

# *Extreme Nephrotic-Range Proteinuria in Mixed Lupus Nephritis with Low Histologic Activity: Potential Contribution of Obesity-Related Hyperfiltration in a Triple Autoimmune Overlap Syndrome* \_\_\_\_\_

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***Vilma CADRI*** \_\_\_\_\_

Contact Author: vilma.cadri@gmail.com

DEPARTMENT OF NEPHROLOGY

UNIVERSITY HOSPITAL CENTER "MOTHER TERESA", TIRANA, ALBANIA

\_\_\_\_\_  
***Ilda NASUFI*** \_\_\_\_\_

DEPARTMENT OF NEPHROLOGY

UNIVERSITY HOSPITAL CENTER "MOTHER TERESA", TIRANA, ALBANIA

\_\_\_\_\_  
***Nisrin HASA*** \_\_\_\_\_

DEPARTMENT OF NEPHROLOGY

UNIVERSITY HOSPITAL CENTER "MOTHER TERESA", TIRANA, ALBANIA

\_\_\_\_\_  
***Irda RRUGEJA*** \_\_\_\_\_

DEPARTMENT OF ANATOMICAL PATHOLOGY

UNIVERSITY HOSPITAL CENTER "MOTHER TERESA", TIRANA, ALBANIA

\_\_\_\_\_  
***Ervin RRAPUSHI*** \_\_\_\_\_

DEPARTMENT OF RHEUMATOLOGY

UNIVERSITY HOSPITAL CENTER "MOTHER TERESA", TIRANA, ALBANIA

## Abstract

**Background:** Mixed lupus nephritis (LN), combining proliferative and membranous lesions, is frequently associated with substantial proteinuria and increased risk of kidney injury. However, the occurrence of massive nephrotic-range proteinuria despite minimal histologic activity, persistently negative anti-double stranded DNA (anti-dsDNA) antibodies, and preserved serum creatinine represents an uncommon diagnostic challenge. The coexistence of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis (PsA) in a single patient is exceptionally rare and further complicates disease assessment and management.

**Case Presentation:** We report a 39-year-old man with an 18-year history of triple autoimmune overlap syndrome (SLE, RA, and PsA) who presented with severe nephrotic-range proteinuria (10.7 g/24 h), urinary albumin-to-creatinine ratio (UACR) of 23,538 mg/g, hypoalbuminemia, persistent hypocomplementemia, pancytopenia, and severe obesity BMI 39.2 kg/m<sup>2</sup>. Despite preserved serum creatinine (0.8 mg/dL), measured creatinine clearance was markedly elevated at 216 mL/min, consistent with extreme glomerular hyperfiltration. Serological evaluation demonstrated positive antinuclear antibodies (ANA) but persistently negative anti-dsDNA antibodies. Kidney biopsy revealed mixed lupus nephritis Class III+V according to the 2018 ISN/RPS classification, with full-house immunofluorescence, a low activity index (2/24), and minimal chronicity (0–1). The marked discrepancy between massive proteinuria and limited histologic activity raised the possibility that obesity-related hyperfiltration contributed to urinary protein losses in addition to immune-complex-mediated renal injury. Following treatment with pulse methylprednisolone, mycophenolate mofetil, hydroxychloroquine, and supportive nephroprotective therapy, the patient achieved substantial clinical and biochemical improvement. After nine months of follow-up, proteinuria decreased to 3.8 g/24 h, UACR declined to 238 mg/g, serum albumin improved to the lower limit of normal, and complement levels normalized, while body weight remained unchanged.

**Conclusion:** This case highlights three important clinical messages. First, active lupus nephritis may occur despite persistently negative anti-dsDNA antibodies. Second, severe nephrotic-range proteinuria may be observed in mixed Class III+V lupus nephritis even when histologic activity appears limited. Third, obesity-related glomerular hyperfiltration may amplify proteinuria and contribute to clinicopathological discordance. The marked renal improvement despite unchanged body weight suggests that lupus nephritis represented the principal pathological process, whereas hyperfiltration acted as an important disease modifier. Kidney

*biopsy remains indispensable for diagnosis and therapeutic decision-making in complex autoimmune overlap syndromes.*

**Keywords:** *lupus nephritis; mixed lupus nephritis; overlap syndrome; systemic lupus erythematosus; rheumatoid arthritis; psoriatic arthritis; nephrotic syndrome; glomerular hyperfiltration; obesity-related kidney disease; mycophenolate mofetil.*

## Introduction

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE), affecting approximately 40–60% of patients and representing a major cause of chronic kidney disease and kidney failure [1,2]. The revised 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification recognizes mixed forms of LN in which proliferative lesions (Class III or IV) coexist with membranous involvement (Class V), a histological pattern frequently associated with substantial proteinuria and distinct therapeutic implications [3,4].

Although anti-double stranded DNA (anti-dsDNA) antibodies and complement levels are widely used as markers of disease activity, the correlation between serological findings and renal histopathology is often imperfect. A substantial proportion of patients with biopsy-proven lupus nephritis may present with negative anti-dsDNA antibodies, particularly in longstanding disease or membranous-predominant forms, highlighting the indispensable role of kidney biopsy in diagnosis and treatment decisions [1,5]. Furthermore, the relationship between urinary protein excretion and histological activity is not always linear, particularly in mixed proliferative–membranous disease and in the presence of additional hemodynamic stressors.

The coexistence of multiple autoimmune rheumatic diseases further complicates disease assessment and management. Overlap syndromes involving SLE and rheumatoid arthritis (RA), commonly referred to as “Rhus syndrome,” are uncommon, whereas the simultaneous presence of SLE, RA, and psoriatic arthritis (PsA) has only rarely been described in the literature [6–8]. In such patients, clinical manifestations, serological markers, and therapeutic responses may differ substantially from classical disease patterns.

Obesity has emerged as an important modifier of kidney disease. Severe obesity may induce glomerular hyperfiltration through increased intraglomerular pressure, activation of the renin–angiotensin–aldosterone system, and altered tubuloglomerular feedback [9]. Persistent hyperfiltration may amplify urinary protein losses and obscure clinicopathological correlations in glomerular disease [10].

We report a patient with an exceptionally rare triple autoimmune overlap syndrome (SLE, RA, and PsA) who developed biopsy-proven mixed lupus nephritis Class III+V presenting with massive nephrotic-range proteinuria, persistently negative anti-dsDNA antibodies, preserved serum creatinine, and marked obesity-related glomerular hyperfiltration. The case highlights the diagnostic value of kidney biopsy and suggests that obesity-associated hyperfiltration may have amplified urinary protein losses and contributed to the apparent discrepancy between extreme proteinuria and limited histologic activity.

## Case Presentation

A 39-year-old Albanian man was referred to the Department of Nephrology, University Hospital Center “Mother Teresa” (QSUNT), Tirana, for evaluation of newly detected nephrotic-range proteinuria in the setting of longstanding autoimmune disease.

The patient had been diagnosed with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in 2007 and subsequently fulfilled diagnostic criteria for psoriatic arthritis (PsA), establishing a rare triple autoimmune overlap syndrome. His long-term treatment included glucocorticoids, hydroxychloroquine, non-steroidal anti-inflammatory drugs, and antihypertensive therapy. At presentation, he had severe obesity, with a body weight of 128 kg and BMI 39.2 kg/m<sup>2</sup>.

Three weeks before admission, he developed progressive fatigue, photosensitivity, facial erythema, scalp desquamation, periorbital edema, xerostomia, polyuria, and worsening constitutional symptoms. Physical examination confirmed obesity, facial erythema, and bilateral periorbital edema. Blood pressure was 130/75 mmHg.

**Figure 1.** Cutaneous manifestations at presentation.



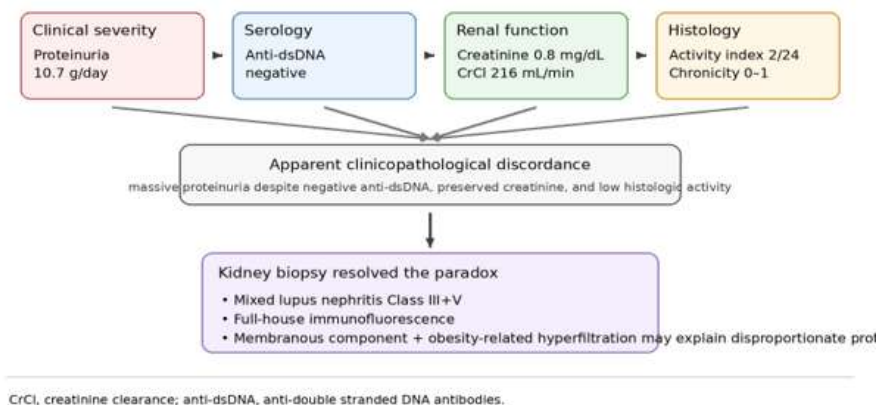
**Figure 1.** Cutaneous manifestations at presentation. (A) Pretibial ulcerative lesion with surrounding erythema and chronic skin changes of the lower extremity. (B) Chronic scalp lesion showing patchy hypopigmentation, alopecic changes, and cutaneous atrophy.

Initial laboratory evaluation revealed nephrotic-range proteinuria of 10.7 g/24 h and a urinary albumin-to-creatinine ratio (UACR) of 23,538 mg/g. Additional findings included hypoalbuminemia, normocytic anemia, thrombocytopenia, and marked hypocomplementemia (C3 34 mg/dL, C4 5.5 mg/dL). Antinuclear antibodies (ANA) were positive, whereas anti-double stranded DNA (anti-dsDNA) antibodies remained negative. Serum creatinine was preserved at 0.8 mg/dL; however, measured creatinine clearance reached 216 mL/min, indicating marked glomerular hyperfiltration

The coexistence of massive nephrotic-range proteinuria, preserved serum creatinine, persistently negative anti-dsDNA antibodies, and marked hyperfiltration represented a significant diagnostic challenge. Therefore, a kidney biopsy was performed.

Histopathological examination demonstrated mixed lupus nephritis Class III+V according to the 2018 ISN/RPS classification. Immunofluorescence revealed a characteristic full-house pattern with deposition of IgG, IgA, IgM, C3, and C1q. The modified NIH activity index was low (2/24), while chronicity was minimal (0–1), indicating limited inflammatory and chronic damage despite extensive urinary protein loss.

**FIGURE 2.** Diagnostic paradox at presentation.



Despite massive nephrotic-range proteinuria, persistently negative anti-dsDNA antibodies, preserved serum creatinine, and marked glomerular hyperfiltration, kidney biopsy demonstrated mixed lupus nephritis Class III+V and resolved the apparent clinicopathological discordance. CrCl, creatinine clearance; anti-dsDNA, anti-double stranded DNA antibodies.

Supportive nephroprotective therapy with losartan and dapagliflozin was initiated. Following exclusion of active infection, induction immunosuppression was started with intravenous methylprednisolone pulses followed by mycophenolate mofetil. Hydroxychloroquine was continued throughout treatment.

The patient demonstrated progressive clinical and biochemical improvement during follow-up. Nine months after treatment initiation, 24-hour proteinuria had decreased from 10.7 g/day to 3.8 g/day, while UACR declined from 23,538 mg/g to 238 mg/g. Serum albumin improved to the lower limit of the normal range, complement levels (C3 and C4) normalized, and anti-dsDNA antibodies remained negative. ANA positivity persisted. Despite substantial improvement in renal and serological parameters, body weight remained unchanged at approximately 128 kg throughout follow-up and BMI 39.2 kg/m<sup>2</sup>.

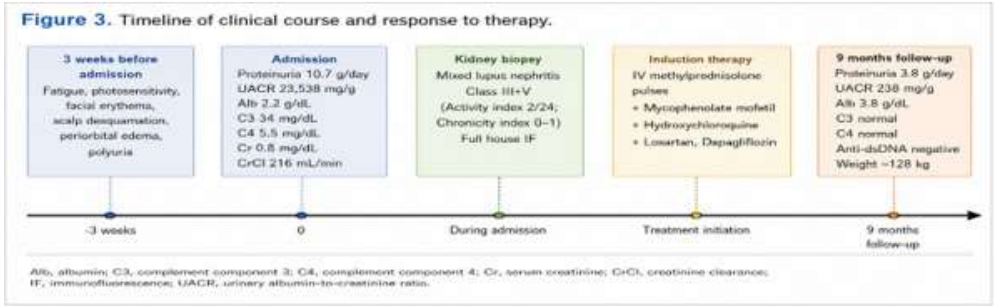
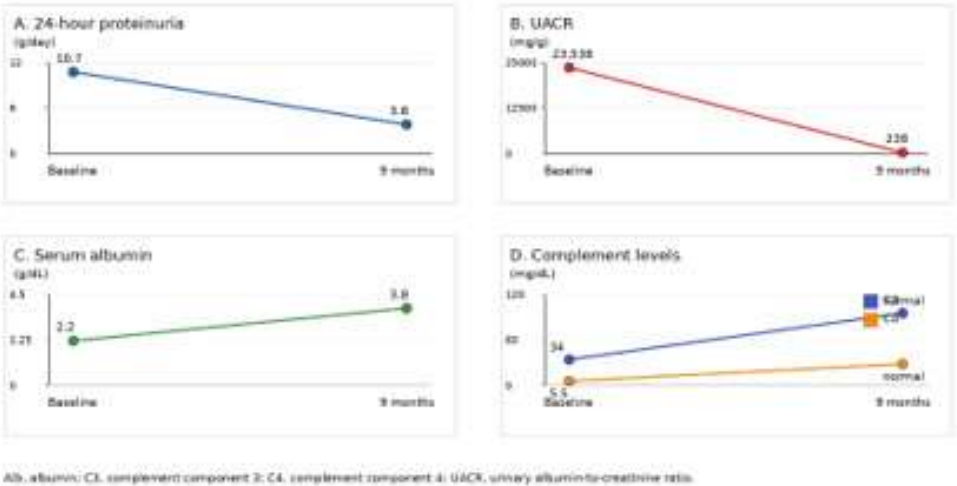


**FIGURE 4.** Trend of key laboratory parameters during follow-up. Changes in (A) 24-hour proteinuria, (B) urinary albumin-to-creatinine ratio (UACR), (C) serum albumin concentration, and (D) complement levels (C3 and C4) between baseline and 9-month follow-up. Marked improvement in proteinuria, albuminuria, hypoalbuminemia, and complement consumption was observed following immunosuppressive and nephroprotective therapy.



## Discussion

This case illustrates the complex interplay between autoimmune disease, renal pathology, and metabolic factors in a patient with an exceptionally rare triple overlap syndrome comprising systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis (PsA). While overlap between SLE and RA (“Rhupus syndrome”) has been increasingly recognized, the coexistence of SLE, RA, and PsA remains exceedingly uncommon and has been described only in isolated reports [6–8]. The simultaneous presence of three autoimmune diseases may generate atypical clinical and serological presentations, complicating diagnostic and therapeutic decision-making. In our patient, nephrotic-range proteinuria represented the first major renal manifestation after nearly two decades of systemic autoimmune disease.

An important feature of this case was the discordance between serological findings and renal histopathology. Despite biopsy-proven lupus nephritis, anti-dsDNA antibodies remained persistently negative throughout the disease course. Although anti-dsDNA antibodies are commonly used as biomarkers of disease activity, their sensitivity for active lupus nephritis is limited, particularly in membranous-predominant disease and in patients receiving chronic immunosuppressive therapy [1,5,11–13]. In contrast, our patient exhibited profound hypocomplementemia at presentation, with markedly reduced C3 and C4 levels that normalized following treatment. This evolution suggests that complement consumption reflected ongoing immune-complex activity more accurately than anti-dsDNA antibodies in this setting. The case therefore reinforces a fundamental principle of lupus nephritis management: serological quiescence does not exclude active renal disease, and kidney biopsy remains essential whenever clinical suspicion persists [3,5,12,13].

In the present case, the coexistence of massive nephrotic-range proteinuria, persistently negative anti-dsDNA antibodies, preserved serum creatinine, and a low histologic activity index created a diagnostic paradox that was ultimately resolved by kidney biopsy. Despite urinary protein excretion of 10.7 g/day, histopathology demonstrated a low activity index (2/24) and minimal chronicity (0–1). At first glance, this degree of proteinuria appeared disproportionate to the biopsy findings. However, the identification of mixed lupus nephritis Class III+V provides a biologically plausible explanation for this apparent discordance. Membranous lupus nephritis is characterized by subepithelial immune-complex deposition and podocyte injury and may produce severe nephrotic syndrome even in the absence of extensive proliferative lesions [4,14,15]. Consequently, the severity of proteinuria and the degree of histological activity do not necessarily correlate

linearly, particularly in mixed proliferative–membranous disease. Importantly, the substantial reduction in proteinuria from 10.7 g/day to 3.8 g/day following immunosuppressive therapy, together with normalization of complement levels and improvement in serum albumin, supports the biological and clinical relevance of the lupus nephritis despite the low activity index observed on biopsy.

A second mechanism may have contributed to the unusually severe proteinuria observed in this patient. At presentation, serum creatinine was normal (0.8 mg/dL), yet measured creatinine clearance reached 216 mL/min, indicating extreme glomerular hyperfiltration. Obesity-related glomerular hyperfiltration is a recognized consequence of severe obesity and results from increased renal plasma flow, activation of the renin–angiotensin–aldosterone system, hyperinsulinemia, and elevated intraglomerular pressure [9,10,16–18]. Persistent hyperfiltration increases mechanical stress on the glomerular filtration barrier and may enhance protein trafficking across damaged glomerular capillary walls [10,16,17]. Although obesity-related glomerulopathy was not demonstrated histologically in our patient, the extraordinary degree of hyperfiltration raises the possibility that obesity acted as a hemodynamic amplifier of proteinuria. We hypothesize that the coexistence of membranous lupus nephritis and severe obesity-related hyperfiltration contributed to the apparent mismatch between extreme urinary protein losses and the limited inflammatory activity observed histologically.

The patient's subsequent clinical evolution further supports this interpretation. Following induction therapy with methylprednisolone and mycophenolate mofetil, combined with hydroxychloroquine and nephroprotective treatment, proteinuria declined from 10.7 g/day to 3.8 g/day, while UACR decreased from 23,538 mg/g to 238 mg/g. Serum albumin improved to the lower limit of the normal range, complement levels normalized, and anti-dsDNA antibodies remained negative. Notably, these improvements occurred despite unchanged body weight of approximately 128 kg throughout follow-up. While lupus nephritis represented the primary pathological process, the patient's marked obesity and extreme glomerular hyperfiltration may have amplified urinary protein losses. Although obesity-related glomerulopathy was not demonstrated histologically, the measured creatinine clearance of 216 mL/min suggests a substantial hyperfiltration state that may have contributed to the apparent discrepancy between nephrotic-range proteinuria and the low histologic activity index observed on kidney biopsy. The case therefore highlights the importance of integrating clinical, serological, metabolic, and histopathological information rather than relying on any single parameter in isolation.

Current KDIGO 2024 and EULAR 2025 recommendations emphasize the importance of early diagnosis, kidney biopsy, hydroxychloroquine therapy, renin–angiotensin system blockade, and timely initiation of immunosuppressive treatment in patients with active lupus nephritis [2,5,19,20]. In the present case,

kidney biopsy proved crucial for establishing the diagnosis despite persistently negative anti-dsDNA antibodies and preserved serum creatinine. Conventional therapy with glucocorticoids and mycophenolate mofetil resulted in substantial clinical and renal improvement, supporting its continued effectiveness in appropriately selected patients, particularly in resource-limited settings.

In conclusion, this case highlights three clinically relevant messages. First, active lupus nephritis may occur despite persistently negative anti-dsDNA antibodies. Second, massive proteinuria may develop in mixed Class III+V lupus nephritis even when histologic activity appears limited. Third, severe obesity-related glomerular hyperfiltration may amplify urinary protein losses and contribute to clinicopathological discordance, thereby obscuring the relationship between proteinuria and histological activity. Recognition of these interacting mechanisms may facilitate earlier diagnosis and more individualized management in complex autoimmune overlap syndromes.

#### **Informed Consent**

Written informed consent was obtained from the patient for the publication of this case report and any accompanying clinical data and images.

#### **Conflict of Interest**

The authors declare no conflict of interest.

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