Case Report

Pneumonitis, appendicitis, and biliary obstruction during toripalimab treatment in a patient with extensive-stage small-cell lung cancer: a case report

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Abstract: In recent years, immune checkpoint inhibitors (ICIs) have become a standard treatment for patients with advanced lung cancers. With the widespread use of immunotherapy in clinical practice, immune-related adverse events (irAEs) have become increasingly common. This case report details a 72-year-old man with small-cell lung cancer (SCLC) who developed pneumonitis, appendicitis, and biliary obstruction during treatment with toripalimab. The patient was initially diagnosed with limited-stage SCLC in January 2019 and completed 5 sequential cycles of etoposide/cisplatin (EP) and radiotherapy (60 Gy/30 F). The overall response was complete response (CR) after first line treatment. He developed radiation pneumonitis after completion of radiotherapy, which responded well to symptomatic treatment. Due to newly diagnosed bone metastasis, he was administered toripalimab intravenously every 3 weeks and 12 mg anlotinib orally once a day from January 2020. By the third cycle, the patient presented with electrocardiographic abnormalities, gingival swelling and pain, and hoarseness, and consequently, the anlotinib was suspended. After 4 cycles, he developed suppurative appendicitis, which was managed successfully with anti-inflammatory agents. He then presented with shortness of breath on exertion and after a comprehensive examination, he was diagnosed with ICI-related-pneumonitis. After 6 weeks of treatment with methylprednisolone, the shortness of breath was mostly relieved and treatment continued. In June 2020, the patient developed severe vomiting. Computed tomography (CT) indicated biliary obstruction, and at endoscopic retrograde cholangiopancreatography (ERCP) there was edema of the major papilla of the duodenum. The patient's symptoms were relieved after treatment with gastric acid suppression and antiemetics. Re-examination by magnetic resonance imaging (MRI) showed that the biliary obstruction had been resolved. Although the disease progressed after immunotherapy, no tumor tissue related to the biliary obstruction was detected, and this was therefore classified as an irAE.

Keywords: Small-cell lung cancer (SCLC); immune checkpoint inhibitors (ICIs); immune-related adverse events (irAEs); case report

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Introduction

Small-cell lung cancer (SCLC) accounts for about 14% of all lung cancers. It is a highly malignant tumor that is prone to recurrence and metastasis, and in approximately 60–70% of patients it is diagnosed at an extensive-stage (ES) that is beyond resection. The main treatment for ES-SCLC is chemotherapy, with etoposide and irinotecan combined with platinum as the first-line therapy. SCLC is particularly sensitive to chemotherapy, but the risk of relapse is significant, and the rate of mortality from recurrent disease is high (1-4). Multiple histological factors have hindered the development of molecular targeted therapies for SCLC (5-8) and the efficacy of these drugs has proven to be poor (9). Unfortunately, in the past 30 years, there has been no substantial breakthrough in the treatment of ES-SCLC (10,11).

With the emergence of novel immune checkpoint inhibitors (ICIs), the management of SCLC with ICIs has attracted more attention. ICIs may be an effective treatment that can dramatically change the therapeutic landscape for SCLC patients (8,12). Toripalimab is a programmed cell death protein 1 (PD-1) humanized IgG4 monoclonal antibody that was the first to be approved as a second-line treatment for melanoma in China in 2018. Toripalimab has higher affinity for programmed death ligand 1 (PD-L1) compared to other PD-1 IgG4 monoclonal antibodies such as pembrolizumab and nivolumab. Phase 1 to 3 clinical trials with toripalimab have been conducted in multiple cancer types, including lung carcinoma, and the results have shown that SCLC patients have a high mutation burden in the PD-L1 (13,14).

We present the following article in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-858).

Case presentation

A 72-year-old man with a history of chronic smoking presented in January 2019 with symptoms of fever, cough, and white sputum. He underwent computed tomography (CT) and bronchoscopy at the local hospital, and pathology confirmed the diagnosis of small-cell carcinoma of the left upper lobe. At positron emission tomography (PET)-CT, the lung lesions showed high uptake, as did multiple mediastinal lymph nodes with suspected metastasis, but at this time there was no sign of metastasis in other organs. After 3 cycles of etoposide/cisplatin (EP) chemotherapy, sequential radiotherapy was performed at 60 Gy/30 F, followed by another 2 cycles of EP chemotherapy. However, a sixth cycle of EP was withheld because the patient experienced a grade 3 gastrointestinal adverse reaction. The patient's overall response (OR) was stable disease (SD) after 2 cycles of EP, partial response (PR) after radiotherapy, and complete response (CR) after 5 cycles of EP. The patient refused prophylactic brain irradiation, and in June 2019 he developed grade 2 radiation pneumonitis (*Figure 1A*), which was significantly improved after treatment with traditional Chinese medicine. By December 2019, the patient developed generalized bone pain and enhanced CT and magnetic resonance imaging (MRI) showed multiple bone metastases in the cervical, thoracic, and lumbar spine and ribs. Enhanced CT of the upper abdomen showed a new lesion of approximately 10 mm in the left lobe of the liver, and liver metastasis could not be ruled out. The patient refused additional chemoradiotherapy, and in January 2020 he commenced a regimen of 240 mg toripalimab intravenously every 3 weeks with 12 mg anlotinib orally once a day. By the third cycle (March 2020), the patient exhibited shortness of breath upon exertion, swollen and painful gingiva, hoarseness, and electrocardiographic abnormalities including paroxysmal atrial tachycardia, short runs of atrial tachycardia, atrial premature beats, bigeminy, trigeminy, and frequent atrial premature, paired atrial premature, and occasional ventricular premature beats. Cardiology consultation recommended discontinuation of anlotinib, and the symptoms improved after symptomatic treatment. On March 22, the patient received the fourth cycle of toripalimab. On April 9, he developed severe pain in the right lower abdomen. Routine blood tests were normal, but CT showed low-density lesions of the left liver and appendicitis (*Figure 1B*) with periappendiceal abscess, which was successfully managed with anti-inflammatory agents. On April 20, the patient experienced recurrence of shortness of breath upon exertion and hoarseness, and CT showed interstitial pneumonia in both lungs as well as enlargement of the lesion in the left lobe of the liver to 18 mm. After consultation with the pulmonologist, infectious pneumonia was ruled out and ICI-related pneumonitis was considered (*Figure 1C*), and toripalimab was discontinued. The pneumonitis responded well to a 6-week course of methylprednisolone (80 mg for 7 days and 40 mg for 7 days intravenously, followed by gradually reduced oral dose for 28 days). By May, the patient was experiencing severe bone pain, and he received radiotherapy (30 Gy/10 F) at C3-C7 from 18 to 29 May, and at T12-L4 starting from 1 June. However, the patient experienced severe vomiting during

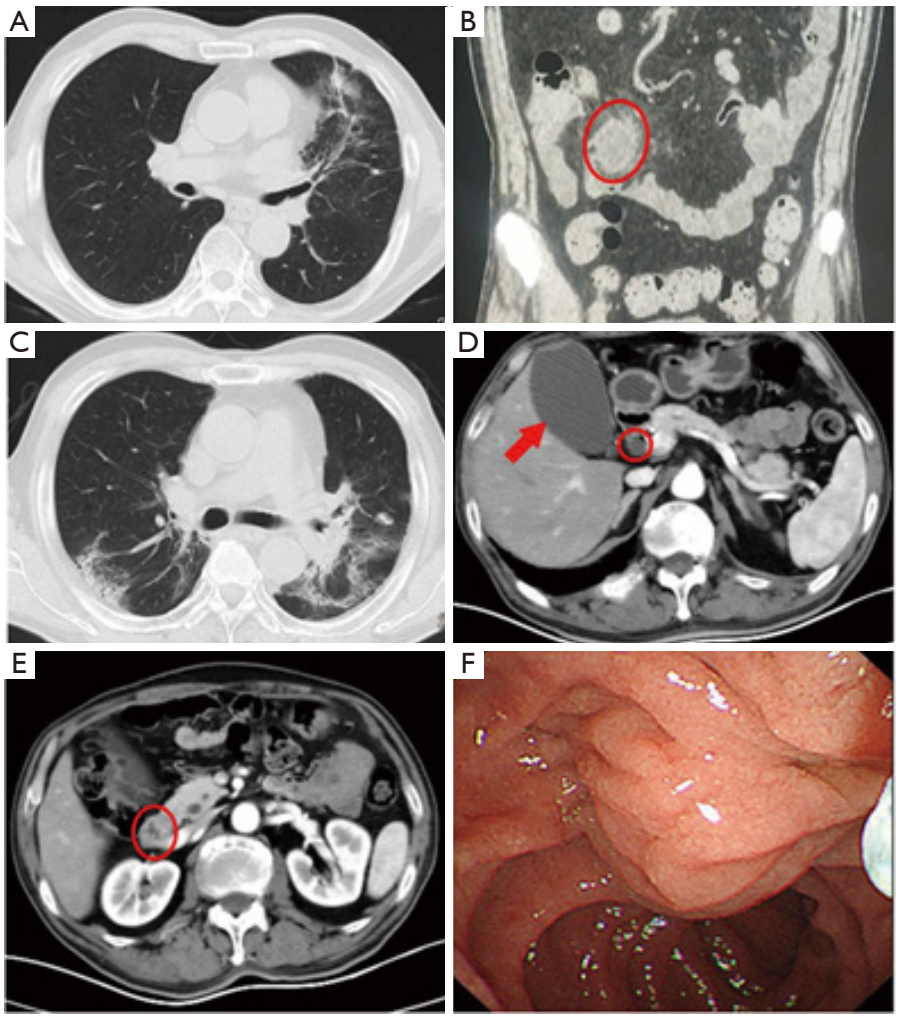

Figure 1 Illustration of each image of patients. (A) The patient had grade 2 radiation pneumonitis, post-radiotherapy CT in June 2019 showing interstitial changes in the radiation field. (B) The patient suffered from appendicitis. Abdominal computed tomography after 4 cycles of toripalimab (April 2020) shows a thickened appendix (red circle in image B) with a dilated lumen containing spot-like high-density shadows, surrounded by round low-density lesions, an absent fat gap, and increased flocculent density. (C) The patient suffered from ICIs related pneumonitis. Chest computed tomography after 3 cycles of toripalimab (April 2020) shows ground glass nodules and interstitial changes in multiple lung fields bilaterally. (D) The patient suffered from biliary obstruction. Enhanced computed tomography shows an enlarged and full gallbladder (red arrow in image D) with an irregular bottom wall and obvious enhancement of small nodules with prominent, dilated intrahepatic and extrahepatic bile ducts (red circle in image D) without any visible obstructions. (E) Enhanced computed tomography shows the pancreatic duct is slightly dilated and there is nodule-like edema of the major papilla of the duodenum (red circle image E) with delayed enhancement. (F) At duodenoscopy, the major papilla of the duodenum was enlarged and edematous, protruding and drooping, with slight sclerosis and a contracted opening. Scope passage was difficult and no stent was placed.

5-fraction lumbar radiotherapy. Abdominal CT showed metastasis in the fourth segment of the left liver, an enlarged appendix, without exception of the formation of fecal stones in the appendix, and nodule-like appearance of the major duodenal papilla with delayed enhancement (*Figure 1D,1E*). At endoscopic retrograde cholangiopancreatography (ERCP) (*Figure 1F*), the papilla was enlarged, swollen and drooping, slightly sclerotic, and without mucosal abnormality. Stenting was not possible. The patient also had an MRI of the brain which showed suspected metastasis in the occipital lobe, but there were no clinical signs or symptoms consistent with the metastatic disease. Laboratory

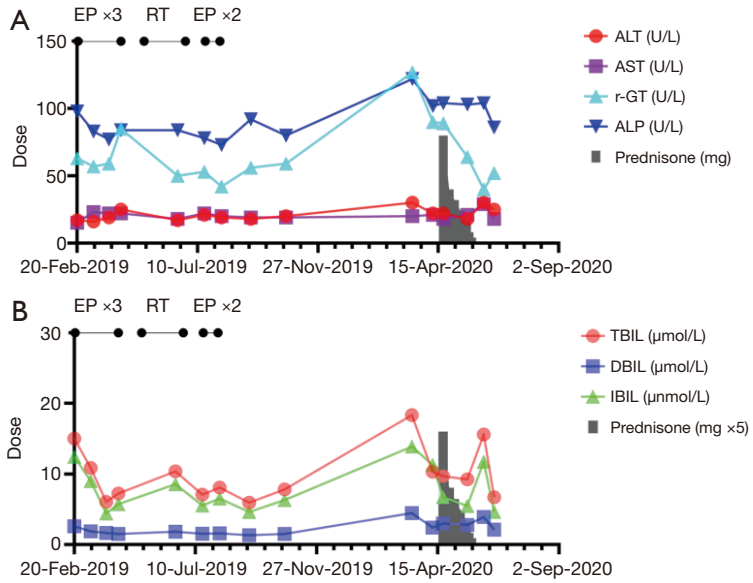

Figure 2 Illustration laboratory data of patients from 20-2-2019 to 2-9-2020. EP: etoposide/cisplatin (5 cycles from 21-2-2019 to 9-8-2019); RT: radiotherapy (60GY/30F from 9-5-2019 to 26-6-2019); Prednisone treatment from 20-4-2020 to 30-5-2020. (A) The changes of hepatic function. (B) The changes in bilirubin indexes. ALT, alanine aminotransferase; AST, aspartate aminotransferase; r-GT, gamma glutamyl transferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin.

tests (*Figure 2*) showed that his alanine aminotransferase (ALT) level was 25 U/L, aspartate aminotransferase (AST) was 18 U/L, alkaline phosphatase (ALP) was 86 U/L, gamma glutamyl transferase (r-GT) was 52 U/L, total bile acid was 5.09 μmol/L, total bilirubin was 6.7 μmol/L, direct bilirubin was 2.1 μmol/L, indirect bilirubin was 4. 6 μmol/L, bile alkaline esterase was 4,650, and lactate dehydrogenase (LDH) was 349 U/L. The biliary obstruction was relieved spontaneously after treatment with gastric acid suppression and the vomiting responded to antiemetic drugs. At the last follow-up, the patient had general body pain and fatigue, and decreased appetite with intolerance to greasy foods. Upon re-examination by MRI, the bile duct obstruction was not detectable but the liver metastasis had enlarged to 35 mm. No other metastases were found.

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 manuscript and any accompanying images.

Discussion

ICIs have enabled treatment breakthroughs in many cancer types, including SCLC (15-18). The IMpower133 study demonstrated that in patients treated with ICI, the median overall survival (OS) was extended by 2 months, median progression-free survival (PFS) was extended by 0.9 months, and the risk of disease progression was reduced by 23% compared to patients in the control group (19). In the CASPIAN study, patients in the experimental group (combination of EP chemotherapy and durvalumab) had significantly prolonged survival compared to the chemotherapy group (median OS 13.0 *vs.* 10.3 months, P=0.0047) (20). In the Keynote 604 study, pembrolizumab combined with EP was able to improve PFS in patients with untreated advanced SCLC (21). After publication of the Keynote 028 and 158 studies, and the CheckMate 032 and 331 reports, the combination therapy of pembrolizumab and nivolumab was recommended as the second-line treatment for SCLC (22-25).

Unfortunately, ICI treatment can also cause irAEs (26-32). ICI-related pneumonitis is a common adverse reaction in patients undergoing ICI treatment for lung cancer. The risk of ICI-related pneumonitis is about 4% with PD-1 inhibitors and is slightly lower (about 2%) with PD-L1 inhibitors (33-35). In the PACIFIC trial, the incidence of pneumonitis among patients receiving immunotherapy after concurrent chemoradiation reached

33.9%, and in the DETERRED and LUN 14-179 trials, the incidence of pneumonitis above grade 2 was 30% in the atezolizumab and pembrolizumab consolidation and maintenance treatment groups (36-38). A Japanese study using real-world data found that following the approval of durvalumab for clinical use, more than 80% of patients with locally advanced NSCLC who received sequential immunotherapy after concurrent chemoradiotherapy developed ICI-related pneumonitis. Half of these cases (48%) were grade 1 pneumonitis, which could be completely relieved with treatment (39).

ICI-pneumonitis must be differentiated from radiation pneumonitis. Radiation pneumonitis occurs 1 to 6 months after radiotherapy, the lesion area is basically the same as the radiation field, and the imaging characteristics are interstitial changes with regular borders. The main treatment is corticosteroids, and fibrosis after corticosteroid treatment is common after the inflammation is absorbed (40,41). ICI-pneumonitis may occur during or after ICI treatment, with the time to occurrence from the start of treatment ranging from 9 days to 19 months (median 2.8 months) (33). ICI-pneumonitis tends to develop earlier in lung cancer patients than in melanoma patients (2.1 *vs.* 5.2 months) (33). New infiltrates on chest imaging, except for new lung infections or tumor progression, are mainly located in the lower lobes of both lungs and are accompanied by dyspnea and other respiratory symptoms including cough, shortness of breath with exertion, and others. Ground glass nodules or patchy nodular infiltration are more common on imaging, which can indicate cryptogenic organizing pneumonia, ground glass pneumonia, interstitial pneumonia, allergic pneumonia, and other non-specific pneumonia (42-44).

The patient in this current case study developed grade 2 radiation pneumonitis after radiotherapy, which was manifested as interstitial inflammation around the radiation field. After symptomatic treatment with traditional Chinese medicine, CT showed that the pulmonary interstitial changes were improved with only minimal fibrotic residue. ICI-related pneumonitis occurred after 4 cycles of immunotherapy and presented as shortness of breath exacerbated by activity. After 6 weeks of corticosteroid therapy, the patient's symptoms abated, and CT showed that the ground glass shadows on the lungs had also resolved.

Biliary obstruction is a less common adverse reaction to immunotherapy. Sclerosing cholangitis caused by nivolumab immunotherapy was first reported in 2017 (45), and subsequent reports of immune-related cholangitis caused by pembrolizumab and other ICIs followed. The main clinical and radiographic features of ICI-related cholangitis are dilation of intrahepatic and extrahepatic bile ducts without obstruction, diffuse thickening of extrahepatic bile ducts, changes in serum levels of liver enzymes, and CD8+ T cell infiltration in the hilar area of the liver on histology. Symptoms should be regressed with corticosteroid therapy or discontinuation of the ICI (45-56). In a report of ICI-related cholangitis caused by pembrolizumab, CT showed edema-like thickening of the gallbladder wall and common bile duct with dilatation of the intrahepatic bile ducts. Magnetic resonance cholangiopancreatography (MRCP) showed irregular stenosis of the intrahepatic bile ducts and dilated peripheral bile ducts, and PET-CT showed increased uptake in the gallbladder wall and the gallbladder (57). In our patient, the CT showed intrahepatic and extrahepatic bile duct dilation and gallbladder enlargement without thickening of the gallbladder and bile duct walls. Delayed enhancement of nodules in the area of the superior papilla of the duodenum was also observed, and the ERCP showed edema with a prominent, drooping, and slightly sclerotic duodenal papilla. The edema of the duodenal papilla made passage of the scope difficult, and thus, additional images and histological specimens could not be obtained for diagnostic confirmation. The patient refused a repeat attempt. Although there was metastasis in the S4 segment of the liver, the lesion was far away from the bile duct, and there was no abnormality of biochemical indicators in the blood. After cessation of the ICI and symptomatic treatment, a repeat MRI indicated that the duodenal papillary edema and biliary obstruction had resolved. Considering the above factors, it is likely that this patient's biliary obstruction was an irAE.

Autoimmune gastroenteritis and enteritis have also been previously reported as adverse reactions to immunotherapy. The clinical manifestations may include bloating, loss of appetite, nausea, vomiting, diarrhea or watery stools, and others (58-63). The symptoms of most patients with ICI-related gastroenteritis progress rapidly, and antibiotic treatment is ineffective. ICI-related gastroenteritis often causes the interruption of immunotherapy, and a small number of serious cases may be related to the direct suppression of T cell activation by immunotherapy and specific microbiota in the intestine (64-67). Histological examination may show epithelial apoptosis and massive neutrophil and lymphocyte infiltration (68-70). In reviewing the course of our patient, it was noted that his purulent appendicitis occurred after the fourth cycle of toripalimab and before he developed ICI-related pneumonitis. The

acute symptoms improved after treatment, but the patient experienced chronic gastrointestinal symptoms afterwards. Following the biliary obstruction, the abdominal CT continued to show diffuse thickening in the area of the appendix. Histological diagnosis of the appendix, gastrointestinal tract, or biliary system was not conducted as it was against the patient's wishes, but according to the series of clinical symptoms it is possible that his appendicitis may be ICI-related.

Immunotherapy has dramatically changed the treatment of lung cancer, but rare adverse reactions are possible, and some have yet to be identified. Therefore, further research is necessary and histological examination, which is the basis of diagnosis, is important. This case study provides valuable information and experience for oncologists and their patients. Indeed, cancer patients receiving immunotherapy should be closely monitored for irAEs, and effective toxicity management and personalized treatment should be administered accordingly.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-858

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-858). Dr. Y Qu reports funding from the Provincial Natural Science Foundation of Liaoning (No. 20180550537 to Y Qu, Expression of PD-1 and PD-L1 immunologic markers in predicting the efficacy of radiotherapy for non-small cell lung cancer) and the Provincial Natural Science Foundation of Liaoning (No. 2019-MS-213 to Y Qu; Relationship between LAIR1 gene expression and radiosensitivity or prognosis in Non-Small Cell Lung Cancer). The other 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 manuscript and any accompanying images.

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