CASE SERIES

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Sjögren's Disease: A True Multisystem Masquerader

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Abstract

We report a series of three cases of a common autoimmune disorder, Primary Sjögrens Disease. The hallmark of this disease is glandular involvement presenting as sicca symptoms in the form of dry eyes and dry mouth. But in our series all three cases did not have sicca symptoms and presented with extraglandular involvement in the form of hypokalaemic paralysis with distal renal tubular acidosis in case 1, autoimmune hepatitis and massive splenomegaly with thrombocytopenia in case 2 and Acute Transverse Myelitis with NMO spectrum disorder in case 3. A lip biopsy led to a confirmed diagnosis in all 3 cases.

All patients responded to immunosuppressive treatment. We wish to highlight the fact that Sjögren's Disease can present without typical sicca symptoms and have solely extraglandular manifestations which a clinician should be aware of, and lip biopsy which is a minor procedure should be done wherever necessary to confirm the diagnosis.

Key words: Primary Sjögren's Disease, sicca symptoms, extraglandular involvement, lip biopsy.

Introduction

Sjögren's Disease is a rheumatological disease with varied clinical manifestations. Although it is classically known to present with glandular manifestations in the form of dry eye and dry mouth in the majority of patients, but it can have many extra-glandular systemic manifestations, as has been reported extensively in literature. It can affect all systems with varying frequency with musculoskeletal and cutaneous being most common followed by renal, haematological, neurological, respiratory and gastrointestinal. However, the majority of patients presenting with extra-glandular systemic involvement have been shown to have sicca symptoms, either on history or on objective evaluation of tear production like Schirmer's test or Tear film Break Up Time (TBUT). We report 3 cases of Sjögren's disease who presented with extra-glandular manifestations affecting renal, GIT and neurological system, respectively, but did not have classical sicca symptoms on history and even on objective evaluation.

Case 1

A 20-year-old woman presented with a 4 months history of bilateral symmetrical polyarthrlagias mainly over large joints like shoulder, hips and knees along with constitutional symptoms like low grade fever, easy fatiguability and generalised weakness. She did not have a history suggestive of connective tissue disorders like oral ulcers, photosensitivity, dry eyes, dry mouth, Raynaud's phenomenon, muscle weakness, etc. However, she had a significant past history of 4 - 5 episodes of hematemesis 4 years back which was managed conservatively and a history of itchy maculopapular rashes over bilateral lower limb. On examination, she had significant pallor, and maculopapular rashes over lower limbs. Abdominal examination revealed moderate splenomegaly, 10 cm below left costal margin till the umbilicus.

On basis of history and examination our diagnostic possibilities were:

Chronic Infections like Malaria, Kala Azar, TB, Brucellosis.

Non-Infectious conditions like Portal Hypertension, and Haematological disorders including malignancies.

Autoimmune Rheumatic Diseases: Rheumatoid Arthritis, SLE, Still's Disease.

Investigations:

CBC, ESR	6.5/3900/49000, 51 mm/hr s/o Pancytopenia P/S - Normocytic and Normochromic RBCs with reduced leucocytes and platelets with no atypical cells.
Reticulocyte Count	1.9%
CRP	18 mg/L (<10 mg/L)
LFT	T Bil 1.2 mg/dL SGOT 187 U/L, SGPT 105 U/L ALP 640 U/L
KFT	Urea 44 mg/dL Cr 0.8 mg/dL
Total Protein Albumin	7.2g/dL 3.3 g/dL
U R/M U C/S	pH 5.8 Protein -ve WBC 1 - 2/hpf RBC 1 - 2/hpf No growth

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Iron Profile	Within Normal Limits
Vit B12/FA	Normal
DCT/ICT	Negative

Ultrasound of abdomen and Doppler showed splenomegaly of 20 cm. Liver echotexture was normal with no evidence of portal hypertension. No lymphadenopathy or ascites were noted.

Upper GI endoscopy was also normal with no evidence of portal hypertension.

Investigations: (Case 1)

rK 39 Antigen, Malarial Antigen, Scrub, Brucella serology	Negative
HBsAg, Anti HCV, HIVI/II	Negative
RF, Anti CCP	Negative
Total IgG levels	1608 mg/dl (<1500)
Serum protein electrophoresis	Polyclonal gamma globulin spike
ANA (IF method)	**1:80 (speckled pattern)**
Anti SMA, LKM, AMA	Negative
ENA profile	
Anti dsDNA	Negative
Anti Sm	Negative
Anti Ro (SSA)	**Positive 66 (<20)**
Anti La (SSB)	**Positive 58 (<20)**
Anti RNP	Negative
Anti Histone	Negative

In view of pancytopenia and splenomegaly, a possibility of haematological malignancy or lymphoma was considered. However, the patient refused a Bone marrow biopsy. Moreover, there was absence of peripheral and intrabdominal lymphadenopathy making lymphoma less likely.

In view of deranged LFT (SGOT/SGPT/ALP) a possibility of autoimmune hepatitis or overlap syndrome was entertained, however considering negative Anti LKM, ASMA and AMA, this possibility was less likely, so a liver biopsy was deferred.

In view of negative history of photosensitivity, oral ulcers, alopecia, etc., and negative results of RF, Anti CCP, anti dsDNA and antiSm and possibility of rheumatoid arthritis and connective tissue disease like SLE were less likely.

Considering high titres Anti Ro/La positivity Sjögren's disease was considered, so further tests were done. Schirmer's Test was negative, F stain did not reveal any abnormality, and Tear film Break Up Time (TBUT) was normal in both eyes (>10 s). Salivary flow estimation could not be done in our centre.

So, to confirm the diagnosis of Sjögren's Disease we did a lip biopsy, which showed extensive lymphoplasmacytic infiltrates around minor salivary glands and ducts with *Focus score* >1 suggestive of Sjögren's Disease.

Final Diagnosis: Sjögren's disease without sicca symptoms with extra-glandular involvement in the form of massive splenomegaly with pancytopenia with hepatitis.

Management: Patient was treated with oral steroids 1 mg/kg. Her symptoms improved after 2 weeks of follow-up; her pancytopenia improved (9.8/4500/1.2), LFT improved (T Bil1.1/SGOT 77/SGPT 55, ALP 360). Spleen size also reduced to 7 cm below left costal margin. Patient is on follow-up and planned for steroid tapering and adding a steroid sparing agent.

Case 2

A 50-year-old women presented to the emergency department with complaints of weakness in all four limbs. She was fine when she went to bed at night. However, she woke up at 2 AM and found that she was not able to move any of her limbs. She had around 2 bowls of food at night. There was no history of any antecedent illness, decreased sensations over her body, fever, slurring of speech, neck pain, headache, vomiting or joint pains. There was no past history of diabetes, hypertension or thyroid disorder and no history of similar complaints in the past.

On examination, she was conscious, oriented with intact higher mental functions. No neck stiffness or Kernig's sign was elicited. Motor examination revealed a power of 1/5 across all 4 limbs with decreased tone, absent deep tendon reflexes, mute plantar reflex and normal sensory examination.

Investigations: (Case 2)

CBC, ESR	9.9/8900/71,000, 25 mm/hr
KFT	Urea 45 mg/dL Cr 0.6 mg/dL
Na/K	139 meq/L/**1.6 meq/L**
Ca/ Mg	8.5 mg/dL/2.1 mg/dL
LFT	T Bil 0.5 mg/dL/SGOT30 U/L/SGPT31 U/L/ALP129 U/L
Blood gas analysis	**pH 7.317** **HCO3 14.2 mmol/L** **pCO2 28.7 mmHg** **Anion Gap 7.5 mmol/L**
Urine pH	**6.5**
Spot Urinary K^+	**30 meq/L (20 - 100)**
Urinary Anion Gap ($Na^+ + K^+ - Cl^- + HCO3^-$)	**Positive**

Viral Markers – HBsAg/Anti-HCV/HIV- 1/2 negative

In view of normal anion gap metabolic acidosis and

hypokalaemia with high urinary pH (>5.5), high normal spot urinary potassium in spite of hypokalaemia, and a positive anion gap we suspected distal renal tubular acidosis (RTA).

Further investigations were done to look for an underlying connective tissue disease.

ANA by IF Method	**1:80 /Speckled Pattern**
ENA Profile	
Anti dsDNA	Negative
Anti Sm	Negative
Anti Ro (SS-A)	**Positive - 58 (<20)**
Anti La (SS-B)	**Positive - 36 (<20)**
Anti RNP	Negative
Anti Histone	Negative

Since patient did not have sicca symptoms, objective tests for tear production were done which were also within normal limits.

Schirmer's Test – Normal (>10 mm in 5 minutes)

Tear Film Break Up Time (TBUT) – Normal

To further evaluate for Sjögren's disease we did ultrasound of head and neck region, a which showed multiple hypoechoic nodules in B/L parotid and submandibular glands. X-ray KUB did not show any nephrolithiasis sometimes seen in cases of RTA. A lip biopsy was carried out which showed extensive lymphoplasmacytic infiltrates around minor salivary glands and ducts with *Focus score >1* suggestive of Sjögren's disease.

Final Diagnosis: Sjögren's disease without sicca symptoms with extra-glandular involvement in the form of distal renal tubular acidosis leading to hypokalaemic periodic paralysis.

Management: The patient was managed with intravenous potassium chloride infusion. Her weakness recovered within a day. Prednisolone was given at dosage of 1 mg/kg for 4 weeks with plan to taper after 4 weeks. She was also started on, potassium citrate solution to which patient responded. She was discharged with proper dietary instructions.

Case 3

A 35-year-old woman presented with sudden onset weakness of both lower limbs with loss of touch and cold sensation till nipples, and had difficulty in perceiving bladder and bowel sensation. On examination, she had a power of 1/5 in both lower limbs and absent deep tenon reflexes with positive Babinski's response. Sensory system showed reduced pain and temperature sensation till nipples (T-4 leval).

A diagnosis of Acute Transverse Myelitis was made and patient was given pulse intravenous methylpred nisolone injection.

Investigations: (Case 3)

CBC, ESR	10.5/8900/249000, 35 mm/hr P/S -Normocytic and Normochromic smear
CRP	14 mg/L (<10 mg/L)
LFT	T Bil 1.2 mg/dL SGOT 47 U/L, SGPT 42 U/L ALP 140 U/L
KFT	Urea 32 mg/dL, Cr 0.7 mg/dL
Serum Protein, Albumin	6.5g/dL, 3.8 g/dL
HbsAg, Anti HCV, HIV	Negative
CSF Examination	Protein 65 mg/dL Sugar 76 mg/dL Total Cells 30/hpf, DLC L90 N10
CSF Gram stain, C/S	Negative
ADA / Gene xpert	Negative
PCR (HSV, CMV, EBV, JE)	Negative

CSF evaluation showed mild lymphocytic pleocytosis with mildly elevated proteins, and an Infective work-up was negative. MRI of the Spine showed evidence of long segment myelitis from D2 to D6 thoracic vertebrae. Her NMO IgG/AQP4 levels were raised. She did not have evidence of optic neuritis, and a diagnosis of NMO spectrum disorder was made (NMOSD).

Other Investigations: (Case 3)

ANA by IF Method	**1:160 /Speckled Pattern**
ENA Profile	
anti dsDNA	Negative
Anti Sm	Negative
Anti Ro (SS-A)	**Positive 42 (<20)**
Anti La (SS-B)	**Positive 34 (<20)**
Anti RNP	Negative
Anti Histone	Negative

On further evaluation, ANA was positive and ENA profile revealed Anti Ro and Anti La positivity. However, she did not complain of sicca symptoms but gave history of intermittent joint pains with morning stiffness.

Her Schirmer's test and Tear film Break up time (TBUT) were normal. A Lip biopsy was done which showed extensive chronic lymphoplasmacytic infiltrates around glands and ducts with focus score >1 consistent with Sjögren's disease. She was administered 2 doses of Rituximab 1 gram 2 weeks apart to which she responded. Her power improved to 4/5 within 1 month and sensory symptoms also improved. Repeat MRI and continuation of immunosuppression is planned.

Discussion

Sjögren's disease (SD) is an autoimmune disorder affecting mainly glandular organs like major and minor salivary glands with prototypic manifestations such as dry eye and dry mouth, also known as sicca symptoms.

The interesting point in this case series is the absence of classical sicca symptoms even on objective evaluation like Schirmer's test, Tear film Break Up Test (TBUT) and F test suggesting normal tear production. However, salivary flow estimation could not be done. We want to highlight that all our patients presented with extra-glandular manifestations only.

In most of the case series of SD in Western literature, patients presented with classical sicca symptoms and parotitis[1,2]. Although it has been reported that almost 40 - 50% of cases presenting with neurological symptoms may not present with classical sicca symptoms, especially those presenting with CNS manifestations like demyelination or encephalopathy as compared to those presenting as peripheral neuropathy; however, they generally develop sicca symptoms later or show positive result on objective evaluation like Schirmer's and Tear film Break Up Test[3].

As far as Indian population is concerned, in a retrospective analysis *et al* 332 Indian patients by Sandhy, *et al* it was seen that sicca symptoms were the presenting manifestation in only 8 - 10% cases, although by further evaluation it was present in the majority (94%) of patients[4]. The authors divided their cohort into 2 groups, one with more sicca symptoms but with milder extra-glandular manifestations mainly musculoskeletal symptoms, while the other group of patients had less of sicca symptoms but more severe systemic manifestations, and higher titres of anti-Ro and La. Our patients resemble the latter group of patients.

Various studies have shown that extra-glandular manifestations are observed in 20 - 25% cases with musculoskeletal being the most common followed by cutaneous, renal, respiratory and neurological involvement[5,6].

In our first case a young patient presented with predominantly large joint polyarthralgia, pancytopenia, hepatitis (likely autoimmune), moderate splenomegaly, past history of upper GI bleed and purpuric skin rashes which are uncommon manifestations of SD. She also did not have sicca symptoms. However, arthralgias are the most common extra-glandular manifestation of SD but other manifestations such as moderate splenomegaly with pancytopenia and hepatitis are rare. Other differential diagnoses like portal hypertension, haematological disorders, tropical infections, RA, SLE, AIH and overlap syndrome were ruled out by appropriate investigations. High titres of anti-Ro and La made us suspect SD which was later confirmed by a lip biopsy.

Another unusual manifestation in these case was the presence of massive splenomegaly and transaminitis with bleeding manifestations. Very few case reports have mentioned such findings in SD. In one case report, the patient of SD had manifestations of type 2 autoimmune hepatitis along with massive splenomegaly which responded to steroids[7].

Renal involvement in SD varies from 5 - 10% all cases. It can occur in the form of distal RTA, tubulointerstitial nephritis, glomerulonephritis or IgA nephropathy. Diabetes insipidus and nephrocalcinosis have been observed in a few cases[8].

In the second case, patient presented with hypokalaemic paralysis. Generally, hypokalaemia is associated with metabolic alkalosis, so whenever it is associated with metabolic acidosis suspect distal RTA by measuring serum anion gap which should be normal along with a positive urinary anion gap and alkaline urinary pH (>5.5) in the presence of metabolic acidosis. SD was suspected in this case after serology showed high titres of anti-Ro and anti-La and was later confirmed by doing ultrasound evaluation of salivary glands and lip biopsy. She responded to potassium replacement and steroids.

In case 3, the patient presented with features suggestive of non-compressive myelopathy, diagnosed as Longitudinally Extensive Transverse Myelitis with NMOSD (NMO IgG and Aquaporin 4 positive) and responded to steroids and Rituximab.

Neurological manifestations in are common extra-glandular presentation with a prevalence of 8.5 - 70% in various case series[3], most common of which includes peripheral neuropathy, especially sensory polyneuropathy. Although motor neuropathy, mononeuritis multiplex, sensory ganglionopathy, and cranial neuropathy can also occur. CNS involvement is less common (2 - 25%)[9]. SD presenting as transverse myelitis has been reported in literature as case reports[10,11].

Cases of LETM with NMO spectrum disorder in a known case of SD have been reported[12,13], while in our patient it was the presenting feature. Also, in 30 - 40% cases, NMO antibody may be negative[14]. So, we should rule-out SD in all cases of LETM even if NMO antibody is negative and without classical sicca symptoms.

By reporting this case series we want to focus attention of readers to the fact that SD is not an uncommon disease as previously thought. Indian patients may not present with classical sicca symptoms but with various extra-glandular organs involvement like renal, neurological, respiratory,

hepatobiliary, and cutaneous. As a physician, it is important to be aware of these organs involvement and consider workup of serology, and USG of parotids which are simple non-invasive tests. Also, lip biopsy should be done in suspected cases as it is a OPD based minor procedure, with gratifying results.

Conclusion

SD is a common autoimmune connective tissue disorder with varying clinical presentations. It is a true multisystem disease. Diagnosis is easy to make in cases presenting with classical features. However, in our cases none of the patients had typical sicca symptoms, but all were serologically positive. A high index of suspicion especially in cases with hypokalaemic periodic paralysis, peripheral neuropathy and demyelinating diseases like myelitis should be there and awareness of various extra-glandular organs involvement is very essential. The importance of porforming a lip biopsy a minor procedure to confirm the diagnosis, us emphosised.

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