Case report

Polyarthritis and angioimmunoblastic lymphadenopathy

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SUMMARY Angioimmunoblastic lymphadenopathy (AILD) is a lymphoproliferative disorder with well established clinical and histological features, one of the clinical manifestations being a peripheral polyarthritis. A case of AILD with a symmetrical non-erosive peripheral polyarthritis is described, including the findings in the synovial fluid and histology of the synovium. There was a marked reduction in the number of peripheral blood T lymphocytes bearing the CDT8 phenotype in both the peripheral blood and synovial fluid. The arthritis was difficult to control, requiring large doses of corticosteroids, which produced significant side effects. Levamisole 150 mg, one day each week, was effective in controlling the arthritis and returning the numbers of CDT8 lymphocytes to normal. The aetiology of AILD is unknown, though a defect in T cell regulation, in particular T cell suppression, with a secondary B cell proliferation has been postulated. The demonstration of reduced numbers of lymphocytes bearing the CDT8 phenotype in this patient supports that theory.

Angioimmunoblastic lymphadenopathy (AILD) is a lymphoproliferative disorder with well described characteristic clinical and histological features. It has a clinical similarity to several connective tissue disorders, including Sjögren’s syndrome and systemic lupus erythematosus (SLE), with which it has been associated. Infrequently there may be an associated arthritis, which is usually seronegative, only three cases having been reported as being seropositive for IgM rheumatoid factor. In the few cases in which the arthritis has been fully described it was symmetrical, peripheral, and non-erosive.

The aetiology of AILD is unknown, though a defect in T cell regulation, probably T cell suppression with secondary B cell proliferation, has been postulated. This paper describes a case of AILD and associated polyarthritis in which the histology of the lymph node and synovium is recorded. Characteristics of the peripheral blood and synovial fluid lymphocytes were examined using monoclonal antibodies to cell surface markers. The arthritis was difficult to treat and was effectively controlled with levamisole, which also corrected the peripheral blood lymphocyte abnormalities. This case draws further attention to the aetiology and treatment of arthritis in this condition.

Case report

A 52 year old woman presented in April 1983 with a three week history of lethargy, nausea, anorexia, night sweats, and breathlessness. She had been previously well and was not taking any medication. She was febrile, temperature 38.2°C, and had a generalised lymphadenopathy, photosensitive malar rash, hepatosplenomegaly, and oral candida. A chest x ray showed right hilar lymphadenopathy and fine scattered miliary calcification. Haemoglobin was 112 g/l, white cell count 32.2×10⁹/l, 22.5×10⁹/l neutrophils, 3.9×10⁹/l lymphocytes, 1.0×10⁹/l monocytes, 0.07×10⁹/l eosinophils, 1.6×10⁹/l plasma cells, 1.6×10⁹/l atypical plasma cells with a few myelocytes and metamyelocytes. Erythrocyte sedimentation rate (ESR) was 85 mm/h.

Accepted for publication 2 December 1986.
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The Paul-Bunnell test was negative, the Mantoux test negative to 100 T.U. IgG was 22.5 g/l (normal 4.8–16.7), IgA 8.7 g/l (normal 0.6–3.7), and IgM 4.2 g/l (normal 0.3–2.8). Cervical lymph node histology (Fig. 1) showed features of AILD. Immunoperoxidase staining of the lymphocytes demonstrated all immunoglobulin classes, 60% staining for IgG, 5% for IgA, 3% for IgM, 1% for IgG, 25–30% for λ, and 5% for κ chains.

Over the following two months the patient developed a symmetrical polyarthritis involving all the peripheral joints, sparing only the distal interphalangeal joints and hips. The Rose-Waaler test was negative and antibodies to nuclear antigens and double stranded deoxyribose nucleic acid were not detected. Radiographs of the hands and feet showed only soft tissue swelling. In July 1983 the patient was given two short courses of chlorambucil and prednisone. The prednisone was continued, and over the next six months a minimum prednisone dosage of 30 mg/day was required to control the arthritis. Because of persisting lymphadenopathy and weight loss the patient was given two further courses of chemotherapy in early 1984. These consisted of cyclophosphamide, BiCNU, vincristine, Melphalan, and prednisone. This controlled the lymphadenopathy and weight loss, but once again when the prednisone was reduced below 30 mg/day the arthritis flared. At this time the ESR was 132 mm/h and the C reactive protein 86 mg/l.

Peripheral blood lymphocytes and synovial fluid were examined before chemotherapy (Table 1) using monoclonal antibodies to cell surface markers, the striking feature being a marked reduction in numbers of lymphocytes bearing the CD8 phenotype, which includes the suppressor T cell population (Table 2). Synovial biopsy of the left knee showed an absence of proliferation in the lining synoviocytes and a sparse infiltrate of mononuclear cells in the subsynovial layer (Fig. 2).

More aggressive chemotherapy using cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP regimen) was used with regression of the lymphadenopathy but with a return of the synovitis when the prednisone was reduced below 30 mg/day. This regimen produced a hypogammaglobulinaemia, IgG 3.6 g/l, IgA 0.06 g/l, and IgM 0.3 g/l, which has persisted. Over the next few months the patient’s illness was complicated by recurrent breast abscesses, right upper lobe pneumonia, proximal myopathy, and osteoporosis with vertebral fractures. It was thought that these complications were corticosteroid induced. In May 1984 she was given gold salts to try and control the arthritis so that the prednisone dosage could be reduced. This had to be discontinued after four months (total dose 800 mg) because of gold induced neutropenia. A bone marrow showed abnormal development of myeloid cells, and a bone scan showed increased uptake in the left hip.

### Table 1 White cell count and lymphocyte subsets in synovial fluid before chemotherapy

<table>
<thead>
<tr>
<th>Cell count×10⁹/l</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WCC*</td>
<td>56.6</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>52.1</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2.8</td>
</tr>
<tr>
<td>Monocytes</td>
<td>1.7</td>
</tr>
<tr>
<td>CDT3</td>
<td>32.8</td>
</tr>
<tr>
<td>CDT4</td>
<td>28.4</td>
</tr>
<tr>
<td>CDT8</td>
<td>3.4</td>
</tr>
<tr>
<td>Surface immunglobulin</td>
<td>13.0</td>
</tr>
<tr>
<td>Monoclonal Ig typing</td>
<td>Kappa 12% Lambda 10%</td>
</tr>
</tbody>
</table>

*WCC=white cell count.
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Table 2  Peripheral blood white cell count and lymphocyte subsets (1) before chemotherapy, (2) four months after chemotherapy, and (3) after four months and (4) 15 months of levamisole treatment

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Cell count×10⁹/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WCC*</td>
<td>4·0–11·0×10⁹/l</td>
<td>14·4</td>
</tr>
<tr>
<td>Total lymphocytes</td>
<td>1·0–4·0×10⁹/l</td>
<td>1·3</td>
</tr>
<tr>
<td>Surface immunoglobulin</td>
<td>0·1–0·8</td>
<td>0·04</td>
</tr>
<tr>
<td>CDT3</td>
<td>0·6–3·2</td>
<td>1·17</td>
</tr>
<tr>
<td>CDT4</td>
<td>0·6–1·1</td>
<td>1·16</td>
</tr>
<tr>
<td>CDT8</td>
<td>0·2–0·5</td>
<td>0·03</td>
</tr>
<tr>
<td>OKT4/OKT8</td>
<td>38·7</td>
<td>79</td>
</tr>
</tbody>
</table>

*WCC=white cell count.

Fig. 2  Synovium showing minimal changes in the synovial cells, with a mild mononuclear cell infiltrate in the subsynovial layer.

cells with marked nuclear abnormalities, but the other cell precursors were normal.

Because of persisting arthritis the patient was started on levamisole 150 mg/day for one day a week. Over three months this produced slow improvement in her arthritis and allowed the prednisone to be reduced to 5 mg/day. Two months after starting levamisole the patient had herpes zoster involving the right T4, T5 dermatomes. Four months after starting levamisole the patient had only minimal early morning stiffness with mild synovitis in the metacarpophalangeal and proximal interphalangeal joints of both hands, with an ESR of 28 mm/h. The prednisone dosage has continued to be reduced and is now 3 mg/day. Peripheral blood white cell count is now 10·4×10⁹/l and there has been an increase in the number of cells bearing the CDT8 phenotype (Table 1).

The patient remained on levamisole, 50–150 mg/day, for one day a week to control her arthritis. There were some fluctuations in her white cell count and lymphocyte subsets, the last relatively normal result being in February 1986 (Table 2). Over subsequent months there was a recurrence of the lymphadenopathy with a progressive pancytopenia, and in June the patient died from sepsicaemia. Levamisole was discontinued at the time of the recurrence of the lymphadenopathy, without any recurrence of the arthritis.

Discussion

The clinical features of AILD, fever, weight loss, lymphadenopathy, hepatomegaly, skin rash, hypergammaglobulinaemia, and polyarthritis, were all present in this patient. In addition, there was fine miliary calcification in the lungs consistent with chicken pox lung. This patient had a marked reduction in the numbers of CDT8 cells in the peripheral blood and synovial fluid with a hypergammaglobulinaemia. The total lymphocyte count was at the lower limit of the normal range. This would be consistent with the hypothesis of an impairment of T cell suppression.
Other studies have mentioned a reduction in peripheral blood total T cell numbers but not commented on a selective reduction in CDT8 cells. Synovial fluid was obtained in two previous cases, one contained a moderate number of leucocytes with 88% neutrophils and the other 15300 leucocytes, of which 70% were neutrophils and 29% large mononuclear leucocytes and 1% small lymphocytes. Synovial biopsy in a third case with bilateral carpal tunnel syndrome and polyarthropathy showed a mononuclear cell infiltrate, but no other features were mentioned. The synovial histology in this case was non-specific, but the important feature was the lack of an inflammatory cell infiltrate.

AILD and SLE share many clinical manifestations as well as hypergammaglobulinaemia and lymphopenia. In addition, in vitro T suppressor cell defects have been reported in patients with SLE. Although lymph node histology and autoantibody profiles differentiate the two conditions, it is possible that they could form a continuous spectrum of disease that may share a common pathogenic mechanism. One of these mechanisms may be a T suppressor cell defect which could also predispose towards development of an arthritis. Although initially thought to be benign, it is now known that AILD carries a 50% mortality at 12 months, reaching 90% if no remission is achieved with chemotherapy.

In this patient an aggressive chemotherapeutic regimen was effective in controlling the disease but not the polyarthritis. The high dose of prednisone (>30 mg/day) required to control the polyarthritis resulted in severe side effects. Gold salts produced only a partial clinical improvement before they were discontinued because of neutropenia. The interesting observation was the beneficial effect of levamisole which occurred over a three months' period, the clinical improvement being associated with an improvement in the numbers of T suppressor cells. This enabled the prednisone dosage to be significantly reduced to a maintenance dose of 3 mg/day.

Levamisole has been previously used in the treatment of AILD with or without an arthritis and may correct a lymphopenia. It has been assumed that it corrects the defect in T cell suppression, the dosage of levamisole being 150 mg two or three days a week. We used a smaller dose of 150 mg one day a week, because it has been shown to be adequate in controlling rheumatoid arthritis.

Therefore this case shows how polyarthritis in AILD may be a major symptomatic manifestation of the condition which can be difficult to control. Levamisole was effective in controlling the polyarthritis and correcting the lymphocyte subset abnormality, allowing a reduction in the corticosteroid dosage. Levamisole probably had little influence on the angioimmunoblastic lymphadenopathy.

References

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Ann Rheum Dis 1987 46: 555-558
doi: 10.1136/ard.46.7.555

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