Termination of Hemodialysis Treatment on the 5th Month of Mycophenolate Mofetil in Type 4 Lupus Nephritis with Serious Renal Failure: A Case Report

Ciddi Böbrek Yetmezlikli Tip 4 Lupus Nefritli Hastada Mikofenolat Mofetil Uygulamasının 5. Ayında Hemodiyaliz Tedavisinin Sonlandırılması: Olgu Sunumu

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic, occasionally life-threatening, multisystem disorder, and renal involvement is one of the most common and most serious complications of SLE. Among the various histological types of lupus nephritis, diffuse proliferative nephritis carries the worst prognosis. A 28-year-old woman was admitted to Baskent University Adana Hospital with the complaints of dyspnea, chest pain, and fatigue. The patient had active lupus manifestations including generalized pleural and pericardial effusion, hypoalbuminemia, anemia, leucopenia, hypocomplementemia, markedly elevated ANA, acute kidney injury, and uncontrolled hypertension. Renal biopsy had been performed at another institute and shown type 4 lupus nephritis. She had been managed with methylprednisolone and cyclophosphamide (CYP) for 6 months. We started immunosuppressive therapy with intravenous methylprednisolone (1 gr/day) for 3 days as an induction therapy. The treatment was continued with oral methylprednisolone 0.5 mg/kg/day and mycophenolate mofetil (MMF) 1 gr/day. Hemodialysis (HD) therapy was initiated because of progressive renal failure and hypervolemia during the clinical course. Despite the improvement in her general condition, the patient underwent HD treatment three times a week for 5 months. On the fifth month of MMF therapy the renal function and diuresis were progressively improved and HD treatment was terminated. Management with MMF may be effective for remission of lupus nephritis in patients who are nonresponders to initial CYC therapy.

KEY WORDS: Lupus nephritis, Renal failure, Immunosuppressive therapy, Cylophosphamide, Mycophenolate mofetil

ÖZ

Sistemik lupus eritematozus (SLE) kronik, nadiren yaşamı tehdit eden multisistemik bir hastalıktır ve böbrek tutulumu SLE'nin en yaygın ve ciddi bulgularından birisidir. Lupus glomerülonefritinin değişken histopatolojik tiplerinden olan diffüz proliferatif nefrit en kötü prognoza sahiptir. 28 yaşında bayan hasta kliniğimize nefes darlığı, göğüs ağrısı ve halsizlik şikayetiyle başvurdu. Hasta başka bir merkezde 6 aydır tip 4 lupus nefriti nedeniyle metilprednizolon ve siklofosfamid içeren immunsüpresif tedavi almaktaydı. Hasta yaygın plevra ve perikard efüzyonu, hipoalbuminemi, anemi, lökopeni, kompleman düşüklüğü, yüksek titrede ANA pozitifliği, böbrek yetmezliği, kontrolsüz hipertansiyon gibi aktif sistemik lupus bulguları nedeniyle kliniğimize yatırıldı. İmmünsupresif olarak 3 gün yüksek doz (1 gr/gün) iv metilprednizolon sonrası peroral 0.5 mg/kg/gün metilprednizolon ile birlikte günlük 1 gr mikofenolat mofetil (MMF) tedavisi başlandı. Aynı zamanda sıvı yüklenmesi ve ilerleyici akut böbrek hasarı nedeniyle hemodiyaliz (HD) tedavisine alındı. İmmünsüpresif tedavi başlandıktan sonra hastanın klinik durumu düzelmesine rağmen 5 ay süresince haftada 3 kez HD tedavisi devam etti. MMF tedavisinin 5. ayında böbrek fonksiyonları ve diürez progresif olarak düzeldi ve HD tedavisi sonlandırıldı. Başlangıç siklofosfamid tedavisine yanıtsız lupus nefriti remisyonunda MMF etkili bir tedavi olabilir.

ANAHTAR SÖZCÜKLER: Lupus nefriti, Böbrek yetmezliği, İmmünsüpresif tedavi, Siklofosfamid, Mikofenolat mofetil

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, occasionally life-threatening, multisystem disorder. Histological type 4 nephritis (diffuse proliferative nephritis) and a younger age are the worst prognostic factors for patient and renal survival.

The issue of renal recovery is certainly complex. The presence of diffuse proliferative lupus nephritis and resistance to immunosuppressive therapy indicates a poor prognosis for renal survival and is associated with an increased risk of end-stage renal failure (1).

This article presents a case of a young woman with progressive renal failure due to severe type 4 lupus nephritis. She became hemodialysis (HD)-dependent despite immunosuppressive therapy with Methylprednisolone and Cyclophosphamide (CYC). However, it was possible to discontinue HD treatment after 5 months of Mycophenolate Mofetil (MMF) therapy.

RESULT

A 28-year-old woman was admitted to Baskent University Adana Hospital with complaints of dyspnea, chest pain, and fatigue. She had been diagnosed with lupus nephritis at another institute six months prior to presentation. Renal biopsy had revealed findings of diffuse global proliferative lupus nephritis. She had been managed with methylprednisolone pulse therapy (3 pulses of 1 gr/day) followed by 0.5 mg/kg oral methylprednisolone tapering according to the clinical response and intravenous CYC (0.5 gr/m^2) given monthly for 6 months.

On her physical examination she was afebril. Her blood pressure was 150/100 mmHg, heart rate was 90 beats/min, and respiratory rate was normal. Thyroid gland , liver, spleen, and lymphoid node examination were normal. Respiration sounds were bilaterally decreased at the middle of the lungs. A systolic murmur was heard at the cardiac apex and bilateral +2 pitting edema was detected on the legs.

Blood tests at admission revealed the following results: hemoglobin: 7.16 g/l, blood urea nitrogen (BUN) 43 mg/dl, serum creatinine 1.43 mg/dl, sodium 137 mEq/l, potassium 6.79 mg/dl, calcium 7.63 mg/dl, phosphorus 5.46 mg/dl, and albumin 2.29 g/dl. Her peripheral white blood cell count was 3200/mm^3, and the differential count showed 71.3% neutrophils, 14.1% eosinophils, 8.4% lymphocytes, 5.6% monocytes and 0.5% basophils. A dipstick urinalysis test revealed many white cells and proteinuria. Examination of the urinary sediment showed hematuria, leucocyturia and a few red cell casts. Repeated urine and blood cultures were sterile. The patient's glomerular filtration rate calculated with the MDRD formula was 48 ml/min and the urine protein-to-creatinine ratio was 3.5.

Serological tests for anti-nuclear antibodies and anti-dsDNA were markedly elevated while complement C3 and C4 levels were both low. The ANA titer was 1/640 and the anti-dsDNA titer was 1404 by ELISA. Other autoimmune markers for ANCA, Anti-GBM, and anti-phospholipids antibodies were negative. Results of viral serology for hepatitis B, C, and HIV were all negative.

The size and parenchyma of both kidneys were found to be normal at ultrasonography. Chest radiography revealed bilateral massive pleural effusion. Echocardiography revealed normal systolic function (EF > %60, left ventricular hypertrophy, 2-3/6 mitral regurgitation and 1/4 tricuspid regurgitation.

A renal biopsy had been performed six-month ago when she was admitted with active systemic lupus manifestation. Histopathological examination showed diffuse segmental or global endocapillary and extracapillary proliferative glomerulonephritis in 29 glomeruli, together with focal lymphocytic infiltration and acute tubular necrosis. Hyaline droplets in segmental capillaries as well as a wire loop pattern on capillary basement membrane were present. IgA, IgG, IgM, and intense C1q and C3 depositions, the so-called full house pattern, was detected on immunofluorescence microscopy. Therefore, the diagnosis was very active diffuse global proliferative lupus nephritis (WHO IV-A).

The patient was hospitalized with active lupus manifestations including generalized pleural and pericardial effusion, hypoalbuminemia, anemia, leucopenia, hypocomplementemia, markedly elevated ANA and anti-dsDNA, acute kidney injury, and uncontrolled hypertension. Immunosuppressive therapy was started with IV methylprednisolone (1 gr/day) for 3 days as an induction therapy. The treatment was continued with oral methylprednisolone 0.5 mg/day and mycophenolate mofetil (MMF) 1 gram/day. Hemodialysis was initiated because of progressive renal failure (serum creatinine increased from 1.43 to 3.8 mg/dl), and hypervolemia during the induction therapy. Despite improvement of the general condition, the patient underwent HD treatment three times a week for 5 months for ongoing renal dysfunction. On the fifth month of MMF therapy, the renal function and diuresis was progressively improved and HD treatment was terminated.

One year after the termination of HD therapy, the patient is still in partial remission under immunosuppressive therapy (MMF 2x500 mg/day combined with methylprednisolone 8 mg/day) and antihypertensive medication (valsartan 160 mg/day). Her serum creatinine level was 1.23 mg/dl and urinary protein excretion was 1.6 gr/day at the last follow-up visit. The patient's clinical and biochemical parameters during the follow-up are summarized in Table I.

DISCUSSION

The most striking finding of this case is the relief of dialysis-dependent renal failure at the fifth month of MMF treatment in a young woman with severe diffuse proliferative lupus nephritis.

Lupus nephritis usually develops in the first few years of disease; the cumulative incidence of renal disease is 60% at 5

Table I: The patient's clinical and biochemical parameters during the follow-up.

	Basal	1st Month	3rd Month	5th Month	1st Year
BP (mmHg)	150/100	180/110	140/80	150/100	130/90
BL Pleural effusion	+	+	-	-	-
Peripheral Edema	++	+++	-	-	-
Treatment	3 day IV MP + oral MP+MMF	MP+MMF	MP+MMF	MP+MMF	MP+MMF
HD treatment	-	Started	Continued	Termination	Without HD
BUN (mg/dl)	43	76	63	25	28
Creatinine (mg/dl)	1.43	3.8	3.3	1.84	1.23
Sodium (mEq/l)	137	129	138	137	136
Potassium (mg/l)	6.79	5.1	3.3	4.02	4.6
Calcium (mg/l)	7.63	8.09	9.9	9.38	9.09
Phosphorus (mg/dl)	5.46	5.08	2.5	4.02	4.4
Albumin (g/dl)	2.29	2.6	3.6	4.59	3.7
Hb (g/dl)	7.16	6.5	10.1	12.2	11.4
WBC (mm^3)	3200	7800	13.000	5200	3700
PLT (mm^3)	296	298	283	256	249
CRP (mg/l)	35.80	8.4	30.2	<3	3.19
C3/C4 (mg/dl)	52.7/7.5	53/9.8	55/12.1	82/18.9	64.1/19
ANA	1/640			1/160	
Anti-dsDNA (IU/ml)	1404			416	
UPCR	3.5			1.0	1.6
eGFR (ml/min)	48	15	18	36	60

BP: Blood pressure, **MP:** Methylprednisolone, **MMF:** Mycophenolate mofetil, **HD:** Hemodialysis, **BUN:** Blood urea nitrogen, **Hb:** Hemoglobin, **WBC:** White blood count, **PLT:** Platelet, **CRP:** C-Reactive protein, **ANA:** Anti-nuclear antibody, **UPCR:** Urine-protein-creatinine ratio, **eGFR:** Estimated glomerular filtration rate

years after the SLE diagnosis. Renal involvement is the most important prognostic factor associated with patient and renal survival. When diffuse proliferative lupus nephritis is present, the risk of end-stage renal failure is as high as 11-33% at 5 years (1).

The aim of immunosuppressive treatment in lupus nephritis is long-term preservation of renal functions, reduction of renal flares, prevention of treatment -related complications, and, ultimately reduction of mortality. Despite many studies in this area and the use of new immunosuppressive drugs, management of the disease continues to be a huge challenge. There are variable treatment protocols in different centers, but no approach provides a definitive treatment. Proliferative lupus nephritis (types 3 and 4) and more serious class 5 (proteinuria in the nephrotic range and renal dysfunction) are usually managed with aggressive induction therapy combined with high-dose corticosteroids and CYC (2-4). Mycophenolate mofetil is an antiproliferative drug that can be used as a first-line therapy combined with prednisolone to reduce gonadal and bladder toxicity of CYC in serious forms of lupus nephritis. In addition, it can be used in patients who are resistant to the CYC regimen.

There is no consensus on the definition of treatment resistance lupus nephritis.

The prevalence of the resistance lupus nephritis arises depending on the clinical criterias. Resistant lupus nephritis is defined as no improvement of clinical or histological findings after the initial conventional treatment with or without CYC (5). Mok and colleagues reported the prevalence of resistant lupus nephritis is up to 20% in their study (6). According to

NIH study the clinical criteria for the diagnosis of treatment resitant lupus nephritis are less than fifty percent reduction of proteinuria from the basaline value or to less than 3 gr/d, active urine sediment, elevated serum creatinine level with or without positive selogical markers (7). Another study using the NIH criteria conducted by Mok and colleagues found that the prevalence of resistance to oral or intravenous CYC induction therapy for diffuse prolipherative lupus nehritis was 14% (8). Using the similar renal response criteria as suggested by the NIH investigators, the patient was accepted as resistant to initial immunosuppressive therapy because of progressive renal impairment with persistent proteinuria. As regards complete or partial remission, the efficacy of CYC and MMF treatment has been reported to be comparable in the induction phase (9). A randomized controlled study that was conducted by Chan and et al showed that the risk of death and end-stage renal failure is lower in patients managed with MMF than in the CYC group (10).

The issue of renal recovery is certainly complex. The presence of histological diffuse proliferative lupus nephritis and resistance to immunosuppressive therapy are known to be associated with increased risk of end-stage renal failure (11). The rate of renal function recovery in patients with dialysis-dependent lupus nephritis is approximately 10-28%, and occurs at a median of 3-18 months (12-13). A dialysis-dependent severe proliferative lupus nephritis patient with complete recovery of renal function has been reported (14).

In conclusion, these findings suggest that MMF may be an effective option for remission of lupus nephritis and decreasing the risk of end-stage renal failure in patients who are nonresponders to initial CYC therapy.

REFERENCES

1. Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD: Factors predictive of outcome in severe lupus nephritis. Lupus nephritis collaborative study group. Am J Kidney Dis 2000;35(5):904-914
2. Gourley MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, Boumpas DT, Klippel JH, Balow JE, Steinberg AD: Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996;1:125(7):549-557
3. KDIGO, Clinical Practice Guideline for Glomerulonephritis. Lupus Nephritis. Kidney Int Suppl 2012;2:221-232
4. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, Karpouzas GA, Merrill JT, Wallace DJ, Yazdany J, Ramsey-Goldman R, Singh K, Khalighi M, Choi SI, Gogia M, Kafaja S, Kamgar M, Lau C, Martin WJ, Parikh S, Peng J, Rastogi A, Chen W, Grossman JM: American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64(6):797-808
5. Mok CC: Therapeutic options for resistant lupus nephritis. Semin Arthritis Rheum 2006;36:71-81
6. Mok CC: Prognostic factors in lupus nephritis. Lupus 2005;14:39-44
7. Boumpas DT, Balow JE: Outcome criteria for lupus nephritis trials: A critical overview. Lupus 1998;7:622-629
8. Mok CC, Ying KY, Ng WL, Lee KW, To CH, Lau CS, Wong RW, Au TC: Long-term outcome of diffuse proliferative lupus glomerulonephritis treated with cyclophosphamide. Am J Med 2006;119(4):25-33
9. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR: Mycophenolate mofetil for induction therapy of lupus nephritis: A systematic review and meta-analysis. Clin J Am Soc Nephrol 2007;2(5):968-975
10. Chan TM, Tse KC, Tang CS, Mok MY, Li FK; Hong Kong Nephrology Study Group: Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2005;16(4):1076-1084
11. Mojcik CF, Klippel JH: End stage renal disease and systemic lupus erythematosus. Am J Med 1996;101(1):100-107
12. Coplon NS Diskin CJD, Petersen J, Swenson RS: The long term clinical course of systemic lupus erythematosus in end stage renal disease. N Eng J Med 1983;27;308(4):186-190
13. Kimberly RP, Lockshin MD, Sherman RL, Beary JF, Mouradian J, Cheigh JS: End-stage lupus nephritis: Clinical course to and outcome on dialysis: Experience with 39 patients. Medicine (Baltimore) 1981;60(4):277-287
14. Ross S, Benz K, Sauerstein K, Amann K, Dötsch J, Dittrich K: Unexpected recovery from longterm renal failure in severe diffuse proliferative lupus nephritis. BMC Nephrol 2012;13:81