Case report

Angioimmunoblastic lymphadenopathy associated with polyarthritis

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SUMMARY A patient with angioimmunoblastic lymphadenopathy with dysproteinaemia is described. The patient had a severe clinical illness with a pronounced haemolytic anaemia, which followed well-established polyarthritis and gold therapy. It was accompanied by in-vitro evidence of suppressed cell-mediated immune responses and by development of serum antismooth muscle antibodies. These features are unusual and support theories that this disease has an immunological basis. Improvement occurred with prednisone and azathioprine therapy, suggesting that combined use of these agents is useful in some patients with AILD. The patient subsequently developed a lymphoma.

Angioimmunoblastic lymphadenopathy with dysproteinaemia (AILD) is a recently described benign lymphoproliferative disorder characterised by fever, sweats, weight loss, a rash, generalised lymphadenopathy, hepatosplenomegaly, haemolytic anaemia, polyclonal hypergammaglobulinaemia, and diagnostic histological abnormalities.^{1,2} Its aetiology remains uncertain, though immune processes have been implicated. The best treatment is unknown. We describe a patient whose disease followed well-established arthritis and sodium aurothiomalate (Myocrysin) therapy and which was accompanied by an unusually severe haemolytic anemia. In-vitro cell-mediated immune responses were suppressed, and serum contained antismooth muscle antibodies. These findings support an immunological aetiology for AILD. Marked clinical improvement followed the use of immunosuppressive therapy, suggesting that this form of treatment has an important role in some patients with this disease.

Case report

A 60-year-old woman presented at the University of Alberta Hospital in April 1977 for treatment of an acute seronegative polyarthropathy involving both

upper and lower limbs. She responded well to enteric-coated acetylsalicylic acid (ASA) and indomethacin until June 1977, when she experienced increasing shoulder pain and fatigue and developed a pruritic maculopapular rash on her extremities. She was admitted to hospital for further treatment of active synovitis in her hands, ankles, and shoulders. At that time subcutaneous nodules were present distal to both elbows; however, there was no adenopathy. Radiographs showed periarticular osteoporosis and soft tissue swelling but no erosions. Tests for rheumatoid factor and fluorescent antinuclear antibodies (FANA) were negative and the ESR was 5. Haemoglobin was 10.9 g/dl and leucocytes $4.8 \times 10^9/l$, with a normal differential count. A skin biopsy showed chronic nonspecific dermatitis.

She continued with indomethacin and enteric-coated ASA, and subsequently started on a course of chrysotherapy. Her dermatological symptoms responded to topical steroids.

The joint symptoms had shown no improvement by August in spite of 510 mg of sodium aurothiomalate, yet the only evidence of active synovitis was in both ankles. She developed fatigue, anorexia, and lost 5 kg in weight. The following week rapidly progressive generalised lymphadenopathy occurred, involving the supraclavicular, axillary, hilar, and inguinal regions.

She was readmitted to hospital, where she developed fever to 39.5°C and a severe haemolytic

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anaemia (haemoglobin as low as 5.6 g/dl, a reticulocytosis, and hyperbilirubinaemia) requiring transfusion of up to 1 unit of packed cells daily to maintain her haemoglobin above 7 g/dl. Her platelets fell to $38 \times 10^9/l$ and her leucocytes transiently to $2 \times 10^9/l$. Peripheral blood films showed increased rouleaux formation, occasional myeloid precursors and nucleated red cells, atypical lymphocytes, and a variable monocytosis (highest count $1.1 \times 10^9/l$). A polyclonal gammopathy (IgG 3340 mg/dl, IgA 768 mg/dl, and IgM >2000 mg/dl) developed. (SI: mg/l = mg/dl $\times 10$). The direct Coombs test was negative, but the indirect Coombs test was positive. Erythrocyte survival studies with 51 chromium showed splenic sequestration with a survival time of 14.5 days (normal 26–32 days). Antismooth muscle antibodies were positive, but rheumatoid factor, FANA, anti-DNA antibodies, and anti-mitochondrial antibodies were negative. Complement levels and liver function tests (LDH, SGOT, and alkaline phosphatase) were normal.

Supraclavicular lymph node biopsies showed replacement of normal architecture by a pleomorphic infiltrate of plasma cells and immunoblasts, prominent arborising blood vessels, and periodic acid Schiff (PAS) positive interstitial amorphous material. A bone marrow aspirate showed non-specific abnormalities with hypercellularity. In the trephine biopsy focal areas of hypocellularity with

Fig. 1 Lymph node showing proliferation of small vessels, intercellular amorphous PAS-positive material, and abundant immunoblasts (PAS, $\times 50$).

Fig. 2 Detail of node (H and E, $\times 120$)

fibroblastic and endothelial proliferation with increased reticulin were found. A diagnosis of AILD was made (confirmed by Dr H. Rappaport, who kindly reviewed the histology).

The patient was treated with prednisone 80 mg daily. Over 4 weeks her symptoms improved, her nodes regressed, her fever resolved, and her haemoglobin rose to 10.1 g/dl. Transfusions were no longer required. Because of persistent haemolysis and the high dose of prednisone needed, azathioprine 100 mg daily was added and the prednisone was reduced. With this combined therapy her general state improved, particularly the rash and the residual arthritis, and her haemoglobin rose to normal over a 2 month period. Apart from intermittent fever, for which no infectious aetiology could be found, she remained well on azathioprine 100 to 150 mg daily and prednisone 10 mg daily until mid 1978. She then developed progressive lymphadenopathy followed by fatigue and fever with chills and sweats. A node biopsy showed non-Hodgkin's malignant lymphoma, which has not yet been definitely characterised, though it is not an immunoblastic lymphoma.

During the course of the acute illness cell-mediated immune responses were measured by in-vitro lymphocyte transformation tests. Responses to mitogens (PHA, Con-A, and PWM) and antigens (*Herpes simplex* and *Candida*) were either absent or markedly reduced when compared to normals (Table 1).

Table 1 *Lymphocyte transformations expressed as a stimulation ratio of counts per minute (c.p.m.) in antigen-treated culture: c.p.m. in spontaneous transformation culture*

	PHA	Con-A	PWM	Herpes simplex I	Candida
Patient	5.4	9.2	3.6	2.6	1.7
Normal	>30	>30	>10	>12	>2

PHA=phytohaemagglutinin. Con-A=concanavalin A. PWM=pokeweed mitogen.

Discussion

The 2 major theories regarding the aetiology of AILD are that it is a hyperimmune condition of B cells, possibly resulting from exposure to exogenous antigens in an abnormal reactor; or that it is an autoimmune condition with defective T-cell regulation.^{1 2} These theories are supported by its histological similarity to antigenically stimulated nodes; by reduced numbers of circulating and lymph node T-cells; by the occasional presence of reduced complement levels, vasculitis, and amyloid; and by its frequent progression to immunoblastic lymphoma.³⁻⁷

In our patient seronegative polyarthritis preceded the development of AILD. In addition, in-vitro cell-mediated immune responses were suppressed, and the serum contained antismooth muscle antibodies. These associations are consistent with an autoimmune aetiology. Concomitant AILD and persistent arthritis appear to be rare, with only 3 well-documented examples.⁸⁻¹⁰ At least 1 patient in whom AILD occurred with Sjögren's syndrome and a positive rheumatoid factor has also been reported.¹¹ The typical serology of connective tissue disorders (for example, RF, FANA) is rarely found in AILD.^{2 12 13} Although our patient's serology was also negative, an unexpected finding was a positive result for antismooth muscle antibodies in the absence of biochemical evidence of liver dysfunction. We could locate only 1 previous case in which this test was positive.¹⁴ Although the arthritis in our patient antedated the lymphadenopathy, it is possible that the joint problems were the first manifestation of AILD.

Our patient's disease also followed gold therapy (as well as indomethacin and ASA). Angioimmunoblastic lymphadenopathy has followed treatment with penicillin, diphenylhydantoin, thiazide diuretics, amphetamines, and alphamethyldopa.^{1 11 15 16} Sodium aurothiomalate does not appear to have been previously implicated as a potential aetiological agent. It is noteworthy that most of these drugs implicated as possible causative factors in AILD, and also gold, have been associated with other

presumed immune phenomena. The role of gold therapy in the AILD in our patient must remain speculative. However, if it were in part responsible, this would support the theory that AILD represents a hyperimmune response to foreign antigens.

The haemolytic anaemia in our patient was particularly severe. Although the direct Coombs test was negative, an autoimmune basis is likely. It responded dramatically, though slowly, to combined prednisone and azathioprine therapy, as did the patient's other symptoms. The predominant splenic sequestration on ⁵¹chromium RBC survival studies suggests that splenectomy might have a place in the management of the haemolytic anaemia of this disorder if it fails to respond to more conservative measures. Optimal treatment of this disorder has not yet been clarified. No therapy, prednisone alone, and chemotherapy have all been suggested. It appears that therapy should be adapted to the individual patient. However, in those patients with a clinical course similar to that in our patient immunosuppressive therapy appears to be worth a trial.

The eventual development of a malignant lymphoma, as occurred in this patient, is unfortunately relatively common.^{2 7} In fact, its appearance supports the view that a defect in immune regulation is important in the genesis of AILD. This condition can therefore probably be considered as another example of a premalignant disease. In addition AILD would appear to be yet another condition in which arthritis may be a systemic and presenting feature.

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