A Case of Delayed Immune Checkpoint Inhibitor Hepatitis in a Patient with Malignant Melanoma

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Abstract
Immune checkpoint inhibitors are an increasingly utilized class of medications in oncology. Significant adverse effects have been reported, including hepatitis which mostly occurs early after initiating treatment. We present a case of a 78-year-old male with past medical history of recurrent sinusoidal mucosal malignant melanoma on pembrolizumab for three years that presented with painless jaundice of 72-hour duration. Laboratory evaluation demonstrated alkaline phosphatase at 1780 IU/L, aspartate aminotransferase at 2290 IU/L, alanine aminotransferase at 1224 IU/L, and bilirubin of 10.0 mg/dL with direct bilirubin of 7.4 mg/dL. The patient underwent interventional radiology transjugular liver biopsy demonstrating features of drug-induced liver injury secondary to pembrolizumab therapy. He was started on steroid therapy and completed six-week course with resolution in liver enzymes. This is a unique case in which pembrolizumab-induced hepatitis occurred three years after initiation of treatment. Due to the increased use of immune checkpoint inhibitors for oncologic treatment, it is important for clinicians to recognize their immune-related adverse effects and varying timing in which these toxicities may occur.

Keywords
Case Report; Gastroenterology; Hepatology; Oncology; Hepatitis; Melanoma; Pembrolizumab

Introduction
Immune checkpoint inhibitors are a frequently used class of medications that have transformed therapies in the field of oncology, specifically for lung cancers and melanoma. Immune checkpoints function by downregulating immune functions and therefore allowing cancer cells to proliferate [1]. Blocking immune checkpoints via cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand (PD-L1) will increase antitumor activity [1]. This can be done through a variety of monoclonal antibodies, including CTLA-4 antibodies (ipilimumab and tremelimumab), PD-L1 antibodies (atezolizumab and durvalumab), and anti-PD-1 antibodies (pembrolizumab and nivolumab). Pembrolizumab is a humanized monoclonal anti-PD-1 antibody approved by the Food and Drug Administration (FDA) for treatment of unresectable or metastatic melanoma [2]. Although these medications have reshaped cancer treatment in oncology, they can have significant side effects occurring within the gastrointestinal system, termed immune-related adverse events (irAEs) [3]. Immune checkpoint inhibitor toxicity specifically to the liver is rare and accounts only for 5-16% in clinical trials [4, 5]. There is no specific checkpoint inhibitor that has higher predilection to cause hepatitis. Review of literature suggests that hepatitis occurs in 5% of patients treated with anti-PD-1 or anti-PD-L1 and 5% of patients treated with CTLA-4 inhibitors [6]. Specifically, for metastatic melanoma patients treated with anti-PD-1 therapy, hepatitis occurred in 4% of cases compared to 18-19% of metastatic melanoma patients receiving combined anti-PD-1 and anti-CLTA-4 therapy [7]. Additionally, hepatitis varies by dose and duration of therapy [8, 9]. We present a unique case in which the patient developed hep-
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Patient Information
A 78-year-old male was admitted on January 3, 2022, with new-onset painless jaundice appearing 72 hours prior to admission. His medical history included recurrent sinusoidal mucosal malignant melanoma, status post osteomyelitis of nasopharynx, on pembrolizumab for three years with surgery and radiation nine years prior, coronary artery disease with stents placed three years prior, diastolic heart failure, spinal meningitis, type II diabetes mellitus, hypertension, and hyperlipidemia. He received pembrolizumab for the past three years at a dose of 200 mg intravenously (IV), with a dose increase to 400 mg IV 12 months prior to presentation. Social history was notable for no significant alcohol use, tobacco use, or recreational drug use. He took no new medications, over-the-counter medications, or herbal supplements. He was adopted and did not know his family history. He denied any recent illnesses or sick contacts.

Clinical Findings and Diagnostic Assessment
On physical exam, the patient was in no acute distress, alert, and oriented with no asterixis. He was hemodynamically stable with no evidence of hypotension. He was jaundiced with icteric sclera. His abdomen was non-distended and non-tender. His initial work-up revealed alkaline phosphatase at 1780 IU/L, aspartate aminotransferase at 2290 IU/L, alanine aminotransferase at 1224 IU/L, and bilirubin of 10.0 mg/dL with direct bilirubin of 7.4 mg/dL. White blood cell count was normal, and he had hemoglobin of 11.7 g/dL with the International Normalized Ratio (INR) of 1.0. His acute elevated liver enzymes in the thousands prompted consideration of ischemic hepatitis, viral hepatitis A immunoglobulin M (IgM) antibody, hepatitis B core antibody IgM, hepatitis B surface antigen, hepatitis C antibody. Human immunodeficiency virus was non-reactive. However, cytomegalovirus (CMV) IgM and IgG were positive with a negative CMV polymerase chain reaction (PCR). COVID-19 PCR was negative. Varicella zoster IgG, herpes simplex virus (HSV) IgM, and Epstein-Barr virus (EBV) DNA were all elevated. Labs were negative for causes of chronic liver disease, including negative antinuclear antibody, anti-smooth muscle antibodies, anti-mitochondrial antibodies, and liver kidney microsomal antibody. The patient underwent interventional radiology transjugular liver biopsy (Fig. 1) that demonstrated expanded portal tracts with evidence of fibrosis and infiltrates composed mostly of lymphocytes with scattered neutrophils. There was notable bile ductal reaction at the periphery with brisk lobular hepatitis characterized by numerous foci of lobular inflammation and lobular disarray as well as injury to the interlobular bile ducts. These findings were characteristic of checkpoint inhibitor hepatitis secondary to pembrolizumab. There was no evidence of microvesicular steatosis. Infectious disease was consulted on the case due to multiple viral antibodies being positive. It was determined that there was no acute viral hepatitis as CMV PCR was negative, varicella was elevated in setting of immunization, there was no acute HSV infection as the patient was afebrile, and the EBV viral load was negative.

Therapeutic Intervention
The decision was made to start the patient on intravenous methylprednisolone 1 mg/kg/day for three days and send him home on prednisone taper for pembrolizumab-associated liver injury. The taper included prednisone 60 mg for seven days, 50 mg for seven days, 40 mg for seven days, 30 mg for seven days, 20 mg for seven days, followed by 10 mg for seven days for a total of 6 weeks of steroids.

Figure 1. Pathology of immune checkpoint inhibitor hepatitis: A. Hematoxylin and eosin stain of hepatocytes demonstrating lymphocytic aggregation (red arrow) and fibrosis (black arrow). B. Magnified hematoxylin and eosin stain further demonstrating lobular necrosis (red arrow) and inflammation with lymphocytes and neutrophils (black arrow). Scale bars are 100 microns (0.1 mm).
Follow-up and Outcomes
Six weeks following presentation, liver enzymes normalized with alkaline phosphatase at 104 IU/L, aspartate aminotransferase at 42 IU/L, alanine aminotransferase at 25 IU/L, and bilirubin at 1.0 mg/dL. Due to patient’s significant irAEs secondary to pembrolizumab therapy, checkpoint inhibitor therapy was discontinued indefinitely. The patient received no further treatment for malignant melanoma, and he continues to be followed-up by the oncology team with restaging positron emission tomography (PET)-CT scans every 6 months.

Discussion
Immune checkpoint inhibitors are commonly used medications in the field of oncology; however, they have been associated with significant gastrointestinal side effects, including hepatitis [10]. Most irAEs have been shown to occur 8-12 weeks after starting treatment, and there have been reports of elevated liver enzymes as early as 8 days and up to 21 months after starting treatment [11]. Our case involved a patient who presented with asymptomatic jaundice secondary to pembrolizumab therapy three years after receiving the first dose.

Although there are no identifiable biomarkers with predictive value for irAEs, elevated liver enzymes are an initial marker that may initially predict liver injury [12]. Therefore, a complete blood panel, a comprehensive metabolic panel, and thyroid tests are recommended before initiation of treatment. Liver enzymes should continue to be monitored prior to each treatment infusion and weekly if there is any grade 1 liver dysfunction [12-14]. The majority of checkpoint inhibitor liver injuries are found on routine lab work; however, our patient presented with jaundice and no elevated liver enzymes.

The specific immunopathogenesis causing hepatitis is currently unknown [1]. However, there are a variety of proposed mechanisms. Firstly, T cell activity against antigens occurs not only on cancer tissue, but also on healthy tissue that can lead to damage to organs like the liver. Specifically, PD-1 inhibits T cells at later stages in immune response [15, 16]. Secondly, it is believed that there may be increasing level or pre-existing autoantibodies as anti-PD-1/anti-PDL-1 therapy may modulate humoral immunity, as this has been demonstrated in enhancing pre-existing antithyroid antibodies [17]. Lastly, there may be an increase in the level of inflammatory cytokines such as interleukin-17 and enhancement of complement-mediated inflammation [18]. All these mechanisms may play a role in causing damage to healthy tissues such as the liver.

If irAE is suspected in a patient, it is pertinent to first work-up causes of acute elevated liver enzymes. The patient should undergo serologic liver investigation to rule out other causes of liver pathology, while monitoring liver enzymes [4]. Liver toxicity can be graded on scale of 1-5 and differs based on aminotransferase and alkaline phosphatase levels, bilirubin, and coagulopathy as shown in Table 1. If grade 3-4 hepatitis is present, liver biopsy should be performed, as was done in our case [10].

Histological findings in checkpoint inhibitor hepatitis are not pathognomonic, therefore a thorough evaluation to rule out other potential causes of hepatitis is warranted. Histological features can be like those seen in viral hepatitis, autoimmune hepatitis, or other causes of drug-induced liver injury [8]. Liver histology of irAEs often reveals focal or confluent necrosis with lymphocytic infiltrates of activated T cells with the distribution of hepatic injury, usually panlobular [10]. However, histological findings can differentiate between anti-PD-1/anti-PDL-1 and anti-CTLA-4 antibody toxicity. Histological findings of anti-PD-1/anti-PDL-1 such as pembrolizumab is characteristic of lobular hepatitis, whereas anti-CTLA-4 antibody toxicity demonstrates granulomatous hepatitis with fibrin ring granulomas and central vein endothelitis [8].

Grade ≥ 2 liver toxicity should be initiated on prednisone at 0.5-1 mg/kg/day [12]. For grades 3-4 hepatitis, individuals should be started on methylprednisolone 1-2 mg/kg/day and the checkpoint inhibitor should be discontinued [12] (Table 1). Steroids should be appropriately tapered for 4-6 weeks after liver enzymes have improved

Table 1. Grade of drug-induced liver injury derived by the Drug-Induced Liver Injury Network (DILIN) [12, 13, 19].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Description</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>- Raised aminotransferases or alkaline phosphatase and Bilirubin &lt;2.5 and No coagulopathy (INR &lt;1.5)</td>
<td>Monitoring liver enzymes</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>- Raised aminotransferases or alkaline phosphatase and Bilirubin ≥2.5 or Coagulopathy (INR ≥1.5) without hyperbilirubinemia</td>
<td>Prednisone at 0.5-1 mg/kg/day</td>
</tr>
<tr>
<td>3</td>
<td>Moderate to severe</td>
<td>- Raised aminotransferases or alkaline phosphatase and Bilirubin ≥2.5 and Hospitalization because of drug-induced liver injury</td>
<td>Methylprednisolone 1-2 mg/kg/day and discontinuation of checkpoint inhibitor</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>- Raised aminotransferases or alkaline phosphatase and Bilirubin ≥2.5 and One of the following: - Prolonged jaundiced and symptoms beyond 3 months - Signs of hepatic decompensation - Organ failure believed to be related to drug-induced liver injury</td>
<td>Methylprednisolone 1-2 mg/kg/day and discontinuation of checkpoint inhibitor</td>
</tr>
<tr>
<td>5</td>
<td>Fatal</td>
<td>Death or liver transplant from drug-induced liver injury</td>
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to grade ≤ 1. However, if liver enzymes do not decrease in 10-14 days, immunosuppression such as mycophenolate mofetil should be considered [12]. To our knowledge, there is no described rebound after cessation of therapy if immune checkpoint inhibitor has been discontinued and steroids have been appropriately tapered. Pembrolizumab is used for metastatic melanoma and is usually continued until disease progresses or toxicities occur [2]. In our case, pembrolizumab therapy was permanently discontinued and the patient underwent surveillance with no current treatment as of June 06, 2023.

Conclusions

Due to the increased use of immune checkpoint inhibitors for oncologic treatment, it is important for clinicians to recognize their irAEs and varying timing of their occurrence. We present a case of checkpoint inhibitor drug-induced liver injury three years after our patient started pembrolizumab therapy. He was successfully treated with steroids and resolution of his liver enzymes. This case demonstrates the varying timeline in which irAEs may arise secondary to commonly used checkpoint inhibitors.

Ethical Statement

This research conducted in accordance with ethical standards outlined in the Helsinki Declaration and adhered to ethical guidelines.

Informed Consent

Written and verbal informed patient consent was obtained for this case report.

Data Availability

This report presents the clinical details and management of an individual clinical episode; data sharing not applicable.

Conflict of Interest

The authors declare that no conflicts exist.

Financial Disclosure

The authors declared no financial support.

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