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CASE REPORT

Pneumocystis pneumonia in stage IIIA lung adenocarcinoma with immune-related acute kidney injury and thoracic radiotherapy: A case report

Ya-Wen Zheng, Jia-Chao Pan, Jin-Feng Wang, Jian Zhang

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Abstract

BACKGROUND

Immune checkpoint inhibitors (ICIs) are therapeutic agents for advanced and metastatic non-small cell lung cancer (NSCLC) with high clinical antitumor efficacy. However, immune-related adverse events occur in 20% of these patients and often requiring treatment with immunosuppressive agents, such as corticosteroids. Consequently, this may increase the risk of patients to opportunistic infections. *Pneumocystis jirovecii* pneumonia (PJP), a rare but serious opportunistic infection typically observed in patients with human immunodeficiency virus, can also occur in cancer patients undergoing long-term glucocorticoid treatment.

CASE SUMMARY

We report a case of a 56-year-old male with squamous NSCLC treated with triplimab combined with paclitaxel, carboplatin, and radical thoracic radiation therapy. Following this regimen, he developed acute kidney injury (AKI) with elevated creatinine levels. After concurrent radical chemoradiotherapy ended, he developed a grade 3 immune-related AKI. High-dose corticosteroids were administered to treat AKI, and renal function gradually recovered. Corticosteroids were reduced to a dose of 10 mg prednisone equivalent daily eight weeks later; however, he developed severe pneumonia with spontaneous pneumothorax. Next-generation sequencing of the bronchoscopic lavage revealed PJP co-infection with herpes simplex virus 1 and cytomegalovirus. The inflammation was more

severe in areas exposed to radiation. Piperacillin-tazobactam, acyclovir, sulfamethoxazole, and trimethoprim were used to control the infection. The patient recovered, and immunotherapy was terminated.

CONCLUSION
PJP is rare but can occur in patients with ICI adverse events and should be differentiated from tumor progression or immune-related adverse events. Thoracic radiation may increase risk, necessitating careful monitoring and prevention.

Key Words: *Pneumocystis* pneumonia; Immunerelated adverse events; Immunotherapy; Thoracic radiotherapy; Acute kidney injury; Case report

Core Tip: A patient with squamous lung cancer was treated with triplimab combined with paclitaxel, carboplatin, and radical thoracic radiation therapy. Despite the good therapeutic effect, he developed a grade 3 immune-related acute kidney injury, prompting high-dose corticosteroids treatment. Eight weeks later, the patient developed severe pneumonia with spontaneous pneumothorax, and was diagnosed with *Pneumocystis jirovecii* pneumonia (PJP) co-infection with the herpes simplex virus 1 and cytomegalovirus. PJP is rare but might occur in patients with immune checkpoint inhibitor adverse events, highlighting the need to be differentiated from tumor progression or immune-related adverse events.

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INTRODUCTION

Immunotherapy-related adverse reactions have increased owing to the widespread use of immunotherapies. Glucocorticoid therapy is an effective method for inhibiting overactivated immune responses[1]. Long-term glucocorticoid therapy renders the patient immunocompromised, and more patients with cancer are at risk of opportunistic infections[2]. *Pneumocystis jirovecii* (*P. jirovecii*) pneumonia (PJP) is an opportunistic infection caused by *P. jirovecii*. PJP is prevalent among patients with human immunodeficiency virus (HIV) infection but rarely in patients with cancer. Patients presenting with PJP may exhibit fever, cough, dyspnea, and respiratory failure in severe cases.

Here, we report a rare case of PJP with spontaneous pneumothorax in a 56-year-old male patient with advanced non-small cell lung cancer (NSCLC) who received eight weeks of glucocorticoid therapy to treat an immune-related acute kidney injury (AKI). Owing to prompt diagnosis and use of sulfamethoxazole, trimethoprim, and other antipathogenic drugs, the patient recovered fully.

CASE PRESENTATION

Chief complaints

The patient diagnosed with squamous lung cancer 4 months ago presented with sudden dyspnea for the past 3 days.

History of present illness

A 56-year-old man who was a former smoker with an Eastern Cooperative Oncology Group performance status of 0 was diagnosed with stage IIIA NSCLC (cTabN2M0, squamous lung cancer, PD-L1 10%; Figure 1A). After multidisciplinary discussion, including consideration of the patient's will, triplimab (a PD-1 inhibitor) combined with radical chemoradiotherapy was chosen as the treatment regimen. After one cycle of induction treatment, the patient received triplimab and concurrent chemoradiotherapy from May 15, 2023, to June 23, 2023. After completing thoracic radiation therapy, AKI was observed on June 24, 2023. The level of creatinine suddenly increased to 226 μmol/L, increasing further to 358 μmol/L two days later. Computed tomography (CT) revealed that the volume of the bilateral kidney increased by approximately 20% without hydronephrosis (Figure 1B), and the patient refused a renal biopsy. The patient subsequently received methylprednisolone (60 mg) twice per day and antibiotics for bacterial infection prevention. The creatinine level decreased gradually, and methylprednisolone was slowly tapered in tandem (Figure 1C). On July 20, 2023, chest imaging revealed a partial response without radiation pneumonia. The timeline of treatment is showed in Figure 1D.

In August 2023, the patient was administered prednisone (10 mg) once daily (equivalent to 8 mg of methylprednisolone). On August 24, 2023, he suddenly developed fever and dyspnea, which worsened over three days, and the patient was urgently admitted to the hospital.

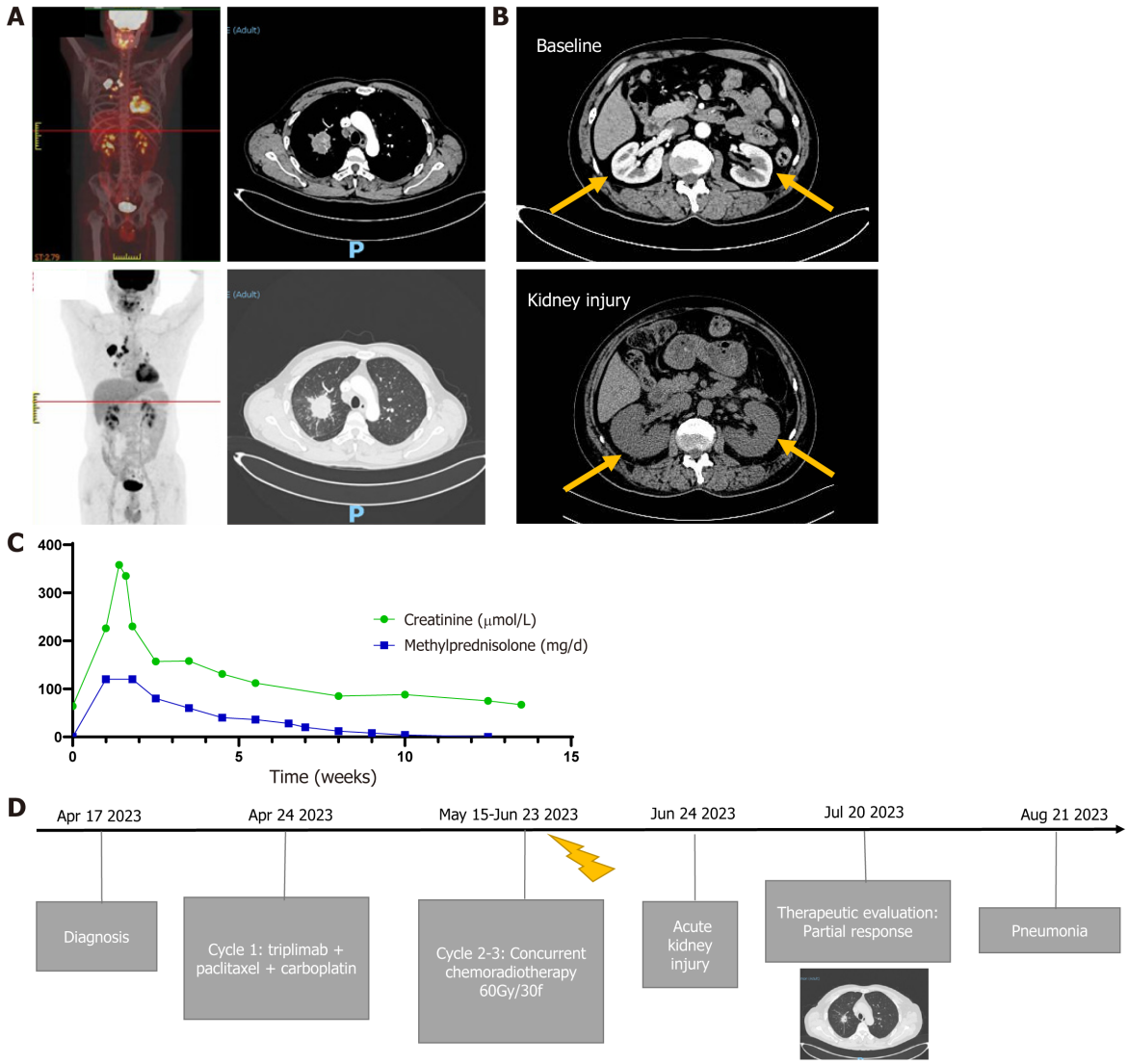

Figure 1 Time line of treatment. A: Positron emission tomography image at diagnosis; B: Images of acute kidney injury; C: Changes in creatinine and methylprednisolone levels; D: Treatment timeline.

History of past illness
The patient had no significant medical history.

Personal and family history
No family history of any malignant disease was reported.

Physical examination
Upon admission, his vital signs were unstable: Blood pressure, 138/89 mmHg; body temperature, 38.2 °C; heart rate, 115 beats/minute; and breathing rate, 24 breaths/minute. The oxygen saturation during oxygen inhalation was 95%. Breath sounds over the right lung were diminished, and moist rales were heard on the left lung.

Laboratory examinations
Blood test results were as follows: White blood cell count: 5.06 × 10^9/L; lymphocyte count: 0.65 × 10^9/L; C-reactive protein: 52.58 mg/L; and procalcitonin level: 0.077 ng/mL. The tests for pathogens (traditional laboratory test results) were negative. Serological test results for Aspergillus were normal.

Imaging examinations
CT showed diffuse lesions in both lungs and right pneumothorax (Figure 2A). After closed drainage of the right thoracic cavity, diffuse lesions in the right lung became more severe. Bronchoscopy with bronchoalveolar lavage was performed since no neoplasm was observed, and transbronchial biopsy deemed unnecessary. Bronchoscopy revealed numerous yellowish-white secretions in the bronchus, bronchial mucosal hyperemia, erosion, and bleeding (Figure 2B).

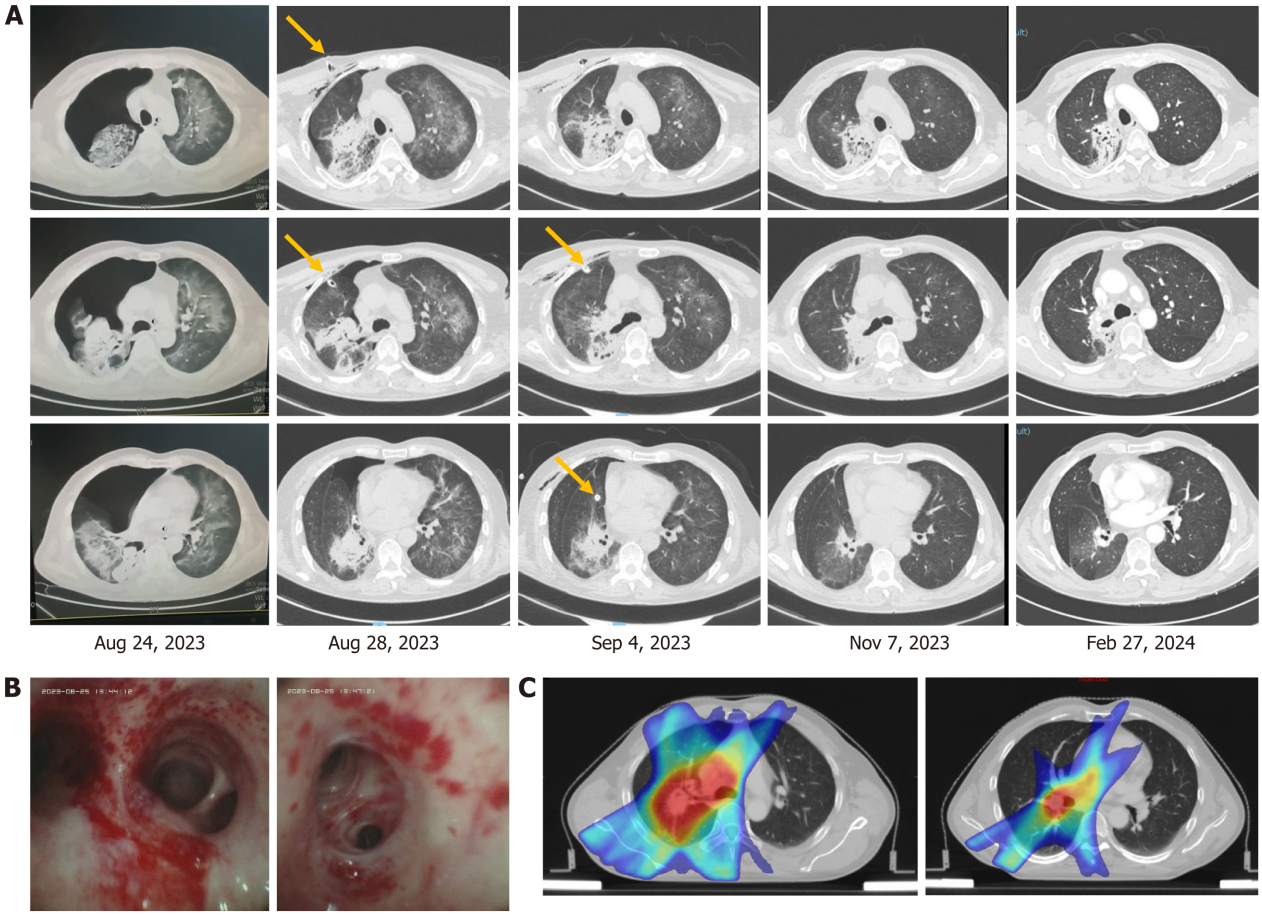

Figure 2 Radiographic and tracheoscopy findings. A: The computed tomography image changes before and after PJP treatment. The orange arrow shows the drainage tube. B: Tracheoscopy findings. C: Tumor irradiation field.

FINAL DIAGNOSIS

PJP infection was suspected, and thus the patient received piperacillin-tazobactam (4.5 g) three times per day combined with sulfamethoxazole and trimethoprim (TMP-SMX) (1.2 g/0.24 g) three times per day as empiric antibiotic therapy. The lavage fluid was sent to KingMed Diagnostics for targeted sequencing of multiple respiratory pathogens. Three days later, the next-generation sequencing of the lavage fluid confirmed PJP, herpes simplex virus 1, and cytomegalovirus.

TREATMENT

Acyclovir (0.25 g) was administered twice a day. One week later, the inflammation and symptoms were alleviated. Piperacillin-tazobactam and acyclovir were used for two weeks, and TMP-SMX was used continuously. Two months later, the inflamed bilateral lung was absorbed; however, the area with radiation developed chronic inflammation, with slight displacement of the mediastinum (Figure 2A and C).

OUTCOME AND FOLLOW-UP

On February 27, 2024, chronic inflammation was absorbed further and TMP-SMX was discontinued. The patient's daily activities eventually returned to the previous level. No further immunotherapies were administered. The patient remains alive without recurrence as of April 01, 2024.

DISCUSSION

PJP is a fungal infection that commonly affects immunocompromised patients and can be life-threatening in severe cases. The World Health Organization has listed it as one of 19 priority invasive fungal diseases, calling for increased research and public health action[3]. Typically, at-risk patients are those with underlying disease states that alter host immunity,

Table 1 *Pneumocystis jirovecii* pneumonia after steroid use due to immune-related adverse reactions

References	Country	Age and Sex	Cancer type	Patient condition	Treatment	AE and immunosuppression	Pathogens	Prognosis
Schwarz *et al* [23], 2019	Austria	79, Male	NSCLC	ECOG performance status 2, history of smoking, COPD	Chemotherapy-thoracic radiation-nivolumab	Immune-related pneumonitis, steroids for 6 weeks	*Pneumocystis jirovecii*	Died
		53, Male	NSCLC	ECOG performance status 0, history of smoking	Chemotherapy-thoracic radiation + nivolumab	Immune-related pneumonitis, steroids, and mycophenolate mofetil for 5 weeks	*Pneumocystis jirovecii*, cytomegalovirus	Died
Duarte *et al* [15], 2020	Belgium	68, Male	Melanoma	NA	Nivolumab-ipilimumab	Immune-related hepatitis and colitis, steroids for 10 weeks and infliximab	*Pneumocystis jirovecii*	Recovered
		24, Female	Hodgkin's lymphoma	NA	Multi cycle chemotherapy-pembrolizumab	Macrophage-activating syndrome, steroids for 6 months	*Pneumocystis jirovecii*	Recovered
Arriola *et al* [24], 2015	England	69, Female	Melanoma	Chronic lymphocytic leukemia	Chemotherapy-ipilimumab	Immune-related colitis, steroids for 12 weeks, and infliximab	*Pneumocystis jirovecii*	Recovered
		63, Female	Melanoma	NA	Ipilimumab	A capillary leak syndrome, steroids for 4 weeks	*Pneumocystis jirovecii*	Recovered

NSCLC: Non-small cell lung cancer; ECOG: Eastern cooperative oncology group; COPD: Chronic obstructive pulmonary disease; AE: Adverse event; NA: Not available.

such as HIV infection, transplant recipients, or those taking immunosuppressive therapies and medications[4]. The incidence of PJP in patients with solid tumors was documented at 0.013% (20/151718)[5].

Over the past 20 years, immune checkpoint inhibitors (ICIs) have been widely used[6]. However, these therapies can result in a variety of immune-related adverse events that can occur in any organ, including the kidneys[7]. AKI is the most common form of nephrotoxicity and is classically related to acute interstitial nephritis[8]. A noninvasive modality for the definite diagnosis of ICI-AKI remains unavailable[9,10]; however, CT imaging showed that the volume of the bilateral kidney increased in our patient. The estimated incidence of AKI directly related to ICI is approximately 3–5% [11]. Most patients had stage 1 or 2 while 10% had stage 3 AKI[12]. In our case, the patient had stage 3 AKI; fortunately, efficient and timely glucocorticoid therapy resulted in the recovery of kidney function. However, glucocorticoids can significantly impact both the innate and adaptive immune responses, and long-term steroid use increases the risk of opportunistic infections.

Our patient developed PJP and viral infection after receiving glucocorticoids for more than two months. PJP prophylaxis is recommended for patients expected to receive ≥ 20 mg daily prednisone equivalent for ≥ 4 weeks in the National Comprehensive Cancer Network guidelines of Management of Immunotherapy-Related Toxicities (Version 1.2024). Additionally, a study by Shah *et al*[13] highlighted the degree of immunosuppression and the relative risk of opportunistic infections. In 112 patients who received 20 mg daily of a prednisone equivalent for four weeks to manage immune-related adverse events, only eight had opportunistic infections; among them, one patient developed PJP[13]. Similarly, Sadek *et al*[14] revealed that only two PJP cases were found in patients treated with an ICI (480 patients received ICIs during that period). The incidence of PJP after steroid use due to immune-related adverse reactions is considerably low, and only six cases have been reported in the literature (Table 1). Considering the relatively common adverse effects of TMP-SMX at prophylactic doses[4], we wonder whether PJP prophylaxis is efficacious or necessary in all patients with cancer receiving steroids for immune-related adverse events. Conversely, steroids were frequently used in patients with cancer for a variety of other reasons. PJP has also been observed in patients with cancer receiving corticosteroids for malignant spinal cord compression[15] and weight loss[16]. Miyake *et al*[17] reported that the incidence of PJP in immunosuppressed non-HIV patients was 0.18% (32/17733), a monthly average dose of ≥ 13.7 mg daily prednisolone was a significant independent risk factors for PJP, and prophylaxis with ≥ 34.3 mg/day of TMP-SMX is to be recommended[17].Therefore, further studies are required to determine whether patients with cancer require precise PJP prophylaxis.

In addition to steroids, multiple other factors, such as lymphocytopenia and radiation to the chest, may contribute to PJP in patients with solid tumors in a composite manner[3]. In patients with lymphocytopenia, especially those with low CD4+ T cell counts, *P. jirovecii* can proliferate, causing a mononuclear cell response with inflammation. McAleese *et al*[18] advocated prophylaxis in patients with a lymphocyte count < 0.6 × 10^9/L. Fu *et al*[19] reported seven patients with thoracic neoplasms experiencing radiation pneumonitis complicated by PJP. Similar to radiation pneumonia, PJP presents with various atypical radiographic characteristics, including the relationship between photographic findings and the planning target volume. Similarly, the right side of the lung that received radiation had a more severe infection in our

case, which resulted in pneumothorax. Pneumothorax is a rare complication of PJP, occurring in only 3% of the HIV-positive patients with PJP[20]. This finding indicates that thoracic radiation may worsen the risk of PJP.

With the emergence of targeted therapies and immunotherapies, as well as the continuous development of novel radiotherapies, we have entered an era of novel treatment paradigms for locally advanced NSCLC[21]. The feasibility of induction with ICIs and chemotherapy before definitive chemoradiotherapy for locally advanced-NSCLC has been explored[22]. Notably, multiple factors interacted with each other in our case; although radiation pneumonia did not occur, handling immune-related adverse events leading to opportunistic infections still worsened the lung injury. In addition, we also differentiated PJP from immune and radiation pneumonia during treatment. Because no sign of inflammation was evident one month before the symptoms, immune and radiation pneumonia were not initially considered. A short-term reexamination after anti-inflammatory treatments confirmed the validity of our judgment.

CONCLUSION

A special feature of our case was that the patient developed double-lung PJP complicated by viral pneumonia accompanied by spontaneous pneumothorax during immune-related adverse event treatment. The patient's prognosis was good after timely anti-inflammatory treatments. Appropriate chemoprophylaxis to reduce the risk of PJP is necessary with comprehensive consideration of steroid use, lymphocytopenia, other chemotherapies, immunotherapies, and radiation therapy.

FOOTNOTES

Author contributions: Zheng YW and Zhang J conceived the manuscript; Zheng YW, Wang JF and Zhang J treated the patient; Zheng YW and Pan JC collected the patient information and acquired the data; Zheng YW and Pan JC analyzed the data and wrote the manuscript; Zheng YW and Zhang J jointly formulated the patient's treatment plan, with equal contributions to the manuscript as co-corresponding authors; Zheng YW takes primary responsibility for communication with the journal during the manuscript submission, peer review and publication processes; all authors reviewed the manuscript critically and approved the content.

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