Acute liver failure due to natural killer-like T-cell leukemia/lymphoma: A case report and review of the Literature

Evan S. Dellon, Shannon R. Morris, Wozhan Tang, Cherie H. Dunphy, Mark W. Russo

Abstract
Acute liver failure (ALF) is a medical emergency requiring immediate evaluation for liver transplantation. We describe an unusual case of a patient who presented with ascites, jaundice, and encephalopathy and was found to have ALF due to natural killer (NK)-like T cell leukemia/lymphoma. The key immunophenotype was CD2+, CD3+, CD7+, CD56+. This diagnosis, which was based on findings in the peripheral blood and ascitic fluid, was confirmed with liver biopsy, and was a contraindication to liver transplantation. A review of the literature shows that hematologic malignancies are an uncommon cause of fulminant hepatic failure, and that NK-like T cell leukemia/lymphoma is a relatively recently recognized entity which is characterized by CD3+ and CD56+. This case demonstrates that liver biopsy is essential in diagnosing unusual causes of acute liver failure, and that infiltration of the liver with NK-like T-cell lymphoma/leukemia can cause acute liver failure.

CASE REPORT
A previously healthy 63-year-old man was admitted for three mo of fatigue, one mo of increasing abdominal girth and peripheral edema, two weeks of jaundice, and one week of confusion. He noted recent fevers, anorexia, weight loss, and day-night reversal. He had never received a blood transfusion or used intravenous or intranasal drugs. He had no tattoos or recent travel. He did not take prescription or over-the-counter medications, or nutritional supplements. He admitted using alcohol heavily in the past, but had been sober for more than 10 years. His family corroborated this information. There was no family history of liver disease.

On physical examination he was jaundiced and had findings consistent with hepatic encephalopathy including slurred speech and asterixis. He had moderate ascites, peripheral edema, and scattered spider angiomata. The liver was normal in size, but splenomegaly was detected.

Routine laboratory tests revealed hyponatremia, hypoalbuminemia, hyperbilirubinemia, thrombocytopenia, and prolonged prothrombin time not due to vitamin K deficiency (Table 1). The white blood cell count was 5.1 × 10^9/L with atypical lymphocytes comprising 53% of the differential (Figure 1). Other diagnostic testing found a negative toxicology screen, 90% iron saturation, negative serologies for hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and human T-cell lymphotrophic virus (HTLV) types I and II. Serologies were also negative for anti-nuclear antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies. Serum protein electrophoresis, alpha-1 anti-trypsin levels, ceruloplasmin levels, and alpha-fetoprotein were normal. Serum ammonia level was not measured. Abdominal ultrasound showed a normal liver size with heterogeneous echotexture, splenomegaly, and patent vasculature. Head CT scan excluded mass lesions and infiltrating disease.
Diagnostic paracentesis at a site in the left-lower-quadrant demonstrated a serum albumin-ascites gradient of 12 g/L, 12475 red blood cells (RBCs)/mm$^3$ and 1875 white blood cells (WBCs)/mm$^3$ with a differential of 1% neutrophils, 4% monocytes and 95% lymphocytes. Because the lymphocytes were described as atypical with mitotic figures, a repeat paracentesis was performed at a right-lower-quadrant site. This revealed 1550 RBCs/mm$^3$ and 250 WBCs/mm$^3$ with the same differential and atypical cells. A sample of the ascitic fluid was sent for cytology (Figure 2). The peripheral blood flow cytometric immunophenotypes were as follows: CD2+, CD3+, CD7+, CD56+, CD4-, CD5-, CD8-, CD57-, and CD16-. A bone marrow biopsy revealed the same findings. Cytogenetic analysis of the bone marrow aspirate revealed the following karyotypes: 43, X, -Y, add (4) (q35), -5, dic (6;19) (q23; q13.4), -10, -11, -13, -14, -16, -18, add(22)(p11), +6 mars.

Since the patient’s coagulopathy prohibited percutaneous liver biopsy, transjugular liver biopsy was performed for definitive diagnosis. There was no evidence of cirrhosis, but there was diffuse hepatic infiltration by a malignant lymphoid population (Figures 3A and 3B) which was immunohistochemically stained as follows: CD3+, CD20-, Epstein-Barr virus (EBV)-, granzyme B+, TIA-1+, and TdT-. The paraffin block of the liver biopsy was analyzed for a T-cell receptor (TCR) gamma gene rearrangement by polymerase chain reaction, and there was no evidence of a clonal TCR gamma gene rearrangement.

The patient was diagnosed with NK-like T-cell lymphoma/leukemia as the cause of liver failure on hospital d 4. This was deemed a contraindication to transplantation. His course was complicated on d 3 by bleeding duodenal ulcers amenable to standard endoscopic treatment. On d 4-6, high-dose methylprednisolone failed to induce remission, and his hepatic synthetic function and mental status worsened. On d 10 and 11, a salvage regimen of gemcitabine was unsuccessful in inducing remission. On d 12, neutropenia, fever, and hypotension developed, and the patient’s jaundice and encephalopathy progressed. The patient expired on hospital d 12.

**DISCUSSION**

The diagnosis of acute liver failure is a medical emergency because mortality is high without liver transplantation$^3$. However, thorough evaluation is mandatory to exclude contraindications to liver transplantation such as...
underlying malignancy,[13] Natural killer killer cells, typically identified morphologically as large granular lymphocytes, are recognized for their role in cell-mediated immunity.[34] They have characteristic immunophenotypes (CD3-, CD56+) which distinguish them from T cells (CD3+, CD56-). Other markers such as CD8 and the additional so-called NK-cell antigens (CD16 and CD57) are variably present.[31-33] Over the past two decades, it has been noted that NK cells undergo clonal expansion and malignant transformation.[35] This is believed to be a rare event, accounting for only a small fraction of all T-cell malignancies, which themselves are thought to comprise approximately just 15% of all non-Hodgkin's lymphoma.[36] NK-cell leukemia/lymphomas are categorized as either immature (and more aggressive) or mature (with an indolent course), and more commonly affect the nasopharynx and sinuses though they have also been reported to involve the skin, mucosa of the gastrointestinal (GI) tract, testes, kidneys, and orbit.[36,37] They are seen more frequently in Asia, Mexico, and South America, ostensibly due to associations with EBV and HTLV.[38-40] Of note, while they are commonly associated with hepatosplenomegaly they have not been reported to present with acute liver failure.[11,36-41]

In contrast to NK cells, NK-like T-cells expressing features of both T cells and NK cells, are defined by a CD3+, CD56+ immunophenotype, and tend not to be associated with EBV.[40] The first reports of NK-like T-cell leukemias and lymphomas[41,42] have described presentations including typical “B” symptoms such as fever, chills, night sweats and weight loss, as well as lymphadenopathy and splenomegaly. Disease involves the spleen, blood, marrow, GI tract, lung, kidneys, and liver, but none of the patients presented with frank liver dysfunction. In most instances, the disease is aggressive and rapidly fatal, regardless of treatment regimen. A large series identified 49 Chinese patients with extra-nasal CD56+ disease, 34 of whom are also CD3+.[43] Of the 5 patients with liver involvement, all had reactive hemophagocytic syndrome but none presented with hepatic failure. Of the 29 patients with follow-up information available, 24 died in a median time of 3.5 mo. A recent phenotypic analysis of 408 Japanese cases of peripheral T/NK cell lymphoma had not described any with liver failure.[44]

In this paper we present the clinical course, immunophenotype, and cytogenetics of what we believe to be the first reported case of a patient with acute liver failure due to NK-like T-cell leukemia/lymphoma. This has implications beyond the rarity of this particular patient’s condition. Because this patient had a history of alcohol consumption, his liver disease might have been ascribed to alcoholic hepatitis from a relapse of alcohol use. However this case illustrates the importance of fully analyzing unexpected findings. The atypical lymphocytes seen on the peripheral smear and in the ascitic fluid cell count differential were not attributed to a reactive process. Rather, they led to the transjugular liver biopsy which is essential in making the diagnosis, and underscores the role of and importance of liver biopsy when the etiology of liver failure is unknown.

In conclusion, a hematologic malignancy infiltrating the liver, although rare, is a contraindication to liver transplantation. It is mandatory to exclude such processes in the correct clinical context. In our case, liver biopsy allowed prompt diagnosis and recognition of NK-like T-cell leukemia/lymphoma as the cause of acute liver failure.

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