Case Report

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Rapid temporal improvement of pembrolizumab-induced pneumonitis using the anti-TNF-α antibody infliximab

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Summary **Immune checkpoint inhibitors are associated with a wide spectrum of immune-related adverse events (irAEs) that are typically transient but are sometimes severe or even fatal. No consensus exists for the treatment of severe immune-mediated pneumonitis that is refractory to corticosteroids. Here, we report an autopsy case of pembrolizumab-induced pneumonitis that was transiently improved using infliximab. A 67-year-old male with advanced lung adenocarcinoma developed pneumonitis two weeks after a single dose of first-line pembrolizumab. The pneumonitis was refractory to corticosteroids, and the patient required mechanical ventilation. Addition of a single dose of infliximab rapidly improved the respiratory status and chest CT showed resolution of ground-glass opacities in the right upper and middle lobes. However, the patient died from re-exacerbation of pneumonitis 17 days after infliximab administration. The autopsy confirmed organizing phase diffuse alveolar damage in the right lower lobe, while the right upper lobe remained almost intact consistent with the CT findings, which is suggestive of the therapeutic effect of infliximab. The half-life of infliximab is 7-12 days, and a second dose of infliximab two weeks after the first dose is sometimes required for the treatment of gastrointestinal toxicity induced by anti-CTLA4 antibodies. Although the current guidelines do not recommend repeated administration of infliximab for immune-mediated pneumonitis, the present case suggests that repeated infliximab therapy may be beneficial in the treatment of immune-mediated pneumonitis.**

Keywords: Immune-related adverse events, diffuse alveolar damage, lung adenocarcinoma

1. Introduction

Pembrolizumab monotherapy has shown survival benefit as a first-line therapy for patients with metastatic non-small cell cancer (NSCLC) with a programmed death ligand 1 (PD-L1) tumor proportion score of 50% or greater and without *epidermal growth factor receptor* (*EGFR*) mutation or *anaplastic lymphoma receptor tyrosine kinase* (*ALK*) translocation (*1*). The addition of pembrolizumab to pemetrexed and a platinum-based chemotherapy also prolongs overall survival in patients with metastatic non-squamous NSCLC without *EGFR* or *ALK* alterations regardless of the tumor proportion score (*2*).

Although pembrolizumab is generally well-tolerated compared to cytotoxic chemotherapy, immune-related adverse events (irAEs) are sometimes severe or even fatal. The severity of irAEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (*3*). The incidence of immune-mediated pneumonitis of any grade was 5.8% and that of grade ≥ 3 was 2.6% in the phase 3 KEYNOTE-024 trial (*1*). For grade ≥ 3 pneumonitis, the guidelines of the European Society for Medical Oncology (ESMO) (*4*) and American Society of Clinical Oncology (*5*) recommend intravenous methylprednisolone at 2-4 mg/kg/day and

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1-2 mg/kg/day, respectively. If pneumonitis does not improve within 48 hours, the guidelines recommend addition of an immunosuppressant such as infliximab, mycophenolate mofetil or cyclophosphamide (*4,5*). The guidelines also recommend gradual tapering of corticosteroids over at least six weeks. In contrast, there are no guidelines for the repeated administration of immunosuppressants for immune-mediated pneumonitis. The increasing use of immune-checkpoint inhibitors requires the accumulation of case reports to determine the best management strategies for severe immune-mediated pneumonitis.

2. Case Report

A 67-year-old man with a 45-pack-year history of tobacco use presented with a massive left pleural effusion. He had undergone sigmoidectomy for colon cancer at the age of 37, and had had transient thyrotoxicosis at the age of 55. A chest computed tomography (CT) scan revealed a mass in the left upper lobe with left pleural effusion, enlarged mediastinal and contralateral hilar lymph nodes and intrapulmonary metastatic nodules in the right lung (Figure 1).

Adenocarcinoma cells were detected in the left pleural effusion and in the subcarinal lymph node tissue obtained using endobronchial ultrasonography-guided transbronchial needle aspiration. The adenocarcinoma cells in the subcarinal lymph node were positive for thyroid transcription factor 1 (TTF-1), and the patient was diagnosed with stage IVA (cT4M3M1a) lung adenocarcinoma (*6*).

The tumor was negative for both *EGFR* mutation and *ALK* and *ROS1* rearrangement. The tumor proportion score in the 22C3 PD-L1 assay was 95% in the subcarinal lymph node. The patient had no obvious past history of autoimmune disease, and the chest CT scan showed no underlying interstitial pneumonia, with normal serum KL-6 levels. Although anti-thyroid antibodies (anti-thyroglobulin and anti-thyroid peroxidase) were both positive and a thyroid ultrasound revealed chronic thyroiditis, thyroid function test parameters, including thyroid-stimulating hormone, free T4 and T3, were all normal.

After drainage of the left pleural cavity, the patient received 200 mg pembrolizumab as first-line treatment. On day 5, the patient presented with an erythematous maculopapular rash on the body trunk. The skin irAE was grade 2 (*3*), and resolved one week later following topical corticosteroid and oral antihistamine treatment. On day 14, the patient developed acute respiratory failure requiring 10 L/min of oxygen, and chest CT showed bilateral non-segmental ground-glass opacities (Figures 2A and 2B). The patient was diagnosed with immune-mediated pneumonitis, and administration of a high-dose intravenous corticosteroid (125 mg methylprednisolone) with a broad spectrum antibiotic for possible bacterial infection was initiated.

On day 15, however, the patient was transferred to the intensive care unit with worsening hypoxia requiring mechanical ventilation. As pneumonitis was refractory to corticosteroid treatment (250 mg methylprednisolone on days 15-17), we administered 5 mg/kg infliximab on day 17. The addition of infliximab

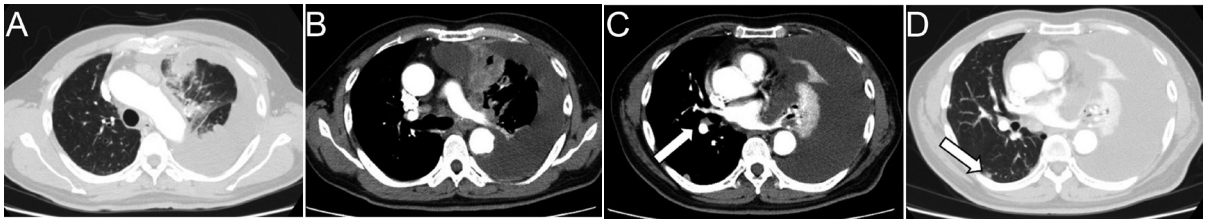

Figure 1. Chest CT scan on admission. Primary tumor in the left upper lobe showed direct invasion into the mediastinum with left pleural effusion and pleural nodules **(A** and **B)**. Contralateral hilar lymph node metastasis (**C**, arrow) and contralateral pulmonary metastasis (**D**, arrow) were also suspected.

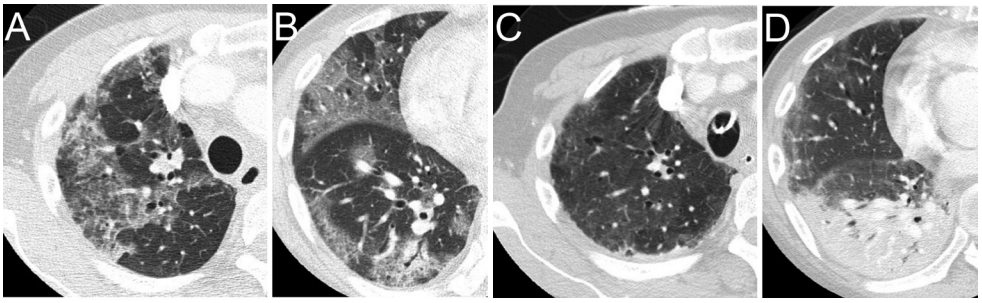

Figure 2. Radiological response of immune-mediated pneumonitis to infliximab. Chest CT scan on day 14 showed non-segmental diffuse ground-glass opacities consistent with immune-mediated pneumonitis **(A** and **B)**. Chest CT scan on day 23 demonstrated resolution of the ground-glass opacities in the right upper lobe **(C)**, and consolidation in the dependent part of the right lower lobe **(D)**.

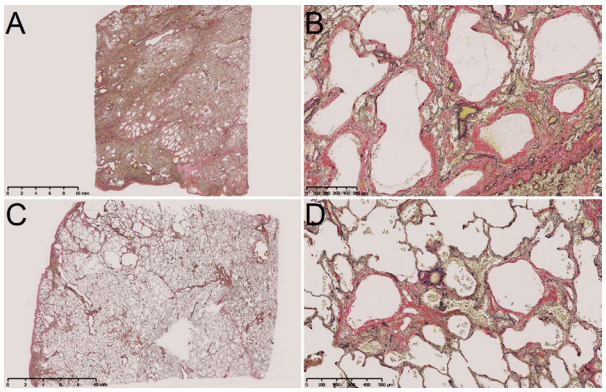

Figure 3. Autopsy findings. The right lower lobe showed organizing phase diffuse alveolar damage with extensive collapse of alveolar spaces **(A** and **B)**. In contrast, the lung parenchyma remained mostly intact with focal organization in the right upper lobe **(C** and **D)**.

rapidly improved respiratory status, and the PaO2/FiO2 ratio increased from 91 mmHg (day 16) to 169 mmHg (day 21). Although the consolidation in the right lower lobe did not improve, the resolution of the ground-glass opacities in the right upper and middle lobes was observed on day 23. (Figures 2C and 2D). The intravenous methylprednisolone dose was gradually tapered from 125 mg on days 18-20, to 60 mg on days 21-27, and 50 mg on day 28 and thereafter. On day 31, however, the patient's respiratory status deteriorated again and he died on day 34.

Autopsy revealed organizing phase diffuse alveolar damage in the right lower lobe with extensive collapse of alveolar spaces (Figures 3A and 3B). In contrast, the right upper lobe remained mostly intact with focal organization (Figures 3C and 3D). No infectious etiology was identified, and the tumor in the left lung showed no pathological response to pembrolizumab.

3. Discussion

The radiological pattern of immune-mediated pneumonitis are associated with mortality and response to corticosteroid. In the retrospective report by Nishino *et al*. (*7*), 65% of patients (13/20) had a cryptogenic organizing pneumonia (COP) pattern, and none of them died (0/13). All but one patient with COP pattern were treated with only corticosteroids, while the one patient was administered a corticosteroid and infliximab. Acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern was observed in 10% (2/20) of patients. Although the two patients with the AIP/ARDS pattern were treated with corticosteroid and infliximab (5 mg/kg), one patient died.

In the current case, the pembrolizumab-induced pneumonitis with AIP/ARDS pattern on CT (*8*) did not respond to corticosteroid treatment, but respiratory status improved one week after administration of infliximab. Although consolidation in the right lower lobe showed no response to infliximab, the improvement in the right upper lobe observed by CT were confirmed by autopsy.

There is no consensus on the dosing schedule of infliximab for the treatment of severe immune-mediated pneumonitis. Based on a retrospective report (*9*), the current ESMO guideline states that gastrointestinal toxicity induced by anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies may require a second dose of infliximab two weeks after the first administration (*4*). To our knowledge, the present case is the first report of immune-mediated pneumonitis that demonstrated transient improvement and re-exacerbation two weeks after infliximab therapy. Considering that infliximab has a half-life of 7-12 days (*10*), elimination of infliximab might have led to re-exacerbation of the pneumonitis in the current patient.

In conclusion, infliximab induced rapid improvement of immune-mediated pneumonitis that lasted for two weeks. Repeated administration of infliximab for a certain period may be beneficial in the treatment of immune-mediated pneumonitis. The present case highlights the need for further research on the choice and optimal dose and duration of immunosuppressants in the treatment of severe immune-mediated pneumonitis.

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