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Angioimmunoblastic Lymphadenopathy with Dysproteinemia in Thailand

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SUMMARY **Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) is a disease of unknown etiology and pathogenesis. It has the features of hyperimmunity and immune deficiency, and its behavior resembles malignant lymphoma. We report a review of 16 patients with AILD seen at Ramathibodi Hospital from 1982 to 1986. Thirteen patients had fever and seven had pruritus and rashes. Lymphadenopathy was found in all 16 cases; generalized in 14 and localized in 2. Hepatomegaiy was present in 14 patients while only 7 had splenomegaly. Laboratory findings included autoimmune hemolytic anemia, lymphocytosis and polyclonal hypergammaglobulinemia. Pulmonary involvement was seen in 5 cases, and bone marrow showed the characteristic features of the disease in 9 cases. Two patients went on to develop diffuse lymphocytic, poorly differentiated lymphoma. Fourteen patients were treated with prednisolone initially. Five responded with complete recovery, eight responded with partial recovery, and one died with extensive involvement of the disease. Six of the patients that recovered partially were later treated with cyclophosphamide, vincristine and prednisolone. One patient recovered completely and two partially. Three died from extensive involvement. Two patients with malignant lymphoma were treated by combination chemotherapy. One case went to complete remission while the other died from infection. One patient was lost to follow up before any treatment was started.**

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) is a clinicopathologic entity of unknown etiology occurring predominantly in middle-aged and older persons. It is characterized clinically by constitutional symptoms and generalized lymphadenopathy. Hepatosplenomegaly and skin lesions are also common. Several immunologic abnormalities have been documented in patients with this disease, including the presence of a Coombs' positive hemolytic anemia,[1-3] dysgammaglobulinemia,[2,3] cryoglobulinemia[4] and abnormal cellular immune response.[5,6] Although the etiology of AILD remains undetermined, it has been attributed to prolonged antigenic stimulation by drugs[2,4,7-10] and infectious agents such as bacteria,[11,12] viruses[13-17] or parasites.[18,19]

The diagnosis of AILD is based on a specific histopathological triad of lymph node changes: (1) the effacement of lymph node architecture with pleomorphic cellular infiltration comprising immunoblasts, plasma cells, macrophages and lymphocytes, (2) proliferation of small blood vessels and (3) interstitial amorphous acidophilic deposition.

The purpose of this report is to present the clinical course, laboratory findings and result of treatment of 16 patients with AILD seen at Ramathibodi Hospital.

PATIENTS AND METHODS

The present series included 16 cases seen at Ramathibodi Hospital between 1982 and 1986. In all cases the diagnosis was confirmed by the histological examination of lymph nodes. The detailed characteristics of the histological picture and radiographic findings will be reported in two separate papers. The clinical records were reviewed in detail in all cases with a specific search for features suggesting autoimmune disorders, prior drug exposure or allergic history. The extent of disease involvement was described according to clinical stages as outlined in the Ann Arbor

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staging classification for Hodgkin's disease.[20] Combination chemotherapy with cyclophosphamide, vincristine and prednisolone was used.[21] The response was considered complete when all the symptoms disappeared and the organomegaly was completely resolved; it was considered partial when the symptoms subsided and/or the organomegaly decreased by at least 50% in size; it was considered negative when symptoms persisted or progressed and when the organomegaly did not decrease or even increased in size.

RESULTS

The representative histologic picture of the lymph node biopsy is shown in Figure 1. The clinical findings based on history, physical examination and laboratory studies are summarized in Tables 1 and 2. The age range was 23-72 years (median 54.5). There were 11 males and 5 females. There was no history of drug or allergy in any patient. Three patients had evidence of multiple autoantibody suggestive of systemic lupus erythematosus.

Tables 3 and 4 compare the clinical and laboratory findings of our patients with data obtained from a literature review of 215 cases.[2-6,22] Thirteen of the patients had fever. Seven of the patients had pruritus and rashes. Hepatomegaly was present in 14 patients while splenomegaly was found in only 7 cases. Anemia was present in 11 patients but only 7 cases had Coombs' positive hemolytic anemia. Twelve patients had polyclonal gammopathy.

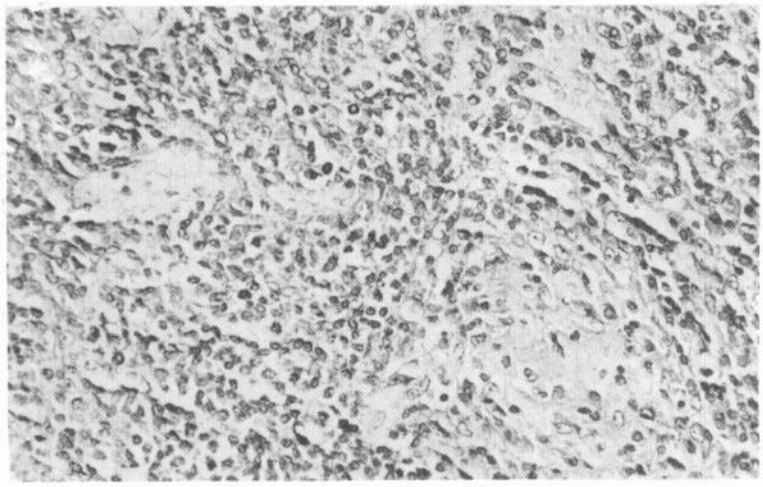

Fig. 1 Lymph node (HE, original manification × 100) showing clusters of epithelioid histiocytes, polymorphic lymphoid cell proliferation and hyperplastic endothelial cells in blood vessels.

Table 5 outlines the response to treatment and survival data of 16 patients. Fourteen patients were treated with prednisolone at 60 mg daily initially. Five patients (cases 4,7,10,11,12) gave complete responses

Table 1 Clinical findings in 16 patients with AILD

Patient	Sex	Age	Weight loss	Fever	Pruritus	Clinical node	Splenomegaly	Hepatomegaly	Ascites	Pulmonary involvement	Skin rash
1	F	23	+	+	+	III	–	+	–	–	+
2	M	33	–	–	–	III	–	–	–	–	–
3	F	60	–	+	+	III	–	+	–	+	+
4	F	70	+	+	+	III	–	+	–	+	+
5	M	31	–	–	–	II	–	–	–	–	–
6	M	35	+	+	+	III	+	+	–	+	+
7	M	55	–	+	–	III	+	+	–	–	–
8	M	62	+	+	+	III	+	+	–	+	+
9	M	67	–	–	–	III	–	+	+	–	–
10	M	72	+	+	+	III	–	+	–	+	+
11	F	34	+	+	–	II	+	+	–	–	–
12	F	42	+	+	–	III	–	+	—	–	–
13	M	54	+	+	+	III	+	+	+	–	+
14	M	59	+	+	–	III	–	+	–	–	–
15	M	64	+	+	–	III	+	+	-	–	–
16	M	48	+	+	–	III	+	+	+	–	–

Table 2 Laboratory findings in 16 patients with AILD

Patient	% Hct	Wbc ($x10^3$)	%Eos	Plt ($x10^3$)	P.B.	BM	Coombs'	ANA	R.F.	Immunoelectrophoresis
1	34	4.0	2	230	–	–	+	+	–	Polyclonal gammopathy
2	39	12.5	12	200	–	–	ND	–	–	Polyclonal gammopathy
3	42	11.8	6	200	+	+	+	–	–	Polyclonal gammopathy
4	31	8.8	3	210	+	+	–	–	–	Polyclonal gammopathy
5	37	6.5	1	220	–	–	–	ND	ND	Normal
6	20	15.0	19	200	+	+	+	ND	ND	Polyclonal gammopathy
7	34	4.8	0	70	+	–	–	ND	ND	Polyclonal gammopathy
8	33	17.7	0	200	–	–	–	ND	ND	Polyclonal gammopathy
9	45	18.2	1	121	+	+	–	ND	ND	Normal
10	30	11.4	10	166	+	+	–	ND	ND	Polyclonal gammopathy
11	39	4.0	14	176	–	+	–	–	–	Polyclonal gammopathy
12	29	4.1	1	221	–	–	+	+	–	Polyclonal gammopathy
13	30	5.4	2	70	–	+	+	+	–	Polyclonal gammopathy
14	38	10.2	4	646	–	ND	ND	ND	ND	ND
15	9	4.7	0	89	–	+	+	ND	ND	ND
16	10	4.9	2	80	+	+	+	ND	ND	Polyclonal gammopathy

ND = Not done
P.B. = Peripheral blood lymphocytosis, plasmacytoid cells or immunoblasts
BM = Bone marrow involvement by AILD
ANA = Antinuclear antibody
RF = Rheumatoid factor
Hct = Hematocrit
Wbc = White blood cell count
Eos = Eosinophils
Plt = Platelets

and eight patients gave partial responses (cases 1,2,6,8,9,13,15,16). One patient failed to respond to prednisolone and died. Extensive involvement of AILD was found at autopsy in almost every organ examined. Patients 6,8,9,13,15 and 16 were later treated with cyclophosphamide, vincristine and prednisolone. Only patient 9 gave a complete response. Patients 6 and 15 gave partial responses while patients 8, 13 and 16 gave no responses and died of extensive involvement. Two patients (cases 2 and 5) later developed diffuse lymphocytic poorly differentiated lymphoma. They were treated with cyclophosphamide, vincristine and prednisolone. Patient 2 did not respond and died of sepsis 4 months after diagnosis. Patient 5 had a complete remission and remains well. At the time of writing, seven patients remain alive (cases 4,5,6,7,9,11,12) and three patients have been lost to follow up (cases 1,10,14) at 10, 3 and 1 months respectively after diagnosis. There was no correlation between the clinical findings, the laboratory abnormalities and the response to treatment.

Table 3 Signs and symptoms of patients with AILD at presentation

Signs and symptoms	Present series (%)	Literature review %
Lymphadenopathy	16 (100)	100
Generalized	14 (88)	83
Localized	2 (12)	17
Fever	13 (81)	67
Hepatomegaly	14 (88)	67
Splenomegaly	7 (44)	68
Weight loss	10 (63)	58
Pruritus	7 (44)	32
Rash	7 (44)	32
Peripheral neuropathy	1 (6)	
Ascites	3 (19)	31

Table 4 Laboratory findings in 16 patients with AILD as compared to previous reports in the literature

	Present series (%)	Literature review (%)
Anemia	11 (69)	75
Positive Coombs' test	7 (50)	46
White count $\geq$ 10,000/cu.mm.	7 (44)	38
Lymphocyte count $\geq$ 3,000/cu.mm.	5 (31)	17
Lymphocyte count $\leq$ 1,000/cu.mm.	3 (19)	47
Eosinophil count $\geq$ 600/cu.mm.	4 (25)	33
Plasmacytoid cells in blood	7 (44)	34
Hypergammaglobulinemia	12 (86)	89
Lesions in bone marrow	9 (56)	40
Pulmonary involvement	5 (31)	54

Table 5 Response to treatment in 16 patients with AILD

Patient	Initial treatment	Response	Subsequent treatment	Result	Survival (mo)	Cause of death
1	Prednisolone	PR	Prednisolone	PR	10+	—
2	Prednisolone	PR	CVP	NR	4	Infection
3	Prednisolone	NR	—	dead	1	Extensive involvement
4	Prednisolone	CR	Prednisolone	CR	3+	—
5	CVP	CR	CVP	CR	15+	—
6	Prednisolone	PR	CVP	PR	13+	—
7	Prednisolone	CR	Prednisolone	CR	3+	
8	Prednisolone	PR	CVP	NR	3	Extensive pulmonary involvement
9	Prednisolone	PR	CVP	CR	3+	—
10	Prednisolone	CR	Prednisolone	CR	3+	—
11	Prednisolone	CR	Prednisolone	CR	9+	—
12	Prednisolone	CR	Prednisolone	CR	9+	—
13	Prednisolone	PR	CVP	PR	5	Extensive involvement
14	—	—	—	—	1	—
15	Prednisolone	PR	CVP	PR	5	Septicemia
16	Prednisolone	PR	CVP	PR	12	Extensive involvement

CR = Complete response; PR = Partial response; NR = No response; CVP = cyclophosphamide, vincristine, prednisolone

DISCUSSION

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) appears to be a distinct clinical and morphologic entity within a broad group of undefined abnormal immune reactions. It is situated in an intermediate position between benign compensatory immunoblastic reactions and lymphomas of immunoblasts (immunoblastic sarcoma).[23,24] The nonspecific clinical presentation which can resemble collagen vascular disease, a hyperimmune disorder, or lymphoma, underscores the requirement for lymph node biopsy as the only definitive diagnostic procedure. The basic defect responsible for the development and evolution of AILD is still not known. In some instances the triggering agent has been attributed to drugs[2,4,7-10] or infectious agents such as bacteria,[11,12] viruses[13-17] or parasites.[18,19]

Although other reports have stressed the association of AILD with a variety of autoimmune and allergic phenomena, autoimmune hemolytic anemia and antinuclear antibody were the only two such features among the patients in the present series. In contrast to other reports, prior drug exposure was not noted in this series. The frequencies of the other clinical and laboratory features were similar to those obtained from a reveiw of 215 reported cases[2-6,22] (Tables 3 and 4). Two of our patients had progression of the disease into malignant lymphoma; this finding is similar to the previously reported incidence of 10 – 30%.[1,2,25]

The therapeutic measures for AILD include prednisolone alone,[1-3,26,29] single agent chemotherapy,[2,3] combination chemotherapy,[1,4,25,30] high dose methylprednisolone,[31] levamisole,[32,33] and plasmapheresis.[34] These therapeutic modalities, however, have not provided the best treatment of the disease. Randomized clinical trials are necessary to provide and answer.

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