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CASE REPORT

A case of acute liver failure due to aggressive natural killer-cell leukemia with a rapid course

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Abstract

An 87-year-old man consulted a former doctor with a complaint of black stool and was admitted to hospital because of anemia and multiple gastric ulcers. The laboratory findings showed that his hepatobiliary enzyme levels and inflammatory response were elevated. Computed tomography showed hepatosplenomegaly and enlarged intra-abdominal lymph nodes. Two days later, he was transferred to our hospital due to deterioration of his liver function. Since he had low level of consciousness and his ammonia level was high, we diagnosed him with acute liver failure (ALF) with hepatic coma, and started on-line hemodiafiltration. As the cause of ALF, we suspected hepatic involvement of a hematologic tumor because of high lactate dehydrogenase and soluble interleukin-2 receptor levels and large abnormal lymphocyte-like cells in the peripheral blood. Because of his poor general condition, bone marrow and other histological examinations were difficult, and he died on the third day of hospitalization. Pathological autopsy showed marked hepatosplenomegaly and the proliferation of large abnormal lymphocyte-like cells in the bone marrow, liver, spleen, and lymph nodes. Immunostaining revealed aggressive natural killer-cell leukemia (ANKL).

We herein report a rare case of the development of ALF with coma due to ANKL with a review of the relevant literature.

Keywords Aggressive NK cell leukemia · Acute liver failure · EBER-ISH

Abbreviations

NK	Natural killer
ANKL	Natural killer-cell leukemia
PSL	Prednisolone
CT	Computed tomography
PT	Prothrombin time
LDH	Lactate dehydrogenase
INR	International normalized ratio
EBV	Epstein-Barr virus
ALF	Acute liver failure
HDF	Hemodiafiltration
DIC	Disseminated intravascular coagulation syndrome
sIL-2R	Soluble interleukin-2 receptor
CD	Cluster of differentiation
EBER-ISH	In situ hybridization with EBV-encoded small ribonucleic acid
LGL	Large granular lymphocyte
ENKL	Extranodal NK/T-cell lymphoma, nasal type
LMP1	Latent membrane protein 1
PD-L1	Programmed cell death-ligand 1 (PD-L1)

Introduction

Aggressive natural killer (NK)-cell leukemia (ANKL) is a rare disease in which mature NK cell-derived leukemia cells proliferate mainly in the liver, spleen, and lymph nodes [1]. It has a poor prognosis.

Acute liver failure (ALF) is defined as a normal liver or a liver with normal hepatic reserve, and a prothrombin time of ≤ 40% or a PT-international normalized ratio of 1.5 due to severe hepatic dysfunction within 8 weeks from the onset

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of the first symptoms. Liver failure without liver inflammation (e.g., drug intoxication, circulatory failure, fatty liver of pregnancy, and metabolic abnormalities) is also diagnosed as ALF, including liver failure associated with tumor infiltration [2].

We herein report a case of acute liver failure caused by ANKL that followed a rapid course.

Case report

The patient was an 87-year-old man who had stayed in a long-term care health facility after experiencing subcortical hemorrhage. Hepatic dysfunction had not been pointed out previously. He had been taking prednisolone (PSL), acetaminophen and loxoprofen for pseudogout for 37 days before admission. Two days before admission, he visited a previous doctor because of black stool, and was admitted to the hospital due to anemia. Upper gastrointestinal endoscopy revealed multiple gastric ulcers. Blood tests also showed elevated hepatobiliary enzymes and inflammatory responses. Fever and abdominal pain appeared. An arterial blood gas analysis revealed metabolic acidosis, while computed tomography (CT) revealed hepatosplenomegaly and intra-abdominal lymphadenopathy. He was transferred to our hospital because of an extended prothrombin time (PT) and further increases in his hepatobiliary enzyme levels and inflammatory response.

At the time of admission, his consciousness level had dropped to Japan Coma Scale 20–30. His body temperature was 36.6 ℃, his blood pressure was 101/60 mmHg, and his pulse was 92 bpm. Saturation of percutaneous oxygen was 100% under the administration of 4L of oxygen. He had jaundice in his conjunctiva and marked tenderness in his upper abdomen. Asterixis was unclear. He had no skin lesions.

Table 1 shows the laboratory data at the time of hospitalization. In detail, blood tests showed hyperbilirubinemia, markedly abnormal liver function and abnormally high lactate dehydrogenase (LDH). His liver enzyme levels were as follows: total bilirubin, 4 mg/dL; aspartate aminotransferase, 1574 U/L; alanine transaminase, 409 U/L; LDH, 2153 U/L; alkaline phosphatase, 2728 U/L; and γ-glutamyl transpeptidase, 289 U/L. His ferritin level rose to 1936 ng/mL. His white blood cell count was 15,200/μL, his C-reactive protein level was 14.1 mg/dL, and his inflammatory response was elevated. His PT decreased to 41%, his PT-international normalized ratio (INR) was prolonged to 1.76, and his ammonia level was elevated. His platelet count decreased to 93,000/μL and his blood fibrinogen/fibrin degradation products level was elevated to 28.1 μg/mL. Large abnormal lymphocyte-like cells appeared in the peripheral blood. Tests for hepatitis A, B, C, and E viral infection were negative, while tests for Epstein-Barr virus (EBV), cytomegalovirus, and herpes simplex virus showed pre-existing infection patterns. His antinuclear antibody titer was < 40-fold and his immunoglobulin G level was 1458 mg/dL (within the normal limits).

Table 1 Laboratory data at the time of hospitalization

Hematology		Biochemistry	
WBC, /μL	14,750	Alb, g/dL	2.3
Neutro, /μL	9990	T-Bil, mg/dL	4.3
RBC, $\times 10^4$/μL	361	D-Bil, mg/dL	3.8
Hb, g/dL	9.7	AST, U/L	1669
Plt, $\times 10^4$/μL	9.3	ALT, U/L	432
		LDH, U/L	2128
Coagulation		ALP, U/L	3030
PT%	41	γ-GTP, U/L	218
PT-INR	1.76	NH3, μg/dL	133
fibrinogen, mg/dL	93	CK, U/L	444
AT-III%	24	BUN, mg/dL	71.3
FDP, μg/mL	28.1	Cr, mg/dL	2.28
D-dimer, μg/mL	14.2	Na, mEq/L	142
		K, mEq/L	4.1
Viral marker		Cl, mEq/L	96
HBsAg	(−)		
HCVAb	(−)	Serology	
EBV.VCAIgG	1:640	CRP, mg/dL	15.35
EBV.VCAIgM	Below 1:10	Ferritin, ng/mL	1936
EBV.EBNA	1:40	sIL-2R, U/mL	7246

WBC white blood cell, *Neutro* neutrophil, *RBC* red blood cell, *Hb* hemoglobin, *Plt* platelet count, *PT* prothrombin time, *PT-INR* prothrombin time-international normalized ratio, *AT-III* anti-thrombin III, *FDP* fibrin-fibrinogen degradation products, *HBsAg* hepatitis B surface antigen, *HCVAb* HCV antibody, *EBV* Epstein-Barr virus, *VCA* virus capsid antigen, *IgG* immunoglogulin G, *IgM* immunoglobulin M, *EBNA* Epstein-Barr virus nuclear antigen, *Alb* albumin, *T-Bil* total bilirubin, *D-Bil* direct bilirubin, AST, aspartate aminotransferase, ALT, alanine aminotransferase, LDH, lactate dehydrogenase, *ALP* alkaline phosphatase, *γ-GTP* γ-glutamyltransferase, *NH3* ammonia, *CK* creatine kinase, *BUN* blood urea nitrogen, *Cr* creatinine, *Na* sodium, *K* potassium, *Cl* Chlorine, *CRP* C-reactive protein, *sIL-2R* soluble interleukin-2 receptor

Non-contrast CT showed hepatosplenomegaly (Fig. 1a, b), edematous changes in the ascending colon, and intra-abdominal lymphadenopathy (Fig. 1c, d). A moderate amount of ascites was also observed. Abdominal Doppler ultrasonography did not detect intrahepatic portal flow.

We diagnosed the patient with acute liver failure (ALF) with coma based on his prolonged PT-INR, high ammonia level, and impaired consciousness. He was admitted to the intensive care unit (ICU) and started on on-line hemodiafiltration (HDF). He also matched the diagnostic criteria for disseminated intravascular coagulation syndrome (DIC), and was treated with anti-thrombin III. Although the CT scan and urinary findings showed no evidence of bacterial infection, we started antibiotic therapy with piperacillin/tazobactam

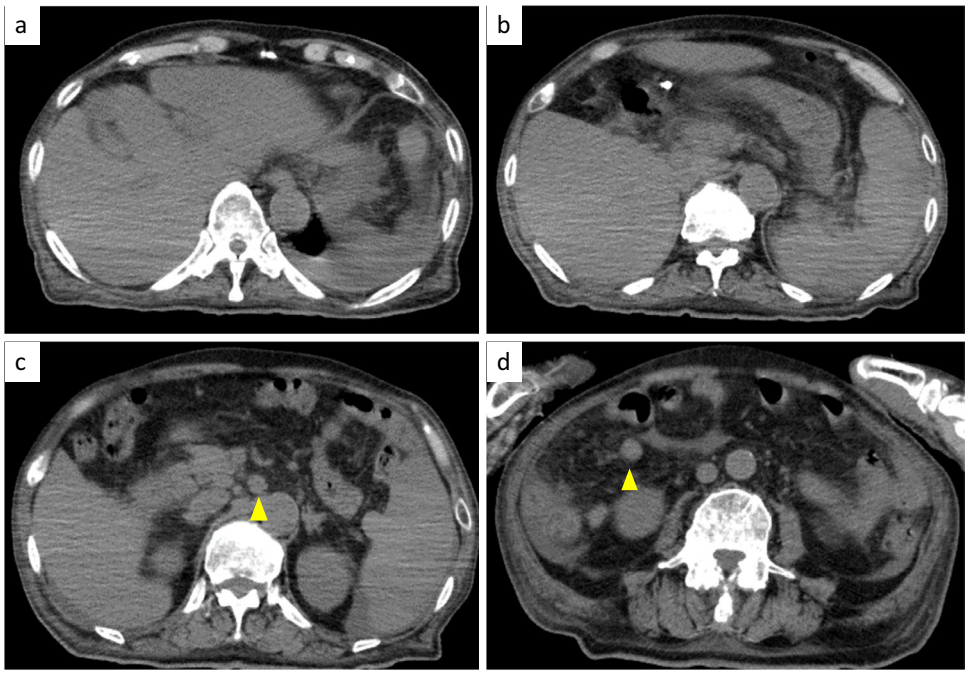

Fig. 1 Abdominal plain CT. **a** The liver was enlarged. **b** The spleen was markedly enlarged. **c**, **d** Multiple enlarged intra-abdominal lymph nodes were observed

because of his high inflammatory response. We ruled out viral hepatitis as a cause of ALF, and suspected hepatic infiltration of a hematologic tumor due to the abnormally high LDH level, hepatosplenomegaly, and intra-abdominal lymphadenopathy. We also considered drug-induced liver injury and multiorgan failure triggered by infection. The blood test on day one after admission showed a high soluble interleukin-2 receptor (sIL-2R) level of 7246 U/L and the presence of large abnormal lymphocyte-like cells in the peripheral blood, which led us to strongly suspect hepatic infiltration of a hematologic tumor. However, we could not examine the bone marrow or organs histologically because his general condition was poor. He required noradrenaline and hydrocortisone to maintain his blood pressure. On the evening, his respiratory condition rapidly worsened, and he was intubated and ventilated. His hepatobiliary enzyme levels were rapidly exacerbated, and his DIC—which appeared to be neoplastic—worsened over time. On day 2 after admission, his blood pressure dropped and his anemia progressed, which did not improve with blood transfusion; however, there was no obvious source of bleeding. He died on day 3 after admission.

An autopsy was performed with the informed consent of his family. Macroscopically, the liver and spleen weighed 2484 g and 436 g, respectively, and marked hepatosplenomegaly with massive necrosis was observed. Multiple infarction was seen on the cut surface of the spleen (Fig. 2a–d). Histologically, large atypical lymphoid cells diffusely infiltrated in the bone marrow, liver (Fig. 3a), spleen, and lymph nodes. Atypical lymphoid cells were positive for cluster of differentiation (CD)3 (Fig. 3b), CD56 (Fig. 3c), granzyme B, TIA-1 (Fig. 3d), negative for CD4, CD5, CD8 (Fig. 3e), CD20, CD79a, CD16 by immunostaining and positive for in-situ hybridization with EBV-encoded small ribonucleic acid (EBER-ISH) (Fig. 3f). The diagnosis of ANKL was made based on the distribution of the tumor in the liver, spleen, bone marrow, and lymph nodes, and the rapid progression of the disease. In particular, marked ANKL cell infiltration of the sinusoids, liver parenchyma, and mesenteric lymph nodes, with partial invasion of the small intestine and colon from the serosal side, was observed. The colon showed widespread ischemic enteritis, which was thought to be the main cause of the colonic edema observed on CT. There was no thrombus formation in the portal vein or sinusoids. Hemophagocytosis was observed in the lymph nodes and bone marrow. The multiple gastric ulcers occurred due to non-steroidal anti-inflammatory drugs without atypical cells infiltration.

Discussion

We experienced a rare case of ALF caused by ANKL that followed a rapid course. ANKL is a very rare disease, accounting for only 0.1% of lymphoid malignancies [3]. East Asians account for 70% of people affected by ANKL, and a male predominance is observed [4, 5]. The median age was 40 years and the two peaks of distribution were observed in younger and elderly populations [5]. Tumor cells are found in the bone marrow and peripheral blood, and many cases present with anemia and thrombocytopenia, sometimes complicated by DIC. Hepatosplenomegaly, enlarged lymph

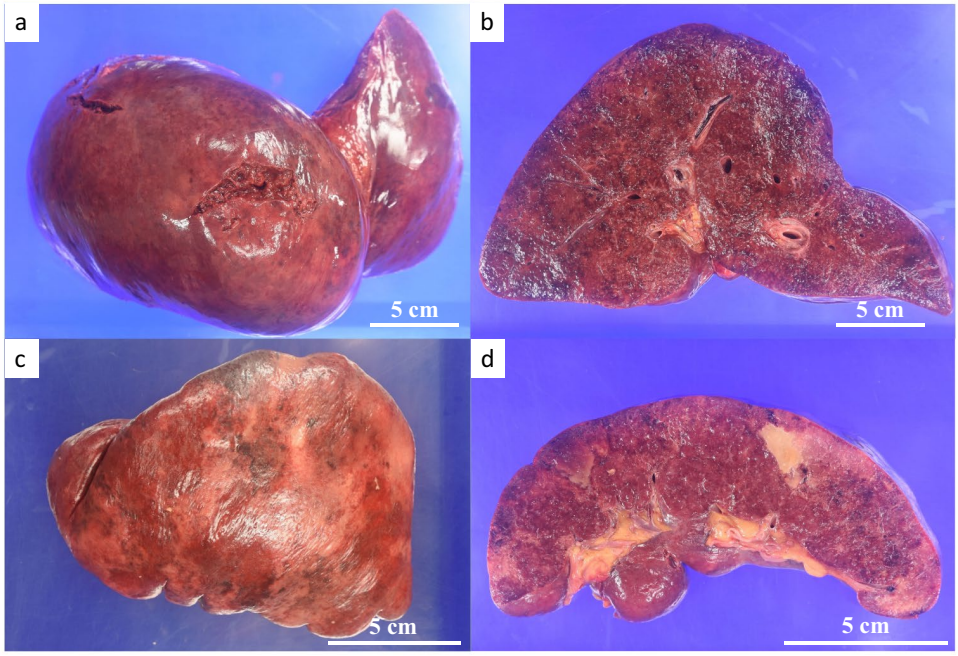

Fig. 2 Macroscopic findings of the liver and the spleen (bar = 5 cm). a The liver was markedly enlarged (2484 g). **b** On the cut surface of the liver, reddish black with extensive hemorrhagic necrosis was present. **c** Splenomegaly was noted (436 g). **d** On the cut surface of the spleen, infarction were observed as well-circumscribed white areas

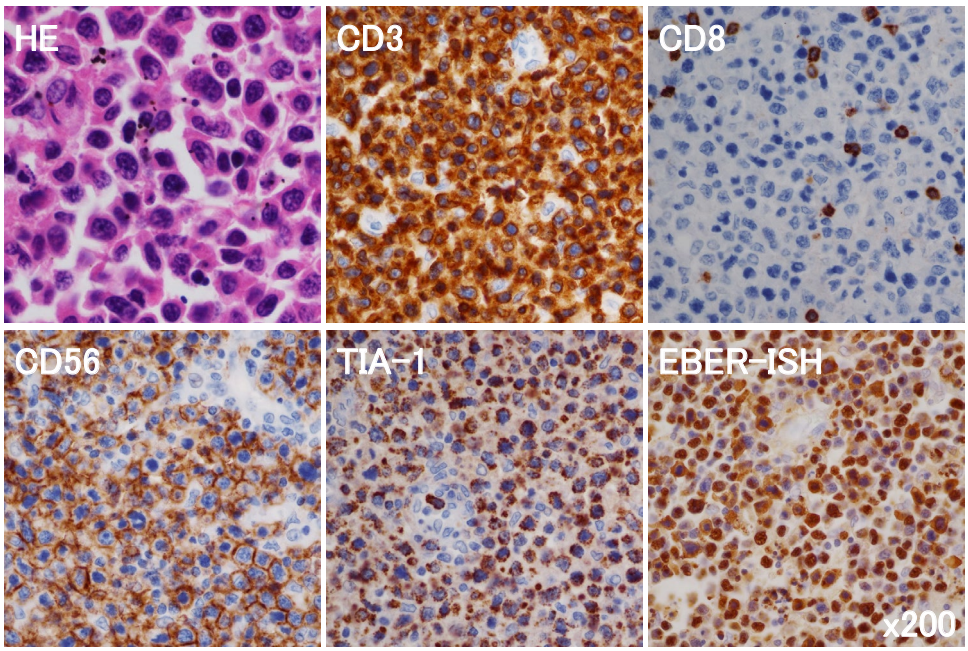

Fig. 3 Microscopic findings of the liver. Large atypical lymphoid cells were diffusely infiltrated by Hematoxylin and eosin stain (**a**). Large atypical lymphoid cells were positive for CD3 (**b**), CD56 (**c**), TIA-1 (**d**), negative for CD8 (**e**), by immunostaining and positive for EBER-ISH (**f**). *CD* cluster of differentiation, *TIA-1* T-cell intracellular antigen 1, *EBER-ISH* in-situ hybridization with Epstein-Barr virus-encoded small ribonucleic acid

nodes and symptoms such as fever, night sweats, and weight loss are frequently observed [2, 6].

Ishida classified the tumor cell morphology of ANKL into three types. Type I has a large granular lymphocyte (LGLs) appearance, in which the cytoplasm is slightly basophilic and has larger cytoplasmic granules in comparison to normal LGL. In type III, the cells exhibit a pleomorphic-like appearance, together with basophilic cytoplasm and a bizarre nucleus containing one or two nucleoli. Type II is a mixture of types I and III in the patient, or shows intermediate characteristics, which include monocyte-like features [5]. The leukemic cells in this case were similar to type II because they had no cytoplasmic granules and no conspicuous nucleoli.

The surface immunophenotype of ANKL is characterized by positivity for NK cell markers (e.g., CD2, sporozoite CD3, and CD56) and cytotoxic molecules (e.g., granzyme B and TIA-1), with 75% of cases being positive for CD16 [7]. In the present case, immunostaining was positive for CD3, CD56, granzyme B, TIA-1, and negative for T-cell markers

(e.g., CD4, CD5, CD8) and B cell markers (e.g., CD20 and CD79a). The CD16 negativity suggested the possibility of extranodal NK/T-cell lymphoma, nasal type (ENKL), but the localization of the lesions—primarily in the liver, spleen, bone marrow, and lymph nodes—and the absence of involvement of the nasopharyngeal region or skin, were consistent with ANKL.

Approximately 90% of ANKL cases are associated with EBV infection, but the mechanism is not fully clarified [8, 9]. In NK/T-cell lymphoma, an analogous disease, the expression of latent membrane protein 1 (LMP1) due to EBV infection has been reported to contribute to the overexpression of programmed cell death-ligand 1 (PD-L1), suggesting that it may be associated with tumorigenesis [10]. In the present case, blood tests showed a pre-existing EBV infection pattern, but tissue immunostaining was positive for EBER-ISH. The majority of ANKL cases show a de novo onset, but some cases have a history of mosquito bite hypersensitivity since childhood or chronic active EBV infection [4]. A subacute form with infectious mononucleosis-like symptoms for more than 90 days has also been reported [11]. No such history was observed in the present case.

Hemophagocytosis was observed in the lymph nodes and bone marrow, with low platelet levels and high LDH and ferritin levels, suggesting that ANKL caused secondary hemophagocytic syndrome.

There were a few similar cases of liver failure due to histologically diagnosed ANKL [12, 13]. In these cases, hepatosplenomegaly was observed, and ANKL cell infiltration into the liver sinusoids or liver parenchyma was pathologically observed. Similarly, in the present case, marked ANKL cell infiltration of the sinusoids in addition to the liver parenchyma was observed, which was considered to be the cause of the decreased portal flow observed on ultrasonography. There was no thrombus formation in the portal vein or sinusoids. Therefore, we speculated that the infiltration of ANKL cells into the liver parenchyma and sinusoids and the consequent reduction of portal flow led to liver failure.

This patient was treated with PSL, acetaminophen, and loxoprofen for pseudogout prior to admission to previous hospital. Autopsy showed that ANKL cells infiltrated the bone marrow. It is possible that the pain that was suspected to be due to pseudogout occurred as an effect of bone infiltration by ANKL cells.

Because ANKL is a rare disease, treatment guidelines for hematopoietic tumors have not yet been established. Ishida et al. demonstrated the possibility of improving the prognosis of ANKL with chemotherapy including L-asparaginase in a Japanese-Korean multicenter retrospective study of a total of 34 cases [5]. In Japan, SMILE therapy (Steroid, Methotrexate, Ifosfamide, L-asparaginase, Etoposide), which is used in the advanced stages of ENKL, is often the treatment of choice for ANKL [4]. In 2021, Fujimoto analyzed the results of allogeneic hematopoietic stem cell transplantation for 59 ANKL cases in Japan. She reported that approximately 30–40% of the patients who were sensitive to chemotherapy at the time of transplantation or in whom initial induction of remission failed but who showed complete remission after transplantation achieved long-term survival [7]. The median overall survival of ANKL patients is reported to be approximately 2 months [2, 5], but it is expected that the prognosis will be prolonged with the establishment of new treatment methods in the future. On the other hand, rapid disease progression often leads to death from multiple organ failure in a short period of time. The present case developed ALF with coma at the time of admission to our hospital, and it was difficult to perform liver biopsy due to marked coagulation abnormalities and the rapid deterioration of the patient's general condition. The patient died within 4 days of admission. Due to the rapid progression of the disease, it was difficult to introduce treatment.

We experienced a case of ANKL that caused ALF with coma, which was diagnosed at autopsy. Although ANKL is a disease with rapid progression and a poor prognosis, an early histological diagnosis may lead to therapeutic intervention, and consequently improve the prognosis.

Declarations

Conflict of interest The authors declared that there is no conflict of interest.

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