Immunosuppression for Immune Checkpoint-related Toxicity Can Cause *Pneumocystis Jirovecii* Pneumonia (PJP) in Non–small-cell Lung Cancer (NSCLC): A Report of 2 Cases

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Clinical Practice Points

- Immune-related adverse events occur in up to 20% of patients with non–small-cell lung cancer treated with immune checkpoint inhibitors and often require treatment with immunosuppressive agents, depending on the grade of severity.
- Pneumocystis jirovecii pneumonia (PJP) is a common opportunistic infection affecting immunosuppressed patients.
- In PJP, the radiographic findings tend to be nonspecific and are difficult to differentiate from the underlying immune-related pneumonitis or other differential diagnosis as viral pneumonitis.
- In cases of prolonged immunosuppression, and especially in high-risk constellations with different potentially pneumonitis-inducing therapies, PJP prophylaxis should be considered.

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Introduction

Immune checkpoint blockade (ICB) has evolved as standard therapy in advanced non–small-cell lung cancer (NSCLC) and showed high clinical efficacy.[1] Here, we present 2 cases that developed immune-related pneumonitis requiring immunosuppression during ICB therapy, consequently leading to *Pneumocystis jirovecii* pneumonia (PJP). Both cases were lethal.

Case 1

A 79-year-old male with a history of smoking (Eastern Cooperative Oncology Group performance status 2, 50 pack-years, chronic obstructive pulmonary disease grade II), was diagnosed with bilateral NSCLC in April 2017. The left tumor was identified as adenocarcinoma, 4.7 cm in diameter, with mediastinal lymphadenopathy (T2bN2M0), ALK/ROS1 negative, EGFR wildtype, and programmed death ligand 1 (PD-L1) expression of 1%. The right tumor was identified as a squamous cell carcinoma, 1.8 cm in diameter (T1bN0M0), ALK/ROS1 negative, and PD-L1 expression of 20%. The patient was evaluated for surgical intervention but deemed inoperable owing to reduced pulmonary function. From April to August 2017, the patient underwent 6 cycles of palliative chemotherapy with carboplatin and gemcitabine, followed by radiotherapy of the left tumor and the mediastinum. Subsequent computed tomography (CT) detected progression of the left tumor and stable disease regarding the right. Based on PD-L1 expression of 1% of the left and 20% of the right, tumor therapy with ICB was offered.

Treatment with nivolumab was initiated in January 2018 but had to be postponed twice because of recurrent respiratory infections. On admission for the fourth treatment cycle in March 2018, the patient presented with moderate dyspnea and dry cough without fever. Chest x-ray was inconclusive, but a thoracic CT scan showed reticular and nodular thickening, indicating pneumonitis (Figure 1A). Nivolumab was withheld, and immunosuppressive treatment with corticosteroids was initiated, resulting in clinical

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improvement. The patient was discharged with ongoing corticosteroids after 5 days. Four weeks later, a thoracic CT scan showed regression of the reticular and nodular thickening (Figure 1B). Corticosteroids were further tapered, and treatment reinitiation was scheduled within 2 weeks.

On readmission, the patient presented with severe dyspnea, dry cough, hypotension, tachycardia, and fever. Laboratory tests showed elevated white blood cell count and lactate dehydrogenase. In the chest CT, bilateral ground-glass patterns and progressive septal thickening were seen (Figure 1C). As differential diagnoses, either aggravated pneumonitis following corticosteroid tapering or PJP were considered. Prednisolone dosage was increased as recommended in grade III pneumonitis treatment, and antibiotic therapy with piperacillin-tazobactam as well as trimethoprim/sulfamethoxazole (TMP/SMX) was initiated. Owing to progressive respiratory deterioration, the patient was transferred to the intensive care unit on the day of admission. The quantitative polymerase chain reaction results of the sputum revealed positivity of PJ on day 2 after admission. The patient was deceased 2 weeks later owing to respiratory failure.

Case 2

A 53-year-old man with a medical history of hypercholesterolemia, a former smoker, and atherosclerosis with an Eastern Cooperative Oncology Group performance status of 0, was diagnosed with stage IIIA NSCLC (cT1N2M0, adenocarcinoma, ALK/ROS1 negative, EGFR wildtype, and PD-L1 70%). Neoadjuvant therapy with 2 cycles of chemotherapy with cisplatin and vinorelbine was initiated in December 2017, followed by a right upper lobe resection in February 2018 (pathologic staging: ypT2a, pN2 (7/29), L0, V0, R0, grade 3, adenocarcinoma). Adjuvant radio-chemotherapy was planned. Owing to suspicion of residual mediastinal tumor persistence, the treatment was changed to ICB (nivolumab) combined with radiotherapy (off-label use and not recommended). The patient received 3 cycles of nivolumab and concomitant radiotherapy from March until April 2018. After the third cycle, the patient developed dyspnea and high fever. Antibiotic therapy with meropenem was started. The CT scan showed ground-glass infiltrates, indicating pneumonitis, with predominance on the right lung (Figure 2A). Radiotherapy and nivolumab therapy were discontinued and corticosteroid therapy was initiated. The patient's symptoms improved, and he was discharged on day 10 with planned corticosteroid tapering approximately for a month. One month after discharge, the patient deteriorated dramatically, and he was readmitted to the hospital. Follow-up CT scan showed increasing diffuse ground-glass opacities. Therefore, worsening of pneumonitis under tapering was suspected, and high-dose corticosteroid in combination with mycophenolate mofetil as an additional immunosuppressive agent was initiated under broad-spectrum combinational antibiotic therapy. Owing to progressive respiratory deterioration, the patient

Figure 1 **Chest Computed Tomography (CT) of Case 1 Undergoing Immune Checkpoint Blockade Therapy for bilateral Lung Cancer. A, CT Scan After 3 Cycles of Nivolumab. Patient Exhibited Moderate Dyspnea Without Signs of Infection. Patient Received Corticosteroids for Grade III Pneumonitis. B, CT Scan 4 Weeks Later Showed Improvement of the Pulmonary Lesions. Tapering of Steroids Was Continued. C, Admission 2 Weeks Later With Severe Dyspnea. Bilateral Ground-glass Patterns and Septal Thickening, Compatible With Pneumocystis Jirovecii Pneumonia**

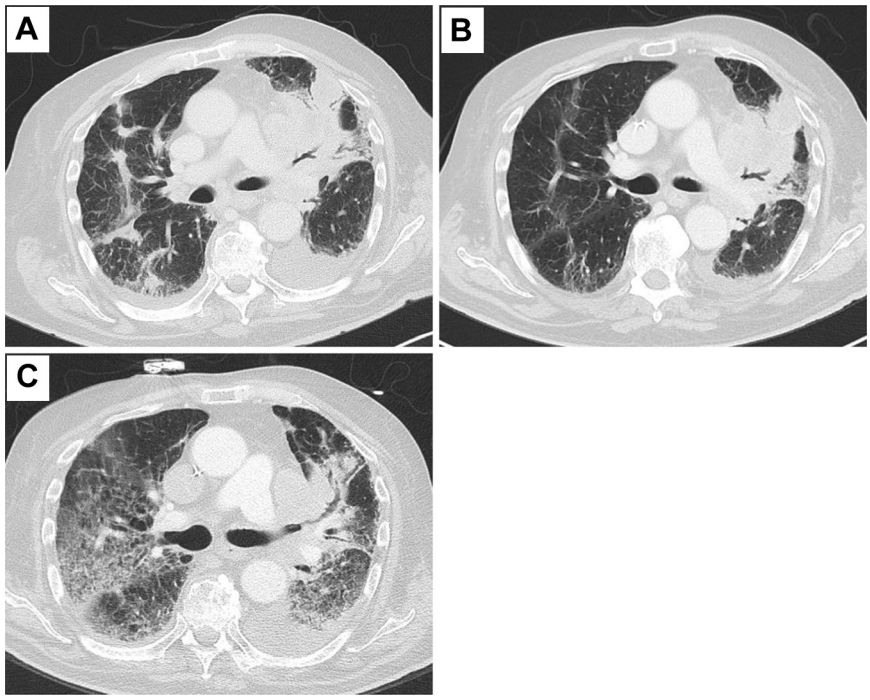
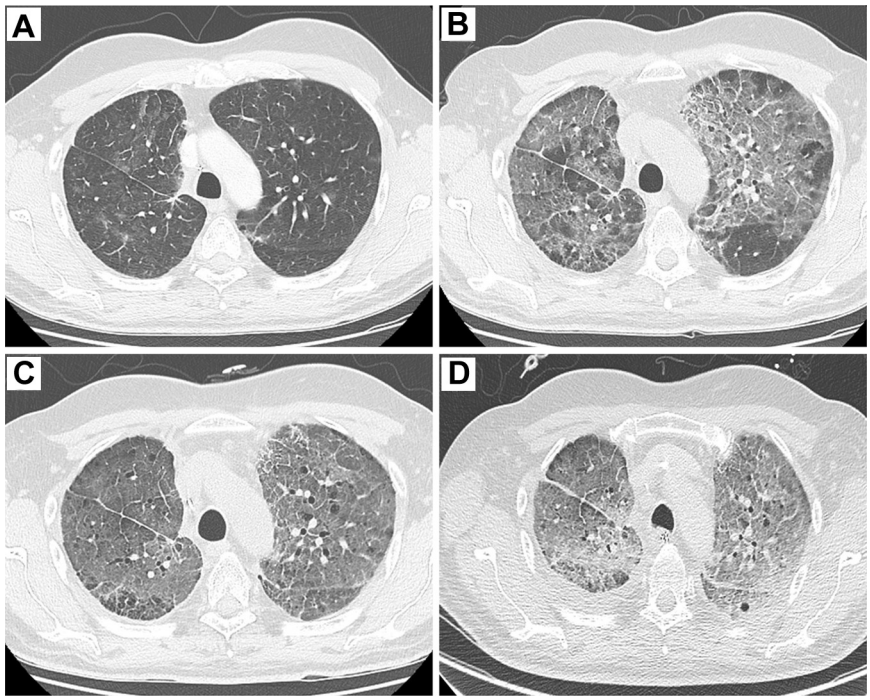


Figure 2 Chest Computed Tomography (CT) of Case 2 Undergoing Immune Checkpoint Blockade Therapy and Concomitant Radiotherapy. A, CT Scan after 3 Cycles of nivolumab. Patient Exhibited Dyspnea, Fever, and Reduced Performance Status. Patient Received Corticosteroids for Grade II Pneumonitis. B, CT Scan 4 Weeks Later after Cortisone Tapering With Worsening of the Immune-related Adverse Event/Radiation Pneumonitis With First Signs of Pneumocystis Infection. C, D, Follow-up CT Scans Under Maximal Anti-infective and Immunosuppressive Therapy. Worsening of Radiologic Findings



was transferred to the intensive care unit and required ventilation support. A chest CT scan showed the formation of pulmonary cystic lesions, septal lines with and without intralobular lines superimposed by ground-glass opacity (crazy paving), and consolidations, all typical features of PJP (Figure 2B).[2] Therefore, the anti-infective therapy was escalated including TMP/SMX, antibiotics, and antifungal therapy. Bronchial alveolar lavage identified PJ infection as well as an accompanying cytomegalovirus positivity. Pre-empiric TMP/SMX therapy was continued and ganciclovir added. The pneumonitis aggravated over time, going along with a dramatic impairment of the clinical situation requiring invasive respiratory assistance. Follow-up CT scans (Figure 2C, D) described a severe pneumonitis. The immunosuppressive therapy strategy was reevaluated and reduced to corticosteroids alone without mycophenolate mofetil; TMP/SMX and ganciclovir were continued. After adapting the therapeutic strategy, the clinical situation of the patient improved, and he stabilized for 1 week. Despite appropriate antibiotic treatment and maximal therapy, the patient died 1 week later owing to respiratory failure.

Discussion

Herein we present the medical course of 2 patients with NSCLC who developed fatal PJP while undergoing immunosuppressive therapy for immune-related pneumonitis. *Pneumocystis jirovecii* pulmonary infections usually affect patients with compromised immunologic states like human immunodeficiency virus-positive patients, solid organ transplant recipients, or patients with hematologic malignancies.[3] The risk for developing PJP is highest among patients undergoing allogeneic hematologic stem cell transplantation (from 0.3% to 15%) or treatment for acute lymphoblastic leukemia (up to 16%).[3] However, it is estimated that if PJP prophylaxis is administered, the risk of PJP infection is below 1%, even in patients undergoing allogeneic hematologic stem cell transplantation.[4] According to a meta-analysis of randomized trials, prophylaxis with TMP/SMX is warranted in non-human immunodeficiency virus immune-compromised patients if the risk for PJP exceeds 6%.[5] For patients with cancer receiving an equivalent of at least 20 mg prednisone per day for more than 4 weeks, oral PJP prophylaxis is suggested.[6-8]

Immune-related pneumonitis occurs in about 2% to 4% of patients undergoing ICB.[9,10] Toxicities of grade 2 or higher require immunosuppression through high-dose corticosteroids with prolonged tapering over weeks. According to a series of patients who developed pneumonitis owing to ICB, corticosteroids were administered in 65% of patients.[11]

Besides ICB-associated pneumonitis, immune-mediated pneumonitis also has been reported in patients with NSCLC undergoing chemotherapy or targeted therapy.[12,13] Another crucial pillar in NSCLC treatment is radiation therapy, and radiation-induced lung injury is one of its well-known side effects. In patients undergoing radiotherapy for the treatment of NSCLC, the rate of symptomatic

pneumonitis is estimated to be 15% to 40%.[14] Radiation-induced lung injury is treated with high-dose corticosteroids and generally tapered over 3 to 12 weeks.[14] Thus, patients who develop pneumonitis upon pulmonary irradiation and ICB therapy, which requires treatment with glucocorticoids, have to be considered at increased risk for PJP.

Interestingly, in a phase III randomized trial evaluating durvalumab (PD-L1 antibody) consolidation therapy after radiochemotherapy in stage III NSCLC, no increased rate of severe pneumonitis compared with placebo was observed (3.4% vs. 2.6%). However, pneumonitis was the most common adverse event leading to discontinuation of the trial regimen, with 4.8% and 2.6% in the durvalumab and placebo arm, respectively.[15,16] A total of 15.1% of patients in the durvalumab arm received glucocorticoids (8.8% high-dose glucocorticoids) compared with 6.8% in the placebo arm (5.1% high-dose glucocorticoids). Two patients in the durvalumab arm developed PJP. Therefore, this study provides a rough estimation on the prevalence of pneumonitis and corticosteroid treatment in patients undergoing pulmonary irradiation with subsequent ICB. In an early interim safety analysis of 21 patients of a phase II trial investigating radio-chemotherapy with concurrent ICB, no cases of pneumonitis $\geq$ grade 3 were observed by the end of a 3-month post-radiotherapy follow-up period.[17] Even though the authors state that the addition of nivolumab to radio-chemotherapy is safe and tolerable, further evidence is desirable.

Conclusion

In our point of view, the risk of pneumonitis and subsequent need of corticosteroids might be increased in patients receiving radiotherapy and ICB. Moreover, such special treatment scenarios might require more aggressive or prolonged immunosuppressive treatment in case of pneumonitis because 2 independent toxicities (immune-related pneumonitis, radiation pneumonitis) might coexist and aggravate the severity of symptoms. We think that in situations with prolonged immunosuppression, and especially in high-risk constellations with 2 potentially pneumonitis-inducing therapies, PJP prophylaxis has to be considered.

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Disclosure

D.N.B. declares that she has served on the advisory board for Roche, MSD, and Merck, and has received speaker honoraria from Roche, BMS, MSD, and Bayer. J.R. declares that he has received honoraria and speaker's fee from BMS, Roche, MSD, AstraZeneca, and Amgen and has served as an advisor for BMS, Roche, MSD, Astra Zeneca, Amgen, and Gilead/Kite. M.H. declares that he has received honoraria from Roche, BMS, MSD, and Astra Zeneca. W.H. has received speaker's fee and honoraria for advisory boards from Astra Zeneca, Roche, BMS, and MSD. A.P. has received speaker's fee and honoraria for advisory boards from Astra Zeneca, Roche, MSD, and Pfizer. All other authors state that they have no conflicts of interest.

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