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Case Report

Lethal Immune-Related Pneumonitis after Durvalumab Therapy for Small Cell Lung Cancer: A First Case in China

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Keywords

Pneumonia · Small cell lung carcinoma · Immune checkpoint inhibitors · Programmed death ligand 1 · Durvalumab

Abstract

Introduction: Although programmed death ligand 1 (PD-L1) inhibitor plus chemotherapy regimen is a promising strategy for malignant tumors, it can induce significant immune-related adverse events, such as immune-related pneumonitis. Here, we report the first case of lethal immune-related pneumonitis in an Asian patient receiving anti-PD-L1 treatment. ***Case Presentation:*** A 68-year-old man was diagnosed with small cell lung cancer and interstitial pneumonia. After his pulmonary infection was relieved by comprehensive treatment, the patient received first-line treatment with durvalumab plus etoposide and carboplatin. Two weeks after starting durvalumab treatment, the patient had chest pain and shortness of breath. He was diagnosed with immune-induced pneumonia and treated with methylprednisolone, cefoperazone, and sulbactam, followed by oxygen and pirfenidone. Oxygen partial pressure decreased to 58 mm Hg within next the 4 days and laboratory assessment suggested cytokine storm. The patient underwent 2 plasma exchanges, one double filtration plasmapheresis and oxygen saturation decreased continuously. The patient died 1 month after durvalumab treatment. ***Conclusion:*** Immune-related pneumonitis induced by PD-L1 inhibitors is rare but life-threatening. Infection should be ruled out before starting immunotherapy.

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 14% of all lung cancers [1, 2]. Immune checkpoint inhibitors (ICIs) in combination with chemotherapy have become the new standard of care for the first-line treatment of extensive-stage SCLC, such as durvalumab plus platinum and etoposide [3]. However, despite the exciting clinical benefits of ICIs [4, 5], they are associated with a number of uncontrolled immune responses, known as immune-related adverse events (irAEs), due to imbalances in immunological tolerance [6]. The main irAEs include diarrhea, colitis, hepatitis, skin toxicities, and endocrinopathies [7]. Pulmonary toxicity is one of the few irAEs, occurring in less than 10% of patients receiving anti-PD-1/programmed death ligand 1 (PD-L1) therapy alone or in combination, and appears to be more common in patients with lung cancer [6]. In addition, although pulmonary toxicity can often be successfully treated with ICIs withdrawal and prednisolone, pneumonitis is an AE of special interest that was associated with drug-related deaths in early clinical trials [6, 8].

In this report, we describe a first case of lethal hormone-resistant immune-related pneumonitis following the treatment of durvalumab in Asian population. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538429).

Case Presentation

A 68-year-old man was admitted on September 6, 2021, with complaints of cough with white sputum; no blood was found in the sputum, no fever, or chest tightness. The condition of patient was generally good (ECOG PS 1). A chest computed tomography (CT) scan in the local hospital showed bilateral chronic bronchitis, emphysema, infection in the right lung, and solid nodules in the upper lobe of the left lung. An enhanced chest CT suggested interstitial pneumonia and a tumor in the upper lobe of the left lung with multiple lymph node metastasis in the mediastinum and bilateral hilum (Fig. 1a, b, c, g, h, i). Pathological examination of the tumor puncture showed SCLC. According to the 8th edition of the UICC/AJCC TNM staging system, the patient was diagnosed with extensive-stage SCLC (cT4N3M0). Comprehensive treatment was given, including ceftazidime injection, antitussives, acetylcysteine inhalation solution, budesonide inhalation suspension, ipratropium bromide metered-dose inhaler, and doxofylline injection. Antinuclear antibodies, dsDNA, anti-myositis antibodies profile, and antineutrophil cytoplasmic antibodies were negative. Serum amyloid A and C-reactive protein were in the normal range. The patient's cough was relieved, and his general condition was stable.

According to the assessment of the Department of Respiratory and the Department of Critical Care, the patient was considered to be able to tolerate the chemotherapy and immunotherapy. On September 21, 2021, the patient received one cycle of first-line therapy of etoposide (170 mg, days 1–3, q3w) plus carboplatin (500 mg, q3w) plus durvalumab (1,000 mg, q3w). Meanwhile, anti-infection therapy with ceftazidime and anti-cough treatment was continued. Two weeks after starting durvalumab treatment, the patient had left chest pain and shortness of breath. A chest CT scan in October 2021 showed new interstitial inflammation in the right lung, with a larger area than before durvalumab treatment (Fig. 1d, e), while the tumor in the left lung and lymph nodes in the mediastinum and bilateral hilum were smaller (Fig. 1f, j, k, l). In addition, the partial pressure of oxygen was 58 mm Hg, indicating hypoxia. Serum amyloid A and C-reactive protein levels were significantly elevated. However, sputum culture, coproculture, and virus detection were negative. On the basis of these

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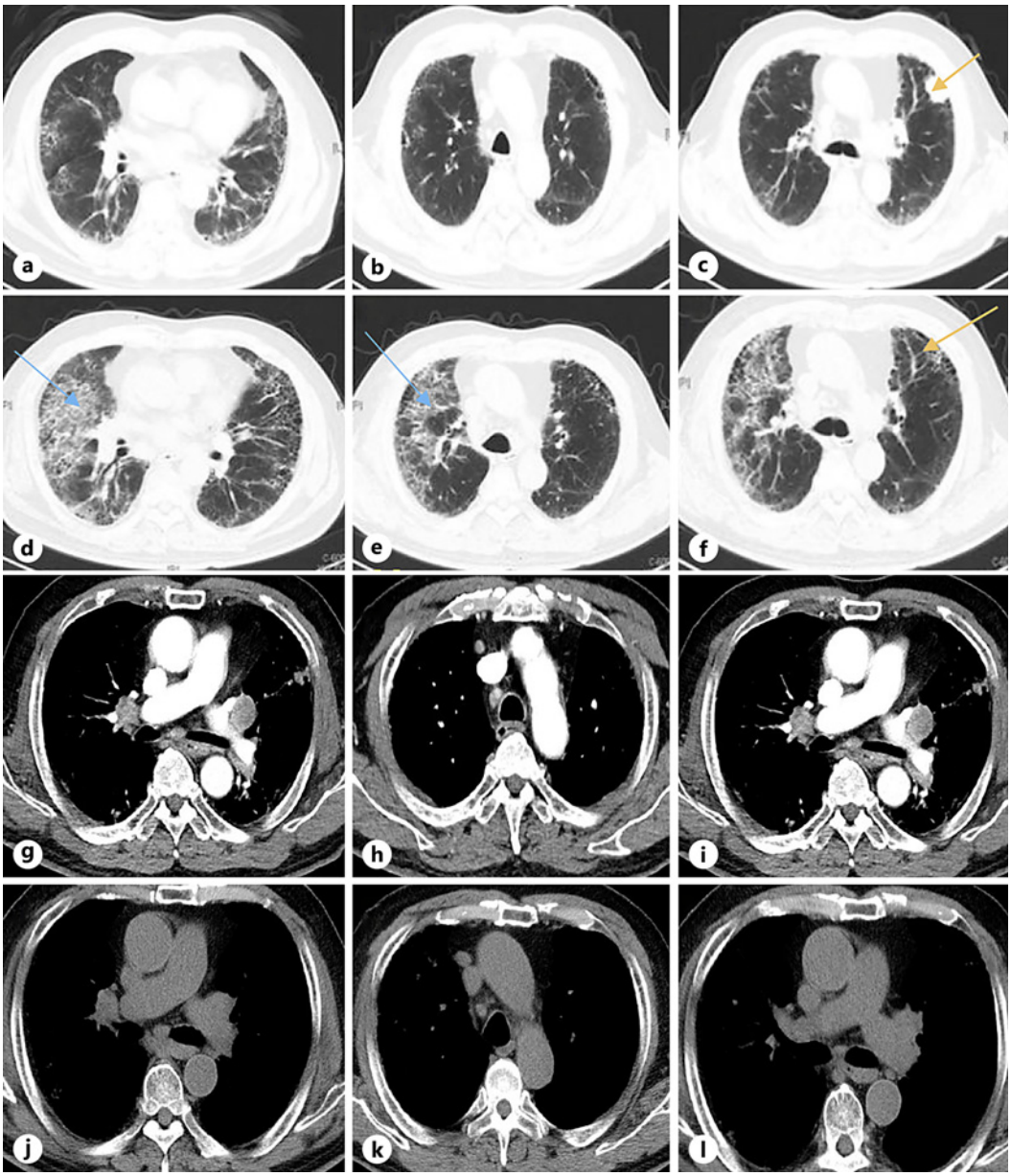

Fig. 1. Computer tomography (CT) scan dated September 2021, before patient started durvalumab. **a**, **b** Emphysema and infection in the right lung. **c** A tumor in the upper lobe of the left lung (red arrow). **g**, **h**, **i** Multiple lymph node metastasis in the mediastinum and bilateral hilum. CT scan dated October 2021, after patient started durvalumab. **d**, **e** New interstitial inflammatory lesions in a large area of the right lung (green arrows). **f** The tumor in the left lung was smaller after treatment start. **j**, **k**, **l** Multiple mediastinum and double lung door lymph node metastasis were smaller than before.

findings, the patient was diagnosed with immune-related pneumonitis of grade 3, without excluding bacterial and viral infections.

High-dose intravenous methylprednisolone (240 mg bid), cefoperazone sodium, and sulbactam sodium (3g ivdrip) were applied immediately, but the symptoms were worsened on the next day. After multidisciplinary discussion, intravenous methylprednisolone (240 mg bid) was continued, and oxygen inhalation and pirfenidone (200 mg tid) were added. However, the symptoms did not improve and the partial pressure of oxygen dropped to 58 mm Hg within 4

days. Laboratory test results showed that he was in the cytokine storm phase, which can cause multiple organ damage (Table 1). He continued to receive steroids, and immunoglobulin (2 $g \cdot kg^{-1} \cdot day^{-1}$ for 5 days) and immunosuppressive agents including infliximab (5 mg/kg) and tocilizumab (8 mg/kg) were added. After the above anti-infective and immunosuppressive treatment, dyspnea did not improve significantly and oxygen saturation continued to decrease. High-flow humidified oxygen, liver protection, coronary expansion, anticoagulation, phlegm-resolving, and anti-asthma therapies were used. Two rounds of plasma exchange treatment and one round of double filtration plasmapheresis were used to eliminate autoimmune antibodies. Unfortunately, the patient did not respond to treatment and eventually died 1 month after starting dulvalizumab treatment (Fig. 2). The changes in blood pressure and oxygen saturation during the cytokine storm phase are shown in Figure 3.

Discussion

Pulmonary toxicity is a rare but dangerous side effect of PD-1/PD-L1 inhibitors which can be usually treated by ICI withdrawal and high-dose prednisolone [6, 8]. In this case, we report a first case of lethal hormone-resistant immune-related pneumonitis after durvalumab treatment in Asian population. A retrospective study from the USA showed that 18.5% (12/65) of the 65 patients with ICI pneumonitis were found to have steroid-refractory ICI pneumonitis, and 67% (8/12) of these patients died of steroid-refractory ICI pneumonitis or infectious complications [9]. Another retrospective French study reviewed 1,187 patients receiving ICI therapy. The study showed that 4% (48/1,187) of patients had pneumonitis treated with corticosteroids, and five of these (5/48; 10%) had corticosteroid-refractory/resistant disease [10].

The patient in this case report experienced grade 3 immune-related pneumonitis after 2 weeks of combination therapy with etoposide, carboplatin, and durvalumab. A retrospective study from the USA included 34 patients with clinical stage IIB to IIIC NSCLC treated with definitive chemoradiation followed by consolidation durvalumab, and the results indicated that there were 9 patients (26.5%) with grade >2 pneumonitis in the entire cohort. Seven patients (20.6%) developed grade 2 pneumonitis and 2 patients (5.9%) developed grade 3 pneumonitis. No patients developed grade 4 or 5 pneumonitis [11]. In PACIFIC study, the most common grade 3 or 4 AE was pneumonia, with 4.4% of patients in the durvalumab group and 3.8% of patients in the placebo group [12]. It is worth noting that both pneumonitis and radiation pneumonitis of any grade were reported together as these entities are difficult to distinguish, with a combined pneumonitis rate of 33.9% in the durvalumab group compared to 24.8% in the placebo group [12]. In addition, a meta-analysis of 22 clinical trials showed that the incidence of any grade pneumonitis in PD-1 and PD-L1 inhibitor therapy was significantly higher than that in chemotherapy (OR = 2.35, 95% CI, 1.32–4.20, $p = 0.004$) [13]. Several clinical studies have shown that the incidence of pneumonia in patients receiving PD-1/PD-L1 inhibitor monotherapy is less than 5%, and the incidence of grade 3 or higher pneumonitis is 0–1.5% [14]. In Naidoo's study [15] among 915 patients who received anti-PD-1/PD-L1 monoclonal antibodies, pneumonitis developed in 43 (approximately 5%) patients, five of them worsened clinically and died during treatment (one of pneumonitis, three of infections associated with immunosuppression, and one of progressive cancer). Due to the rarity, both diagnosis and therapy are challenging in cancer patients who may develop PD-1/PD-L1 inhibitor-related pneumonitis.

Time to onset of ICI-associated pneumonitis ranges from 9 days to 24 months, and known risk factors for pneumonitis include high PD-L1 expression, interstitial lung disease (ILD), preexisting asthma and chronic obstructive pulmonary disease, combined ICIs, treatment in

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Table 1. Indicators of cytokine storm and organ damage in this patient

Indicators	Levels						Reference interval	
	10.13	10.15	10.16	10.18	10.19	10.20		
LDH, U/L	396.50	–	588.00	–	632.00	–	120–250	↑
CRP, mg/L	134.10	–	38.00	–	24.00	–	0–10	↑
PCT, ng/mL	–	1.25	–	–	–	–	0–0.05	↑
WBC, ×109/L	8.09	16.44	13.06	12.69	36.19	20.43	3.5–9.5	↑
RBC, ×1,012/L	3.45	3.42	3.37	3.19	3.36	2.67	4.3–5.8	↓
PLT, ×109/L	452	673	570	400	444	219	125–350	↑
HGB, g/L	102	100	99	95	100	80	130–175	↓
SAA, mg/mL	–	296.03	–	–	–	–	1–10	↑
HBDH, U/L	305.10	538.60	539.2	–	387.50	571.10	72–182	↑
MYO, ng/mL	–	122.10	–	–	–	181.30	17.4–105.7	↑
HS-Tnl, pg/mL	17.80	3,478.10	1,698.3	–	725.50	541.50	0–17.5	↑
TNF-α, pg/mL	–	445.59	–	–	–	–	≤4.50	↑
G-CSF, pg/mL	–	237.20	–	–	–	–	≤10.26	↑
IL-6, pg/mL	–	175.46	–	–	365.99	210.24	≤11.09	↑
IL-17A, pg/mL	–	93.56	–	–	–	–	≤4.74	↑
IL-4, pg/mL	–	104.60	–	–	–	–	≤4.19	↑
IL-2, pg/mL	–	50.60	–	–	–	–	≤6.64	↑

LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood count; RBC, red blood count; PLT, platelets count; HGB, hemoglobin; SAA, serum amyloid A; HBDH, hydroxybutyrate dehydrogenase; MYO, myoglobin; HS-Tnl, high-sensitivity troponin I; TNF-α, tumor necrosis factor alpha; G-CSF, granulocyte colony stimulating factor; IL, interleukin.

combination with EGFR-TKIs, and lung radiation therapy [14, 15]. Even though there were cases reporting successful durvalumab treatment for patients with NSCLC and ILD [16], the safety and efficacy of ICIs for patients with ILD remain unclear because patients with ILD are often excluded from clinical trials involving ICIs. In addition to emphysema and pulmonary fibrosis, this case was also burdened by pulmonary infection. Even though the patient's cough was relieved and inflammatory indicators were recovered before starting durvalumab, imaging examinations were not performed to ensure the patient's lung infection had completely disappeared, and levels of inflammatory factors were not tested, which might be a risk factor for irAEs. Since the patient's general condition was stable and his family had a strong desire for him to receive antitumor treatment early, immunotherapy in combination with chemotherapy was initiated shortly after the remission of the lung infection. Considering the relatively low incidence of pneumonia in patients treated with durvalumab reported in previous studies (any grade, 4%; grade 3 or 4, 2%) [17], durvalumab was chosen for the present case. However, chemotherapy with etoposide and platinum can lead to

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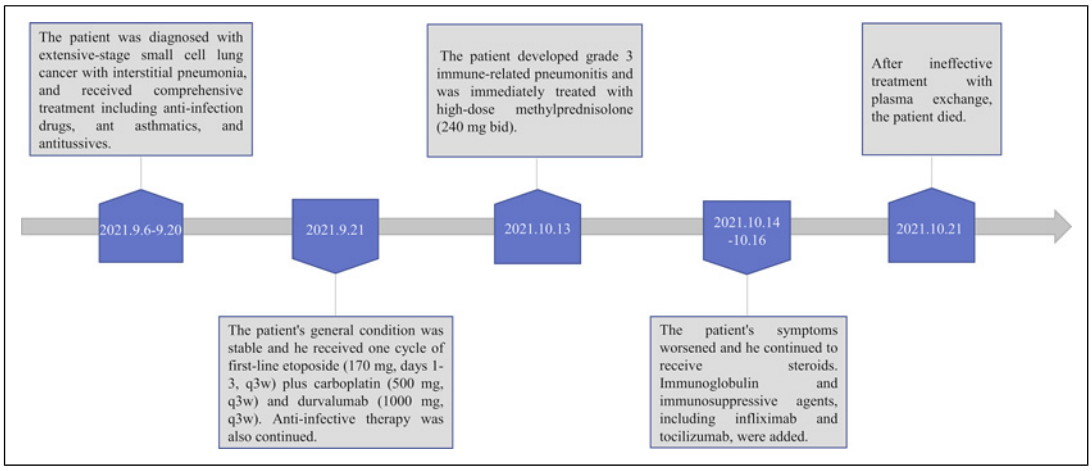

Fig. 2. Timeline of the present case.

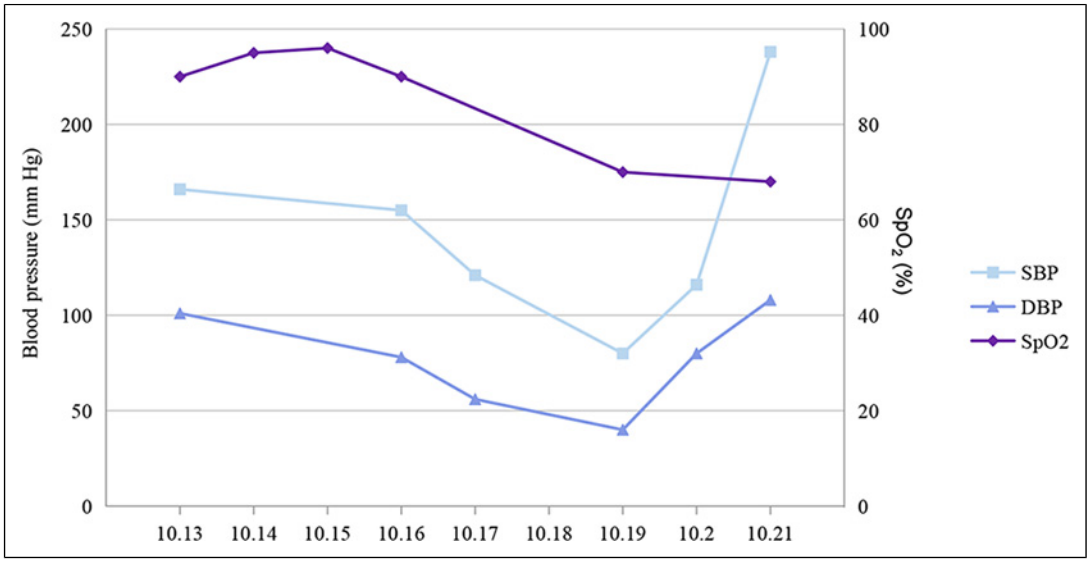

Fig. 3. Blood pressure and oxygen saturation of the patient. SBP, systolic blood pressure; DBP, diastolic blood pressure.

granulocytopenia. We hypothesize that chemotherapy may have contributed to recurrence of underlying lung infections in this patient, elevating inflammatory factor levels in the lungs and promoting the development of immune-related pneumonia as well as the progression of consequent cytokine storm.

To date, no prospective clinical trial has been established to determine the best treatment for pneumonia and other serious irAEs of ICI treatment. In most patients, corticosteroids alone can be used to resolve pulmonary toxicity secondary to anti-PD-1/PD-L1 therapy [18]. However, even rarer steroid-refractory conditions require additional suppressive approach. According to the National Comprehensive Cancer Network (NCCN) guidelines, discontinuation of immunotherapy is required for severe pneumonitis and high-dose steroids are advised. If no improvement is obtained after 48 h, infliximab, mycophenolate mofetil, or intravenous immunoglobulin should be considered [19]. In our case, durvalumab-related

pulmonary toxicity was challenged by high-dose corticosteroids and only after 4 days resistance to steroid therapy was recognized. After that, immunoglobulin treatment was added in lines with alternative therapy for steroid-refractory immune-related pneumonia, as well as infliximab and tocilizumab. Eventually, plasma exchange treatment was applied, but it did not achieve any noteworthy benefits for patient. Experience derived from this case suggests that continuing symptomatic and supportive treatment might be safer for patients with a history of pulmonary infection, and immunotherapy might be delayed until the patient's condition is improved and imaging results indicate that the lung infection had completely disappeared. Notably, the delay should not be too long to avoid rapid progression of the tumor.

Till now, optimal time to durvalumab initiation in real-world practice remains undetermined. In order to establish the best clinical practice in the field of immuno-oncology, prospective research is needed to define appropriate timeframes for delaying immunotherapy as well as to study the consequences of early steroids and immunosuppressive agents use in the treatment of severe ICI-related pneumonia.

In conclusion, the present case suggests that it is very important to completely rule out the presence of infection before starting PD-1/PD-L1 immunotherapy, as this might aggravate related pulmonary toxicity. Clinicians should assess and closely monitor patients with high-risk factors before, during and after PD-1/PD-L1 inhibitor use, and regularly monitor cytokines and inflammatory indicators to reduce the risk of irAEs and improve patient's prognosis.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the wife of the deceased patient for the publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Wen Zhang and Zhe Yang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Yunxia Liu and Qiang Li were involved in the study concepts and design. All authors (Qian Li, Mei Liu, Yunxia Liu, Feng Shi, Shan Yuan, Guojie Di, Haobin Jin, Yaru Shi, Wen Zhang, and Zhe Yang) involved in the acquisition, analysis, and interpretation of data. Mei Liu and Feng Shi supervised the analysis. Yunxia Liu and Shan Yuan involved in the draft of the manuscript. All authors read, critically revised, and approved the manuscript.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article; further inquiries can be directed to the corresponding author.

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