J Korean Med Sci 2004; 19: 134-6
ISSN 1011-8934

Appearance of Systemic Lupus Erythematosus in Patients with Myasthenia Gravis following Thymectomy : Two Case Reports

We report two cases of systemic lupus erythematosus (SLE) in myasthenia gravis (MG) patients who had undergone thymectomy. SLE developed in the patients 3 months or 13 yr after thymectomy, and polyarthritis was the main clinical manifestation of SLE. Both patients fulfilled at least four of the revised criteria for the classification of SLE. In this report, we describe two postthymectomy lupus patients and perform a comparative review of previous cases.

Key Words : *Myasthenia Gravis; Lupus Erythematosus, Systemic; Thymectomy*

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Received : 15 January 2003
Accepted : 26 March 2003

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INTRODUCTION

The systemic lupus erythematosus (SLE) and myasthenia gravis (MG) show certain similarities, in that they occur mainly in young women, are manifested by cycles of improvement and exacerbation, and share positivity for antinuclear antibodies (ANA) and thymus hyperplasia. The co-existence of SLE and MG is well documented (1, 2). Thymectomy is a common therapeutic option in the treatment of MG, and systemic autoimmune disorders have been detected in MG patients several years after thymectomy. The development of SLE in MG patients after thymectomy has been reported infrequently, and to our knowledge has not been reported previously in Korea (3-8). We describe two cases of SLE in MG patients who had undergone thymectomy.

CASE REPORTS

Case 1

A 36-yr-old woman developed fatigue and polyarthralgia that involved the wrists, proximal interphalangeal (PIP) joints, left knee, and left ankle, over a period of 2 months. She had stiffness of joints in the morning lasting 3 hr. Eight months previously, she had been diagnosed with MG based on the typical history of diplopia, right eye ptosis, generalized muscle weakness, positive response to edrophonium, and increased decremental response after repetitive nerve stimulation. Five months later, a thymectomy was performed to remove her hyperplastic thymus, as her symptoms were not adequately controlled with pyridostigmine. Pathological examination of the thymus revealed focal lymphoid hyperplasia.

Examination of the patient showed the evidence of polyarthritis of the wrists, right 3rd, 5th PIPs, left 2nd, 3rd PIPs, left knee, and left ankle. There was no malar rash, photosensitivity, oral ulcer, hair loss, or Raynaud's phenomenon. Laboratory data revealed an ESR of 45 mm/hr, anemia of 9.9 g/dL hemoglobin, leukopenia of 1,600/μL, thrombocytopenia of 91,000/μL, and elevated LDH. The patient had a positive ANA of 1:1,280 (homogeneous), positive anti-dsDNA level of 57.3 IU/mL (normal <7), and decreased complement (C_3, C_4, CH_{50}) levels. The tests for cryoglobulin, lupus anticoagulant, and anticardiolipin IgG and IgM antibodies were negative. The remaining biochemical tests, coagulation profile, and urinalysis were normal. This patient displayed four of the revised criteria for SLE classification (9), i.e., polyarthritis, hematological findings, positive ANA, and anti-dsDNA antibodies. She was treated with prednisolone (1 mg/kg) and hydroxychloroquine, with gradual tapering off of the treatment, and remained stable during the 3 yr of follow-up.

Case 2

A 34-yr-old woman presented with aggravated polyarthralgia of the shoulders, PIPs, and knees, which had persisted for 2 yr. She had morning stiffness of both hand joints lasting 2 hr. Thirteen years previously, the patient had been diagnosed as suffering from MG, and underwent thymectomy of a hyperplastic thymus.

Examination revealed that the patient had polyarthritis of the PIPs, and a malar rash and photosensitivity that had started 1 yr earlier. There was no oral ulcer, hair loss, or Raynaud's phenomenon. Laboratory data revealed an ESR of 13 mm/hr, a positive ANA test of 1:640 (homogeneous), a positive anti-dsDNA antibody level of 11.1 IU/mL (normal <7), and decreased levels of complements (C_3, C_4, and CH_{50}). The results of the CBC, urinalysis, and chemical analyses were normal. The patient had five of the revised criteria for SLE (9): polyarthritis, malar rash, photosensitivity, positive ANA, and anti-dsDNA antibodies. A non-steroidal anti-inflammatory drug and hydroxychloroquine were administered to the patient, and her symptoms improved. During the 2-yr follow-up period, the patient was stable and did not suffer from any specific symptoms of SLE.

DISCUSSION

Surgical removal of the thymus gland is used successfully to manage MG, which is an autoimmune disease in which antibodies against the acetylcholine receptor inhibit neuromuscular transmission (10, 11). Although the precise mechanism by which thymectomy produces a benefit to MG patients is still unclear, this therapeutic option is indicated in all patients with generalized MG between the age of puberty and at least 55 yr. However, in recent years, evidence has emerged of systemic autoimmune disorders including SLE, Hashimoto's thyroiditis, cutaneous vasculitis, and antiphospholipid syndrome occurring many years after thymectomy in patients with MG or other immunological diseases (12).

The evidence that thymectomy induces autoimmune disease is based primarily on animal studies. New Zealand black × New Zealand white F_1-crossed (NZB × NZW F_1) mice spontaneously develop a lupus-like disease with increasing age, which is associated with uninhibited activation of polyclonal B cells (13). When neonatal NZB × NZW F_1 mice were subjected to thymectomy, there was a marked acceleration of disease, possibly due to the elimination of the thymic T-suppressor cell population. Furthermore, reconstitution of these mice with young syngeneic thymic grafts retarded the development of autoimmunity (14). Studies have also been performed on normal mice, in which the features of autoimmunity were induced by the administration of polyclonal B cell activators. The effects of neonatal thymectomy and long-term administration of polyclonal B cell activators were synergistic in provoking anti-DNA antibody production, which suggests that the intact thymus protects against the induction of autoimmunity by environmental stimuli (15).

In humans, long-term thymectomized MG patients display mild T-cell lymphopenia, which is associated with hypergammaglobulinemia and evidence of B cell hyperreactivity. In addition, many of these patients have high titers of a variety of autoantibodies, including anti-dsDNA and anticardiolipin antibodies (12). The high frequency (1.2-2.5%) of co-existence of thymoma and SLE may reflect the loss of thymic function in the presence of a tumor (16).

In this report, we described two cases of SLE in MG patients following thymectomy. Based on both the animal and human studies, thymectomy is expected to facilitate the development of autoimmune disease in an age-dependent manner in the setting of continuous environmental stimulation, particularly in genetically predisposed individuals. This sequence of events may be initiated by the loss of suppressor T cells and immune surveillance after thymectomy in patients with MG. Thus, it is unlikely that postthymectomy lupus occurs by coincidence in MG patients.

In our two patients, thymectomy had been performed 3 months or 13 yr before the occurrence of SLE. In other studies, SLE developed at highly variable time intervals of between 3 months and 18 yr after thymectomy (8). Polyarthritis and polyarthralgia are the most common manifestations of postthymectomy lupus (combined data from several case reports). Other frequent manifestations include skin rashes, fever, cytopenia, and pleuritis. The rare SLE manifestations of optic neuritis and transverse myelitis have been reported in two cases (17, 18). In our patients, polyarthritis was the main manifestation of SLE. Owing to the limited number of cases examined, it is impossible to compare the clinical features with those of other SLE patients.

In conclusion, although thymectomy is the effective treatment modality in patients with MG, our findings and the observations of others support the view that this surgical option may be a precipitating factor for other autoimmune diseases, such as SLE. Further investigations will reveal the effects of thymectomy on the immune system in humans. Nonetheless, the possibility that novel autoimmune diseases emerge following thymectomy cannot be ignored.

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