Grade 3 Severe Liver Injury Secondary to Pembrolizumab

Paola López-Marte, MD*; Bárbara Rosado-Carrión, MD†;

Over the last years, pembrolizumab has been one of the checkpoint inhibitors that have revolutionized the management of unresectable malignancies given its successful rate of disease control. This drug has become part of the standard of care in several types of cancers, however, the side effects are an emerging concern for physicians managing patients with cancer. Immune mediated injury of these drugs can target virtually any organ. Liver injury is an important side effect of these drugs that can be life threatening and needs to be well recognized. Here we report a case of an 85-year-old male with medical history of stage 3 laryngeal carcinoma who presented with severe liver injury secondary to pembrolizumab. [*P R Health Sci J 2023;42(3):254-255*]

Key words: Pembrolizumab, DILI, Immunotherapy

Drug induced liver injury (DILI) is one the most common causes of elevated liver enzymes and the leading cause of acute liver failure in many countries (1). DILI occurs in 1: 10,000-100,000 persons taking prescription or over the counter (OTC) medications including health and nutritional supplements (1). DILI is the most common serious adverse event which often derails the development of potential new medications in clinical trials and is the most common reason medications are removed from the marketplace or restricted by the FDA (2). Checkpoint inhibitors revolutionized cancer management particularly in patients with non-resectable malignancy or not candidates for surgery since it has improved survival on these patients (3)(4). Pembrolizumab is a programed cell death -1 (PD-1) inhibitor and is a type of checkpoint inhibitor, which was initially approved for metastatic melanoma and non-small cell lung cancer but over last years it has been authorized for multiple non-resectable malignancies (5). However, it can cause serious immune mediated adverse effects which remain a clinical challenge, since the profile of these events can vary depending on the tumor histology for which the drug is target (6). Checkpoint inhibitors are drugs that can cause liver injury (7). Severe liver injury secondary to pembrolizumab is a rare entity that often goes underrecognized. Here we present a case of a life- threatening grade-3 pembrolizumab-induced liver injury in an elderly man.

Case Report

We report a case of a 85-year-old male with past medical history of laryngeal carcinoma stage 3 treated with chemotherapy and radiotherapy in the past. He was on immunotherapy with pembrolizumab for 6 months due to residual disease. Patient comes, referred by his oncologist, to the Hepatology clinic after increased liver function tests were noted. He reported decreased appetite, fatigue, jaundice, and mild right upper quadrant (RUQ) abdominal pain. He denied alcohol abuse. Physical exam was remarkable for palpable hepatomegaly and RUQ tenderness on palpation. Laboratory results are summarized on table 1. Liver profile demonstrated a mixed cholestatic and hepatocellular injury pattern (R factor: 2). Differential diagnosis included biliary obstruction, metastatic disease, viral, autoimmune, and metabolic causes versus DILI (RUCAM causality score: 8). Magnetic Resonance Cholangiopancreatography (MRCP) was negative for infiltrative disease and biliary duct obstruction. Other causes of elevated liver tests including viral hepatitis (HBV, HCV, HAV) were excluded. An immune mediated drug induced liver injury secondary to pembrolizumab was strongly suspected. A liver biopsy was not obtained due to patient's age, comorbidities, severity of liver injury, and to avoid delay in the management. The drug was discontinued, and he was started on high dose intravenous corticosteroids (1-2mg/kg/day) daily for 3 days followed by oral corticosteroids along with ursodeoxycholic acid, given for severe cholestasis. He underwent close follow up at the clinic. At 2 weeks he was feeling better and liver function tests were trending down. Two months later, his liver enzymes are within normal limits. Currently, he is off oral corticosteroids, asymptomatic and has persisted with normal liver tests.

Discussion

Pembrolizumab is a humanized monoclonal antibody that exerts its function by blocking PD-1 receptor on T cells to block PD-L1 and PD-L2 ligands on tumor cells from binding, acting like a checkpoint inhibitor by reversing T cell suppression, inducing antitumor response and delaying tumor growth (8). The mechanism of action of this drug can also cause the

*University of Puerto Rico, School of Medicine, Division of Gastroenterology Research, San Juan, Puerto Rico; †Ponce Health Sciences University, Division of Gastroenterology-Transplant Hepatology, Ponce, Puerto Rico

The authors have no conflict of interest to disclose.

Address correspondence to: Bárbara Rosado- Carrión, MD, Ponce Health Sciences University, Division of Gastroenterology-Transplant Hepatology, 2431 Ave. Las Americas Edif. Porrata Pila Suite 308-310, Ponce, PR, 00717. Email: barbararos@yahoo.com

Table 1. Laboratory results during the first visit and two months after starting treatment.

Laboratory	1st Visit	2 months later
AST (IU/L)	637	23
ALT (IU/L)	350	15
ALP (IU/L)	3438	87
GGT (U/L)	935	-
Albumin (g/dL)	3.4	
T. Bilirubin (mg/dL)	7.62	0.57
PT/ INR	12.0/1.0	
AFP (ng/mL)	16.59	-
CA 19-9 (U/mL)	75.7	-
ASMA	POSITIVE	-

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyltransferase; T. Bilirubin: total bilirubin; AFP: alpha-fetoprotein; ASMA: anti-smooth muscle antibody

activation of the immune system to attack healthy organs leading to an "autoimmune like picture" as it was seen in our patient (9). Checkpoint inhibitors can cause colitis, dermatitis, myocarditis and hepatitis as shown on several case reports, however, grade 3 liver related adverse events occurred in less than 1% of cases on the clinical trials for pembrolizumab (10). Zhang, et al performed a case series evaluating histological patterns of liver injury in patients on anti-PD-1 therapy, and the most common pattern of hepatic injury found was acute lobular hepatitis followed by steatohepatitis and cholestatic injury (9). Mild cases of DILI secondary to checkpoint inhibitors are often treated in a conservative manner with discontinuation of the offending drug and corticosteroids but sometimes this might not be enough to treat moderate to severe cases (11). In fact, cases of fulminant hepatic failure have been reported and advanced age (>65) might be an independent factor related to severe hepatitis (12). Indications for checkpoint inhibitors are expected to increase in the upcoming years. With the concomitant use of other hepatotoxic therapies that often patients with advanced malignancy receive, incidence of cases with severe DILI secondary to these drugs will possibly arise. Thus, it becomes imperative for physicians to promptly recognize this entity since the diagnosis and management can be challenging. Treatment delays could be potentially fatal, taking into account that orthotopic liver transplant in cases of acute liver failure it is contraindicated in the setting of an uncontrolled extrahepatic malignancy. Our case highlights that although rare, a grade 3, severe liver injury can occur. Therefore, close monitoring of liver enzymes is essential before, during and after starting these types of immunotherapies.

Resumen

En los últimos años, pembrolizumab ha sido uno de los inhibidores de puntos de control que ha revolucionado el manejo de las neoplasias malignas irresecables dada su exitosa tasa de control de la enfermedad. Este medicamento se ha convertido en parte del estándar de cuidado en varios tipos de cáncer, sin embargo, los efectos secundarios son una preocupación emergente para los médicos que tratan a pacientes con cáncer. El daño mediado a través del sistema inmune por estos fármacos pueden afectar prácticamente a cualquier órgano. El daño a nivel hepático es un efecto secundario importante de estos medicamentos que puede poner en peligro la vida y debe reconocerse bien. Presentamos el caso de un varón de 85 años con antecedentes de carcinoma de laringe en estadio 3 que presentó con daño hepático severo secundario al pembrolizumab.

References

1. Haque T, Sasatomi E, Hayashi PH. Drug-induced liver injury: Pattern recognition and Future Directions. Gut and Liver [online]. January 2016;10(1):27-36. Available from: PubMed. Accessed April 30, 2022. Doi:10.5009/gnl15114
2. Babai S, Auclert L, Le-Louët H. Safety data and withdrawal of hepatotoxic drugs. Therapie [online]. December 2021;76(6):715–723. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.1016/j.therap.2018.02.004
3. Cheng M, Wang H, Zhao Y, Li G. Efficacy and prognostic factors for response to PD-1 inhibitors in advanced cervical carcinoma: A retrospective study. Drug Des Devel Ther [online]. March 2022;16:887–97. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.2147/DDDT.S358302.
4. Yao J, Zhu X, Wu Z, et al. Efficacy and safety of PD-1 inhibitor combined with antiangiogenic therapy for unresectable hepatocellular carcinoma: A multicenter retrospective study. Cancer Med [online] April 2022;00: 1-11 Available from Pubmed. Accessed April 30, 2022. Doi:10.1002/cam4.4747
5. Palmer AC, Izar B, Hwangbo H, Sorger PK. Predictable clinical benefits without evidence of synergy in trials of combination therapies with immune-checkpoint inhibitors. Clin Cancer Res [online]. January 2022;28(2):368–77. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.1158/1078-0432.CCR-21-2275
6. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol [online]. October 2017;28(10):2377–23785. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.1093/annonc/mdx286.
7. Ortland I, Mirjalili M, Kullak-Ublick GA, Peymani P. Drug-induced liver injury in Switzerland: an analysis of drug-related hepatic disorders in the WHO pharmacovigilance database VigiBaseTM from 2010 to 2020. Swiss Med Wkly [online]. May 2021;151: w20503. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.4414/smw.2021.20503.
8. Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Mol Cancer [online]. January 2022;21(1):28. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.1186/s12943-021-01489-2.
9. Zhang D, Hart J, Ding X, et al. Histologic patterns of liver injury induced by anti-PD-1 therapy. Gastroenterol Rep (Oxf) [online]. September 2019;8(1):50-55. Available from Pubmed. Accessed April 30, 2022. Doi:10.1093/gastro/goz044
10. Suzman DL, Pelosof L, Rosenberg A, Avigan MI. Hepatotoxicity of immune checkpoint inhibitors: An evolving picture of risk associated with a vital class of immunotherapy agents. Liver Int [online]. June 2018;38(6):976–987. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.1111/liv.13746
11. Al-Nattah S, Lata Sharma K, Caldis M, Spengler E, Nicholas Rose W. Plasmapheresis for pembrolizumab-induced hepatitis in a patient with squamous cell carcinoma and prior orthotopic liver transplantation. Case Reports Hepatol [online]. January 2022; 2022: 5908411. Available from: Pubmed. Accessed April 30, 2022. Doi: 10.1155/2022/5908411
12. Vozy A, De Martin E, Johnson DB, Lebrun-Vignes B, Moslehi JJ, Salem JE. Increased reporting of fatal hepatitis associated with immune checkpoint inhibitors. Eur J Cancer [online]. December 2019;123:112-115. Available from Pubmed. Accessed April 30, 2022. doi:10.1016/j.ejca.2019.09.022]