Salazosulfapyridine-Induced Angioimmunoblastic Lymphadenopathy

Atsushi NAKANO, Kazuhiro HATTA, Yoichiro KOBASHI*, Masashi GOTO and Takanobu IMANAKA

A 20-year-old man with ulcerative colitis was admitted because of fever, eruption and lymphadenopathy. He had started taking salazosulfapyridine one month previously. Lymph node biopsy revealed angioimmunoblastic lymphadenopathy. Autoantibody titers were all negative, and viral antibody titers were not increased retrospectively. Rearrangement of T-cell receptor β and chromosomal aberration were not seen on the lymph node. This case is considered not to be a peripheral T-cell lymphoma but rather salazosulfapyridine-induced angioimmunoblastic lymphadenopathy (AIL), which is the second case in English language literature. (Internal Medicine 35: 894–897, 1996)

Key words: angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), immunoblastic lymphadenopathy (IBL), lymphoproliferative disease, drug-allergy

Introduction

Angioimmunoblastic lymphadenopathy (AIL), proposed by Frizzera et al (1), is mostly considered as a clinicopathological entity of peripheral T-cell lymphoma called AIL-like T-cell lymphoma. But some antiepileptics, viruses or collagen diseases sometimes induces a similar state which can not be distinguished from AIL-like T-cell lymphoma. The present patient displayed a rare case of AIL induced by salazosulfapyridine.

Case Report

A 20-year-old male college student was admitted to this hospital on July 6, 1994 because of fever, eruption and lymphadenopathy. A month previously, under the diagnosis of ulcerative colitis, he had been given salazosulfapyridine and mepenzolate bromide every day. After starting the medication, he felt general fatigue, fever, eruption and lymphadenopathy. Dicrofenac sodium suppository further worsened the fever up to 40°C and eruption expanded, and he was admitted to our hospital. There was past history of hereditary spherocytosis since the age of 19. Family history was unremarkable. On physical examination, his temperature was 38.8°C. There was rice-grain-sized wide-spread erythema spread on his trunk and extremities. Edema was present on the neck, shoulder and lateral side of chest (Fig. 1). The mucous membrane of conjunctiva, oral angle, nose and glans penis were erosive. There was

wide-spread lymphadenopathy of submandibular, cervical, axillary and inguinal lymph nodes. The liver was palpable 3 cm below the right costal margin and the spleen was felt 2 cm below the left costal margin.

As Table 1 shows, laboratory data were as follows: hemoglobin 10.6 g/dl; platelet 206,000/mm³; white cell count 8,800/mm³; C-reactive protein 2.0 mg/dl; lactate dehydrogenase 1,446 IU/l; and hepatobiliary enzyme was increased – aspartate aminotransferase 55 IU/l; alanine aminotransferase 118 IU/l; total bilirubin 1.4 mg/dl; γ -glutamyl transpeptidase 300 IU/l; leucine aminopeptidase 125.9 IU/l; and alkaline phosphatase 983 IU/l. Rheumatoid factor, antinuclear antibody or anti-DNA antibody were negative (Table 2). Titer against measles, EB virus, rubella, adenovirus and cytomegalovirus are shown in Table 2. Abdominal ultrasonic examination and computed tomography disclosed mild splenomegaly and several swelling of lymph nodes less than 1 cm in diameter. The lymphocyte stimulating tests (LST) for salazosulfapyridine, dicrofenac sodium and mepenzolate bromide were all negative (Table 3).

Biopsy of the right inguinal lymph node sampled on the 4th day of admission showed typical features of AIL, that is, effacement of lymph node architecture and numerous reactive cells and lymphoid cells of varying size and appearance. At high magnification, there was prominent mitotic activity and some lymphocytes showed clear cytoplasm mixed with eosinophils and neutrophils. Proliferation of post-capillary venules with high endothelial cells were seen at impregnation for reticulin

From the Departments of Comprehensive Care and Education, and *Pathology, Tenri Hospital, Tenri

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Reprint requests should be addressed to Dr. Atsushi Nakano, the Departments of Comprehensive Care and Education, Tenri Hospital, 200 Mishima, Tenri 632

Figure 1. A) There was rice-grain-sized wide-spread erythema with fusing tendency spread on trunk and extremities. Edema was present on the neck, shoulder and lateral side of chest. B) All symptoms disappeared after treatment.

Table 1. Laboratory Data on Admission

CBC			
RBC	$3.59 \times 10^6/\mu\text{l}$	T.P	5.7 g/dl
Hb	10.6 g/dl	Alb	3.5 g/dl
Ht	31.6 g/dl	Glob	2.2 g/dl
WBC	8,800/ μl	α_2	6.1%
Lymp	19.0%	β	10.1%
Mono	6.0%	γ	17.1%
Eos	3.0%	LDH	1,466 IU
Baso	1.0%	GOT	55 IU
N. Seg	60.0%	GPT	118 IU
N. Band	11.0%	T. Bil.	1.4 mg/dl
CRP	2.0 mg/dl	γ GTP	300 IU
		ALP	983 IU

CBC: complete blood count, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, WBC: white blood cell, Lymp: lymphocytes, Mono: monocytes, Eos: eosinophils, Baso: basophils, N. Seg: neutral segments, N. Band: neutral bands, CRP: C reactive protein, T.P: total protein, Alb: albumin, Glob: globulin, LDH: lactate dehydrogenase, GOT: glutamic-oxaloacetic transaminase, GPT: glutamic-pyruvic transaminase, T. Bil: total bilirubin, γ GTP: γ glutamyl transpeptidase, ALP: alkaline phosphatase.

Table 2. Immunoserological Data

RA	<0.5
ANA	(-)
anti-DNA	<2.5
anti-ENA	(-)
Hp	27.8
CH50	38.1
C3	90.7
C4	27.9
Coombs test	(-)
anti-mitochondrial antibody	(-)
anti-smooth muscle antibody	(-)

RA: rheumatoid antibody, ANA: antinuclear antibody.

Table 3. Lymphocyte Stimulation Test

Salazosulfapyridine	1.09(-)
Diclofenac sodium	1.10(-)
Mepenzolate bromide	1.16(-)

fiber. All of these findings are consistent with AIL (Figs. 2, 3).

The diagnosis of AIL was made from the clinical course, laboratory data, and lymph node biopsy. Because the rearrangement of T-cell receptor β or chromosomal abnormality was not seen in the lymph node, this case was considered to present the reactive state. He was treated with corticosteroids. All drugs were stopped on the day of admission and 500 mg of methylprednisolone was administered for 3 days followed by prednisolone 60 mg per os. All the symptoms disappeared.

Discussion

Angioimmunoblastic lymphadenopathy (AIL) is a lymphoproliferative disease with clinical presentation of acute fever, erythema, lymphadenopathy and hepato-splenomegaly first recognized by Frizzera et al in 1974 (1, 2). Immunoblastic lymphadenopathy (IBL) advocated by Lukes and Tindle was

Figure 2. Lymph node architecture was widely destroyed and proliferation of venules were prominent (HE stain, $\times 40$).

Figure 3. A) There was prominent mitotic activity and some lymphocytes showed clear cytoplasm mixed with eosinophils and neutrophils (HE stain, $\times 400$). B) Proliferation of post-capillary venules with high endothelial cells were seen at impregnation for reticulin fiber (Gitter stain, $\times 200$).

recently used almost synonymously (3, 4). AIL is characterized by its histology: 1) the proliferation of post-capillary venules with high endothelial cells and PAS-positive thickened walls. 2) the presence of clear cell which is a middle to large lymphocyte with clear cytoplasm. 3) proliferation of immunoblast and plasma cell. 4) diffuse effacement of lymph node architecture.

At first, AIL was considered to be of an entity of lymphoproliferative disease with a broad spectrum ranging from reactive lymphadenopathy to peripheral T-cell lymphoma (AIL-like T-cell lymphoma) (5, 6). But recently, AIL is considered to include two entities: one is neoplastic AIL, a hyperimmunity state of peripheral T-cell lymphoma which presents symptoms of B-cell activation, and the other is reactive AIL induced by drug allergy, viral infection or some type of collagen diseases, presenting strikingly resembling findings

(7–11). Actually, some studies show 49% of AIL led to complete remission (CR) and almost all of the case of the CR group include survived more than 5 years (12, 13). The CR group and non-CR group follow apparently different courses. These data suggest that AIL is divided into two entities, neoplastic AIL and reactive AIL. The rearrangement of T-cell receptor β and chromosomal abnormality are useful to differentiate the two entities (14, 15).

The present case is thought to be a reactive AIL because there was no cluster of clear cells in histology, no rearrangement of T-cell receptor β and no chromosomal abnormality. Because the viral titers were not increased and there was no immunoserological findings suggesting collagen disease, some kind of drug is thought to have induced AIL in this case. Phenytoin is well known as a cause of drug-induced AIL; it develops several months after starting medication. However, phenytoin was not used in the present case. Among the three possible drugs in this case, diclofenac sodium and mepenzolate bromide were not reported so far. Smith et al (16) reported a case of salazosulfapyridine-induced AIL in 1985. The dramatic effectiveness of corticosteroid is consistent with reactive AILD. The interval between starting salazosulfapyridine and the onset of symptoms is about a month, which is also compatible with drug-induced AIL. The secondary polyclonal gammopathy was not seen in this case but that is not significant as the essence of AIL is hyperreactivity or neoplasia of T-cell. In the present case, although whether salazosulfapyridine induction of AIL was not proven by the lymphocyte stimulating test and challenge test was not performed, the clinical course in this case apparently presents salazosulfapyridine-induced AIL. This case emphasizes that not all cases of AIL need chemotherapy and the diagnosis of AIL-like T-cell lymphoma must be made carefully.

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