A Case of *Pneumocystis jirovecci* in a Patient with Non-Small Cell Lung Cancer Treated with Immunotherapy

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ABSTRACT

Immune checkpoint inhibitors have become the standard of care in the management of metastatic non-small cell lung cancer (NSCLC) and are associated with improved outcomes when compared to traditional chemotherapy regimens. However, they present with their own unique set of immune-related side effects. One immune-related adverse effect that can arise is pneumonitis, where patients present with dyspnea with nonspecific radiologic findings, making it challenging to differentiate from other etiologies causing dyspnea.

We present a case of a 58-year-old woman with NSCLC previously treated with immunotherapy, who presented with shortness of breath. She was initially thought to have immune-related pneumonitis and was treated with immunosuppressive therapy. After several days of treatment, bronchoscopy demonstrated a positive polymerase chain reaction (PCR) for *Pneumocystis jirovecii* (PJP) after an initial negative direct fluorescent antibody (DFA). The patient was started on appropriate management for PJP and no further immunosuppressive therapy was given.

KEYWORDS: *Pneumocystis jirovecci,* checkpoint inhibitor pneumonitis, non-small cell lung cancer

INTRODUCTION

Non-small cell lung cancer (NSCLC) constitutes approximately 80% of all new lung cancer diagnoses. Over the past decade, treatment of NSCLC has evolved greatly. Previously, platinum-based chemotherapy regimens were used in the treatment of advanced NSCLC. These regimens only had a response rate of 20–40%, progression-free survival (PFS) of 4–6 months, and overall survival (OS) of 12–18 months.[1]

Over the past decade, immunotherapy has revolutionized the management of NSCLC. Immune checkpoint inhibitors have now become the standard of care in the treatment of metastatic NSCLC. Immunotherapy is associated with higher response rates and improved OS compared to traditional chemotherapy regimens.[2]

Immune checkpoints are surface proteins on T cells that act as negative regulators by preventing T cell activation by antigen presenting cells, which may include tumor antigens. Immune checkpoint inhibitors work by blocking these negative regulators and allowing the natural immune cascade to occur via T cell activation by antigen presenting cells.[3]

Monoclonal antibodies targeting the programmed death-1 (PD-1) checkpoint pathway, such as pembrolizumab and nivolumab, have been studied extensively in clinical trials for NSCLC. As a complication of activating the immune system, checkpoint inhibitors may activate T cell attack on self- antigen as well, leading to a set of toxicities called immune-related adverse events (i.e., pneumonitis, colitis, hypophysitis, thyroiditis, arthritis, etc.).[3]

Checkpoint inhibitor pneumonitis (CIP) typically presents as dyspnea with new infiltrates on chest imaging. This can be a very serious illness, in which patients usually require treatment with empiric high-dose steroids while concomitantly undergoing work-up for other etiologies.[3]

It can be challenging to diagnose CIP, as patients present with non-specific symptoms such as dyspnea and cough, which can also be caused by other processes such as infection, progression of cancer, or side effects of radiation therapy.

We report a case of a patient with NSCLC previously treated with an immune checkpoint inhibitor who presented to the emergency room with dyspnea. She was initially thought to have checkpoint inhibitor pneumonitis and was treated for such, but was ultimately found to have *Pneumocystis jirovecii* (PJP) pneumonia.

CASE PRESENTATION

A 58-year-old woman with metastatic adenocarcinoma of the lung, hypertension, hyperlipidemia, depression, multiple sclerosis not actively on treatment, and a 30-pack year smoking history, presented to the emergency department (ED) for weakness and shortness of breath.

For her oncological treatment history, she was initially treated with pembrolizumab, pemetrexed, and carboplatin, but had developed worsening nausea and fatigue with an associated 20-pound weight loss after three cycles and was started on a corticosteroid dose of 50 mg prednisone equivalent (PEQ) daily for failure to thrive two months prior to her presentation in the emergency room. She was not initiated on PJP prophylaxis at this time. In addition, she was then transitioned to second-line therapy with nanoparticle albumin-bound paclitaxel (nab-paclitaxel).

One week after her eighth cycle of nab-paclitaxel, she

presented to the ED with shortness of breath. She was tachycardic to 140 beats per minute and required 4 liters (L) of oxygen via nasal cannula. The remainder of her vital signs were normal. Her physical exam was significant for cachexia, dry mucous membranes, diffuse wheezing throughout all lung fields, and ulcers over her left arm.

Computerized tomography (CT) imaging was negative for a pulmonary embolism but revealed significant worsening of extensive bilateral ground-glass opacities with subpleural reticulations, compared to a CT image one week prior to her presentation.

Additional workup on presentation was significant for a negative respiratory pathogen panel, negative blood cultures, negative Chlamydia and Mycoplasma testing, and a negative urine legionella.

The patient was started on empiric, high-dose methylprednisolone (2 mg/kg daily) for a suspected immune-related pneumonitis from pembrolizumab. She was also empirically started on piperacillin-tazobactam and azithromycin. She underwent a bronchoscopy with studies sent off to assess for PJP, gram stain, fungal cultures. Despite empiric treatment with steroids and antibiotics, the patient's oxygen requirement continued to increase to 30L of oxygen via high-flow nasal cannula (HFNC).

After discussion with the consulting teams and the patient, a decision was made to treat for steroid-refractory pneumonitis with infliximab and increased methylprednisolone dosing to every eight hours. Due to the concern for PJP pneumonia given her immunosuppression, the patient was also started on treatment dosing with trimethoprim-sulfamethoxazole. With these changes, her oxygen requirements improved to 14L HFNC.

Studies from the patient's bronchoscopy revealed a positive Fungitell and negative PJP direct fluorescent antibody (DFA). Given these findings, PJP treatment was decreased to prophylactic dosing and she was continued on treatment for presumed immune-related pneumonitis along with the addition of intravenous immunoglobulins (IVIG) for two daily doses.

However, two days later, the patient's PJP polymerase chain reaction (PCR) was positive and treatment doses of trimethoprim-sulfamethoxazole was resumed with tapering of her high-dose steroids to PJP level of treatment. IVIG and infliximab was discontinued.

Despite PJP directed therapy, her oxygen requirements escalated with repeat CT imaging showing worsening airspace disease with new multifocal nodular airspace opacities throughout right lung and left lower lobe superimposed on diffuse background ground glass attenuation. The patient had previously been made "do not intubate" at the start of her admission and was ultimately transitioned to hospice and passed away.

DISCUSSION

This case describes a patient whose respiratory failure was believed to be due to either infection or immune-related pneumonitis. Although the management strategies are quite different, both have surprisingly similar clinical presentations that are difficult to distinguish.

CIP is a rare but very serious complication that can arise as a result of immune checkpoint inhibitor therapy, such as pembrolizumab, which this patient had been treated with months prior to presenting to the ED. The time to onset of symptoms of CIP is highly variable. In one study that looked at patients who received anti–PD-1/PD-L1 immunotherapy at Memorial Sloan Kettering Cancer Center (MSKCC) and the Melanoma Institute of Australia, the time to symptom onset ranged between 9 days to 19 months.[4] Furthermore, the typical presenting symptoms of CIP are dyspnea, cough, fever, and chest pain. Physical exam may be normal; however, some patients with advanced pneumonitis can present with crackles on lung exam.[3]

In large clinical trials, the incidence of CIP has been reported to be around 3 to 5%.[3] In the real world, the incidence of CIP has been higher. One study done at the University of North Carolina looked at 315 patients with lung cancer who received immune checkpoint inhibitors between 2004 to 2017 and demonstrated a CIP incidence of 9.5%, which is higher than the incidence reported in the initial clinical trials.[5] Given this higher than reported incidence of CIP, the medical community should have heightened awareness of this clinical entity.[3]

The diagnosis of CIP can be very challenging to make, as it is a diagnosis of exclusion. Typically, patients with CIP present with nonspecific symptoms, such as cough, fever, and shortness of breath. Diagnostically, the preferred imaging modality for CIP is CT chest. One study at MSKCC reviewed the imaging of CIP among 27 cases at their institution. These patients exhibited a wide array of findings on their CT imaging – 37% of the 27 patients had ground glass opacities, 19% of the patients had discrete patchy or confluent consolidation consistent with organizing pneumonia, 22% had interstitial markings, and 7% had evidence of hypersensitivity reactions.[4] CIP may present with a variety of phenotypes on radiographic imaging.

Management of CIP is based on retrospective data as there are no prospective trials comparing different treatment modalities. Initial treatment of CIP is with empiric high-dose corticosteroids if there is suspicion for CIP, given the associated high morbidity and mortality. Patients with lower grade CIP (grade 1–2) are initiated with a dose of prednisone 1 mg/kg/day, while patients with higher grade CIP (grade 3–4) are started on prednisone 2–4 mg/kg/day.[3] Patients generally show clinical improvement in 48–72 hours after corticosteroid initiation, and patients who do not improve are considered steroid-refractory and started on second-line immunosuppressive agents.

Patients with CIP who are steroid-refractory are a highly-morbid population, and show variable rates of response to second-line immunosuppressive agents. These agents include infliximab, IVIG, and tocilizumab. However, there is no evidence suggesting superiority of one treatment choice compared to another in patients with steroid-refractory CIP.

CIP is a diagnosis of exclusion. Its presentation is non-specific and overlaps with many other entities such as radiation pneumonitis, cancer progression, other immune-related adverse effects, and, most importantly, infectious etiologies. Therefore, while it is important to start empiric treatment for CIP if there is clinical suspicion, it is equally as important to undergo a rigorous evaluation for other etiologies. Oftentimes, a bronchoalevolar lavage (BAL) is critical in ruling out infectious etiologies.[3] In this case, the DFA was negative but the PCR was positive from the BAL for PJP. One study done in Thailand looked at 222 patients who were concomitantly tested by both DFA and PCR for PJP. Among non-HIV patients, a sensitivity of 91.94% was reported for PCR testing, whereas a sensitivity of 8.06% was reported for DFA testing.[6]

PJP occurs commonly as an opportunistic infection in immunosuppressed patients. Patients with NSCLC often receive corticosteroids for a number of reasons, including appetite stimulation, brain or spinal metastases, underlying history of COPD, immune-related adverse effects, or concurrent autoimmune disorders. Clinicians should consider PJP prophylaxis in patients who are on PEQ doses of 30 mg or greater for over four weeks or for patients who are receiving a corticosteroid dose of between 15 to 30 mg PEQ daily for over eight weeks.[7]

There are two case reports in the literature of patients with NSCLC who required treatment with corticosteroids for CIP, and later developed PJP. The presenting symptoms in these patients were dyspnea, cough, and fever. CT findings included bilateral ground-glass patterns and septal thickening and the diagnosis was made based on BAL findings from a PJP PCR test.[8]

The mainstay of treatment of PJP is antibiotics, usually a 21-day course of trimethoprim-sulfamethoxazole. Adjunctive glucocorticoids are added for patients with severe PJP, defined as having a partial pressure of oxygen less than 70 on room air, or with evidence of hypoxemia. There is some data supporting the use of adjunctive glucocorticoid therapy in patients with severe PJP who do not have HIV. One retrospective study examining patients with severe PJP without HIV, showed that the patients who received adjunctive prednisone therapy had a shorter duration on mechanical ventilation and intensive care admission.[9] Adjunctive glucocorticoid therapy in PJP consists of prednisone 40 mg orally twice daily for five days, followed by 40 mg orally once daily for five days, followed by, 20 mg orally once daily for 11 days.

CONCLUSION

Overall, when a patient with NSCLC who has been treated with immunotherapy and immunosuppression presents with nonspecific symptoms such as dyspnea, it can be very challenging to determine the etiology of these symptoms. We present a case of a patient presenting with respiratory failure, whose symptoms were initially thought to be due to CIP, but later were found to be due to infection. CIP is a diagnosis of exclusion, and these patients often need a bronchoalveolar lavage to rule out an infectious etiology of their symptoms. It is crucial to tease out whether the symptoms are caused by a pneumonitis or an infectious etiology, as this can change the management and ultimately alter the clinical course of a patient.

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