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Letter to the Editor: New Observation

Coexisting Stiff Limb Syndrome, Myositis, and Myasthenia Gravis in a Patient with Thymoma

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Thymoma is associated with a high prevalence of paraneoplastic syndromes that exhibit a wide range of autoimmune disorders, the most prominent of which is myasthenia gravis (MG),[1,2] whereas the occurrence of myositis is rare,[2,3] and that of stiff person syndrome (SPS) is extremely rare.[4,5] Here, we report the first case of a triple combination of MG, myositis, and stiff limb syndrome (SLS) associated with thymoma.

A 41-year-old female initially presented with recurrent migratory pruritic macular rash. Eleven months later, symmetric weakness, edema, and myalgias occurred on the arms and legs, most prominent on the proximal aspects of the extremities. Simultaneously, persistent flexion of the arms and hands and dorsiflexion of the feet appeared. One week later, she had difficulty in chewing and swallowing food and experienced fluctuating ptosis and diplopia. Upon admission at a local hospital, her serum creatine kinase (CK) level was 1465 U/L. Myositis was considered and she was placed on a low dose of prednisone for 2 weeks. She was then transferred to our hospital. Physical examination revealed restricted ocular movement, muscle atrophy, and contractures of the distal upper and lower limbs. Muscle tone was remarkably increased at the elbow and wrist flexors, and ankle dorsiflexors, but not at neck flexors or extensors. The muscle strength was 4/5 at neck flexion/extension, 3/5 at shoulders and hips, and 4/5 at wrist flexion/extension and ankle dorsiflexion/plantarflexion. Muscle stretch reflexes were decreased in both upper and lower extremities. Blood tests showed CK 631 U/L (normal range 0–140), CK-MB 7.65 ng/ml (0.1–4.94), ESR 50 mm/h (normal <20), ANA 1:100 (normal <1:40), positive antibodies against acetylcholine receptor (AchR), striated muscle and myocardium, and increased level of glutamic acid decarboxylase (GAD) antibody 23.74 U/ml (0–0.9). Her full myositis-specific antibody panel (Mi-2, Jo-1, SRP, PL-7, PL-12, EJ, and OJ) and myositis-associated antibodies (Ku, PM-Scl 100, PM-Scl 75, and Ro-52) were negative. The serum tumor markers showed an increased level of squamous cell carcinoma-associated antigen (SCCA) 28.4 ng/ml (<1.5). Serum paraneoplastic antibodies revealed strongly positive CV2, and the others (amphiphysin, Ma2, Ri, Hu, and Yo) were negative. Electrocardiography indicated minimal voltage criteria for left ventricular hypertrophy. Echocardiography showed mild mitral regurgitation and impaired left ventricular diastolic function. Electromyography (EMG) revealed irritable myopathy and continuous muscle discharge at rest and during maneuvers in extensor digitorum communis and anterior tibial muscles, as well as in their antagonist muscles. Repetitive nerve stimulation (RNS) on facial nerves, accessary nerves and axillary nerves revealed a more than 15% decrementing amplitude of compound muscle action potentials to low rates of stimulation (3–5 Hz), and no incrementing response to high rates of stimulation (20 Hz–50 Hz). Single-fiber EMG showed increased jitter (≥40 us) in extensor digitorum communis, suggesting a neuromuscular junction transmission defect. Magnetic resonance imaging of both legs at the thigh level indicated edema and inflammatory changes with diffusely hyperintense lesions on T2-weighted images. A left bicep muscle biopsy showed features of polymyositis (Figure 1). Chest computerized tomography (CT) revealed a large lobular nonhomogeneous anterior mediastinal mass, several nodes on the left pleura and right upper lung lobe, with enhancement of the mediastinal mass and left pleural nodes. Positron emission tomography (PET) demonstrated increased fluorodeoxyglucose uptake in the mediastinal mass and the adjacent pleura and pericardial membrane. Accordingly, concomitant myositis, GAD-positive SLS, and MG associated with malignant thymoma were diagnosed.

Due to the extensive invasion of the thymoma, thymectomy was deferred. In addition to oral pyridostigmine, the patient received pulse intravenous methylprednisolone 500 mg daily for 3 d followed by a gradual steroid taper. Intravenous immunoglobulin was simultaneously administered at 0.4 g/kg/day over 5 days. Within 2 weeks of treatments, her myalgias and limb edema dramatically improved and serum CK and CK-MB levels were restored to the normal range. Twenty-three days after the initiation of the aforementioned treatments, she was started on intravenous cyclophosphamide (CTX), together with radiotherapy. Muscle strength slowly improved. The elevated muscle tone, however, was only slightly reduced. Her serum level of GAD antibody increased to 78.62 U/ml. Two months later, chest CT revealed significant shrinkage of thymoma. Extended thymus and thymoma resection were performed, and the thymoma-invaded upper lobe of left lung was dissected. The pathological diagnosis was

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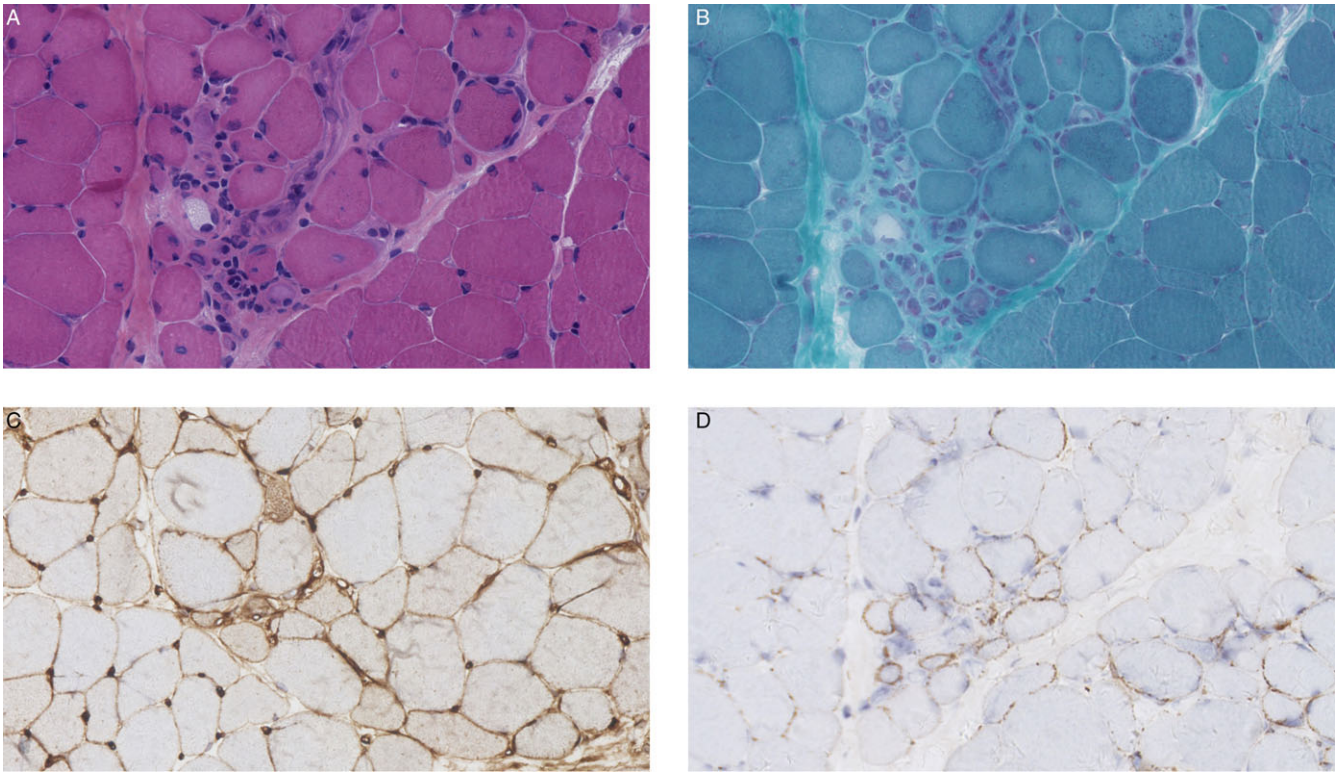

Figure 1: Muscle biopsy appearance of the patient. Multi-foci inflammatory cell infiltration in endomysium and perimysium, and scattered necrotic fibers visualized by hematoxylin–eosin stain (A)and trichrome stain (B). Universal sarcolemmal MHC-1-positive immunostain (C) and scattered sarcolemmal C5b-9-positive immunostain in muscle fibers (D) (magnification × 400).

WHO-type B2 thymoma invading lung, pleura, and pericardium. Right after the operation, the persistent flexion of arms and dorsal flexion of feet disappeared. Four months later, symptoms of ptosis, dysphagia, and limb weakness disappeared. Sixteen months later, however, she relapsed with recurrence of her symptoms, and ventricular tachycardia occurred. Chest CT revealed diffuse spreading of thymoma on mediastinal pleura, chest pleura, and multiple lymph nodes. Twelve months later, the patient died. The immediate family refused autopsy of the deceased patient.

Our patient presented myositis-related symptoms 11 months prior to the initiation of MG, as well as SLS, the latter in the subgroup of stiff-person spectrum disorders (SPSDs). Currently, six SPSD-related autoimmune antibodies have been identified.[6] Among them, GAD antibodies are positive in approximately half of SPSD patients.[6] The correlation between SPS and thymoma has been described in very few case reports.[4,5] In addition to GAD antibody-associated SLS, our patient had positive CV2 antibodies in serum, which occur with small cell lung cancer and thymoma. Her PET-CT revealed no other tumors except for an invasive thymoma. Her SLS manifestations dramatically disappeared immediately following the thymoma resection. Thus, SLS, myositis, and MG were taken as thymoma-related paraneoplastic syndromes.

Because MG and myositis both involve the neck and the proximal predominant limb muscles, as well as the pharyngeal muscles, the concurrence of MG and myositis may be missed.[7] Fatigability with fluctuating weakness is a hallmark of MG, whereas muscle weakness in myositis is stable and unresponsive to acetylcholinesterase inhibitors. When MG and myositis develop concurrently, the characterized ocular weakness suggests the diagnosis of MG and myositis may be ignored. On the other hand, MG may be underdiagnosed when patients initially present with pharyngeal and limb weakness, which are frequently seen in muscle-specific kinase (MuSK) antibody-positive MG patients. In these conditions, serum CK and MG-specific antibody detection and complete EMG examinations, including needle EMG and RNS, are helpful for the differentiation between myopathy and MG.

In MG-myositis patients, serum CK level is slightly or remarkably increased but can also be normal. Muscle biopsy reveals inflammatory cell invasion in the endomysium and sometimes perimysium with various necrosis, degeneration, and regeneration but can also show mild pathological changes.[7] In the latter, diffuse MHC-1 positivity in both necrotic and non-necrotic muscle cells could provide evidences of autoimmune myopathy.[7,8] Myocarditis can also coexist with MG-myositis, increasing the mortality rates in patients.[2] Myocarditis diagnosis is typically based on increased levels of CK and CK-MB, ST-T wave abnormalities, arrhythmia, and/or heart failure. Multinucleated giant cells are not uncommonly found in the skeletal and/or cardiac muscles of these patients consistent with the association of thymoma and giant cell myositis/myocarditis.[2,9] On admission, our patient showed increased level of CK-MB and impaired left ventricular diastolic function. In the late stage of the disease, she developed ventricular tachycardia, likely indicative of myocarditis.

Our patient was positive for striated muscle antibodies, but negative for inflammatory myopathy-specific autoantibodies, which are used for the identification of a heterogeneous group of idiopathic inflammatory myopathies.[8] These differences in autoimmune antibodies between thymoma-associated myositis and

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idiopathic inflammatory myopathies have been noticed in a few previous studies.[2,3] Anti-striated muscle antibodies may serve as useful biomarkers for myositis in MG patients.

In summary, thymoma can induce MG, myositis, and SLS. The early detection and efficient treatment of thymoma is critical for clinical recovery.

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Conflicts of Interest. The authors have no conflicts of interest to declare.

Statement of Authorship. YJ and SH managed the patient's treatment. YJ followed the patient and drafted the manuscript. HZ and HG reviewed the manuscript. JZ performed thymus pathology.

Ethical Publication Statement. The patient's husband agreed and provided written informed consents for publication of the case. This study was a retrospectively analysis of clinical data and was granted an exemption from requiring ethics approval by Medical Ethics Committee of Beijing Hospital.

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