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Malignant Progression of Angioimmunoblastic Lymphadenopathy

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Summary. In a 79-year-old woman, the progression of angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) to malignant lymphoma was observed within one year after diagnosis. Three biopsy specimens from lymph nodes and one tonsil, obtained at intervals of several months, showed an increasing destruction of the tissue architecture and the development of histological criteria for a lymphoid neoplasm, which at autopsy was confirmed as a malignant non-Hodgkin's lymphoma. The demonstration of a chromosomally abnormal clone in lymph node derived and the laboratory findings were in agreement with the histological changes and the sequential clinical deterioation. Initially, a symptom-free interval of eight months was achieved with prednisone therapy. However, this treatment failed after the malignant transformation had become evident.

Key words: Angio immunoblastic lymphadenopathy – Chromosomal abnormalitis – Non Hodgkins lymphoma

AILD or immunoblastic lymphadenopathy is a systemic disease clinically characterized by generalized febrile lymphadenopathy often with splenomegaly, dysproteinemia, anemia and skin rash (Frizzera et al., 1974; Lukes and Tindle, 1975). The histological picture of the lymph nodes shows a proliferation of small vessels, immunoblasts and plasma cells. Interstitial depositions of PAS positive material is frequently seen.

An evolution to immunoblastic sarcoma of three cases of immunoblastic lymphadenopathy was first described by Lukes and Tindle (1975). Although AILD is generally regarded as a benign disease according to clinical and histological findings (Frizzera et al., 1974, 1975; Horne et al., 1974; Radaszkiewicz and Lennert, 1975; Rappaport and Moran, 1975), a few cases with neoplastic conversion into sarcoma have been reported (Fisher et al., 1976; Frizzera et al., 1977; Howarth and Bird, 1976; Kurtz, 1977; Nathwani et al., 1978; Toth and Garam, 1977; Yataganas et al., 1977). We present a further case of AILD with progression into malignant lymphoma.

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The patient, a 79-year-old woman, was referred to our hospital in December 1976, with enlarged bilateral cervical lymph nodes and splenomegaly. Small lymph nodes were found in both axillary and inguinal regions. She had no fever, weight loss or pruritus, but complained of weakness, malaise, and pain in swallowing. Bilateral cervical lymph node biopsies (December 1976) showed the distinct histological characteristics of angio-immunoblastic lymphadenopathy.

Two months before admission, an enlarged lymph node had developed on the left side of her neck which had been treated with penicillin. A consecutive extensive rash with pruritus receded after medication had been changed to tetracycline. Allergy to penicillin or other drugs was not observed before. Medication in the last years consisted of digoxin and, occasionally, headache tablets containing aminophenazone. Liver function and size were normal. In the chest X-rays no intrathoracic involvement was seen.

Laboratory investigations in December 1976, gave the following results: hemoglobin 13.3 g per 100 ml, hematocrit 37%, white-cell count 6000 with 78% neutrophils, 15% lymphocytes, 5% monocytes, 2% eosinophils, platelet count 92000 and erythrocyte sedimentation rate (ESR) 14 mm/h (Westergren). Total serum proteins were 6.8 g per 100 ml, with 4 g albumin and 2.8 g globulins. Immunoglobulin assay revealed an IgA level of 734 mg per 100 ml (normal 90–450 mg). IgM and IgG were within normal range.

Serum alkaline phosphatase, transaminases, total lipids, blood urea, serum glucose, and serum electrolytes were in the normal range. Lactic dehydrogenase was slightly increased to 321 U (normal 95–195 U) and the serum copper level to 192 μg per 100 ml (normal 65–165 μg).

The direct Coombs' test and assay for rheumatoid factor were negative, but C-reactive protein was present. Other serum proteins, such as haptoglobulin and coeruloplasmin, were consistently increased during the course of the disease. Levels of α-1-fetoprotein and carcino-embryonic antigen (CEA) gave no indication for a neoplasm. Lymphocyte transformation (phytohemagglutinin, pokeweed mitogen and concanavalin A) and phagocytic ability (NBT-test) were diminished. There was no indication for an auto-immune process. Antibodies against native DNA, leukocytes, and nuclear factors were not detected. Lymphotropic and other viral infections were excluded serologically. Antibody determination with virus antigens revealed no signs of acute or recent infection.

Clinical Course

We started treatment with prednisone at a dose of 50 mg per day. The patient's condition improved, and the enlarged lymph nodes became considerably smaller within two weeks. The prednisone dosage was optimized to 25–30 mg per day. Lower doses resulted in recurrent swelling of the involved lymph nodes. For five months following therapy, the patient was free of clinical symptoms. In May 1977, a painful lymphadenopathy gradually developed on the left side of her neck, although the dose of prednisone had been increased. As an additional measure, we applied a focal dose of 12.60 Gy (1260 rads) ^{137}telecesium to the cervical region, given in nine single fractions over a period of three weeks. This small dose effected an almost complete reduction of the fist-sized lesion, so that it was scarcely palpable. Occasional fevers, occurring at that time, were effectively treated with tetracycline. After a second symptom-free interval of three months, a large lymph node appeared in the left inguinal region. A second biopsy from this lymph node confirmed the diagnosis of AILD. A part of this lymph node was used for chromosome analysis.

In October 1977, the patient's condition suddenly worsened, and she was admitted to stationary care. Again, she had fever and her right tonsil was en-

Table 1. Concentration of serum proteins during clinical course of disease. The determination was done by radial immunodiffusion test according to Mancini (Partigen-plates, Behring-Werke, Marburg)

Serum proteins	mg-% (10. 6. 77)	mg-% (27. 10. 77)	mg-% (normal)
Immunoglobulin G	1083	859	800–1800
Immunoglobulin A	764	554	90– 450
Immunoglobulin M	95	60	60– 280
Haptoglobulin	250	408	160– 300
Coeruloplasmin	72	45	20– 60
β1A (C3)	68	78	80– 120
β1E (C4)	39	52	20– 50

larged. A third biopsy confirmed the diagnosis AILD but with malignant changes in addition.

A painful local recurrence in the irradiated area was treated with a second series of 19 Gy (1900 rad). Following this therapy, the lymph nodes were no longer palpable. During her stay in hospital, the patient suffered from recurring pneumonia, which we could not control. She died in December 1977, twelve months after the diagnosis of AILD.

Repeated laboratory investigations performed between December 1976 and December 1977, showed normal values for the parameters tested, except for a moderate thrombocytopenia and an increase of the erythrocyte sedimentation rate to 60 mm/h. No eosinophilia could be detected in subsequent differential blood cell counts. For the last two months before her death, the leukocytes and lactic dehydrogenase were markedly increased. Urinalysis repeatedly showed infection with E. coli and Providencia.

Analysis of serum proteins, six and two months before the patient died, showed a continouus decrease of immunoglobulins. IgG and IgM levels decreased to low normals values, while IgA levels remained pathologically elevated, with falling tendency. A polyclonal paraprotein was identified immunoelectrophoretically as being IgA (Table 1).

Histological Findings

First Biopsy in December 1976

The three cervical lymph nodes measured up to 5 cm in diameter and showed a grayish-white cut surface. The histological pattern displayed a distinct proliferation of venules (Fig. 1). Sometimes a few remaining follicles with germinal centers were observed. A mixed population of lymphocytes, plasma cells, eosinophilic granulocytes, and epitheloid cells was found between the arborizing vessels. In addition, many large immunoblastic cells with basophilic cytoplasm and one or more prominent nucleoli were seen. There were also some scattered blasts with pale cytoplasm. Occasionally, multinucleated cells were observed. Mitoses were frequent (Fig. 2). Amorphous interstitial PAS-positive material was present in variable amounts.

Diagnosis: Angioimmunoblastic lymphadenopathy.

Second Biopsy in July 1977

The architecture of the inguinal lymph node was completely destroyed without any remaining follicular structure. The cellular picture varied considerably consisting of differently sized lymphocytes, plasma cells and immunoblasts between the prominent venules. Blasts with large polymorphous nuclei were numerous. The number of mitoses had increased. Many epitheloid cells with a wide faintly eosinophilic cytoplasm were seen. The capsula of the lymph node was infiltrated, but not destroyed.

Diagnosis: Angioimmunoblastic lymphadenopathy with increased mitotic activity.

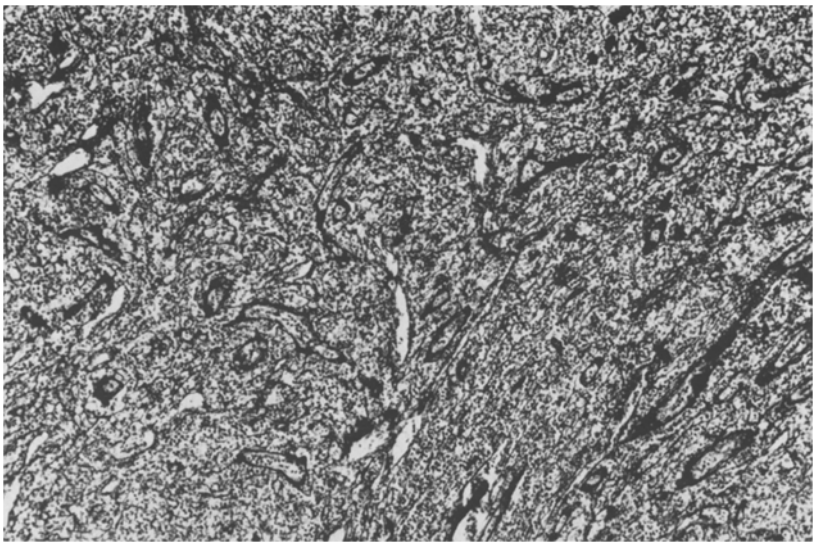

Fig. 1. First Biopsy: AILD with massive proliferation of arborized vessels. (Ag, × 100)

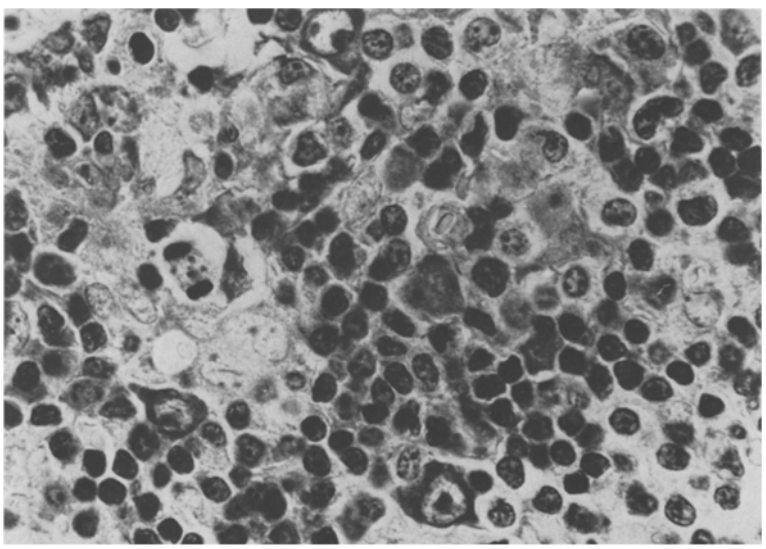

Fig. 2. First Biopsy: AILD with immunoblasts, plasma cells and mitoses. (Giemsa, × 1000)

Third Biopsy in October 1977

The excision of the right tonsil showed a total loss of normal lymphatic structure. The dominent feature was a diffuse infiltration with large lymphoid cells resembling so-called histiocytic cells. The nuclei of such cells showed polymorphy and an irregular distribution of chromatin. Some tumor cells showed plasmacytoid features. Proliferation of venules was still remarkable. The numerous plasma cells varied in form and size. Small lymphocytes and epithelioid cells were markedly diminished (Fig. 3).

Diagnosis: AIL with evolution of diffuse malignant non-Hodgkin's lymphoma.

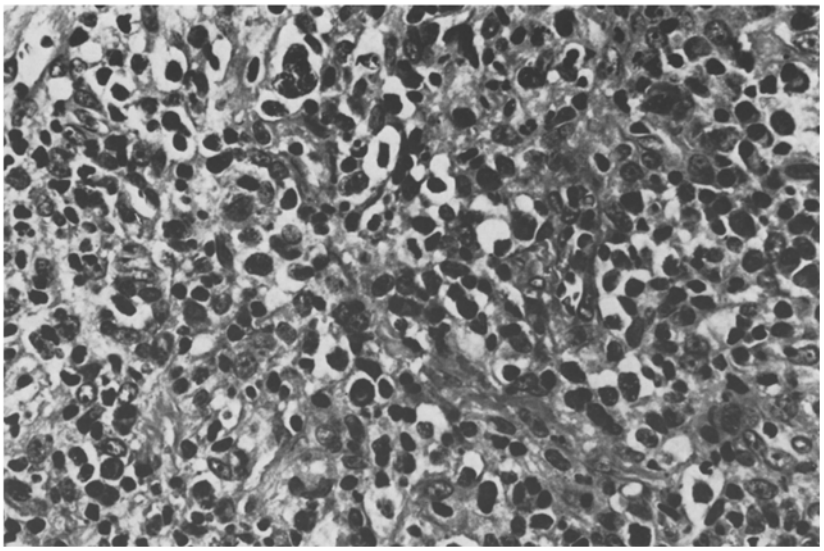

Fig. 3. Third Biopsy: Polymorphous sarcomatous pattern with multinucleated tumor cells, mitoses and obliterated vessels. (H.E., × 400)

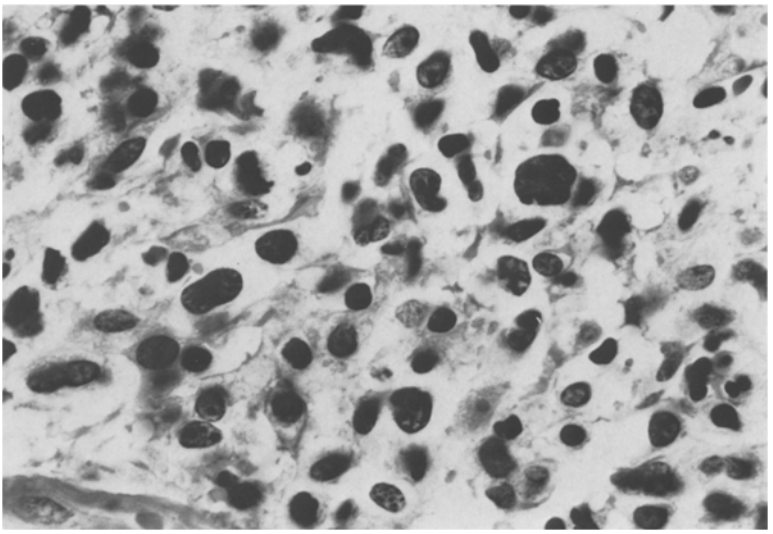

Fig. 4. Autopsy: Lymph node with loosely structured Cellular Pattern with polymorphous lymphatic cells. (H.E., × 1000)

Postmortem Findings

At autopsy, conglomerates of grayish-white lymph nodes, up to 4 cm in diameter, were found in all lymph node areas. The capsular and pericapsular tissue of the lymph nodes were infiltrated. A prominent vascularity was consistently visible, but the endothelial cells now were flat and inconspicuous. The cell infiltrates consisted of numerous large lymphoid cell with oval or polymorphous, often

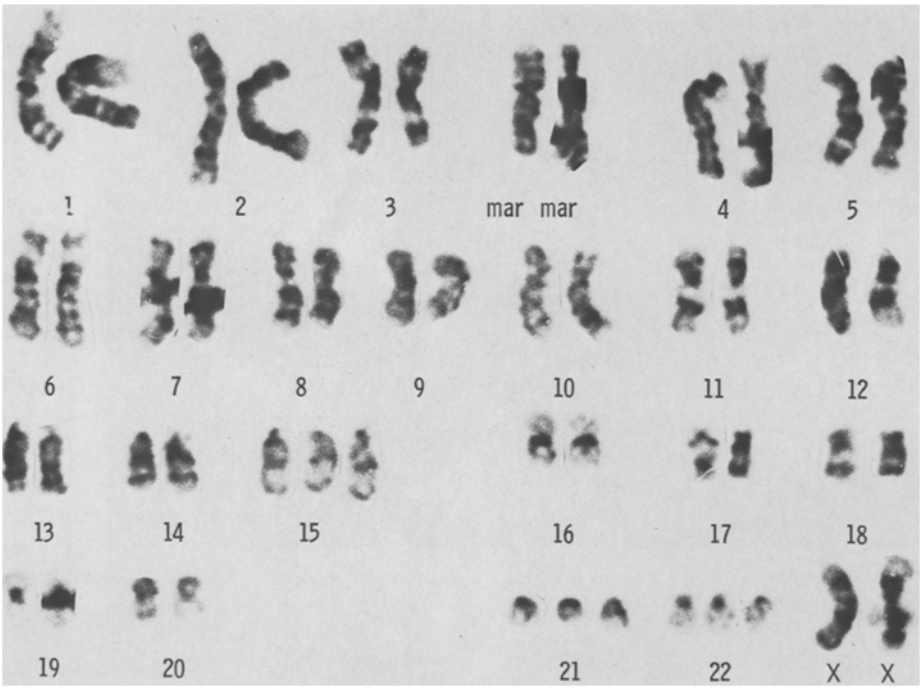

Fig. 5. Representative karyotype with 51, XX, +15, +21, +22, +mar 1, +mar 2

hyperchromatic nuclei (Fig. 4). Giant tumor cells were not infrequent. Among the blast-like cells were plasma cells with varying degrees of nuclear atypia. Compared with the previous biopsy specimens the lymph nodes now had a more incoherent structure and contained fewer small lymphocytes. In some areas, there was an increase of reticulin fibers within the lymph nodes. The spleen (400 g) contained an abundance of infiltrating tumor cells among a few normal follicles. Polymorphous lymphoid infiltrates with distinct cell atypias were found also in the periportal areas of the liver and patchy in the bone marrow. There were old thrombi in both femoral veins, and recurrent, finally fulminant pulmonary embolism was found. The lower left and the upper right lobe of the lung showed areas of infarction pneumonia, which were connected with multiple abscesses. Secondary mycosis was also seen.

Cytogenetic Studies

The chromosome constitution of lymph node cells was studied on July 27, 1977. Cells were prepared for chromosome analysis after a 2 h incubation time.

Trypsin was used for G-banding. A total of 74 metaphases was analyzed under the microscope, and 14 metaphases were karyotyped. Of the metaphases 77% had a normal karyotype and 9% had 51 chromosomes and an identical karyotypic pattern, i.e., 51, XX, +15, +21, +22, + mar 1, + mar 2 (Fig. 5). One metaphase with 48 and two metaphases with 49 chromosomes showed the characteristics of

the hyperdiploid clone but lacked various chromosomes. Of the metaphases 9% were hypodiploid, apparently due to random loss of chromosomes.

Discussion

The clinical and laboratory findings in our case are similar to those described by Frizzera et al. (1974, 1975) and Lukes and Tindle (1975). AILD chiefly occurs in the elderly and rapidly develops, with marked general symptoms, generalized lymphadenopathy, splenomegaly, malaise, and weight loss. Coombs' positive hemolytic anemia, thrombocytopenia, lymphocytopenia, eosinophilia and polyclonal gammopathy are found frequently (Horne et al., 1974; Lapes et al., 1976; Matz et al., 1977; Radaszkiewicz and Lennert, 1975; Spector and Miller, 1977). Regarding the dignity of AILD, Rappaport and Moran (1975) and Radaszkiewicz and Lennert (1975) favored the benign character of the disease. Therefore, the distinction to malignant lymphomas, especially Hodgkin's disease and the Lennert lymphoma (1977) is important. Other authors (Dorfman and Warnke, 1974; Moore et al., 1976) prefer to postpone the decision until more is known about this entity. On the basis of morphological and clinical similarities, Twomey (1974) considers AILD to be as malignant as Hodgkin's disease.

In recent years several case reports of AILD with progression to malignant lymphoma have been reported (Fisher et al., 1976; Frizzera et al., 1977; Howarth and Bird, 1976; Kurtz, 1977; Nathwani et al., 1978; Toth and Garam, 1977; Yataganas et al., 1977). Meanwhile, Nathwani et al. (1978) published a report on 36 patients whose lymph nodes revealed, in addition to AILD, histologic features interpreted as malignant lymphoma of the immunoblastic type. Progression into immunoblastic lymphoma was observed in eight of 23 patients with AILD. They consider the term immunoblastic lymphoma to be applicable to large cell lymphomas developing in AILD even if the cytologic picture varies considerably from large lymphoid cells with extreme plasmacytoid differentiation to clear cells.

In our case, too, the follow-up biopsies showed a marked progression with an increasing lymph node destruction and the development of a malignant non-Hodgkin's lymphoma which, following the suggestion of Nathwani et al. (1978), should also be called immunoblastic lymphoma. Under this wide-spread conception of immunoblast one can also subsume such cases of malignant evolution from AILD which we described as plasmoblastic lymphomas (Donhuijsen et al., 1977; Leder and Donhuijsen, 1978). The progression into a small-cell (lymphoplasmacytic) lymphoma has been reported by Frizzera et al. (1977). The subsequent development of Hodgkin's disease was also seen (Yataganas et al., 1977). Such evolution into different malignant lymphomas seems to make the decision whether or not a malignant evolution had occurred more difficult than reported recently (Nathwani et al., 1978). In our case, malignancy was suspected in the second biopsy but only in the third specimen the malignant lymphoma was evident. Thus AILD may transform into a large variety of lymphomas. The demonstration of a chromosomally abnormal clone in this case confirms previous reports (Castoldi et al., 1976; Hossfeld et al., 1976). Chromosomal findings in AILD resemble those seen in Hodgkin's disease, where also only a minority of the metaphases is abnormal. It is interesting to note that at the time when the chro-

mosomes were studied, the lymph node histology suggested a change into a more "malignant" picture. The results of chromosome analysis in the present case and in the cases previously studied, support the view that AILD has the potential to develop into a neoplastic disease.

The etiology of AILD is not known. In the opinion of Lukes and Tindle (1975) and Schoengen et al. (1977), AILD represents a hyperimmune proliferation of the B-cell system, whereas Matz et al. (1977) speak of a primary B-lymphocyte abnormality. Medication with various drugs has also been discussed as a cause of AILD (Frizzera et al., 1975; Lapes et al., 1976; Lukes and Tindle, 1975; Schultz and Yunis, 1977). In our patient, however, an allergic reaction to penicillin was not observed until after the onset of the disease. Up to now, there is no conclusive evidence that any of the drugs mentioned played a decisive role in the etiology of AILD (Iseman et al., 1976; Schoengen et al., 1977).

Favorable therapeutic results in AILD have been achieved with low doses of corticosteroids (Frizzera et al., 1975; Radaszkiewicz and Lennert, 1975). Although in a great number of patients complete and partial remissions were observed following cytostatic therapy, the responses often were of short duration (Lapes et al., 1976; Nathwani et al., 1978; Rudders and Long, 1978; Schultz and Yunis, 1975; Spector and Miller, 1977). In a review of Symmers (1978) the mortality of 111 patients with AILD ranged 44–80%.

In some cases, an exacerbation of disease developed after cytostatic therapy, since the susceptibility to infections is increased by these drugs (Lukes and Tindle, 1975; Rappaport and Moran, 1975). Some authors (Frizzera et al., 1975; Radaszkiewicz and Lennert, 1975; Schoengen et al., 1977) hold the view that aggressive treatment with cytostatic agents, radiotherapy or high-dosed corticosteroids should be avoided, because of the lack of histologic evidence of malignancy in most cases of AILD.

Clinical course in the cases with malignant transformation of AILD that have been reported as yet (Fisher et al., 1976; Frizzera et al., 1977; Howarth and Bird, 1976; Kurtz, 1977; Lukes and Tindle, 1975; Nathwani et al., 1978; Toth and Garam, 1977; Yataganas et al., 1977) was similar to those of other AILD cases. While in some patients with AILD longer remissions could be achieved by cytotoxic treatment and symptomatic therapy with low doses of corticosteroids supplement by local radiotherapy (Matz et al., 1977; Moore et al., 1976), none of the patients with malignant progressions survived more than 14 months after such therapy. In our case, prednisone therapy alone was effective before the malignant transformation of AILD. Once that malignancy has been confirmed by biopsy, combination chemotherapy appears to be indicated.

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