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Lymph Node Pathology in Patients with a Clinical Diagnosis of Angioimmunoblastic Lymphadenopathy with Dysproteinemia (AILD): An Analysis of 37 Cases

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SUMMARY **Lymph node pathology was analyzed in 37 patients clinically diagnosed as having angioimmunoblastic lymphadenopathy with dysproteinemia (AILD). Results confirmed AILD in 11 cases and were compatible with AILD in 2 cases. Reactive lymphoid hyperplasia was found in 15 cases, 2 cases had angiofollicular lymphoid hyperplasia or Castleman's disease, atypical lymphoid hyperplasia suggestive of malignant lymphoma was observed in 3 cases, and malignant lymphoma was diagnosed in the remaining 4 cases. The histopathologic features of AILD which differed from reactive lymphoid hyperplasia were effacement of lymph node architecture, vascular arborization, high endothelial venules, and capsular infiltration (p-value < 0.05). Lymphodepletion and PAS-positive interstitial material were occasionally found in both groups (p-value > 0.05). Among the 15 cases with pathology of reactive lymphoid hyperplasia, we identified 8 cases with hyperplastic lymphoid follicles, interfollicular plasmacytosis and hypervascularity which we designated as a hyperimmune reaction. This study emphasizes the necessity of lymph node examination in all patients with a clinical suspicion of AILD.**

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) is a disorder of atypical lymphoproliferation which is thought to be a hypersensitivity or hyperimmune reaction.[1,2] Patients frequently present with clinical manifestations mimicking malignant hematologic diseases such as fever, anorexia, weight loss, generalized lymphadenopathy, and hepatosplenomegaly.[1-3] Laboratory abnormalities include Coombs-positive hemolytic anemia, polyclonal hypergammaglobulinemia, leukocytosis, eosinophilia and thrombocytopenia.[3] Recent exposure to drugs, particularly penicillin, sulfonamides and anticonvulsants, is noted in about one third of cases and recovery follows cessation of the offending drug.[3] Some cases are preceded by viral infections:- rubella, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus have been reported.[4-7] However, the cause of AILD remains unknown. Most AILD cases have clonal T-cell receptor-beta gene rearrangement, resulting in monoclonal T-cell proliferation.[8-10] Patients with AILD have distinct histopathologic changes, and the definite diagnosis of AILD requires histologic confirmation. This study was performed to characterize lymph node pathology in Thai patients diagnosed clinically as AILD.

MATERIALS AND METHODS

Lymph node biopsies performed at Siriraj hospital between 1989 and 1995 from patients with clinically suspected AILD were reviewed. Signs and symptoms suggestive of AILD were fever, anorexia, weight loss, generalized lymphadenopathy and hepatosplenomegaly plus one or more of the fol-

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lowing findings: skin rash, history of drug intake or drug allergy, presence of plasma cells, plasmacytoid cells, or immunoblasts in a buffy coat of a bone marrow aspirate or peripheral blood, anemia, positive Coombs' test, and hyperglobulinemia. Sixty-two patients were found to fulfill the above criteria, but necessary pathologic materials were only available for 37 patients.

Lymph node biopsy specimens were fixed in formalin, processed, sectioned and stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and methyl green pyronine (MGP). In some cases, paraffin immunoperoxidase studies for immunophenotyping were performed. The following features of the lymph nodes were histologically evaluated or graded: lymph node architecture (complete, partial, or no effacement), absence or presence of lymphoid follicles and their texture (normal, burned-out, or hyperplastic follicles), vascular proliferation (graded 1+, 2+, and 3+), presence or absence of vascular arborization and high endothelial lining of postcapillary venules. Cellular components evaluated were immunoblasts, plasma cells, lymphocytes, histiocytes, eosinophils and neutrophils (1+, 2+, and 3+), presence or absence of eosinophilic PAS-positive interstitial material, capsular infiltration, foci of necrosis, clusters of immunoblasts, and cytologic atypia. Vascular or cellular proliferation was graded 1+, 2+, or 3+ if blood vessels or cellular components were present in <25%, 25% - 50% or >50% of areas or cells examined under high powered microscopy, respectively. Lymphodepletion was present if lymphocytes were less than 50% of total cells in low power fields.

The histopathological features of AILD (Fig. 1) followed the criteria of Frizzera *et al.*[1] Classical AILD is a diffuse effacement of lymph node architecture. Some sinuses may be open and in some areas residual "burned-out" germinal centers can be identified. Prominent arborizing vasculatures with high endothelial linings are present. The cellular composition of AILD is polymorphous. Immunoblasts and large transformed lymphocytes are frequently found, but they do not form a distinct sheet-like aggregation. Instead, they are interspersed among polymorphous infiltrates of

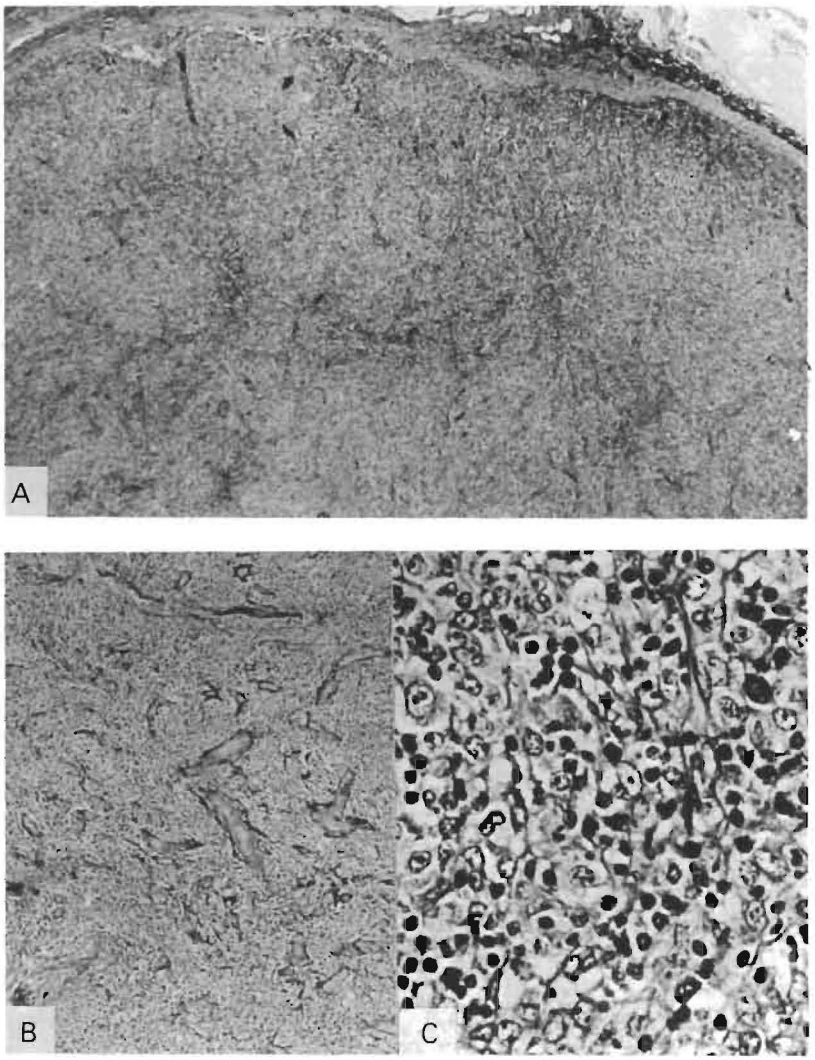

Fig. 1. Histopathologic features in angioimmunoblastic lymphadenopathy (AILD): A) low magnification of classical AILD showing diffuse effacement of lymph node architecture. No lymphoid follicle is left (hematoxylin & eosin, x10); B) typical arborizing postcapillary venules with high endothelial lining (PAS, x40); and C) admixture of lymphoid cells, transformed lymphocytes, immunoblasts, and plasma cells (hematoxylin & eosin, x200).

plasma cells, lymphocytes, eosinophils, and histiocytes. An additional feature is the presence of an interstitial amorphous proteinaceous material which stains pink with H&E and bright pink with PAS. Capsular infiltrates are always present but foci of necrosis are uncommon. Data were analyzed by the Chi-square test; p values < 0.05 were considered significant.

RESULTS

Lymph node pathologies varied markedly in patients with similar clinical presentations (Table 1) and were only diagnostic of AILD in 13 out of the 37 cases (35%). The histopathologic features of AILD which differred from reactive lymphoid hyperplasia were effacement of lymph node architecture, vascular arborization, high endothelial venules, and capsular infiltration ($p < 0.05$) (Table 2). Most AILD cases showed complete or nearly complete effacement of lymph node architecture and absence of lymphoid follicles. Lymphoid follicles, if present, were "burned-out" with accumulations of follicular dendritic cells. Rarely,

Table 1. Pathologic diagnosis of lymph node biopsies in patients with clinical diagnosis of AILD

Pathologic diagnosis	Number of cases (%)
AILD	11 (30%)
Compatible with AILD	2 (5%)
Reactive lymphoid hyperplasia	15 (41%)
Angiofollicular lymphoid hyperplasia	2 (5%)
Atypical lymphoid hyperplasia	3 (8%)
Malignant lymphoma	4 (11%)
Total	**37 (100%)**

Table 2. Histologic comparison between AILD and reactive lymphoid hyperplasia

Histologic features	No. of cases with specific feature per total cases (%)		
	AILD	Reactive hyperplasia*	p-values
1. Architecture			<0.05
- complete effacement	9/11 (82%)	2/14 (14%)	
- partial effacement	2/11 (18%)	5/14 (36%)	
- no effacement	0/11 (0%)	7/14 (50%)	
2. Remnant lymphoid follicles			<0.05
- absent	6/11 (55%)	2/14 (14%)	
- normal	3/11 (27%)	9/14 (64%)	
- burned-out	3/11 (27%)	2/14 (14%)	
- hyperplastic	0/11 (0%)	6/14 (43%)	
3. Vascular proliferation	2+ to 3+	2+ to 3+	
- arborization	9/11 (82%)	6/14 (43%)	<0.05
- high endothelial lining	11/11 (100%)	9/14 (64%)	<0.05
4. Cellular proliferation	polymorphous	polymorphous	
5. Lymphodepletion	4/11 (36%)	3/14 (21%)	>0.05
6. PAS+ interstitial material	3/11 (27%)	1/14 (7%)	>0.05
7. Capsular infiltration	10/11 (91%)	3/14 (21%)	<0.001
8. Necrosis	1/11 (9%)	1/14 (7%)	>0.05

* Excluding tuberculous lymphadenitis which showed distinct granulomas

normal small follicles without active germinal centers were seen. Capsular infiltration was more frequent in AILD than in reactive nodes (91% versus 21%, respectively). Four of the 11 AILD cases (36%) showed lymphodepletion and in one of these cases there was accompanying leukopenia. PAS-positive interstitial material was found in 27% of AILD cases while necrosis was rare in both groups.

Half of the reactive nodes did not show effacement of the lymph node architecture. Those with partial effacement had variable unaffected areas. Two reactive nodes disclosed complete effacement due to markedly increased fibrosis in one case (end stage of reactive lymphadenitis) and paracortical expansion in the other. The majority of lymphoid follicles in the reactive nodes were normal or hyperplastic. Marked vascular proliferation and polymorphous cellular component were present in both groups.

There was a hyperimmune reaction in 8 of the 15 cases of reactive lymphoid hyperplasia; characterized by follicular hyperplasia, interfollicular vascular proliferation and plasmacytosis (Fig. 2).[11] PAS-positive interstitial material was found in one case. The other seven reactive cases included two cases proven to be compatible with systemic lupus erythematosus, one case of tuberculous lymphadenitis, and four cases of reactive non-specific lymphoid hyperplasia with a mixed pattern.

The two cases of angiofollicular lymphoid hyperplasia or Castleman's disease were of the hyaline-vascular type. Three cases were designated as atypical lymphoid hyperplasia. Despite the suspicion of lymphoma by histology, monoclonal immunophenotypes could not be identified. Among the four cases of malignant lymphoma, there was one case with histopathologic features of AILD accompanied by large aggregates of clear cells which were positive for T-cell markers, indicative of AILD-like T-cell lymphoma.[12] The other cases were follicular lymphoma of large cell type (1 case), diffuse large cell type (1 case), and Hodgkin's disease (1 case).

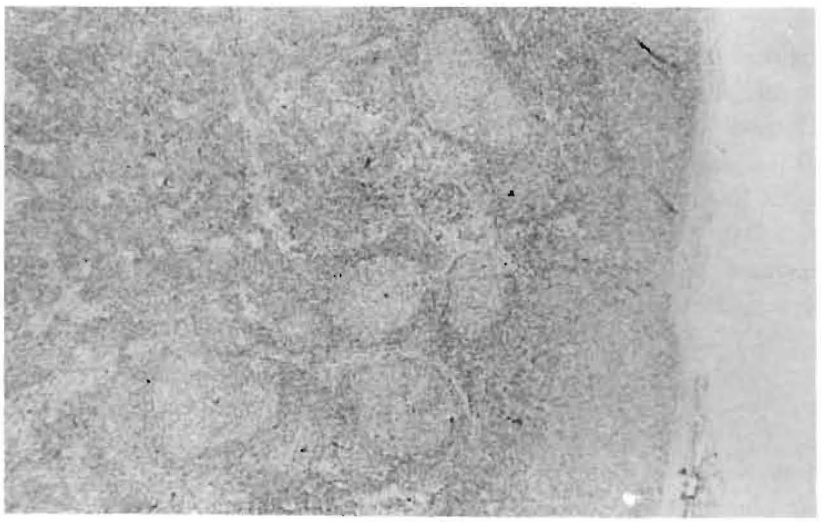

Fig. 2. Low magnification of lymph node showing "hyperimmune reaction." Note the prominent hyperplastic follicles (hematoxylin & eosin, x10). Plasmacytosis is distinct in the interfollicular areas (not shown).

AILD showed a predilection towards elderly males; the mean age was 53 years and the male to female ratio was 3.3:1 (Table 3). Other manifestations were similar except that AILD patients more often had generalized lymphadenopathy. Most patients had taken medication by history; ampicillin, chloramphenicol, cotrimoxazole and prednisolone were the drugs identified by patients with hyperimmune reactions. Positive Coombs tests in non-AILD cases occurred mainly in the hyperimmune reaction group (4 out of 5 cases tested). Polyclonal hypergammaglobulinemia was a feature of only half the AILD cases evaluated.

DISCUSSION

The diagnosis of AILD was confirmed by lymph node biopsy in only one third of clinically suspected cases (13 of 37). This emphasizes that AILD is a clinicopathologic entity whose diagnosis includes both clinical and pathologic features.[12,13] There was considerable overlap between the clinical and laboratory findings-but not the histopathologic features, of AILD and other lymphoproliferative disorders.[11] Complete effacement is characteristic of AILD while the presence of many hyperplastic lymphoid follicles is a cardinal feature

Table 3. Clinical comparison between AILD and non-AILD (reactive and atypical lymphoid hyperplasia Including malignant lymphoma)

Clinical features and laboratory findings	No. of cases with specific feature or finding per total cases (%)		
	AILD	Reactive hyperplasia	Atypical hyperplasia*
Male : female	10 : 3	8 : 7	2 : 7
Mean age (years)	53.3	33.1	43.8
Fever	11/13 (85%)	11/15 (73%)	6/9 (67%)
Lethargy and/or weight loss	8/13 (62%)	3/15 (20%)	4/9 (44%)
Skin rash	7/13 (54%)	6/15 (40%)	2/9 (22%)
Lymphadenopathy			
- localized	2/13 (15%)	7/15 (47%)	3/9 (33%)
- generalized	11/13 (85%)	6/15 (40%)	6/9 (67%)
Hepatomegaly	10/13 (77%)	7/15 (47%)	6/9 (67%)
Splenomegaly	9/13 (69%)	4/15 (27%)	6/9 (67%)
Drug history	2/13 (15%)	9/15 (60%)	3/9 (33%)
Anemia	7/13 (53%)	11/15 (73%)	6/9 (67%)
Thrombocytopenia	2/13 (15%)	0/15 (0%)	0/9 (0%)
Elevated ESR	7/8 (88%)	11/12 (92%)	5/5 (100%)
Positive Coombs' test	3/8 (38%)	6/12 (50%)	1/7 (14%)
Hyperglobulinemia	3/11 (27%)	1/14 (7%)	1/7 (14%)
Polyclonal hypergamma globulinnemia	2/4 (50%)	0/2 (0%)	1/1 (100%)

* Atypical lymphoid hyperplasia other than AILD. Malignant lymphoma was also included.

of hyperimmune reactions.[11] Interestingly, a history of previous exposure to medication was elicited from patients with both AILD and hyperimmune reactions. The initial histopathologic changes in some AILD cases may therefore be those of a hyperimmune reaction but later develop the classical features of AILD. This speculation is supported by case reports of hyperimmune reactions evolving into AILD.[10] In these cases, germline configuration of the T-cell receptor genes was initially observed and rearrangement of the T-cell receptor genes was detected in subsequent biopsy. It is therefore recommended that lymph node biopsy be repeated within 4 to 6 weeks in cases with persistent lymph node enlargement where the initial lymph node biopsy is not diagnostic of AILD. Transformation of AILD into malignant lymphomas-immunoblastic lymphoma, peripheral T-cell lymphoma and Hodgkin's disease, has been clearly documented.[12-15] Repeat lymph node biopsies in patients with AILD whose clinical course worsens is also recommended.

In conclusion, this study emphasizes the distinct histopathologic features of AILD. Lymph node biopsy is crucial both for confirming the diagnosis of AILD and for excluding other conditions.

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