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Analysis of a Case of Immune-Related Myocarditis Combined with Myasthenia Gravis and Liver Injury Induced by Tislelizumab

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Abstract: Immune checkpoint inhibitors (ICIs) have demonstrated significant advantages and potential in tumor immunotherapy, but immune-related adverse events (irAEs) are becoming increasingly important safety issues. This article analyzes and discusses a case of a patient with esophageal cancer who developed bilateral lower limb weakness, bilateral ptosis, loss of appetite, nausea, and vomiting after four cycles of treatment with tislelizumab. The patient was considered to have immune-related myocarditis, myasthenia gravis, and liver injury involving multiple organs caused by tislelizumab treatment. As multi-organ damage caused by tislelizumab is rarely reported domestically and internationally, this article will analyze and discuss domestic and foreign literature, hoping to provide some help to clinicians who subsequently use tislelizumab.

Keywords: Immune checkpoint inhibitors; Immune-related adverse reactions; Myocarditis; Myasthenia gravis; Liver injury

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1. Introduction

In recent years, immune checkpoint inhibitors (ICIs) have been used to treat various types of tumors. Programmed death-1 (PD-1) and programmed death ligand 1 (PD-L1) immune checkpoint inhibitors represent one of the most important breakthroughs in the treatment of advanced malignancies [1]. However, they can potentially cause a series of unique side effects, known as immune-related adverse events (irAEs) [1,2]. irAEs include skin, gastrointestinal, liver, endocrine events, and other uncommon inflammatory events. Although uncommon, ICIs can cause fulminant and even fatal toxic reactions [3]. Therefore, irAEs must be identified and managed promptly. This article reports a case of multi-organ irAEs: myocarditis, myasthenia gravis, and liver injury, that occurred in a patient with advanced esophageal cancer after the application of tislelizumab. The patient's symptoms did not improve after glucocorticoid treatment, ultimately leading to death. The study will summarize the clinical characteristics and treatment strategies of immune-related multi-organ damage caused by ICI inhibitors, hoping to provide references for the prevention and management of clinically relevant adverse reactions.

2. Case information

The patient, a 69-year-old male, presented with symptoms of nausea and vomiting in March 2022. A gastroscopy was performed, and a biopsy was taken, although the pathological results were not detailed. On July 6, 2022, the patient underwent radical surgery for esophageal cancer, followed by three cycles of immunotherapy combined with chemotherapy using Tislelizumab, Albumin-bound Paclitaxel, and Cisplatin. The patient underwent a fourth cycle of chemotherapy on November 5, 2022, with Tislelizumab (200 mg), Albumin-bound Paclitaxel (400 mg), and Cisplatin (40 mg). The process went smoothly without any significant adverse reactions.

On November 27, 2022, the patient woke up to find bilateral eyelid ptosis and weakness in lifting, which was more pronounced in the evening than in the morning. He also experienced nausea, vomiting, a slightly hoarse voice, intermittent spitting of white mucus, double vision, weakness in both lower limbs, and poor appetite, but denied having headaches, palpitations, chest tightness, or chest pain. Past medical history includes a 14-year history of diabetes mellitus, treated with Metformin Sustained-Release Tablets and Gliclazide Sustained-Release Tablets, with controllable blood glucose levels. The patient denied having hypertension, coronary heart disease, cerebrovascular disease, hepatitis, or any other relevant medical history. There is no significant family history or history of drug or food allergies.

On December 1, 2022, a physical examination was performed upon admission, revealing a temperature of 36.5℃, a heart rate of 110 beats per minute, a respiratory rate of 20 breaths per minute, and a blood pressure of 160/106 mmHg. The patient had a fast heart rate of 110 beats per minute, with a regular rhythm. No significant heart murmurs were heard in the valve auscultation areas. The nervous system examination showed that the patient was conscious, mentally stable, had unclear speech but normal intelligence, bilateral eyelid ptosis, and fixed bilateral eyeballs with limited upward, downward, left, and right gaze. The pupils were 3 mm in diameter, equal in size and round, with a normal pupillary light reflex. The patient had a hoarse voice, dysphonia, normal bilateral pharyngeal reflexes, and no abnormalities in other cranial nerves. The flexor muscle strength of both upper limbs was normal, while the extensor muscle strength was grade 4. The muscle strength of both lower limbs was grade 4. The finger-to-nose test and heel-to-knee-to-shin test were stable and accurate on both sides. The sensation was normal, and tendon reflexes of the extremities were reduced, with negative pathological signs.

Auxiliary examinations were performed on December 1, 2022, including a craniocerebral MRI+MRA, which indicated multiple cerebral ischemic lesions, brain atrophy, craniocerebral arteriosclerosis, and changes in the paranasal sinuses. Laboratory tests showed creatine phosphokinase levels of 3610.0 U/L, lactate dehydrogenase levels of 802.0 U/L, creatine kinase isoenzyme mass of 73.2 μg/L, troponin I levels of 5.51 ng/mL, and B-type natriuretic peptide precursor levels of 2795 pg/mL. Upon urgent examination, the patient showed no significant symptoms such as chest tightness or chest pain, dyspnea or shortness of breath. An electrocardiogram revealed significant ST-segment depression in some leads, and no obvious heart murmurs were heard during the physical examination. Considering acute myocardial damage, the patient was treated with aspirin, ticagrelor dual antiplatelet therapy, statins, and vasodilators.

On the second day of the patient's admission (December 2, 2023), their condition worsened with significant dyspnea, inability to lie flat, persistent bilateral ptosis, slurred speech, increased oral secretions, weakness in all four limbs, decreased muscle strength and reflex, and non-cooperation in gait examination. Electromyography showed damage to the peripheral nerves in both lower limbs. Laboratory tests revealed elevated alanine transaminase (101.8 U/L) and aspartate transaminase (1185.4 U/L). Given the patient's acute onset, previous immunotherapy combined with chemotherapy, and medical history, acute immune-related adverse reactions were suspected, including myocardial injury, liver damage, and severe myasthenia affecting swallowing muscles and eyelids. Therefore, the patient was treated with methylprednisolone sodium succinate 1000 mg qd, recombinant

human brain natriuretic peptide infusion, and nitroglycerin infusion. At approximately 3:30 on December 3, 2023, the patient became unconscious and unresponsive to calls. Physical examination showed equal and round pupils bilaterally with sluggish light reflex, suggesting type II respiratory failure. The patient was intubated and connected to a ventilator for assisted respiration. ECG indicated sinus tachycardia, left axis deviation, and complete left bundle branch block.

On December 4, 2023, the patient's condition remained critical, requiring continuous ventilator-assisted respiration with no signs of dyspnea. Norepinephrine infusion was maintained to stabilize blood pressure, while continuous infusions of butorphanol, propofol, amiodarone, and ulinastatin were administered for sedation, analgesia, ventricular rate control, and reducing cardiac workload, respectively. Laboratory tests showed improved liver function with alanine transaminase at 84.0 U/L and aspartate transaminase at 84.9 U/L, but elevated lactate dehydrogenase (665.0 U/L), creatine phosphokinase (619.0 U/L), creatine kinase isoenzyme mass (5.32 μg/L), N-terminal pro-brain natriuretic peptide (9763 pg/mL), and cardiac troponin I (16.51 ng/mL). The patient continued to receive high-dose corticosteroid therapy with reduced dosage (500 mg/dose qd) and treatments to improve myocardial blood supply, nourish the myocardium, reduce cardiac workload, and enhance cardiac function. However, on December 6, 2023, at 3:08, the patient's blood pressure dropped, and despite aggressive resuscitative efforts, the patient passed away three hours later.

3. Discussion

Tislelizumab is a humanized recombinant monoclonal antibody targeting programmed death receptor (PD)-1, which demonstrates good tolerability and antitumor effects in patients with advanced solid tumors [4]. While treating tumors, it may excessively stimulate the body's immune function, leading to multi-system immune-related adverse events (irAEs). Currently, there are reports of myocarditis and myasthenia gravis caused by immune checkpoint inhibitors (ICIs) both domestically and internationally. Although the clinical incidence of such adverse reactions is low, they can cause fulminant and even fatal toxic reactions. This article reports a case of a patient with esophageal cancer who developed myocarditis, myasthenia gravis, and multi-organ damage including liver injury after four cycles of tislelizumab treatment. Clinicians should be vigilant about the occurrence of multi-system damage irAEs during the application of this drug. This aims to remind clinicians to promptly manage patients using ICIs who show symptoms or signs of adverse reactions.

Myocarditis is a rare immune-mediated adverse event. According to previous reports, its incidence is low, ranging from only 0.06% to 1%, but the mortality rate it causes is very high, between 20% and 50% [4,5]. Observational studies have also shown that the incidence of myocarditis with combination immunotherapy is higher than that with monotherapy. ICI-related myocarditis manifests in various ways, commonly including shortness of breath, chest pain, and ventricular arrhythmias [6]. At the same time, there are also many nonspecific symptoms, such as edema, fatigue, nausea, and myalgia [7]. These nonspecific symptoms are atypical and can be easily overlooked, leading to serious consequences.

The pathological mechanism of myocarditis has not been fully elucidated. Some researchers believe that there may be common antigens between tumor cells and cardiomyocytes [8]. Another proposed mechanism is the relative weakening of immune tolerance in the periphery of the heart [9]. The diagnosis of myocarditis is primarily based on the 2013 European Society of Cardiology Guidelines. Patients presenting with symptoms or signs related to myocarditis should promptly undergo electrocardiography, troponin testing, echocardiography, and cardiac magnetic resonance imaging. Endomyocardial biopsy may be performed if necessary [10].

Currently, high-dose glucocorticoids (prednisone 1–2 mg/kgd) are used for pulse therapy in cases of

immune checkpoint inhibitor (ICI)-related myocarditis. However, despite aggressive treatment, the condition may still progress [10]. For patients who do not respond immediately to high-dose corticosteroids, a steroid regimen targeting heart transplant rejection (methylprednisolone 1 g/d) should be promptly initiated, along with the addition of mycophenolate mofetil, infliximab, or antithymocyte globulin therapy. In life-threatening cases, immunosuppression with abatacept or alemtuzumab may be added [11].

The incidence of ICI-related myasthenia gravis is between 0.1% and 0.2%. It may sometimes occur concurrently with inflammatory myopathy and myocarditis and has a high fatality rate [12,13]. Common clinical symptoms include ptosis or diplopia, muscle weakness in the limbs, difficulty breathing, and swallowing. Research on the specific pathogenesis of ICI-related myasthenia gravis is currently very limited. Some studies have found changes in the CD8/CD4 ratio of peripheral blood lymphocytes and inhibition of T-regulatory cell activity [14].

In patients with immune checkpoint inhibitor (ICI)-related myasthenia gravis, the positive rate of anti-acetylcholine receptor antibodies ranges from 57% to 83%. Positive results may be observed in the ice pack test and neostigmine test [15]. If the patient simultaneously presents with hypercreatinekinemia, it suggests that the patient may also have ICI-related myositis. Once ICI-related myasthenia gravis occurs, ICI treatment should be immediately discontinued, and corresponding treatment should be administered as soon as possible. ICI-related myasthenia gravis should be treated with glucocorticoids. If symptoms do not improve or worsen after 3 days, plasma exchange and intravenous immunoglobulin should be considered [16]. Early identification and intervention are key to reducing the severity and duration of toxicity.

4. Conclusion

This article reports a case of cardiovascular, neurological, and liver injury after four cycles of treatment with Tislelizumab. By summarizing the diagnostic and treatment measures for such adverse reactions at home and abroad, the study aimed to remind clinicians to comprehensively monitor immune indicators in patients receiving ICIs. For patients with multi-organ immune-related adverse events (irAEs) or those with life-threatening complications, early diagnosis and timely glucocorticoid treatment are crucial for prognosis.

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