Nonrandom Chromosome Abnormalities in Angioimmunoblastic Lymphadenopathy

By Yasuhiko Kaneko, Richard A. Larson, Daina Variakois, J. Marie Haren, and Janet D. Rowley

Cytogenetic and pathologic studies were performed on six patients with angioimmunoblastic lymphadenopathy (AILD). All six had diffuse lymphadenopathy; five had fever, four had weight loss, and four had a diffuse erythematous rash. All patients except one had a polyclonal elevation of immunoglobulin. All patients had diagnostic findings in lymph node (LN) and bone marrow (BM) biopsies. Two patients died of progressive AILD; one patient died after transformation of AILD to immunoblastic sarcoma (IBS); one patient died of gastrointestinal bleeding of unknown cause. The remaining two patients, who have achieved complete remission with intensive chemotherapy, are alive 20 and 8 mo after the diagnosis; one of these had AILD and the other, both AILD and IBS. Despite diagnostic BM biopsy findings, none of the patients had chromosome abnormalities in their BM cells. In studying LN cells of 5 patients, however, we found chromosome abnormalities in each; clonal abnormalities were detected in two, both clonal and nonclonal abnormalities in two, and only nonclonal single-cell abnormalities in one. An extra chromosome 3, seen in four patients, was clonal in two and nonclonal in the two others. Cells with +5, +15, +19, +21, +22 were seen in two patients. All patients had 50% or more normal dividing cells in their LN. The mosaicism of unrelated abnormal karyotypes that was seen in four patients suggests that this malignant tumor is not necessarily monoclonal in its early stages, but that one clone may be selected and predominate in the late stage. Because nonrandom acquired clonal chromosome abnormalities are a consistent feature of malignancies, our data suggest that AILD may be a malignant disease despite its original description as a benign proliferative process. Therefore, it may require aggressive chemotherapy.

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), also referred to as immunoblastic lymphadenopathy (IBL), is a systemic disease characterized by generalized lymphadenopathy, hepatosplenomegaly, skin rash, fever, and anemia.\(^{1-3}\) The characteristic pathologic changes in lymph nodes (LN) are a diffuse effacement of nodal architecture,\(^{1-3}\) marked proliferation of polymorphic cells, including lymphocytes, plasma cells, and immunoblasts, and an abundance of small vessels.

Most patients with AILD have a progressive clinical course with a fatal outcome.\(^{3,4}\) Frizzera et al.\(^{1,2}\) and Lukes and Tindle,\(^{3}\) however, considered AILD a non-neoplastic disease because of the benign histologic appearance. Chromosome abnormalities, which are one of the features characteristic of neoplastic disease, have been reported in AILD patients.\(^{5-10}\) However, no detailed histologic description of the biopsy specimens, or information on the subsequent clinical course, has been provided on these patients.

Here, we describe the chromosome pattern as well as the precise clinical and pathologic features in six patients with AILD. We found chromosome abnormalities in all five patients whose LNs were examined. Although it may be difficult to diagnose AILD as a neoplastic disease on the basis of the histologic findings, the presence of chromosome abnormalities and the fatal clinical course suggest that AILD is a neoplastic disease.

CASE REPORTS

The six patients described in this report were admitted to the University of Chicago Hospitals and Clinics (UCHC) between February 1976 and August 1981.

Patient 1

A 69-yr-old woman was admitted in February 1976 after 12 mo of fatigue, weight loss, and peripheral edema. She had fever up to 38.6°C as well as hepatosplenomegaly and generalized lymphadenopathy. A chest x-ray showed mild hilar and mediastinal adenopathy, and a gallium scan was positive in multiple LNs. Her past history was unremarkable. Biopsies of LNs and bone marrow (BM) were diagnostic for AILD. Skin testing demonstrated anergy. Her symptoms resolved spontaneously, and no treatment was begun.

Three months later, shortly after a course of ampicillin, the patient developed fever, rash, pulmonary infiltrates, bilateral pleural effusions, and leukocytosis with 26,000 leukocytes/cu mm and 8%-14% eosinophils. A work-up for infection was negative except for Candida in the pharynx and in the urine. Thoracentesis and paracentesis revealed exudative sterile effusions with mononuclear cells and neutrophils. Polyclonal gammaglobulins were elevated to 3.3 g/dl. The patient was noted to be profoundly hypothyroid [free thyroxine index less than 1.0 (normal range 6.4-10.5), TSH = 56 (normal range 0-6 μU/ml)] with titers of antithyroglobulin antibodies greater than 1:5280. Prednisone and azathioprine were begun, but there was no significant response. Three weeks after the start of this regimen, and 3 mo after the diagnosis of AILD, she died of progressive respiratory insufficiency. An autopsy demonstrated extensive involvement with AILD in LNs, BM, liver, spleen, lungs, thyroid, kidney, pancreas, stomach, myocardium, and muscle. No infectious agents were identified.
### Table 1. Laboratory Data on Six Patients With AILD at the Time of Diagnosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Hb (g/dl)</th>
<th>Platelets (x 10^9/μl)</th>
<th>WBC (x 10^9/μl)</th>
<th>PMNs (%)</th>
<th>Lymphocytes (%)</th>
<th>Eosinophils (%)</th>
<th>ESR (mm/hr)</th>
<th>Coombs Test</th>
<th>Albumin (g/dl)</th>
<th>Globulin (g/dl)</th>
<th>ANIF</th>
<th>Anti-DNA Antibodies</th>
<th>IgG (mg/dl)</th>
<th>IgA (mg/dl)</th>
<th>IgM (mg/dl)</th>
<th>Survival</th>
<th>Immunelectrophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/F</td>
<td>10.6</td>
<td>236</td>
<td>14.4</td>
<td>85</td>
<td>5</td>
<td>0</td>
<td>85</td>
<td>Pos.</td>
<td>2.78</td>
<td>2.70</td>
<td>Neg.</td>
<td>Neg.</td>
<td>2.370</td>
<td>204</td>
<td>603</td>
<td>3</td>
<td>Polyclonal IgG</td>
</tr>
<tr>
<td>2</td>
<td>49/F</td>
<td>11.7</td>
<td>251</td>
<td>3.8</td>
<td>67</td>
<td>17</td>
<td>8</td>
<td>77</td>
<td>Neg.</td>
<td>3.08</td>
<td>1.84</td>
<td>Neg.</td>
<td>Neg.</td>
<td>2.000</td>
<td>480</td>
<td>710</td>
<td>15</td>
<td>Polyclonal IgM</td>
</tr>
<tr>
<td>3</td>
<td>58/M</td>
<td>12.3</td>
<td>258</td>
<td>6.1</td>
<td>70</td>
<td>16</td>
<td>1</td>
<td>73</td>
<td>Pos.</td>
<td>3.36</td>
<td>1.35</td>
<td>Neg.</td>
<td>Neg.</td>
<td>2.750*</td>
<td>1.450*</td>
<td>1.280*</td>
<td>15</td>
<td>Polyclonal lambda</td>
</tr>
<tr>
<td>4</td>
<td>70/F</td>
<td>11.8</td>
<td>401</td>
<td>6.7</td>
<td>78</td>
<td>9</td>
<td>4</td>
<td>115</td>
<td>Neg.</td>
<td>1.82</td>
<td>4.24</td>
<td>Neg.</td>
<td>Neg.</td>
<td>4.210</td>
<td>1.270</td>
<td>66</td>
<td>20+</td>
<td>Polyclonal lambda</td>
</tr>
<tr>
<td>5</td>
<td>63/M</td>
<td>14.0</td>
<td>124</td>
<td>14.4</td>
<td>53</td>
<td>16</td>
<td>9</td>
<td>33</td>
<td>ND</td>
<td>3.24</td>
<td>0.92</td>
<td>ND</td>
<td>ND</td>
<td>911</td>
<td>148</td>
<td>135</td>
<td>6</td>
<td>Polyclonal IgM</td>
</tr>
<tr>
<td>6</td>
<td>64/M</td>
<td>10.2</td>
<td>216</td>
<td>5.1</td>
<td>76</td>
<td>6</td>
<td>0</td>
<td>129</td>
<td>Pos.</td>
<td>1.97</td>
<td>3.48</td>
<td>Neg.</td>
<td>Neg.</td>
<td>3.750</td>
<td>985</td>
<td>502</td>
<td>8+</td>
<td>Polyclonal IgG</td>
</tr>
</tbody>
</table>

**Immunoelectrophoresis**

- **Serum**
- **Urine**

- Polyclonal IgG
- Polyclonal IgM
- Monoclonal kappa
- Polyclonal IgA
- Polyclonal gamma globulins

**Survival**

- 3 months
- 15 months
- 20+ months

---

**ANIF**, anti-nuclear immunofluorescence; **ESR**, erythrocyte sedimentation rate; **ND**, not done.

*Eight months after diagnosis.

A "+" after survival indicates that the patient is alive.
Patient 2
A 49-yr-old woman was admitted in October 1977 with weakness and malaise, a generalized pruritic macular-papular rash, lymphadenopathy, and fever up to 38.2°C. Her past history included Grave’s disease, which had been treated with radioactive iodine in 1961; she subsequently was given desiccated thyroid extract. Biopsies of LN and BM revealed AILD. Skin testing documented anergy.

Symptoms waxed and waned for 8 mo without requiring specific therapy. In the ninth month of her illness, the patient developed increased lymphadenopathy, bilateral pleural effusions, and ascites. Transformed lymphocytes and immunoblasts consistent with AILD were present in both pleural and ascitic fluids. Because smears were positive for acid-fast bacilli, she received isoniazid and ethambutol for 2 mo until tuberculosis was ruled out by cultures. Skin tests, including tuberculin, remained nonreactive. Administration of prednisone (40 mg/day) was begun, and all clinical evidence of disease resolved for 3 mo. She later survived an episode of staphylococcal sepsis. In the 13th month of her illness, the patient developed a disseminated Herpes zoster infection, which progressed despite therapy with adenine arabinoside. Terminally, the rash, fevers, and adenopathy recurred, together with pancytopenia, despite continued prednisone therapy. She died of zoster pneumonia 15 mo after the diagnosis of AILD; no autopsy was performed.

Patient 3
A 58-yr-old man was admitted in November 1979 following 2 mo of malaise with intermittent fevers and rigors and an evanescent pruritic, erythematous papular rash. He was found to have generalized lymphadenopathy and mild splenomegaly. His past history was unremarkable except for recent exposure to intravenous pyelogram dye and ampicillin for urinary tract infections. Four years earlier, he had been found to be skin-test-positive for tuberculin at a time when his wife had active pulmonary tuberculosis; he received INH for 1 yr without encountering any difficulty.

A BM biopsy was initially interpreted as showing multiple lymphohistiocytic nodules of unknown origin. An LN biopsy in January 1980 demonstrated classical changes of AILD; in retrospect, the initial BM biopsy was considered to be consistent with this diagnosis. His skin reaction to tuberculin was again positive.

An attempt at plasmapheresis therapy was discontinued when a cold agglutinin with anti-I specificity (titer 1:8) was found in association with significant hemolysis. Four months after the diagnosis, cytotoxic therapy was begun because the patient had debilitating fevers. There was no sustained response to any of several chemotherapy regimens: prednisone alone, chlorambucil and prednisone, COMLA (cyclophosphamide, vincristine, methotrexate with leucovorin rescue, and cytosine arabinoside), or ABV-MLA (doxorubicin, bleomycin, vinblastine, methotrexate with leucovorin rescue, and cytosine arabinoside). A trial with human leukocyte interferon (2.5 x 10^6 U i.m. daily for 8 doses) also was not beneficial. His course was marked by frequent prolonged febrile episodes with debilitating rigors and weakness.

Two months prior to his death, three intrapulmonary masses were noted on a chest x-ray; a needle biopsy demonstrated large-cell (immunoblastic) lymphoma. The patient refused further chemotherapy, and he died due to sepsis and pulmonary insufficiency from progressive lymphoma 15 mo after the initial diagnosis. No autopsy was performed.

Patient 4
A 70-yr-old woman was admitted in June 1980 after 4 mo with bilateral leg weakness, fatigue, lymphadenopathy, and edema and 3 wk with a generalized erythematous macular rash. Two years earlier, a paraganglioma meningioma had been resected, and phenytoin (200 mg/day) had been prescribed for seizure prophylaxis. She also had been taking doxepin (Sinequan). She had a low-grade fever up to 38°C as well as mild splenomegaly, marked bipedal edema, and bilateral pleural effusions. A diagnostic thoracentesis yielded an exudative effusion with numerous eosinophils and immunoblasts. A chest x-ray was otherwise normal and gallium scan was positive only in multiple LNs. Marked hypoalbuminemia and mild hyponatremia (133 meq/liter) were present. Skin testing revealed anergy. An electroencephalogram was normal, and the phenytoin was discontinued. Biopsy findings in LNs and BM were consistent with AILD.

Because of the patient’s debilitating weakness, 6 mo of cytotoxic chemotherapy were begun with COPP (cyclophosphamide, vincristine, prednisone, and procarbazine). Within 3 mo after the beginning of therapy, all evidence of disease had disappeared. The patient has remained in complete remission for more than 14 mo, and the results of all laboratory tests have returned to normal values.

Patient 5
A 63-yr-old man developed intermittent fevers to 40°C, rigors, generalized lymphadenopathy, and an erythematous confluent macular, necropruritic rash in November 1980. The findings in cervical LN biopsy in January 1981 were consistent with AILD. The spine tip was palpable 3 cm below the left costal margin at that time. Skin testing documented anergy. The patient’s past history was remarkable only for a known penicillin allergy and for frequent contact with petroleum solvents. The rash and adenopathy waxed and waned over 8 mo, and epidosic fevers were adequately controlled with Tylenol (3.9 g/day). No cytotoxic therapy was given. In July 1981, he was admitted to another hospital with sudden upper gastrointestinal bleeding and hypotension. He died of shock and ventricular fibrillation several hours after admission. This was 6 mo after the initial diagnosis of AILD. Whether the bleeding was related to AILD is unknown, because no autopsy was performed.

Patient 6
A 64-yr-old man first noted swelling in both inguinal areas in July 1981. He denied having had any other symptoms except for a 5 kg weight loss over the preceding few months. He was taking no medications and had had no significant exposure to chemicals or toxins. His past medical history was unremarkable. His LNs were diffusely enlarged up to 6 cm in diameter; the spleen was palpable 3 cm below the left costal margin. A chest x-ray was normal, but a gallium scan was positive in multiple LNs and in the spleen. A skin test was negative with tuberculin, but reactive with mumps, Candida, and Trichophyton antigens. The serum albumin was markedly decreased, and gamma globulins were increased, with a polyclonal pattern.

An LN biopsy revealed malignant lymphoma with large noncleaved cells (immunoblastic sarcoma), together with features of AILD. On biopsy, the BM was normocellular, with normal hematopoietic elements and moderately increased numbers of lymphocytes, plasma cells, and a few immunoblasts. Exudative ascites was present, with benign cells, including 51% reactive lymphocytes and 43% macrophages. The cerebrospinal fluid was normal.

Because of the morphological evidence of malignant transformation in the biopsy specimen, the patient was placed on a COPP chemotherapy regimen. Within 1 wk, his lymphadenopathy and splenomegaly had diminished dramatically. This therapy is currently being continued.
MATERIALS AND METHODS

Patients

All six patients underwent LN biopsies. Repeated LN biopsies were performed on three patients, because of studies on the progress of the disease in two cases (2 and 3) and because of a small initial sample and an infarcted second sample in one case (5). All patients except patient 5 had bone core biopsies; two of these patients (2 and 3) had repeated biopsies. Skin biopsies were done on three patients (1, 2, and 3) and lung biopsies on two (2 and 3). An autopsy was performed only on patient 1.

Pathologic Studies

The tissues were processed routinely, and biopsied LNs were also stained with periodic acid Schiff (PAS), methyl green pyronin (MGP), and reticulin. Stains for reticulin and iron were also carried out on all bone core biopsy specimens. The cells from PB, BM aspirates, ascites, and pleural effusions were stained with Wright-Giemsa. The cytochemical reactions tested included peroxidase, naphthol ASD chloroacetate esterase, and acid phosphatase (ACP).

Chromosome Studies

A cytogenetic sample was obtained from LNs of five patients, from BM of four, from PB of three, and from ascites of one. Cells from PB were cultured for 24 hr without phytohemagglutinin (PHA) or for 72 hr with PHA. The cells from BM, LN, and ascites were prepared directly or after 24-hr culture. Lymph node cells of patient 2 were cultured for 7 days without mitogen. Chromosomes were analyzed with regular Giemsa stain and with the Q-banding method.

We define abnormal clones as two or more metaphase cells with identical extra chromosomes or with identical structural rearrangements, or three or more metaphase cells with identical missing chromosomes. Karyotypes were identified according to the International System for Human Cytogenetic Nomenclature. Marker chromosomes of totally unidentified origin were designated according to the system devised by Sakurai and Sandberg; the size of the chromosome and then its centromeric position are given in parentheses following the word “mar.” The centromeric position was designated according to the system proposed by Levan et al., in which M, m, sm, st, and T stand, respectively, for median point, median portion, submedian portion, subterminal portion, terminal portion, and terminal point.

RESULTS

The laboratory data on the six patients at the time of diagnosis of AILD are summarized in Table 1. Five patients were mildly anemic; three had a positive Coombs antiglobulin test, but none had significant hemolysis. Two patients had leukocytosis and three had eosinophilia. Five patients had an elevated sedimentation rate. All six patients were hypoalbuminemic and, with the exception of patient 5, all had a polyclonal elevation in immunoglobulins, but none had antinuclear antibodies.

Pathologic Studies

Pathology data on the six patients are summarized in Table 2. In LN biopsies of all patients, the architecture of the node was effaced, and there were no residual germinal centers. Vascularity was moderately increased in all cases. The amount of intercellular PAS-positive material varied in amount and intensity and was most pronounced in patients 1, 2, and 5. In all cases, the infiltrate was polymorphic, consisting of lymphocytes, immunoblasts, histiocytes, plasma cells, and eosinophils. The lymphocyte population showed a spectrum of stimulation and pleomorphism. The most pleomorphic-appearing lymphoid cells were seen in patients 3 and 6. The cells of these two patients also showed the most numerous mitoses per high-power field. Three consecutive LN biopsies at approximately 1.5-mo intervals and the last biopsy after 8 mo in patient 3 showed progression toward a more neoplastic-appearing process. The last biopsy specimen contained features of immunoblastic sarcoma (IBS) (Fig. 1 and 2). In contrast, patient 2, who also had 3 LN biopsies at approximately 4 mo intervals, showed no apparent change in histologic findings.

The BM biopsies revealed involvement with AILD, consisting of polymorphic infiltrates with apparent...
vascular proliferation, in all 5 patients who were examined (Table 2). Patient 2 had a marked increase in eosinophils in the BM and increased reticulin within the involved areas (Fig. 3); the increase in eosinophils was also seen in the LNs and PB. All bone marrow aspirations in this patient were dry taps. The repeated biopsies of patients 2 and 3 showed progression in the involvement of marrow space with AILD.

A lung biopsy specimen of patient 3 showed prominent necrosis and only a small aggregate of viable cells, which consisted predominantly of large cells, in keeping with IBS. Skin biopsies showed the typical appearance of AILD which was described previously.\textsuperscript{14}

The PB contained stimulated lymphocytes of various sizes in 4 patients. Patient 3 had the most bizarre lymphoid cells, with marked nuclear irregularities (Fig. 4). The ACP reaction in these large cells was positive in a granular pattern usually seen in T cells. The PAS stain was negative in these cells, and the esterase reaction was inadequate.

**Chromosome Studies**

The karyotypes of the six patients are summarized in Table 3. Chromosomes were examined in LN cells of five patients, and all five had both abnormal and normal metaphase cells. Patient 2 had 3 abnormal cells; one had +3 and the other two had marker chromosomes in addition to +3. Serial analyses of LN biopsy specimens were performed in patient 3. In the first sample, obtained before the initiation of chemotherapy (February 1980), two unrelated clones were observed. Six cells belonged to one clone; one cell had
obtained in April, after chemotherapy with prednisone and chlorambucil. The other clone had a karyotype of 47, XY, +3 and related abnormalities; these abnormalities were similar to those noted in PB cells obtained in March 1980. The other clone had a karyotype of 51, XY, +5, +15, +19, +21, +22 (Fig. 5). A second sample was obtained in April, after chemotherapy with prednisone and chlorambucil. One clone with +5, +15, +19, +21, +22 was present, but the other with +3 was not. In the third LN sample, obtained after intensive chemotherapy, the clone with +5, +15, +19, +21, +22 was still present.

Patient 4 had three cells each with a different abnormality; one had +3, another had a 14q- chromosome with the breakpoint at band q32, and the third had a marker chromosome of unknown origin. Patient 5 had one cell with +3, as well as a clone with a 6q- chromosome and other aberrations; the +3 cell and the cells with 6q- were unrelated. Patient 6 had two cells with an identical karyotype, 56, XY, +5, +5, +6, +10, +15, +15, +19, +20, +21, +22, and three cells each with a different abnormality; one had a marker chromosome of unknown origin, another had a 6;14 translocation, and the third had a marker chromosome of unknown origin and loss of a chromosome 20.

Chromosomes were also examined in BM cells of four patients (1–3 and 6). Although BM biopsy specimens obtained from the same site showed features characteristic of AILD, no chromosome abnormalities were detected in them. Chromosomes were examined in PB cells of three patients. Patients 2 and 4 had no abnormalities. Patient 3 had 47, XY, +3 and related karyotypes in pretreatment PB cells cultured for 72 hr with PHA (March 1980). He had one cell with +X in the sample obtained in April. No abnormalities were detected in them.

Table 3. Chromosome Findings on Six Patients With AILD

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Date of Study</th>
<th>Source of Cells</th>
<th>Cytoxic Therapy</th>
<th>No. of Cells Studied</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2/11/76</td>
<td>BM</td>
<td>–</td>
<td>8 (7)*</td>
<td>N(7)†</td>
</tr>
<tr>
<td></td>
<td>3/17/76</td>
<td>BM</td>
<td>–</td>
<td>37 (19)</td>
<td>N(19)</td>
</tr>
<tr>
<td></td>
<td>4/13/76</td>
<td>BM</td>
<td>+</td>
<td>14 (7)</td>
<td>N(7)</td>
</tr>
<tr>
<td>2</td>
<td>11/7/77</td>
<td>BM</td>
<td>–</td>
<td>25 (24)</td>
<td>N(24)</td>
</tr>
<tr>
<td></td>
<td>11/7/77</td>
<td>PB, PHA+</td>
<td>–</td>
<td>13 (7)</td>
<td>N(7)</td>
</tr>
<tr>
<td></td>
<td>4/14/78</td>
<td>LN</td>
<td>–</td>
<td>6 (6)</td>
<td>N(3)/47, XX, +3 (1)/47, XX, +3, -5, +mar(A1, st) (1)/48, XX, +3, -5, +2 mar(A1, st) (1)</td>
</tr>
<tr>
<td></td>
<td>4/17/78</td>
<td>Ascites</td>
<td>–</td>
<td>20 (13)</td>
<td>N(13)</td>
</tr>
<tr>
<td>3</td>
<td>2/27/80</td>
<td>LN</td>
<td>–</td>
<td>41 (23)</td>
<td>N(15)/47, XY, +3 (1)/48, XY, +3, + 18 (2)/48, XY, +3, +mar (X, sm) (3)/51, XY, +5, +15, +19, +21, +22 (2)</td>
</tr>
<tr>
<td></td>
<td>3/3/80</td>
<td>PB, PHA+</td>
<td>–</td>
<td>84 (20)</td>
<td>N(14)/47, XY, +3 (3)/48, XY, +3, + 18 (2)/48, XY, +3, +mar (X, sm) (1)</td>
</tr>
<tr>
<td></td>
<td>4/7/80</td>
<td>LN</td>
<td>+</td>
<td>36 (18)</td>
<td>N(10)/51, XY, +5, +15, +19, +21, +22 (7)/52, same, +77 (1)</td>
</tr>
<tr>
<td></td>
<td>4/25/80</td>
<td>PB, PHA-</td>
<td>+</td>
<td>40 (20)</td>
<td>N(10)/47, YY (1)</td>
</tr>
<tr>
<td></td>
<td>8/7/80</td>
<td>PB, PHA+</td>
<td>+</td>
<td>10 (10)</td>
<td>N(10)</td>
</tr>
<tr>
<td></td>
<td>8/12/80</td>
<td>BM</td>
<td>+</td>
<td>16 (15)</td>
<td>N(15)</td>
</tr>
<tr>
<td></td>
<td>11/21/80</td>
<td>PB, PHA+</td>
<td>+</td>
<td>29 (15)</td>
<td>N(15)</td>
</tr>
<tr>
<td></td>
<td>12/8/80</td>
<td>LN</td>
<td>+</td>
<td>8 (7)</td>
<td>N(4)/51, XY, +5, +15, +19, +21, +22 (2)/51, XY, +5, +15, +19, +21 (1)</td>
</tr>
<tr>
<td>4</td>
<td>6/27/80</td>
<td>PB, PHA+</td>
<td>–</td>
<td>31 (15)</td>
<td>N(15)</td>
</tr>
<tr>
<td></td>
<td>7/7/80</td>
<td>LN</td>
<td>–</td>
<td>120 (13)</td>
<td>N(10)/47, XX, +3 (1)/47, XX, +mar (C12, sm) (1) 44, XX, +3, -14, +der(14) t(14); ? (q32; ?) (1)</td>
</tr>
<tr>
<td>5</td>
<td>3/12/81</td>
<td>LN</td>
<td>–</td>
<td>32 (23)</td>
<td>N(19)/47, XY, +3 (1)/47, XY, -9, del(6) (q21q23 or 25), +mar 1(A3, m), +mar 2(G, t) (3)</td>
</tr>
<tr>
<td>6</td>
<td>8/7/81</td>
<td>LN</td>
<td>–</td>
<td>61 (28)</td>
<td>N(23)/56, XY, +5, +5, +6, +10, +15, +15, +19, +20, +21, +22 (2)/47, XY, +mar (C, sm) (1)/46, XY, +mar(F, st) (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>–</td>
<td>9 (9)</td>
<td>N(9)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are numbers of cells studied with banding.
†Numbers in parentheses are numbers of cells with the particular karyotype.
N, normal karyotype.
CHROMOSOME ABNORMALITIES IN AILD

883

clonal and nonclonal abnormalities in two, and only nonclonal single-cell abnormalities in one. Cells with +3 were found in four patients; this abnormality was clonal in two and nonclonal in two others. Cells with +5, +15, +19, +21, +22 were found in two patients. All patients had normal metaphases in 50% or more of the dividing cells in their LNs.

DISCUSSION

Chromosome Pattern in AILD

In studying LN cells, we found chromosome abnormalities in all five patients with AILD; clonal abnormalities were detected in two and both clonal and nonclonal abnormalities in two. Only nonclonal abnormalities were found in LN cells of patient 4. Whether these cells, especially single cells with +3, had true nonclonal abnormalities, or whether other cells with the same abnormality would have been detected if more dividing cells had been analyzed, is unknown. It is apparent, however, that there was no predominant aneuploid clone in patient 4 at the time of chromosome study.

Chromosome abnormalities have been reported in 8 patients with AILD,5–10 but precise documentation of AILD or information regarding the subsequent clinical course has not been provided. We reviewed the chromosome pattern in 13 patients with AILD, including our 5 patients who had an abnormal karyotype; the karyotypes of the 8 patients with AILD reported previously are summarized in Table 4. With the exception of our patient 4, all patients had clonal chromo-

Fig. 4. Peripheral blood from patient 3 obtained on April 23, 1980. Very large lymphoid cells with bizarre nuclei were abundant. All of these cells showed a positive acid phosphatase reaction in the granular pattern usually seen in T cells rather than the diffuse pattern seen in monocytes (Wright Giemsa, ×1100).

thus, among five patient with chromosome abnormalities, clonal abnormalities were found in two, both found in two other PB samples obtained in August and November 1980. Chromosomes in ascites of patient 2 were normal.

Fig. 5. Karyotype, with Q-banding, of a lymph node cell from patient 3 obtained on February 27, 1980. The arrow shows an extra chromosome 3. The karyotype is 47, XY, +3.
some abnormalities. Ten patients had hyperdiploidy (47–56 chromosomes), and 3 others had pseudodiploidy. An extra chromosome 3 with or without additional abnormalities was seen in 6 patients; the cells with +3 were clonal in 4 (31%) cases and nonclonal in 2. Goedde et al. reported on one patient with T-zone lymphoma and +3; the LN biopsies showed a gradual change from “lymphogranulomatosis X” (AILD) to T-zone lymphoma.9 This case is included as 1 of the 6 cases with +3 in the review of the 13 patients. An extra chromosome 5 was seen in 5 patients (38%). Patients 3 and 6 in the present report and one patient reported previously by Kaneko et al.10 had similar karyotypes; +5, +19, and +22 were seen in all 3 patients, +15 in 2, and +21 in 2. A partial deletion of 4q was seen in two patients and a partial deletion of 6q in two patients. A nonclonal abnormality involving a 14q+ chromosome with a break point in 14q 32 was seen in 2 patients. Evolution of the karyotype, as evidenced by the presence of 2 or more abnormal karyotypes that are

Table 4. Chromosome Findings on the Eight Patients With AILD Reported on Previously

<table>
<thead>
<tr>
<th>Age and Sex of Patient</th>
<th>Source of Cells</th>
<th>Karyotype</th>
<th>Comments</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>68 M</td>
<td>LN</td>
<td>48; XY, +5, −15, +del(4) (q21), +der(15) t(15;7) (q25;?) (9)/47, XY, +5, −15, +del(4), +der(15), −21 (6)/48, XY, +5, −15, +19, −21, +del(4), +der(15) (3)/48, XY, +5, −15, +19, +der(15) (8)/47, XY, +5, −15, +der(15) (7)</td>
<td>70% of LN cells formed E-rosettes</td>
<td>5</td>
</tr>
<tr>
<td>32 M</td>
<td>LN</td>
<td>47, XY, +3 (11)/47, XY, +3, −9, +21 (1)/48, XY, +3, +8, +9, −20 (1)</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>45 M</td>
<td>LN</td>
<td>47, XY, +8, +C(35)/47, XY, +C (15)</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>52 M</td>
<td>PF</td>
<td>46, X, +q+, +2/3, −G/Y*</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>59 F</td>
<td>LN</td>
<td>46, XX, t(1p−; 2p+) (41)/47, XX, +5, t(1p−; 2p+) (8)</td>
<td>LN had features transitional to IBS</td>
<td>8</td>
</tr>
<tr>
<td>24 M</td>
<td>LN</td>
<td>47, XY, +3 (3)</td>
<td>LN had features transitional to T-zone lymphoma</td>
<td>9</td>
</tr>
<tr>
<td>57 M</td>
<td>LN</td>
<td>46, XY, del(4) (q33), del(6) (q23), t(5;7) (q33; q22) (9)</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>65 F</td>
<td>LN</td>
<td>49, XX, +5, +19, +22 (11)</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate numbers of cells with the particular karyotype.

PF, pleural fluid.

*The number of cells with this karyotype was not described.
related to each other, was observed in 6 patients. Thus, chromosome abnormalities in AILD may be characterized by hyperdiploidy with an extra chromosome 3 or 5, and by the frequent occurrence of karyotypic evolution. As can be seen in Table 5, these changes are uncommon in other malignant lymphomas.

In the present study, four patients had unrelated abnormal metaphase cells in the LN which was biopsied at an early stage of AILD. Patient 3 had two unrelated abnormal clones in the pretreatment LN. After 1 mo of chemotherapy with prednisone and chlorambucil, one clone with + 3 disappeared, and only the second clone, with + 5, + 15, + 19, + 21, + 22, was present. Despite more aggressive chemotherapy (COMLA and ABV-MLA), the latter clone persisted. The presence of two karyotypically distinct populations has been reported in experimentally induced mouse plasmacytomas;\(^5,17\) in the analysis of one of these cell lines (63–1), Yoshida et al. observed that one population eventually replaced the other in the course of transplantation passages.\(^6\) This finding of mosaicism both in our four patients and in mouse plasmacytomas suggests that these tumors are not necessarily monoclonal at early stages or passages. A selective advantage of one particular karyotypic pattern may account for the presence of the single malignant clone that is detected in the advanced stage of AILD or in the later passages of mouse plasmacytomas.

In addition to abnormal metaphase cells, we found many normal metaphase cells, presumably nonmalignant, in the involved LNs. The frequency of normal metaphase cells is usually low in non-Hodgkin's lymphoma.\(^10\) Although the data in Hodgkin's disease are more limited, our own results resemble those seen in AILD. Of 13 Hodgkin's patients whose lymph nodes provided mitotic cells, 3 had only normal metaphase cells and 7 others had some normal cells with the percentage ranging from 10% to 89%.\(^18\)

We found chromosome abnormalities in LN cells of AILD patients, but not in BM aspirates, although the bone marrow biopsy specimens, which were obtained simultaneously, showed features typical of AILD. A possible explanation for this discrepancy is that we could not detect the relatively small number of abnormal mitotic cells in the BM. Thus, the most suitable source for chromosome studies on AILD is an involved LN rather than the BM.

Patients with AILD have lymphoma-like clinical signs and symptoms, and many of them have a progressive clinical course with a fatal outcome.\(^1,4\) The median survival of 18 patients reported by Lukes and Tindle was 18 mo,\(^3\) and 47 of 98 patients (48%) reviewed by Cullen et al. died within 12 mo after diagnosis.\(^4\) Frizzera et al. and Lukes and Tindle, however, considered AILD to be a non-neoplastic disease because of the benign histologic appearance.\(^1,3\)

Our findings and our review of the data on eight other patients\(^5-10\) showed that most AILD patients had clonal chromosome abnormalities. Cells with acquired clonal chromosome abnormalities are usually considered to be malignant. We recognize, however, that some patients who have myeloid diseases and clonal abnormalities, for example, + 8 and + 9 in polycythemia vera,\(^19\) or a 5q- in refractory anemia\(^20\) may have a long stable course without a transition to leukemia. Because of the presence of clonal chromosome abnormalities and because of the frequently fatal clinical course, we believe that AILD is a neoplastic disease, although the histologic appearance may be more benign than that of other malignant lymphomas.

**Correlation of Chromosome Pattern With Clinical and Histologic Features of AILD**

First Lukes and Tindle,\(^1\) and subsequently Nathwani et al.,\(^21\) observed that, in a substantial number of patients, AILD evolved to immunoblastic sarcoma (IBS) or immunoblastic lymphoma, although many patients died due to AILD itself without its evolution to IBS. Both groups of investigators hypothesized that malignant transformation of benign cells occurs in some AILD patients.\(^2,21\)

The serial studies of LNs from patient 3 can provide evidence on this point. In the first LN biopsy, which showed the features of AILD without evidence of IBS, only 2 of 23 banded cells were found with a karyotype of 51, XY, + 5, + 15, + 19, + 21, + 22. Six cells with

---

**Table 5. Incidence of Extra No. 3, Extra No. 5, or 14q+ in Various Lymphoproliferative Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number of Patients</th>
<th>Number Extra No. 3 (％ of Patients)</th>
<th>Number Extra No. 5 (％ of Patients)</th>
<th>Number 14q+ (％ of Patients)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AILD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Present report</td>
</tr>
<tr>
<td>Univ. of Chicago</td>
<td>5</td>
<td>80</td>
<td>40</td>
<td>40</td>
<td>Present report</td>
</tr>
<tr>
<td>Literature</td>
<td>8</td>
<td>25</td>
<td>38</td>
<td>0</td>
<td>5-10</td>
</tr>
<tr>
<td>DHL</td>
<td>28</td>
<td>11</td>
<td>7</td>
<td>54</td>
<td>15</td>
</tr>
<tr>
<td>PDL</td>
<td>28</td>
<td>18</td>
<td>4</td>
<td>89</td>
<td>15</td>
</tr>
<tr>
<td>T-cell dyscrasias</td>
<td>17</td>
<td>0</td>
<td>6</td>
<td>53</td>
<td>15</td>
</tr>
</tbody>
</table>
+3 and related karyotypes formed another clone; 15 additional cells had a normal karyotype. The first clone predominated and the second clone had disappeared in the second LN biopsy specimen, which had features of both AILD and IBS. In the third LN biopsy, which showed the presence of AILD and IBS with an increase in fibrosis, the clone with 51 chromosomes still persisted, although there were fewer mitotic cells. Thus, the chromosome pattern was correlated with the histologic changes in this case, although chromosome abnormalities had already been detected before the evolution to IBS.

On the other hand, in an LN biopsy of patient 6 at diagnosis, which showed IBS together with features of AILD, only 2 cells with a karyotype of 56, XY, +5, +5, +6, +10, +15, +15, +19, +20, +21, +22 were found among 28 banded cells. Three other cells each had a different abnormality, and the remaining 22 cells had a normal karyotype. The LN biopsy of patient 5 showed AILD without evolution to IBS; a small abnormal clone, an unrelated single-cell abnormality, and many normal metaphase cells were observed. Lymph node biopsies of two other patients, one (2) with a clonal abnormality and the other (4) with only single-cell abnormalities, also showed AILD without IBS. These findings suggest that clonal abnormalities are usually present in the LNs of AILD patients regardless of evolution to IBS and that the chromosome pattern is not necessarily correlated with the histologic appearance. In one instance, however, total replacement of one aneuploid clone was correlated with the evolution of a more malignant histologic pattern.

Two patients (2 and 3) with clonal chromosome abnormalities died 15 mo after diagnosis without achieving a complete remission. Patient 2 was treated with prednisone alone. Patient 3 was treated initially with prednisone alone and subsequently with prednisone and chlorambucil; intensive chemotherapy was initiated after one aneuploid clone had become predominant. On the other hand, two patients (4 and 6) who received intensive cytotoxic chemotherapy before the predominance of an aneuploid clone achieved complete remission and are alive 20 and 8 mo after the diagnosis, respectively. The other patient (5) without predominance of an aneuploid clone died due to gastrointestinal bleeding of unknown cause during a period of observation without cytotoxic chemotherapy. These findings suggest that intensive cytotoxic chemotherapy should begin immediately if cells with chromosome abnormalities are detected. Prednisone alone, prednisone with a mild cytotoxic drug, as well as a period of observation without cytotoxic chemotherapy, may allow the development of an aggressive malignant clone that may be unresponsive to any treatment later on.

Although many investigators still consider AILD to be a non-neoplastic disease, we have provided evidence by chromosome studies that AILD is a neoplastic disease whether or not it evolves to IBS. Chromosome studies are essential if we are to increase our understanding of the processes that lead to the development and evolution of this disease.

ACKNOWLEDGMENT

The authors thank Dr. Stanley Yachnin for providing sequential LN samples from patient 3; Elisabeth Lanzl for editorial review; Susan Morin for secretarial assistance; and Peter Eckert for the photography.

REFERENCES

Nonrandom chromosome abnormalities in angioimmunoblastic lymphadenopathy
Y Kaneko, RA Larson, D Variakojis, JM Haren and JD Rowley