Hepatic Peripheral T-cell Lymphoma : A Spectrum of Liver Pathology and Clinical Correlation

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Abstract

Thirty-two patients with fever of unknown origin, weight loss, anemia, elevated serum levels of alkaline phosphatase and/or lactate dehydrogenase were evaluated. Histopathologic findings of the liver showed T-cell infiltration in the hepatic sinusoids and portal tracts. The cellular morphology varied from mature lymphocyte to malignant lymphoid cells. We divided the cases into four groups on the basis of cellular atypia. Group A and group B showed mature lymphoid cell infiltration, however, only group B had multiple large areas of hepatocellular necrosis. Group C showed atypical lymphoid cell infiltration. In group D, definite malignant lymphoid cell infiltrates were demonstrated. Groups B, C, and D patients had a very poor prognosis. All of them died despite chemotherapy. Group A patients had a better prognosis. Those who had chemotherapy achieved a complete remission. Progression to a higher group occurred in two of six patients with group B lesions and one of seven patients with group C lesions. The EBV-RNA genomes were found increasingly in the higher groups. This study supports the concept that these groups of disease represent a spectrum of peripheral T-cell proliferations.

Peripheral (post-thymic) T-cell lymphomas are less commonly found in Western countries than in Asia[1,2]. They exhibit considerable heterogeneity in morphology, immunology, and prognosis [3-9]. Currently, a generally accepted classification theme for T-cell lymphoma is unavailable. In April 1993, there was a meeting of the International Lymphoma Study Group in Berlin, Germany. They proposed the new classification for lymphoid neoplasms, entitled, "A Revised European-American Classification of Lymphoid Neoplasms, (REAL classification)" by using morphologic, immunologic, and genetic techniques[10,11]. T-cell and putative NK-cell neoplasms are classified separately to be a unique group. This group of lymphoid neoplasms is composed of 10 different types, e.g., mycosis fungoides/Sezary syndrome; angioimmunoblastic T-cell lymphoma (angioimmunoblastic lymphadenopathy with dysproteinemia, AILD); angiocentric lymphoma (angiocentric immunopro-

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liferative lesions, AIL); subcutaneus panniculitic T-cell lymphoma; and hepatosplenic gamma-delta T-cell lymphoma. Some of the so-called "malignant histiocytosis, (histiocytic medullary reticulosis)" have proved to be peripheral T-cell lymphoma by immunophenotyping studies[12-15].

Peripheral T-cell lymphomas and the so-called malignant histiocytosis can manifest with nodal and/or extranodal involvement[14-17]. The clinical findings include a prolonged intermittent fever, profound weight loss, lymphadenopathy, splenomegaly, jaundice, and skin lesions. The laboratory findings are anemia, pancytopenia, abnormal liver function tests, and coagulopathy. Hepatosplenic gamma-delta T-cell lymphoma also has similar clinical and laboratory findings[18-21].

Liver involvements in peripheral T-cell lymphoma are demonstrated by lymphoid cells infiltrated in the hepatic sinusoids and portal tracts [11,16-21]. The morphology of lymphoid cells vary from mature lymphocytes, atypical lymphoid cells, to malignant lymphoid cells. Hepatic sinusoidal lymphocytosis has been reported in patients with tropical splenomegaly syndrome[22,23], non-tropical idiopathic splenomegaly[24,25], Felty's syndrome[26], hairy cell leukemia[27], and intrahepatocellular erythrocyte inclusions with hepatic sinusoidal infiltrates and splenomegaly[28]. To our knowledge, there is no classification of liver pathology in patients with peripheral T-cell lymphoma. We describe thirty-two patients who presented with fever of unknown origin, hepatosplenomegaly, anemia, elevated serum alkaline phosphatase and/or lactate dehydrogenase, and hepatic sinusoidal lymphoid infiltrates. Some patients had peripheral T-cell lymphoma in other organs, e.g., lymph nodes, skin, head and neck region. We classify liver pathology into four groups depending on the morphology of lymphoid cells.

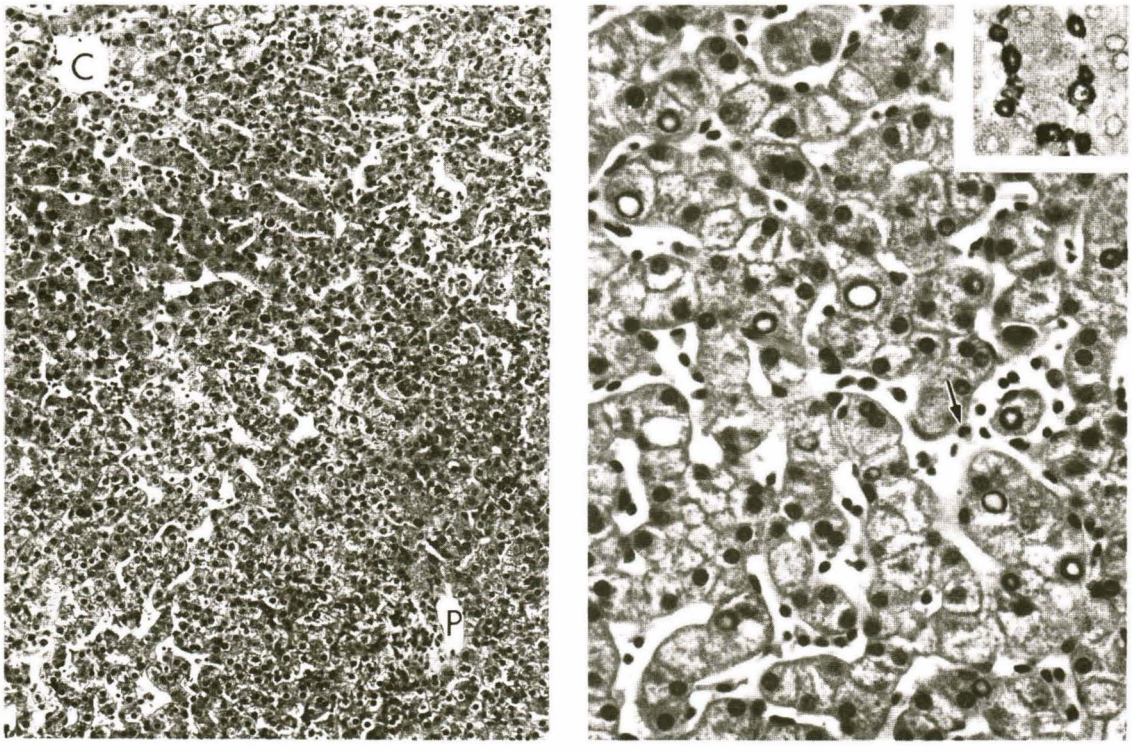

Fig. 1. Group A. Left, Low-power view of liver showing cellular infiltration of sinusoids, central vein region (C), and portal tract (P) (X100). Right, high power view showing mature lymphocytes and neutrophil (arrow) in the dilated sinusoids (X300). Inset, liver tissue stained by immunohistochemical technique reveals positive reaction for CD45R0 at the cell surface of lymphocytes (X300).

MATERIAL AND METHOD

This retrospective study was conducted in Songklanagarind University Hospital, Songkhla, Thailand, during the 7-year period of 1989 through 1995. The liver tissues from biopsy, necropsy, or both, were made available from thirty-two patients with a prolonged fever of unknown origin. These patients also had high serum levels of alkaline phosphatase and/or lactate dehydrogenase. Details of physical findings, laboratory findings, treatments, and the follow-up are summarized in Tables 1-4. The liver tissue sections were reviewed and were classified into 4 groups in order of severity; group A, group B, group C, and group D, with group A being the least severe.

Morphologic criteria

Group A. (Fig. 1)- The histopathology of liver tissue in this group revealed cellular infiltration in the sinusoids and portal tracts. The degree of infiltration varied from minimal to massive. Scattered areas of sinusoidal dilatation, pseudopeliotic pattern, were observed. The hepatocytes in these areas usually had a smaller size than the other areas. Most of the infiltrates were mature small or medium-sized lymphocytes. They had scant cytoplasm, small round or oval nuclei and some of these nuclei showed slight indentations. The other types of cellular infiltration which may be found were neutrophils, eosinophils, plasma cells, and monocytes. In some areas, the collections of lymphocytes and monocytes formed pseudogranulomas which were found. The sinusoidal infiltrate was more prominent in zones 1 and 2, and less prominent in zone 3 of the hepatic acinus. The Kupffer's cells were hypertrophic and showed minimal hemophagocytosis. The liver architectures were intact. Hepatocellular necrosis was usually absent except for a few cells. There was no large area of hepatocellular necrosis. Cholestasis in the liver tissue was minimal or absent.

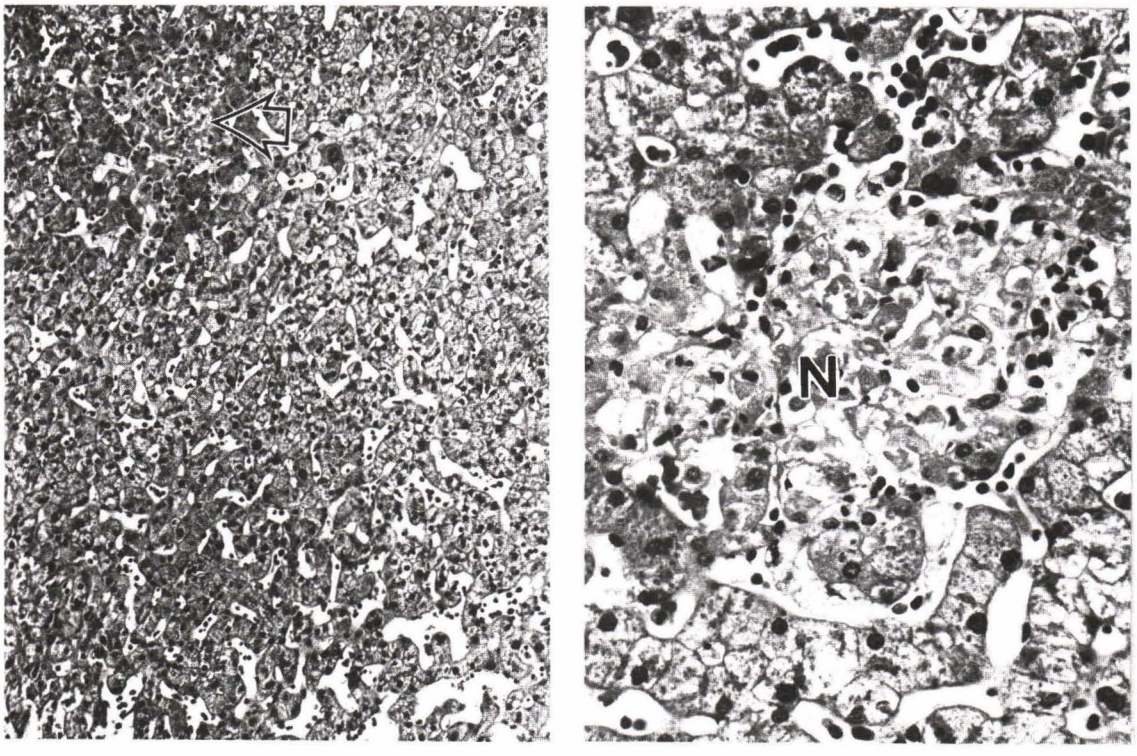

Fig. 2. Group B. Left, low-power view of liver showing cellular infiltration in the dilated sinusoids. There is an area of hepatocellular necrosis (arrow) (X100). Right, high power view showing the area of hepatocellular necrosis (N). The sinusoids are infiltrated with mature lymphocytes (X300).

Group B. (Fig. 2)- The histopathology of liver tissue in this group was similar to group A except for the presence of large areas of hepatocellular necrosis. The Kupffer's cells were hypertrophic and showed frequent hemophagocytosis. Cholestasis in liver tissue was more severe than in group A.

Group C. (Fig. 3)- Histopathology of liver tissue revealed scattered dilatation of hepatic sinusoids. Hepatocytes in these areas were atrophic. The cellular infiltration was more prominent in portal tracts than in the hepatic sinusoids. The lymphoid infiltrate was polymorphous. Some lymphocytes show cytologic atypia with features of immature bizzare large cells. The nuclei were round, cleaved, or cerebriform pattern. Occasional mitotic figures were seen. Lymphoid cells were admixed with a few neutrophils, plasma cells, and monocytes. The Kupffer's cells were hypertrophic and showed massive hemophagocytosis. Large areas of hepatocellular necrosis was usually present and cholestasis was usually severe.

Group D.- There was no problem in the diagnosis of non-Hodgkin's lymphoma in this group. Two types of histopathologic features were noted; the monomorphic pattern and the polymorphic pattern.

Monomorphic pattern (Fig. 4A)- The malignant lymphoid cells were the uniform medium-sized or large cells with frequent mitosis. The nuclei of these cells were round, cleaved, or cerebriform pattern. The malignant lymphoid cell infiltrates were mainly located in the portal tracts and some were seen in the dilated sinusoids. The hepatocytes showed marked atrophy. Multiple large areas of hepatocellular necrosis were observed throughout the liver tissue. The Kupffer's cells were hypertrophic and showed massive hemopha-

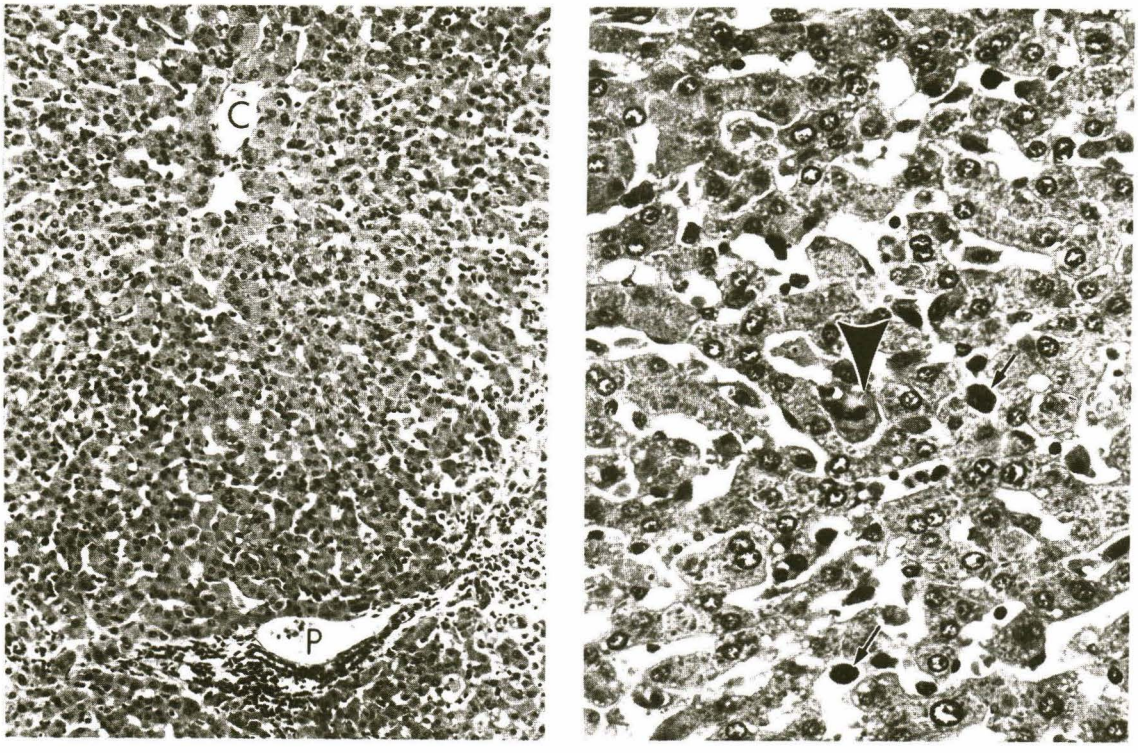

Fig. 3. Group C. Left, low-power view of liver showing cellular infiltration in the dilated sinusoids and portal tract (P), central vein region (C) (X100). Right, high power view showing polymorphous lymphoid infiltrates. Some lymphoid cells show cytologic atypia (arrows). The hepatocytes are atrophic. The Kupffer's cells are hypertrophic and show hemophagocytosis (arrowhead) (X300).

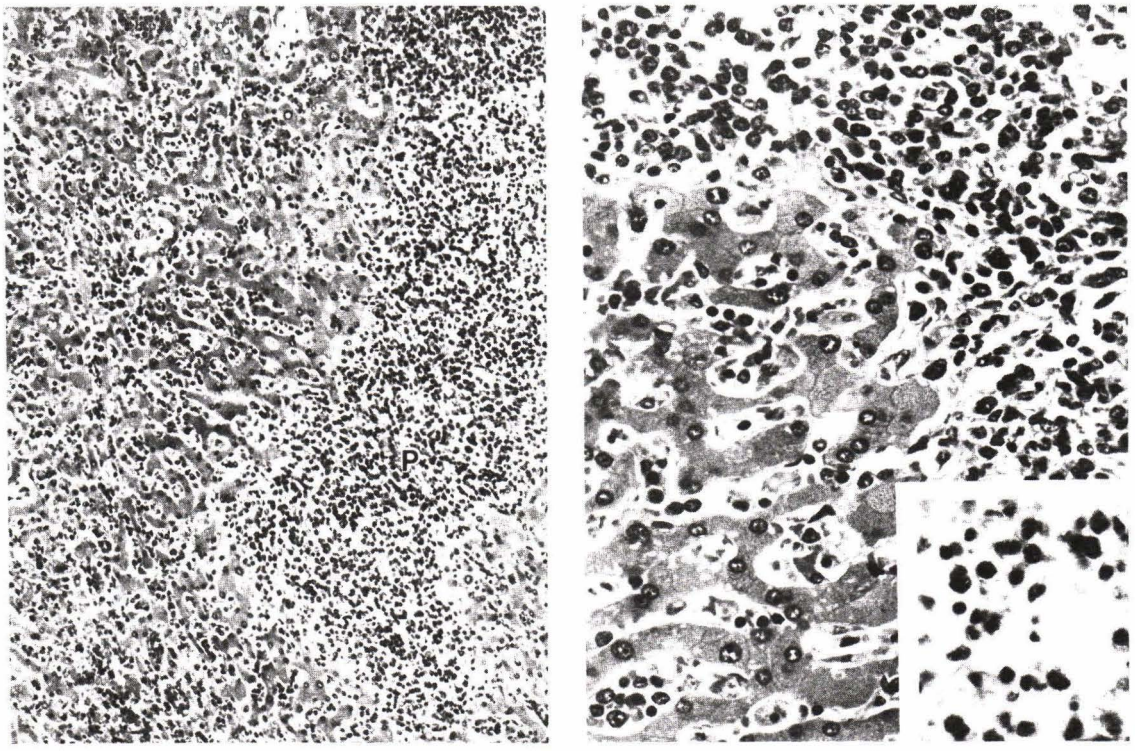

Fig. 4A. Group D, Monomorphic Pattern. Left, low-power view of liver showing malignant lymphoid cell infiltration in the sinusoids and portal tract (P) (X100). Right, high power view showing a uniform malignant lymphoid cells. The hepatocytes are marked atrophic. Inset, the *in situ* hybridization showing strongly EBV-RNA positive in the nuclei of malignant lymphoid cells (X300).

gocytosis. There was no hemophagocytosis by the malignant lymphoid cells.

Polymorphic pattern (Fig. 4B)- The neoplastic cell population included small irregular lymphoid cells, atypical cells, and large bizzare cells with prominent nucleoli. Some of these large cells were histologically similar to Reed-Sternberg's cells. The other features appeared to be the same as the monomorphic pattern.

Immunohistochemistry

Immunohistochemical stainings for leukocyte common antigen (LCA), CD20, CD45RO, CD30 and p53 protein of liver tissue from paraffin blocks were performed using the following antibodies : monoclonal mouse antihuman LCA (CD45) (Dako, Denmark, 1:100), monoclonal mouse antihuman CD20 (Dako, 1:100), monoclonal mouse antihuman CD45R0 (UCHL-1) (Dako, 1:100), monoclonal mouse antihuman CD30 (Ber-H2) (Dako, 1:50), p53 protein (CM1) (Novo Castra, Newcastle, 1:700), rabbit antimouse immunoglobulin (Dako, 1:50), and horseradish peroxidase-mouse antiperoxidase (Dako, 1:50). The staining procedure was performed as previously described[29,30].

In situ hybridization

In situ hybridization study for Epstein-Barr virus (EBV) genomes was performed on formalin-fixed, paraffin embedded tissue using the fluorescein-conjugated EBV (EBER) oligonucleotides, complementary to nuclear RNA portions of the EBER genes that are actively transcribed in latently infected cells. Briefly, tissue sections 5-microns were deparaffinized with xylene, rehydrated in graded water-ethanol solutions, and digested with proteinase K (3 mg/L in 0.05 M Tris/HCL, *p*H 7.6) for 30 minutes at 37°C. After dehy-

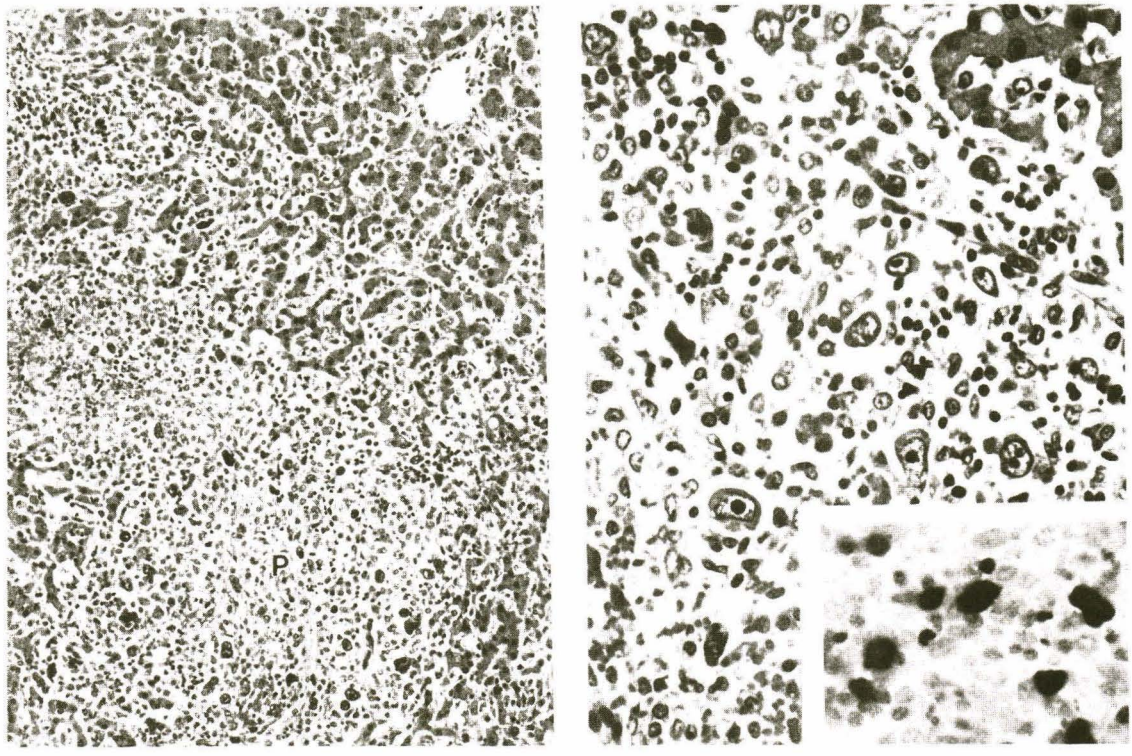

Fig. 4B. Group D, Polymorphic Pattern. Left, low-power view of liver showing malignant lymphoid cell infiltration in the sinusoids and portal tract (P) (X100). Right, high power view showing a polymorphous malignant lymphoid cell infiltrates. Some of these cells are large with prominent nucleoli (X300). Inset, the *in situ* hybridization showing EBV-RNA positive in the nuclei of the large-sized malignant cells (X300).

dration and air-drying, the fluorescein-conjugated (FITC) EBER oligonucleotide probes (Y 0017, Dako) were applied on the sections for 2 hours at 37°C. The following immunohistochemical detection system (K 046, Dako) was used : rabbit F(ab') anti-FITC/AP for 30 minutes and a solution containing 5-bromo-4-chloro-3-indolyphosphate (BCIP) and nitroblue tetrazolium (NBT) for 30-60 minutes. Then the slides were washed in running tap water and mounted in glycergel[31].

RESULTS

The patients were twenty-five men and seven women, age ranged from 17 years to 85 years. All of the patients had a prolonged fever which varied from one month to three months. The body temperature was up to 42°C. Thirteen patients had weight loss of more than 5 kilograms. Six patients had central nervous system symptoms.

The hemograms revealed anemia in all cases. The average hemoglobin was 8.7 g/dl (range 4.9-11.6 g/dl). Sixteen patients had leukopenia and sixteen patients had thrombocytopenia. Pancytopenia was found in 1 patient of group A, 3 patients of group B, 5 patients of group C, and 3 patients of group D. Atypical lymphocytes from peripheral blood was observed in twelve patients. Bone marrow aspirates and biopsies showed immature lymphoid cells; 5 of 8 cases in group A, 4 of 5 cases in group B, 5 of 6 cases in group C and 5 of 6 cases in group D.

The antibodies to HTLV-1 by particle agglutination tests were performed in 19 cases and all of them gave negative results. The anti-HIV tests were also negative in all of 20 cases. None of the patients had hypercalcemia. Serum proteins were in the normal range except for one patient who had polyclonal hypergammaglobulinemia.

Table 1. Clinical and laboratoric summary of group A.

Case	Age (yr)/sex	Presenting symptoms	Liver cm below RCM	Spleen cm below LCM	Lymph nodes diameter up to (cm)	Other findings	T.bili/D.bili (mg/dl)	SGOT IU/L	SGPT IU/L	ALP IU/L	LDH IU/L	Abnormal coagulo-grams	Chemo-therapy	Follow-up
1.	37/F*	Fever	3	0	Neck, 0.5	Maculopapular rash	1.0/0.4	630	210	1140	1190	No	No	Alive 2 yr
2.	69/M*	Fever, weight loss	0	0	Para aortic, 4.0	-	0.9/0.4	57	69	1350	670	No	Yes	Alive 2 yr
3.	23/F*	Fever, weight loss	3	12	Neck, 2.0	Lymph node, AILD	1.0/0.5	131	70	385	1065	Yes	Yes	Alive 4 yr
4.	54/F*	Fever	3	5	Groin, 1.0	Lymph node, AILD	0.6/0.1	34	10	573	1130	No	Yes	Alive 2 yr
5.	64/M*	Fever, weight loss	3	5	Neck, 0.5	-	1.1/0.6	18	36	819	385	Yes	Yes	Alive 10 mo
6.	33/F*	Fever, weight loss	3	3	Axilla, 0.5	Subcutaneus panniculitic T-cell lymphoma, B-cell lymphoma in lymph node	1.0/0.6	49	43	433	990	No	Yes	Alive 6 yr
7.	25/M*	Fever, arthralgia	0	0	No	-	2.4/1.8	39	42	572	360	No	No	Loss follow-up
8.	60/M**	Fever, weight loss	1	3	No	-	1.9/1.0	41	31	500	965	Yes	No	Died 12 d
9.	52/M**	Fever, confusion	5	0	No	-	2.5/1.4	187	95	2300	ND	Yes	No	Died 28 d
10.	68/M**	Fever, weight loss	3	10	Neck, 2.5	Lymph node, AILD	1.2/0.4	64	87	530	1170	Yes	No	Died 3 mo
11.	52/F**	Fever	0	0	No	Angiocentric T-cell lymphoma in kidney, uterus	ND	36	14	322	ND	Yes	No	Died 2.5 mo

ND = not done; SGOT = aspartate aminotransferase (normal, 0-35); SGPT = alanine aminotransferase (normal, 0-35): RCM = right costal margin; LCM = left costal margin; ALP = alkaline phosphatase (normal, 30-120); LDH = lactate dehydrogenase (normal, 230-460); AILD = angioimmunoblastic lymphadenopathy; * = liver tissue obtained by biopsy; ** = liver tissue obtained by necropsy; *** = liver tissues obtained by biopsy and necropsy.

Table 2. Clinical and laboratoric summary of group B.

Case	Age (yr)/sex	Presenting symptoms	Liver cm below RCM	Spleen cm below LCM	Lymph nodes diameter up to (cm)	Other findings	T.bili/D.bili (mg/dl)	SGOT IU/L	SGPT IU/L	ALP IU/L	LDH IU/L	Abnormal coagulo-grams	Chemo-therapy	Follow-up
1.	66/M**	Fever	5	0	No	-	3.9/1.8	164	99	251	ND	Yes	No	Died 16 d
2.	69/M**	Fever	3	0	No	Cutaneus T-cell lymphoma	0.3/0.1	12	5	700	473	Yes	No	Died 14 mo
3.	19/M**	Fever, weight loss	5	0	Neck, 1.0	-	2.9/1.9	810	281	721	4075	Yes	No	Died 48 d
4.	50/M**	Fever	7	3	Neck, 0.5	-	7.5/5.0	49	37	533	ND	Yes	No	Died 12 d
5.	35/M***	Fever	8	6	Neck, 1.0	-	10.1/4.9	348	64	1150	3650	Yes	No	Died 22 d
6.	83/M***	Fever, confusion	0	0	No	-	1.1/0.6	108	113	1020	556	Yes	No	Died 2 mo

ND = not done; SGOT = aspartate aminotransferase (normal, 0-35); SGPT = alanine aminotransferase (normal, 0-35): RCM = right costal margin; LCM = left costal margin; ALP = alkaline phosphatase (normal, 30-120); LDH = lactate dehydrogenase (normal, 230-460); * = liver tissue obtained by biopsy; ** = liver tissue obtained by necropsy; *** = liver tissues obtained by biopsy and necropsy.

Table 3. Clinical and laboratoric summary of group C.

Case	Age (yr)/sex	Presenting symptoms	Liver cm below RCM	Spleen cm below LCM	Lymph nodes diameter up to (cm)	Other findings	T.bili/D.bili (mg/dl)	SGOT IU/L	SGPT IU/L	ALP IU/L	LDH IU/L	Abnormal coagulo-grams	Chemo-therapy	Follow-up
1.	20/M**	Fever	3	6	No	-	6.6/3.9	1130	363	122	ND	Yes	No	Died 1 d
2.	17/M**	Fever	5	0	Neck, 1.0	-	14.4/8.0	563	117	435	ND	Yes	No	Died 2 d
3.	50/M***	Fever	2	2	No	-	17.3/12.4	616	143	953	ND	Yes	No	Died 7 d
4.	37/M*	Fever	5	5	Neck, groin, 0.5	-	2.1/1.0	298	610	855	2381	Yes	Yes	Died 3 mo
5.	48/F***	Fever, weight loss, paraplegia	5	0	No	-	6.7/3.9	302	107	1320	2600	Yes	Yes	Died 19 d
6.	25/M**	Fever, exopthalmos	3	0	No	Orbit, angiocentric T-cell lymphoma	17.9/13.8	893	644	257	1965	Yes	Yes	Died 2 mo
7.	62/M**	Fever, weight loss	3	0	Neck, 2.0	Lymph node, AILD	1.0/0.3	22	14	201	563	ND	No	Died 10 d

ND = not done; SGOT = aspartate aminotransferase (normal, 0-35); SGPT = alanine aminotransferase (normal, 0-35): RCM = right costal margin; LCM = left costal margin; ALP = alkaline phosphatase (normal, 30-120); LDH = lactate dehydrogenase (normal, 230-460); AILD = angioimmunoblastic lymphadenopathy; * = liver tissue obtained by biopsy; ** = liver tissue obtained by necropsy; *** = liver tissues obtained by biopsy and necropsy.

Table 4. Clinical and laboratoric summary of group D.

Case	Age (yr)/sex	Presenting symptoms	Liver cm below RCM	Spleen cm below LCM	Lymph nodes diameter up to (cm)	Other findings	T.bili/D.bili (mg/dl)	SGOT IU/L	SGPT IU/L	ALP IU/L	LDH IU/L	Abnormal coagulo-grams	Chemo-therapy	Follow-up
1.	40/M**	Fever, weight loss	0	0	Neck, 1.0	T-cell lymphoma in lymph node	2.4/1.5	306	229	1290	675	Yes	No	Died 30 d
2.	46/F**	Fever, epistaxis	0	0	No	Maxillary sinus, angiocentric T-cell lymphoma	0.5/0.2	67	27	ND	1290	Yes	Yes	Died 36 d
3.	29/M**	Fever, confusion	0	0	Neck, 2.0	T-cell lymphoma in lymph node, pleura	1.2/0.5	481	121	978	1140	ND	Yes	Died 5 mo
4.	85/M**	Fever, confusion	3	3	Neck, 1.0	T-cell lymphoma in lymph node	0.9/0.4	94	24	342	876	ND	Yes	Died 3 mo
5.	33/M*	Fever, weight loss	3	5	No	-	9.1/5.4	224	154	261	3820	Yes	Yes	Died 1 mo
6.	79/M***	Fever	7	5	No	-	7.3/5.0	112	44	1200	ND	Yes	No	Died 12 d
7.	67/M**	Fever	3	6	No	-	1.4/0.8	174	18	1070	ND	Yes	No	Died 6 d
8.	43/M**	Fever, weight loss	7	5	Neck, groin, 3.0 axilla, 10.0	-	5.4/4.0	99	47	702	1070	ND	No	Died 4 d

ND = not done; SGOT = aspartate aminotransferase (normal, 0-35); SGPT = alanine aminotransferase (normal, 0-35): RCM = right costal margin; LCM = left costal margin; ALP = alkaline phosphatase (normal, 30-120); LDH = lactate dehydrogenase (normal, 230-460); AILD = angioimmunoblastic lymphadenopathy; * = liver tissue obtained by biopsy; ** = liver tissue obtained by necropsy; *** = liver tissues obtained by biopsy and necropsy.

The pertinent findings of these patients were the high serum levels of alkaline phosphatase and/or lactate dehydrogenase.

Other laboratory results, e.g., the initial blood cultures, serological tests for salmonellosis, melioidosis, leptospirosis, scrub and murine typhus, Epstein-Barr virus, and cytomegalovirus which were performed in some patients were negative. There was no seasonal predilection. The causes of death in these patients were hepatic failure, metabolic acidosis, adult respiratory distress syndrome, abnormal bleeding, and sepsis. There was no infection-associated hemophagocytic syndrome in an autopsy case.

Group A. (Table 1)

There were six male and five female patients ranging in age from 23 to 69 years. Six patients had hepatosplenomegaly and two patients had only hepatomegaly. Seven patients had lymphadenopathy ranging in size from 0.5 to 4.0 cm. Three of these 11 patients were diagnosed to have angioimmunoblastic T-cell lymphoma (AILD). Case no. 1 had mycosis fungoides. Interestingly, case no. 6 had subcutaneus panniculitic T-cell lymphoma in the skin of the leg and B-cell non-Hodgkin's lymphoma in the axillary lymph node. An autopsy was performed on case no. 9 and showed angiocentric (T-cell) lymphoma of the visceral organs. Most of these patients had elevated serum levels of alkaline phosphatase and lactate dehydrogenase. Coagulopathy was found in six patients. Five patients received multiagent chemotherapy. All of them achieved a complete remission, alive without disease from 10 months to 6 years. Seven patients did not have chemotherapy; in one patient (case no. 1), the disease spontaneously regressed; one patient was lost to follow-up; and four patients died within 12 days to 3 months.

Group B (Table 2)

All of the six patients in this group were males ranging in age from 19 to 83 years. Two patients had hepatosplenomegaly and three had only hepatomegaly. Three patients had lymphadenopathy ranging in size from 0.5 to 1.0 cm. Case no. 2 had cutaneus T-cell lymphoma. Coagulopathy was observed in all of the patients. Two patients (case no. 5 and no. 6) showed the progression to group C on the later liver necropsied tissues. None of them received chemotherapy and all of them died within 12 days to 14 months.

Group C (Table 3)

This group composed of seven patients, 6 males, 1 female, ranging in age from 17 to 62 years. Three patients had hepatosplenomegaly and four patients had only hepatomegaly. Case no. 6 had orbital angiocentric (T-cell) lymphoma and case no. 7 had angioimmunoblastic T-cell lymphoma (AILD). One patient (case no. 5) showed the progression to group D on the later liver necropsied tissue. All of them died within 1 day to 3 months despite the use of chemotherapy in some cases.

Group D (Table 4)

This group composed of 7 males and 1 female ranging in age from 29 to 85 years. Five patients had hepatosplenomegaly. Three patients (case no.1, 3, 4) had peripheral T-cell lymphoma in lymph nodes. Case no. 2 had angiocentric (T-cell) lymphoma in maxillary sinuses. Liver tissue in case no. 1 had histopathologic features of polymorphic pattern and the rest showed monomorphic pattern. All of the patients died within 4 days to 5 months.

Ultrastructural appearance

Ultrastructural variability of lymphoid cells from hepatic sinusoids are demonstrated in Fig. 5. Lymphocytes from group A and group B (Fig. 5a, 5b) showed round to oval contour nuclei; no sharply angled nuclear invaginations. Some lymphocytes showed slight indentation of the nuclear membrane. The cytoplasm was scant; few cellular organelles were seen. There was no cytoplasmic granule. Fig. 5c showed atypical lymphoid cell from group C. This cell had an irregular, sharply angled nuclear invaginations. The cytoplasm was abundant with more cellular organelles. Fig. 5d showed a large lymphoid cell with abundant cytoplasm from group D. There was no cytoplasmic granule. The nucleus showed marked angulations, lobulated appearance, and had the prominent nucleolus.

Electron microscopy of hepatocytes displayed many bleblike structures that contained cytoplasmic content at the sinusoidal surface of the cell. Stacks of rough endoplasmic reticula were seen and some were dilated (Fig. 6).

Immunohistochemistry and *in situ* hybridization

Results of immunohistochemistry and *in situ* hybridization for EBV-RNA genomes are

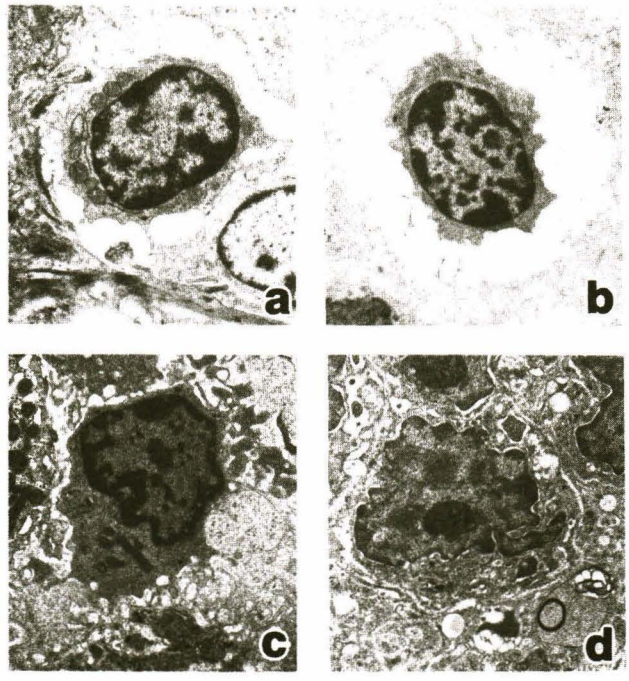

Fig. 5. Ultrastructure of lymphocytes which are infiltrated in the hepatic sinusoid. "a" is a lymphocyte from group A patient. "b" is a lymphocyte from group B patient. "c" is a lymphocyte from group C patient. "d" is a lymphocyte from group D patient (X4000).

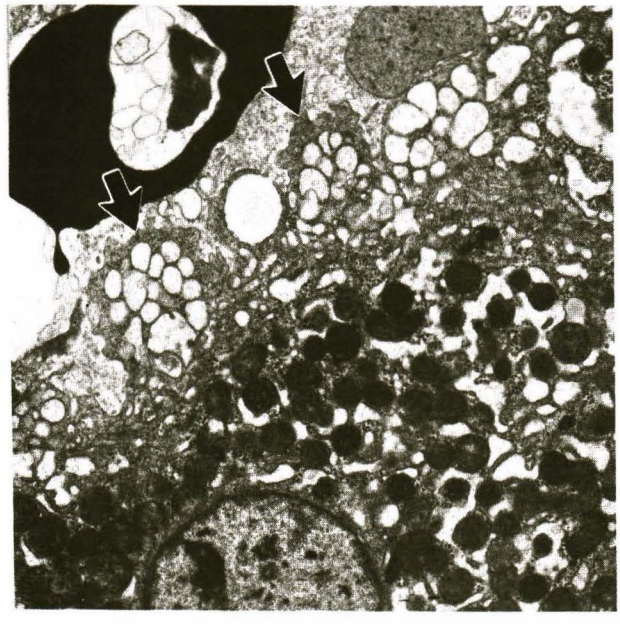

Fig. 6. Electron microscopy of a hepatocyte shows bleblike structures (arrows) at the sinusoidal surface (X6000).

Table 5. Immunohistochemical staining and *in situ* hybridization for Epstein-Barr virus.

Group/cases	LCA	CD 45RO positivity	CD 20 positivity	CD 45RO+CD20 positivity	CD 30 and p53 positivity	EBV *in situ* hybridization positivity
A/11	11/11	11/11	0/11	0/11	0/11	0/11
B/6	6/6	6/6	0/6	0/6	0/6	1/5
C/7	7/7	7/7	0/7	0/7	0/7	4/7
D/8	8/8	5/8	0/8	3/8	0/8	5/8

summarized in Table 5. All of the lymphoid cells in the livers were LCA-positive. CD45R0 (T-cell antigen) were positive in all cases except three patients from group D which gave expression in both CD45R0 and CD20 (B-cell antigen) in the same malignant lymphoid cells. Stainings for CD30 and p53 protein gave negative results.

The presence of EBV-RNA genomes was detected in 10 of the 31 cases; none in group A, 1 of 5 cases in group B, 4 of 7 cases in group C, and 5 of 8 cases in group D.

DISCUSSION

The Revised European-American Lymphoma Classification (1994) has classified peripheral T-cell lymphomas into ten different types [10,11]. From our studied patients, we believe that some of these types, such as, mycosis fungoides/ Sezary syndrome; peripheral T-cell lymphomas, unspecified; angioimmunoblastic T-cell lymphoma; and angiocentric lymphoma are the same disease entity with different manifestations. As it begins with a localized disease, and then progresses to a systemic disease. Diseases in the liver and bone marrow are considered to be a systemic involvement.

Adult T-cell leukemia/lymphoma (ATLL), which is a type of peripheral T-cell lymphoma, has been reported from south-west Japan and the West Indies[32,33]. This type of malignancy is related to human retrovirus HTLV-1 infection[33,34]. However, only a small minority (less than 4 per cent) of HTLV-1 seropositive patients develop ATLL, and then only after a prolonged latent period[35]. From clinical, serological and pathological findings, none of our patients was considered to have ATLL, nor CD30-positive anaplastic large cell lymphoma which is another type of peripheral T-cell lymphoma[36].

This group of patients had clinical signs and symptoms similar to the previously described as so-called "malignant histiocytosis"[16]. These included fever, weight loss, weakness and malaise, jaundice, lymphadenopathy and skin lesions. Laboratory investigations revealed anemia, pancytopenia, abnormal coagulograms, high serum levels of alkaline phosphatase and lactate dehydrogenase. Histopathology of liver tissue displayed infiltration of lymphoid cells in hepatic sinusoids and portal tracts. The morphologic spectrum of lymphoid cells varied from benign mature cells to malignant cells. We classified liver pathology into four groups. Group A composed of mature lymphoid cells, and group D composed of malignant lymphoid cells. This corresponds to the classification of angiocentric lymphoma (angiocentric immunoproliferative lesion)[37]. Because of the wide morphologic spectrum of the T-cell infiltrates, we prefer to call this group of diseases **"Peripheral T-cell Proliferative Diseases"**.

The histopathological changes of liver tissue in group A and group B may be difficult for interpretation. The clues for this are the presence of T-cell lymphocytes or mixed cells in the dilated hepatic sinusoids; in combination with clinical signs of fever, weight loss, anemia; and laboratory results showing elevated serum alkaline phosphatase and/ or lactate dehydrogenase. In some cases, the concomittance of peripheral T-cell lymphoma in other organs may be found. Electron microscopy of hepatocytes displayed bleblike structures at the sinusoidal surface of hepatocytes. We believe that the damage of hepatic cell sinusoidal membrane may lead to an elevation of alkaline phosphatase in the serum[38].

Groups B, C, and D patients had a poor prognosis. All of them died in a short period of time despite receiving multidrug chemotherapy.

Group A patients had a better prognosis. Chemotherapy is effective and some of them were cured of the disease. In suspected patients, liver biopsy and bone marrow examination are helpful for the diagnosis and to classify the severity of the disease.

In peripheral T-cell lymphomas, the positive cases for EBV-RNA genomes in malignant cells ranged from 36 per cent to 100 per cent[39-43]. The presence of viral genomes correlates with a poor prognosis[39]. In our patients, we did not find EBV-RNA genomes in group A. We found 20 per cent in group B, 57 per cent in group C, and 62 per cent in group D. The pathogenesis of peripheral T-cell proliferative diseases is unclear. We believe that Epstein-Barr virus infection plays a role in the pathogenesis.

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เฮปาติค เพอริเฟอรัล ที-เซลล์ ลิมโฟมา : ลักษณะทางจุลพยาธิวิทยาของตับและอาการทางคลินิก

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คณะผู้รายงานได้ศึกษาผู้ป่วย จำนวน 32 ราย ที่มีไข้โดยไม่ทราบสาเหตุ มีน้ำหนักตัวลดลง ซีด และมีการเพิ่มขึ้นของเอ็นซัยม์ alkaline phosphatase และ/หรือ lactate dehydrogenase ในเลือด ผู้ป่วยทุกรายได้รับการตรวจทางจุลพยาธิวิทยาของตับ ผลการตรวจพบว่ามีการ infiltrate ของกลุ่ม T-cell lymphocyte เข้าไปใน sinusoid ที่ขยายกว้างและเข้าไปในบริเวณ portal tract ของตับ, lymphocyte มีลักษณะของเซลล์ที่แตกต่างกัน ตั้งแต่เป็น lymphocyte ที่มีขนาดรูปร่างปกติ ไปจนถึงเซลล์ที่มีลักษณะเป็นมะเร็งอย่างชัดเจน คณะผู้รายงานได้แบ่งลักษณะทางจุลพยาธิวิทยาออกเป็น 4 กลุ่มตามลักษณะของ T-cell lymphocyte, กลุ่ม A และกลุ่ม B พบว่า lymphocyte มีลักษณะเป็นเซลล์ปกติ เฉพาะกลุ่ม B พบว่ามีการเน่าสลายของเซลล์ตับเป็นบริเวณกว้าง กลุ่ม C พบว่า lymphocyte มีลักษณะ atypia, ส่วนกลุ่ม D พบว่า lymphocyte มีลักษณะเป็นเซลล์มะเร็งชัดเจน จากลักษณะทางจุลพยาธิวิทยา กลุ่ม A มีความรุนแรงน้อยที่สุด และกลุ่ม D มีความรุนแรงมากที่สุด

การติดตามผู้ป่วย พบว่ากลุ่ม B, C และ D มีการพยากรณ์โรคไม่ดี ผู้ป่วยทุกรายเสียชีวิตในเวลาอันสั้น ถึงแม้จะได้รับการรักษาโดยเคมีบำบัด กลุ่ม A มีการพยากรณ์โรคที่ดีกว่า ผู้ป่วยที่ได้รับการรักษาโดยเคมีบำบัดก็จะหายจากโรค ส่วนผู้ป่วยที่ไม่ได้รับการรักษามักเสียชีวิตในเวลาอันสั้น อัตราการพบยีน (RNA) ของ Epstein-Barr virus ใน T-cell lymphocyte ที่อยู่ในตับมีมากขึ้นตามลำดับจากกลุ่ม B ถึงกลุ่ม D

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