Case Report

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Pulmonary Arterial Hypertension Induced by Immune Checkpoint Combined Therapy in an Intrahepatic Cholangiocarcinoma Patient: A Case Report

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ABSTRACT

Immune Checkpoint Inhibitors (ICIs) have dramatically revolutionized the therapeutic approaches by which we treat a series of cancers accompanied by immune-related adverse events (irAEs). Herein, we reported an intrahepatic cholangiocarcinoma male patient with a history of ankylosing spondylitis developing pulmonary arterial hypertension (PAH) under ICI combined therapy with pembrolizumab and lenvatinib. The indirect measurement of cardiac ultrasound showed a pulmonary artery pressure (PAP) of 72mmHg after 21 three-week cycles of ICI combined therapy. The patient partially responded to the treatment of glucocorticoid and mycophenolate mofetil. The PAP decreased to 55mmHg 3 months after the ICI combined therapy was discontinued, but increased to 90mmHg after the ICI combined therapy was rechallenged. We treated him with adalimumab -an antitumor necrosis factor-alpha (ani-TNF-α) antibody- combined with glucocorticoid and immunosuppressants under lenvatinib monotherapy. The patient responded again with PAP decreasing to 67mmHg after 2 two-week cycles of adalimumab. Accordingly, we diagnosed him to have irAE-related PAH. Our findings supported the use of glucocorticoid disease-modifying antirheumatic drugs (DMARDs) as a treatment option in refractory PAH.

Keywords: Ankylosing Spondylitis; Immune-Related Adverse Events; Immune Checkpoint Inhibitors; Intrahepatic Cholangiocarcinoma; Pulmonary Arterial Hypertension

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INTRODUCTION

Immune Checkpoint Inhibitor (ICI) combined therapy improved the cholangiocarcinoma (CCA) outcome with a disease control rate (DCR) of 68% for pembrolizumab combined with lenvatinib as the second-line treatment (1). Pembrolizumab is a humanized monoclonal IgG4 anti-programmed cell death-1(anti-PD-1) antibody, prolonging the survival of advanced CCA patients by enhancing antitumor immunity via blocking negative regulators of T cells. It is also accompanied by the occurrence of immune-related adverse events (irAEs) (2). The incidence of irAEs for pembrolizumab treatment is no more than 60%, with less than 10% being grade 3-4 irAEs, similar to many diseases such as gastrointestinal diseases, endocrine diseases, pneumonia, and rheumatism with the most common symptoms of fatigue, pruritus, rash, pyrexia, decreased appetite, nausea, and diarrhea (3). However, pulmonary arterial hypertension (PAH) caused by ICI is rarely reported (4).

PAH is defined as the pulmonary artery pressure (PAP) exceeding 20mmHg (assessed by the invasive method of the right heart catheterization (RHC)). It leads to further right heart failure with an annual incidence of 0.0287% and 5-year mortality of 62.4% approximately (5). PAH is also practically measured by an indirect method of cardiac ultrasound, in which the velocity of the tricuspid regurgitation jet is used to measure the right ventricular systolic pressure, thereby estimating PAP (5). The most common pathological manifestation of PAH is the infiltration of the pulmonary arterial vasculature with immune cells, which could produce proinflammatory cytokines to induce excessive pulmonary vascular remodeling (PVR) and PAH deterioration (6). Supportive treatments with a limited effect on PAH include diuretics, vasodilators, and combined with the targeted therapy (7). We have reported here a case of irAEs-related PAH.

CASE REPORT

A 55-year-old Chinese male was admitted to the Fourth Hospital of Hebei Medical University on March 13, 2020, with complaints of right upper abdominal pain for more than one month. The thoracoabdominal enhanced computed tomography (CT) 4 days ago in the

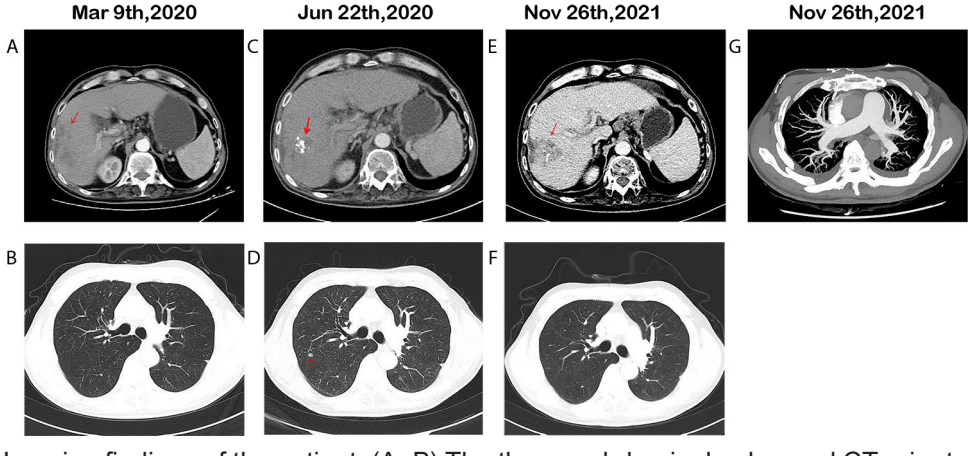

Figure 1. Imaging findings of the patient. (A, B) The thoracoabdominal enhanced CT prior to treatment on March 9, 2020. (A) Abnormal enhancement lesions in the right lobe of the liver (red arrow). (B) No metastatic nodule in the right lung. (C, D) The thoracoabdominal enhanced CT after the fourth administration of albumin-bound paclitaxel on June 22, 2020. (C) Deposits of lipiodol in the liver lesions, no obvious enhancement (red arrow). (D) New metastatic nodule in the right lung (red arrow). (E, F) The thoracoabdominal enhanced CT after Pulmonary arterial hypertension emerged on November 26, 2021. (E) Deposits of lipiodol in the liver lesions, no obvious enhancement, no change in size (red arrow), no portal vein tumor thrombus. (F) Metastatic nodule in the right lung disappeared. (G) Pulmonary artery CT angiography on November 26, 2021. No pulmonary thromboembolism.

Second Hospital of Hebei Medical University revealed multiple abnormal enhancement lesions in the right lobe of the liver and no lesions in both lungs (Figures 1A and 1B). The patient had a history of ankylosing spondylitis for more than 30 years with spinal ankylosis and activity limited of the waist, but no history of basic cardiopulmonary disease.

The hepatitis B surface antigen (HBsAg) was positive for hepatitis B virus (HBV) copies of 6.85×10^3 IU/mL. Tumor markers including alpha-fetoprotein (AFP) and carbohydrate antigen 19-9 (CA19-9) also increased (Figure 2), but the antinuclear antibody spectrum was negative. No esophageal and gastric fundus varices were observed by gastroscopy (Figures 3A, and 3B). Adenocarcinoma cells from the liver lesions were found by ultrasound-guided needle biopsy (Figure 3E), and subsequent immunochemical examination suggested that these tumor cells originated from the bile duct with AE1/AE3(+), TTF-1(-), CDX2(-), CK7(+), CK19(+), Ki67(number of positive cells: 30%), Hep-1(-), and Glypican-3(-). The mismatch repair (MMR) protein status was MLH1 (+), PMS2 (+), MSH2 (+), and MSH6 (+).

The patient was diagnosed with stage IIIB (cT2N1M0) intrahepatic cholangiocarcinoma based on the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system for intrahepatic cholangiocarcinoma, along with HBV-related cirrhosis (Child-Pugh class A), and ankylosing spondylitis.

Transcatheter arterial embolization (TAE) of the liver was performed for a large tumor near the liver margin to prevent the rupture and bleeding of the liver tumor on March 23, 2020, followed by mono-chemotherapy of 200mg albumin-bound paclitaxel with a cycle of three weeks. After 4 cycles of treatment, a new metastatic nodule appeared in the right lung, while the primary lesions in the liver responded stably by enhanced CT scan assessment (Figures 1C, and 1D). We evaluated the disease as a progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. The patient refused the second-line chemotherapy since it could aggravate hepatic cirrhosis, but he preferred ICI combined with the targeted drug even after being informed that ICI may aggravate ankylosing spondylitis. Therefore, treatment of 200 mg pembrolizumab intravenously with a cycle of three weeks in combination with

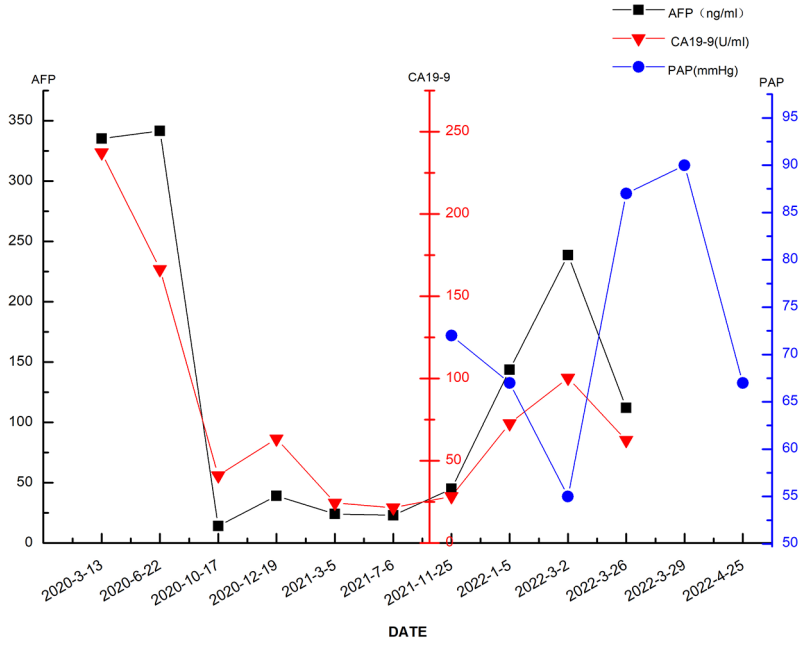

Figure 2. Changes in tumor markers and pulmonary arterial pressure during treatment. AFP, alpha fetoprotein. CA19-9, carbohydrate antigen 19-9. PAP, pulmonary arterial pressure.

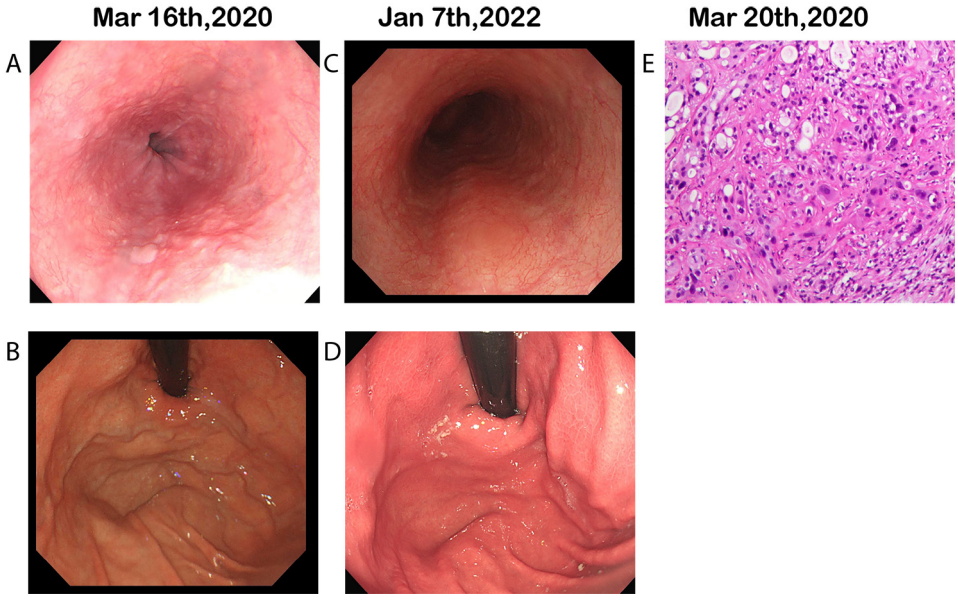

Figure 3. Gastroscopic and pathological findings of the patient. (A, B) Gastroscopy prior to treatment on March 16, 2020**.** No esophageal and gastric fundus varices. (A) Esophagus. (B) Gastric fundus. (C, D) Gastroscopy after Pulmonary arterial hypertension emerged on January 7, 2022. Slight exposure of esophageal and gastric fundus vein. (C) Esophagus. (D) Gastric fundus. (E) The histopathological examination of liver lesion on March 20, 2020. Adenocarcinoma cells（Liver tumor tissue was fixed with 10% formalin, dehydrated, paraffin embedded, and sectioned (4μm) for hematoxylin and eosin staining, magnification, ×20).

oral administration of lenvatinib 8 mg daily was performed for 21 cycles, during which the disease was evaluated as a stable disease (SD). The patient suddenly developed dyspnea at rest with a saturation of percutaneous oxygen (SpO_2) of 93% on November 25, 2021. He later developed cyanosis and systemic edema. The arterial blood gas in the room air revealed a PaO_2 of 56.8 mmHg and $PaCO_2$ of 27.1 mmHg, and the chest radiography revealed cardiomegaly. Echocardiography, which measured the tricuspid regurgitation pressure difference and right atrial pressure, revealed an estimated PAP of 72 mmHg (Figure 2), with a right heart enlargement and a left ventricular ejection fraction (EF) of 42%. We discontinued pembrolizumab and lenvatinib considering that the elevated PAP might be related to pembrolizumab. Further pulmonary artery CT angiography revealed no evidence of pulmonary thromboembolism (Figure 1G). The laboratory examination showed an increased prothrombin time (PT) of 19s, an activated partial thromboplastin time (APTT) of 45.3s, a positive antinuclear antibody with a ratio of 1:1000, a decreased complement C3 of 0.41 g/L, and a decreased complement C4 of 0.08 g/L. Other laboratory test results including those of myocardial enzyme, myoglobin, troponin I, and erythrocyte sedimentation rate (ESR) were all within the normal ranges. The patient and his wife refused the invasive RHC to measure PAP. The thoracoabdominal-enhanced CT showed that the liver lesions were evaluated as "stable" without portal vein (PV) tumor thrombus, metastatic nodule in the right lung disappeared and no interstitial pneumonia was observed (Figures 1E, and 1F). The PV was in the normal range (0.9 cm) as shown by ultrasound measurement. Gastroscopy reexamination revealed slight exposure of esophageal and gastric fundus veins in (Figures 3C, and 3D). Based on the above, we concluded that the patient did not develop PV-related, inters pneumonia-related, or connective tissue disease-related PAH. Dyspnea and systemic edema improved after ventilator-assisted ventilation and a 2-week symptomatic diuretic treatment, but exertional dyspnea remained. We believed that the first cause of PAH was pembrolizumab

and the second was lenvatinib. Considering that the vasodilators treatment for PAH generally takes effect slowly, and the heavy tumor burdens of the patient, we started with methylprednisolone 8mg once a day for 2 weeks with no improvement of exertional dyspnea and PAP, an additional oral mycophenolate mofetil dispersible 0.5 g twice a day was performed for three weeks. The exertional dyspnea of the patient significantly improved, and the estimated PAP decreased to 55 mmHg. The patient showed a strong willingness to rechallenge with ICI combined therapy even after being informed about the possible PAH recurrence. After he was rechallenged with pembrolizumab and lenvatinib for the first three-week cycle based on glucocorticoid and mycophenolate mofetil, the estimated PAP increased to 90 mmHg, and the left ventricular EF increased to 67% with an aggravation of exertional dyspnea. We terminated pembrolizumab again but continued the lenvatinib, increased the dose of methylprednisolone to 20mg once a day, and the dose of mycophenolate mofetil to 0.75 g twice a day. The adalimumab 40mg subcutaneous injection once every two weeks was also performed. Four weeks later, the estimated PAP was reduced to 67 mmHg, and the left ventricular EF to 61% with significantly improved exertional dyspnea. The patient is still receiving regular treatment of mycophenolate mofetil and adalimumab under continuous observation.

DISCUSSION

According to the 6th PAH world symposium of 2018, PAH is diagnosed if the mean PAP exceeds 20 mmHg by RHC measurement. Considering the trauma and risk of RHC, PAH is also identified by the Doppler ultrasound (5). PAH may be caused by a variety of factors such as basic cardiopulmonary disease, pulmonary embolism (PE), portal hypertension (PH), connective tissue diseases, hereditary factors, and drugs (8). The patient did not have any previous history of cardiopulmonary diseases, predisposing factors of PAH such as infection or inflammation, or evidence of PE based on the pulmonary artery CT angiography. Although the patient had a history of HBV-related cirrhosis, there was no evidence of PH such as a widened PV trunk diameter, PV thrombosis, or ascites. In addition, PAH is a rare complication of tyrosine kinase inhibitors (TKIs), and severe PAH was reversible upon discontinuation of TKI (9). Lenvatinib is a small-molecule TKI whose terminal half-life is 28 h, whereas the PAP was still at a high level of 75 mmHg after 2 weeks of lenvatinib discontinuing. The PAP also tends to decrease during the lenvatinib monotherapy, so we excluded this cause of PAH. The patient's ankylosing spondylitis was stable without aggravated low back pain symptoms and inflammatory markers changing, thereby we ruled out the possible causes of ankylosing spondylitis activation for PAH. The PAH responded to glucocorticoid and immunosuppressant after pembrolizumab was discontinued and increased again after rechallenging, which was controlled again with additive Tumor Necrosis Factor inhibitors (TNF-i) application based on the glucocorticoid and immunosuppressant. We diagnosed this irAE-related PAH as "probable" with a score of 6 using the Naranjo criteria (10).

ICIs can initiate irAEs by increasing the T-cell activity against antigens present in healthy tissue. The abnormal activation of T cells produces a large number of inflammatory cytokines in infiltrating pulmonary arterial vasculature to both remodel PVR and increase pulmonary vascular resistance, a process that promotes the occurrence of PAH (11). The $CD8^+$ T cells trigger local inflammatory responses through cytolytic activity and promote PAH development through a Tumor Necrosis Factor-alpha (TNF-α) mediated inhibition of pyruvate dehydrogenase. The $CD4^+$ T-cells including Th1, Th2, Th17, and regulatory T-cells (Tregs) were also involved in

PAH. The changes in the tumor immune microenvironment (including $CD8^+$, $CD4^+$ T cells, and cytokines) induced by ICI may mimic the microenvironment changes in PAH to initiate PAH onset. The PD-1 inhibition could abrogate the protection of Treg and activate pathogenic self-reactive T cells to initiate PAH (12). The cytokines released in the tumor immune microenvironment also participated in PAH to a large extent upon ICI treatment. The upregulation of Interleukin-6 (IL-6) and IL-6 receptor mediates the thickening of the pulmonary vasculature in idiopathic PAH (iPAH). TNF-α signaling drives PAH development by suppressing bone morphogenic protein receptor-2 (BMPR2) signaling, as well as by increasing endothelial-leukocyte cell interaction (13). Bargagli E et al. reported a case of systemic sclerosis with PAH experiencing a significant decrease in PAP after 1 year of treatment with an anti-TNF-α antibody of infliximab (14). Considering that there is no insurance coverage outside the hospital, our patient also refused the cytokines measurement. We would try an anti-IL-6 antibody of Tocilizumab in the case of TNF-i failure. In addition, whether the existing autoimmune disease is a risk factor for irAE-related PAH needs to be further proved.

This is the second case of ICI-related PAH. A squamous cell lung cancer patient under durvalumab (an antibody for programmed death-ligand 1) treatment was previously diagnosed as the first case of ICI-related PAH, overlapping with systemic lupus erythematosus (SLE) and Sjogren's syndrome (4). The present report describes a case of PAH induced by pembrolizumab in an intrahepatic cholangiocarcinoma patient, where the PAP decreased after treatment with glucocorticoid, immunosuppressant, and TNF-α antagonist. Considering the possible immune factors in the formation of PAH, the application of glucocorticoid, immunosuppressant, and inflammatory cytokine antagonist may be a therapeutic option for other refractory PAH.

Competing Interests: The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTION

JZ collected the data and wrote the manuscript. SZ contributed to the literature collection and manuscript writing. SX collected the pathological data. XZ collected the radiographic data. JS L collected the endoscopic data. ZJ collected and revised the Figures. ZG and QL contributed to the project design, data collection, and manuscript review. All authors read and approved the final manuscript.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

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PATIENTS' INFORMED CONSENT

Written informed consent was obtained from the patient for the publication of this case report and any potentially identifying images/ information.

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Conflict of Interest: None declared.

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