

[CASE REPORT]

Acute Liver Injury Due to T-cell Infiltration into the Liver as an Initial Clinical Finding of Adult T-cell Leukemia/Lymphoma

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Abstract:

Acute liver injury (ALI) has been rarely reported as a clinical finding of adult T-cell leukemia/lymphoma (ATLL). A 74-year-old Japanese female patient who was histologically diagnosed as having autoimmune hepatitis (AIH) one year earlier, showed elevations in her aminotransferase and total bilirubin levels, and this was considered to be an exacerbation of AIH. Liver biopsy revealed interface hepatitis. Because atypical lymphocytes and human T-cell leukemia virus 1 immunoglobulin G antibody were positive, the patient was diagnosed to have ATLL. The biopsy revealed CD4+ and CD8+, but not CD20+ lymphocytes. Thus, the ALI in the patient was due to T-cell infiltration into the liver, and not due to an exacerbation of AIH.

Key words: ATLL, acute liver injury, AIH, HTLV-1

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Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a rare and distinct T-cell malignancy associated with human T-cell leukemia virus 1 (HTLV-1) infection. HTLV-1 is endemic in Japan, the Caribbean basin, South America, and Central Africa (1). ATLL presents with diverse clinical features and it has a poor prognosis. It can be divided in four clinical subtypes: acute, chronic, smoldering, and lymphoma types (2). Although several studies have reported that diffuse infiltration of leukemia cells induce acute liver failure (3, 4), acute liver injury has rarely been reported as an initial clinical finding of ATLL. We herein report that acute liver injury presented as a first clinical finding in an ATLL patient who was previously diagnosed to have autoimmune hepatitis (AIH).

Case Report

A 74-year-old Japanese female patient who was histologically diagnosed to have AIH one year earlier [score of Re-

vised Original Scoring System of the International Autoimmune Hepatitis Group (5) before treatment was 15: probable (Table 1)] and had thus been treated with 5 mg prednisolone to sustain normal liver enzyme levels after liver biopsy (Fig. 1, 2A), complained of body weight loss, appetite loss, and general fatigue. Laboratory data showed elevations in aminotransferase and total bilirubin, although there was no elevation of the immunoglobulin G level (Table 2). Additionally, there was no evidence for disseminated intravascular coagulation, phagocytic syndrome, or infection. However, atypical lymphocytes were observed in a peripheral blood smear, and an elevation of CD4 to CD8 ratio was also detected due to an increase in CD8+ lymphocytes in the peripheral blood. Notably, the levels of markers associated with viral infection were not elevated. Elevated levels of soluble interleukin-2 receptor were detected after admission. Upon comparing computed tomography (CT) scans performed at the time of AIH diagnosis to those obtained at the time of admission, imaging at the time of admission revealed swelling of the intraabdominal lymph nodes and hepatomegaly, but there was no evidence of obstructive jaundice (Fig. 3). A liver biopsy performed at admission re-

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vealed lymphocyte infiltration into the portal tract and interface hepatitis (Fig. 4A). We considered that the acute liver injury was an exacerbation of AIH. The liver injury improved after the dose of prednisolone was increased to 0.5 mg/kg. After increasing the dosage of prednisolone, atypical lymphocytes were detected in a routine complete blood count analysis. An examination of a peripheral-blood smear revealed a few atypical lymphocytes which were medium-sized with pronounced nuclear pleomorphism. Serological

tests were positive for HTLV-1 immunoglobulin G antibody. A flowcytometric analysis showed atypical lymphocytes that were positive for T-cell markers CD2, CD3, CD4, and CD5, with the co-expression of CD25, and negative for CD8. Monoclonal integration of HTLV-1 was recognized by the Southern blot method. Re-evaluation by CT scans revealed multiple lymphadenopathy in thoracic and abdominal area without an enlargement of the liver. Overall, these findings are consistent with the diagnosis of ATLL (acute type). At 1 month after making a diagnosis, she developed dyspnea due to massive pleural effusion by ATLL cell invasion to the mediastinal region. Intensified chemotherapy was started using a CHOP-like regimen. Four months after the start of chemotherapy, she died of intracranial metastasis of ATLL. Informed consent for this case report was obtained from the patient and her daughter.

Liver tissue of the second biopsy was compared with that of the first used for the initial diagnosis of AIH. Both tissues showed interface hepatitis and the infiltration of both CD4+ and CD8+ lymphocytes (Fig. 2C, D, 4C, D). Although CD20+ lymphocytes existed in the first biopsy, these cells were not observed in the second biopsy (Fig. 2B, 4B). Based on these findings, the acute liver injury in the patient was deemed to be due to T-cell infiltration into the liver, and not due to an exacerbation of AIH.

Table 1. International Autoimmune Hepatitis Group Score in the Present Case.

International AIH group score		
Sex	Female	2
ALP/AST	<1.5	2
IgG	1.0 - 1.5	1
ANA	<1:40	0
AMA	Negative	0
Virus marker	Negative	3
Drug exposure	Negative	1
Alcohol intake	<25 g/day	2
Histological findings		
Interface hepatitis	Positive	3
Infiltration of plasma cell	Positive	1
Total		15

ALP: alkaline phosphatase, ANA: anti-nuclear antibody, AMA: anti-mitochondrial antibody, AST: aspartate transaminase, IgG: immunoglobulin G

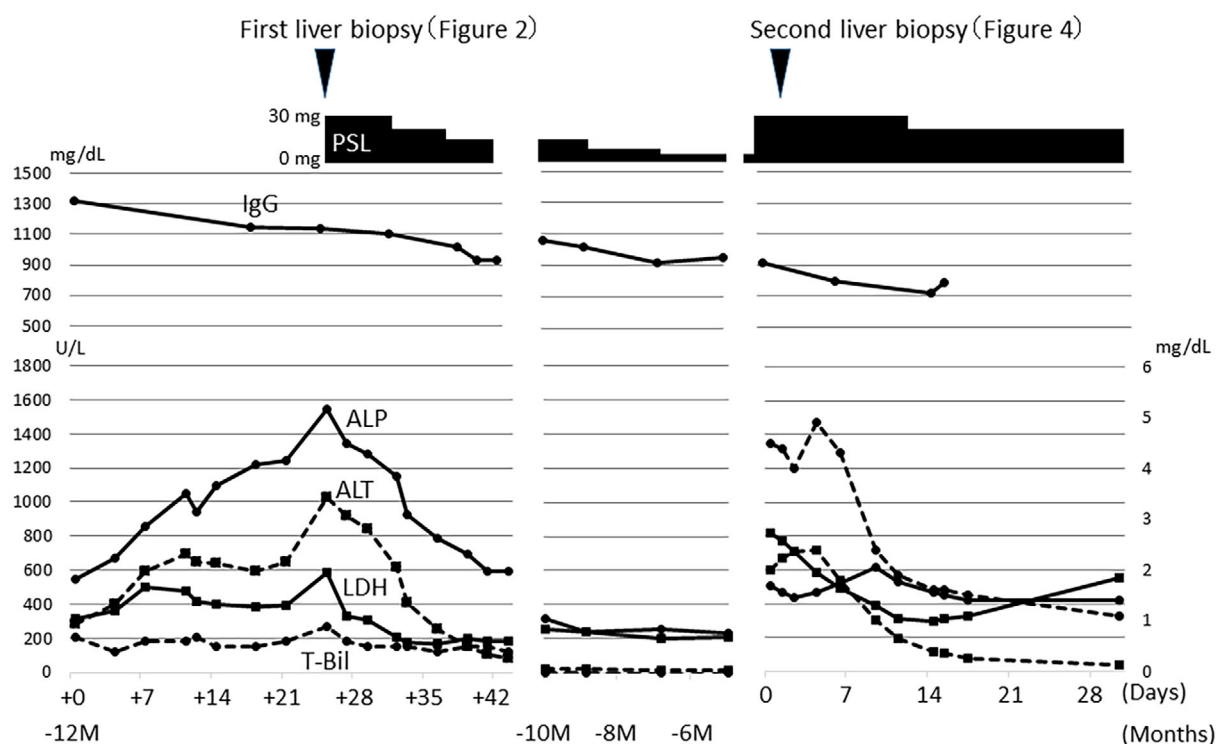


Figure 1. Clinical course of the present case. The upper line chart shows serial changes in immunoglobulin G. The bottom line chart shows serial change in alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and total bilirubin (T-Bil). The black arrowheads indicated the dates of liver biopsy. The black boxes indicate the dosage of prednisolone (PSL).

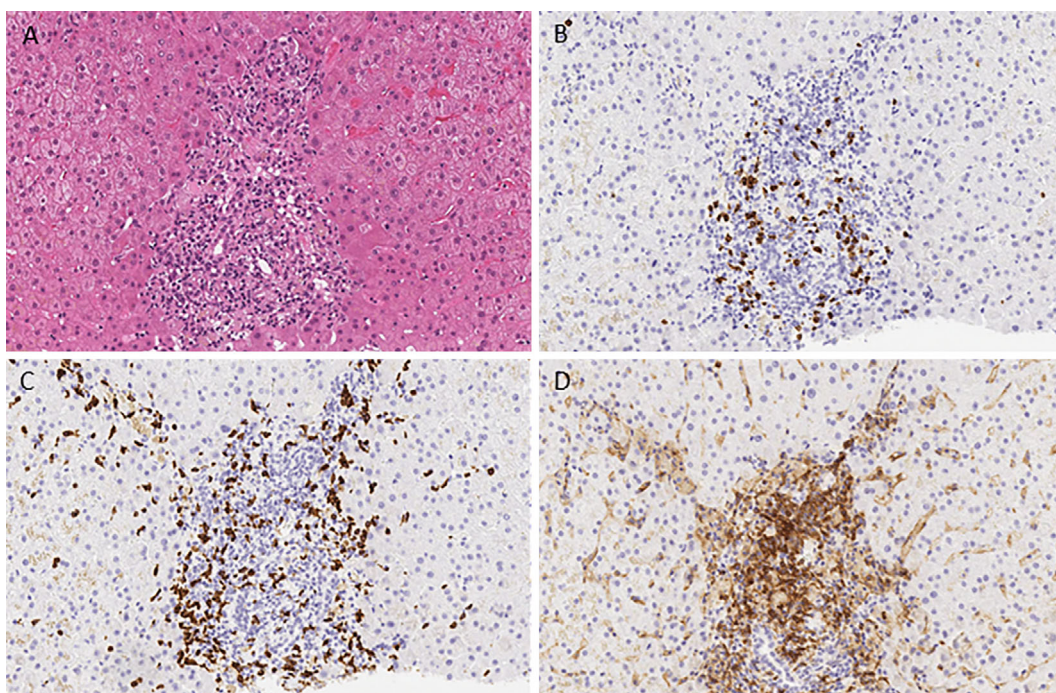


Figure 2. Histological findings of the first liver biopsy. A: Hematoxylin and Eosin staining section; B, C and D: Immunohistochemistry for CD20 (B), CD4 (C), and CD8 (D) using appropriate antibodies. These slides were serial sections. Mild inflammation and interface hepatitis were found in the portal tract (A). CD20+ cells (B), CD4+ cells (C) and CD8+ cells (D) were detected in the portal tract.

Table 2. The Laboratory Data of the Patient in the Admission.

Hematology		Fibrosis marker	
WBC	6.41 10^3 /mL	Type IV collagen7S	7.2 ng/mL
LUC	3.3 %		
Aty. lymph	+	Blood coagulation	
RBC	4.10 10^6 /mL	PT-INR	0.95
Hb	12.9 g/dL	APTT	34.2 sec.
Plt	212 10^3 /mL	Fib	316 mg/dL
Renal function		D-dimer	2.0 μ g/mL
BUN	10.3 mg/dL	Virus marker	
Cre	0.69 mg/dL	CMV IgM	(-)
Blood chemistry		CMV IgG	(+)
T-Bil	4.5 mg/dL	EBV VCA IgM	<10
AST	856 IU/L	EBV VCA IgG	40
ALT	599 IU/L	EBV EBNA	10
LDH	821 IU/L	Tumor markers	
γ -GTP	93 IU/L	sIL2R	3,920 U/mL
ALP	508 IU/L		
Albumin	3.6 g/dL	CD3CD4	56.2 %
Na	138 mmol/L	CD3CD8	10.4 %
Ca	9.2 mg/dL	CD4/CD8 ratio	5.43
IgG	918 IU/L		
IgM	42 IU/L		
CRP	0.48 mg/dL		

ALP: alkaline phosphatase, ALT: alanine aminotransferase, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CD: cluster designation, CMV: cytomegalovirus, Cre: creatinine, CRP: C-reactive protein, EB: Epstein-Barr virus, Fib: fibrinogen, γ -GTP: γ -glutamyl transpeptidase, Hb: hemoglobin, Ig: immunoglobulin, Plt: platelets, PT-INR: prothrombin time international ratio, RBC: red blood cells, sIL2R: soluble interleukin-2 receptor, T-Bil: total bilirubin, WBC: white blood cells

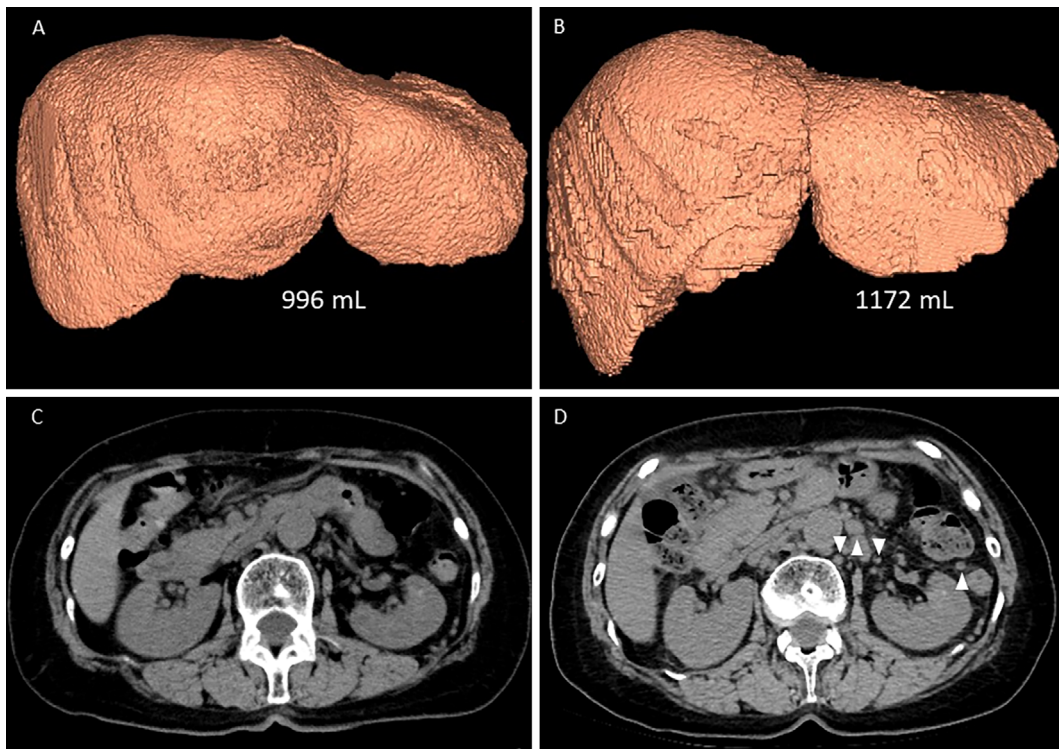


Figure 3. Computed tomography imaging at the time of AIH diagnosis and at the time of admission. The liver volume assessed at the time of AIH (A) and at admission (C). Intraabdominal lymph node assessment at the time of AIH (B) and at admission (D). The arrow heads indicated lymph nodes with swelling.

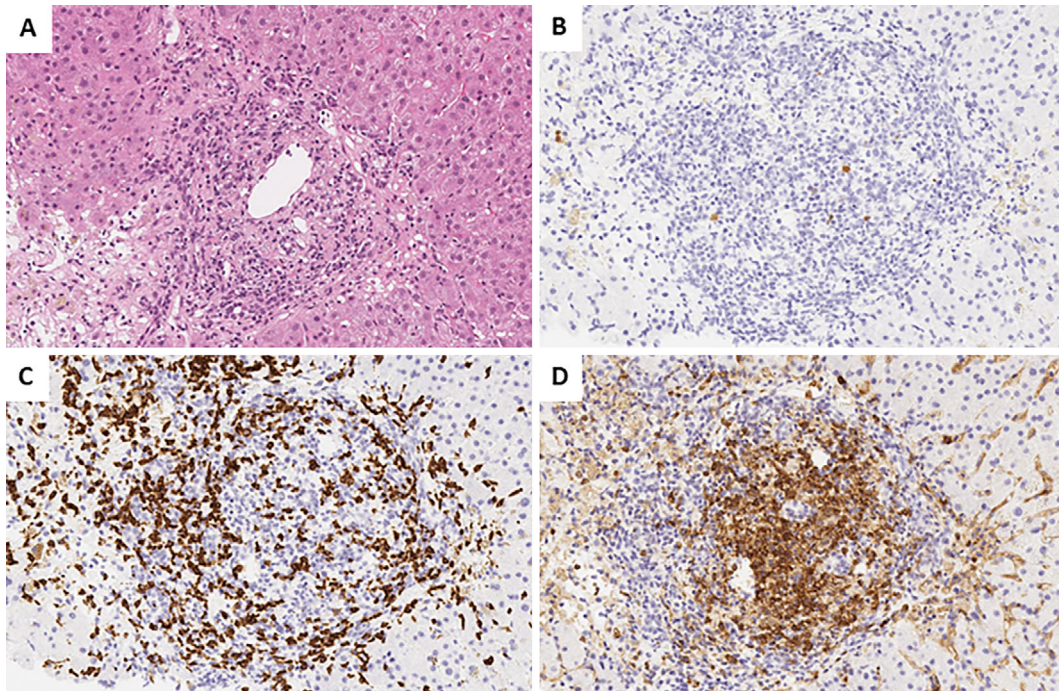


Figure 4. Histological findings of the second liver biopsy. A: Hematoxylin and Eosin staining section; B, C and D: Immunohistochemistry for CD20 (B), CD4 (C), and CD8 (D). These slides were serial sections. Mild interface hepatitis and infiltration of cells were found in the portal tract (A). There were few CD20+ cells (B). CD4+ cells (C) and CD8+ cells (D) were abundantly found in the portal tract and liver parenchyma.

Discussion

Acute liver injury in the present case was due to T-cell infiltration into the liver, as CD20+ cells were absent in the liver tissue (Fig. 4B, C, D). A liver biopsy at the time of the diagnosis of AIH showed abundant infiltration of CD20+ cells at the portal tract (Fig. 2B), which is known to be evidence of active AIH (6, 7). Thus, the elevation in the liver enzyme level in the present case was not mediated by a humoral mechanism, which is believed to be involved in the pathophysiology of AIH (8). As there was no overt evidence of ATLL when the acute liver injury appeared, we could not conclude that leukemia cells mediated the liver injury at the time of the second biopsy. However, the patient was diagnosed to have acute-type ATLL only two months after the second biopsy, and symptoms sustained until the time of ATLL diagnosis. Therefore, we consider that acute liver injury can be a clinical finding of ATLL.

The pathophysiology of liver injury associated with ATLL has been rarely studied. In contrast, HTLV-1-associated myelopathy (HAM) has been researched and the hypothetical pathophysiology has been reported by others (9). The hypothetical mechanism of HAM is as follow. HTLV-1-specific cytotoxic T lymphocytes (CTL) are stimulated by the HTLV-1 antigens and accumulate in the spinal cord. These CTLs recognize viral antigens on the HTLV-1-infected CD4+ T cells which infiltrate into the spinal cord, resulting in the secretion of proinflammatory cytokine. HTLV-1-specific CTLs lead to apoptosis of neural cells in the nerve system. As a result, the nervous system is destructed. Although there is no evidence associated with a similar mechanism in this case, this hypothetical mechanism may have played a role in this case.

Prednisolone improved the liver injury caused by T-cell infiltration in this case. We consider two hypothetical mechanisms. First, prednisolone might induce apoptosis in CD4+ and CD8+ cells (10), and liver injury would have improved after the infiltrated cells had decreased. Second, prednisolone might suppress the autoimmune response (11, 12). HTLV-1 infection is reportedly associated with autoimmune diseases, as HTLV-1 modifies the behavior of CD4+ cells and alters their cytokine production (13, 14). Prednisolone induces CD4+ and CD8+ cell populations, which synthesize high levels of IL-10, but reduces the amounts of autoimmune disease-promoting IL-4 and IL-5 (12). As a result, prednisolone may reduce HTLV-1-infection associated with liver injury.

A misdiagnosis had occurred in this case during the initial assessment of the patient, due to the presence of elevated levels of transaminase. Acute liver failure occurring due to infiltration of the liver by malignant cells is well-known, and leukemia or lymphoma are common causes of malignant infiltration of the liver (15). Thus, we hypothesized that malignant infiltration of the liver could be considered for the differential diagnosis of patients with acute liver failure.

However, in this study, we did not predict ATLL as a potential cause of ALI since the patient had originally been diagnosed with AIH. This case study highlighted the need to perform a differential diagnosis of patients with ALI, even in patients previously diagnosed with a chronic liver disease.

A prior study had reported that upon comparison of the frequency of liver infiltration between ATLL and non-Hodgkin lymphoma patients, ATLL was found to be a more common etiology of liver infiltration (16). Additionally, when a patient presents with multiple lymphadenopathy and hepatomegaly, ATLL, rather than non-Hodgkin lymphoma should be suspected.

In Japan, the east coast of northern Tohoku as well as Kyushu island are known to be regions with a high prevalence of HTLV-1 infection. After making a diagnosis of AIH, we enquired the patient about her and her parents' place of birth. The patient and her parents were not born in the regions with high prevalence of HTLV-1. However, the patient was breastfed by a woman who was born in such a region but had no relationship with the patient, since the patient's mother died after the birth of the patient. Although there was no information regarding the HTLV-1 infection status of the woman who breastfed the patient, we suspected that the woman might have been infected with HTLV-1. The anamnesis detailed above was obtained after diagnosis of ATLL. Since HTLV-1 transmission mainly occurs during breastfeeding from a mother infected with HTLV-1, we enquired the patient about her nursing and family history as well as the place of her birth once the patient was suspected to be infected with HTLV-1.

There are some limitations associated with this case study. We did not confirm how infiltrated T-cells in the liver injured the hepatocytes, and we did not evaluate any cytokines. Thus, precisely how prednisolone improved liver injury in this case remains unclear. As mentioned above, HTLV-1 infection is associated with autoimmune disease. However, whether the pre-existing AIH in this case was associated with HTLV-1 infection remains unknown. As AIH has never been reported as a complication of HTLV-1 infection, we suspect that AIH was not associated with HTLV-1 infection.

The authors state that they have no Conflict of Interest (COI).

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