Successful Management of Generalized Myasthenia Gravis Induced by Atezolizumab in a Patient With Extensive-Stage SCLC: A Case Report

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Received 30 March 2022; revised 24 May 2022; accepted 29 May 2022

Available online - 2 June 2022

ABSTRACT

Immune checkpoint inhibitors including atezolizumab and durvalumab have been approved as the first-line treatment in extensive-stage SCLC. However, immune checkpoint inhibitors can cause immune-related adverse events, which will lead to the shelving of follow-up treatment and the progression and deterioration of SCLC. Myasthenia gravis (MG) is a relatively rare and fatal presentation of immune-related adverse events, and experience with immune-related MG in patients with SCLC is limited. Herein we present a patient who developed generalized MG after receiving three cycles of atezolizumab. Fortunately, he responded to intravenous immunoglobulin and glucocorticoids, and chemotherapy for SCLC continued.

Case Presentation

A 56-year-old man presented with fever, cough, and expectoration. Chest enhanced computed tomography (CT) revealed an irregular nodule mass with a size of about 3 by 4 cm in the lower lobe of the left lung with uneven enhancement, which surrounded the left lower pulmonary artery and vein. Endobronchial ultrasonound-guided fine-needle aspiration biopsy confirmed a diagnosis of SCLC. Positron emission tomography–CT further revealed metastases in bilateral hilar, mediastinal, and clavicular lymph nodes, and contralateral lung lobe, indicating a clinical stage of T4N3M1b. He was treated

Introduction

Immune-related myasthenia gravis (irMG) is a rare and fatal adverse event, usually leading to a poor prognosis. Experience with irMG in patients with SCLC is limited. We present a case with SCLC who developed irMG after receiving three cycles of atezolizumab. Fortunately, he responded to intravenous immunoglobulin and glucocorticoids, and chemotherapy for SCLC continued.
with etoposide 190 mg on days 1 to 3 (100 mg/m²), carboplatin 500 mg on day 1 (area under the blood concentration time curve of 5 mg/mL/min), and atezolizumab 1200 mg on day 2. After three cycles of treatment, he developed eyelid ptosis, diplopia, and ocular motor disturbances, and then displayed symptoms of dysphagia, slurred speech, choking, and weakness in neck muscles and limbs. Neurologic examination revealed a marked decline in systemic muscle strength without tenderness to palpation. Serum muscle enzymes were normal. No thymic mass was found on chest CT, and no abnormality was found on cranial magnetic resonance imaging. Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and antineuronal antibodies were all negative. Neuromuscular antibody testing revealed an elevated serum antiacetylcholine receptor (AChR) antibody titer of 0.576 nmol/liter, and normal levels of antivoltage-gated calcium channels antibody, antimuscle-specific tyrosine kinase antibody, and antititin antibody. A repetitive nerve stimulation test revealed that the amplitude of low-frequency stimulation was markedly decreased. No abnormal signs in myogenic damage and nerve conduction velocity were found on electromyography. Generalized MG induced by atezolizumab was considered. Pyridostigmine bromide 60 mg/day every 6 hours orally and intravenous immunoglobulin (IVIG) 30 g/day (500 mg/kg/day) for 5 days were administered, and his MG was notably ameliorated. The fourth cycle of antitumor therapy without immune checkpoint inhibitors (ICIs) was given immediately. He received intravenous methylprednisolone 40 mg/day for 5 days about 1 week after chemotherapy, followed by prednisone acetate 40 mg/day orally. The reduction scheme of glucocorticoid is as follows: prednisone acetate was reduced to 30 mg/day after 2 weeks, and then reduced by 5 mg every 2 weeks. The retest of anti-AChR antibody titer was still high (0.796 nmol/liter), and a second and third round of IVIG with a dosage of 20 g/day for 3 days and 10 g/day for 3 days were given separately, and the interval between the second and third round of IVIG was about 3 weeks. His muscle strength continued to improve and basically returned to normal. He received follow-up chemotherapy as scheduled, and maintained partial response with the pulmonary mass continuing to shrink (Fig. 1).

**Discussion**

irMG is a rare but fatal neurologic adverse event. In a single-center experience, only 14 of 5898 patients with cancer (0.24%) treated with ICIs experienced irMG.⁴ Compared with Lambert-Eaton syndrome, MG is a rarer paraneoplastic syndrome in SCLC, and ICIs may exacerbate preexisting MG.⁵ In our case, auxiliary examinations support a diagnosis of MG induced by atezolizumab rather than Lambert-Eaton syndrome as a paraneoplastic syndrome. Although irMG has been

![Clinical course of the present case. IVIG, intravenous immunoglobulin; MP, methylprednisolone; NSE, neuron-specific enolase; PAT, prednisone acetate tablets; proGRP, progastrin-releasing peptide.](image-url)
reported in multiple malignancies, experience in the management of irMG in SCLC is extremely rare. In the phase I and phase II trial of nivolumab alone or nivolumab combined with ipilimumab in recurrent SCLC, one patient developed MG 16 days after treatment with ipilimumab and nivolumab. He initially responded to treatment with prednisone and plasmapheresis; however, his condition soon deteriorated, and he had no response to glucocorticoids, plasmapheresis, and IVIG, and eventually died because of MG-associated respiratory failure. In a systematic review of 65 cases with irMG, 24 patients (37%) died, with MG complications and cancer progression as the main causes of death. In our case, pyridostigmine bromide and IVIG were preferentially administered in the first place, which was in line with the recent view of early administration of IVIG or plasma exchange in the management of irMG. Fortunately, the patient responded to our above treatments, and chemotherapy was promptly conducted after his MG was ameliorated. To avoid the deterioration of MG caused by the early usage of glucocorticoids and an increased risk of infection during the period of myelosuppression caused by chemotherapy, half a dose of glucocorticoids was administered 1 week later after the completion of chemotherapy. As the patient was not completely recovered from MG and retested anti-AChR antibody titer was still high, another two rounds of IVIG were given for consolidation. Finally, his muscle strength improved to normal, and chemotherapy was continued as scheduled. The discrepancy in treatment response and outcome between this case and the previously reported case indicated the existence of heterogeneity of irMG. MG is a life-threatening adverse event induced by immunotherapy, and its prognosis is poor as a whole. Our present case’s good response to treatment may be caused by chance, and the absence of elevated muscle enzymes in our case may partly explain his better prognosis. In addition, our treatment schedule took both irMG and SCLC into account, avoiding delays in antitumor therapy because of the incidence of irMG and striving for a chance to prolong the patient’s survival.

Conclusions
In general, MG is a relatively rare immune-related adverse event and is fatal with a poor prognosis. Heterogeneity exists in patients’ clinical presentations and responses to treatment. Early usage of IVIG may be effective. Antitumor therapy should be restarted whenever possible once irMG is ameliorated.

CRediT Authorship Contribution Statement
Shuang Wu: Wrote the initial manuscript, Depicted the figure, Manuscript preparation.
Jiayu Shi, Yuzhou Guan: Assisted in the diagnosis and treatment of atezolizumab-induced myasthenia gravis of this case.
Li Zhang, Hanping Wang: Guided the writing, Revised of this manuscript.
Shuang Wu, Jiayu Shi, Yuzhou Guan, Li Zhang, Hanping Wang: Contributed to data evaluation and manuscript revision.

Acknowledgments
This work was supported by the National Key Research and Development Program of the People’s Republic of China (grant number 2016YFC0901500). This work obtained informed consent from the patient.

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