A Rare Potential Cause of Mononeuropathy Multiplex

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Introduction

The clinical presentation of multifocal involvement of two or more noncontiguous peripheral or cranial nerves which impairs the motor, sensory, sensorimotor, or somatic function defines mononeuropathy multiplex (MNM).[1] If the underlying pathology is progressive in nature, patients may evolve to have overlapping multifocal neuropathies in contiguous areas (overlapping multifocal neuropathy) which may be extensive enough to obscure the original anatomical pattern of multifocal features. While the differential for such presentations is broad and includes various inflammatory, autoimmune (i.e. multifocal acquired demyelinating sensory and motor neuropathy), infectious, drug-induced, genetic, mechanical, or neoplastic etiologies; the syndrome is often concerning for an underlying vasculitic neuropathy, especially when other systemic signs and features are present.[1,2] In this clinical scenario, consideration of potential mimics of vasculitic neuropathy is important as the underlying treatment may differ and affect clinical outcomes.[3,4] Here we present a case of mononeuropathy multiplex associated with a rare entity in a 58-year-old male in whom standard treatment with immunosuppression is contraindicated.

Case Report

A 58-year-old male reported symptom onset 4 months prior to neuromuscular consultation with numbness on his right foot and shin as well as left arm hypersensitivity and discomfort. He had no preceding illnesses but did report receiving the flu vaccine approximately 3 weeks prior to the onset of his initial symptoms. Symptoms began to progress over the course of 1-2 weeks with ascending numbness in his right leg as well as a knot-like sensation and pain in the back of the calf for which he presented to the ED with a negative workup for DVT. He continued to have progression of symptoms over the following weeks to include his right leg feeling heavier with exercise or longer drives as well as a similar knot-like sensation/pain in his left calf. His hypersensitivity also progressed to include his right arm. Throughout the second month of symptoms, he had a repeat emergency room visit as well as an appointment with his primary care manager with additional workup demonstrating a negative lumbar X-ray and brain MRI. Notable lab findings were a negative Lyme antibody titer as well as a positive ANA (titer 1:320) and borderline low B12 level (278 ng/mL) for which he was started on oral supplementation.

His numbness and hypersensitivity progressed to include his bilateral thumbs and forearms. Ultimately, he was referred to an outside neurologist two months after symptom onset where he was documented to have asymmetric distal sensory loss in his right greater than left lower extremities. A C-Spine MRI and EMG were ordered. He developed the acute onset of right foot drop two weeks after his initial neurology consultation (2.5 months after symptom onset). An EMG showed an asymmetric neuropathy, prompting an urgent neuromuscular evaluation at the University of Kansas Medical Center due to concern for mononeuropathy multiplex.

His initial exam demonstrated mild lower facial weakness (4/5) as well as left upper extremity elbow extensor weakness (4+/5), right ankle dorsiflexion/plantar flexion weakness (dorsiflexion 0/5, plantar flexion 3/5), and mild left dorsiflexion weakness (4/5). Reflexes were symmetric in the upper extremities and at the knees; however, his right Achille's reflex was diminished (1/4) as compared to the left (2/4). He had a multifocal pattern of decreased pinprick sensation including over the bilateral thumbs (left worse than right), bilateral lateral forearms, lateral thighs, and diffusely below the knees with the exception of some sensation in the lateral feet, bilaterally, and the left sole of the foot. Vibration and proprioception were diminished at the toes, and his gait was steppage.

EMG performed on the day of presentation was consistent with an asymmetric sensorimotor axonal peripheral neuropathy (Table 1). Given his history, examination, and electrophysiologic findings, he was admitted for expedited workup for a possible vasculitic neuropathy. Laboratory workup was notable for an elevated ANA at 1:160, Vascular Endothelial Growth Factor (VEGF) of 99.6 pg/mL (reference <=96.2 pg/mL), and Kappa/Lambda free light chain ratio of 1.81 (reference

0.26-1.65). Additional studies, including other typical vasculitic labs, were negative (Table 1). CSF was evaluated and unremarkable and an abdominal fat pad aspirate, obtained due to the slightly elevated Kappa/Lambda ratio, was normal (Table 1).

A PET CT, obtained to rule out malignancy in the setting of the unexpected kappa/lambda ratio, demonstrated hypermetabolic lesions in the lung left upper and lower lobes and a pleural lesion adjacent to the right lower lobe, concerning for metastatic disease (Figure 1). These findings prompted a biopsy of the hypermetabolic left lower lobe lung lesion in addition to his previously planned right sural nerve and peroneus brevis muscle biopsies (biopsy sites chosen based on surgeon preference). He was started on empiric high dose steroids and mycophenolate mofetil while biopsy results were pending. However, he tolerated this treatment poorly, and it was stopped within 30 days with no additional immunosuppression started. He remained on symptomatic treatment for his neuropathic pain while initial biopsy results were pending.

The right peroneus brevis muscle biopsy demonstrated an inflammatory neuropathy with perivascular and endomysial chronic inflammation and increased sarcolemmal MHC class I expression (Figure 2) while the right sural nerve biopsy demonstrated an inflammatory neuropathy with vascular and parenchymal inflammation and one poorly formed granuloma. A Fite stain was negative

Table 1. Initial electrodiagnostic findings and summary of hospital laboratory workup.
Abbreviations: Lat. Latency, Amp. Amplitude, Dur. Duration, Dist. Distance, CV Conduction Velocity. R. Right, L. Left, EDB extensor digitorum brevis, TA tibialis anterior, FH fibular head, APB abductor pollicis brevis, ADM abductor digit minimi, PL peak latency, MAC median antebrachial cutaneous nerve, PSW positive sharp waves, Fibs fibrillation potentials, Poly polyphasia, NML normal, MUAPs motor unit action potentials

Initial EMG							
Motor NCS							
Nerve/Sites	Lat. (ms)	Amp. (mV)	Dur. (ms)	Dist. (mm)	CV (m/s)		
R. Peroneal-EDB	**NR**	**NR**	**NR**	**NR**	**NR**		
L. Peroneal-EDB	4.6	**0.4**	6.0	80	**30** (FH-ankle) **45** (Knee-FH)		
L. Peroneal-TA	3.9	3.1	16.5		45		
R. Peroneal-TA	**5.0**	**0.5**	17.5		**23**		
R. Tibial-AH	4.9	**0.9**	8.3	80	45		
L. Tibial-AH	4.2	**2.2**	8.0	80	48		
Normal Studies	R. Median-APB, R. Ulnar-ADM						
Sensory NCS-all antidromic unless otherwise specified							
Nerve/Sites	PL (ms)	Amp (μV)		Segment			
R. MAC	2.7	5.9		Elbow-forearm			
L. MAC	3.1	**2.9**		Elbow-forearm			
L. Sural	4.4	**2.4**		Lower leg-ankle			
R. Sural	**4.8**	**1.9**		Lower leg-ankle			
R. Sup. Peroneal	4.64	**1.8**		Lateral leg-ankle			
L. Sup. Peroneal	**NR**	**NR**		Lateral leg-ankle			
Normal Studies	R. Median (wrist-digit II), R. Ulnar (wrist-digit V), R. Radial (forearm-snuffbox)						
Needle Electrode Examination							
Muscle	Insertional Activity	Spontaneous Activity		Volitional Activity			
		PSWs	Fibs	Poly	Amp	Dur	Recruit
R. Tibialis Anterior	NML	4+	4+	No MUAPs			
R. Gastrocnemius	NML	3+	3+	No MUAPs			
R. Vastus Lateralis	NML	None	None	None	NML	NML	Mild
Normal Muscles	R. Semitendinosus, R. Gluteus medius, R. mid and low paraspinals, R. first dorsal interosseous, R. Biceps brachii, R. Deltoid						
Additional Workup (obtained as part of initial hospitalization)							
Blood Tests	**Abnormal:** ANA 1:160, VEGF 99.6 pg/mL, Kappa/Lambda FLC 1.81						
	Negative/Normal: ACE, SSA/SSB, B12, Cryoglobulins, Anti-DS-DNA, Copper, Hepatitis A/B/C serology, HIV 1 and 2 Ag Ab, SIFE, RF, Anti-Smith, Anti-RNP, MPO/PR3, Syphilis, T Spot, LDH, CEA, AFP						
Cerebrospinal Fluid	Protein: 39, Glucose: 63, WBC: 2, Cytology: negative						
Other	Abdominal Fat Pad Biopsy: negative for amyloid deposition						

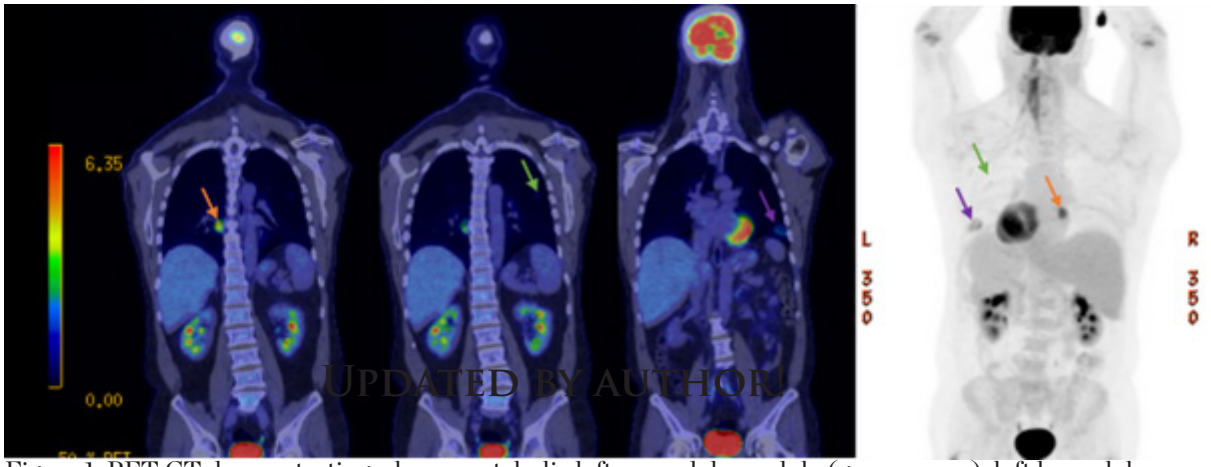

Figure 1. PET CT demonstrating a hypermetabolic left upper lobe nodule (green arrow), left lower lobe mass (purple arrow) and right lower lobe pleural-based mass (orange arrow).

for Mycobacterium leprae. No vasculitis was observed. The inflammatory infiltrates in both the nerve and muscle consisted predominantly of mature T cells, rare mature B cells, and macrophages (Figure 3). A Ki-67 antibody demonstrated rare mitotically active mononuclear cells in the endomysial and perivascular infiltrates. No Epstein-Barr virus encoding region (EBER) positive cells were seen in the nerve or muscle. Though these findings showed no neoplasm in the nerve or muscle, his lung biopsy showed an atypical angiocentric lymphoid infiltrate with large atypical B cells, some of which were EBV positive, diagnostic of lymphomatoid granulomatosis, grade 2.

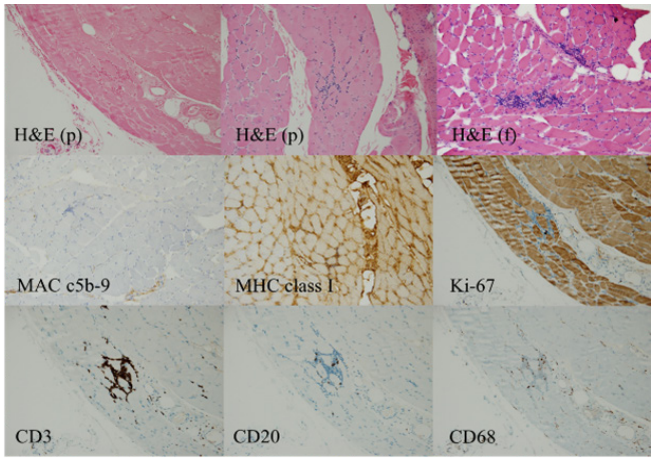

Figure 2. Right peroneus brevis muscle biopsy. H&E: focal perivascular and endomysial inflammation. MAC C5b-9: no endomysial capillary staining. MHC Class I: increased sarcolemmal and weak sarcoplasmic expression. Ki-67: rare endomysial/perivascular positive nuclei. CD3: numerous endomysial/perivascular aggregates of small lymphocytes. CD20: rare endomysial/perivascular small lymphocytes. CD68: few endomysial/perivascular macrophages. EBER-ISH staining: negative (not shown). P – paraffin section. F – frozen section.

Given the lung biopsy results, he was referred to the NIH after consultation with Hematology/Oncology for discussion of treatment options and enrollment in a clinical trial. Unfortunately, he developed side effects to the experimental therapy which prompted cessation, however, he achieved remission of his lymphomatoid granulomatosis at the time his therapeutic drug trial was discontinued and remains under watch for a recurrence. At last follow up, approximately 16 months after onset of symptoms, he had regained right lower extremity function, no longer with a complete foot drop, only needing a soft brace for support rather than a carbon fiber ankle foot orthotic. He is able to drive. He still had some bilateral foot numbness, though improved, and only had some mild intermittent pains in his feet, mostly in the evenings. He was back to driving, including his motorcycle, and was regularly walking or riding a bike for exercise.

Discussion

Lymphomatoid granulomatosis (LYG) was initially described in 1972 and mistaken for a T-cell disorder because of the predominance of T-cells on pathologic examination.[5] Subsequent evaluations determined that LYG is a rare Epstein-Barr (EBV) associated B-cell lymphoproliferative disorder whose histology and clinical features distinguish it from other EBV associated B-cell lymphoproliferative disorders, post-transplant lymphoproliferative disorders, and lymphomas.[6-9]

The disorder typically affects adults in the fourth to sixth decades with a male predominance of approximately 2:1.[8-10] While there is near universal lung involvement at diagnosis, greater than 90%, only one- to two-thirds of patients present with pulmonary symptoms, such as cough or shortness of breath. Non-specific systemic symptoms such as fever, weight loss, and fatigue often lead to initial

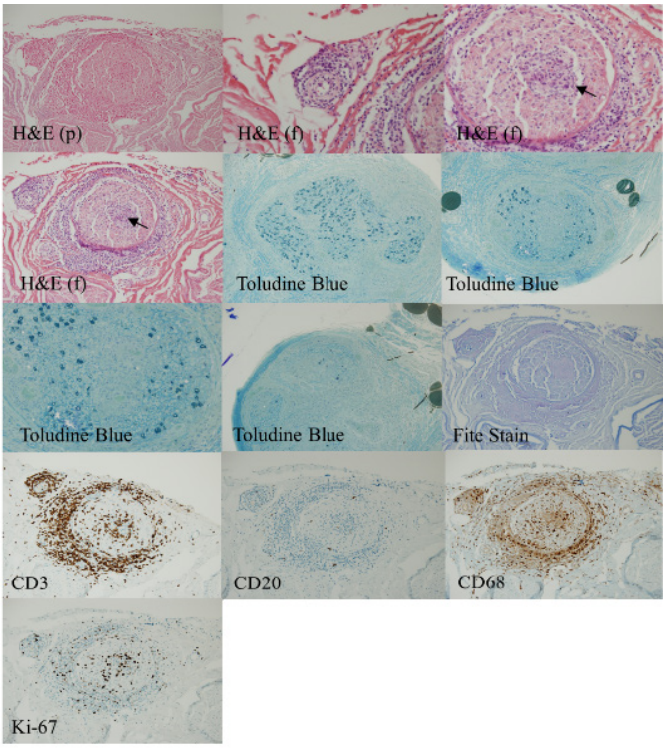

Figure 3. Right sural nerve biopsy. H&E stain: epineurial, perineurial, and endoneurial blood vessels with perivascular lymphocytic infiltrates and a poorly formed granuloma (arrow). Toludine blue: variable loss of myelinated axons within fascicles. Fite Stain: negative for organisms. CD3: many endoneurial/perineurial/epineurial/perivascular lymphocytes. CD20: rare endoneurial/perineurial/epineurial lymphocytes. CD68: many perineurial/epineural/perivascular macrophages; no well-formed granulomas. Ki-67: few positive nuclei.

medical evaluation.[9,11,12] Extrapulmonary manifestations are common and include cutaneous findings such as erythematous papules and/or subcutaneous nodules (25-50%). Central nervous system involvement (26-40%) can include various symptoms depending on the site affected with imaging demonstrating intraparenchymal lesions with or without linear enhancement or enhancement of the cranial nerves/leptomeninges. Other potential disease sites include renal (19-40%), hepatic (17-29%), and rarely the peripheral nervous system/cranial nerves (0-15%).[9,10,13-15]

Disease pathogenesis is secondary to defective immune surveillance of EBV-infected B cells with a functional defect in $CD8^+$ cytotoxic T cells thought to be the inciting event.[9] The pathology of LYG demonstrates angiocentric, destructive infiltrates of neoplastic and reactive lymphocytes with variable degrees of parenchymal necrosis. The predominant infiltrate consists of CD3 positive T cells with CD4 positive cells representing the majority subtype and a variable population of large, atypical B cells.[7,9,10] Due to the angiocentric nature of the pathology and the multi-system involvement, LYG can be difficult to distinguish from other forms of primary or secondary vasculitis, notably granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis, and sarcoidosis.[3,4] Key distinguishing features of LYG include areas of necrosis sparing the blood vessel wall as well as the presence of large, atypical B-cells which are EBV positive. Despite the presence of macrophage and histocytes, well-formed granulomas are absent.[3,16] Histologic grading of lymphomatoid granulomatosis is based on the number of EBV+ atypical B cells present and the degree of coagulative necrosis. Lower grades are characterized by rare EBER+ atypical B cells and focal or absent coagulative necrosis while higher grades have an increased number and size of EBER+ atypical B cells and often-extensive coagulative necrosis. An increased frequency of monoclonality by molecular analysis of EBV-infected B cells is also seen with higher grades.[9,10]

While the case presented above lacked EBV positive B cells in both the muscle and nerve biopsy, it remains unclear whether his MNM reflects direct LYG involvement of the peripheral nervous system or an epiphenomenon/paraneoplastic process. While no published studies confirm neoplastic infiltrates in peripheral nerves in LYG, direct involvement remains a possibility, similar to the skin. Cutaneous lesions of LYG, though common, show neoplastic cells only in a subset of cases.[10,17] Prior case series reviewing skin biopsies from patients with cutaneous manifestations of LYG demonstrated that while all biopsies consisted of a subcutaneous infiltrate composed of small T-cells and histiocytes with variable degrees of necrosis, only 19 – 37.5% had large, atypical B cells that were EBER positive, compared to greater than 75% in comparable lung biopsies. This discrepancy has been attributed to either sampling error or the possibility that some cutaneous manifestations may be an epiphenomenon related to the upregulation of cytokines and chemokines in relation to the immune response to EBV. Prior studies have linked the vasculitis of LYG to this phenomenon.[10,17,18] Outside of the skin having a similar inflammatory infiltrate but lacking EBER positive atypical B-cells, there is a single case report of a muscle biopsy with similar findings in a patient who presented with a nodular rash and cutaneous ulcerations, significant proximal weakness, and weight loss who was ultimately diagnosed with LYG with presumed paraneoplastic polymyositis.[19]

Given the lack of definitive findings described in peripheral nerves, pathologic evaluation of sites outside of the peripheral nervous system remain the definitive diagnostic standard for LYG, even if the primary symptoms are in the peripheral nerves. There are only two additional

case reports describing mononeuropathy multiplex in patients ultimately diagnosed with LYG, with both being diagnosed post-mortem.[4,13] One of the cases was treated presumptively for vasculitis prior to death based on perivascular and intramural lymphocytic inflammation of small vessels on the muscle and nerve biopsy.[4] Given its multiorgan involvement and histological features of angiocentric inflammation, LYG is a potential mimic for vasculitis.[1-4]

As the underlying pathology is that of dysregulated immune surveillance and immunosuppression, accurate diagnosis is important as treatment varies from other systemic vasculitities. As LYG is related to dysregulated immune surveillance of EBV infected B cells, immunotherapy such as corticosteroids or single-agent chemotherapy, which have been trialed in the past, fail to provide disease control and lead to a high rate of progression to higher grade disease or lymphoma.[3,9] Treatment of low-grade LYG consists of withdrawal of any immunosuppressants, interferon alpha or intravenous gamma globulin to enhance the immune response, and possibly immune checkpoint inhibitors. While observation and immunosuppression withdrawal has been trialed for those with iatrogenic immune suppression, most eventually require disease-directed therapy.[9] High grade disease is less likely to respond to augmentation of the immune system and often requires therapies akin to those used for other aggressive EBV-associated malignancies such as diffuse large B-cell lymphoma. Immunochemotherapy such as dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) as well as high dose chemotherapy and stem cell transplantation have been used for high grade disease.[9] Even with immune modulation or immunochemotherapy, relapse with low-grade disease or progression to high grade disease remains common due to the defective immune surveillance of EBV-infected cells in LYG cases. In these cases, crossover treatment to a treatment available but not previously received for LYG has been shown to be effective.[9] Prognosis is variable with a more favorable prognosis for lower grade disease. With the advent of pathobiological based therapies over the past 20 years, survival has improved from the historical median overall survival of 2 years to half of treated patients now living at least 10 years.[9]

In conclusion, LYG is an extremely rare angiodestructive lymphoproliferative disease secondary to EBV associated B-cell lymphoproliferation. Given its propensity for multi-organ involvement and the angiocentric nature of its pathology, it is a potential mimic of both primary and secondary vasculitides. Evaluation for subclinical sites of involvement, particularly pulmonary, may be required to secure a definitive diagnosis given that cutaneous, muscle, and peripheral nerve pathology may not allow for a definitive diagnosis of LYG and prove misleading. A pathological clue to the LYG diagnosis in our case is the absence of vessel wall fibrinoid necrosis. Appropriate diagnosis is highlighted by the fact that treatment for LYG does not include immunosuppression as typically prescribed for other causes of MNM.

This case has been presented previously at the virtual 43rd Carrell-Krusen Neuromuscular Symposium held from February 18-19, 2021 and at the Peripheral Nerve Society (PNS) Virtually Anywhere Conference from June 13, 2021.

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