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 polyarthritis 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 anti-nuclear antibodies (FANA) were negative and the ESR was 5. Haemoglobin was 10·9 g/dl and leucocytes 4·8 × 109/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 supravacuicular, axillary, hilar, and inguinal regions.

She was readmitted to hospital, where she developed fever to 39·5°C and a severe haemolytic
anaemia (haemoglobin as low as 5.6 g/dl, a reticulo-
cytosis, and hyperbilirubinaemia) requiring trans-
fusion of up to 1 unit of packed cells daily to main-
tain her haemoglobin above 7 g/dl. Her platelets fell
to 38 x 10^9/l and her leucocytes transiently to
2 x 10^9/l. Peripheral blood films showed increased
rouleaux formation, occasional myeloid precursors
and nucleated red cells, atypical lymphocytes, and
a variable monocytes (highest count 1.1 x 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 x 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. Compl-
iment 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
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 haemo-
globin 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 resi-
dual 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 lymphad-
lenopathy 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 immuno-
blastic 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).

Fig. 1 Lympb node showing proliferation of small
vessels, intercellular amorphous PAS-positive material,
and abundant immunoblasts (PAS, x 50).

Fig. 2 Detail of node (H and E, x 120)
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

<table>
<thead>
<tr>
<th></th>
<th>PHA</th>
<th>Con-A</th>
<th>PWM</th>
<th>Herpes simplex 1</th>
<th>Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>5-4</td>
<td>9-2</td>
<td>3-6</td>
<td>2-6</td>
<td>1-7</td>
</tr>
<tr>
<td>Normal</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;2</td>
</tr>
</tbody>
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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 antis主帅 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 antis主帅 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 alphamethylldopa.1 11 15 16 Sodium aurothiomalate does not appear to have been previously implicated as a potential aetiologic 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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References

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