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# Seronegative lupus membranous nephropathy

Mandya Chikkalingaiah Kiran

## ABSTRACT

**Introduction: Lupus nephritis represents the greater part of systemic lupus erythematosus (SLE) involvement. Antinuclear antibody (ANA) is positive in more than 95% of SLE population. Literature depicts the prevalence of ANA negativity around 1–5% and more prevalent in young females as seropositive lupus. Existence of full-house nephropathy is generally associated with lupus nephritis. Case Report: We present a case of full-house nephropathy in a 24-year-old female patient with negative serology for SLE presenting with nephrotic syndrome. Renal biopsy revealed tubuloreticular inclusions (TRIs) in endothelial cells differentiating itself from rarer C1q nephropathy. Patient had partial response with conventional immunotherapy with mycophenolate mofetil (MMF) and prednisone. Conclusion: The role of B cell depleting therapy in seronegative lupus; this population needs to be explored in future.**

**Keywords: Full house nephropathy, Lupus nephritis, Seronegative lupus, Tubuloreticular inclusions**

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## INTRODUCTION

Systemic lupus erythematous (SLE) renal involvement is referred to as 'lupus nephritis' and is generally associated with antinuclear antibody (ANA) positivity. Antinuclear antibody is negative in approximately 5% of patients diagnosed with SLE. The existence of full-house nephropathy is generally associated with lupus nephritis. We present an interesting case of nephrotic syndrome with full house nephropathy with persistent negative lupus serology.

## CASE REPORT

A 24-year-old Caucasian woman presented with swelling of feet and face since 2–3 months. On referral visit she was examined for proteinuria. Patient denies joint pain, rashes, oral ulcer, hair loss and usage of NSAIDS. Workup revealed nephrotic range proteinuria 5.51 grams per day, serum creatinine 1.2 mg/dl and urinalysis of occasional RBC, with no active sediments. Serology tests for ANA, double stranded DNA <5 IU/ml (normal 0–9), smith antibody <0.2 IU/ml (normal 0–9),

hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), rheumatoid factor and A1c were negative. Serum complement levels were within normal limits [C3 152 mg/dl (normal 90–180 mg/dl), C4 24 mg/dl (normal 9–36 mg/dl)]. Renal biopsy (34 glomeruli) revealed immune complex mediated glomerulonephritis (GN) with marked glomerular basement membrane duplication and interstitial fibrosis (5–10%) (Figure1). Immune deposits were present in all compartments. There was no evidence of proliferative, amyloidosis, diabetic or paraproteinemia nephropathy. Immunofluorescence (IF) of nine glomeruli featured IgG3+ (Figure 2), IgA1+, IgM1-2+, C3 2+, C1q 2+ staining with absent monoclonal element. Electron microscopy of three glomeruli showed loops of sub epithelial (98%), sub endothelial (20%), mesangial (1-2+) deposits with diffuse foot process effacement. Numerous TRIs within endothelial cell cytoplasm were also seen (Figure 3). Patient was treated with MMF, prednisone, ace inhibitor (ACEI) and statin. Two weeks later patient developed severe arthritis involving both shoulder and left hip. Patient was hospitalized for intravenous steroids and repeat lupus serology were negative. Arthritis settled down and she was continued on above medications. At two year follow-up her proteinuria has improved from 5.51 to 1.1 gram per day (Figure 4) with stable renal function (Scr 1.1 mg/dl). Repeat lupus serology is negative and complement levels are normal. No lupus flares were seen in these two years. We did not have opportunity to test anti C1q antibodies in our patient.

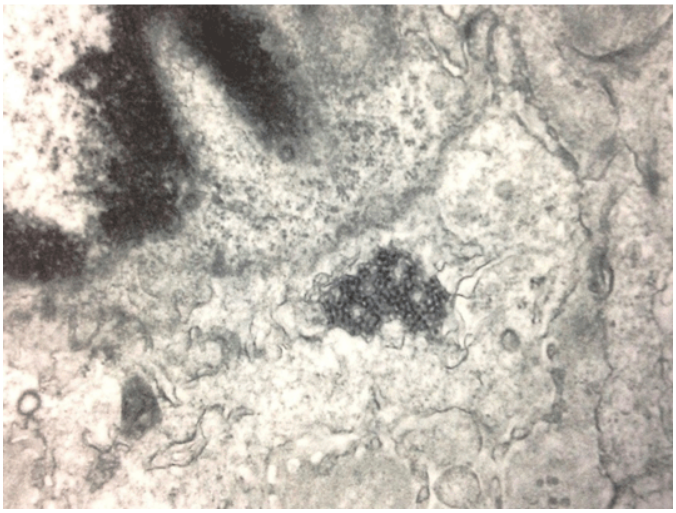

Figure 3: EM: tubulo reticular inclusion (x22, 000).

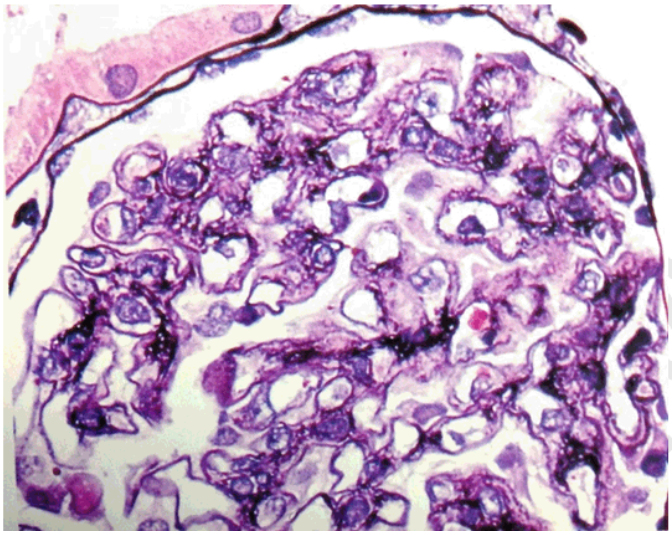

Figure 1: Marked glomerular basement membrane duplication (Jones x40).

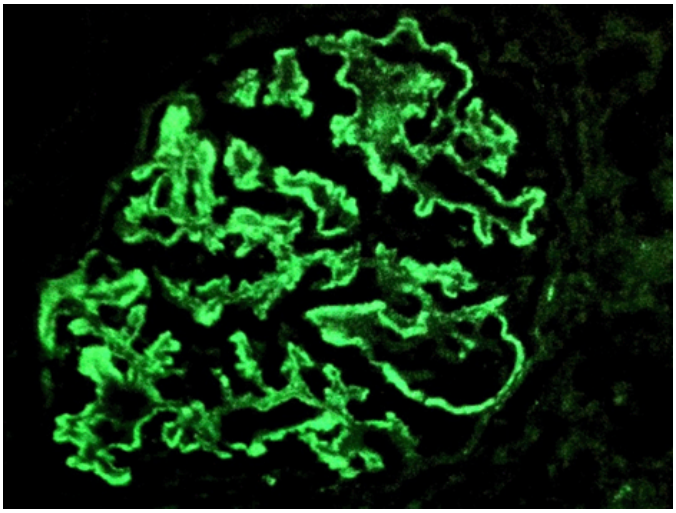

Figure 2: 3+ granular and peripheral IgG IF staining (x20).

## DISCUSSION

Lupus nephritis represents about 50% of SLE population. Existence of 'full house nephropathy' defined as the presence of IgG, IgA, IgM, C1q and C3 deposits at the same time on the IF examination is generally associated with lupus nephritis [1, 2]. Full-house nephropathy can also be seen in clinical conditions such as post hepatic cirrhosis, diabetic nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis and C1q nephropathy [3]. Wen et al. observed non lupus full house nephropathy in 24 patients without endothelial TRIs. Their clinicopathological spectrum included membranous glomerulonephritis (46%), IgA nephropathy (21%), membranoproliferative GN (12.5%), Post infectious GN (12.5%), C1q nephropathy (4%), and unclassified mesangial glomerulonephritis (4%) [4]. Our patient too had full house nephropathy with immune mediated glomerulonephritis, with endothelial tubuloreticular inclusion bodies.

C1q nephropathy is often reported as seronegative lupus nephritis due to under recognition. C1q nephropathy is an uncommon pathological entity accounting for 0.4–

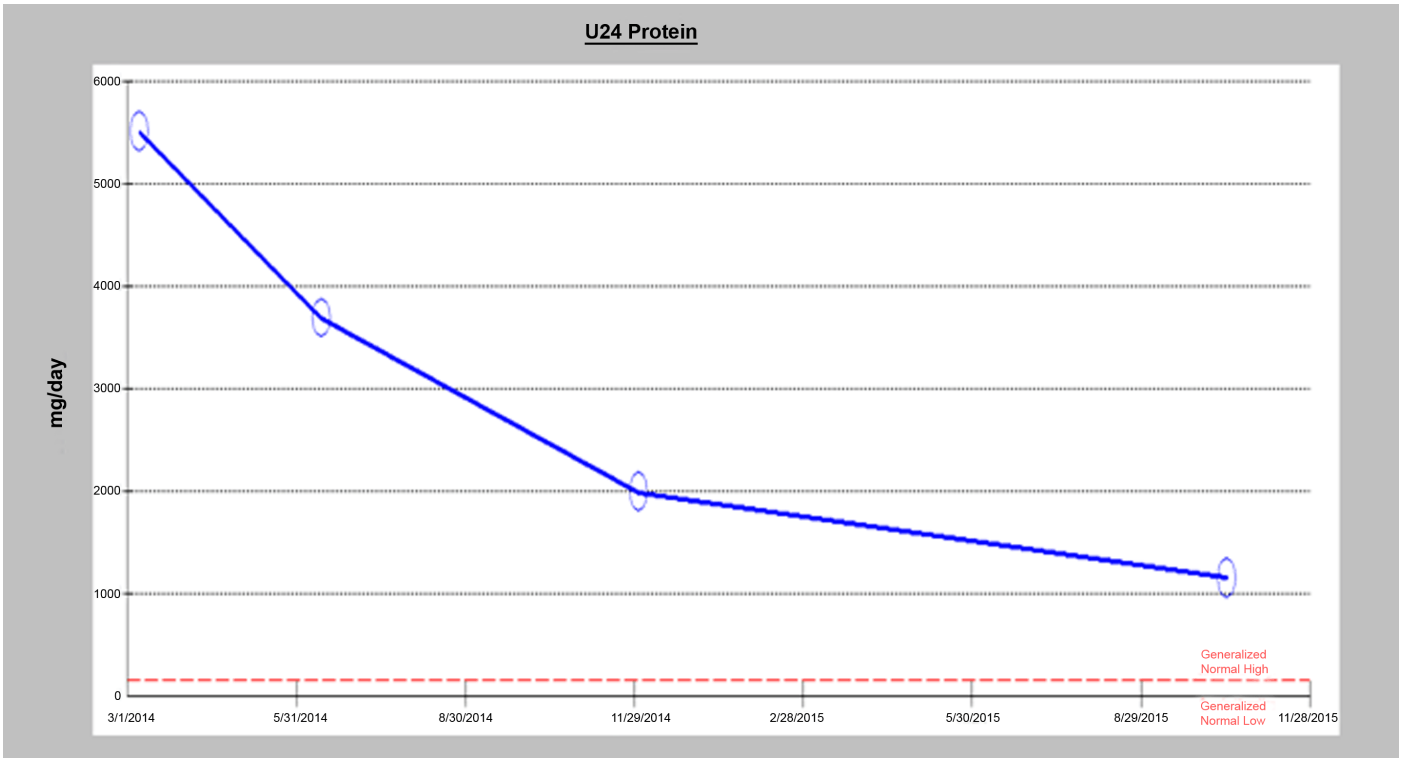


Figure 4: 24 hr urinary protein levels (mg/day) trends.

2.0% of all consecutive native kidney biopsies [5–7]. The distinguishing characteristics of C1q nephropathy are robust staining of C1q on immunofluorescence, absence of endothelial cell TRIs [8] and anti C1q antibodies [9]. Even though our index patient had C1q 2+ on IF, the presence of TRIs with sub endothelial deposits excludes C1q nephropathy. Anti C1q antibody could not be tested on our patient.

The presence of TRIs in endothelial cells always evokes suspicion of an association with underlying viral infections or autoimmune diseases. Lee et al. studied 104 renal biopsies for TRIs expression. Lupus nephritis represented 60% whereas viral infections of HBV, HCV and HIV were 19%. TRIs were also seen in membranous glomerulonephritis (7%), IgA nephropathy (7%) and Henoch-Schonlein purpura (2%) [10]. In spite of strong association of TRIs with lupus nephritis, its presence in seronegative pathological situations like our patient can be expected.

Seroconversion from negative to positive lupus serology over years follow-up has been reported in the literature. Cairns et al. reported 11 patients of whom four developed overt lupus over 1–7 years of follow-up [11] and Adu et al., reported 17 patients of whom five developed definite evidence of lupus over 1–10 years follow-up [12]. In contrast, Jones and Maggil described five patients who remained seronegative lupus over a five-year follow-up [13]. Similarly Enriquez et al. [14] described three children who remained seronegative over short follow-up of two years. Our patient shows no seroconversion at two years follow-up. Does the seroconversion over years determine the clinical outcome, needs to be explored. What's the importance of differentiation of C1q nephropathy from full house nephropathy with or without serology positiveness? The immunosuppressive therapy response of C1q nephropathy is dismal. Immunological response of seronegative lupus matches with that of seropositive lupus. These seronegative patients with full house nephropathy and TRIs should be treated as seropositive lupus nephritis [15]. Our index case showed partial response with reduction of proteinuria from 5.5 to 1.1 g/d with MMF and prednisone. The follow-up will determine the response and renal survival.

## CONCLUSION

We conclude that high index of suspicion and ruling out rarer pathological entities like C1q nephropathy is needed. So far immunosuppressive therapies have shown good response in seronegative lupus nephropathy. The future will underscore the role of other immunosuppressive armamentarium including anti-CD 20 monoclonal antibody (rituximab) and needs to be explored.

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## Author Contributions

Mandya Chikkalingaiah Kiran – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

## Guarantor

The corresponding author is the guarantor of submission.

## Conflict of Interest

Authors declare no conflict of interest.

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