Cytomegalovirus pneumonia complicating immune checkpoint inhibitors-induced pneumonitis: A case report

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Abstract. A 63-year-old man was hospitalized for immune check-point inhibitors (ICIs) medicated pneumonitis, secondary to treatment with pembrolizumab for non-small cell lung cancer. He was treated with high dose steroids, mycophenolate mofetil, empiric broad spectrum antibiotics and empiric trimethoprim-sulfamethoxazole and intravenous immunoglobulin. Despite the aforementioned treatment, his condition continued to deteriorate. The patient was admitted to the intensive care unit. While intubated, he underwent bronchoscopy and lavage, which was analyzed for potential infectious agents. Cytomegalovirus (CMV) pneumonia was diagnosed and treated. He passed away despite antiviral treatment and maximal supportive care. CMV infection should be suspected in patients failing to recover from toxicities of ICIs with appropriate immunosuppression.

Introduction

Immune checkpoint inhibitors (ICIs), either alone or in combination, increase survival of patients with several types of malignant tumor and are currently being studied in the context of neoadjuvant and adjuvant care for multiple diseases. However, these monoclonal antibodies, targeting programmed cell death (PD)-1, PD-1 ligand (PDL-1) and cytotoxic T-lymphocyte antigen (CTLA)-4, are associated with a unique spectrum of adverse consequences that can affect virtually every organ in the body. These include autoimmune inflammation in the digestive tract, lung, skin, endocrine glands and peripheral and central nervous systems (1,2). ICIs have been shown to increase survival of patients with metastatic non-small cell lung cancer (NSCLC) without activating genetic alteration in EGFR, ALK or reactive oxygen species and are now standard of care for these patients (3,4).

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ICI-related pneumonitis (ICI-P) affects 3-5% of patients treated with checkpoint inhibitors (5,6). It appears to be more prevalent in patients with NSCLC than in those with other types of cancer (6,7). Similarly, it is more common in patients treated with PD-1/PDL-1 inhibitors than in those treated with CTLA-4 inhibitors alone (6). The frequency of ICI-P is higher when anti-PD-1 and anti-CTLA-4 are administered concomitantly (6,7). Despite the low fatality rate of ~1%, pneumonitis is one of the leading causes of ICI-associated morbidity (8).

Treatment of ICI-P depends on its severity: The majority of patients experience only mild to moderate pneumonitis and improve with withdrawal of immunotherapy and/or a course of corticosteroids (9,10). However, certain patients worsen during treatment of pneumonitis and require additional immunosuppressive therapy, such as infliximab, mycophenolate mofetil (9,10) or immunomodulatory agents, such as intravenous immunoglobulin (IVIG) (11). The clinical course may be further complicated by opportunistic infection, secondary to prolonged treatment with steroids and immunosuppressants (12,13).

The clinical course of cytomegalovirus (CMV) pneumonia is typically indolent but fulminant disease may be observed in immunocompromised patients and carries a mortality risk mortality >30% (14). CMV pneumonia has been infrequently described in patients receiving cancer immunotherapy. Here, we describe a patient that developed fatal CMV pulmonary infection following treatment for pneumonitis induced by the anti PD-1 antibody pembrolizumab.

Case report

A 63-year-old man with a medical history of chronic obstructive pulmonary disease, hyperlipidemia and diabetes mellitus was diagnosed with metastatic squamous cell lung carcinoma in May 2017 (Fig. 1). Tumor cells stained positively for PDL-1 with a count >50%, and the patient started treatment with pembrolizumab in June 2017.

In February 2019, a PET-CT scan showed no pathological uptake and the patient was in complete remission. The only side effect noted at that time was hypothyroidism, which was treated with levothyroxine.

In June 2019, the patient was admitted to Galilee Medical Center (Nahariya, Israel) due to respiratory distress and pulmonary infiltrates. He was treated with prednisone

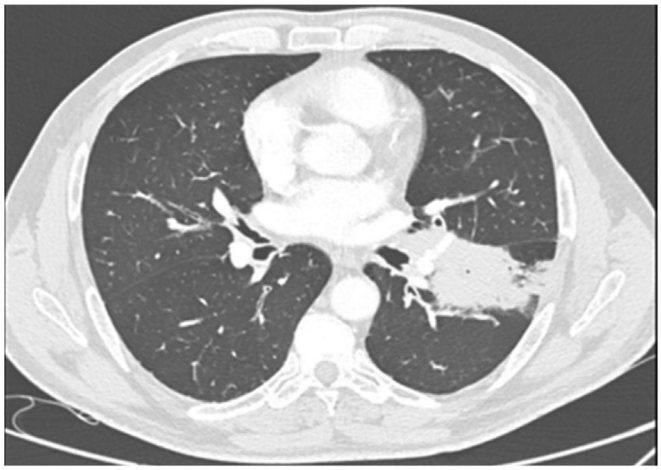

Figure 1. CT scan at diagnosis, showing left lung tumor mass.

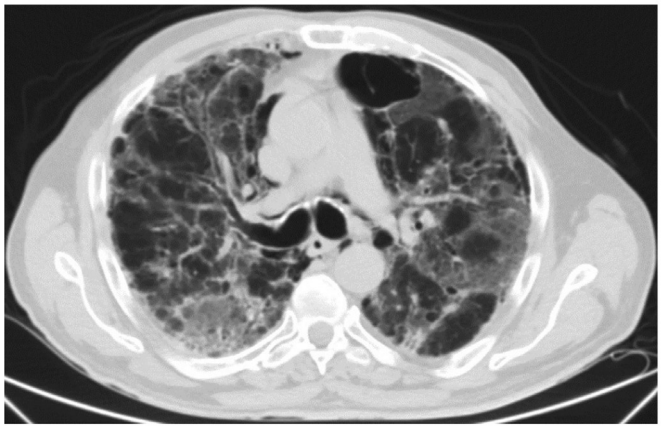

Figure 2. CT scan showing bilateral reticular opacity and disappearance of the left lung tumor mass.

(1 mg/kg) and levofloxacin and discharged following improvement with a recommendation to taper the dose of prednisone. While receiving 10 mg prednisone, he experienced worsening dyspnea and was re-admitted.

On admission, the patient was tachypneic, but other vital signs were within the normal range. Blood oxygen saturation was 82% on ambient air. CT angiography demonstrated bilateral reticular opacities (Fig. 2).

The clinical course and imaging studies were consistent with grade 4 autoimmune pneumonitis secondary to ICIs in a patient with chronic obstructive pulmonary disease. The patient was treated with Prednisone 2 at a dose of 2 mg/kg, mycophenolate mofetil, empiric broad-spectrum antibiotics and trimethoprim-sulfamethoxazole. Despite these measures, his condition worsened and the patient was intubated and mechanically ventilated due to respiratory failure.

The patient was admitted to the intensive care unit and IVIG was added to his treatment regimen. While intubated, he underwent bronchoscopy and lavage, which was analyzed for potential infectious agents. Following PCR analysis, CMV DNA was detected in the lavage fluid and CMV IgM was detected in the serum. Both tests supported the diagnosis of CMV pneumonia. Additionally, workup for *Pneumocystis carinii* (PCP), Ziehl-Neelsen staining and bacterial and fungal cultures were negative, and anti-viral treatment with Ganciclovir was added to his treatment regimen.

The patient was weaned off mechanical ventilation after two weeks and admitted to the Department of Oncology with high flow oxygen support and continued antiviral therapy, prednisone (slowly tapered to 0.5 mg/kg) and prophylactic trimethoprim-sulfamethoxazole. However, despite these measures, his condition continued to deteriorate. After discussion with the patient and his family, the decision was made to avoid repeat intubation. The patient died 3 weeks later.

Discussion

We describe a patient that suffered from ICI-P complicated by CMV pneumonia, diagnosed by serology and a positive PCR test using pulmonary lavage. An autopsy with pathology review of lung tissue would constitute a definitive diagnostic test to support CMV pneumonia diagnosis, however the family declined this procedure. The clinical course, consisting of an initial improvement with steroids and subsequent deterioration and unresponsiveness to aggressive immune suppression, together with positive serological and PCR tests, support the diagnosis of CMV pneumonia in this patient. To the best of our knowledge, this is the first published report of CMV pneumonia complicating ICI-P.

Although the majority of patients with pneumonitis secondary to ICIs recover with corticosteroid treatment, fatalities may occur. It is important to recognize factors that may complicate the clinical course in these patients so they can be diagnosed and promptly treated. The clinical and radiological findings suggestive of CMV pneumonia are non-specific, overlapping with those of immune-mediated pneumonitis (15-17). Thus, a high degree of clinical suspicion is needed for early diagnosis. The present patient was treated with steroids for several weeks before diagnosis of CMV pneumonia, and doses were tapered, as aforementioned, suggesting that this complication can occur even after a relatively short course of steroids.

The range of clinical diseases due to CMV in immunocompromised patients is broad and includes hepatitis, retinitis, encephalitis, esophagitis and colitis (18). Our case demonstrates that workup for CMV infection should be administered in patients failing to improve with steroids for immune-mediated toxicity.

We report a case of fatal CMV pneumonia complicating ICI-P. A high degree of clinical suspicion and prompt evaluation for CMV infection is recommended in cases that do not improve with steroids for treatment of immunotherapy-associated adverse effects and in patients that relapse following initial improvement.

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Authors' contributions

AS was responsible for conception of the work, data acquisition and analysis, revising and finalizing the manuscript. OB was responsible for data acquisition and analysis, drafting and revising the manuscript. AO was responsible for acquisition and analysis.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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