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Acute Liver Failure Precipitated by Diffuse Liver Infiltration of Metastatic Breast Cancer: A Case Report

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ABSTRACT

We report a case of acute liver failure induced by metastatic cancer that is not identified on radiologic studies in a 53 year old female with a history of treated breast cancer.

Keywords

Acute liver failure (ALF), Metastatic breast cancer.

Introduction

Acute liver failure is defined by acute liver damage, impaired liver function (jaundice and coagulopathy) and clinically apparent hepatic encephalopathy in patients with no underlying chronic liver disease [1]. The condition of patients who develop coagulopathy but do not have an alteration in their level of consciousness is defined as acute liver injury.

In fact, virally induced ALF remains the most common cause worldwide although it has declined substantially in Europe [1].

Although the liver is a common location for hematogenous spread of solid tumors, clinically severe liver failure with coagulopathy and encephalopathy as a result of metastatic infiltration is rare [2].

There have been few reports of acute liver failure due to infiltration of the liver by malignant cells. In a large, multi-center ALF registry 1.4% of ALF were attributed to malignancy and in a large single center study performed at the King's College in London, only 18 patients (0.44%) with this condition were identified over an 18-year period (1978–1995). The malignancies included lymphoma or leukemia (33%), breast cancer, (30%), and colon cancer (7%). Unlike the usual pattern of liver metastases, imaging studies may not reveal discrete hepatic lesions and the diagnosis can be challenging [2,3]. Therefore, most cases are diagnosed post mortem by autopsy [4,5].

Case Presentation

A 53 years-old female with medical relevant story of poorly differentiated infiltrating ductal breast carcinoma metastatic to bones submitted to hormonal therapy and to 6 cycles of chemotherapy (Docetaxel, Herceptin, Pertuzumab), last session was 1 week prior to her presentation, was admitted to the hospital due to jaundice, right upper quadrant abdominal pain and weight gain. The patient was scheduled for mastectomy wich was delayed due to her symptoms. There was no history of alcohol, drugs or natural products consumption. The patient also denied recent travels.

On admission to the hospital, she was hemodynamically stable and afebrile. Physical examination was significant for icteric sclera, mild right upper quadrant abdominal tenderness and hepatomegaly. No other relevant findings including ascites or hepatic encephalopathy were found. Also, there were no lymphadenopathies or rash. Blood tests revealed leukocytosis of 12.8 × 10 9 (4.0-11.0 × 10 9) with left shift. Platelets count was normal of 170.000. Liver enzymes were disturbed with a cholestatic pattern predominance: AST 145 IU/L (<34 IU/L), ALT 89 IU/L (<49 IU/L), GGT 658 IU/L (<38 IU/L), alkaline phosphatase (AP) 402 IU/L (<104 IU/L), total bilirubin 3.7 mg/dl (<1.0 mg/dl) and direct bilirubin 3.5 mg/dl (<0.2 mg/dl), as well as prolonged INR: 1.31. Abdominal ultrasound was done initially to determine whether the problem of cholestasis is intrahepatic or extrahepatic. It showed hepatomegaly (the liver is enlarged measuring 17.7 cm at the midclavicular line) with a coarse liver echotexture with no hepatic duct's dilation. MRI then was done and showed huge hepatomegaly. To note PET scan was

done 2 weeks prior to presentation and showed increase in size of breast nodules, resolution of the bone lesions without evidence of hepatomegaly or any liver uptake indicating metastatic lesions.

An extensive workup diagnosis including viral serologies (HAV, HBV, HCV, CMV), autoimmune and metabolic studies was done although the patient has a cholestatic liver disease and failed to show an etiology. A presumptive diagnosis of vascular disorder of the liver (Budd Chiari syndrome or SOS) was assumed. Abdominal doppler ultrasound showed patent portal and hepatic veins. Liver biopsy was considered as serologic testing and imaging fails to elucidate a diagnosis. The patient's condition deteriorated and the liver function tests results also worsened (peak values…). Microscopic examination revealed very few foci of preserved liver tissue extensively infiltrated by tumoral elements arranged in small nets of carcinomatous cells showing mild to moderate nuclear pleomorphism and frequent mitotic figures. These results support the diagnosis of primary breast carcinoma. Unfortunately, Immunohistochemical stains, E-cadherin and CD44 stains weren't tested. The patient's condition deteriorated rapidly and the she died within 10 days of presentation.

Discussion

ALF is a rare diagnosis with the vast majority of cases are related to drug toxicity [3]. Of these, acetaminophen is the leading cause of acute liver failure in the United States and Europe [3]. Viral hepatitis, such as hepatitis B, as well as autoimmune liver disease and hypoperfusion or shock are also causes of many cases of acute liver failure [3,6]. Although the liver is a common location for hematogenous spread of solid tumors, ALF as a result of metastatic tumor involvement is rare [7]. Rowbotham and associates analyzed 4,020 ALF cases over an 18-year period and attributed only 0.44% of these cases to malignant hepatic infiltration [5,8,9]. Furthermore, hematologic malignancies have been described more than solids tumors in particular non Hodgkin lymphoma [3,10-13]. And the solid malignancies included breast, colon, and small cells lung cancer [3,11-13].

Breast cancer usually spreads to the bones, lungs, and/or liver [3,4,14]. Approximately 40–50% of women with metastatic breast cancer will have liver metastasis at some point during the course of their disease [3,14]. In the case of ALF caused by metastatic breast cancer, most cases have a prior history of known and adequately treated breast cancer [3,15]. Ductal carcinomas of different degrees of invasiveness are by far the most frequently described [3,15].

The majority of patients present with 2–6 weeks of fatigue, nausea, anorexia, jaundice, worsening ascites, and different levels of altered mental status [3,16]. The degree of hepatic enzyme elevation varies upon presentation, but is often found to correlate with the degree of intrasinusoidal hepatic involvement [2]. Most patients showed predominantly cytolytic jaundice with modest elevation of alkaline phosphatase. In our case, serum aminotransferase level was not as high as has been found in other cases of ALF [10].

In a handful of cases such as the one described by Goswami and associates, patients present with significant hepatic dysfunction but no hepatic encephalopathy [3,8]. In our case, acute onset of jaundice associated with hepatomegaly, progressive elevation of LFTs and evidence of coagulopathy drew attention toward primary liver pathology and even possible hepatic failure, however there was no evidence of encephalopathy. The presentation however, clinically mimicked ALF. Considering radiologic studies, typical radiologic features of liver metastases are target lesions on ultrasound and irregular areas of low attenuation on CT [8,17]. In case of ALF the diffusely infiltrating type of metastases has been most commonly described. As with our patient radiological studies are typically not able to detect this type and the diagnosis can be challenging [4] especially that in most cases the history of cancer is not necessarily recent [2]. Subsequently, hepatomegaly and ascites may be the only radiologic findings, and most cases are diagnosed post mortem by autopsy.

The underlying mechanism of diffuse parenchymal metastasis remains unknown [3,4]. Allison et al proposed a loss of cell surface adhesion molecule expression; the three cases in their study described as diffuse intrasinusoidal hepatic metastasis did not express both E-cadherin and CD44, which are glycoproteins involved in cell-cell and cell-extracellular matrix adhesion [3,4]. In the present case, a difference in E-cadherin expression in the two different areas of metastasis was observed; the tumor cells in the metastatic nodule in the lung stained positive for E-cadherin, while the infiltrating tumor cells in the liver stained negative [3,4]. These findings support the hypothesis that a loss of cell surface adhesion molecule expression is involved in facilitating diffuse parenchymal metastasis [3,4,9]. Various mechanisms have been suggested to explain the association of hepatic infiltration and ALF including tumour infiltration of the biliary tree, hepatic vasculature, and hepatic parenchyma [11]. Invasion of the extrahepatic biliary system leads to obstructive jaundice rather than ALF, but infiltration of small intrahepatic bile ducts may result in extensive cholangitis, duct necrosis, and ALF [10,18]. In addition, obstruction of hepatic venules by tumour may result in hepatocyte ischaemic injury and subsequent hepatocellular necrosis [8,10,19]. Alternatively, rapid replacement of vast areas of hepatic parenchyma by malignant cells may lead to a critical mass of hepatocyte destruction and subsequent ALF is possible that massive release of cytokines from malignant cell populations anatomically distinct from the liver may lead to ALF in a similar way, since occasional instances of fulminant hepatic failure have been described in non-metastatic renal cell carcinoma [10,19,20].

Because clinical presentation and noninvasive investigations may not be diagnostic, histological examination is necessary and a liver biopsy may be useful [9,5,21]. Many authors report that in ALF caused by metastatic breast cancer, the most common histologic finding was widespread intrasinusoidal infiltration of the tumor with extensive fibrous tissue [2,3]. Necrosis is also commonly seen and is associated with intravascular invasion and thrombus formation affecting tissue perfusion [2,3].

Finally, the prognosis of ALF from neoplastic infiltration is

extremely poor (90% mortality rate) with death occurring within several days of clinical presentation [3,7,8]. Myszor and Record reviewed 25 cases of ALF from hepatic infiltration secondary to hematologic and solid organ malignancies and reported a 100% mortality rate at a mean period of 7.8 days from the time of hospitalization [8,22].

Conclusion

Although malignant infiltration of the liver is rare, it ought to be considered as a differential diagnosis in patients with acute hepatic failure. Hepatomegaly may be one of the only clues. Imaging is often non-diagnostic. Liver biopsy may be the most effective technique to confirm the diagnosis during the patient's life.

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