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CASE REPORT

Myasthenia Gravis-Like Symptoms Following Immune Checkpoint Inhibitor Therapy for Hepatocellular Carcinoma: A Case Report

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Abstract: We describe the case of an older male patient with hepatocellular carcinoma and a history of hepatitis B virus-related cirrhosis and type 2 diabetes mellitus. At 12 weeks after treatment with transcatheter arterial chemoembolization (TACE) combined with systemic therapy using lenvatinib and camrelizumab, the patient was found to have progressive disease, based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. He also exhibited symptoms such as left eyelid ptosis and limitations in inward, upward, and downward movements of the left eye. The possibility of immune checkpoint inhibitor-induced myasthenia gravis was considered. After relevant examinations including electromyography and repetitive nerve stimulation, a diagnosis of oculomotor nerve palsy induced by diabetes-related microvascular dysfunction was ultimately considered. Subsequently, the patient was treated with camrelizumab combined with regorafenib and TACE therapy and was concurrently subjected to stricter glycemic control and neurotrophic treatment. Three months later, the ocular symptoms disappeared, and the mRECIST assessment revealed the achievement of a partial response. At the time of manuscript submission, the overall survival of the patient had reached 81 months.

Keywords: immunotherapy, hepatocellular carcinoma, checkpoint inhibitor, immune adverse event, myasthenia gravis, oculomotor paralysis, diabetes mellitus

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer deaths worldwide. It is characterized by a high degree of malignancy, high mortality rate, rapid progression, and rapid recurrence and metastasis.[1] The prognosis of HCC is generally poor because most patients are diagnosed with mid-to-late-stage disease and are thus denied the opportunity for radical treatment.[2] Immune checkpoints comprise a normal part of the immune system, with a vital role in preventing immune responses toward normal, healthy cells through the suppression of T cell responses.[3] Tumor cells can utilize immune checkpoints for the evasion of immune surveillance. Accordingly, the advent of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape of HCC. However, immune-related adverse events (irAEs) have also posed considerable challenges to clinicians and patients.[4] irAEs involve almost every system of the human body and cause difficulties in single-discipline diagnosis and treatment. In particular, neurological immune-related adverse events (NAEs) are rare complications of ICI therapy. Certain NAEs, such as myasthenia gravis (MG), can lead to undesirable consequences, including a high mortality rate, severe dysfunction, or symptom persistence;[5,6] however, there is currently a widespread lack of awareness of such conditions among clinicians. Therefore, the correct identification of irAEs, particularly NAEs, is of utmost importance.

Case Presentation

The patient, a 65-year-old man, had a history of hepatitis B virus (HBV)-related cirrhosis and type 2 diabetes mellitus. In May 2018, contrast-enhanced abdominal computed tomography (CT) combined with ultrasound imaging of the liver revealed

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the presence of a lesion with a diameter of 1.7 cm in the left medial liver lobe. A diagnosis of HCC was considered. The serum alpha-fetoprotein (AFP) level was 140 ng/mL, and no signs of bone metastasis were observed during an emission CT examination. The patient was diagnosed with stage Ia disease based on the China Liver Cancer Staging (CNLC) system and underwent local radiofrequency ablation therapy. Findings of a subsequent pathological examination were consistent with HCC. The patient underwent regular postoperative outpatient re-examinations and long-term entecavir therapy for anti-HBV treatment. In 2023, contrast-enhanced abdominal CT and ultrasound imaging of the liver indicated HCC recurrence, manifesting as three intrahepatic lesions with a maximum area of 3.2 cm × 2.5 cm and accompanied by a tumor thrombus in the middle hepatic vein. The recurrence was classified as CNLC stage IIIa disease. Transcatheter arterial chemoembolization (TACE) combined with systemic antitumor treatment using lenvatinib and camrelizumab was administered, with intravenous camrelizumab administered for 12 cycles. In December 2023, the patient experienced left eyelid ptosis and diplopia. He sought medical attention at the neurology department of another hospital, where magnetic resonance imaging (MRI) and magnetic resonance angiography of the head did not reveal significant abnormalities. Subsequently, the patient sought medical attention at our hospital. Examination results showed a serum AFP level of 454 ng/mL and the presence of new intrahepatic cancer lesions, based on contrast-enhanced abdominal CT. The patient was found to have progressive disease based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Considering the patient's history of ICI treatment, the possibility of ICI-induced MG was considered. A confirmed diagnosis would indicate a risk of fatality and influence subsequent HCC treatment regimens for the patient; therefore, assistance in diagnosis and treatment was immediately sought from experts of the ophthalmology and neurology departments. The results of specialized examinations were as follows: (1) Ophthalmology, pupil size, 3 mm in both eyes, pupillary light reflex (+), left upper eyelid margin covered half of the pupil range, limitations in outward, inward, upward, and downward movements of the left eye; (2) Neurology, symmetrical facial and tongue muscles, absence of nuchal rigidity, grade 5 muscle strength in all four limbs, normal muscle tone, positive tendon reflex in all four limbs, stable and accurate coordination among the four limbs, symmetrical and normal bilateral superficial pain sensation and tuning fork vibration sensation, Babinski reflex not elicited on both sides. The patient did not experience the gradual worsening of symptoms over the day and showed negative results in the fatigue and ice pack tests. Based on the opinions expressed during the consultation, plain orbital MRI scanning was performed, which revealed the absence of definite space-occupying lesions. An electromyography (EMG) examination of repetitive nerve stimulation (RNS) in the bilateral facial nerves showed the absence of a decreasing trend in low-frequency stimulation and an increasing trend in high-frequency stimulation. The bilateral facial nerves exhibited normal motor conduction, and the results of the muscle enzyme tests were normal. The patient had a history of diabetes mellitus, chronic irregular dietary habits, and poor glycemic control, with postprandial blood glucose fluctuations being approximately 15–20 mmol/L. A final clinical diagnosis of diabetes-related oculomotor nerve palsy was made, and the possibility of irAEs was excluded. The patient subsequently received a treatment regimen that included stricter glycemic control and neurotrophic treatment with B vitamins and methylcobalamin. TACE treatment was performed twice on an as-needed basis, and regorafenib was used in place of lenvatinib as the targeted drug, combined with camrelizumab for systemic antitumor therapy. Three months later, the ocular symptoms of the patient disappeared completely, and a contrast-enhanced abdominal CT re-examination showed the absence of active cancer lesions. The serum AFP level was reduced to 42.8 ng/mL. The patient also achieved a performance status score of 0 and a partial response as assessed using the mRECIST criteria. At the time of manuscript submission, the patient had received 21 cycles of camrelizumab therapy, and overall survival (OS) had reached 81 months.

Discussion

ICIs can cause overactivation of the non-specific immune system, thereby leading to the occurrence of irAEs,[7,8] which can affect any system of the body, including the skin, heart, lungs, liver, kidneys, nerves, gastrointestinal tract, endocrine system, musculoskeletal system, and blood.[9] In particular, NAEs have a low incidence but usually lead to severe consequences.[10] Moreover, an awareness of such conditions among clinicians is generally lacking. The diagnosis of NAEs requires careful differentiation from the neurological dysfunction caused by tumors, infection, metabolic and iatrogenic (non-immune mediated) complications, and other diseases.[11,12] Therefore, a multi-disciplinary treatment (MDT) approach is extremely important for the diagnosis and treatment of such diseases.

The patient in the present case study exhibited unilateral eyelid ptosis accompanied by limitations in outward, inward, upward, and downward movements of the eye on the same side. Given the patient's history of ICI treatment, the possibility of ICI-related ophthalmoplegia and MG were considered. Previous research indicates that most cases of ICI-related ophthalmoplegia are accompanied by myositis or myocarditis.[13] In the present case, the patient had normal muscle enzyme levels, which led to the exclusion of this diagnosis. MG induced by ICI neurotoxicity, which has an estimated incidence of approximately 0.1%–0.2%,[14] is an extremely rare but life-threatening adverse event related to the use of ICIs. Further, it tends to affect men, with a median age of 70 years,[14] and its symptoms most commonly appear at 2–12 cycles after the start of ICI treatment.[14] Moreover, anti-programmed cell death protein 1 therapy is more likely to cause MG than other ICIs.[5] Symptoms might be initially limited to the orbicularis oculi muscle, levator muscle, and extraocular muscles and mainly manifests as eyelid ptosis and diplopia. ICI-related MG also has a greater tendency to cause respiratory weakness than classic MG.[5] From the disease course in the present case, the symptoms of eyelid ptosis and diplopia progressed slowly. In addition, the patient did not experience the gradual worsening of symptoms over the day and showed negative results in the fatigue and ice pack tests. An EMG examination based on RNS in the bilateral facial nerves also showed the absence of a decreasing trend in low-frequency stimulation and an increasing trend in high-frequency stimulation. These findings were inconsistent with the manifestations of MG. Chronic poor glycemic control in the patient could have led to microvascular dysfunction of the oculomotor nerve, which is manifested as eyelid ptosis and impaired inward, upward, and downward eyeball movements. However, pupil size and pupillary light reflex remained normal, which is known as the pupillary escape phenomenon.[15,16] The corresponding mechanism can be attributed to the nutrient artery of the oculomotor nerve being located in the central part of the nerve trunk, whereas the parasympathetic nerve involved in pupillary control is located on the surface, where it is nourished by the blood vessels in the pia mater.

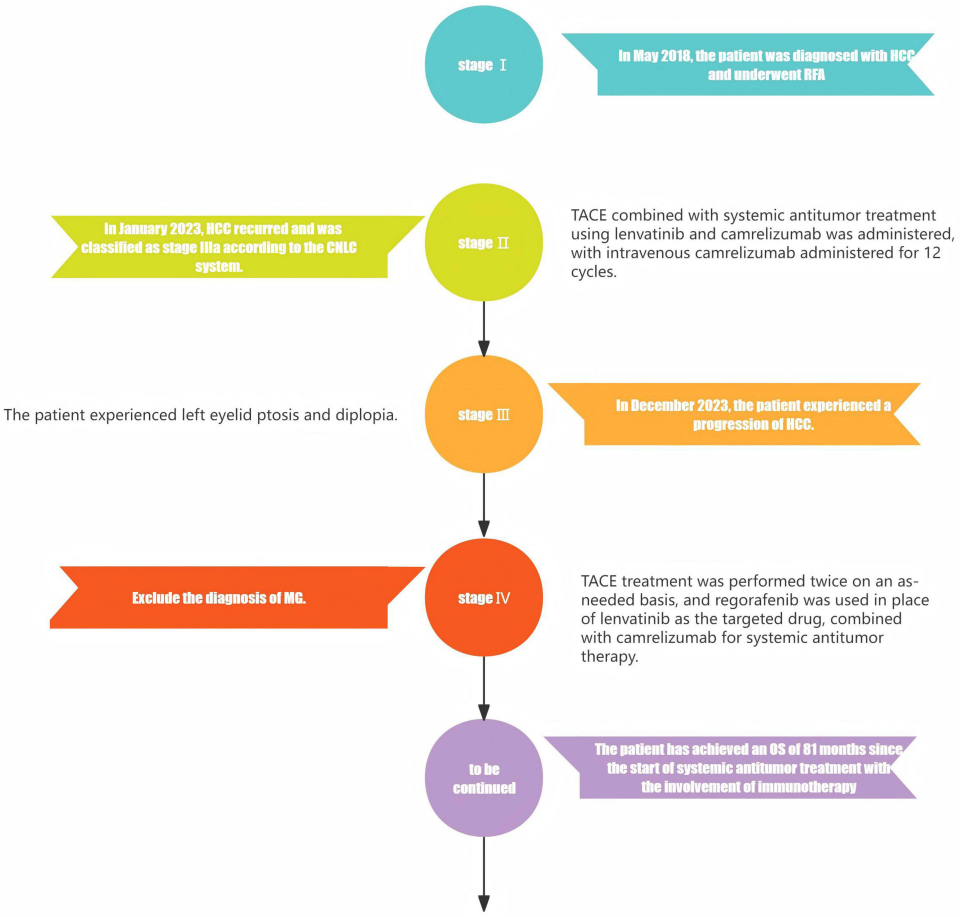

Figure 1 Timeline figure.

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The onset of this condition can be accompanied by mild periorbital swelling and pain; however, its symptoms usually self-resolve after 3–4 months.[15,16] Patient presentations in this case study were consistent with the characteristics of microvascular dysfunction of the oculomotor nerve. Moreover, symptoms were alleviated after glycemic control and neurotrophic treatment, and the subsequent ICI treatment regimen for the management of HCC was not affected. The patient has achieved an OS of 81 months since the start of systemic antitumor treatment with the involvement of immunotherapy (Figure 1).

Conclusion

The advent of ICIs has greatly improved the treatment outcomes for patients with HCC. However, irAEs arising from ICI treatment can involve multiple systems of the body and are characterized by a wide variety of manifestations. In particular, NAEs are rare and highly likely to cause undesirable consequences. Moreover, an awareness of such conditions among clinicians is also generally lacking, which poses huge difficulties in timely diagnoses. In addition to increasing the vigilance and awareness of irAEs among clinicians during the diagnosis and treatment process, the adoption of the MDT approach can also have an important role in the differential diagnosis and treatment of irAEs. Finally, during the HCC treatment process, the diagnosis and treatment of concomitant underlying diseases of the patient are of equal importance to avoid focusing only on the tumor and neglecting the overall condition of the patient.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are notpublicly available due to privacy or ethical restrictions.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of The Third Central Hospital of Tianjin (October, 18, 2024).The approval covers collection, analysis of case data, and publication of the report, ensuring compliance with ethical standards for patient privacy protection and information disclosure.

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The case report follows the CARE guidelines. Written informed consent was obtained from the patient for the publication of this case report, including any accompanying clinical data and images.

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Disclosure

The authors declare no competing interests in this work.

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