CLINICAL VIGNETTE

Diabetic Amyotrophy: A Case Report

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An 83-year-old female presented to the emergency room with worsening abdominal distension and left lower extremity swelling. The patient has a history of lymphoma, DM, HTN, and hypothyroidism. She was recently discharged from the hospital with new diagnoses of diastolic heart failure, hyponatremia secondary to SIADH, hypoalbuminemia from proteinuria and anemia of chronic disease. She was also noted to have elevated inflammatory markers during her first hospitalization for which extensive outpatient workup was planned. When she presented again to the emergency department, she reported progression of her lower extremity edema and abdominal distension despite compliance with furosemide. In addition, she reported feeling extremely "tired" and having diffuse arthralgias. She explicitly denied any chest pain, paroxysmal nocturnal dyspnea or orthopnea. She reported mild dyspnea on exertion but felt it was overall fatigue rather than true shortness of breath. She had no cough, rashes, dysphagia or diplopia. She had a poor appetite but no other gastrointestinal symptoms. She also reported low-grade elevated temperatures, without focal infectious symptoms.

Outside records indicate that the patient was diagnosed almost five years ago with diffuse large B cell lymphoma. She was treated with chemotherapy and had been undergoing surveillance by her oncologist, without evidence of recurrence.

Her initial exam was notable for a temperature of 100.7° F, HR 79, BP 109/58 and pulse oximetry 99% on room air. Her cardiopulmonary exam was normal. Her abdomen was without an appreciable fluid wave. Examination of her lymph nodes was unremarkable. She had no tenderness over her temporal skull. She had pitting edema of her left thigh greater than her right thigh. Her musculoskeletal exam was remarkable for muscle tenderness on palpation without synovitis. She had proximal muscle weakness, most prominent in her bilaterally upper extremities as well as her hip flexors, with left being weaker than right.

Hospital Course:

Because of progressive worsening symptoms, the patient was admitted and additional diagnostic studies obtained. These included blood and urine cultures, which were without significant growth. Negative testing for: mycoplasma pneumonia, MTB-Quantiferon Gold, HIV, Cocci, Aspergillus and Histoplasma. Chest radiographs were done and noted bronchial wall thickening. On standard labs, it was noted that the patient had anemia with a hemoglobin nadir of 6.7, and thrombocytopenia with platelet nadir of 61,000.

In light of her symptoms of weakness, elevated ESR and possible focal myopathies, rheumatology and neurology consultations were obtained with additional tests to evaluate for polymyalgia rehumatica, inflammatory myositis, and paraneoplasic myopathies. Her statin medication was also discontinued.

Labs:

	Prior hospitalization	Current hospitalization
BNP	501	181
CK (total)	Not available	441 (peak)
LD	581	403
Ferritin	2856	4019
CRP	3.5	7.1
ESR	>100	>100

Her rheumatological workup included:

Rheumatoid factor 18 (<25 IU/mL); **Antinuclear Ab Titer >= 1:1280** ; dsDNA Ab EIA <200 (<200 IU/mL), Centromere B Antibody negative; Smooth Muscle Ab negative; SM Antibody negative, RNP Antibody negative; **SSA Antibody 63 (<20 U);** SSB Antibody negative; Scleroderma Antibody negative; MI-2 Autoantibodies negative; Jo 1 Antibody negative; Cyclic Citrulline Ab IgG negative; Cardiolipin IgA negative, Cardiolipin IgG negative, **Cardiolipin IgM 19 (<12.5 MPL)**; C3 89 (71-141 mg/dL); C4 32 (12-34 mg/dL)

Serum Immunofixation showed that no monoclonal immunoglobulins were present.

A neuro paraneoplastic panel was sent which was negative for NMDA, Hu Immunoreactivity, VGKC Antibody Titer, Yo Immunoreactivity, Ri Immunoreactivity, CAR Immunoreactivity, and LEMS Immunoreactivity.

Additional invasive tests were performed to evaluate for occult infection or malignancy. Bronchoscopy was negative for infectious or malignancy findings, bone marrow biopsy was negative for lymphoma and showed a hypercellular marrow. MRIs of her brain and spine yielded no findings that would explain her weakness. A lumbar puncture yielded clear CSF fluid with no increased cellularity but a mildly elevated protein count at 61. An MRI with and without contrast of her left femur was obtained and showed diffuse heterogeneous but bilaterally symmetric muscle edema.

Given the possibility of a myositis, a surgical biopsy of the patients left quadriceps muscle was performed, which showed no inflammatory cells or evidence of vasculitis (Insert Figure 1).

Based on the pathology, the diagnosis of diabetic amyotrophy was made.

Discussion

This case had a number of factors that pointed towards myositis, including elevated inflammatory markers, positive ANA and SSA antibodies, and hyperintensity and edema on extremity MRI imaging. Differential diagnosis included polymyalgia rheumatica, statin-induced myopathy, vasculitis, diabetic muscle infarction, and inflammatory myositis (due to either autoimmune or paraneoplastic etiology). However, surgical biopsy interestingly showed no inflammatory cells, necrosis, or vasculitis. Single fiber atrophy was identified, suggestive instead of neurogenic origin and a diagnosis of diabetic amyotrophy was made based on the pathologic and clinical picture.

Diabetic amyotrophy, otherwise known as Bruns-Garland syndrome, was first described by Bruns in 1890 and the term was coined by Garland in 1955[1]. It is characterized by acute or subacute onset of asymmetric pain in the proximal lower extremities[2]. The process can progress to weakness and atrophy, and can extend distally or to the contralateral muscle groups. It often occurs in well-controlled or newly diagnosed diabetics, and can even be the presenting symptom in someone whom has yet to be diagnosed with diabetes. This contrasts the more common diabetic peripheral neuropathy, which primarily affects distal sensory fibers in a symmetric fashion and has a more gradual onset in longstanding poorly controlled disease.

The syndrome has a number of other names, including diabetic lumbosacral radiculoplexus neuropathy, diabetic myelopathy, diabetic mononeuritis multiplex, and diabetic polyradiculopathy, which reflects the uncertainty in the anatomical etiology of the disease[2]. Nerve conduction studies show decreased amplitudes of lower limb motor and sensory action potentials. Electromyography shows evidence of denervation in affected muscles, and surgical muscle biopsy is characterized by neurogenic changes, denervation, and microvascular hyalinization (also referred to as pipestream microangiopathy). Sural nerve biopsy shows ischemic injury and inflammatory infiltrates with immune complex and complement deposition, indicating an immune mediated microvasculitis as the etiology of the disease[3]. Laboratory studies supportive of the diagnosis include elevated ESR and elevated protein levels in CSF fluid without pleocytosis[2].

Treatment generally involves immunosuppressive medications primarily with corticosteroids (either oral prednisone or intravenous methylprednisolone), but symptomatic improvement has also been reported in case reports or retrospective case series with intravenous immunoglobulin therapy, plasma-pheresis, and cyclophosphamide[4]. A 2012 Cochran review found only one randomized control trial that had been completed, comparing intravenous methylprednisolone to placebo[5]. The results of this study were only presented in abstract form, and although the primary endpoint of time to improve by four points on the Neuropathy Impairment Scale of Lower Limbs was not significantly different between the two groups, many of the subscores of the Neuropathy Symptom and Change score were better in the treatment arm. Additional symptomatic management can include narcotic analgesics, neuropathic pain treatments, and antidepressants.

Conclusion

Diabetic amyotrophy is a clinically and pathophysiologically distinct entity from the more

common diabetic peripheral neuropathy, causing asymmetric pain and weakness in primarily proximal muscles in well controlled or recently diagnosed diabetics. The disease is thought to be due to ischemic injury and immune mediated microvasculitis, and diagnosis can be confirmed with nerve conduction studies and sural nerve biopsy. Muscle biopsy findings show neurogenic muscle atrophy and can help in ruling out alternative diagnoses. While no compelling evidence exists to guide treatment strategies, symptomatic improvement has been suggested with immunosuppressive medications.

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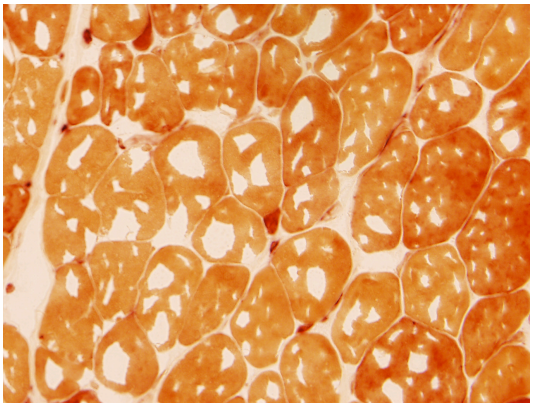

Figure 1: Nonspecific enolase histochemical stain of muscle. Small atrophic myofiber is demonstrated in the center of the image as a dark-brown triangle. 400x original magnification.