Pauci-immune Lupus Nephritis: A Case Report

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A 26-year-old female with systemic lupus erythematosus was admitted because of dyspnea and progressive lower extremity edema. Laboratory testing showed blood urea nitrogen levels of 147 mg/dL, creatinine of 6.7 mg/dL, serum albumin of 1.7 g/dL and the daily protein loss was 12.7 g. Her C3 level was 60.4 mg/dL and C4 level was 10.2 mg/dL. The antinuclear antibody titer was 1:320, with a homogeneous pattern, but she was negative for anti-dsDNA. ELISA testing for anti-PR3 antibodies and anti-MPO antibodies were all negative. She was also negative for circulating lupus anticoagulant. Renal biopsy revealed diffuse proliferation of glomerular cells, but immunofluorescent microscopy showed no immune deposits and electron microscopy revealed only scanty electron-dense deposits. She received 1 g/day of methylprednisolone intravenously for 3 days, followed by 60 mg/day of prednisolone. She was discharged with serum creatinine decreased to 4.7 mg/dL, and a great improvement in dyspnea. Diffuse proliferative lupus nephritis that contains little or no subendothelial deposits is rare. The differential diagnosis, possible mechanisms and treatment are discussed.

Key Words: crescentic glomerulonephritis, lupus nephritis, pauci-immune glomerulonephritis, systemic lupus erythematosus
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Lupus nephritis is believed to result from the formation of glomerular immune deposits. However, the mechanisms by which autoantibodies form the immune deposits are still unclear [1], although the amount and the location of these immune deposits determine the histologic pattern of lupus nephritis [2,3]. Focal or diffuse proliferative lupus nephritis are characterized by deposits in both the glomerular capillary loops and in the mesangial areas [2].

The presence of immune deposits within the subendothelial space of glomerular capillary loops appears to be critical for the induction of severe glomerular injury in systemic lupus erythematosus (SLE) and the number of subendothelial deposits generally correlates with the degree of intracapillary or extracapillary proliferation and necrosis [4]. It is extremely rare for patients with diffuse proliferative lupus nephritis to have little or no subendothelial deposits [3,5,6]. We report one rare case with diffuse proliferative lupus nephritis but without comparable amounts of immune deposits.

Case Presentation

A 26-year-old Chinese female presented with dyspnea and bilateral lower extremity edema. Tracing back her history, she was diagnosed with SLE in March 2005, with an initial presentation of fever, skin rashes, and bilateral lower extremity edema. Her lupus had been controlled by prednisolone, but she stopped medication for 1 week before admission in July 2005. Physical examination revealed a body temperature of

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36.6°C, pale appearance, bilateral basilar lung rales and marked, pitting edema over bilateral lower extremities. No skin rashes were noted and no oral ulcer was found. Chest radiography performed at admission showed bilateral upper lobe infiltrate and cardiomegaly.

Admission laboratory tests showed hemoglobin of 4.8 g/dL, hematocrit of 15.5%, white blood cell count of 6,680/μL, platelet count of 110,000/μL, erythrocyte sedimentation rate of 80 mm/hour, blood urea nitrogen of 147 mg/dL, creatinine of 6.7 mg/dL, and serum albumin of 1.7 g/dL. Urinalysis showed 4+ protein and 5–10 red blood cells per high-power field, and daily protein loss was 12.7 g. Additional laboratory values included C3 level of 60.4 mg/dL (reference range, 83.1–125.5 mg/dL), and C4 level of 10.2 mg/dL (reference range, 17.2–32.8 mg/dL). Haptoglobin was less than 5.83 mg/dL (reference range, 13–163 mg/dL) with evidence of hemolysis. Antinuclear antibody (ANA) titer was 1:320, with a homogeneous pattern, but the patient was negative for anti-dsDNA. ELISA testing for anti-proteinase 3 antibodies and anti-myeloperoxidase antibodies were all negative. She was negative for a circulating lupus anticoagulant.

Renal sonography showed 12-cm kidneys with no hydronephrosis. A renal biopsy was performed on August 5, 2005, which revealed features of World Health Organization (WHO) class IV lupus nephritis. Thereafter, she was given 1 g/day of methylprednisolone intravenously for 3 days, followed by 60 mg/day of prednisolone. She was discharged on August 23, 2005, with serum creatinine decreased to 4.7 mg/dL, and a great improvement in dyspnea. However, she was lost to follow-up 1 week after discharge and refused further treatment. She died 2 months later.

Renal biopsy findings showed prominent global hypercellularity and lobulation in a total of nine glomeruli, and fibrocellular crescents were also present in all of the glomeruli. There was distinct intracapillary cell infiltration, but no necrotizing lesion was found. No feature of thrombotic microangiopathy was identified. There was also a moderate degree of diffuse interstitial cell infiltration (Figure 1). Immunofluorescence microscopy showed no staining for IgG, IgA, IgM, C1q, C3 or C4. Electron microscopy revealed only a scanty amount of subepithelial electron-dense deposits. The glomerular basement membrane was not thickened and the foot processes were effaced (Figure 2).

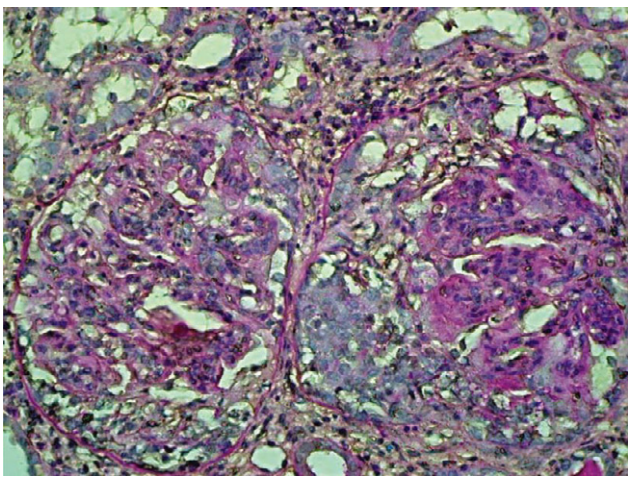

Figure 1. *Both glomeruli revealed prominent endocapillary hypercellularity, lobulation, and fibrocellular crescent formation. Note the interstitial lymphocytic infiltrate (Periodic acid-Schiff, magnification 400×).*

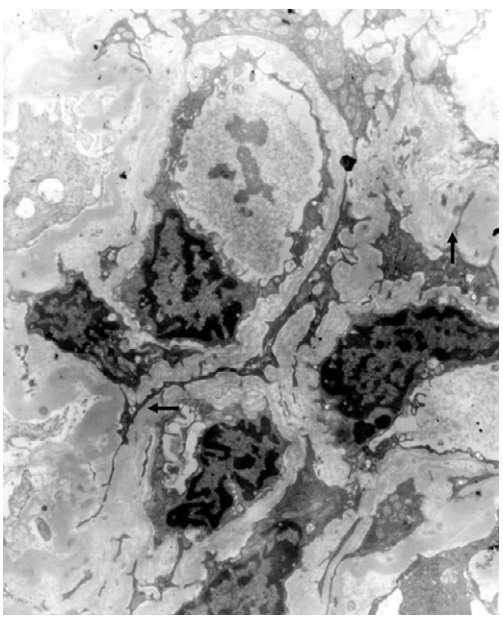

Figure 2. *Electron micrograph shows the glomerular capillary loop and mesangial area with only scanty subepithelial electron-dense deposits (arrows) (uranyl acetate and lead citrate, magnification 4,000×).*

Discussion

We have presented a case of lupus nephritis with histologic features compatible with diffuse proliferative lupus nephritis (WHO class IV), but immunofluorescent microscopy showed no immune deposits and electron microscopy revealed only scanty electron-dense

deposits. Such "pauci-immune" diffuse proliferative lupus nephritis is quite rare [3,5,6].

The most important differential diagnosis for pauci-immune lupus nephritis is the antineutrophilic cytoplasmic antibodies (ANCA)-associated pauci-immune glomerulonephritis occurring in patients with SLE with minimal renal involvement, especially when the patients had either normal or only mildly abnormal serum levels of C3, C4 and anti-dsDNA, such as the cases reported by Schwartz et al [6]. The major ANCA-associated pauci-immune glomerulonephritis to be considered include Wegener's granulomatosis, microscopic polyangiitis, and renal-limited microscopic polyangiitis [7]. Characteristics of these three diseases were not found in our renal specimen and ELISA test for ANCA was also negative in our patient. Histologically, Charney et al indicated that the glomerular feature of pauci-immune lupus nephritis is intracapillary hypercellularity with occasional crescents, rather than necrotizing lesions [5]. In contrast, ANCA-associated pauci-immune glomerulonephritis is characterized by focal segmental necrotizing glomerulonephritis associated with extracapillary proliferation of cells in Bowman's space to form glomerular crescents with no or minimal intracapillary hypercellularity. There is greater disruption of Bowman's capsule than in those occurring in immune complex crescentic glomerulonephritis [5,7,8].

The mechanisms by which the diffuse proliferative lupus nephritis with scanty immune deposits developed remain a mystery. Delayed-type hypersensitivity (DTH) that was reported in ANCA-associated pauci-immune glomerulonephritis may also be involved. DTH is a manifestation of cell-mediated immunity that is induced by sensitized T cells that recruit and activate macrophages at the site of antigen challenge [9]. Several studies have shown that sensitized cells can cause severe glomerular injury, which is independent of humoral immune responses, and are likely to be the principal mediators of crescent formation [10]. Cunningham et al [9] had found that the glomeruli of patients with ANCA-associated pauci-immune glomerulonephritis exhibit prominent features of DTH, in combination with the absence of antibody and complement, which suggests an important pathogenic role for cell-mediated immunity. Therefore, it becomes an interesting question whether pauci-immune lupus nephritis is also a manifestation of T cell-directed cognate immune injury.

There is no standard treatment for pauci-immune necrotizing lupus nephritis because cases are rare. Both of the cases reported by Akhtar et al [3] apparently responded to steroid and cyclophosphamide treatment. One case received pulse methylprednisolone and six cycles of monthly intravenous cyclophosphamide, and the other patient was treated with prednisone 30 mg/day initially and later maintained on prednisone and cyclophosphamide. The protocol of cyclophosphamide was not mentioned. Three of the five patients presented by Charney et al [5] also responded to therapy. Two received daily cyclophosphamide and prednisone, and one received not only cyclophosphamide and prednisone but also plasma exchange. Our patient presented a modest initial response after high-dose methylprednisolone and was maintained on prednisolone, although she was lost to follow-up later. Although clinical experience is limited, it seems that steroids and cyclophosphamide are effective in treating pauci-immune lupus nephritis as for regular proliferative lupus nephritis.

In conclusion, pauci-immune lupus nephritis is extremely rare and testing for ANCA and the difference in histologic features are helpful to distinguish it from ANCA-associated pauci-immune glomerulonephritis. Although the precise pathogenesis is unclear and the treatment protocol is not conclusive, evidence suggests that steroids and cyclophosphamide may be the most effective treatment.

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稀少免疫沈積狼瘡腎炎 — 病例報告

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二十六歲紅斑性狼瘡女性病患因呼吸困難及下肢水腫住院。生化檢查發現血清尿素氮為 147 mg/dL，肌酸酐為 6.7 mg/dL，每天尿蛋白流失 12.7 公克。血清補體，C3、C4 皆下降，抗核抗體效價為 1:320，但抗雙鏈 DNA 抗體為陰性。以酵素連結免疫吸附分析檢查發現 anti-PR3 抗體及 anti-MPO 抗體皆為陰性。血中 lupus anticoagulant 亦為陰性。腎臟切片在光學顯微鏡下可發現細胞廣泛增生的腎絲球，但是螢光顯微鏡檢及電子顯微鏡並無發現任何或僅發現極稀少的免疫沈積。患者接受甲基類固醇脈衝治療，每天 1 公克注射 3 天後，維持口服類固醇每天 60 毫克治療。出院時腎功能及呼吸困難皆獲得改善。廣泛增生性狼瘡腎炎卻僅能發現極少，甚至沒有免疫沈積的情形非常少見。本文在此討論此罕見病例的鑑別診斷，可能的機轉以及治療方式。

關鍵詞：新月型腎絲球腎炎，狼瘡腎炎，稀少免疫沈積腎絲球腎炎，紅斑性狼瘡

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