Immune Checkpoint Inhibitor-Induced Myasthenia Gravis in a Patient with Advanced NSCLC and Remote History of Thymoma

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Clinical Practice Points

- Antibodies that block programmed death-ligand 1 are highly active against advanced non–small-cell lung cancer (NSCLC) and many other tumor types.
- We report on a patient with advanced NSCLC with remote history of curatively resected thymoma and no prior history of autoimmune disease who developed severe immune-related myasthenia gravis following treatment with pembrolizumab.
- This case suggests caution must be exercised when treating cancer patients with immune checkpoint inhibitors, including NSCLC, who have a remote history of curatively treated thymoma.

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Introduction

Programmed death-ligand 1 (PD-L1) inhibitors have revolutionized the treatment of advanced non–small-cell lung cancer (NSCLC), with improved survival in randomized clinical trials. However, immune-related adverse events (irAEs) remain a concern.[1]

Accurately predicting irAEs is important; among the exclusionary conditions that preclude treatment is the presence of active autoimmune disease. Underlying disease states that predispose to irAEs remain under-recognized.

Thymoma is often associated with autoimmune diseases such as myasthenia gravis, which typically remits when the underlying thymoma is curatively treated.[2] However, autoimmunity can persist. Here, we report a case of remote history of a patient with a resected thymoma who developed severe irAEs on pembrolizumab for metastatic NSCLC.

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Case Report

A 63-year-old woman, a never-smoker, was diagnosed with stage IV NSCLC-adenocarcinoma after presenting with cough. Positron emission tomography/computed tomography showed a right pleural effusion, fluorine-18 fluorodeoxyglucose-avid right para-mediastinal mass and ascites (Figure 1). Pleural fluid cytology and mediastinal lymph node biopsy demonstrated lung adenocarcinoma (Figure 2). PD-L1 expression was 5% by DAKO 22C3. Broad genomic profiling was negative for oncogenic driver mutations including EGFR, ALK, ROS1, and BRAF V600E/K.

Past medical history revealed a history of thymoma, curatively resected 15 years previously. She also received postoperative radiation therapy. She had no history of autoimmune disease including myasthenia gravis.

She was initially treated with carboplatin/pemetrexed followed by pemetrexed maintenance. Upon progression, she initiated pembrolizumab. After 2 cycles, she developed bilateral (left > right) ptosis (Figure 3), extraocular muscle palsies, shortness of breath, and fatigue that worsened towards the end of the day. Magnetic resonance imaging of the brain was unremarkable. She was admitted to the intensive care unit with diagnosis of myasthenia gravis. Pembrolizumab was discontinued, and the patient was treated with intravenous immunoglobulins, high-dose corticosteroid therapy, and pyridostigmine with clinical improvement. Laboratories were notable for negative for acetylcholine blocking, modulating, and receptor antibodies, but positive for highly elevated striatal muscle IgG antibody titer (1:1280). The patient's neurologic symptoms

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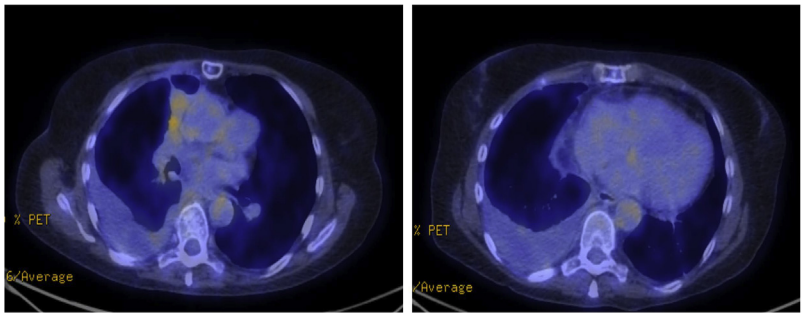
Figure 1 Positron Emission Tomography/Computed Tomography With Right-sided Paramediastinal Mass and pleural Effusion



improved, and she was discharged home and subsequently elected hospice care without follow-up imaging to assess response.

Discussion

Thymomas originate from the lympho-epithelial cells of the thymus and account for about one-half of primary anterior mediastinal tumors.[3] They are associated with unique autoimmune diseases such as myasthenia gravis; over 10% to 30% of patients with myasthenia gravis concurrently have a thymoma.[4,5]

The role of immunotherapy for thymic malignancies has been investigated. In a clinical trial of pembrolizumab, 71% of thymoma patients experienced grade $\geq$ 3 irAEs, including myasthenia gravis

Figure 2 A, Tumor Cells Positive for CK7; B, Tumor Cells Positive for TTF1; C, Hematoxylin and Eosin Stain Tissue Section From Cell Block at 200×; and D, Tumor Cells With Weak Positive Staining (less than 10%) for Programmed Death-ligand 1 by DAKO 22C3 Antibody

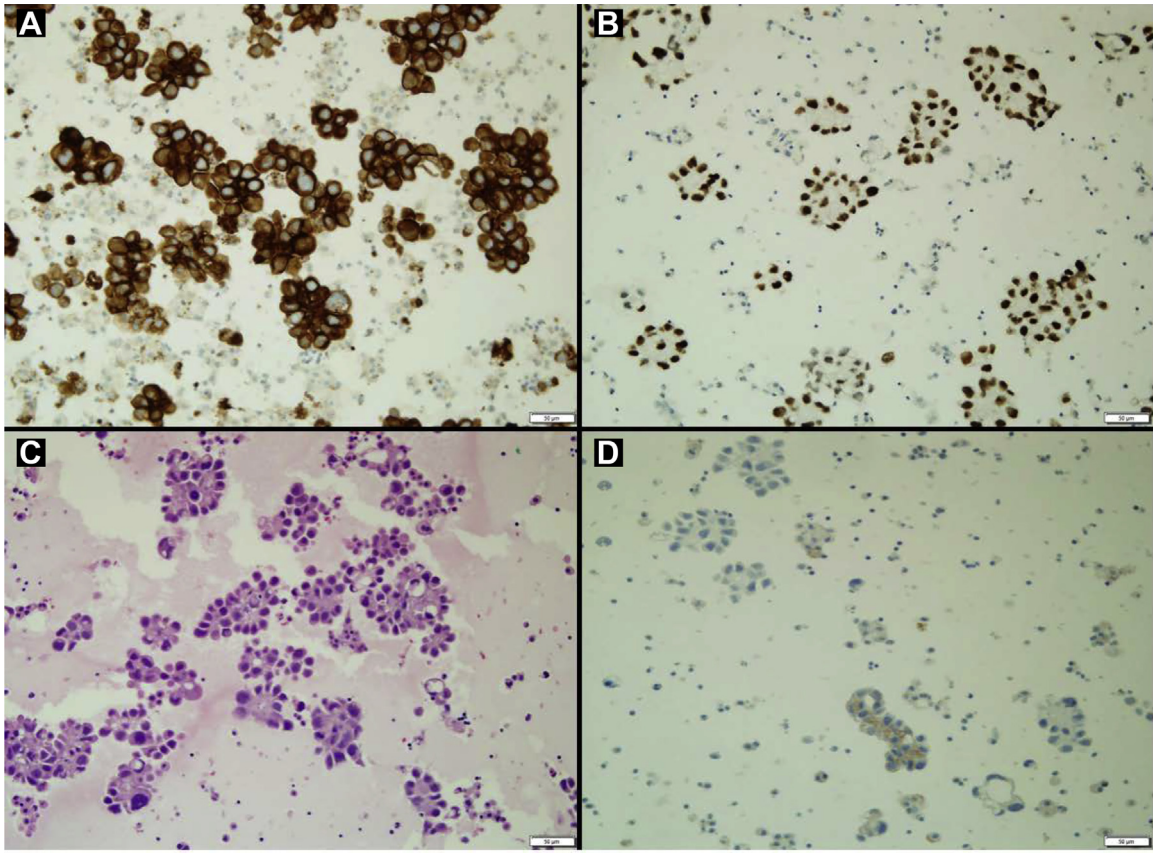


Figure 3 Bilateral Ptosis Consistent With Myasthenia Gravis

and myositis.[6] In a trial with the PD-L1 antibody avelumab in thymic malignancies, 5 of 8 patients had irAEs including 3 (38%) of 8 patients with grade $\geq$ 3 irAEs.[7]

Pembrolizumab-related myasthenia gravis has led to fatal outcomes despite early aggressive treatment such as corticosteroids, pyridostigmine, intravenous immunoglobulin, and plasmapheresis.[8] In one review, pembrolizumab-related myasthenia gravis was reported to result in a mortality rate of 30%.[9]

Conclusion

Our case suggests that patients with a remote history of thymoma, even without evidence of recurrence or history of autoimmune diseases, may develop severe irAEs such as myasthenia gravis typically associated with treatment of active, malignant thymoma. Thus, caution must be observed when treating NSCLC or other malignancies with immune checkpoint inhibitors in patients with a prior history of thymoma.

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Disclosure

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