Case Report

Hypoproteinemia being a manifestation of immunotherapy-related liver dysfunction

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Abstract: Immunotherapy has changed the pattern of treatment in cancer. The interaction between programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibits the activation of T cells, and PD-1/PD-L1 inhibitors can increase the immune response to cancer cells by inducing the immune cells, which has become an important clinical method to treat cancer. However, the alteration in the activation of T cells might lead to misidentification between the body's own cells and tumor cells and induce immune-related adverse events (IRAEs), such as pneumonitis, liver dysfunction, rash, colitis, nephritis, and endocrinopathies. And the IRAEs might lead to serious consequences. Studies have reported that PD-1/PD-L1 inhibitor–related hepatotoxicity is one of these adverse events. Most of the studies reported that hepatitis resulting from PD-1 inhibitor was manifested as elevated liver enzymes and bilirubin. Quite a few patients experienced lower degree of hepatotoxicity treated with checkpoint inhibitors, which indicated that it was necessary to focus on immunotherapy-related liver dysfunction. Here, we report a case of immunotherapy-related liver dysfunction with hypoproteinemia as the first manifestation under the treatment of PD-1 inhibitors combined with chemotherapy. This case suggests that hypoproteinemia was one of the manifestations of immunotherapy-related liver dysfunction, which helps us better understand the immunotherapy-related disease.

Keywords: Hypoproteinemia; liver dysfunction; programmed death-1/programmed death-ligand 1 inhibitor (PD-1/PD-L1 inhibitor); immunotherapy; lung cancer

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Introduction

Immunotherapy has revolutionized the treatment of cancers such as melanoma, renal cancer, and non-small cell lung cancer (NSCLC) (1,2). NSCLC is a serious disease with high mortality. Recently, immunotherapeutic agents targeting the immune checkpoint pathways to enhance the anti-tumor immune reaction have shown great promise in cancer treatment and have been incorporated into the standard treatment (3). Due to checkpoint pathway-mediated immune suppression, the immune system becomes tolerant to tumor formation, and so blocking the checkpoints can activate the T cells and enhance the anti-tumor reaction (4). However, excessive immune response may cause the immune cells to attack normal tissue, leading to the occurrence of immune-related adverse events (irAEs) (1,5-11). Programmed death-1 (PD-1) is one of important immune checkpoint receptors. PD-1 is expressed in T cells, while programmed death-ligand 1 (PD-L1) is overexpressed in specific types of tumor cells (12), and the interaction of PD-1 and PD-L1 decreases

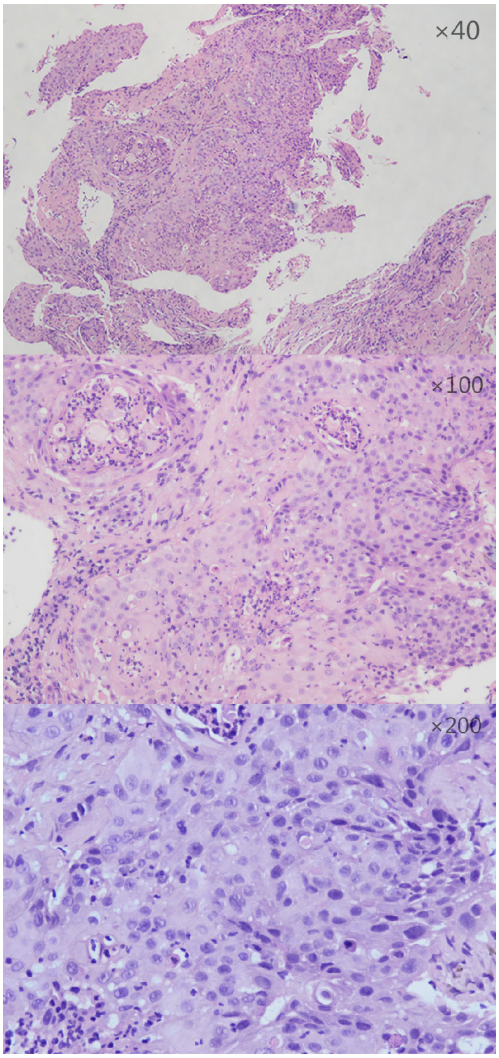

Figure 1 Pathology of the lung biopsy. Hematoxylin and eosin slides showing lung squamous cell carcinoma.

T cell immune response and maintains the toleration to the tumor cells (13). Researches have demonstrated that PD-1/PD-L1 inhibitors could prolong the survival of patients with NSCLC by enhancing the immune reaction to tumor cells to take effect in the NSCLC treatment (9). A meta-analysis confirmed that patients with NSCLC receiving anti-PD-1/PD-L1 treatments had higher OS rate both in second-line therapy (HR =0.689, 95% CI: 0.635–0.747, P<0.001) and first-line therapy (HR =0.600, 95% CI: 0.407–0.884, P=0.010) than patients receiving chemotherapy (13). With the widespread use of PD-1/PD-L1 inhibitors, it is necessary to pay attention to side effects, such as pneumonitis, liver dysfunction, rash, colitis, nephritis, and endocrinopathies (14-21). Liver dysfunction is one of the most common irAEs. Most of the studies reported that hepatitis resulting from PD-1 inhibitor was manifested as elevated liver enzymes and bilirubin (22,23). Here, we report a case of immunotherapy-related liver dysfunction with hypoproteinemia. The case indicates that hypoproteinemia was manifestation of immunotherapy-related liver dysfunction. Our case also suggested that the possibility of immune-related liver dysfunction should be considered when liver damage occurs during treatment.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4980).

Case presentation

A NSCLC patient was admitted to Shanghai pulmonary hospital (*Figure 1*). The patient was treated with anti-PD-1 monoclonal antibody combined with chemotherapy and subsequently suffered severe hypoproteinemia and edema. And then, he progressed to grade 3 hepatic dysfunction. After receiving magnesium isoglycyrrhizinate injection to protect the liver, bile capsule to decrease bilirubin, and methylprednisolone to inhibit inflammation, the levels of liver enzyme declined, and the patient felt better. The patient had no history of liver disease, alcohol consumption, and viral hepatitis. No other hepatotoxic medications were taken during the treatment.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

Discussion

Immunotherapy has become a promising approach for cancer patients, with immune checkpoint inhibitors demonstrating remarkable achievements in clinical trials. Among them, PD-1/PD-L1 inhibitor can strengthen the function of effector T cells and increase antitumor reaction. At the same time, however, these inhibitors precipitate T cells to infiltrate normal tissue, resulting in irAEs, in a fashion similar to autoimmune disorder (24). The specific pathogenic mechanisms of irAEs still need to be explored. IrAEs occur in up to 70% of cancer patients with the treatment of PD-1/PD-L1 immune checkpoint

inhibitors (24). A meta-analysis assessed that grade 3 and above irAEs occurred in 7.1% of cancer patients treated with PD-1 inhibitors and 6.3% treated with PD-L1 inhibitors. As for the incidence of death related to irAEs, it was reported that the death rate in patients treated with PD-1 inhibitor was higher than that in patients treated with PD-L1 inhibitor (25). When treated with checkpoint inhibitors, nearly 8–21% of patients experienced a lower degree of hepatotoxicity while grade 3–4 hepatitis was rare (9). Studies have shown that the median time of hepatic dysfunction appearing from starting PD-1 inhibitor is about 41 days (range, 21–120 days) (26).

Liver enzyme, bilirubin and serum protein were tested to observe liver function. Different from previous studies reporting that hepatitis caused by PD-1 inhibitor manifest as elevated liver enzymes and bilirubin (22,23), in this case, hypoproteinemia was the manifestation of immunotherapy-related liver dysfunction.

Albumin is synthesized and secreted by hepatocytes and is then released into extracellular space. Albumin enters into systemic circulation from interstitial space by way of the lymphatic system, with 40% of albumin being located in plasma and 60% being located in the extravascular space (27,28). PD-1 is expressed on intrahepatic T cells while PD-L1 is expressed on hepatocytes, Kupffer cells, hepatic stellate cells, and liver sinusoidal endothelial cells. The interactions between PD-1 and PD-L1 induce liver immune tolerance (29). Thus, blocking this pathway makes the autoimmune system attack the liver, which reduces the production of albumin, leading to the liver enzymes and bilirubin inside the hepatocytes being released. Patients with a serum albumin level of less than 28 g/L have been found to have a significantly increased risk of early death (30).

As immunotherapy has become a standard treatment in NSCLC, it is very important to pay attention to its adverse effects. This is the first report concerning PD-1 inhibitor–related liver dysfunction mainly manifesting as hypoproteinemia. The poor prognosis of the patient suggests that irAE of liver dysfunction, especially with hypoproteinemia, should not be ignored during treatment, and that early liver protection and glucocorticoids suppressing inflammation are necessary. Further exploration of PD-1 inhibitor–related liver dysfunction is needed to ensure oncologists perform immunotherapy more safely.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4980

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4980). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

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