Case report

Spontaneous bacterial peritonitis in hepatocellular carcinoma after PD-1 inhibitor therapy: two clinical cases

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ABSTRACT

With the recent advances in immunotherapy, especially programmed cell death protein 1 (PD-1) inhibitors, the treatment of hepatocellular carcinoma (HCC) patients has entered a new stage. However, few reports have focused on spontaneous bacterial peritonitis (SBP) after PD-1 inhibitor treatment of intermediate-to advanced-stage HCC. In this article, we report two clinical cases of SBP after successful PD-1 inhibitor therapy. The patient's condition was assessed as a complete response (CR) according to the mRECIST criteria. Based on these two cases, we found that patients with large or giant HCC who have large tumour diameter should be closely monitored for SBP after successful PD-1 inhibitor therapy, especially when the imaging shows the rapid development of marked necrosis and depression at the tumour site. Early and active treatment is necessary to reduce the suffering caused by SBP.

1. Introduction

Primary liver cancer is the seventh most common malignancy and has the fourth highest cancer-related mortality rate worldwide, with approximately 841,080 new cases and nearly 781,631 deaths annually [1]. China has a particularly high incidence of liver cancer, accounting for approximately 50% of new cases and deaths worldwide [2]. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Globally, most HCC patients are diagnosed in the intermediate or advanced stage [3]. The prognosis of these patients is poor. In recent years, with advances in immunotherapy, especially programmed cell death protein 1 (PD-1) inhibitors, the treatment of intermediate-to advanced-stage HCC patients has entered a new stage. While the application of PD-1 inhibitor therapy has positive clinical results, PD-1 inhibitors also lead to various immune-related adverse events [4, 5]. However, few case reports have focused on the occurrence of spontaneous bacterial peritonitis (SBP) after using PD-1 inhibitor treatment of intermediate-to advanced-stage HCC. In the present report, we describe two typical cases of SBP after PD-1 inhibitor therapy.

2. Case presentation

2.1. Case 1

A 54-year-old male patient was admitted to our hospital because of a liver tumour on 8 August 2020. The patient showed protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels of 5930 mAU/mL on admission, but his other tumour indicators were normal. The patient had no drinking history. He also had positive results for hepatitis B surface antigen, e antibody, and core antibody. The HBV-DNA level was <50 IU/ml. Renal and hepatic functions were normal. On 10 August 2020, magnetic resonance imaging (MRI) showed a tumour in the right lobe of the liver, which was diagnosed as HCC with left branch, right branch and main trunk cancer emboli (Figures 1A, 1B, 1C, and 1D). The admission diagnosis of the patient was HCC with portal vein cancer thrombi (Barcelona Clinic Liver Cancer (BCLC) stage C). The patient signed the informed consent form for treatment. The total bilirubin (TBIL), alanine aminotransferase (ALT) and albumin (ALB) levels before transarterial chemoembolization (TACE) were 14.6 μmol/L, 25.6 IU/L and 38.7 g/L,
respectively. Then TACE was performed on 10 August 2020. Ten millilitres (mL) of iodine oil, 30 mg of pirarubicin, 1/6 vials of microspheres and 1/6 vials of gelatine sponge pellets were injected into the tumour through the superselective right hepatic artery. Three days later, reexamination of liver function showed that TBIL, ALT and ALB after TACE were 20.1 μmol/L, 55.8 IU/L and 37.4 g/L, respectively. The patient was discharged uneventfully. On 4 September 2020, lenvatinib (12 mg/day) was orally administered in combination with PD-1 inhibitor therapy (240 mg/21 days). The TBIL, ALT and ALB levels before and after PD-1 inhibitor therapy were 16.8 μmol/L and 20.5 μmol/L, 33.7 IU/L and 36.8 IU/L, 39.6 g/L and 39.4 g/L, respectively. There was no rash, diarrhea or other adverse reactions except for hypertension during the comprehensive treatment. Antihypertensive drugs were given as indicated, and the blood pressure was finally controlled at normal levels.

On 3 October 2020, the patient visited a local hospital because of abdominal pain and fever. Ultrasonography and CT of the abdomen were performed, which suggested massive ascites (Figures 2A and 2B). At the same time, a routine blood test showed elevated leukocyte and neutrophil percentages, albumin was 35.2 g/L, the level of transaminase was increased slightly, and other hepatic and renal function tests showed no significant abnormalities. Abdominal cavity puncture drainage was performed, and 1600 mL of ascites was drained repeatedly. The abdominal puncture drainage fluid was subjected to cytological and pathogenic examinations. Abdominal cavity puncture drainage fluid was analyzed to determine the presence of ascites. The ascites fluid analysis showed that the specific gravity was 1.009, the protein content was 5 g/L, the pondus hydrogenii (PH) was 7.23, the white blood cell count was 0.9×10^9/L, and the polymorphonuclear leukocytes was 0.43×10^9/L. The ascites fluid analysis results showed that Escherichia coli was the pathogenic bacteria. The final diagnosis was SBP. Anti-infective, albumin therapy and intravenous nutrition support were given, and the patient's targeted therapy and immunotherapy were suspended during the treatment period. The patient recovered after 16 days of symptomatic treatment. After discharge, oral lenvatinib (8 mg/day) was continued. On 2 December 2020, his PIVKA-II was 46 mAU/mL. MRI of the liver showed patchy hypointense and hyperintense mixed signal shadows in the right liver lobe. Using contrast agent, no enhancement was observed, and the lesion measured 8.8 × 5.8 cm. A dendritic filling defect was seen in the right branch of the portal vein. The diagnosis based on the MRI was HCC after comprehensive treatment, and no obvious activity was found in the tumour, with possible thrombosis of the right portal vein and multiple encapsulated effusions in the abdominal cavity (Figures 1E, 1F, 1G, and 1H). The patient’s current condition was assessed as a complete response (CR) according to the mRECIST criteria and a CR according to the RECIST 1.1 criteria [6, 7].

2.2. Case 2

A 50-year-old male patient was admitted to our hospital on 9 December 2019. The patient had no drinking history. His levels of AFP and PIVKA-II were 4605 μg/L and 271,522 mAU/mL, respectively. The other tumour indicators were normal. Hepatitis B surface antigen, e
antibody, and core antibody were positive. The HBV-DNA level was 1.86 \times 10^6 \text{ IU/ml}. The levels of alanine aminotransferase and aspartate aminotransferase were 113 U/L and 113 U/L, respectively. And the other remaining hepatic and renal functions were normal. Enhanced CT of the liver was performed in our hospital and the diagnosis based on CT was giant HCC in the right lobe of the liver with a diameter of was 14.4 \times 12.6 cm, possible invasion of the subbranches of the right portal vein, and cirrhosis (Figures 3A, 3B, 3C, and 3D). The admission diagnosis of the patient was HCC with portal vein invasion (BCLC stage C). The patient signed an informed consent form for treatment. TACE was performed on 19 December 2019. Giant tumour staining and disorganized vessels were observed after TACE, which involved the injection of 20 mL iodine oil, 30 mg pirarubicin, 1/4 vial of microspheres and 1/4 vial of gelatine sponge pellets into the tumour through the superselective right hepatic artery. Because of the COVID-19 epidemic, the patient did not visit our hospital again until 27 April 2020. At that time, enhanced CT of the liver was performed. The diagnosis based on CT was giant HCC after TACE. Multiple active foci measuring approximately 12.8 \times 11.8 \text{ cm} were found, invasion of the subbranches of the right portal vein and right hepatic vein was not excluded, and cirrhosis was observed (Figures 3E, 3F, 3G, and 3H). The TBIL, ALT and ALB levels before TACE were 21.5 \text{ μmol/L}, 48.2 \text{ IU/L} and 39.4 \text{ g/L}, respectively. On 28 April 2020, the patient underwent TACE again. A total of 7 mL iodine oil, 30 mg pirarubicin, and a small amount of microspheres and gelatine sponge pellets were injected into the tumour through the superselective right hepatic artery. Five days later, reexamination of liver function showed that TBIL, ALT and ALB after TACE were 25.4 \text{ μmol/L}, 65.1 \text{ IU/L} and 38.2 \text{ g/L}, respectively. The patient was discharged uneventfully. On 6 May 2020, oral lenvatinib (12 mg/day) was started, combined with PD-1 inhibitor therapy (240 mg/21 days). The TBIL, ALT and ALB levels before and after PD-1 inhibitor therapy were 23.6 \text{ μmol/L} and 24.7 \text{ μmol/L}, 55.9 \text{ IU/L} and 58.3 \text{ IU/L}, 39.0 \text{ g/L} and 38.7 \text{ g/L}, respectively. The patient had no adverse reactions, such as rash, gastrointestinal reactions, or hypertension during this period. On 8 Jun 2020, the patient presented with lower abdominal pain accompanied by fever (maximum temperature: 39.2°C). MRI of the abdomen was performed at a local hospital and it indicated profuse fluid accumulation in the abdominal cavity (Figures 2C and 2D). At the same time, a routine blood test showed elevated leukocyte and neutrophil percentages, albumin was 31.7 \text{ g/L}, and other hepatic and renal function tests showed no significant abnormalities. Abdominal puncture was performed, during which 1900 mL of ascites was repeatedly drained. Cytological and pathogenic examinations were performed on the drainage fluid. The ascites fluid analysis showed that the specific gravity was 1.005, the protein content was 8 \text{ g/L}, the PH was 7.25, the white blood cells was 0.8 \times 10^9/L, and the polymorphonuclear leukocyte count was 0.40 \times 10^9/L. The ascites culture results showed that Escherichia coli was the pathogenic bacteria. The final diagnosis was SBP. Anti-infective and other symptomatic treatments including albumin therapy and

Figure 3. A/B/C/D: Images of case 2 before PD-1 inhibitor therapy. E/F/G/H: Images of case 2 before PD-1 inhibitor therapy. I/J/K/L: Images of case 2 after PD-1 inhibitor therapy.
intrahepatic metastases and HCC. However, neither had ascites prior to PD-1 inhibitor treatment, and large ascites were not seen in these patients. Both patients also had a history of cirrhosis. In case 1, the images showed that there was significant hepatomegaly, which measured 11.3 cm. No abnormal enhancement was seen using contrast agent and invasion of the subbranches of the right portal vein and right hepatic vein was not excluded (Figures 3I, 3J, 3K and 3L). The level of PVIVKA-II was 78 mAU/mL, and the other remaining tumour indicators were normal. The patient's condition was assessed as a CR according to the mRECIST criteria and a partial response (PR) according to the RECIST 1.1 criteria.

3. Discussion

PD-1 inhibitors, as second-line drugs to treat liver cancer, have survival benefits but still have many problems to be solved. They play an antitumour role by activating specific T cells, but the activated T cells also attack normal cells, tissues, and organs while they are killing tumour cells, resulting in immune-related adverse events. A study involving 4766 patients who accepted PD-1 inhibitors found that the incidence of immune-related adverse events was 26.82%, and the mortality rate associated with immune-related adverse events was 0.17% [8]. The most common immune-related adverse events reported clinically are skin and joint reactions, neurotoxicity, endocrine toxicity, cardiopulmonary adverse reactions, and gastrointestinal reactions [4, 5, 9, 10]. However, few studies have reported on the occurrence of SBP while using the PD-1 inhibitor. There is a lack of discussion on the treatment effect of PD-1 inhibitors under the circumstances in which spontaneous bacterial peritonitis (SBP) occurs. This study reported two cases of SBP after PD-1 inhibitor therapy in patients with intermediate-to advanced-stage HCC. The patients' final condition was assessed as a CR or PR according to the mRECIST criteria and RECIST 1.1 criteria. The two patients had very good antitumour treatment effects, which may be related to the abscopal effect. The abscopal effect was initially used to describe situations in which radiotherapy was applied to a tumour lesion, and lesions that were not irradiated began to spontaneously shrink. In other words, local therapy for tumours could act on distant tumours. A previous study showed that ablation could not only lead to local tumour destruction but also abscopal effects in distant lesions, which was most likely mediated by an antitumour immune response [11]. Another study showed that yttrium-90 radioembolization induced an abscopal effect on HCC [12]. In addition, nonthermal histotripsy tumour ablation promotes abscopal immune responses that enhance cancer immunotherapy [13]. Therefore, in this study, it is highly possible that TACE released the tumour antigen and subsequently enhanced the effect of the anti-PD-1 antibody (an abscopal effect). Therefore, the two HCC patients reported in this study experienced complete tumour necrosis and obvious antitumour effects.

In addition, the two patients experienced SBP. SBP mainly refers to ascites due to infections that occur without any perforation of the organs in the abdominal cavity or the presence of abdominal inflammatory lesions [14]. Previous studies reported that the prevalence of SBP can be as high as 8–27% in hospitalized patients with cirrhotic ascites [15]. In these cases, both patients were hepatitis B virus carriers, and their tumour were very large, described as large or even giant HCC. Case 2 had cirrhosis. However, neither had ascites prior to PD-1 inhibitor treatment, and neither of these patients had the typical risk factors for SBP, such as low ascites protein, prolonged prothrombin time, elevated total bilirubin, hypoproteinaemia, or decreased platelet or sodium levels [16, 17]. Both patients in this report had a large tumour mass before treatment, a large or even giant HCC. In case 1, the images showed that there was a significant depression of cells at the tumour site after treatment, which indicated that lots of tumour cells may have undergone necrosis and their debris was shed into the abdominal cavity, which may have caused the symptoms of SBP. These two cases mean that SBP can occur in patients with intermediate-to advanced-stage HCC after PD-1 inhibitor treatment, even if the patients have none of the known risk factors for SBP. Moreover, a relatively good clinical outcome can be obtained in these patients.

Of course, there was insufficient evidence that the SBP in these two cases was caused by the PD-1 inhibitors alone. We speculated that the SBP was related to the PD-1 inhibitors for the following reasons. First, according to the current research, the occurrence of SBP is related to low ascites protein, prolonged prothrombin time, elevated Tbil, hypoproteinaemia, and decreased platelet or sodium levels. However, these two patients did not have any of these risk factors before the occurrence of SBP. Therefore, the causes of SBP in these two patients may be different from the causes of most of SBP. Second, the SBP in these two cases occurred at least 1 month after TACE. The long interval time indicates that the SBP had little relationship with the TACE. Third, the only new therapy for these two cases before the SBP occurred was PD-1 inhibitor therapy. Both SBPs occurred approximately one week after the second cycle of PD-1 inhibitor therapy. Fourth, after recovery from the SBP, oral lenvatinib was continued, and SBP did not re-occur. Therefore, SBP may have little relationship with lenvatinib. Of course, SBP caused by PD-1 treatment is very rare. The above views are all our inferences, which need more clinical studies for further confirmation. In addition, for HCC patients with portal vein invasion, ascites is often formed due to the increase in portal vein pressure. However, SBP is closely related to ascites. In this study, both patients had portal vein invasion and eventually experienced SBP. Therefore, a relationship between portal vein invasion and SBP cannot be completely excluded.

A limitation of this study was that the use of iodized oil in TACE may increase the risk of infection and increase the risk of SBP for giant HCCs.

4. Conclusion

HCC patients with large tumour should be closely monitored for SBP after successful PD-1 inhibitor therapy, especially when imaging shows the rapid development of marked necrosis and depression at the tumour site. Early and active treatment is necessary to reduce the suffering caused by SBP.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.
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