Small fibre neuropathy in sarcoidosis

Jenna-Lynn Senger[1], Ashley W.M. Chan[2], Simon Wu[3], Mary Cheuk[3], Rajive Jassal[4]

[1] Division of Plastic Surgery, Faculty of Medicine and Dentistry, University of Alberta
[2] Division of Physical Medicine and Rehabilitation, Faculty of Medicine and Dentistry, University of Alberta
[3] Faculty of Medicine and Dentistry, University of Alberta
[4] Division of Neurology, Faculty of Medicine and Dentistry, University of Alberta

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

Glossary

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

Correponding author: Simon Wu, sizhesim@ualberta.ca,
5-005C Katz Group Centre, University of Alberta,
11361-87 Avenue, Edmonton, Alberta, Canada
T6G 2E15-005C

albertaacademicreview.com

ISSN 2561-5327 (print)
ISSN 2561-5335 (online)

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

Page 2 / Volume 2 / Issue 1 / DOI: 110.29173/aar31

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%),

Table1.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)

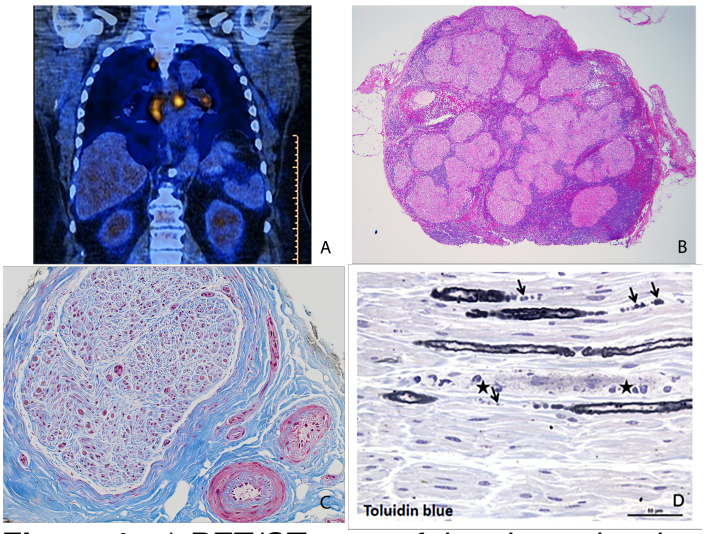

Figure 1. a) PET/CT scan of the chest showing increased radioisotope uptake in the mediastinum. b) Lymph node biopsy revealed non-caseating granulomas supportive of a diagnosis of sarcoidosis. c) Hematoxylin and eosin stain of sural nerve biopsy. At low magnification (100x), two fascicles showing axon loss. d) At higher magnification (1000x), toluidine blue-stained semithin section of sural nerve biopsy confirmed marked reduction of myelinated fibers. Arrows: 'myelin ovoids' (sign of axonal damage). Asterisks: phagocytosing macrophages.

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. Tthis 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

Page 4 / Volume 2 / Issue 1 / DOI: 110.29173/aar31

effects. 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 neurosarcoidosis. 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

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.

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 dioagnosis of predomiantly small fiber neoropathy

Idiopathic	
Metabolic	Diabetes Uremia
Monoclonal Gammopathy	Amyloidosis Multiple myeloma
Vitamin B12 deficiency	
Autoimmune	Celiac Sjogren Vasculitis Guillain-Barré Syndrome
Sarcoidosis	
Infectious	HIV HCV Leprosy Lyme Disease
Neurotoxicity	Alchohol B6 Toxicity Chemotherapy
Paraneoplastic	
Hereditary	Fabry's Tanglers

Acknowledgment

The author is thankful of the anonymous reviewers whose valuable comments help in refined and improved the manuscript. The authors declare no competing interests; this case report received no external funding.

Cite as:

Senger J-L., Chan A.W.M., Wu S., Cheuk, M., Jassal, R. 2019. Small fibre neuropathy in sarcoidosis. Alberta Academic Review, Vol 2 (1) 1-6, DOI: 110.29173/aar31

Reference

Burns TM, Dyck PJB, Aksamit AJ, Dyck PJ. 2006. The natural history and long-term outcome of 57 limb sarcoidosis neuropathy cases. Journal of the Neurological Sciences. 244(1):77-87.

Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS et al. 2015. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. The Lancet Neurology. 14(2):162-173

Galassi G, Gibertoni M, Mancini A, Nemni R, Volpi G, Merelli E, Vacca G. 1984. Sarcoidosis of the peripheral nerve: Clinical, electrophysiological and histological study of two cases. European Neurology. 23 (6):459-465.

Heij L. 2016.Ara290 : A novel treatment for neuropathic pain in sarcoidosis. Leiden University**.**

Heij L, Niesters M, Swartjes M, Hoitsma E, Drent M, Dunne A, Grutters JC, Vogels O, **Brines M**, Cerami A et al. 2012. Safety and efficacy of ara 290 in sarcoidosis patients with symptoms of small fiber neuropathy: A randomized, double-blind pilot study. Molecular Medicine. 18(11):1430-1436.

Hoitsma E, Marziniak M, Faber CG, Reulen JPH, Sommer C, De Baets M, Drent M. 2002. Small fibre neuropathy in sarcoidosis. The Lancet. 359(9323):2085-2086.

Hoitsma E, Reulen JPH, de Baets M, Drent M, Spaans F, Faber CG. 2004. Small fiber neuropathy: A common and important clinical disorder. Journal of the Neurological Sciences. 227(1):119-130.

Iannuzzi MC, Fontana JR. 2011. Sarcoidosis: Clinical presentation, immunopathogenesis, and therapeutics. JAMA. 305(4):391-399.

Lower EE, Weiss KL. 2008. Neurosarcoidosis. Clinics in Chest Medicine. 29(3):475-492.

O'Regan A, Berman JS. 2012. Sarcoidosis. Annals of Internal Medicine. 156(9):ITC5-1.

Parambil JG, Tavee JO, Zhou L, Pearson KS, Culver DA. 2011. Efficacy of intravenous immunoglobulin for small fiber neuropathy associated with sarcoidosis. Respiratory Medicine. 105(1):101-105.

Themistocleous AC, Ramirez JD, Serra J, Bennett DLH. 2014. The clinical approach to small fibre neuropathy and painful channelopathy. Practical Neurology. 14(6):368.