

Effective Treatment of Rapidly Deteriorated Renal Function with Methylprednisolone Pulse Therapy and High Dose Mycophenolate Mofetil in A Patient with Lupus Nephritis

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Abstract

A 30 year old African American female with Graves' disease and unspecified connective tissue disorder was admitted because of orthopnea and general edema. Laboratory testing showed blood urea nitrogen levels of 60 mg/dL, creatinine of 4.6 mg/dL, serum albumin of 2.1 g/dL and the daily urinary protein loss was 4.6 g. C3 level was 78 mg/dL and C4 level was 36 mg/dL. The antinuclear antibody titer was 1:640, with a speckled pattern, and anti-ds DNA was positive. She was negative for lupus anticoagulant. Renal biopsy revealed focal segmental proliferative lupus nephritis, and immunofluorescent microscopy showed full house immune deposits and electron microscopy revealed diffusely enlarged podocytes with foot process effacement and characteristic tubuloreticular inclusions in endothelial cells. She received 1 g/day of pulse methylprednisolone intravenously for 3 days, followed by 60 mg/day of prednisone. She was also started with mycophenolate mofetil 1000mg twice a day and followed by decreased dosage. Heavy proteinuria and serum creatinine level started improving after 5 days of treatment and nephrotic syndrome remitted completely in 3 weeks. The differential diagnosis, clinical risk factors and manifestations, prognostic predictors and treatment are discussed. (J Intern Med Taiwan 2012; 23: 59-65)

Key Words: Lupus nephritis, Systemic lupus erythematosus, Nephrotic syndrome

Introduction

Lupus nephritis (LN), one of the most common manifestations of systemic lupus erythematosus (SLE), usually arises within 5 years of diagnosis; however, more than half of patients have not had other symptoms of SLE when they were diagnosed with LN¹⁻². Clinical manifestations of LN range

from asymptomatic proteinuria or hematuria, hypertension, to overt nephritic and nephrotic syndromes, rapidly progressive glomerulonephritis, and chronic renal failure. The most frequently observed abnormality in patients with lupus nephritis is proteinuria with or without elevated serum creatinine³. The incidence and time course of development of LN in SLE patients varies with age,

gender, and ethnicities. The reported cumulative incidence was 55% in Asian, 51% in Africans and 43% in Hispanic populations compared with 14% in Caucasians⁴⁻⁵. In another observational study, males, younger patients, and non-European Americans are at higher risk of developing LN earlier in the disease course of SLE⁶.

Case Presentation

A 30 year old African American female was well until 3 years earlier, when Graves' disease developed and unspecified connective tissue disorder presented with both hands joints swelling and polyarthralgia. One week before admission, nausea and watery diarrhea developed and followed with abdominal distension and anasarca. Pre-admission medications were levothyroxine 175 mcg a day, plaquenil 200 mg twice a day and OTC acetaminophen use as needed for arthralgia. On admission, her legs, ankles, and eyelids were edematous and she complained of orthopnea accompanied with left sided pleuritic like chest pain. There was no sclerodactylia and no Raynaud's phenomenon. Elevated blood pressure (systolic BP 150-175 mmHg, diastolic BP 91-110 mmHg) was newly noticed. Her lungs were clear to percussion and auscultation; her heart demonstrated a regular rhythm without murmurs, gallops, or friction rubs.

The diagnostic laboratory tests were performed. The sodium was 132 mEq/L, potassium 4.9 mEq/L, chloride 105 mEq/L, CO₂ 20.4 mEq/L, blood urea nitrogen 60 mg/dl, and the creatinine at this time had risen to 4.6 mg/dl (serum creatinine was normal one year before admission).

The glucose was 84 mg/dl, calcium 8.1 mg/dl, and magnesium 2.5 mg/dl. The white count was normal at $4.6 \times 10^3/\mu\text{L}$, hemoglobin was 11.6 g/dl, and hematocrit was 33%. The platelet count was $311,000 \times 10^3/\mu\text{L}$. Hepatitis B and C serologies were negative. Serum lipid profile

revealed total cholesterol 220 mg/dL, triglyceride 129 mg/dl, low-density cholesterol (LDL) 110 mg/dL, and high-density cholesterol (HDL) 44 mg/dL. Urinalysis showed heavy proteinuria (6.4g/day), but urinary sediment showed no abnormality. Immunological examination showed positive antinuclear antibody, determination at a titer of 1:640 with a speckled pattern. Rheumatoid factor was negative. Anti-ds. DNA and anti-Sm antibody were positive. Anti-CCP (cyclic citrullinated peptide) antibody, anti-cardiolipin antibody, and anti-neutrophil cytoplasmic antibodies were negatives. C3 was slightly low 78 mg/dl (normal range: 88 to 206 mg/dl) and C4 was normal 36 mg/dl (normal range 12 to 72 mg/dl). Chest X-ray disclosed bilateral moderate pleural effusions. Renal ultrasonography revealed normal renal parenchyma echogenicity and no hydronephrosis. Minimal improvement of clinical symptoms resulted in renal biopsy performed on admission day 7. Light microscopy showed increase of mesangioproliferative changes, focal segmental karyorrhexis, and glomerular tip lesion which is podocyte prominence, capsular adhesion, and intracapillary foam cell (Figure 1A, 1B). Electron microscopic study showed diffusely enlarged podocytes with foot process effacement. Tubuloreticular inclusions, which is accumulation of ribonucleoprotein and membrane, in endothelial cells was detected on electron microscopy. It is a characteristic finding specific for lupus nephritis (Figure 1C). Immunofluorescence study, the glomeruli are positive for full house immunofluorescence including IgG, IgA, IgM, C1q, C3, and kappa and lambda light chains (Figure 1D). In addition, focally mild tubulointerstitial injury pattern was also observed. The diagnosis of lupus nephritis associated with focal segmental proliferative LN ISN/RPS Class III-A/S was made and administration of pulse methylprednisolone 1g/day for 3 days was started and followed by

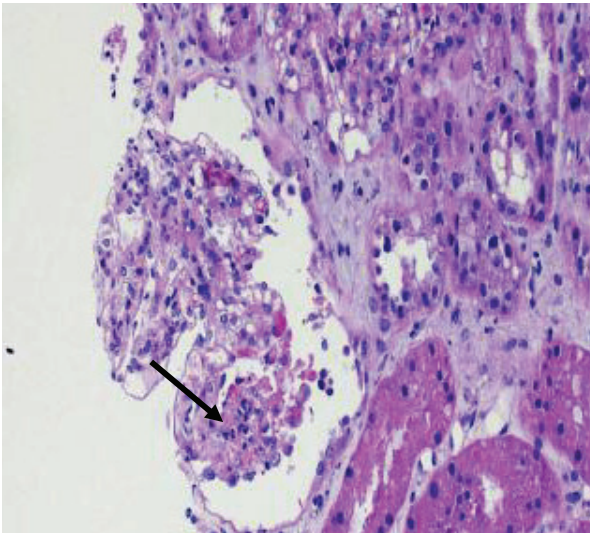


Fig 1A. Glomeruli with leukocytic infiltrates and karyorrhexis. Nuclear fragmentation is present in a segmental distribution (arrow). (hematoxylin and eosin, Magnification, 40X).

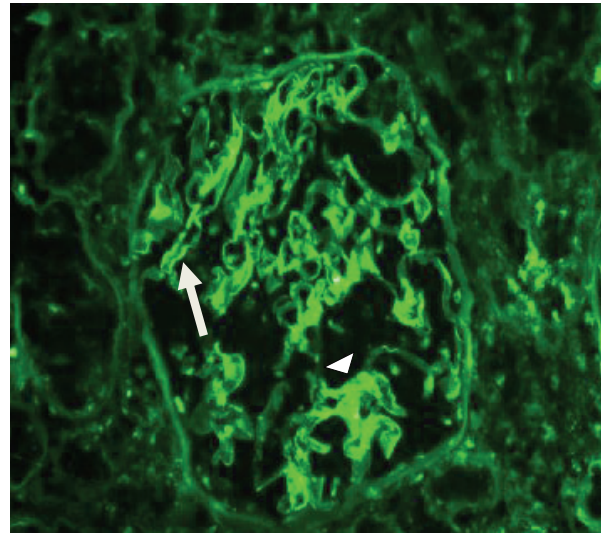


Fig 1B. Immunofluorescence micrograph shows prominent subendothelial deposits (arrow), accompanied by immune deposits in the mesangium (arrowhead). (Direct immunofluorescence for IgG with anti-IgG human antibodies marked with fluorescein, 400X).

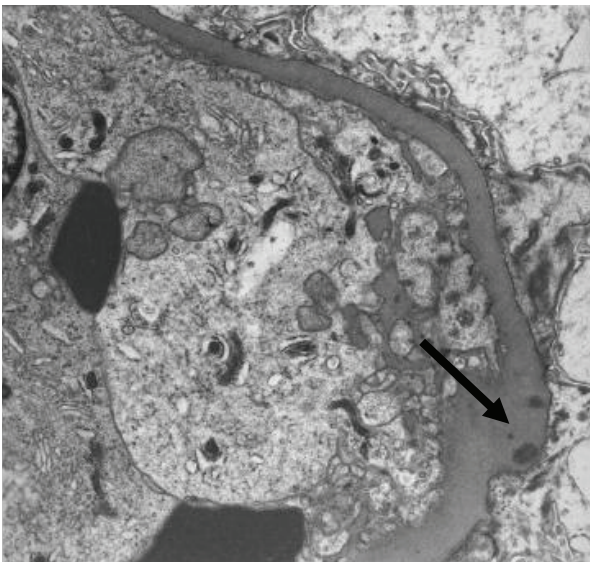


Fig 1C. Electron micrograph shows subepithelial electron-dense deposits (arrows) (uranyl acetate and lead citrate, magnification 4,000X).

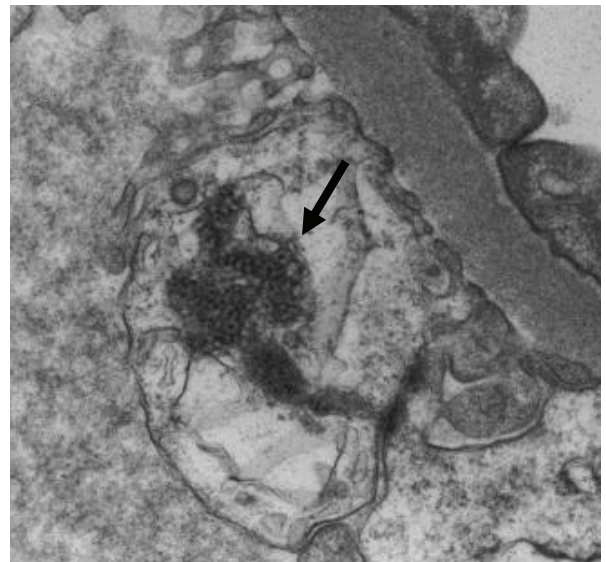


Fig 1D. Electron micrograph shows characteristic tubuloreticular inclusions (arrow) in the endothelial cells (uranyl acetate and lead citrate, magnification 25,000X).

Prednisone 60 mg/day. In the meantime, she was treated with mycophenolate mofetil 1000mg twice a day and followed by decreased dosage. Heavy proteinuria and serum creatinine level started improving after 5 days and nephrotic syndrome remitted completely in 3 weeks (Figure 2).

Discussion

We have presented a case of lupus nephritis with histologic features compatible with focal segmental proliferative lupus nephritis (ISN/RPS Class III-A/S), with immunofluorescent microscopy

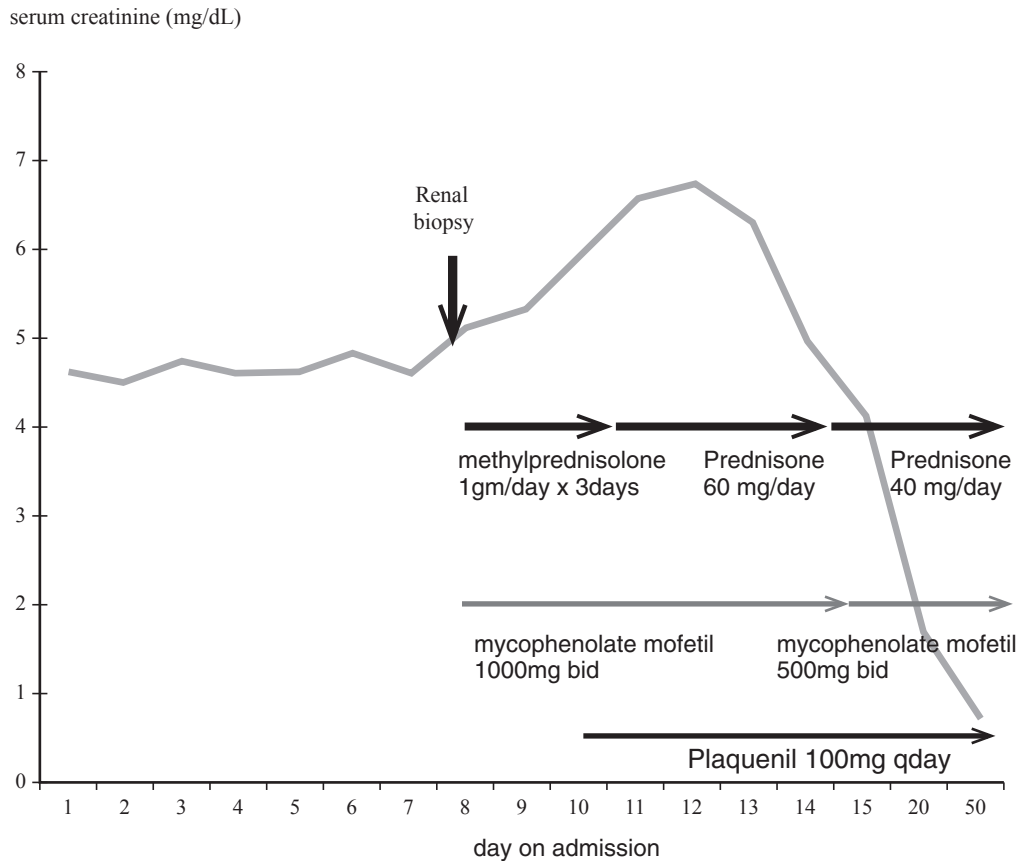


Fig 2. Time course change of serum creatinine (mg/dL) since admission and after immunosuppressive therapy.

showed typical full house pattern of immune deposits and electron microscopy revealed diffusely enlarged podocytes with foot process effacement, dense electron deposits, and characteristic tubuloreticular inclusions. When patient clinically presented with edema and nephrotic syndrome, the initial differential diagnosis should have included: i) systemic disease related (e.g. diabetes mellitus, amyloidosis, SLE), ii) medications related, especially non-steroid anti-inflammatory drugs induced acute interstitial nephritis and nephrotic syndrome; iii) unknown primary (e.g. minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy); and iv) post-infectious glomerulonephritis (e.g. membranous proliferative glomerulonephritis and IgA nephropathy).

The International Society of Nephrology

(ISN) pathologic classification scheme for LN and the Renal Pathology Society (RPS)⁷⁻⁸ provided a modified classification of LN from an older system that was developed by the World Health Organization (WHO) in 1982⁹⁻¹⁰. The ISN classification focused on the new clinicopathologic and pathogenic information with advantages of using light, immunofluorescent and electron microscopy to classify each biopsy into clearly distinctive categories and utilizing well defined criteria, allowing different investigators to compare and communicate the results of patient at different centers.

Class I, minimal mesangial LN, is the earliest and mildest form of glomerular involvement. Patients usually have normal urinalysis finding and plasma creatinine concentration. The glomeruli are normal by light microscope, but immune deposit in

mesangium can be detected in immunofluorescence and electron microscopy. Class II, mesangial proliferative LN, reveals mesangial hypercellularity and mesangial matrix expansion on light microscopy, and subendothelial deposit on immunofluorescence or electron microscopy. Patients typically present with hematuria and /or proteinuria; hypertension and nephrotic syndrome occasionally. Class III, focal proliferative LN, presents with less than 50% glomeruli having segmental (S) or global (G) active (A) or chronic (C) glomerulonephritis on light microscopy. Focal subendothelial deposit can be observed in electron microscopy. Our patient presented in this report is focal segmental proliferative LN Class III A/S. Almost all patients in this class of disease have hematuria and proteinuria. Nephrotic syndrome, hypertension and elevated serum creatinine are present in some patients. Class IV, diffuse proliferative LN, presents with more than 50% glomeruli having segmental or global glomerulonephritis, including necrotizing lesions and crescent formations, on light microscopy. Immunofluorescence microscopy reveals diffuse immunoglobulin and complement deposition and electron microscopy reveals subendothelial deposit. All patients will have hematuria and proteinuria. Hypertension, nephrotic syndrome, elevated plasma creatinine concentration and significant hypocomplementemia are commonly seen in patients. Class V, membranous LN, is characterized with diffuse thickening of the glomerular capillary wall on light microscopy and subepithelial immune deposits on immunofluorescence or electron microscopy. Hypertension and nephrotic syndrome are commonly seen in this class of patients, however, serum creatinine level is usually normal or slightly elevated. In class VI, advanced sclerosing LN, more than 90% glomeruli are globally sclerosed. Patients in this class of disease presents with slowly progressive renal dysfunction,

hematuria and / or proteinuria, and will not benefit from immunosuppressive therapy.

Immunosuppressive therapy is typically indicated in patients with focal and diffuse proliferative LN and in some patients with membranous LN including those with a severe nephrotic syndrome and usually not indicated for minimal mesangial and mesangioproliferative LN. It consists of two phases of treatment: first, induction therapy, which typically involves administering potent immunosuppressive drugs to achieve disease remission with duration as short as 3 months or as long as a year; second, maintenance therapy, which usually applies less aggressive maintenance immunosuppressive drugs for a prolonged period to prevent disease relapse. The choice of induction therapy includes glucocorticoid, cyclophosphamide, mycophenolate mofetil (MMF), and tacrolimus. For mild focal proliferative LN, a trial of glucocorticoids alone is suggested rather than combined with MMF or cyclophosphamide. However, for moderate to severe proliferative LN, initiation of glucocorticoids with either intravenous cyclophosphamide or oral MMF is recommended. The choice of intravenous cyclophosphamide or oral MMF depends on patients' clinical features. For example, MMF may be preferred in blacks and Hispanics and women prefer avoiding ovarian toxicity from cyclophosphamide. For severe active LN, intravenous cyclophosphamide with intravenous pulse methylprednisolone are recommended to induce rapid immunosuppressive effect to achieve disease remission¹¹⁻¹².

For the choice of maintenance therapy, patients who have been successfully induced with MMF or cyclophosphamide are recommended maintenance therapy with MMF or azathioprine. For patients who have been successfully induced with MMF, maintenance with MMF rather than azathioprine is recommended. For patients who have been successfully induced with cyclophosphamide, MMF

rather than azathioprine for maintenance therapy is recommended. However, azathioprine is preferred to MMF in women who are in complete remission and want to become pregnant¹³⁻¹⁵.

In conclusion, we have presented a case of INS RPS Class III-A/S lupus nephritis with risk factors of preexisted connective tissue disorder, younger age, and African Americans ethnicity. Renal biopsy should be considered in patients, with prior clinical history of SLE or other autoimmune disorders, who have clinical or laboratory evidence of active nephritis and / or nephrotic syndrome. Prompt diagnosis and therapy to attain clinical remission of active LN and detecting clinical risk factors of disease progression (e.g., elevated serum creatinine at the time of renal biopsy, crescents and concurrent tubulointerstitial disease on renal biopsy, hypertension, nephrotic range proteinuria, anemia, black or Hispanic) are associated with an improved and predicted long-term prognosis.

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使用甲基類固醇脈衝療法和高劑量 Mycophenolate Mofetil 有效治療一位狼瘡腎炎病人之迅速惡化腎功能

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摘 要

三十歲非洲裔美國女性病患過去曾有 Graves' 疾病及未明確性結締組織疾病，因呼吸困難及全身性水腫住院。生化檢查發現血清尿素氮為 60 mg/dL，肌酸酐為 4.6 mg/dL，血清白蛋白 2.1 g/dL，每天尿蛋白流失 4.6 公克。血清補體 C3 78 mg/dL 輕度下降，C4 36 mg/dL 在正常範圍值。抗核抗體效價為 1:640 呈現斑點狀型態，而且抗雙鏈 DNA 抗體為陽性。血中狼瘡抗凝劑試驗為陰性。腎臟切片在光學顯微鏡下呈現局部分段式增生性狼瘡腎炎，螢光顯微鏡檢發現 full house 免疫沈積，電子顯微鏡發現廣泛性增大型足細胞以及足禿的退化跡象，以及在內皮細胞內發現極具有特徵性管泡狀網狀內含體。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。同時合併施與 mycophenolate mofetil 口服 1000 毫克每天兩次，隨後逐漸減少劑量。治療後第五天尿蛋白流失情況及血清肌酸酐明顯改善，病患之腎變病綜合症也於治療後三周改善消失。本文將進一步探討此臨床病案之鑑別診斷，疾病相關之危險因子，狼瘡腎炎之臨床表現與病理診斷分類及特徵，以及討論狼瘡腎炎的治療方式與預後相關因子。