

## Case Report

# Myasthenia gravis and dyspnea associated with Castleman's disease

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**Abstract:** Castleman's disease is a rare lymphoproliferative disorder. It is usually benign and the resection of the tumor is curative. However, Castleman's disease is occasionally associated with autoimmune diseases such as paraneoplastic pemphigus, POEMS syndrome (polyneuropathy, organomegally, endocrinopathy, monoclonal gammopathy, and skin changes), which usually leads to poor outcomes. Here we report a patient with Castleman's disease who developed progressive myasthenia gravis and dyspnea. Myasthenic symptoms were responsive to acetylcholinesterase inhibitors and corticosteroids, but the patient's respiratory functions continued to decline in spite of intensive medical therapy. To our knowledge, this is the second case of Castleman's disease associated with simultaneous myasthenia gravis and dyspnea. Considering the immunostimulatory nature of the tumor, we propose that the myasthenia gravis and bronchiolitis obliterans are both components of the aberrant systemic immunoreaction.

**Keywords:** Castleman's disease, myasthenia gravis, bronchiolitis obliterans, respiratory insufficiency

### Introduction

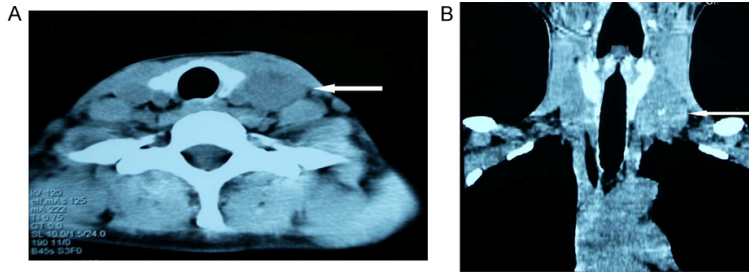
Myasthenia gravis is an acquired autoimmune disorder characterized by skeletal muscle fatigue and weakness. The clinical features of myasthenia gravis are mediated by antibodies to the nicotinic acetylcholine receptor (nAChR) at the neuromuscular junction. Myasthenia gravis is often associated with thymoma or thymic hyperplasia. Other diseases that are known to be associated with myasthenia gravis include rheumatoid arthritis, pernicious anemia, systemic lupus erythematosus, sarcoidosis, Sjogren's disease, and mitochondrial myopathy [1]. These associated conditions suggest an autoimmune basis for myasthenia gravis. Although rare, a few myasthenia gravis cases have been reported to be associated with Castleman's disease, a lymphoproliferative disorder [2, 3]. We present the case of a patient with myasthenia gravis and progressive dyspnea related to Castleman's disease. Furthermore, the onset of the myasthenic symptoms occurred 5 months after the resection of the tumor. This phenomenon suggests that the patient suffered from a progressive systematic immune disturbance.

### Case report

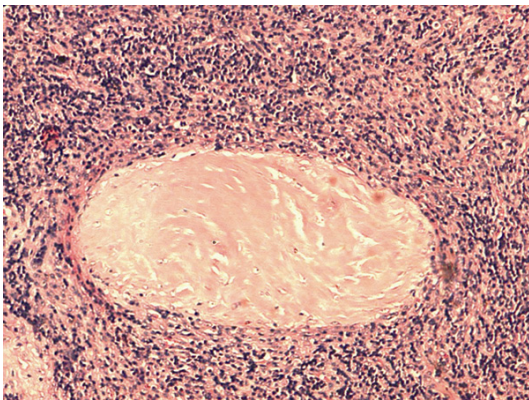
A 25-year old woman presented to our clinic with dyspnea of ten months' duration. She had no recent infections and her medical history was unremarkable. She experienced increasing inspiratory dyspnea on exertion. She also experienced a nonproductive cough and oral mucosa ulcerations. A neck computed tomography (CT) confirmed the presence of a well-defined and margined mass near the trachea (**Figure 1**). Excision of the mass was performed, and a 3.3 × 2 × 5.3 cm uniformly solid lobulated mass was removed. Histologic evaluation of the mass showed immunoproliferative changes with abnormal follicular architecture, obliteration of sinuses, hypervascular interfollicular tissue, and concentric perivascular arrangement of the mantle zone (**Figure 2**). The patient was diagnosed with Castleman's disease.

Unfortunately, the dyspnea did not subside postoperatively. Her respiratory symptoms gradually progressed to the point that she required ventilatory support. Physical examination revealed three depressions sign and rhonchi. Pulmonary function test showed severe ob-

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**Figure 1.** (A) Neck CT scan and (B) CT reconstruction image of neck. Neck computed tomography (A) and the reconstructive imagine (B) showing a well-defined and margined homogeneous mass at the right of the trachea (arrow).



**Figure 2.** Histology of a patient with Castleman's disease. Histopathologic sections (hematoxylin & eosin stain) show typical features of hyaline vascular Castleman disease with hyalinized vessels within germinal follicles that are surrounded by onion-like lymphocytes. (hematoxylin and eosin staining,  $\times 400$ ).

structive ventilatory disturbances. There was bronchiectasis, but no evidence of multicentric or residual tumors on computed tomography scan. No enlarged lymph nodes were found around the neck, axillary fossa, or retroperitoneal under ultrasonic tomography. The computed tomography findings and clinical symptoms were characteristic of bronchiolitis obliterans. Furthermore, she gradually developed generalized weakness and bilateral ptosis three months after the operation. The neurologic examination, electromyography, neostigmine test, and fatigability test were suggestive of myasthenia gravis.

Because she was receiving ventilatory support and could not easily swallow, she was treated with continuous intravenous administration of neostigmine (4 mg/d) and prednisolone (40 mg) in the morning. The myasthenia was con-

trolled by these drugs, but the pulmonary symptoms progressively worsened. The condition of the patient deteriorated in spite of intensive drug treatment. She died four weeks later from respiratory insufficiency.

### Discussion

Castleman's disease is a rare lymphoproliferative disease characterized by non-clonal lymph node hyperplasia. This tumor may adopt a unicentric or multicentric presentation. The former is usually asymptomatic and amenable to surgical treatment, and the latter often exhibits complicated symptomatic manifestations. The most common location of these tumors is retroperitoneal or mediastinal. Pathologically it is classified into the common hyaline vascular type, the rarer plasma cell type, and the mixed type. About 20-40% of the tumors are discovered incidentally. Similar to the present case, it usually manifests as a solitary mass with marked enhancement on computed tomography. The etiology and pathogenesis of Castleman's disease are poorly understood. Our current understanding of the pathogenesis of Castleman's disease points to reactive follicular hyperplasia in response to an unknown antigenic stimulus [4].

An association of multicentric Castleman's disease with HIV infection has been demonstrated. In spite of the fact that unicentric Castleman's disease is frequently asymptomatic, there is a remarkable association of Castleman's disease with other diseases, such as lichen planus, pemphigus vulgaris, POEMS syndrome, myasthenia gravis, nephrotic syndrome, amyloidosis, plasmacytoma, and rheumatoid arthritis [4-6]. The association of Castleman's disease with various immune phenomena and immunological diseases presents a challenging pathophysiological model of antibodies and variable immunodeficiencies.

We present this case because of the rare association of myasthenia gravis, bronchiolitis obliterans, and Castleman's disease. Myasthenia gravis is caused by autoantibodies against nAChRs at neuromuscular junctions, resulting in symptoms of muscular weakness and fatiga-

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bility. However, the mechanisms that initiate and maintain the autoimmune response are not well understood. In addition to the antibody-mediated autoimmune response, T-cells are also thought to participate in the pathogenesis of this disease. Several cases of Castleman's disease associated with myasthenia gravis have been reported [2, 3, 5]. In one case the myasthenic symptoms improved after removal of the tumor, but the condition deteriorated after several months [2]. In another case, the myasthenic symptoms were well controlled by drugs. In our case, the myasthenic symptoms emerged five months after the surgery. These cases suggest that the association between the two diseases is more than coincidental, but they share common underlying autoimmune mechanisms.

Bronchiolitis obliterans is particularly noteworthy because it is the most severe concomitant disease state of Castleman's disease [5-8]. Bronchiolitis obliterans is characterized by inflammation of the bronchioles with elaboration of fibrous granulation tissue and bronchial exudates into the lumens. It is a lethal condition with the common endpoint of functional obstruction of the bronchioles. Indeed, all reported cases of Castleman's disease with bronchiolitis obliterans have been fatal, the most serious pathological manifestation being rapidly progressive respiratory insufficiency [5-7]. Our patient died eleven months after the appearance of the first symptoms of bronchiolitis. The fatal outcome was the result of the bronchiolitis obliterans. The most common mucocutaneous manifestation of Castleman's disease is paraneoplastic pemphigus [9, 10]. The mucous membrane of the mouth was observed in our case, but we did not observe polymorphous mucocutaneous eruptions, which are pathognomonic of paraneoplastic pemphigus.

Castleman's disease is an essentially benign condition. Surgical resection is the mainstay of treatment for uncomplicated cases. However, complications may develop even after removal of the tumor. This may create a diagnostic and therapeutic dilemma for surgeons. Castleman's disease-associated myasthenia gravis may be controlled by acetylcholinesterase inhibitors and corticosteroids. However, bronchiolitis obliterans is not responsive to any

medication and lung transplantation is the only potential treatment. It should be noted that bronchiolitis obliterans is also a common devastating complication of lung transplantation, which affects up to 50-60% of patients who survive five years after surgery [11]. Theoretically, the underlying autoimmune disease should be well controlled before the lung transplantation to decrease the risk of development of bronchiolitis obliterans in the transplanted organ [6].

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### Disclosure of conflict of interest

None.

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