Sjögren’s syndrome presented with severe motor neuron disease

Abdulrahman A. Khormi¹, Fajer Al Tamimi¹, Sami Alrasheedi¹, Talal Al Kuhaimi¹, Ahmed Al-Shaikh¹

King Faisal Specialist Hospital and Research Center – Riyadh¹

Introduction

Sjögren’s syndrome (S.S.) is a chronic, systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. It is an elaborate involvement of the lacrimal and salivary glands, which eventually lead to keratoconjunctivitis sicca and xerostomia. It occurs in two forms, primary or secondary (associated with another autoimmune disease, most commonly rheumatoid arthritis). The American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee have approved classification criteria that aids at primary Sjogren’s Syndrome diagnosis. It includes labial salivary gland biopsy with evidence of lymphocytic infiltrate, positive ant SSA, ocular staining score of 5 or more, Shirmer’s test positivity and unstimulated whole saliva flow less than or equal to 1ml/minute. The application of this criteria requires exclusion of conditions that may mimic S.S. such as hepatitis C infection, AIDS, IgG4 disease, and Sarcoidosis.¹

S.S. has many neurological manifestations. In Sjögren’s syndrome-associated neurological complications, neurological symptoms often precede the manifestation of sicca symptoms. (2) Motor neuron disease (MND) is a rarely recognized complication in Sjögren’s syndrome. (3) Here in we present a case of lady with primary Sjogren and this rare neurological manifestation.

Case presentation

A 37-year-old lady presented ten years ago to her local hospital with dry eyes and mouth. She was labeled as Sjögren’s syndrome and started on steroid. She was followed up for two years then lost her follow up. Six years later, she presented to the same hospital while she is eight months pregnant with bilateral parotid swelling. She was started on Hydroxychloroquine 400 mg q.d and Prednisolone 20 mg q.d. Then the parotid swelling has subsided. She gave birth to a healthy child, but her neck swelling increased. After that, she had a regular follow up, but was not compliant with her medications. Eight months later, she had surgical removal of right submandibular gland and lymph node at a private hospital in patient local area and showed lymphocytic sialadenitis with prominent lymphoepithelial lesion, which supports Sjogren Syndrome. The lymph nodes were reactive with no malignancy. However, the patient shows poor compliance to medications and stopped all her medications.

One month later, she was presented to her local hospital with generalized body ache and gradual onset of muscle
weakness mainly proximal involving upper and lower limbs. All her examinations were unremarkable apart from neurological examination which revealed: Right and left upper limb power of 1/5, right lower limb power of 1/5, and left lower limb power 2/5. Her reflexes were absent in the upper limb and weak in the lower limb, while the plantar reflexes were equivocal. She has normal tone in all muscles. She was admitted for evaluation.

Her investigations were unremarkable apart from: IgM 4, IgG 18, IgA 25. Anti SSA 89.6 U/ml and Anti SSB were positive 45.8 U, while antiDNA, anti JO1, anti RNP, and antiCCP were negative. The cryoglobulin was negative and MRI brain and spine was normal. Her EMG was done at her local hospital and showed Asymmetric axonal motor neuropathy with denervative changes in both proximal upper limbs. Gastroenterology team at her local hospital (GI) was consulted because of high liver function tests (LFT) and she was diagnosed with primary liver cirrhosis. Neurology team was involved and started her on IVIG on Februray13, 2016. She was discharged on prednisolone 60 mg PO OD and Azathioprine 50 mg OD.

After one month, she was admitted again at her local hospital with similar complains, so she was started on IV Methylprednisolone therapy 1 gram per day for three days. The patient was advised for neuromuscular biopsy to confirm definitive vascular neuropathy, so to consider rituximab and cyclophosphamide. She was referred to our center for further evaluation

On the same month, she was seen in our outpatient clinic and advised direct admission for evaluation. She gave similar history of progressive weakness, initially in her lower limbs, right more than the left. Then, her upper limbs became involved. Upper limbs weakness was severe, more proximal than distal with no diurnal variation. The weakness was affecting her daily activities e.g. eating, drinking, combing her hair, etc. She had no headaches, seizures, visual symptoms, or sphincter dysfunction. She has no sensory impairment. She has dry eyes and mouth, dental caries, and generalized fatigue. No history of rash, joint pain, or stiffness. No myalgia. No palpitations, chest pain, syncope, dyspnea, or orthopnea. No history of nausea, vomiting, constipation, diarrhea, and no history of recent GI or genitourinary. No evidence of upper respiratory tract infection. No weight loss, night sweats, or fevers.

She is a housewife and mother of three healthy children with no history of abortion. All her deliveries were spontaneous vaginal deliveries with no maternal or fetal complications. Her antenatal and postnatal cares were unremarkable. She never smokes. Family history of Rheumatological illnesses was not identified.

On examinations, her vital signs were Temp: 36.7, HR: 108, BP: 126/83, RR: 20, Sat: 96% RA, and body mass index 23.8. She was alert, conscious, oriented to time, place, and person, and not in acute distress. Her speech fluency and coherence were intact. She has intact short and long-term memory. Her cranial nerves and fundus examination were normal. Her tone was normal all over. There was no body rash. Eyes, ears, nose, and throat examinations were unremarkable. Schirmer test is 2 mm in right eye, 3 mm in the left eye, dry tongue, absence of salivary pool, and poor dental hygiene with dental caries. No parotid gland enlargement. No lymphadenopathy. Her systems examinations were unremarkable.

Her muscle power examinations revealed the upper limbs biceps and triceps 0/5 bilaterally. Left arm wrist extension is 3/5, wrist flexion is 4/5, and the grip is 5/5. Right arm wrist extension is 3/5; wrist flexion is 2/5; and the grip 4/5. The lower limbs hip extension and flexion, knee extension and flexion were 5/5, plantar flexion and extension 4/5 bilaterally. Her reflexes showed upper limb absent reflexes in biceps and triceps bilaterally. The lower limbs plantar reflex is down-going on the left side and mute in the right. Her Sensory examination was intact, while the gait cannot be assessed. Her blood investigations showed, LFTs (Alb: 35.8 g/l, Bili: 4.2 umol/l, ALT: 69.9U/l, AST: 41.3 U/l, ALP: 276.1 HI, GGT: 140 IU/l), and unremarkable others. The autoimmune workup showed anti Ro was positive 89.6 U/ml, ANA positive and negative SLE and antiphospholipid markers. TSH 0.285 mu/l, T3 1.4 nmol/l, FT4 17.2 pmol/l, IgG 11 g/l, IgA 2.2 g/l, IgM 3.2 g/l, and cryoglobulin absent. The chest x-ray was unremarkable. Her echocardiography showed normal ejection fraction and no evidence of pulmonary artery systolic hypertension.

To summarize her problems, she sustained Sjögren’s syndrome which was confirmed clinically by positive keratoconjunctivitis sicca, xerostomia, and anti Ro. The minor salivary gland at the lower lip was biopsied and showed lymphocytic infiltrates, which was consistent with Sjögren’s syndrome.
She suffered of both upper and lower extremities weakness, which the neurologist assessed and their differential diagnosis were motor neuron disease, para-neoplastic syndrome, motor neuropathy, or myopathy. They advised MRI brain and spine, which showed the following: Brain, There was a small nonspecific elongated focus of T2/FLAIR hyper-intensity in the right frontal white matter. The brain parenchyma has otherwise normal signal characteristics. The ventricles were normal in size and position. There was no extra-axial fluid collection, mass effect, or midline shift. Incidentally noted prominent developmental venous anomaly in the region of the right basal ganglia. Vascular flow voids were present. Spine MRI revealed normal vertebral alignment, vertebral body heights and bone marrow signal. The lumbar spinal canal was congenitally narrow. There was transitional anatomy at the lumbosacral junction with partial lumbarization of S1. The spinal cord has normal size and signal. The conus medullaris terminated normally at L1. There was multilevel facet and ligamentum flavum thickening at the lumbar levels as well as a small disc bulge at L5-S1 without significant central canal or neural foraminal stenosis at any level. Ectopic right kidney was noted. CSF analysis was unremarkable for hematology and protein CSF was 1289 mg/l, albumin 773 mg/l, IgG 362 mg/l, glucose 5.26 mmol/l; and opening pressure was 19 cm of water. Nerve conduction study was normal, while EMG showed severe motor unit loss with significant denervation.

Also she has proteinuria, she underwent kidney biopsy, which showed tubulointerstitial nephritis. She had high liver function test with positive AMA. The Gastroenterologist couldn’t establish the diagnosis of primary biliary cirrhosis, as the patient refused liver biopsy. She was started on Ursodiol 500 mg o.d. The abdominal MRI showed hemangioma in segment 4 in the liver, so the GI consult recommended repeating the abdominal MRI annually.

We have commenced her on our plan of management of 5 sessions of plasma exchange, then 3 days of IV methylprednisolone 1 g and then continued on oral prednisolone 50 mg. The pain in her lower limbs has improved. Then she received 5 doses of IVIG 0.4 g/kg. After that, she received the 1st dose of rituximab. Her lower limbs weakness were partially improved.

She was discharged with plan to receive four cycles of IVIG and four doses of rituximab. We kept her on maintenance medications as follows; prednisolon 60mg o.d, calcium carbonate 600 mg o.d, cholecalciferol 1000 U o.d, trazodone 100 mg q.h.s, metformin 1000 mg b.i.d, Omeprazole 20 mg o.d, gliclazide 60 mg o.d, ferrous gluconate 300 mg B.I.D., and acetoaminophine 650 P.R.N. and refresh plus 1bid for the eyes.

On her first visit to Day Medical Unit for her first post discharge cycle, she reported severe pain in her right lower limb. She was found to have right hip fracture. Our orthopedics admitted her and she had bipolar hemiarthroplasty, and then discharged in good condition. She has resumed her scheduled IVIG therapy. She was on osteoporosis prophylaxis (Cholecalciferol 1000 units daily and Calcium Carbonate 600mg PO Daily)

She was seen at outpatient clinic after her second cycle of IVIG, she was maintained on prednisolone 25mg o.d, calcium 600 mg o.d, cholecalciferol 1000 U o.d, trazodone 100 mg q.h.s, metformin 1000 mg b.i.d, Omeprazole 20 mg o.d, gliclazide 60 mg o.d, ferrous gluconate 300 mg b.i.d, and paracetamol P.R.N.

She looked clinically cushingoid. She was still complaining of weakness in her upper and lower extremities, power of around 1-2/5. She complained of chest pain below the chest and mild lower limb edema with orthopnea. She was afebrile. Her pulse was around 120 beats per minute, regular. Her blood pressure on the higher side 155/109 mmHg and her respiratory rate was around 18 per minute with oxygen saturation of 99% in room air.

Her blood investigations showed normal CBC. Normal coagulation profile. D-dimer of 0.8 mg/l, ESR 17 mm/hr. Normal renal profile. Her albumin is 33 g/l. CK is normal 21 U/l. AST has normalized, while ALT has reduced to 59.2 U/l. Her urinalysis is negative for protein. CRP was normal. Chest x-ray showed no evidence of congestion and mild haziness of the right border of the heart. She continued to complain of shortness of breath during her 2nd, 3rd and 4th cycles, in which D-Dimer was measured and was elevated. Accordingly, she had CT angiography of the chest was negative for pulmonary embolism. During her last IVIG cycle, she developed allergic reaction to Octagam IVIG which was replaced later by Biotest IVIG.

www.ijasrjournal.org
The patient was advised about the need to be on extensive physiotherapy preferably under rehabilitation care for full mobilization and strengthening of her muscles as tolerated and informed about the need to do incentive spirometry to avoid atelectasis. She was scheduled for next dose of rituximab and the plan is to continue on rituximab every 6 months with monthly IVIG and to gradually taper down her prednisone and keep her on 10 mg of prednisone. Thereafter, she lost her follow up. Her caring physician phoned her family and found that she sustained outside hospital arrest. Unfortunately, she ended under long-term facility in coma and ventilator dependant.

**Discussion**

A wide variety of neurological complications are described in Sjögren’s syndrome. In Sjögren’s syndrome-associated neurological complications, neurological symptoms often precede the manifestation of SICCA symptoms. Classically, peripheral neuropathy in patients with primary S.S. responds poorly to treatment. (2) Motor neuron disease (MND) is a rarely recognized complication in Sjögren’s syndrome (3). Upon reviewing literature, we found case reports of similar presentation at two patients. Both had mild or absent Sicca symptoms. Lower motor neuron signs were observed only in their late follow-up period, and upper motor neuron signs were markedly predominant throughout the entire follow-up period. IVIG were used to treat both cases and showed some efficacy to improve their symptoms (3). Unfortunately, our patient did not get much benefit of the treatment with IVIG. More optimal maintenance treatments should be sought rather than simply repeating IVIG. One treatment option that might be tried is Rituximab. It is, an anti-CD20 antibody, may be useful in systemic complications in primary S.S. patients and in some cases of refractory neuropathy. (3) Rituximab was initiated at our patient and showed some efficacy.

**Conclusion**

Motor neuron disease (MND) is a rarely recognized complication in Sjögren’s syndrome. Treatment options include steroid, IVIG and in resistant cases Rituximab might be used. Multidisciplinary teams approach is needed to treat this complication. Further studies are needed to find more optimal therapies.

**Competing interests**
The author(s) declare that they have no competing interests.

**References**

1) ARTHRITIS & RHEUMATOLOGY Vol. 00, No. 00, Month 2016, pp 00–00 DOI10.1002/art.39859 VC 2016, American College of Rheumatology. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren’s Syndrome.
2) Neurological disorders in primary Sjogren Syndrome ( Autoimmune Diseases 2012. 645967 ).
3) Upper motor neuron syndrome associated with subclinical Sjogrens syndrome ( Inter Med 47: 1047-1051, 2008 DOI: 10.2169/internalmedicine.47.0846)