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Myasthenia Gravis and co-existing autoimmunity in a thymoma after radiotherapy

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Abstract:
Myasthenia Gravis is the most frequent neurological disorder associated with thymoma, which encompasses Thymoma associated Myasthenia Gravis (TAMG) [1]. Thymoma-associated Myasthenia gravis (TAMG) is associated with autoantibodies to the nicotinic acetylcholine receptor (AChR-Ab) presenting with fatigable weakness of skeletal muscles [2]. The thymus is abnormal in 75% of the patients with antibody-positive MG, in 65%of the patients it is usually hyperplastic and in an additional 10%, there are thymoma [3]. The prognosis of Myasthenia Gravis (MG) in patients with thymoma is equal or less malignant when compared to Myasthenia without a thymoma probably attributable to the early detection and remission with thymectomy [7]. We hereby present the manifestation of Generalized myasthenia in a young female after successful radiotherapy of thymoma and its association with autoimmune antibodies.

Keywords: *MG (Myasthenia Gravis), thymoma, autoimmunity.*

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I. INTRODUCTION

Myasthenia Gravis is the most frequent paraneoplastic neurological disorder associated with thymoma, which encompasses Thymoma Associated Myasthenia Gravis (TAMG), characterized by the presence of autoantibodies to nicotinic Acetylcholine receptors, Muscle-specific Kinase, Lipoprotein receptor protein-4(LRP4), titin, and Ryanodine receptor [3]. The myoid cells in the thymus act as a trigger for this autoimmune response, because the transcripts of Acetylcholine receptors are found in it [2]. So, acetylcholine receptor antibodies are found in 85% of myasthenic patients but only in 50% of ocular disease patients. So, a thymoma can give rise to several autoimmune disorders like myasthenia, acquired neuromyotonia, encephalitis, Morvan's Syndrome, and myositis [3]. Myasthenia is graded according to Osserman staging, type 1a-confined to ocular muscles,2a- Mild generalized weakness, 2b- severe generalized MG, 3-fulminant MG. They are low-grade malignant tumours treated with thymectomy or extended resection [4]. Complete surgical resection is the gold standard but in case of extensive metastases or unresectable tumours, radio and chemotherapy are opted for with or without thymectomy [6].

The onset of Myasthenia Gravis after total thymoma removal occurred in 15-25% of the cases, classified as postoperative MG [5]. It occurs due to a large number of mature T cells in peripheral blood leading to autoimmune disease. The Thymoma associated Myasthenia Gravis has titin

and Ryanodine receptor antibodies in 95% of cases, which has a genetic association with HLA-DR3[3]. The presence of these antibodies is associated with bulbar weakness and severe disease in MG [6]. Myasthenia is the first manifestation of an underlying thymoma but in our case, it developed post-radiotherapy of thymoma. TAMG is equally frequent in males and females, can occur at any age but with a peak at 50years [6]. They can relapse at pleural/intrathoracic sites, extra thoracic metastases are rare6.

II. CASE PRESENTATION:

The data of the patient is taken after informed consent from her. A 27-year female presented with easy fatiguability and drooping of both upper eyelids along with double vision from 20 days. She also had pain in both thighs which aggravated on climbing upstairs, the weakness gradually progressed towards evening, the drooping of both upper eyelids more towards the evening. There are no complaints of weakness of the neck and difficulty in breathing. In 2014, she was diagnosed with invasive thymoma, she received external beam radiotherapy and responded well. A Follow-up Computed Tomogram of the Chest showed volume loss in the right lung and mediastinal shift to the right side. In 2018, she developed sputum-positive Pulmonary tuberculosis completed anti-tubercular therapy.

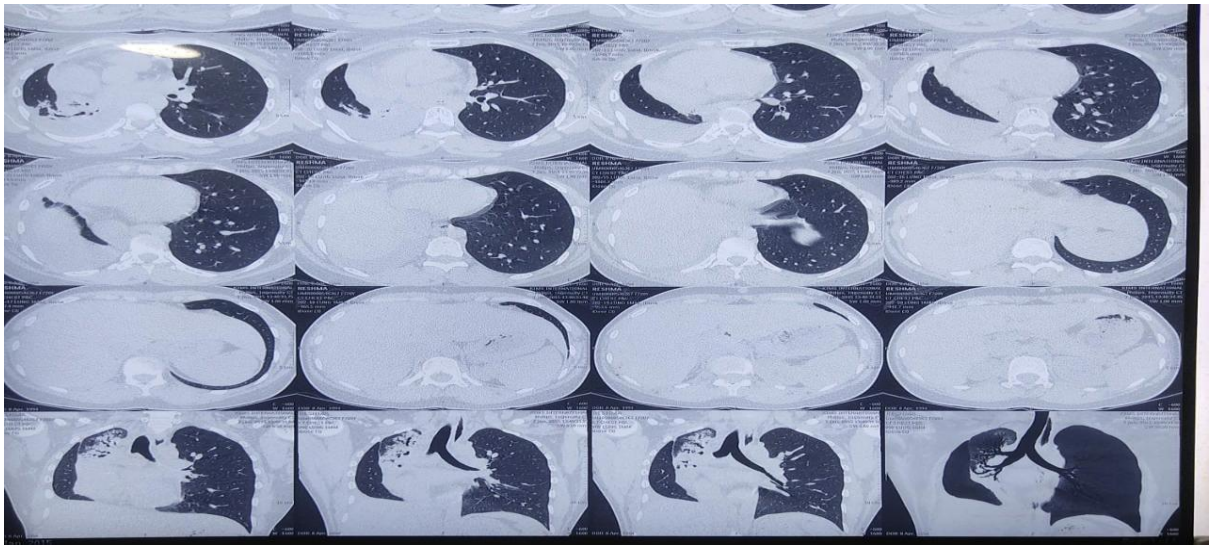
The general examination revealed mild pallor, vital signs were normal except respiratory examination

showed signs of volume loss on the Right side. The Nervous System Examination showed ptosis of both upper eyelids with an eye in normal position without nystagmus. The Motor System revealed normal bulk, tone, reflexes. The power in all other muscles was normal except power in hip flexors which was +4/5, The icepack test was positive. Sensory, cerebellum, and gait are normal. A Provisional Diagnosis of Generalized Myasthenia secondary to thymoma after radiotherapy was made and she was admitted for further evaluation. The peripheral smear shows normocytic normochromic anaemia normal liver, and renal function, thyroid function is normal, normal parathormone levels, she had low vitamin D levels and the classical Acetylcholine receptor antibody titres with enzyme immunoassay were elevated(>8nm/L). The IgM dsDNA ELISA shows a positive titre (20.34U/ml). The contrast CT chest showed a heterogeneously enhancing lesion with peripheral calcification measuring 2.3×1.7cm in the anterior mediastinum with loss of right lung parenchyma and mediastinal shift to right, linear calcification in the right atrium extending along superior vena cava suggesting calcified thrombus. Repetitive Nerve Stimulation shows a decremental response.

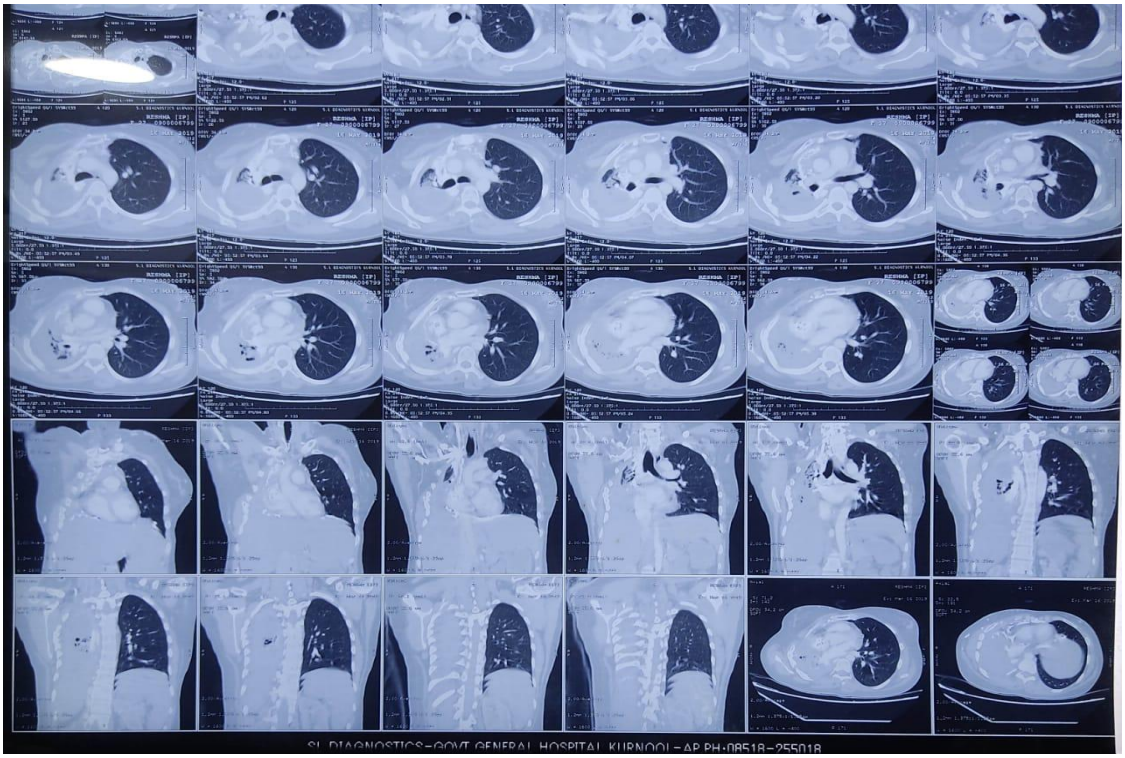
A definitive diagnosis of Generalized myasthenia in a thymoma after radiotherapy is made and put on pyridostigmine 60mg 6th hourly, after which she improved clinically. She is susceptible to future SLE and another spectrum of auto-immune diseases due to elevated ANA titre.

The patient before and after the ice pack test.

The Computed tomogram of the patient after radiotherapy



The Computed tomogram Chest of the patient at presentation



III. Conclusion

Myasthenia Gravis is the initial commonest presentation of a thymoma., but can occur as post-operative MG, after the excision of the thymus. It can be the initial paraneoplastic manifestation of an indolent thymoma[6]. The mechanism of development of myasthenia initially is autoimmunity due to the presence of myoid cells which have nicotinic Acetylcholine receptors to which t cells are sensitized [2]. It has a biphasic age distribution, that is it occurs in women in twenties and thirties, but in men at their fifties and sixties [3]. The ratio in women and men is 3:2, a thymoma is found in 10% of the cases, but in a few populations, it is reported to be 10-30%. The mechanism by which thymoma induces auto-immunity is damage induced by tumour growth diminishes its ability to maintain self-tolerance and opens up a "window of opportunities" for other autoimmune diseases [6]. A variety of auto-immune diseases have been described with thymoma other than myasthenia like systemic lupus erythematosus, red cell aplasia, neutropenia, thrombocytopenia, Syndrome of Inappropriate Antidiuretic Hormone secretion, Autoimmune dermatoses like autoimmune blistering disease, pemphigus Vulgaris, paraneoplastic Vulgaris, bullous pemphigoid, Polymyositis, Dermatomyositis, Myopathy, Pernicious anemia, less common are Rheumatoid arthritis, Ulcerative Colitis, Takayasu syndrome, Scleroderma, Autoimmune hemolytic anemia, Cortical Encephalitis, etc.,9

Our case is a Generalized Myasthenia in a thymoma treated with radiotherapy presenting after 7 years of a radiological cure. The patient has antibodies to Nicotinic Acetylcholine receptor and also to ds -DNA, the antibodies to Ryanodine receptor and titin were not measured. The frequency of second autoimmune disease is 13-22% in Myasthenia Gravis, highest in early-onset MG. The commonest to be associated is Systemic lupus erythematosus, frequency is 1-8% [10]. This susceptibility to develop autoimmune disorders does not decrease even after complete resection or radiotherapy [10]. The overlap with autoimmune diseases reflects common pathogenic mechanisms, immunological factors leading to activation of autoreactive B and T cells, genetic susceptibility and specific candidate genes and specific factors, understanding these mechanisms is vital for targeted treatment [10]. So, a thymoma's association with an auto-immune disorder should be viewed as a syndrome .10

Mineo TC, Biancari F have described post-operative MG in two patients operated on for invasive thymoma and cured completely [7]. Saa Yoon Kang et al described myasthenia gravis after thymectomy in a 39-year patient with no recurrence, which responded well to treatment.[4]

Generalized myasthenia is pharmacologically treated and the patient is maintained in remission phase but must be aware of the long-term progression and the development of other autoimmune disorders like Systemic lupus erythematosus, encephalitis, neuromyotonia, autoimmune enteropathies., There is a need for regular follow-up of the patient for the development of auto-immune diseases and prompt management with immunosuppressant drugs which can improve the person's quality of life.

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