Hepatotoxicity Following Immune Checkpoint Inhibitor Therapy in Metastatic Lung Adenocarcinoma: A Case Report

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Research Article

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Abstract

Immune checkpoint inhibitors (ICIs) are mAbs against cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death-1 receptor (PD-1) and programmed death-ligand 1 (PD-L1), which the inhibitory pathways that leads to T cell inactivation. Here, we report a case of ICI-induced immune-mediated hepatotoxicity with liver biopsy. A 63-year-old man with brain metastasis from lung adenocarcinoma was treated with three times of g knife treatment, following by a combination of chemotherapy [carboplatin and (550 mg) + pemetrexed (1000 mg)] plus bevacizumab (anti-VEGF monoclonal antibody) (600 mg D1) and camrelizumab (anti-PD-1 mAb) (200 mg D1). Around 21 days later, abnormal liver function was detected. He received a diagnosis of ICI-induced liver injury after liver biopsy. The liver function of this patient was recovered, following methylprednisolone treatment. Such data offers useful information for clinicians to deal with cancer patients for ICI treatment, suggesting that liver function must be closely monitored.

Introduction

Immune checkpoint inhibitors (ICI) has been wildly used for anti-cancer therapy in various malignancies [1], however, the outcomes of ICI have been compromised in some degree among a number of patients with serious immune-related adverse events (irAE) [2], including skin, gastrointestinal tract, endocrine glands and liver. Hepatotoxicity may be one of the most dangerous complications with ICI, occurring in up to 16% of patients receiving ICIs [3]. However it was not fully demonstrated the case of ICI-induced immune-mediated hepatotoxicity from the literature. We reported here a case of ICI-induced immune-mediated hepatotoxicity with liver biopsy.

Case

A 63-year patient was admitted to neurosurgery for neurological symptoms due to lung adenocarcinoma brain metastasis. Histopathology of his tumor showed PD-L1 tumor proportion score (TPS) 20% and KRAS mutation in Exon2, but EGFR mutations and ALK rearrangements were negative. This patient was discharged on the same day following a combination of chemotherapy [carboplatin and (550 mg) + pemetrexed (1000 mg)] plus bevacizumab (anti-VEGF monoclonal antibody) (600 mg D1) and camrelizumab (anti-PD-1 mAb) (immune check point inhibitor) (200 mg D1). However on the third day, this patient had maculopapular rash on the chest with itching and tongue ulcers, but was resolved spontaneously 3 days later. Abnormal liver function was discovered during his second admission for the anti-cancer therapy, showing that ALT, AST, ALP or GGT was 268IU/L, 280 IU/L, 259IU/ L or 344IU/L, respectively; TB or DB was 12.7 or 3.9 μ mol/L, respectively (Figure1). He had no viral hepatitis nor autoimmune liver disease. B ultrasound and magnetic resonance revealed a normal liver and bile duct structure. Notably, DILI susceptible gene screened from this patient showed a RS72631567 mutation with RUCAM score at 6.

Liver biopsy of this patient demonstrated that focal necrosis, acidophilic body and mild steatosis and cholestasis (Figure 2). Lymphocyte, but not eosinophil infiltration, was observed primarily in the liver sinusoids and mild inflammation in the portal area. These infiltrating lymphocytes were CD3⁺ or CD8⁺, but not CD20⁺. CK19 immuno-staining showed normal small bile ducts. HBsAg, HbcAg, Copper and Perls blue were all negative.

Thus the cause of the liver injury was finally diagnosed as ICI-induced immune-mediated hepatotoxicity at level 3, according to the Common Adverse Reaction Toxicity Criteria (CTCAE 4.03 criteria) from National Cancer Institute [4]. ICI was discontinued and corticosteroid was initiated. The liver function of this patient was recovered, following methylprednisolone treatment. Finally, the patient's liver function almost recovered, showing that ALT, AST, ALP or GGT was 44, 32, 326 or 367 IU/L, respectively, prior to discharge (Figure 3).

Discussion

ICI-induced immune-mediated hepatotoxicity is manifested as elevated AST and ALT or symptomatic hepatitis [5], and > 50% of the cases are cholestatic hepatitis [6], then mixed liver injury are more common than hepatocellular liver injury [7].

In the current case, the patient has received pemetrexed and carboplatin initially, followed by anti-PD1. Thus, it is rather challenging for the clinicians to clarify whether such liver injury was caused by pemetrexed and carboplatin and/or PD-1. This patient presented with chest maculopapular with itching and tongue ulcer, more favorable in ICI induced liver injury, which is supported with liver biopsy of the histopathology. We can't exclude the liver injury from this patient caused by paclitaxel and carboplatin, which often resulted in more severe liver damage at histopathological level, i.e. fusion necrosis and bile duct damage [8]. Our finding, however, is more favorable to ICI induced liver damage, showing that quite large number of CD3⁺ or CD8⁺ lymphocyte, but not eosinophils, infiltration in the damaged liver, which is in agreement with other report of ICI injured liver [9][10]. Some researchers further showed that portal vein inflammatory cells are composed of CD4⁺ and CD8⁺ T cells, and the lobules are dominated by CD8⁺ cells[5]. In this case, the histological morphology is manifested by punctate necrosis of hepatocytes and inflammation in the portal area, accompanied by infiltration of CD4⁺ and CD8⁺ T cells. These histological characteristics are consistent with ICI injured liver.

Summary

Here, we reported a case of ICI induced liver injury, with clinical manifestations and pathology. The pathology demonstrated that this patient included focal necrosis, acidophilic body, mild steatosis, mild cholestasis and portal inflammation, as well as infiltrating leucocytes in portal area, mainly CD4⁺ and CD8⁺ lymphocytes. This ICI induced liver injury patient responded well to corticosteroid. Such data offers useful information for clinicians to deal with cancer patients with ICI treatment, suggesting that liver function must be closely monitored.

Declarations

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Authors' contributions

S.K.L, K.H.L, and Y.Z.D conceived of the case and collected data, S.K.L , X.L.W and F.Y drafted the manuscript. G.D.Z , L.Y.L and Q.X assisted with manuscript writing, editing and detailed search of references. H.W and S.S.B as the co-corresponding authors, were involved in the study design and revision of *the draft and all authors commented on previous versions of the manuscript*. All authors read and approved the final manuscript.

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Data availability

All related datas are presented in this paper, further information or datas are available on a reasonable request.

Code availability

Not applicable.

Compliance with ethical standards

Ethics approval

The case report comply with the current laws of the country in which he was performed.

Consent to participate

The patient declared to consent to participate in this study.

Consent for publication

The patient declared to consent to the publication of the current paper.

Conflicts of interest

The authors declare that they have no conflict of interest.

Research involving human participants

This work was performed in humans with approval from the Institutional Review Board.

Informed consent

The Institutional Review Board granted a waiver for this retrospective study.

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Figures

Figure 1

The changes of specific indicators of liver function before and after immunotherapy.

Figure 2

Liver biopsy showed spotted focal necrosis (Figure A) infiltrated inflammatory cells, mainly lymphocytes in portal area (Figure B), and the enrichment of CD4 (Figure C) and CD8 (Figure D) in portal area.

Figure 3

The changes of specific indicators of liver function before and after methylprednisolone treatment.