Atezolizumab-induced myositis and myocarditis in a patient with metastatic urothelial carcinoma

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SUMMARY

Immune checkpoint inhibitors have revolutionised cancer therapy in the past decade. Although they have been indicated to treat a diverse range of malignant neoplasms, they are also associated with various immune-related adverse effects. We report the case of a 74-year-old man with a history of urothelial carcinoma who had atezolizumab-induced myocarditis and myositis resulting in acute hypercapnic respiratory failure, despite the discontinuation of atezolizumab and aggressive treatment with corticosteroids. This case highlights the importance of a multidisciplinary approach for early diagnosis and treatment of immune-related adverse events. Physicians must be aware of the risks associated with immune checkpoint inhibitors and have a basic knowledge regarding their management.

BACKGROUND

The discovery of immune checkpoint inhibitors has revolutionised cancer therapy in the past decade. Originally approved for the management of metastatic melanoma, they have since been indicated to treat a diverse range of malignant neoplasms, including urothelial carcinoma, non-small cell lung cancer, head and neck squamous cell carcinoma and other advanced neoplasms.

These monoclonal antibodies work by blocking immune checkpoint proteins, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) and PD-1 ligand 1 (PD-L1). The checkpoint proteins are present on T cells and tumour cells and are crucial for tumours to avoid immune destruction and treatment. Approved immune checkpoint inhibitors include pembrolizumab and nivolumab (anti-PD-1); atezolizumab, durvalumab and avelumab (anti-PD-L1); and ipilimumab (anti-CTLA-4).[1 2]

Although these agents represent an important development in cancer treatment, immune checkpoint inhibition can lead to non-specific immune activation of T cells, which can result in unique immune-related adverse events (irAEs) that can be life-threatening.[1 2] These irAEs can involve any organ system and commonly include dermatological effects, pneumonitis, gastrointestinal effects and endocrinopathies.[3 4] Neurological irAEs are rare, occurring in less than 3% of patients, but they, along with cardiac effects, have the highest fatality rates among all of the irAEs.[1]

As the indications for and usage of immune checkpoint inhibitors continue to increase, the number of patients with cancer who are exposed to these medications continues to rise.

Correspondingly, increased rates of irAEs are expected. It is therefore imperative that clinicians be aware of the risks and have knowledge regarding their management.[1] Diagnosis can be challenging because the symptoms may be generalised and mimic those directly related to cancer.[5] Early diagnosis and treatment are crucial to improve prognosis and require a multidisciplinary approach.[1 2 4] Hence, clinicians should have a low threshold of suspicion for irAEs if the patient's health deteriorates after the administration of an immune checkpoint inhibitor.[6]

We report a rare case of atezolizumab-induced myocarditis and myositis resulting in acute hypercapnic respiratory failure in a patient with metastatic urothelial cell carcinoma.

CASE PRESENTATION

A 74-year-old man sought care at the emergency department (ED) with a chief concern of shortness of breath. His medical history included urothelial carcinoma of the proximal ureter and renal pelvis, initially treated with Bacillus Calmette–Guérin (BCG) vaccine. Approximately 1.5 years before initial evaluation in our ED, he was diagnosed with cancer recurrence and high-grade papillary urothelial carcinoma and underwent nephroureterectomy and chemotherapy with gemcitabine and cisplatin. He was recently found to have lung metastases and had started immunotherapy with atezolizumab (840 mg intravenous), receiving his second cycle of treatment approximately 2 weeks before his initial evaluation in our ED.

A few days after receiving atezolizumab, he had development of dyspnoea, which was preceded by influenza-like symptoms. He was then seen at an outside institution, where he was found to have increased troponin levels and underwent cardiac catheterisation with stent placement to the left anterior descending artery. He initially had some relief; however, his dyspnoea continued to progress, prompting his seeking care at our ED. Initial laboratory results showed a troponin level greater than 4000 ng/L, and he was admitted to the hospital with concern for in-stent restenosis. However, serial troponin values were largely unchanged, which supported the diagnosis of myocarditis rather than an ischaemic process. Electrocardiography (ECG) indicated right bundle-branch block but showed no acute ischaemic changes or signs of pericarditis.

Echocardiography showed a normal left ventricular ejection fraction with no wall-motion abnormalities.

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Further history was obtained, which revealed that the patient had also been experiencing dysphonia, diplopia, dysphagia, ptosis and proximal muscle weakness, in addition to shortness of breath. Neurological examination showed proximal and axial weakness, as well as a component of fatigability. The patient became more dyspneic with minimal exertion. Electromyography (EMG) and an autoimmune panel were recommended, and immunotherapy was discontinued, per oncologist recommendations, until the patient could be stabilised. His creatine kinase level was found to be increased, at 1763 U/L (reference range, <300 U/L). Chest imaging showed no evidence of thymoma. CT of the head without intravenous (intravenous) contrast showed no evidence of acute cortical infarction, intracranial haemorrhage, cerebral metastasis or other focal mass lesions. These findings were suggestive of a possible neuromuscular junction disorder and myopathic process secondary to the immune checkpoint inhibitor (atezolizumab) therapy.

On day 3 of hospitalisation, the patient experienced acute respiratory decompensation with shallow, agonal breathing and hypoxia, along with hypotension. Arterial blood gas analysis showed pH 7.14, arterial carbon dioxide tension 77 mm Hg and arterial oxygen tension 53 mm Hg on 100% fractional inspired oxygen. His clinical picture at this point was concerning for atezolizumab-related neuromuscular junction disorder causing acute hypercapnic respiratory failure.

EMG was performed and, although technically limited, showed an abnormal pattern and distribution of fibrillation potentials compatible with a proximal myopathic process. Because motor unit potentials could not be examined, a widespread neurogenic process causing the observed abnormalities was not specifically excluded by this study. Although there was no evidence of a disorder of neuromuscular transmission in this study, false-negative repetitive nerve stimulation results have been reported in acute, severe myasthenic crisis.[7] The autoimmune laboratory study results were negative. These tests include the serum AChR, MuSK,and striational antibodies.

After consultations among neurology, cardiology and oncology specialists, the patient was diagnosed with atezolizumab-induced myocarditis and myositis resulting in acute hypercapnic respiratory failure.

TREATMENT

The patient was started on high-intensity corticosteroid therapy with 1 g intravenous methylprednisolone daily, with a plan to eventually transition to a prednisone taper starting at 60 mg daily after clinical improvement.

OUTCOME AND FOLLOW-UP

The patient's respiratory status continued to worsen, and he was subsequently intubated and transferred to the intensive care unit. Bronchoscopy done at the bedside showed minimal secretions. Chest CT without intravenous contrast showed bilateral lower lobe atelectasis with superimposed aspiration pneumonia, right lower lobe bronchiolitis and bilateral upper lobe nodules consistent with pulmonary metastasis.

The risk of extubation failure due to the underlying immune-related organ dysfunction was discussed with the family. The patient was successfully extubated after weaning him off sedatives. The patient elected to change his code status to 'do not resuscitate/do not intubate'.

The patient died approximately 12 hours after extubation. The family agreed to a limited autopsy, including the heart in its entirety, a diaphragm biopsy and a psoas muscle biopsy.

Postmortem microscopic examination of the heart showed biventricular active lymphocytic myocarditis, in addition to ischaemic heart disease, with recent myocardial infarction and global microscopic ischaemic injury. The diaphragm and psoas muscle biopsies showed lymphocytic myositis on microscopic examination.

DISCUSSION

Atezolizumab, a humanised monoclonal antibody, activates tumour-specific T cells by specifically targeting PD-L1 and blocking its interaction with its receptor. It has been indicated in the treatment of various advanced malignant processes, but it is also associated with irAEs. The exact mechanism of these adverse events remains undefined, but various mechanisms have been proposed implying an autoimmune process. These can occur alone or in combination and include increased T-cell activity, autoantibodies or inflammatory cytokines.[1]

To our knowledge, this is the first premortem and postmortem proven report of a patient with atezolizumab-induced myositis with myocarditis. One other case has been reported of immune checkpoint inhibitor-induced concomitant myositis and myocarditis associated with a different agent.[8] The epidemiological data on atezolizumab with regard to irAEs is limited; only five other cases have been published to date.[9–13]

Our case highlights a rare occurrence of myositis-induced respiratory weakness causing hypercapnic respiratory failure. Atezolizumab was previously linked with the exacerbation of myasthenia gravis, causing hypercapnic respiratory failure[10]; however, this is the first reported case of myositis-induced hypercapnic respiratory failure due to atezolizumab. Similar to our case, in the three reported cases of atezolizumab-induced myositis, the patients had increased creatine kinase levels, with a median value of 1542 U/L, and the autoimmune panels were negative.[10–12] EMG in immune-related myositis will show a myopathic pattern, but, if inconclusive, a muscle biopsy is used to confirm the diagnosis.[1 4] The postmortem diaphragm and psoas muscle biopsies in our case showed lymphocytic myositis on microscopic examination, thus confirming the diagnosis, which was also consistent with other reported cases of immune-mediated myositis.[14]

The differential diagnosis of immune-related myositis includes myasthenia gravis and inflammatory myopathies (paraneoplastic).[8] Currently, there is no distinct definition for immune-related myositis and myasthenia gravis. These syndromes can overlap. Thus, the patients can present with a wide array of symptoms—as evidenced in our patient who had a myositis-induced weakness with a component of fatigability.[1] It can mimic myasthenia gravis by being confined to the oculobulbar muscles.[1] Immune-related myositis is unique in relation to its idiopathic counterpart because there are no extra muscular manifestations, and the serum myositis-specific antibodies can be negative.[4] If a patient taking an immune checkpoint inhibitor has weakness, neuroimaging should also be done to rule out cerebral metastasis, acute cortical infarction or other focal mass lesions.

Only two other cases of atezolizumab-induced myocarditis have been reported to date. Atezolizumab has been reported to cause arrhythmias and cardiac arrest.[10 13] Prompt workup with ECG, echocardiography, cardiac MRI, and serum cardiac troponin and brain natriuretic peptide measurement are needed.[1 15] Although ECG can demonstrate conduction abnormalities, echocardiography findings can be normal, as noted in our patient.

Diagnosis in our case was based on persistently increased cardiac troponin levels, unrelated to the obstruction of coronary arteries. The diagnostic standard for confirming immune-related myocarditis is endomyocardial biopsy.[16] In our case, the finding of multifocal, patchy lymphocytic myocarditis on postmortem microscopic examination of the heart supports the diagnosis of immune checkpoint inhibitor-associated myocarditis.[17]

The major clinical guidelines addressing the management of irAEs are those given by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology.

Discontinuation of the immune checkpoint inhibitor and starting treatment with corticosteroids forms the basis of management of immune-related myocarditis and myositis. Moderate (1–2 mg/kg) to high-dose (>2 mg/kg) intravenous methylprednisolone is given, followed by an oral corticosteroid taper after the resolution of symptoms. Regarding the treatment of myocarditis, the NCCN recommends adding infliximab for life-threatening symptoms. In the case of myositis, if it doesn't improve or deteriorates after starting corticosteroid treatment, intravenous immunoglobulin, plasmapheresis or other immunosuppressant therapy can be considered.[18]

Common Terminology Criteria for Adverse Events (CTCAE), which is used for reporting adverse events, characterises them into four grades in the order of increasing severity. This patient's acute respiratory failure and myositis are described as grade 4 as they were life-threatening. On the other hand, myocarditis in this patient is reported as grade 3. Recommendations have been made by the Society for Immunotherapy of Cancer (SITC) for the management of toxicities associated with immune-checkpoint inhibitors. Under SITC, management of CTCAE grade 3 and grade 4 events involves starting the treatment with prednisone 1–2 mg/kg/day, and if there is no improvement in 2–3 days, immune suppressants like infliximab is added. Immunotherapy is put on hold for grade 3 events, but if there is no improvement of the symptoms within 4–6 weeks, it is discontinued. Under grade 4, immunotherapy is promptly discontinued.[18 19]

Learning points

- With increased utilisation of immune checkpoint inhibitors, increased rates of immune-related adverse events (irAEs) are expected; therefore, it is imperative for physicians to be aware of these adverse events and have a basic understanding of their management.
- Physicians should have a low threshold of suspicion for irAEs if a patient's health deteriorates after the administration of an immune checkpoint inhibitor.
- Discontinuation of the immune checkpoint inhibitor and starting treatment with corticosteroids form the cornerstone of managing irAEs.
- Early diagnosis and treatment are crucial to improving the prognosis of the patient and require a multidisciplinary approach.

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