Acute liver failure secondary to metastatic liver infiltration : case report and review of the literature

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Abstract

We present the case of a patient who died from multiple organ failure due to acute liver failure as a result of malignant hepatic infiltration by an adenocarcinoma. A review of the literature revealed that the clinical picture, laboratory examination, and imaging studies do not contribute to the diagnosis of this rare cause of liver failure. Therefore, liver biopsy should be considered early in the process, as this diagnosis is a contraindication for orthotopic liver transplantation. (Acta gastroenterol. belg., **2013**, 76, **436-438**).

Key words : acute liver failure, metastasis, sinusoidal infiltration.

Case report

A 59-year-old man was admitted to the hospital with a 3-day history of non-specific pain in the peri-umbilical area and right upper quadrant. The patient did not complain of fever, chills, nocturnal sweating, or weight loss, but he had recently experienced deep venous thrombosis of the lower limb. The patient was a moderate smoker and occasionally drank alcohol.

A review of the patient's medical history revealed vascular arteritis treated by bilateral femoro-popliteal bypass, lung emphysema, hypothyroidism, arterial hypertension, and dyslipidemia.

At the time of his clinical examination, the patient appeared subicteric and slightly cachectic with digital clubbing. His vital signs were in the target range. Cardiopulmonary and neurological examinations were normal. Light hepatomegaly and ascites was noted. Laboratory tests revealed a mild inflammatory response (C-reactive protein 38.7 mg/l), conjugated hyperbilirubinemia (total level 24.8 mg/l, conjugated level 19.8 mg/l), cytolysis (AST 151 U/l, ALT 121 U/l), and cholestasis (gamma GT 936 U/l). The patient's LDH level reached 595 U/l and his albumin level was low at 36 g/l, but blood coagulation, complete blood count, renal function, and ionogram were in the normal ranges.

Although the patient was stable for a few days, his situation then dramatically worsened. The total bilirubin levels increased over 6 days from 49 to 430 mg/l. His PTT levels dropped from 120% to 28%, and his platelet count decreased from 90000 to 12000/mm^3. Accordingly, the clinical status of the patient acutely worsened and encephalopathy appeared. The patient developed acute liver and renal failure. The patient did not have a history of acetaminophen, antimicrobial agent, antiepileptic agent, recreational drug, or herbal agent use or abuse. Common viral hepatic etiology was excluded, and cardiac echography ruled out right heart failure.

Liver echography was inconclusive except for a lack of focal lesions or signs of cirrhosis. The biliary tracts were not dilated. The gallbladder exhibited uncomplicated cholelithiasis. Ascites was present, but no splenomegaly or portal obstruction was found.

Contrast enhanced multidetector computed tomography (MDCT) revealed rare non-specific hypodense areas within the hepatic parenchyma (Fig. 1a), but no evident signs of tumoral infiltration or cirrhotic change were found. We found no signs of portal hypertension, but ascites was clearly demonstrated. The examination did not reveal signs of carcinomatosis. At the time of analysis, the ascites appeared to be transudative with weak neoplastic invasion.

Positron emission tomography/computed tomography (PET/CT) revealed a diffuse hypermetabolic liver with maximal activity in the left lobe and inferior portion of the right inferior lobe, contrasting with the low physiological activity of the heart (Fig. 1b). Diffuse hypermetabolic foci were present in the bone marrow, but without osteolytic or osteosclerotic counterparts on CT. The thoracic component of the PET/CT was normal except for an not systematized right upper pulmonary lobe infiltration.

Although the general and coagulation status of the patient was declining quickly, an emergency coelioscopic liver biopsy was performed after 48 hours of hepatic failure. Logistic reasons prevented us from performing a transjugular liver biopsy, as this technique is not available at our care center. The fundamental purpose of the biopsy was to exclude a treatable lymphoma. Histology (Fig. 2) revealed massive parenchymal and sinusoidal infiltration by a moderately differentiated adenocarcinoma, probably pulmonary in origin. The patient died 4 days after the biopsy due to multiple organ failure.

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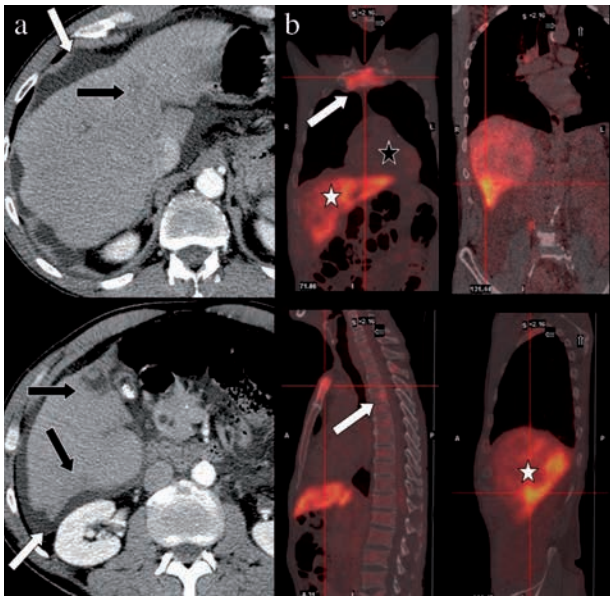

Fig. 1. — a) Selected contrast enhanced axial MDCT views demonstrate aspecific areas of hypodensity in the hepatic parenchyma (black arrows). Diffuse ascites is present (white arrow). b) Sagittal and coronal integrated PET/CT views through the left and right posterior hepatic lobes illustrate an extremely "hot" liver with diffusely increased activity throughout the hepatic parenchyma (white star), in contrast to the extremely low physiological activity of the heart (black star). Numerous spots of hyperactivity are also present throughout the bone marrow (white arrows).

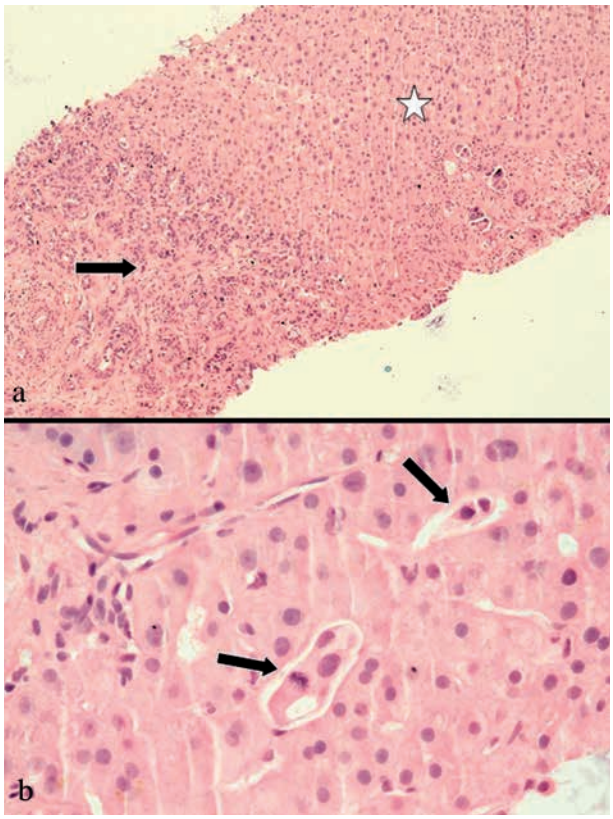

Fig. 2. — Photomicrographs (hematoxylin-eosin stain) of the hepatic sample obtained through celioscopic biopsy. a) Low power field view (×5) in which the hepatic parenchyma (white star) appears to be infiltrated by adenocarcinoma cells (black arrow). b) Higher power field view (×40) in which numerous hepatic sinusoids appear to be infiltrated by neoplastic cells (black arrows).

Discussion

Introduction

Acute liver failure is defined as a rapid decline in the synthesis function of the liver in a patient without preexisting liver disease. Coagulopathy (international normalized ratio ≥ 1.5), hepatic encephalopathy (any altered mental status), and jaundice appear less than 26 weeks after the onset of hepatic impairment (1).

Various etiologies are known for acute liver failure. Acetaminophen toxicity accounts for the majority of cases, whereas other drugs (e.g., antimicrobials, antiepileptics, amiodarone, recreational drugs, herbal agents) and viral agents (e.g., hepatitis A or B, Epstein-Barr, and cytomegalovirus, as well as hepatitis E and herpes simplex) can also be responsible. Autoimmune and ischemic hepatitis, Wilson's disease, Reye's syndrome, portal or hepatic vein thrombosis, pregnancy-associated liver failure, and sepsis can also be causal (2). Metastatic liver infiltration is rarely a cause of liver failure, though the liver is the most frequent site of metastatic spread ; almost 50% of patients with solid malignant disease eventually develop hepatic metastases. These liver lesions remain asymptomatic in the vast majority of cases with the retention of sufficient hepatic function (3). Thus, acute liver failure secondary to metastatic liver infiltration is rare. When this complication does occur, it results from diffuse sinusoidal infiltration rather than the classical tumoral focal deposits. This infiltration induces hepatic ischemia, hepatic necrosis, and tumoral portal vein thrombosis (4).

Neoplasms causing acute liver failure secondary to metastatic liver infiltration can be solid or hematological in origin. The gastrointestinal tract, breast, urothelium, lung, and nasopharynx are known tissues of origin, as well as Hodgkin and non-Hodgkin lymphomas, leukemias, and malignant histiocytosis (5).

Clinical presentation

In addition to the rarity of acute liver failure secondary to malignant hepatic infiltration, its presentation often remains obscure, causing diagnostic uncertainty and requiring a thorough general and liver investigation. The symptoms are general and non-specific : fatigue, abdominal tenderness, and weight or appetite loss. Jaundice, ascites, and hepatomegaly are present in most cases before the onset of liver insufficiency. The only remarkable point is the absence of cerebral edema, a common complication of liver failure (6). The increase in serum aminotransferase indicates hepatocyte destruction, but

without correlation between the measured levels and disease severity (7). Elevated LDH levels reflect uncontrolled tumor expansion and, thus, liver cell destruction in hepatocellular carcinomas (8). These findings appear to be prodromic to the acute liver failure, developing in less than 2 weeks and being fatal in the same time span (6). An important point is to differentiate symptoms from the underlying disease and liver failure. Lymphadenopathies can raise suspicion of hematological neoplasia and digital hippocratism can point to pulmonary disease, whereas paraneoplastic syndromes can narrow down the diagnosis.

Imaging techniques and further evaluation

Hepatic ultrasound and magnetic resonance imaging (MRI) have approximately the same accuracies as MDCT for the detection of focal hepatic masses, but they are less effective for the evaluation of the other abdominal organs (9). The limits of these techniques are reached when trying to demonstrate the presence of small metastases. All case reports to date, most often using MDCT, have concluded that imaging techniques are unable to demonstrate the sinusoidal infiltration causing acute liver failure, as no nodular lesions are found and only marked hepatomegaly is observed. This homogeneous aspect is due to the diffuse sinusoidal invasion. The differential diagnosis should include hepatitis, lymphoma, storage disease, granulomatosis, and diffuse hepatocellular carcinoma (10). However, Doppler ultrasound can contribute to a tentative diagnosis by providing information on the hemodynamic status of the portal venous system. Sinusoidal obstruction will lead to increased portal pressure. Portal flow velocity will decrease and the flow may become hepatofugal. The portal vein will then appear narrow and the hepatic artery prominent (11) ; Liver infiltration must be considered if this finding is seen in the absence of signs of cirrhosis.

Fluorine-18-labeled fluorodeoxyglucose PET/CT imaging is able to detect liver metastases from several origins, sometimes in an equal or even more sensitive manner than MDCT and MRI (12,13). PET/CT has been performed rarely in cases of diffuse metastatic liver infiltration, probably because of the limited availability of the test and the acute clinical deterioration of the patients. The “hot liver sign”, also termed “hepatic superscan”, refers to intense diffuse hepatic tracer uptake with low brain and cardiac tracer uptake. This finding has been described as an early indicator of extensive metastatic involvement of the liver (14)

Because of these alarming findings, the absence of etiology for acute liver failure and the predictable mortality, the patient should undergo a liver biopsy early in the diagnostic process. The window of opportunity for this invasive procedure is narrow, as coagulation abnormalities will appear (15). A transjugular liver biopsy carries less hemorrhagic risk than percutaneous biopsy and should be favored if available.

Outcome and management

The focus of managing acute liver failure of any origin is to determine its etiology (as specific treatments or antidotes can be proposed) and to have the case managed in an intensive care unit (ICU) of a care center with liver transplant capabilities, where specific measures can be applied and the need for liver transplantation identified (16). Without optimal treatment, acute liver failure results in multiple organ failure syndrome.

Acute liver failure resulting from malignant infiltration has a very poor prognosis, leading to death a few days after rapid deterioration. Only a few patients have been reported to survive after suffering from a promptly treated hematological malignancy (6). Despite the rarity of the diagnosis, it is important to consider it, as secondary malignant liver disease clearly contraindicates orthotopic liver transplantation. The known outcome will help avoid unnecessarily aggressive patient care, including transfer to the ICU of a transplant-capable center under sometimes delicate conditions.

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