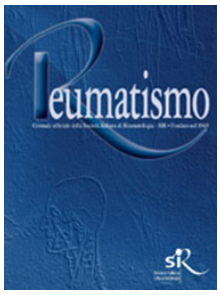

Reumatismo - The Italian Journal of Rheumatology

https://www.reumatismo.org/reuma

eISSN 2240-2683

Please cite this article as:

Kaynar K, Serdar Kılıçaslan S, Mungan S, et al. **Membranous nephropathy in a patient with Sjögren's disease**. *Reumatismo* doi: 10.4081/reumatismo.2025.1794

Submitted: 19-08-2024
Accepted: 26-03-2025

Membranous nephropathy in a patient with Sjögren's disease

Kubra Kaynar,[1] Şeymanur Serdar Kılıçaslan,[2] Sevdegül Mungan,[3]
Seda Akduman,[2] Vildan Kumcu,[2] Nihan Yazıcı[2]

[1]Department of Nephrology, School of Medicine, Karadeniz Technical University, Trabzon; [2]Department of Internal Medicine, School of Medicine, Karadeniz Technical University, Trabzon; [3]Department of Pathology, School of Medicine, Karadeniz Technical University, Trabzon, Turkey

Correspondence: Kubra Kaynar, Department of Nephrology, School of Medicine, Karadeniz Technical University, Tıp Fakültesi, Nefroloji Bilim Dalı, 61080 Trabzon, Turkey.
Tel.: + 90 542 241 58 79. Fax: +90 462 325 22 70.
E-mail: kkaynar@yahoo.com

Key words: erythema, glomerulonephritis, membranous, Sjögren's syndrome.

Contributions: all authors have read and agreed to the final manuscript. KK, participated in the conception, design, interpretation of data of the patient as well as drafting the article and its revision; SSK, contributed to the design, interpretation of data, and drafting the article; SA, reviewed the literature and participated in writing the manuscript; SM, contributed to the interpretation of the pathological findings of patient's kidney biopsy; VK, reviewed the literature; NY, participated in writing the manuscript.

Conflict of interest: all authors declare no conflicts of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: informed consent was obtained from the patient.

Availability of data and materials: all data underlying the findings are fully available.

Funding: none.

Summary
Sjögren's disease (SjD) was first described in a middle-aged female patient with chronic rheumatism in 1930. Membranous nephropathy (MN) is the most commonly identified type of glomerulonephritis in older adults with nephrotic syndrome. One of the autoimmune diseases that causes secondary MN is SjD. A 68-year-old female patient with a medical history of 25 years of hypertension, 9 years of SjD, depressive mood disorder, and intracoronary stent placement applied with peripheral edema. Hypoalbuminemia, hypothyroidism, hematuria, proteinuria, and albuminuria were also detected. In the autoantibody panel, antinuclear antibodies, anti-Ro-52 antibody, anti-Ro/SS-related antigen A antibody, and anticentromere antibody were positive. Kidney biopsy revealed MN. Anti-phospholipase A2 receptor antibody was negative. Methylprednisolone, cyclosporine, hydroxychloroquine, nifedipine, metoprolol, valsartan, L-thyroxine, acetylsalicylic acid, artificial tear drops, and fluoxetine were administered. Partial remission was detected in the first month of treatment. However, the patient, who had all vaccinations, developed swine flu infection and subsequently widespread candidiasis, and despite amphotericin B treatment and discontinuation of immunosuppressives, died in the 5th month due to septic shock. Anti-PLA2R antibody negative MN is one of the kidney manifestations of SjD. The poor prognosis of our patient was due to high SjD disease activity and severe infectious complications, which are independent risk factors for overall mortality.

Introduction

Sjögren's disease (SjD) was first described in a middle-aged woman with hyposecretion of lacrimal, salivary, and sweat glands and chronic rheumatism by a Swedish ophthalmologist, Henrik Sjögren, in January 1930 (1). This chronic autoimmune disease is derived from an abnormal immune response, which results from genetic predisposition, epigenetic factors (mostly infections), and hormonal (particularly estrogen) deficiency (2). One of the extra-glandular manifestations of SjD is nephritis, mostly in the form of interstitial nephritis. However, there is an increasing number of reports regarding the presence of glomerulonephritis in SjD patients (3). Membranous nephropathy (MN) was also reported in patients with SjD, most of whom were from Asia (4).

Here, a recently diagnosed MN in a 68-year-old female patient who had been followed up with SjD for nine years is presented.

Case Report

A 68-year-old female patient had a medical history of hypertension for 25 years treated with metoprolol (25 mg/d), valsartan (80 mg/d) and hydrochlorothiazide (12.5 mg/d), SjD for 9 years treated with hydroxychloroquine (200 mg/d), artificial tears, and prednisolone (2.5 mg/d), pantoprazole (40 mg/d), depressive mood disorder treated with fluoxetine (20 mg/d), coronary artery disease treated with acetylsalicylate (100 mg/d), and stents after balloon angioplasty 10 years ago. The patient was left unfollowed for 4 years (2019-2023) during the pandemic. Her physical examination revealed a blood pressure of 130/80 mmHg, hypertensive retinopathy (grade 2), sausage fingers (dactylitis), and erythema (Figure 1). Schirmer test showed a wetting of 25 mm in the right eye and 30 mm in the left eye. Unstimulated saliva production was measured at 0 mL/15 minutes. Laboratory tests showed normal serum creatinine level (0.88 mg/dL), hypoalbuminemia (34 g/L), and hypothyroidism (thyroid-stimulating hormone: 6.7 mIU/L, free T4: 0.8ng/dL). Urine sediment evaluation revealed hematuria without casts. Analysis of 24-hour urine samples revealed proteinuria (4.1 g/day) and albuminuria (3.28 g/day) (Figure 2). Tests for auto-antibody panel resulted in positive antinuclear antibodies (ANA) with centromere staining pattern (titer of 1/3200-1/10000), anti-Ro-52 antibodies (+++), anti-Ro/SS-related antigen A antibodies (+++), and anti-centromere antibodies (+++) by immunofluorescent assay. The other autoantibodies [anti-double-stranded DNA, antineutrophil cytoplasmic antibody (ANCA), anti-La/SSB, anti-Scl 70, and anti-Smith] and rheumatoid factor were not detected. In addition, serum complement fractions 3 and 4 levels were normal. European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) was 21, showing high disease activity at admission (5).

The size of the right kidney was 98×39 mm, and that of the left kidney was 90×44 mm, with normal echogenicity. Kidney biopsy was performed based on the indications for nephrotic syndrome. Global sclerosis in 4 out of 19 glomeruli, diffuse basal membrane thickening, mesangial matrix expansion, and interstitial fibrosis (30%) were found by light microscopy (Figure 3). The depositions of Immunoglobulin G (+3), complement component 1q (+1), fibrin, light chains (+3), and complement 4d were detected by immunofluorescence microscopy. These results were compatible with MN (Figure 3). Anti-phospholipase A_2 receptor (anti-PLA_2R) antibody levels of our patient were 14.9 RU/mL by enzyme-linked immunosorbent assay. The generally accepted cut-off value for positive anti-PLA_2R antibody is 20 RU/mL (6). The biopsy of the cutaneous lesions revealed leukocytoclastic vasculitis morphology (epidermis with hyperparakeratosis, microabscess foci, vacuolar degeneration in the basal layer, formation of necrotic keratinocytes, lymphocyte exocytosis, and upper dermis with perivascular band-like chronic inflammation) (Figure 4). Osteopenia was diagnosed by bone mineral densitometry.

After MN, osteopenia, and hypothyroidism were diagnosed, methylprednisolone (1 mg/kg/day, 64 mg/day) and cyclosporine (dose adjusted to achieve trough levels of 120-200 ng/mL), nifedipine 30 mg 1*1, furosemide 20 mg, L-thyroxine 25 mg, and Vit D 800 IU+calcium 1 g were also administered to the patient. After one month of treatment, partial remission (more than 50% reduction in proteinuria) was obtained (proteinuria decreased from 9.6 g/day to 2.9 g/day and serum albumin

levels increased from 2.26 g/dL to 3 g/dL). However, the patient applied to the emergency room 10 days after her last visit. *Escherichia coli* was detected both in urine and blood cultures, and *Klebsiella pneumoniae* was found in sputum cultures. Ceftriaxone (2*1 g) was added to the treatment according to the antibiogram test results. Herpes simplex virus type 1 was positive from the specimen taken from the lesion around the lips. In addition, she had dysphagia. Gastroesophagoscopy revealed white exudative plaques with multiple fragile ulcerative lesions. Swabs taken from these lesions revealed *Candida glabrata*. Acyclovir (5 mg/kg every 8 hours intravenously) and caspofungin (70 mg /day) were administered to the patient, and cyclosporine ceased as soon as these opportunistic infections were diagnosed. *Influenza* A/swine flu was detected by real-time polymerase chain reaction (RT-PCR) test. Caspofungin was changed to liposomal amphotericin B (5 mg/kg/day) due to the presence of *Aspergillus fumigatus* in sputum cultures, and ceftriaxone was replaced with piperacillin and tazobactam (4.5g four times a day) due to acute oxygen desaturation. The patient was transferred to the intensive care unit. Linezolid (600 mg every 12 hours) was added to the treatment regimen due to *Staphylococcus hominis* positivity in central venous catheter tip cultures. *Pneumocystis jirovecii* was also detected by RT-PCR. Co-trimoxazole (20 mg/kg/day) was given. The patient did not respond to high-flow oxygen delivery and had noninvasive ventilation. She had to be intubated due to the persistence of desaturation. Endotracheal aspirate cultures were positive for *Aspergillus fumigatus* despite 14 days of liposomal amphotericin B treatment. Unfortunately, the patient died 2 days after intubation.

Discussion and Conclusions

The dysregulation of the immune system leads to the occurrence of SjD, which is defined as primary (if there is no association with other autoimmune diseases) or secondary (if there is another underlying disorder like lupus, systemic sclerosis, *etc.*) (7). Our patient had primary SjD due to the presence of salivary hypofunction and anti-Ro antibodies without other connective tissue disorders (8). Salivary hypofunction, a measurement of timely produced saliva, is different than xerostomia, a subjective symptom of the patient (9). The patient had also extraglandular involvement of SjD, which included cutaneous leukocytoclastic vasculitis, Raynaud phenomenon, and glomerular disease (10). Qui *et al.* recently reported that the frequency of both anti-PLA_2R antibody positive and negative MN cases among SjD patients increased during the last years (11). Dry eyes were found in 59.46% of cases, while dry mouth was found in 77.03% of the patients in this retrospective analysis. Our patient had dry mouth but not dry eyes. The positivity of anti-Ro antibody was found in 95.95% of patients with SjD and MN, while anti-La antibody positivity was found in 32.43% of them (11). Our patient had positive anti-Ro antibodies.

Kidney involvement usually occurs in 1-33% of patients with SjD (12). The most common kidney disease among patients with primary SjD who underwent kidney biopsy was tubulointerstitial nephritis. Distal renal tubular acidosis, hypokalemic salt-losing tubulopathy, and diabetes insipidus were also commonly associated with SjD (12, 13). Nevertheless, glomerular diseases are less frequently observed in SjD, and the clinical spectrum is wide. The most common glomerular involvements in SjD are membranoproliferative glomerulonephritis (GN) secondary to cryoglobulinemia and ANCA-associated pauci-immune GN (13). Anti-PLA_2R antibody-negative secondary MN cases due to SjD have rarely been reported. Our patient had anti-PLA_2R antibody-negative MN and full-blown SjD at the same time. Chen *et al.* reported 13 patients with MN and SjD; eight of them were anti-PLA_2R antibody positive, and five of them were negative (3). Eight patients had nephrotic-range proteinuria, while the rest did not have nephrotic-range proteinuria. Our patient presented with nephrotic syndrome. The secondary form of MN should be considered in patients with both PLA_2R-negative MN and SjD (3, 14). Exostosin 1 and 2 (EXT1 and EXT2) were reported as markers of MN associated with systemic autoimmune disease, such as SjD (15). It would have been better if we could have searched these markers in our patient. Polyarthritis vasculitis, and fatigue were reported as the most powerful predictors of nephritis development in patients with primary SjD (14).

The patients with severe nephrotic syndrome secondary to MN and SjD were treated with prednisone, cyclophosphamide, and hydroxychloroquine (3). Mycophenolate and calcineurin inhibitors are also commonly used for secondary MN treatment combined with corticosteroids (15, 16). The time to remission after treatment among patients with primary SjD and MN varied from 3 to 20 months (3). However, patients without remission after 15 months of treatment were also reported. Infections both trigger the development of SjD and complicate the disease (17). A recently published retrospective cohort study, which analyzed data of 11,372 patients with primary SjD, reported high systemic disease activity (determined by ESSDAI), positivity of oral tests, ANA, and cryoglobulins as the independent risk factors for SjD-related death (18). Our patient had a high ESSDAI score due to highly active renal involvement, and positivity of oral tests and ANA serology. In this study, presenting the data of nearly 12,000 patients followed for an average of 9 years, almost 900 deaths were identified. Deaths were due to SjD disease activity (14%), infections (28%), cardiovascular events (27%), solid organ malignancies (18%), and other causes (14%). In addition, higher mortality was reported in those with nephritis (14, 19). As nephritis is a well-known life-threatening complication and diagnosis of nephritis needs an invasive procedure (kidney biopsy), other reliable and less invasive methods for its diagnosis, such as model establishment for a nomogram, have been searched (19).

This case had some limitations: the inability to search the markers showing the association of autoimmune diseases with MN (EXT1 and EXT2) was the shortcoming of this case report. Future studies to clarify these associations are needed.

In conclusion, anti-PLA_2R antibody-negative MN is one of the kidney manifestations of SjD. The poor prognosis of our patient was due to high SjD disease activity and severe infectious complications, which are independent risk factors for overall mortality.

References

1. Murube J. Henrik Sjögren, 1899-1986. Ocul Surf 2010; 8: 2-7.
2. Nair JJ, Singh TP. Sjögren's syndrome: review of the aetiology, pathophysiology & potential therapeutic interventions. J Clin Exp Dent 2017; 9: e584-9.
3. Chen R, Wang J, Xie Q, Xue J, Hao C. Sjögren's syndrome complicated with membranous nephropathy, a cause or coincidence? Int J Rheum Dis 2021; 24: 1086-94.
4. Yang HX, Wang J, Wen YB, Fei YY, Jiang MD, Zhou MY, et al. Renal involvement in primary Sjögren's syndrome: a retrospective study of 103 biopsy-proven cases from a single center in China. Int J Rheum Dis 2018; 21: 223-9.
5. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015; 1: e000022.
6. Jurubiță R, Obrișcă B, Achim C, Micu G, Sorohan B, Bobeică R, et al. Anti-phospholipase A2 receptor antibody screening in nephrotic syndrome may identify a distinct subset of patients with primary membranous nephropathy. Int Urol Nephrol 2022; 54: 1713-23.
7. Negrini S, Emmi G, Greco M, Borro M, Sardanelli F, Murdaca G, et al. Sjögren's syndrome: a systemic autoimmune disease. Clin Exp Med 2022; 22: 9-25.
8. Baer AN. Diagnosis and classification of Sjögren's syndrome. 2024. Available from: https://www.uptodate.com/contents/diagnosis-and-classification-of-sjogrens-disease? Accessed on: 14/03/2024.
9. Retamozo S, Baldini C, Bootsma H, De Vita S, Dörner T, Fisher BA, et al. Therapeutic recommendations for the management of older adult patients with Sjögren's syndrome. Drugs Aging 2021; 38: 265-84.
10. Baer AN. Clinical manifestations of Sjögren's disease: extraglandular disease. 2024. Available from: https://www.uptodate.com/contents/clinical-manifestations-of-sjogrens-disease-extraglandular-disease? Accessed on: 26/03/2024.
11. Qiu DD, Li Z, Wang JJ, Chen DQ, Tu YM, Liang SS, et al. The spectrum and prognosis of Sjögren's syndrome with membranous nephropathy. Clin Kidney J 2024; 18: sfae384.
12. Aiyegbusi O, McGregor L, McGeoch L, Kipgen D, Geddes CC, Stevens KI. Renal disease in primary Sjögren's syndrome. Rheumatol Ther 2021; 8: 63-80.
13. Radhakrishnan J. Kidney disease in primary Sjögren's disease. 2024. Available from: https://www.uptodate.com/contents/kidney-disease-in-primary-sjogrens-disease? Accessed on: 26/03/2024.
14. Chatterjee R, Balakrishnan A, Kharbanda R, Rathore U, Gupta L, Misra DP, et al. Renal involvement in Sjőgren's syndrome: predictors and impact on patient outcomes. Rheumatol Int 2023; 43: 1297-306.
15. Alsharhan L, Beck LH Jr. Membranous nephropathy: core curriculum 2021. Am J Kidney Dis 2021; 77: 440-53.
16. Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjögren's syndrome: clinical presentation and outcome. Arthritis Rheum 2013; 65: 2945-53.
17. Utomo SW, Putri JF. Infections as risk factor of Sjögren's syndrome. Open Access Rheumatol 2020; 12: 257-66.
18. Brito-Zerón P, Flores-Chávez A, Horváth IF, Rasmussen A, Li X, Olsson P, et al. Mortality risk factors in primary Sjögren syndrome: a real-world, retrospective, cohort study. EClinicalMedicine 2023; 61: 102062.
19. Guo L, Zhao S, Liu X. Development of a nomogram for membranous nephropathy prediction in patients with primary Sjögren's syndrome: a 6-year retrospective study. Front Immunol 2024; 15: 1320880.

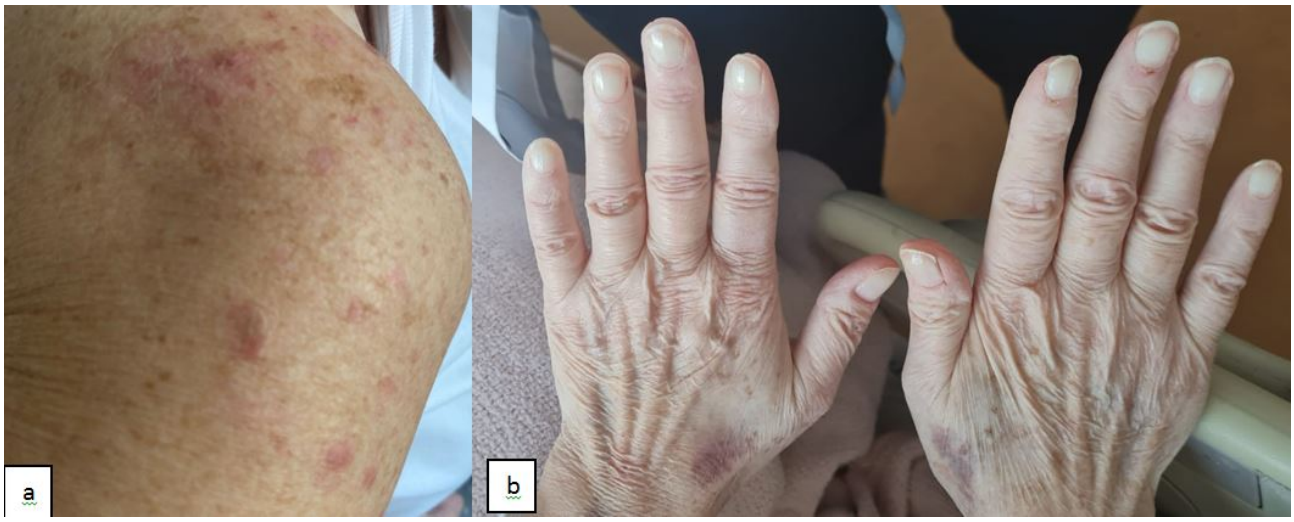

Figure 1. a) Cutaneous erythema; b) sausage fingers of the patient.

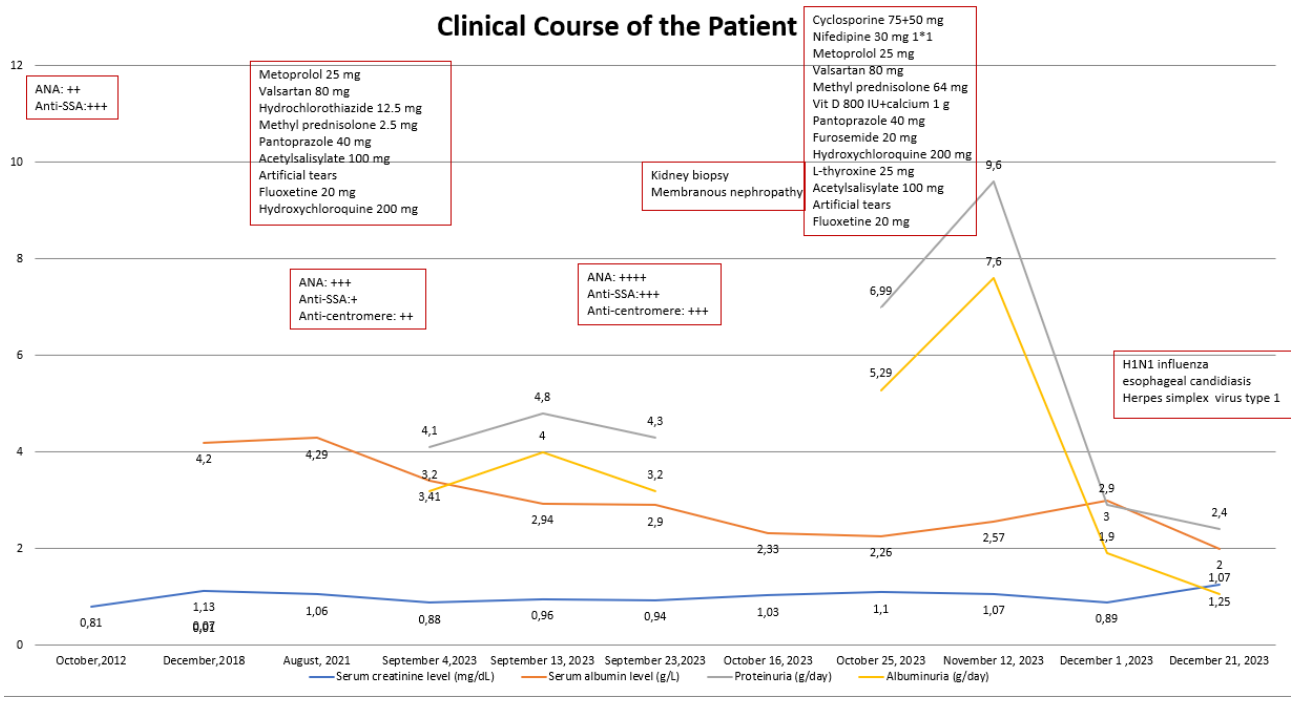

Figure 2. Clinical course of the patient.

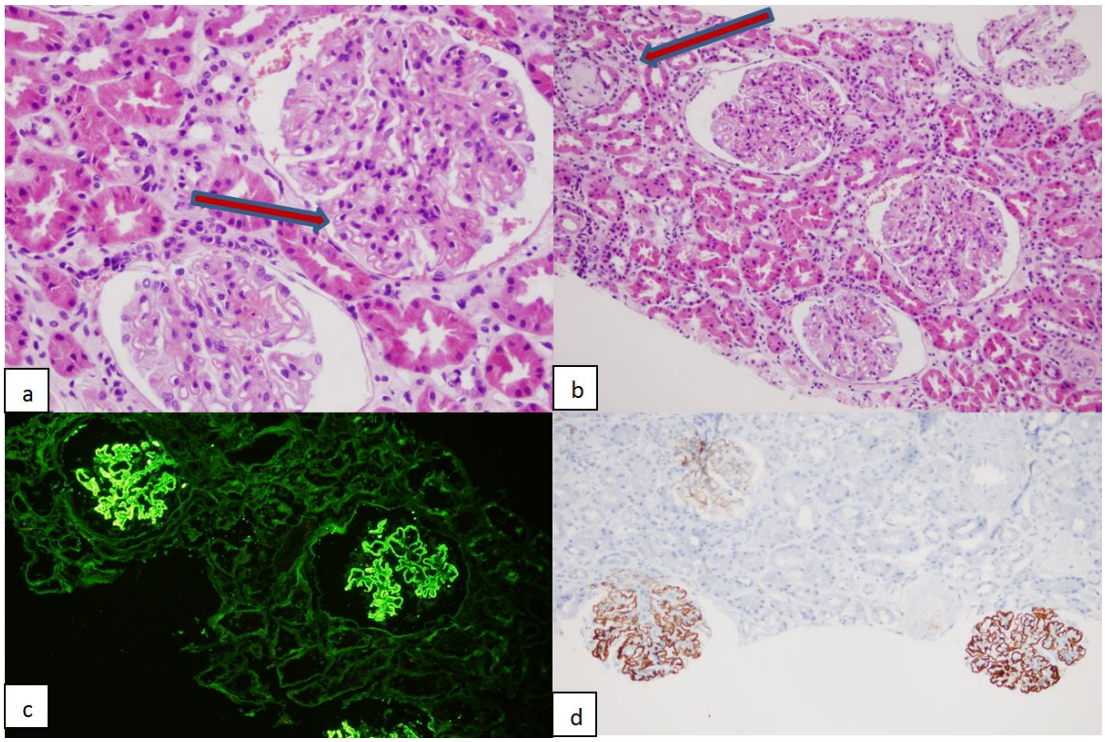

Figure 3. Kidney biopsy showing (a) diffuse basal membrane thickening and mesangial matrix expansion (arrow) H&E ×400, (b) global sclerosis (arrow) by light microscopy H&E ×200, (c) the depositions of immunoglobulin G, and (d) complement 4d by immunohistochemistry stain ×200.

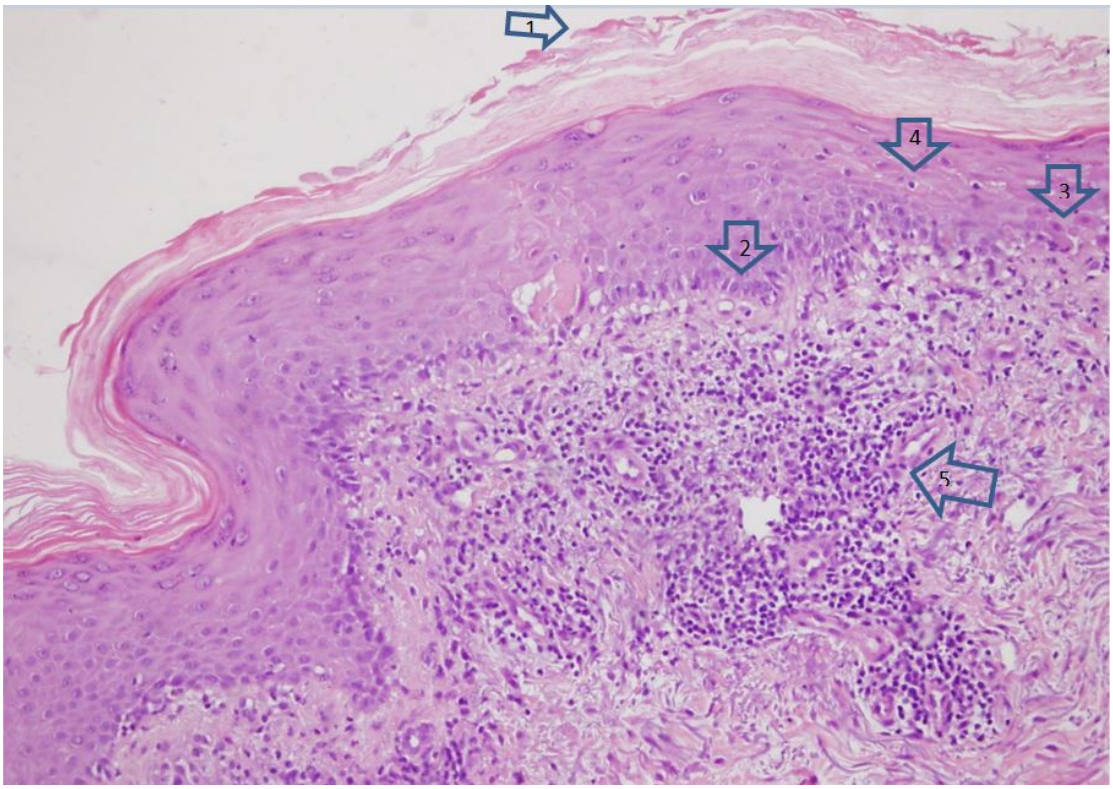

Figure 4. The biopsy taken from the cutaneous lesions revealed subacute cutaneous lupus erythematosus (epidermis with hyperparakeratosis,[1] vacuolar degeneration in basal layer,[2] formation of necrotic keratinocytes,[3] and lymphocyte exocytosis,[4] upper dermis with perivascular band-like chronic inflammation[5]).