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Case Report

A Case of True Renal Lupus Vasculitis Combined with Pauci-immune Glomerulonephritis in a Patient with Systemic Lupus Erythematosus

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Renal lupus vasculitis is a rare vascular lesion complicated with systemic lupus erythematosus (SLE). We report an unusual case of true renal lupus vasculitis with antineutrophil cytoplasmic antibodies (ANCA)-negative pauci-immune glomerulonephritis in a patient with SLE. A 32-year-old woman presenting with hematuria and overt proteinuria was admitted to the hospital. She had been diagnosed with SLE at 16 years of age and treated with prednisolone, hydroxychloroquine, and methotraxate. A kidney biopsy revealed 42 glomeruli with ischemic wrinkling, and segmental loop necrosis with fibrin deposition. Prominent inflammatory cell infiltration of interlobular arteries and afferent arterioles with severe necrosis was demonstrated. No electron-dense and immune deposits in the glomeruli were observed by immunofluorescent and electron microscopy; in contrast, those in the renal vascular wall showed a full-house pattern. Antiphospholipid antibodies and ANCA were negative. The patient was treated with monthly intravenous cyclophosphamide pulses and high dose steroid, and showed good response on further follow-up. **(J Rheum Dis 2015;22:34-38)**

Key Words. True renal lupus vasculitis, Pauci-immune glomerulonephritis, Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease affecting various organs and particularly the kidney. Lupus nephritis (LN) develops in up to 60% of patients with SLE during the course of the disease, which is closely associated with different clinical characteristics, treatment response, and outcomes, including renal and patient survival [1]. Not only glomerulonephritis but also renal vascular lesions are encountered frequently in renal biopsy and can adversely affect the prognosis of the renal disease in SLE [2,3]. However, the significance of lupus vasculopathy has been overlooked in actual renal biopsy specimen because the primary focus on the classification of LN is glomerular lesion. In particular, true renal lupus vasculitis (TRLV) is a rare vascular lesion associated with LN that has been infrequently reported in the medical literature. We report a case of TRLV combined with antineutrophil cytoplasmic antibodies (ANCA)-negative pauci-immune glomerulonephritis in a patient with SLE.

CASE REPORT

A 32-year-old woman was admitted to the hospital with complaints of fatigue, generalized edema, and proteinuria of several weeks' duration. The patient was initially diagnosed with SLE at the age of 16 years with symptoms of fever, malar rash, arthritis, hair loss, and oral ulcer in another hospital and has been followed in our institution for the past 7 years. She had been treated with low dose prednisolone, hydroxychloroquine, and methotraxate with stabilization in the last several years. She has a history of tuberculous lymphadenitis, and abdominal aortic dis-

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section related to newly diagnosed Marfan's syndrome, treated with aortic stent insertion about 3 years ago. The patient had no hypertension, diabetes mellitus or viral hepatitis.

She had no fever, and blood pressure was 145/92 mmHg. Pretibial pitting edema was detected; otherwise, there were no specific findings on head and neck, abdomen, chest, skin and joints on physical examination. Laboratory examination revealed white blood cell count 5,400 cells/mm^3, hemoglobin 10.8 g/dL, hematocrit 33.9%, and platelet 290,000 cells/mm^3 with an unremarkable blood smear. Erythrocyte sedimentation rate was 32 mm/h and C-reactive protein was 0.08 mg/dL. Blood chemistry showed blood urea nitrogen (BUN) 27.1 mg/dL, creatinine 1.23 mg/dL, total protein 3.6 g/dL, and albumin 1.6 g/dL. Liver enzymes, prothrombin time, and activated partial thromboplastin time were unremarkable. Urinalysis and urine microscopy demonstrated proteinuria 4+, hematuria 20 to 29 erythrocytes/high power field, and no cast. The 24-hour urine protein and 24-hour urine creatinine were 4.17 g/d and 1.03 g/d, respectively. Serum C3 level was 46 mg/dL (normal 90 to 180 mg/dL), C4 level 5 mg/L (normal 10 to 40 mg/dL), and anti-double strand DNA 2,831 IU/mL (normal≤4 IU/mL). Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was score 12, and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index was score 1. Antinuclear antibody was positive (1:640, speckled pattern). Anti-Ro antibody and anti-Smith antibody were positive. Otherwise, anti-ribonucleoprotein antibody and anti-La antibody were negative. ANCA immunofluoresence, anti-proteinase 3 antibody, anti-myeloperoxydase antibody and antiphospholipid antibodies including lupus anticoagulant, anti-cardiolipin antibody immunoglobulin (Ig) M/IgG, and anti-β2 glycoprotein IgM/IgG were negative.

On the second day following her admission, renal biopsy was performed. Biopsy specimen included 42 glomeruli, of which 13 glomeruli (31%) showed segmental loop necrosis with fibrin deposits and 32 glomeruli (76%) demonstrated either ischemic wrinking or mild to moderate mesangial cell proliferation (Figure 1A and 1B). Additionally, interlobular arteries and afferent arterioles frequently demonstrated circumferential, transmural, and prominent inflammatory cells infiltration of the vessel wall with severe necrosis and fibrinoid deposits, focally occluding the lumen (Figure 2A and 2B). Tubules revealed focal severe atrophy or loss with heavy infiltration of lymphocyte, plasma cell and macrophage on interstitium. Immunofluorescent microscopy demonstrated renal vessel wall with a marked staining for IgG, IgM and IgA, indicating a full-house pattern and C3 and C1q deposition (Figure 3). In contrast, necrotizing glomeruli showed an absence of significant immune deposits (Figure 1C). On electron microscopy, no electron-dense deposit was observed in glomeruli, in contrast to those in the vessel wall which presented periarteriolar heavy electron-dense diposits (Figure 2C).

Based on the pathologic findings, the patient was diagnosed with TRLV with ANCA-negative pauci-immune glomerulonephritis. The patient was treated with 6 monthly cycles of intravenous cyclophosphamide 750 mg pulses and high dose steroid. Spot urine protein/crea-

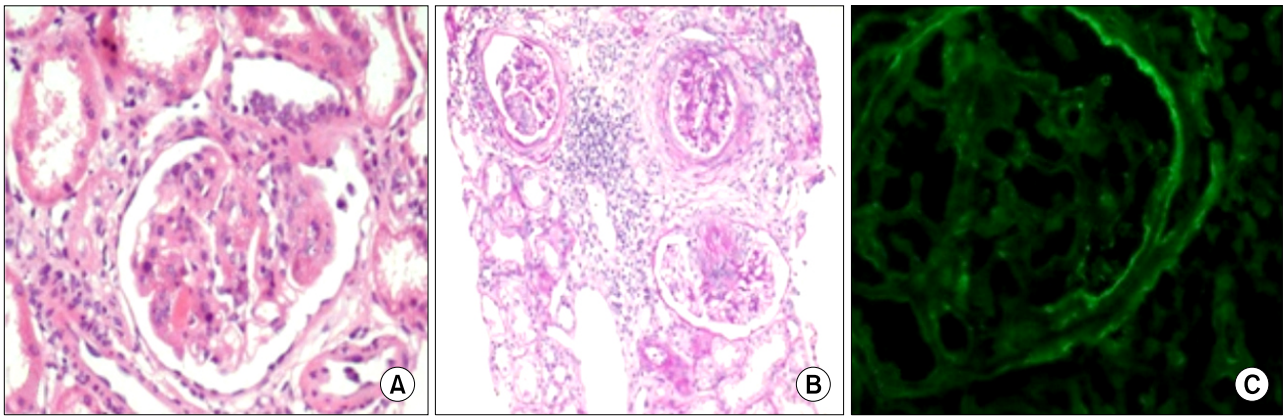

Figure 1. Pauci-immune glomerulonephritis. (A) Glomeruli show segmental necrosis with fibrinoid deposits and (B) ischemic wrinkling (H&E; A: ×400, B: ×200). (C) Immunofluoresence demonstrates absence of significant immune-complex deposits (×400).

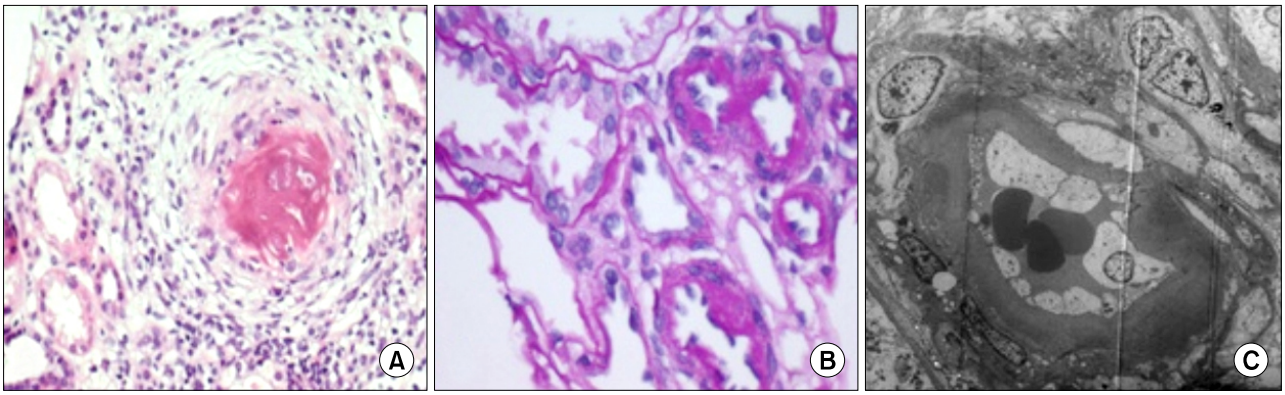

Figure 2. True renal lupus vasculitis. (A) Interlobular arteries shows prominent and transmural inflammatory cell infiltration with (B) severe necrosis and fibrinoid deposits (A, B: H&E, ×400). (C) Electron-dense deposits demonstrated in arteriolar wall (electromicroscopy, ×3,000).

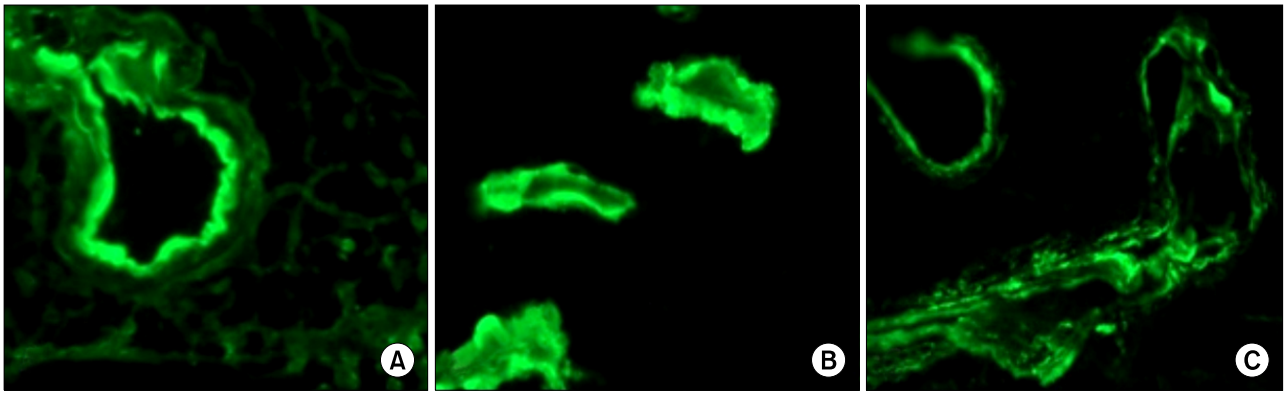

Figure 3. A full-house pattern immune-complex deposits in vessel wall including (A) immunoglobulin G (×400), (B) immunoglobulin M (×400), and (C) C1q, by immunofluoresence microscopy (×400).

tinine ratio and serum albumin level was improved to 0.9 and 3.0 g/dL respectively; blood chemistry showed the serum BUN and 18 mg/dL andcreatinine of 1.0 mg/dL; serum C3 level was 57 mg/dL, C4 level 5 mg/L (normal 10 to 40 mg/dL), and anti-double strand DNA 404 IU/mL; SLEDAI was improved to score 8 after completion of cyclophosphamide pulse treatment. The patient was treated with myclphenolate mofetil for remission maintenance with low-dose steroid. She has been followed in our out-patient clinic with stable disease activity.

DISCUSSION

The kidney is one of the most commonly involved organs in SLE and closely related to renal and patient survival. Renal vascular lesions are encountered frequently on renal biopsy specimen and have been reported in the literature in up to 27.7% to 37.6% in patients with SLE [2,3]. However, in view of the particular importance of glomerular findings for the classification of lupus nephritis, and the lack of an established classification and few pathological studies for vascular lesions, the latter is often overlooked. Previous studies showed that the presence of renal vascular lesions adversely affects renal outcomes in patients with SLE [2-4]. In particular, the presence of TRLV or thrombotic microangiopathy was closely related to poor renal outcome in previous studies.

Appel et al. [5] described five morphologic forms of lupus vasculopathy, including uncomplicated vascular immune deposits, non-specific arteriosclerosis, non-inflammatory necrotizing vasculopathy, thrombotic microangiopathy, and true renal vasculitis. Among these, TRLV ranging from 0.3% to 2.8% in these biopsies has rarely been reported in the literature and has not been studied systematically owing to the rarity of the lesion [2,5]. It is

characterized histologically as prominent infiltration of the blood vessel wall with inflammatory cells, combined with or without necrosis, fibrinoid changes, or thrombosis. Electron microscopic descriptions of this lesion are lacking and it is still unknown whether TRLV contains immune complex deposits.

The biopsy specimen of the renal vessels in the presenting patient demonstrated an active vasculitis process, with profound infiltration of inflammatory cells in the interlobular arteries and afferent arterioles. Additionally, the vascular lesions showed immune complex deposits with positive staining for all Igs and complement factors, indicating full-house pattern by immunofluorescence, on the contrary to glomerular lesion. This is compatible with the pathologic finding of TRLV in SLE. The biopsy finding in the presenting case differentiated from the lesion of other lupus vasculopathy including uncomplicated vascular immune deposits, non-inflammatory necrotizing vasculopathy and thrombotic microangiopathy. These forms of vasculopathy do not show overt inflammatory cell infiltration of the vessels walls even though uncomplicated vascular immune deposits reveal abundant immune deposition; and, non-inflammatory necrotizing vasculopathy and thrombotic microangiopathy share the morphological spectrum characterized by fibromyxoid intimal thickening with or without thrombosis. In addition, thrombotic microangiopathy may occur with distinct clinical syndromes associated with vascular endothelial damage and IgG usually is absent [6]. Laboratory results of patient were repeatedly negative for the antiphospholipid antibodies, making it unlikely that antiphospilipid antibody syndrome was not involved in the renal vascular lesions.

The biopsy finding of the glomeruli in this case represents pauci-immune glomerulonephirits with 32 of 41 glomeruli showing segmental loop necrosis and fibrinoid deposits along with mesangial cell proliferation, and negative staining for all Igs and complement factors. However, ANCA test by enzyme-linked immunosorbent assay was negative. Nasr et al. [7] recommended that ANCA testing should be considered when renal biopsy shows prominent necrosis and crescent formation without significant endocapillary proliferation or subendothelial deposits in patients with SLE, because ANCA-associated glomerulonephritis may occur superimposed on LN. ANCA has been reported in 15% to 20% in patients with SLE and is usually p-ANCA [8]. Positive rate of ANCA was higher in patients with than without renal involvement in SLE, in other studies [9,10]. Several previous studies described ANCA-positive pauci-immune glomerulonephritis combined with LN [10,11]. Our case is distinct from previous reports for ANCA-associated glomerulonephritis in SLE because the case revealed negativity of ANCA and also combined with TRLV.

The role of ANCA in TRLV remains controversial. Although inflammatory cell infiltration of the vessels is overlapping feature between TRLV and ANCA-associated vasculitis, the latter is not accompanied with Ig, complement components or electron dense deposits. Previous study [5] has suggested the immune deposit is not essential in vessel damage from inflammatory cell infiltration because immune complex might be related to non-specific trapping of circulating plasma proteins from the damaged vessels in SLE. In addition, immune complex deposits may be detected without vasculitic lesions. Further study is required to establish the role of ANCA in TRLV. Two cases of TRLV with absence of ANCA in lupus patients were reported in previous studies [12,13]. The presenting case is distinct from those because previous reports of TRLV with combined with proliferative LN, whereas our case showed TRLV with pauci-immune glomerulonephirits.

Several studies demonstrated that the presence of renal vasculitis was associated with unfavorable outcomes in patients with SLE [2-4]. Active serology, hypertension, renal failure or mortality was higher in SLE patients with than without renal vasculitis, particularly in TRLV. Furthermore, TRLV are usually accompanied with proliferative LN in patients with SLE. It is known that active urinary sediments, increased in serum creatitine, hypertension, and renal failure were features differentiating patients with renal vascular lesion from those without renal vasculitis in SLE. However, descried clinical manifestations are overlapped with those in SLE patients with LN and renal vascular lesion shows highly variable clinical course. Thus, suspicion of TRLV, as well as LN, is important in SLE patients with proteinuria and/or hematuria.

When the suggesting pathogenesis of TRLV is taken into consideration, treatment of TRLV is generally followed treatment protocol of LN or ANCA-associated vasculitis, with potential induction of remission by short-course cytotoxic drugs and a high dose glucocorticoid, and maintenance of remission by a safer immunosuppressant for a longer period [14]. Several case reports of renal vasculitis in patients with SLE showed favorable outcomes with re-

mission induction with intravenous cyclophosphamide pulse therapy and high dose steroid [12,13]. A recent case of refractory TRLV was reported achievement of remission induction with rituximab [15]. Further study of TRLV according to pathologic phenotype is essential to establish clinical outcomes and treatment response in different stages of the disease.

SUMMARY

This case indicates that the presence of TRLV should be considered in lupus patients with proteinuria, hematuria, or renal failure, and that pauci-immune glomerulonephritis may occur superimposed on SLE. Diagnostic approach and aggressive immunosuppressive therapy are needed early in the course of the disease in SLE patients.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Cameron JS. Lupus nephritis: an historical perspective 1968-1998. J Nephrol 1999;12 Suppl 2:S29-41.
2. 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;18:240-8.
3. Wu LH, Yu F, Tan Y, Qu Z, Chen MH, Wang SX, et al. Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions. Kidney Int 2013;83:715-23.
4. Grishman E, Venkataseshan VS. Vascular lesions in lupus nephritis. Mod Pathol 1988;1:235-41.
5. Appel GB, Pirani CL, D'Agati V. Renal vascular complications of systemic lupus erythematosus. J Am Soc Nephrol 1994;4:1499-515.
6. Gelfand J, Truong L, Stern L, Pirani CL, Appel GB. Thrombotic thrombocytopenic purpura syndrome in systemic lupus erythematosus: treatment with plasma infusion. Am J Kidney Dis 1985;6:154-60.
7. Nasr SH, D'Agati VD, Park HR, Sterman PL, Goyzueta JD, Dressler RM, et al. Necrotizing and crescentic lupus nephritis with antineutrophil cytoplasmic antibody seropositivity. Clin J Am Soc Nephrol 2008;3:682-90.
8. Sen D, Isenberg DA. Antineutrophil cytoplasmic autoantibodies in systemic lupus erythematosus. Lupus 2003;12: 651-8.
9. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
10. Pan HF, Fang XH, Wu GC, Li WX, Zhao XF, Li XP, et al. Anti-neutrophil cytoplasmic antibodies in new-onset systemic lupus erythematosus and lupus nephritis. Inflammation 2008;31:260-5.
11. Marshall S, Dressler R, D'Agati V. Membranous lupus nephritis with antineutrophil cytoplasmic antibody-associated segmental necrotizing and crescentic glomerulonephritis. Am J Kidney Dis 1997;29:119-24.
12. Moeckel GW, Jabs K, Fogo AB. An 11-year-old African-American girl with systemic lupus erythematosus and ANCA-negative renal vasculitis. Am J Kidney Dis 2002;39: 433-8.
13. Benz K, Büttner M, Rosenthal K, Amann K. Lupus nephritis and fibrinoid vasculitis of the kidney: a very rare alliance. J Clin Pathol 2010;63:950-2.
14. Abdellatif AA, Waris S, Lakhani A, Kadikoy H, Haque W, Truong LD. True vasculitis in lupus nephritis. Clin Nephrol 2010;74:106-12.
15. Kadikoy H, Haque W, Ahmed S, Abdellatif A. Rituximab in the treatment of refractory lupus nephritis with vasculitis. Saudi J Kidney Dis Transpl 2012;23:334-7.