Case Report

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Internal Medicine Section

ANA-Negative Class V Lupus Nephritis with Isolated Anti-Smith Antibody Positivity: A Case Report

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ABSTRACT

Lupus Nephritis (LN) is a severe manifestation of Systemic Lupus Erythematosus (SLE) and is typically associated with Antinuclear Antibody (ANA) positivity. ANA-negative LN is exceedingly rare and may delay diagnosis, especially when renal disease is the initial presentation. We report a case of a 38-year-old woman presenting with nephrotic syndrome who was diagnosed with biopsy-proven pure Class V LN despite repeatedly negative ANA and anti-double-stranded DNA antibodies. Extended serological testing revealed strongly positive anti-Smith (anti-Sm) antibodies with markedly reduced complement levels. The patient achieved partial remission following treatment with Mycophenolate Mofetil (MMF) and corticosteroids. This case highlights the diagnostic importance of renal biopsy and extended Extractable Nuclear Antigen (ENA) testing in suspected SLE with negative ANA serology and underscores the need for heightened clinical suspicion in atypical presentations.

Keywords: Autoantibodies, Glomerulonephritis, Hypocomplementaemia, Immune complex diseases, Renal biopsy

CASE REPORT

A 38-year-old previously healthy woman presented with a six-week history of progressive bilateral lower-limb oedema, frothy urine, and fatigue. There was no history of photosensitivity, malar rash, oral ulcers, arthritis, serositis, Raynaud's phenomenon, neurological symptoms, or prior autoimmune disease. She denied exposure to herbal medicines, non-steroidal anti-inflammatory drugs, or cosmetic products containing mercury or hydroquinone, and family history was unremarkable.

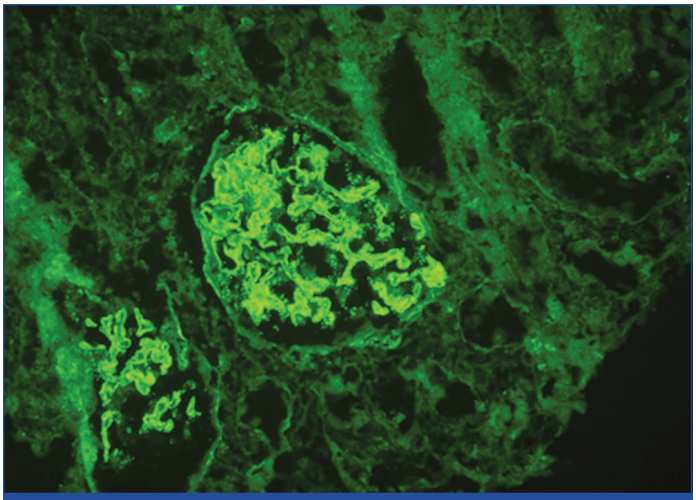
On examination, she had bilateral pitting pedal oedema up to the knees. Blood pressure was 142/88 mmHg. There was no prior history of hypertension, and previously documented readings within the past year were within normal limits, suggesting new-onset elevation at presentation. Pulse was 84/min, and body mass index was 22 kg/m^2. There were no mucocutaneous lesions, synovitis, or neurological deficits. Cardiovascular and respiratory examinations were normal. Baseline laboratory and serological parameters are summarised in [Table/Fig-1]. Complement levels (C3 and C4) were markedly reduced. Total complement activity (CH50) could not be assessed due to non-availability of the assay.

Test	Result	Reference Range	Interpretation
Haemoglobin (g/dL)	10.8	12-16	Mild anaemia
Total leukocyte count (/µL)	6,800	4,000–11,000	Normal
Platelet count (/L)	230 × 10^9	150–450 × 10^9	Normal
ESR (mm/hr)	68	<24	Markedly elevated
CRP (mg/L)	2.1	<6	Normal
Serum creatinine (mg/dL)	1.3	0.6–1.1	Mildly elevated
eGFR (CKD-EPI)	62 1.73 mL/min/1.73 m^2	>90	CKD stage 2
Serum albumin (g/dL)	2.5	3.5–5.0	Hypoalbuminamia
24-hour urine protein (mg/day)	4.2	<150	Nephrotic range
Urine PCR	4.25	<0.2	Severe proteinuria
Urine ACR (mg/g)	628	<30	Severe
ANA (IIF)	Negative	Negative	ANA-negative
ANA (ELISA)	Negative	Negative	Confirms ANA-negative profile
Anti-dsDNA (ELISA)	Negative	Negative	Negative
Anti-Sm antibody	Strongly positive	Negative	Highly specific for SLE
Anti-Ro/SSA, Anti-La/SSB, Anti-RNP	Negative	Negative	Normal
C3 complement (mg/dL)	42	90-180	Low
C4 complement (mg/dL)	6	10-40	Low
Renal biopsy	Class V Lupus Nephritis (LN)	—	Confirmatory
Direct immunofluorescence	Granular IgG, C3 along GBM	—	Consistent with LN

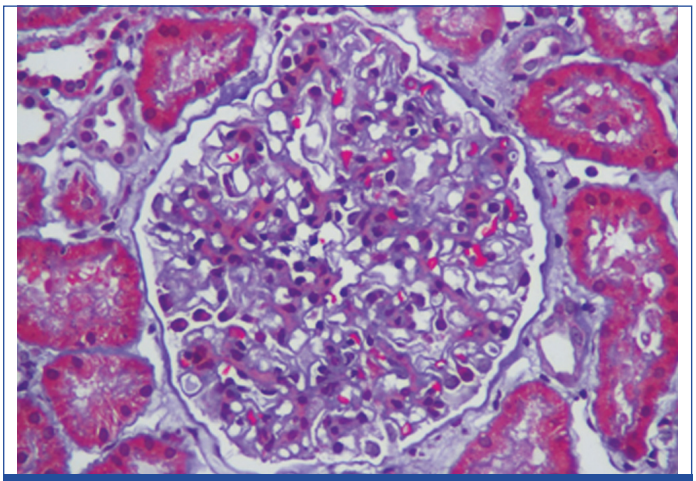
[Table/Fig-1]: Summary of laboratory and diagnostic investigations.
ANA: Antinuclear antibody; IIF: Indirect immunofluorescence; ELISA: Enzyme-linked immunosorbent assay; Anti-dsDNA: Anti–double-stranded deoxyribonucleic acid antibody; Anti-Sm: Anti-Smith antibody; Anti-Ro/SSA: Anti-Ro (Sjögren's syndrome-related antigen A) antibody; Anti-La/SSB: Anti-La (Sjögren's syndrome-related antigen B) antibody; Anti-RNP: Anti-ribonucleoprotein antibody; C3: Complement component 3; C4: Complement component 4; GBM: Glomerular basement membrane; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; PCR: Protein–creatinine ratio; ACR: Albumin–creatinine ratio; LN: Lupus nephritis; SLE: Systemic lupus erythematosus.

Renal biopsy was performed within two weeks of presentation. Light microscopy revealed eight glomeruli, none of which were globally sclerotic. The glomeruli showed mild mesangial hypercellularity with spikes and pinhole lesions along the glomerular basement membrane, without endocapillary hypercellularity, wire-loop lesions, hyaline thrombi, crescents, segmental sclerosis, or necrotising lesions. There was no interstitial inflammation, interstitial fibrosis, tubular atrophy, or significant vascular pathology. Immunofluorescence microscopy demonstrated granular deposition of IgG and C3 along the mesangium and glomerular capillary walls, with negative IgA and no light-chain restriction. Electron microscopy confirmed subepithelial immune-complex deposits, consistent with pure Class V LN (ISN/RPS classification) [1]. The modified NIH LN activity index was 0/24 and the chronicity index was 0/12. The immunofluorescence and light microscopy findings are illustrated in [Table/Fig-2,3].

Serum anti-PLA2R antibodies were negative, excluding primary membranous nephropathy [2].



[Table/Fig-2]: Direct immunofluorescence microscopy of renal biopsy showing granular IgG and C3 deposition along the glomerular basement membrane (immunofluorescence stain, x400 magnification), consistent with immune-complex–mediated Lupus Nephritis (LN).



[Table/Fig-3]: Light microscopy of renal biopsy demonstrating diffuse glomerular basement membrane thickening consistent with membranous nephropathy (Periodic acid–Schiff stain, x400 magnification).

Although the patient did not fulfill the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria due to negative ANA (a mandatory entry criterion) [3], she satisfied the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria based on clinical renal involvement along with immunologic features including strongly positive anti-Sm antibodies and hypocomplementaemia [4].

The patient was treated with MMF 1 g twice daily and oral prednisolone 1 mg/kg/day (60 mg/day). Prednisolone was tapered by 10 mg every two weeks until a dose of 20 mg/day was reached. Thereafter, the dose was reduced by 5 mg every two weeks to 10 mg/day, followed by reduction of 2.5-5 mg every two weeks until a maintenance dose of 5 mg/day was achieved over six months. Losartan 50 mg once daily was initiated for proteinuria reduction, and atorvastatin 20 mg daily for dyslipidaemia. Sodium restriction and loop diuretics were prescribed. Calcium and vitamin D supplementation were initiated for bone protection. Pneumocystis jirovecii pneumonia prophylaxis with trimethoprim-sulfamethoxazole was initiated during high-dose steroid therapy.

At six months, the patient achieved partial remission, defined as ≥50% reduction in proteinuria with stable renal function, as per consensus criteria [5]. Serial changes in laboratory and urinary parameters are summarised in [Table/Fig-4]. Proteinuria decreased to 1.2 g/day, serum albumin normalised, and creatinine remained stable. Complement levels normalised, while anti-Sm antibodies remained positive on ELISA. No drug-related adverse effects or extra-renal disease manifestations were observed.

Parameter	Baseline	6 months
Serum creatinine (mg/dL)	1.3	1.0
eGFR (mL/min/1.73 m²)	62	68
Serum albumin (g/dL)	2.5	3.8
24-hour urine protein (g/day)	4.2	1.2
Urine protein–creatinine ratio	4.25	1.1
Urine RBC (per HPF)	Nil	Nil
Urine WBC (per HPF)	Nil	Nil
Urinary casts	Absent	Absent
C3 complement (mg/dL)	42	128
C4 complement (mg/dL)	6	22
Anti-Smith antibody (ELISA)	Strongly positive	Persistently positive
ANA (IIF)	Negative	Negative

[Table/Fig-4]: Comparison of baseline and 6-month follow-up parameters.
eGFR: Estimated glomerular filtration rate; RBC: Red blood cells; HPF: High-power field; WBC: White blood cells; C3: Complement component 3; C4: Complement component 4; ANA: Antinuclear antibody; IIF: Indirect immunofluorescence; ELISA: Enzyme-linked immunosorbent assay

DISCUSSION

ANA-negative SLE is an uncommon but recognised entity accounting for approximately 2-5% of patients [6]. True ANA negativity should be confirmed using indirect immunofluorescence on Human epithelial type 2 (HEp-2) cells to exclude technical limitations, prozone effects, or low-titre antibodies below detection thresholds [6]. In such cases, diagnosis may be delayed, particularly when renal involvement is the initial or dominant manifestation.

Published reports of ANA-negative LN remain limited and are largely confined to isolated case reports and small series. Bakshi N et al., described biopsy-proven LN in the absence of ANA positivity, emphasizing the diagnostic importance of renal histology and extended autoantibody testing [7]. Similarly, Simmons SC et al., reported ANA-negative full-house nephropathy presenting with nephrotic syndrome, highlighting that negative screening serology does not exclude immune-complex-mediated renal lupus [8]. Other reports have documented hypocomplementaemia and Extractable Nuclear Antigen (ENA) positivity as key diagnostic clues in seronegative presentations [9,10]. Compared with previously published cases, the present patient demonstrated persistent ANA negativity confirmed by two methodologies, isolated strong anti-Smith (anti-Sm) antibody positivity without other ENA antibodies, and pure Class V histology without proliferative features - a distinctly uncommon constellation.

Class V LN appears to be disproportionately represented among ANA-negative LN cases. Membranous patterns may reflect predominant subepithelial immune-complex deposition with relatively limited circulating nuclear antigen-antibody complexes detectable by conventional ANA assays [11]. This hypothesis remains speculative but has been proposed to explain discordance between renal immune-complex deposition and negative systemic serology. Anti-Sm antibodies, which are highly specific for SLE, may contribute directly to immune-complex formation and complement activation, potentially explaining the marked hypocomplementaemia observed in this case [12].

The differential diagnosis included primary membranous nephropathy, infection-related glomerulonephritis, and malignancy-associated nephropathy. These were excluded based on negative anti-PLA2R antibodies, absence of clinical or laboratory evidence of infection or malignancy, and renal biopsy findings consistent with LN. Partial rather than complete remission at six months may reflect delayed presentation, high baseline proteinuria, or the natural course of membranous LN [13].

In the present case, MMF was selected as first-line induction therapy due to preserved renal function, pure Class V histology, and its favourable safety profile compared to cyclophosphamide, in accordance with contemporary LN management recommendations [14]. Hydroxychloroquine was deferred initially given the absence

of extra-renal manifestations at presentation, although it remains an important adjunct in long-term SLE management and relapse prevention.

Long-term prognosis in pure Class V LN is generally favourable with appropriate immunosuppression; however, progression to proliferative disease and development of systemic manifestations have been reported, necessitating continued surveillance [12,14,15]. This case reinforces that persistent ANA negativity does not exclude LN and that extended autoantibody testing and timely renal biopsy are essential in patients presenting with nephrotic syndrome and hypocomplementaemia.

CONCLUSION(S)

ANA-negative LN, although uncommon, should be considered in patients presenting with nephrotic syndrome and hypocomplementaemia even in the absence of classic serological markers. Persistent negativity of ANA does not exclude SLE when other highly specific antibodies such as anti-Smith are present and renal histology is supportive. This case highlights the importance of extended ENA testing and timely renal biopsy in atypical presentations. Pure Class V LN may be overrepresented among seronegative cases and can respond favourably to appropriate immunosuppressive therapy. Early recognition of this rare serological phenotype can prevent diagnostic delay and allow prompt initiation of treatment. Continued surveillance is essential to monitor for disease progression or development of systemic manifestations.

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