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Treatment of class II lupus nephritis with combination therapy of mycophenolic acid and corticosteroid; a case report

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ABSTRACT

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE). Despite available guidelines recommendations on appropriate therapeutic agents, up to one-third of LN patients still do not meet expected response to initial corticosteroid or immunosuppressive treatment. We report a 17-year-old Indonesian female who was diagnosed LN with persistent proteinuria manifestations. Renal biopsy was suggestive of class II LN. Corticosteroid was given for a month without therapeutic response, and the patient was given combination of moderate dose methylprednisolone and mycophenolic acid resulted in complete remission after nine months therapy. Despite the existing guidelines, choices of LN treatment might be individual depends on disease severity (clinical, laboratory and histopathological findings) and demographic factors. The combination of mycophenolic acid and corticosteroid might be better option than high dose corticosteroid to treat class II LN for minimizing the adverse event of corticosteroid.

Implication for health policy/practice/research/medical education:

Despite the existing guidelines, choices of LN treatment might be individual depends on disease severity and demographic factors. The combination of mycophenolic acid and corticosteroid might be better option than increasing the dose of corticosteroid to treat class II LN unresponsive to corticosteroid therapy alone to minimize the adverse event of corticosteroid.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that damage cells and organs through binding of autoantibodies and immune complexes in tissues (1). One of the affected organs is kidney or better known as lupus nephritis (LN). Nearly 50% of people with SLE developed LN, which could reach to end-stage renal disease (2). Around 20% to 70% of LN patients are reported to be resistant to corticosteroid or immunosuppressive therapy (3). We report a case of LN in young Indonesian female who do not respond to corticosteroid therapy and had to be switched to combination therapy.

Case Report

A 17-year-old Indonesian woman presented to our hospital

with swollen of her feet, hands and eyelids since three months. Patient did not complain of hair loss, stiff joints, and mouth ulcer or skin rashes. Patient was diagnosed with SLE with LN based on clinical appearance and laboratory results that meet Systemic Lupus International Collaborating Clinics (SLICC) criteria [lymphopenia, thrombocytopenia, high ANA (antinuclear antibody) titers, proteinuria, and hypocomplementemia]. ANA profiles was obtained positive results for native SS-A, SS-B, Ro-52 recombinant, and nucleosomes. Anti-dsDNA was negative. Proteinuria in 24-hours urine sample was 6.03 grams, while albumin-to-creatinine ratio was ≥ 300 mg/g. A renal biopsy showed proliferation of mesangial cells, since capillary walls were normal, tubular atrophy, infiltration of inflammatory cell in interstitial are by light-

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microscopy with PAS staining (Figure 1A). Furthermore, immunofluorescence of renal tissue revealed immune deposit of C1q (Figure 1B), C3 (Figure 1C), and IgG (Figure 1D) in mesangial and capillary wall. All of these findings lead to LN ISN/RPS class II.

According to KDIGO (Kidney disease: Improving global outcomes) recommendation, patient should be given corticosteroid (methylprednisolone 24 mg/d). Despite this treatment, she still had swelling in both of her feet, hands and eyelids. Her proteinuria also did not improve. We changed the therapy to mycophenolic acid (MPA) 360 mg/d in combination with methylprednisolone (24 mg/d equivalent with 30 mg prednisone), and after five days the swelling in the patient appeared to be reduced. Urine examinations still revealed proteinuria but had improved. Patient was discharged after seven days combination therapy without any swelling. Patient's therapy was continued and planned for a 3-month evaluation because patient's home was too far from our hospital. After four months of combination therapy, swelling in the patient was not seen, and proteinuria had improved. Evaluation after nine months combination therapy (Table 1), swelling in the patient was not seen, and laboratory parameters showed complete response (normal creatinine serum plus urine protein to creatinine ratio (uPCR) revealed <500 mg/g).

Discussion

LN is one of clinical manifestations of SLE. LN may manifest in persistent proteinuria (>0.5 g/d or urine dipstick >3+), and/or cellular casts including erythrocyte, granular, tubular, or mixed. The most common clinical manifestation of LN is proteinuria, which causes edema (1). Extra-renal lupus manifestations are also important for establishing diagnosis of LN (4).

The diagnostic of SLE refers to SLICC criteria with the finding of at least four clinical and laboratory criteria (5). This patient had edema as chief complaint and persistent proteinuria. Further examinations showed five criteria that met the SLICC criteria (proteinuria, lymphopenia, thrombocytopenia, high ANA titers and

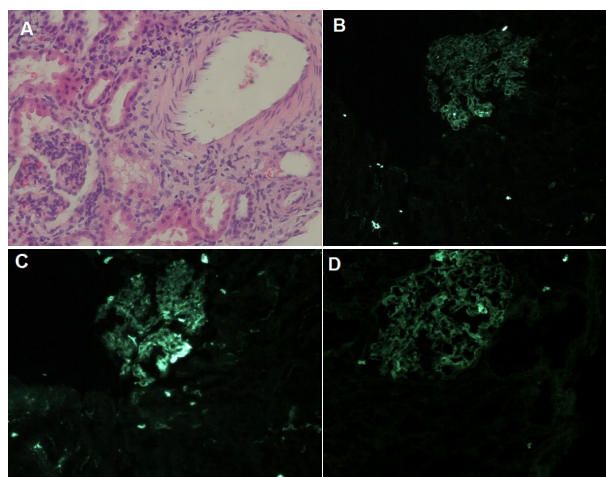


Figure 1. Histopathology of renal biopsy sample. (A) Light-microscopy PAS staining showing proliferation mesangial matrix and cell, capillary wall was normal, atrophy tubulus, infiltration of inflammatory cell in interstitial ($\times 400$). (B) Immunofluorescence of renal tissue revealed immune deposit of C1q in mesangial and capillary wall ($\times 400$). (C) Immunofluorescence of renal tissue revealed immune deposit of C3 in mesangial and capillary wall ($\times 400$). (D) Immunofluorescence of renal tissue revealed immune deposit of IgG in mesangial and capillary wall ($\times 400$).

hypocomplementemia). Renal biopsy is recommended when there is a suspicion of renal involvement, while clinical and laboratory parameters cannot accurately predict the histological class (6). Renal histopathology is also the basis for determining the disease class and treatment options for LN (7). Recently, clinical data supported the opinion that mycophenolate mofetil (MMF) with corticosteroids may be first-line therapy instead of cyclophosphamide for all serious forms of LN (class III, IV, and V) (8). However, in general, additional therapy for LN also can be given renin-angiotensin-aldosterone system inhibitor including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blocker (ARB) to treat proteinuria (1).

KDIGO glomerulonephritis work group has recommended that the selection of LN therapy should be based on histopathology (Table 2). Administration of corticosteroid or calcineurin inhibitor (CNI) induction can be administered to class II LN if proteinuria more

Table 1. Clinical course of lupus nephritis, changes in serum and urinary findings

	Before treatment	1 Month after steroid therapy	5 Days after MPA and steroid therapy	4 Months after MPA and steroid therapy	9 Months after MPA and steroid therapy
Serum creatinine (mg/dL)	1.58	0.9	0.7	0.8	0.78
Dipstick urine	+4	+4	+3	+2	+1
Albumin/creatinine urine	≥ 300 mg/g	≥ 300 mg/g	300 mg/g	300 mg/g	Normal
Protein/creatinine urine	≥ 1500 mg/g	≥ 1500 mg/g	1500 mg/g	1500 mg/g	Normal
Protein Esbach	3 g/L				0.1 g/L
Protein excretion (urine)	6.03 g/24 h				

Table 2. KDIGO recommendation for lupus nephritis therapy (6)

Class of Lupus Nephritis	Recommendation Therapy
Class I: Minimal mesangial lupus nephritis	Therapy for extra renal manifestation
Class II: Mesangial proliferative lupus nephritis	<ul style="list-style-type: none"> • If proteinuria <1 g/dL: therapy for extra renal manifestation • If proteinuria >3 g/dL: corticosteroid or calcineurin inhibitors (CNIs)
Class III: Focal lupus nephritis & Class IV: Diffuse lupus nephritis	<ul style="list-style-type: none"> • Initial therapy with corticosteroid combine with cyclophosphamide or MMF • If getting worse in 3 months therapy, initial therapy can be changed or re-biopsy
Class V: Membranous lupus nephritis	Therapy with corticosteroid and other immunosuppressant if there is persistent nephritic proteinuria
Class VI: Advanced sclerosing lupus nephritis	Therapy with corticosteroid or other immunosuppressant if there are extra renal manifestations.

than 3.0 g/d detected (6). Renal histopathology in our patient demonstrated LN class II. According to this recommendation, the patient was given corticosteroids for four weeks, however, no clinical and laboratory improvement was detected. We could not give CNI because the drug was not available in the area where the patient lives. Considering the patient is in childbearing age, we decided to give MPA combination with methylprednisolone and ARB. Evaluation after nine months using MPA and corticosteroids showed complete remission. In our case, there was a discrepancy between the expected results of treatment with a recommended therapy guideline, since in LN class II, corticosteroid did not show successful treatment. Some factors that can influence the results of therapy and prognosis include; demographic factors, genetic and immunology, histopathology, clinical and laboratory parameters (3,9).

The presence of certain autoantibodies is characteristic of SLE. Some autoantibodies and histopathological feature are known to be related to the course and the prognosis of LN. The study by Cortés-Hernández et al showed that patients with anti-dsDNA (anti-double stranded DNA) and anti-histone reactivity have tendency to develop proliferative glomerulonephritis compared to patients without these autoantibodies (10). There is an increase of anti-C1q immune complex along with increased anti-C1q titers which can predict LN flares (9). The presences of interstitial infiltration, tubular atrophy, and interstitial fibrosis have poor prognosis for renal survival (11). In our case, there were not positive anti-dsDNA, anti-C1q, and anti-histone titers, since on histopathological examination, the patient met the criteria for LN class II with partial tubular atrophy and minimal inflammatory cell infiltration of interstitial area. Based on these data, it was possible that these are the reason she did not showed any clinical and laboratory improvement after treatment corticosteroid even though her renal histopathology revealed LN class II.

SLE is a complex autoimmune disease, very

heterogeneous with activity and prognosis of diseases that can differ depending on age, gender, race and ethnicity. The results of the Aspreva Lupus Management Study (AMLS) showed that the response rate of administration of MMF and cyclophosphamide was the same in Asian populations and white people (12). Younger age at the onset of nephritis has a worse prognosis than late onset (after the age of more than 50 years old). Male patient also has a worse prognosis than women (9). In our case, the patient is Asian female with 17 years old age when she was first diagnosed with SLE. The combination of MPA and methylprednisolone resulted in complete response after nine months therapy for our patient.

This case showed that a combination of moderate dose corticosteroids and MPA can successfully induce complete remission LN class II unresponsive to corticosteroids alone. Mycophenolic acid is an active drug that is a potent inhibitor of T- and B-lymphocyte proliferation via a reversible inhibition of inosine 5-monophosphate dehydrogenase (13). While moderate doses of corticosteroids have anti-inflammatory activity through genomic mechanisms. Genomic effects are activated with low (<7.5 mg prednisone equivalent per day) to moderate (7.5–30 mg prednisone equivalent per day) glucocorticoid doses. Genomic mechanisms are activated after glucocorticoid, as lipophilic molecules, cross the cell membranes and bind to the intracellular cytoplasmic glucocorticoid receptor (cGR). The complex GC-cGR translocates to the nucleus and binds to DNA binding sites known as glucocorticoid response elements. The result is a decreased transcription of genes encoding inflammatory cytokines, a process known as trans-repression and an increased transcription of anti-inflammatory genes, known as transactivation (14). Based on these mechanisms, the combination of MPA and moderate dose corticosteroid has a synergistic effect in reducing the inflammatory response and damage to the nephrons.

As patients with higher degree of disease activity are usually treated with higher corticosteroid doses. Both

disease activity and corticosteroid exposure have been associated with organ damage in SLE (e.g., bone disease, insulin resistance and peptic ulcer). Organ damage occurs in 50% of patients with SLE within five years of SLE diagnosis, with reported increased risk of 2.8% for each 1 mg prednisone per day (14). The addition of MPA to corticosteroid in the LN management aims to improve kidney outcomes while minimizing adverse events.

Conclusion

We report a case of class II LN who did not respond to corticosteroid therapy in a young Asian female. After switching therapy to MPA and moderate dose methylprednisolone, a complete response was obtained after nine months. We recommend that despite the existing guidelines, choices of LN treatment might be individualized depends on disease severity (based on clinical, laboratory and histopathological findings) and demographic factors. The combination of moderate dose corticosteroids and MPA might be better option than high dose corticosteroid to treat Class II LN for minimizing the adverse event of corticosteroid.

Authors' contribution

FAN was the principal investigators of the study. All authors were included in preparing the concept and design. All authors revisited the manuscript, critically evaluated the intellectual contents, and participated in preparing the final draft of the manuscript. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

No conflict of interest declared.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patient gave the consent to publish as a case report.

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