Tirelizumab-induced immune encephalitis:A case report

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Tirelizumab-induced immune encephalitis:An Unusual Case Report

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Key Clinical Message: A 65-year-old male patient with lung squamous cell carcinoma, treated with chemotherapy and the PD-1 inhibitor (tirelrelizumab), exhibited abnormal confusion, drowsiness, and other symptoms. After a comprehensive analysis of the clinical manifestations and auxiliary examination, the final diagnosis was immune-mediated encephalitis related to tirellizumab.

Abstract: In the contemporary landscape of oncology, immune checkpoint blockade therapy has emerged as a paramount therapeutic modality. However, concomitant with the pervasive deployment of immune checkpoint inhibitors (ICIs), there has been an escalating incidence of adverse drug reactions over the years.Immunological encephalitis, a prevalent form of central nervous system toxicity, poses a significant threat to the lives of affected patients.A 65-year-old male patient, diagnosed with squamous cell carcinoma of the lung, experienced an atypical immune-mediated encephalitis of clinical nature subsequent to the administration of a PD-1 inhibitor, specifically tirecizumab.The present investigation delved into the clinical presentations and suitable therapeutic protocols for immune-mediated encephalitis.

Keywords:Lung cancer; Tirellizumab; Drug-related adverse reactions; Immune encephalitis

Introduction

Immune checkpoint blockade therapy for PD-1/PD-L1 serves as a breakthrough in the field of antitumor treatment. However, by increasing immune system activity, this therapy can lead to inflammatory side effects, which are often known as immune-related adverse events (irAEs)[1]. In recent years, the increasing use of immune checkpoint inhibitors (ICIs) has led to an annual increase in the incidence of irAEs. Although immune-mediated encephalitis was previously considered rare, a pharmacovigilance study of 48,650 patients with adverse events revealed an incidence of 0.51% for this specific neurotoxicity associated with immune checkpoint inhibitors[2]. Larkin et al. found that immune-mediated encephalitis typically manifests around 55 days after treatment (ranging from 18 to 297 days)[3], with symptoms that are often diverse and atypical.

Case History/examinatian

A 65-year-old male diagnosed with poorly differentiated squamous cell carcinoma of the left hilum in December 2023, with PD-L1 (SP 263) with a tumor cell positive rate of approximately 80%. Due to the ineligibility

for a direct surgery, a combination of chemotherapy and immunotherapy was recommended before revaluation. The patient has a medical history of hypertension for 30 years, with a maximum recorded blood pressure of 170/90 mmHg. He is currently taking 1 sustained-release nifedipine tablet daily. He also has a 30-year history of diabetes, with postprandial blood glucose levels reaching as high as 13 mmol/L, for which he has been administering long-acting insulin subcutaneously once a week. In addition, he experienced an old cerebral infarction 2 years ago, for which he did not receive thrombolysis or stent treatment, and continues to have residual neurological symptoms. From January 25, 2024, to February 25, 2024, the patient underwent 2 cycles of chemotherapy combined with immunotherapy. The treatment regimen included paclitaxel (albumin-bound type 260 mg/m^2) 400 mg on days 1 and 8, along with carboplatin (AUC=5-7) at 400 mg on day 1, administered every 21 days, in combination with immunization (tirelizumab 200 mg every 21 days).

On the morning of March 8, 2024, the patient had sudden confusion, poor speech, drowsiness, and other manifestations. The physical examination was uncooperative. An emergency CT scan was performed upon admission, revealing the following findings: (1) Possible ischemic infarctions in the bilateral lateral ventricles, left basal ganglia, and brainstem; and (2) swelling of the left top subcutaneous soft tissue. Brain diffusion-weighted imaging (DWI) indicates abnormal signals in the left thalamus and pons, suggesting an old cavity infarction. The patient's main blood biochemistry upon admission was as follows: (1) Blood cell analysis: white blood cell count: 10.8 * 10ˆ9/L; red blood cell count: 3.31 * 10ˆ12/L; hemoglobin: 99.0 g/L; platelet count: 256.0 * 10ˆ9/L; platelet ocrit: 0.201%; neutrophil percentage: 86.6%; absolute neutrophil value: 9.4 * 10ˆ9/L; hypersensitivity C-reactive protein: 95.68 mg/L. (2) Liver function: alanine aminotransferase: 15.7 U/L; aspartate aminotransferase: 16.5 U/L; albumin: 37.4 g/L; total bilirubin: 10.09 μmol/L; direct bilirubin: 4.25 μmol/L; indirect bilirubin: 5.84 μmol/L; alkaline phosphatase: 65.1 U/L; r-glutamyltransferase: 17.7 U/L; (3) Serum electrolytes: sodium: 130.8 mmol/L; and (4) Arterial blood gas analysis: lactic acid: 0.5 mmol/L; Negative log of hydrogenion concmtra ion: 7.28; Partial pressure of carbon dioxide: 35.50 mmHg; actual bicarbonate: 16.20 mmol/L; standard bicarbonate: 16.40 mmol/L; anion gap: 19.20 mmol/L; residual base: 9.40 mmol/L; arterial blood oxygen partial pressure 35.00 mmHg; blood oxygen saturation: 67.20%; arterial blood oxygen content: 2.66 mmol/L; hemoglobin concentration: 62.00 g/dL; oxygen partial pressure in the alveoli and arteries: 53.00 mmHg; and potassium: 4.71 mmol/L.

3. Differential diagnosis and treatment

From March 8, 2024, to March 12, 2024, based on the clinical manifestations, the patient has a history of hypertension combined with cerebral infarction, and transient ischemic attacks (TIAs), indicating cerebral blood insufficiency. The patient is prescribed oral aspirin (enteric-coated), clopidogrel sulfate, and atorvastatin calcium tablets to provide antiplatelet therapy, lipid stabilization, and antihypertensive treatment. After initiating treatment, the symptoms initially improved, and there was no significant worsening. However, on March 13, 2024, the patient experienced a progressive aggravation in consciousness and drowsiness and was given a red injection Chinese medicine to promote blood circulation and remove blood stasis to prevent and treat cerebral infarction. On March 15, 2024, the patient entered a shallow coma. On March 15, 2024, a cranial plain MRI (Fig. 1) revealed the following findings: (Artifacts) (1) Left temporoparietal swelling and abnormal signal, nature to be determined, recommended for follow-up review; (2) Ponte, bilateral thalamus, basal ganglia, lateral ventricle, hemioval center, and frontal multiple lacunar cerebral infarctions, with partial softening noted; (3) bilateral lateral paraventricular ischemia demyelination changes; (4) senile brain changes; and (5) occipital arachnoid cyst. Clinical considerations indicated the possibility of immune-related encephalitis or brain metastases. On the same day, the patient was given methylprednisolone sodium succinate 40 mg IV hormone treatment once and mannitol injection 125 mL ivgtt q12h once. On March 16, 2024, the patient regained consciousness and was able to eat autonomously. Hormonal and mannitol therapies were continued, and the patient was able to move independently and maintain a normal diet.

Cranial MRI of March 19, 2024 (Fig. 2): 1. Multiple lacunar cerebral infarctions in the brainstem and bilateral basal ganglia; 2. diffuse swelling of the left temporoparietal gyrus and mild enhancement in the left temporal lobe. The review found that there was no obvious enhancement, and brain metastasis was excluded.

Given the clinical characteristics and the comparison of imaging examination, immune encephalitis was finally considered. March 19, 2024 CT chest scan (Fig. 3): 1. Left hilar space (5.0*3.9 cm), considering malignancy; 2. Multiple slightly large lymph nodes in the mediastinum; 3. Left lower lobe inflammation, mild interstitial changes; 4. Multiple micro and small nodules in both lungs (larger short diameter of approximately 1.1 cm) are recommended for regular review; 5. Left 5,6 anterior rib, left 7,10 posterior rib, and right 6-8 side ribs irregular, suggestive of old fractures; 6. The left adrenal gland shown is slightly thickened. Chest CT revealed inflammation of the left lower lung lobe, considering immunological pneumonia, except for infectious pneumonia, and adding cefoperazone sulbactam sodium for injection based on hormone (methylprednisolone sodium succinate 40 mg iv) treatment.

Outcome and follow-up

On April 3, 2024,during ward rounds, the patient presented with a stable general condition, clear consciousness, and the ability to exercise independently, while cooperating in the physical examination. Cranial MRI findings (April 3, 2024) (Fig. 4): 1. Possible necrosis of the left parietal and temporal cortex, combined with clinical practice; 2. bilateral cerebral hemisphere white matter changes indicative of cerebral ischemia and demyelination; 3. Abnormalities in the left lateral paraventricular region, thalamus, and pons; 4. senile brain changes; 5. posterior fossa cyst. Chest CT scan (April 3, 2024) (Fig. 5) findings: 1. Left hilar occupancy (4.8*3.6 cm), Considering the malignancy, Compared with images March 19,2024, Similar to before; 2. Larger lymph nodes are seen in the mediastinum, Part is slightly smaller than before; 3 inflammation of the original left lower lobe. This time, the absorption is significantly improved; Mild interstitial changes in the lower lobe of both lungs, and the left side is clearly visible compared with the front; 4. Multiple micro and small nodular foci in both lungs, some have reduced in size, while others have newly appeared, regular follow-up is recommended; 5. left 5 and 6 anterior ribs, left 7 and 10 posterior ribs, and right 6-8 lateral ribs with irregular morphology, suggestive of an old fracture, consistent with the prior scans; 6. The left adrenal gland slightly thickened, similar to previous assessments.

After treatment on April 3, 2024, the patient was allowed to be discharged. The regimen included oral prednisone acetate tablets 15 mg (3 tablets) once daily for 3 days, followed by a reduction to 10 mg (2 tablets) once daily and 5 mg (1 tablet) once daily before discontinuation. Blood routine analysis and coagulation function were monitored for 1 week. The patient was reviewed after 1 month to assess the potential for surgery.

Case Discussion

This patient is an elderly male with a history of hypertension for 30 years and an old cerebral infarction for 2 years. Based on the clinical manifestations, he had an early diagnosis of new lacunar cerebral infarction or a primary infarction leading to the recurrence of cerebral infarction dementia (MID), but improved cerebral circulation treatment after consciousness, drowsiness symptoms have not been significantly improved. Later, the patient was treated with the PD-1 checkpoint inhibitor tirellizumab. This treatment activated T cell-mediated tumor cell killing, which led to the release or stimulation of numerous inflammatory mediators, enhancing the immune response and promoting the inflammatory response. A brain MRI of the patient showed patchy lesions in the brain, indicative of brain parenchymal inflammation. The laboratory examination of the patient during the onset. The laboratory tests revealed increased CSF cell count, elevated protein levels, and increased IL-6 levels, all of which are clinically relevant. This patient's immune-mediated encephalitis manifested on day 10 after the second cycle of treatment. Through the clinical manifestations, the encephalitis patient has rapid onset, the pathological activity developed rapidly in a short period, abnormal consciousness, accompanied by drowsiness and other symptoms, more atypical. The patient developed immunoencephalitis and immunopneumonia, both of which improved significantly following small-dose hormone treatment (0.5-1 mg/kg).

Patients with mild to moderate irAEs have found significant improvements in progression-free survival, overall survival, and overall response rate compared with patients without irAEs[4]. Immune-related adverse events caused by ICIs can affect any organ, most commonly in the skin, colon, endocrine organs, liver, and

lung. Neurological disorders are rare and even life-threatening[5]. During the first 4 weeks of treatment, the risk of first developing irAEs was 3 times higher than between 4 weeks of treatment and end of treatment[6]. Neurological irAEs are estimated in 4.2% of patients with diverse clinical manifestations with central and peripheral dysfunction[7]. In central irAEs, encephalitis should be considered ICIs infusiona rare, sometimes occult, and potentially fatal AE[8]. Patients of any age and sex can experience acute encephalitis as an irAE, which can be life-threatening. In a multicenter cohort analysis of "lung cancer immunotherapy-related encephalitis", 9 male patients, all smokers, with a median age of 67 (48-77) years were studied. Of these, 78% had adenocarcinoma, and 5 patients were treated with second-line ICIs. Two patients had inactive brain metastases at the onset of ICIs. A median of 5 (1-22) ICIs infusions preceded the onset of neurological symptoms, most commonly confusion (78%), fever (45%), and cerebellar ataxia (33%)[8]. Case fatality rate was reported between 6% and 12%)[9]. In addition, the unfavorable prognosis of encephalitis may lead to neurological sequelae, such as cerebrovascular diseases and epilepsy. The pathogenesis of immune-related encephalitis is unclear. The inhibition of immune checkpoints by PD-1, PD-L1, and CTLA-4 may induce or aggravate irAEs through various mechanisms, such as tumor and normal nerve, muscle tissue cross immune reaction, interactions between specific intestinal microbes and immune system, immune cell changes, and genetic factors (genetic susceptibility and polygenic risk), all of which are potential mechanisms contributing to irAEs.

At present, the diagnosis of irAEs, which is mainly based on the experience of autoimmune neurological diseases. Reference to the Chinese autoimmune encephalitis diagnosis and treatment of autoimmune encephalitis expert consensus[10](2022 edition), summarizes the following four conditions: A. With acute onset, use of immune checkpoint inhibitors within 1 year, clinical characteristics of consciousness disorders, autonomic dysfunction; severe coma, seizures, and mental behavior abnormalities. B. Early imaging examination can improve the accuracy and timeliness of the diagnosis of immune-related encephalitis, and brain MRI shows leptomeningeal enhancement or brain parenchyma inflammation. C. Histological examination of brain biopsy is the gold standard for the diagnosis of encephalitis, but there are clinical risks and realization. Therefore, inflammatory reaction in cerebrospinal fluid (CSF), brain parenchymal abnormalities in CSF bacterial culture, or neuroimaging can be used as surrogate indicators of immune-related encephalitis; IL-6, IL-17, C-reactive protein are the three inflammatory mediators related to immune-related encephalitis for monitoring and evaluating the condition. D. Antineuronal antibodies were negative, while reasonably excluding other causes. The diagnostic conditions include four aspects: clinical manifestations, auxiliary examination, confirmed experiment, and exclusion of other causes. First, comprehensive analysis is needed to identify the encephalitis with irAEs. In addition, the diagnosis of ICIs-related encephalitis requires sufficient exclusion of meningeal carcinoma, infectious diseases (such as viral encephalitis, neurosyphilis, CNS infections caused by bacteria, fungi, and parasites), and metabolic encephalopathy (Wernick encephalopathy, hepatic encephalopathy, and pulmonary encephalopathy).

In a case of atenlibizumab and bevacizumab for advanced hepatocellular carcinoma-associated encephalitis, high-dose hormone shock was selected and multiple plasmapheresis was performed, resulting in improvement of clinical symptoms and abnormal remission of CSF[11]. In one case of autoimmune encephalitis during Nivolumab monotherapy (Nivolumab 3 mg/kg Q14d), the symptoms occurred 28 weeks after treatment, with no significant improvement despite antiepileptic treatment. After methylprednisolone 80 mg, the patient's neurological symptoms disappeared within 24 hours[12]. Glucocorticoid shock therapy is commonly used as the first line treatment for irAEs encephalitis, methylprednisolone 1000 mg/day, continuous intravenous infusion for 3 days, followed by 500 mg/day, intravenous infusion for 3 days. Afterward, the treatment transitioned to oral prednisone acetate 1 mg $kg^{-1}{\cdot}day^{-1}$. After 2 weeks, the amount was reduced by 5 mg every 2 weeks, and the total course was approximately 6 months[13]. Although most of the irAEs are usually controlled with corticosteroids, serious events that induce the development of immune encephalitis, or even final death, may complicate treatment[14]. The best treatment strategy is based on drug efficacy and its dose (hormones, infliximab, IVIG, rituximab, and plasma exchange).

Therefore, patients receiving PD-1 or PD-L1 inhibitor drugs should be alert to sleep abnormalities and altered consciousness, and the possibility of encephalitis after ICIs treatment. An early multidisciplinary

approach to diagnosis and management is crucial in effectively addressing this condition. Referring to this patient, MRI examination mostly showed leptomeningeal enhancement or brain parenchymal inflammation, showing abnormal signals in one or both medial temporal lobes, which provided a more reliable and effective imaging basis for the early diagnosis and prognosis evaluation of irAEs. Early detection of immune-mediated encephalitis and early administration is likely to avoid large hormonal impact, and low-dose hormone use may be used as an early clinical path. At present, it is difficult to measure and evaluate individual-level exposure to immune-related encephalitis in large-scale population studies. The vast majority of studies are from animal experimental data. Just like other pharmacovigilance studies, it is necessary to conduct prospective clinical studies for long-term validation of ICI-induced irAEs in the future. Due to the lack of detailed clinical information and clear diagnostic criteria, it is currently difficult to evaluate cases reported by clinicians (for example, cerebrospinal fluid data to confirm the reported diagnosis). The natural outcome of adverse events under standard supportive care, comparing the impact of nonspecific and targeted immunomodulatory therapy on the clinical outcomes of patients with tumors developing irAEs still needs further exploration[15].

Statement of Ethics

Ethical approval was not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Conflict of Interest Statement

There are no competing interests for any author.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the author.

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