

Seronegative Lupus Nephritis Revealing Male Lupus: A Case Report and Literature Review

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Abstract

The diagnosis of systemic lupus erythematosus (SLE) classically relies on the association of clinical manifestations with positive serological tests, particularly antinuclear antibodies (ANA) and anti-dsDNA antibodies. Seronegative lupus is a rare entity characterized by negative immunological markers despite characteristic clinical features. Its prevalence is estimated between 2% and 10% of all lupus cases, with a higher frequency observed in male patients. We report the case of a 55-year-old man who presented with an isolated renal manifestation of lupus, in the absence of any other clinical or biological signs of systemic disease. The diagnostic work-up ruled out other etiologies, and the renal biopsy revealed a class IV proliferative glomerulonephritis with a characteristic "full-house" immunofluorescence pattern. This case highlights the diagnostic challenges of seronegative lupus and the central role of renal biopsy in establishing the diagnosis. A review of the literature on seronegative lupus and male lupus is presented.

Keywords: Seronegative lupus, lupus nephritis, male lupus, diffuse proliferative glomerulonephritis, class IV lupus nephritis, full-house pattern.

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic,

multisystemic autoimmune disease characterized by the production of autoantibodies directed against nuclear antigens, including antinuclear antibodies (ANA) and anti-DNA antibodies [1, 2]. The diagnosis of SLE is based on a combination of clinical and biological criteria, as defined by the American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinics (SLICC), and more recently by the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria[2,3]. A positive ANA test is a mandatory entry criterion for these classification systems [2,3].

However, seronegative lupus is a rare but well-recognized entity defined by the absence of ANA and anti-dsDNA antibodies despite the presence of characteristic clinical manifestations [4,5]. The prevalence of seronegative lupus is estimated at 2% to 10% of all lupus cases, with a higher frequency observed in male patients [5, 6]. A systematic review of 152 patients with ANA-negative SLE found that cutaneous manifestations, photosensitivity, and joint complaints were the most common clinical features [5].

Lupus nephritis is a major cause of morbidity and mortality in SLE, affecting approximately 40% to 60% of patients [7, 8]. The histopathological classification of lupus nephritis, based on the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification, distinguishes six classes, with class IV (diffuse proliferative glomerulonephritis) being the most severe and most commonly associated with renal failure [7,9].

The characteristic "full-house" immunofluorescence pattern, with glomerular deposits staining for IgG, IgA, IgM, C1q, and C3, is a hallmark of lupus nephritis but can occasionally be seen in other conditions such as endocarditis, HIV, or hepatitis C infection [9, 10].

We report a case of seronegative lupus nephritis revealing male lupus, highlighting the diagnostic challenges and the importance of renal biopsy in establishing the diagnosis.

2. Case Report

A 55-year-old male patient, with a history of chronic obstructive pulmonary disease on bronchodilators and a perforated gastric ulcer operated 15 years ago, was hospitalized for evaluation and management of deep nephrotic syndrome with moderate renal failure. There was no significant family history of autoimmune or renal

disease. The patient had no history of photosensitivity, malar rash, oral ulcers, arthritis, or serositis. The patient was retired, living with his spouse, and had no significant psychosocial stressors.

Clinical examination revealed a patient in good general condition with moderate edema of the lower limbs. Blood pressure was 140/85 mmHg. Laboratory findings showed serum creatinine at 15 mg/L (normal: 6-12 mg/L) with a clearance at 45 mL/min, serum albumin at 18 g/L (normal: 35-50 g/L), and proteinuria at 4.5 g/24h (normal: <0.15 g/24h). Complement levels (C3, C4) were normal. Immunological work-up was negative for antinuclear antibodies, anti-dsDNA antibodies, anti-Sm antibodies, anti-RNP antibodies, and anti-SSA/Ro antibodies. Viral serologies (HIV, hepatitis B and C) and cryoglobulins were negative. Serum protein electrophoresis showed no monoclonal peak. The differential diagnosis included primary membranous nephropathy, IgA nephropathy, focal segmental glomerulosclerosis, and infection-related glomerulonephritis. These were excluded based on the absence of viral serologies (HIV, hepatitis B and C), negative cryoglobulins, and the specific histological findings on renal biopsy.

A renal biopsy was performed. Light microscopy revealed diffuse endocapillary and extracapillary hypercellularity with cellular crescents, consistent with class IV (diffuse proliferative) lupus nephritis [7, 9]. Immunofluorescence showed a "full-house" pattern with dominant mesangial and capillary loop deposits of IgG (3+), IgA (2+), IgM (2+), C1q (3+), and C3 (3+) [9, 10]. The main diagnostic challenge in this case was the absence of serological markers (ANA and anti-dsDNA antibodies) despite the presence of a severe nephrotic syndrome. This led to a delay in considering the diagnosis of lupus nephritis. The diagnosis was only established after renal biopsy, which revealed the characteristic 'full-house' immunofluorescence pattern and class IV proliferative glomerulonephritis. The patient was started on oral prednisone at 1 mg/kg/day (60 mg/day) with a gradual taper over 6 months, and mycophenolate mofetil at 2 g/day. Due to digestive intolerance (nausea and diarrhea), mycophenolate mofetil was discontinued and the patient was switched to the EuroLupus regimen: intravenous cyclophosphamide at 500 mg every 2 weeks for 6 doses, combined with oral prednisone [11]. He achieved partial response within three weeks and recovered normal renal function but developed corticosteroid-induced osteoporosis, which

was managed with calcium and vitamin D supplementation. At 6 months follow-up, the patient remained in partial remission with proteinuria at 0.8 g/24h (from 4.5 g/24h) and serum creatinine at 12 mg/L (from 15 mg/L). Serum albumin had normalized to 38 g/L. The patient continued on tapering doses of

prednisone (10 mg/day) and completed the cyclophosphamide regimen. No relapse of nephrotic syndrome was observed. The corticosteroid-induced osteoporosis was managed with calcium (1000 mg/day) and vitamin D (800 IU/day) supplementation.

See Timeline Table below

Date/Event	Key Clinical Biological Data and	Interventions
Presentation	Lower limb edema, serum creatinine at 15 mg/L, proteinuria at 4.5 g/24h	Hospitalization, etiological work-up
Immunological work-up	ANA, anti-ds DNA, anti-Sm, anti-RNP, anti-SSA/Ro: negative	Renal biopsy indicated
Renal biopsy	Diffuse proliferative glomerulonephritis (class IV), "full-house" immunofluorescence pattern	Diagnosis of seronegative lupus nephritis established
Induction therapy (Week 1)	Decreasing proteinuria, stable creatinine	Prednisone 60 mg/day + mycophenolate mofetil 2 g/day
Therapy change (Week 2)	Digestive intolerance to MMF (nausea, diarrhea)	Switch to intravenous cyclophosphamide 500 mg every 2 weeks
Response (Week 3)	Partial response, creatinine at 12 mg/L, albumin at 38 g/L	Continuation of treatment
6-month follow-up	Proteinuria at 0.8 g/24h, creatinine at 12 mg/L	Prednisone 10 mg/day, calcium, vitamin D

3. Discussion

3.1. Seronegative Lupus

Seronegative lupus is a rare entity defined by the absence of ANA and anti-dsDNA antibodies despite the presence of characteristic clinical manifestations of SLE [4, 5]. The prevalence of seronegative lupus is estimated at 2% to 10% of all lupus cases, with a higher frequency in male patients [5, 6]. The diagnosis is challenging because the absence of serological markers delays recognition and treatment [4, 5]. A systematic review of 152 patients with ANA-negative SLE found that cutaneous manifestations, photosensitivity, and joint complaints were the most common clinical features [5]. The most frequently detected autoantibodies in these patients were anti-SSA/Ro and anti-dsDNA [5].

Several hypotheses have been proposed to explain the seronegative status in these patients [5, 12]. First, the antibodies may be present at low titers that are not detected by conventional assays. Second, the antibodies may be bound to tissues, leading to false-negative serological tests. Third, the disease may be caused by other autoantibodies such as anti-ribosomal P antibodies, anti-Sm antibodies, or anti-RNP antibodies. Fourth, in some cases, the disease may be mediated by other immunological mechanisms not involving ANA [12].

Seronegative lupus nephritis is an even rarer entity. A case of a 28-year-old male with nephrotic syndrome and negative ANA was diagnosed with class IV/V lupus nephritis on renal biopsy [13]. A 31-year-old male with anasarca, nephrotic-range proteinuria, and negative autoimmune work-up was diagnosed with seronegative lupus nephritis based on renal biopsy showing diffuse proliferative glomerulonephritis with full-house staining [1]. In a 19-year-old male with mild proteinuria and microscopic hematuria, renal biopsy revealed class V membranous lupus nephritis despite negative serology [14]. These cases underscore the diagnostic significance of renal biopsy in seronegative lupus nephritis [1, 13, 14].

3.2. Male Lupus

SLE predominantly affects women, with a female-to-male ratio of approximately 9:1 [15]. Male lupus is less common and may present with atypical clinical features [16]. While some studies suggest that men less frequently display the typical mucocutaneous features of SLE at disease onset, the incidence of renal involvement and the severity of nephropathy may be higher in men [16]. However, other studies have found no significant

difference in major organ involvement between male and female patients [15]. Our patient, a 55-year-old man, presented with isolated renal involvement, which is consistent with the pattern of male lupus [16].

3.3. Lupus Nephritis

Lupus nephritis affects approximately 40% to 60% of patients with SLE [7, 8]. The ISN/RPS classification distinguishes six classes, with class IV (diffuse proliferative glomerulonephritis) being the most severe and most commonly associated with renal failure and progression to endstage renal disease [7, 9]. The "full-house" immunofluorescence pattern, characterized by glomerular deposits of IgG, IgA, IgM, C1q, and C3, is a hallmark of lupus nephritis [9, 10].

Although this pattern is highly suggestive of lupus nephritis, it can infrequently be seen in patients with endocarditis, HIV, hepatitis C virus infection, a portosystemic shunt, and poststreptococcal glomerulonephritis [9, 10]. However, the work-up in our patient was negative for all these conditions, confirming the diagnosis of lupus nephritis.

The management of lupus nephritis requires aggressive immunosuppressive therapy. According to the 2019 EULAR/ERA-EDTA recommendations, induction therapy with mycophenolate mofetil or low-dose cyclophosphamide, combined with glucocorticoids, is recommended for active proliferative lupus nephritis [11]. Our patient was treated with corticosteroids and mycophenolate mofetil, but due to intolerance, he was successfully switched to the Euro lupus regimen [11].

3.4. Implications for Clinical Practice

This case underscores several important points for clinical practice. First, seronegative lupus should be considered in patients with suggestive clinical features even with negative serology, as the diagnosis of lupus cannot be excluded based on serology alone [4, 5]. Second, renal biopsy is essential for diagnosis, as it not only establishes the diagnosis but also determines the histopathological subtype and guides treatment [7, 9]. Third, male lupus may present with isolated renal involvement, and clinicians should be aware that male patients may have atypical presentations [16]. Fourth, the "full-house" immunofluorescence pattern, while characteristic of lupus nephritis, requires exclusion of other causes [9, 10]. Finally, treatment should be individualized based on the severity of renal involvement, the patient's tolerance, and the

histopathological findings [11].

3.5. Strengths and Limitations

The strength of this case report lies in the comprehensive diagnostic work-up, including renal biopsy with immunofluorescence, which confirmed the diagnosis of seronegative lupus nephritis. The case highlights the importance of renal biopsy in atypical presentations and the need to consider lupus in the differential diagnosis of nephrotic syndrome, even in the absence of serological markers.

The main limitation is that this is a single case report, which limits the generalizability of the findings. In addition, long-term follow-up data are limited to six months, and the patient's response to treatment was assessed over a relatively short period. Further studies with larger cohorts are needed to confirm these observations and to better understand the pathophysiology of seronegative lupus nephritis.

4. Conclusion

The diagnosis requires a high index of suspicion and is confirmed by renal biopsy, which reveals characteristic histological features and the "full-house" immunofluorescence pattern [9,10]. This case highlights the diagnostic challenges of seronegative lupus and the central role of renal biopsy in establishing the diagnosis [4,5]. Early diagnosis and treatment are essential to prevent progression to end-stage renal disease [7, 11].

Take-away Lessons

This case demonstrates that the diagnosis of lupus nephritis cannot be excluded based on negative serology alone. Renal biopsy is essential in patients with unexplained nephrotic syndrome, as it can reveal the characteristic histological and immunofluorescence findings of lupus nephritis. Clinicians should be aware that male patients may present with isolated renal involvement without systemic manifestations. The 'full-house' immunofluorescence pattern on renal biopsy is highly suggestive of lupus nephritis, but requires exclusion of other causes such as infection or malignancy.

5. Patient Perspective

The patient was initially surprised by the diagnosis of lupus, as he had no typical symptoms such as skin rash or joint pain. He expressed that the renal biopsy was a decisive step in understanding his condition. Although he

was concerned about the treatments, he noted a rapid improvement in his condition and is grateful to have received a complete diagnostic and therapeutic work-up. He agreed to share his case in the hope of helping other patients with similar presentations.

6. Informed Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying data. The patient was informed that his identity would remain anonymous. A copy of the consent form is available for review by the Editor-in-Chief of this journal.

7. Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this manuscript.

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