CASE STUDIES

Thrombotic microangiopathy in membranous lupus nephritis

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Abstract

Renal vascular lesions in SLE are grouped into uncomplicated vascular immune deposits, non-inflammatory necrotizing vasculopathy, thrombotic microangiopathy (TMA) and renal vasculitis. Thrombotic microangiopathy (TMA) is a rare finding in patients with SLE and is associated with poor prognosis. Treatment approach for TMA with membranous nephritis is highly challenging. The present case study discusses the case of a young woman with SLE and membranous lupus nephritis, complicated by TMA.

Keywords: thrombotic microangiopathy, membranous lupus nephritis, SLE

Introduction

Systemic lupus erythematous (SLE) is a systemic autoimmune disease having various clinical and pathological manifestations. The vascular manifestations of SLE range from most common uncomplicated vascular immune deposits to rare renal vasculitis. The non-immune, non-inflammatory thrombotic microangiopathy (TMA) is a rare vascular manifestation of SLE, which is therapeutically challenging. We present here a unique case of a young female with lupus membranous nephropathy, complicated by TMA.

Case report

An 18-year-old African American female with prior diagnosis of SLE and biopsy-proven lupus membranous nephropathy (Fig. 1 and 2) presented to the emergency room with shortness of breath, and headache for the past 2 days. She had been on treatment with hydroxychloroquine 200 mg bid and prednisone (dose ranged between 15 mg and 60 mg daily) for seropositive SLE (ANA, anti dsDNA, anti-Smith positive) and had achieved remission (U Pr/Cr 0.36 gm/day) around 6 months ago. Physical examination revealed blood pressure 220/120 mm Hg, alopecia, and synovitis of knees. Laboratory evaluation showed: significant microscopic hematuria (RBC 30-35/hpf), proteinuria (urine protein/creatinine ratio: 13.4 gm/day), creatinine: 3.4 mg/dl (creatinine 1.1 mg/dl one month prior to admission), hemoglobin: 9.7 g/dl, and platelet count: 534 $\times 10^9$/L. Lactate dehydrogenase level, reticulocyte count and peripheral smear were normal. Her complement levels were low (C3 27 mg/dl and C4 <8 mg/dl), ANA 1:640, anti-dsDNA was >300 IU/mL (normal range 0-99 IU/mL), anticardiolipin antibody IgM: 47 U/mL (normal 0-12 MPL U/mL) and IgG was 23 U/mL (normal 0-14 GPL U/mL). She was negative for HBV, HCV, HIV, VDRL, lupus anti-coagulant, and beta-2 glycoprotein. Renal biopsy showed glomerular TMA, membranous nephritis, and severe interstitial fibrosis (Fig. 3 and 4).

The patient was initially treated with combined intravenous methylprednisolone (500 mg daily for 3 days) and plasmapheresis (three cycles). This was followed by prednisone (60 mg q day), and monthly intravenous cyclophosphamide (750 mg) treatment. However, her renal function did not improve even after 4 months (creatinine: 2.7 mg/dl). She was subsequently treated with mycophenolate mofetil, but no response was noted. Renal function continued to deteriorate (creatinine 5.5 mg/dl), and she continued to have active SLE with arthritis and serositis. Immunoglobulin IgG level was 2411 mg/dl (normal 549-1584 mg/dl). Rituximab (1000 mg) was infused twice with an interval of 2 weeks. The follow-up conducted at second week showed that the creatinine had stabilized at 4.5 mg/dl. However, the follow-up at 6th month

Fig. 1: Membranous lupus glomerulopathy class V (electron microscopy)

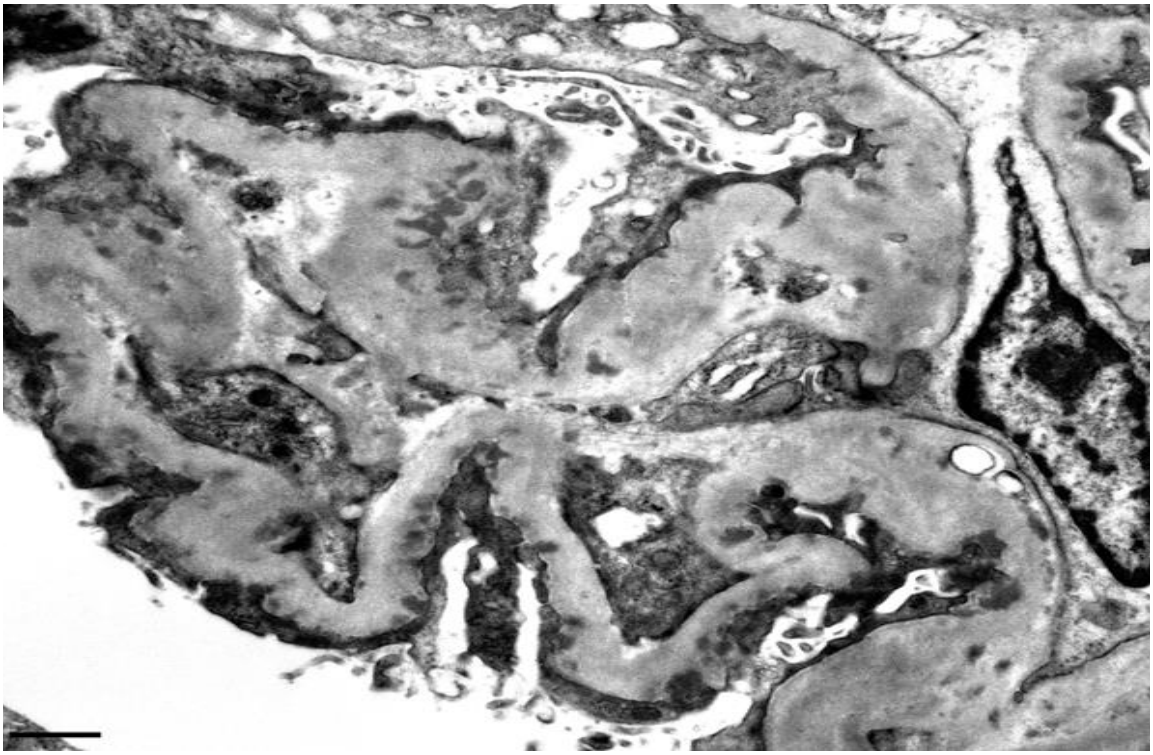


Fig. 2: Granular IgG deposit along the glomerular basement membrane (immunofluorescence)

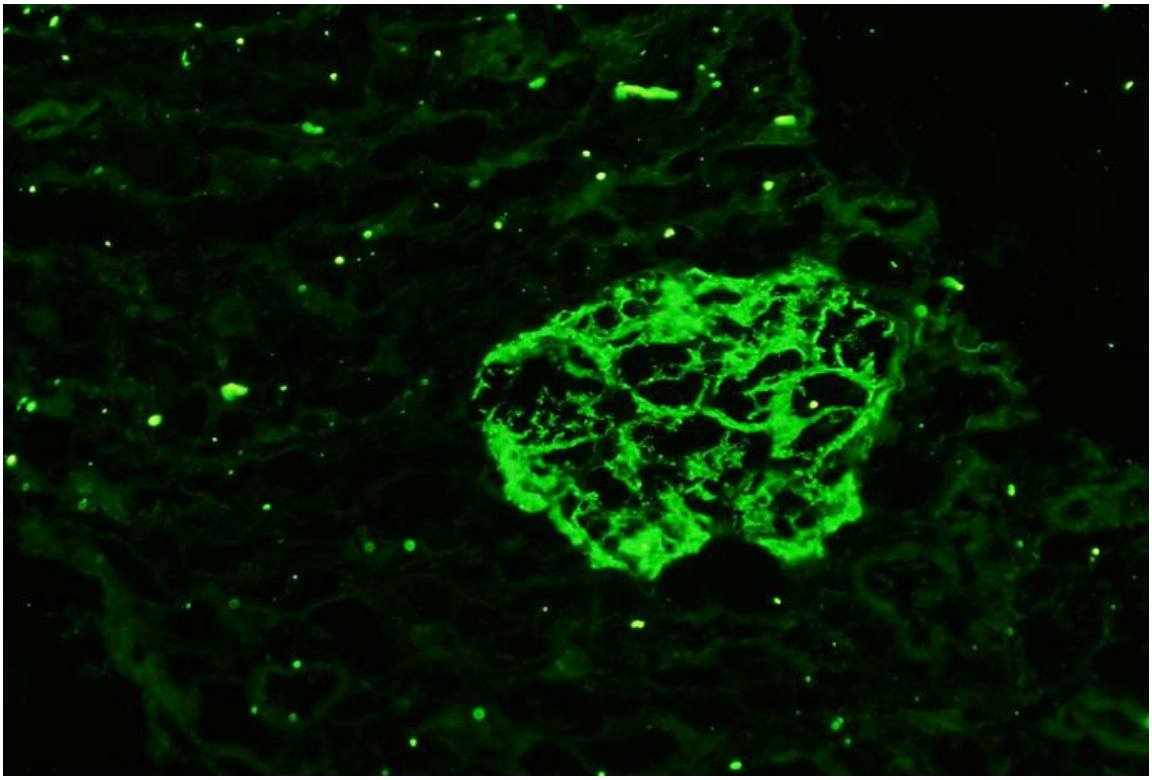


Fig. 3: Renal biopsy showing severe glomerular TMA

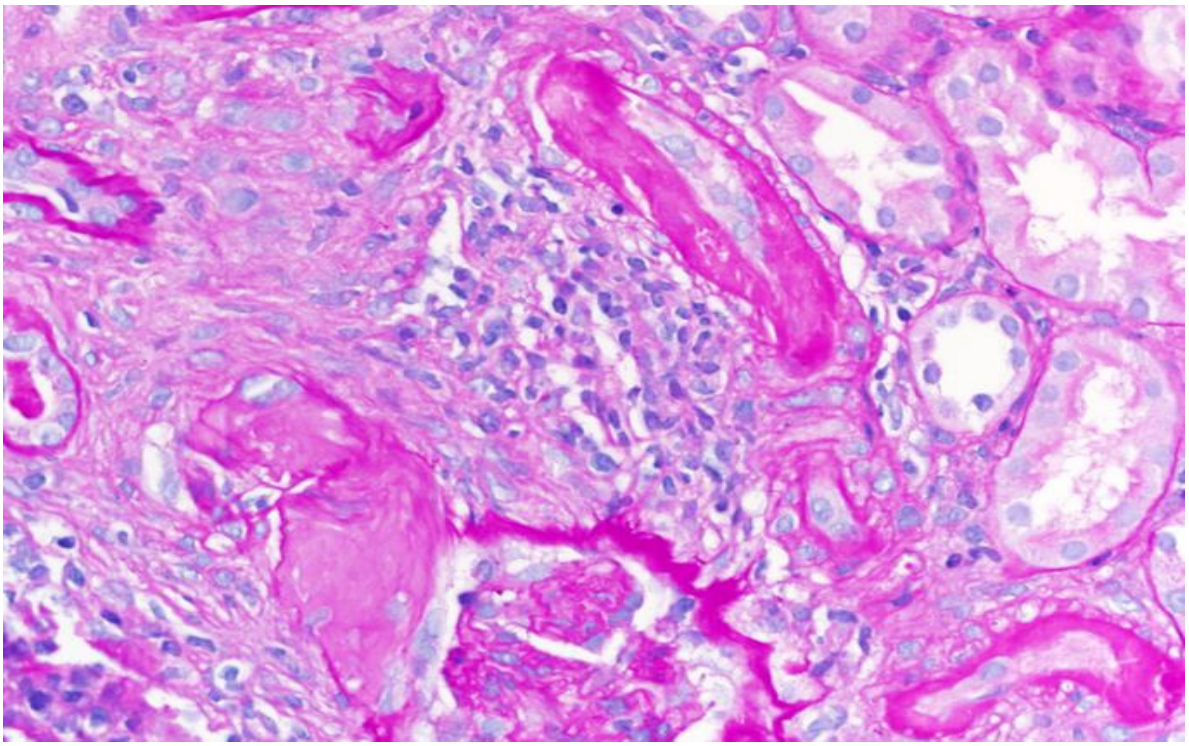
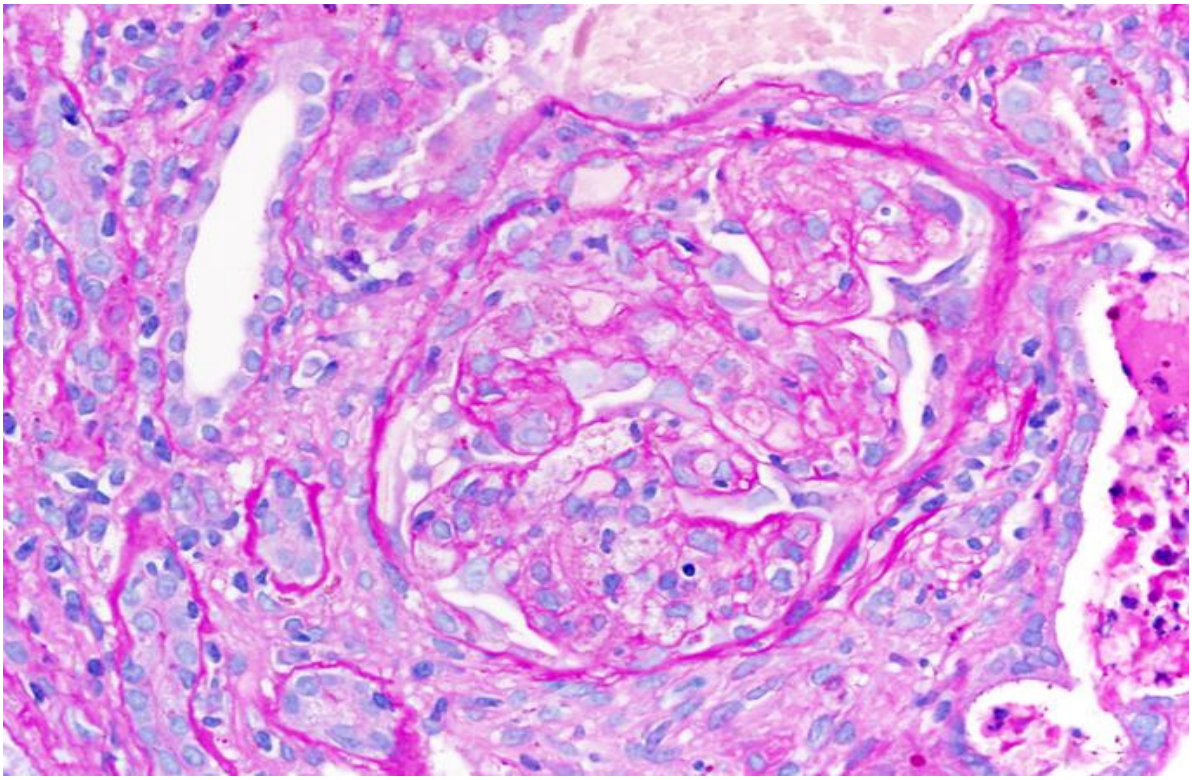


Fig. 4: Renal biopsy showing severe glomerular TMA



showed impairment in renal function with uremia, resulting in end stage renal disease requiring hemodialysis.

Discussion

TMA in SLE is a rare non-immune and non-inflammatory vascular complication. As per the literature evidence, the prevalence of TMA varies with geographical location and population. The prevalence reported by Banfi *et al.* in a series of 285 biopsied lupus patients is 8.4%, while the prevalence noted by Grishman *et al.* in autopsy and lupus biopsy specimens is 0.7%.[1, 2] The study by Devinsky *et al.* reported that out of 50 SLE patients, 14 with terminal illness developed TMA.[3] TMA is a clinicpathophysiological entity without any associated lupus activity or increased ANA levels.[4, 5] TMA is frequently associated with the presence of antiphospholipid antibodies (APL) such as anticardiolipin (ACL) antibodies or lupus anticoagulant (LA).[5, 6] The present case had pathological evidence of TMA along with membranous nephropathy and renal dysfunction. The poor prognostic outcome of this challenging condition underscores the need of newer immunosuppressive armamentarium for effective management.

Recent reports have focused on SLE-associated intrarenal 'non-immune' and non-inflammatory vasculopathy characterized by arterial and/or arteriolar thrombosis with endothelial thickening, in the absence of vascular parietal immune deposits or infiltrating inflammatory cells.[1, 5-7] These pathological characteristics are identical to the lesions of renal TMA. APL antibodies, involved in the generation of renal TMA in primary APL syndrome, are considered as a main factor for the promotion of intrarenal arterial thrombosis in SLE.[8, 9]

Renal vascular lesions in SLE are grouped into uncomplicated vascular immune deposits, non-inflammatory necrotizing vasculopathy, thrombotic microangiopathy and renal vasculitis. The clinical syndromes associated with TMA include hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), antiphospholipid antibody syndrome (APS), systemic sclerosis and malignant hypertension. The finding of TMA in renal biopsy with lupus nephritis could indicate the possible co-existence of these syndromes. However, TMA can occur in lupus nephritis without other associated conditions or systemic involvement.[10] APL syndrome is well recognized as a major complication in SLE patients. The APL antibodies include anticardiolipin, anti-β2 microglobuin and lupus anticoagulant. The study by Daugas *et al.* has reported the occurrence of anticardiolipin and lupus anticoagulant in 44% and 34% of SLE patients, respectively, and the development of APS in one third of these patients.[11]

The prognosis of TMA in lupus is poor. The study conducted by Ming *et al.* in a cohort of Taiwan population has identified old age (>50 years), low complement value, presence of infection, and acute renal failure as significant risk factors for higher mortality in SLE patients with TMA.[12] The overall mortality rate of SLE patients with TMA, reported by Bell *et al.*, was 52.0%, which was much higher than that in TMA patients without SLE (<10%).[13] Patients receiving plasma exchange 7 times or more possess a significantly higher rate of improvement in renal function and hematological abnormalities.

To the best of the authors' knowledge, the present study is the first to report the occurrence of lupus membranous nephropathy with TMA. The present case had poor prognostic risk factors of low complement, acute renal failure and nephrotic range proteinuria. In spite of aggressive immunosuppressive therapy, the patient developed end-stage renal disease. We conclude that TMA complicated by membranous lupus nephritis portends a poor prognosis. A customized treatment regimen should be considered for managing TMA in lupus patients.

Competing interests
The authors declare that they have no competing interests.

Citation
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References

1. Banfi G, Bertani T, Boeri V, Faraggiana T, Mazzucco G, Monga G, et al. Renal vascular lesions as a marker of poor prognosis in patients with lupus nephritis. Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL). Am J Kidney Dis. 1991 Aug;18(2):240–8.
2. Grishman E, Venkataseshan VS. Vascular lesions in lupus nephritis. Mod Pathol. 1988 May;1(3):235–41.
3. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. Ann Neurol. 1988 Apr;23(4):380–4.
4. Appel GB, Pirani CL, D'Agati V. Renal vascular complications

of systemic lupus erythematosus. J Am Soc Nephrol. 1994 Feb;4(8):1499–515.
5. Farrugia E, Torres VE, Gastineau D, Michet CJ, Holley KE. Lupus anticoagulant in systemic lupus erythematosus: a clinical and renal pathological study. Am J Kidney Dis. 1992 Nov;20(5):463–71.
6. Kincaid-Smith P, Fairley KF, Kloss M. Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. Q J Med. 1988 Oct;68(258):795–815.
7. Nesher G, Hanna VE, Moore TL, Hersh M, Osborn TG. Thrombotic microangiographic hemolytic anemia in systemic lupus erythematosus. Semin Arthritis Rheum. 1994 Dec;24(3):165–72.
8. D'Agati V, Kunis C, Williams G, Appel GB. Anti-cardiolipin antibody and renal disease: a report three cases. J Am Soc Nephrol. 1990 Nov;1(5):777–84.
9. Piette JC, Cacoub P, Wechsler B. Renal manifestations of the antiphospholipid syndrome. Semin Arthritis Rheum. 1994 Jun;23(6):357–66.
10. Jennette JC, Heptinstall RH. Heptinstall's pathology of the kidney. 6th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2007.
11. Daugas E, Nochy D, Huong DLT, Duhaut P, Beaufils H, Caudwell V, et al. Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. J Am Soc Nephrol. 2002 Jan;13(1):42–52.
12. Chen M-H, Chen M-H, Chen W-S, Mu-Hsin Chang P, Lee H-T, Lin H-Y, et al. Thrombotic microangiopathy in systemic lupus erythematosus: a cohort study in North Taiwan. Rheumatology (Oxford). 2011 Apr;50(4):768–75.
13. Bell WR, Braine HG, Ness PM, Kickler TS. Improved Survival in Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome. New England Journal of Medicine. 1991 Aug 8;325(6):398–403