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Case Report

Immune checkpoint inhibitor (ICI)-induced hepatitis diagnosed by liver biopsy followed by ICI-free chemotherapy leading to therapeutic effect: A case of lung cancer treatment

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ABSTRACT

In recent years, the combination of platinum-based chemotherapy and immune checkpoint inhibitors (ICIs) has become the standard treatment for patients with lung cancer. Hepatitis is one of the common toxicities following ICI/chemotherapy. When drug-induced hepatitis occurs, the suspected drug must be discontinued. Since it may be difficult to determine the exact drug causing the hepatitis, liver biopsy may help identify this. We report the case of a patient diagnosed with immune-related adverse event hepatitis from liver biopsy and clinical course.

A 45-year-old man with lung adenocarcinoma (stage IV, cT4N3M1c) negative for driver gene mutation was treated with carboplatin (CBDCA), pemetrexed (PEM), and pembrolizumab. Elevated blood aspartate aminotransferase and alanine aminotransferase levels after chemotherapy indicated hepatitis induced by cytotoxic anticancer agents and ICIs. As autoimmune hepatitis was also suspected, liver biopsy was performed and the findings suggested ICI-induced hepatitis. Pembrolizumab was discontinued and CBDCA/PEM was resumed, following which, the primary lesion shrank. When drug-induced hepatitis is suspected, clinicians should actively perform liver biopsy to confirm the diagnosis, so that appropriate therapeutic regimen can be administered.

1. Introduction

In recent years, the combination of platinum-based chemotherapy and immune checkpoint inhibitors (ICIs) such as pembrolizumab has become the standard treatment for patients with driver gene mutation-negative non-small cell lung cancer [1–4]. The combination of pembrolizumab and platinum-doublet chemotherapy markedly improved the 1-year survival rate and progression-free survival compared to platinum-doublet chemotherapy alone in patients with advanced lung cancer in the KEYNOTE-189 placebo-controlled randomized phase III clinical trial [5]. As the combined pembrolizumab and platinum-doublet chemotherapy regimen is being widely used in daily practice, many immune-related adverse events (irAEs) have been reported.

Abbreviations: ICI, immune checkpoint inhibitor; PEM, pemetrexed; CBDCA, carboplatin; irAE, immune-related adverse event; AIH, autoimmune hepatitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CT, computed tomography; CTCAE, Common Terminology for Adverse Events; PSL, prednisolone.

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Hepatitis is one of the common toxicities following ICI/chemotherapy. When pembrolizumab and platinum-doublet chemotherapy are used together, hepatitis develops in 1.2% of the cases, of which 1.0% is Grade 3–5 [5]; this is an adverse event that cannot be overlooked.

When drug-induced hepatitis occurs, the suspected drug must be discontinued. However, the active drug must not be stopped groundlessly as there are only a few effective treatment regimens for lung cancer. It may be difficult to determine the exact drug causing the hepatitis.

Here, we report a case in which irAE hepatitis, autoimmune hepatitis (AIH), and drug-induced hepatitis could be differentiated by considering liver biopsy results and clinical course.

2. Case report

A 45-year-old man was referred to our hospital because of left shoulder pain. He had a 56 pack-year smoking history and a daily alcohol intake of 60 g. Following lung biopsy, computed tomography (CT), positron emission tomography-CT, and head magnetic resonance imaging, he was diagnosed with stage IV (cT4N3M1c) adenocarcinoma with brain and bone metastases. Genetic tests showed that driver gene mutations and PD-L1 expression were negative. His general condition was good, and he had a performance status of 1. Pre-treatment blood test results were as follows: white blood cell count, 10,320/ μ L; hemoglobin, 12.9 g/dL; platelets, 473×10^3 / μ L; total protein, 6.9 g/dL; albumin, 3.3 g/dL; aspartate aminotransferase (AST), 75 U/L; alanine aminotransferase, (ALT) 35 U/L; lactate dehydrogenase (LDH), 353 U/L; and C-reactive protein, 4.19 mg/dL. AST and LDH levels were slightly elevated. He had no hepatitis B or C virus infection. Carboplatin (CBDCA)/pemetrexed (PEM)/pembrolizumab was started as first-line regimen.

On day 5 after chemotherapy initiation, blood test result showed grade 2 hepatitis based on the Common Terminology for Adverse Events (CTCAE) ver. 5 (AST 155 U/L; ALT 258 U/L). Fatigue, jaundice, loss of appetite, arthralgia, fever, hepatosplenomegaly, and ascites were not observed. As hepatitis resolved spontaneously without any treatment, the second course was started on day 22. Blood AST and ALT levels increased again to CTCAE grade 2 (AST 178 U/L; ALT 189 U/L), and hepatitis duration was prolonged. At this time, the patient was asymptomatic. Blood tests ruled out hepatitis B and C. There was no history of blood transfusion or travel abroad; no raw food was consumed; and the possibility of hepatitis A, D, and E was low. There was no malaise, fever, sore throat, swollen lymph nodes, rash, or immunodeficiency, and there was no suspected Epstein-Barr virus or cytomegalovirus infection. CT and abdominal echocardiogram showed no notable findings and no liver metastasis. The patient had abstained from drinking alcohol since he was hospitalized. Thus, alcoholic liver disease was excluded. He had been taking acetaminophen and psychotropic drugs for a long time, but he had no hepatitis. Because liver impairment appeared consistently after chemotherapy, we hypothesized that it was due to ICI or a cytotoxic anticancer drug. An ultrasound-guided liver biopsy was performed by a hepatologist on day 40 (day 19 of cycle 2) to identify the cause, and a pathologist made a pathological diagnosis by performing normal formalin fixation. The specimens were stained for CD138, CD4, and CD8 to distinguish between irAE and AIH.

The pathological findings were mild lobular hepatitis (Fig. 1A) and small spotty–focal necrosis, which are distinct from the findings of drug-induced hepatitis (confluent lobular necrosis). There was no cholestasis, cholangitis, steatosis, eosinophil infiltration, or neutrophil infiltration, commonly noted in drug-induced hepatitis [6,7]. Therefore, drug-induced hepatitis was ruled out.

A small number of plasma cells (Fig. 1B) and piecemeal necrosis was found in the portal vein area (Fig. 1C). Immunostaining showed that CD4⁺ lymphocytes were present in higher quantities than CD8⁺ lymphocytes (Fig. 1D and E). Past studies have reported

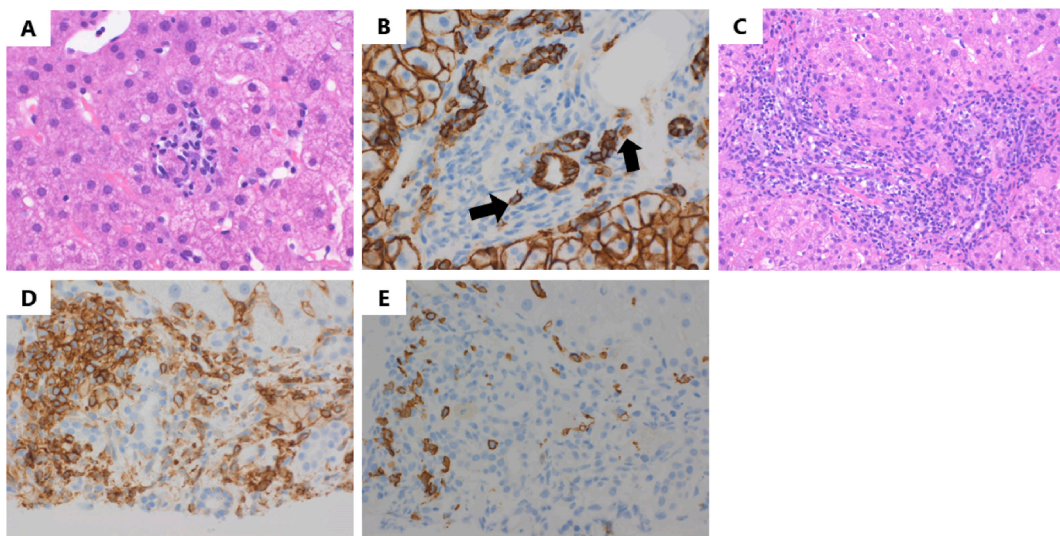


Fig. 1. Pathological findings showing mild lobular hepatitis on Hematoxylin & Eosin (H&E) staining (400x) (A), differing from the findings of drug-induced liver injury. Immunohistochemical staining showing few CD138⁺ plasma cells. Majority of CD138⁺ cells were hepatocytes and bile duct epithelial cells. Only two plasma cells (arrows) are found in the lymphocyte population infiltrating the portal vein area (400x) (B). Piecemeal necrosis found in the portal vein area on H&E staining (200x) (C). Immunohistochemical staining showing more infiltrative CD4⁺ lymphocytes (D) than CD8⁺ lymphocytes (400x) (E).

that AIH is CD4⁺-lymphocyte predominant while irAE hepatitis is CD8⁺-lymphocyte predominant. According to the 2016 Autoimmune Hepatitis Practice Guidelines, in order to diagnose AIH, hepatitis due to other causes should be excluded. In addition, it is necessary to satisfy 3 of the following 4 items: 1) antinuclear antibody positive or anti-smooth muscle antibody positive; 2) high IgG value: >1.1 times the upper limit of the standard value; 3) histologically, piecemeal necrosis and plasma cell infiltration are observed; and 4) corticosteroids are very effective [8]. In this case, the antinuclear antibody was positive ($\times 40$) at the onset of liver impairment but subsequently turned negative; further, IgG, anti-smooth muscle antibody, and anti-liver kidney microsome type 1 antibody were also negative. Piecemeal necrosis and plasma cell infiltration were mild and not typical. Thus, this was not typical AIH. It was concluded that hepatic damage was not due to AIH because hepatitis did not recur and the antinuclear antibody turned negative.

45 mg of prednisolone (PSL; 0.6 mg·kg⁻¹·dose⁻¹) was started on day 46 based on the treatment guidelines for conventional AIH [8]. AST and ALT levels declined quickly and returned to normal on the day 111 (Fig. 2). PSL dose was gradually reduced and stopped on day 138. CT and chest radiography showed that the primary lesion shrank significantly after two courses of CBDCA/PEM/pembrolizumab (Fig. 3A and B) but was increasing again due to the discontinuation of chemotherapy (Fig. 3B and C). CBDCA/PEM without pembrolizumab was restarted on the day 111 (90 days after the last administration of chemotherapy). Hepatitis was not noted, and the primary lesion shrank again (Fig. 3C and D).

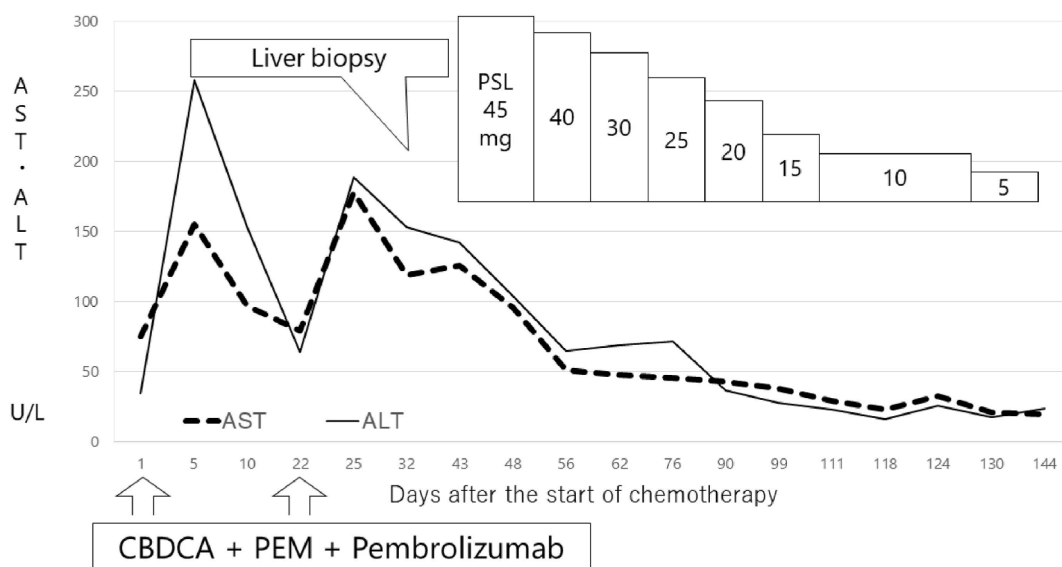


Fig. 2. After administration of the first course of CBDCA/PEM/pembrolizumab, an increase in blood AST and ALT levels was observed. After the second course of drug administration, AST and ALT increased again but did not decrease. We suspected irAE hepatitis, and administration of 45 mg of PSL (0.6 mg·kg⁻¹·dose⁻¹) was started. AST and ALT levels decreased immediately after the start of PSL. The dose of PSL was decreased about every two weeks and was finally discontinued. No relapse of hepatitis was noted.

ALT: alanine aminotransferase.

AST: aspartate aminotransferase.

CBDCA: carboplatin.

PEM: pemetrexed

irAE: immune-related adverse event.

PSL: prednisolone.

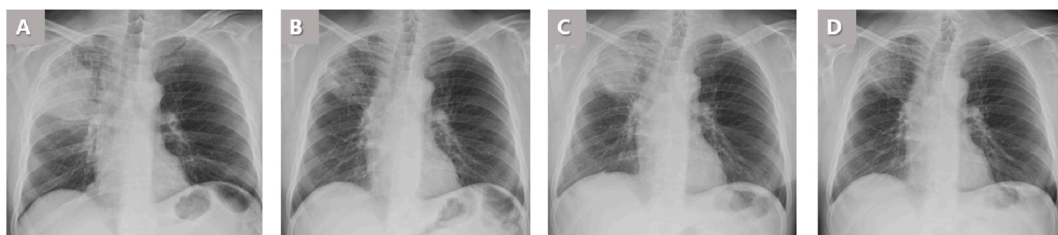


Fig. 3. Chest radiography findings (A) before treatment and (B) after two courses of chemotherapy with CBDCA/PEM/pembrolizumab showing marked reduction in the primary lesion. (C) The lesion grew again after the cessation of drug therapy. (D) After two courses of chemotherapy with CBDCA/PEM, a reduction in the size of the primary lesion is observed again.

CBDCA: carboplatin, PEM: pemetrexed.

3. Discussion

Liver biopsy provided useful information for differentiating irAE hepatitis, AIH, and drug-induced hepatitis in this case. IrAE hepatitis and drug-induced hepatitis can be differentiated histologically [7]. Recent pathological studies have revealed that irAE hepatitis and AIH have similar but not identical histopathological features and can be distinguished to some extent. Lymphocyte infiltration is significantly less in irAE hepatitis than in AIH [9]. AIH and irAE hepatitis can be distinguished by immunostaining of lymphocytes [6,9–11]. AIH has predominantly CD20⁺ and CD4⁺ lymphocytes, whereas irAE has predominantly CD3⁺ and CD8⁺ lymphocytes [9,12–16].

In general, piecemeal necrosis and plasma cells are characteristic of AIH, but in our case, piecemeal necrosis, lymphocyte infiltration, and plasma cells were less, which is consistent with irAE hepatitis rather than AIH. CD4⁺ T-cells were predominant in this case. CD4⁺ T-cell predominance is consistent with AIH, and CD8⁺ T-cell, with irAE hepatitis [9]. However, not all irAE hepatitis cases are predominantly CD8⁺. Further, the small number of cases precludes complete understanding. We comprehensively determined that it was irAE hepatitis rather than AIH by considering that IgG, anti-smooth muscle antibody, and anti-liver kidney microsome type 1 antibody were negative; that hepatitis did not recur; and that antinuclear antibody turned negative.

CBDCA/PEM and pembrolizumab are key drugs in the treatment of stage IV driver mutation-negative lung cancer. It is important to discontinue the causative drug of hepatitis and use an effective drug to ensure long-term survival. No preventive drug for fulminant irAE hepatitis is known. The guidelines state using steroids in case of grade 2 or higher irAE. In this case, administration of PSL 0.6 mg·kg⁻¹·dose⁻¹ improved the hepatitis rapidly; in case the effect of PSL had been inadequate, the use of mycophenolate mofetil or an immunosuppressant would have been considered.

While liver biopsy is useful for differentiating liver disorders, it is an invasive procedure. Pathological evaluation also takes time, which delays the start of treatment. Therefore, liver biopsy is not recommended for all patients in the event of liver damage. However, there are only a few effective treatment regimens for patients with driver mutation negative lung cancer. Therefore, a liver biopsy should be performed to distinguish between the drug that is causing hepatitis and the active drug, thereby allowing for the active drug to be continued.

4. Conclusion

The pathological differences between irAE and AIH are not fully understood because liver biopsies have rarely been performed. Clinicians should actively perform liver biopsies to confirm the diagnosis, so that appropriate therapeutic regimen can be administered.

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Declaration of competing interest

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