

CASE REPORT

Metastatic breast cancer presenting as acute liver injury: diagnostic dilemma in the setting of suspected hemochromatosis

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Abstract

A 70-year-old female with a history of lobular carcinoma of the breast, status post-mastectomy followed by adjuvant radio-chemotherapy in remission for 4 years was admitted with the features of acute liver failure (ALF). Iron studies revealed a hemochromatosis picture and the CT and MRI scans of the abdomen suggested cirrhosis. An extensive workup failed to identify an etiology. A trans-jugular liver biopsy was obtained and revealed poorly differentiated carcinoma consistent with the metastasis of breast primary. The patient's condition deteriorated and died within a week following the onset of acute hepatic failure. DNA testing revealed that the patient was heterozygous for H63D mutation. In cases of ALF with the suspicion of malignancy, liver biopsy should be obtained to evaluate an infiltrative hepatic disease.

INTRODUCTION

Acute liver failure (ALF) is defined as acute liver dysfunction manifesting as coagulopathy (INR \geq 1.5) and presence of hepatic encephalopathy of any degree with less than 26 weeks duration, in a patient without pre-existing liver disease [1]. Malignancy is an uncommon cause of ALF and, in very rare cases (0.44–1.4%), can occur due to a diffuse pattern of metastatic infiltration to the liver [1]. The diagnosis of infiltrative liver metastasis can be challenging, and most cases of ALF from neoplastic infiltration have an extremely poor prognosis. Early recognition at presentation will help to avoid a battery of investigations and help providers to convey vital information, such as prognosis and scarcity of treatment, to their effected patients. Here, we will appraise the clinical and laboratorial findings, discuss treatment and prognosis and review the available literature.

CASE PRESENTATION

We present a 70-year-old female with a history of lobular carcinoma of the breast, status post-mastectomy followed by adjuvant radio-chemotherapy who remained disease free for 4 years, referred to our hospital with the finding of hypotension. She was also complaining of right upper quadrant pain, jaundice and asthenia. No complaint of dizziness, weakness or change in mentation was noted during the initial encounter. Upon admission, her mean arterial pressure was 63 mmHg, and she had scleral icterus and ascites. She did not have fever, abdominal pain, pruritus, hepatomegaly or hepatic encephalopathy. Her hemoglobin was 8.8 gm/dl; mean corpuscular volume of 90.5 fl; ferritin of 5485 ng/ml; iron saturation of 74% and transferrin of 126 mg/dl; all suggestive of hemochromatosis. Additional labs included aspartate aminotransferase (AST) 240 IU/l; alanine aminotransferase (ALT) 431 IU/l; gamma glutamyl transferase

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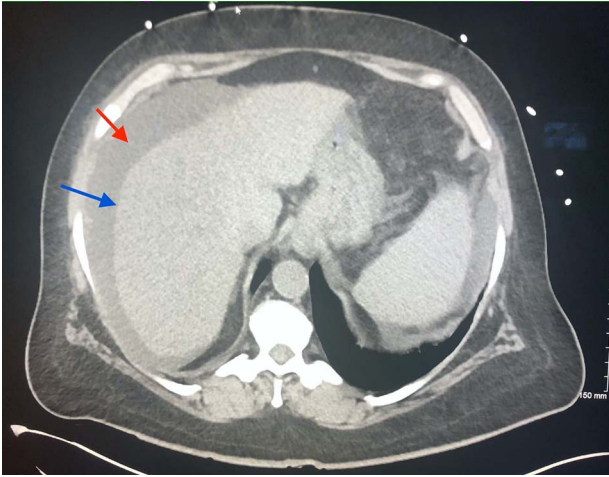


Figure 1: Cross-sectional imaging of the CT abdomen pelvis without contrast showed lobulated contour to heterogeneous attenuation of the liver (Blue arrow) and moderate ascites (Red arrow).

550 IU/l; alkaline phosphatase (ALP) 431 IU/l; total bilirubin (TBili) 11.6 mg/dl; direct bilirubin (DBili) 6.7 mg/dl and INR 1.8. CT scan of the abdomen without contrast showed ascites and heterogeneous attenuation of the liver suggestive of cirrhosis without any specific hepatic lesions (Fig. 1). She was started on maintenance fluids and conservatively managed. We started an extensive workup including MR abdomen, viral serologies (HAV, HBV, HCV and CMV), paracentesis and autoimmune panels. Metabolic studies failed to identify an etiology. MR abdomen confirmed the findings of a cirrhotic liver without overt focal hepatic lesions and excluded pancreatic/biliary mass. After 4 days in the hospital, she developed a bleeding diathesis from intravenous catheter sites. Her TBili increased to 16 mg/dl with DBili of 9 mg/dl and INR increased to 2.1. At this time, a working diagnosis of rapidly progressive liver failure due to hemochromatosis or autoimmune hepatitis was assumed. A trans-jugular liver biopsy was performed after transfusion of fresh frozen plasma to correct her bleeding to find a definite diagnosis. Tissue biopsy revealed poorly differentiated carcinoma consistent with metastasis from a breast primary. She then developed clinical hepatic encephalopathy with an ammonia of 94 $\mu\text{mol/l}$. She deteriorated further with no response of blood pressure to three different vasopressor agents. Eventually, the patient and family decided to withdraw medical care. DNA testing revealed that the patient was heterozygous for H63D mutation.

Microscopic examination of the trans-jugular liver biopsy showed an extensive involvement of the tissue by the aggregates of malignant cells (Fig. 2). A trichrome stain highlighted prominent fibrosis surrounding the malignant infiltrate (Fig. 2). It was difficult to establish if the fibrosis was secondary to metastatic carcinoma or arising in background cirrhosis. Immunohistochemical stains were performed and showed positivity for cytokeratin AE1/AE3, CK7, GATA-3 (Fig. 3) and focal staining for GCDFP-15 (Fig. 4) and Mammaglobin, confirming breast origin.

DISCUSSION

Liver metastasis is a common phenomenon in breast, stomach, colon, pancreatic and lung solid tumors [2]. However, it

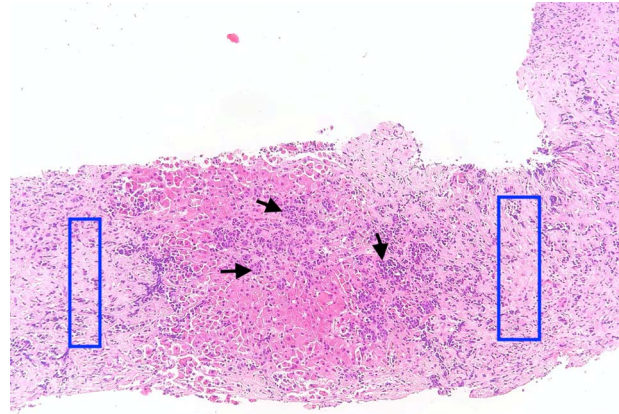


Figure 2: Core biopsy of hepatic tissue showing the aggregates of malignant cells (Black arrows) and dense fibrosis (Blue boxes) (H&E, 10 \times magnification).

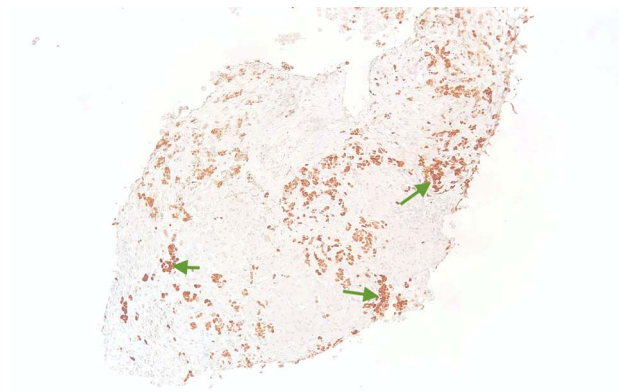


Figure 3: GATA3 Immunohistochemical stain showing strong nuclear positivity in malignant cells (Green arrows) (10 \times magnification).

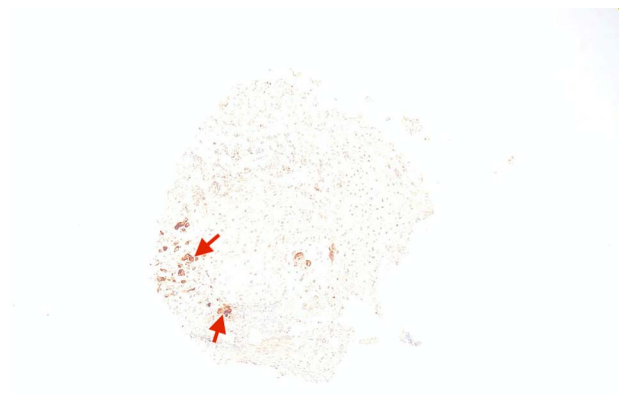


Figure 4: GCDFP-15 Immunohistochemical stain showing focal cytoplasmic positivity in malignant cells (Red arrows) (10 \times magnification).

presenting as ALF, after a disease-free interval of a breast cancer, can create a diagnostic challenge. In the review of ALF by Mogrovejo et al. between 1950 and 2014, diagnosis was made post-mortem in 24 cases and ante-mortem in eight cases, with a statistically significant trend of increasing pre-mortem diagnosis since 2000 [3]. This could possibly be due to earlier intervention with trans-jugular biopsy as well as the evolution of immunohistochemistry.

Immunohistochemistry is a unique ancillary examination for the evaluation of metastatic tumors from unknown sites. A single marker may be used to support a suspected site of origin; however, here, a constructed panel helped to determine the tissue of origin. Cytokeratin (i.e. AE1/AE3 antibody) are commonly seen in carcinomas. Nonepithelial tumors such as melanomas and sarcomas, and hepatocellular carcinomas are often negative for pankeratin [4]. Gross cystic disease fluid protein 15 (GCDFFP-15; BRST-2), also known as prolactin-inducing protein, is a glycoprotein present in various body fluids including saliva, milk and seminal fluid and is positive in breast carcinoma. Mammaglobin is a marker that is overexpressed in 48–84% of breast carcinomas. It is more sensitive but less specific than GCDFFP-15 for diagnosis of a breast primary tumor. For metastatic carcinoma, GCDFFP-15 has a high (>95%) specificity for breast primary tumor if the other mentioned sites are clinically excluded [5]. GATA3 is also a very sensitive marker for breast carcinoma and is more sensitive than GCDFFP15 [6]. The utility of this marker is somewhat limited by a lower (50–74%) sensitivity; therefore, the absence of staining does not exclude a breast primary tumor [7].

The most common pattern of liver metastasis is the formation of discrete multiple nodules. A single nodule formation is next most common, while diffuse tumor invasion into the liver parenchyma is less common [8]. In typical cases, contrasted CT or MRI would identify the dense or nodular pattern of the metastases larger than 1–2 cm; however, with diffuse metastasis, imaging may be non-specific. A diffuse pattern of spread to the liver surface tends to be smooth without nodularity, despite a significant degree of tumor invasion.

Most individuals with hereditary hemochromatosis are homozygous for the C282Y or H63D mutation. However, our patient's genetic architecture consisted of one copy of H63D (heterozygous), which has no associated risk for hemochromatosis [9]. Nevertheless, studies have shown that the presence of a heterozygous H63D mutation results in a significant increase in serum transferrin saturation and alters iron indexes without significant iron overload [10]. Our patient's initial iron studies and the progression of the liver failure raised suspicion for hemochromatosis; however, liver biopsy revealed no hepatic hemosiderosis or iron staining in the hepatocytes. The clinical presentation, the blood testing pattern of a hemochromatosis phenotype and radiological evidence in our patient obscured the malignant infiltration of the liver until tissue biopsy was obtained.

Diffuse parenchymal metastasis is an unusual pattern of liver metastasis that can cause liver failure. In this case, a CT scan and MR of the abdomen failed to detect liver metastasis, while microscopic examination revealed diffuse tumor cells. In cases of ALF with suspicion of malignancy, liver biopsy should be obtained to evaluate an infiltrative hepatic disease. This case highlights the importance of keeping a broad differential and the avoidance of premature closure or anchoring when determining the etiology of ALF.

AUTHOR CONTRIBUTIONS

R.C. helped conceptualize the paper, contributed to data acquisition, wrote the manuscript and reviewed and approved the final manuscript.

H.T. and B.H. helped conceptualize the paper, contributed to data acquisition and reviewed and approved the final manuscript.

K.F. contributed the pathology slides, reviewed pathology portion and approved the final manuscript.

M.D. is the investigator of this project and responsible for the overall conduct, results and conclusions of the paper. He conceptualized the paper, contributed to the manuscript and reviewed and approved the final manuscript.

FINANCIAL DISCLOSURE/CONFLICT OF INTEREST

The authors have no financial relationships relevant to this article to disclose. The authors have no conflicts of interest to disclose.

FUNDING/SPONSORSHIP

There are no financial conflicts of interest to disclose.

ETHICAL APPROVAL

This study was approved by graduate medical education at Northside Hospital Gwinnett.

CONSENT

We have taken the patient's written consent to publish the case report. The patient accepts the publication of this case report.

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