Case of Vasculitic Neuropathy and Myelopathy

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Introduction

Eosinophilic granulomatous polyangiitis (EGPA) is a rare form of antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. Vasculitic peripheral neuropathy could be the sole or the first and most prominent manifestation of systemic vasculitis. Here, we present a case with cervical spondylotic myelopathy and vasculitic neuropathy which was initially misdiagnosed as statin-induced myopathy and later diagnosed as EGPA following nerve biopsy.

Case

A 61-year-old female with coronary artery disease status post coronary artery bypass surgery 3 years ago presented with a 4-month history of numbness with severe burning pain that started in the toes and ascended up the legs and then into the hands. She also had proximal and distal weakness worse in the arms, headaches, myalgia, and arthralgia. The onset coincided with the initiation of amlodipine for hypertension; she presented to an outside hospital 1 month later due to persistent symptoms, where she was diagnosed with statin-induced myopathy, and both amlodipine and atorvastatin (that she had been taking for 3 years) were stopped at that time. Her headaches resolved, however her numbness, pain, and weakness progressed. She noted 20-pound weight loss in the initial month. She also reported odynophagia and Raynaud's phenomenon. Interestingly, she had similar symptoms when she took amlodipine in the past that spontaneously resolved after discontinuation of the drug. Social history and family history were non-contributory.

Review of outside records revealed that her highest creatine kinase (CK) was 55 U/L. Physical exam showed normal vital signs, no rashes, intact cranial nerves, symmetric proximal and distal weakness (medical research council (MRC) scales: shoulder abduction 4, elbow flexion 4, elbow extension 5, wrist extension 5, wrist flexion 5, finger flexion 5, finger extension 4+, finger abduction 4, thumb abduction 5, hip flexion 4-, knee extension 5, knee flexion 4, ankle dorsiflexion 4, plantar flexion 4+, eversion 4+, and inversion 4+, toe flexion 4, toe extension 3), diminished sensation to pinprick up to ankles, decreased proprioceptive and vibratory sense at the interphalangeal joint of the great toes bilaterally (timed vibratory sense: 12 and 9 seconds). Tone was normal. Deep tendon reflexes were prominent in upper extremities, 3 at brachioradialis and biceps with finger flexions, 3 at triceps, 2 at patella, 1 at ankle bilaterally; plantar responses were flexor, and Hoffman's sign was mildly positive bilaterally. Jaw jerk was absent. Coordination and gait were intact.

Initial admission labs showed anemia, thrombocytosis, leukocytosis with elevated nucleated cells, monocytosis ($0.87x10^3$/mL), and eosinophilia ($1.63x10^3$/mL); elevated C-reactive protein (16.45 mg/dL) and sedimentation rate (68 mm/hr); CK was below 5 U/L and aldolase 42 U/L. MRI of the cervical spine revealed multilevel cervical spondylosis most pronounced at C6-C7 with severe central spinal stenosis with a signal change in the spinal cord, as well as multilevel neural foraminal stenosis bilaterally. She was evaluated by orthopedic surgery and deemed not a surgical candidate as it was felt not to be the primary driver of her pain and weakness. MRI thoracic and lumbar spine, and vitamin B12 were normal. Serum immunofixation revealed IgG k paraproteinemia and elevated IgG (1,672 mg/dL) and IgE (368 IU/mL). PET-CT scan of the whole body showed diffuse nonspecific marrow and splenic hypermetabolism, and mildly hypermetabolic lymph nodes. Anti-HMG-CoA reductase (HMGCR) antibody was negative. Due to concern for autoimmune neuropathy including systemic vasculitis, cryoglobulinemia, and Sjögren's syndrome, as well as hematologic malignancy causing paraproteinemia, Rheumatology and Hematology were consulted; extensive workup revealed positive rheumatoid factor (97 IU/mL), P-ANCA (320 titer), and myeloperoxidase antibody (MPO-ANCA) (1.3 AI), anti-SS-A 52 kD antibody IgG (105 U). Negative results included cryoglobulin, vascular endothelial growth factor, anti- SS-A and SS-B antibodies, and lip and bone marrow biopsies. Nerve conduction study showed moderate, primarily axonal, sural-sparing, distal motor neuropathy or neuronopathy; mild, non-irritative myopathy; and right demyelinating median neuropathy with axonal loss (**Table 1**).

Table 1. Nerve conduction study.

Sensory nerve conduction study

Nerve / Sites	Onset Lat	Peak Lat	NP Amp	PP Amp	Segments	Distance	Velocity
	ms	ms	µV	µV		mm	m/s
R Median - Digit II (Antidromic)							
Wrist	NR	NR	NR	NR	Wrist - Dig II	130	NR
R Ulnar - Digit V (Antidromic)							
Wrist	2.71	3.44	12.2	30.6	Wrist - Dig V	110	41
R Radial - Anatomical snuff box (Forearm)							
Forearm	1.88	2.40	22.2	23.7	Forearm - Wrist	100	53
R Sural - Ankle (Calf)							
Calf	3.18	3.85	2.4	8.6	Calf - Ankle	140	44

Motor nerve conduction study

Nerve / Sites	Muscle	Latency	Amplitude	Segments	Distance	Velocity	Temp.
		ms	mV		mm	m/s	ºC
R Median - APB							
Wrist	APB	5.16	1.4	Wrist - APB	70		32
Elbow	APB	10.10	1.2	Elbow - Wrist	193	39	32
R Ulnar - ADM							
Wrist	ADM	2.97	6.0	Wrist - ADM	70		31.9
B.Elbow	ADM	5.99	5.6	B.Elbow - Wrist	158	52	31.9
A.Elbow	ADM	7.71	5.4	A.Elbow - B.Elbow	100	58	31.9
R Peroneal - EDB							
Ankle	EDB	3.70	0.8	Ankle - EDB	80		29.4
Fib head	EDB	10.36	0.5	Fib head - Ankle	275	41	28
Pop fossa	EDB	12.55	0.6	Pop fossa - Fib head	100	46	28
R Tibial - AH							
Ankle	AH	3.80	2.2	Ankle - AH	80		
Pop fossa	AH	10.36	1.4	Pop fossa - Ankle	325	50	
R Peroneal - Tib Ant							
Fib Head	Tib Ant	3.54	1.8	Fib Head - Tib Ant			25.9
Pop fossa	Tib Ant	5.83	1.7	Pop fossa - Fib Head	100	44	25.9

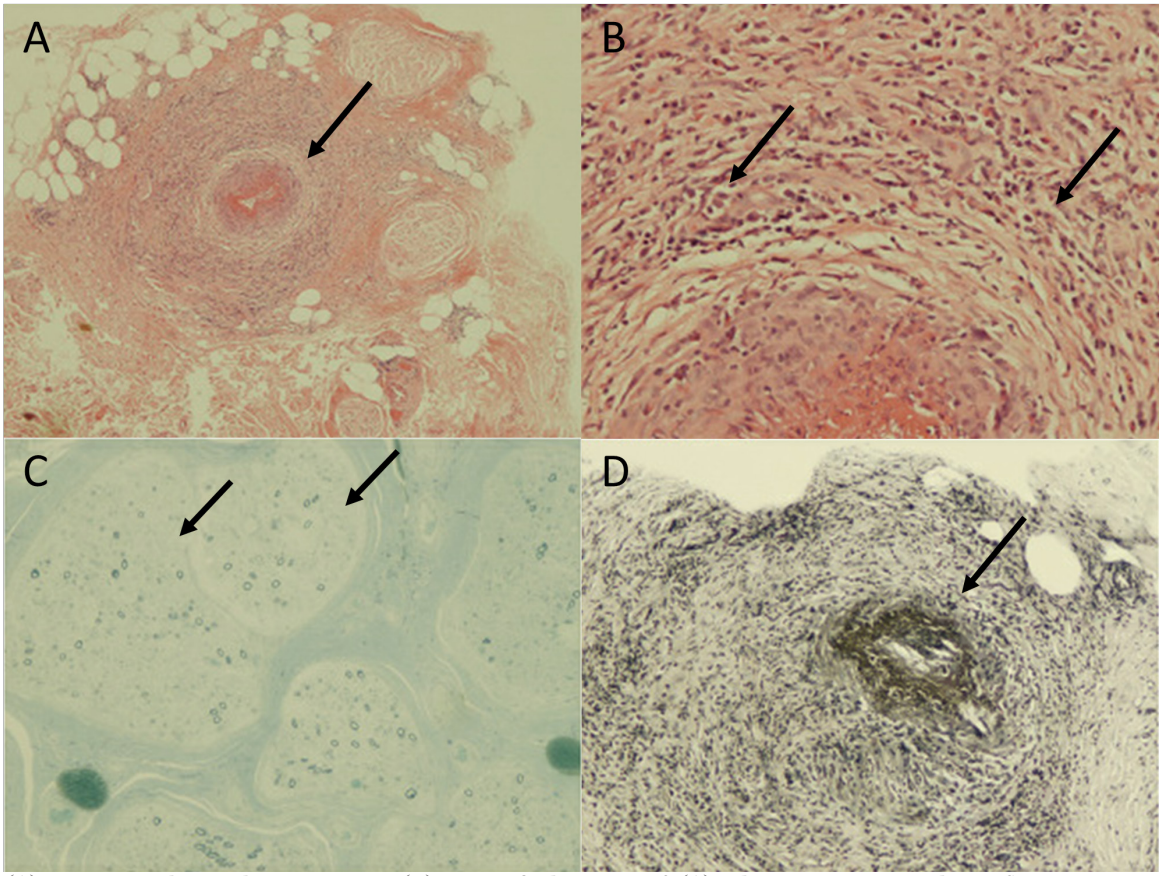
MRI of lower extremities showed heterogenous increased short T1 inversion recovery (STIR) signal intensity involving multiple muscles. She proceeded with muscle and nerve biopsies. Muscle biopsy from the left vastus lateralis showed nonspecific type 2 fiber atrophy and epimysial perivascular inflammation. Sural nerve biopsy showed vasculitis consistent with eosinophilic granulomatosis with polyangiitis and axonal neuropathy.

She was diagnosed with EGPA on the basis of nerve biopsy findings shown in **Figure 1**. Intravenous methylprednisolone was initiated resulting in spontaneous symptom resolution. Patient is currently undergoing protracted oral prednisone taper without signs of recurrence.

Discussion

We report a case of cervical spondylotic myelopathy and vasculitic neuropathy from EGPA preceded by amlodipine use, initially misdiagnosed as statin-induced myopathy despite absence of elevation in CK. Symmetric proximal weakness with myalgia and hyperreflexia in arms and preserved reflexes in Achilles tendon that did not go along with neuropathy likely led to confusion between myopathy and neuropathy. However, statin induced myalgia, myopathy, or necrotizing myositis are unlikely to present without hyperCKemia[1]. Negative anti-HMGCR antibody also supported against statin-induced myopathy. Neuromuscular exam favored neuropathic weakness than myopathic weakness in presence of distal weakness

Figure 1. Sural Nerve Biopsy.



(A) Hematoxylin and eosin stain, (B) magnified image of (A), showing perivascular inflammation in epineural vessels containing eosinophils (arrows). (C) Toluidine blue semithin EM stain showed severe loss of large myelinated axons (arrows). (D) Verhoeff EVG stain showed loss of internal elastic lamina in the epineural arteries (arrow).

and paresthesia; vasculitic neuropathy could present as symmetric length-dependent polyneuropathy and not limited to mononeuritis multiplex[2]. Mild proximal weakness and preserved reflexes were likely due to concurrent severe cervical spondylotic myelopathy. Workup at our institution showed elevated aldolase, positive anti-SS-A 52 kD antibody, heterogenous STIR hyperintensity in lower extremities involving multiple muscle groups, non-irritative myopathy on needle electromyography, and nonspecific findings on muscle biopsy; all suggested nonspecific muscle involvement. We believe that all those nonspecific muscle findings were likely from disuse or ischemia in the muscles, not from inflammatory myositis or necrotizing myositis in the absence of hyperCKemia, especially with the fact that muscle involvement in EGPA is exceedingly rare with only 8 cases reported to date, ranging from eosinophilic myositis to necrotizing eosinophilic vasculitis[3].

EGPA is an ANCA-associated vasculitis defined as eosinophil-rich with necrotizing granulomatous inflammation often involving the respiratory tract, necrotizing vasculitis predominantly affecting small to medium vessels, and associations with asthma and eosinophilia[4]. The incidence is estimated as 10.7 to 14 in 1,000,000, with median age of symptom onset at 40 years. P-ANCA and MPO-ANCA are seen in 40% of vasculitic type associated with myalgia, migrating polyarthralgia, weight loss, mononeuritis multiplex, and renal involvement either as crescentic or necrotizing glomerulonephritis. ANCA negative EGPA is associated with hypereosinophilic syndrome with myocarditis[5]. Peripheral neuropathy is commonly seen up to 80% of cases; central nervous system involvement is reported at a lower frequency, leading to ischemia and hemorrhage, granulomatous lesions, and hypertrophic pachymeningitis. Prognosis is favorable with 5-year survival of 90%; recurrence could occur in 20 to 30 % of all cases[6]. Poor prognostic factors include elevated serum creatinine (>1.58 mg/dL), proteinuria (> 1 g/day), severe gastrointestinal tract involvement, cardiomyopathy, and central nervous system involvement[7,8]. In the absence of poor prognostic factors, initial induction treatment consists of either oral or intravenous corticosteroids with

protracted taper; in the presence of poor prognostic factors, cyclophosphamide has been traditionally added[9]. In recurrent cases, methotrexate (10 to 25 mg per week), cyclosporin A (1.5 to 2.5 mg/kg per day), and azathioprine (2 mg/kg per day) have been used; in refractory cases, plasma exchange, intravenous immunoglobulin, interferon-alpha, tumor necrosis factor inhibitors, rituximab, mepolizumab, and omalizumab have been reported in literature[5, 9].

It is interesting that the initiation of amlodipine coincided with the symptom onset in our patient. Drug-induced vasculitis has been reported with agents such as antibiotics, anti-thyroid drugs, and anti-tumor necrosis factor-α agents[10]. Traditionally, drug-induced vasculitis involves skin and subcutaneous tissue, occasionally lung and kidney, and multi-organ involvement is rare. The specificity of ANCA antibodies is also helpful to discriminate drug-induced vasculitis from idiopathic ANCA-associated vasculitis. In drug-induced vasculitis, ANCA tends to be multi-specific with MPO-ANCA being most common but HLE-ANCA, lactoferrin-ANCA could be seen concurrently, although these ANCA are not available for routine testing at the University of Kansas Medical Center. In idiopathic ANCA-associated vasculitis, ANCA usually has only one target as in EGPA and MPO-ANCA[11]. Vasculitis would resolve after cessation of the causative agent in most cases. There has been only one case report that initiation of amlodipine preceded leukoclastic vasculitis of the skin, but no report was found with EGPA[12]. Collectively, we believe that the timing of amlodipine initiation at symptom onset was a coincidence rather than a plausible causative agent of drug-induced vasculitis.

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