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MALIGNANCY CAN PRESENT AS ACUTE LIVER FAILURE – A CASE REPORT OF B-CELL LYMPHOMA WITH ACUTE LIVER FAILURE AS ITS FIRST PRESENTATION

Catarina Melita[1], Joaquim Tinoco[2], Rita Theias Manso[2], Liliana Antunes[3], Mónica Palma Anselmo[3], Paulo Telles de Freitas[3]

[1] Internal Medicine Department 2, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal
[2] Surgical Pathology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal
[3] Intensive Care Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

Corresponding author's e-mail: catarina.melita@ulsasi.min-saude.pt

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ABSTRACT

Malignant infiltration of the liver is a rare cause of acute liver failure and is associated with an exceedingly high mortality rate. We describe the case of an elderly woman presenting with fulminant hepatitis and simultaneous type B lactic acidosis, with near-normal imaging findings, who was later demonstrated to have non-Hodgkin lymphoma. The presence of acute liver failure, hepatomegaly, markedly elevated lactate dehydrogenase and/or lactic acidosis should raise suspicion for lymphoma infiltration of the liver and prompt liver biopsy early in the course of disease. We hope to raise awareness for this uncommon and elusive presentation of lymphoma, in the hope that it will help achieve earlier diagnoses and improvements in patient survival.

KEYWORDS

Acute liver failure, lactic acidosis, non-Hodgkin lymphoma, fulminant hepatitis, hepatic malignant infiltration

LEARNING POINTS

- Lymphoma presenting as fulminant hepatitis is rare and frequently fatal.
- Malignant infiltration of the liver should be suspected in cases of acute liver failure, particularly when no clear aetiology is present, and liver biopsy should be performed promptly.
- The internist should be aware of lymphoma as a potential cause of type B, non-hypoxemic lactic acidosis.

BACKGROUND

Acute liver failure (ALF) is defined by the presence of liver injury that has been progressing for less than 26 weeks, accompanied by hepatic encephalopathy and coagulopathy (international normalized ratio, INR >1.5), in the absence of preexisting liver disease[1]. The main causes of ALF include viral infections, drugs and toxins, metabolic disorders, vascular diseases and autoimmune injury. Liver infiltration

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by malignancy accounts for <1% of all ALF cases and often portends a poor prognosis[2].

CASE DESCRIPTION

A hypertensive 80-year-old woman, with no significant medical history, presented to the emergency department with headache and asthenia for the last 2 weeks, followed by gait imbalance, lower back pain, confusion, hypersomnolence and vomiting. There was no evidence of fever, weight loss or night sweats, but she had been in a rural area for a week at the time of symptom onset. Her family denied the patient's intake of drugs, alcohol and other potentially toxic substances.

On examination, the patient was initially normotensive, afebrile and anicteric, but showed disorientation, bradykinesia and slurred speech, with a Glasgow Coma Scale score of 13 points. No asterixis, meningeal or focal neurological signs were present, and the remainder of the physical examination was unremarkable except for mild right upper quadrant abdominal discomfort. Laboratory workup was notable for elevated lactate levels (12,8 mmol/l) despite no signs of hemodynamic instability or hypoxemia, as well as liver transaminases five times the upper-range limit and markedly elevated lactate dehydrogenase (LDH), with an international normalized ratio (INR) of 1.4 and mild hyperbilirubinemia (*Table 1*, results on admission). She also had mild leucocytosis with neutrophilia, elevated C-reactive protein (10 mg/dl) and acute kidney injury, with hypercreatininemia (3.44 mg/dl) and oliguria. Cerebrospinal fluid (CSF) analysis showed moderate cellularity with 168 nucleated cells/µl (80% polymorphonuclear leukocytes), and hyperproteinorrachia of 162 mg/dl, with mild glucose consumption. Concerns for bacterial meningitis led to initiation of broad-spectrum empirical antibiotics, including coverage for zoonoses.

There was no response to initial therapy and the patient was admitted to the intensive care unit two days later, as grade IV encephalopathy and shock developed. Her lactate levels continued to rise, as did aminotransferases and LDH despite adequate supportive care and antibiotics, as seen in day 5 results *(Table 1)*.

Computed tomography scan with contrast revealed hepatomegaly and a small, hypodense, focal area in the liver *(Fig. 1)*, with no other discernible liver abnormalities. Small, intra-abdominal lymphadenopathies and a thickening of peritoneal surfaces were described as reactive inflammatory findings, and no vascular abnormalities were present. Magnetic resonance imaging of the brain revealed only mild, diffuse pachymeningitis.

CSF cultures and viral panel results all came negative, as did blood cultures, hepatotropic viruses, other infectious agents (including human immunodeficiency virus, Herpesviridae, Leptospira, Brucella, Rickettsia, Borrelia, arboviruses) and an extensive antibody panel. Subsequently, new-onset cold

Laboratory parameters	Reference range	Admission	Day 5	Day 10
Serum lactate (mmol/l)	<2	12.8	24.7	6.4
Aspartate aminotransferase (U/l)	<32	164	3763	71
Alanine aminotransferase (U/l)	<33	120	768	84
Gama-glutamyl transferase (U/l)	<40	168	157	61
Alkaline phosphatase (U/l)	35-105	223	193	70
Lactate dehydrogenase (U/l)	135-214	1102	4634	479
Total bilirubin (mg/dl)	<1.2	2	3.5	9.1
INR	<1.2	1.4	2.1	1.7
Hemoglobin (g/dl)	>12	12	8.4	6
Leukocytes (×10^3/µl)	4.5-11	15.2	18.9	8.1
Platelet count (×10^3/µl)	>150	128	31	55
C-reactive protein (mg/dl)	<0.5	10.9	9.5	4.6
(CSF) Nucleated cells (cells/µl)	<5	168 (80% PMN)	-	-
(CSF) Protein (mg/dl)	<45	162	-	-
(CSF) Glucose (mg/dl)	>60	59	-	-
(CSF) β2-microglobulin (mg/l)	<1.3	2.4	-	-

Abbreviations: INR, international normalized ratio; CSF, cerebrospinal fluid.

Table 1. Laboratory parameters upon admission, and progression over days 5 and 10.

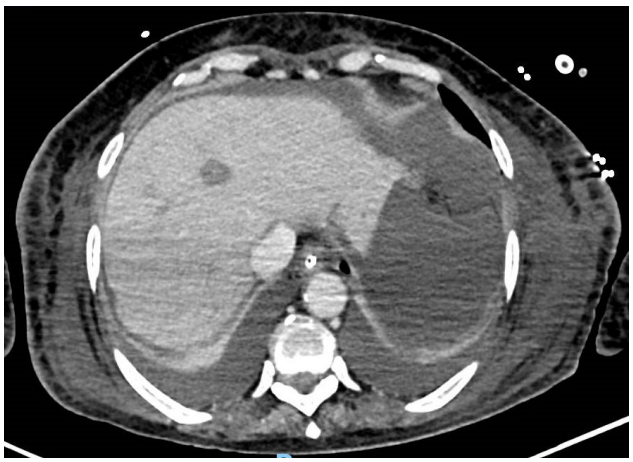

Figure 1. Computed tomography scan of the upper abdomen showing liver enlargement, ascites and a hypodense nodule in segment IV.

agglutinin haemolytic anaemia and hypercalcemia with low parathyroid hormone (PTH) and vitamin D levels developed. β2-microglobulin levels were moderately elevated in the serum and CSF, as well as angiotensin-converting enzyme (ACE). Much later, results of PTH-related protein were confirmed elevated (3.40 pmol/l, reference <2.5). There was a brief period of clinical improvement upon initiation of IV methylprednisolone on day 7, with lactate amelioration, reduction of vasopressor support and dramatic improvement in liver enzymes by day 10, despite elevated bilirubin and coagulopathy. Unfortunately, this was soon followed by rapid deterioration with septic shock, multiorgan dysfunction and aggravated disseminated intravascular coagulation (DIC), with death ensuing on day 15.

Autopsy showed widespread hepatic parenchymal distortion caused by nodular lymphoid proliferation, predominantly centred around portal tracts, and numerous areas of hepatocellular necrosis surrounded and infiltrated by predominantly intermediate size atypical lymphoid cells, positive for CD79a and BCL2 *(Fig. 2)*, also showing weak positivity for CD20 and PAX-5. Ki-67 proliferation index was 30% and immunohistochemistry markers CD3, CD23, CD10, BCL6, CD5, MUM1, CD138, CD30, TdT, CD34, AE1/AE3 and CAM 5.2 were all negative. These findings were consistent with B-cell non-Hodgkin lymphoma (NHL) with generalized involvement of the liver. Pathology analysis similarly identified involvement of CSF and meninges, lymph nodes, bone marrow, spleen, intra-abdominal adipose tissue, pancreas and heart by the lymphoma. However, due to extensive autolysis artifacts, inherent to normal postmortem tissue autolytic process, further morphological and immunophenotypic characterization were not feasible in this case.

DISCUSSION

Hepatic involvement secondary to lymphoma is common and is found in approximately 16-43% of NHL patients[3]. However, secondary liver dysfunction is usually found in later stages of the disease, and ALF as the main initial presentation is rare. This is associated with an extremely poor outcome, with reported mortality rates of 94% and many cases only diagnosed on autopsy[2,4].

Lymphoma can involve the liver with discrete mass lesions or as a diffusely infiltrative process, as in this case. Patients with ALF most commonly present diffuse disease and imaging frequently shows only hepatomegaly, with

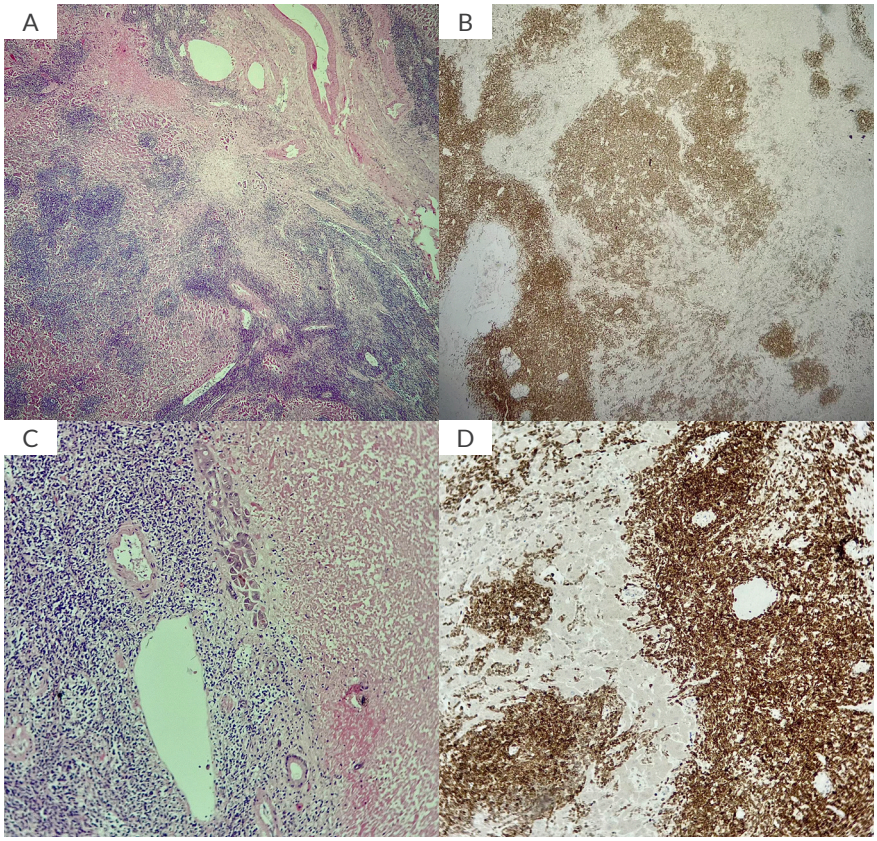

Figure 2. Hepatic infiltration by non-Hodgkin B-cell lymphoma with architectural distortion, portal tract lymphoid proliferation and necrosis. (A) Haematoxylin and eosin (25× magnification); (B) Immunohistochemistry marking with BCL2 (25×); (C) Haematoxylin and eosin, (100×); (D) Immunohistochemistry marking with CD79a (40×).

minimal alterations in parenchymal density or architectural distortion, sometimes with low-density areas reflecting necrosis[1,2,4]. Symptoms are often vague and include nausea, vomiting, upper abdominal pain or discomfort, as well as fever and other constitutional symptoms[2,4].

Our patient exhibited some of these symptoms, as well as considerable hyperlactataemia upon presentation, despite adequate oxygenation and peripheral perfusion, which raises suspicion for a non-hypoxemic, type B, lactic acidosis. Causes include thiamine deficiency, intoxication with ethanol and other alcohols, certain drugs, such as metformin or acetaminophen, and inborn errors of metabolism, none of which seemed to be the case[5]. Malignant neoplasms, most commonly haematological malignancies, in particular NHL, also cause type B lactic acidosis. Mechanisms include reduced lactate clearance caused by extensive liver involvement; focal areas of ischemia; concurrent thiamine deficiency (the consumption of thiamine is increased by the high tumoral cell turnover); and the Warburg effect, where malignant cells shift their metabolism towards anaerobic glycolysis, granting them a proliferative advantage. Albeit a rare finding, lactic acidosis occurring in the setting of malignancy often indicates a high tumour burden and sombre prognosis[5]. Additional clues pointing towards a lymphoproliferative disorder in this case included the elevated LDH, β2-glycoprotein and ACE levels in both serum and CSF, none of which are, however, specific. The development of haemolytic anaemia with cold agglutinins and non-PTH mediated hypercalcemia further raised suspicion.

Since early initiation of chemotherapy may potentially improve the patient's outcome in the setting of lymphoproliferative malignancy, it is vital to promptly and correctly establish the diagnosis as the underlying cause of ALF[3,4]. Our patient should have undergone early liver biopsy, but this was hindered by the misleading initial presentation, directing towards infectious multisystemic causes, associated with rather inconspicuous imaging findings, and by the persistent coagulopathy, later complicated by DIC. Transjugular liver biopsy was also not feasible since this technique is not available at our centre and the patient's instability precluded transport. As suspicion of lymphoproliferative disease arose, concurrent neurological involvement was hypothesized and a biopsy of the eye fundus was arranged, yet the patient's condition deteriorated before this was possible.

The primary or secondary nature of the lymphoma should also be considered, concerning its primary location in the liver with subsequent systemic dissemination, versus a systemic lymphoma with extra-hepatic sanctuary and secondary involvement of the liver. The authors favour the last hypothesis, taking into consideration the diffuse and homogenous parenchymal infiltration, rather than one or multiple individualized masses as seen in primary lymphomas of the liver, and the absence of immunosuppression or hepatotropic virus infection to drive chronic stimulation of B cells, in particular hepatitis C or B viruses[6].

This case illustrates that liver involvement by lymphoma should be considered among the differential diagnoses of ALF, even in the absence of recognizable extrahepatic involvement, and reminds us to consider non-hypoxemic causes for lactic acidosis, including haematological malignancy. Timely histological confirmation should be sought whenever possible.

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