MAEDICA – a Journal of Clinical Medicine
2020; 15(4): 543-548
https://doi.org/10.26574/maedica.2020.15.4.543

MÆDICA - a Journal of Clinical Medicine

CASE REPORT

Subacute Onset Sensorimotor Axonal Neuropathy with Sicca Syndrome

Ioan-Cristian LUPESCU[a], Mirela Ramona DRAGHICI[a], Oana Maria OBRISCA[a], Basel TORON[a], Adriana Octaviana DULAMEA[a, b]

[a]Neurology Department, Fundeni Clinical Institute, Bucharest, Romania

[b]Neurology Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

We present the case of a 65-year-old female, with no prior medical history, who came to our attention for painful paresthesias involving the distal lower limbs and progressive gait disturbance, accompanied by fatigue, involuntary weight loss, xerophthalmia and xerostomia. Due to a right-sided cervical tumefaction, cervical MRI was performed and revealed an enlarged right parotid gland. Electroneurography confirmed the presence of a chronic sensorimotor axonal neuropathy with active denervation. Blood and urinary samples were collected, highlighting the presence of anti SS-A and SS-B antibodies, with cryoglobulinemia, IgM monoclonal band and kappa light chain monoclonal band. No malignancies were found after extensive workup and bone marrow aspiration was normal. Consequently, a diagnosis of Sjögren syndrome-associated peripheral neuropathy with cryoglobulinemia was established, and after plasma exchange, partial improvement of the patient's gait was noted.

Keywords: Sjögren syndrome, sicca, polyneuropathy, plasma exchange.

Abbreviations (in alphabetical order):

anti-Sm	anti-Smith
CMV	Cytomegalovirus
CT	Computer Tomography
dsDNA	double stranded DeoxyribonucleicAcid
HIV	Human Immunodeficiency Virus
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IVIG	Intravenous Immunoglobulin
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MUP	Motor Unit Potential
SS-A	Sjögren Syndrome A
SS-B	Sjögren Syndrome B

Address for correspondence:
Ioan-Cristian Lupescu
Neurology Department, Fundeni Clinical Institute, Sos. Fundeni, No. 258, Bucharest, Romania
Email: ioan.cristian.lupescu@gmail.com

Article received on the 2nd of November and accepted for publication on the 9th of December 2020

INTRODUCTION

There is a large spectrum of acute or subacute polyneuropathies, which can be caused by nutritional factors (*e.g.*, alcoholism, vitamin B12 deficiency, malabsorbtion syndromes), toxic exposure (*e.g.*, heavy metal poisoning, drug-induced), diabetes, uremia, vasculitis (*e.g.*, polyarteritis nodosa, Wegener, Churg-Strauss), autoimmune conditions (*e.g.*, acute or subacute Guillain-Barre syndrome), paraneoplastic neurologic syndromes, sarcoma, HIV or Lyme disease (1).

The term „sicca" is a Latin word that means dryness (2). Sicca syndrome refers to the presence of xerophthalmia and xerostomia, and it is used in conjunction with Sjögren syndrome; however, the two entities are not synonymous (3). Symptoms of dry eye and dry mouth are frequent in persons aged >65 and can have many causes, the most common being medication side-effects (4).

Sjögren syndrome (SS) is one of the main diagnostic considerations in an elderly woman with symptoms of sensory neuropathy or neuronopathy (1).

Diagnosis of primary SS is based on the 2016 ACR/EULAR classification criteria (Table 1). Scores ≥ 4 are considered diagnostic in patients who meet the inclusion criteria (*i.e.*, at least one symptom of ocular or oral dryness) and exclusion criteria (positive history of head/neck radiotherapy, active hepatitis C infection, AIDS, sarcoidosis, amyloidosis, graft-*versus*-host disease or IgG4-related disease) (5). ❑

CASE PRESENTATION

We present the case of a 65-year-old woman, non-smoker, non-alcohol consumer and with no prior medical history. In August 2018, she started developing in involuntary weight loss (~20 kilograms) with anorexia, fatigue, xerophthalmia and xerostomia. In October 2018, these were followed by painful paresthesias of the distal lower limbs, extending proximally and later involving both upper limbs. There was also a progressive gait disturbance and the patient started noticing a right-sided cervical tumefaction. Cervical MRI was performed in February 2019 and highlighted an enlarged right parotid gland, multiple right-sided lymph nodes and a thyroglossal cyst.

When the patient came to our attention, she presented bilateral steppage gait, distal paraparesis 3-4/5 MRC, diminished patellar and ankle reflexes as well as tactile and proprioceptive hypoesthesia with bilateral "glove and stocking" distribution. Walking was possible only with support.

We have first performed an electroneurography, which confirmed the presence of a severe chronic sensory-motor axonal polyneuropathy with active denervation (Table 2).

Lumbar puncture with cerebrospinal fluid examination showed slightly raised protein level (0.4 g/L) and diminished glycorrhachia (54.6 mg/dL).

In search for an etiology, blood samples were collected and a series of abnormal parameters were noted (Table 3).

TABLE 1. Diagnostic criteria of primary Sjögren syndrome. Reproduced from Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/ European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* 2017;69(1):35-45.

Item	Value
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm^2	3
AntiSS-A/Ro positive	3
Ocular Staining Score ≥5 (or van Bijsterveld score ≥4) in at least one eye	1
Schirmer's test ≤5 mm/five minutes in at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 mL/minute	1

TABLE 2. Electroneurographic abnormalities in our patient

Nerves	**Compound muscle action potentials (CMAP)**
Tibial (bilateral)	No motor responses
Common peroneal (bilateral)	Greatly reduced amplitude and conduction velocity Conduction block at the left fibular head
Median (right sided)	Within normal range
Ulnar (right sided)	Within normal range
Nerves	**Sensory nerve action potentials (SNAP)**
Superficial peroneal (bilateral)	No sensory responses
Sural (right sided)	No sensory responses
Median (right sided)	Reduced amplitude and conduction velocity
Ulnar (right sided)	Reduced amplitude and conduction velocity
Muscles	**Needle examination (electromiography)**
Tibialis (bilateral)	Spontaneous activity (fibrillations, fasciculation potentials) No obtainable motor unit potentials (MUPs)
Gastrocnemius (right sided)	No spontaneous activity Neurogenic MUPs

All other markers, including glycated hemoglobin, thyroid hormones, tumoral markers, auto-antibodies (antiphospholipid, anti-dsDNA, anti-Sm, anti-topoisomerase, anti-gliadin, anti-transglutaminase) and viral serologies for hepatitis B, hepatitis C, *Borrelia*, Epstein-Barr, HIV and syphilis were all negative. Chest x-ray, electrocardiogram and urinary cultures were also within normal range.

A Sjögren syndrome-associated polyneuropathy was established as diagnosis. Under methylprednisolone 16 mg qd, there was a partial remission of both neuropathic symptoms and right-sided cervical enlargement.

At discharge, the patient received treatment with methylprednisolone 8 mg qd, pregabalin 75 mg bid, alpha-lipoic acid 600 mg qd, omeprazole 20 mg qd, aspirin 75 mg qd and pentoxifylline 400 mg bid.

Given the whole clinical picture, extensive paraclinical workup was recommended, to exclude a paraneoplastic Sjögren syndrome.

Further laboratory workup highlighted additional abnormal findings:

Contrast-enhanced CT of the thorax-abdomen-pelvis was performed, revealing non-specific pulmonary micronodules, inhomogeneous appearance of the thyroid gland, non-enhancing bilateral mammary nodules (with signs of benignity on mammography), subserous uterine leiomyoma, right ovarian cyst and also an osteosclerotic lesion of the left femoral neck, with demineralization of the sacrum and iliac wings. No intrathoracic or intraabdominal enlarged lymph nodes were noted. Transvaginal ultrasound highlighted multiple uterine leiomyomas and anechoic images of the right ovary. Cervical ultrasound indicated the presence of bilateral hypoechoic nodules involving the thyroid, bilaterally enlarged cervical lymph nodes and cystic dilation of the parotid glands with microcalcifications. Spirometry and upper digestive endoscopy were normal. Ophthalmological exam confirmed the presence of sicca syndrome based on a positive Schirmer test. Finally, a bone marrow aspiration was performed and was within normal range.

Based on all these findings, we established a diagnosis of Sjögren syndrome and severe cryoglobulinemia with cutaneous, renal, and neurologic involvement. There was also the occurrence of a monoclonal gammopathy, for which

TABLE 3.1. Abnormal laboratory findings in our patient

	Biomarkers	Value	Reference interval
Autoimmune	Antinuclear antibodies	6.1 U/mL	0–1.1 U/mL
	Anti SS-A	>200 U/mL	0–25 U/mL
	Anti SS-B	55 U/mL	0–25 U/mL
	Rheumatoid factor	3270 IU/mL	0–15 IU/mL
Inflammatory	Procalcitonin	0.11 ng/mL	0–0.05 ng/mL
	C-Reactive Protein	3.86 mg/L	<3 mg/L
Infectious	IgM CMV	4.11	<1.1
	IgG CMV	188.4	<10
Metabolic-nutritional	Vitamin B12	181 pg/mL	<211 pg/mL

TABLE 3.2. Abnormal laboratory findings in our patient

	Biomarkers	Patient value	Normal range
Immunology	Cryoglobulinemia	Present (+++)	Absent
	Immunoglobulin M	588 mg/dL	40–230 mg/dL
	C4 complement	0.0	0.1–0.4 g/L
	β2-microglobulin	3.35 mg/dL	0.8–2.2 mg/dL
Protein electrophoresis	IgM monoclonal band	Present	Absent
	Kappa light chain band	Present	Absent
Urinalysis	24 hour proteinuria	282 mg/24 h	0–150 mg/24 h
	Microscopic examination	Hematuria	Absent
		Leukocyturia	Absent

bone marrow biopsy was performed (to exclude myeloproliferative disorders).

Given the absence of immunoglobulin treatment, the patient received plasma exchange (a total of five sessions , each given every other day) and pulse-therapy with cyclophosphamide 200 mg qd (given daily for four days). At discharge, there was a moderate improvement of gait (the patient being now able to walk without support), although with persistence of paresthesias in the distal territories of both upper and lower limbs. ❑

DISCUSSIONS

It is worth mentioning that SS can produce a wide spectrum of neuropathic syndromes. The *sensory axonal form*, which is the most common, is associated in the beginning with symmetric paresthesias in the distal parts of the lower extremities, followed by sensory loss with a "glove and stocking" distribution and abolished deep tendon reflexes (6). Or the clinical picture may be dominated by lancinating pains, often felt as a burning sensastion, sometimes in a "non-length dependent" distribution (*i.e., small fiber neuropathy*) (7), while in others, the main complaint is an abrupt or insidious onset of sensory ataxia with loss of proprioception (*i.e., dorsal root ganglionitis*) (8). The *sensorimotor form* affects both sensory and motor fibers, and it is usually associated with lymphomatous or systemic manifestations such as purpura and cryoglobulinemia (9). Other neuropathic syndromes include mononeuropathy multiplex, multiple cranial neuropathies, trigeminal neuropathy, autonomic neuropathy and radiculoneuropathy (10). *Motor predominant*

Maedica 2020 | A Journal of Clinical Medicine, Volume 15, No. 3, 2020 546

neuropathies, resembling Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP), have also been described in association with SS (11).

Epidemiologic studies have given variable estimates for the frequency of SS-associated neuropathy. First, we should mention that the overall incidence of Sjögren syndrome is estimated at about seven cases/ 100 000 persons/ year, with a prevalence of 43 cases/ 100 000 persons (12). In two representative studies (each with over 500 patients), the prevalence of neuropathic syndromes was low: 1.8% in the first one and 10% in the other (13, 14). However, in another series, while 27% of patients had clinical signs of neuropathy, nerve conduction studies were abnormal in 55%, suggesting that a larger proportion of patients had subclinical neuropathy (15).

Although primary SS affects mostly women, peripheral nerve involvement due to SS is more evenly distributed between genders, with a median age of onset of 63-year-old (16).

Regarding treatment, a recent review (based mainly on case series and case reports) established that intravenous immunoglobulins (IVIG) have been effective in the sensory, motor and sensorimotor forms, while cyclophosphamide was useful in mononeuritis multiplex, and rituximab or glucocorticoids improved autonomic neuropathies (17).

Of course, therapeutic responses have varied between studies. One case series noted an objective improvement of the sensory ataxic form in four out of five patients, following administration of intravenous immunoglobulins (18); the regimen consisted of 0.4 g/ kg body weight/ day, given for five consecutive days, and patients received three such courses, at two week intervals each. In another study comprising 13 patients, IVIGs performed poorly, while better outcomes were observed with corticosteroids combined with immunosuppressive drugs (particularly mycophenolate mofetil) (19).

Rituximab was also shown to be effective in primary SS patients with peripheral nerve involvement, especially in the setting of vasculitis and cryoglobulinemia (20).

Not many works have been published regarding plasma exchange (the treatment used in our patient). Chen et al found it effective in two out of four patients with sensory ataxic neuropathy, suggesting that it could be considered and used in such cases (21). Rapid improvement following plasma exchange has been also noted in a 58-year-old patient with rapidly progressive sensorimotor distal neuropathy and new-onset seizures, in the setting of primary SS (22). ❑

CONCLUSIONS

Our case presented a double challenge. First of all, there was the difficulty in establishing a correct diagnosis and determining the etiology, given the many abnormal findings (autoimmune markers, paraproteinemia, cryoglobulinemia). Even after confirming the diagnosis of Sjögren syndrome, it was important to determine its type (primary *versus* secondary/paraneoplastic). The second challenge was that of choosing an appropriate treatment, since there are not many publications available on the subject. Unfortunately, immunoglobulin treatment was not available in our hospital at that time, so we opted for plasma exchange, which is usually regarded as a similarly effective alternative. ❑

Conflicts of interest: none declared.
Financial support: none declared.
Acknowledgements: All authors would like to thank each of the following doctors from Colentina Clinical Hospital (in particular dr. Ramba Doina) for their contribution and assessment in establishing the final diagnosis: Dr. Ramba Doina, Rheumatology & Internal Medicine Department; Dr. Enache Mirela, Abdominal & thyroid ultrasound; Dr. Ifrim Silvi, Doppler ultrasound of lower limb arteries; Dr. Parcalabu Irina, Transvaginal ultrasound; Dr. Budileanu Oana, Ophtalmological examination; Dr. Popov Viola Maria, Hematological examination; Dr. Forminte Nicolae-Marian, Cervical lymph node & salivary gland biopsy.

References

1. **Allan HR, Martin AS, Joshua PK, Sashank P.** Diseases of the Peripheral Nerves In: Allan HR, Martin AS, Joshua PK, Sashank P. Adams and Victor's Principles of Neurology – 11th Edition. *McGraw-Hill Educational*, 2019:1319-1348.
2. **Ghafoor M.** Sjögren's Before Sjögren: Did Henrik Sjögren (1899-1986) Really Discover Sjögren's Disease? *J Maxillofac Oral Surg* 2012;3:373-374. doi:10.1007/s12663-011-0303-0.
3. **Richey TK, Bennion SD.** Etiologies of the sicca syndrome: primary systemic amyloidosis and others. *Int J Dermatol* 1996;8:553-557. doi:10.1111/j.1365-4362.1996.tb03653.x.
4. **Baer AN, Walitt B.** Sjögren Syndrome and Other Causes of Sicca in Older Adults. *Clin Geriatr Med* 2017;1:87-103. doi:10.1016/j.cger.2016.08.007.
5. **Shiboski CH, Shiboski SC, Seror R, et al.** 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* 2017;1:35-45. doi:10.1002/art.39859.
6. **Perzyńska-Mazan J, Maślińska M, Gasik R.** Neurological manifestations of primary Sjögren's syndrome. *Reumatologia* 2018;2:99-105. doi:10.5114/reum.2018.75521.
7. **Birnbaum J.** Peripheral nervous system manifestations of Sjögren syndrome: clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. *Neurologist* 2010;5:287-297. doi:10.1097/NRL.0b013e3181ebe59f.
8. **Griffin JW, Cornblath DR, Alexander E, et al.** Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. *Ann Neurol* 1990;3:304-315. doi:10.1002/ana.410270313.
9. **Pavlakis PP, Alexopoulos H, Kosmidis ML, et al.** Peripheral neuropathies in Sjögren's syndrome: a critical update on clinical features and pathogenetic mechanisms. *J Autoimmun* 2012;1-2:27-33. doi:10.1016/j.jaut.2012.01.003.
10. **Mori K, Iijima M, Koike H, et al.** The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. *Brain* 2005;Pt 11:2518-2534. doi: 10.1093/brain/awh605. Epub 2005 Jul 27.
11. **Mochizuki H, Kamakura K, Masaki T, et al.** Motor dominant neuropathy in Sjögren's syndrome: report of two cases. *Intern Med* 2002;2:142-146. doi:10.2169/internalmedicine.41.142.
12. **Qin B, Wang J, Yang Z, et al.** Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;11:1983-1989. doi:10.1136/annrheumdis-2014-205375.
13. **Pavlakis PP, Alexopoulos H, Kosmidis ML, et al.** Peripheral neuropathies in Sjögren syndrome: a new reappraisal. *J Neurol Neurosurg Psychiatry* 2011;7:798-802. Epub 2010 Dec 16.
14. **Brito-Zerón P, Akasbi M, Bosch X, et al.** Classification and characterisation of peripheral neuropathies in 102 patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 2013;1:103-110. Epub 2012 Sep 27.
15. **Gøransson LG, Herigstad A, Tjensvoll AB, et al.** Peripheral neuropathy in primary Sjögren syndrome: a population-based study. *Arch Neurol* 2006;11:1612-1615. doi:10.1001/archneur.63.11.1612.
16. **Seeliger T, Prenzler NK, Gingele S, et al.** Neuro-Sjögren: Peripheral Neuropathy With Limb Weakness in Sjögren's Syndrome. *Front Immunol* 2019;10:1600. Published 2019 Jul 11. doi:10.3389/fimmu.2019.01600.
17. **Humă AC, Kecskeş EM, Tulbă D, et al.** Immunosuppressive treatment for peripheral neuropathies in Sjögren's syndrome – a systematic review. *Rom J Intern Med* 2020;1:5-12. doi:10.2478/rjim-2019-0022.
18. **Takahashi Y, Takata T, Hoshino M, et al.** Benefit of IVIG for long-standing ataxic sensory neuronopathy with Sjögren's syndrome. IV immunoglobulin. *Neurology* 2003;3:503-505. doi:10.1212/01.wnl.0000046680.47883.7d.
19. **Pereira PR, Viala K, Maisonobe T.** Sjögren Sensory Neuronopathy (Sjögren Ganglionopathy): Long-Term Outcome and Treatment Response in a Series of 13 Cases. *Medicine (Baltimore)* 2016;19:e3632. doi:10.1097/MD.0000000000003632.
20. **Mekinian A, Ravaud P, Hatron PY, et al.** Efficacy of rituximab in primary Sjögren's syndrome with peripheral nervous system involvement: results from the AIR registry. *Ann Rheum Dis* 2012;1:84-87. doi: 10.1136/annrheumdis-2011-200086. Epub 2011 Sep 16. PMID: 21926185.
21. **Chen WH, Yeh JH, Chiu HC.** Plasmapheresis in the treatment of ataxic sensory neuropathy associated with Sjögren's syndrome. *Eur Neurol* 2001;4:270-274. doi:10.1159/000052142.
22. **Ging K, Mono ML, Sturzenegger M, et al.** Peripheral and central nervous system involvement in a patient with primary Sjögren's syndrome: a case report. *J Med Case Reports* 2019;13:165. https://doi.org/10.1186/s13256-019-2086-8.