, and she was subsequently given azathioprine 100 mg daily. On this drug her joint symptoms improved, her ESR fell to 52 mm/h, and her haemoglobin rose to 11.5 g/dl.

In February 1979 she complained of anorexia and lethargy. She was found to have palpable left axillary and supraclavicular nodes with hepatosplenomegaly. Leg oedema and ascites were also noted. Haemoglo-

bin was 9.1 g/dl, white cell count $8.9 \times 10^9/l$ (73% neutrophils, 13% lymphocytes, 4% monocytes, and 6% plasma cells). The platelet count was $57 \times 10^9/l$ and reticulocytes 4%. The Coombs test was positive. The latex test for rheumatoid factor and ANA were again negative. Her blood urea had risen to 32.8 mmol/l. Serum albumin was 25 g/l and globulin 65 g/l. Fibrin degradation products were elevated at 160 mg/l.

A diagnosis of disseminated intravascular coagulation was made and her haemoglobin continued to fall to 7 g/dl. She remained ill with an intermittent fever and lymphadenopathy. A lymph node biopsy was performed, and the histology showed the features of angioimmunoblastic lymphadenopathy with replacement of normal lymph node architecture with immunoblasts, plasma cells, and arborising blood vessels.

She was treated with prednisolone 20 mg t.d.s. and transfused with 4 pints (2.3 l) of blood in all. Despite this there was no sustained increase in haemoglobin or platelets. The oedema became more pronounced and she became weaker over the following few months; she finally developed bronchopneumonia and died in April 1979.

Discussion

These 2 cases demonstrate that AILD, although rare, has a place in the differential diagnosis of seronegative polyarthritis, though seropositive cases have also been described.^{4-6, 10} AILD shares many features with systemic lupus erythematosus (SLE) and adult-onset Still's disease. The rarity of a positive ANA in this disorder allows differentiation from systemic lupus erythematosus.¹²⁻¹³ However, a definite diagnosis can be made only from the histological appearance of a lymph node or skin biopsy.¹⁴ The characteristic histological features are: effacement of lymph node architecture; proliferation of arborising small vessels; polymorphic cellular infiltrate with immunoblasts, plasma cells, lymphocytes, eosinophils, and histiocytes; and the presence of amorphous acidophilic interstitial material.^{2, 3}

In case 1 the arthritis appeared in association with the other major features of this disorder. Analysis of the reported cases in which arthritis and AILD have been described⁴⁻¹³ shows that this is the usual time for the arthritis to appear. It is likely, because of this timing, that the arthritis in these cases is a true clinical manifestation of AILD.

In case 2 the arthritis antedated the onset of AILD by 18 months. It is interesting to speculate whether this arthritis was separate from AILD or a prodroma of AILD. Three cases of AILD have previously been reported in which the arthritis appeared before the major manifestations of this disorder. Flandrin,⁶ in a series of patients with AILD, had one patient with a past history of rheumatoid arthritis. Goudsmit *et al.*⁷ described a patient who developed a rash and arthritis 4 months before the main features of AILD developed. And Rothwell *et al.*¹³ have recently reported a well documented case in which a seronegative polyarthritis developed 4 months before the apparent onset of AILD, though a rash appeared 2 months after the arthritis. In these last 2 cases it would seem probable that the arthritis was a prodroma of AILD. The gap between the arthritis and the onset of AILD was considerably longer than 4 months in our second case, but it would seem likely that the arthritis and AILD are in some way related.

The aetiology and pathogenesis of AILD are unclear, but 2 pathogenetic mechanisms have been proposed. Frizzera *et al.*² have suggested that it is an autoimmune disorder with defective T cell regulatory function, which may predispose to an abnormal pro-

liferative and autoaggressive reaction of B cells. However, Lukes and Tindle³ labelled it a hyperimmune entity with B cell proliferation and proposed that it may be triggered by a hypersensitivity reaction to drugs.

In case 2 AILD followed 11 months of treatment with azathioprine. Although there are no previous reports of AILD following azathioprine therapy, this possible association needs consideration in view of this drug's oncogenic potential.

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