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Anaplastic T-cell Lymphoma Presenting as Fatal Acute Liver Failure

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Acute liver failure (ALF) is an uncommon manifestation of liver disease and constitutes a medical emergency for which early identification is necessary. Hepatic involvement by hematologic malignancies although frequent, rarely causes severe hepatic dysfunction. Even more, acute hepatic failure as the first manifestation of a hematologic malignancy is extremely uncommon, although some cases have been reported in the literature. We describe the case of a 61 y/o puertorrican veteran who developed acute hepatic failure secondary to massive infiltration of the liver by a recurrent non-Hodgkin's lymphoma.

Key words: Liver failure, Acute, Lymphoma, Large cell, Hematologic, Neoplasms

Hepatic parenchymal infiltration by malignancies is common. In adults, metastatic infiltration of the liver from adjacent or distant malignancies or from other secondary malignancies like leukemia's and lymphomas is more common than primary liver tumors. Nevertheless, it is rare for infiltrating malignancies such as lymphomas to cause hepatic dysfunction and even more uncommon to present solely as fulminant liver failure (1-2). For unknown reasons the incidence of liver lymphomatous involvement have been increasing. There have been near forty cases reported in the literature with this clinical presentation (1-2).

Acute hepatic failure is a rare complication of liver disease, which represents the final pathway of a myriad of diseases that may rapidly produce severe liver injury. Although this injury is most commonly associated to significant hepatocellular necrosis, it has also been associated to massive hepatocellular replacement by malignancies, as seen in this case.

Case Report

A 61 y/o man presented to the Veterans Affairs Medical Center Satellite Ambulatory Clinic complaining of general malaise, weakness, dry cough and poor appetite. He referred a 15-pound weight loss over the previous two and a half weeks. He had previous history of an anaplastic large cell lymphoma (in remission after chemotherapy 8 yrs before), coronary artery disease with coronary artery bypass grafting and Saint Jude aortic valve replacement (one year before presentation), diabetes mellitus type 2, gastroesophageal reflux disease and hypothyroidism. He was treated with a first generation cephalosporin and antitussives for a suspected upper respiratory tract infection. He returned two days later to the outpatient clinics complaining of progressive shortness of breath and jaundice. He also stated having fever, chills, nausea and general malaise over the past week. He was noted to be on respiratory distress and for this reason he was transferred to the San Juan Veterans Administration Hospital for admission. There was no history of use of acetaminophen, alcohol, drugs usage other than the prescribed medications, use of herbal remedies or over-the counter medications, sexual risk factors, personal or family history of liver disease or exposure to jaundiced patients.

Upon examination he was found febrile with temperature of 102.1° F, normotensive with blood pressure of 119/69 mm/Hg, tachycardic (124/bpm) and tachypneic (24/min). He was agitated and confused; and presented appreciable jaundice. Abdominal exam disclosed diffuse tenderness over both upper abdominal quadrants. The liver was palpable 2-3 cm below the mid right clavicular line and

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tender. There was also evidence of splenomegaly. There was no ascites. No lymphadenopathies were noted.

Upon admission laboratory studies (Table 1) revealed a white blood cell count of 12.1, with a monocyte predominance; platelet count, 129, 000; alanine aminotransferase (ALT), 236 U/L; aspartate aminotransferase (AST), 309 U/L; alkaline phosphatase, 814 U/L; a total bilirubin of 12.5 mg/dl; LDH, 1683 U/L, moderate anion gap metabolic acidosis; prolongued prothrombin time 64.3 and an international normalized ratio (INR) >10 in the presence of a previous INR within therapeutic values for a patient with a mechanical heart valve 1 wk before admission. Previous liver function tests were normal one month before. Drug screen was negative.

Chest X ray showed no infiltrates. An abdominal ultrasound revealed changes consistent with hepatocellular disease without biliary tree dilation or hepatosplenomegaly.

All medications including warfarin and metformin were discontinued and aggressive medical management for hypoglycemia, coagulopathy, and encephalopathy was instituted. Prophylactic broad spectrum antibiotics were provided as well.

Two days after admission he had no evidence of improvement and his clinical course continue to deteriorate manifesting refractory hypoglycemia, worsening coagulopathy, severe metabolic acidosis and respiratory failure. Three days after admission (12 days after the initial presentation of symptoms) the patient died due to severe multiple organ failure caused by the acute liver failure.

The autopsy revealed systemic anaplastic large cell lymphoma with marked retroperitoneal and abdominal lymphadenopathy. Prominent extranodal disease was present in the liver and spleen. The enlarged liver weighed 3,800 grams, showed usual consistency without nodularity and a subtle pale brown mottling appearance. The sinusoids were markedly dilated and filled with large pleomorphic cells with occasionally lobulated nucleus, vesicular nuclear chromatin, conspicuous nucleoli and moderately abundant cytoplasm (Figure 1).

The neoplastic cells showed immunoreaction for CD3 and CD30 and were negative for CD20, CD15, and the ALK-1 protein.

In addition to the liver and spleen; lymphomatous infiltrates were identified in the lung, heart and thyroid gland. The bone marrow was also involved.

Table 1. Laboratory data

	Normal Values	Day 1 Admission	Day 2	Day 3	Day 4 (Death)
WBC (x10-3)	4.28-9.3	12.1	10.4	10.2	18.4
Hgb (g/dl)	12.6-17.8	14.1	10.9	12.6	8.3
Hct (%)	37.9-54.5	40.4	31.4	37.3	27.2
PLT's (x10-3)	155-371	129	106	107	107
PMN's (%)	34-74	39		62	50
Bands (%)		6		14	20
Lymph (%)	16.9-47.7	22		9	10
Mono (%)	0.2-1	26.7		8	18
Eos (%)	0-0.4	0		0	0
Baso (%)	0-0.1	0.2		0	1
Na (mEq/L)	135-145	128	130	133	140
K (mEq/L)	3.5-5	5.4	5.0	5.5	6.4
Cl (mEq/L)	100-110	90	93	94	98
CO2 (mEq/L)	24-32	17.6	18.7	21.3	9.8
BUN (mg/Dl)	10-26	34.8	43.2	29.6	56.9
Creatinine (mg/dl)	0.7-1.5	1.3	1.2	0.9	2.2
Glucose (mg/dl)	72-128	114	80	40	3
Ca (mg/dl)	8.5-10.5	8.9	8.5	8.7	8.4
Mg (mg/dl)	1.8-2.4				3.5
Pho (mg/dl))	2.5-4.5				4.3
Albumin (mg/dl)	2.6-5.2	3.2	2.8	2.7	2.1
Tot Prot (mg/dl)	6-8.5	6.4	5.5	5.1	4.1
AST (U/L)	0-40	309	273	269	982
ALT (U/L)	0-45	236	150	141	239
Alk Phos (U/L)	30-115 U/L	814	509	473	379
G-GT (U/L)	0-60			199	115
LDH (U/L)	60-200 U/L	1683			3854
T Bil (U/L)	0.2-1.3	12.5	11.2	12.9	16.2
D Bil (U/L)	0-.2			9.6	11.3
INR		>10	5.27	9.10	8.17
PT (Secs)	11.8-14.3	200	47.9	48.5	67.2
PTT (Secs)	24.7-36.7 Sec	64.3	44.6	73.1	

Discussion

The liver is a major component of the reticuloendothelial system for which liver involvement in the presence of hematological malignancies is not rare. Lymphomatous infiltration of the liver can be either primary or secondary. Primary hepatic lymphoma, usually presents as hepatic masses mimicking primary hepatocellular carcinomas or metastatic disease, rather than manifesting as an infiltrative process. On the contrary, secondary liver involvement by lymphomas is usually diffusely infiltrative with intra-sinusoidal propagation, for which manifestation is based on clinical suspicion in the presence of altered liver function tests, specially alkaline phosphatase, which is usually moderately increased and lactic dehydrogenase which can be markedly elevated (1).

Anaplastic large cell lymphoma (ALCL) is an aggressive, but potentially curable T-cell lymphoma, originally called Ki-1 lymphoma due to its characteristic immunoreaction with

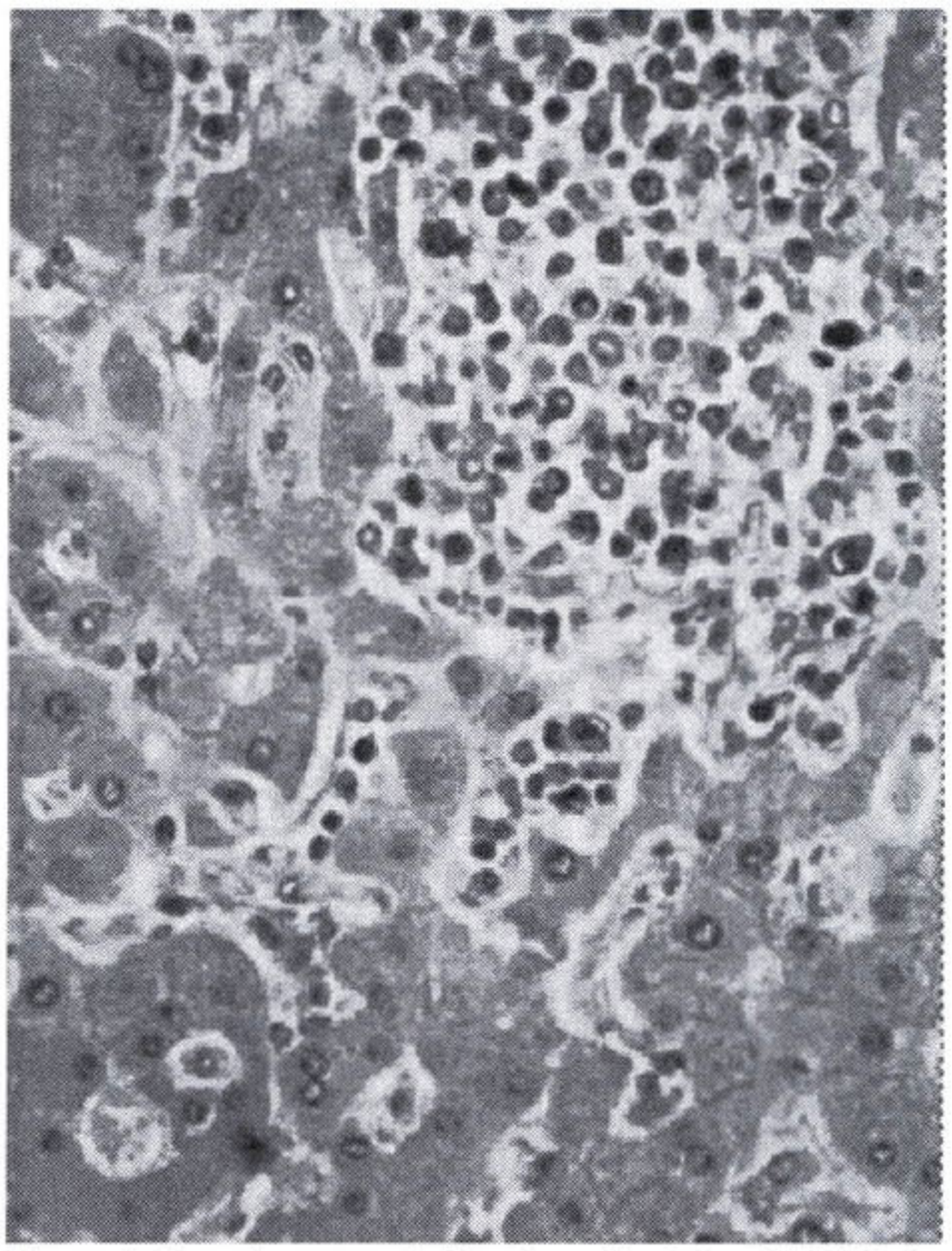

Figure 1. Lymphomatous Infiltration of the Liver (H&E Stain, Original Magnification 400x)

the activation antigen CD30 (Ki-1) (2,3,4). ALCL is a rare disease, comprising approximately 3% of adult non-Hodgkin's lymphomas (5) and is often associated with genetic alterations involving the anaplastic lymphoma kinase (ALK) locus on chromosome 2 (6). The most common of these alterations is the t(2;5) which results in a fusion product involving the nucleophosmin (NPM) gene on chromosome 5 (7). Approximately 60 to 85% of ALCL express the ALK protein. Expression of the ALK protein carries a favorable prognosis (8) with overall five year survival of 80% and occurs more frequently in younger patients, while ALK negative cases are more prevalent in the elderly and are associated with a 40% five year survival. Future genetic studies may aid in defining these groups as two distinct disease entities.

Acute liver failure is an infrequent manifestation of acute liver injury. This condition carries a high mortality rate even in countries where liver transplantation is available. Acute liver failure is manifested by rapid deterioration of liver function and the presence of encephalopathy in the absence of preexisting liver damage. The development of hepatic failure has been further named and characterized by the time of development of encephalopathy in hyperacute, acute and subacute.

The most common causes of acute liver failure are drug toxicity, as seen with acetaminophen intoxication and viral hepatitis. Other less common causes are initial presentation of Wilson's disease and/or autoimmune hepatitis, less common infectious agents such as herpes and Epstein Barr virus, toxins, acute fatty liver of pregnancy and malignant infiltration by leukemia's, lymphomas and other tumors such as melanoma and breast carcinoma.

Lymphomas rarely infiltrate the hepatic parenchyma massively inducing liver insufficiency (1,9). It is also extremely rare to present as fulminant liver failure (1,9). Massive lymphomatous infiltration causes hepatocellular ischemia, necrosis and cell death. When occurs, presents in a rapid course and the prognosis in most instances is fatal (10). Early diagnosis and treatment is essential to prevent death and possibly cure this disease (1,11-12). To establish the diagnosis a high index of suspicion is required, becoming a diagnostic challenge for the clinician due to the similarity to the presentation of other more common hepatic conditions.

These common signs and symptoms are: type B symptoms, lactic acidosis, lymphadenopathy, hyperbilirubinemia, elevated alkaline phosphatase and LDH, coagulopathy, thrombocytopenia and hepatosplenomegaly (1,9). Further more, in acute liver failure, severe coagulopathy and thrombocytopenia develop rapidly, leaving a small window for liver biopsy, an important tool for establishing a diagnosis in some cases (1,9,13). Immediate suspicion and early consultation should be considered when the previously mentioned factors are seen. Although the prognosis is poor, the chance of survival and even remission makes early diagnosis crucial (1,9,14).

Recent literature has described several cases of acute liver failure induced by massive lymphomatous involvement. Interesting is the fact, that around two thirds of the reported cases are due to non-Hodgkin's lymphoma. Even more, in a recent publication by Lettieri et al, three of the five cases reported as developing acute liver failure were T-cell lymphomas, as the case hereby presented, suggesting that maybe aggressive T-cell lymphomas are more likely to induce acute liver failure than the B-cell lymphomas. In all these cases acute liver failure was the initial presentation of the T-cell lymphoma. Our case is different in the fact that he had a prior history of an anaplastic large cell lymphoma which was in remission for 8 years until the fatal presentation of acute liver failure.

Resumen

El Fallo Hepático Agudo es una manifestación poco común de enfermedad hepática y constituye una

emergencia médica. Aunque el envolvimiento hepático por malignidades hematológicas es frecuente, rara vez causa disfunción hepática severa. Es también extremadamente inusual que la presentación inicial de una malignidad hematológica sea fallo hepático agudo aunque un número limitado de casos han sido reportados en la literatura. Describimos el caso de un veterano puertorriqueño de 61 años que desarrolló fallo hepático agudo, debido a una infiltración masiva del parénquima hepático por un linfoma recurrente tipo no-Hodgkin.

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