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Case Report
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Case Report: Sarcoidosis with Peripheral Neuropathy

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Abstract

Background: Peripheral neuropathy is a broad term that encompasses various disorders of the peripheral nervous system. This includes granulomatous neuropathy and non-granulomatous Small Fiber Neuropathy (SFN). The most prevalent clinical manifestations of granulomatous neuropathy are distal symmetric polyneuropathy and asymmetric polyradiculoneuropathy. Common causes of peripheral neuropathy include glycometabolic disturbance, infection, inflammation, and intoxication. However, cases of sarcoidosis are rare.

Case Report: A 58-year-old female driving instructor with no previous medical history presented to the hospital with initial numbness in her left foot, followed by numbness and weakness in her right foot and both feet. A month later, she experienced bilateral numbness below the wrist. The patient underwent a lumbar puncture and further testing for auto-antibodies in both the Cerebrospinal Fluid (CSF) and serum. The results showed negative findings for seventeen antibodies related to peripheral neuropathy and Anti-MAG antibody. Enhanced chest CT revealed multiple swollen lymph nodes in the neck, mediastinum, and bilateral hilar area. Ultrasonography also confirmed enlarged lymph nodes in the bilateral supraclavicular, subclavian region, and mediastinum. Electromyography (EMG) and Nerve Conduction Studies (NCS) indicated asymmetric motor and sensory polyneuropathy. Additionally, the histological examination of a supraclavicular lymph node revealed characteristic Non-Caseating Granulomas (NCG).

Conclusion: This case report highlights the potential of peripheral neuropathy as a clinical manifestation of sarcoidosis. It emphasizes the importance of considering sarcoidosis as a possible diagnosis in patients presenting with peripheral neuropathy, thereby contributing to increased knowledge and reducing the risk of misdiagnosis.

Keywords: Sarcoidosis; Peripheral neuropathy; biopsy; Clinical manifestations; Treatment; Corticosteroids

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Introduction

Sarcoidosis is a phenotypically heterogeneous, a multisystemic granulomatous disease of unknown cause that can cause organ dysfunction and diminished quality of life, which exhibits a spectrum of manifestations from asymptomatic or cause severe or life-threatening organ dysfunction resulting in multiple and diverse symptoms [1].

The prevalence reported from 1.0 to 64 per 100,000 per year, varied depending on the geographic region, the mortality is thought to be up to 5% to 10% [2,3]. The lung is affected in 83.6% to 91.7% of patients, extrapulmonary sarcoidosis is observed in about 30% to 50% of patients. The most frequent extrapulmonary localizations are skin (15.9%-16.4%), peripheral lymph nodes (11.3%-15.2%), eye (6.9%-11.8%), and liver (2.5%-11.5%) [4-6]. Biopsy reveals the presence of noncaseating granuloma on histopathologic examination to confirm the diagnosis [7]. Peripheral neuropathy includes granulomatous neuropathy and non-granulomatous Small Fiber Neuropathy (SFN). While distal symmetric polyneuropathy and asymmetric polyradiculoneuropathy are the most common clinical manifestation of granulomatous neuropathy [8]. The clinical features of sarcoidosis are highly heterogeneous, including Asymptomatic, Pulmonary Sarcoidosis, Skin sarcoidosis, Löfgren syndrome, Ocular sarcoidosis, Musculoskeletal, Cardiac sarcoidosis, Neurosarcoidosis. The prevalence of neurologic involvement is reported 3% to 10%. Any part of the nervous system can be affected, the most frequently affected sites are the cranial nerves, meninges, and brain parenchyma, however, the pituitary gland, spinal cord, and peripheral nerves is far less affected [9-11]. However, peripheral nerves are rarely seen. Here, we described a patient presenting with numbness as the first symptom and had been misdiagnosed several times. She was finally diagnosed as sarcoidosis based on the supraclavicular lymph nodebiopsy. This case report describes a rare clinical manifestation

of sarcoidosis, which will contribute to a better understanding of the clinical characteristics of sarcoidosis for better diagnosis in the future.

Case Presentation

A 58-year-old female driving instructor with no previous medical history visited the hospital on August 30th, 2022, following a 2-month history of limb numbness that significantly impacted her daily life. Initially, she experienced numbness on the left dorsum of the foot and decreased sensation in pain and temperature. After three to four days, she also developed numbness on the lateral surface and bottom of the left foot, along with weakness in distal and dorsiflexion movements. One week later, she began experiencing numbness on the right sole and dorsum of the foot. When walking, she suffered foreign body sensation on the soles of feet; she had numbness in hands after 10 days. During the course of the disease, the patient had no other discomforts, such as headache, muscle atrophy, fasciculation, myalgia, limb convulsions, etc. The patient was otherwise healthy and had no signs of a systemic disease. Neurological examination and patient's history were unremarkable. On neurologic examination, she had asymmetric weakness of the low extremity, muscle strength was evaluated as 4/5 in the left lower limbs and as 4+/5 in the right lower on the Medical Research Council (MRC) scale. Hypoesthesia to pinprick below the wrist and ankle was detected. Deep tendon reflexes could be weakening in lower limbs.

Blood routine, routine urine, stool testing, biochemical indicators, coagulation function, thyroid function, glycosylated hemoglobin, tumor markers, serum immunoglobulin, serum complement (C3, C4) and Bence Jones Protein (BJP) was normal. Anti-double-stranded DNA, anti-CCP, anti-SSA, ANCA, and other autoantibody tests were negative. The electrophysiological evaluation revealed multiple peripheral neuropathy in common peroneal nerve, tibial nerve, ulnar nerve, median nerve. A Lumbar Puncture (LP) showed an intracranial pressure of 130 mm H_2O, nucleated cell counts of 4 × 10^6 cells/L, total protein level of 345.0 mg/L, glucose level of 2.80 mmol/L, and chloride level of 127.00 mmol/L. Peripheral neuropathy seventeen antibodies and Anti-MAG antibody in both the CSF and serum negative. The electrophysiological evaluation revealed that the motor and sensory conduction velocity was generally slower than normal of common peroneal nerve with an average conduction velocity of 30.7 or 35 m/s, and tibial nerve with an average conduction velocity of 37 or 40 m/s, respectively. Bilateral common peroneal nerve and tibial nerve conduction velocity slowed down, wave amplitude decreased, bilateral ulnar nerve conduction velocity slowed down, wave amplitude decreased, there was conduction block, bilateral median nerve latency prolonged. The bone imaging showed that bone salt metabolism was increased in the knee, nonspecific inflammation (Figure 1). Enhanced chest CT showed multiple swollen lymph nodes at the root of the neck, mediastinum, and bilateral hilar area (Figure 2). Ultrasonography also showed enlarged lymph nodes in the bilateral supraclavicular, subclavian region and mediastinum. The supraclavicular lymph nodebiopsy founded presence of sarcoid-type granulomas with epithelioid cells and macrophages without necrosis in the center, surrounded by lymphocytes, plasma cells, and mast cells (Figure 3). The patient was administered intravenous methylprednisolone (500 mg per day, intravenously, for 5 days, 250 mg per day for 3 days, 120 mg per day for 3 days) at the same time, vitamin B1, mecobalamine improved symptoms. One month later, prednisone tablets were reduced to 30 mg qd; the symptoms of the patient were significantly improved, the degree of numbness was reduced; only the fingers and distal toes were numb, the left foot weakness was improved, the dorsiflexor muscle strength was V-grade, and the right foot muscle strength returned to normal.

Discussion

In this article, we report a rare case of a patient diagnosed with sarcoidosis and peripheral neuropathy. Based on the supraclavicular lymph nodebiopsy founded presence of sarcoid-type granulomas with epithelioid cells and macrophages without necrosis in the center, surrounded by lymphocytes, plasma cells, and mast cells [12]. There is no diagnostic gold standard of sarcoidosis, and the diagnosis is most likely in the presence of compatible clinical and radiological features coupled with evidence of noncaseating granulomatous inflammation at disease sites and after exclusion of other diseases that may present similarly [13]. Mentioned in this article definite diagnostic criteria for Central Nervous System and Peripheral Nervous System Neurosarcoidosis as follows: 1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings

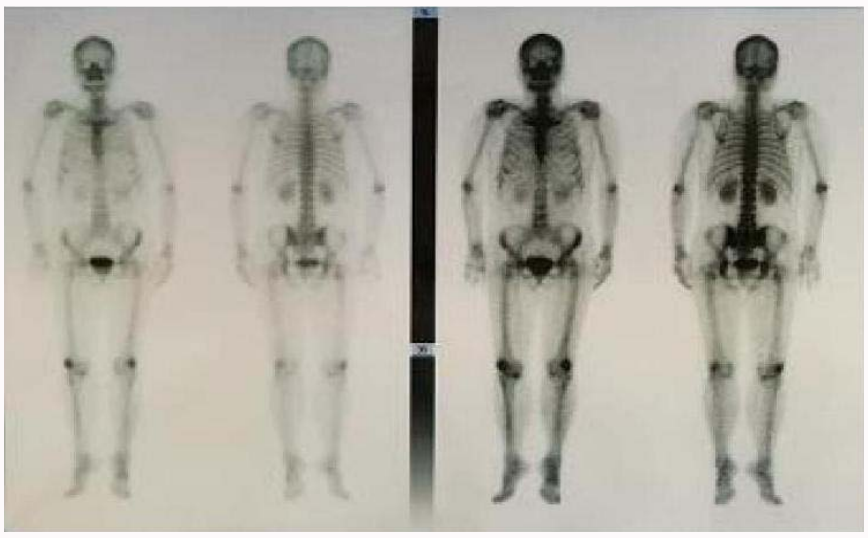

Figure 1: The bone imaging showed that bone salt metabolism was increased in the knee, nonspecific inflammation.

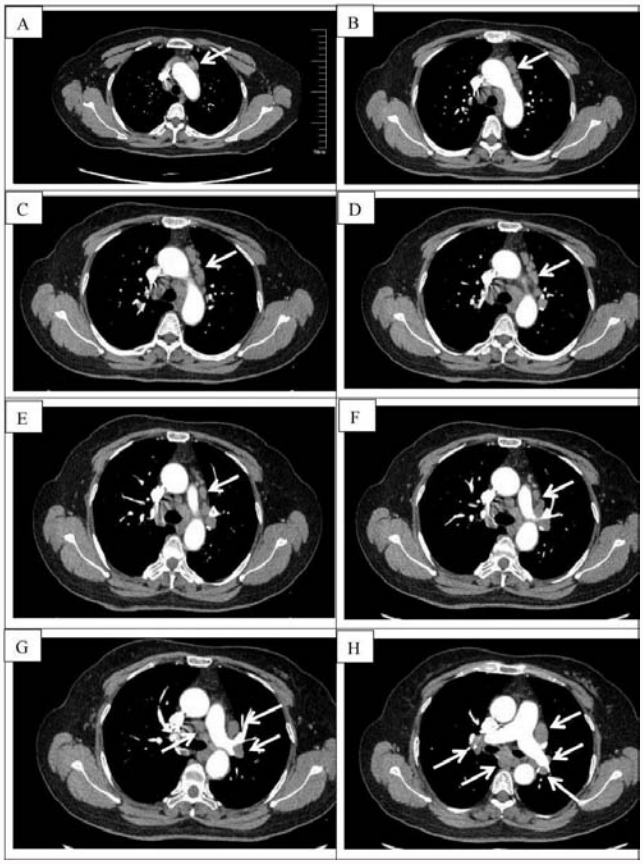

Figure 2: The enhanced chest CT results of the patient. A) Cervical root lymph node enlargement. B) Enlargement of lymph nodes in the left hilar area. C). Enlargement of lymph nodes in the left hilar area and mediastinal. D) Enlargement of lymph nodes in the left hilar area and mediastinal. E) Enlargement of lymph nodes in the left hilar area and mediastinal. F) Enlargement of lymph nodes in the left hilar area and mediastinal. G) Enlargement of lymph nodes in the left hilar area and mediastinal. H) Enlargement of lymph nodes in the left hilar area and mediastinal.

typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes. 2. The nervous system pathology is consistent with neurosarcoidosis. We diagnosed sarcoidosis excluding other diseases and confirmed it pathologically.

At present, the peripheral nervous system is exposed to many environmental, metabolic, and genetic predispositions and affected by a large of diseases; they can be axonal, demyelinating, or mixed. Hereditary peripheral Neuropathies include Charcot-Marie-Tooth (CMT) disease, Hereditary Neuropathy with liability to Pressure Palsies (HNPP), Hereditary Sensory and Autonomic Neuropathy (HSAN), Familial amyloid Neuropathy, Polyglucosan body disease. Inflammatory neuropathies include Autoimmune, Sarcoidosis, Guillain-Barre syndrome/Acute Inflammatory Demyelinating Polyneuropathy (AIDP), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Vasculitis, Celiac disease, Multifocal motor neuropathy, cryoglobulinemia. Neuropathies associated with neoplasias and related disorders include paraneoplastic neuropathy, monoclonal gammopathy/POEMS and amyloidosis. Metabolic neuropathies include diabetic neuropathy, neuropathy caused by thyroid gland dysfunction, uremic neuropathy, and liver failure and vitamin deficiencies. Toxic neuropathies include alcohol abuse, chemotherapeutic agents and heavy metals [14,15]. Approach to the evaluation of peripheral neuropathies, Mononeuropathy? Mononeuropathy multiplex? Polyneuropathy? Axonal? Demyelinating? Or Mixed? Different tests were performed for different types of lesions [16]. In our patient, The Electromyography (EMG) and Nerve Conduction Studies (NCS) revealed asymmetric motor and sensory polyneuropathy, sarcoid granulomas caused direct compression and distortion of nerve fibres morphologically, and Nerve compression can induce focal demyelination. Demyelinating neuropathies show decreased conduction velocity, temporal dispersion, and prolonged distal and F-wave latencies. Histological examination of a supraclavicular lymph node showed noncaseating epithelioid cell granulomas consistent with the diagnosis of sarcoidosis. Peripheral neuropathy may be a clinical manifestation of sarcoidosis. Thus far, rare case report of the numbness and weakness of sarcoidosis similar to our case has been published in PubMed.

Sarcoidosis is a rare inflammatory disease characterized by the development of granulomas in various organs, especially in the lungs and lymph nodes. The incidence rate of sarcoidosis varies depending on the geographic region and age. High incidence rates in Northern European, however, less common in Asians. It more commonly occurs in people younger than 40, with a peak in the age-group from 25 to 40 years [17]. Pulmonary sarcoidosis, skin sarcoidosis, Löfgren syndrome, ocular sarcoidosis, musculoskeletal, cardiac sarcoidosis and neurosarcoidosis are the main clinical findings of sarcoidosis [18]. The etiology of sarcoidosis is still unknown but some studies have reported that an unidentified antigen processed by activated macrophages instigates an immune response regulated by T-cells and macrophages. These activated cells discharge various mediators, including cytokines, chemokines, and reactive oxygen species that may be involved in the progression of disease. Many studies hypothesized that genetic susceptibility, environmental factors, putative antigens and autoimmunity in the development of these diseases [19]. Infectious agents, noninfectious agents, immune-related diseases and cancer were mentioned for differential diagnosis of sarcoidosis [20]. Neurological involvement in sarcoidosis is relatively uncommon, with a reported prevalence of 3% to 10% [21]. Neurological manifestations are rarely the first or only symptom of sarcoidosis,

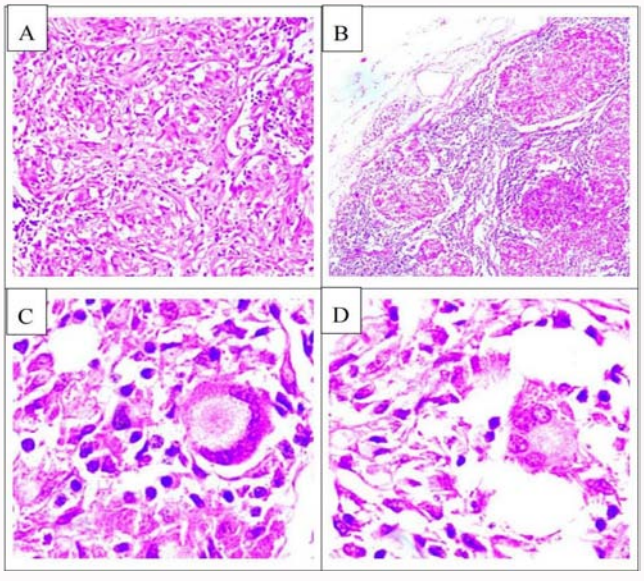

Figure 3: The supraclavicular lymph node biopsy founded granulomatous inflammation, granuloma nodules were consistent in size, and partially blended intranodal necrosis was not seen.

with 84 to 94 percent of cases experiencing coexisting systemic manifestations, especially in the lungs and intrathoracic lymph nodes [22]. Common and uncommon neurological manifestations and evolution of sarcoidosis as follows [23,24]: Cranial nerve (Optic nerves, oculomotor nerves, Trigeminal nerves, Facial nerves, Auditory nerves, Accessory nerves, sublingual nerves); Meningeal (meningeal irritation, CSF usually reveals mild monocyte pleocytosis and a protein elevation >1 g/L); Brain parenchyma (a solitary mass or multiple nodules and may cause focal neurologic deficits, seizures, or increased intracranial pressure); Spinal cord (Cervical >thoracic >conus involvement, On MRI, transverse myelitis with cord swelling and spinal cord atrophy); Pituitary (Infundibulum< pituitary stalk thickness< pituitary gland, Hypogonadism, TSH deficiency, diabetes insipidus and hyperprolactinemia); Peripheral neuropathy (Chronic axonal sensory and/or motor neuropathy polyneuropathy, multiplex mononeuropathy, radiculopathy, brachial/lumbar plexitis, subacute demyelinating polyneuropathy mimicking Guillain-Barré syndrome, chronic demyelinating inflammatory neuropathy); Stroke (ischemic >hemorrhagic). In this case, peripheral neuropathy was manifested as asymmetric motor and sensory polyneuropathy.

Over half of patients with sarcoidosis are mild or self-limited or never have clinical manifestations. However, in particularly severe cases of neurologic, ophthalmic, or cardiac involvement, more aggressive therapeutic management can be needed. What medicines are used to treat inflammation in sarcoidosis? First-Line Agents: Corticosteroids; Second Line Agents: Methotrexate, Hydroxychloroquine, Leflunomide, Azathioprine, Mycophenolate; Third-Line Agents: Infliximab, Adalimumab [25,26].

The patient in this case recovered well, after a period of treatment, her daily life significantly unaffected. Nevertheless, the study has some limitations. First, this is a case study of one individual. Secondly, we did not perform biopsy of gastrocnemius and sural nerve, whether it is characteristic non-caseating granulomas.

Conclusion

This was a rare case of sarcoidosis with peripheral neuropathy, the underlying mechanism remains elusive, we suggest that target antigen presentation, T cell activation, cytokine/chemokine profiles, propagation of granulomatous inflammation, T-regulatory balance, and the fibrotic response involved in the pathology of sarcoidosis, caused peripheral neuropathy.

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