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Case Report

Immunotherapy

Lessons from the diagnosis and treatment of severe immune checkpoint inhibitor-associated pneumonia: a case report

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Herein, we report a case of an elderly male patient who underwent extended radical resection of cardiac carcinoma after regular chemotherapy combined with sintilimab (PD-1 monoclonal antibody) immunotherapy complicated with severe pneumonitis postoperatively. We performed several treatments for aspiration pneumonitis; however, the patient's pulmonary infection and oxygenation were not efficiently improved. The multidisciplinary team considered it an immune checkpoint inhibitor-associated pneumonitis after diagnosis and treatment and then modified the treatment regimen. The pulmonary inflammation was effectively controlled with improved oxygenation; the patient was gradually weaned from the ventilator and finally discharged. The possibility of immune checkpoint inhibitor-associated pneumonitis should be fully considered particularly for patients with a history of immunosuppressive therapy with clinical symptoms of severe pneumonitis.

Plain language summary: Pneumonia is well known. Immune pneumonia may be a new problem. It occurs in 2–5% of patients with immune therapy. It is a bad reaction with low incidence. If this disease is not treated in time, it will cause a relatively terrible result. The fatality rate can reach 12.8–22.7%. The most severe cases can be life threatening. At present, the reason for immune pneumonia is not clear. Some experts believe that it is related to immune change. Dyspnea, cough, fever and chest pain are symptoms of this disease. Although the incidence of immune pneumonia is very low, it should be noted. If you are on immunotherapy, consult your doctor when you feel unwell.

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Immune checkpoint inhibitors (ICIs), as novel immunotherapy, provide significant clinical benefits to patients with malignant tumors and prolong their overall survival [1]. However, immune system overactivation predisposes immune checkpoint inhibitor-associated pneumonitis (CIP) [2,3], which is a lung injury caused by ICIs and has various clinical, imaging and pathological manifestations. CIP has an incidence of 3–5% [4–6], severe incidence of 1.4% [7] and mortality of 12.8–22.7% [8–11]. Patients with CIP do not have typical symptoms and usually present with emerging or worsening dyspnea, cough, chest pain, fever and fatigue [12–14]; patients with severe CIP present with life-threatening respiratory symptoms that require ventilator support [15]. However, as many as a third of patients with CIP have atypical symptoms at onset, and clinicians can easily neglect therapeutic measures for CIP due to the presence of other clinical manifestations similar to aspiration pneumonitis [12]. The patient's hospital stay will be prolonged and mortality will be increased if the disease is not diagnosed accurately and in a timely manner [8]. The distinctiveness of this case is that the patient took timely and effective treatment measures for unimproved pulmonary infection after showing poor oxygenation in the early stage following the diagnosis of severe pneumonitis. Furthermore, severe CIP was diagnosed after discussion by the multidisciplinary team; the dose of hormone therapy was increased, and finally, the patient was effectively treated.

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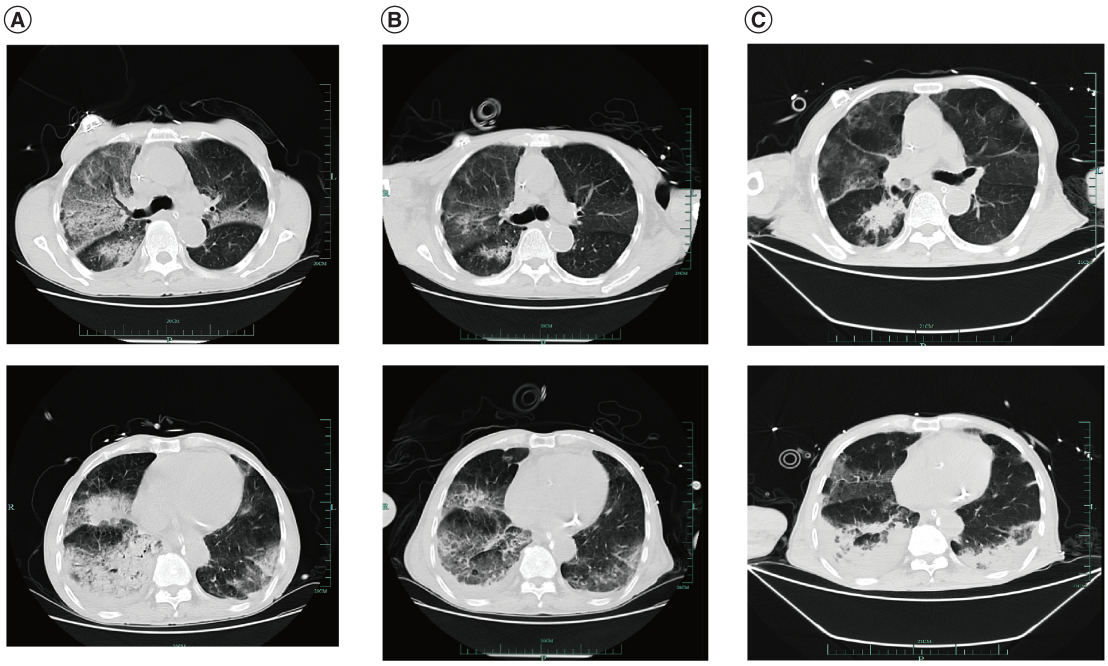

Figure 1. CT images of this patient at different stages of treatment. (A) The CT image on 19 June showing bilateral lung inflammation. **(B)** The CT image on 23 June showing that the bilateral lung inflammation was slightly improved compared with that on 19 June. The oxygenation of the patient was slightly improved, but there was more sputum in the trachea. **(C)** The CT image on 29 June showing patchy high-density shadows in the bilateral lung, progressed inflammation and deteriorated oxygenation again, indicating that the patient's condition was not improving even after adjusting antibiotics.
CT: Computed tomography.

Case description

A 73-year-old male patient was diagnosed with gastric cancer in February 2022 and regularly treated with chemotherapy combined with sintilimab (PD-1 monoclonal antibody) immunotherapy. After preoperative preparation, he underwent laparoscopic extended radical resection of cardiac carcinoma (total gastrectomy + lymph node dissection + Roux-en-Y anastomosis anastomosis) + intestinal adhesiolysis on 2 June 2022. A nasogastric tube was used postoperatively for nutritional support therapy. He had an intermittent delirium attack, which was improved after using antipsychotics. On 19 June, the patient showed a progressive decrease in oxygen saturation, with an oxygen partial pressure of 54.9 mmHg; he was given oxygen inhalation via an oxygen storage bag mask at 10 l/min and transferred to an intensive care unit (ICU). After establishing the artificial airway, the ventilator was mechanically ventilated. Bronchoscopy revealed milky white fluid in the main airway and the right main bronchus that was blocking the bronchi, considering mistaken inhalation; thus, severe pneumonitis was diagnosed (Figure 1A).

However, there was considerable sputum in the airway, and daily bronchoscopic sputum suction was performed. On 23 June, his lung computed tomography (CT) showed bilateral lung inflammation, which was slightly improved compared with that on 19 June (Figure 1B). However, on 24 June, the patient's oxygenation became worse. Acute respiratory distress syndrome was caused by aspiration pneumonitis considering his medical history; thus, prone position ventilation was started.

On 27 June, the patient's sputum pathogen metagenome sequencing test report suggested *Enterococcus faecium*, *Candida albicans* and human herpes virus 1 type, with 99% confidence in identification. Thus, piperacillin sodium and tazobactam sodium combined with micafungin were continued. On 29 June, the patient's oxygenation further declined. Auscultation revealed low breath sounds in the right lower lung, and CT showed bilateral lower lung consolidation, predominantly in the right lung (Figure 1C); thus, prone position ventilation was given for 16 h. The patient had persistent airway hyperreactivity, barrel chest and a smoking history of >20 years, which was considered to be acute exacerbation of chronic obstructive pulmonary disease; thus, methylprednisolone 40 mg every 12 h was added. After the patient was treated with prone ventilation combined with steroids, his oxygenation was slightly improved with an oxygenation index up to 290 mmHg, but poor transient oxygenation still existed.

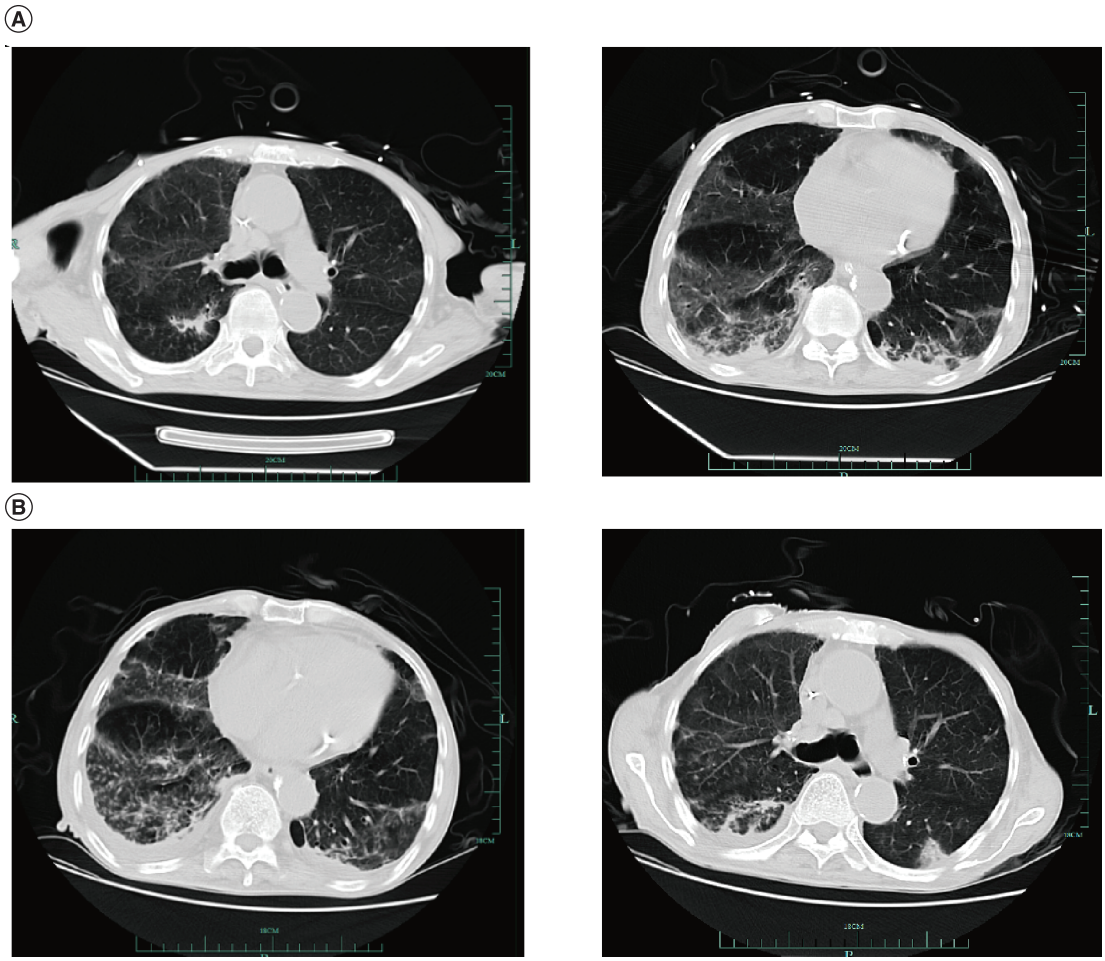

Figure 2. A CT image of the patient's lungs after treatment. (A) The computed tomography image on 20 July 2022 showing that the patient's bilateral lung inflammation was significantly improved and **(B)** predischarge computed tomography image on 17 August 2022.

The patient still required ventilator-assisted ventilation after adding antibiotics, with a ventilator pressure of 22 cm H_2O, a positive end-expiratory pressure of 5–8 cm H_2O and an oxygen concentration of 35–50%; his oxygenation and respiratory function did not improve significantly. Moreover, several consecutive CT imaging scans showed that there were no obvious or only slight improvements in the patient. Therefore, on 6 July, a multidisciplinary team was organized to discuss the case and enhance the patient's therapeutic efficiency. The patient had a history of therapy; thus, immune checkpoint inhibitor-associated pneumonia could not be excluded, and T-cell subset assessment was supplemented. The test results were as follows: total lymphocyte count: 1861, T cells ($CD3^+$): 82.21% and T helper cells ($CD3^+$, $CD4^+$): 53.95%; this was treated with methylprednisolone 80 mg every 12 h. Considering the patient's long time of tracheal intubation and difficulty in weaning from the ventilator in the future, a tracheotomy was performed on 11 July. On 21 July, his lung CT showed an improvement in the lung infection compared with that before (Figure 2A), and oxygenation was also further improved. On 22 July, the patient was weaned from the ventilator, and oxygen inhalation was performed by mask at the pneumonectomy site. On 29 July, the patient was transferred from the ICU to a specialized ward for continuous treatment. On 17 August, his lung CT showed multiple inflammations in the bilateral lung, which was improved compared with the previous CT scan (Figure 2B). The laboratory parameters and ventilator-assisted ventilation settings are shown in Table 1.

Table 1. The clinical tests and ventilator settings of this patient.

Date (year 2022)	White blood count (10^9/l)	Neutrophils (%)	C reactive protein (mg/l)	Procalcitonin (ng/ml)	Ventilator pressure (cm H_2O)	Positive end-expiratory pressure (cm H_2O)	Oxygenation index
19 June	19.77	85.3	118.45	2.98	22	4	220
24 June	31.46	84.5	221	0.74	30	10	130
29 June	–	–	–	–	28	7	110
1 July	17.27	91.3	123.05	0.33	22	5	170
21 July	12.34	70.3	21.38	0.11	12	3	320
21 August	8.95	72.4	4.14	0.06	–	–	–

From 19 June to 29 June 2022, the patient's condition gradually progressed, and it was observed that oxygenation index decreased and inflammation-related indicators increased. After changing the treatment regimen, the patient's condition gradually improved from 1 July to 21 August 2022, with an increase in oxygenation index and a decrease in inflammation-related indicators.

Discussion

Our patient was treated with a nasogastric tube for nutritional therapy after total gastrectomy due to an intermittent delirium attack, which could be a risk factor for aspiration pneumonitis [16,17]. Aspiration pneumonitis refers to adverse pulmonary consequences caused by gastric or oropharyngeal fluids or xenobiotics (e.g., ingested food pellets or fluids, mineral oil, salt or freshwater) that may contain bacteria and/or have low pH while entering the lower airways; chest imaging studies of aspiration pneumonitis show obstructive stenosis or foreign bodies in gravity-dependent areas or segmental involvement of the lungs [16,18]. It is clinically frequently accompanied by common symptoms of pneumonitis, comprising cough, fever, purulent sputum and dyspnea [19,20]. In our case, on transfer to ICU, the CT images showed tracheal patchy shadows and bronchoscopy showed milky fluid obstructing the main airway and right main bronchus; the initial diagnosis considered by the ICU doctor was severe pneumonitis caused by aspiration, that is, aspiration pneumonitis. During treatment, the patient's oxygenation did not improve as expected, and even after adding multiple antibiotics, the infection symptoms did not subside. After discussion with the multidisciplinary team, severe CIP was considered and diagnosis and treatment were adjusted accordingly. The conventional thinking of ICU doctors at the early stage of treatment for this patient resulted in an unclear diagnosis; however, the issues were found in time during the process and the treatment regimen was adjusted.

CIP is commonly observed when patients are treated with PD-1 or PD-L1 inhibitors [21–25]. A meta-analysis of 5038 patients from 19 clinical studies involving PD-1 and PD-L1 inhibitors showed a higher incidence of CIP and severe CIP in patients taking PD-1 inhibitors [26]. The onset of CIP differs from hours to 24 months after the first administration of ICIs, with a median onset of 2–3 months [3]. Severe CIP occurs 6 months after immunotherapy [27]; however, considering the interval and persistence of the immune response, CIP can occur at any time during immunotherapy. Therefore, close monitoring and follow-ups are important. Clinicians should be aware that patients with a history of treatment with ICIs may develop CIP [28].

Dyspnea (53%) and cough (15%) are the most common symptoms of CIP [29], and the imaging findings of CIP are varied and may demonstrate scattered or diffuse ground-glass opacities, patchy consolidation, interlobular septal thickening, reticular opacities, traction bronchiectasis and fibrous streak opacities in both lungs [30]. The few variances from other lung diseases or inflammations and the lack of typical symptoms can easily be confused with other diseases, resulting in neglect or even missed diagnosis of CIP [31,32].

In our patient, the bronchoscopy results were obtained on admission to ICU, indicating the presence of aspiration pneumonitis; moreover, its clinical manifestations and imaging findings were consistent with the diagnosis of aspiration pneumonitis. Thus, consequent treatment improved the oxygenation of the patient to some extent. The oxygenation of the patient decreased at the middle stage of treatment; therefore, prone ventilation and hormone therapy were given after considering acute respiratory distress syndrome and acute exacerbation of chronic obstructive pulmonary disease, which improved the symptoms of CIP to some extent [33,34]. After forming the diagnosis of CIP, the treatment regimen was further adjusted. The patient's condition greatly improved, he was gradually weaned from the ventilator and finally discharged. Since 2018, the China National Medical Products Administration has successively permitted the applications of >10 s such as PD-1 in China. However, at present, due to the short-term applications and lack of experience in the treatment, those similar complications require further summary and analysis. In clinical practices, ICU doctors tend to diagnose severe pulmonary infections similar to aspiration pneumonitis and ignore the history of immunosuppressive therapy. Therefore, we wanted to highlight this particular concern and help doctors to better diagnose CIP.

Conclusion

It is difficult to clinically diagnose CIP. During the diagnosis and treatment of patients with a history of treatment with ICIs, the differential diagnosis of patients should be considered more carefully. If necessary, a relevant assessment of CIP should be performed as early as possible to allow patients to receive the most successful treatment.

Summary points

- Immune checkpoint inhibitors, as novel immunotherapy, provide significant clinical benefits to patients with malignant tumors and prolong their overall survival.
- However, immune system overactivation predisposes immune checkpoint inhibitor-associated pneumonitis (CIP), which is a lung injury caused by immune checkpoint inhibitors and has various clinical, imaging and pathological manifestations.
- This report describes an elderly male patient who underwent extended radical resection of cardiac carcinoma after regular chemotherapy combined with sintilimab (PD-1 monoclonal antibody) immunotherapy complicated with severe pneumonitis.
- The patient's hospital stay will be prolonged and mortality will be increased if the disease is not diagnosed accurately and in a timely manner.
- The few variances from other lung diseases or inflammations and the lack of typical symptoms can easily be confused with other diseases, resulting in neglect or even missed diagnosis of CIP.
- In clinical practices, intensive care unit doctors tend to diagnose severe pulmonary infections similar to aspiration pneumonitis and ignore the history of immunosuppressive therapy.
- Therefore, we wanted to highlight this particular concern and help doctors to better diagnose CIP.

Author contributions

F Weng conceived this study. J Wei designed the study. F Weng and M Sang acquired and analyzed the data. X Gao and P Zhang contributed analysis tools. F Weng wrote the paper. Q Fu was of immense help in the preparation of the manuscript. All authors read and approved the final manuscript.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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