[症例報告]An autopsy case report of T-cell lymphoma accompanied by hemophagocytic syndrome and acute hepatic failure

An autopsy case report of T-cell lymphoma accompanied by hemophagocytic syndrome and acute hepatic failure

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ABSTRACT

An autopsy case of T-cell lymphoma complicated with hemophagocytic syndrome (HPS) is reported. A 60-year-old woman presenting with fever and jaundice was transferred to our hospital. On admission, she showed bicytopenia, severe liver dysfunction and coagulopathy. She subsequently developed pancytopenia. At first, she was suspected of having aplastic anemia. Methylpredonisolone pulse therapy was therefore initiated, and the leukopenia improved. But she later developed leukopenia again, and died of septic shock. At autopsy, proliferation of histiocytes with hemophagocytosis was observed in the reticuloendothelial system. Moreover, T-cell lymphoma was observed. Hence diagnosis of T-cell lymphoma with HPS was made pathologically. *Ryukyu Med. J., 17(1)57~60, 1997*

Key words: T cell lymphoma, hemophagocytosis, hepatic failure

INTRODUCTION

Hemophagocytic syndrome (HPS) is a non-neoplastic generalized histiocytic proliferation disorder with marked hemophagocytosis in the reticuloendothelial system. The characteristic clinical findings of the syndrome include fever, pancytopenia, liver dysfunction and disseminated intravascular coagulation (DIC). Now, we report a rare case of T-cell lymphoma accompanied by HPS and acute hepatic failure[1], and review the previous literature.

CASE REPORT

A 60-year-old woman was admitted to our hospital in July 1993 for fever, jaundice and cold sweats. The patient had been well until first signs of jaundice had appeared six days prior to hospitalization. Two days after this episode, fever and cold sweat followed. The patient had no history of drug or alcohol abuse.

Physical examination included height 145cm; weight 52.9 kg; temperature 39.0℃ and pulse 90/min. Her eyes showed marked icterus without anemia. Hepatosplenomegaly and superficial lymph node swelling were not observed. Purpuras were observed on the upper extremities, and tenderness was noted on the right lower chest.

The laboratory findings on admission are shown in Table 1. Leukocytopenia and thrombocytopenia were observed in peripheral blood. Red blood cell count was

Table 1 Laboratory data on admission

Peripheral blood			Blood chemistry		
WBC	1800	/μl	TB	17.3	mg/dl
stab	50	%	DB	15.1	mg/dl
seg	40	%	GOT	1659	IU/L
ly	10	%	GPT	2002	IU/L
RBC	420×10⁴	/μl	ALP	366	IU/L
Hb	13.2	g/dl	LDH	2123	IU/L
Hct	37.3	%	γ-GTP	108	IU/L
Reticulocyte	1	‰	LAP	383	IU/L
PLT	9.7×10⁴	/μl	TP	6.0	g/dl
ESR	7	mm/hr	ALB	3.4	g/dl
Serology			**Bone marrow**		
CRP	3.88	mg/dl	NCC	8500	/μl
IgG	1801	mg/dl	pro	2.0	%
IgM	148	mg/dl	met	1.0	%
IgA	170	mg/dl	stab	4.0	%
RA	(−)		seg	4.0	%
ANA	(−)		lybl	2.0	%
HBsAg	(−)		ly	74.0	%
IgM-HBcAb	(−)		histiocyte	(±)	
IgM-HAAb	(−)		reticulum	12	%
HCV-Ab	(−)		megakaryo	1	%
HCV-RNA	(−)				
Parvovirus B19	(−)		**Coagulation test**		
EBV-VCA(IgM)	10	>	PT%	52	%
EBV-VCA(IgG)	×160		Fib	36	mg/dl
EBV-EBNA	10	>	HPT	32	%
CMV-Ab(IgM)	0.8	>	FDP	35	μg/dl
HTLV-I Ab	4096	<			
Ferritin	3000	ng/ml<			
TNF-α	2.0	pg/ml>			
IF-γ	0.5	U/ml >			
IL-1β	15.6	pg/ml>			
HGF	10.0	ng/ml<			

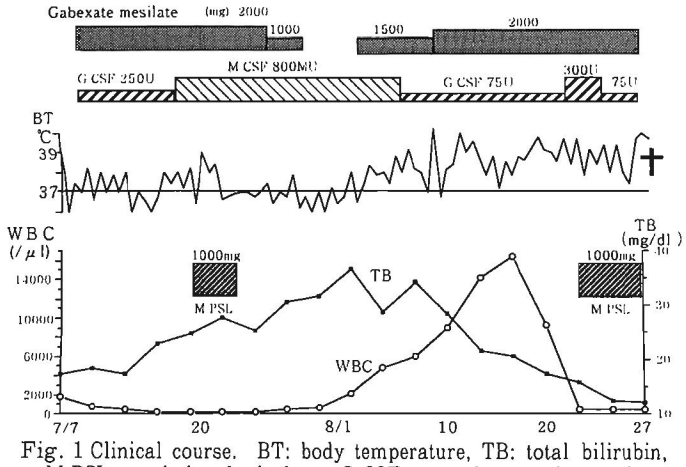

Fig. 1 Clinical course. BT: body temperature, TB: total bilirubin, M-PSL: methylpredonisolone, G-CSF: granulocyte-colony stimulating factor, M-CSF: macrophage-colony stimulating factor.

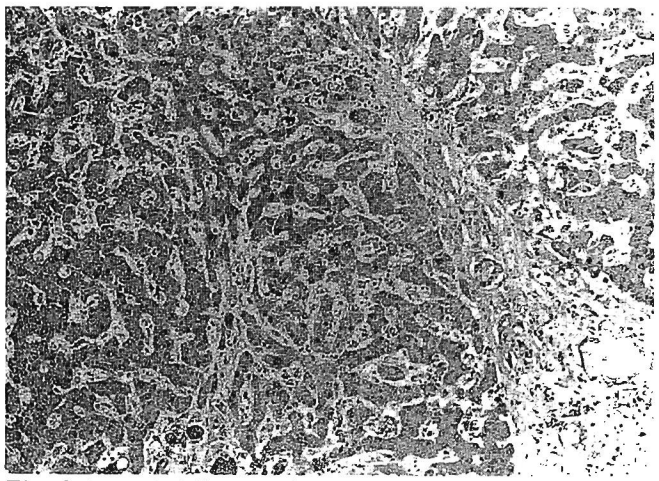

Fig. 2 Autopsied liver specimen shows fibrotic change within portal area and bridging fibrosis (HE stain, ×80).

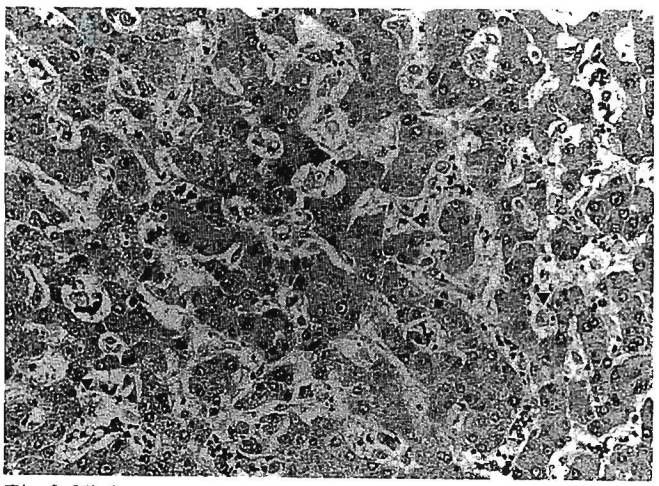

Fig.3 Higher magnification showing dilated sinusoid of the liver with proliferation of histiocytes (arrows) (HE stain, ×200).

within the normal range, but reticulocyte count was decreased. Coagulation test showed a decrease in prothrombin time activity, hepaplastin test and fibrinogen, and an increase in fibrinogen degradation products. Liver biochemical test revealed markedly elevated total bilirubin, moderately elevated serum aspartate transaminase, alanine transaminase and lactate dehydrogenase, and elevation in biliary tract enzymes. In serology, a mild elevation in C-reactive protein was observed. The viral markers of hepatitis A, B and C were all negative. No significant elevation of the antibody titers of Epstein-Barr virus and cytomegalovirus was noted. A test for antinuclear antibody was negative. Serum human T-lymphotropic virus type-I (HTLV-I) antibody was positive in high titer. Moreover, serum levels of hepatocyte growth factor (HGF) and ferritin were extremely elevated.

The bone marrow aspirate revealed markedly decreased nucleated cell count, but no invasion of malignant nor abnormal cells. Since severe liver dysfunction and DIC were seen on admission, administration of gabexate mesilate and fresh frozen plasma, and glucagon-insulin therapy were initiated. Thereafter, serum levels of transaminases, FDP and D dimer decreased, but serum concentration of total bilirubin contrarily increased. During the three week period of therapy, serum levels of HGF decreased to 1.96 ng/ml as compared to the initial level of more than 10 ng/ml.

Although no pathogens were identified, administration of antibiotics was initiated for the high fever, but without subsequent improvement, high fever persisted. Granulocyte-colony stimulating factor was administered for leukocytopenia, but peripheral leukocyte counts did not increase.

From the bone marrow findings, she was first suspected of having aplastic anemia. Therefore, administration of high dose methylpredonisolone and macrophage-colony stimulating factor was initiated, which led to increase in neutrophil counts. However, she once again developed leukocytopenia 15 days after methylpredonisolone pulse therapy. Consequently, she died of sepsis resulting from lung abscess in the left lower lobe, which was due to methicillin-resistant *Staphylococcus aureus* (MRSA) infection on the 44th day of hospitalization (Fig. 1).

At autopsy, the liver weighed 1580g, and the surface was slightly irregular. The spleen weighed 70g, and only the mediastinal lymph nodes were found to be swollen.

Histopathologically, the liver specimen showed fibrotic change in the portal area and parenchyma forming bridging fibrosis and slight liver cell damage, a feature similar to that of early stage of liver cirrhosis and different from that of acute hepatic failure (Fig. 2). Higher magnification revealed histiocyte proliferation in the dilated sinusoid with phagocytosis of red blood cells and other blood elements (Fig. 3). In the spleen, proliferation of histiocytes with phagocytosis of red blood cells was also observed. The tissue specimen of the hilar lymph node showed diffuse infiltration of abnormal lymphocytes

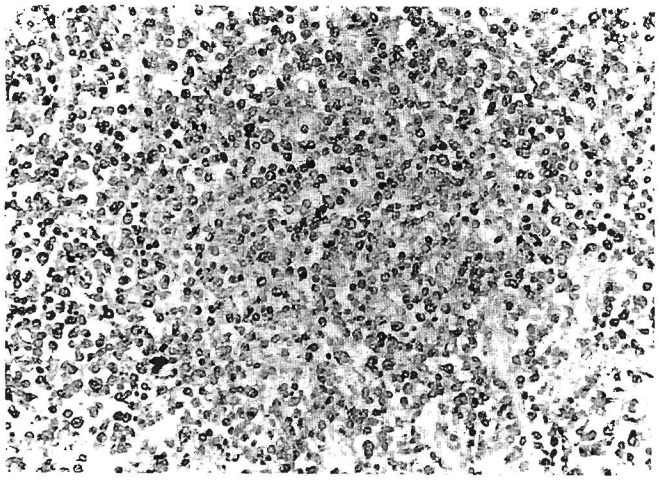

Fig. 4 Atypical lymphocytes, which are positive with the UCHL-1 stain, diffusely infiltrate in the lymph node (diffuse lymphoma, mixed type according to the Lymphoma Study Group classification, ×200).

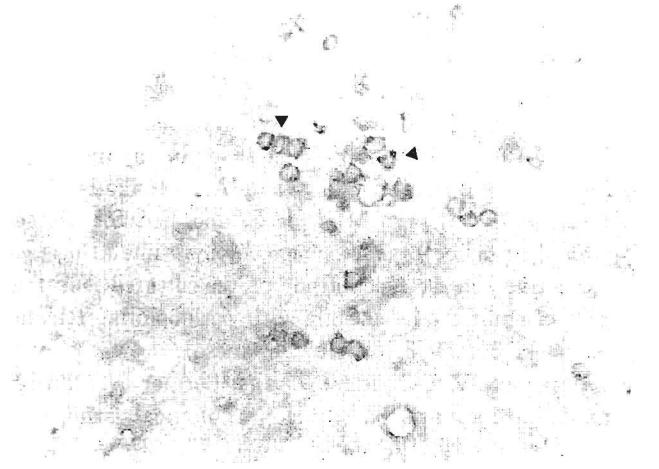

Fig. 5 The lymph node sinuses showed proliferation of histiocytes, which were positively stained with lysozyme (lysozyme stain, arrows, ×400).

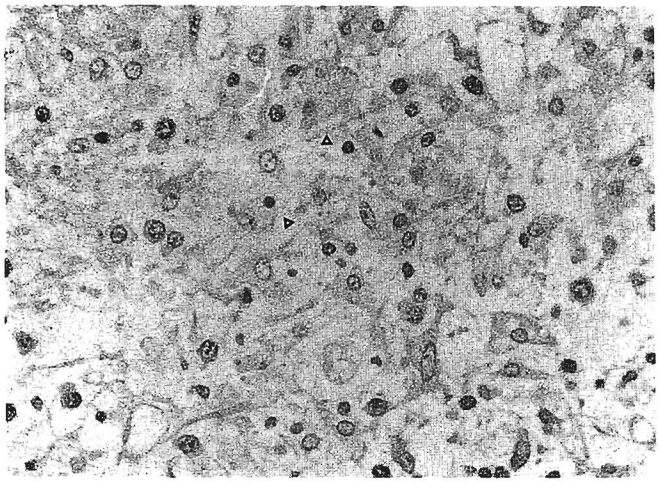

Fig.6 Higher magnification showing phagocytosis of red blood cells by histiocytes (arrows) (HE stain, ×400).

with nuclear atypia which were positively stained with UCHL-1 (Fig. 4). The lymph node sinuses showed proliferation of histiocytes with hemophagocytosis, which were positively stained with lysozyme and α 1-antichymotrypsin, but negatively stained with pan-T and pan-B cell marker (Fig. 5). The bone marrow specimen revealed proliferation of histiocytes with hemophagocytosis despite the hypocellularity of the other cellular elements of the bone marrow (Fig. 6). In the lung, features of bronchial pneumonia with scattered foci of bacterial colonies were observed.

DISCUSSION

The present patient followed an aggressive fatal course manifesting fulminant hepatitis and clinical features, such as, high fever, severe liver dysfunction, pancytopenia and DIC. All hepatitis virus markers and antibodies against other viruses which are sometimes responsible for liver cell damage were negative. In addition, autoimmunity, alcohol and drug abuse seemed unlikely to have caused the liver injury in this patient.

Initially, we assumed the pathogenesis of the present patient as follows; severe infection complicated with aplastic anemia causing DIC and microcirculation injury in the liver, leading to subsequent hepatic failure. Based on response to methylpredonisolone pulse therapy, it was suggested that aplastic anemia may be mediated by an immunopathological mechanism.

Although she died of sepsis as a terminal event of bacterial infection, the high fever noted in the early stage showed no response to antibiotic therapy. Furthermore, repeated blood cultures and endotoxin test were all negative. There were no significant elevation in the antibody titers of several viral markers. We therefore conclude that the high fever observed in the early stage may not have been due to infection.

Hemophagocytic syndrome is the most likely disorder compatible with the histological findings and clinical course in the present case. The syndrome is characterized by histopathological findings of proliferating histiocytes with hemophagocytosis, and clinical manifestations of fever, leukocytopenia, thrombocytopenia, liver dysfunction, hyperferritinemia[2] and coagulopathy. It is believed that either activated T-lymphocytes by virus or other kinds of infection or lymphoma cells produce cytokines, and consequently cause HPS[3-8].

In this case, as mentioned above, there was no evidence of virus or other kinds of infection. Although lymph node swelling was not noted clinically, the patient was diagnosed as having adult T-cell leukemia (ATL) in the early stage because of histological findings of T-cell lymphoma and elevation in serum HTLV-I antibody. From these findings, it is suggested that HPS occurred simultaneously with the onset of ATL, but the possibility of an unknown viral infection could not be discounted. Elevated

levels of tumor necrosis factor-α, interferon-γ and interleukin-1β were not observed in the present case. However, it has been reported that various cytokines other than the above mentioned ones are secreted in patients with ATL[9,10]. Therefore, it is possible that other cytokines were responsible for the occurrence of HPS in the present case. The histological liver cell damage observed was mild in spite of the severe clinical course. It is therefore conceivable that the mechanism of hepatic failure differed from that due to hepatitis viruses. Such differences between severe clinical course and hepatic histological findings has been previously reported in patients with HPS[1,11].

The administration of gabexate mesilate led to a decrease in serum levels of total bilirubin and HGF. It is reported that protease inhibitors such as gabexate mesilate have an inhibitory effect on inflammatory cytokines[12].

Finally, we surmise that hypercytokinemia was responsible for hepatic failure due to hepatic endothelial cell damage, and pancytopenia due to enhanced phagocytosis.

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