Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Unusual presentations in systemic lupus erythematosus with concurrent IgA nephropathy lesion: a rare case report from Eastern Nepal

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Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organs. While lupus nephritis (LN) is seen in SLE, concurrent IgA nephropathy lesion is rare. Uncommon manifestations like cutaneous ulcers and orbital involvement present diagnostic challenges, and this case from Nepal emphasizes careful diagnostic approach in such cases.

Case presentation: A 42-year-old female presented with bilateral lower limb swelling, gum bleeding, and epistaxis. Initial evaluation revealed pancytopenia and suspected renal involvement. Renal biopsy showed IgA nephropathy lesions, but clinical and laboratory findings favored lupus nephritis. Treatment with immunosuppressive agents was initiated. Despite therapy, the patient developed cutaneous ulcers and orbital cellulitis. Decreasing anti-ds DNA levels were noted during the course of treatment.

Discussion: The diagnosis of lupus nephritis in the presence of IgA nephropathy lesions emphasizes the complexity of SLE diagnosis. Treatment with immunosuppressive agents targeting the underlying autoimmune process, yet the development of cutaneous ulcers and orbital cellulitis highlights the importance of timely intervention in managing SLE complications. In resource-limited settings, clinicians should initiate interventions based on clinical and lab findings while awaiting detailed biopsy results.

Conclusion: This case highlights diagnostic challenges in SLE and emphasizes the necessity for careful monitoring and timely intervention in managing complications. The interplay between SLE and IgA Nephropathy (IgAN) suggests that SLE may trigger or exacerbate it, complicating disease management. Further exploration is needed to enhance the understanding and management of complex autoimmune disorders like SLE.

Keywords: autoimmune disorder, case report, IgA nephropathy, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement and the production of autoantibodies against nuclear antigens[1]. Lupus nephritis (LN), is a form of glomerulonephritis that constitutes one of the most severe organ manifestations of the SLE[2]. Association of SLE with LN is frequent, but those showing lesions of IgA nephropathy is unexpected and has not been reported often in the literature[3]. Orbital involvement and cutaneous ulcers in SLE are rare and this case from Nepal highlights the overall importance of a diligent diagnostic approach in managing complex autoimmune conditions, especially when unusual laboratory findings are seen[4,5]. This case report is reported according to CARE checklist 2013[6].

HIGHLIGHTS

- This case presents an atypical pattern of multiple systemic manifestations in a female with systemic lupus erythematosus (SLE).
- Occurrence of IgA nephropathy lesion alongside SLE is rare highlighting the complexity of autoimmune disorders.
- In a limited resource setting, management of SLE can be challenging, especially when pathological, laboratory findings and clinical correlations do not show similarity; and this case emphasizes the necessity of appropriate provisional diagnosis and treatment modality when the patient has multiple complexities.

Case presentation

A 42-year-old female presented to the emergency ward of the tertiary care center with complaints of bilateral lower limbs swelling for two weeks, gum bleeding on/off for three weeks, and epistaxis two episodes in one week. A known case of systemic hypertension under medication, no significant family history, and

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:6140–6144

Received 30 April 2024; Accepted 11 July 2024

Published online 23 July 2024

http://dx.doi.org/10.1097/MS9.0000000000002401

Table 1

Laboratory findings at the time of first presentation.

S.N.	Laboratory findings	Results	Reference values
1	Hemoglobin (Hb)	5.4 gm/dl	12–16 gm/dl
2	TLC	2600/mm^3	4000–11 000/mm^3
3	Neutrophils	62%	40–75%
4	Leukocytes	32%	20–45%
5	Platelets	37 000/mm^3	150 000-450 000/mm^3
6	MCV	84.7 fl	80–100 fl
7	RBC	1.9 million/mm^3	4.2–5.4 million/mm^3
8	PT	16.1 sec	11–13 sec
9	INR	1.2	0.8–1.2
10	AST	131 IU/l	10–40 IU/l
11	ALP	115 IU/l	44–147 IU/l
12	ALT	43.6 IU/l	7–56 IU/l
13	Serum albumin	3 gm%	3.5–5 gm%
14	Serum urea	63.2 mg/dl	7–20 mg/dl
15	Serum creatinine	1.2 mg/dl	0.6–1.2 mg/dl
16	C3	81.89 mg/dl	90–180 mg/dl
17	C4	12.62 mg/dl	10–40 mg/dl

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio; MCV, mean corpuscular volume; PT, prothrombin time; RBC, red blood cell; TLC, total leukocyte count.

no history of alcohol consumption, tobacco, and smoking was reported. She had previously visited a primary health center for these symptoms and was referred to our hospital.

On examination, she had a patent airway, SpO2 98%, respiratory rate 20 breaths per min, pulse 114 beats per min, and blood pressure 150/90 mmHg. Her pupils were bilaterally symmetrical and the AVPU scale was alert. Laboratory findings at the time of presentation is shown as tabulated [Table 1]. Urinalysis showed plenty of pus, nil red blood cells (RBCs), and traces of albumin. Based on lab findings, pancytopenia was seen with suspected renal involvement, and the patient was managed symptomatically with Injection Ceftriaxone 1 g IV twice a day (BD), Tablet Folic acid 5 mg per oral (PO) BD , Tablet Paracetamol 1 g PO as per requirement (SOS), 1-pint packed red blood cells transfusion and asked for renal biopsy with anti-nuclear antibodies (ANA) test, USG, routine blood examination, urinalysis for follow-up after 1 month due to unavailability of quick biopsy results; then she was discharged being hemodynamically stable.

Significant laboratory findings of the second visit, her first follow-up was noted as tabulated [Table 2]. USG revealed mild hepatomegaly. The renal biopsy revealed multiple sections stained with Hematoxylin and Eosin (H&E), Periodic acid-Schiff, Silver methenamine, Masson's Trichrome, and Congo red including renal medulla and cortical parenchyma containing up to 12 glomeruli. Among these, 5 (41.6%) were globally sclerosed. Among the remaining, 6 (53%) revealed secondary segmental tuft sclerosis. Viable areas showed focal/segmental increase in mesangial matrix/cellularity. There was no evidence of crescent formation, tuft necrosis, or endocapillary hypercellularity. Focal chronic interstitial inflammation and a moderate increase in tubulointerstitial chronicity were observed. Overall, significant global and segmental tuft sclerosis was seen [Figure 1A]. Direct immunofluorescence studies revealed dominant glomerular mesangial staining for IgA and mild mesangial staining of IgG, C3, and C1q with segmental entrapment of IgM [Figure 1B]. All the findings demonstrated lesions of IgA nephropathy (with Oxford MEST-C score of M0E0S1T1C0) [Table 3].

However, clinical manifestations and lab findings of proteinuria, elevated serum urea and creatinine, and absence of hematuria indicated lupus nephritis rather than IgA nephropathy. According to EULAR/ACR criteria, with a score of 14, SLE was diagnosed but clinical criteria for lupus nephritis was not fulfilled in the score as it was not supported by pathological findings [Table 4]. She was prescribed Tablet Prednisolone 15 mg PO OD, Tablet Mycophenolate Mofetil 500 mg PO BD, Tablet Hydroxychloroquine 400 mg PO OD, Tablet Ramipril 12.5 mg PO OD, Supplemental Calcium, Vitamin D3 and Vitamin B12.

After one month of diagnosis, she again visited with multiple reddish painful lesions with pus discharges over the chin for 4 days [Figure 1C]. Local examination revealed multiple abscesses on the forehead, chin, and buttocks. Multiple erythematous plaques were seen over the skin [Figure 1D]. Significant lab findings were ANA titer 1:100 and anti-ds DNA 4.29 IU/ml. She was managed with IV antibiotics, IV fluids, and supportive treatment. Five months later, she presented with complaints of swelling and pain over the left eye along with mucopurulent discharge for three days. A significant lab finding was anti-ds DNA 1.09 IU/ml. Drainage for orbital cellulitis was done with a pint packed cell volume transfusion. Throughout the disease progression, serum creatinine and urea were above normal. All the significant findings during her subsequent follow ups have been tabulated below [Table 2]. Since then, the patient has been stable and is under continuous medications.

Discussion

SLE is known for its diverse and serious organ manifestations, among which nephritis is one of the most common and severe, affecting 50% of adults and 80% of children with SLE. Diagnostic protocols typically include urine and blood tests alongside kidney biopsy, with elevated serum levels of creatinine and urea serving as key indicators of kidney function impairment in lupus nephritis[1]. Lupus nephritis typically occurs within 5 years of SLE and being one of the most serious organ manifestations of SLE, requires appropriate clinicopathological findings for proper diagnosis[2].

Table 2

Significant laboratory findings of first, second and third follow up.

Parameter	1st follow-up	2nd follow-up	3rd follow-up	Reference values	Units
Urea	48	203	96.82	7–20	mg/dl
Anti-ds DNA	24.3	4.29	1.09	< 10	IU/ml
Creatinine	1.5	1.12	1.52	0.6–1.2	mg/dl
C3	81.89	107.09	125.11	90–180	mg/dl
C4	16.62	23.79	37.43	10–40	mg/dl

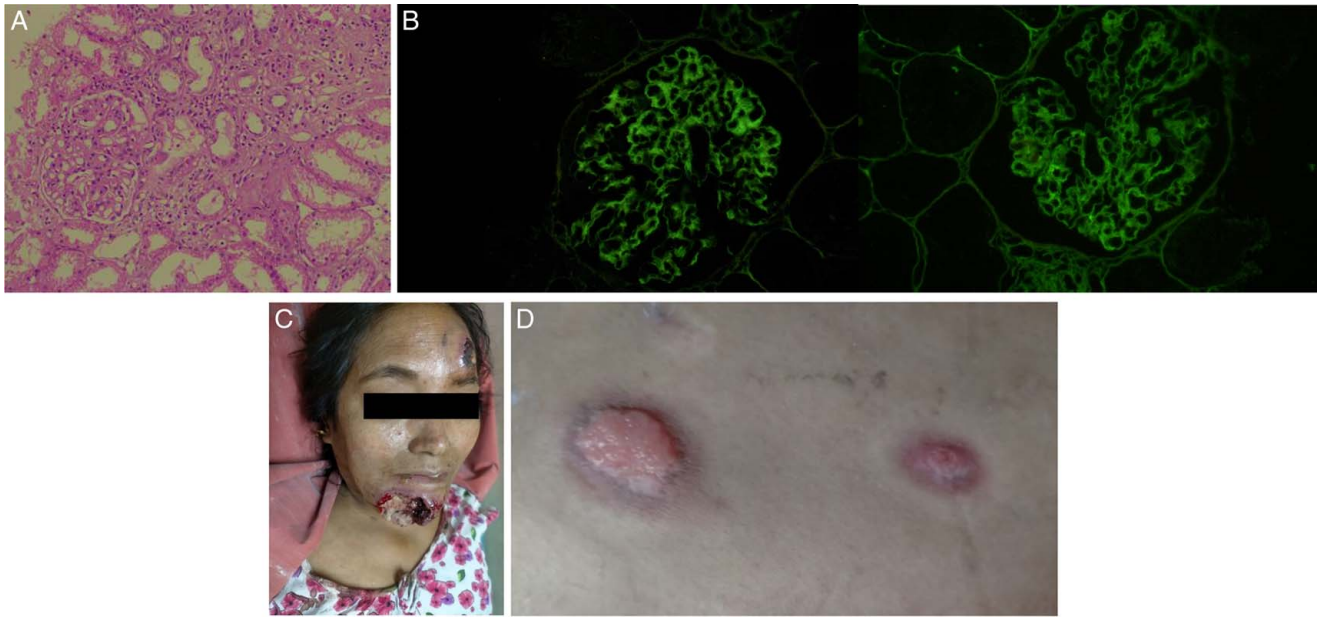

Figure 1. (A) Hematoxylin and Eosin staining obtained by renal biopsy with hypercellularity and expansion of mesangium. (B) Diffuse immunofluorescence staining revealing IgA and IgG deposits in glomerular mesangium (from left to right). (C) Ulcerative lesion over the chin and forehead. (D) Multiple erythematous plaques over the skin.

Most of the patients diagnosed with lupus have asymptomatic clinical signs of nephritis. Initial signs of proteinuria reflecting tubular or glomerular dysfunction as indicated by foamy urine or nocturia with grossly not visible microscopic hematuria are the significant findings in nephritis that indicate the underlying pathology[7]. Diagnosing lupus nephritis can be challenging due to the often subtle and nonspecific early-stage kidney involvement. Definitive diagnosis is typically achieved through kidney biopsy, revealing immune complex-mediated glomerulonephritis with characteristic glomerular deposits that dominantly stain for IgG, along with co-deposits of IgA, IgM, C3, and C1q. Immune deposits may also be found in tubular basement membranes, interstitium, and blood vessels, with ultrastructural findings of co-existent electron-dense deposits in mesangial, sub-endothelial, and sub-epithelial regions[8]. In this case, however, the renal biopsy findings indicated dominant IgA staining with mild deposits of IgG, IgM, C3, C1q and both light chains.

Table 3

Immunostaining pattern

S.N	Parameter	Result
1	IgA	3+ mesangial: granular
2	IgG	1+/+ mesangial; granular
3	IgG subclasses:	
	IgG1	2+ mesangial; granular
	IgG2	Negative
	IgG3	1+ mesangial; granular Negative
	IgG4	Negative
4	IgM	Segmental entrapment
5	C3	1+ mesangial; granular Negative
6	C1q	1+ mesangial; granular Negative
7	Kappa Light chains	1+/2+ mesangial; granular Negative
8	Lambda Light chains	2+ mesangial; granular Negative

This atypical presentation led to the suspicion of IgA nephropathy. IgA nephropathy typically presents with macroscopic hematuria, edema, facial puffiness, prior infections (pharyngitis, gastrointestinal, urinary, and respiratory tract), and hypertension. IgA nephropathy is characterized by granular IgA deposits in the mesangium, often with C3, properdin, and lesser amounts of IgG or IgM[9]. Oxford classification/ MEST-C score is the histopathologic scoring system for patients with IgA nephropathy involving examination of mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T) with recent addition of crescents (C) with over 32 different combinations[10]. With histopathological picture demonstrating mild mesangial hypercellularity in viable glomerular areas, focal chronic interstitial inflammation and tubulointerstitial chronicity with global and secondary segmental sclerosis seen in capillary tufts, IgA nephropathy was the finding in our case with a MESCT-C score of M0E0S1T1C0 . According to the EULAR/ACR criteria, with a score of 14, SLE was diagnosed; however, the absence of classic lupus nephritis in this patient raised the hypothesis that SLE can present with concurrent or predominant IgA nephropathy, an association rarely reported in literature.

The co-existence of SLE and IgA nephropathy (IgAN) is an exceptionally rare clinical phenomenon with only eight cases reported till date. Classical nephritis in SLE typically involves lupus nephritis, making IgAN a rare and unexpected finding. Inconsistent proteinuria and normal serum complement levels are common in IgAN, whereas low serum complement levels are characteristic of SLE nephritis[11]. Our case presented with low serum complement levels at diagnosis, which gradually increased, aligning with the observations of Da Silva and colleagues, Mac-Moune and colleagues and Corrado and colleagues, who reported similar cases[3,11,12]. This is the first case from Nepal with such findings.

Table 4

EULAR/ACR criteria for the classification of systemic lupus erythematosus (SLE)

S.N.	Domain	Clinical feature	Score
1	Hematologic	Thrombocytopenia (platelet count <100 000/mcl)	4
2	SLE-specific antibodies	Anti-dsDNA antibody	6
3	Complement proteins	Low C3 and low C4	4
Total score			14
Conclusion			Score $\geq$ 10 (SLE positive)

Mac-Moune *et al.*[3] described three patients with SLE and IgAN without features of lupus nephritis. Da Silva and colleagues reported a similar association, emphasizing the indolent renal course and systemic presentations in these patients, which mirrors our case where the patient presented with cutaneous ulcers and orbital cellulitis but maintained stable kidney function[11].

Kobak *et al.*[13] identified co-existence of Hashimoto's thyroiditis, IgAN, and SLE, further supporting the rare but possible overlap of these conditions. Additionally, Da Silva and colleagues and Corrado and colleagues noted complement consumption in their cases, likely due to extrarenal lupus activity. Similar complement consumption was observed in our patient, suggesting a systemic lupus influence on IgAN[11,12]. Fujikura and colleagues and Horino and colleagues reported IgAN flares triggered by inflammatory insults without SLE, indicating that in our case, SLE may have acted as the trigger for IgAN flare[14,15].

ANAs refer to the class of antibodies that bind to cellular components in nucleus like DNA, RNA, nucleic acid-protein complexes and proteins. These are present in up to 30% of normal individuals and co-relation with clinical manifestations should be done while diagnosing autoimmune connective tissue disorders and is often the initial step while making diagnosis. Besides SLE, Scleroderma, Myositis, Sjogren's syndrome, Psoriatic Arthritis are some of the autoimmune conditions where ANA titers are elevated and their specific diagnosis require matching with corresponding clinical features and other specific antibodies[16]. While identification of ANAs like anti-ds DNA and Smith antibody (Sm), antiphospholipid antibodies (APLA) and low complement levels are crucial for diagnosis of SLE, positive ANA test of titer greater than or equal to 1:80 is the current immunological domain for classification of patient having SLE[17]. Serum level of anti-ds DNA antibodies, a type of ANAs are an excellent indication of disease activity of lupus with their levels rising simultaneously with flares of SLE; particularly in nephritis and decreasing in response to treatment[16].

Immunosuppressants, glucocorticoids, non-corticosteroids, antimalarials, biologics, and Janus Kinase/ Bruton's tyrosine kinase/ proteasome inhibitors are some of the drugs used in the treatment of SLE[18]. Our initial treatment regimen included Hydroxychloroquine and immunosuppressive agents such as Mycophenolate Mofetil and Prednisolone to target the underlying autoimmune process, including supportive measures for renal function and symptom control.

Extreme cutaneous manifestations, such as ulcers, are associated with significant morbidity and require timely intervention to prevent complications[5]. Similarly, orbital involvement in SLE can lead to vision loss and requires close monitoring and timely treatment[4]. In our case, though with ongoing treatment, a subsequent decline in anti-ds DNA levels was noted; flares of cutaneous ulcers and orbital cellulitis were seen. Since IgA nephropathy is not associated with anti-ds DNA levels, establishing a typical relationship between renal pathology and anti-ds DNA levels in such cases, becomes complex. While SLE activity, as indicated by anti-dsDNA levels, may be controlled, the renal pathology due to IgAN may maintain a state of chronic inflammation. This persistent inflammatory milieu can contribute to non-renal SLE manifestations such as cutaneous ulcers and orbital cellulitis.

Based on the observed clinical course and diagnostic findings in our patient, it is possible that SLE may act as a trigger for IgAN, resulting in a distinct and complex interaction between these two conditions. The low serum complement levels at diagnosis, gradual normalization, and the presence of SLE-specific antibodies suggest an underlying SLE activity that may influence the manifestation and progression of IgAN. This hypothesis is supported by the patient's clinical presentation, the decline in anti-ds DNA levels with ongoing treatment, and the persistent inflammatory state contributing to non-renal manifestations such as cutaneous ulcers and orbital cellulitis.

In resource-limited settings, where detailed biopsy results are awaited, it is suggestive to start quick interventions based on clinical and laboratory findings. There may occur diagnostic dilemmas as in our case but it is essential for clinicians to start accessible intervention as early as possible. As evidenced by our case, laboratory and pathological findings do not always coincide with disease diagnosis and progression. Our case underscores the inconsistency between laboratory/pathological findings and disease diagnosis/progression, emphasizing the requirement for further research.

Conclusion

This case highlights a rare co-existence of SLE and IgAN, presenting with atypical clinical and pathological features and adds critical evidence to the limited existing literature. Despite initial diagnostic challenges and the absence of classic lupus nephritis, the patient exhibited significant systemic involvement including cutaneous ulcers and orbital cellulitis. The clinical course suggests that SLE may have triggered or exacerbated IgAN, complicating the disease presentation and management. The observed decline in anti-ds DNA levels alongside persistent renal inflammation underscores the complex interplay between these autoimmune conditions. Immediate action based on clinical and lab findings is crucial, especially in resource-limited settings. Further research is necessary to explain the mechanisms underlying this rare association and develop targeted therapeutic strategies for managing patients with concurrent SLE and IgAN.

Ethical approval

A written consent form was signed from the patient and this case report did not intervene with patient's treatment plans and hence it did not require ethical approval.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-In-Chief of this journal on request.

Source of funding

None.

Author contribution

Conceptualization: P.P. Patient management: P.P., G.P., A.K.Y., N.C. Writing—original draft: P.P., N.N., N.K.K., A.N. Writing—review and editing: P.P., N.N., N.K.K., G.P., A.K.Y. ,N.C., A.N. Visualization and supervision: A.K.Y. All authors have read and agreed to the final version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

None.

Guarantor

Popular Pokhrel.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgement

The authors appreciate the cooperation of the patient party during the preparation of the case report.

References

[1] National Institute of Diabetes and Digestive and Kidney Diseases. Lupus Nephritis [Internet]. Bethesda, MD: U.S. Department of Health and Human Services; 2022. Accessed 17 Aug 2024.https://www.niddk.nih.gov/health-information/kidney-disease/lupus-nephritis

[2] Anders HJ, Saxena R, Zhao M, *et al*. Lupus nephritis. Nat Rev Dis Prim 2020;6:1–25.

[3] Mac-Moune Lai F, Li EK, Tang NL, *et al*. IgA nephropathy: a rare lesion in systemic lupus erythematosus. Mod Pathol 1995;8:5–10.

[4] Musa M, Chukwuyem E, Ojo OM, *et al*. Unveiling ocular manifestations in systemic lupus erythematosus. J Clin Med 2024;13:1047.

[5] Shinji Izuka TY. Cutaneous ulcerations with systemic lupus erythematosus. CMAJ Canadian Med Assoc J 2021;193:E1734.

[6] Riley DS, Barber MS, Kienle GS, *et al*. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol 2017;89:218–35.

[7] Musa R, Brent LH, Qurie A. Lupus Nephritis. [Updated 2023 Jul 31]. StatPearls [Internet]. StatPearls Publishing; 2024.

[8] Bomback AS. Nonproliferative forms of lupus nephritis: an overview. Rheum Dis Clin North Am 2018;44:561–9.

[9] Rout P, Limaiem F, Hashmi MF. IgA Nephropathy (Berger Disease). StatPearls [Internet]. StatPearls Publishing; 2024.

[10] Haaskjold YL, Bjørneklett R, Bostad L, *et al*. Utilizing the MEST score for prognostic staging in IgA nephropathy. BMC Nephrol 2022;23:26.

[11] Sales L, Laiza B, Karla A, *et al*. IgA nephropathy in systemic lupus erythematosus patients: case report and literature review. Revista Brasil Reumatol 2016;56:270–3.

[12] Corrado A, Quarta L, Di Palma AM, *et al*. IgA nephropathy in systemic lupus erythematosus. Clin Exp Rheumatol 2007;25:467–9.

[13] Kobak S, Hudaverdı O, Keser G, *et al*. Coexistence of systemic lupus erythematosus, Hashimoto's thyroiditis and IgA nephropathy in the same patient. Mod Rheumatol 2011;21:89–91.

[14] Fujikura E, Kimura T, Otaka A, *et al*. [IgA nephropathy in the patient with systemic lupus erythematosus in remission]. Nihon Naika Gakkai zasshi. J Japanese Soc Intern Med 2002;91:3282–4.

[15] Horino T, Takao T, Terada Y. IgA nephropathy in a patient with systemic lupus erythematosus. Lupus 2010;19:650–4.

[16] Nosal RS, Superville SS, Amraei R, *et al*. Biochemistry, Antinuclear Antibodies (ANA). StatPearls [Internet]. StatPearls Publishing; 2024.

[17] Aringer M, Costenbader K, Daikh D, *et al*. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthrit Rheumatol 2019;71:1400–12.

[18] Katarzyna Pawlak-Buś, Schmidt W, Dudziec Ewa, *et al*. Current treatment of systemic lupus erythematosus: a clinician's perspective. Rheumatol Int 2023;43:1395–407.