Fulminate Hepatic Failure as an Initial Presentation of Non-Hodgkin Lymphoma: A Case Report

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ABSTRACT

Viral hepatitis and toxins comprise most common causes of fulminate hepatic failure that are often diagnosed with standard laboratory tests. Herein we discuss a rare, difficult to diagnosis etiology of acute liver failure (ALF). A 62-year-old man presented with a two-week history of fever and fatigue. At four days before admission he became lethargic. His past medical and drug histories were unremarkable. Physical examination revealed generalized jaundice, fever and loss of consciousness. Laboratory tests showed elevated liver transaminases with direct hyper-bilirubinemia. Abdominal ultrasonography and CT scan showed hepatosplenomegaly and para-aortic abdominal lymphadenopathy. A further work-up included liver biopsy. The histopathology and imunohistochemistry was compatible with diffuse large B-cell lymphoma. He underwent high dose glucocorticoid therapy but his condition deteriorated rapidly and he died eight days after admission. ALF as an initial manifestation of malignant hepatic infiltration is extremely rare yet should be considered in all patients with unknown hepatic failure that are highly suspicious for malignant neoplasm.

KEYWORDS
Acute liver failure; Fulminate hepatic failure; Neoplasm; Lymphoma

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INTRODUCTION

Fulminant hepatic failure is defined as the presence of a complex number of symptoms, signs and laboratory abnormalities indicative of liver failure in a patient in previously good health or compensated liver function. The etiology of fulminate hepatic failure varies among different age groups and in different geographic regions.[1,2] Although viral hepatitis, drugs and toxins compose the most common causes of acute liver failure (ALF), uncommon disorders such as autoimmune hepatitis, metabolic liver disease, vascular abnormalities and infiltrative malignancies such as lymphoma must be considered.[2]

In patients with lymphoma, ALF has been reported in prolonged, advanced disease or as a consequence of cancer treatment. However hepatic failure as an initial manifestation is extremely rare and more difficult to diagnose.[3,4] Liver biopsy is often necessary to confirm the diagnosis of an unknown infiltrative malignancy that solely presents with hepatic failure.[5]

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Herein, we present the case of a previously healthy 62-year-old man with ALF due to infiltrative non-Hodgkin lymphoma (NHL) followed by a review literature.

CASE REPORT

A 62-year-old man was admitted to our emergency department with loss of consciousness that began gradually from 5 days prior to admission. He complained of generalized body pain, disabling fatigue, night spiking fever and sweating during the preceding two weeks before admission. The patient became jaundiced from ten days before hospitalization. His past medical history was unremarkable and he had no history of any significant disease, alcohol abuse, cigarette smoking, substance addiction, blood transfusion, intravenous drug abuse, and tattooing. He had not taken any prescriptions or over-the-counter medications, or herbal or nutritional supplements during the previous six months. The patient lived in resided in Kerman he and had no history of any recent travel. There was no significant family history of liver disease.

In general appearance, he seemed ill, toxic and icteric. His vital signs included a blood pressure of 110/85 mmHg, pulse rate of 110/min, respiratory rate of 19/min and temperature of 39.1°C. The sclera were icteric and conjunctiva were pale, but there was no cervical lymph node enlargement. Heart and lung exam was normal. There was mild tenderness in the epigastric area upon deep abdominal palpitation. He did not have any signs of clubbing. In neurological assessment, he was in a lethargic state and had asterixis. Other examinations were unremarkable.

Routine laboratory tests revealed hyperbilirubinemia and elevated liver aminotransferases. Laboratory tests on the first day and during hospitalization are shown in Table 1. All serology tests for hepatitis A, B, C and human immunodeficiency viruses (HIV 1 and 2) were negative. Blood and urine tests for toxicology were not performed. Serology tests were also negative for anti-nuclear, anti-smooth muscle and anti-mitochondrial antibodies. All body fluid cultures were negative, in multiple analyses.

Both his brain CT scan and lumbar puncture test were normal. Abdominal and pelvic ultrasonography revealed hepatosplenomegaly. Para-aortic lymphadenopathy was seen in the abdominal and pelvic CT scan (Figure 1). Both chest X ray and chest CT scan were normal.

Due to the presence of para-aortic lymphadenopathy and hepatosplenomegaly, a biopsy of the liver was performed on the second day after admission. On histological examination of the liver specimen, diffuse sinusoidal infiltration with typical medium to large lymphocytes was observed (Figure 2). Immunohistochemistry (IHC) results were as follows: CD 3 negative and CD20 positive with Ki67 >80% (Figure 2). Likewise, involvement of bone marrow with malignant lymphocyte cells was reported in his bone marrow aspiration specimen. Consequently, diffuse large B cell lymphoma was diagnosed for the patient.

On the fourth day after hospitalization, high-dose glucocorticoid was started however the patient's clinical and mental status, and liver and kidney function tests worsened rapidly. Subsequently, there was progressive coagulopathy and azotemia. Due to increased respiratory failure, the patient was intubated and underwent mechanical ventilation. Hemodialysis was performed. Unfortunately the patient died on the eighth day after admission due to severe refractory hypotension.

DISCUSSION

Malignant hepatic infiltration is a rare cause of ALF that is mostly undiagnosed in primary clinical assessment.[6] It usually occurs in patients with previous medical histories of malignancy but in initial manifestation of cancer, as with our patient, is extremely rare.[6,7]

Hematological malignancies are the most common causes for malignant hepatic infiltration; among these, NHL is more prevalent.[7] Liver involvement in NHL has been seen in 16%–22% of

Table 1: Laboratory results during hospital admission.

Variable	Reference range, age-adjusted	On Admission	Day 4	Day 8
Hemoglobin (g/dl)	14–16.5 (men)	8.6	8	7.7
White-cell count (mm^3)	4000–11000	8700	12000	18400
Differential count (%)				
Neutrophils	32-65	80		
Lymphocytes	6-20	23		
Other		2		
Platelet count (mm^3)	150,000-450,000	157,000	100,000	43000
Random blood glucose (mg/dl)	100-180	67	90	76
Creatinine (mg/dl)	0.5 -1	1.4	4.4	6.3
Albumin (g/dl)	3.5-4.5	2.8		
Lactate dehydrogenase (LDH) (U/liter)	150-230	956		
Erythrocyte sedimentation rate (mm/h)	<20	80		
Bilirubin (mg/dl)				
Total	0-1	22.7	25	31
Direct	0-0.4	11.4	11.7	18
Prothrombin time (sec)	12-13	14	20	38
International normalized ratio for prothrombin time	1-1.1	1.2	3	7.7
Alanine aminotransferase (U/l)	18-34	6381	3458	141
Aspartate aminotransferase (U/l)	12-30	1043	980	288

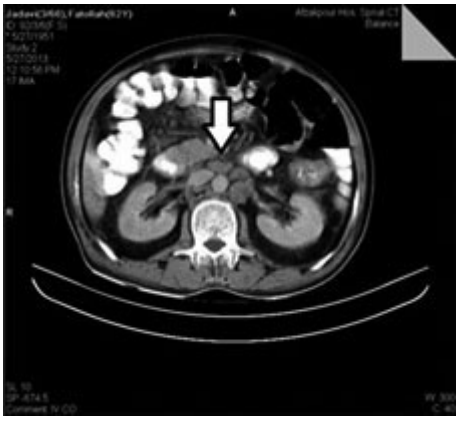

Fig. 1: Arrow shows para-aortic lymphadenopathy in abdominal CT scan.

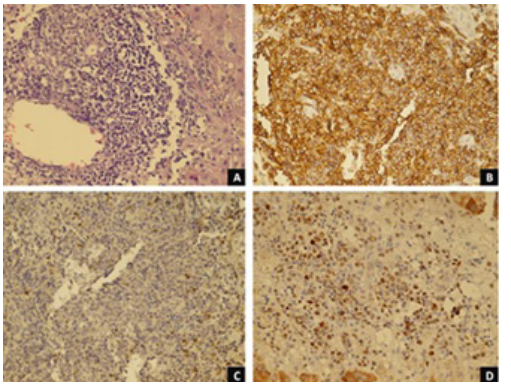

Fig. 2: Histology and immunohistochemistry (IHC) staining. (A): Liver biopsy specimen shows distortion of hepatic architecture and portal infiltration by malignant lymphocyte cells (Hematoxylin & eosin stain; 400x). (B): Immunostaining for CD 20, malignant lymphoid cells stain as membranous pattern (CD 20 staining for B cell origin). (C): Immunostaining for CD 3 (CD 3 staining considers T cell origin). (D): Immunostaining for Ki67, >80% of cells stained positive. (Ki67 staining shows mitosis activity in tumor cells).

untreated cases.[7,8] Although this is often asymptomatic, sometimes hepatomegaly, impaired liver enzymes, particularly mild to moderate elevations in alkaline phosphatase and lactate dehydrogenase (LDH) and rarely ALF occur.[6-9]

Three major causes explain the underlining pathophysiological mechanism of ALF in malignant infiltrative liver disease. The first one is tumor involvement of the small intrahepatic biliary tree which can cause progressive cholangitis, duct necrosis, and finally ALF.[10] Second, extensive infiltration of sinusoids and hepatic vasculature by

malignant cells cause diffuse hepatic necrosis.[11] Finally, cytokines such as interleukin 2, which is particularly secreted from lymphomatous tumor cells may damage interlobular bile ducts and cause portal fibrosis either directly or by an immunological mechanism.[12,13]

Due to the lack of evidence of the underlying primary malignancy, the diagnosis of ALF etiology is more difficult in malignant infiltrative liver disease. In an assessment of 18 patients with ALF due to tumor involvement of the liver, there were no signs and symptoms that distinguished it from the other usual causes of ALF.[7] However, the presence of palpable peripheral, intra-thoracic or abdominal lymphadenopathy, hepatosplenomegaly, lactic acidosis, high LDH and serum ferritin levels may be valuable clues to a suspected hematologic malignancy.[14-16] As with our patient, diagnosis is usually confirmed by biopsy of involved liver, bone marrow or lymph nodes.

Often the prognosis of ALF following malignant infiltrative liver disease is poor and the mortality has been reported as 94% in one study.[7] Frequently, death occurs within six days following hospital admission and is the result of multi-organ failure.[7,17] By starting suitable treatment prior to the onset of multi-organ failure, patients with NHL have better prognosis than other malignancies.[16,18]

Although orthotropic liver transplantation is the only life-saving therapy for all end stage liver diseases,[19] malignant metastatic lymphoma is considered a contraindication to liver transplantation. However there is limited information about this contraindication.[6,7] Despite the fact that liver failure can impact the metabolism of most drugs, appropriate chemotherapy should be started as soon as possible according to the clinical situation, underlying histology and degree of hepatic insufficiency.[16-18] CHOP-Rituxan chemotherapy is the most common chemotherapy regimen prescribed in NHL. Its success has been reported in cases of ALF secondary to malignant hepatic lymphoma.[16-18] A study in 41 patients with lymphoma and severe liver dysfunction showed that intravenous mechlorethamine, high-dose corticosteroids, and rituximab were safe and suitable therapeutic options for these groups.[20]

Nevertheless, our patient with multi-organ failure and refractory hypotension received high dose intravenous hydrocortisone alone and eventually died.

Although ALF as the initial manifestation of malignant lymphoma hepatic infiltration is extremely rare, it should be considered in patients who present with acute hepatic failure of unknown etiology. Specific therapy, particularly in the early stages of liver failure may be life-saving.

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Dr. Ahmadi: Diagnosis and treatment of patient and collecting data.
Dr. Akhavan Rezayat: Writing the article.
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CONFLICT OF INTEREST
The authors declare no conflict of interest related to this work.

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