CASE SERIES

Atypical initial presentations of Sjogren's syndrome: a case series

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Abstract

Primary Sjogren's syndrome (pSS) typically presents with Sicca symptoms xerostomia and xeropthalmia. This study highlights atypical presentations of Primary Sjogren's syndrome posing diagnostic and therapeutic challenges.

Four female patients (median age 30 years, IQR = 15.5) with atypical pSS features, confirmed by positive Anti-Ro antibodies and negative lupus or rheumatoid arthritis tests, were treated between February and August 2023. PSS presented as erythema nodosum, soft tissue swelling with medium-vessel vasculitis, palpable purpura, and severe thrombocytopenia in these cases prior to Sicca symptoms. Initial treatment included steroids and hydroxychloroquine. Azathioprine, Methotrexate, and Cyclophosphamide were added as steroid-sparing agents. Three patients achieved remission. One patient with co-existing pulmonary tuberculosis (TB) died. Atypical features can occur in SS, requiring vigilance for diagnosis and individualised treatment.

Our series demonstrates the diverse atypical clinical features of Sjogren's syndrome, encompassing radiologic, histopathologic, laboratory abnormalities, and treatment guidelines, expanding the known spectrum of disease presentation and management.

Keywords: Primary Sjogren's syndrome, Takayasu arteritis, Medium vessel vasculitis, Palpable purpura, Thrombocytopenia.

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Introduction

Primary Sjogren's syndrome (pSS) is a systemic autoimmune disease, characterised by lymphocytic infiltration of exocrine glands. Usual manifestation of Sjogren's syndrome (SS) is Sicca symptoms such as xerostomia and xeropthalmia.[1] PSS also causes extra-glandular manifestations and maybe associated with the development of lymphoma. Secondary SS is associated with underlying systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).[1,2]

The prevalence of pSS in Europe is 0.05%-0.72%, annual prevalence is 3-10 new cases/100,000 population/year, female to male ratio is 14:1, and the most common age of onset is between the fourth and sixth decades of life.[2]

In this series we are presenting four patients who had atypical initial presentation of primary Sjogren's syndrome without typical initial manifestation of Sicca symptoms, while two of the patients developed Sicca symptoms later during the course of the disease.

Case Series

These patients were seen and managed at the Rheumatology Department, Shalamar Hospital, Lahore, between January 2023 and December 2023 from initial visit to subsequent follow-ups, except for Case-1, who was first seen in June 2020 with subsequent follow-ups later on. All four patients were females with median age of 30 years (IQR = 15.5). Autoimmune profile of all patients was suggestive of pSS with different and atypical initial presentations. One of the four patients (Case-3) unfortunately died, probably due to the complications of pSS and co-existing tuberculosis, although exact cause of mortality is not known. The rest of the three patients improved clinically. Lab data, autoimmune profile, and treatment regimen with doses of all patients are mentioned in Table-1.

Case-1: A 25-year-old female with no comorbidity, presented with red, tender nodules (erythema nodosum; EN) on both shins for 20 days with a history of low-grade fever and fatigue for one month without any Sicca symptoms. Systemic and musculoskeletal examinations were normal. Her autoimmune profile was suggestive of primary SS (Table 1), after infection causing EN, malignancy, drugs (penicillin, oral contraceptives, etc.), autoimmune disorders (SLE, Behcet's disease, Sarcoidosis, etc.) which may cause EN were ruled out. Her vitals were stable. Chest X-Ray was normal. Primary SS with EN was treated with Hydroxychloroquine (HCQ) and Prednisolone. She clinically improved on HCQ. She came for follow-up after two years when she was four-weeks pregnant and had signs and symptoms of dry mouth and dry eyes. On examination, she had a blood pressure of

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Table 1: Laboratory investigations performed for all the patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age (Years)	25	43	35	22
Initial Presentation	Primary Sjogren syndrome (pSS) with Takayasu arteritis: Initial presentation of pSS with Erythema Nodosum (EN)	Medium vessel vasculitis as initial presentation of pSS	Palpable purpura as initial presentation of pSS	Immune thrombocytopenia as initial presentation of pSS
Treatment	Pre-pregnancy: Prednisolone 40mg & HCQ 400mgDuring Pregnancy: Azathioprine 2mg/kg/day, Prednisolone 4omg/day, Methyldopa 1.5g/day, Nifedipine 60mg/day & HCQ 400mg/day	IV Methylprednisolone cumulative dose 3500mg, Prednisolone 1mg/kg/day in tapering dose, HCQ 5mg/kg/day Intravenous cyclophosphamide 500 mg bi-monthly for three months for induction remission then methotrexate was started for maintenance of remission.	IV Methylprednisolone cumulative dose 1500mg, Prednisolone 0.5/mg/kg/day, HCQ 400mg, IV Meropenem 2g/day for 5 days, Anti-Tubercular Therapy, and planned Azathioprine as a steroid sparing drug after 1 month of ATT.	IV Methylprednisolone pulse dose of one gram for 3 days followed by 750 mg for 4 days then oral prednisolone 1mg/kg/day in slow tapering dose with azathioprine 50mg/day. HCQ 5m/kg/day was also added to her treatment. Stable on Prednisolone and Azathioprine 100mg/day
Investigations				
Haemoglobin (n=12-16 g/dl)	12.1	11.9	7.4	8.8
Coomb's test	—-	——	Negative	Negative
Reticulocyte Count (n=0.2-2%)	—-	——		0.2
TLC (n=4-11x103/UL)	7.2	8.2	11.5	5.76
Lymphocytes (n=20-40%)	26	24	12	45
ALC (1000-4800 cell/mm^3)	1872	1968	1380	2265
Neutrophils (n=40-60%)	57	70	83	42
Platelets (n=150-450x103/UL)	295	300	414	2
ESR (n=10-20 mm/1^{st} hr)	30	40	42	80
CRP mg/dl (n=<5)	3.4	5	182	2.2
LFT:ALT (n= 5-40U/L)AST (n= 5-40U/L)	3328	2532	2724	3538
Creatinine (n=0.5-1.3 mg/dl)	0.9	0.8	3.2	0.5
Urine complete examination	Normal	Normal	Protein++Pus cell 20-22RBC 20-22P:C 0.8 (n=<0.2)	Normal
Blood culture & sensitivity	——	No growth	No growth	No growth
Urine culture & sensitivity	——-	No growth	Klebsiella(Sensitive to Meropenem)	——
BAL AFB/fungal/gram stainingculture & sensitivity	——	——-	AFB Staining & culture positive	——

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BAL GENE EXPERT MTB/RIF	———	———-	Positive, RIF sensitive	———-
Complement Level				
C3 (normal 83-193 mg/dl)	95	———	65	———
C4 (normal 15-57 mg/dl)	14	———-	7	———
ANA by IFA	1:100000 speckled	1:160 speckled	Negative	Negative
ENA by QUANTRIX				
Anti-Ro Antibodies (Positive > 1)	100	97	83	117
Anti-La antibodies (Negative < 6)	———-	67	12	————
Anti-dsDNA antibodies	Negative	Negative	Negative	Negative

150/100mmhg in right arm and 110/80mmhg in left arm. Feeble radial and brachial pulses were palpable on her left side as compared to the right with no audible bruit. Her systemic and musculoskeletal examinations were unremarkable.

Doppler ultrasound of the right upper limb arteries revealed irregular wall thickening and luminal narrowing in the distal radial and ulnar arteries, displaying biphasic arterial flow. On the left, a persistently monophasic blood flow pattern in all upper limb arteries indicated reduced peak systolic velocity, suggesting stenosis in both the subclavian arteries, as confirmed by magnetic resonance angiogram (Figure 1). Bilateral diffuse arterial changes with irregular luminal narrowing were observed in the lower limbs, with preserved blood flow up to the dorsalis pedis. Renal arterial Doppler ultrasound was normal. This patient with primary SS was diagnosed with Takayasu's Arteritis (TA) during the fourth week of pregnancy, and received treatment with Azathioprine, Prednisolone, and anti-hypertensives along with HCQ. Her pregnancy was complicated with pre-eclampsia and intrauterine growth retardation; she underwent a lower segment caesarean section at 32 weeks, delivering a healthy baby with a normal Apgar score. The patient remained in remission during pregnancy and afterwards on regular OPD follow-ups.

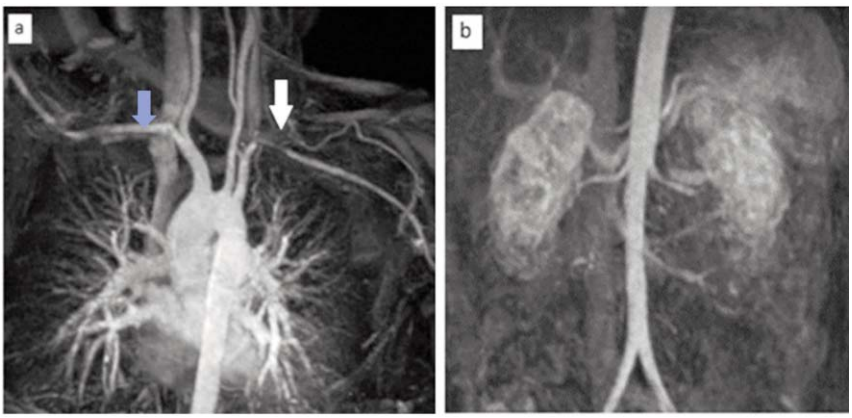

Figure-1: (Patient 1): Magnetic Resonance Angiogram (MRA); Chest (Figure 1a): considerable narrowing of the origin of left subclavian artery (white arrow) over a segment of 1.8 cm and mild narrowing of the right subclavian artery (blue arrow). Abdomen (Figure 1b): normal abdominal aorta, renal, and iliac arteries.

Case-2: A 43-year-old hypertensive housewife, initially suspected of medium vessel vasculitis based on a histopathology biopsy of a soft tissue swelling (Figure 2a, 2b & 2c), presented with a one-month history of painful swelling on the right jawline. Despite a prior 14-day antibiotic, the swelling persisted, accompanied by undocumented fever, migraines, fatigue, and insomnia. After two weeks she developed symptoms of mesenteric ischaemia, including severe post-prandial abdominal pain, diarrhoea, and vomiting. She had no current and past history of recurrent upper respiratory tract infection, tuberculosis, nephritis (haematuria/proteinuria), drug use (Minocycline, Hydralazine, Simvastatin, Allopurinol, Propylthiouracil, Isoniazid, Ethambutol, and anti-tumour necrotic factor (TNF) drugs). She had postural hypotension and tachycardia. Her examination revealed maxillary sinus

tenderness, and a 2 × 2cm oval, firm, tender, and mobile swelling over the right jaw, not adherent to underlying bone and overlying skin, no discolouration of overlying skin, with biopsy scar, and generalised abdominal tenderness. She had negative anti-HCV, HBsAg, HIV, stool culture, and a normal CT-angiogram of abdomen, chest X-ray, and echocardiography. This patient with primary SS and medium vessel vasculitis was treated with intravenous Methylprednisolone pulse and was later switched to oral Prednisolone 1mg/kg/day, HCQ, and Cyclophosphamide for induction of remission. She was switched to Methotrexate for maintenance of remission. Gastrointestinal symptoms were refractory to intravenous antibiotics but were improved on treatment with intravenous Methylprednisolone, and her jaw swelling gradually resolved without relapse, but on follow-up OPD visits she had complaints of dry mouth and dry eyes which were managed accordingly.

Case-3: A 35-year-old lady with no comorbidities presented with acute gastroenteritis, high-grade fever, and palpable purpura on legs for three to four days. She had a history of similar rash on legs, low-grade fever on-and-off for the last four months and arthritis. She was previously misdiagnosed as Henoch-Schoenlein purpura which was treated with oral steroids. She had no past history of recurrent respiratory tract infections refractory to antibiotic treatments, genital ulcers, or current or past history of viral illness (COVID-19). She had no history of haematological or visceral malignancy, no history of drug intake which may cause palpable purpura (Beta-lactams, Erythromycin, Clindamycin, Vancomycin, Sulphonamides, Furosemide, Allopurinol, NSAIDs (non-steroidal anti-inflammatory drugs), Amiodarone, Thiazides, Phenytoin, beta-blockers, TNF-alpha inhibitors, selective serotonin reuptake inhibitors, Metformin, Warfarin, Valproic acid, etc.).

On examination, the patient was febrile, hypertensive, having tachycardia and tachypnoea, dry tongue and oral cavity, oral ulcers, poor oral hygiene, and palpable purpura on both legs. Chest examination revealed bilateral decreased air entry and decrease vocal resonance. Bilateral pleural effusion was confirmed on chest X-ray. During work-up (Table 1) she was diagnosed with tuberculosis on broncho-alveolar lavage. Her skin biopsy showed leukocytoclastic vasculitis (Figure 2 d & e) along with the presence of primary SS on the basis of autoimmune profile.

She was given intravenous Methylprednisolone, antibiotic, and anti-tubercular therapy on admission along with HCQ. The patient's Sicca symptoms and rash improved. Rash, however, had previously recurred on tapering the steroid dose; therefore, she was discharged on oral steroid. Unfortunately, the planned initiation of Azathioprine treatment after one month of anti-tuberculosis therapy was not possible due to the patient's sudden and fatal decline from worsening dyspnoea, which occurred at home before the scheduled follow-up appointment.

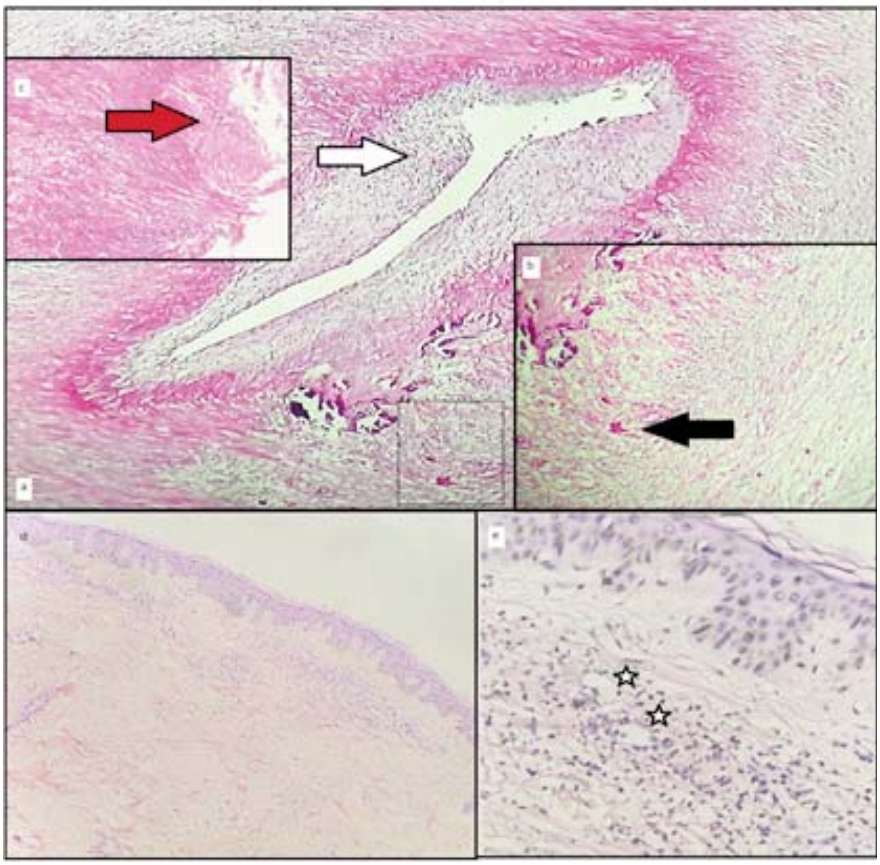

Figure-2: Figure 2a, b & c show Haematoxylin and Eosin (H&E) stained slide with a muscular artery showing lymphocytic infiltrate in vessel wall. A few ill-formed granulomas, one of which magnified (x50) to view multinucleated giant cells marked with a black arrow (Fig 2b). Vascular lumen is occluded partially by neutrophilic infiltration (white arrow). Disrupted internal elastic lamina (red arrow) (Fig 2c). Patient 3: Fig 2d & e show H&E stained biopsy of the skin showing a neutrophilic infiltration of the dermis (Fig 2d). Fig 2e (x100) shows dermal neutrophilic debris, showing karyorrhexis around small vessels which are showing distortion (Star).

Case-4: A 22-year-old young female came with a history of gum and heavy vaginal bleeding for one week during her postpartum period after the birth of her first child, without history of dry mouth and dry eyes, fever, and other signs or symptoms of infection. She had no current or previous history of arthritis, rash, weight loss, fever, diarrhoea, malaria, dengue, recurrent pregnancy losses, arterial or venous thrombosis, haematological malignancy. Drug history was also not significant for Furosemide, NSAIDs, Penicillin, Quinidine, Quinine, Statins, Sulfonamides, Linezolid, etc.

She was pale but the rest of the general, systemic, and musculoskeletal examinations were normal. Ultrasound of the abdomen was unremarkable and no evidence of transaminitis during pregnancy. This patient with primary SS and severe thrombocytopenia was treated with intravenous Methylprednisolone pulse followed by oral Prednisolone. Azathioprine and HCQ was also added to her treatment. She also received a whole blood transfusion and a mega unit of platelets. Gradual increase in platelets was observed without any relapse on current therapy.

Discussion

Erythema nodosum (EN) is a rare cutaneous manifestation of Sjogren syndrome occurring in only 4% of the cases compared to subcutaneous nodules (9%) and purpura (60%).[3] EN is a common acute nodular septal panniculitis, characterised by the sudden onset of painful erythematous, firm, solid, deep nodules or plaques, localised on extensor surfaces of the legs. Most common aetiologies of EN includes infections, drugs, malignancy, and inflammatory bowel disease.[4]

Systemic vasculitis is one of the rarest and most severe extra-glandular manifestations of primary Sjögren's syndrome (pSS) reported in only 10% of the cases, accounting for the increased morbidity and mortality of the disease, cryoglobulinaemic vasculitis is the most frequent type of systemic vasculitis in pSS. Anti-neutrophil cytoplasmic antibody-associated, large- and medium- vessel vasculitis are described only in sporadic cases.[5] Case-1 developed Takayasu arteritis (diagnosed on ACR/EULAR classification criteria)[6] after diagnosis of pSS. This was also seen in a Japanese girl who was diagnosed as seronegative pSS at nine years of age with evidence of lymphocytic sialadenitis on lip biopsy who developed TA at the age of 14 years, five years later.[7] Rarely, medium vessel vasculitis resembling polyarteritis nodosa without aneurysm can occur in pSS.[8] Likewise, palpable purpura with leukocytoclastic vasculitis is occasionally the initial presentation of pSS.[9]

In literature, recommended treatments for vasculitis in pSS, regardless of the organ involved, is immunosuppression with high dose intravenous Methylprednisolone for three days, in combination of Azathioprine, Mycophenolate Mofetil, or Cyclophosphamide. Treatment of cutaneous vasculitis may be initially carried out with an oral Glucocorticoid (0.5–1mg/kg/day) or with intravenous Methylprednisolone (depending on the severity of the condition) plus steroid-sparing immunosuppressant. Cases refractory to initial treatment can be treated with Rituximab.[10] Case-1, SS with Takayasu arteritis, was treated with Prednisolone and Azathioprine. Case-2, SS with medium vessel vasculitis and mesenteric ischaemia, was treated with intravenous Methylprednisolone pulse followed by oral Prednisolone and bi-monthly intravenous Cyclophosphamide for induction of remission and Methotrexate for maintenance of remission Case-4 SS with immune thrombocytopenia with intravenous Methylprednisolone pulse, then oral Prednisolone, HCQ and Azathioprine. Initiation of DMARDS was delayed in Case-3 due to pulmonary TB; however, the patient died due to complication of TB.

Wu J, et al reported that mild to severe thrombocytopenia (≤50 ×109/L) was noted in 5.1% in pSS, affecting females (95.3%) with mean age of 51.69 (±12.43) years. Patients with thrombocytopenia had hypocomplementaemia, and low prevalence of Sicca symptoms.[11] First line therapy for immune thrombocytopenia in pSS includes glucocorticoid with immunoglobulins. Cyclophosphamide, cyclosporine, and Azathioprine can be used as steroid sparing agents. Refractory cases can be treated with Rituximab, Eltrombopag, and Splenectomy.[12] Case-4 had severe thrombocytopenia with history of bleeding, but she did not have Sicca symptoms, constitutional or other extra-glandular features of pSS initially. Her complement levels were not done due to affordability issues. She responded well to Glucocorticoid and Azathioprine without any relapse.

Strength and limitations: This is a first-of-its-kind study in Pakistan highlighting the spectrum of atypical features of pSS. Moreover, no recent data is available on the management of vasculitis in pSS. The limitations of the study identified were: limited lip biopsy specimens, unavailability of focus scoring, and limited expertise available for clinical assessment of Sicca symptoms (Schirmer test, Ocular staining test, and salivary flow rate). Moreover, CT angiogram protocols required to detect mesenteric ischaemia/vasculitis were not available in most of the centres. In future well-designed studies are needed to explore the impact of these presentations on

the disease's natural progression and patient outcomes, addressing the limitations.

Conclusion

Young to middle aged females with symptoms of cutaneous or systemic vasculitis, or unexplained thrombocytopenia should be evaluated for underlying pSS even in the absence of predominant Sicca symptoms. Prompt diagnosis should be made and extracted nuclear antigen testing should be performed after excluding all related causes. Early initiation of treatment with steroids and DMARDs can minimise morbidity and mortality in such patients.

Consent: Consent of all patients was obtained for publishing their cases.

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FN: Conceived ideas, designed, case summaries, clinical and lab data, and editing final draft.
SKI: Literature review and writing.
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