CLINICAL VIGNETTE

Sarcoidosis-Associated Lambert-Eaton Myasthenic Syndrome in a Patient with Dysphagia and Recurrent Bell's Palsy

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the neuromuscular junction. It is caused by antibodies against voltage-gated calcium channels on the presynaptic membrane which interfere with calcium influx required for quantal release of acetylcholine into the neuromuscular junction. Reduced acetylcholine release at the neuromuscular endplate produces decreased endplate potentials, reducing the compound muscle action potential. Discovery of LEMS via clinical evaluation of proximal muscle weakness and confirmation by presence of antibodies to voltage-gated calcium channels raises the concern for underlying malignancy. Small cell lung cancer and lymphoproliferative disorders are associated with the expression of voltage-gated calcium channel antibodies which manifest as paraneoplastic LEMS. In the absence of malignancy, LEMS is associated with immune-mediated disorders. We present a case of sarcoidosis associated with LEMS.

Case Description

A 52-year-old female with a past medical history significant for right-sided Ramsay Hunt syndrome and Bell's palsy presented to clinic with dysphagia, partial right facial paresis, and phonophotophobia. Initial neurological evaluation demonstrated decreased sensation to light touch on the right side of her face with mildly decreased right palate elevation and difficulty with guttural and palatal sounds. MRI brain without contrast was negative for infarction, hemorrhage, mass effect, or hydrocephalus. Head and Neck evaluation revealed mild pharyngeal dysmotility during a swallow study. An extensive auto-immune and paraneoplastic workup was initiated. Voltage-gated calcium channel binding antibodies, P/Q-type (0.06 nmol/L) and N-type (0.16 nmol/L) returned elevated, concerning for LEMS. She was started on prednisone with symptomatic resolution except for her right-sided hearing loss. A chest computed tomography (CT) obtained to evaluate for occult malignancy revealed moderate mediastinal, hilar, and interlobar adenopathy (Figure 1). Bronchoscopy with endobronchial ultrasound guided needle biopsies as well as intranodal forceps biopsies were obtained and revealed noncaseating granulomas consistent with sarcoidosis (Figure 2).

Discussion

LEMS is a rare neurologic disorder, with incidence falling well below one per million.[1] Approximately half of all cases of LEMS are associated with malignancy, the majority being small cell lung cancer. Rare additional cases of LEMS associated with neuroendocrine forms of prostate carcinoma, leukemias, and lymphomas have been reported. These malignancies themselves express P/Q-type calcium channels, leading to likely immunization by the tumor.[2]

In the absence of malignancy, LEMS tends to present in young females with comorbid immune-mediated disorders including myasthenia gravis, pernicious anemia, hypothyroidism, and systemic lupus erythematosus. Demographics of patients without underlying cancer tend to be similar to those diagnosed with myasthenia gravis.[3]

LEMS diagnosis is based on a clinical triad of proximal muscle weakness, areflexia, and autonomic features such as orthostatic dysfunction. In addition, voltage-gated calcium channel antibody panels are positive or repetitive nerve stimulation studies show a low compound muscle action potential followed by increments at higher frequencies of stimulation. While pharyngeal dysmotility is less commonly described compared to the typical presentation of lower extremity weakness, ocular and bulbar involvement of the disease is inconsistently reported based on the timing of assessment.[4] Regarding the antibody panel, antibodies to the P/Q-type are highly specific to LEMS and have been rarely reported in patients with small cell lung cancer without co-occurring neurologic dysfunction.[5]

LEMS associated with sarcoidosis has been described in one other documented case report.[6] Sarcoidosis as an immune-mediated disorder classically involves the accumulation of noncaseating granulomas secondary to chronic cytokine production by CD4+ type 1 helper T cells transforming macrophages into epithelioid histiocytes. This model of autoimmunity has been made more complex by evidence of anergy secondary to CD25+ regulatory cells resulting in immune response suppression to tuberculin as well as proposed mechanisms behind pulmonary fibrosis linked to the shift in cytokine production by CD4+ type 1 helper T cells to type 2 helper T cells.[7-9] As such,

aberrant cellular immunity may lead to the appearance of LEMS autoantibodies as in other immune-mediated conditions.

The majority of patients can be successfully treated with prednisone and azathioprine to induce immunosuppression, while addressing any existing underlying malignancy. Pyridostigmine, a medication used to treat myasthenia gravis, may be utilized to inhibit acetylcholinesterase activity and amplify amounts of acetylcholine capable of causing endplate potentials. Additionally, 3,4-diaminopyridine is a fast voltage-gated potassium channel blocker that prolongs presynaptic depolarization to increase release of acetylcholine has shown success in trials for maintain remission and for patients with mild weakness. Acutely, intravenous immunoglobulin or plasmapheresis may be utilized for respiratory distress along with supportive ventilator care as needed.[10] Additionally, on detection of the neurologic disease, screening for small cell lung carcinoma with chest CT followed by FDG-PET is recommended.[2]

Conclusion

LEMS is a rare disease of the neuromuscular junction commonly associated with malignancy secondary to antibody formation against voltage-gated calcium channels. In the absence of underlying malignancy, LEMS has been associated with immune-mediated disorders. Following screening for occult malignancies, immunologic disorders should be considered as potential etiologies for the formation of autoantibodies. LEMS associated with sarcoidosis is a rarely reported phenomenon highlighting the complexity of dysregulated immune response in autoimmune diseases.

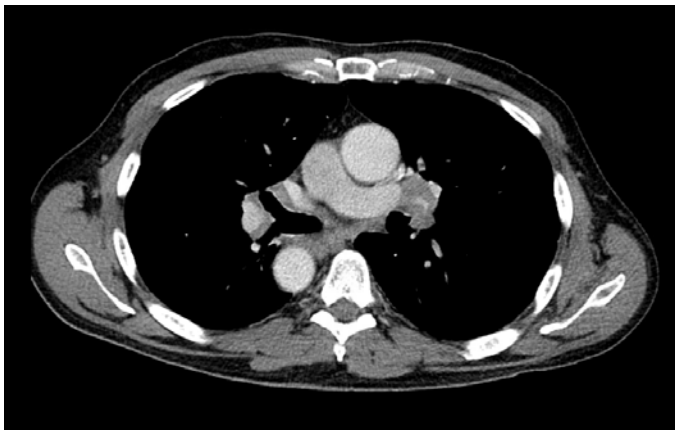

Figure 1. Chest CT with contrast demonstrating moderately-sized, roughly symmetric mediastinal and bilateral hilar and interlobar lymphadenopathy.

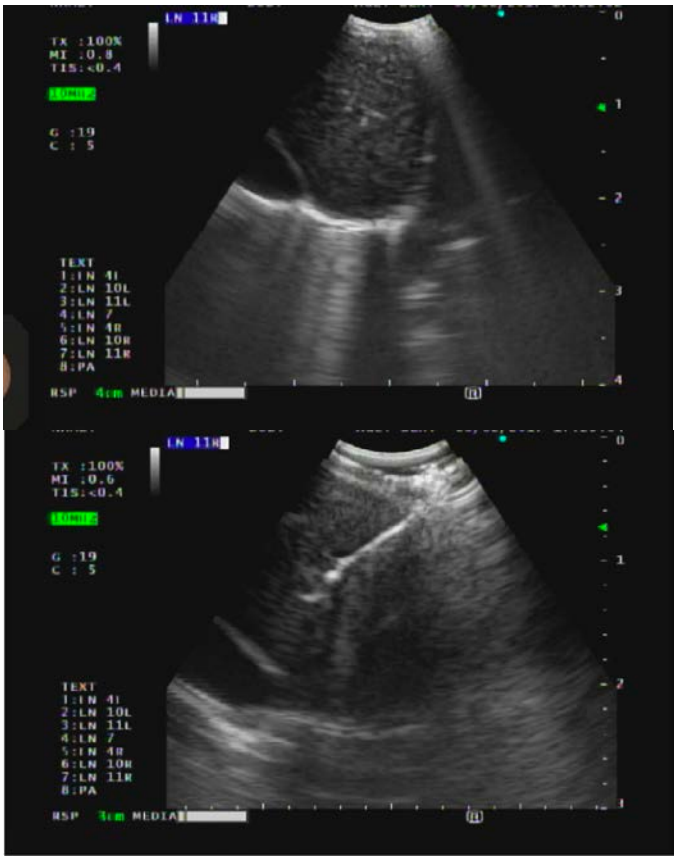

Figure 2. Endobronchial ultrasound-guided transbronchial needle aspiration of a lymph node at 11R station greater than 5 mm in size later revealing non-caseating granulomas with negative AFB and GMS stains.

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