CASE REPORT

Cholestatic Liver Injury Induced by Pembrolizumab in a Patient with Lung Adenocarcinoma

Kana Kurokawa¹, Munechika Hara², Shin-ichiro Iwakami², Takuya Genda³, Naoko Iwakami³, Yosuke Miyashita⁴, Masahiro Fujioka¹, Shinichi Sasaki¹ and Kazuhisa Takahashi¹

Abstract: The anti-programmed cell death-1 protein monoclonal antibody, pembrolizumab is an immune checkpoint inhibitor. While it improves the prognoses of patients with advanced non-small-cell lung cancer, it has been reported to induce various kinds of immune-related adverse events, including hepatotoxicity. Despite the frequency of hepatotoxicity, there is only limited information available regarding the pathophysiology and treatment. We herein report a 48-year-old man with lung adenocarcinoma who was treated with pembrolizumab and developed cholestatic liver injury. In this case, the importance of evaluating the histology of hepatotoxicity and the effectiveness of ursodeoxycholic acid for cholestatic liver injury is indicated.

Key words: immune checkpoint inhibitor, hepatotoxicity, cholestatic liver injury, ursodeoxycholic acid

(Intern Med 58: 3283-3287, 2019) (DOI: 10.2169/internalmedicine.2591-18)

Introduction

The development and rapid advance of immunotherapy, especially of immune checkpoint inhibitors targeting programmed death-1 (PD-1) and PD-1 ligand (PD-L1), have dramatically changed the therapeutic strategy of non-small-cell lung cancer (NSCLC). In certain previous reports, anti-PD-1 antibodies (nivolumab and pembrolizumab) and anti-PD-L1 antibodies (atezolizumab and durvalumab) have shown effects of improving the progression-free and overall survival of NSCLC patients (1-4). However, a high occurrence of immune-related adverse events (irAEs) has been reported, and such severe toxicities can become life-threatening (5). Furthermore, it is difficult to manage irAEs in some cases because their underlying pathogeneses are not fully understood.

We herein report the case of a patient with lung adenocarcinoma who developed severe hepatotoxicity following the administration of pembrolizumab and whose pathological findings revealed cholestatic liver injury.

Case Report

A 48-year-old man with a 28-year history of smoking was referred to our hospital because of an abnormal shadow in the left lung. He was diagnosed with lung adenocarcinoma in the left upper lobe with left adrenal metastasis (cT2aN2M1b, Stage IVA) that did not harbor an epidermal growth factor receptor mutation or the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase fusion gene, however, it showed a tumor proportion score of PD-L1 of 1-49%.

Four cycles of first-line therapy using cisplatin, pemetrexed and bevacizumab were administered, followed by pemetrexed and bevacizumab as maintenance therapy. After two cycles of such therapy, an increase in the size of the primary lesion was observed. Therefore, the patient was treated with pembrolizumab (200 mg/kg every 3 weeks) as second-line therapy. Eleven days after the second admini-
stration of pembrolizumab, he presented a fever and progressive fatigue and was admitted to our hospital. His conjunctiva and his skin were icteric. Laboratory examinations revealed the following: aspartate aminotransferase (AST) 413 U/L, alanine transaminase (ALT) 175 U/L, alkaline phosphatase (ALP) 1,033 U/L, gamma-glutamyl transpeptidase (γ-GTP) 649 U/L, total bilirubin 5.4 mg/dL (including 3.9 mg/dL direct bilirubin) with a deranged coagulation profile (platelets 27,000/μL and fibrin degradation products 61.3 μg/mL). Neither a viral etiology (hepatitis B and C virus or cytomegalovirus) nor autoimmune origin (antinuclear and antimitochondrial antibodies) were proven.

On admission, chest X-ray showed a nodular shadow in the left upper lung field (Fig. 1A). Thoracic computed tomography revealed a 2.6×3.0 cm nodular shadow in the left upper lobe (Fig. 1B). Splenomegaly was detected on enhanced abdominal computed tomography (CT), although dilatation of the bile duct and thickening of the gallbladder wall were not observed (Fig. 1C). Abdominal ultrasonography showed a finding suggesting a fatty liver. The patient denied having consumed alcohol recently, and there had been no recent changes in his medication, except for pembrolizumab.

Prednisolone 80 mg (1 mg/kg) was administered once daily, because drug-induced liver injury caused by pembrolizumab was suspected. After the administration of prednisolone, his serum ALP and γ-GTP did not improve, although decreases in his bilirubin, AST and ALT were observed. The patient subsequently underwent a diagnostic liver biopsy to clarify the cause of the prolonged biliary tract involvement. Histopathology of the liver revealed inflammatory cell infiltration of the portal tract and destruction of the interlobular bile duct, whereas the parenchyma displayed a normal architecture (Fig. 2A and B). Immunohistopathological staining showed that those inflammatory cells were represented by CD8+ lymphocytes (Fig. 2C). These pathological findings suggested cholestatic liver injury.

The administration of ursodeoxycholic acid (UDCA) 900 mg daily was commenced after a pathological finding was obtained, and biliary tract enzymes were consequently improved (Fig. 3). After 4 weeks of taking prednisolone 80 mg daily, the dosage was tapered to about 10 mg every 2 weeks without any recurrence of hepatitis. However, the primary lesion of the left upper lobe rapidly became enlarged after the improvement of his liver injury. Although the patient received docetaxel and ramucirumab as a third-line therapy, his general condition quickly worsened due to the progress of lung cancer.

**Discussion**

Immune checkpoint inhibitors, including anti-PD-1 monoclonal antibody, have improved the outcomes of NSCLC (1, 2, 6, 7). However, collateral damage to normal organs and tissues, including skin, gastrointestinal, hepatic, pulmonary and endocrine systems, caused by irAEs, has been reported in association with these drugs (8). It is reported that severe (grade 3 or 4) irAEs associated with anti-PD-1/PD-L1 antibodies occur in 7% to 12% of patients. While the development of irAEs is associated positively with the response to immune checkpoint inhibitors (9), the management of irAEs is often difficult because of their diversity and a poor understanding of the underlying pathogeneses.
Figure 2. A, B: Histopathology of the liver showing infiltration due to inflammatory cells in the portal tract (white arrow) and destruction of the interlobular bile duct (yellow arrow), while the parenchyma and centrlobular zone showed a normal architecture (A: Hematoxylin and Eosin staining ×100, B: ×400). C: Immunohistochemical staining showing that infiltration due to inflammatory cells is by CD8+lymphocytes (CD8 staining by monoclonal anti-human CD8 mouse antibodies ×400).

Figure 3. Serum alanine transaminase (ALP) and gamma-glutamyl transpeptidase (γ-GTP) did not improve after the administration of prednisolone 80 mg (1 mg/kg), while decreases in aspartate aminotransferase (AST), alanine transaminase (ALT) and total bilirubin (T-Bil) were observed. However, biliary tract enzymes were consequently improved after the administration of UDCA 900 mg daily was commenced.
Hepatic irAEs with immune checkpoint inhibitors mostly consist of asymptomatic elevations in AST and ALT levels, although some patients have an associated fever (10). The incidence of hepatic irAEs due to anti PD-1/PD-L1 antibodies has been described as ≤ 5% in previous reports, with events of grade 3 or 4 occurring in 1-2% of patients (5). Among patients who develop hepatitis, the most common onset timing is 8 to 12 weeks after commencing treatment, although early or delayed events may also be observed (8). For a definitive diagnosis of hepatic irAEs, viral, other autoimmune and other drug-induced causes should be excluded.

Generally, drug-induced liver injury is classified as either hepatocellular injury or cholestatic liver injury based on its principal changes (11). While anti-cytotoxic T lymphocyte antigen 4 showed panlobular hepatitis and granulomatous hepatitis associated with severe lobular necrotic and inflammatory activity, only a few reports have described the histopathology of anti-PD-1/PD-L1 induced hepatic injury (12, 13). Five cases of predominantly lobular hepatitis with mild portal inflammation caused by nivolumab have been described (14). In addition, Martin et al. reported the histology of hepatitis related to anti-PD-1/PD-L1 antibodies (five cases due to pembrolizumab, three due to nivolumab and one due to durvalumab) characterized by lobular hepatitis (13). Pembrolizumab-induced hepatitis with a histopathology of inflammation centering on the bile ducts has also been documented (15). Doherty et al. also reported three cases of anti-PD-1 antibody-induced hepatitis, mostly characterized by impairment of the biliary tract. The clinical courses of these cases were prolonged and severe (16). Similarly, our patient had infiltration of inflammatory cells mainly around the portal tract and destruction of the interlobular bile duct and showed resistance to corticosteroid therapy. These findings suggest that biliary injury due to immune checkpoint inhibitors is less sensitive to immunosuppressive therapy containing corticosteroids than hepatocellular injury and is associated with a protracted clinical course.

The most important differential diagnosis for immune checkpoint inhibitor-induced hepatitis is autoimmune hepatitis. These two conditions have some similarities: immunological processes are involved in the pathogenesis, and both require immunosuppressive therapy for treatment. However, regarding pathological immunostaining findings, some differences between the two conditions have been reported. CD8+ lymphocytes were mainly observed on immunostaining of specimens of liver injury caused by immunotherapy (14). Furthermore, immunotherapy-induced liver injury was associated with markedly smaller numbers of CD4+ lymphocytes than autoimmune hepatitis (14). Immunostaining in the present case showed a similar CD8+-predominant pattern, and these findings support the notion that CD8+ expressing PD-1 proliferated after the blockade of the PD-1 inhibitory pathway in mice (17).

In the present case, prolonged cholestasis was observed after the administration of steroid therapy and was successfully treated with the additional administration of UDCA. Over the past three decades, UDCA has been used as a potential therapeutic approach for chronic cholestatic liver disease, particularly primary biliary cholangitis. It was proposed that UDCA exerted its cytoprotective effect in chronic liver disease mainly by removing hydrophobic biliary acids from the circulating biliary acid pool and by stimulating impaired hepatobiliary secretion (18). Besides the maintenance of adequate cell surface pH by biliary HCO3 secretion, antioxidative action through the upregulation of glutathione synthesis was thought to be associated with the cytoprotective effect of UDCA (19).

In addition to these direct cytoprotective actions in cholestasis, some immunomodulatory effects of UDCA have been proposed (20). UDCA inhibits the production of interleukin-2 by mononuclear cells, suggesting its interfering effect for the activation of both B lymphocytes and CD8+ cytotoxic T lymphocytes (21). UDCA also represses the expression of major histocompatibility complex and intercellular adhesion molecule-1, which are involved in the recognition of autoantigens by CD8+ lymphocytes during autoimmune response (22, 23). Taken together, these findings suggest that UDCA might function not only as a cytoprotective agent but also as an immunomodulator against the CD8+ cytotoxic T lymphocyte-associated autoimmune response during pembrolizumab-induced cholestasis. Although the guidelines for the treatment of severe immune-related hepatitis involve the discontinuation of immune therapy and the use of steroids in order to reduce the immune reaction and inflammation (5), UDCA remains a viable candidate treatment, as improvement in the liver function was observed in our patient after its administration.

One limitation of this report is that the liver biopsy was performed after the administration of steroids. However, it was obvious that inflammatory cells were present around the portal tract without evidence of parenchymal inflammation. These pathological findings are still valid as an indication for cholestatic liver injury. Epidemiology, pathophysiology and treatment of liver injury induced by immune checkpoint inhibitors are not well documented. Further research is needed in order to further understand liver injury induced by immune checkpoint inhibitors and its subsequent treatment.

We encountered a case of severe cholestatic liver injury induced by pembrolizumab that was successfully treated with UDCA. The present case suggests that accurately establishing the type of liver injury leads to appropriate subsequent treatment. Clinical features are important for determining the type of hepatitis, in addition to a liver biopsy (e.g., considerable elevation of biliary tract enzyme such as ALP, γ-GTP and total bilirubin compared with AST and ALT, which indicates cholestatic liver injury). UDCA may be best applied in such situations even if a liver biopsy cannot be carried out, due to severe liver damage, which increases the risk of complications when conducting such a biopsy.

In conclusion, pembrolizumab was shown to be capable of causing severe and prolonged cholestatic liver injury.
UDCA is a viable therapeutic option for such a pathological condition due to its cytoprotective and immunomodulatory effects.

The authors state that they have no Conflict of Interest (COI).

References

1. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373: 1627-1639, 2015.
2. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016.
3. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389: 255-265, 2017.
4. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 377: 1919-1929, 2017.
5. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 26: 2375-2391, 2015.
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373: 123-135, 2015.
7. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387: 1540-1550, 2016.
8. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol 2: 1346-1353, 2016.
9. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol 4: 374-378, 2018.
10. Postow MA. Managing immune checkpoint-blocking antibody side effects. In: Am Soc Clin Oncol Educ Book. 2015: 76-83.
11. Mosedale M, Watkins PB. Drug-induced liver injury: advances in mechanistic understanding that will inform risk management. Clin Pharmacol Ther 101: 469-480, 2017.
12. Karamchandani DM, Chetty R. Immune checkpoint inhibitor-induced gastrointestinal and hepatic injury: pathologists’ perspective. J Clin Pathol 71: 665-671, 2018.
13. De Martin E, Michot JM, Papouin B, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 68: 1181-1190, 2018.
14. Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison with autoimmune hepatitis and idiopathic cryptogenic drug-induced liver injury. Mod Pathol 31: 965-973, 2018.
15. Aivazian K, Long GV, Sinclair EC, Kench JG, McKenzie CA. Histopathology of pembrolizumab-induced hepatitis: a case report. Pathology 49: 789-792, 2017.
16. Doherty GJ, Duckworth AM, Davies SE, et al. Severe steroid-resistant anti-PD1 T-cell checkpoint inhibitor-induced hepatotoxicity driven by biliary injury. ESMO Open 2: e000268, 2017.
17. Im SJ, Hashimoto M, Gerner MY, et al. Defining CD8+ T cells that provide the proliferative burst after PD-1 therapy. Nature 537: 417-421, 2016.
18. Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. J Hepatol 62 (1 Suppl): S25-S37, 2015.
19. Arisawa S, Ishida K, Kameyama N, et al. Ursodeoxycholic acid induces glutathione synthesis through activation of PI3K/Akt pathway in HepG2 cells. Biochem Pharmacol 77: 858-866, 2009.
20. Roma MG, Toledo FD, Boaglio AC, Basiglio CL, Crocenzi FA, Sanchez Pozzi EJ. Ursodeoxycholic acid in cholestasis: linking action mechanisms to therapeutic applications. Clin Sci (Lond) 121: 523-544, 2011.
21. Yoshikawa M, Tsujii T, Matsumura K, et al. Immunomodulatory effects of ursodeoxycholic acid on immune responses. Hepatology 16: 358-364, 1992.
22. Terasaki S, Nakanuma Y, Ogino H, Unoura M, Kobayashi K. Hepatocellular and biliary expression of HLA antigens in primary biliary cirrhosis before and after ursodeoxycholic acid therapy. Am J Gastroenterol 86: 1194-1199, 1991.
23. Yokomori H, Oda M, Wakabayashi G, Kitajima M, Ishii H. Ursodeoxycholic acid therapy attenuated expression of adhesion molecule in primary biliary cirrhosis. Intern Med 42: 1259-1261, 2003.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).

© 2019 The Japanese Society of Internal Medicine

Intern Med 58: 3283-3287, 2019 DOI: 10.2169/internalmedicine.2591-18