# Severe steroid-refractory immune checkpoint inhibitor-associated pneumonitis and exploration of potential biomarkers: A case report

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**Abstract.** Immune checkpoint inhibitor-associated pneumonitis (CIP) is a severe and potentially fatal immune-related adverse event. Its clinical management is highly challenging, especially in severe cases that are refractory to steroid therapy, making the exploration of biomarkers for assessing disease severity and predicting treatment response critically important. A 66-year-old male patient with stage IV lung adenocarcinoma developed acute fever and dyspnea after treatment with the anti-programmed cell death protein-1 inhibitor tislelizumab and was subsequently diagnosed with severe (grade 4) CIP. During the acute phase of the disease, laboratory tests revealed that the patient's peripheral blood absolute eosinophil count (AEC), interleukin-6 (IL-6) and C-reactive protein (CRP) concentrations were significantly and synchronously elevated. The patient responded poorly to initial empirical anti-infective and low-dose steroid therapy, leading to rapid clinical deterioration. After the treatment was upgraded to methylprednisolone pulse therapy (500 mg/day) combined with intravenous immunoglobulin, the condition was effectively controlled and the clinical symptoms gradually alleviated. Follow-up revealed that while CIP inflammation resolved, the underlying stage IV lung adenocarcinoma progressed, leading to the re-initiation of systemic chemotherapy in February 2025. In conclusion, dynamic changes in the combination of AEC, IL-6 and CRP may serve as biomarkers for assessing the severity, immune phenotype and treatment response of CIP. A comprehensive strategy for the successful management of severe, steroid-refractory CIP should involve early recognition, rapid pathogen exclusion via targeted next-generation sequencing and the timely escalation of immunosuppression combined with multiorgan function support. The clinical value of the aforementioned biomarkers requires further research for validation.

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## Introduction

Immune checkpoint inhibitors (ICIs) have recently been widely used to treat malignant tumors, significantly prolonging the survival of patients with various advanced cancers. However, immune-related adverse events (irAEs) triggered by ICIs, activating the systemic immune system, have become a major challenge in clinical management. Among these, ICI-associated pneumonitis (CIP) is a life-threatening complication, with an overall incidence of 2-5%. Severe (grade 3-5) CIP has a high mortality rate and occurs more frequently in patients with lung cancer (1,2). Although most patients with CIP respond well to corticosteroid therapy, ~10-20% of patients exhibit steroid-refractory or steroid-dependent characteristics. This group of patients has a poor prognosis, representing a major clinical challenge (3,4). CIP is essentially a diagnosis of exclusion and can occur at any time-point following ICI therapy. Owing to an incomplete understanding of its exact pathogenesis and a lack of specific clinical manifestations, imaging features and reliable biomarkers, diagnosis is challenging. In severe cases, CIP is highly susceptible to being confused with conditions such as severe community-acquired pneumonia, acute respiratory distress syndrome or cytokine release syndrome, which may delay treatment past the optimal timing (2,5). Therefore, identifying biomarkers that can assist in the early identification, severity assessment and treatment response prediction of CIP is clinically important. In addition to comprehensive clinical judgment, reliable monitoring tools for assessing CIP activity, immune subtypes and the risk of 'steroid-refractory' disease remain insufficient.

This report describes a case in which acute, rapidly progressive severe CIP was induced by the programmed cell death protein-1 inhibitor tislelizumab. This case exhibited steroid-refractory characteristics, and during the acute phase of the illness, a significant and synchronous increase in peripheral blood absolute eosinophil count (AEC), interleukin-6 (IL-6) concentration and C-reactive protein (CRP) concentration was observed. Through a systematic review of the diagnosis and treatment process of this case, an in-depth analysis of the key clinical decision points was performed and the potential role of the combination of AEC, IL-6 and CRP in the occurrence,

progression and outcome of CIP was explored. This study aimed to provide new diagnostic and therapeutic insights and a reference framework for the clinical management of severe, complex CIP and to explore the possibility of assessing disease progression on the basis of dynamic changes in biomarkers.

## Case report

The patient was a 66-year-old male with a nine-year history of stage IV lung adenocarcinoma who had undergone multiple lines of antitumor therapy. Before the initiation of tislelizumab, the patient was in a good general condition, with an Eastern Cooperative Oncology Group performance status score (6) of 1 and a body mass index (BMI) of 28.1 $kg/m^2$. Pulmonary metastases were identified on tumor restaging. The patient received 16 cycles of an antitumor regimen containing tislelizumab, resulting in a partial response to treatment. The patient's past medical and personal history included a history of sinusitis, myocardial bridging, aortic valve stenosis, hypertension and a smoking index of 1,600 pack-years. Approximately 3 months after the completion of treatment, the patient was admitted to the Department of Medical Oncology at Zibo Central Hospital (Zibo, China), due to fever for 20 days. A chest computed tomography (CT) scan revealed multiple ground-glass opacities in both lungs (Fig. 1A). After 3 days of ineffective empirical anti-infective therapy, the patient was transferred to the respiratory intensive care unit (RICU) because of newly developed dyspnea.

After the patient was transferred to the RICU, an arterial blood gas analysis was performed, which revealed an oxygenation index of 127 mmHg (normal index, >400 mmHg; consistent with type I respiratory failure when <300 mmHg), a value that met the diagnostic criteria for type I respiratory failure (7). Laboratory tests revealed that the patient had an AEC of $1.37x10^9$/l (reference range, 0.00-$0.80x10^9$/l); an IL-6 concentration of 1,019 pg/ml (reference range, 0-7 pg/ml); a CRP concentration of 174 mg/l (reference range, 0.00-5.00 mg/l); a normal procalcitonin concentration; a normal coagulation panel; normal D-dimer, N-terminal pro-brain natriuretic peptide (NT-proBNP), and antinuclear and anti-extractable nuclear antigen antibody profiles; normal cardiac markers; and negative results on severe acute respiratory syndrome coronavirus-2 nucleic acid and influenza A/B nucleic acid tests and on serum fungal (1,3)-β-D-glucan/galactomannan assays. On the basis of the patient's history of ICI use, clinical presentation and imaging characteristics, the initial differential diagnosis included fungal pneumonia (mucormycosis, aspergillosis and *Pneumocystis jirovecii*), CIP and chronic eosinophilic pneumonia. The initial treatment regimens included prone positioning ventilation, high-flow nasal cannula oxygen therapy, intravenous isavuconazole sulfate (a loading dose of 200 mg every 8 h for the first 48 h, followed by a 200 mg once-daily maintenance dose), piperacillin-tazobactam (4.5 g every 8 h) and methylprednisolone (40 mg/day, ~0.5 mg/kg/day). Because of high suspicion of superimposed infection and complex comorbidities, a cautious low-dose protective regimen was adopted. This strategy aimed to prevent fatal septic shock, which can occur when high-dose glucocorticoids accelerate pathogen proliferation (8). Oral trimethoprim-sulfamethoxazole (four double-strength tablets every 6 h, each containing 800 mg sulfamethoxazole and 160 mg trimethoprim) was also initiated. After 3 days of the aforementioned treatment regimen, the patient's body temperature returned to normal; however, dyspnea progressively worsened. A repeat chest CT scan performed on day 6 revealed the progression of pulmonary lesions (Fig. 1B). During the treatment period, the patient underwent bronchoscopy. Bronchoalveolar lavage fluid (BALF) was subjected to targeted next-generation sequencing (tNGS) and pathogen culture. The tNGS assay employed a multiplex PCR-based enrichment strategy coupled with high-throughput sequencing, covering hundreds of clinically relevant pathogens (including bacteria, fungi, viruses and atypical pathogens). Nucleic acids (DNA and RNA) were extracted from the specimen, and targeted pathogen-specific amplicons were generated and sequenced. The obtained sequences were aligned against a curated pathogen reference database for pathogen identification. The tNGS report showed no definitive pathogenic microorganisms in the pathogenic microorganism list, and conventional cultures also yielded negative results; only a few commensal or opportunistic organisms at very low abundance were detected, which were considered clinically insignificant. Follow-up tests revealed that AEC had decreased to $0x10^9$/l, the IL-6 concentration had decreased to 66 pg/ml and the CRP concentration had decreased to 46 mg/l; however, the oxygenation index had decreased to 120 mmHg. On the basis of the ineffectiveness of anti-infective therapy and low-dose glucocorticoid treatment, the negative BALF-tNGS results, the exclusion of other noninfectious interstitial lung diseases and the patient's clear history of tislelizumab use, the clinical diagnosis was 'severe ICI-related pneumonitis (Grade 4)'. At that point, isavuconazole sulfate and trimethoprim-sulfamethoxazole were discontinued, and methylprednisolone was increased to 80 mg every 12 h (160 mg/day, equivalent to 1.86 mg/kg/day), reaching the recommended starting dose for grade 4 irAEs (1-2 mg/kg/day) in the National Comprehensive Cancer Network (NCCN) (9) guidelines. However, the patient's condition continued to deteriorate. Then, 3 days later, the patient's oxygenation index decreased to 87 mmHg and chest CT revealed further progression of the inflammatory lesion (Fig. 1C). Follow-up tests revealed an AEC of $0x10^9$/l, an IL-6 concentration of 27 pg/ml, a CRP concentration of 26 mg/l, a normal D-dimer concentration and an NT-proBNP concentration of 6,870 pg/ml. Physical examination revealed diffuse Velcro crackles in both lungs. After 3 days of high-dose corticosteroid therapy (160 mg/day), the patient's condition deteriorated with progression of the pulmonary imaging findings, which met the criteria for steroid-refractory CIP. The following day, the patient received methylprednisolone pulse therapy at 500 mg/day for 3 days combined with intravenous human immunoglobulin (IVIG) (20 g/day for 5 consecutive days) and recombinant human BNP (administered as a continuous intravenous infusion at 0.0075 $\mu$g/kg/min for 72 h to improve cardiac function). During pulse therapy, the patient's oxygenation index acutely deteriorated to 55 mmHg; however, the patient declined endotracheal intubation. After methylprednisolone was reduced to 160 mg every 12 h and high-flow humidified oxygen therapy combined with an oxygen mask [fraction of inspired oxygen ($FiO_2$), 61%] was maintained for respiratory support, the oxygenation index gradually improved.

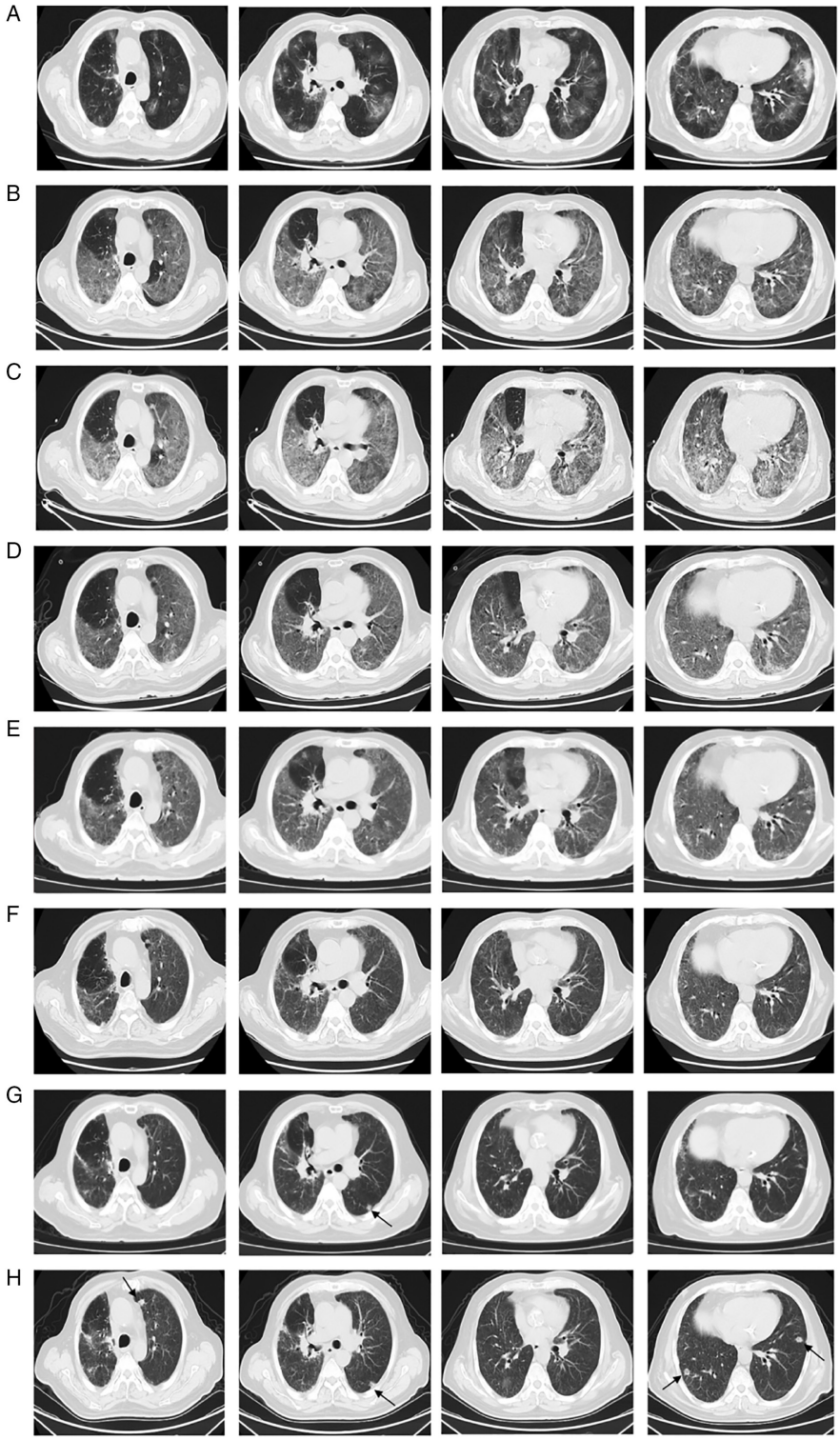



Figure 1. Serial axial chest CT images at representative mid-thoracic levels, showing the complete disease course: From initial presentation and progression of CIP, to gradual resolution of inflammatory lesions, and subsequent tumor progression. All images are displayed with standard lung window settings. Black arrowheads indicate new or enlarging pulmonary nodules suggestive of tumor progression. (A) May 2024: Initial presentation of CIP. Multiple patchy GGOs are visible in both lungs. (B) May 2024: 6 days after admission. Compared with panel A, the GGOs have increased in extent and density, indicating progression of CIP despite empirical anti-infective and low dose steroid therapy. (C) May 2024: After escalation to high-dose methylprednisolone (160 mg/day), further progression is observed. The bilateral diffuse GGOs remain similar in extent but show focally increased density, involving >50% of the lung parenchyma, consistent with grade 4 CIP. (D) May 2024: Following methylprednisolone pulse therapy (500 mg/day for 3 days) combined with IVIG. The extent of GGOs remains similar, but the density is largely decreased compared with previous imaging. (E) June 2024: 25 days after admission. Continued resolution of pulmonary infiltrates is observed, with the extent of GGOs remaining similar but density further decreased. (F) July 2024: 1 month after discharge (during oral prednisone tapering). Persistent resolution of pulmonary infiltrates is noted, with decreased extent and density of GGOs. The underlying lung architecture is largely preserved. (G) November 2024: 5-month follow-up. Complete radiographic resolution of pneumonitis is achieved, and prednisone has been discontinued. However, an enlarged nodule is observed in the left upper lobe (black arrowhead), suggesting possible tumor progression. (H) February 2025: 8-month follow-up. The left upper lobe nodule has further enlarged, and multiple new bilateral nodules are observed (black arrowheads), confirming disease progression. No active inflammatory lesions are present. GGOs, ground-glass opacities; CIP, Immune checkpoint inhibitor-associated pneumonitis; IVIG, intravenous human immunoglobulin.

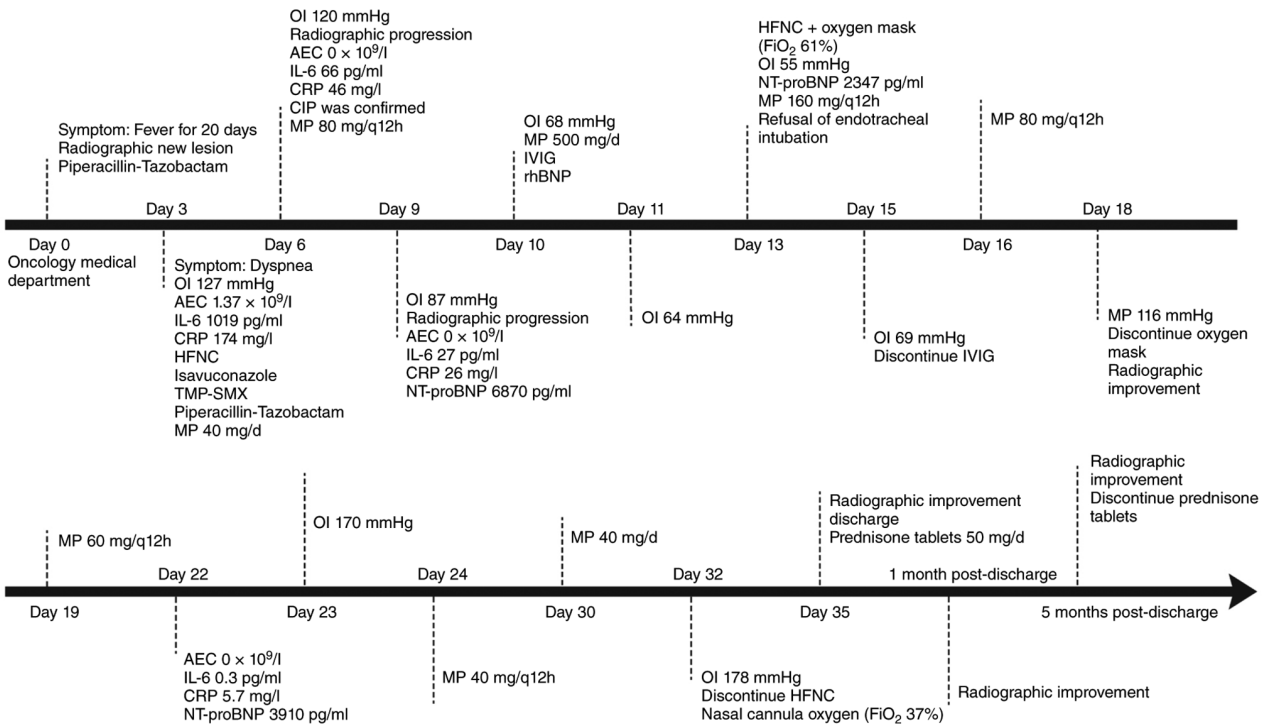



Figure 2. Patient clinical course timeline. AEC, refers to absolute eosinophil count; CIP, checkpoint inhibitor-associated pneumonitis; CRP, C-reactive protein; $FiO_2$, fraction of inspired oxygen; HFNC, high-flow nasal cannula; IL-6, interleukin-6; IVIG, intravenous immunoglobulin; MP, methylprednisolone; NT-proBNP, N-terminal pro-brain natriuretic peptide; OI, oxygenation index; rhBNP, recombinant human brain natriuretic peptide; RICU, respiratory intensive care unit; TMP-SMX, trimethoprim-sulfamethoxazole.

By day 8, the oxygenation index increased to 116 mmHg, and compared with previous imaging, a repeat chest CT showed absorption of the inflammatory lesions (Fig. 1D). By day 22, the patient's oxygenation index had increased to 178 mmHg, and oxygen therapy was switched to a nasal cannula ($FiO_2$, 37%). The resting oxygen saturation could then be maintained >95%, although daily activities remained limited. A chest CT scan on day 25 revealed continued absorption of the inflammatory lesions (Fig. 1E), and the patient was discharged in a relatively stable condition. Given the severity of Grade 4 CIP, tislelizumab was permanently discontinued, and no oncological restaging was performed during the acute phase to prioritize life-saving measures.

After discharge, the patient was prescribed oral prednisone tablets at 50 mg/day, gradually tapered by 5 mg per week. After 1 month, outpatient follow-up chest CT showed significant absorption of the pulmonary inflammatory lesions (Fig. 1F), and the patient's daily activities were unrestricted, while the underlying tumor lesions remained stable. At the 5-month follow up, chest CT revealed near-complete resolution of the pneumonitis lesions (Fig. 1G), and prednisone tablets were discontinued (Fig. 2 provides a detailed timeline of the patient's clinical course and therapeutic interventions). However, the scan showed slight enlargement of certain pulmonary nodules, which was considered tumor progression, but the patient declined further antitumor intervention at that time. At the 8-month follow up, repeat chest CT demonstrated further enlargement and an increased number of bilateral pulmonary nodules (Fig. 1H), confirming disease progression, after which the patient received systemic antitumor therapy with nab-paclitaxel (200 mg on days 1 and 5 of each 21-day cycle) in combination with bevacizumab (600 mg on day 1 of each cycle).

## Discussion

CIP diagnosis is inherently a diagnosis of exclusion. In the case presented here, the patient was elderly and had a long-term history of smoking and underlying lung disease. The clinical presentation of acute fever, dyspnea and multiple ground-glass opacities is highly prone to confusion with conditions such as severe community-acquired pneumonia (e.g., fungal infection, *Pneumocystis jirovecii* infection) or acute interstitial pneumonia (2,5). In the present case, the negative results for traditional infection markers (such as procalcitonin), along with the failure of empirical anti-infective therapy, prompted clinicians to rapidly perform tNGS analysis of BALF. A negative tNGS result, combined with negative conventional microbiological cultures and fungal markers, provided crucial evidence to rule out the most clinically suspected opportunistic infections covered by the targeted gene panel. This diagnosis shifted the focus of treatment rapidly from anti-infection to intensified immunosuppression. Notably, tNGS has been shown to have high diagnostic accuracy in ICU patients with lower respiratory tract infections, with a pathogen detection rate superior to that of conventional methods and comparable to mNGS, while offering advantages in turnaround time and cost-effectiveness (10). Therefore, the clinical value of combined monitoring of AEC, IL-6 and CRP must be based on strict infection exclusion by tNGS rather than serving as an independent diagnostic gold standard.

The most prominent laboratory finding in this case was the synchronous and significant elevation of the AEC, IL-6 and CRP concentrations during the acute phase of the disease. This combination pattern warrants in-depth discussion. Multiple studies suggest that an elevated baseline AEC is a potential risk factor for the development of irAEs and CIP (11-13). In the present case, the significant increase in AECs ($1.37x10^9$/l) during the acute phase may suggest the activation of the type 2 T-helper (Th2) cell-mediated immune pathway, which aligns with certain CIP phenotypes that are relatively sensitive to corticosteroids (12-14). However, a paradoxical phenomenon was observed: After treatment with methylprednisolone (40 mg/day) was initiated, the patient's AEC rapidly decreased to normal levels; however, the clinical symptoms and imaging findings continued to deteriorate. These findings suggest that in the case of severe CIP, eosinophilia may merely be a marker of the early disease stage or a specific subtype rather than the sole or dominant factor driving sustained injury.

This patient had an IL-6 concentration of as high as 1,019 pg/ml and a CRP concentration of 174 mg/l, indicating a strong systemic inflammatory response, which could be referred to as a 'cytokine storm' (15-17). Accumulating evidence indicates that elevated IL-6 concentrations in both the serum and BALF of patients with severe CIP are associated with diffuse alveolar damage and poor prognosis (18-22). CRP is an acute-phase protein, which further confirms the activation of systemic inflammation. Initial steroid therapy rapidly decreases the concentrations of IL-6 and CRP, reflecting the inhibitory effect of the treatment on systemic inflammatory pathways. However, the delayed alleviation of clinical symptoms revealed a potential dissociation between the resolution of local lung tissue inflammation and changes in systemic biomarkers. The initial steroid therapy in this case was ineffective, which may be attributed to either an insufficient dose of steroids or the need for a longer time for the local inflammatory response to resolve. In the retrospective analysis, the patient's oxygenation index (127 mmHg) upon admission to the RICU met the diagnostic criteria for grade 4 (severe) CIP. However, the initial methylprednisolone dosage (40 mg/day, ~0.5 mg/kg/day) was lower than the recommended starting dose for grade 4 irAEs (1-2 mg/kg/day) as per guidelines such as the NCCN guidelines (9). This may have resulted in insufficient immunosuppressive intensity during the initial stage to adequately contain the already erupted inflammatory cascade.

Based on the clinical course characteristics of this case, a hypothetical framework (23) may be proposed to explain the above phenomena: Severe CIP may involve the sequential or overlapping activation of multiple immune pathways in its pathophysiological process. In the initial stage, the activation of specific T cells (such as Th2 cells) triggered by ICIs may drive early events such as eosinophil infiltration (manifested as an elevated AEC). In the subsequent stage, damaged alveolar epithelial cells release damage-associated molecular patterns, further activating the innate immune system (such as alveolar macrophages), thereby releasing large amounts of proinflammatory cytokines such as IL-6 and triggering a systemic inflammatory storm (manifested as a sharp increase in IL-6 and CRP concentrations). This stage may dominate the subsequent tissue injury. In this model, although corticosteroids effectively inhibit the activity of upstream lymphocytes (manifested as rapid decreases in the AEC, IL-6 concentration and CRP concentration), they may only delay or insufficiently suppress the already activated downstream effector pathways mediated by innate immune cells and the complement system. This finding explains the asynchrony between clinical symptom improvement and changes in systemic biomarkers. This hypothesis provides a possible perspective for understanding steroid-refractory disease. For patients with mixed immune phenotypes and cytokine storm characteristics, early combination therapy with second-line immunosuppressants targeting specific pathways (such as the IL-6 receptor antagonist tocilizumab) in addition to adequate corticosteroids may interrupt the vicious inflammatory cycle. This has been previously reported (20,24-26). Meanwhile, evidence suggests that nintedanib plays a potential role as an adjuvant treatment for corticosteroid-refractory CIP, especially in patients with early interstitial changes indicating fibrotic progression. However, clinical experience remains limited, and further studies are required to confirm its efficacy and safety (27).

A key limitation of this study is the lack of data concerning the alveolar microenvironment. Owing to the patient's critical condition (type I respiratory failure with an oxygenation index of 127 mmHg), the emergency bronchoscopy focused solely on obtaining samples for pathogen detection to guide life-saving decisions; BALF cytological classification and cytokine profiling were not performed. The proposed sequential immune activation framework is therefore derived solely from peripheral blood trends and should be validated through future studies in which local BALF data are paired with systemic biomarkers.

This case was ultimately controlled through pulse therapy with methylprednisolone (500 mg/day) combined with IVIG. IVIG exerts its immunomodulatory effects through multiple mechanisms and its combination with corticosteroids is a common salvage regimen for refractory CIP (9,28). Notably, during the treatment process, the patient's NT-proBNP level significantly increased, indicating that the severe hypoxemia induced by CIP led to cardiac insufficiency. The timely addition of recombinant human BNP to improve cardiac function underscores the importance of multiorgan function support in the management of severe CIP. Additionally, an interesting observation in this case was that the patient's condition began to stabilize and improve only when the steroid dosage was tapered to 160 mg every 12 h after pulse therapy. This finding suggests that after the passage of the acute inflammatory stage for certain patients with refractory CIP, the focus of treatment may need to shift appropriately from merely intensifying immunosuppression to providing adequate respiratory support and time, allowing the lung tissue to repair itself. Up-to-date guidelines also emphasize the need to balance immunosuppression intensity with organ function support (29). Although the clinical focus was entirely directed toward managing the severe irAEs, the patient's tumor status remained stable during the steroid tapering and early follow-up periods. This indicates that the prior 16 cycles of tislelizumab provided a durable anti-tumor response even after permanent discontinuation. More importantly, the evolution of CIP-related inflammatory lesions and tumor lesions in this case was independent: The near-complete resolution of pneumonitis following immunosuppressive therapy did not alter the natural course of the

underlying Stage IV lung adenocarcinoma. This underscores the necessity of distinguishing irAEs treatment responses from true tumor progression during long-term follow-up.

The findings of this study offer three key implications for the diagnosis and management of severe glucocorticoid-refractory CIP: i) Establishing a standardized rescue strategy for early recognition, rapid pathogen exclusion (via tNGS), timely escalation of immunosuppression and multiorgan support; ii) proposing a pathophysiological hypothesis for glucocorticoid resistance; and iii) providing guidance for targeted therapy in patients with CIP characterized by a cytokine storm.

This study was a single-case report. The observed biomarker patterns and the proposed pathophysiological hypotheses were derived from individual experience and their generalizability awaits validation through more cases. In the present study, it was not possible to determine the causal relationships among the AEC, IL-6 concentration and CRP concentration, nor to completely rule out the influence of other undetected factors. With respect to the temporal relationship between steroid dose adjustments and clinical turning points, individual differences also exist and should be interpreted with caution.

In conclusion, this case highlights the complexity of managing severe, steroid-refractory CIP. Dynamic monitoring of the combined changes in the AEC, IL-6 concentration and CRP concentration may provide clues for assessing disease activity and immune phenotype. When combined with conventional microbiological assays, tNGS offers a rapid and reliable means of excluding major opportunistic pulmonary infections, thereby facilitating diagnostic clarification in patients with suspected CIP. Successful rescue relies on early recognition, rapid escalation of treatment based on a precise diagnosis, and a comprehensive strategy that encompasses immunosuppression, organ support and long-term management. Further research is needed to validate the predictive value of different biomarker combinations and, on the basis of a deeper understanding of immune phenotypes, to explore individualized and precise treatment pathways.

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**Availability of data and materials**

The tNGS datasets generated in the present study have been deposited in the China National GeneBank Sequence Archive (CNSA; https://db.cngb.org/cnsa/) under accession number CNP0009941. The data generated in the present study are not publicly available due to the restrictions imposed by the *Regulations of the People's Republic of China on Human Genetic Resources* and the sensitive clinical nature of the data but may be requested from the corresponding author. Other data generated during this study may be requested from the corresponding author.

**Authors' contributions**

YX designed the study, collected clinical data, drafted the manuscript and prepared the related figures. AX participated in the clinical management of the patient and revised the manuscript. XY analyzed the biomarker data. LW supervised the study design, revised the manuscript critically and approved the final version. All authors have reviewed the raw data and confirm their authenticity. YX and LW had full access to all raw data in this study and take responsibility for the integrity and accuracy of the data analysis. All the authors have read and agreed to the final version of the manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. The patient was informed that all identifying information would be removed to ensure anonymity.

**Competing interests**

The authors declare that they have no competing interests.

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