CASE REPORT

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Anti-ds DNA Negative Lupus Nephritis with Secondary Sjogren's Syndrome

P Rajesh, Meenakshi Kalyan**, Dwarabandham S Rakshaha Siridhan*, Raghunandhan****

Abstract

Systemic lupus erythematosus and Sjogren's syndrome co-exist with presence of multiple circulating autoantibodies and variable prognosis. A middle-aged female presented with polyarthralgia, photosensitivity rash on the face and ear lobules, dyspnoea, swelling of both lower limbs with reduced urine output since few months. General physical examination showed pallor, poedal oedema, skin hyperpigmentation in malar prominence and both ears, BP - 160/90 mmHg. Eye examination showed grade 3 hypertensive retinopathy and positive Schirmer's test. Investigations revealed anaemia with leucopenia, creatinine - 1.48 mg/dl, low C3 levels, urine routine examination showed proteinuria and hematuria. USG abdomen showed bilateral grade 2 renal parenchymal disease. Echocardiography showed moderate conc LVH, minimal pericardial effusion. RA factor was positive. ANA showed RO 52 positive, SSA RO 60 positive and anti-ds DNA negative which was confirmed by ELISA. Renal biopsy confirmed diffuse proliferative glomerulonephritis lupus nephritis class IV. Labial biopsy revealed Sjogren's syndrome. She was treated with intravenous methylprednisolone, cyclophosphamide and hydroxychloroquine, leading to remission.

Key words: Systemic lupus erythematosus, secondary Sjogren's syndrome.

Introduction

The association of Sjogren's syndrome (SS) and systemic lupus erythematosus (SLE) was first highlighted in a case series published by Heaton in 1959[1]. The link between these 2 diseases was strengthened by positive anti-Ro and anti La antibodies in common to both diseases. The relationship between the 2 disease processes is debated. SS may be a secondary manifestation of SLE with autoimmune exocrinopathy. The anti-double stranded DNA antibodies (anti-ds DNA) are a specific marker for SLE associated with renal involvement by their deposition in glomeruli, subendothelial an subepithelial spaces, mesangium, basement membrane and tubules. The interaction with toll like receptor 9 (TLR 9), anti-ds DNA complexed with DNA could determine the activation of dendritic cells with consequent B and T-cells activation and the release of proinflammatory cytokines[2]. Despite the central role of these antibodies in the disease pathogenesis, a percentage of SLE patients ranging from 2 to 30% result negative for anti-ds DNA[3]. Association of Anti-Ro antibody alone with lupus nephritis is less known in literature. The prevalence of secondary Sjogren's syndrome (sSS) in SLE is 14 % - 17.8%[4]. We report a rare case of Anti-ds DNA negative lupus nephritis with sSS.

Case report

A 42-year-old female with no past medical history presented with pain in bilateral interphalangeal joints, dryness of mouth and eyes for 6 months, photosensitivity rash on the face (Fig. 1) and ear lobules (Fig. 2) for 3 months, facial puffiness, dyspnoea on exertion, swelling of both lower limbs and reduced urine output for 2 months. There was no significant family history or drug history. She was married with 3 children and had regular menstrual cycles. General physical examination showed pallor, bilateral pitting pedal oedema, facial puffiness, skin hyperpigmentation in malar prominence and both ears. P - 86/min, regular, BP - 160/90 mmHg, JVP not raised. Joint tenderness was present in bilateral proximal and distal interphalangeal joint of index finger and 3rd finger without redness or swelling. Fundus showed grade 3 hypertensive retinopathy. Respiratory, cardiovascular, abdomen and neurological system were within normal limits. Investigations revealed Hb - 7.9 g/dl, WBC - 3,500/cumm, platelets - 1,50,000, DLC - N 67, L20 M8 E3, ESR - 56 mm/hr. Peripheral smear showed microcytic hypochromic anaemia with leucopenia, creatinine - 1.48 mg/dl, urea - 49.2 mg/dl, uric acid - 7.4 mg/dl. LFT, electrolytes, lipids, thyroid profile, ECG, CXR were normal. RA factor was positive. ANA by ELISA showed 2+ (Titres > 1: 160), ANA 15 screen by Line Immuno assay method (LIA) showed RO 52 positive, SSA RO 60 positive, anti-ds DNA and anti-U1 RNP were negative. HIV, HbsAg, Anti-HCV and Anti-CCP were negative. Anti-ds DNA confirmed by ELISA was negative and positive for RO 52 and SSA RO 60 antibodies. Urine routine microscopy

Post-Graduate Student, **Professor, ***Assistant Professor, Department of Medicine, Vydehi Institute of Medical Science and Research Centre, Whitefield, Benguluru - 560 066.

Corresponding Author: Dr Meenakshi Kalyan, Professor, Department of Medicine, Vydehi Institute of Medical Science and Research Centre, Whitefield, Benguluru - 560 066. Phone: 9850342276, E-mail: drmeenakshikalyan@gmail.com.

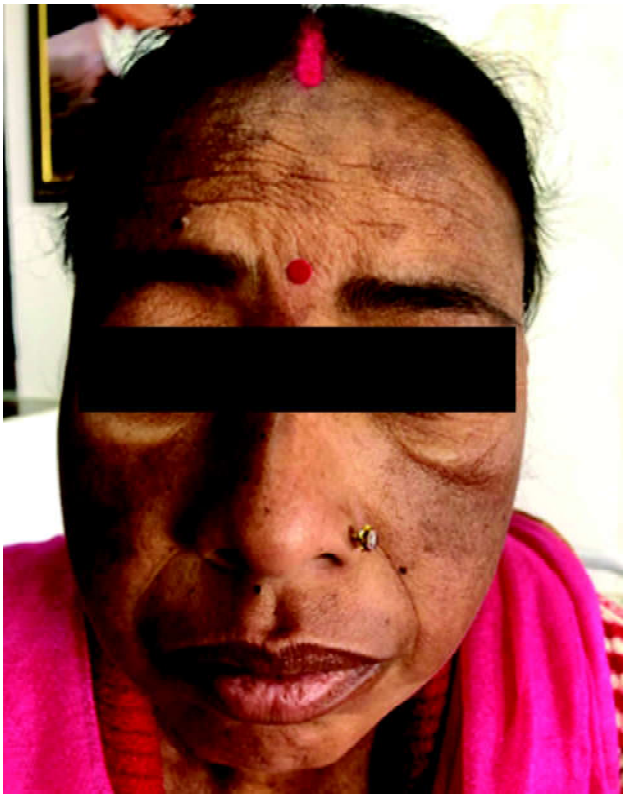

Fig. 1: *Hyperpigmented skin lesion with photosensitivity on malar prominence.*

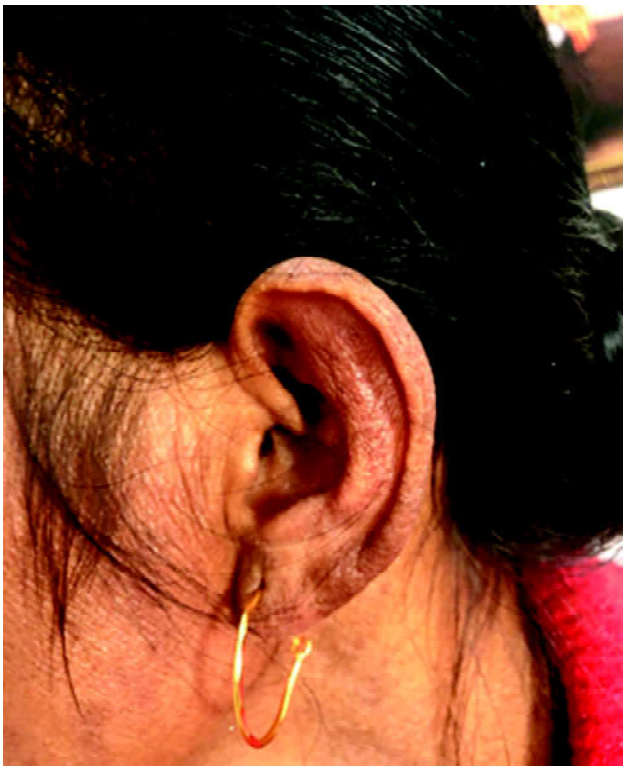

Fig. 2: *Hyperpigmented skin lesion with photosensitivity on ear lobules.*

showed protein - 500 mg/dl, RBC - 33 - 34/hpf. There were no dysmorphic RBCs or casts. Urine micro total protein - 783 mg/dl, urine protein: creatinine ratio of 7.04, complement levels of C3 were 14.7 mg/dl (Low) and C4 - 2.38 mg/dl (Low). Urine culture showed no growth. USG abdomen showed both kidneys normal in size, shape and maintained cortico-medullary differentiation with bilateral grade 2 renal parenchymal disease. Echocardiography showed moderate conc LVH, minimal pericardial effusion, grade 2 diastolic dysfunction, EF - 58%. Eye examination revealed severe dry eyes, tear film breakup time of 4 seconds in both eyes, tear meniscus height of 0.5 mcm in both eyes, Schirmer's test was 4 mm in right and left eye. There was no evidence of parotid gland enlargement or salivary gland swelling. Renal biopsy revealed diffuse

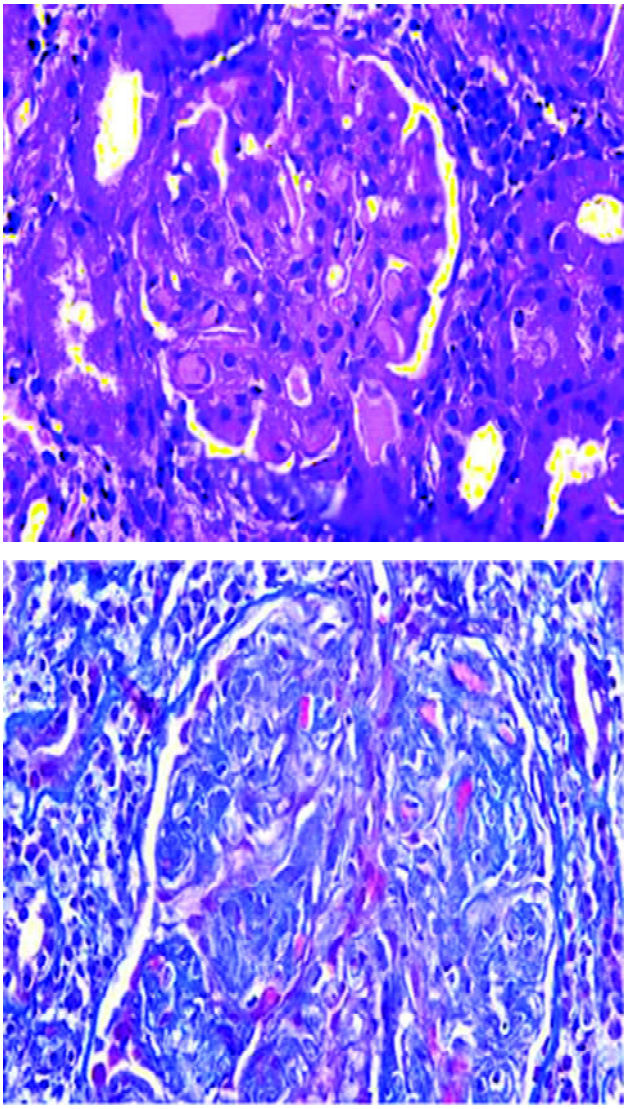

Fig. 3 and 4: *Renal biopsy showing diffusely thickened glomerular basement membrane and 13/18 glomeruli showing wire loop lesions and hyaline thrombi in majority of the glomeruli.*

endocapillary hypercellularity with lobular accentuation. 1/18 glomerulus showed partial cellular crescent, diffusely thickened glomerular basement membrane and 13/18 glomeruli showed wire loop lesions and hyaline thrombi in majority of the glomeruli (Fig. 3 and 4). Tubulointerstitial findings in renal biopsy revealed no chronic damage within the cortex, tubules containing uromodulin casts, no RBC casts seen, interstitium with moderate mixed inflammatory infiltrate consisting of few polymorphs, lymphocytes, and abundant plasma cells. Active tubulitis was present. Morphological and immunofluorescence features of diffuse proliferative glomerulonephritis, lupus nephritis class IV with activity index of 13/24 (Fig. 5). SLEDAI score was 16 (Presence of arthritis, haematuria > 5 RBCs/HPF excluded infection, stone, presence of proteinuria, new rash, low complement). Labial biopsy measuring 1.2 x 1 x 0.5 cm in dimensions with hematoxylin (Fig. 6) and eosin stain (Fig. 7) showed non keratinised squamous epithelium with connective tissue of salivary gland consisting of mucous acini. At least 2 foci (> 50 mononuclear infiltrate) of periductal lymphocytic infiltrate seen adjacent to normal acini. Calculated focal score of 3 suggestive of Sjogren's syndrome. Systemic lupus erythematosus Disease Activity Index (SLEDAI) score was 16. Score of 6 and above are considered to be consistent with active disease requiring therapy. Based on the above findings of renal biopsy, labial biopsy, positive anti-RO 52 and SSA RO 60 antibodies, SLEDAI score of 16, diagnosis of anti-ds DNA negative lupus nephritis with secondary Sjogren's syndrome was made. She was treated with intravenous pulse therapy with methylprednisolone 500 mg for 3 days followed by injectable cyclophosphamide 500 mg i.v., once a month for 6 months, T. hydroxychloroquine 200 mg BD, T. cilnidipine 10 mg OD, T. Prednisolone 40 mg OD, and subsequently started on Telmisartan 20 mg OD. Follow-up after 6 months showed s. creatinine of 1.2 mg/dl and urine micro total protein was 360 mg/dl.

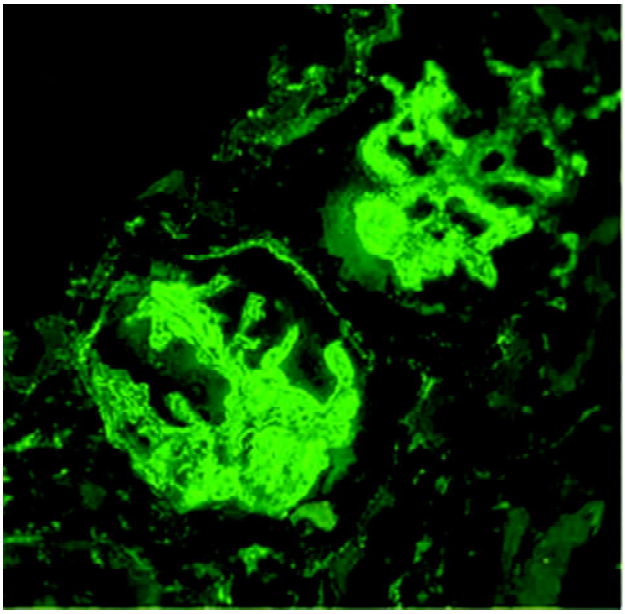

Fig. 5: *Immunofluorescence features of diffuse proliferative glomerulonephritis – lupus nephritis class IV.*

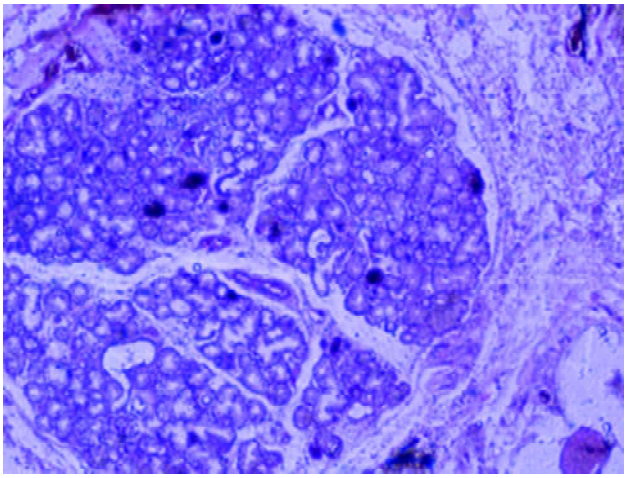

Fig. 6: *Labial biopsy haematoxylin stain showing > 50 mononuclear infiltrates of periductal lymphocytic infiltrate suggestive of Sjogren's syndrome.*

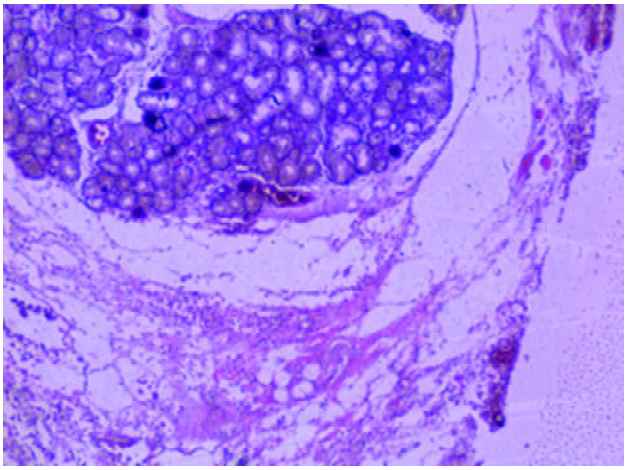

Fig. 7: *Labial biopsy eosin stain showing > 50 mononuclear infiltrates of periductal lymphocytic infiltrate suggestive of Sjogren's syndrome.*

Discussion

SLE, a serologically diverse, chronic autoimmune disease involving multisystem is diagnosed after consideration of clinical, laboratory, pathological findings, and validated classification systems which include the revised American College of Rheumatology (ACR) criteria and the Systemic Lupus International Collaborating Clinics (SLICC) criteria[5].

The 2 main types of renal injury identified on renal pathology are immune complex deposition disease as characterised by the known classifications of lupus nephritis (LN) and non-immune complex disease including thrombotic microangiopathy, podocytopathy and tubulointerstitial disease. Immunofluorescence (IF) is characteristic for the presence of the 3 classes of immunoglobulins (IgG, IgM, IgA) and classic and alternative complement pathway deposits (C3, C4, C1q). This patient presented with simultaneous renal and extrarenal manifestations of SLE. Very few patients were identified in the literature with renal and extra-renal manifestations and absent serologies for SLE. Among the autoantibodies which have been detected in the sera of patients with autoimmune disease are anti-Ro60 (anti-SSA) and anti-Ro52 (TRIM21)[6]. It is reported that anti-Ro60 is detected in SLE and Sjogren's syndrome with a much higher percentage in cutaneous lupus erythematosus while anti-Ro52 is associated with more diseases as interstitial lung disease, congenital heart block, neoplastic diseases and infections. Elsayed *et al*[7] reported that patients with LN class-III and class-IV (focal and diffuse) had the highest frequency of positivity for the five autoantibodies, where 66.6% for anti-dsDNA, 61% for anti-nucleosome, 67.38% for anti-histone, 52.37% for anti-Ro60, and 44.72% for anti-Ro52. Fabrizio *et al*[8] reported that renal involvement was more frequent in anti-ds DNA positive and serositis was more frequent in anti-ds DNA negative SLE. Our patient had negative anti-ds DNA negative lupus nephritis proved in renal biopsy. Jain *et al*[9] reported a case of negative anti-ds DNA and positive anti-Ro antibodies LN with its possible role in the pathogenesis of LN. SS may be classified as primary Sjogren's syndrome (pSS), or secondary Sjogren's syndrome (sSS) (also called polyautoimmunity), due to its association with other autoimmune disorders, especially SLE, rheumatoid arthritis (RA) and Systemic sclerosis. The classification criteria of the American-European Consensus Group (2002)[10] for sSS are based on association with other autoimmune diseases and combination of the following items: 1) dry eye symptoms; 2) dry mouth symptoms; 3) abnormalities in objective ocular tests; 4) alterations in objective oral tests; 5) positive circulating anti-Ro (SSA) and/or anti-La (SSB) antibodies; and 6) histological analysis of the minor salivary glands revealing a focal lymphocytic sialadenitis (focus score $\geq$ 1/4 mm^2 of glandular tissue). The prevalence of secondary Sjogren's syndrome ranges between 6% and 19% in SLE[11]. To be classified with secondary Sjogren's syndrome, patients must have symptoms of keratoconjunctivitis sicca or xerostomia and objective evidence of decreased tear or salivary flow which is present in this patient. Symptoms of dry eye and dry mouth for > 3 months, and/or feeling the presence of foreign bodies in the eyes, and/or use of artificial tears more than three times a day and/or recurrent or persistent parotid gland enlargement, and/or difficulty swallowing solid foods, requiring fluid intake for relief of this symptom. Prevalence of autoantibodies of Anti-ds DNA in SLE is 60% and Anti-Ro/SSA in SLE is 30% which is associated with Sjogren's syndrome, photosensitivity, subacute cutaneous lupus erythematosus, neonatal lupus, congenital heart block[12]. ACR/European League Against Rheumatism (EULAR) 2016[13] have proposed new classification criteria for pSS validated specifically. The Johns Hopkins Lupus cohort study conducted by Baer *et al*[14] showed that 14.5% patients had sSS with SLE and had a higher frequency of photosensitivity, oral ulcers, ocular involvement, Raynaud's phenomenon, and anti-Ro antibodies, and a lower frequency of renal disease, anti-dsDNA antibodies, and RNP antibodies. In SLE patients, anti-Ro antibody associates to haematological manifestations (anaemia, leucopoenia, lymphopenia, and thrombocytopenia), palpable purpura and sSS. Careful analyses of the clinical features and investigations are important for the differential diagnosis between both syndromes.

Conclusion

The possible development of sSS in SLE patients should be considered in patients with positive anti-Ro (SSA) antibody. sSS-SLE patients have a peculiar profile of clinical and serological manifestations, such as higher prevalence in females, older age of disease onset, and longer disease duration.

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