

Managing severe dermatitis and grade 4 pneumonitis in a patient with non-small-cell lung cancer following pembrolizumab treatment: A case report

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Abstract. Inhibitors of the programmed death receptor 1 (PD-1) or its ligand PD-L1 are widely used in cancer treatment. Despite their efficacy, these immunotherapies can induce adverse effects, particularly dermatitis and pneumonitis. However, the prognosis of these conditions is infrequently reported. The present study discusses a case of a patient with non-small-cell lung cancer (NSCLC) who developed severe dermatitis and grade 4 pneumonitis following treatment with pembrolizumab. Initially, the patient was administered methylprednisolone at a dosage of 4 mg/kg/day. Reducing the dosage to 1 mg/kg/day exacerbated the pneumonitis, following which the patient was administered mycophenolate mofetil (MMF), which notably ameliorated both conditions. The methylprednisolone dosage was then gradually reduced to 4 mg daily. The present case represents a rare instance of simultaneous severe dermatitis and grade 4 pneumonitis in a patient with NSCLC following immunotherapy. The conditions were successfully managed with a combination of MMF with methylprednisolone, resolving the steroid-dependent dermatitis and pneumonitis. The patient maintained a partial remission, with a tumor size of >30% smaller compared with the initial tumor size, for >3 years following the cessation of immunotherapy.

Introduction

Lung cancer represents one of the most prevalent and lethal malignancies worldwide. Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer cases (1). The advent

of immune checkpoint inhibitors (ICIs) has transformed the therapeutic landscape for advanced NSCLC, establishing immunotherapy as a cornerstone in lung cancer treatment (2,3). ICIs include the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody and the programmed cell death protein-1 (PD-1) or its ligand (PD-L1) monoclonal antibodies. These agents disrupt the interaction between the PD-1 receptor on T lymphocytes and the PD-L1 ligand on tumor cells, thereby hindering tumor immune evasion and enhancing the anti-tumor immune response (4).

CTLA-4, predominantly expressed on the surface of activated T lymphocytes, competes with co-stimulatory receptors on T cells, inhibiting T cell proliferation and activation during early tumorigenesis, thus protecting tumor cells from T cell-mediated destruction and promoting tumorigenicity. CTLA-4 antibodies effectively block the binding of CTLA-4 to ligands on antigen-presenting cells, reducing its inhibitory effect on T cell activation and potentially decreasing the capability of regulatory T cells through inhabiting its interaction with macrophages, thereby enhancing tumor cytotoxicity (5,6). However, the use of ICIs may cause activated T cells to target normal tissues expressing antigens shared with tumor cells, leading to compromised immune tolerance and manifesting as immune-related adverse effects (irAEs) (7), which can affect the skin, digestive tract, liver, endocrine system, lungs and other organs (8). Dermatological adverse events are prevalent and readily identifiable in clinical settings (9).

Emerging evidence suggests that frequent skin adverse events can significantly impair patients' quality of life and erode treatment adherence (10,11). Moreover, patients with lung cancer exhibit a higher incidence of immuno-related pneumonitis compared with patients with other tumor types (12,13), with this condition representing a primary cause of mortality among immunotherapy-treated patients (14). Therefore, vigilant monitoring for dermatological adverse effects and immuno-related pneumonitis is essential in the immunotherapies for lung cancer.

The present report presents a rare NSCLC case complicated by severe dermatitis and grade 4 pneumonitis following immunotherapy, which was successfully managed with a combination of mycophenolate mofetil (MMF) with methylprednisolone, overcoming steroid-dependent dermatitis and

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pneumonitis. The patient had maintained a partial response for >3 years after the cessation of immunotherapy. The study was approved by the Ethics Committee of the Affiliated People's Hospital of Ningbo University (approval no. 2024-N-004; Ningbo, China).

Case report

A 64-year-old man was diagnosed with advanced pulmonary adenocarcinoma with intrapulmonary metastasis (cT4N2M1a, stage IV) at Ningbo Medical Centre Lihuili Hospital (Ningbo, China) in January 2021. The patient then immediately underwent the aforementioned genetic testing and testing the expression of PD-L1. The actionable gene mutations, such as EGFR, anaplastic lymphoma kinase, ROS proto-oncogene 1, receptor tyrosine kinase and MET proto-oncogene, were negative detected by next-generation sequencing. Sample processing and sequencing were performed in a CLIA-certified and CAP-accredited laboratory (Geneseeq Technology Inc.). DNA extraction, library preparation, and targeted capture enrichment were carried out following the methods as previously described with modifications (15). Formalin-Fixed Paraffin-Embedded (FFPE) samples were de-paraffinized with xylene, and genomic DNA was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen GmbH). DNA was quantified by Qubit 3.0 using the dsDNA HS Assay Kit (Thermo Fisher Scientific, Inc.) and the quality was evaluated by a Nanodrop 2000 (Thermo Fisher Scientific, Inc.). Libraries were prepared by KAPA Hyper Prep kit (Kapa Biosystems; Roche Diagnostics), as previously described (16). Briefly, 1–2 µg of genomic DNA was sheared into ~350 bp fragments using a Covaris M220 instrument. End repair, A-tailing, and adaptor ligation of fragmented DNA were performed using the KAPA Hyper DNA Library Prep kit (Roche Diagnostics), followed by size selection with Agencourt AMPure XP beads (Beckman Coulter, Inc.). DNA Libraries were then amplified by PCR and purified using Agencourt AMPure XP beads (Beckman Coulter, Inc.). Customized xGen lockdown probes (Integrated DNA Technologies, Inc.) targeting NSCLC-related genes were used for hybridization enrichment. Human cot-1 DNA (Thermo Fisher Scientific, Inc.) and xGen Universal Blocking Oligos (Integrated DNA Technologies, Inc.) were added as blocking reagents. The capture reaction was performed with Dynabeads M-270 (Thermo Fisher Scientific, Inc.) and the xGen Lockdown Hybridization and Wash kit (Integrated DNA Technologies, Inc.). Captured libraries were subjected to PCR amplification with KAPA HiFi HotStart ReadyMix (Kapa Biosystems; Roche Diagnostics). The purified library was quantified using the KAPA Library Quantification kit (Kapa Biosystems; Roche Diagnostics) and its fragment size distribution was analyzed using a Bioanalyzer 2100. Target enriched libraries were sequenced on the HiSeq4000 platform (Illumina, Inc.) with 2x150 bp pair-end reads. Sequencing data were demultiplexed by bcl2fastq (v2.19; Illumina, Inc.), analyzed by Trimmomatic (<http://www.usadellab.org/cms/index.php?page=trimmomatic>) (17) to remove low-quality (quality<15) or N bases. Then the data were aligned to the hg19 reference human genome with the Burrows-Wheeler Aligner (bwa-mem) (18) and further processed using the Picard suite (available at: <https://broadinstitute.github.io/picard/>)

and the Genome Analysis Toolkit (GATK) (19). SNPs and indels were called by VarScan2 (20) and HaplotypeCaller/UnifiedGenotyper in GATK, with the mutant allele frequency (MAF) cutoff as 0.5%. Common variants were removed using dbSNP and the 1000 Genome project. Germline mutations were filtered out by comparing to patient's whole blood controls. Gene fusions were identified by FACTERA (21) and copy number variations (CNVs) were analyzed with ADTEX (22). The log2 ratio cut-off for copy number gain was defined as 2.0 for tissue samples. A log2 ratio cut-off of 0.6 was used for copy number loss detection. Allele-specific CNVs were analyzed by FACETS (23) with a 0.2 drift cut-off for unstable joint segments.

Additionally, immunohistochemistry (IHC) of the tumor tissue showed negative expression for PD-L1. The methodological details of IHC were as follows: i) Sample Preparation: FFPE sample were collected from patients. Tissue sections with a thickness of 4 µm were cut using a microtome and mounted on positively charged glass slides. Sections were dried overnight at 60°C and then deparaffinized with xylene and rehydrated through a graded alcohol series (100, 95, 80 and 70% ethanol) for 5 min each. ii) Heat-induced epitope retrieval (HIER): Antigen retrieval was performed by placing slides in a cooker pressure and immersing them in EDTA-based retrieval solution (pH 8.0) for 10 min at 120°C. After cooling for 20 min at room temperature, slides were washed twice with phosphate buffered saline (PBS; pH 7.4) for 5 min each. iii) Blocking and antibody incubation: Endogenous peroxidase activity was quenched by incubating slides in 3% hydrogen peroxide in methanol for 30 min at room temperature. Then, slides were washed twice with PBS for 5 min. Non-specific binding was blocked using a protein blocking reagent (Coomassie Brilliant Blue G-250; 0.1% in PBS) for 15 min at room temperature. The primary antibody, anti-PD-L1 clone 22C3 (Thermo Fisher Scientific, Inc.), was diluted at 1:50 in antibody diluent (0.1% bovine serum albumin in PBS). Slides were incubated with the primary antibody overnight at 4°C in a humidified chamber. iv) Secondary antibody and detection: After incubation with the primary antibody, slides were washed three times with PBS for 5 min each. The secondary antibody, a horseradish peroxidase (HRP)-conjugated goat anti-mouse IgG antibody (cat. no. 115-035-003; Jackson ImmunoResearch Laboratories, Inc.) was diluted at 1:200 in antibody diluent. Slides were incubated with the antibody secondary for 30 min at room temperature. Detection was performed using a DAB substrate kit (cat. no. K066; Agilent Technologies) according to the manufacturer's instructions. Slides were developed for 5–10 min until brown precipitates were visible under a light microscope. After development, slides were rinsed with distilled water and counterstained with hematoxylin for 1 min. Slides were then dehydrated through a graded alcohol series (70, 80, 95 and 100% ethanol) for 5 min each and cleared with xylene. v) Scoring and analysis: Stained slides were reviewed and scored by two independent pathologists who were blinded to the clinical information. PD-L1 expression was assessed based on the percentage of tumor cells showing membrane staining and the intensity of staining. Staining intensity was scored as 0 (no staining), 1 (weak), 2 (moderate), and 3 (strong). A combined positive score (CPS) was calculated as follows: CPS=(number of PD-L1 positive tumor cells/total number

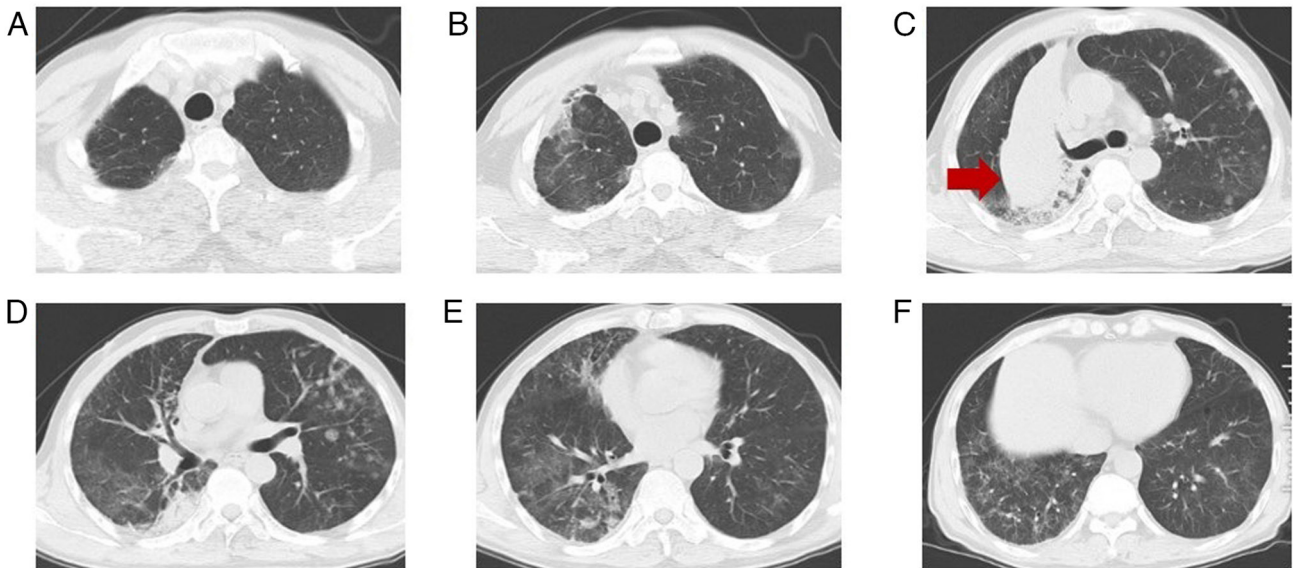


Figure 1. Chest CT conducted in April 2021. (A) Patchy shadows in the right upper lung. (B) Multiple patchy shadows in both upper lungs, predominantly involving the right upper lobe. (C) An irregular soft tissue mass in the right hilum of the lung. The red arrow in the image indicates the tumor. (D) Multiple patchy shadows with unclear boundaries and uneven density in the lingular segment. (E) Multiple patchy shadows and grid-shaped high-density shadows in the right lower lobe and right middle lobe. (F) Multiple patchy shadows scattered in both lower lobes.

of tumor cells) $\times 100$. A CPS ≥ 1 was considered positive for PD-L1 expression.

Subsequently, 7 days later, the patient was treated with a pemetrexed and carboplatin chemotherapy regimen [pemetrexed 800 mg on day (d)1 and d8, and carboplatin 500 mg (area under curve=5) on d1, with a 21-d cycle], combined with pembrolizumab 200 mg on d1, also with a 21-d cycle. On the 15th day following the initiation of treatment, the patient experienced myelosuppression, which delayed the subsequent chemotherapy. Chemotherapy was terminated after this point due to the patient subsequently experiencing a series of immune-related adverse events, such as fever, immune-related cystitis, immune-related pneumonitis and severe cutaneous irAEs. However, on the 26th day, the patient developed a fever with a peak temperature of 38.4°C and exhibited typical urinary irritation symptoms such as dysuria, urgency and frequency accompanied by intense bladder pain. The patient was successively administered a levofloxacin injection (0.5 g/day) and a piperacillin tazobactam injection (4.5 g/8 h) for anti-infection treatment, but the symptoms did not improve. Multiple urine routine tests indicated an increase in red and white blood cell counts, with the highest red blood cell count being $1,279/\mu\text{l}$ and the highest white blood cell count being $3,620/\mu\text{l}$, while the normal ranges are $<17/\mu\text{l}$ and $11/\mu\text{l}$, respectively. The urine cultures were negative for bacterial growth. Computed tomography urography revealed no apparent signs of infection or tumor metastasis. The patient was unwilling to undergo an invasive procedure, therefore a cystoscopy was not performed.

Due to the absence of clear evidence of infection and tumor metastasis, a diagnosis of immune-related cystitis was likely. Starting from February 2021, the patient was administered methylprednisolone injection at a dose of 40 mg/d. After 5 days, a routine urine examination showed that the red and white blood cell counts had turned negative under a high-power field, and the patient's urinary tract irritation symptoms were

markedly improved. According to standard medical protocols, high-dose medications are administered intravenously, while low-dose ones are given orally. Therefore, the oral dose of methylprednisolone was sequentially decreased to 28 mg/d. The dose was gradually reduced 8 mg per week and the total duration of administration was ~ 5 weeks.

In April 2021, the patient experienced a recurrence of fever, accompanied by coughing, dyspnea and hypoxia. The patient was then admitted to the Affiliated People's Hospital of Ningbo University (Ningbo, China). A chest CT scan (Fig. 1) showed multiple patchy and grid-shaped high-density shadows with unclear borders and uneven bilateral density in the lungs. Arterial blood gas analysis (without oxygen inhalation) yielded the following results: pH 7.46 (normal range, 7.35-7.45), partial pressure of carbon dioxide (PCO_2) 30 mmHg (normal range, 35-45 mmHg), partial pressure of oxygen (PO_2) 56 mmHg (normal range, 80-100 mmHg) and oxygenation index 266. The non-invasive blood oxygen saturation was 90%. A blood routine test showed white blood cells of $8.91 \times 10^9/\text{l}$ (normal range, $3.5\text{--}9.5 \times 10^9/\text{l}$), red blood cells of $4.97 \times 10^{12}/\text{l}$ (normal range, $3.8\text{--}5.1 \times 10^{12}/\text{l}$), hemoglobin of 122 g/l (normal range, 115-150 g/l), platelets of $213 \times 10^9/\text{l}$ (normal range, $125\text{--}350 \times 10^9/\text{l}$), neutrophil count of $5.14 \times 10^9/\text{l}$ (normal range, $1.8\text{--}6.3 \times 10^9/\text{l}$), C-reactive protein (CRP) of 28.0 mg/l (normal range, <10 mg/l) and procalcitonin of 0.24 ng/ml (normal range, 0.00-0.05 ng/ml). Based on the medication history of the patient and the fact that blood routine and CRP were not elevated at the onset of fever, it was deemed probable that the patient was suffering from immune-related pneumonitis.

Upon admission, the patient was administered an 80 mg methylprednisolone injection, supplemented by oxygen inhalation, alongside other symptomatic and supportive measures including fever reduction, fluid replacement and nutritional support. Concurrently, a comprehensive suite of diagnostic tests was initiated to exclude alternative diagnoses. These included

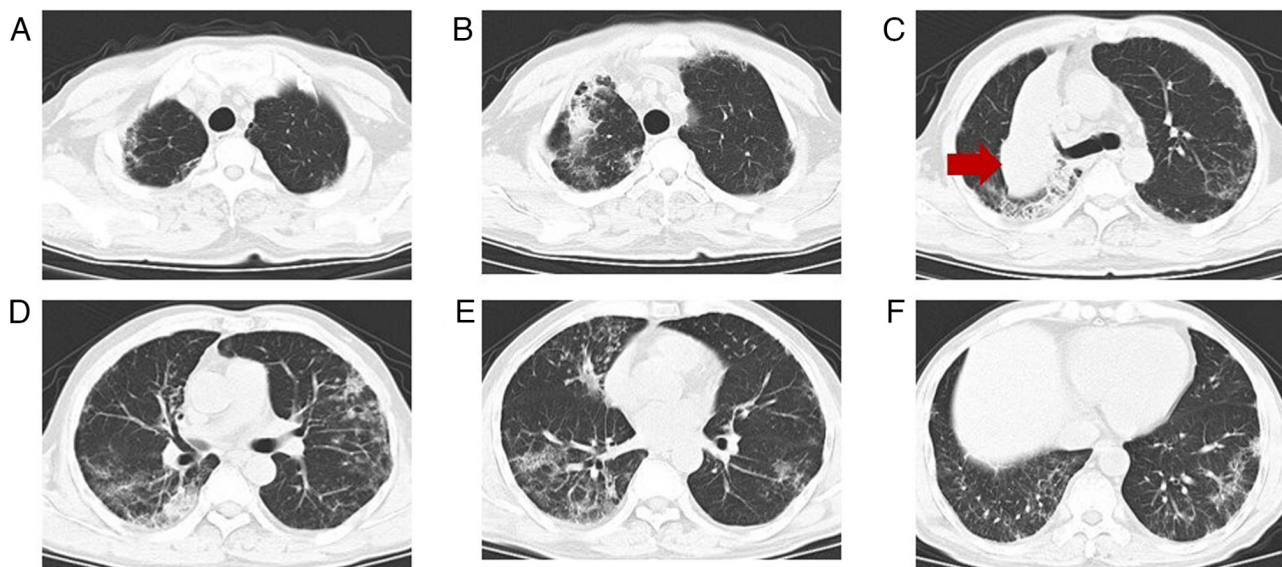


Figure 2. Follow-up CT scan at 14 days. (A) Patchy shadows in the right upper lung. (B) Multiple patchy shadows and grid-shaped high-density shadows with unclear boundaries and uneven density in both upper lungs, predominantly involving the right upper lobe. (C) A mass in the right hilum. The red arrow in the image indicates the tumor. (D) Multiple patchy shadows and grid-shaped high-density shadows in the lingular segment and the right lower lobe. (E) Multiple patchy shadows and grid-shaped high-density shadows in the right lower lobe. (F) Multiple patchy shadows scattered in both lower lobes. All shadows were more extensive than previously observed.

multiple sputum cultures, 1-3- β -D glucan test, galactomannan assays, assessment of brain natriuretic peptide, coagulation function, D-dimer and respiratory pathogen nucleic acid detection for a range of pathogens including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, coxsackie virus, coronavirus, echovirus, influenza A and B viruses, respiratory syncytial virus, adenovirus and parainfluenza virus. Additionally, electrocardiogram and echocardiography were performed to rule out pulmonary fungal infection, tumor progression, pulmonary embolism, cardiac events and pleural carcinomatosis.

On the second day of treatment, the patient's temperature normalized and there was an improvement in cough, dyspnea and hypoxia, with non-invasive blood oxygen saturation increasing to 96%. This indicated that the initial treatment was effective, prompting the continuation of the prescribed therapies for 2 weeks. However, in the following week, the patient experienced persistent low-grade fever, dyspnea and hypoxia, which necessitated a follow-up chest CT scan. The scan, conducted 14 days after admission (Fig. 2), indicated the progression of the lesion compared with earlier imaging.

The patient was classified as G3 according to the grading of immune-related pneumonitis in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (24). Moreover, in line with the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for the management of toxicities from immunotherapy (25), which provides recommendations for diagnosis, treatment and follow-up, patients graded G3 or G4 are advised to discontinue the immunotherapy permanently and be administered with methylprednisolone at a dosage of 1-2 mg/kg/d. The guidelines suggest initiating tapering corticosteroids after improvement to grade <1, over 4-6 weeks for grade 2 and over 6-8 weeks for grade 3. Therefore, the dosage of methylprednisolone injection was adjusted to 240 mg (equivalent to 4 mg/kg/d) daily. The

patient's temperature normalized, and symptoms of dyspnea and hypoxia improved within the following 72 h. Subsequently, the dosage of methylprednisolone injection was reduced to 160 mg daily, then gradually decreased to 80 mg daily over 2 weeks. Concurrently, compound sulfamethoxazole tablets (SMZ) at 1.2 g twice per week were administered to prevent *Pneumocystis jirovecii* pneumonia, omeprazole 40 mg daily was used to prevent stress ulcers and vitamin D 60 IU daily and calcium 300 mg daily were used to prevent osteoporosis, along with symptomatic and supportive treatments including fever reduction, fluid replacement and nutritional support. At ~1 month after admission, the administration of methylprednisolone was changed to oral due to the patient's intention to be discharged and the oral dose of methylprednisolone was to 56 mg daily for 2 weeks. In May 2021, a follow-up chest CT (Fig. 3) indicated focal absorption. After a brief observation period, the patient's symptoms did not recur, leading to their discharge from the hospital.

In June 2021, when the oral methylprednisolone dosage was reduced to 44 mg daily within 1 week, the patient experienced a relapse characterized by fever, dyspnea, cough, tachypnea and cyanosis of the lips, hands and feet. Severe cutaneous symptoms also emerged, including canker sores and perianal ulcers (Fig. 4). A chest CT (Fig. 5) revealed significant lesion progression compared with the scan taken in May 2021. Arterial blood gas analysis (performed without oxygen inhalation) indicated a pH of 7.43, a PCO_2 of 34 mmHg, a PO_2 of 36 mmHg, a blood oxygen saturation of 72% and an oxygenation index of 171. Non-invasive oxygen saturation was measured at 78%. The patient was diagnosed with immune-related pneumonitis and respiratory failure and was classified as grade 4 (G4) according to the CTCAE version 5.0 (24).

Upon readmission to the Affiliated People's Hospital of Ningbo University (Ningbo, China), the patient received a 240 mg methylprednisolone injection (4 mg/kg/d) and

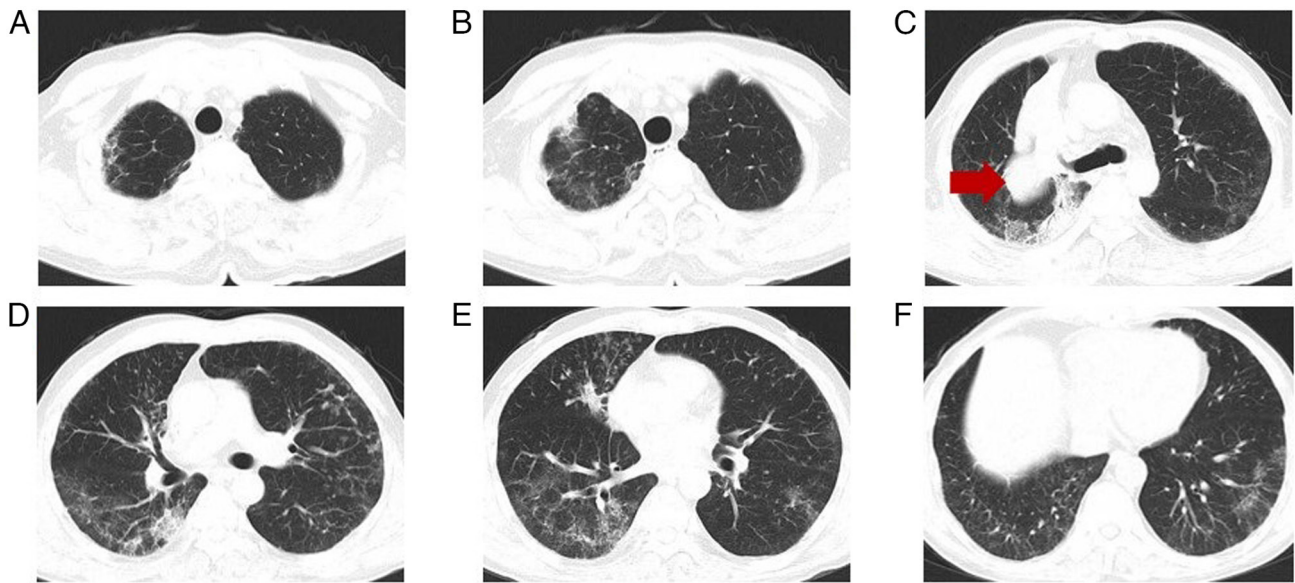


Figure 3. Chest CT conducted in May 2021. (A) Compared with Fig. 1, patchy shadows in the right upper lung demonstrated partial absorption. (B) Multiple patchy shadows in both upper lungs demonstrated partial absorption. (C) An irregular soft tissue mass in the right hilum of the lung. The red arrow in the image indicates the tumor. (D) Multiple patchy shadows in the lingular segment demonstrated partial absorption, leaving behind some fibrous cord shadows. (E) Multiple patchy shadows and grid-shaped high-density shadows in the right lower lobe and right middle lobe demonstrated partial absorption, leaving behind some fibrous cord shadows. (F) Multiple patchy shadows in the right lower lobe were almost completely absorbed compared to Fig. 1.

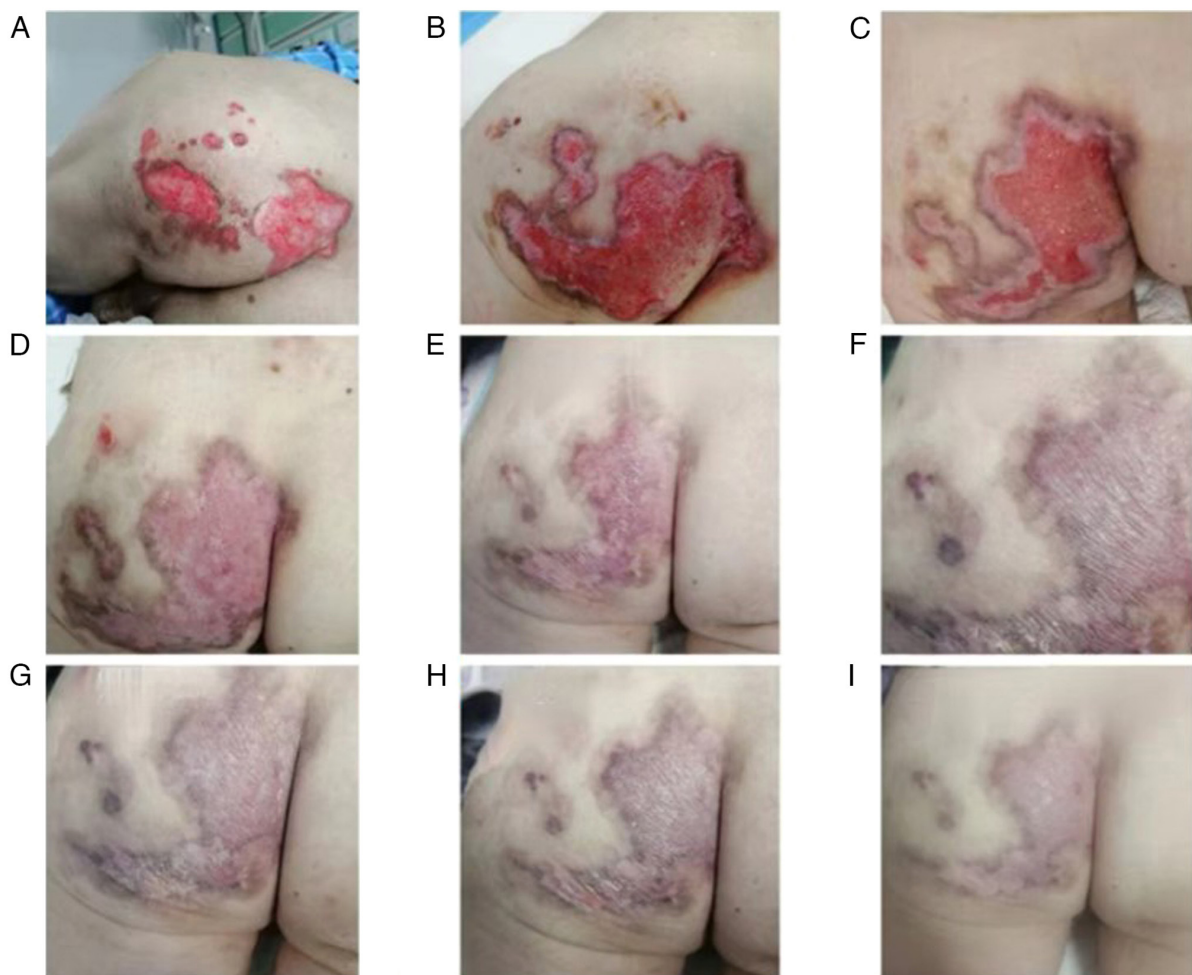


Figure 4. Severe perianal ulcers of the patient, which progressively healed with appropriate treatment. (A) June 2021, (B) September 2021, (C) October 2021, (D) November 2021, (E) December 2021, (F) February 2022, (G) March 2022, (H) March 2022 and (I) May 2022. (A and B) Initial expansion of the ulcerative lesions. (C) Formation of granulation tissue around the ulcers, indicating a reduction in their size. (D-I) Gradual healing process of the perianal ulcers over time.

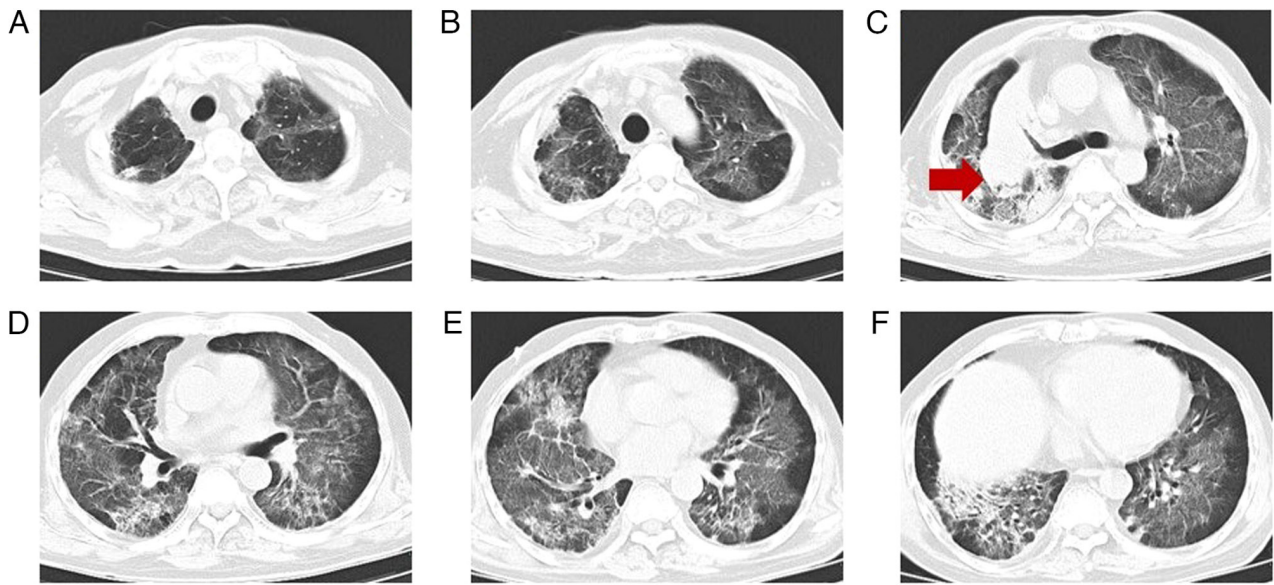


Figure 5. Chest CT conducted in June 2021. (A) Hazy shadows in both upper lungs. (B) Diffuse ground glass and hazy shadows in both upper lungs. (C) Reduction in the size of the mass indicated by the red arrow. Diffuse ground glass in the left upper lobe. (D) Diffuse ground glass and hazy shadows in both lower lungs. (E) Diffuse ground glass and hazy shadows in both lower lungs. (F) Pulmonary interstitial fibrosis in the right lower lobe.

was treated with intravenous immunoglobulin 20 g/d for 5 days. Supporting therapy was also provided through non-invasive ventilator-assisted ventilation (oxygen concentration, 50%), which improved the non-invasive oxygen saturation to 94%. The symptoms of tachypnea and cyanosis were alleviated. Considering the patient's history of tumor treatment and prolonged glucocorticoid use, co-infections, particularly fungal infections, were a concern. Consequently, Piperacillin-tazobactam (4.5 g daily for 2 weeks) and Caspofungin (50 mg daily for 1 week, 1st day 70 mg) were administered. Various tests were conducted to exclude pulmonary embolism, cardiac events and fungal infections. Due to the patient's condition, bronchoscopy was not performed, precluding the submission of bronchoalveolar lavage fluid for culture and next-generation sequencing. However, multiple sputum cultures, 1-3- β -D glucan tests, galactomannan tests, cryptococcus capsular antigen tests and respiratory pathogen nucleic acid detections were all negative for bacterial, fungal or respiratory viral infections.

A dermatologist was consulted for specialized advice to address the severe cutaneous symptoms. Due to the concurrent presence of canker sores and perianal ulcers, the dermatologist did not rule out Behçet's syndrome and recommended an ophthalmic examination and skin biopsy. However, the patient did not exhibit eye symptoms, such as uveitis, dry eyes, floater signs or vision distortion. Further examination showed that the patient was negative for antinuclear, anti-myeloperoxidase, anti-protease 3 and anti-glomerular basement membrane antibodies. Notably, the reaction to the pathergy test, which is currently the only particular diagnostic procedure for Behçet's syndrome, was also negative. A skin biopsy of the perianal ulcer (Fig. 6) revealed the absence of skin epidermis, surface ulcers and dermal vascular hyperplasia, as well as minimal neutrophil infiltration. The biopsy sample was fixed in 10% neutral buffered formalin for ≥ 24 h at room temperature before being embedded in paraffin and sectioned into 3 μ m

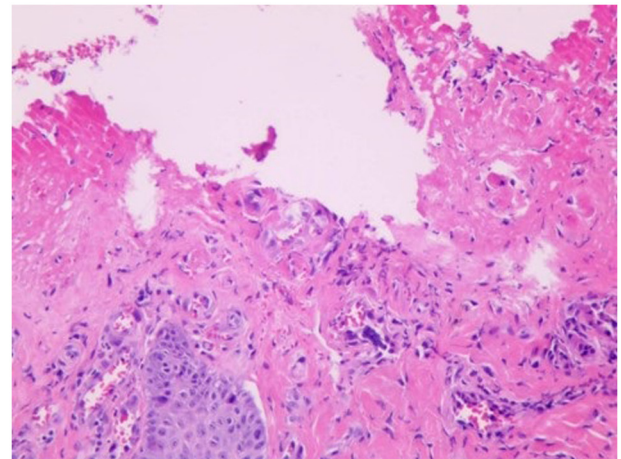


Figure 6. Skin biopsy of the perianal ulcer showing the absence of skin epidermis, surface ulcers and dermal vascular hyperplasia, and a small amount of neutrophil infiltration. Magnification, x50.

thick slices. Hematoxylin staining was performed for 5-15 min at room temperature followed by counterstaining with eosin for 1-3 min at room temperature. A light microscope (magnification, x50) was used to image the samples.

These findings deviate from the typical pathological features of Behçet's syndrome, leading to the conclusion that the canker sores and perianal ulcers were severe cutaneous irAEs. In response, the patient was treated with thalidomide tablets (50 mg once daily) and topical treatments, including methylprednisolone, human epidermal growth factor (5,000 IU daily) and silver ion antibacterial gel, applied to the perianal ulcer for 8 months.

In the following days, the patient's respiratory symptoms, non-invasive oxygen saturation, oxygenation index and cutaneous symptoms gradually improved. As the symptoms subsided, the dosage of methylprednisolone was gradually

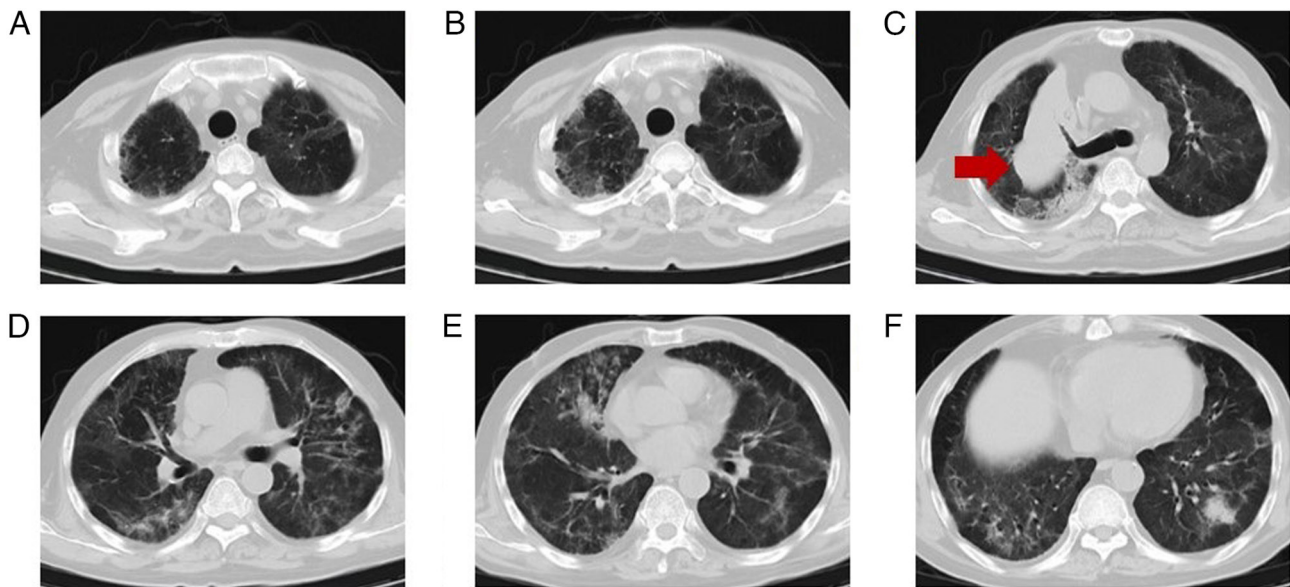


Figure 7. Chest CT conducted in July 2021. (A) Focal ground-glass shadows in the right upper lung. (B) Multiple ground-glass shadows in the bilateral upper lungs. (C) The mass as the red arrow indicated was further reduced in size. (D) Multiple ground-glass shadows in the bilateral lower lungs. (E) Multiple ground-glass shadows in the bilateral lower lungs. (F) No pulmonary interstitial fibrosis is shown. All shadow lesions were improved compared with those in June 2021.

decreased as follows: 240 mg for 1 week, 160 mg for 1 week, 120 mg for 1 week, 80 mg for 1 week, 60 mg for 1 week and 40 mg for 1 week. However, due to the patient's previous recurrence of pneumonitis during glucocorticoid tapering, it was concluded that the disease was corticosteroid-dependent. Therefore, the immunosuppressive drug MMF (1 g twice daily) was introduced during glucocorticoid reduction. Subsequently, 1 month later, the patient's canker sores had healed. Then, 6 weeks later, the patient was free from cough, phlegm, dyspnea and cyanosis of the lips, hands and feet. The non-invasive oxygen saturation was >90% without oxygen inhalation. An arterial blood gas analysis (with an oxygen concentration of 29%) revealed a pH of 7.49, PCO_2 of 35 mmHg, PO_2 of 75 mmHg, blood oxygen saturation of 94% and an oxygenation index of 258. A review of the chest CT (Fig. 7) showed reduced interstitial changes in the bilateral pulmonary fields compared with the previous scan. The perianal ulcer did not progress further. Based on these improvements, the patient was discharged from the hospital in July 2021 with instructions to take methylprednisolone tablets at 32 mg once daily and maintain the original MMF dosage. In the next months, the dosage of methylprednisolone was gradually reduced to 12 mg daily. Throughout methylprednisolone reduction, the perianal ulcer gradually healed (Fig. 4), and the respiratory symptoms did not recur.

Over the subsequent year, the methylprednisolone tapering was conducted cautiously, with an average reduction of 4 mg every 3 to 4 months. By October 2022, the methylprednisolone dosage was reduced to 4 mg once daily, and the MMF was decreased to 250 mg twice daily. In December 2022, a chest CT scan revealed multiple bilateral pulmonary interstitial lesions. The patient discontinued methylprednisolone on their own initiative, but within a few days, they experienced moderate polyarthralgia and myalgia, which impaired their ability to perform instrumental activities of daily living. Consequently,

the patient was referred to a rheumatologist. A series of assessments were conducted, including measurements of erythrocyte sedimentation rate, CRP, rheumatoid factor, anti-cyclic citrullinated peptide and antinuclear antibodies to rule out myositis. However, X-rays and ultrasound of the affected joints were not performed.

Due to the medical and medication history of the patient, they were diagnosed with immune-related inflammatory arthritis. The patient was advised to resume methylprednisolone at 4 mg once daily and MMF 250 mg twice daily. Additional medications prescribed included SMZ to prevent *P. jirovecii* pneumonia, omeprazole 40 mg daily to prevent stress ulcers and vitamin D 60 IU daily and calcium supplements 300 mg daily to prevent osteoporosis. The patient continued the aforementioned treatments to September 2024.

Given the patient's notable improvement in irAEs following effective treatments, anlotinib 12 mg daily for 2 weeks followed by 1 week off treatment, was initiated as the second-line treatment in June 2022. The patient maintained a partial remission, as the tumor was >30% smaller compared with the initial tumor size, for >3 years after discontinuing immunotherapy in January 2021. The patient returned to the hospital for follow-up visits every 2-3 months and the last follow-up of the patient was conducted in July 2024. In September 2024, the patient succumbed to severe co-infection (with COVID-19 and bacterial sepsis).

Discussion

With the rapid development and cross-development of oncology, immunology and other related disciplines, immunotherapy has made rapid progress and has become an important antitumor method after surgery, radiotherapy and chemotherapy. Particularly, ICIs have achieved breakthrough progress in tumor immunotherapy. However, with the

widespread application of PD-1/PD-L1, an increasing number of adverse effects caused by ICIs have raised concerns (26).

PD-1/PD-L1 inhibitors function by blocking the negative regulatory signals of T cells, alleviating immunosuppression and enhancing the antitumor activity of T cells (4). Simultaneously, these inhibitors may abnormally amplify the body's autoimmune responses, leading to an imbalance in immune tolerance (8). When these inhibitors accumulate in non-cancerous tissues, they can induce an autoimmune-like inflammatory response, termed irAEs. irAEs can affect multiple organs, including the skin, digestive tract, liver, endocrine system and lungs (4,8). In the present case, there were concurrent occurrences of immune-related cystitis, cutaneous lesions and pneumonitis, which is a rare phenomenon and sparsely documented in the literature. A recent retrospective study identified co-occurring irAEs, classifying them into seven distinct clusters: Endocrine, cutaneous, respiratory, gastrointestinal, hepatic, musculoskeletal and neurological (27). Notably, in the present case, the patient exhibited irAEs that spanned the cutaneous, respiratory and urinary systems, showing the complex and multifaceted nature of the immune response triggered by PD-1/PD-L1 blockade.

Currently, no specific grading standards exist for irAEs. The grading of irAEs still follows the CTCAE version 5.0 (24). The ESMO (25) and the National Comprehensive Cancer Network (28) have published guidelines for irAEs based on expert consensus. These guidelines provide general treatment options for the most common irAEs and detail the use of immunosuppressive drugs and the course of treatment according to the severity of irAEs. The treatment principles vary for different grades of toxic reactions. For grade 1, it is recommended to closely observe and intervene on time to avoid further changes in toxicity. For grade 2, if necessary, withhold ICI therapy and glucocorticoids (prednisone 0.5 to 1 mg/kg/d or equivalent per day) and resume ICI therapy upon improvement. For grades 3 and 4, a high dose of glucocorticoids should be given (prednisone 1 to 2 mg/kg/d or equivalent). When symptoms subside to grade 1 or below, glucocorticoids should gradually decrease. Whether to resume ICI therapy for grade 3 toxicity requires a complete evaluation of the patient's tumor status and a careful weighing of the risks and benefits before resuming ICI therapy. For grade 4 toxicity, except for endocrine disease controlled by hormone replacement therapy, ICIs should be permanently discontinued. For corticosteroid-dependent or refractory or ineffective cases, other immunosuppressive drugs can be considered, including tumor necrosis factor- α inhibitors (infliximab), conventional synthetic disease-modifying antirheumatic drugs (such as MMF) and anti-interleukin 6 receptor therapies (such as tocilizumab or sarilumab).

In the present study, MMF was crucial in the steroid tapering process. MMF functions by inhibiting the proliferation of T and B lymphocytes, thus modulating the immune responses that lead to irAEs. The use of MMF during glucocorticoid tapering is not traditionally regarded as a standard treatment approach (29). However, a previous report has demonstrated that MMF can consistently reduce the cumulative dose of glucocorticosteroids in patients with IgA nephropathy (30). MMF is increasingly recognized as an important option in managing severe irAEs. Recent research supports the use

of MMF in the treatment of corticosteroid-resistant irAEs in patients with cancer, particularly as a first-line treatment for severe hepatitis (31). Additionally, MMF is a widely used immunosuppressive drug for several conditions, including dermatomyositis and IgA-associated nephropathy (32). MMF is generally well-tolerated but can cause gastrointestinal issues such as diarrhea and nausea in ~30% of patients; it has a lower rate of hepato-nephrotoxicity compared with other immunosuppressants, such as calcineurin inhibitors and azathioprine (33), which is an important advantage (34). However, MMF is classified as a reproductive toxin and is suspected of causing genetic defects, so it should be used with caution in pregnant patients (35).

The patient in the present study initially exhibited typical symptoms of urinary irritation. After ruling out infection and tumor metastasis, the development of cystitis was associated with the duration of ICI use and could not be attributed to the adverse reactions of chemotherapy drugs or the progression of the patient's disease. Consequently, the patient was diagnosed with immune-related cystitis. Immune-related cystitis is a rare condition, with limited published cases and no detailed information in the relevant management guidelines, such as the ESMO (25) and the National Comprehensive Cancer Network (28) guidelines. Additionally, to the best of our knowledge, there are no clear, quantifiable indicators to assess the severity of this condition. In the present case, the symptoms improved after discontinuing ICIs and glucocorticoid treatment. It can be confirmed that glucocorticoids are effective for immune-related cystitis, but there is no consensus on the specific dosage yet. Therefore, clinicians must pay attention to immune-related cystitis. The experience in diagnosing and treating cystitis is valuable for discussion and reference.

Cutaneous irAEs are the most common adverse events related to immune ICI therapy, affecting >50% of all patients in all grades. Although the precise pathogenesis remains unclear, the reported mechanisms underlying these cutaneous irAEs involve the non-specific activation of the immune system by ICIs, leading to autoimmune-like or inflammatory conditions (36). T cell-mediated immunopathology is central to these reactions, with varying effector cells and cytokines depending on the clinical phenotype (37). Cutaneous irAEs manifest in the skin, mucous membrane and skin appendages such as fingernails, toenails and hair. They often present with rashes, pruritus and maculopapular eruptions; some are similar to common skin diseases, such as vitiligo, psoriasis, lichen planus and hemangioma. Although severe cases are rare and generally do not interfere with the continuation of treatment, it is important to monitor and manage these symptoms (9,38). According to the CTCAE version 5.0, the present patient experienced a severe perianal ulcer, classified as grade 3 or grade 4. The diversity of immune-related skin illnesses necessitates their distinction from other typical skin diseases. Therefore, consultation with a dermatologist for specialist advice and treatment planning is essential. Mild cases of skin irAEs can affect patients' quality of life, increase economic burden and reduce compliance with formal immunotherapy. These adverse events can threaten the safety of the patients' life in severe cases.

Immune-related pneumonitis is a relatively rare but potentially life-threatening adverse effect of ICI therapies (13). The pathophysiology of immune-related pneumonitis is not fully

understood; however, it is considered to involve increased T cell activity, autoantibody production, inflammatory cytokine levels and complement-mediated inflammation (39). A previous study reported an increased presence of lymphocytes in the bronchoalveolar lavage fluid of patients with immune-related pneumonitis, suggesting a role for T lymphocytes and macrophages in its pathogenesis (39). The incidence of any-grade immune-related pneumonitis in clinical studies is ~4% for anti-PD-1 therapies, with high-grade pneumonitis occurring at a rate of ~1% (40).

Diagnosing immune-related pneumonitis primarily relies on clinical symptoms, laboratory findings and imaging. When immune-related pneumonitis is suspected, a chest CT scan is essential. The most common imaging findings include patterns similar to organizing pneumonia, with multiple bilateral pulmonary lesions, such as ground-glass opacities and interstitial lung involvement (41). In the present case, the chest CT lesions initially showed ground-glass opacities and interstitial involvement, and >1 year later, lung consolidation was observed. In this case, the characteristics of immune-related pneumonitis include an early acute onset after the application of ICIs and a relatively severe degree. After the exclusionary examination, the condition of the patient improved with sufficient glucocorticoid treatment. However, during the process of glucocorticoid reduction, the symptoms recurred and were aggravated, requiring non-invasive ventilator-assisted ventilation. Considering the rapid reduction of glucocorticoids and corticosteroid dependence, the use of MMF was added, leading to a rapid reversal of the disease and achieving good prognosis.

In conclusion, the patient experienced multiple organ adverse effects, which were effectively alleviated with proper treatment, leading to a favorable prognosis. After discontinuing immunotherapy, the patient has maintained a partial response for >3 years.

IrAEs can affect various organs and exhibit notable variability in their onset times. Due to the complexity and diversity of irAEs, clinicians are increasingly encountering both common and rare types. The characteristics of different diseases and the treatment trajectories of various cancers can complicate the outcomes of current retrospective studies. It is crucial to enhance interdisciplinary cooperation to improve the identification and management of irAEs. This approach is particularly important for continuously optimizing the handling of rare adverse effects such as immune-related cystitis and severe skin-related adverse events. Recent research has deepened the understanding of the relationship between irAEs and the efficacy of immunotherapy. A previous study found that the occurrence and progression of irAEs are associated with improved immunotherapy responses (42). Patients who develop irAEs generally show improved treatment responses compared with those who do not experience such adverse events (43).

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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

YW and XC designed the study. YW was the principal person responsible for the study and wrote the original manuscript. ZF performed analysis and interpretation of CT imaging data. YW, HW and WY performed a critical literature review and contributed to the acquisition, analysis and interpretation of data. ZF and WY 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 study was conducted according to the ethical standards of The Declaration of Helsinki and its later amendments. Local ethical approval was obtained from the Ethics Committee of the Affiliated People's Hospital of Ningbo University (approval no. 2024-N-004; approval date, March 2024; Ningbo, China).

Patient consent for publication

Written informed consent was obtained from the patient for the case information and images to be published in this case report.

Competing interests

The authors declare that they have no competing interests.

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