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CASE REPORT | LIVER

Natural Killer–Like T-Cell Lymphoma: A Rare Cause of Acute Liver Failure

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ABSTRACT

Acute liver failure is characterized by encephalopathy and disruption of hepatic function, often requiring liver transplantation to prevent fatal consequences. We present a 33-year-old man with recurrent lymphoma presenting with acute liver failure, which was initially thought to be from drug-induced liver injury associated with his chemotherapy medication, asparaginase. However, liver biopsy revealed malignant infiltration by lymphoma. The subtype of lymphoma was natural killer–like T-cell lymphoma, which is an uncommon variant, and has rarely been associated with hepatic infiltration. His condition rapidly worsened with development of multiorgan failure leading to death.

INTRODUCTION

Acute liver failure (ALF) is a life-threatening emergency, which can require liver transplantation for survival or which can result in death if left untreated. Although uncommon, several hematologic malignancies are now recognized as possible causes of ALF. We present one such case of a rare variant of natural killer–like T-cell (NKT) lymphoma presenting with ALF due to malignant hepatic infiltration.

CASE REPORT

A 33-year-old man was first diagnosed with nasal-type NKT cell lymphoma 1 year before admission and underwent surgical resection, followed by adjuvant chemotherapy with steroid–methotrexate–ifosfamide–L-asparaginase–etoposide and radiation therapy. He developed recurrence 6 months before this hospitalization for which he was started on L-asparaginase and gemcitabine, which were continued until 3 weeks before admission. He presented to our hospital with nausea, vomiting, fever, jaundice, and generalized fatigue for a duration of 5 days. Physical examination revealed stable vital signs, scleral icterus, jaundice, and tender hepatomegaly. Laboratory testing revealed the following: white blood cell count 2,000/μL, hemoglobin 8 g/dL, platelet count 20,000/μL, alanine aminotransferase 100 U/L, aspartate aminotransferase 194 U/L, alkaline phosphatase 794 U/L, total bilirubin level 15.4 g/dL, and international normalized ratio 1.6. Antimicrobial therapy was empirically started. Abdominal ultrasound and magnetic resonance imaging revealed hepatomegaly with no evidence of biliary obstruction. Acetaminophen and alcohol levels were undetectable, whereas viral serologies were negative. Review of laboratory tests from 10 days before presentation revealed normal liver enzymes and bilirubin level.

We initially suspected that the cause of his abnormal liver enzymes could be drug-induced liver injury from recent L-asparaginase use, for which we started treatment with vitamin B complex, N-acetylcysteine, and L-carnitine. His blood cultures remained negative. The patient's liver function worsened over the next week with laboratory tests revealing the following: alanine aminotransferase 304 U/L, aspartate aminotransferase 1,062 U/L, alkaline phosphatase 576 U/L, total bilirubin 20.8 g/dL, platelets 14,000/μL, and international normalized ratio 2.0. He eventually developed hepatic encephalopathy and hepatorenal syndrome. A transjugular liver

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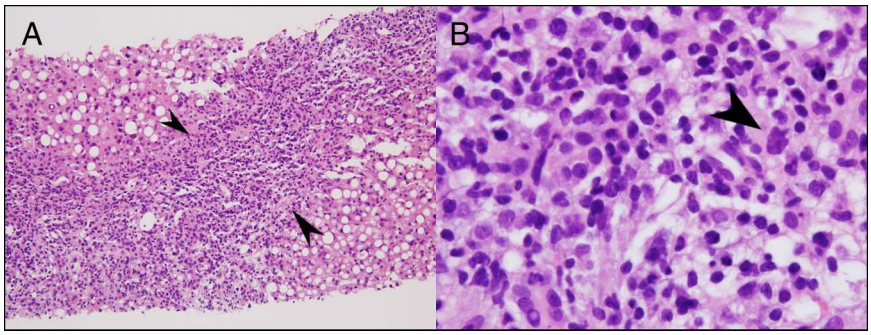

Figure 1. (A) Low-power magnification hematoxylin and eosin stain section of core liver biopsy showing disruption of the hepatic architecture due to portal tract expansion from lymphocytic infiltration (arrowheads), associated with portal-portal linkage. (B) High-power magnification hematoxylin and eosin stain section showing portal tract infiltration with medium-sized atypical lymphocytes with moderate amounts of clear eosinophilic cytoplasm. The arrowhead points to a large neoplastic lymphoreticular cell in the center surrounded by several smaller benign lymphocytes.

biopsy showed infiltration of portal sinusoids with atypical lymphocytes, concerning for malignant infiltration of the liver (Figure 1). Immunohistochemical stains revealed atypical lymphocytes, which were CD3+ and CD56+. Granzyme-1 stain, T-cell intracytoplasmic antigen-1 stain, and in situ hybridization of Epstein-Barr virus (EBV) were found to be positive. These findings represented extensive hepatic infiltration by NKT lymphocytes, manifesting as ALF in our patient. Although hemophagocytic lymphohistiocytosis presents similarly, absence of fever and hemophagocytic activity on liver biopsy in addition to presence of high NKT cell activity made it less likely in our patient. Liver transplantation was contraindicated by active malignancy, and he ultimately died of multiorgan failure.

DISCUSSION

ALF is characterized by disruption of hepatic synthetic function in the absence of preexisting liver disease and is a medical emergency that frequently requires prompt and thorough evaluation for liver transplantation. Acetaminophen toxicity is the most common cause (39%) of ALF in the United States, followed closely by idiosyncratic drug reactions (13%), viral hepatitis (12%), indeterminate causes (17%), autoimmune hepatitis, and ischemic necrosis.[1,2] However, in recent years, malignant infiltration of the liver by hematologic malignancy has been recognized as a possible cause of ALF.[3–9]

ALF from hepatic infiltration by hematologic malignancies is rare (0.44%) and carries a high mortality rate (94%).[4] According to one study in the United Kingdom, non-Hodgkin lymphoma has more commonly been shown to involve the liver compared with other malignancies.[4] Although hepatic involvement has been seen in 16%–22% cases of non-Hodgkin lymphoma, very few present as ALF.

NKT cells are a subpopulation of T cells that carry characteristics of both T cells and NK cells. In addition to having the surface markers of NK cells, they have the conventional antigen receptor present in T cells. Although T cells carry CD3+ and CD56− surface markers, NK cells are known to have CD3− and CD56+ surface markers. NKT cells, on the other hand, show combined features from both the groups and carry CD3+ and CD56+ immunophenotype markers.[10,11] NKT cells have 2 subsets, namely Type I and Type II, both of which play an important role in pathogenesis of autoimmune, infectious, and malignant disorders. Interestingly, both these subsets play antagonizing roles in the mechanism of liver injury, with Type I cells creating a proinflammatory state and Type II cells playing a protective role against Type I–mediated liver inflammation.[12] As seen in our case, NKT cells tend to have a strong association with EBV and commonly involve extranodal sites, specifically the nasal and nasopharyngeal regions.[11] EBV-associated nasal NKT cell lymphoma can be aggressive in its presentation and tends to be resistant to conventional chemotherapeutic agents involving anthracyclines.[13,14]

Treatment with L-asparaginase is associated with various adverse effects, such as hypersensitivity reactions, hepatotoxicity, pancreatitis, neurotoxicity, and coagulopathy.[15] Although mild hepatotoxicity can be expected after L-asparaginase chemotherapy, ALF has been reported to present with a cholestatic liver enzyme profile.[15–18] Histopathological evaluation typically reveals diffuse hepatic steatosis along with some degree of hepatic necrosis and presence of inflammatory cell infiltrate in the portal tracts.[18] Several case reports have suggested a role for L-carnitine and vitamin B complex as safe and effective treatment options in such cases.[19,20]

In conclusion, ALF can be a fatal condition that warrants close attention and timely evaluation for liver transplantation, where indicated. Ours is a unique case of NKT cell lymphoma leading to ALF by means of hepatic infiltration, with only one other similar case reported in the literature.[3] Our case also highlights the importance of distinguishing drug-induced liver injury from malignant hepatic infiltration from the standpoint of guiding treatment and determining prognosis and goals of care.

DISCLOSURES

Author contributions: I. Shah wrote and edited the manuscript and is the article guarantor. N. Vyas and JA Reynolds edited the manuscript.

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Informed consent could not be obtained from the family of the deceased. All identifying information has been removed from this case report to protect patient privacy.

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