Case report

Severe pulmonary toxicity from immune checkpoint inhibitor treated successfully with intravenous immunoglobulin: Case report and review of the literature

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ABSTRACT

Immune checkpoint inhibitors are known to cause a variety of immune-related adverse events, including pneumonitis. When symptomatic, treatment typically consists of temporary or permanent cessation of the checkpoint inhibitor and several weeks of corticosteroid therapy. However, a subset of patients may suffer from severe pneumonitis, and the optimal treatment for this group is not known. Here we describe the case of a patient receiving pembrolizumab for non-small cell lung cancer who developed severe checkpoint inhibitor pneumonitis. After treatment with high-dose corticosteroids failed to produce a response, a course of intravenous immunoglobulin catalyzed rapid and durable improvement. In this review, we discuss the current evidence regarding the incidence and outcomes of severe checkpoint inhibitor pneumonitis and propose a role for intravenous immunoglobulin as a possible treatment strategy.

1. Case presentation

A 76-year-old woman with metastatic lung adenocarcinoma receiving palliative chemoimmunotherapy presented with acute onset fevers, dyspnea, and cough.

The patient had a past medical history remarkable for invasive ductal carcinoma of the right breast treated with lumpectomy followed by an aromatase inhibitor, which was diagnosed eight months prior to the lung cancer. She had a prior 20 pack-year tobacco use history, but had ceased smoking 35 years ago. She had recently traveled to the Southwest United States. She had no known occupational or environmental exposures. Notably, there was no history of chest radiation.

Lung cancer had been diagnosed three months prior to the current presentation, when she presented with hypoxemia on exertion and computed tomography (CT) showed a right upper lobe mass with evidence of lung and liver metastases. Biopsy of the lung and liver revealed metastatic adenocarcinoma consistent with lung origin and no actionable mutations on standard tumor molecular profiling. Palliative systemic therapy with carboplatin, pemetrexed, and pembrolizumab administered intravenously every 21 days was commenced as per the evidence-based standard of care. Imaging following the first two cycles of therapy showed stable disease.

Midway through the fourth cycle of therapy, the patient developed fevers, dyspnea on exertion, and cough. CT angiogram of the chest showed no pulmonary embolism, but revealed confluent regions of consolidation in the lungs bilaterally – significantly worse on the left – and a small left pleural effusion on a background of known bilateral cavitary lung lesions (Fig. 1).

She was admitted to the intensive care unit with severe hypoxemic respiratory failure and PaO2/FiO2 ratio of 87. She was treated with broad-spectrum antibiotics due to concern for a primary infectious process, but experienced worsening hypoxemia on day three necessitating endotracheal intubation and mechanical ventilation. Positive end-expiratory pressure was titrated, and lung protective ventilation utilizing a low tidal volume strategy was employed.

Bronchoscopy on day three revealed thin secretions in the left lower lobe, but was otherwise unremarkable. Bronchoalveolar lavage studies showed slight neutrophilic predominance (70% and 54% polymorphonuclear cells in two separate samples). Negative microbiology studies included gram stain and bacterial, viral, legionella, fungal,

Fig. 1. Representative axial image from CT chest obtained on presentation showing bilateral consolidations bilaterally, significantly worse on the left, and a small left pleural effusion.

nocardia, and acid-fast bacteria cultures. Aspergillus galactomannan antigen from the bronchoalveolar lavage fluid was negative, as were blood and urine markers of infection. A transthoracic echocardiogram showed mild symmetric left ventricular hypertrophy with normal right ventricular size and systolic function without significant valvular disease, signs of increased filling pressures, or atrial septal defect. Additional invasive diagnostic procedures (i.e. lung biopsy) were deferred due to clinical instability.

Immune checkpoint inhibitor (ICI) pneumonitis was suspected, and she was initiated on intravenous methylprednisolone at a dose of 2 mg/kg/day on day three. On day nine, the patient continued to have significant desaturations despite an FiO2 of 0.8, positive end-expiratory pressure of 10 cmH2O, and negative total body fluid balance.

Due to concern for steroid-refractory pembrolizumab-induced pneumonitis, intravenous immunoglobulin (IVIg) dosed at 2g/kg was administered on days 9–13 for a five-day course. This therapy was chosen due to its relatively mild toxicity profile in comparison to other more aggressive immunosuppressive agents, i.e. infliximab, cyclophosphamide, and mycophenolate mofetil. The patient experienced rapid and significant clinical and radiographic improvement allowing for successful extubation on day 12. Repeat chest CT imaging on day 12 demonstrated a marked improvement in the severe interstitial abnormality felt to represent an organizing phase of acute lung injury, consistent with a clinical response to immunomodulatory therapy (Fig. 2).

After two weeks of high-dose methylprednisolone, she was transitioned to prednisone 1 mg/kg/day. Her supplemental oxygen requirement decreased, she was weaned to an oxymizer device and ultimately discharged on day 23. At a follow-up visit three weeks later, oxygen needs had decreased to 1.5 L per minute via nasal cannula, and her exercise tolerance had improved substantially. Her prednisone was decreased to 0.5mg/kg/day with plans for a continued slow taper completed over the course of 2 months. Re-staging CT of the torso performed six weeks after her admission to reassess malignant tumor burden demonstrated continued improvement of the predominantly left-sided infiltrate, but a remaining bilateral subpleural interstitial fibrotic abnormality; the malignant disease burden was noted to be stable (Fig. 3).

2. Discussion

ICI pneumonitis is a rare, but potentially fatal complication of programmed cell-death 1 (PD-1), programmed cell-death ligand (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) blockade, occurring in 3–5% of patients – though some studies have reported a frequency of up to 11.8% [1–6]. Fortunately, the majority of these patients experience only mild or moderate pneumonitis and will improve with withdrawal of the immunotherapy and/or a course of corticosteroids [6,7].

However, a subset of patients will develop severe pneumonitis, classified as grade 3 or higher by the Common Terminology Criteria for Adverse Events (version 5.0), defined by: requiring hospitalization, involving > 50% of lung parenchyma, limiting activities of daily living, or requiring supplemental oxygen. In general, severe pneumonitis accounts for approximately 30% of ICI pneumonitis cases. Severe manifestations of this toxicity have been associated with tumor histology (i.e. non-small cell lung cancer (NSCLC), renal cell carcinoma (RCCA) – both of which are the most common current indications for ICI use) and underlying lung disease, though larger datasets are needed to establish these risk factors more definitively [5,6,8,9]. Overall, severe pneumonitis represents a distinct category of patients, for which the prognosis is more variable and for which the management may differ.

Current understanding of the incidence, natural history, and treatment of severe pneumonitis is limited to several small retrospective series, summarized in Table 1.

In a study of 64 ICI-induced pneumonitis cases, Delaunay and colleagues reported that 45% (29/64) were classified as severe, including six fatalities [7]. Of note, deaths occurred only in NSCLC patients treated with PD-1/PD-L1 inhibitors. No patient in this cohort was treated with immunosuppression beyond corticosteroids, and in the 43 patients who improved or were stable, 41.9% (18/43 patients) had had grade 3 or 4 pneumonitis.

Naidoo and colleagues studied 43 patients treated with ICIs [6]. In this cohort, 12 patients (27%) experienced grade 3 or higher pneumonitis, including one fatal case. Pneumonitis improved or resolved in seven of these 12 patients with severe pneumonitis. The remaining five patients were treated with additional immunosuppression, including

Fig. 2. Representative axial image from CT chest obtained after three days of IVIg therapy showing marked improvement in severe interstitial abnormality.

infliximab with and without cyclophosphamide. Ultimately, all five patients died, most often from infectious complications. One death was attributed to pneumonitis alone.

Khunger and colleagues performed a systematic review and meta-analysis of nineteen clinical trials of PD-1 and PD-L1 inhibitors that included 5,038 NSCLC patients accounting for 140 cases of pneumonitis, and 49 cases grade 3 or higher [8]. Patients treated with PD-1 inhibitors had a higher incidence of pneumonitis of any grade (3.6% vs. 1.3%) and severe pneumonitis (1.1% vs 0.4%) when compared to those treated with PD-L1 inhibitors. Roughly 30% of all pneumonitis cases associated with PD-1 or PD-L1 inhibitors were considered severe. Additionally, patients who had had no prior cancer therapy had a higher rate of pneumonitis (4.2% vs. 2.8%), though treatment status did not confer a higher rate of severe pneumonitis. This report did not examine treatment strategies.

Nishino and colleagues performed a systematic review and meta-analysis of clinical trial data to evaluate the incidence of pneumonitis related to PD-1 inhibitors specifically across NSCLC, melanoma, and RCCA trials [5]. Here, they reported an incidence of severe pneumonitis (grade 3 or higher) of 0.8% with immune monotherapy (30% of pneumonitis cases), and 1.5% with combination immunotherapy (23% of pneumonitis cases). This report also did not examine treatment strategies.

Finally, Suresh and colleagues recently published a retrospective study of 205 patients with advanced NSCLC who received PD-1 or PD-L1 inhibitors through clinical trials or standard of care [10]. Here, they reported a much higher rate of ICI pneumonitis compared to prior studies: ICI pneumonitis ≥ grade 2 severity occurred in 39 of 205 (19%) patients, including 25 cases (64%) ≥ grade 3 and five deaths. Of ICI pneumonitis cases, fourteen were steroid-refractory or steroid-
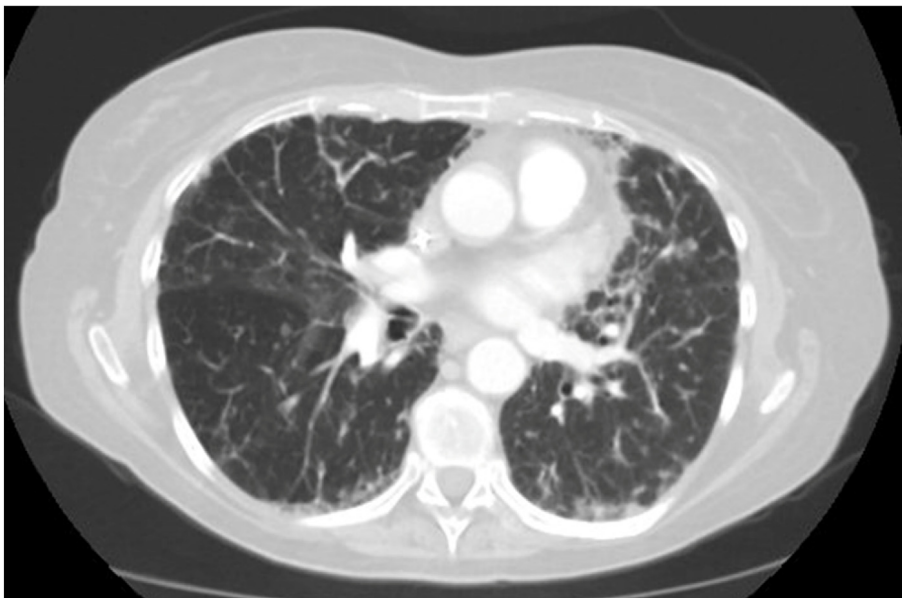

Fig. 3. Representative axial image from CT chest performed six weeks after admission showing near resolution of infiltrates with residual bilateral subpleural interstitial fibrosis.

Table 1
Summary of studies of ICI pneumonitis and treatments included in this review.

Source	ICI used	Tumor type	Incidence of pneumonitis (%)	Incidence of severe pneumonitis (%)	Treatment
Delaunay et al.	CTLA-4, PD-1, PD-L1 inhibitors	NSCLC, melanoma, others	64/1826 (3.5%)	29/64 (45%)	Corticosteroids
Naidoo et al.	PD-1, PD-L1 inhibitors ± CTLA-4 inhibitor	NSCLC, melanoma, others	43/915 (4.7%)	12/43 (27%)	Corticosteroids; infliximab ± cyclophosphamide
Khunger et al.	PD-1, PD-L1 inhibitors	NSCLC	140/5038 (2.8%)	49/140 (33%)	Not discussed
Nishino et al.	PD-1 inhibitor	NSCLC, melanoma, RCCA	154/4496 (3.4%)	44/154 (29%)	Not discussed
Suresh et al.	PD-1, PD-L1 inhibitors	Advanced NSCLC	39/205 (19%)	25/39 (64%)	Corticosteroids; mycophenolate mofetil or infliximab

unresponsive despite 72 hours of high dose steroids. Four patients went on to receive additional immunosuppressive therapy with mycophenolate mofetil or infliximab. Three of these four patients improved with additional therapy. In this study, the occurrence of ICI pneumonitis negatively impacted patients' overall survival.

A challenge to the practitioner in making treatment decisions is the unknown biological mechanisms that lead to ICI pneumonitis. Current understanding includes contributions from increased immune surveillance and decreased self-tolerance with resultant autoimmunity via T-cell recognition of antigens. This leads to cytokine production, increased humoral immunity, and the production of autoantibodies whose activity results in the activation of tissue degrading enzymes that finally lead to tissue injury [11]. The impact of common environmental and therapeutic factors (i.e. tobacco, radiation, and prior chemotherapeutic exposure) remains uncertain. Additional studies are needed to further elucidate this proposed pathophysiology and to better establish risk factors and models for predicting toxicity, as increasing use of ICIs across the spectrum of oncologic care is a growing reality.

Recommendations for the treatment of ICI pneumonitis are drawn from consensus opinion, as there have been no prospective trials establishing the preferred regimen. According to American Society of Clinical Oncology guidelines, pneumonitis of grade 3 or higher should prompt treatment with intravenous corticosteroids and permanent withdrawal of the ICI [9]. Clinical improvement is expected within the first 48 hours of treatment, otherwise the pneumonitis is considered steroid-refractory. Clinicians may then consider additional immunosuppression, usually with infliximab, mycophenolate mofetil, or cyclophosphamide. We advocate that IVIg should be included amongst these agents.

To our knowledge, there are no published reports of utilizing IVIg for the treatment of ICI pneumonitis. However, IVIg has been used successfully in other ICI-related toxicities, such as myasthenia gravis [12], thrombocytopenia, and other neurological syndromes [13,14]. Additionally, IVIg has an evolving role in the treatment of interstitial lung disease (ILD), including ILD-associated with connective tissue disease and idiopathic pulmonary fibrosis [15–17]. As detailed recently by Hallowell and colleagues, IVIg is felt to exert its immunomodulatory effect via three mechanisms: (1) regulating the function of immune cells causing inflammation, (2) binding and neutralizing autoantibodies and (3) downregulating expression of various chemokines, cytokines, chemo-receptors and adhesion molecules [18]. Other benefits to the use of IVIg include a relatively modest toxicity profile, (i.e. headache, myalgias, nausea and fever), though more serious events such as venous thromboembolism, aseptic meningitis, and anaphylaxis may occur [19]. Finally, IVIg has been postulated to have more immunomodulatory rather than immunosuppressive effects. Therefore, in light of multiple reports of infectious complications related to additional immunosuppression used for steroid-refractory pneumonitis [6], clinicians should consider IVIg as a potentially effective agent with a more favorable therapeutic index.

3. Conclusion

Our case demonstrates the safety and efficacy of the addition of IVIg to high-dose corticosteroid therapy as a treatment for steroid-refractory ICI pneumonitis. We acknowledge the difficulty in ascertaining how much of the patient's improvement can be attributed to the corticosteroids versus IVIg; however, the lack of improvement despite one week of high-dose intravenous corticosteroids and subsequent rapid improvement within 72 hours of IVIg administration suggests a meaningful impact from this adjunctive therapy. We believe that IVIg represents an attractive treatment option for steroid-refractory pneumonitis, with a favorable toxicity/benefit profile as compared to other traditional immunosuppressive agents. Rigorous prospective evaluation of IVIg and other immunosuppressive agents in the treatment of severe ICI pneumonitis is needed to establish best practice in

this evolving field.

Declarations of interest

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Appendix A. Supplementary data

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