CASE REPORT

Abrupt respiratory insuciency presenting initially as myasthenia gravis crisis with thymic carcinoma – a case report

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ABSTRACT

Myasthenia gravis (MG) is frequently complicated by respiratory insufficiency, which is known as an MG crisis. It can appear as the initial presenting symptom of myositis-MG overlap. Here we report a case of a 67-year-old woman with previously underdiagnosed MG, who presented with acute respiratory insufficiency. A bulky mass in the right lung was pathologically suspected to be a lymphoepithelioma-like carcinoma of the thymus. Due to high expression of programmed death-ligand 1 (PD-L1) (70%–80%) on the tumor, the immune checkpoint inhibitor (ICI) pembrolizumab was administered as second-line therapy. However, the patient died of ICI-induced myocarditis, which was confirmed by autopsy. Immunohistochemistry showed an overexpression of PD-L1 on the myocardial sarcolemma as well as the diaphragm. PD-L1 overexpression on the diaphragm might have contributed to the pathogenesis of myositis-MG overlap with acute respiratory insufficiency.

Key Words: Crisis, Myasthenia gravis, Respiratory insufficiency, Thymic carcinoma

1. INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease. MG crisis is defined as an exacerbation of MG weakness that provokes an acute episode of respiratory insufficiency leading to mechanical ventilation. It is an uncommon, life-threatening neurological emergency.[1] Typically, from 10%–20% of patients with MG will experience an MG crisis episode, which occur most commonly during the first year after diagnosis, and will have other neurological signs and symptoms.[2] In some patients, MG crisis can be the initial presentation of MG.[3,4] One rare case of myositis-MG overlap had some characteristic features, including respiratory insufficiency.[5]

About 20% of MG cases are associated with thymic neoplasms, whereas 50% of thymomas present with MG. Very few reports have described MG associated with thymic carcinoma.[6] Thymic carcinoma responds poorly to chemotherapy. Carboplatin plus paclitaxel combination therapy is the first-line treatment with the highest response rate in patients with thymic carcinomas.[7] There are scarce data regarding single-agent targeted therapy as second-line systemic treatment including sunitinib, pemetrexed, paclitaxel, octreotide, gemcitabine, 5-FU, etoposide, and ifosfamide. Pembrolizumab, which is an immune checkpoint inhibitor (ICI), is also used as second-line therapy in patients with thymic carcinoma and as programmed death 1 (PD1)/PD-ligand 1 (PD-

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L1) inhibitor therapy.[7] Along with myocarditis, myositis, and hepatitis, MG has been reported to be a severe immune-related adverse event (irAE) in 3%–14% of cases of thymic carcinoma treated with permbrolizumab.[8,9]

Here, we report a case of myositis-MG overlap initially presenting as respiratory insufficiency followed by ICI-induced myocarditis, confirmed by autopsy.

2. CASE PRESENTATION

A 67-year-old woman presented with 1 week of progressive, non-fluctuating back pain, and dyspnea. She had no medical history and was taking no medication. In the family history, no neurological disorders were reported. She visited our hospital and lost consciousness in the entrance hall. Her respiration was extremely weak, and her oxygen saturation level was unmeasurable on room air. The arterial blood gas analysis was pH 7.05, $PaCO_2$ 120 torr, and PaO_2 25.8 torr. After 10L oxygen administration, her blood pressure was 134/72 mmHg, her heart rate 108 beats/min, and her oxygen saturation level 98%. Cranial nerve examination showed that the light reflex was prompt and ocular movement was full without a ptosis.

Due to respiratory arrest, mechanical ventilation was started on assist control mode of 14 breaths/min with a tidal volume of 450 mL, 30% FiO_2, and a positive end expiratory pressure of 5 mmHg, and she subsequently regained her normal physiological respiration rate. The laboratory evaluation showed a white blood cell count of 14,300/μL, hemoglobin of 13.7 g/dL, and platelet count of 31.3 $\times$ 104/μL. Blood chemistry showed an aspartate transaminase/alanine transaminase ratio of 113/170 U/L, brain natriuretic peptide (BNP) 566 pg/mL, and creatine kinase (CK) level 636 U/L. Other blood parameters were within normal limits of blood urea nitrogen/creatinine of 18.0/0.42 mg/dL Thyroid function testing showed free T4 of 1.08 ng/dL and thyroid stimulating hormone of 0.62 μIU/mL. Computed tomography showed an anterior mediastinal tumor 78 mm in diameter, right pleural effusion, and pleural dissemination (see Figure 1A & B). Her echocardiography showed hypokinesia of the left ventricle lower wall. However, a cardiac catheterization demonstrated normal findings in her coronary arteries.

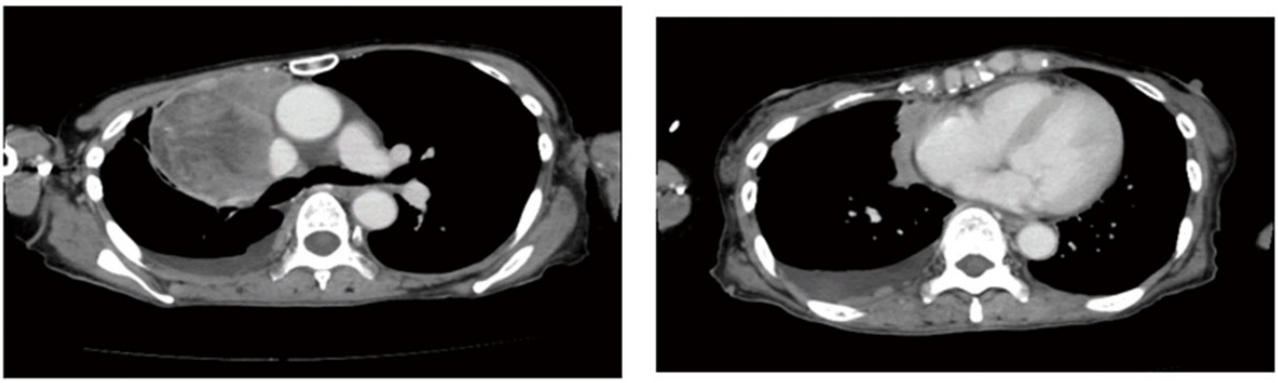

Figure 1. Computed tomography reveals an anterior mediastinal tumor, 78 mm in diameter, at the carina level (A)(left), and right pleural effusion and pleural dissemination at the heart level (B)(right).

We were suspicious of other causes of respiratory insufficiency, such as neuromuscular disorders, Guillain-Barre syndrome, or MG. There were normal findings of the physical and neurological examination and cerebrospinal fluid analysis. A diagnosis of MG was achieved based on the neurophysiological studies. Electromyography showed no decrement on 3 Hz repetitive nerve stimulation in various muscles. During weak contractions, electromyography showed low amplitude and myopathic changes. She was diagnosed with MG based on high titers of anti-acetylcholine receptor antibody (anti-AchRAb) (5.4 nmol/L; normal < 0.40 nmol/L), and positive anti-titin Ab. After the diagnosis of myositis-MG overlap, intravenous immunoglobulin was administered to the patient for 5 days.

On the 10th day of admission, she was scheduled to undergo a tracheostomy and a pathological examination of the percutaneous tumor biopsy, which revealed lymphoepithelioma-like carcinoma of the thymus. According to the Masaoka staging system, the patient was diagnosed with thymic carcinoma stage IVa (pleural dissemination). We administered carboplatin and paclitaxel as first-line therapy. However, the tumor increased after 2 chemotherapy cycles. On the 91st day after admission, due to high expression of PD-L1 (70%–80%) on the tumor, pembrolizumab, which is an ICI, was administered as second-line therapy. On the 8th day after administration of pembrolizumab, the patient's serum CK and CK-muscular

brain level were significantly elevated to 4,635 IU/L and 5.91 IU/L, respectively, along with a BNP level of 288.8 pg/mL. Bedside echocardiogram showed a significantly reduced ejection fraction of left ventricle 30% and extensive wall motion abnormality. Methylprednisolone 1,000 mg was administered due to suspected myocarditis. However, on the 10th day after administration of pembrolizumab, the patient died of heart failure despite active management in collaboration with the cardiology team. Pathological views on autopsy revealed squamous cell carcinoma in the thymus (see Figure 2A) and a T-cell-predominant lymphocytic diffuse infiltration into the myocardium (see Figure 2B) and diaphragm (Figure 2C). As the PD-1/PD-Ls pathway was considered to play crucial roles in acute respiratory insufficiency due to myositis-MG overlap, immunohistochemistry with PD-L1 was performed on diaphragm. Immunohistochemistry demonstrated high expression of PD-L1 in the thymic carcinoma (Figure 2D), myocardium (Figure 2E), and diaphragm (Figure 2F). We confirmed ICI-induced myocarditis with myositis-MG overlap.

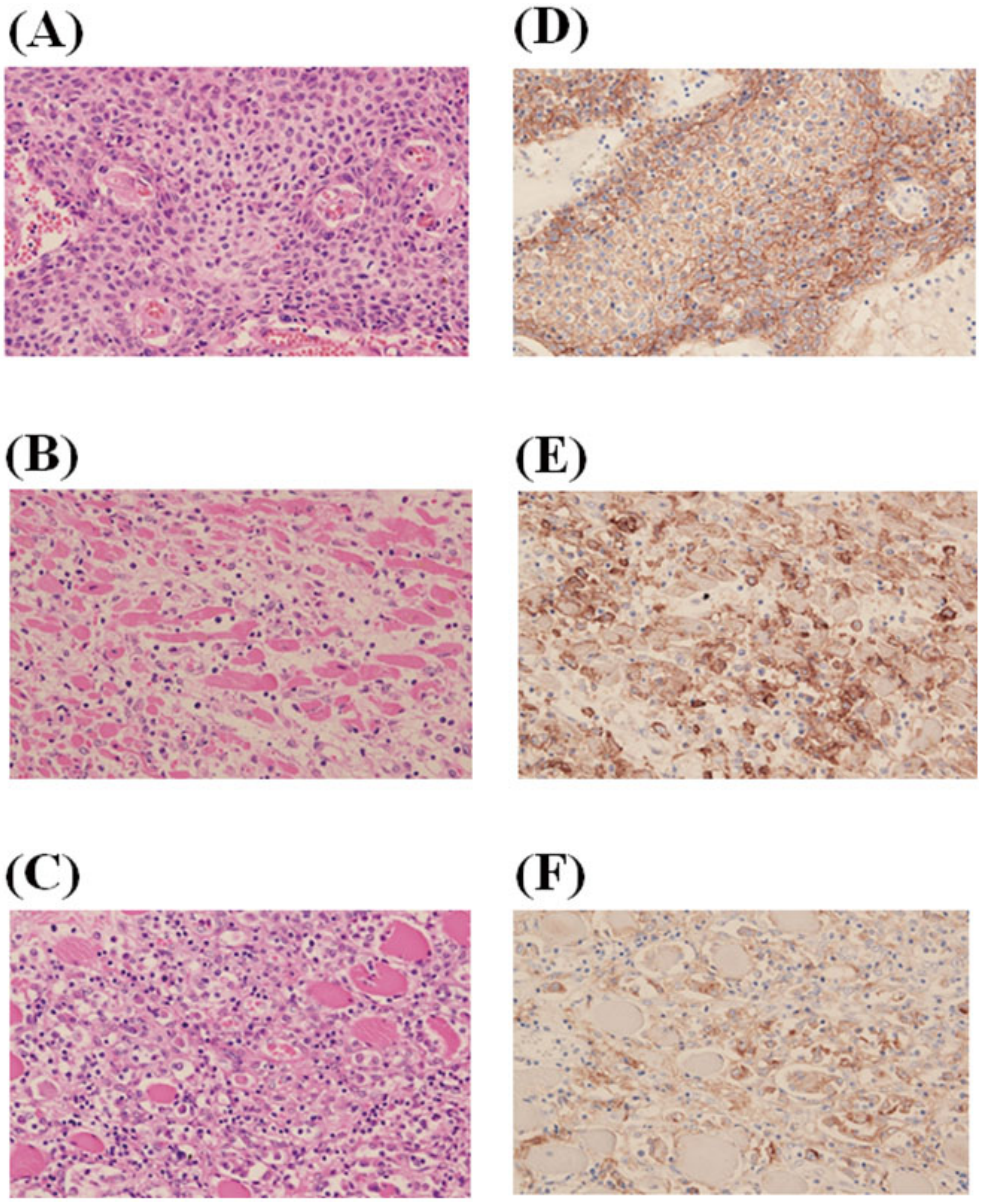

Figure 2. Histological examination obtained from autopsy revealed poorly differentiated, nonkeratinizing squamous cell carcinoma of the thymus (A), and lymphocytic infiltrate in the myocardium (B) and the diaphragm (C) (hematoxylin and eosin staining, X100). Immunohistochemistry with PD-L1 (X100) showed overexpression on the squamous cell carcinoma of the thymus (D), the myocardium (E), and the diaphragm (F).

3. DISCUSSION

The current case report demonstrates that acute respiratory insufficiency can be an initial presentation of myositis-MG overlap. Respiratory insufficiency can be a complication during the early course of MG in approximately 3%–8% of cases, known as an MG crisis,[10] which is reported to occur during the first year after diagnosis. With respiratory insufficiency in MG without a history of generalized weakness, this is a rare occurrence.[3,4]

Given our patient showed no other neurological symptoms which are quite usual with MG, we did not initially suspect it. However, due to evidence of hypoxemic respiratory failure, we attempted to determine the cause of the respiratory insufficiency. The frequent thymoma association in patients with myositis-MG overlap indicates that the association between these 2 diseases is not coincidental but is caused by thymoma-related immunopathogenic mechanisms.[11] In our case, despite non-fatigable muscle weakness unresponsive to acetylcholinesterase inhibitors, CK levels were elevated after admission. She also showed a muscular disorder pattern on the electromyography and was anti-titin Ab positive. These findings might lead to suspicion of myositis-MG overlap.[12] Consequently, titin Ab and, particularly, ryanodine receptor-Ab, might be associated with myositis-MG overlap cases.

We report here a case with ICI-induced myocarditis. The high level of PD-L1 expression on the tumor indicates that PD-L1 might play a role in the pathogenesis of the tumor and that PD-L1/PD-1 blockade could be a viable therapeutic option for patients with PD-L1-positive thymic carcinoma who have failed other first-line therapies.[13] Patients with MG initially have a higher prevalence of cardiac manifestations in the presence of thymoma (10%–15%).[14] It was reported that myocarditis developed in patients with MG with anti-striational antibodies, including anti-titin Ab.[15] The occurrence of severe irAEs, especially myocarditis, myositis and hepatitis, following pembrolizumab administration in patients with thymic carcioma has been a major concern and could lead to death. PD-L1 expression in muscle cells in patients with MG may influence autoimmune reactivity with disease severity, and the gene expression of PD-L1 is not influenced by the presence of tumors in the thymus.[16] Pre-existing anti-AchRAbs and B-cell lymphopenia put patients with thymomas at high risk for developing myositis after treatment with ICIs.[17] The learning point is to avoid using ICIs in patients with thymic carcinomas having auto-immune manifestations, especially in those positive for anti-AchRAb and anti-titin Ab.

We demonstrated that there was an overexpression of PD-L1 in the diaphragm of our patient. In some patients with autoimmune diseases, including Sjögren's syndrome, it was hypothesized that the PD-1/PD-Ls pathway participates in the pathogenesis of the diseases.[18] To the best of our knowledge, our case is the first report of PD-L1 overexpression in the diaphragm that may have contributed to respiratory insufficiency in a patient with myositis-MG overlap.

In conclusion, we have reported the case of a 68-year-old woman who presented with acute respiratory insufficiency as the initial presentation of myositis-MG overlap. Thus, in an emergency room setting, overexpression of PD-L1 in the diaphragm should be suspected in a patient with myositis-MG overlap.

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CONFLICTS OF INTEREST DISCLOSURE

There is no conflict of interest.

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