Long-term survival with tocilizumab treatment for tislelizumab-related pneumonitis in a patient with non-small cell lung cancer: A case report

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Abstract. Tislelizumab, an immune checkpoint inhibitor (ICI) that is approved for the treatment of non-small cell lung cancer (NSCLC), has shown superior overall and progression-free survival benefits compared with chemotherapy in clinical trials. However, like other ICIs, tislelizumab administration may lead to a series of immune-related adverse events (irAEs), including checkpoint inhibitor pneumonitis. Corticosteroids are recommended as the first-line treatment for the management of irAEs. However, biological immunomodulatory agents, such as infliximab and tocilizumab, are often needed in patients with steroid-refractory or steroid-resistant irAEs. The present study reports the case of a patient with NSCLC and tislelizumab-related pneumonitis, who showed complete resolution of symptoms and clear computed tomography imaging after tocilizumab treatment, and achieved a long-term survival period of >5 years. In the current patient, the involvement of interleukin-6 (IL-6) in corticosteroid-refractory pneumonitis was demonstrated by elevated serum IL-6 levels, and subsequent treatment with the IL-6 receptor inhibitor tocilizumab achieved complete resolution and long-term survival. The present case suggests that IL-6 may be involved in the pathogenesis of irAEs and that tocilizumab may be an effective option for treating steroid-refractory or steroid-resistant irAEs.

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Introduction

The emergence of immune checkpoint inhibitors (ICIs) has been a breakthrough in the treatment of various types of cancer, including melanoma and non-small cell lung cancer (NSCLC). Programmed cell death-1/programmed death-ligand 1 (PD-L1) inhibitors are the most commonly used ICIs and have shown excellent efficacy in a variety of advanced diseases, including NSCLC (1,2). Tislelizumab, an immune checkpoint inhibitor approved for the treatment of NSCLC, has been reported to be associated with superior progression-free survival (PFS) and overall survival (OS) compared with chemotherapy in clinical trials (3,4). While ICIs have achieved a breakthrough in treatment efficacy, immune-related adverse events (irAEs) due to ICI administration have also received widespread attention. Among all types of irAEs that may damage different organs of the body, checkpoint inhibitor pneumonitis (CIP) is one of the potentially life-threatening AEs, particularly in patients with NSCLC (5,6). A large-scale clinical trial reported a 3-5% incidence of CIP in patients with NSCLC, whereas a higher incidence of 19% was reported in a real-world study (7,8). Corticosteroids are recommended as the first-line treatment for the management of a wide variety of irAEs according to the European Society For Medical Oncology and American Society of Clinical Oncology guidelines (9,10). However, biological immunomodulatory agents, such as infliximab and tocilizumab, are recommended in patients with steroid-refractory or steroid-resistant irAEs.

Interleukin-6 (IL-6) is a well-known proinflammatory cytokine with pleiotropic biological functions that is considered to have a prominent role in the development of irAEs (11,12). Tocilizumab, a novel recombinant humanized anti-IL-6-receptor (anti-IL-6R) monoclonal antibody, inhibits the IL-6 signaling pathway by binding both membrane-bound and soluble forms of the IL-6R (13). At present, tocilizumab is mainly used for the treatment of inflammatory autoimmune diseases, such as rheumatoid arthritis and systemic onset juvenile idiopathic arthritis (13). In 2017, the U.S. Food and Drug Administration approved tocilizumab for the treatment

of severe or potentially life-threatening cytokine release syndrome (CRS) induced by chimeric antigen receptor-T cells in adults and children ≥2 years of age (14). Additionally, tocilizumab has shown good efficacy in the treatment of steroid-refractory irAEs. For instance, in a single-center study involving 34 patients with steroid refractory irAEs receiving tocilizumab treatment, 79.4% of patients exhibited clinical improvement (15). However, there are limited reports on the treatment of CIP with tocilizumab. The present study reports a clinical experience of using tocilizumab to treat tislelizumab-related pneumonitis after ineffective corticosteroid therapy in a patient with stage IV lung cancer.

Case report

A 62-year-old man was admitted to Qingdao Central Hospital, University of Health and Rehabilitation Sciences (Qingdao, China) after complaining of lower back pain that had persisted for 1 month in June 2020. The patient had a 40-pack-year history of smoking and a 10-year history of refractory type 2 diabetes. A chest computed tomography (CT) scan indicated a 2.1x2.0-cm cavitary mass in the right lower lung alongside vertebral metastases (Fig. S1). ^{18}F-FDG positron emission tomography revealed right-sided lung cancer with right hilar lymph node metastasis and vertebral metastases ranging from the 10th thoracic vertebra to the 1st lumbar vertebra (Fig. 1). Magnetic resonance imaging (MRI) of the thoracic and lumbar spine also showed vertebral metastasis (Fig. S2). The histological diagnosis was obtained by a CT scan-guided biopsy of the thoracic vertebral lesions. The specimen was fixed in 10% neutral buffered formalin at room temperature for 24-48 h, sectioned at 4 μm and stained with hematoxylin and eosin at room temperature for 5 and 1 min, respectively. The stained slides were examined under a light microscope (ECLIPSE Ci-plus; Nikon Corporation), confirming metastatic squamous cell carcinoma (Figs. S3 and S4). The PD-L1 expression was assessed by immunohistochemistry using the 22C3 pharmDx assay on the Dako Autostainer Link 48 platform (cat. no. PRDT_711205; Agilent Technologies, Inc.). Formalin-fixed, paraffin-embedded tissue sections (4 μm) were stained according to the manufacturer's protocol. Tissues were fixed in 10% neutral buffered formalin (room temperature; 24-48 h). After deparaffinization, antigen retrieval was performed at 97˚C for 20 min, followed by washing with wash buffer and rehydration through a descending alcohol series according to the manufacturer's protocol. The stained slides were examined under a light microscope (ECLIPSE Ci-plus), and the tumor proportion score (TPS) was evaluated. The result was interpreted as the TPS defined as the percentage of viable tumor cells exhibiting partial or complete membrane staining. The PD-L1 (22C3) immunohistochemistry assay indicated that the TPS was 40% (Fig. S4). Immunohistochemical analysis of p40, cytokeratin (CK)5/6, CK7 and thyroid transcription factor 1 (TTF1) (Fig. S4) was performed on formalin-fixed, paraffin-embedded tissue sections from the thoracic vertebral lesion using the same automated immunostainer and following the same protocol as described for PD-L1. After antigen retrieval, sections were blocked with 5% normal goat serum (Vector Laboratories, Inc.) at room temperature for 30 min. The following primary antibodies were applied at 4˚C overnight: Anti-p40 (1:100; GT233807; Gene Tech Biotechnology Co., Ltd.), anti-CK5/6 (1:200; MAB-0744; Fuzhou Maixin Biotechnology Development Co., Ltd.), anti-CK7 (1:50; GM701807; Gene Tech Biotechnology Co., Ltd.) and anti-TTF1 (1:100; MAB-0599; Fuzhou Maixin Biotechnology Development Co., Ltd.). HRP-conjugated secondary antibody was applied using the ultraView Universal DAB Detection Kit (cat. no. 760-500; Roche Tissue Diagnostics; Roche Diagnostics, Ltd.) without additional dilution. After incubation at room temperature for 1 h, staining was visualized with 3,3'-diaminobenzidine and counterstaining was performed with hematoxylin at room temperature (25˚C) for 2 min. Positive staining for p40, CK5/6 and CK7, and negative staining for TTF1 confirmed the diagnosis of metastatic lung squamous cell carcinoma. Consequently, the patient was diagnosed with stage IV (cT2N1M1; 8th edition of the American Joint Committee on Cancer Cancer Staging Manual) lung squamous cell carcinoma with right hilar lymph node and vertebral metastases (16).

To alleviate pain and prevent skeletal-related events, the patient first received hyperfractionated radiotherapy for the vertebral metastases at doses of 30 and 40 Gy in 10 fractions to the planning target volume and the planning gross target volume, respectively. After radiotherapy, the patient began receiving treatment with albumin-bound paclitaxel (300 mg on day 1), nedaplatin (120 mg on day 1) and tislelizumab (200 mg on day 1) every 3 weeks starting from August 2020. Nedaplatin was removed from the second cycle due to grade 3 myelosuppression (Common Terminology Criteria for Adverse Events 5.0) (17). Imaging after two cycles of chemo-immunotherapy showed stable disease. After receiving the third cycle, the patient presented with a fever, cough and shortness of breath. A chest CT scan in late October 2020 demonstrated ground-glass opacities (GGOs), reticular opacities and consolidations predominantly in the peripheral and lower lung (Fig. 2A and B). The plasma IL-6 levels were markedly elevated and reached 299.45 ng/l (normal range, 0-5.4 ng/l). CT-guided lung biopsy from the consolidation of the lower lobe of the right lung, processed in the same manner as the previous specimens, showed inflammation of the lung tissue and fibrous tissue hyperplasia (Fig. S5). Considering the treatment history combined with the negative results from the pathogenic microbiological tests, the patient was diagnosed with grade 2 CIP according to the American Society of Clinical Oncology (ASCO) guideline with a cryptogenic organizing pneumonia pattern (10). The chemo-immunotherapy was subsequently suspended. The patient received an initial intravenous dose of methylprednisolone at 60 mg per day (~1 mg/kg), which was then gradually tapered off over 12 days until discontinuation, with close monitoring of blood glucose changes to control hyperglycemia. CT images collected in November 2020 showed notable radiographic improvement after corticosteroid treatment (Fig. 2C and D). The patient also experienced marked clinical improvement of the cough and shortness of breath. After this, the dosage of corticosteroid was gradually decreased until it was discontinued.

However, 1.5 months after the discontinuation of corticosteroids and without restarting systemic therapy, the patient developed dyspnea and a worsening cough again. The chest

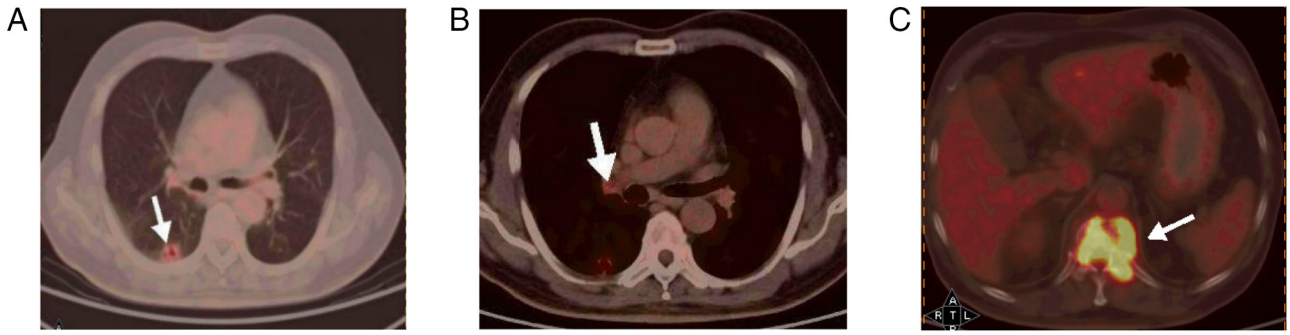

Figure 1. Positron emission tomography-computed tomography scan on patient admission. (A) The primary tumor in the right lower lobe of the lung (arrow). (B) Right hilar lymph node metastasis (arrow). (C) Vertebral metastasis (arrow).

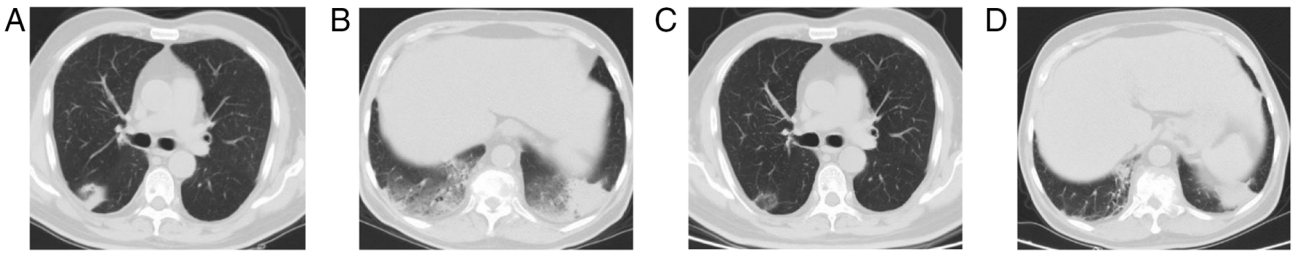

Figure 2. CT images of checkpoint inhibitor pneumonitis before and after corticosteroid therapy. (A) CT image at the level of the intermediate bronchus showing pneumonitis after three cycles of immunotherapy (October 2020). (B) CT image at the level of the bilateral lower lung showing pneumonitis after three cycles of immunotherapy (October 2020) (C) CT image at the level of the intermediate bronchus showing notable improvement of pneumonitis after administration of corticosteroids (November 2020). (D) CT image at the level of the bilateral lower lung showing notable improvement of pneumonitis after administration of corticosteroids (November 2020). CT, computed tomography.

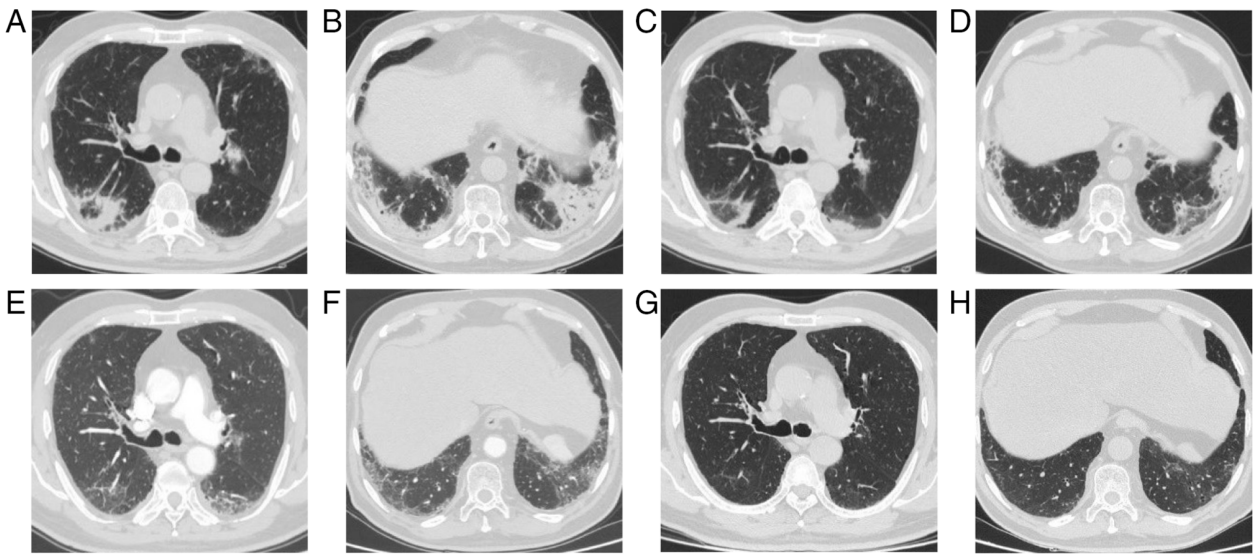

Figure 3. Radiological response of checkpoint inhibitor pneumonitis following tocilizumab treatment. (A) CT image at the intermediate bronchus level showing pneumonitis relapse (December 2020), which was more serious than when it first occurred. (B) CT image at the bilateral lower lung level from the same date (December 2020) also showign the relapsed pneumonitis. (C) After one cycle of tocilizumab (January 2021), the CT image at the intermediate bronchus level showed notable improvement. (D) The corresponding CT image at the bilateral lower lung level after one cycle (January 2021) also demonstrated improvement. (E) Following two cycles of tocilizumab (March 2021), further regression of pneumonitis was observed at the intermediate bronchus level. (F) The CT image at the bilateral lower lung level after two cycles (March 2021) showed continued resolution. (G) After four cycles of tocilizumab (May 2021), complete resolution of pneumonitis was achieved at the intermediate bronchus level. (H) The CT image at the bilateral lower lung level after four cycles (May 2021) confirmed complete resolution. CT, computed tomography.

CT scan collected in December 2020 demonstrated multifocal areas of consolidation, reticular opacities and GGOs in the peripheral and bilateral lower lungs, which were more pronounced than when they first appeared (Fig. 3A and B). Additionally, the plasma IL-6 levels were markedly elevated and reached 209.72 ng/l (Fig. 4). To block the IL-6R, the

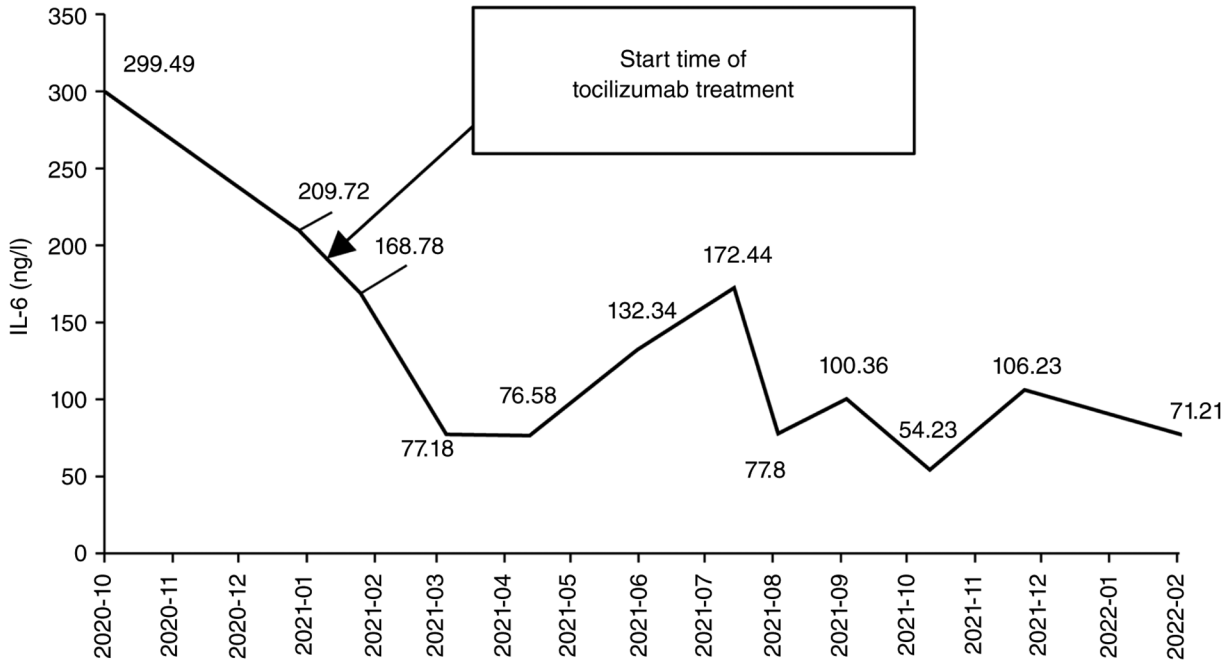

Figure 4. Changing plasma levels of IL-6 in the patient. The IL-6 level was 209.72 ng/l when the pneumonia relapsed (December 2020). After administration of tocilizumab, the IL-6 level markedly decreased to 76.58 ng/l (March 2021). The IL-6 level was 71.21 ng/l at the last testing (February 2022). Il-6, interleukin-6.

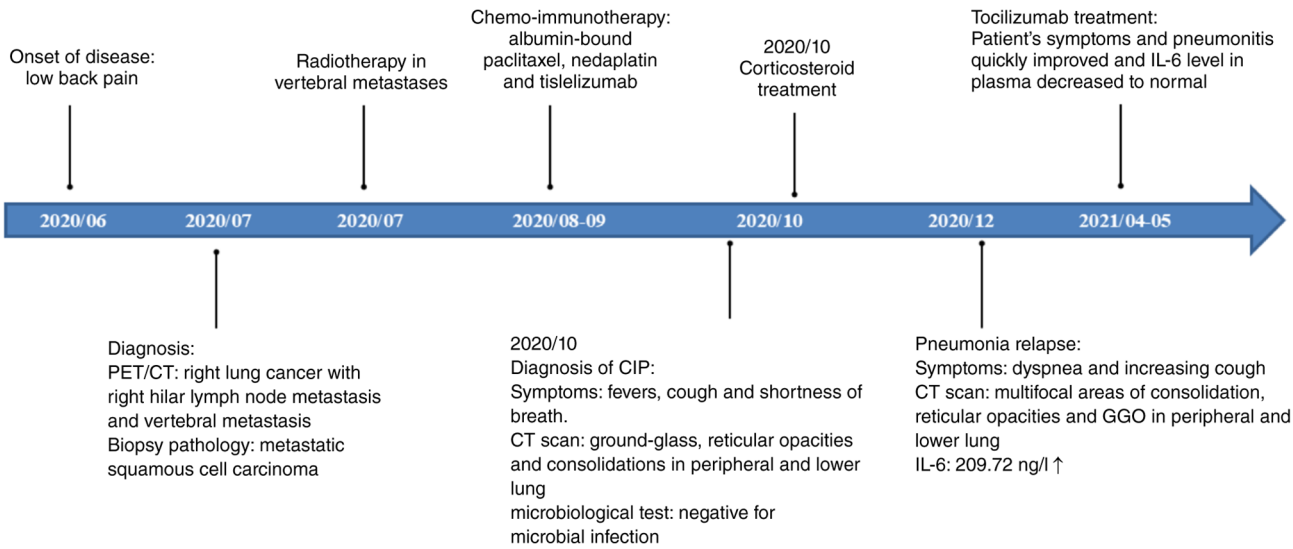

Figure 5. Treatment timeline. PET, positron emission tomography; CT, computed tomography; CIP, checkpoint inhibitor pneumonitis; GGO, ground glass opacity; IL-6, interleukin-6.

patient received four cycles of tocilizumab at 4 mg/kg every 3 weeks from January 2021 to April 2021. After treatment with tocilizumab, the clinical symptoms and pneumonitis rapidly and notably improved and then disappeared (Fig. 3C-H). A marked decrease in the plasma IL-6 levels was also observed (Fig. 4).

During the follow-up period until February 2022, the plasma IL-6 levels fluctuated, with a transient increase to near pre-tocilizumab levels between May and July 2021 (peak, 172.44 ng/l), followed by a gradual decline to 71.21 ng/l by February 2022. Throughout this period, the CT images showed that the pneumonitis remained in complete remission (Fig. S6). No AEs related to tocilizumab were observed. Although the patient refused any anticancer therapy from the first incidence of CIP, the tumor has remained in a stable state and there has been no recurrence. As of the submission of the manuscript, the PFS and OS times of the patient have both exceeded 60 months. The treatment timeline is shown in Fig. 5.

Discussion

Several published guidelines, including the European Society for Medical Oncology Clinical Practice Guideline and the ASCO Guideline Update, recommend corticosteroids as a first-line treatment for the management of irAEs (9,10). For most steroid-refractory and steroid-resistant irAEs,

the guidelines recommend biological immunomodulatory agents, such as infliximab, mycophenolate mofetil or intravenous immunoglobulin, as second-line treatment (18,19). Furthermore, emerging evidence suggests that different immunopathogenic mechanisms, such as breach of self-tolerance, cross-antigen reactivity, cytokine production, off-target effects and microbiome-related factors (including bacterial, fungal and viral components), result in irAEs (9). Therefore, a personalized treatment strategy beyond the first-line regimen has been proposed for the management of irAEs.

A number of inflammatory factors, such as IL-6 and TNF-α, released during tumor immunotherapy can result in irAEs (20,21). Among the inflammatory factors, IL-6 serves the most crucial role in the development of irAEs (including CIP) (22,23). Tocilizumab, a novel recombinant humanized anti-IL-6R monoclonal antibody, can block the IL-6 signaling pathway and thus disrupt the continuous development of CIP and restore the damaged alveoli (13). A retrospective multicenter study evaluated the effectiveness and safety of anti-IL-6R antibodies. A total of 92 patients with irAEs received therapeutic anti-IL-6R antibodies (sarilumab or tocilizumab), 73% of whom experienced resolution or a reduction to grade ≤1 irAEs at a median time of 2.0 months after the initiation of anti-IL-6R therapy (24). This study provided indirect evidence of IL-6 as one of the essential mediators of irAEs. In the present study, the patient was diagnosed with CIP (grade 2) after receiving three cycles of tislelizumab in combination with chemotherapy. The patient then received a high dose of intravenous corticosteroids in the first-line treatment of CIP. The patient initially responded to this treatment but subsequently developed recurrent pneumonitis (grade 3) after discontinuation of corticosteroids in the absence of ICI rechallenge. Considering the notably elevated plasma IL-6 levels, the patient received tocilizumab treatment, which resulted in a subsequent decrease in IL-6, as well as a marked improvement in the symptoms and radiological findings. For this patient, the clinical decision to use tocilizumab instead of guideline-recommended alternatives, such as mycophenolate mofetil or tacrolimus, was guided by a distinct biomarker profile (25). Specifically, the observation of a notably elevated serum IL-6 level offered a compelling biological rationale for selectively inhibiting the IL-6 pathway, rather than initiating non-specific, broad-spectrum immunosuppression. This approach exemplifies the shift toward a biomarker-directed, personalized management strategy for steroid-refractory irAEs, which aims to target dominant inflammatory pathways over empirical treatment. Evidence from the present case suggests that blocking IL-6R can be beneficial for mitigating CIP and that the anti-IL-6R antibody, tocilizumab, may be an effective approach for the management of CIP.

Tocilizumab has a marked effect in the management of irAEs, but the optimal dose and frequency of tocilizumab for their treatment remains unknown. The recommended dose of 8 mg/kg tocilizumab has been approved for systemic juvenile idiopathic arthritis (14). The current evidence regarding the dosing of tocilizumab for irAEs is primarily derived from retrospective case reports (15,26), with no standardized guidelines established. The most commonly reported regimen involves a single intravenous dose of 4 mg/kg, which may be repeated at intervals of 2-4 weeks depending on the clinical and radiological responses of the patients. Most patients exhibit a response within 1 to 2 cycles of treatment. The total number of treatment cycles is tailored to individual patient response and clinical judgment, allowing for multiple cycles when deemed necessary. In the present case, the patient was treated with four cycles of 4 mg/kg tocilizumab. However, further study is still needed to evaluate the optimal dose and frequency of tocilizumab for the treatment of CIP. The safety of tocilizumab in the treatment of irAEs is also a main concern. However, there is a lot of available evidence supporting the safety of tocilizumab. The most common AEs observed in tocilizumab studies are headaches, upper respiratory tract infections and gastrointestinal events, but most of them can be well tolerated (27). In a single-dose tocilizumab (10 or 20 mg/kg) study involving healthy subjects, neutropenia was the only main dose-related toxicity (28). A retrospective analysis also established the safety of 8 mg/kg tocilizumab for the treatment of patients with T cell-induced CRS (14). A large retrospective study also highlighted the efficacy and safety of tocilizumab in the treatment of irAEs without hindering the ICI-induced tumor response (4). In the current patient with NSCLC, short-term treatment with four cycles of tocilizumab was demonstrated to be safe, with no treatment-related AEs observed. To determine the optimal dosing regimen and timing of administration, future studies should focus on prospective dose-finding trials designed to evaluate the safety and efficacy of different dosing strategies, such as comparing 4 vs. 8 mg/kg, and to establish the most effective and safe treatment protocol.

Although irAEs are potentially life-threatening, effective management of irAEs has been shown to be associated with improved long-term survival in patients with NSCLC (29). A multicenter retrospective study showed that patients with NSCLC whose CIP was successfully managed achieved a significantly longer PFS time than those who did not develop CIP (30). A meta-analysis of 54 studies demonstrated that patients whose irAEs were successfully managed achieved a significantly higher objective response rate (odds ratio, 3.44), longer PFS time (HR, 0.51) and longer OS time (HR, 0.58) than those without irAEs (31). In the present study, the observed long-term PFS and OS are fundamentally attributed to the successful management of CIP. This supports a key principle that effective control of severe irAEs is a crucial foundation for ensuring patient safety and the potential survival benefits of immunotherapy. The present case demonstrates that tocilizumab may serve as an effective salvage therapy for a specific subset of steroid-refractory CIP characterized by significant activation of the IL-6 pathway. Compared with long-term, high-dose corticosteroid use, its targeted mechanism of action offers a potentially more favorable risk-benefit profile. In contrast to other biological agents or broad-spectrum immunosuppressants in this specific context, tocilizumab exerts a more selective effect, which may better align with the underlying disease pathophysiology. This highlights the importance of individualized treatment approach rather than a uniform strategy in the management of irAEs.

In conclusion, the present case suggests that IL-6 may be involved in the pathogenesis of irAEs and that tocilizumab

may be an effective treatment option for the personalized management of CIP. As a single-case report, the findings may lack generalizability. The response to tocilizumab observed in this patient may not be representative of the entire population of patients with NSCLC and CIP, and therefore, validation in larger patient cohorts is necessary to confirm its efficacy, establish the optimal dosing regimen and comprehensively evaluate its safety profile. Furthermore, factors such as the patient's age, underlying medical conditions, tumor characteristics and prior corticosteroid use, as well as the timing and dosage of tocilizumab administration, may have influenced the treatment outcomes. Therefore, caution should be exercised when generalizing these findings to other patients. Future rigorously designed prospective studies are warranted to validate the association between biomarkers such as IL-6 and treatment response to tocilizumab in a broader patient population. Additionally, the management of irAEs will become an important challenge for clinicians. Further exploration of effective biomarkers for adverse reactions and therapeutic targets is also needed to improve patient prognosis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LY was the attending physician for the patient and drafted the manuscript. QMG was responsible for testing and analyzing the patient's plasma IL-6 levels and modified the manuscript. YW and LL performed the treatment and follow-up of the patient. FC collected the clinical data and obtained the CT and MRI images. XTZ guided the treatment of the patient and conceptualized the work. QMG and XTZ confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Qingdao Central Hospital, University of Health and Rehabilitation Sciences (approval no. KY202600401).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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