Late-Onset Myasthenia Gravis in an Elderly Female After Thymectomy: A Case Report

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ABSTRACT

Late-onset myasthenia gravis is characterized with onset after 60 years of age and has a male predominance. Myasthenia gravis may develop after surgery on any thymic mass hence questions as to the role of thymectomy in individuals without myasthenia gravis symptoms have been raised and is still controversial. We now present a rare case of a 75 year old female who was initially asymptomatic but had incidental finding of a thymic mass on routine chest x-ray and subsequently had thymectomy done when she was 65 years old. Two months after thymectomy, she developed fluctuating generalized muscle weakness, diplopia and ptosis more pronounced in the afternoon. She was diagnosed to have myasthenia gravis confirmed by positive results on both repetitive nerve stimulation and Tensilon tests. She was maintained on Pyridostigmine and Prednisone as well which provided improvement of her symptoms. She remained stable until 7 years and 9 months after thymectomy when she again had fluctuating muscle weakness as well as ptosis and diplopia.

***Key Words**: Myasthenia gravis; Late-onset myasthenia gravis; Thymectomy; Post-thymectomy myasthenia gravis; elderly female*

INTRODUCTION

Myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission. It is an autoimmune disease characterized by autoantibodies against different components of the neuromuscular junction (NMJ), thereby eliciting muscle fatigability and weakness.[1,2] It is characterised clinically by fluctuating painless muscle weakness, which worsens with exercise and towards the end of the day, and improves with rest. Its clinical hallmark is the fluctuating pronounced weakness limited to the voluntary muscles. It is usually caused by antibodies to postsynaptic proteins, of which three have been identified: nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK), and the low density lipoprotein receptor- related protein 4 (LRP4). Myasthenia gravis includes heterogeneous autoimmune diseases, with a postsynaptic defect of neuromuscular transmission as the common feature.

The annual incidence of MG is reported to range between 3 and 30 per million population, with the rates at the upper end of the range reported by prospective studies probably providing the most accurate estimates.[3] Prevalence of MG is reported to be approximately 200 per million population now,[4] compared with about 5 per million population between 1915 and 1934.

Myasthenia gravis can be classified as to onset of symptoms. Early-onset MG appears before the age of 50 and is characterized by female predominance (60-70%) whereas between the age of 50 and 60, there is no gender difference.[5] Late-onset MG appears after the age of 60 and this form is characterized by a clear male predominance.[6]

The thymus is thought to play an important pathogenic role in anti-AChR antibody positive MG, with thymic hyperplasia present on 65 percent of cases and thymoma in 10 percent of cases.[7] Furthermore, MG occurs in 30 percent of patients with a thymoma as a paraneoplastic phenomenon.[8] Studies have shown evidences implicating the thymus as the main site of autosensitisation with acetylcholine receptor in the presence of an inflammatory environment leading to induction and maintenance of the anti-acetylcholine receptor auto-immune response in MG.

Concerns regarding the need to perform thymectomy on patients noted to have a thymic mass whether a thymoma or thymus hyperplasia had been raised in recent years. Thymoma occurs in approximately 10% of patients with MG and, in turn, MG occurs in approximately one-third of patients with thymoma.[9] Few thymoma patients without myasthenia gravis (MG) have been observed to develop MG after total removal of the thymoma (postoperative MG). However, the cause of this is not yet known because of the rarity of postoperative MG patients. There has been little information regarding postoperative MG in the literature. It has been said in previous reports that the onset of MG after total thymoma removal occurs only in 1.5–28% of cases without MG.[10] Thymectomy is generally recommended for patients with thymoma. However, myasthenia gravis occasionally develops postoperatively in patients who have had thymoma despite no signs of myasthenia gravis before the surgery. Some studies have reported post-thymectomy myasthenia gravis (PTMG); however, its mechanism and risk factors remain unclear.

We now report a rare case of a late-onset myasthenia gravis in an elderly female after thymectomy admitted at our institution.

CASE PRESENTATION

This is a case of EDR, a 75 year old female who was admitted at our institution last March 23, 2014 due to drooping of eyelids. Patient was asymptomatic until 10 years prior to admission (at 65 years of age) she had routine chest x-ray done for screening for pulmonary tuberculosis which later revealed a suspicious mediastinal mass. Chest CT scan was subsequently done which revealed right mediastinal mass. Patient was asymptomatic, had regular surveillance of chest CT scan which did not show any changes until 8 years prior to admission, on regular follow up chest CT, there was an increased in size of the mediastinal mass. She then had thymectomy done (March 2006) and was discharged with no complications with biopsy results showing a benign thymic hyperplasia. Seven years 10 months prior to admission (May 2006), 2 months post-thymectomy, she noted to have fluctuating generalized muscle weakness, more in the afternoon, associated with

diplopia and ptosis. Consult was done due to persistence of symptoms. Tensilon test as well as repetitive nerve stimulation test both showed positive results. She was managed as Myasthenia Gravis and given Pyridostigmine and Prednisone of unrecalled dosage. Patient noted improvement of symptoms, medications subsequently tapered off and Prednisone discontinued 6 years after onset of myasthenia gravis. Seven years and 6 months post-thymectomy, patient then noted saliva to be thick and had difficulty in swallowing it. She was then advised to discontinue Pyridostigmine by her attending physician. She remained stable with no symptoms until 7 years and 9 months after thymectomy, she again had recurrence of fluctuating weakness in the afternoon as well as ptosis and diplopia. Patient again took Pyridostigmine 60mg four times a day. There was still progression of symptoms despite intake of Pyridostigmine hence consult at our institution and subsequent admission. Pertinent neurologic examination during admission showed (+) ptosis of both eyes, right more than left; (+) lid lag after one minute and (+) fatigable muscles on repetitive movements as well as weakness of proximal muscles of both upper and lower extremities. Patient was admitted at a regular room and observed for difficulty of breathing and motor weakness. She was started on Mycophenolate Mofetil 500mg twice a day, Prednisone 60mg once a day, Pyridostigmine 60mg every 4 hours. She then had difficulty of breathing, dysphagia and increased motor weakness on the 5th hospital day hence intubated and transferred to the ICU due to myasthenic crisis. She had 3 cycles of plasmapheresis done wherein improvement of symptoms were noted after each cycle. She was worked up on a possible recurrence of mediastinal mass wherein a high resolution chest CT scan (Figures 1 and 2) done showed patchy pneumonia, bilateral anterior and posterior upper lobes, no evidence of recurrent anterior or superior mediastinal mass; no mediastinal, hilar or axillary lymphadenopathy; no sign of pulmonary mass or metastasis. No improvement of motor strength was noted. Patient was subsequently transferred out of the ICU after 9 days. Prednisone was then tapered down to 50mg once a day, Pyridostigmine decreased to 60mg three times a day, Mycophenolate Mofetil maintained on 500mg twice a day. She continued to improved, was weaned off the mechanical ventilator and extubated subsequently. Motor strength also improved, and was noted to be able to stand and walk with assistance. She was discharged improved on the 19th hospital day with Mycophenolate Mofetil 500mg twice a day, Pyridostigmine 60mg three times a day and tapering dose of Prednisone starting at 45mg once a day. Subsequent follow-ups were done 2 months after discharge, noted to have slight weakness of the quadriceps and deltoid muscles with lid lag after prolonged upward gaze. Prednisone was tapered off, Pyridostigmine three times a day. Recent follow up showed less fatigable muscle strength, no lid lag and was able to do squats. Pyridostigmine was now discontinued and was maintained only on Mycophenolate 500mg three times a day.

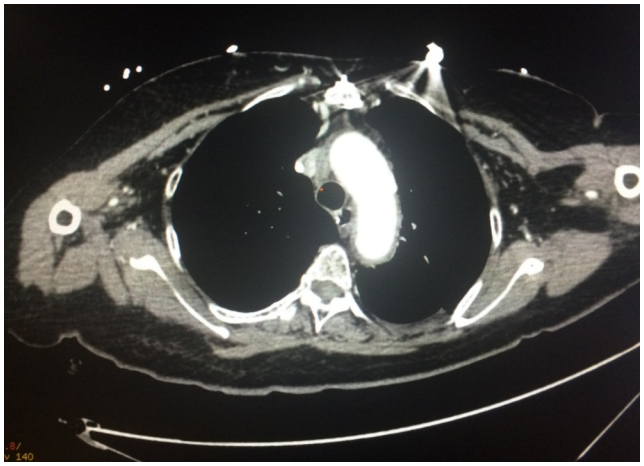

Figure 1. High resolution chest CT showing no evidence of recurrent anterior or superior mediastinal mass

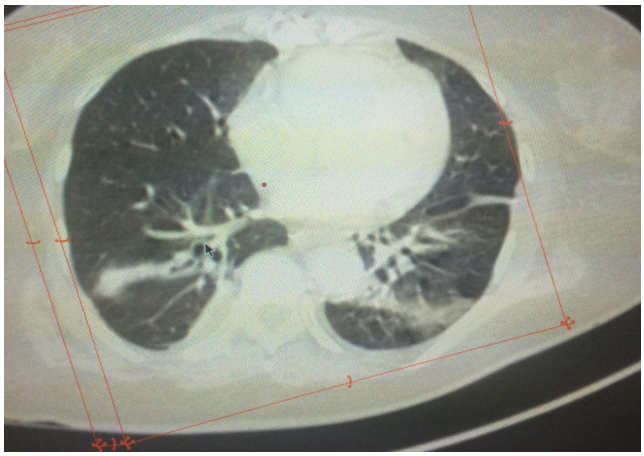

Figure 2. High resolution chest CT showing patchy pneumonia, bilateral anterior and posterior upper lobes

DISCUSSION

Myasthenia gravis (MG) is caused by antibodies against proteins in the neuromuscular junction postsynaptic membrane. Late-onset myasthenia gravis occurs after the age of 60 and is characterized by a clear male predominance. Three postsynaptic neuromuscular junction antigenic target proteins have been identified in myasthenia gravis, namely: nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK) and low density lipoprotein receptor-related protein 4 (LRP4). The thymus gland plays a role in myasthenia gravis and is the main site of autosensitisation in anti-AChR MG. Thymic hyperplasia (65%) and thymoma (10%) as a paraneoplastic phenomenon is seen in anti- AChR antibody positive MG.

According to the Philippine Neurological Association (PNA) Consensus Guidelines report of the Neuromuscular Council issued last last March 2012 on treatment for myasthenia gravis, thymectomy is one option for MG patients. The inclusion criteria for patients given the option of thymectomy are: 1. presence of thymoma in all ages; and 2. non-thymomatous MG that is generalized at the onset with a high level of antibodies to AchR, rapid progression of disease, aged 18-55 years and within 3-5 years of MG duration. Based from the study of Berrih-Aknin, etal, thymectomy is frequently used treatment for myasthenia gravis. It is always indicated in MG patients who have a thymoma. Evidence for thymectomy in non-thymomatous MG remains less certain-no randomised controlled trials have been published to date, although one is currently underway (results expected to be available in 2016).[11] A study reviewed the management and clinical outcome of patients with MG who underwent thymectomy over a 12 year period wherein 89 patients who underwent transsternal thymectomy were identified. A thymoma was subsequently identified on histology in 24 %, whereas 48, 9 and 19 % had hyperplastic, atrophic and normal thymic histology, respectively. One patient developed postoperative myasthenic crisis but generally the procedure was well tolerated. Outcome was favourable for the majority of patients, with 34 % achieving complete stable remission (CSR) and an additional 33 % achieving pharmacological remission. Moreover, steroid requirements fell progressively during follow-up. Patients with a hyperplastic gland had a significantly greater chance of achieving CSR compared to other histological subtypes and the incidence of CSR increased with a longer duration of follow-up. Thymectomy for MG is generally safe and well tolerated and is associated with a sustained improvement of symptoms in the majority of patients.[12] Imaging of the mediastinum should be repeated using high resolution chest CT in the context of a MG relapse after a period of stable disease to exclude the development of a thymoma, which can occur later in the disease course.[7]

Late-onset myasthenia gravis is characterized by a clear male predominance. It is frequently associated with the presence of a thymoma, a tumor of the thymic epithelial cells and most patients would present generalized and severe symptoms such as bulbar involvement. A recent article of Aarli defined myasthenia gravis (MG) in the elderly as onset after the age of 50 years. MG is diagnosed more often today than previously. The increase is mainly found in patients over the age of 50 years. Neurologists therefore see more old patients with MG now than before. Prevalence of the early-onset form of MG seems to be unchanged. Recent data indicate that MG may still be substantially underdiagnosed in very old people.[13] This study also stated that thymomatous MG is more common among older patients than it is in younger onset. Approximately 30% of patients with late-onset, nonthymoma MG have antibodies to titin, while such antibodies are extremely scarce in early-onset MG. Titin antibodies in MG patients seem to be associated with a higher frequency of DR7 antigen and a decrease of DR3 antigen. They also noted that the age peak for late-onset MG (onset after age 50) is now the same for both sexes, between 70 and 80 years, mainly because of a relative increase in the onset of MG among older women. Late -onset MG is seen only slightly more often in men than in women. The female-to-male ratio, which is near 3:1 in the early-onset form, is 1:1.1 in late-onset MG. An important cause for the increase is the demographic change. The age group from which late-onset MG is recruited, has expanded during the last 30 years.

Thymoma is usually seen in late-onset myasthenia gravis (LOMG), however, a study showed some "LOMG" thymuses show lymphoid follicles like most in

early onset myasthenia gravis (EOMG) even in patients over 60, particularly in females.[14] Lympho-epithelial tissue of the aging thymus is gradually replaced with fat, but residual parenchyma may continue exporting some T-cells at least into middle age. Remnants may rarely show signs of expansion and even infiltration, however morphometric analysis did not reveal significant difference between LOMG and normal thymuses.[14] Thymectomy appears to be of benefit in elderly patients with EOMG-like immunological features but not in those with striational antibodies.

A few thymoma patients without myasthenia gravis (MG) have been observed to develop MG after total removal of the thymoma (postoperative MG). However, the cause of this is not yet known because of the rarity of postoperative MG patients. A study conducted by Kazuya Kondo, etal[10] evaluated the clinical characteristics of the 8 postoperative MG patients. They compiled 1089 thymoma patients treated between 1990 and 1994 in 115 institutes in Japan, and found 8 cases of postoperative MG. This study showed postoperative MG was found in 8 (0.97%) of 827 thymoma patients without preoperative MG. The postoperative MG patients included 1 male and 7 females, with a mean age of 50.5 +/-15.0 years. The thymoma was completely resected in all cases. The surgical method used was extended thymectomy in 2 cases and thymothymectomy in 6 cases. There were 2 cases (0.7%) of postoperative MG in the extended thymectomy group (n=275), 6 (1.9%) in the thymothymectomy group (n=321), and none in the tumor resection group (n=137).[10] The interval between thymectomy and the onset of postoperative MG varied (6 days–45 months). The type of MG was ocular in 2 cases and general in 5 cases, according to the modified Osserman classification. The postoperative MG was responsive to anti-cholinesterase compounds and/or steroids. The improvement rate was 86%.[10] The study concluded that the onset of MG after total thymoma removal occurred in 1–3% of thymoma patients without MG. Although the resection of the thymus gland does not prevent the onset of postoperative MG, the patients who underwent thymectomy showed a good prognosis. They recommend thymothymectomy or extended thymectomy as a surgical procedure for thymoma patients without MG.[10]

Myasthenia gravis symptoms appearing post-thymectomy is a rare occurrence. On literature review, one case report entitled Post-thymectomy myasthenia gravis with an episode of Osserman stage III by Kuwata, etal[15] published last 2012 was seen . They reported a case of an 81 year old female admitted for an abnormal shadow seen in a chest radiograph with no symptoms of myasthenia gravis. Chest CT showed a bulky anterior mediastinal tumor (thymoma on biopsy) and subsequently had thymothymectomy, left upper lobectomy, pericardial resection, and phrenicectomy. Pathological examination of the tumor identified it as a thymoma (type B2, Masaoka stage II). Two months after the surgery, she experienced the onset of post-thymectomy myasthenia gravis with Osserman stage III and started steroid pulse therapy (prednisolone 1g/day for 3 days). Additionally, the patient was treated with immunoadsorption to shorten the duration of the steroid therapy. At three months after the admission, she was removed from the ventilator with a drug regimen of 60 mg/day prednisolone.

The current hypothesis of the pathogenic mechanism of post- thymectomy myasthenia gravis (PTMG) includes: thymoma recurrence; surgical exposure to larval MG; and activation of peripheral lymphocytes from thymoma after surgery. Hoffacker et al.[16] demonstrated that thymoma releases mature autoantigen- specific T-cells into the periphery, using T-cell proliferation assays for a fragment of the acetylcholine receptor, the midsize neurofilament protein, and tetanus toxoid. Buckley etal on the other hand states that T-cells in the thymoma are exported to the peripheral blood, and that these T-cells can persist in the periphery for many years.[17] These studies suggest that thymoma actively exports large numbers of mature T-cells into the peripheral blood and that, following export, the cells persist in the periphery, potentially stimulating autoantibody production and subsequent autoimmune disease.

CONCLUSION

Late-onset myasthenia gravis in an elderly female was once a rare neurologic occurrence but is now becoming more common due to the increasing number of elderly population. Asymptomatic

individuals with thymic mass who have undergone thymectomy may develop myasthenia gravis. Signs and symptoms of myasthenia is easily detected thus an increase in the index of suspicion should be made even if it is seen in an elderly female. Since there are still no evidence as to whether thymectomy is warranted for asymptomatic patients and for non-thymomatous MG, careful considerations and further research should be done as to whether thymectomy should be recommended as a standard of care. A thorough and detailed pre- and postoperative work up for myasthenia gravis to screen for likelihood of a post-thymectomy myathenia gravis should be done for all patients who would have surgery of any thymic mass.

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