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Sarcoid polyneuropathy masquerading as chronic inflammatory demyelinating polyneuropathy

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ABSTRACT

Introduction: Sarcoid polyneuropathy is a rare and clinically heterogeneous disorder that may be the initial presentation of sarcoidosis. *Methods*: We report the clinical, electrophysiological, and pathological findings of a patient who carried a diagnosis of sensory-predominant chronic inflammatory demyelinating polyneuropathy (CIDP) for over a decade but was ultimately found to have sarcoidosis. *Results*: A 36-year-old man presented with a several week history of gait difficulty and muscle cramps. He had a diagnosis of CIDP but had not received lasting benefit from steroid-sparing immunosuppressive drugs. Electrodiagnostic studies were consistent with a chronic demyelinating polyradiculoneuropathy with conduction blocks. After he developed systemic symptoms, tissue biopsies revealed granulomatous disease. His symptoms improved with steroid therapy. *Conclusions*: Sarcoid polyneuropathy presents a diagnostic challenge, but in patients with atypical neuropathy, , characteristic systemic symptoms, or a poor response to standard treatment, nerve and muscle biopsies can help diagnose this treatable disorder.

Key Words: sarcoidosis, polyneuropathy, CIDP, nerve biopsy, muscle cramps

INTRODUCTION

Sarcoidosis is a rare multisystem granulomatous disorder that typically affects lungs, lymph nodes, skin, and eyes. It affects women more commonly than men, with a prevalence of approximately 10/100,000 in Caucasian populations and approximately 35/100,000 in African Americans.[1] Clinical involvement of the central or peripheral nervous system occurs in 5-15% of cases, although there is likely a significant proportion of subclinical neurosarcoidosis.[2] Isolated neurosarcoidosis without systemic signs may occur in 20% of patients with neurological involvement. The most common neurological manifestations of sarcoidosis include optic neuritis, cranial neuropathies, and myelopathies. Peripheral polyneuropathy is rare, although there are reports of acute Guillain-Barré Syndrome (GBS)-like presentations, focal or multifocal axonal polyneuropathies, and demyelinating polyneuropathies.[2,3] Peripheral nervous system involvement is usually accompanied by systemic signs of sarcoidosis,[4] but sometimes it is the presenting symptom.[5] We report the clinical course and histological findings of a patient with sarcoid polyneuropathy masquerading as chronic inflammatory demyelinating polyneuropathy (CIDP).

CASE REPORT

A 36 year-old African-American man with a diagnosis of CIDP for the past decade presented with several weeks of muscle pain and cramps, weakness in his lower extremities leading to falls, and dysesthesias. The patient had tapered off prednisone 2 months earlier without resuming other immunomodulatory therapy. A review of prior records revealed that the diagnosis of CIDP was based on serological testing, lumbar

punctures, and several electrodiagnostic studies. His initial presentation 10 years earlier was notable for distal weakness, numbness, and areflexia. Serologic studies were unrevealing, and cerebrospinal fluid (CSF) demonstrated elevated protein (166 mg/dl) without pleocytosis. Previously performed electrodiagnostic studies showed partial conduction block in multiple motor nerves, temporal dispersion, reduced sensory nerve action potential amplitudes, and prolonged F-wave latencies. Magnetic resonance imaging (MRI) of the brain and spinal cord were unremarkable. He had been treated with intravenous immunoglobulin (IVIg) followed several weeks later by plasmapheresis without improvement in weakness and numbness. Subsequently, he began taking oral steroids, which resulted in symptom improvement. The diagnostic work-up was revisited at 3 and 8 years following initial presentation after multiple steroid-sparing immunosuppressive agents including azathioprine, rituximab, and mycophenolate mofetil (MMF) failed to control persistent weakness, paresthesias, and muscle cramps. Diagnostic testing performed following his initial visit revealed similar CSF and electrodiagnostic findings to those seen previously. The patient thought that IVIG was beneficial for 3 to 4 weeks before dysesthesias and muscle pains returned. He reported feeling his best when taking high dose daily corticosteroids.

Upon examination, there was limited abduction of the right eye, but other eye movements and facial strength were normal. There was decreased bulk of intrinsic muscles of the hands and feet. There was no muscle tenderness. Muscle tone and power were normal except for slight distal lower extremity slight weakness, graded 4/5 on the Medical Research Council scale. Reflexes were absent in arms and legs. Muscle pain and cramps were triggered by movements of the upper and lower extremities. Choreoathetoid

movements of the fingers were noted with arms outstretched. Gait was mildly wide-based, and he used a cane to ambulate. He had difficulty walking on his heels and could not perform tandem gait. The Romberg sign was present. Pinprick sensation was absent in the distal limbs; vibration sense and position sense were absent at the toes and decreased at the ankles.

Serum creatine kinase was 393 (reference value 30-235 IU/L). Erythrocyte sedimentation rate, serum cortisol, thyroid stimulating hormone, vitamin B12, anti-nuclear antibody, C-reactive protein, rheumatoid factor, angiotensin converting enzyme, hepatitis serologies, and HIV antibodies all were normal or negative.

Nerve conduction testing (Table 1 and Figure 1) revealed reduced amplitude of left fibular, tibial, and median compound muscle action potentials (CMAPs). The left fibular, tibial, ulnar, and bilateral median distal motor latencies were prolonged. There were prolonged left median and ulnar minimum F-wave latencies and slowing of nerve conduction velocities with conduction block in left tibial (popliteal fossa-ankle), fibular (ankle-fibular head), ulnar (wrist-below elbow), and bilateral median (wrist-elbow) nerve segments. The left median nerve sensory nerve action potential (SNAP) was low amplitude, and left sural, superficial fibular, and ulnar SNAPs were absent. Needle electromyography showed low density fibrillation potentials in the left tibialis anterior, medial gastrocnemius, and vastus lateralis muscles and reduced recruitment of long-duration motor unit action potentials in those muscles. In summary, electrodiagnostic studies were consistent with a chronic acquired demyelinating sensorimotor polyneuropathy with secondary axonal loss.

SUBSEQUENT COURSE

The patient was treated with IVIg, 2 g/kg every 4 weeks, which resulted in moderate improvement of gait and dysesthesias. The motor exam remained stable, but muscle cramps continued to be bothersome. Six months after initial consultation, he presented to an urgent care clinic with hematemesis and was found to have hilar and mediastinal lymphadenopathy on chest X-ray. Follow-up PET/CT scan raised a question of sarcoidosis. On further evaluation several hyperpigmented nodular skin lesions were noted in his lower back and shoulder. Punch biopsy of skin lesions and endoscopic biopsy of esophageal lymph nodes confirmed the diagnosis of sarcoidosis. MRI of the brain and entire spine was normal. Attempted sural nerve biopsy did not contain any identifiable peripheral nerve tissue, but it showed non-necrotizing granulomatous inflammation (Figure 2) that was infiltrating adjacent skeletal muscle. Special stains for acid fast bacilli and fungal microorganisms were negative.

The diagnosis was changed to sarcoidosis with peripheral nerve and muscle involvement. Due to poor long-term control of neurologic symptoms and multi-organ manifestations of systemic sarcoidosis, he was given 1 g intravenous methylprednisolone daily for 5 days followed by 60 mg prednisone daily, which resulted in decreased muscle cramps and paresthesia and improved gait. On maintenance treatment with 10 mg prednisone every other day and 1 g MMF twice daily, cramps continue to be bothersome, but neurological examination has not changed without worsening in strength, gait, or functional status for 2 years.

DISCUSSION

This patient had symptoms and electrodiagnostic findings consistent with sensory-predominant CIDP, which preceded systemic non-neurological symptoms of sarcoidosis by more than 10 years. Although sensory-predominant CIDP is well-known, the myalgias and muscle cramps and poor response to steroid-sparing immune modulators, were not typical of CIDP. In addition, given the efficacy of IVIg in improving symptoms of CIDP,[6,7] the failure of IVIg and corticosteroid-responsiveness of this patient's prominent sensory symptoms should have triggered consideration of an alternative diagnosis. However, it was not until chest X-rays showed findings suspicious for sarcoidosis that further workup, including biopsies of skin, lymph node, and muscle led to the correct diagnosis of sarcoid polyneuropathy. The patient responded well previously to corticosteroids, and treatment was again changed to corticosteroids, with good results.

Peripheral neuropathy is a rare manifestation of sarcoidosis, affecting only 2% of patients.[8] Patterns of peripheral nerve involvement due to sarcoidosis are varied and include distal symmetric polyneuropathy, focal or multifocal neuropathy, and mononeuritis multiplex.[9,2] Sarcoidosis has also been reported to present with an acute GBS-like inflammatory polyneuropathy, and as in this case, associated with electrodiagnostic evidence of demyelinating neuropathy and conduction block.[10-12,3] In a retrospective cohort of 57 patients with biopsy-proven sarcoid neuropathy, positive neuropathic sensory symptoms, including pain, were more prominent than weakness and sensory loss.[4] In this cohort, asymmetric, non-length dependent axonal polyneuropathy predominated, although an acquired demyelinating process with conduction block was

observed in 3 patients. Patients typically had associated systemic symptoms and a chronic progressive disease course, but good functional outcomes with steroid treatment.

A neuropathological analysis of 11 cases of sarcoidosis with nerve granulomas observed on sural nerve biopsy also revealed a wide range of peripheral nerve abnormalities.[5] Five patients had predominantly sensory findings on clinical examination, and 8 patients had axonal sensory-motor multifocal neuropathy on electrophysiological studies; nerve biopsy studies showed endoneurial infiltrates and epineurial granulomata in all specimens. It is unclear how granulomatous disease causes neuropathic symptoms and demyelination, although it may be significant that granulomata may remain asymptomatic if they are confined to the epineurium.[13] In addition, necrotizing vasculitis was observed in association with granulomata in 6 patients. Thus, symptoms of neuropathy may be secondary to vasculitis-related nerve ischemia and granuloma-associated inflammation, which may lead to axonal degeneration or demyelination following infiltration of the endoneurium. Others have posited that patchy demyelination may be the result of neural compression by granulomata.[3] Larger clinical and neuropathological studies correlating patient symptoms with granuloma location and inflammation are necessary to better understand the varied clinical scope and pathophysiology of sarcoid polyneuropathy. Muscle biopsy showed granulomata in 9 of 10 patients, 8 of whom also had lymph node or lung involvement. Muscle granulomata have been reported previously to be common in sarcoidosis and are often asymptomatic[14], but they can provide a clue to the diagnosis if a muscle biopsy is performed. Interestingly, concurrent central nervous system involvement is relatively

uncommon; fewer than 25% of cases of peripheral neuropathy due to sarcoidosis have associated brain, meningeal, or spinal cord pathology.[4]

Evidence-based guidance for treatment of neurosarcoidosis is limited by its rarity. Glucocorticoids are considered the first-line treatment, although in refractory cases a second immune modulator is often added. Methotrexate is usually second line treatment in pulmonary sarcoidosis, and a few studies suggest it may be useful in neurosarcoidosis. There are also reports of benefit from IVIg.[9] Treatment with infliximab, which inhibits tumor necrosis factor-alpha, has demonstrated benefit in a randomized controlled trial when it was given to 138 patients with extrapulmonary sarcoidosis (8% of whom had peripheral nerve involvement).[15] Fewer than 10 % of patients do not respond to any immune modulatory therapy.

In summary, we describe a patient sarcoid polyneuropathy mimicking sensory-predominant CIDP for over a decade until he developed systemic symptoms that led to the correct diagnosis. Sarcoid polyneuropathy is not only rare, but it also presents with a variety of clinical syndromes which often delay the diagnosis of this challenging disorder. Thus, in patients with atypical symptomatology or poor response to therapy, particularly in the setting of systemic symptoms, we recommend a clinical and laboratory search for sarcoidosis. In cases of suspected peripheral nerve sarcoidosis, biopsy of both nerve and muscle tissue may increase the diagnostic yield and help rule out other rare inflammatory, infectious, or neoplastic causes of neuropathies.

ABBREVIATIONS

CIDP- chronic inflammatory demyelinating polyneuropathy

CMAP- compound muscle action potentials

CSF- cerebrospinal fluid

CT- computed tomography

GBS- Guillain-Barre syndrome

IVIg- intravenous immunoglobulin

MMF- mycophenolate mofetil

MUAP- motor unit action potentials

PET- positron emission tomography

SNAP- sensory nerve action potentials

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Table 1. Motor nerve conduction studies

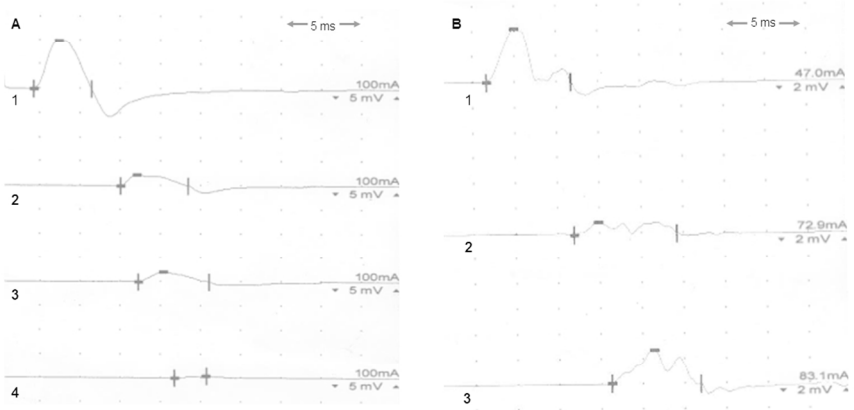
Nerve and site	Onset latency (ms)	Amplitude (mV)	F-latency (ms)	Conduction velocity (m/s)
Ulnar L				
Wrist	4.2 (3.9)	9.9 (4.5)	54.3 (26.3)	
Below Elbow	15.0	2.3		19 (44)
Above Elbow	17.2	2.1		45 (40)
Axilla	21.7	0.4		22 (50)
Median L				
Wrist	5.3 (4.5)	7.3 (4.8)	57.3 (25.4)	
Elbow	15.0	4.0		24 (44)
Axilla	10.6	4.0		28 (50)
Median R				
Wrist	6.6 (4.5)	4.3 (4.8)	NR (25.4)	
Elbow	16.9	1.1		24 (44)
Axilla	21.2	2.7		23 (50)
Fibular L				
Ankle	6.5 (6.5)	0.4 (1.5)	NR (43.5)	NR (36)
Fibular head	NR	NR		
Tibial L				
Ankle	6.9 (7.0)	1.1 (2.0)	NR (44.0)	
Popliteal fossa	31.8	0.1		17 (36)

NR indicates non-recordable. Normal values in parentheses. Normal F-latency values based on patient height of 69 inches.

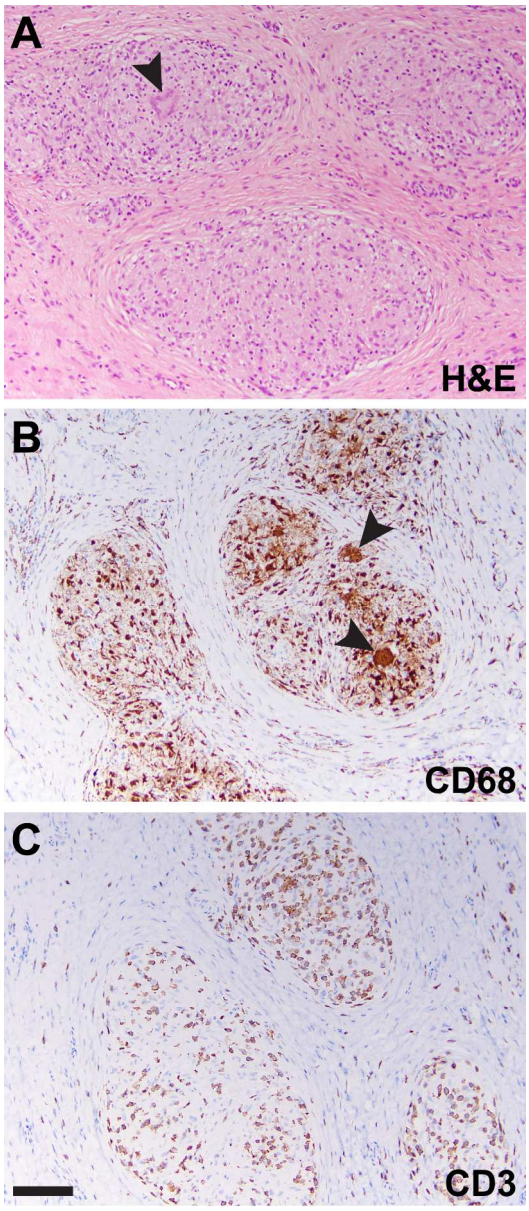
Figure Legends

Figure 1. Nerve conduction studies. A: Ulnar motor nerve study recorded from abductor digiti minimi with stimulation at the wrist (1), below the elbow (2), above the elbow (3), and at the axilla (4). (B) Median motor nerve study recorded from abductor pollicis brevis with stimulation at the wrist (1), elbow (2), and axilla (3). Of note, the greater amplitude at the axilla may be due to technical factors or submaximal stimulation at the elbow.

Figure 2. Nerve biopsy findings. Sural nerve biopsy showed no peripheral nerve tissue but revealed multiple non-caseating, well-formed granulomata **(A)** that were highlighted by immunoperoxidase stains for macrophage marker CD68 **(B)** and T-lymphocyte marker CD3 **(C)**. Multinucleated giant cells were also present (arrowheads, **A** and **B**). Scale bar, 100 μm.



Nerve conduction studies. A: Ulnar nerve recorded from abductor digiti minimi with stimulation at the wrist (1), below the elbow (2), above the elbow (3), and at the axilla (4). (B) Median nerve recorded from abductor pollicis brevis with stimulation at the wrist (1), elbow (2), and axilla (3).
115x86mm (300 x 300 DPI)



Nerve biopsy findings. Sural nerve biopsy showed no peripheral nerve tissue but revealed multiple non-caseating, well-formed granulomas (A) that were highlighted by immunoperoxidase stains for macrophage marker CD68 (B) and T-lymphocyte marker CD3 (C). Multinucleated giant cells were also present (arrowheads, A and B). Scale bar, 100 μm.
175x403mm (300 x 300 DPI)