Case Report

Liver biopsy role in ICI-associated liver injury

HEPATOLOGY FORUM

doi: 10.14744/hf.2021.2021.0036

Liver biochemical flare with immune checkpoint therapy in metastatic Merkel cell carcinoma: A liver biopsy is always necessary

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Abstract

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin. Treatment for locoregional MCC includes local excision with regional lymphadenectomy, followed by adjuvant radiotherapy. Immune checkpoint inhibitors (ICI) have emerged as a breakthrough treatment of metastatic MCC. Nevertheless, T-cell immune response is triggered against self-antigens resulting in immune-mediated toxicities, including ICI-mediated hepatotoxicity. We report a case of recurrent metastatic MCC treated with avelumab, a PD-L1 inhibitor, with subsequent significant liver biochemical flare. The initial clinical diagnosis was ICI-mediated hepatotoxicity. Workup to rule out competing causes of liver injury came back negative. Hence, avelumab was discontinued, and the patient was initiated on steroid therapy with stepwise escalation. Owing to clinical and laboratory deterioration, it was then decided to perform a percutaneous liver biopsy to document steroid-refractory ICI-mediated hepatotoxicity and/or rule out other causes of potential liver injury. The liver biopsy showed MCC tumor cells almost entirely infiltrating the hepatic parenchyma, confirmed by immunohistochemistry. At that point, steroid therapy was discontinued, and the patient was transitioned into palliative care. In conclusion, patients with apparent ICI-related hepatotoxicity should always be considered for a liver biopsy to exclude massive infiltrative malignancy as the true cause of liver dysfunction.

Keywords: Hepatotoxicity; immune checkpoint inhibitors; immunotherapy; Meckel cell carcinoma.

Introduction

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin, which typically affects the sun-exposed skin of elderly Caucasians.[1] Predisposing factors for MCC include male gender, fair-colored skin, exposure to ultraviolet (UV) radiation, immunosuppression and advanced age.[2] MCC presents clinically as a fast-growing, painless, reddish/purple nodule or plaque.[1]

The treatment of choice for locoregional MCC includes local excision with regional lymphadenectomy, followed by adjuvant radiotherapy.[2] Based on the recognized immune susceptibility of MCC, immune checkpoint inhibitors (ICI) have emerged as a breakthrough treatment of metastatic MCC. Avelumab is a fully human monoclonal antibody targeting the programmed death-ligand 1 (PD-L1). Blockade of PD-L1, whose expression is upregulated in MCC, can sensitize tumors to cytotoxic T lymphocyte activity.[3]

Case Report

We present a mid-50's year old man with chronic hepatitis B viral (HBV) infection on tenofovir and MCC of the left thigh, who developed recurrence in the left thigh after surgical excision at the excisional site that was treated with radiotherapy. He was later found to have retroperitoneal lymphadenopathy and was started on ICI therapy with avelumab. Prior to initiating ICI, baseline liver biochemistry and bilirubin were completely normal. He subsequently developed a significant liver biochemical flare after initiating ICI therapy.

The patient was initially admitted to a community hospital with the complaint of diffuse myalgia. Upon admission, initial workup revealed alanine aminotransferase (ALT) of 132 U/L [n<50 IU/L], aspartate aminotransferase (AST) 324 U/L [n<38 IU/L], total bilirubin of 36 µmol/L [n<22 µmol/L], gamma-glutamyl transferase (GGT) 158 U/L [n<50 IU/L], alkaline phosphatase of 211 U/L [n<120 IU/L] and an International Normalized Ratio (INR) of 1.2 [n<1.2]. The initial clinical diagnosis was ICI-mediated myositis and hepatitis.

Avelumab was subsequently discontinued, and the patient was started on oral prednisone therapy (45 mg/day) two weeks after avelumab exposure. An initial improvement in muscle soreness was observed to some extent, but not in the liver biochemistry. Three days later, the prednisone dose was increased to 90 mg/day, but with no improvement of the liver biochemistry. One week later, therapy was further escalated to IV methylprednisolone 2 mg/kg/day because of worsening liver function tests with a rise in the total bilirubin to 93 µmol/L, ALT of 257 U/L, AST of 615 U/L, GGT of 422 U/L, alkaline phosphatase of 374 U/L and an INR of 1.4. The patient was then transferred to our tertiary referral hospital for further management.

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How to cite this article: Al-Rajhi I, Omar M, Farnell D, Jayakumar S, Sohi D, Yoshida EM. Liver biochemical flare with immune checkpoint therapy in metastatic Merkel cell carcinoma: A liver biopsy is always necessary. Hepatology Forum 2022; 3(1):27–29.

Received: November 09, 2021; **Accepted:** November 24, 2021; **Available online:** December 28, 2021

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Additional investigations to rule out other etiologies of acute liver injury included negative serology for Hepatitis A Virus, Hepatitis C Virus, Epstein Barr Virus, Cytomegalovirus, and Human Immunodeficiency Virus. HBV DNA was undetectable. Serum ceruloplasmin and alpha-1 antitrypsin levels were normal. Serology was negative for autoimmune diseases of the liver, including negative anti-mitochondrial antibody, anti-smooth muscle antibody, normal immunoglobulin G and M levels. Abdominal ultrasound of the liver with Doppler showed no focal lesions in the liver and patent hepatic vasculature.

The patient gradually became jaundiced, developed ascites and hepatic encephalopathy along with worsening liver biochemistry and coagulopathy. His total bilirubin peaked at 153 µmol/L, ALT at 461 U/L, AST at 843 U/L, GGT at 1133 U/L, and INR at 2.1.

In the context of the worsening clinical condition and laboratory parameters, it was decided to perform a percutaneous liver biopsy, to document steroid-refractory ICI-hepatotoxicity and/or rule out other competing etiologies of liver injury. The biopsy showed the hepatic parenchyma completely replaced by metastatic Merkle cell carcinoma tumor cells with positive immunohistochemistry (Fig. 1). Based on the liver biopsy results, methylprednisolone was discontinued, and the goal of care was changed to palliation.

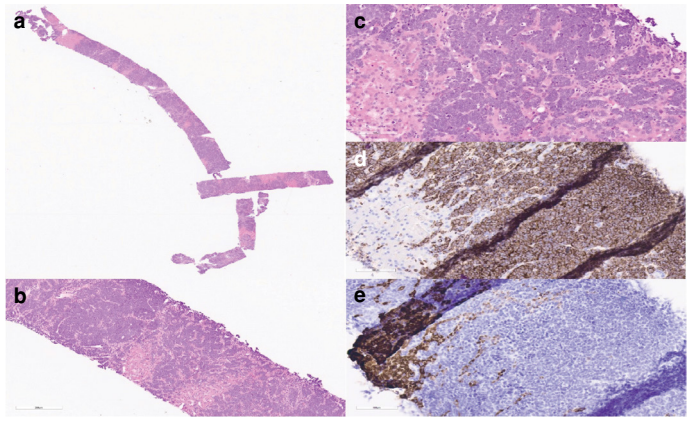

Figure 1. Non targeted liver biopsy showing hepatic parenchyma almost entirely replaced by metastatic Merkel cell carcinoma (a) Higher magnifications (b, c) showing tumor cells replacing the hepatic parenchyma. The tumor cells are positive for synaptophysin immunohistochemistry (d) and negative for HSA immunohistochemistry (e).

Discussion

MCC is an aggressive cutaneous tumor of neuroendocrine origin.[1] MCC is associated with MCPyV infection in more than 80% of patients. In MCPyV-negative MCCs, the oncogenic stimulus appears to be UV radiation-induced genetic damage.[4] The main prognostic factor for survival in patients with MCC is the clinical stage of the tumor. The 5-year survival rates for localized MCC, MCC with nodal metastases, and those with distant metastases are 51%, 35%, and 14%, respectively.[1,2]

ICI with avelumab (PD-L1 inhibitor) was started in our patient. After receiving the first dose of avelumab, the patient presented with a picture presumed to be secondary to ICI-mediated myositis and hepatitis.

T-cell immune activity against self-antigens is triggered in response to ICI targeting PD-1 or PD-L1, resulting in a broad spectrum of ICI-related autoimmune toxicities, which can sometimes yield life-threatening outcomes. The skin, endocrine organs, GI tract, liver, and lungs are the most common organs to be affected with ICI toxicity.[5] ICI-mediated hepatotoxicity manifests as elevated ALT or AST, with or without raised bilirubin. The onset is typically 6-14 weeks after starting ICPI treatment, with most patients being asymptomatic and only a minority presenting with fever.[6]

Our patient presented mainly with aberrant liver biochemistry with the elevation of both hepatocellular and cholestatic liver enzymes. Synthetic liver function was preserved at first presentation. Since the AST was ≥5 times the upper limit of normal, which was presumed to be consistent with Grade 3 ICI-hepatotoxicity, it was decided to permanently discontinue avelumab and start oral steroid therapy. The time frame between initiation of avelumab and starting steroid therapy was approximately two weeks.

Clinical practice guidelines, including the American Society of Clinical Oncology and the European Society of Medical Oncology, endorse introducing corticosteroid therapy for Grade ≥2 hepatotoxicity and permanent discontinuation of ICIs for Grade ≥3. In patients with inadequate response to these measures, the use of an immunosuppressive agent, including mycophenolate mofetil, azathioprine and/or tacrolimus, should be considered. For severe or persistent cases of ICI-mediated hepatoxicity, consultation with a hepatologist and consideration of liver biopsy are warranted.[7,8]

A liver biopsy can aid in the diagnosis of ICI hepatotoxicity but is not routinely performed, possibly because it is invasive and of the belief that a clinical diagnosis is sufficient. The most common histopathologic pattern is lobular hepatitis with features mimicking those of autoimmune hepatitis. The inflammation is mostly panlobular, but can be confined to zone 3 in some cases.[9]

In our patient, the liver biopsy was key to making an accurate diagnosis and showed that Merkel cell carcinoma tumor cells had almost entirely infiltrated the hepatic parenchyma. Additionally, immunohistochemistry confirmed the diagnosis. At that point, methylprednisolone therapy was discontinued, and the patient was then appropriately transitioned into palliative care. This clearly underscores the importance of liver biopsy in all patients with advanced cancer on ICI presenting with liver injury, particularly in steroid-refractory cases. ICI-mediated hepatotoxicity is most likely to be the cause, but a metastatic cancer to the liver remains a possibility that needs to be ruled out.

Another interesting aspect of this case is the absence of reported cases of metastatic MCC to the liver. Upon careful review of literature, we found only one case report of metastatic MCC to the liver and lung,[10] suggesting that our case is the second to be reported in the literature.

In conclusion, our experience suggests that all cases of apparent immune checkpoint inhibitor therapy hepatotoxicity should be considered for a liver biopsy to exclude massive infiltrative malignancy as the true cause of the liver dysfunction.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – IAR, MO, DF, SJ, DS, EY; Design – IAR, MO, DF, SJ, DS, EY; Supervision – IAR, MO, DF, SJ, DS, EY; Data Collection and/or Processing – IAR, MO, EY; Analysis and/or Interpretation – IAR, MO; Literature Search – IAR, MO; Writing – IAR, MO, EY; Critical Reviews – IAR, MO, DF, SJ, DS, EY.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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