American Journal of Medical Case Reports, 2025, Vol. 13, No. 2, 9-11
Available online at http://pubs.sciepub.com/ajmcr/13/2/2
Published by Science and Education Publishing
DOI:10.12691/ajmcr-13-2-2

The Pembrolizumab Puzzle: Hepatic Complications of Immunotherapy

Jasdeep Bathla[1,*], George Kidess[2], Kenan Abouchaer[1], Ayman Salem[1], Dana Kabbani[1]

[1]Department of Internal Medicine, Detroit Medical Center/Wayne State University, Detroit, MI, USA
[2]Wayne State University School of Medicine, Detroit, MI, USA
*Corresponding author: jasdeepsbathla@gmail.com

Received February 10, 2025; Revised March 11, 2025; Accepted March 18, 2025

Abstract Immune checkpoint inhibitors, or ICI's, are an advanced immunotherapy that is increasingly used in a range of malignant disorders. Given such widespread use, attention to the side effect profile of these agents is needed given an array of complications, specifically, drug-induced liver injury (DILI). Although rarely encountered, DILI can be life-threatening given the precarious prognosis of this patient population. We present a case of DILI due to a specific subset of ICI's known as programmed cell death protein 1 (PD-1) inhibitors which unfortunately resulted in a fatal outcome. The patient had history of relapsed Hodgkin's lymphoma on salvage immunotherapy with pembrolizumab and despite appropriate management, ultimately succumbed to multiorgan failure. Despite potential for such disastrous outcomes, this class of medications remains relatively safer than alternative therapies. This case highlights a specific deleterious effect of this drug class while advocating for further investigation into the link between ICI use and DILI.

Keywords: *pembrolizumab, immune checkpoint inhibitor, immunotherapy, drug induced liver injury*

Cite This Article: Jasdeep Bathla, George Kidess, Kenan Abouchaer, Ayman Salem, and Dana Kabbani, "The Pembrolizumab Puzzle: Hepatic Complications of Immunotherapy." *American Journal of Medical Case Reports*, vol. 13, no. 2 (2025): 9-11. doi: 10.12691/ajmcr-13-2-2.

1. Introduction

Immune checkpoint inhibitors (ICI's) are a novel class of immunotherapy medications that include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors and programmed cell death protein 1 (PD-1) inhibitors. This class of drugs is commonly used as a biologic agent to target cancer cells in a variety of advanced stage malignancies, however, with increased use, more attention to the side effect profile of these medications is needed. Drug-induced liver injury (DILI) secondary to ICI use is more common with the CTLA-4 inhibitors and very rarely associated with PD-1 inhibitors, such as pembrolizumab. When caught early and addressed appropriately, most cases of DILI secondary to ICI use have good prognosis with complete resolution of hepatic function, however, few fatal cases have been reported. Here, we present a case of DILI secondary to pembrolizumab use that resulted in rapidly deteriorating hepatic function and eventually death, despite appropriate therapy.

2. Case

A 62-year-old patient with a history of relapsed Hodgkin's lymphoma, on salvage immunotherapy with pembrolizumab, was transferred to our facility due to acute liver injury noted by transaminitis with ALT of 2153 U/L, AST of 2085 U/L, hyperbilirubinemia of 15.44 mg/dL, and coagulopathy with INR of 2.01. He was otherwise asymptomatic but did endorse fatigue and jaundice. His last dose of pembrolizumab was roughly forty days prior to presentation and acute causes of liver failure such as autoimmune, viral, or infection had returned negative prior to facility transfer. Given the risk of drug-induced liver toxicity, he was started on steroids promptly with IV Methylprednisolone 2 mg/kg twice daily dosing along with Bactrim for infectious prophylaxis. Following steroid initiation, his liver enzymes and

hyperbilirubinemia acutely worsened demonstrating progression to grade IV hepatotoxicity. Mycophenolate mofetil 1 g oral twice daily dosing was added with reduction in steroid dose to daily dosing due to concerns of possible steroid-induced cholestasis. A liver ultrasound was obtained and showed cirrhotic liver morphology suspected to be from steatohepatitis and subsequent MRCP showed an acute vs chronic cholecystitis picture, cirrhotic liver, and a non-dilated biliary tree. He ultimately underwent a liver biopsy which showed portal and lobular inflammation consisting of mostly lymphocytes with some plasma cells, few neutrophils and macrophages, along with hepatocyte injury with occasional acidophil bodies and hepatocellular cholestasis (Figure 1 and Figure 2). Overall, these findings were consistent with moderate hepatitis supporting a diagnosis of checkpoint inhibitor treatment induced liver injury. Ultimately, despite

appropriate treatment with steroids, his liver failure progressed to multiorgan involvement with the development of hemodynamic shock, and he was then terminally weaned in the ICU per family's wishes.

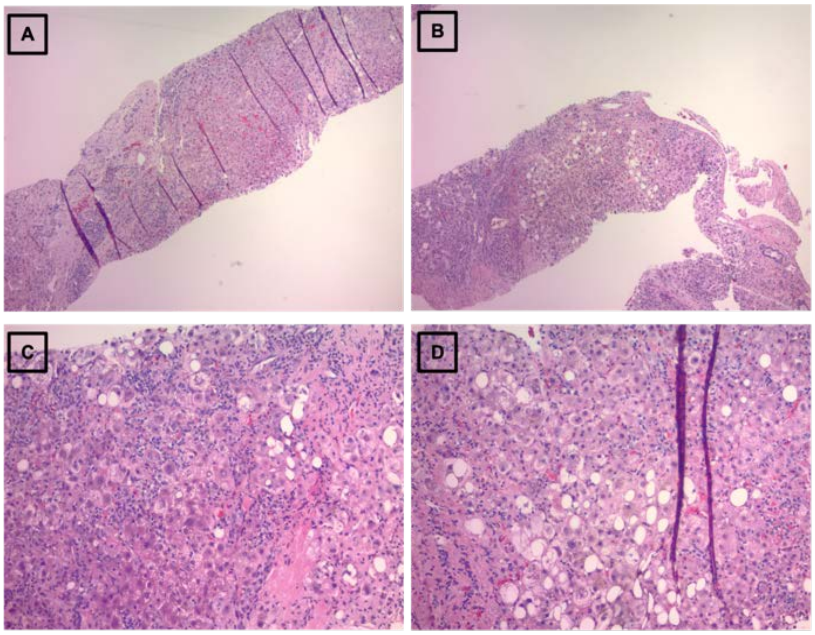

Figure 1. Hematoxylin & Eosin (H&E) stain of hepatic tissue both in 3X (A, B) and 10X (C, D) showing lymphocytic infiltration, hepatic necrosis, and vacuolization

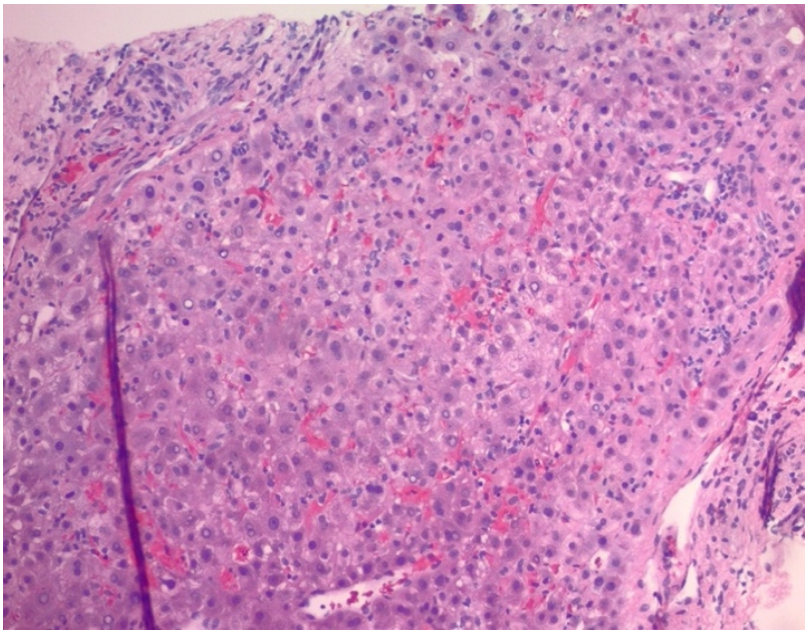

Figure 2. Trichrome staining of hepatic tissue showing several areas of fibrosis (stained blue)

3. Discussion

Although no specific mechanism of DILI secondary to ICI use has been reported, some theories have suggested possible involvement of their inhibition of T-cell downregulators. While this may be beneficial in producing an increased immune activation against cancer cells, it conversely may lead to unwanted exposure to autoimmune reactors, especially in tissue that has high capacity for immune tolerance such as the liver [1]. Information about risk factors for developing DILI is limited with few studies completed however one such study found an increased incidence of DILI caused by PD-1 inhibitors in those with a history of non-alcoholic steatohepatitis, similar to our patient [2,3].

Clinical suspicion and exclusion alone may be sufficient to diagnose DILI, however, histopathological analysis of liver biopsy can be pursued for confirmation. Pathologic manifestations are generally broad, including panlobular hepatitis, centrilobular necrosis, portal inflammation, and nodular regenerative hyperplasia [4]. One case report on the histopathology of pembrolizumab-induced DILI showed dense inflammatory cell infiltrate, bile duct inflammation, and endothelialitis, similar to findings seen in our case which additionally showed vacuolization and fibrosis on trichrome staining [5].

Our patient presented acutely with a relatively recent

use of ICI therapy, however, different studies have shown a varying length of time between last ICI use and symptom presentation ranging from sixty days to fourteen weeks [6,7]. Overall cases of DILI caused by specifically PD-1 inhibitors occur very rarely in less than 3% of cases, with an even fewer amount, less than 1%, resulting in fatal outcomes, such as our case described above [3].

Oftentimes, cessation of ICI use or appropriate therapy with steroids is sufficient for resolution of symptoms, however, patients can often decompensate quickly despite therapy. Initial management involves cessation of ICI use, along with corticosteroid use for DILI, although current data suggests questionable efficacy. In severe cases, patients may qualify for liver transplant as well. Typically, patients with favorable prognosis and normalization of liver enzymes may be continued on the inciting ICI therapy with close monitoring thereafter [3,8]. Thus, this further highlights the infrequency of refractory and potentially fatal complications of ICI use.

While DILI secondary to ICI use has the potential for serious complications, it is incredibly important to emphasize that these medications have much lower rates of complications than other oncologic therapies and fatal events are dwarfed by deaths due to untreated malignancy [9]. With rising use of ICI's due to their excellent utility as an oncological immunotherapy agent, clinicians must remain vigilant of potential serious adverse effects and complications such as DILI. Further studies and clinical trials on the development of these drugs must be done to evaluate advanced associations between ICI use and DILI.

References

[1] Shojaie L, Ali M, Iorga A, Dara L. "Mechanisms of immune checkpoint inhibitor-mediated liver injury". *Acta Pharmaceutica Sinica B*. 2021; 11(12): 3727-3739.

[2] Sawada K, Hayashi H, Nakajima S, Hasebe T, Fujiya M, Okumura T. "Non‐alcoholic fatty liver disease is a potential risk factor for liver injury caused by immune checkpoint inhibitor". *Journal of Gastroenterology and Hepatology*. 2019; 35(6): 1042-1048.

[3] Remash D, Prince DS, McKenzie C, Strasser SI, Kao S, Liu K. "Immune checkpoint inhibitor-related hepatotoxicity: A Review". *World Journal of Gastroenterology*. 2021; 27(32): 5376-5391.

[4] Patil PA, Zhang X. "Pathologic manifestations of gastrointestinal and hepatobiliary injury in immune checkpoint inhibitor therapy". *Archives of Pathology & Laboratory Medicine*. 2020; 145(5)571-582.

[5] Aivazian K, Long GV, Sinclair EC, Kench JG, McKenzie CA. "Histopathology of pembrolizumab-induced hepatitis: A case report". *Pathology*. 2017; 49(7): 789-792.

[6] Tsung I, Dolan R, Lao CD, et al. "Liver injury is most commonly due to hepatic metastases rather than drug hepatotoxicity during pembrolizumab immunotherapy". *Alimentary Pharmacology & Therapeutics*. 2019; 50(7): 800-808.

[7] Phan T, Patwala K, Lipton L, Knight V, Aga A, Pianko S. "Very delayed acute hepatitis after pembrolizumab therapy for advanced malignancy: How long should we watch?" *Current Oncology*. 2021; 28(1): 898-902.

[8] Chaudhry H, Lin J, Sohal A, Gulati A, Roytman M. "S3271a rare case of pembrolizumab-induced hepatitis". *American Journal of Gastroenterology*. 2022; 117(10S).

[9] Wang DY, Salem J-E, Cohen JV, et al. "Fatal toxic effects associated with immune checkpoint inhibitors". *JAMA Oncology*. 2018; 4(12): 1721.