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メタデータ	<p>言語: English</p> <p>出版者: Springer</p> <p>公開日: 2013-07-30</p> <p>キーワード (Ja):</p> <p>キーワード (En): peripheral T-cell lymphoma, acute liver failure, hemophagocytic syndrome</p> <p>作成者: Konno, Naoki, Takahashi, Atsushi, Watanabe, Kenya, Katsushima, Fumiko, Monoe, Kyoko, Kanno, Yukiko, Saito, Hironobu, Abe, Kazumichi, Ohira, Hiromasa</p> <p>メールアドレス:</p> <p>所属:</p>
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## **A case of peripheral T-cell lymphoma presenting with acute liver failure**

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## **Abstract**

A 68-year-old woman was evaluated by her primary physician for swelling and pain in the right neck. Treatment with antibiotics failed to achieve any improvement. Two weeks later, she was hospitalized to the gastroenterology service because of liver dysfunction and pneumonia. Disseminated intravascular coagulation (DIC) was diagnosed, and protease inhibitor and steroid pulse therapy were started. She was transferred to our department for further evaluation the following day. Bone marrow examination revealed hemophagocytosis and infiltration of CD3-positive cells. Multiple masses were identified in the liver. Her prothrombin time was 35.7% of the standard value 17 days from disease onset, despite improvement of DIC. She was diagnosed with acute liver failure based on the Japanese diagnostic criteria. Her general condition worsened quickly, which prevented use of chemotherapy, and she died after a total course of 19 days. Autopsy revealed atypical lymphocytes in the liver. The diagnosis was peripheral T-cell lymphoma.

Key words: peripheral T-cell lymphoma, acute liver failure, hemophagocytic syndrome

## **Introduction**

Acute liver failure is caused by many etiologies including malignant lymphoma. Peripheral T-cell lymphoma of unspecified type (PTCL-U) is a rare disorder that accounts for about 7% of all malignant lymphomas.<sup>1</sup> PTCL-U carries a poor prognosis, with a 1-year survival rate of 44%.<sup>2</sup> Affected organs include bone marrow in 30% of cases and liver in 12.9%.<sup>2</sup> We report a case of a patient with PTCL-U who presented with swollen cervical lymph nodes, followed by a rapidly declining course, including hemophagocytic syndrome (HPS) and acute liver failure.

## **Case**

This 68-year-old woman was diagnosed with depression and hypertension at age 66 and was receiving treatment for these conditions. She noticed right cervical lymph node swelling and pain and 2 days later was evaluated by her primary physician. Treatment with cefditoren pivoxil failed to achieve any improvement. Two weeks later, computed tomography (CT) demonstrated pneumonia. Blood tests revealed severe hepatic dysfunction: aspartate aminotransferase (AST) of 5530 IU/L (normal, 10-35 IU/L), alanine aminotransferase (ALT) of 2660 IU/L (normal, 12-33 IU/L), total bilirubin (TB) of 7.8 mg/dL (normal, <1.1 mg/dL) and prothrombin time (PT) of 40.1% (normal, 70-125%). The patient was hospitalized on the gastroenterology ward.

Disseminated intravascular coagulation (DIC) was diagnosed, and protease inhibitor and steroid pulse therapy was started with addition of 8 units of fresh frozen plasma (FFP). On the following day, she was transferred to our department for further evaluation. Laboratory tests on admission to our service showed abnormalities including coagulopathy and abnormal liver function by peripheral blood and biochemical tests

(Table 1)

Chest radiograph showed bilateral infiltrates. CT revealed bilateral cervical lymphadenopathy, multiple nodules in the liver with poor contrast effect, and splenomegaly (Fig. 1). Bone marrow examination showed hemophagocytosis and infiltration of CD3-positive cells (Fig. 2A, B). Treatment with thrombomodulin, FFP and plasma exchange proved ineffective. PT was elongated to 35.2 on hospital day 3 and the patient died on hospital day 4 (Fig. 3). On autopsy, the liver showed hepatocellular necrosis and infiltration of CD3-positive malignant cells in the lobular and portal areas (Fig. 4A). The malignant cells were medium-sized lymphoid cells with round hyperchromatic nuclei and were positive for granzyme B, but negative for TIA-1 (Fig. 4B, C). Based on clinical and histological findings, the diagnosis was unspecified PTCL (PTCL-U).

## Discussion

PTCL-U accounts for about 7% of malignant lymphomas and carries a poor prognosis, with a 1-year survival rate of 44%.<sup>1-2</sup> According to the Ann Arbor classification, stages III and IV account for 76% of cases. As in our patient, most cases are diagnosed at an advanced stage, with invasion most often to the bone marrow (30.6%), spleen (24.6%), and liver (12.9%).<sup>2</sup> When malignant lymphomas form tumors in liver parenchyma, the margins are well defined.<sup>3</sup> In primary cases, solitary tumors often form, whereas multiple tumors and diffuse infiltration are seen in secondary invasion.<sup>4</sup> Contrast CT usually shows homogeneous low-density areas, and based on imaging findings, secondary invasion by malignant lymphoma was also suspected in our patient.

In this patient, based on lymph node enlargement and elevated lactate dehydrogenase (LDH) and ferritin levels, malignant lymphoma was suspected at the time of hospital admission, and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy was considered. However, the patient was already in poor general condition, with a rapidly declining clinical course, so this treatment could not be administered. In primary hepatic malignant lymphoma, the diagnosis is even more difficult than in our case, and taking a patient's general condition into consideration, urgent liver biopsy is important for diagnosis and treatment.<sup>5-11</sup> Malignant lymphoma, either hepatic primary or secondary, must be considered as a cause of acute liver failure.

Recently, the definition and diagnostic criteria for acute liver failure were established for Japanese patients.<sup>12</sup> Based on these criteria, patients showing prothrombin time values of 40% or less of the standard value or international normalized ratio (INR) of 1.5 or more, caused by severe liver damage, within 8 weeks of onset of symptoms are diagnosed as having acute liver failure. In addition, the causes of acute liver failure are classified into 9 categories. This patient had a PT value of 35.2% of the standard value 17 days from disease onset. As such, the patient was diagnosed with acute liver failure due to circulatory failure and hepatic infiltration of malignant lymphoma.

Our patient had DIC on admission and we cannot rule out the possibility that PT had been elongated by DIC. However, serum fibrin degradation products (FDP) were improved from 43.2 to 29.6 mg/dL, in spite of deterioration of PT and TB. According to the Child-Pugh scoring system, the patient's score changed from 9 to 13, indicating development of liver failure despite improvement of DIC. Therefore, it is reasonable to conclude that PT elongation was caused by liver failure rather than DIC.

Mechanisms of liver injury due to malignant lymphomas include: liver injury due to

the tumor cells themselves; liver injury due to ischemia, endotoxemia, or DIC associated with tumor cell invasion; and liver injury due to hemophagocytic syndrome (HPS), a complication of malignant lymphoma.<sup>13-16</sup> Rowbotham et al. reported a 0.45% incidence of acute liver failure associated with malignant lymphoma,<sup>5</sup> and onset of lymphoma in association with acute hepatitis has also been reported.<sup>5-11</sup>

In our patient, findings of tumor cell invasion in hepatic tissue suggested liver injury by the tumor cells, while findings of hemophagocytosis on bone marrow examination and high ferritin levels suggested that the liver injury was also related to HPS. Malignant lymphoma is a cause of HPS, and the prognosis of malignant lymphoma associated with HPS is poor. Among cases of HPS related to malignant T-cell lymphomas, 79% are associated with PTCL-U.<sup>17-18</sup> Hino et al. also reported a case of malignant T-cell lymphoma with HPS, which like our case also presented with liver failure. That patient died 1 week after admission.<sup>6</sup> Hepatosplenic gamma/delta T-cell lymphoma also has a poor prognosis, with similar symptoms and clinical course to those seen in our patient.<sup>19</sup> Our patient had cervical lymph node swelling. In addition, malignant cells had infiltrated mostly in the portal areas on liver examination at autopsy and were TIA-1 negative. These findings led to the diagnosis of PTCL-U.

Four prognostic factors in PTCL-U are age ( $\geq 60$  years), performance status ( $\geq 2$ ), elevated LDH levels, and bone marrow involvement. In contrast to a 1-year survival rate of 92% in patients without any of the above factors, the 1-year survival rate is only 40% in patients with all of the above factors.<sup>2</sup> In cases like ours, with HPS and acute liver failure, survival is unlikely.<sup>6,7</sup> However, Schmitz et al. recently proposed COHP plus etoposide (CHOEP) therapy as a novel treatment strategy for T-cell lymphoma.<sup>20</sup> In conclusion, we should understand the differences of clinical course by subtypes of

lymphoma. Careful evaluation and early treatment are therefore important.

## References

- 1) The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. Lymphoma Study Group of Japanese Pathologists. *Pathol Int* 50: 696-702, 2000.
- 2) Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. *Blood* 103: 2474-2479, 2004.
- 3) Maher MM, McDermott SR, Fenlon HM, Conroy D, O'Keane JC, Carney DN, et al. Imaging of primary non-Hodgkin's lymphoma of the liver. *Clin Radiol* 56: 295-301, 2001.
- 4) Gazelle GS, Lee MJ, Hahn PF, Goldberg MA, Rafaat N, Mueller PR. US, CT, and MRI of primary and secondary liver lymphoma. *J Comput Assist Tomogr* 18: 412-415, 1994.
- 5) Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut* 42: 576-580, 1998.
- 6) Hino T, Sata M, Arima N, Nouno R, Kumashiro R, Koga Y, et al. A case of malignant lymphoma with hemophagocytic syndrome presenting as hepatic failure. *Kurume Med J* 44: 53-60, 1997.
- 7) Kusano H, Higaki K, Kondo R, Sakai T, Kage M, Oshima K, et al. Hepatosplenic T-cell lymphoma presenting as untreatable hepatic failure and hemophagocytic syndrome. *Kanzo* 51: 28-34, 2010.
- 8) Saló J, Nomdedeu B, Bruguera M, Ordi J, Ginès P, Castells A, et al. Acute liver

- failure due to non-Hodgkin's lymphoma. *Am J Gastroenterol* 88: 774-776, 1993.
- 9) Thompson DR, Faust TW, Stone MJ, Polter DE. Hepatic failure as the presenting manifestation of malignant lymphoma. *Clin Lymphoma* 2: 123-128, 2001.
- 10) Haider FS, Smith R, Khan S. Primary hepatic lymphoma presenting as fulminant hepatic failure with hyperferritinemia: a case report. *J Med Case Reports* 2:279, 2008.
- 11) Morali GA, Rozenmann E, Ashkenazi J, Munter G, Braverman DZ. Acute liver failure as the sole manifestation of relapsing non-Hodgkin's lymphoma. *Eur J Gastroenterol Hepatol* 13: 1241-1243, 2001.
- 12) Mochida S, Takikawa Y, Nakayama N, Oketani M, Naiki T, Yamagishi Y, et al. The definition and diagnostic criteria for 'acute liver failure' in Japan. *Kanzo* 52: 393-398, 2011
- 13) Roos E, Dingemans KP, van de Pavert IV, van den Bergh-Weerman M. Invasion of lymphosarcoma cells into the perfused mouse liver. *J Natl Cancer Inst* 58: 399-407, 1977.
- 14) Jaffe ES, Costa J, Fauci AS, Cossman J, Tsokos M. Malignant lymphoma and erythrophagocytosis simulating malignant histiocytosis. *Am J Med* 75: 741-749, 1983.
- 15) Zafrani ES, Leclercq B, Vernant JP, Pinaudeau Y, Chomette G, Dhumeaux D. Massive blastic infiltration of the liver: a cause of fulminant hepatic failure. *Hepatology* 3: 428-432, 1983.
- 16) Falini B, Pileri S, De Solas I, Martelli MF, Mason DY, Delsol G, et al. Peripheral T-cell lymphoma associated with hemophagocytic syndrome. *Blood* 75: 434-444, 1990.
- 17) Tong H, Ren Y, Liu H, Xiao F, Mai W, Meng H, et al. Clinical characteristics of T-cell lymphoma associated with hemophagocytic syndrome: comparison of T-cell

lymphoma with and without hemophagocytic syndrome. *Leuk Lymphoma* 49: 81-87, 2008.

18) Han AR, Lee HR, Park BB, Hwang IG, Park S, Lee SC, et al.

Lymphoma-associated hemophagocytic syndrome: clinical features and treatment outcome. *Ann Hematol* 86: 493-498, 2007.

19) Belhadj K, Reyes F, Farcet JP, Tilly H, Bastard C, Angonin R, et al. Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood* 102: 4261-4269, 2003

20) Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood*. 116:3418-25, 2010

## **Figure Legends**

### **Figure 1**

Abdominal contrast CT showed multiple masses in the liver with poor contrast effect and splenomegaly.

### **Figure 2**

Microscopic findings of bone marrow aspiration demonstrate hemophagocytosis of red blood cells (A, magnification,  $\times 400$ , Giemsa staining) and diffuse infiltration of CD3-positive malignant cells (B, magnification,  $\times 200$ , Immunohistochemical staining for CD3).

### **Figure 3**

Summary of the patient's clinical course. mPSL, methylprednisolone; CTRX, ceftriaxone; MEPM, meropenem; FFP, fresh frozen plasma.

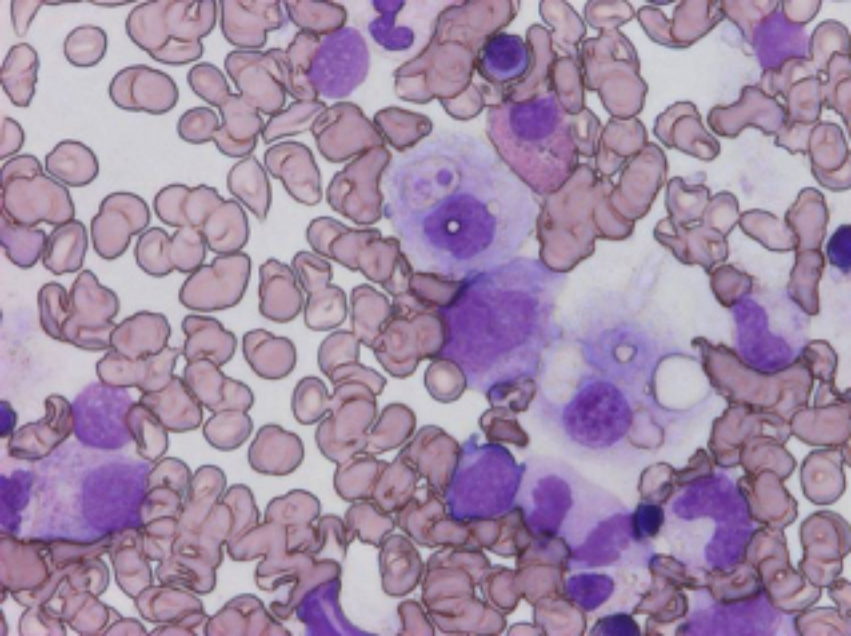
### **Figure 4**

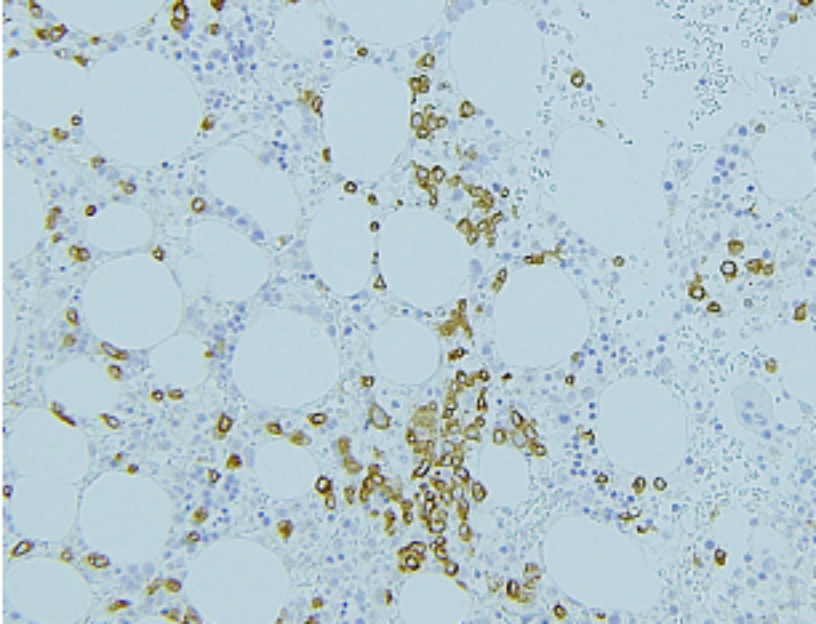
Malignant cell infiltrates in the portal area and hepatic necrosis on liver biopsy specimen at autopsy (A, magnification  $\times 100$ , hematoxylin and eosin staining). Infiltrated malignant cells in the portal area are positive for CD3 and granzyme B (B, magnification,  $\times 100$ , immunohistochemical staining for CD3; C, magnification,  $\times 400$ , immunohistochemical staining for granzyme B).

Table 1

blood count			biochemistry			BUN	41	mg/dL
WBC	3700	/ $\mu$ L	Alb	2.9	g/dL	Crea	2.15	mg/dL
RBC	$380 \times 10^4$	/ $\mu$ L	AST	4561	IU/L	CRP	4.81	mg/dL
Hb	11.3	g/dL	ALT	2113	IU/L	NH3	68	$\mu$ g/dL
PLT	$7.1 \times 10^4$	/ $\mu$ L	LDH	2698	IU/L	ferritin	71400	ng/mL
coagulation			ALP	592	IU/L	sIL-2R	43000	U/mL
PT	50.7	%	GTP	253	IU/L	Virus marker		
APTT	48.7	sec	TB	10.2	mg/dL	HBsAg	-	
FDP	43.2	$\mu$ g/dL	DB	8.4	mg/dL	HCVAb	-	







# Figure 3

