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Mononeuropathy Multiplex – Case Report of An Unusual Manifestation of Primary Sjögren's Syndrome

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ABSTRACT

Sjögren's Syndrome (SS) is a chronic autoimmune disease characterized by exocrinopathy, with xerophthalmia and xerostomia. Patients with SS may exhibit extra-glandular features such as neurologic symptoms. Peripheral neuropathy is the most common neurological complication of primary SS (pSS). We report a case of a 71-year-old female with pSS admitted to the Internal Medicine ward due to sensorimotor symptoms and petechiae. From the extensive study carried out, emphasis is given to elevation of inflammatory markers and to nerve conduction study compatible with mononeuritis of multiple nerves. The diagnosis of mononeuropathy multiplex (MM) secondary to pSS was made. She was started on corticosteroid therapy, which allowed complete regression of the petechiae as well as symptomatic and functional improvement. However, new sensorimotor deficits were noted a few days later. The decision was made to start cycles of cyclophosphamide in association with corticosteroid and physical therapies, leading to deficit improvement. Currently, the patient is in remission with low-dose corticosteroid therapy.

Keywords: Sjögren's Syndrome; Mononeuropathy Multiplex; Peripheral Nervous System; Autoimmune Diseases; Vasculitides

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Introduction

Sjögren's Syndrome (SS) is a chronic autoimmune disease characterized by lacrimal and salivary glands inflammation and dysfunction, with subsequent xerophthalmia and xerostomia [1]. SS can occur alone (primary SS) or in association with another systemic rheumatic disease (secondary SS). Patients with SS may exhibit extra-glandular features such as neurologic symptoms [2]. The prevalence of neurological involvement in primary SS (pSS) described in literature varies widely (18-45%), according to different cohorts [3, 4]. Peripheral neuropathy is the most common neurological manifestation of pSS (5-21%) [3, 5, 6, 7] and it is associated with a complex and extensive range of phenotypes that derive from the involvement of different sections of the peripheral nervous system (PNS) [8]. Different forms of peripheral neuropathy may coexist in the same individual. Axonal sensory and sensorimotor neuropathies are the most common phenotypes of PNS involvement in pSS [5, 8, 9, 10] and derive from damage of large myelinated fibers. Mononeuropathy multiplex (MM) is a rare type of sensorimotor neuropathy characterized by simultaneous or consecutive asymmetric damage of at least two discontiguous nerves [6]. Symptoms include acute onset of sensory and/or motor progressive deficits in an area innervated by individual nerves (usually on the lower limbs). Pain in very common and constitutional symptoms may be present.

Case Presentation

A 71-year-old woman with personal history of hypertension, dyslipidemia, venous thromboembolism and recently diagnosed pSS presented to the emergency department of our hospital with progressive complaints of pain in her lower limbs and paresthesias. The patient had no other relevant personal history nor known toxiphilic habits and was, at that time, medicated with lansoprazole, simvastatin, telmisartan, lorazepam, fluoxetine and warfarin. In the beginning, the paresthesias only involved the plantar aspect of the right foot and the fourth and fifth fingers of the right hand, but they progressively spread to all right hand. Diminished strength of the right hand developed in the next days. A few days after the onset of these symptoms, purpuric lesions emerged in the lower limbs. In the emergency department, neurological examination revealed sensorimotor compro-mise. Manual muscle strength testing, described using Medical Research Council (MRC) grades, disclosed the following abnormalities: flexion of the fourth and fifth fingers grade four/five (right flexor digitorum profundus and right flexor digitorum superficialis muscles; right ulnar and median nerves); fifth finger abduction two/five (right abductor digiti minimi muscle; right ulnar nerve); thumb adduction three/five (right adductor pollicis muscle; right ulnar nerve); first to third fingers flexion three/five (right flexor digitorum profundus, right flexor digitorum superficialis, flexor pollicis longus and flexor pollicis brevis muscles; right ulnar and median nerves); wrist and fingers extension four/five (extensor carpi radialis longus, extensor carpi radialis brevis, extensor carpi ulnaris, extensor digitorum and extensor digiti minimi muscles; right radial nerve). Neurological examination also revealed bilateral plantar and lateral edge hypoesthesia of the right foot (left and right tibial nerve and right sural nerve), decreased right brachioradialis deep tendon reflex (right radial nerve) and abolition of Achilles reflex bilaterally (left and right tibial nerve). No other neurologic abnormalities were found. The remaining physical examination revealed petechiae on the lower limbs. The patient was admitted to the Internal Medicine ward for clinical surveillance, symptomatic control and to continue etiological study.The blood analysis results are displayed in table 1.

The remaining study showed negative Human Immunodeficiency, Hepatitis C and Hepatitis B Viruses serologies, negative Antineutrophil Cytoplasmic and Antinuclear Antibodies, negative cryoglobulins and rheumatoid factor, and normal complement and immunoglobulins

levels. Urinalysis was unremarkable. Blood cultures were also negative.

In the electromyographic study, the activity of the following muscles was evaluated: abductor pollicis brevis, first dorsal interosseous, flexor digitorum superficialis, extensor digitorum communis, brachialis and triceps, bilaterally; right abductor hallucis and abductor digiti minimi; soleus, peroneus longus, extensor digitorum brevis and tibialis anterior, bilaterally; and right vastus medialis and vastus lateralis. No spontaneous activity was detected (resting muscles were all electrically silent). The abnormalities observed are described in table 2. All the previously stated muscles that are not mentioned in the table showed completely normal results.

Table 1: Relevant laboratory findings of blood analysis

Blood analysis	Result	Normal range values
Hemoglobin	12,9 g/dL	12.0 – 16.0 g/dL
Platelets	315 x 10E3/uL	150 – 440 x 10E3/uL
Creatine	0,66 mg/dL	0.51 – 0.95 mg/dL
Creatine kinase	89 U/L	26 – 174 U/L
Erythrocyte Sedimentation Rate	71 mm/hour	0 – 20 mm/hour
C-Reactive Protein	7.99 mg/dL	0 – 0.5 mg/dL

Table 2: Electromyography abnormal results

Muscle	Abnormalities on voluntary activity
Right abductor pollicis brevis	Absent (complete denervation)
Right first dorsal interosseous	Reduced recruitment pattern despite maximal activation; reduced amplitude at maximal activation; normal duration
Right flexor digitorum superficialis	Absent (complete denervation)
Right extensor digitorum communis	Very reduced recruitment pattern despite maximal activation; normal amplitude and duration
Right abductor digiti minimi	Absent (complete denervation)
Right abductor hallucis	Very reduced recruitment pattern despite maximal activation; reduced amplitude at maximal activation; normal duration
Right soleus	Very reduced recruitment pattern despite maximal activation; normal amplitude and duration
Left soleus	Very reduced recruitment pattern despite maximal activation; normal amplitude and duration
Left extensor digitorum brevis	Very reduced recruitment pattern despite maximal activation; normal amplitude and duration
Right extensor digitorum brevis	Very reduced recruitment pattern despite maximal activation; reduced amplitude at maximal activation; normal duration

In the nerve conduction study, the following nerves were evaluated: right and left median nerve (sensorimotor); right and left ulnar nerve (sensorimotor); right and left radial nerve

(sensory); right and left tibial nerve (sensorimotor); right and left peroneal nerve (motor); right superficial peroneal nerve (sensory); right and left sural nerve (sensory). The abnormalities observed are described in table 3. All the previously stated nerves that are not mentioned in the table showed completely normal results.

Table 3: Nerve conduction study abnormal results

Nerves evaluated	Latency (ms)	Amplitude (uV)	Velocity (m/s)	Interpretation
Right median (sensorimotor)	Indeterminable distal motor latency and sensory conduction velocity due to absent sensorimotor correspondent response to stimulation			
Right ulnar (sensorimotor)				
Right radial (sensory)	1.85 [N < 2.9]	10 [N > 20]	48.6 [N > 49]	Normal sensory conduction velocity with reduced amplitude of the correspondent sensory potential
Right superficial peroneal nerve (sensory)	2.4 [N < 4.2]	3.3 [N > 5]	33.3 [N > 49]	The superficial nerve sensory conduction velocity is reduced, with reduced amplitude of the correspondent sensory potential
Right sural nerve (sensory)	2.4 [N < 3.9]	3.2 [N > 10]	43.8 [N > 39]	Very reduced amplitude of the correspondent sensory potential
Right tibial nerve (motor)	3.7 [N < 6.1]	0.6 [N > 4]		The amplitude of the evoked compound muscle action potential is very reduced

The presented results reflect the presence of MM affecting the nerve trunks of the right hemisphere with involvement of the right median, radial, cubital, peroneal and tibial nerves.

Thoraco-abdominopelvic Computerized Tomography scan did not show relevant abnormalities. Brain and spinal cord Magnetic Resonance Imaging excluded central nervous system involvement.

Symptoms were very difficult to control and negatively impacted patient's daily living activities. Corticosteroid therapy was initiated (1 g/day of methylprednisolone for three days and, after that, 1 mg/kg/day of prednisolone). The patient showed complete regression of the petechial rash, as well as symptomatic and functional improvement, allowing her to be discharged. However, even under high-dose corticosteroid therapy (60 mg/day of prednisolone), a new sensory-motor deficit in the left hand and left foot was noted a few days after. Given the partial response to corticosteroid therapy decision was made to start cyclophosphamide (15 mg/kg for two to three weeks) in addition to corticosteroid and physical therapies, leading to deficit improvement. Currently, three years after diagnosis, the patient is able to walk independently, although presenting evident impairment mainly on pinching movement in the right hand and flexion/extension of the left first toe. The patient is in remission with low-dose corticosteroid therapy (2.5 mg/day of prednisolone).

Discussion

The exact prevalence of neurologic involvement in pSS is still not clear since available data is extremely variable. These discrepancies can be credited to various factors such as referral biases, evolution of the diagnostic criteria of SS over time, heterogeneity of study designs and low quality of the studies, which were mainly retrospective and with a relatively small number of participants [7]. The true percentage of

patients affected by MM is also still unknown, although this condition is certainly an uncommon manifestation of pSS [6, 8]. Neurologic manifestations of pSS, contrary to what was observed in our patient, usually precede the diagnosis of pSS [8, 9].

Patients with symptoms and signs suggestive of neuropathy should undergo nerve conduction studies to confirm PNS involvement and to better characterize the disease. Likewise, differential diagnoses must be excluded in patients exhibiting neurological symptoms. In this particular case, cryoglobulinemic vasculitis should be ruled out, as mononeuropathy multiplex in the setting of pSS is commonly associated to cryoglobulinemic vasculitis [7].

In general, the precise pathogenic mechanisms of nervous system involvement in pSS have not yet been fully elucidated [9]. MM seems, however, to result from necrotising vasculitis of the vasa nervorum with associated T-cell and macrophage infiltration that leads to ischaemia-induced nerve injury [11]. Biopsy of the affected nerves often shows axonal degeneration and perivascular inflammatory infiltrates [9]. Regarding the present clinical case, skin and nerve biopsies were requested upon admission of the patient to the hospital but they were not performed promptly.

Our patient presented with palpable purpura and polyneuropathy with asymmetric involvement on examination and on electrodiagnostic studies, with rapid onset and stepwise progression of the neurologic deficits; additionally, increased levels of inflammatory markers were noted, with a negative workup for infectious and other types of primary vasculitis. Taken together, these findings are highly suggestive of a vasculitic neuropathy secondary to pSS, a not so prominent feature of the disease (less than 10% of patients) [12]. Female sex, normal complement fractions and absence of cryoglobulinemia predict a less severe clinical picture [13, 14].

Treatment of MM in pSS is supportive but also aims to minimize ongoing nerve injury and prevent involvement of additional nerves. Likewise, treatment also relies on immunosuppressive therapy. There are no randomized controlled trials evaluating immunosuppressive therapies in patients with pSS and peripheral or central nervous system involvement. Often, treatment recommendations for neurologic manifestations of pSS are extrapolated from those of other pSS organ involvement and from other autoimmune diseases, or based on limited evidence from small, uncontrolled series [2, 5, 15, 16]. MM is usually treated with high-dose corticosteroids (prednisolone 1 mg/kg/day) and cyclophosphamide [17, 18]. However, even combined therapy does not always yield fully satisfactory therapeutic results. Treatment of neurologic involvement in pSS depends on the presence of vasculitis, on the severity of the disease, and on failure of symptomatic treatments. Treatment is also symptomatic and includes concomitant use of gabapentin, pregabalin or opioids [19, 20]. The use of tricyclic antidepressants is generally inadvisable due to their anticholinergic side effects that can contribute to pre-existing sicca symptoms.

Conclusions

Neurological manifestations may be part of the clinical spectrum of SS, with a various range of signs and symptoms. The authors present a case of pSS with extra-glandular disease affecting the PNS due to vasculitis, which must be recognized and treated promptly to prevent involvement of additional nerves. Clinicians should be aware of this possible complication and assess SS patients who exhibit neurologic signs or symptoms. It is also important to evaluate and exclude differential diagnoses.

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Abbreviations

SS – Sjögren's Syndrome; pSS - primary Sjögren's Syndrome; PNS - peripheral nervous

system; MM – mononeuropathy multiplex; MRC – Medical Research Council

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