Sjogren's syndrome with multi-organ extraglandular manifestations - a case report

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ABSTRACT

Background: Primary Sjogren's syndrome is an autoimmune disorder characterized by diminished lacrimal and salivary gland functions. Other than the exocrine gland involvement, it is also known to affect other visceral organs, resulting in extraglandular manifestations. Obvious cardiac involvement is rare, with pericardial effusions being the commonest feature. Sjogren's syndrome is also known to cause renal involvement, with tubulointerstitial nephritis being the most typical.

Case Presentation: We report of a 37-year-old female with primary Sjogren's syndrome who developed bilateral parotid swelling, generalized edema, palpable purpura, arthralgias, and dyspnea. Skin biopsy of the purpuric lesions demonstrated leukocytoclastic vasculitis. Echocardiography revealed a low left ventricular ejection fraction (~45%) and a small pericardial effusion (10 mm). These findings together with an abnormally raised NT-proBNP of 2,424 pg/ml were highly suspicious for an autoimmune myocarditis. Proteinuria (1.8 g/24 hours) was present and renal biopsy confirmed membranoproliferative glomerulonephritis. Cryoglobulins were positive. Upon commencement of the treatment, with intravenous bumetanide, pulsed methylprednisolone, and enalapril, the patient experienced rapid symptom resolution.

Conclusion: The extraglandular manifestations of primary Sjogren's syndrome are many and may affect more than one organ at the same time. Although rare, autoimmune myocarditis is an important differential in Sjogren's syndrome patients who present with dyspnea.

Keywords: Sjogren's syndrome, cryoglobulinemia, vasculitis, myocarditis, glomerulonephritis, case report.

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Background

Primary Sjogren's syndrome is a connective tissue disorder characterized by lymphocytic infiltration of exocrine glands resulting in diminished lacrimal and salivary gland functions. It is also known to affect other visceral organs, resulting in extraglandular manifestations [1]. These arise secondary to diverse pathogenetic mechanisms, often due to autoimmune-induced inflammation of ductal epithelial structures of various organs. More severe forms of the extraglandular disease less commonly arise from immune complex deposition, often in the context of cryoglobulinemia with higher degrees of morbidity and mortality [2].

Case Presentation

We report of a 37-year-old Maltese female who was first diagnosed with primary Sjogren's syndrome (pSS) in 2016, following the subacute development of xerostomia and keratoconjunctivitis sicca. Autoantibody profile at the time revealed the presence of antinuclear antibodies (ANA) (1/640), as well as anti-Sjogren's syndrome type A antibody (anti-SSA) (3.4; normal range: 0.1-1.0 ratio). A labial gland biopsy was performed, which showed focal lymphocytic sialadenitis, confirming the diagnosis of pSS.

One year following the diagnosis, the patient reported of bilaterally swollen parotid glands and the recurrent development of palpable non-pruritic lesions over both lower limbs. These lesions were episodic in nature and typical, which lasted up to a week prior to spontaneous resolution. She denied any history of weight loss, fever, or night sweats. Physical examination confirmed bilateral firm and non-tender symmetrical parotid swellings. No organomegaly or lymphadenopathy was detected. An ultrasound scan of her parotid glands showed extensive multi-cystic replacement in the presence of glandular atrophy. Immunosuppressive therapy was not initiated at this stage as the patient preferred to omit treatment.

She was reviewed again in June 2018 after developing worsening, generalized edema, persistent palpable purpura (Figure 1), arthralgias and dyspnea, which was worse on lying down. Examination revealed an elevated blood pressure of 150/90 mmHg and a regular tachycardia at 108 bpm. She was afebrile, heart sounds were normal, and chest auscultation was clear. Bilateral pitting edema of both lower limbs was present up to the thighs and included the genitalia.

Laboratory investigations reconfirmed the presence of ANA (>1/1,000) and anti-SSA antibodies (7.3), together with the present anti-SSB antibodies (7.0; normal range: 0.1-1.0 ratio). Other extractable nuclear antigens, including anti-double stranded DNA, anti-ribonucleoprotein antibodies, and anti-Smith antibodies, were negative. The rheumatoid factor was raised at 70 U/ml (normal range: 0-15 U/ml). Additional laboratory measures included a raised erythrocyte sedimentation rate (ESR) of 53 mm in the first hour (normal range: 10-14 mm; first hour), NT-proBNP of 2,424 pg/mL (normal range: 5-125 pg/ml), a reduced estimated glomerular filtration rate (at 53 mls/minute/1.73 m^2), and a normal serum albumin of 33 g/l (normal range: 32-52 g/l). A chest X-ray demonstrated a small left basal pleural effusion. Complement levels were low with a C3 of 292 mg/l (normal range: 900-1,800 mg/l) and a C4 of <20 mg/l (normal range: 100-400 mg/l). Immunoglobulin levels and serum protein electrophoresis were within normal limits (Table 1). A skin biopsy of the purpuric lesions was consistent with leukocytoclastic vasculitis (LCV).

In view of a rapidly deteriorating clinical picture, the patient required admission to hospital. On admission, the electrocardiogram was normal. An in-patient transthoracic echocardiogram (TTE) was performed, which showed a reduced left ventricular ejection fraction (LVEF) of ~45%, a moderately dilated left ventricle (Figure 2), and a severely dilated left atrium together with a small pericardial effusion (10 mm). TTE findings together with raised cardiac biomarkers and the patient's clinical characteristics were suggestive of heart failure secondary to autoimmune myocarditis.

The 24-hour urinary collection showed a protein estimation of 1.8 g/24 hours (normal range: 1-150 mg/24 hour). Urine output was adequate. An urgent renal biopsy was also performed, confirming a membranoproliferative pattern of glomerulonephritis (MPGN). Type II cryoglobulins were positive. Hepatitis and HIV screens were negative.

Treatment was commenced with intravenous pulsed methylprednisolone (1 g daily for 3 days), bumetanide, and enalapril. After 3 days, corticosteroids were switched

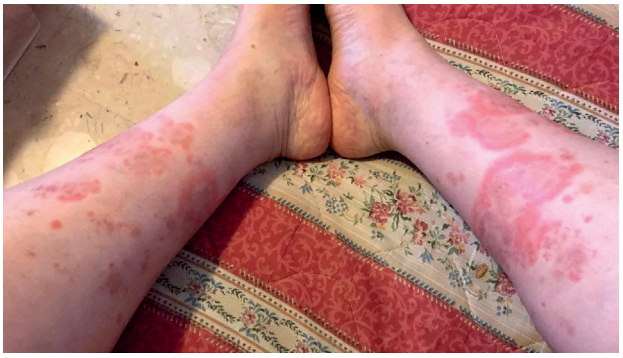

Figure 1. *Purpuric lesions with resultant LCV on skin biopsy.*

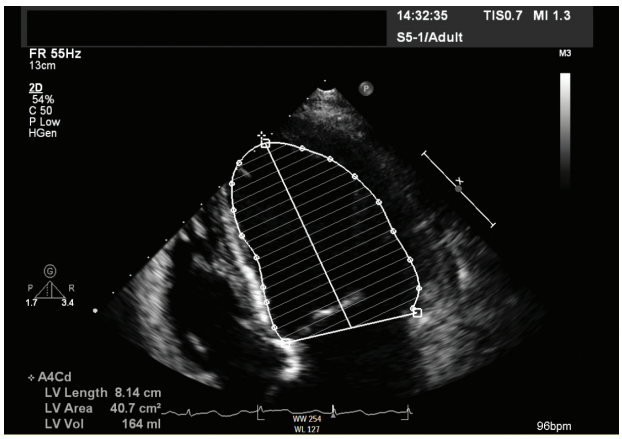

Figure 2. *Pre-treatment echocardiogram shows a moderately dilated left ventricle with an end-diastolic volume of 164 mls.*

Table 1. *Serum immunology results.*

Investigation	Normal range	Patient immunology June 2018
ANA	Absent [titre]	>1/1,000
ENA	0.0-19.9 RU/ml	146.2
Anti-SSA antibody (Ro)	0.0-1.0 index value	7.3
Anti-SSB antibody (La)	0.0-1.0 index value	7.0
Rheumatoid factor	0-15 U/ml	70
C3	900-1,800 mg/l	292
C4	100-400 mg/l	<20
Ig A	0.70-4.00 g/l	2.39
Ig G	7.01-16.0 g/l	8.7
Ig M	0.40-2.30 g/l	0.81
Anti-dsDNA	0.0-100.0 IU/ml	13.7
Anti-Smith	0.0-1.0 index value	0.4
Anti-RNP	0.0-1.0 index value	0.3

ANA, antinuclear antibodies; ENA, extractable nuclear antigen; Anti-SSB antibody, anti-Sjogren's syndrome type B antibody; Anti-SSA antibody, anti-Sjogren's syndrome type A antibody; C3, Complement 3; C4, Complement 4; Ig, Immunoglobulin; Anti-dsDNA, anti-double stranded DNA; Anti-RNP antibodies, anti-ribonucleoprotein antibodies.

Table 2. *Timeline of serum biochemistry results.*

Investigation	Normal range	August 2016 (At diagnosis)	June 2018 (On hospital admission/ before treatment)	August 2018 (Two months after treatment initiation)
NT-proBNP	5-125 pg/ml		2,424	123
ESR	10-14 mm 1st hour	5	53	5
Creatinine	45-84 umol/l	59	107	74
eGFR	90-120 mls/min/1.73m^2	107	53	81
Troponin	3-14 ng/l		12	
Urinalysis proteins	Negative (mg/dl)	Negative	150	Negative
24-hour urinary protein	1-150 mg/24 hour		1,883.4	551.6

NT-proBNP, N-terminal pro b-type natriuretic peptide; ESR, erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate.

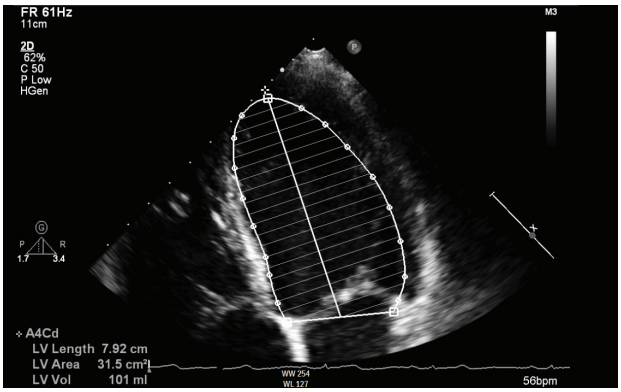

Figure 3. *Post-treatment echocardiogram shows a normal left ventricle with an improved end-diastolic volume at 101 mls.*

to 40 mg of oral prednisolone daily. Over the next few days, the patient experienced rapid resolution of her generalized edema, rash, arthralgias, and dyspnea. She lost a total of 15 kg bodyweight over 14 days. A cardiac magnetic resonance scan performed 6 days after commencing corticosteroids was unremarkable.

Following discharge, the patient remained well. Mycophenolate mofetil (MMF) was started as a steroid-sparing agent. Laboratory measures 2 months later revealed an NT-proBNP of 123 pg/ml, ESR of 5 mm in the first hour, and improvement in complement levels (C3: 478 mg/l; C4: 62 mg/l). Urinary collection after 1 month showed a residual proteinuria of 0.5 g/24 hours (Table 2). A repeat TTE performed 3 months later showed normalization of left atrial and ventricular volumes (Figure 3), and complete resolution of the pericardial effusion with normalization of LVEF (>60%).

Discussion

Severe cardiac involvement is very rarely associated with pSS, with valvular regurgitation, pulmonary hypertension, and asymptomatic pericardial effusions being reported as the most common manifestations [3].

pSS complicated with autoimmune myocarditis is rare and most of what is known of the condition is limited to case reports [4-6]. Recognition and prompt treatment of such cases are important as myocarditis has been the cause of sudden cardiac deaths in around 10% of the cases [7]. The precise mechanism by which cryoglobulinemic vasculitis affects the myocardium remains unclear, but it appears to be secondary to a small vessel vasculitis involving the coronary microcirculation [8]. An endomyocardial biopsy remains the gold standard for the diagnosis of myocarditis [9]; this was not performed in the present report due to the invasive nature of the procedure. The combination of clinical and non-invasive diagnostic findings, however, strongly implicated an autoimmune, steroid-responsive myocarditis.

Immunosuppression with corticosteroids is the main form of treatment of autoimmune myocarditis, together with steroid sparing agents such as cyclosporin, azathioprine, and cyclophosphamide [7]. Lack of proper clinical comparative studies, however, means that the optimal immunosuppressive treatment in such instances remains uncertain. The maintenance of normal LVEF and the absence of symptoms in this case were achieved with a tapering course of prednisolone together with mycophenolate mofetil, demonstrating the latter to be an effective form of immunosuppression in such cases.

In terms of renal involvement, pSS is most associated with an interstitial nephritis. Glomerulonephritis is usually of the membranoproliferative histological subtype, with other forms, such as the mesangial or membranous types, being the less common forms. MPGN, in such cases, is mainly attributed to the inflammation caused by the deposition of circulating immune complexes within the glomerulus, oftentimes with underlying type II cryoglobulins, and is usually a late complication in pSS patients [10].

Immunosuppression is necessary to eliminate the remaining disease in glomerulonephritis and retain normal kidney function. Optimal treatment type and duration vary depending on the patient's characteristics and the physician's judgment; however, corticosteroids together with other agents, such as MMF, rituximab, or cyclophosphamide, are described as reasonable options in glomerulonephritis [10]. MMF in this case resulted in the

normalization of kidney function together with a significant reduction in residual proteinuria.

Few cases have been described where pSS has been associated with multi-organ involvement, especially concurrent cryoglobulinemic glomerulonephritis and myocarditis. The combination of this patient's clinical, cardiac, and renal findings, along with her rapid improvement following immunosuppression, strongly suggest causality. This case demonstrates that autoimmune myocarditis is an important differential to consider in pSS patients who present with dyspnea. Additionally, despite interstitial nephritis being the commonest renal manifestation of pSS, clinicians should remain cautious for the presence of glomerulonephritis, especially in the presence of type II cryoglobulinemia; kidney biopsy remains an essential investigation that should always be considered in such patients.

Conclusion

The extraglandular manifestations of primary Sjogren's syndrome are many and may affect more than one organ at the same time. Although rare, autoimmune myocarditis is an important differential in Sjogren's syndrome patients who present with dyspnea.

What is new?

Pericardial effusions and interstitial nephritis are the commonest heart and kidney complications of Sjogren's syndrome. This case highlights a case of Sjogren's syndrome with concurrent multi-organ involvement - a rare occurrence (cryoglobulinemia, myocarditis, and glomerulonephritis). The best treatment in such cases is unknown. This patient was treated successfully with a high dose of steroids and mycophenolate mofetil. Autoimmune myocarditis is an important differential in Sjogren's syndrome patients who present with dyspnea.

List of Abbreviations

ANA	Anti-nuclear antibodies
Anti-dsDNA	Anti-double stranded DNA
Anti-RNP antibodies	Anti- ribonucleoprotein antibodies
Anti-SSA antibody	Anti-Sjogren's syndrome type A antibody
Anti-SSB antibody	Anti-Sjogren's syndrome type B antibody
C3	Complement 3
C4	Complement 4
eGFR	Estimated glomerular filtration rate
ENA	Extractable nuclear antigen
ESR	Erythrocyte sedimentation rate
Ig	Immunoglobulin
LCV	Leukocytoclastic vasculitis
LVEF	Left ventricular ejection fraction
MMF	Mycophenolate mofetil
MPGN	Membranoproliferative glomerulonephritis
NT-proBNP	N-terminal pro B-type natriuretic peptide
pSS	Primary Sjogren's syndrome
TTE	Transthoracic echocardiogram

Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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References

1. Stefanski AL, Tomiak C, Pleyer U, Dietrich T, Burmester GR, Dorner T. The diagnosis and treatment of Sjögren's Syndrome. Deutsches Arzteblatt Int. 2017;114(20):354–61. https://doi.org/10.3238/arztebl.2017.0354
2. Voulgarelis M, Tzioufas AG, Moutsopoulos HM. Renal involvement in primary Sjögren's syndrome: natural history and treatment outcome. Clin Exp Rheumatol. 2008;26(5 Suppl 51):S66–71.
3. Vassiliou VA, Moyssakis I, Boki KA, Moutsopoulos HM. Is the heart affected in primary Sjögren's syndrome? An echocardiographic study. Clin Exp Rheumatol. 2008;26(1):109–12.
4. Golan TD, Keren D, Elias N, Naschitz JE, Toubi E, Misselevich I, et al. Severe reversible cardiomyopathy associated with systemic vasculitis in primary Sjögren's syndrome. Lupus. 1997;6(6), 505–8. https://doi.org/10.1177/096120339700600605
5. Kau CK, Hu JC, Lu LY, Tseng JC, Wang JS, Cheng HH. Primary Sjögren's syndrome complicated with cryoglobulinemic glomerulonephritis, myocarditis, and multi-organ involvement. J Formosan Med Assoc. 2004;103(9):707–10.
6. Levin MD, Zoet-Nugteren SK, Markusse HM. Myocarditis and primary Sjögren' s syndrome. Lancet. 1999;345(9173):128–9. https://doi.org/10.1016/S0140-6736(99)02251-5
7. Bracamonte-Baran W, Čiháková D. Cardiac autoimmunity: myocarditis. Adv Exp Med Biol. 2017;1003:187–221. https://doi.org/10.1007/978-3-319-57613-8_10
8. Ali MA, Kayani WZ, Linzie BM, Punjabi GV, Wetmore JB. Myopericarditis in a patient with hepatitis C and cryoglobulinemic renal disease. Clin Case Rep. 2017;5(5):616–20. https://doi.org/10.1002/ccr3.788
9. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34(33):2636–48. https://doi.org/10.1093/eurheartj/eht210
10. Goules A, Geetha D, Arend LJ, Baer AN. Renal involvement in primary Sjögren's syndrome: natural history and treatment outcome. Clin Exp Rheumatol. 2019;37 Suppl 118(3):123–32.

Summary of the case

1	**Patient (gender, age)**	Female, 37-year-old
2	**Final diagnosis**	Primary Sjogren's syndrome with cryoglobulinemia causing autoimmune myocarditis and glomerulonephritis
3	**Symptoms**	Generalized edema, persistent palpable purpura, arthralgias, and dyspnea
4	**Medications**	Corticosteroids, bumetanide, enalapril, and mycophenolate mofetil
5	**Clinical procedure**	Methylprednisolone 1 g daily x3 days, prednisolone 40 mg daily with a tailoring regimen, bumetanide 1 mg three times daily, enalapril 5 mg daily, and mycophenolate mofetil 1 g twice daily
6	**Specialty**	Immunology