Hepatocellular Carcinoma Arising In The Non-Cirrhotic Liver Of A Patient With Crohn's Disease Treated With Azathioprine

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Citation

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Abstract

Crohn's disease (CD) and its treatments have several associations with hepatobiliary disorders, including gallstone disease, portal vein thrombosis, and idiosyncratic drug toxicities. However, hepatocellular carcinoma (HCC) has rarely been described. It is unusual to diagnose HCC in a non-cirrhotic liver; this occurs less than 15% of the time [1]. In this case report, we describe a 50-year-old male with longstanding CD treated with azathioprine (AZA). He presented with loose stools and weight loss. Laboratory evaluation identified mildly elevated hepatocellular liver tests. An abdominal CT showed a new, 15 cm heterogeneous tumor and surgical resection revealed a moderately differentiated HCC. Trichrome staining of the non-tumoral parenchyma did not show fibrosis. Eight out of ten case reports of HCC in patients with CD cite the use of AZA. Prior studies show that AZA increases hepatocyte turnover. CD, itself, is a chronic inflammatory condition that has been shown to alter the gut-liver axis. Therefore, we believe that the complex interplay between our patient's AZA use and his CD led to the development of HCC in the absence of liver fibrosis.

INTRODUCTION

CD is a multi-system disease with known hepatobiliary manifestations. Azathioprine is an anti-neoplastic agent often used to treat CD. Its metabolic pathway, however, can lead to bone marrow and liver toxicity. CD patients on AZA are occasionally referred to a hepatologist with abnormal liver function tests. While long-term AZA use can result in malignancies like lymphoma and skin cancer, the association with hepatocellular carcinoma is not well described.Below, we report a case of mild transaminitis leading to a diagnosis of HCC arising in the non-cirrhotic liver of a CD patient on long-term AZA.

CASE REPORT

This 50-year-old male was diagnosed with CD at age 21. Besides a mild sigmoid colon stricture and perirectal fistula in his early 30s, the patient had an uncomplicated disease course. His maintenance drug was AZA, held at a daily dose of 150 mg for 20 years. He presented to clinic with increasing stool frequency. On review of systems, the patient endorsed a 12-pound unintentional weight loss over a 4-month period. The patient's exam was non-focal and negative for hepatosplenomegaly, jaundice, pallor, or RUQ pain. On basic laboratory evaluation, his AST was 101 IU/L, alkaline phosphatase was 309 IU/L, but his other liver tests were within the normal range. His hematocrit was 24% (baseline 30%) and iron, ferritin, and albumin were low. The patient underwent an abdominal CT scan that showed an 11x 10x 15 cm heterogeneous mass arising from the caudate lobe of the liver with arterial enhancement and early washout concerning for HCC (Figure 1).In comparison, a CT scan performed one-year prior was essentially normal with only scattered densities in both lobes consistent with small cysts.

Viral hepatitis serologies, AMA, smooth muscle antibody, CEA, AFP, and CA 19-9 were negative. The patient was taken for tumor resection and histopathology showed a solitary, moderately differentiated hepatocellular carcinoma T3N1 with clean margins (Figure 2a). Histological evaluation of the remaining liver tissue showed normal, well-preserved hepatic parenchyma (Figure 2b).

Figure 1

CT abdomen w/wo contrast shows a large tumor arising from the caudate lobe of the liver. The mass had arterial enhancement and early contrast washout.

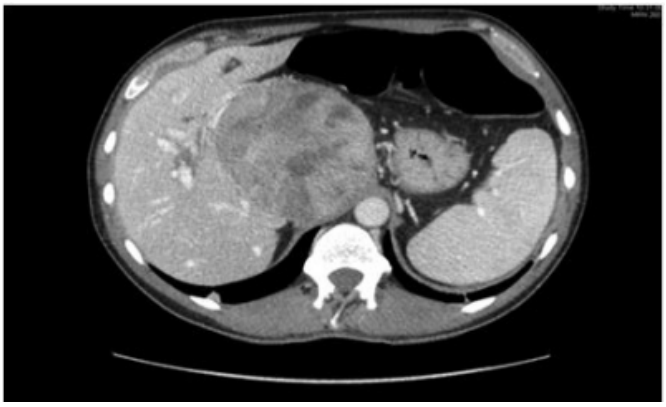
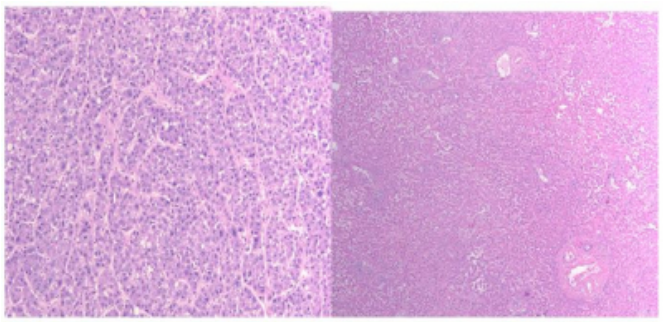


Figure 2

(a) H&E stain showing moderately differentiated HCC. The tumor has round nuclei, prominent nucleoli, and abundant pink cytoplasm. However, unlike normal liver, HCC does not make portal tracts or central veins. (b) The background liver shows no si



DISCUSSION

It is rare for HCC to be diagnosed in an otherwise healthy liver. Considerations were given for alternative hypotheses, including viral hepatitis, toxic/metabolic derangements, and primary sclerosing cholangitis (PSC) [2, 4]. In our evaluation, we did not find evidence of these conditions. The patient did not use IV drugs, drink alcohol, engage in risky sexual practices, have occupational exposures, or a family history of liver disease. The patient had normal biliary contours on imaging to rule out PSC. Furthermore, hepatic stores of iron and glycogen were taken into account and were within normal range [3]. We hypothesize that the patient's CD and AZA use were the drivers of mutagenesis.

Ten cases of HCC in non-cirrhotic livers of CD patients have been reported internationally. Eighty percent of these patients were treated with AZA [5]. There are now enough cases to suggest a possible causal link among CD, AZA, and HCC. The gut-liver axis in inflammatory bowel disease is a field of emerging study, and the hepatotoxic effects of AZA may be priming the hepatocyte for dysplastic changes that are further disrupted in the setting of CD.

This patient's CD was treated for over 20 years with the immunosuppressive drug AZA, a pro-drug antagonist of purine metabolism. AZA is metabolized to 6-TG, which mitigates the drugs therapeutic and toxic effects. Pharmacological studies have shown an association between AZA and lymphoma and skin cancer, however, solid organ tumors have not been extensively documented [6]. A previous study showed that rats treated with AZA had a 218% increase in hepatocyte turnover, which may increase the velocity of somatic mutations [7]. While immunosuppression itself is a risk factor for carcinogenesis, AZA seems to increase that risk.

CD disrupts the gut flora milieu and leads to impaired enterohepatic bile salt circulation, cytokine release, and cellular damage. This may explain CD's involvement of extra-luminal organs including the skin, liver, and joints. New research demonstrates that intestinal colonization with the bacteria Helicobacter hepaticus leads to transcription factor up-regulation and activation of an HCV-like transgene in a mouse model [8]. In addition, H. hepaticus has been isolated more frequently in gastrointestinal samples from an IBD cohort [9]. Therefore, CD may change the gut-liver axis and cause dysplasia in the absence of chronic liver inflammation.

In conclusion, we present a case of HCC in the non-fibrotic liver of a patient with CD on long-term AZA therapy. The association among CD, AZA, and HCC is still unclear, however, a complex interplay between disease and treatment most likely exists. More research is needed to further define this interaction.

References

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