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Peripheral Neuropathy in Sjogren's Syndrome: A Case Report

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Abstract

We report here a case of peripheral nerve complications of Sjogren's syndrome in a 45-year-old Chinese man. To our knowledge, there are presently no studies to provide the best treatment for peripheral neuropathy in Sjogren's syndrome. In our patient, rituximab was particularly effective. However, the mechanism through which rituximab exerts its efficacy in the treatment of neuropathy is unclear. Clinicians should screen other systemic diseases in patients with peripheral neuropathy, and consider Sjogren's syndrome in the differential diagnosis.

Keywords: Sjogren's syndrome; Peripheral neuropathy; Case report

Case Report

A 45-year-old, previously healthy Chinese man with no remarkable family history began to experience numbness in both soles and the right toes on February 10, 2020. The numbness gradually spread upward, up to the right buttocks and was persistent, accompanied by acupuncture-like pain on the right soles when standing, which was alleviated after rest. On February 16, the numbness of the limbs spread till the right waist and gradually also spread to the left toe, with needle-like pain on the soles of both feet that was worsened by activity. On April 10, the numbness of the left foot gradually extended to the left ankle, and the patient had difficulty walking. He had no weakness of the lower extremities, diplopic, eyelid ptosis, choking, slurring speech, or incontinence. There was also no history of trauma, prescription for fever, cough, diarrhea, or diabetes. However, he had a medical history of Raynaud's phenomenon, and there was no significant change in weight. These symptoms gradually aggravated, and he required admission to the hospital on May 1, 2020. The patient was wheelchair-bound upon admission. Cranial nerve functions were normal, and he had no cerebellar ataxia. Motor examination showed muscle strength of distal muscles of lower limbs was gread. He had no dystonia. The Romberg sign was negative, and deep tendon reflexes were normal. His other senses were normal.

Laboratory tests showed the following results: ANA 1:1000, centromere and mitochondrial type, CENP-B antibody++, anti-neutrophil cytoplasmic antibody (P-ANCA) positive (+) at 1:10, anti-myeloperoxidase antibody IgG(MPO-ANCA) <2.00RU/mL. Cold agglutinin test was negative. Other blood test and urinalysis results were all normal. Normal Cerebrospinal fluid (CSF) test result. Cranial MRI and lumbar MRI were both normal. Nerve conduction study showed partially myelinated peripheral nerves and axonal damage. The F-wave results were normal, while the H-reflex was partially decreased. Electromyography (EMG) showed neurogenic impairments (left and right gastrocnemius and quadriceps). Eye tests including Schirmer I test showed 4mm/5 min in the left eye and 3 mm/5 min in the right eye. The fluorescein break-up time was 3s in the left eye and 4s in the right eye. Corneal fluorescent staining was positive in both eyes. Labial gland biopsy revealed five stromal focal lymphocytic infiltrations, and the number of lymphocytes was more than 50 per focus. According to the classification standard of Sjogren's syndrome [1], the diagnosis was Sjogren's syndrome and peripheral neuropathy (immune-mediated peripheral neuropathy).

The treatment included rituximab 500mg, hydroxychloroquine 0.2g twice a day, and vitamin B1, B6, and B12. After treatment with rituximab, the patient's symptoms improved the mean pain VAS score was reduced from 8 points to 4 points. The patient scheduled to be treated with tituximab (500mg) after 2 weeks later. But the second rituximab (500mg) treat-

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ment was administered one month later at visit 2. After treatment, numbness of scope limited to the double foot and the toes, pain VAS score 0. After that, he received two rounds of rituximab treatment, each 500mg, with an interval of 2 months. After six months of follow-up, the numbness and pain in both lower limbs were relieved without recurrence. Review of EMG: no neurogenic damage was observed.

Discussion

Sjogren's syndrome is a chronic, inflammatory autoimmune disease characterized by lymphocyte proliferation and progressive glandular damage. Clinical symptoms not only damage the function of the salivary and lacrimal glands but also involve multiple organs and systems [2]. Kaltreider et al. [3] first reported the peripheral nerve complications of Sjogren's syndrome in 1969. Their study showed that the incidence of Sjogren's syndrome complicated with simple peripheral neuropathy is 10.1% [4]. The immunocytological staining results of this case was suggestive of Sjogren's syndrome, and the dignosis was confirmed by labial gland biopsy. The peripheral neuropathy of Sjogren's syndrome mainly includes the following types [5]: (1) painful sensory small fiber neuropathy, (2) sensory ataxia neuropathy, (3) axonal polyneuropathy, (4) vascular inflammatory neuropathy, (5) brain neuropathy, and (6) autonomic neuropathy. According to the clinical characteristics and electromyographic manifestations of our patient, he appeared to have vascular inflammatory neuropathy.

At present, there are few reports about peripheral neuropathy in Sjogren's syndrome. Differentiation from other diseases that cause peripheral neuropathy is crucial. *Chronic Guillain-Barré syndrome* is a chronic progressive or recurrent peripheral nerve disease. Our patient had a normal tendon reflex, normal F wave in the EMG, and was without albuminocytological dissociation in cerebrospinal fluid examination. Hence, Guillain-Barré syndrome was eliminated from the diagnosis. *Paraneoplastic syndrome* of the nervous system refers to the pathological changes of the nervous system caused by abnormal immune response of tumor products including ectopic hormones or other unknown reasons. The imaging results of chest, abdomen, and pelvic CT scan; tumor marker screening; anti-Hu, Yo, and Ri antibodies test were all normal. Hence, paraneoplastic syndrome was also ruled out. *Nervous system involvement of systemic vasculitis* such as giant cell arteritis, nodular polyarteritis, Anti-neutrophil Cytoplasmic Antibody (ANCA)-related vasculitis, and cryoglobulinemia vasculitis may lead to nervous system involvement, usually caused by inflammatory destruction and ischemic damage of nourishing blood vessels. Our patient did not meet the diagnostic criteria of systemic vasculitis. *Metabolic diseases* such as degeneration of the spinal cord caused by vitamin B12 deficiency and copper deficiency myeloneuropathy. Because our patient's serum vitamin B12 and ceruloplasmin were within the normal range, these diagnoses were ruled out.

The mechanism of Sjogren's syndrome neurological involvement is complex. Vasculitis, immune response induced by antibody-antigen complexes in the nervous system, thrombus due to anti-phospholipid antibodies, and internal environment disturbances due to endothelitis are essential factors in its pathogenesis [6]. Nerve biopsy in patients with peripheral neuropathy of Sjogren's syndrome showed two pathological changes: necrotizing vasculitis and periductal lymphoplasmacytic infiltration [7]. Similar pathogenesis has also been reported in the literature [8]. In both cases, neurological damage may occur in patients with peripheral neuropathy of Sjogren's syndrome. One is the typical vasculitis and the other is non-vasculitis, nonspecific inflammatory cell infiltration around blood vessels, loss of myelinated fibers, and degeneration of axons and myelin. Comparing the characteristics of lymphocytes in Peripheral Neuropathy Sroup (pSS-PNS) and non-peripheral neuropathy group (pSS-nPNS) in Sjogren's syndrome, our findings showed that the ratio of CD4/CD8 in the pSS-PNS group was significantly higher than that in pSS-nPNS group, suggesting that T lymphocytes were involved in the nervous system damage of Sjogren's syndrome [9]. In addition to T lymphocytes, the direct damage of vasculitis and the antibody secreted by B lymphocytes were also involved in the occurrence of PNS. Among the autoantibodies, anti-β2-glycoprotein I antibody (β2-GPI) and perinuclear antineutrophil cytoplasmic antibody (p-ANCA) play a certain cautionary role in the diagnosis of peripheral neuropathy in Sjogren's syndrome [10]. The main symptom endured by this patient included lower-extremity numbness and plantar pain, a history of Raynaud's phenomenon, and p-ANCA positivity, which verified that the vasculitis could be a risk factor for peripheral neuropathy in Sjogren's syndrome.

To our knowledge, there are presently no studies that discuss the optimal treatment for peripheral neuropathy in Sjogren's syndrome. Treatment is mainly supportive with consideration of immunomodulatory therapies such as intravenous Immunoglobulin (IVIg), Plasma Exchange (PE), glucocorticoids, azathioprine, and cyclophosphamide. Mekinian et al. [11] reported that the most significant improvement is observed in the case of pSS-PNS patients with cryoglobulinemia or vasculitis after rituximab treatment. In this case, rituximab is particularly effective. The mechanism of rituximab in the treatment of neuropathy is unclear. Rituximab inhibits the activation of T cells by B-cell depletion and blockade of antigen presentation, which may affect B cell function, resulting in secondary changes in T cell function. For example, rituximab induces the production of immunomodulatory T cells [12].

To conclude, clinicians should screen for other systemic diseases in patients with peripheral neuropathy and consider Sjogren's syndrome in the differential diagnosis. The types of Sjogren's syndrome complicated with nervous system involvement are complex, and the pathogenesis and treatment effect are still not clear. Prospective studies with large sample sizes are needed to obtain more clinical data and experiences. Further research is needed to assess the efficacy of rituximab in the treatment of Sjogren's syndrome with peripheral neuropathy.

Author Statements

Statement of Ethics

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient has provided written informed consent to publish this case report and any accompanying images.

Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

All authors have contributed equally to this report and are in agreement with the contents of the manuscript.

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