Acta Medica Okayama

Volume 35, *Issue* 4 1981 *Article* 4

OCTOBER 1981

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Abstract

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*PMID: 6457513 [PubMed - indexed for MEDLINE]

Acta Med. Okayama 35, (4), 263—272 (1981)

A CASE OF ANGIO-IMMUNOBLASTIC LYMPHADENOPATHY WITH DYSPROTEINEMIA RELATED TO ALLOPURINOL

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Received March 17, 1981

Abstract. A 63-year-old man developed generalized lymphadenopathy with skin rashes, fever, hepatomegaly and polyclonal hypergammaglobulinemia, twice, in February 1972 and in June 1979, after taking allopurinol for gout. Cervical lymph node biopsy, performed each time, showed the presence of immunoblasts and plasma cells, effaced nodal structure with involvement of the pericapsular tissue, rich vascularity and numerous mitoses, indicatve of angio-immunoblastic lymphadenopathy with dysproteinemia (Frizzera, Moran and Rappaport). The existence of hypersensitivity to drugs, in particular, allopurinol in certain patients was emphasized, and induction of immunoblastic lymphadenopathy with various other therapeutic agents was briefly discussed.

Key words : angio-immunoblastic lymphadenopathy, allopurinol.

Lymphoproliferative disorders resembling Hodgkin's disease have been called under various terms, such as lymphoreticulosis hyperglobulinemica (Jahnke and Schotan) (1), immunodysplasia syndrome (Kuroyanagi) (2), diffuse plasmacytic sarcomatosis (Flandrin *et al.*) (3), chronic pluripotential immunoproliferative syndrome (Westerhausen and Oehlert) (4), or immunodysplastic desease (Suchi) (5). However, the terms angio-immunoblastic lymphadenopathy with dysproteinemia (AILD) suggested by Frizzera, Moran and Rappaport (6) and immunoblastic lymphadenopathy (IBL) suggested by Lukes and Tindle (7), are now the most accepted in view of more clear-cut clinico-pathological definition of the lesion.

Although the exact etiology of AILD and IBL remains uncertain, there have been several reports concerning the relationship between the occurrence of these lymphadenopathies and therapeutic agents used for a variety of conditions. We present an elderly male who developed generalized lymphadenopathy twice after taking allopurinol (AP); this is a zanthine oxidase inhibitor with the chemical formula 4-hydroxypyrazolo (3,4-d) pyrimidine, and effective for hyperuricemia associated with gout.

CASE PRESENTATION

This is a 63-year-old male, a businessman, born in 1915. As to past history, the patient underwent a right nephrectomy in 1956 for nephrolithiasis. From 1966 on, he had medications for essential hypertension and gout. Since April 1971, he had been given probenecid 1.5 g and colchichine 1 mg per day for gout in the Department of Internal Medicine, Misasa Hospital, Okayama University Medical School. Because of serum uric acid ranging from 7.5 to 8.0 mg/dl (normal: 2.5-7.0), AP 200 mg per day was added in the end of November. Approximately one month after commencing AP, he noticed lymph node swelling in the neck, which extended further to the axillary and inguinal regions, and by x-rays to the right hilus. Hypersensitivity to AP was highly suspected. In March 1972 when AP was switched to prednisolone 30 mg per day, he had a remission of lymphadenopathy.

In April 1979, he was admitted to the Department of Urology, Tottori University Hospital, for left uretero-lithiasis (uric-acid stones). Because his

TABLE 1. PERIPHERAL BLOOD PICTURE AND MYELOGRAM ON MDMISSION

Peripheral Blood			Bone Marrow (%)			
Hb (g/dl)	9.5		NCC	225,000 (/mm³)		
RBC (/mm³)	285x10⁴		ProErbl		0.4	
Ht (%)	30.5			B	2.6	
Thrombo (/mm³)	19.3x10⁴		Ma	P	0.6	
WBC (/mm³)	11,200			O	0	
Differentials (%)				B	2.8	
St	14.0	} 33.5	No	P	8.6	
Seg	19.5			O	1.0	
Eo	4.5		Mitosis		0.2	16.2
Ba	0		Mybl		1.4	
Mo	4.5			Pr	4.8	
Ly	47.0	} 57.5		My	6.2	
Aty Ly*	10.5		Nt	Mt	11.0	
				St	7.6	
Rouleaux formation (+)				Seg	7.8	38.8
T cell	89.0%			My	1.0	
B cell	10.5%		Eo	Mt	0.2	
Serum Fe (γ/dl)	133			St	0.2	
Cu (γ/dl)	92.5			Seg	1.4	2.8
TIBC (γ/dl)	209		Ba		0	
			Mo		1.6	
			Ly		12.8	
			Aty Ly*		25.8	
			Mitosis		0.2	
			Plasma		1.0	
			Ret		0.8	
			Thrombo		Normal	

* Aty Ly: Atypical lymphocytes.

serum uric acid was 10 mg/dl, he was started on AP 200 mg per day. Approximately one month afterwards, lymphadenopathy was noted again. In May, he was again referred to the Department of Internal Medicine, Misasa Hospital.

On admission, he had a mild fever of 37.5°C, generalized lymphadenopathy up to thumb-tip size involving cervical, axillary and inguinal regions bilaterally, hepatomegaly of two finger breadths and bilateral hilar enlargement on a chest film. As shown in Tables 1 and 2, abnormal laboratory data included serum uric acid 17.0 mg/dl, ESR 120/1 h, moderate anemia (RBC 285 x 10^4/mm ^{3}, Hb 9.5 g/dl and Ht 30.5%), moderate leukocytosis (11,200/mm^3) with relative lymphocytosis (47.0%) and atypical lymphocytes (10.5%), serum protein 10.1 g/dl with high gamma-globulin (59.4%), and IgG 2650, IgA 490, IgM 680 and IgE 600 (mg/dl) indicating polyclonal hypergammaglobulinemia. A myelogram (nuclear cell counts: 225,000/mm^3) showed 25.8% atypical lymphocytes.

Immediately after admission, AP was discontinued. On the ninth hospital day, purpura-like skin rashes with itch devedped all over the body. For about three weeks, his clinical course was carefully watched without any specific treat-

TABLE 2. LABORATORY DATA ON ADMISSION

Uric acid		Total bilirubin	0.6 mg/dl
Serum	17.0 mg/dl	Direct	0.32 mg/dl
Urine	92.5 mg/dl	GOT	41 u
ESR	120/1h, 124/2h	GPT	34 u
Coombs		ALP	9.1 K-A u
Direct	(−)	Gamma-GTP	12 mμ/ml
Indirect	(−)	LAP	138 u
PPD	(−)	Cholin esterase	0.41 ΔPH/h
LE test	(−)	HBs antigen	(−)
LE cells	(−)	Urea-N	11 mg/dl
ANF	(+)∼(++) diffuse	Creatinine	1.39 mg/dl
		CPK	10 IU
CH50	18u/ml	Bleeding time	5'
C3	69	Platelet adhesiveness	37.8%
C4	2.6	Fibrinogen	382.8 mg/dl
RA	(−)	Coagulation time	
RAHA	(±)	(Lee-White)	7'30''
CRP	(−)	Thromboelastogram	
ASLO	12 Todd u	r	7'30''
Cold hemagglut.	x4 (+)	k	6'15''
Thyroid test	(−)	ma	33.5 mm
Microsome test	(−)	Platelet aggregation	
Electrolytes		(ADP)	
Na	134 mEq/l	$2x10^{-6}$	15.4% (1'23'')
K	3.5 mEq/l	$1x10^{(6}$	10.6% (1'17'')
Ca	8.0 mg/dl		
Cl	99 mEq/l		

ment. The blood picture and myelogram improved somewhat, whereas fever, lymphadenopathy and polyclonal hypergammaglobulinemia persisted. Prednisolone was then initiated on the 20th of June (Fig. 1, Table 3). After three months of this treatment, almost all the laboratory data including ESR, serum protein and immunoglobulin had returned to normal, fever and lymphadenopathy had subsided, and he was discharged on the 31st of October. Unfortunately, however, he developed a cerebrovascular accident four days later and died on the 12th of November; necropsy was not permitted.

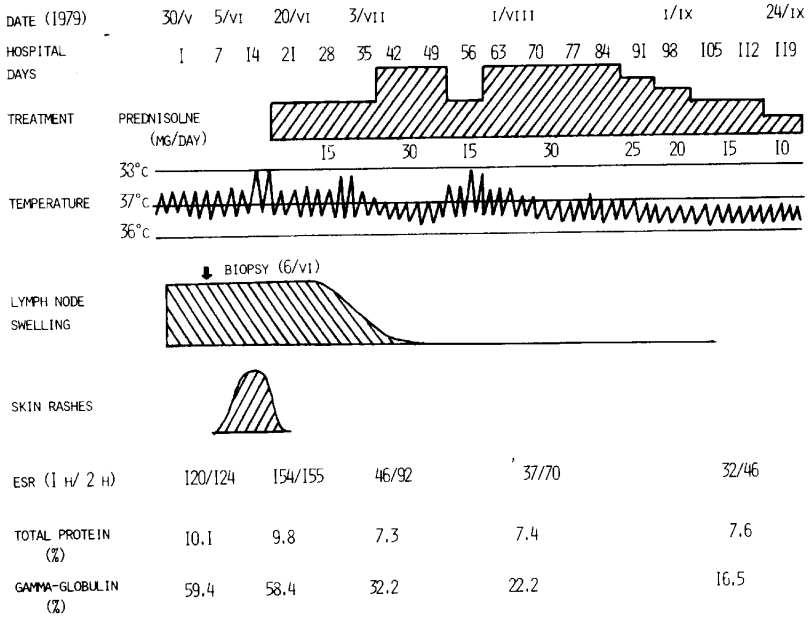


Fig. 1. Clinical course of the patient.

PATHOLOGICAL FINDINGS

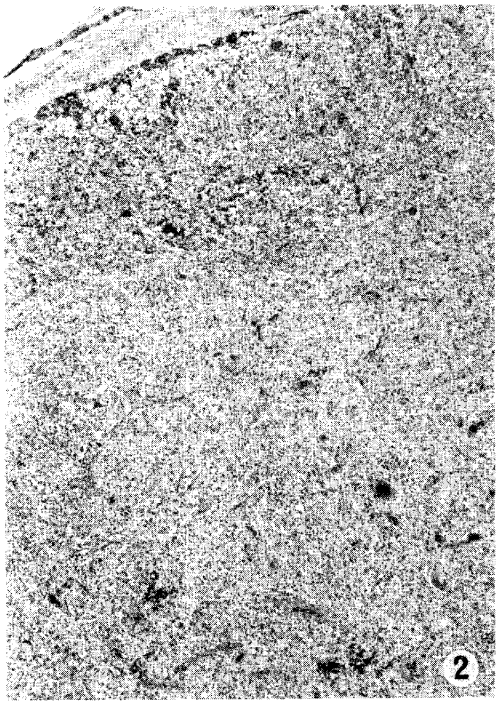
Lymph node biopsy from the neck was done twice, *i.e.*, in February 1972 and in June 1979 at the time when he noticed generalized lymphadenopathy. The first and second specimens were essentially similar to each other in pathological

Fig. 2. Lymph node (the second biopsy) showing effaced nodal structure. H.E., x40.

Fig. 3. Vascular proliferation with pericapsular infiltration. Silver impregnation, x40.

Fig. 4. Blood vessels with thickened vascular wall. Periodic acid-Schiff, x100.

Fig. 5. Numerous immunoblasts with round, vesicular nucleus, one to two prominent nucleoli and deeply basophilic cytoplasm. May-Grünwald-Giemsa, x400.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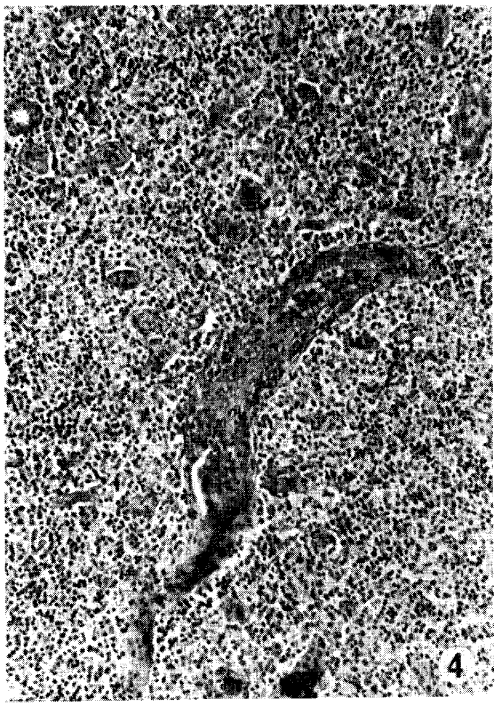
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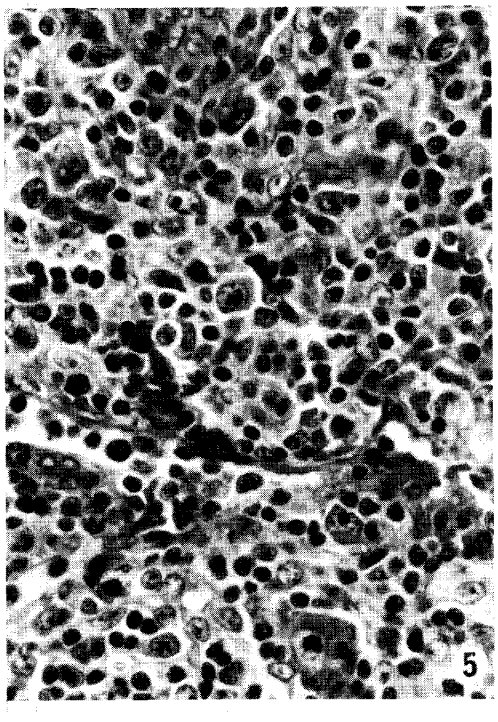
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finding although the second was more characteristic of AILD. The second specimen consisted of a lymph node of small finger-tip size. The nodal architecture was almost completely effaced leaving only one to two abortive lymph follicles and lymphocytes infiltratied to the pericapsular tissue (Fig. 2). With silver impregnation and periodic acid-Schiff staining, vascular proliferation with thickened wall was outstanding (Figs. 3 and 4), although PAS-positive "amor-

TABLE 3. SEQUENCE OF SERUM PROTEIN FRACTION, IMMUNOGLOBULINS AND ERYTHROCYTE SEDIMENTATION RATES*

Date (1979)	May 30	June 18	July 12	Aug. 8	Sept. 12
Protein Fraction (%)					
TP (g/dl)	10.1	9.8	7.3	7.4	7.6
Alub.	29.4	28.0	46.0	49.1	52.4
Alpha-1	0.9	2.5	2.4	4.1	4.2
Alpha-2	5.3	5.9	11.0	14.3	15.7
Beta glob.	4.7	5.0	8.1	10.0	10.9
Gamma glob.	59.4	58.4	32.2	22.2	16.5
A/G	0.41	0.38	0.85	0.96	1.10
Immunoglobulins (mg/dl)**					
IgG	2650	3300	1830	1350	1000
IgA	490	590	500	520	460
IgM	680	900	230	233	146
IgE (IU/ml)	—	600	—	—	—
Erythrocyte Sedimentation Rates (1h/2h)					
	120/124	154/155	46/92	37/70	32/46

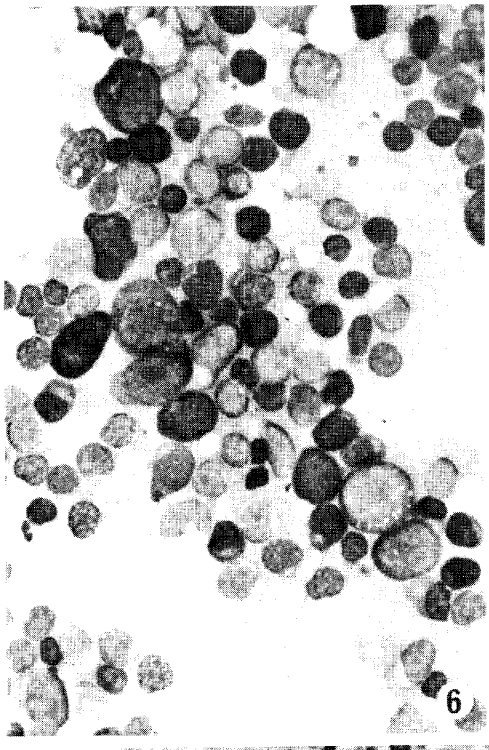
*Prednisolone was started in June 20.

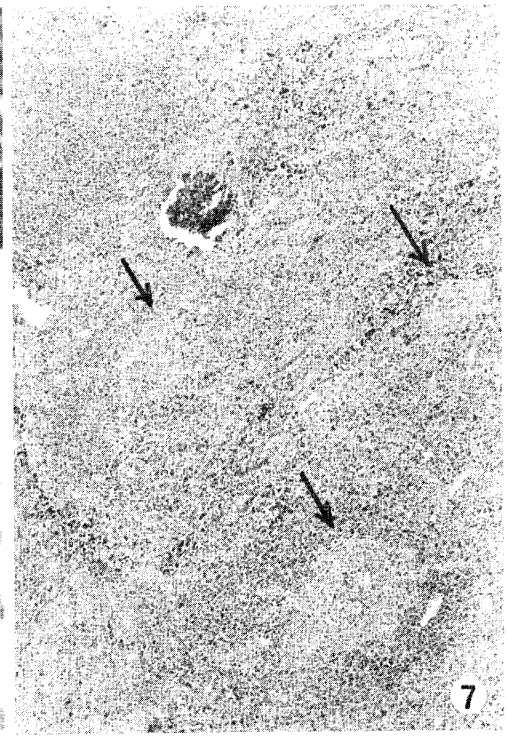
**Normal ranges: IgG 1200 ± 319; IgA 288 ± 121; IgM 80 ± 29; and IgE 15 ∿ 800.

phous material" was hardly evident. Above all, large cells with a round, vesicular nucleus, one to two prominent nucleoli and deeply basophilic cytoplasm, *i.e.,* immunoblasts, were easily recognized among a large number of diffusely infiltrating plasma cells and lymphocytes (Figs. 5 and 6). Eosinophils were sparse, and two to three mitoses per high power field were present.

The first specimen, also of small finger-tip size, had relatively well-preserved nodal structure with scattered prominent lymph follicles (Fig. 7). However, the interfollicular space was rich in vascularity. The involvement of pericapsular tissue and the presence of immunoblasts were less conspicuous than in the second specimen.

Localization of intracytoplasmic immunoglobulins was conducted according to the original method of Taylor (8,9). The second biopsied specimen was positive for IgG, IgM and IgA, and kappa and lambda chains in plasma cells, plasmacytoid lymphocytes and immunoblasts (Fig. 8).





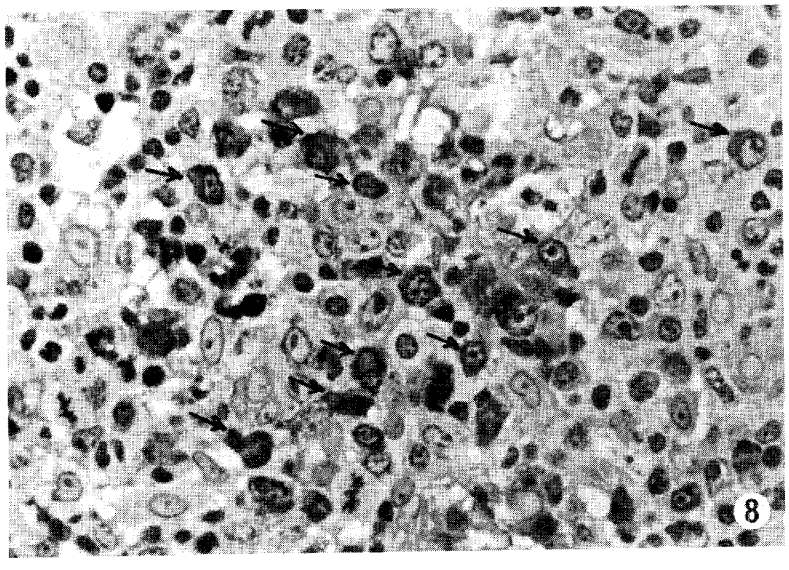


Fig. 6. Imprint of lymph node showing several large immunoblasts. May-Grünwald-Giemsa, x400.

Fig. 7. Lymph node (the first biopsy) showing relatively well preserved nodal structure with a few lymph follicles (arrows). H.E., x40.

Fig. 8. Lymph node (the second biopsy) showing intracytoplasmic kappa-chain-positive cells (arrows). Peroxidase-antiperoxidase method, x400.

DISCUSSION

Frizzera *et al.* (6) in 1975 pointed out the appearance of skin rashes in eight of 24 patients with AILD, following the intake of drugs such as penicillin, sulfonamide, aspirin and halothane. In the same year, Lukes and Tindle (7) mentioned the dramatic onset, particularly of lymphadenopathy, in seven of 22 patients with IBL after the administration of therapeutic agents including penicillin, griseofulvin, diphenyl-hydantoin (DH) and sulfonamide.

Subsequently, Lapes *et al.* (10) reported one case of IBL associated with DH. Schultz and Yunis (11) described a patient with IBL who had received liver extract by injection and by mouth for many years for mild anemia, resulting in the presence of serum antibodies to the liver extract. In other respects, liver extracts, ampicillin and chlorpheniramine maleate (12), DH, phenobarbital and primidon in one patient and chlorthalidone in another (13), and amoxycillin and hetacillin (14) have been implicated as potentially provocative agents of AILD and IBL. Imamura (15) surveyed Japanese cases with AILD and IBL, and concluded that 13 of 38 patients (34.2%) were related to administration of drugs in some way.

We necropsied a patient with IBL who had taken myobutazolidin, a compound of phenylbutazone and carisoprodol (a muscle-relaxant), for more than three years (16). As far as the intake of AP is concerned, Matloff and Neiman (17) in 1978 reported a patient with AILD who had been taking methyldopa and triamterene-hydrochlorthiazide for several years, and AP 200 mg a day approximately for three years. In the following year, Deeg *et al.* (18) emphasized "a striking temporal relationship" between the administration of antibiotics, including dicloxacillin and ampicillin, or administration of AP and exacerbation of AILD.

As noted by Sekiya *et al.* (19), so-called drug-induced lymphadenopathy is almost inevitable, especially in patients who are on anticonvulsant agents such as DH. They admitted, however, histological similarity of their cases I and II to IBL. Furthermore, "a small excess risk" of malignant lymphoma including Hodgkin's disease can occur in patients receiving long-term treatment with DH (20); a case reported by Kikuchi *et al.* (21) supports this view.

At this stage of conflicting issue, Kojima (22) in 1978 and Abe (23) in 1979 proposed the concept of "polyclonal immunoblastosis", in which they emphasized the presence of prominent proliferation of large mononuclear cells with basophilic cytoplasm, *i.e.*, immunoblast and plasmablast, and plasma cells. Our case fulfils the criteria of Kojima and Abe.

Concerning the hypersensitivity to therapeutic agents in IBL, Lukes and Tindle (7) suggested that "an undetected abnormal immune state may have been triggered into an exaggerated response". In this sense, the promising effect of levamisole hydrochloride, known as a macrophage activator, on patients with AILD and IBL by induction of T-helper cells in the immune response is of interest (24, 25).

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