

## CASE REPORT

# Atypical case of Sjögren's syndrome with psychiatric and peripheral neurological disorder

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## Abstract

Sjögren's syndrome is a rare disorder of the immune system characterized by the chronic lymphocytic infiltration of the organs with exocrine secretion (lacrimal, salivary glands), but also of other tissues of the body, that can be primary or secondary and can appear alone or in association with other systemic diseases: rheumatic arthritis, systemic erythematous lupus, scleroderma or polymyositis/dermatomyositis. The case that we are presenting is that of a 40-year-old man, who came to the Department of Rheumatology with articular, muscular, ocular, psychological and neurological symptoms. After multiple biological, immunological, histological, neurological, psychiatric, ophthalmological, digestive investigations, it was reached the conclusion that the patient presents a rare autoimmune disease (primary Sjögren's syndrome) involving mainly peripheral neuromuscular and psychological (small frequency) and the patient was given specific immunomodulatory, anti-inflammatory and anti-depressive treatment, to which he responded well. Thus, after 18 months of investigation, severe depressive episodes and difficult collaboration of the patient with the medical team, it was possible to reach the definitive diagnosis and to perform the appropriate treatment.

**Keywords:** Sjögren's syndrome, autoimmune disease, rheumatology.

## Introduction

The human body is frequently the target of external attacks (viruses, bacteria, allergens, toxic substances) that can weaken him; more seriously is the case when the protection cells of the body fight against the tissues, not recognizing them as their own structures [1]. The result is unpredictable and variable; there are major differences from one patient to another. The involvement of the central and peripheral nervous system is proven in many studies [2]. The psychological symptoms most frequently related are anxiety, depression and somatization, as well as cognitive and memory problems [3]. The peripheral neuropathy is manifested most frequently by muscle weakness, decrease of the muscular strength and seems related to the lymphocyte infiltration of the small blood vessels that serve the nerves [4].

Prevalence of neurological manifestations in Sjögren's syndrome varies widely from 10 to 60%, with pure or predominantly sensory polyneuropathies as the most common neurological manifestation (e.g., sensory ataxic or small fiber sensory painful neuropathy). Mononeuropathy multiplex, polyradiculopathy, symptomatic dysautonomia, cranial neuropathy, myopathy, and central nervous system involvement are less common [4, 5]. Normally, the symptoms are well tolerated by the patient, but there are also aggressive and unclear forms. We report such a case to literature data and discussions on the diagnosis, treatment and results.

## Case presentation

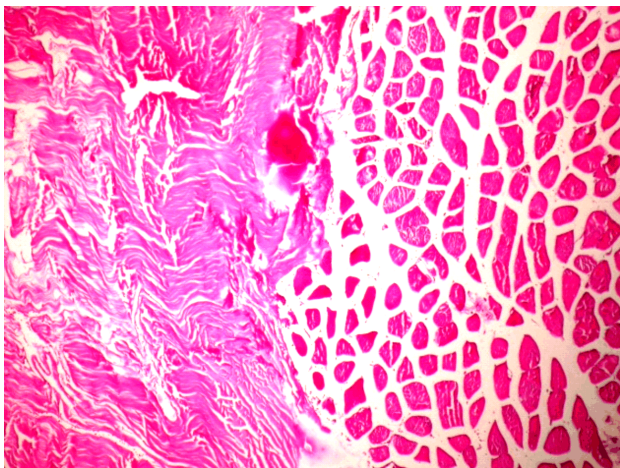
The case that we are presenting is of a 40-year-old man, who came to the Department of Rheumatology with non-specific symptoms: non-systematized arthralgia with inflammation, muscular pain, severe physical asthenia, fatigue, irascibility, depression, insomnia. The presented case is rare from many reasons. The immunological investigations were not eloquent from the beginning, the muscular biopsy showed atrophic inflammatory modifications, the biopsy of the salivary gland was refused by the patient, the Schirmer's test was positive and articular and neurological symptoms were predominant.

The patient noted for the first time, approximately two years ago, muscular weakness at the lower and upper limbs, fatigability, insomnia, articular diffuse pain, with inflammatory character, at the lumbosacral spine, knees, shoulders, without objective clinical modifications. Initially, the patient was evaluated rheumatologically in a university center. A spondylitis was suspected; the antinuclear antibody (ANA) profile was negative, HLA-B27 antibody was positive, the ophthalmological exam was negative, the neurological exam in normal limits, and in the absence of an inflammatory biological process, the articular and vertebral X-rays performed – without modifications, did not sustain the diagnosis. Due to the persistence of the subjective complaints, we initiated treatment with Sulfasalazine in progressively increased doses up to 3 g/day for three months and Medrol 32 mg/day, in progressively

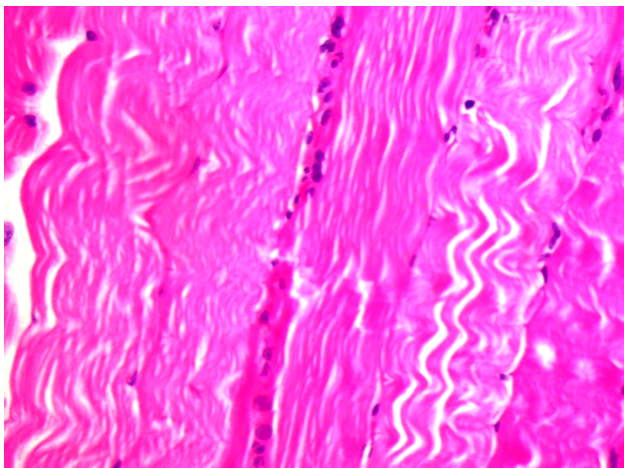
decreased doses, but the patient did not respect the therapy plan. After six months, he came to our Department with the same subjective complaints, to which were added oral ulcerations, dry mouth, alterations of taste, dental decays, sensation of intraocular foreign object, avoidance of bright light, spasm of the eyelid, irritated colon syndrome and muscular atrophies of the lower limbs, affirmatively significant, diffuse and persistent myalgia, decrease of muscular strength of lower limbs, insomnia, arthralgia, significant physical asthenia. He is investigated clinically and paraclinically; from the hematological, immunological [anti-Sjögren's syndrome (SS)-A, anti-SS-B, RF (rheumatoid factor), anti-Epstein-Barr virus antibodies, ANA] and biochemical [hemoleukogram (HLG), hepatic, renal, respiratory, endocrine and inflammatory tests, creatine phosphokinase (CPK), electrophoresis (ELFO), circulating immune complex (CIC), complement fraction 3 (C3)] points of view, the analyses were within normal ranges. Abdominal ultrasound, colonoscopy and magnetic resonance imaging (MRI) of sacral iliac articulations were performed revealing normal relations. The muscular punch biopsy showed striate muscular fibers with an aspect of isolated atrophies; on Hematoxylin-Eosin (HE) staining are observed dystrophic aspects that lead to the loss of nucleus with the partial disintegration of the fibers, other areas presenting interstitial edema that isolate each fiber,

the aspect pleading for a muscular dystrophy (Figures 1–6).

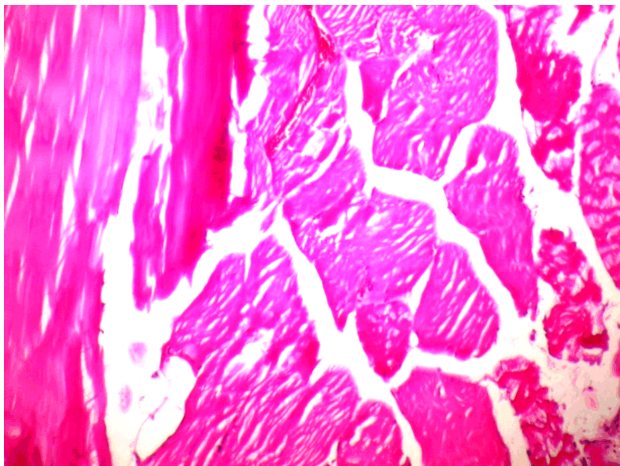
Electromyography underlines a post-inflammatory aspect, a possible chronic polymyositis or myopathy with inclusions, without myasthenic decrement, without the severe character of a muscular dystrophy with debut on the adult. The ophthalmological exam showed a cornea without brightness, with erosions, a lachrymal secretory failure (positive Schirmer's test, both eyes 5 mm, and remained positive after the stimulation with 5% ammonium chloride vapors emitted 20 cm from the nose). The biopsy of the salivary gland was refused by the patient, who was asthenic, recalcitrant, verbally aggressive with the family and the medical staff. The exam of the oral cavity exhibited dry mucus, dental decays, filiform papillae atrophy, easy bilateral increase of the parotid glands that were firm, without pain, irregular on palpation, and decrease of the parotid glands salivary flux. Psychiatric consultation showed a depressive anxious disorder severe form. Endocrine examination eliminated thyroid disease as a possible cause of the persistent physical asthenia. Neurological examination removed other neurological disorders, hereditary or achieved neuropathies, the patient presenting decrease of tendon reflexes, relatively minor cutaneous sensorial deficiency and variable motor dysfunctions. Erythrocyte sedimentation rate (ESR), anti-SS-A, anti-SS-B and anti-HLA-B27 antibodies were positive on the laboratory investigation repeated after 10 months.



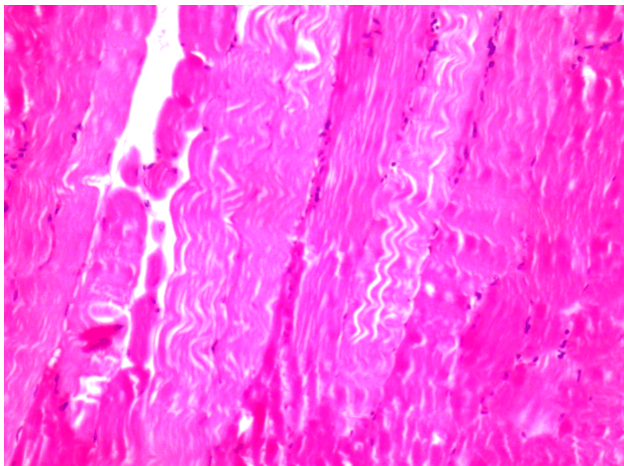
**Figure 1** – Extended interstitial edema, fibrosis, atrophy and intracytoplasmic vacuolization. HE staining,  $\times 40$ .



**Figure 2** – Disorganized muscular fibers and nuclear crowding. HE staining,  $\times 200$ .

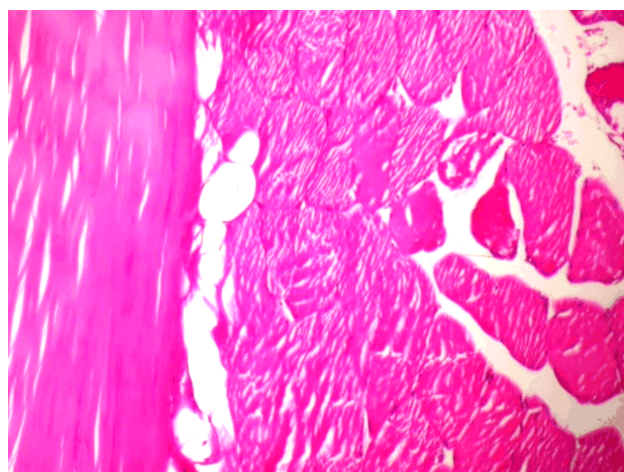


**Figure 3** – Dystrophic fibers and interstitial edema. HE staining,  $\times 200$ .

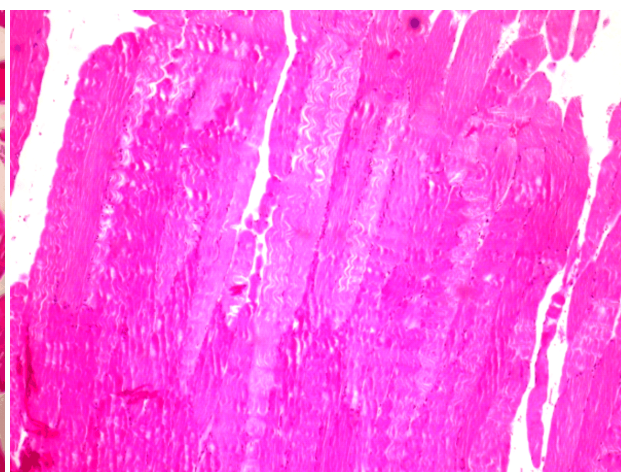


**Figure 4** – Intracytoplasmic vacuolization, nuclear pyknosis and interstitial edema. HE staining,  $\times 40$ .





**Figure 5 – Infiltration of the interstitial tissue with adipocytes. HE staining,  $\times 100$ .**



**Figure 6 – Dystrophic modifications of the fibers with aspect of undulation. HE staining,  $\times 40$ .**

Clinical and laboratory tests excluded a disease with rheumatologic basis (rheumatoid polyarthritis, systemic erythematous lupus, scleroderma, myositis). Initiation of pulse therapy with Methylprednisolonum 1 mg/kg/day three days and Methotrexate 20 mg/week, Esomeprazolium 10 mg/day, psychiatric treatment, with a periodical surveillance of hepatic and renal functions were decided. The treatment of dry eyes was made by frequent ocular instillations with ophthalmological products that contain methylcellulose. The treatment of dry mouth was achieved by severe oral hygiene, avoiding the alimentation with solid food, lubrication with antibiotics and antifungal solution, and by an increased infusion with liquids. In order to modify consistency of saliva and to diminish the sensation of dryness, mucolytics were intermittently administered. A program of specific rehabilitation was started. After six months of therapy, the condition of the patient improved significantly, the outcome of the disease being net favorable without adverse neurological and psychiatric side effects.

## Discussion

Sjögren's syndrome can be primary or secondary to the administration of drugs, radiotherapy or because of other immunological deficiencies and can coexist with other rheumatologic diseases [5, 6]. Because the symptoms can be overlaid and even coexist with the manifestations of other diseases, Sjögren's syndrome diagnosis can be made sometimes with difficulty. Neurological peripheral involvement is unusual and controversial and is characterized by the appearance of peripheral neuropathies secondary to the vasculitis of the vessels that irrigate the nerves in a variable proportion, between 0–60% of the cases [5–7]. In a study on a large number of patients in France [6], the systemic complications were present for more than 74% of the patients. The systemic involvement occurs usually between 5 and 15 years from the first manifestations of the disease, and the secondary muscular neuropathy and hypotrophy are present at approximately 16% of the cases [8].

In the case of our presented patient, the muscular biopsy sampled from the superior region of the right hip

was fixed immediately in 10% formalin; the histological processing was made by the paraffin-embedding method, with HE classical staining. The sections were made at 4  $\mu$ m using MICROM microtome, and the images examination was made with Nikon E200 optical microscope.

The normal muscular fibers in the transversal section have 5–12  $\mu$ m in diameter, with 4–6 peripheral nuclei under the sarcolemma and a parallel orientation with the long axis of the fiber. The nucleoli cannot be seen and the cytoplasm is pale eosinophilic.

In our case, the microscopic examination reveals dystrophic changes without inflammatory aspects. The atrophic aspect of the fibers is predominant; the fibers have different diameter, and in the interstitial space fibrosis is present (Figure 1). Other dystrophic lesions are: intracytoplasmic vacuolization (Figures 2 and 3), fat infiltration in the interstitial tissue (Figure 4), undulated fibers with fewer nuclei (Figure 5) and a central agglomeration of them (Figure 6). The immunohistochemical panel performed (desmin, actin and vimentin) did not reveal pathological aspects. We did not performed any other histoenzymatic and histochemical tests.

In the context of those presented, without having the possibility of performing electron microscopy, our case was interpreted as an injury of muscular dystrophy type. We were not able to include the described lesions in a certain type of neuromuscular dystrophy, because the histological aspects were not sufficient. We cannot exclude a myositis or a neuromuscular dystrophic disease; therefore, it is necessary to correlate with clinical aspects and the serological modifications.

Data from literature sustain the fact that the neuropathies are generally sensitive and affect the patient on the level of the lower limbs symmetrically [9]. The mononeuropathy multiplex is sensitive and motor and can occur associated with Sjögren's syndrome [10]. The myopathies can appear on the level of the lower limbs proximally or distally, are discrete and persistent as it happened in the presented case [11–13]. Polymyositis and myositis can be subclinical in some cases, but the histological changes are presented in a higher percentage of patients investigated [14].

The specialty literature presents possible neurological

and muscular alterations as neuropathies of the hands and feet, myalgia, myopathies or myositis for a variable number of cases [15], probably due to the polymorphic symptoms and the difficulties of making a diagnosis. Neurological involvement frequently preceded the diagnosis of Sjögren's syndrome. The rate of affecting women, compared to men is 9:1 [15].

Some studies underline the diversity of neurological complications of Sjögren's syndrome. The frequency of neurological manifestations revealing Sjögren's syndrome and of negative biological features, especially in the case of nervous system involvement, could explain why this disease is frequently misdiagnosed. Most patients had peripheral nervous system involvement. Symmetric axonal sensorimotor polyneuropathy with a predominance of sensory symptoms or pure sensory neuropathy occurred most frequently [16, 17].

The increasing impact of Sjögren's syndrome as a cause of peripheral neuropathy is underscored in a review article, directed toward neurologist, written by Kaplan *et al.*, in 1990, which stated "Our experience and review of the literature reveal that Sjögren's syndrome is an important, poorly recognized cause of peripheral neuropathy". They note that the "clinical evidence of glandular involvement is often minimal to absent when patients with Sjögren's syndrome develop peripheral neuropathy and the diagnosis of the underlying condition is elusive" [17].

The optimal treatment for peripheral neuropathy in Sjögren's syndrome is unknown. There are no controlled studies of any treatment regimen. Moreover, the use of immunosuppressive therapy (such as corticosteroids or cytotoxic drugs) has met with variable results in the currently reported cases [18]. Therefore, all therapy must be individualized such that the chance for potential benefit outweighs the risk of any proposed treatment. In cases of the commonly occurring distal (fingers and toes) tingling paresthesia it is reasonable to treat conservatively with splints and physical therapy [19]. The pathophysiological basis of peripheral nervous system involvement is still unclear. Few studies have explored the fundamental role of humoral autoimmune mechanisms. Small, uncontrolled, treatment trials with numerous immunomodulatory agents have reported variable benefit in Sjögren's syndrome – associated neuropathy, particularly corticosteroids for mononeuritis multiplex and intravenous immunoglobulin for small fiber or sensory ataxic neuropathy [20]. The treatment of dry eyes and dry mouth depends on the severity of the dryness, which is best assessed by a specialist and is graded according to the degree of symptoms, conjunctival injections and staining, corneal damage, tear quality, and lid involvement [21–28]. Patients with dry mouth can liberally drink sips of water and take bottled water with them on trips. They can also place a glass of water at their bedside for nighttime use, as needed. Sugar-free lemon drops can also be used as needed to stimulate salivary secretion. Artificial saliva can be used as needed, although patient's tolerance varies. Patients should be seen regularly by a dentist, who may advise fluoride treatments. Toothpaste without detergents can reduce mouth irritation in patients with Sjögren's syndrome [29].

## Conclusions

The outcome of Sjögren's syndrome is unpredictable and the peripheral neurological involvement can be differentiated with difficulty from other neurological entities. There are particular situations, as in our case, where the patient has symptoms suggestive of the disease, but the specific biological and clinical investigations do not support the diagnosis suspected from the beginning. This case presentation helps us in recognizing non-specific elements that can become specific to a certain context of symptoms and investigations. We consider that any information regarding the diagnosis, outcome and treatment of Sjögren's syndrome may lead to a better understanding of the pathology of autoimmune diseases, and it will benefit both, the medical community and the patients.

## Conflict of interests

The authors declare that they have no conflict of interests.

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*Received: May 10, 2015*

*Accepted: March 12, 2016*