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CASE REPORT | LIVER

Elevated Liver Enzymes in a Patient With Hepatocellular Carcinoma on Immune Checkpoint Inhibitor Therapy: A Diagnostic and Therapeutic Challenge

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ABSTRACT

We present a patient with untreated hepatitis C virus and metastatic hepatocellular carcinoma treated with combination immunotherapy who developed elevated liver enzymes. The immunotherapy was withheld, and the liver enzymes continued to rise. A liver biopsy was performed, which demonstrated findings consistent with chronic viral hepatitis. Direct-acting antiviral treatment was initiated, and the liver enzymes returned to normal limits. This case demonstrates the diagnostic dilemmas raised among patients with hepatocellular carcinoma on immunotherapy who develop elevated liver enzymes and some of the challenges regarding the use of these medications in patients with viremic hepatitis C virus.

INTRODUCTION

Immunotherapy for hepatocellular carcinoma (HCC) consists of monoclonal antibodies that inhibit immune checkpoint molecules and subsequently activate the immune system against cancer cells. The IMbrave150 study, which included patients with chronic hepatitis C virus (HCV) infection, demonstrated a significant survival advantage of combined atezolizumab/bevacizumab compared with sorafenib for advanced HCC.[1]

The immune system plays an important part in the control of cancer.[2] Liver cancer cells express the programmed death ligand (PD-L1), which leads to regulatory T-cell proliferation and exhaustion of effector cells, allowing tumor cells to evade immune responses.[3] Immune checkpoint inhibitors, such as atezolizumab, are monoclonal antibodies that block the interaction of liver tumor cells with PD-L1, thus preventing the inactivation of T cells and "waking" the immune system.[4] Bevacizumab is a monoclonal antibody that binds the vascular endothelial growth factor to inhibit angiogenesis and potentiate the effects of atezolizumab. Given that immune checkpoint inhibitors activate the immune system, an expected side effect of this process is inflammation of noncancer tissue in any organ, which can complicate the management of advanced HCC and lead to diagnostic uncertainty in patients with underlying chronic liver disease.

CASE REPORT

We report a case of a 66-year-old man with a medical history significant for Child-Pugh class A cirrhosis secondary to untreated HCV and multifocal HCC (Barcelona Clinic Liver Cancer Stage B at the time of diagnosis). After 2 sessions of transarterial radioembolization, the patient was found to have tumor invasion into the portal vein and pulmonary metastases, at which point liver enzymes were normal. He was started on atezolizumab/bevacizumab × 10 cycles and had mild liver enzyme elevations that improved without the need to hold immunotherapy or start steroids. He had a reduction in the size of pulmonary nodules and a stable intrahepatic disease burden. After cycle 11, the patient developed perineal neuropathic pain concerning for immune checkpoint-related neuropathy. Immunotherapy was held, and he was started on prednisone 40 mg daily, with initial improvement in these symptoms. Prednisone was rapidly tapered to 10 mg daily and, given his

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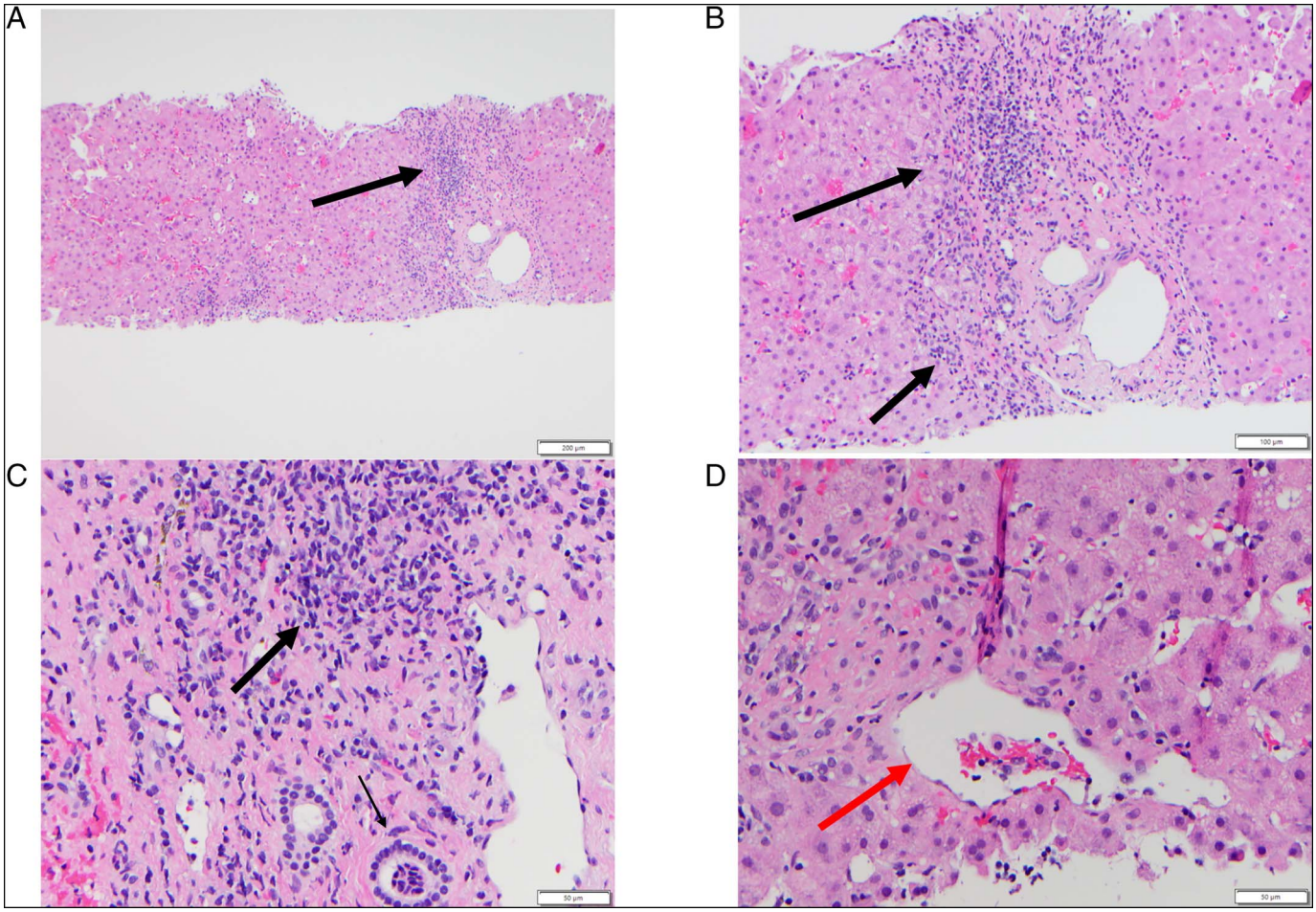

Figure 1. Histologic features of liver core biopsy by a hematoxylin-eosin stain. (A) A representative lower power view of mild-to-moderate hepatitis with dominant portal inflammatory activity (original magnification 100×). (B) A representative view of the portal tract with mild interface hepatitis and eccentrically placed lymphoid aggregate features often seen in chronic hepatitis C virus (original magnification 200×). (C) A closer view of portal inflammatory infiltrates composed of predominantly lymphocytes with rare eosinophils and plasma cells. Bile ducts remain intact (original magnification 400×). (D) A closer view of a central vein with no endothelialitis/venulitis (original magnification 400×). Arrows in black demonstrate lymphocytic infiltrate and lymphoid aggregates. The arrow in red demonstrates the lack of endothelialitis or venulitis arguing against immune checkpoint inhibitor-mediated hepatotoxicity.

excellent treatment response to immunotherapy, he was restarted on atezolizumab/bevacizumab. He developed a recurrence of the perineal pain, and prednisone was increased to 60 mg daily. Given the lack of improvement on high-dose steroids, the diagnosis of immune checkpoint neuropathy was questioned, and his prednisone was subsequently tapered and eventually discontinued. His atezolizumab/bevacizumab was restarted and neuropathy symptoms improved, without recurrence. A month after restarting immunotherapy (after cycle 13), he was noted to have elevated aspartate aminotransferase (245 U/L, ref ≤34) and alanine aminotransferase (157 U/L, ref ≤49) with total bilirubin 1.6 mg/dL (ref ≤1.1) and alkaline phosphatase 110 U/L (ref 46–116). Despite holding the next infusion, his liver enzymes increased the following week to aspartate aminotransferase 343 U/L and alanine aminotransferase 267 U/L with unchanged total bilirubin and alkaline phosphatase. The patient was referred to hepatology where workup included negative hepatitis A and B serologies, normal creatinine kinase, and magnetic resonance imaging of the abdomen showing the unchanged size of hepatic masses with no biliary dilatation. The alpha-fetoprotein level was 17 ng/mL (compared with 83 ng/mL pretreatment). Autoimmune serologies and immunoglobin levels were not obtained given that the suspicion for primary autoimmune hepatitis was low. His HCV RNA was 2.9 million, from 900 thousand before treatment. His only new medications were metformin and insulin. He denied alcohol use. A percutaneous liver biopsy was performed, and histologic findings were more consistent with recurrent viral hepatitis than checkpoint inhibitor hepatitis (Figure 1). The biopsy showed no cytopathic atypia or positive stains for cytomegalovirus or Epstein-Barr virus. He was subsequently started on HCV therapy with sofosbuvir/velpatasvir and completed a 12-week course with subsequent improvement of HCV RNA and normalization of liver enzymes. At the end of direct-acting antiviral (DAA) therapy, immunotherapy was restarted. Three weeks later, the patient had a worsening appetite and fatigue. Subsequent surveillance imaging showed marked progression of his pulmonary disease with mediastinal lymphadenopathy and a new pleural

effusion. Before being checked for sustained virologic response, he opted to pursue hospice care and died shortly thereafter.

DISCUSSION

This case highlights the diagnostic dilemma in approaching a patient with HCC and untreated HCV viremia who presents with elevated liver enzymes after initiation of immunotherapy for metastatic HCC. It is imperative to evaluate alternative causes of transaminase elevation before making a diagnosis of immune checkpoint hepatitis. The differential diagnosis includes drug-induced liver injury, viral hepatitis, biliary obstruction, autoimmune hepatitis, increased tumor burden, and nonhepatic sources (eg, myositis).[5] In this case, there was a concern for HCV reactivation (increase in HCV-RNA level of $\geq$1 $\log_{10}$ IU/mL from baseline)[6] in the setting of corticosteroid use. Although it is possible that immunotherapy itself could have led to HCV flare, this is less likely given that immune checkpoint inhibitors enhance immune function and several studies report reductions in HCV RNA after immunotherapy initiation.[7]

The histological review with liver biopsy may be of value in difficult clinical scenarios. Examination of this patient's liver biopsy reveals a hepatitis pattern of injury with mild-to-moderate interface activity, predominantly lymphocytic infiltrate, accompanied by lymphoid aggregates (Figure 1). These features are often seen in HCV. Of note, there were no characteristic features for immune checkpoint hepatitis including a panlobular pattern of hepatitis, bile duct injury (Figure 1), perivenular infiltrate with endothelialitis (Figure 1), granulomatous inflammation, or histiocytic aggregates.

The incidence of immune checkpoint hepatitis is increased in patients who receive combination therapies (including atezolizumab/bevacizumab).[1] However, based on limited data, the incidence of adverse events from immunotherapy is not higher in patients with active viral hepatitis.[7] Conversely, some evidence suggests that immunotherapy for HCC may be most effective in patients with viral hepatitis [8] and that patients with HCV can safely continue immunotherapy while receiving DAAs.[7]

The management of active HCV in the setting of advanced HCC is controversial. Early concerns that DAAs increased HCC recurrence risk have largely been dispelled and HCV treatment may be reasonable given the improved survival of patients on immunotherapy.[9] Expert reviews suggest a patient-by-patient approach with the use of shared decision making.[9,10] Potential benefits of HCV therapy need to be weighed against the decreased efficacy of DAAs in HCC[11] and limited life expectancy among patients with advanced HCC. Our case additionally raises concerns about DAA therapy increasing the aggressiveness of HCC. Although published data do not definitively demonstrate an association between DAAs and HCC aggressiveness,[9,12] there remains a possibility that HCV treatment could alter the disease phenotype by changing the tumor microenvironment.

In sum, this case demonstrates the importance of maintaining a broad differential diagnosis of elevated liver enzymes in patients with HCC on immunotherapy and selectively considering DAA therapy in patients with advanced HCC.

DISCLOSURES

Author contributions: All authors approved the final version of this manuscript. D. Abbas: study concept and design, interpretation of the case, and drafting and critical revision of the manuscript. L-C Zhu: pathology slide extraction and interpretation and critical revision of the manuscript. AM Moon: study concept and design, interpretation of the case, critical revision of the manuscript, and is the article guarantor.

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