CASE REPORT

ISAAC'S SYNDROME ASSOCIATED WITH MYASTHENIA GRAVIS AND THYMOMA

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ABSTRACT

A 65-year-old male developed fatigable weakness of ocular and bulbar muscle and positive anti-acetyl cholinesterase antibodies suggesting the diagnosis of myasthenia gravis. His condition responded to anticholinesterase and immunotherapy. However, 18 months later, he developed painful paresthesiae, muscle cramps with hyperhiderosis, and was diagnosed as having Isaac's syndrome (neuromyotonia, continuous muscle fibre activity). Computed tomography of the chest revealed a thymic mass, which was confirmed after surgery and histopathology as thymic cell carcinoma. The co-occurrence of myasthenia gravis and continuous muscle fiber activity should prompt the consideration of the occurrence of these disorders as one of the paraneoplastic manifestations, most often due to a thymic neoplasm. Both these conditions respond to treatment of underlying thymoma. This case is a very rare presentation worth reporting.

Key words: *Continuous muscle fibre activity, myasthenia gravis, thymic cell carcinoma*

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder characterized by fluctuating neuromuscular weakness involving the ocular, bulbar, limb, and respiratory muscles. Thymic pathology is frequent in as much as 50% of the individuals with generalized MG. About 50% of these have thymic hyperplasia and in another 15% thymoma is reported. The other uncommon neuromuscular disorders associated with thymoma are Isaac's syndrome (neuromyotonia) and polymyositis.[1]

Neuromyotonia is a neurological disease characterized by spontaneous electromyographic discharges and defined by Isaacs as a syndrome of continuous muscle fiber activity at rest (CMFAS).[2] Clinically neuromyotonia is characterized by hyperexcitability of peripheral nerves manifesting as a CMFA as fasciculation's and muscle cramps. Other clinical presentations of the same syndrome include stiffness of the leg muscles, sensory painful parasthesias as well

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as hyperhidrosis; the latter symptom represents autonomic nervous system involvement. This hyperexcitability is autoantibody-mediated and targeted against voltage-gated potassium channels (VGKC). Anti-VGKC antibodies are found in approximately 40% of patients with acquired neuromyotonia.[3] Diagnosis is made on electromyography; the neuromyotonic discharges are characteristically high frequency (150-250 Hz), decrementing and repetitive discharges of a single motor unit.[4]

Several lines of evidence suggest that these discharges are generated in the peripheral motor axons. Isaac's syndrome is a paraneoplastic in about a quarter of cases; the tumors most often associated with this condition are thymoma and small cell carcinoma of the lung.

The association of CMFAS with thymoma and MG is of very rare occurrence.

Here, we report the occurrence of MG and Isaac's Syndrome in an individual who was eventually diagnosed with thymic cell carcinoma a very rare occurrence of two paraneoplastic syndromes in a same individual.

CASE REPORT

A 65-year-old male initially presented with fatigable ptosis, difficulty in mastication, and mild dysphagia. He was known diabetic and hypertensive. He was also chronic smoker (10 cigarettes per day for last 10 years). A diagnosis of MG was made on the basis of good response of the neuromuscular weakness to anticholinesterases with a positive anti-acetylcholine receptor antibody. His family history was non-contributory for the occurrence of a neuromuscular transmission disorder. Complete blood counts, renal and liver function tests, chest roentgenogram were essentially normal. In view of generalized and bulbar muscle weakness, treatment with pyridostigmine was initiated. Intravenous immunoglobulin (2 g/kg) was also administered. In addition, oral corticosteroids (prednisolone, 1 mg/kg/day) and azathioprine were also started. The dose of azathioprine was increased to 2.5 mg/kg/day over 3 weeks. The subject improved over the first 2 weeks and remained in remission over the next 18 months. During this period, the doses of oral corticosteroids and pyridostigmine were slowly reduced.

About 18 months after diagnosis of MG, the gentleman complained of severe paresthesiaes involving both feet, painful cramps in legs and arms, severe generalized sweating (hyperhidrosis) to the extent that it led to chilly sensation requiring the use of heaters and blankets. In addition, he also complained of constipation and nocturnal diarrhea. The symptoms worsened over 2 months to the extent that he was readmitted for repeat evaluation. Clinical examination at this time revealed rippling movements in the muscles of the calves and thighs at rest along with stiffness of legs. Otherwise, however, power was grade 5/5 (MRC grades) in all muscle groups tested. There was no evidence of fatigable weakness in the ocular or bulbar muscle groups. All deep tendon reflexes were normal. There was no sensory deficit. Postural hypotension was also present with postural fall of 30 mm in systolic and 20 mm in diastolic blood pressure. A small dose of carbamazepine (100 mg b.d) transiently

reduced the painful cramps and fasciculations as well as hyperhiderosis to some extent.

Electrophysiological examination (nerve conduction studies) was done which showed prolonged F-wave latency and multiple F-wave on single stimulation [Figure 1]. Electromyographic evaluation revealed spontaneous activity in the form of fasciculation along with neuromyotonic discharges which were high frequency decrementing and repetitive discharges [Figure 2]. Based on electrophysiological and clinical presentation, possibility of neuromyotonia was made, as neuromyotonia is one of the paraneoplastic manifestations of thymoma. Hence a contrast enhanced CT chest was planned which revealed a well-defined loculated mass seen in the anterior mediastinum, measuring approximately 4.4 x 2.4 cm and invading the aorta, confirming the diagnosis of thymoma. No pulmonary parenchymal or hilar lesion or lymphadenopathy was evident.

Both MG and Isaac's syndrome may be the paraneoplastic neuromuscular manifestation of a thymic neoplasm. In view of the above diagnosis, the plan was to remove thymoma for the control of the neuromuscular disorders. A sternal thoracotomy was performed. Thymectomy was done and postoperative biopsy sampling of the thymic mass revealed cells arranged in lobules separated by fibrous septae. These cells were large having round to oval vesicular nuclei and moderate amount of cytoplasm suggesting mitotic pathology. Paucity of lymphocytes were also observed. Thus, histological findings are suggestive of thymoma type B3 (well-differentiated thymic carcinoma) [Figures 3 and 4].

In the immediate post-operative period, the individual required invasive ventilatory support due to precipitation of myasthenic crisis. The

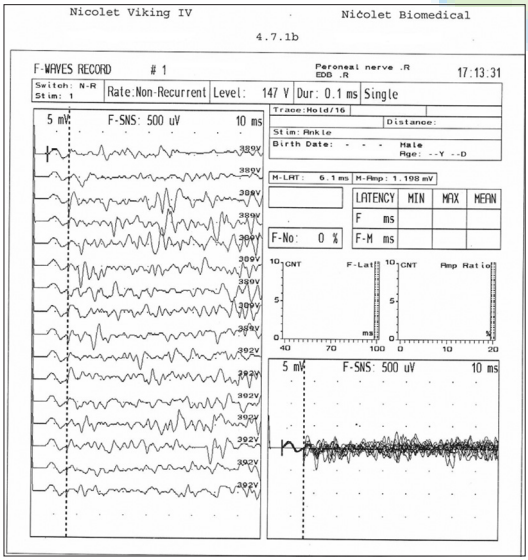

Figure 1: Motor conduction of median showed repetitive discharges on single stimulation. Group of 2 to 6 potentials of decreasing amplitude at regular intervals.

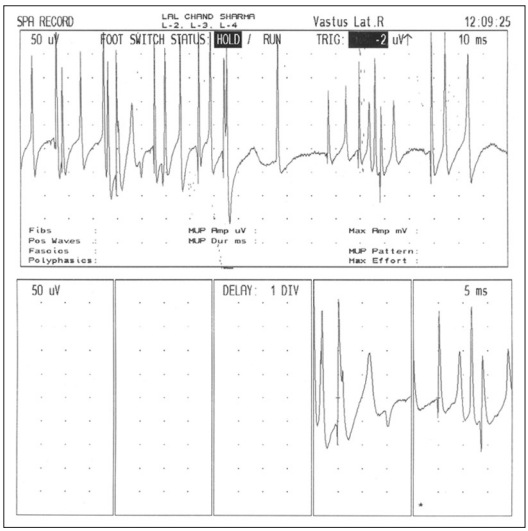

Figure 2: EMG shows decreasing amplitude repeated discharges on voluntary stimulation.

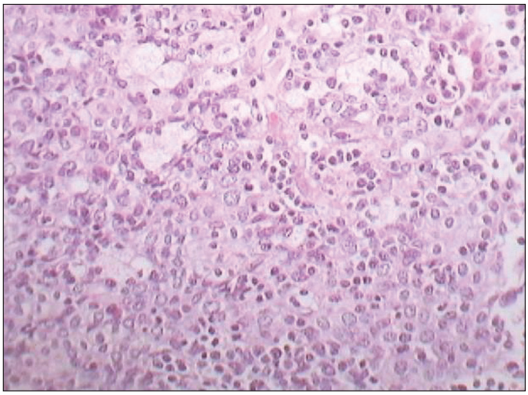

Figure 3: Thymic tumor cells having round to oval vesicular nuclei

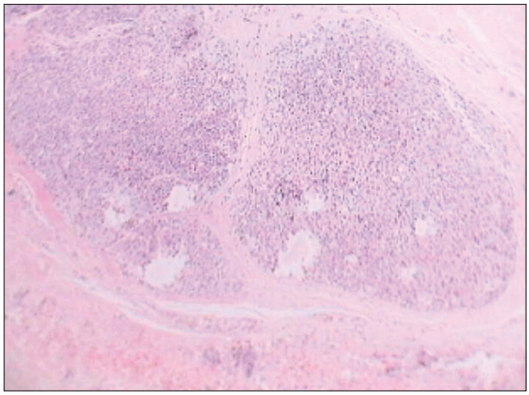

Figure 4: Thymic gland slide showing cells arranged in lobules separated by fibrous septae.

individual also developed postural hypotension. Decision was taken to administer a course of intravenous immunoglobulin (500 mg/kg/day for 5 days). His condition improved over 2 weeks in the post-operative period in as much as there was no demonstrable myasthenic weakness in any muscle group over 2 weeks. However, hyperhiderosis, parasthesiae, and cramps persisted though reduced in intensity after the treatment. He was discharged in a stable condition. On follow up, the patient had well-controlled symptoms of myasthenia and neuromyotonia with medication.

DISCUSSION

Both MG and CMFA have been described in relation to thymoma though is a rare combination.

MG and neuromyotonia are both paraneoplastic manifestation of thymic neoplasm. There were very few case reports in the literature of both these disorders occurring in same patient with thymoma.[5] The patient we reported herein was also shown to have an underlying malignant thymic neoplasm which was confirmed on histopathology.

One noteworthy symptom that merits discussion is the occurrence of hyperhiderosis in association with neuromyotonia in our patient. This may implicit that the occurrence of hyperhiderosis may be due to autonomic dysfunction and involvement of small fibers in peripheral nervous system. Retrospectively, we thought that the hypotension encountered in the post-operative period was also a manifestation of autonomic involvement. Hyperhiderosis though rare has been reported in cases of autoimmune neuromyotonia.

In the patient reported herein, the response to immunotherapy and thymectomy was reasonably good. The patient remained in remission; in the literature also, the response of MG and neuromyotonia is good after removal of tumor.[6,7]

CONCLUSION

The occurrence of myasthenia gravis and neuromyotonia in an individual should prompt a diagnosis of a paraneoplastic syndrome secondary to thymic neoplasm. These individual should also be evaluated for the

occurrence of autonomic dysfunction due to associated involvement of the small nerve fibers. Removal of thymic neoplasm may help in remitting the symptoms of these neuromuscular syndromes. Hence, the high index of suspicion and early treatment is important for management of the neuromuscular disorders.

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