

Muscle-specific receptor tyrosine kinase (MuSK) myasthenia gravis associated with castleman disease

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Received: November 8, 2016

Revised: December 16, 2016

Accepted: December 20, 2016

Muscle specific tyrosine kinase (MuSK) myasthenia gravis (MG) is a rare subtype of MG, which is immunologically distinct and differential therapeutic response. Though MG is often associated with other autoimmune disorders or malignancy, concurrence of other disease and MuSK MG has been infrequently reported. We present a patient of MuSK MG associated with multicentric Castelman disease.

Key words: Castleman disease; Myasthenia gravis; Muscle specific tyrosine kinase

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Castleman disease (CD) is an uncommon lymphoproliferative disorder characterized by lymphadenopathy with unique histological features as well as a broad spectrum of clinical features.¹ While polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a well-known neurological manifestation of CD, myasthenia gravis (MG) has been rarely reported in patients with CD.^{2,3} Furthermore, all previous reports included patients with MG presenting with anti-acetylcholine receptor antibodies and solitary CD of the hyaline vascular type, with the exception of one patient with a mixed type of CD. In the present report, we discuss the case of a patient with multi-centric plasma cell type CD with clinical and laboratory features of anti-MuSK antibody MG.

CASE

A 27-year-old man with a one-year history of recurrent diplopia, dysphagia, and general weakness was referred to our hospital. He had been previously diagnosed with seroneg-

active MG at another hospital, following which he received treatment with 360 mg of pyridostigmine daily, though no clinical improvement was noted. Physical examination revealed that the left cervical (3 × 4 cm), bilateral axilla (4 × 4 cm) and inguinal (3 × 3 cm) lymph nodes were enlarged. Neurologic examination revealed eye movement limitation with diplopia, facial muscle weakness, and dysarthria with fatigue. Limb muscle weakness or fatigue was not remarkable. Chest and abdominal computed tomography revealed numerous lymph node enlargements in the mediastinum and abdominal cavity, although the size of the thymus was normal. Radiological studies revealed an absence of bone changes. Motor and sensory nerve conduction studies performed on the median, ulnar, tibial, peroneal, and sural nerves were normal. Repetitive nerve stimulation studies revealed significant decremental responses in the orbicularis oculi (27%) and nasalis (35%) muscles. Anti-acetylcholine receptor antibody was not detected in repetitive check.

Complete blood cell analysis revealed a hemoglobin level of 9.1 g/dL, hematocrit of 29.1%, white blood cell count of 5,700/ μ L with a normal differential, and platelet count of $4.3 \times 10^5/\mu$ L. The erythrocyte sedimentation rate was 63 mm/hr. Cervical lymph node biopsy revealed lymphoid follicular hyperplasia with interfollicular sheets of plasma cells leading to a diagnosis of multicentric CD, plasma cell type (Fig. 1). Immunohistochemical staining for human herpes virus type 8 was negative.

The direct Coombs test was positive, and cryoglobulin was detected. Serum protein electrophoresis revealed a polyclonal increase in gamma-globulins with immunoglobulin levels as follows: IgG: 7,950 mg/dL; IgA: 584 mg/dL; and IgM: 141 mg/dL. Interleukin 6 level was normal (below 25 pg/mL). Antinuclear antibodies, double strand DNA, LE cell, and human immunodeficiency virus (HIV) antibody tests were negative.

The patient received treatment with 360 mg of oral pyridostigmine and 1,200 mg of cimetidine daily. After 2 months of treatment, lymph node diameter was reduced in the cervical (1 × 2 cm) and axillary nodes (1 × 1 cm), while the inguinal lymph node could not be palpated. Erythrocyte sedimentation rate (ESR) was decreased to 22 mm/hr, and cryoglobulin test results were negative. However, no improvement in myasthenia symptoms was noted, and the dose of pyridostigmine could not be increased due to cholinergic side effects including muscle cramp and excessive salivation. Immunosuppressive treatment including dexamethasone, melphalan, and cyclosporine was initiated. After one year of treatment, CD was almost abolished, and further clinical worsening of MG was not noted with steroid maintenance. The patient occasionally experienced bulbar weakness leading to dose escalation of steroid, and began to exhibit serious clinical deterioration ten years later while on the steroid treatment (prednisolone 40 mg and 10 mg every other day). He complained of difficulty in swallowing and

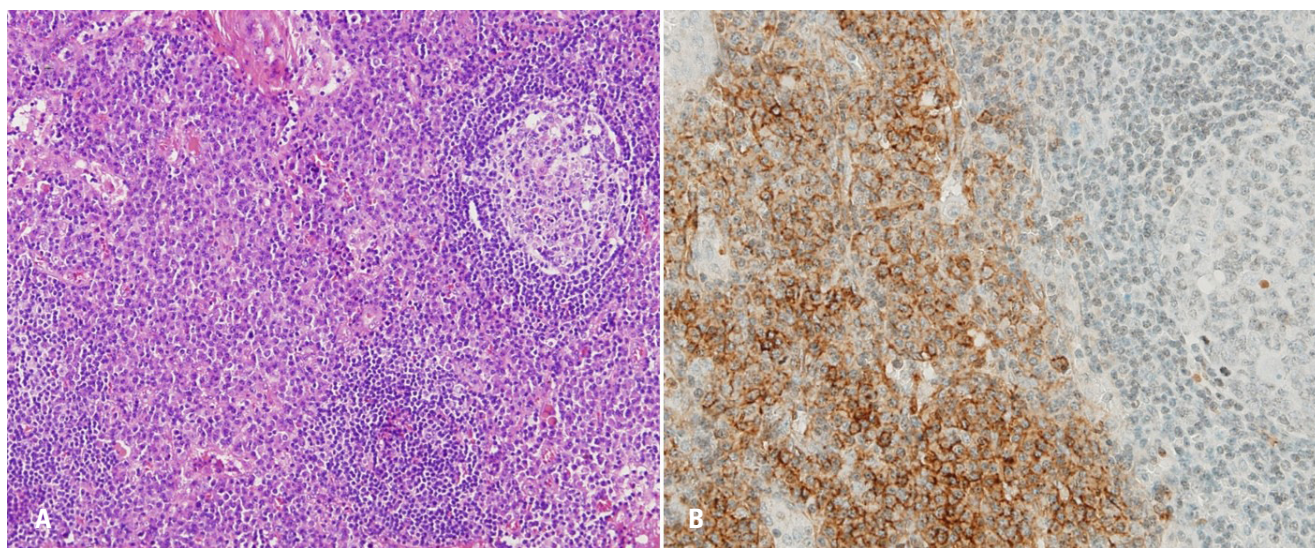


Fig. 1. Cervical lymph node biopsy demonstrates (A) lymphoid follicle hyperplasia with interfollicular sheets of plasma cells (hematoxylin and eosin stain; original magnification $\times 100$) (B) which are positive in CD138 (immunohistochemical stain for CD138; original magnification $\times 200$).

speaking without prominent limb fatigue. Neurologic examination showed nasal voice with bilateral facial weakness. Repetitive nerve stimulation studies revealed significant decremental responses in the orbicularis oculi (59%) and nasalis (46%) muscles with relatively less in the flexor carpi ulnaris (12%) and trapezius (16%) muscles. Hematologic evaluation revealed no evidence of CD relapse. Serum anti-acetylcholine receptor antibody was not detected again, however anti-MuSK antibody was found to be borderline (titer units between 10 and 20, reference < 10 titer units). Oral tacrolimus was added, and his neurological deficits improved again.

DISCUSSION

Our patient exhibited bulbar and neck weakness in relation to limb strength, in addition to rare episodes of ptosis and a poor or even deteriorated response to pyridostigmine. These features are consistent with anti-MuSK MG. Anti-MuSK antibodies may have been low in this patient because the serologic test could be performed after prolonged treatment with immunosuppressant drugs.

To date, all reports of patients with both MG and CD have discussed individuals positive for anti-acetylcholine receptor antibodies with a solitary, hyaline vascular type of CD, with the exception of one individual diagnosed with a mixed type. In contrast, our patient had anti-MuSK antibody MG and multicentric, plasma cell type CD. Though he experienced a relapse of MG after clinical remission of Castleman's disease, the parallel onset of two unusual diseases and initial improvement with immunosuppressive treatment seemed to be more than incidental.

Within the histological classification, multi-centric CD is strongly associated with human herpes virus 8 infection and increased risk of Kaposi's sarcoma.⁴ Furthermore, recent studies have revealed that patients with multi-centric CD exhibit elevated serum concentrations of IgG4 and interleukin-6, and abundant infiltration of IgG4-positive cells in the affected organs.⁵ MuSK antibodies are primarily associated with IgG4, in contrast to acetylcholine receptor antibodies, which are primarily associated with IgG1 or IgG3.⁶ It is possible that common immunologic triggers were responsible for the concurrent development of multi-centric CD and

MuSK MG in this patient.

Complicating autoimmune diseases in MuSK MG are rare and only pemphigus, systemic lupus erythematosus, and multiple sclerosis have been reported.⁶⁻⁸ Due to the rarity of MuSK MG, it is difficult to determine the underlying immunological mechanisms or triggers for additional diseases. Further clinical studies are required in order to determine the unique patterns of immune disorders associated with MuSK MG. Such studies may aid in elucidating the pathogenesis of these conditions and in developing improved methods of treatment.

Acknowledgments

This paper was written as part of Konkuk University's research support program for its faculty on sabbatical leave in 2010.

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