

Dilemma of seronegative lupus nephritis: A case report of diffuse proliferative glomerulonephritis with thrombotic microangiopathy

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Dilemma of seronegative lupus nephritis: A case report of diffuse proliferative glomerulonephritis with thrombotic microangiopathy

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Key word

Case report, Thrombotic microangiopathy, Lupus nephritis.

Abstract

We report a case with clinical presentations of newly onset hypertension, edema, serositis, and nephrotic syndrome, and a kidney biopsy showing diffuse proliferative glomerulonephritis with "full-house" immune deposits and thrombotic microangiopathy (TMA). The findings were suggestive of lupus nephritis (LN). However, despite persistent hypocomplementemia, her serological tests for autoantibodies associated with systemic lupus erythematosus, (including antinuclear antibody, anti-double-stranded DNA antibody, lupus anticoagulant, anticardiolipin antibody, and Coombs' test) were all negative. Although the patient did not meet the diagnostic criteria for LN based on the 2019 EULAR/ERA-EDTA lupus guideline, she was treated as such based on her biopsy results and clinical suspicion. This case report presents a challenging case of seronegative diffuse proliferative glomerulonephritis with "full-house" immune deposits and TMA.

Case report

A 29-year-old Chinese female without prior history or family history of kidney disease presented with eyelid edema for more than one year. She did not have skin rash, arthralgia, photosensitivity, or oral ulcers. During her pregnancy 5 months prior, she was found to have proteinuria on urinalysis. At the current admission, the patient's initial blood pressure and pulse rate were 166/100 mmHg and 110 beats/min, respectively. She did not have fever (36.6°C), and had an intact mental status. Laboratory results revealed a normal leukocyte count ($6.9 \times 10^9/L$) with 81.3% neutrophils, anemia (hemoglobin 70 g/L), mild thrombocytopenia ($130 \times 10^9/L$), hypoalbuminemia (26.2 g/L), normal lactate dehydrogenase (LDH) (391.2 U/L), creatinine (119.3 $\mu\text{mol/L}$), and uric acid (616.4 $\mu\text{mol/L}$), and hyperlipidemia (total cholesterol 7.72 mmol/L). Her serum β_2 -microglobulin was 10.07 mg/L. Daily urinary protein was 3.270 g. Her C3 and C4 levels were 1.17 g/L (reference range, 0.7–1.4 g/L) and 1.16 g/L (reference range, 0.1–0.4 g/L), respectively, with a d-dimer of 4.83 $\mu\text{g/mL}$. Her ANA, anti-double strand DNA antibody, lupus anticoagulant, anticardiolipin antibody,

and Coombs' test were all negative. Computed tomography of her chest and abdomen revealed moderate bilateral pleural effusion with partial atelectasis or consolidation of adjacent lung tissues, massive peritoneal and pelvic effusion, massive pericardium effusion, and extensive subcutaneous soft tissue swelling and effusion involving her chest and abdominal wall (Fig1 A). Since admission, her hemoglobin, platelet, LDH levels showed gradual decline. The presence of red blood cell fragmentation was observed. Despite component therapy, her hemoglobin levels fluctuated between 57 and 72 g/L, and her platelet levels decreased from $130 \times 10^9/L$ to $66 \times 10^9/L$. 3% red blood cell fragmentation, Serum disintegrin, metalloproteinase with thrombospondin motifs 13 (ADAMTS13), and human complement factor H levels were checked and the results were all within normal range.

Subsequently, a kidney biopsy was performed. Under light microscopy, 26 glomeruli were examined, including 1 with global sclerosis, 1 with small cellular crescent, 2 with large fibrocellular crescents, and 1 with fibrous crescent. The remaining glomeruli showed diffuse mesangial and endocapillary hypercellularity with lobulated accentuation. Segmental glomerular capillary loops were obliterated with neutrophil infiltration. Wire-loops and glomerular basement membrane double-contours were present. A few fibrin thrombi were seen in glomerular and focal afferent arterioles. Tubules showed some degree of acute injury (lumen dilatation and vacuolar degeneration) and severe atrophy (~60%). Patchy interstitial fibrosis and inflammation were also observed. The arteriolar wall was thickened with luminal stenosis (Fig1 B,C,D). Immunofluorescence staining showed "full-house" granular deposits along capillary loops and in mesangial areas (3 + IgG, 2 + IgM, 3 + IgA, 3 + C3, 3 + C1q, 1 + Kappa, and 2 + Lambda). Many focal tubular basement membrane deposits were present (Fig1 G,H). Electron microscopy revealed numerous electron dense deposits in the subepithelial, subendothelial, and mesangial areas. Mesangial interpositioning forming glomerular basement membrane double contours were confirmed. Podocyte foot processes were diffusely effaced. Tubuloreticular inclusions were not identified (Fig1 E,F). Pathologically, diffuse proliferative glomerulonephritis (membranoproliferative glomerulonephritis type III pattern) and TMA were suggested. Together with clinical presentations, a diagnosis of seronegative LN type IV + V with superimposed TMA was favored.

Treatment with plasma exchange was initiated, combined with prednisone acetate 50 mg daily, mycophenolate mofetil 0.5 g, and hydroxychloroquine sulfate 0.2 g twice daily, followed by rituximab 500 mg infusion for twice (total 1,000 mg). Hemodialysis was performed during the initial two months. Three months after hemodialysis discontinuation (5 months later), edema was significantly improved with persistent hypoproteinemia and proteinuria. Six months later, hemoglobin recovered and creatinine was normalized.

Discussion

In this report, a young woman presented with acute onset nephrotic syndrome and multi-organ injuries. Her anemia progressed despite stabilized renal function. TMA was clinically indicated based on laboratory findings of microangiopathic hemolytic anemia, thrombocytopenia, increasing LDH, and peripheral red blood cell fragmentation. The biopsy confirmed the presence of TMA in addition to a diffuse proliferative glomerulonephritis with "full-house" deposits. The etiologies of TMA can be divided into primary and secondary causes, the former includes ADAMTS13 deficiency or autoantibodies against ADAMTS13, complement-mediated or factor H autoantibodies-related hemolytic-uremic syndrome, and rare origins of vitamin deficiency. Secondary causes of TMA include infection, malignant hypertension, autoimmune diseases, malignancies, organ transplantation, pregnancy, or medications(1). Thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome were excluded based on her normal ADAMTS13 levels and human complement factor H. Therefore, this patient's TMA was suspected to be secondary to underlying SLE. However, the current classification criteria for SLE do not provide clear guidance on diagnosing LN in patients with negative ANA but suspicious renal pathology.

"Full-house" immunofluorescence depositions upon renal biopsy is characteristic of LN, but this can be also seen in other types of nephropathy. In the 2019 SLE classification criteria published by EULAR and the American College of Rheumatology, at least one episode of positive ANA is designated as a mandatory entry criterion, followed by weighted values from another 7 clinical indicators (general status, hematology, neuropsychology, mucocutaneous, serosa, musculoskeletal, and renal presentations) as well as 3 immunological

indicators (antiphospholipid antibodies, decreased complement levels, and other SLE specific antibodies). A score of [?] 10 combined with at least one clinical criterion is required for SLE diagnosis. Although this guideline does not exclude the possibility of LN with negative ANA, the algorithm for diagnosing LN with negative ANA remains unavailable currently. Moreover, it remains controversial whether LN can be diagnosed solely by renal pathology. A 2013 literature review suggested that LN could be diagnosed without positive SLE-related autoantibodies, which might emerge during subsequent follow-up. In a case of ANA-negative SLE with vasculitis, prolonged serositis, and glomerulonephritis with “full-house” deposits, patient’s renal function and serum albumin normalized after immunosuppression(2). Other reports also revealed that patients might become serologically positive during follow-up with the diagnosis of SLE being made(3). We propose that the speed of emergence of existing autoantibodies may not parallel that of other clinical presentations in our patient, possibly due to a time lag. It could be worthwhile to explore novel or un-identified autoantibodies exhibiting a closer relationship with disease manifestations in similar patients.

Based on our literature review, the main criteria for diagnosis was negative SLE-related autoantibodies with a renal pathology showing “full-house” immune deposits. Though the diagnosis of LN based on pathology alone is not recommended, biopsy findings combined with other clinical presentations can be very helpful for establishing seronegative LN. There are a few pathology findings considered characteristic for LN: “full-house” immunofluorescence staining; intense C1q staining; extraglomerular deposits; subendothelial & subepithelial deposits; and tubuloreticular inclusions. In this patient’s biopsy findings, all features were identified, with the exception of tubuloreticular inclusions. Combined with clinical presentations of thrombocytopenia, hemolytic anemia, serositis, and multi-system damages, LN was reasonably favored despite negative serologic evidence.

The optimal treatment approach for LN with TMA remains unclear. However, early provision of adequate doses of plasma exchange or infusion may effectively improve renal outcomes in LN patients with TMA(4). A retrospective study focusing on SLE with TMA showed that patients’ survival rate was 33.3% and 92.4% in the conventional and immunosuppressive therapy groups, respectively(5). In addition, treatment responses of seronegative LN are better than those of seropositive ones. Such good responses to immunosuppressants were also observed in our patient. Therefore, we administered plasma exchange in combination with glucocorticoids and immunosuppressants to the index patient. She also received hemodialysis for months and saw an improvement in edema. After 6 months of follow-up, both her hemoglobin (110 g/L) and creatinine (99.3 $\mu\text{mol/L}$) returned to normal levels.

In summary, this case highlights the diagnostic challenge of seronegative LN with TMA. The current classification criteria for SLE do not provide clear guidance on diagnosing LN in patients with negative ANA but suspicious renal pathology. More cases are needed to establish a standardized diagnostic strategy and to summarize the phenotypic characteristics and treatment responses of patients with seronegative LN.

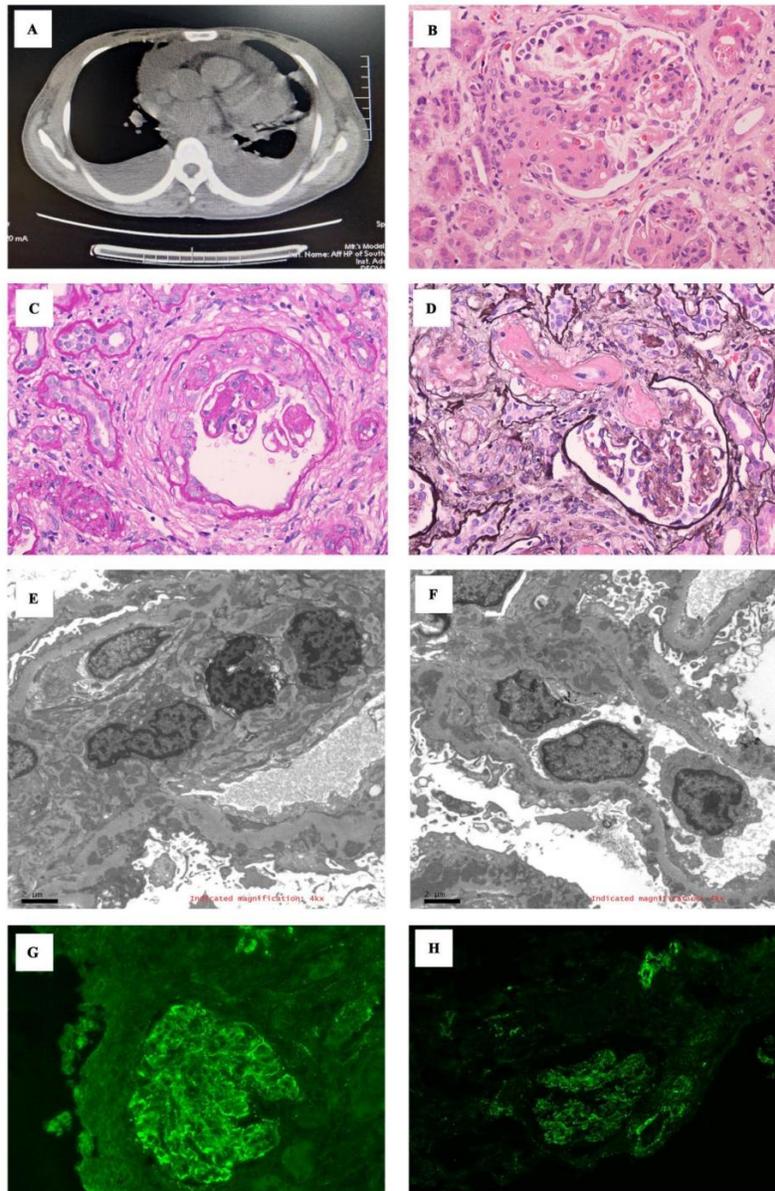


Figure 1: Image findings. A: Chest computed tomography with pleural effusions. B: Kidney biopsy under light microscopy, hematoxylin & eosin stain, glomeruli with diffuse mesangial, and endocapillary hypercellularity with lobulated accentuation. C: Kidney biopsy, light microscopy, periodic acid-Schiff (PAS) stain, a glomerulus with a fibrocellular crescent. D: Kidney biopsy, light microscopy, PAS stain, glomerular arterioles with fibrin thrombi. E and F: Kidney biopsy, electronic microscopy, glomeruli with subepithelial, subendothelial and mesangial deposits. G: Kidney biopsy, IgG immunofluorescence staining with capillary and mesangial granular deposits and a few tubular basement membrane deposits. H: Kidney biopsy, C1q immunofluorescence staining with capillary and mesangial granular deposits.

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