Small fibre neuropathy in sarcoidosis

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Key points:
1) Consider sarcoidosis in patients presenting with acute onset neuropathic pain.
2) Specialized imaging, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canadaautonomic testing with biopsy is required to confirm sarcoidosis.
3) Corticosteroids and immunomodulators may improve patient outcomes.

Abstract
Sarcoidosis is characterized by multisystem granulomatous formation particularly in the chest. In this case report, we present an uncommon case highlighting significant peripheral nerve involvement, a phenomenon that is not well recognized in sarcoidosis. The patient presented with severe incapacitating pain. Sarcoidosis as being the underlying cause was only established after extensive investigations. This case highlights the importance of recognizing small fibre peripheral polyneuropathy as a possible presentation of sarcoidosis. This could help to direct appropriate medical intervention.

Key words:
Sarcoidosis, neuropathy, peripheral nerves

| Acronym | Definition                             |
|---------|----------------------------------------|
| ACE     | Angiotensin-Converting Enzyme          |
| CHEPs   | Contact Heat-Evolved Potential Stimulators |
| CPT     | Current Perception Threshold Testing   |
| CSF     | Cerebrospinal Fluid                    |
| CT      | Computerized Tomography                |
| IENFD   | Intraepidermal Nerve Fibre Density     |
| IVIG    | Intravenous Immunoglobulin             |
| MRI     | Magnetic Resonance Imaging             |
| PET     | Positron Emission Tomography           |
| QST     | Quantitative Sensory Testing           |
| QSART   | Quantitative Sudomotor Axon Reflex Test |
| SNAP    | Sensory Nerve Action Potential         |
| SSR     | Sympathetic Skin Response              |

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1. Introduction

Granulomas lesions in sarcoidosis can affect many organs including lungs, eyes, kidneys, heart and the nervous system (O’Regan and Berman 2012). However, it most commonly presents with lung and skin involvement. In contrast, peripheral nerve involvement in sarcoidosis is much less common (Galassi et al. 1984). This report describes an unusual case with severe subacute incapacitating neuropathic pain. The underlying etiology was only revealed after extensive investigations. This case highlights the importance of being vigilant about the possibility of polyneuropathy with predominantly small fibre involvement due to sarcoidosis as it could have important management implications.

2. Case report

2.1 Initial patient presentation

A 57-year-old, obese, construction worker of Western European origin presented with a two-week history of symmetric pain in his limbs, worse in the legs. He described it as a burning sensation affecting the foot to the mid-thigh and from the hand to the elbow. Over the ensuing two months, the pain progressed to the extent that it severely hampered his daily activities and disrupted his sleep. The patient denied having any constitutional symptoms such as fever, chills, or night sweats. Strength was not affected despite discomfort when trying to move. He denied changes in vision, swallowing, speech or bowel and bladder control. Systemic enquiry was negative for cardiac or respiratory symptoms. A 60-pound weight loss over the prior months was identified. The patient attributed this to a calorie restricted low carbohydrate diet that he had been on for 6 months. At the time of presentation, he remained over 200 pounds. Except for gout, nephrolithiasis, and remote facial melanoma, his past medical history was unremarkable. The melanoma was diagnosed over 10 years ago and was treated with wide margin excision with no sign of recurrence. He was a non-smoker and denied use of alcohol or illicit substances. The patient had no known medication allergies, history of recent foreign travel and had no autoimmune or granulomatous infections. There are no malignancies or autoimmune diseases in his family history.

2.2 Additional examinations and workup

On neurological examination, the patient was allodynic to light touch, especially in distal limbs. Pinprick, temperature and vibration sensations were decreased in a glove-stocking distribution. Strength testing was unremarkable with normal stretch reflexes and no pathologic reflexes. Cranial nerve examination was normal. Romberg sign was mildly positive due to proprioceptive loss, but finger-nose test and heel-shin test were normal. Quantitative sudomotor axon reflex test (QSART), quantitative sensory testing (QST), and cold perception threshold testing (CPT) were unremarkable. However, the heart rate variability test revealed diminished response to deep breathing, Valsalva maneuver indicative of autonomic dysfunction.

With the poorly controlled unrelenting pain, he was admitted to hospital for symptom management and further investigations. He was put on high doses of analgesics including hydromorphone, pregabalin, and duloxetine. Aside from mildly elevated liver enzymes and iron deficiency, hematologic investigations were largely unremarkable. Further investigations including complete blood count, hemoglobin a1c, glucose tolerance, nutritional deficiency (i.e., serum albumin, vitamins B1, B6, B12 and E), virus panel (HIV, Hepatitis B and C, Parvovirus B19 and EBV), immune profile (i.e., ANA, ENA, ANCA, dsDNA, CRP, RF, C3/C4, anti-transglutaminase), and a workup for paraproteinemia (i.e., SPEP, free kappa/lambda fractions) were all negative. Skin, ophthalmic, and back examinations were unremarkable. No tuberculosis or other infections were found. Chest x-rays only demonstrated mild pleural thickening. Computerized tomography (CT) imaging of the abdomen and magnetic resonance imaging (MRI) of the brain and spine were unremarkable. However, cerebrospinal fluid (CSF) analysis revealed albuminocytologic dissociation with elevated protein. Because of the suspicion of an inflammatory polyneuropathy, he was given a 5-day course
of intravenous immunoglobulin (IVIG) but with no benefit.

**2.3 Electrodiagnostic studies and PET/CT scan confirm sarcoidosis**

The patient was then referred for electrodiagnostic studies. Nerve conduction studies confirmed a mild bilateral length dependent sensory axonopathy in the upper and lower extremities (Table 1). While his symptoms were suggestive of small sensory nerve fibre involvement, these findings suggested that large diameter myelinated sensory nerve fibres were also mildly affected. Based on these findings and the clinical presentation, further workup was done for paraneoplastic syndrome (i.e., anti-Hu/Yo and Ri) but the results were negative. Taking the subtle chest x-rays changes into account, a workup for sarcoidosis was started. These included anti-amphiphysin, anti-Ma2 and anti-CV2 and angiotensin-converting enzyme (ACE) levels that turned out to be normal. However, CT of the chest revealed mediastinal lymph node enlargement. He reported no foreign travel and had no autoimmune or granulomatous infections.

There were no malignancies or autoimmune diseases in his family history. A whole-body positron emission tomography (PET)/CT scan was therefore ordered. It confirmed perihilar and mediastinal lymphadenopathy with increased radioisotope uptake (Figure 1a). Lymph node biopsy provided histological evidence of non-necrotizing granulomas consistent with sarcoidosis (Figure 1b). The presence of small nerve fibre neuropathy was further supported by abnormalities on autonomic testing and reduced intraepidermal nerve fibre density on punch skin biopsy. Sural nerve biopsy confirmed marked axonal loss (Figure 1c and d) with no granuloma. Based on these findings, the patient was started on high dose prednisone and methotrexate. His pain showed substantial improvement after a week of treatment, he was then discharged home. Following gradual tapering of prednisone, the patient remained stable with no recurring symptoms. Therefore, no further follow up x-rays or electro-conductive studies were done within the follow up window.

### 3. Discussion

Sarcoidosis is a granulomatous disorder that affects multiple organ systems. With most common onset in the third to fourth decade of life, it has an incidence of 35.5/100,000 in African Americans, which is much higher than in Caucasians (10.9/100,000). By far the most frequently affected organs are lungs (>90%),

**Table 1. Specialized Neuropathy Investigations**

| Electrodiagnostic nerve conduction study | Normal motor, F-wave. Non-recordable peroneal, ulnar & median SNAP. Reduced sural and radial SNAP amplitude |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------|
| Autonomic                               | Diminished cold perception threshold, and significantly diminished heart rate variability to Valsalva maneuver |
| IENFD                                   | Distal leg showed marked decreased fiber density 0.6 fibers/mm\(^{-1}\); mildly decreased at the thigh |
| Nerve biopsy (sural)                    | Acute axonal damage with secondary demyelination (subtotal myelin loss) and collagen pockets (unmyelinated axonal damage) |
heart (25-50%), eyes (25%), and skin (30%) (Iannuzzi and Fontana 2011; Lower and Weiss 2008). Although neurosarcoidosis occurs in around 5% of patients, it frequently involves the central nervous system including cranial neuropathy, pituitary/hypothalamic dysfunction, psychiatric symptoms, hydrocephalus and meningitis. In contrast, involvement of the peripheral nervous system is much rarer. The patient in this case study presented with no symptoms of granulomas in the most frequently affected organs, and only after biopsy of lymph nodes granulomas were found. Typical central nervous system involvement is expected, however, the lack of thoracic lesions indicated the presence of peripheral small fibre neuropathy instead. This demonstrates the significance of the study.

A review of 57 patients with sarcoidosis-associated peripheral neuropathy reported polyradiculoneuropathy (39%), polyneuropathy (33%) and mononeuropathy (10%) (Burns et al. 2006). Even less known is the involvement of small and poor myelinated or unmyelinated nerve fibres, making the accurate diagnosis of neurosarcoidosis challenging.

Electrodiagnostic studies are often non-informative as they only assess large myelinated nerve fibres (Hoitsma et al. 2002). Furthermore, there is currently no "gold standard" diagnostic test for small fibre neuropathy. Therefore, multiple tests to evaluate the somatic and autonomic fibre systems are necessary. These include quantitative sensory testing (QST), cold perception threshold testing (CPT), and sympathetic skin response (SSR). In addition, skin biopsy may be helpful (Hoitsma et al. 2004). Immunofluorescence staining with PGP-9.5 of the skin allows intraepidermal nerve fibre density (IENFD) to be determined. Although it has high specificity (977%), the sensitivity is low (69%) (Hoitsma et al. 2004).

3.1 Other causes of small fibre neuropathy

The differential diagnosis of small fibre neuropathy is wide (Themistocleous et al. 2014). In contrast to sarcoidosis, there are other far more common causes. These include diabetes, alcohol toxicity, nutritional deficiency, malignancy, infection and drug toxicity (Hoitsma et al. 2004) (Table 2). A feature that they have in common is upregulation of pro-inflammatory cytokines (TNF-α, IL-1) that act as mediators of neuropathic pain.

3.2 Management

The most troublesome of small fibre neuropathy are positive symptoms including allodynia, burning, lancinating and thermal hyperalgesia. Patients may additionally complain of myalgia, particularly cramping of the calf muscles, and/or restless leg syndrome.

Symptom management of small fibre neuropathy is challenging, with only 30-50% of patients benefiting from traditional therapies (Finnerup et al. 2015). Even in those individuals, the pain scores usually only improve by 30-50%. Frequently used medications include anticonvulsants, antidepressants, opioids and topical capsaicin/lidocaine. Many of these cause significant side effects and carry potential risks.
There remains a paucity of information regarding long-term outcomes for patients with sarcoidosis-associated small fibre neuropathy. Reports suggest that typical symptoms of small fibre neuropathy worsen within the first weeks to months before plateauing. After that, patients demonstrate variable degrees of improvement. Therefore, definitive management of the underlying sarcoidosis is critical, as rapid initiation of treatment has been shown to be a prognostic feature for pain improvement (Burns et al. 2006). Sarcoidosis is best treated with steroids and steroid sparing agents (methotrexate, azathioprine, cyclosporin), with medications such as anti-cytokines, antimalarials, and monoclonal antibodies reserved for chronic resistance (Heij et al. 2012). Immune-modulating therapies such as intravenous gamma globulin (IVIG) have also shown efficacy in alleviating symptoms (Parambil et al. 2011). ARA290 is a new drug that has been shown promising effects in the treatment of neurosarcoïdosis. By mimicking erythropoietin, it acts on the innate repair receptor to trigger anti-inflammatory and anti-apoptotic processes that limit injury and promote repair. It has been shown to improve pain, neuropathic symptoms, quality of life and exercise capacity (Heij 2016).

3.3 Outcomes

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4. Conclusion

Given the heterogeneity of clinical signs and symptoms, and negative electrodiagnostic studies, small fibre neuropathy is a rare presentation of sarcoidosis that is challenging to recognize. Although we were able to establish the presence of a small fibre polyneuropathy through tests including QST, CPT, CHEPT, SSR, skin biopsies and nerve conduction studies, the underlying cause was only established following a PET/CT scan. This is a valuable test that when combined with a high index of clinical suspicion enable clinicians to make an accurate early diagnosis. Timely recognition is critical for patient management, as early medical intervention portends better outcomes.

Table 2. Differential diaagnosis of predominantly small fibre neuropathy

| Differential Diagnosis       | Predominantly Small Fiber Neuropathy |
|-----------------------------|-------------------------------------|
| Idiopathic                  | Diabetes                            |
| Metabolic                   | Uremia                              |
| Monoclonal Gammopathy       | Amyloidosis                          |
| Multiple myeloma            |                                     |
| Vitamin B12 deficiency      |                                     |
| Autoimmune                  | Celiac                              |
| Sjogren                     | Vasculitis                           |
| Guillain-Barré Syndrome     |                                     |
| Sarcoidosis                 |                                     |
| Infectious                  | HIV                                 |
| HCV                         | Leptosy                              |
| Lyme Disease                |                                     |
| Neurotoxicity               | Alcohol                             |
| B6 Toxicity                 | Chemotherapy                         |
| Paraneoplastic              |                                     |
| Hereditary                  | Fabry’s                              |
| Tanglers                    |                                     |

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