EJCRIM
European Journal
of Case Reports
in Internal Medicine

WHEN SEROLOGY FAILS: RECOGNISING SYSTEMIC LUPUS ERYTHEMATOSUS IN THE ABSENCE OF AUTOANTIBODIES

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Received: 14/05/2025
Accepted: 26/05/2025
Published: 05/06/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for the publication of this case report.
Acknowledgements: We would like to thank American manuscript editors for English editing of our paper.
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How to cite this article: Alghanim KK, Alshammari SO, Albaqshi HT. When serology fails: recognising systemic lupus erythematosus in the absence of autoantibodies. *EJCRIM* 2025;**12**:doi:10.12890/2025_005525

ABSTRACT

The diagnosis of systemic lupus erythematosus (SLE) typically relies on characteristic autoantibodies and standardised classification criteria, and these serological markers guide both diagnosis and treatment decisions. But in rare cases, patients present with seronegative disease, creating significant diagnostic challenges that can delay appropriate intervention. Therefore, we present a case demonstrating the importance of clinical vigilance and histopathological confirmation in seronegative SLE. A 43-year-old woman with hypothyroidism developed inflammatory polyarthritis with consistently negative autoimmune serologies – rheumatoid factor, anti-cyclic citrullinated peptide antibodies, antinuclear antibodies, and anti–double-stranded deoxyribonucleic acid antibodies – despite elevated inflammatory markers. Initial treatment with hydroxychloroquine and corticosteroids elicited a significant therapeutic response. After 5 years, she developed a rapid decline in renal function with nephritic-range proteinuria. Renal biopsy revealed crescentic immune-complex glomerulonephritis with IgG, IgM, C3, and C1q deposits, confirming lupus nephritis. Aggressive therapy with intravenous methylprednisolone, plasma exchange, and cyclophosphamide, followed by maintenance therapy with mycophenolate mofetil, hydroxychloroquine, and oral corticosteroids, achieved clinical improvement and renal stabilisation. This case demonstrates that negative serologies should not preclude a diagnosis of SLE when the clinical presentation suggests systemic autoimmunity. Early renal biopsy and aggressive immunosuppression can prevent irreversible organ damage in seronegative disease. These findings support recognising seronegative SLE as a distinct disease subset and advocate for more inclusive diagnostic approaches beyond serological testing.

KEYWORDS

Seronegative systemic lupus erythematosus, renal biopsy, immunosuppressive therapy, autoantibodies

LEARNING POINTS

- Diagnosing seronegative systemic lupus erythematosus (SLE) relies on both clinical evaluation and histological findings.
- The absence of detectable autoantibodies does not exclude SLE; thus, a renal biopsy can assist in confirming the diagnosis.
- Initiating immunosuppression early is crucial to prevent permanent organ damage.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION/BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by a wide range of clinical manifestations. Diagnosis typically depends on serological markers, such as antinuclear antibodies (ANAs) and anti-double-stranded deoxyribonucleic acid (anti-dsDNA). However, studies have demonstrated that seronegative SLE can present with clinical features consistent with SLE, even in the absence of these markers[1]. The lack of standard autoantibodies complicates diagnosis, delays treatment initiation, and increases the risk of organ damage. Evidence indicates that seronegative SLE represents a small percentage of lupus cases and is often diagnosed through histopathological findings and clinical presentations[2]. This report examines the case of a 43-year-old woman with hypothyroidism, who presented with polyarthritis and elevated inflammatory markers. Despite these findings, autoimmune serologies remained negative. Initially, she was managed as a case of seronegative arthritis, but she later developed acute kidney involvement. Renal biopsy revealed immune-complex-mediated glomerulonephritis. The challenge of diagnosing her severe renal disease, combined with the absence of typical lupus serologies, required a multidisciplinary management approach. This case underscores the significance of recognising seronegative SLE as a distinct clinical entity and the necessity for advanced diagnostic strategies when clinical suspicion is strong, even with negative serological tests.

CASE DESCRIPTION

A 43-year-old woman with a history of hypothyroidism, managed with levothyroxine, presented with polyarthritis, affecting the small joints of the hands, elbows, and shoulders. Her vital signs were stable. During the initial clinic visit, the musculoskeletal examination revealed oedema and tenderness upon palpation of the metacarpophalangeal joint of the right middle finger. Laboratory tests showed mild normocytic, normochromic anaemia (haemoglobin 11.6 g/dl) and significantly elevated inflammatory markers (C-reactive protein, CRP 44.7 mg/L, erythrocyte sedimentation rate,

Parameter	Result	Reference range
Haemoglobin (g/dl)	11.6	Female: 12–16
Mean corpuscular volume, MCV (fl)	85	80–100
Mean corpuscular haemoglobin, MCH (pg)	29	27–33
Leukocyte ($\times 10^3$/l)	7	4.5–11
Lymphocyte ($\times 10^3$/l)	2.7	1–4.8
C-reactive protein, CRP (mg/l)	44.7	<3
Erythrocyte sedimentation rate, ESR (mm/h)	77	Female: 0–20
ANA	Negative	Negative
RF	Negative	Negative
Anti-dsDNA	Negative	Negative
Anti-CCP	Negative	Negative
Lupus anticoagulant	Positive	Negative
ENA	Negative	Negative
Complement 3, C3 (g/l)	1.61	0.83–1.93
Complement 4, C4 (g/l)	0.65	0.15–0.57
Creatinine (µmol/l)	71	Female: 45–84
Protein in urine (mg/dl)	0	0–14
Erythrocytes per high-power field in urine (RBCs/hpf)	0	≤2
24-h urine protein collection (mg/day)	<150	<150

Abbreviations: ANA, antinuclear antibodies; RF, rheumatoid factor; anti-dsDNA, anti-double stranded deoxyribonucleic acid; anti-CCP, anti-cyclic citrullinated peptide; ENA, extractable nuclear antigen; RBCs, red blood cells.

Table 1. Laboratory investigation results upon early presentation to rheumatology clinic.

ESR 77 mm/h). Autoimmune serologies – including ANA, anti-dsDNA, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), extractable nuclear antigen (ENA), and antiphospholipid (aPL) antibodies – were negative, aside from a transiently positive lupus anticoagulant, which later turned negative in repeat testing *(Table 1)*. The patient also reported a history of mechanical back pain. HLA-B27 testing was negative, and magnetic resonance imaging (MRI) of the spine did not indicate spondyloarthropathy.

The patient was thus diagnosed with seronegative inflammatory arthritis and initially treated with a tapered low-dose regimen of prednisolone (10 mg orally once daily) and hydroxychloroquine (300 mg orally once daily). While her adherence to the treatment was suboptimal, she reported notable improvement in joint symptoms and inflammatory markers, leading to maintenance therapy with hydroxychloroquine alone. Five years later, she developed proteinuria, haematuria, and renal impairment *(Table 2)*. Additionally, she presented with oral ulcers, inflammatory polyarthritis, fatigue, hypertension, and oedema in the lower limbs. Laboratory evaluations indicated anaemia associated with positive direct coombs test, leukopenia, elevated erythrocyte sedimentation rate/CRP, proteinuria, haematuria, and erythrocyte casts.

A renal biopsy was conducted, revealing more than 12 glomeruli, with one identified as obsolescent. The remaining glomeruli showed tuft compression by crescents, accompanied by focal segmental fibrinoid necrosis. The composition of the crescents varied: four were cellular, one was fibro cellular, and one was fibrous, indicating different stages of disease progression. Additionally, the tubules displayed patchy epithelial injury, while the interstitium was oedematous with mild, patchy lymphocytic infiltrates. No inflammatory reaction was observed in the arterioles.

Immunofluorescence (IF) staining revealed immune-complex deposition across multiple glomerular compartments. Specifically, IgA showed an equivocal segmental capillary wall deposit in a single glomerulus. IgG was positive in a granular pattern, affecting focal segments and capillary walls. IgM demonstrated granular and coarse segmental deposits within the mesangial and capillary walls. C3 deposits were observed in the glomerular, mesangial, and

Parameter	Result	Reference range
Haemoglobin (g/dl)	8.7	Female: 12–16
Mean corpuscular volume, MCV (fl)	89	80-100
Mean corpuscular haemoglobin, MCH (pg)	29	27-33
Reticulocyte count (%)	2	0.5–2.5(%)
Direct Coombs test	IgG+, C3-	Negative
Leukocyte ($\times 10^9$/l)	16	4.5–11
Lymphocyte ($\times 10^9$/l)	2.04	1–4.8
Neutrophils ($\times 10^9$/l)	14	1.5–8
Platelets ($\times 10^9$/l)	205	140-450
Complement 3, C3 (g/l)	1.5	0.83–1.93
Complement 4, C4 (g/l)	0.56	0.15–0.57
C-reactive protein, CRP (mg/l)	151	<3
Erythrocyte sedimentation rate, ESR (mm/h)	77	Female: 0-20
Serum creatinine (µmol/l)	468	Female: 45–84
Blood urea nitrogen, BUN (mmol/l)	33	2.5-6.7
Protein in urine (mg/dl)	850	0-14
Erythrocytes per high-power field (RBCs/hpf)	>5 (desmorphic RBC cast)	≤2
24-h urine protein collection (mg/day)	1633	<150

Abbreviations: ANA, antinuclear antibodies; RF, rheumatoid factor; anti-dsDNA, anti-double stranded deoxyribonucleic acid; anti-CCP, anti-cyclic citrullinated peptide; ENA, extractable nuclear antigen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; RBCs, red blood cells.

Table 2. Laboratory findings at the time of renal involvement.

capillary walls, and C1q was positive in a segmental pattern. Fibrinogen staining was positive within the crescents, further supporting the presence of active glomerular injury. No monoclonality was detected, as indicated by an X8L ratio of 3:1.

The biopsy findings suggested immune-complex-mediated glomerulonephritis, even though ANA and anti-dsDNA results were negative. The combination of multisystem involvement and histological evidence confirmed the diagnosis of seronegative SLE.

Initial management of the patient's inflammatory polyarthritis involved administering 10 mg of prednisolone daily along with 300 mg of hydroxychloroquine daily. Prednisolone was gradually tapered and eventually discontinued. Five years later, the patient developed acute kidney injury, which was complicated by significant proteinuria and haematuria, necessitating further intervention. Due to concerns about rapidly progressing glomerulonephritis, she was admitted to the Intensive Care Unit for treatment with high-dose intravenous methylprednisolone (1 g daily for 3 days). This was followed by a tapering dose of oral prednisolone.

The Euro-Lupus protocol for cyclophosphamide was initiated to control immune-mediated kidney damage. Plasma exchange was also employed to remove circulating immune complexes and inflammatory mediators. Following this immunosuppressive treatment, the patient showed improved renal function, as evidenced by reduced serum creatinine levels. Under the combined care of rheumatology and nephrology teams, she was discharged with continued cyclophosphamide infusions and a gradual taper of corticosteroids.

A long-term immunosuppressive therapy plan was developed to prevent disease recurrence, underscoring the need for personalised treatment strategies in seronegative SLE with renal involvement. Mycophenolate mofetil (500 mg orally twice daily) was prescribed as maintenance therapy.

DISCUSSION

Seronegative SLE presents a diagnostic challenge, as it diverges from conventional serological criteria. Although ANA positivity is traditionally regarded as a hallmark of SLE, some patients with distinct clinical and histopathological evidence of the disease may test negative for these antibodies[3]. Wajid et al. reported that the prevalence of seronegative SLE is below 2%[4]. This case highlights the need for a more comprehensive diagnostic strategy and illustrates the limitations of relying solely on autoantibody-based criteria. The patient's initial presentation with seronegative inflammatory peripheral polyarthritis led to a misdiagnosis with spondylarthritis being considered. Subsequently, the development of acute renal injury with nephritic-range proteinuria prompted further investigation. Despite persistently negative ANA and anti-dsDNA tests, a renal biopsy confirmed crescentic glomerulonephritis with immune-complex deposition, consistent with lupus nephritis. Standardised diagnostic criteria for seronegative SLE are lacking because the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2019 classification mandates antinuclear antibody (ANA) positivity. This requirement can exclude legitimate cases. Alternative diagnostic criteria, such as the Systemic Lupus International Collaborating Clinics (SLICC) criteria, offer greater flexibility by prioritising clinical presentation and tissue-based findings[5]. In the case described, despite negative autoantibody tests, indications of arthritis, nephritis, and systemic inflammation supported a probable lupus diagnosis. The limited sensitivity of testing methods may fail to detect autoantibodies in some patients, while others could produce antibodies against non-nuclear antigens.

Muralidharan and Rao[6] discussed the difficulties in diagnosing ANA-negative SLE, stressing the need for accurate testing methods and strong clinical judgment. In this case, ANA was assessed using the indirect immunofluorescence (IIF) technique on HEp-2 cells, which is considered the gold standard due to its high sensitivity and broad antigenic representation. A low threshold of 1:80 was used to enhance the detection of low-level antibodies. The patient was not on immunosuppressive therapy, and renal function was preserved, eliminating the possibility that autoantibodies were lost due to medications or renal issues. Altogether, these considerations and the lack of technical errors support the diagnosis of seronegative SLE[6].

Approximately 30–60% of SLE patients develop lupus nephritis, which significantly affects clinical outcomes. Since kidney involvement in seronegative lupus is similar to that in seropositive cases, renal biopsy remains an essential diagnostic tool[7]. The biopsy for this patient showed glomerular crescents, fibrinoid necrosis, and extensive immune-complex deposits – features characteristic of proliferative lupus nephritis. Failure to promptly recognise lupus nephritis in seronegative patients may delay treatment, even when immune-mediated features are present in the absence of ANA. In such cases, delayed identification can postpone necessary treatment initiation. This delay could exacerbate kidney damage before the initiation of immunosuppressive therapy[8].

An analysis of comparable cases demonstrates that seronegative lupus nephritis often presents with inflammatory arthritis, renal involvement, and a delayed diagnosis due to negative serologic findings[9]. Some patients exhibit temporary autoantibody positivity, indicating fluctuations in lupus autoantibody levels over time[10]. Although the patient initially appeared to have seronegative spondylarthritis, the absence of HLA-B27, negative spine MRI, and progression to severe renal disease necessitated clinical reassessment. This case supports recognising seronegative SLE as a distinct clinical entity. The extensive diagnostic approach, including kidney biopsy, was crucial in determining the disease pathology.

Future research should explore novel biomarkers, such as type I interferon signatures, to facilitate earlier identification

of seronegative lupus. This case highlights the drawbacks of relying solely on serologic tests for SLE diagnosis and emphasises the importance of clinical judgment in assessing autoimmune diseases. Although a negative ANA result can complicate diagnosis, specific organ involvement and biopsy results may warrant further investigation into seronegative lupus. Clinicians should remain vigilant for unusual findings and employ a multidisciplinary strategy to ensure timely diagnosis and effective management.

CONCLUSION

This case emphasises the diagnostic challenges associated with seronegative SLE and highlights the necessity of combining clinical and histopathological assessments for diagnosing autoimmune diseases. The lack of autoantibodies should not exclude the possibility of SLE, especially when major organs are involved. Improved diagnostic criteria are urgently needed to facilitate early detection and the timely initiation of suitable immunosuppressive therapy, which is vital for reducing long-term organ damage.

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