Diffuse Hepatic Melanoma Mimicking Acute Alcoholic Hepatitis


Stanley Martin Cohen


Mitchell Kaplan


Shriram Jakate

Acute alcoholic hepatitis (AAH) is a syndrome associated with significant morbidity and mortality. It is generally diagnosed clinically, as coagulopathy and thrombocytopenia that often precludes the use of liver biopsy. However, up to 30% of cases of clinical AAH may be misdiagnosed in the absence of a liver biopsy. We report a case of AAH diagnosed clinically that was found to have diffuse hepatic melanoma on histology. Given this case report, and the significant ramifications associated with the diagnosis of AAH, pathologic confirmation should be considered in these patients.

INTRODUCTION

Alcoholic liver disease is a general term describing a spectrum of liver diseases associated with alcohol use. These range from reversible fatty change to acute alcoholic hepatitis to alcoholic cirrhosis.

Acute alcoholic hepatitis (AAH) is a clinical syndrome seen in patients with significant alcohol intake. AAH is characterized by AST:ALT ratios of 2–3:1, jaundice, coagulopathy, leukocytosis, right upper quadrant pain, tender hepatomegaly, and fever (1). The syndrome presents as a spectrum of diseases ranging from a self-limited illness to a condition with mortality rates ranging from 30%–50% (2,3). Severity of AAH is measured by the Maddrey discriminant function defined as 4.6 (Patient's protime – control protime) + total bilirubin (in mg/dL) (3). "Severe" cases are those with a Maddrey discriminant function of >32 or the presence of hepatic encephalopathy.

Biopsy of AAH is not pathognomonic, but highly suggestive in the appropriate clinical setting. The biopsy classically reveals steatosis, acute polymorphonuclear infiltrates, perivenular fibrosis (and possibly even cirrhosis), and the presence of Mallory bodies (4).

Stanley Martin Cohen M.D., Section of Hepatology; Mitchell Kaplan M.D., Section of Hepatology and Shriram Jakate M.D., Section of Pathology, Rush University Medical Center, Chicago, IL.

A CASE TO REMEMBER

Despite the potential usefulness of liver biopsy for diagnostic and prognostic purposes, AAH is generally diagnosed on clinical grounds. Liver biopsy is often felt to be unnecessary to make the diagnosis. In addition, biopsy is felt to be too dangerous given the presence of coagulopathy and possible thrombocytopenia.

We report a case of presumed severe AAH which on liver biopsy was found to be diffuse hepatic melanoma.

CASE REPORT

A 65-year-old white male presented to a local hospital with a two-week history of jaundice and right upper quadrant pain. He denied any history of prior liver disease. His only risk factor for liver disease was significant alcohol use of at least three to four drinks daily. His past history was only significant for hypertension and hyperlipidemia. His home medications (all of which were stable for at least five years) included atorvastatin, diltiazem hydrochloride, doxazosin mesylate, and lisinopril. His family history was non-contributory for any evidence of liver disease, autoimmune disease, or malignancy. He denied any history of tattoos, illicit drug use, tobacco, or blood transfusions. Admission laboratory data revealed AST 92 U/L, ALT 46 U/L, total bilirubin 9.2 mg/dL (1.3 mg/dL on a routine chemistry panel drawn one month earlier), albumin 2.9 g/dL, alkaline phosphatase 225 U/L, and INR 1.4. Serologies were negative for hepatitis A, B, and C, as well as ANA, SMA, and AMA. An ultrasound revealed a thickened gallbladder wall, and increased echogenicity of the liver, without frank lesions. HIDA scan was inconclusive. MRI with MRCP revealed mild ascites, gallbladder wall edema, heterogeneous enhancement of the liver without focal lesions, and no evidence of a biliary obstructive process. The patient was diagnosed with alcoholic cirrhosis and superimposed alcoholic hepatitis. Due to progressive increase in the bilirubin and INR, he was transferred to our facility for possible liver transplant evaluation.

Upon transfer, the above history was confirmed and the original imaging studies were reviewed. The patient's only medications upon transfer were oral vitamin K, pantoprazole, and pentoxyfilline (for presumed AAH). Physical examination was significant for jaundice, hepatomegaly, and ascites. A healed incision on the right neck (which the patient claimed was due to an intravenous line) was observed. Initial labs at our institution revealed AST 70 U/L, ALT 40 U/L, total bilirubin 18.4 mg/dL, albumin 2.5 g/dL, alkaline phosphatase 187 U/L, total protein 6.1 g/dL, creatinine 0.6 mg/dL, protime 18.7 seconds, INR 1.63, white blood cell count 13.4, hemoglobin 13 g/dL, and platelets of 238,000. Our clinical diagnosis was acute alcoholic hepatitis. The patient was deemed not to be a liver transplant candidate due to his recent alcohol use. He was told of the severity of his alcoholic hepatitis, and the poor prognosis given a Maddrey discriminant function of approximately 49. He was told that a liver biopsy would not be necessary given the classic presentation of acute alcoholic hepatitis. He was started on prednisone at a dose of 40 mg daily.

On hospital day two, family members were able to recall additional history. The patient had had a transjugular liver biopsy at the initial hospital. He was told that he had alcoholic liver disease and "maybe some melanoma." We were able to obtain the reports of the transjugular liver biopsy and the outside biopsy specimen. The wedged hepatic venous pressure gradient was found to be 18 mmHg (normal <4 mmHg). The specimen revealed the presence of a diffusely-infiltrating melanoma in the liver with no evidence of alcohol-induced changes.

Given confusion in the history, and the significant implications of the diagnosis, a repeat transjugular liver biopsy was performed at our institution. The hepatic vein pressure gradient was 11 mmHg, consistent with mild portal hypertension. The biopsy revealed no changes of alcoholic liver disease, but showed diffuse infiltration of poorly-differentiated malignant cells, both in the sinusoids and portal areas (Figure 1). The tumor cells were large and poorly differentiated and contained prominent cytoplasmic melanin-like pigment (Figure 2). Immunohistochemically, the tumor cells were positive for S-100 protein (Figure 3) and HMB-45, diagnostic of melanoma.

Prednisone was discontinued. A complete dermatologic and ophthalmologic evaluation failed to reveal a source for the malignant melanoma. The patient was

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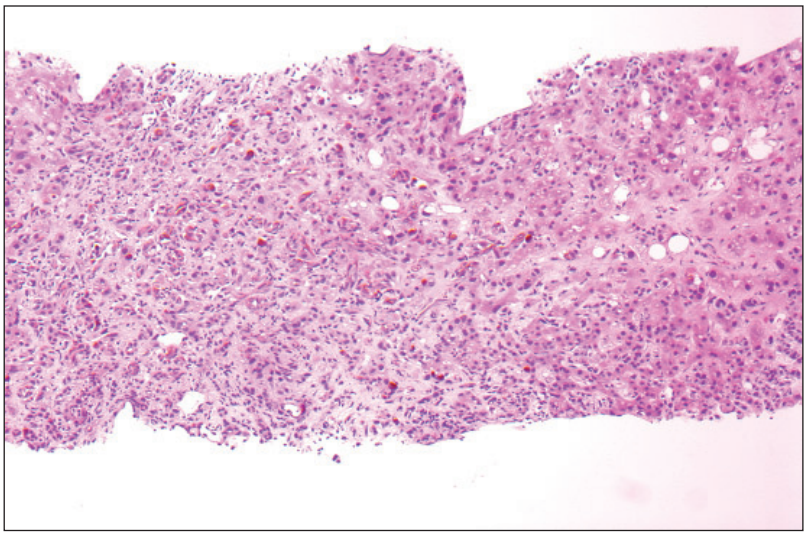

Figure 1. Low power photomicrograph of liver needle biopsy showing diffuse infiltration of the tumor in sinusoids and portal areas (Hematoxylin and Eosin stain, magnification ×100).

seen by oncology but refused to consider any experimental chemotherapy regimens. He developed worsening ascites, hepatic encephalopathy, and subsequent multi-organ failure, and expired within two weeks. The family declined a request for autopsy.

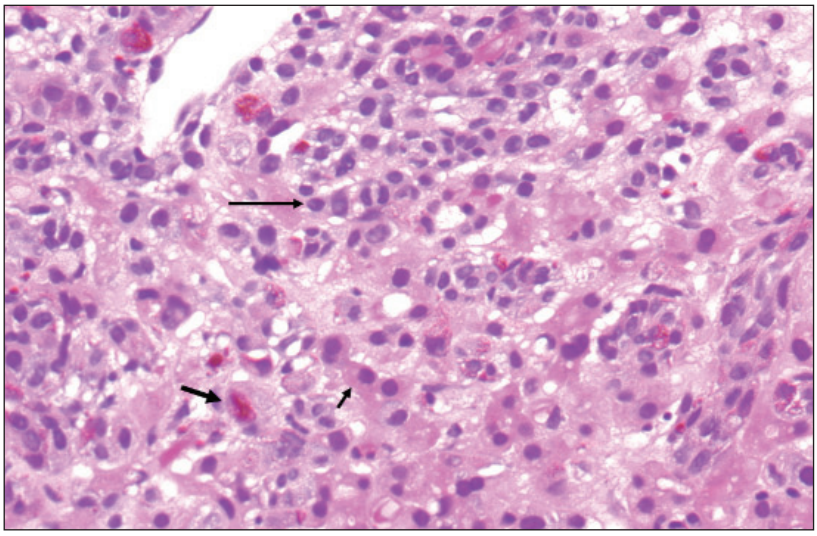

Figure 2. High power photomicrograph of liver needle biopsy showing poorly differentiated tumor cells (long arrow), tumor cells showing melanin-like pigment (thick arrow) and normal hepatocytes (short arrow) (Hematoxylin and Eosin stain, magnification ×400).

DISCUSSION

Liver biopsy can be useful to establish the exact etiology of liver damage, as well as provide information regarding staging and prognosis of various liver-related conditions. For presumed alcoholic liver disease, especially acute alcoholic hepatitis, the diagnosis is usually made on clinical grounds. Liver biopsy has generally been reserved for evaluation of the degree of fibrosis, and the impact of other co-factors such as chronic viral hepatitis.

Whether liver biopsy should be performed in all patients with a clinical diagnosis of alcoholic liver disease is debatable. In a study from the University of Chicago in 1979, as many as 20% of patients with alcohol abuse presenting with abnormal liver tests were found to have a non-alcohol related cause of their liver disease (5). Another study comparing clinical and histologic diagnoses of alcoholic liver disease found that the clinical diagnosis was highly specific (98%) but less sensitive (79%) than liver biopsy (6). An NIH study found the sensitivity and specificity of a clinical diagnosis of alcoholic liver disease to be 91% and 96%, respectively, when compared to histologic specimens (7). While the previous studies show data relating to the diagnosis of general alcoholic liver disease, there is little data comparing clinical and histologic diagnoses with regard to the specific entity of AAH. The only available abstract revealed that in patients with a clinical diagnosis of severe AAH, based on clinical parameters and a Maddrey discriminant function of >32, only 70% were confirmed to actually have AAH on biopsy (8).

The majority of the published therapeutic trials in severe AAH did not require liver biopsy prior to entry, and allowed clinical diagnosis as the sole entry criteria. While the implications of a diagnosis of general alcoholic liver disease may not be that important, the specific diagnosis of AAH has major ramifications. This

includes a very poor prognosis with extremely high mortality rates. In addition, the diagnosis of severe AAH warrants consideration of specific treatment modalities such as corticosteroids or pentoxyfilline (2,3,9–22). However, these treatments can be associated with significant side effects.

In addition to confirming the diagnosis, liver biopsy findings in AAH can have clinical and prognostic significance. One of the large AAH corticosteroid treatment trials which did require histologic confirmation for study entry revealed that marked infiltration of the hepatic parenchyma with neutrophils was independently associated with a favorable outcome (20). In addition, the presence of megamitochondria in a liver biopsy of AAH patients was associated with milder disease, less incidence of cirrhosis, and improved short-term survival (23).

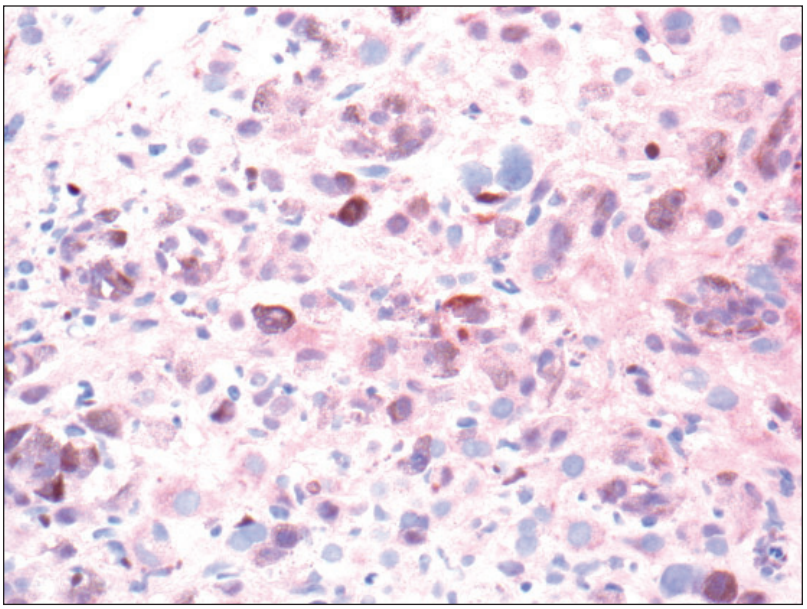

Figure 3. High power photomicrograph showing positive S-100 protein immunostaining (brown color) of tumor cells (magnification ×400).

In average-risk patients, a percutaneous liver biopsy is generally considered safe with morbidity rates of 0.1%–0.6% and mortality rates of 0.01%–0.03% (24,25). In patients with AAH, thrombocytopenia and coagulopathy are often present. Transjugular liver biopsy can offer an alternative technique for obtaining a histologic specimen in these patients with acceptably low procedural risk (26-28).

The patient presented in this case report had a clinical diagnosis of severe AAH based on history and laboratory parameters. The absence of frank lesions on imaging studies, and no known prior history of malignancy further solidified the diagnosis. However, if clinical parameters had been used exclusively in this case, an incorrect diagnosis would have resulted. In this particular patient, no successful treatment would likely have been available due to the diffuse nature of his tumor. However, in other cases masquerading as severe AAH (i.e. lymphoma or drug-induced liver disease), a biopsy-proven diagnosis may allow the use of potentially life-saving therapeutic options.

In summary, AAH is a very serious condition associated with considerable mortality. The available therapeutic options may decrease mortality, but may have significant adverse effects. Up to 30% of cases of AAH may be misdiagnosed on clinical parameters alone. Given the major ramifications of a diagnosis of AAH, pathologic confirmation should be highly considered. ■

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