

Received: 2022.05.10

Accepted: 2022.09.21

Available online: 2022.10.02

Published: 2022.11.07

# Tacrolimus Induction Therapy for Nephrotic Syndrome Caused by Minimal Mesangial Lupus Nephritis with Lupus Podocytopathy: A Case-Based Review

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABCDEF G 1 **Ibuki Kurihara**  
ABDEF 2 **Chihiro Terai**  
ABD 2 **Hiroki Yabe**  
DEF 1 **Hitoshi Sugawara**

1 Division of General Medicine, Department of Comprehensive Medicine 1, Saitama Medical Center, Jichi Medical University, Saitama, Japan  
2 Division of Rheumatology, Department of Comprehensive Medicine 1, Saitama Medical Center, Jichi Medical University, Saitama, Japan

**Corresponding Author:** Ibuki Kurihara, e-mail: [kibui.rahariku@gmail.com](mailto:kibui.rahariku@gmail.com)  
**Financial support:** None declared  
**Conflict of interest:** None declared

**Patient:** Female, 23-year-old  
**Final Diagnosis:** Lupus podocytopathy • minimal mesangial lupus nephritis  
**Symptoms:** Edema • weight gain  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Nephrology • Rheumatology





**Objective:** Unusual clinical course  
**Background:** Nephrotic syndrome caused by minimal mesangial lupus nephritis is considered rare. Nephrotic syndrome can be caused by minimal mesangial lupus nephritis with diffuse epithelial foot-process effacement and lupus podocytopathy.

**Case Report:** A 23-year-old Japanese woman diagnosed with mixed connective tissue disease was admitted because of weight gain and generalized edema for 2 weeks prior to admission. She had butterfly-shaped erythema on her cheeks, proteinuria, leukocytopenia with lymphocytopenia, and hypoalbuminemia. She was positive for antinuclear antibodies, and specific autoantibodies were only positive for the ribonucleoprotein (RNP) antigen. She was diagnosed with systemic lupus erythematosus. Renal biopsy showed minor glomerular abnormalities, and immunofluorescence revealed peripheral deposits of IgM and complement C3c. Electron microscopy revealed diffuse podocyte foot-process effacement of >80% of the capillary loop surfaces, with only a few subendothelial deposits. Consequently, we diagnosed minimal mesangial lupus nephritis with lupus podocytopathy. On hospital day 4, we administered 1000 mg/day of methylprednisolone for 3 days, followed by prednisolone 50 mg/day, but proteinuria persisted. On day 12, we administered tacrolimus (3 mg/day). Proteinuria improved and then disappeared on day 17. Prednisolone was gradually tapered and stopped after 3 years, although tacrolimus 3 mg/day was continued. No flare-up was observed 4 years after admission.

**Conclusions:** Tacrolimus showed good efficacy in this case of minimal mesangial lupus nephritis with lupus podocytopathy. Prospective and randomized controlled trials should be conducted to demonstrate the efficacy of tacrolimus for this indication.

**Keywords:** Calcineurin Inhibitors • Lupus Nephritis • Neonatal Systemic Lupus Erythematosus • Nephrotic Syndrome • Podocytes • Tacrolimus

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/937201>

 1254   3  16



## Background

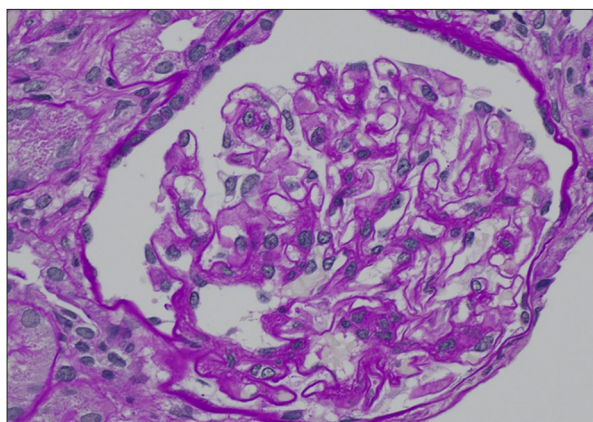
Minimal mesangial lupus nephritis (ISN/RPS classification Class I) occurs in approximately 3.9% of lupus nephritis cases. Of these, only 0.8% are estimated to present with nephrotic syndrome [1]. Nephrotic syndrome in patients with lupus nephritis has been attributed to immune complex deposition and endocapillary proliferation disrupting the glomerular filtration barrier [2]. However, nephrotic syndrome has also been observed in minimal mesangial lupus nephritis with electron microscopy findings of diffuse epithelial foot-process effacement. These cases showed no endocapillary proliferation, necrosis, crescents, or significant immune complex deposits. These lesions are termed lupus podocytopathy [3,4]. A study reported that all cases of minimal mesangial lupus nephritis with lupus podocytopathy demonstrated nephrotic syndrome; 23.1% of patients developed acute kidney injury, only 23.1% showed low serum complement, and 53.8% had nephrotic syndrome relapse, which had a different course from ordinary minimal lupus nephritis [3]. Glucocorticoids are the first-line therapy and immunosuppressive agents, such as calcineurin inhibitors (CNIs), are the second-line therapy for minimal-change nephrotic syndrome [5]. Herein, we report a patient with nephrotic syndrome caused by minimal mesangial lupus nephritis with lupus podocytopathy who attained remission with tacrolimus and steroid pulse therapy.

## Case Report

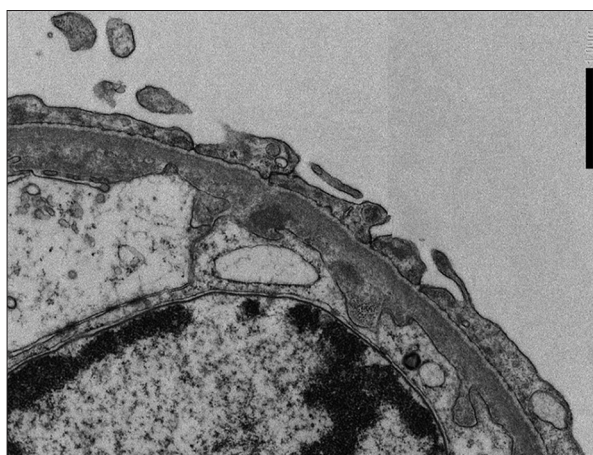
A 23-year-old Japanese woman was admitted to our hospital with a weight gain of approximately 10 kg and generalized edema for 2 weeks. She had been diagnosed with mixed connective tissue disease with symptoms of Raynaud's syndrome, arthralgia in both hands, sclerosis of the fingers, positive anti-RNP antibodies, and elevated creatine kinase 3 years before admission. She was under observation without medication. Otherwise, her medical history and that of her family were unremarkable.

On admission, the patient was 160 cm tall and weighed 66 kg, with a body temperature of 36.5°C, pulse rate of 82 beats/min, respiratory rate of 18 breaths/min, and blood pressure of 107/62 mmHg. With the exception of the butterfly-shaped erythema on her cheeks, her physical examination was unremarkable. Attenuated bilateral lower lung breath sounds and generalized pitting edema were noted.

Laboratory tests showed leukocytopenia (3340/ $\mu$ L, 96% neutrophils) with lymphocytopenia, hypoalbuminemia (0.6 g/dL, normal range, 4.1-5.1 g/dL), normal renal function (blood urea nitrogen, 21 mg/dL; creatinine, 0.69 mg/dL; normal range, 0.46-0.79 mg/dL), and a normal C-reactive protein (CRP) level (0.13 mg/dL, normal range, 0.3-0.6 mg/dL). Antinuclear

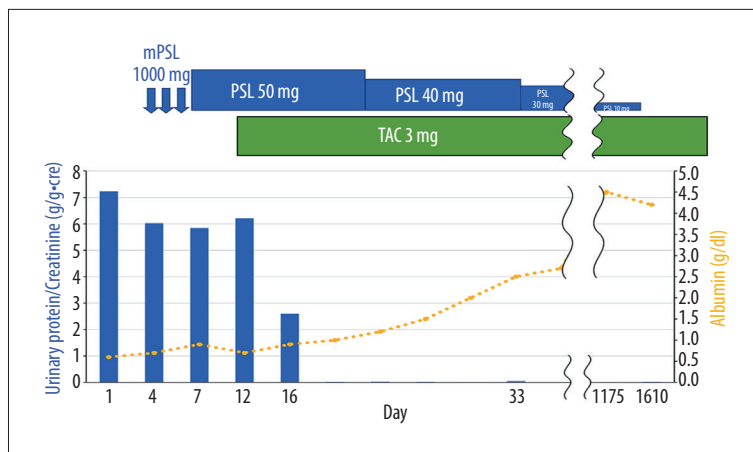


**Figure 1.** Light microscopy examination of the kidney biopsy. There was no increase in the mesangial matrix and cellularity; and no endocapillary proliferation, glomerulitis, thrombosis, necrosis, or crescents were observed (periodic acid-Schiff stain, magnification: 200 $\times$ ).



**Figure 2.** Electron microscopy showed diffuse podocyte foot-process effacement over >80% of the capillary loop surfaces, with only a few subendothelial deposits (magnification: 20 000 $\times$ ).

antibodies (5120-fold, speckled type) were dominant and specific autoantibodies were only positive for RNP antigen. The concentration of complement C3 was 90 mg/dL (normal range, 86-160 mg/dL); C4 was 23 mg/dL (normal range, 17-45 mg/dL); and hemolytic complement activity (CH50) was 29.3 U/mL (normal range, 23-46 mg/dL). Urinalysis showed massive proteinuria (5461 mg/day), a few erythrocytes (1-4/hpf), granular casts (5-9/hpf), and elevated  $\beta$ 2-microglobulin (2638  $\mu$ g/L; normal range, less than 230  $\mu$ g/dL). Chest X-ray showed bilateral pleural effusions, and pleural fluid examination revealed a transudative effusion. The patient was diagnosed with systemic lupus erythematosus according to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus [6].



**Figure 3.** The clinical course of our patient from day 1 to day 1610.

We performed a renal biopsy on hospital day 3. The specimen contained 6 glomeruli. There was no increase in the mesangial matrix or cellularity, and endocapillary proliferation, glomerulitis, thrombosis, necrosis, and crescents were not observed (Figure 1). Immunofluorescence showed a pattern of peripheral depositions of IgM (+) and C3c (++) on the glomerular capillary walls. Electron microscopy showed diffuse podocyte foot-process effacement of >80% of the capillary loop surfaces, with only a few subendothelial deposits (Figure 2). These findings met the criteria for lupus podocytopathy, a minimal-change disease variant proposed by Oliva-Damaso et al [7]. Therefore, we diagnosed minimal mesangial lupus nephritis with lupus podocytopathy. On hospital day 4, we administered methylprednisolone 1000 mg/day for 3 days, followed by 50 mg/day of prednisolone. However, proteinuria persisted, and on day 12 of hospitalization, we added tacrolimus (3 mg/day, target trough of 4-6 ng/ml [8]), which resulted in rapid improvement by day 15 of hospitalization (tacrolimus trough 5.2 ng/ml); proteinuria regressed completely on day 17 of hospitalization, and the facial rash and arthralgias also improved. The patient was discharged on hospital day 33 with instructions to continue prednisolone 30 mg/day and tacrolimus 3 mg/day. Our rheumatologists followed up with the patient. Her body weight decreased by 15 kg. The prednisolone dose was gradually tapered and stopped after 3 years, although tacrolimus was continued at 3 mg/day. The tacrolimus trough range was 3.0-7.2 ng/ml throughout the followup. No flare-ups were observed at the 4-year followup visit (Figure 3). The serum creatinine level was within normal range throughout the followup period.

## Discussion

We report here the efficacy of tacrolimus as a steroid-sparing agent and CNI in a case of nephrotic minimal mesangial lupus nephritis with lupus podocytopathy. Based on the English literature concerning minimal mesangial lupus nephritis (ISN/RPS classification Class I) with podocytopathy in adults [3,4],

immunosuppressive drugs and steroid therapy are necessary to achieve remission. A retrospective cohort study reported a similar remission rate with glucocorticoid treatment alone and glucocorticoid plus additional immunosuppressive drugs (tacrolimus, cyclophosphamide, mycophenolate mofetil, tripterygium glycosides, azathioprine, and leflunomide) in patients with lupus podocytopathy. However, the relapse rate was significantly higher in the glucocorticoid-alone group (89.5% vs 35.7%) [9]. The same study also reported that remission should be maintained with the administration of combination regimens of glucocorticoids and immunosuppressants [9]. In minimal-change nephrotic syndrome, some trials report mean remission times of 15-18 days [10,11], with mean proteinuria decreasing to a quarter of the initial level at 14 days [10].

In the present case, proteinuria did not improve by day 12, and glucocorticoid treatment alone was considered ineffective. However, proteinuria decreased 3 days after the commencement of tacrolimus once a day. The patient had no flare-ups for 4 years, including 1 year without steroids. This observation indicates the efficacy of tacrolimus as a steroid-sparing agent. Tacrolimus is effective and safe for selected young patients with systemic lupus erythematosus, even when administered as a single daily dose. A 2-dose regimen is used for transplant patients who need higher blood levels [5,12]. CNIs are immunosuppressants that inhibit T cell hyperactivation.

Additionally, they effectively improve proteinuria by acting non-immunologically on the intracellular structure of glomerular epithelial cells [13]. Calcineurin alters the podocyte phenotype, which contributes to proteinuria and kidney damage. CNIs reduce proteinuria by stabilizing the cytoskeleton and preventing podocyte apoptosis [14]. The mean time to remission was 2.6 weeks (range: 0.9-16 weeks) in adults with minimal-change nephrotic syndrome treated with tacrolimus monotherapy after intravenous methylprednisolone [15]. The immediate reduction of proteinuria seen in this case could be attributed to this effect of tacrolimus. Additionally, a retrospective

cohort study reported that treatment with CNIs improves the remission rate and has better long-term renal outcomes than treatment with other regimens in patients with lupus nephritis with severe podocyte effacement [16]. Further prospective and randomized controlled trials are necessary to demonstrate the efficacy of CNIs.

## Conclusions

We report a patient with nephrotic syndrome caused by minimal mesangial lupus nephritis with lupus podocytopathy for whom tacrolimus treatment and steroid pulse therapy resulted in remission. CNIs, especially tacrolimus, have shown good efficacy in such cases. Further studies, in the form of prospective and randomized controlled trials, are necessary to demonstrate the efficacy of tacrolimus in cases of minimal mesangial lupus nephritis with lupus podocytopathy.

## References:

1. Lech M, Anders HJ. The pathogenesis of lupus nephritis. *J Am Soc Nephrol.* 2013;24:1357-66
2. Aly R, Zeng X, Acharya R, Upadhyay K. Delayed onset minimal change disease as a manifestation of lupus podocytopathy. *Clin Prac.* 2021;11:747-54
3. Hu W, Chen Y, Wang S, et al. Clinical-morphological features and outcomes of lupus podocytopathy. *Clin J Am Soc Nephrol.* 2016;11:585-92
4. Shea-Simonds P, Cairns TD, Roufosse C, et al. Lupus podocytopathy. *Rheumatology.* 2009;48:1616-18
5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021;100(4S):S1-S276
6. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(9):1151-59
7. Oliva-Damaso N, Payan J, Oliva-Damaso E, et al. Lupus podocytopathy: An overview. *Adv Chronic Kidney Dis.* 2019;26:369-75
8. Tunnicliffe DJ, Palmer SC, Henderson L, et al. Immunosuppressive treatment for proliferative lupus nephritis. *Cochrane Database Syst Rev.* 2018;6(6):CD002922
9. Hu WX, Chen YH, Bao H, et al. Glucocorticoid with or without additional immunosuppressant therapy for patients with lupus podocytopathy: A retrospective single-center study. *Lupus.* 2015;24:1067-75
10. Li X, Liu Z, Wang L, et al. Tacrolimus monotherapy after intravenous methylprednisolone in adults with minimal change nephrotic syndrome. *J Am Soc Nephrol.* 2017;28(4):1286-95
11. Chin HJ, Chae DW, Kim YC, et al. Comparison of the efficacy and safety of tacrolimus and low-dose corticosteroid with high-dose corticosteroid for minimal change nephrotic syndrome in adults. *J Am Soc Nephrol.* 2021;32(1):199-210
12. Tanaka H, Oki E, Tsugawa K, et al. Effective treatment of young patients with pediatric-onset, long-standing lupus nephritis with tacrolimus given as a single daily dose: An open-label pilot study. *Lupus.* 2007;16(11):896-900
13. Faul C, Donnelly M, Merscher-Gomez S, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med.* 2008;14:931-38
14. Rafael-vidal C, Altabás I, Pérez N, Mourino Rodríguez CM, et al. Calcineurin and systemic lupus erythematosus: The rationale for using calcineurin inhibitors in the treatment of lupus nephritis. *Int J Mol Sci.* 2021;22:1263
15. Li X, Liu Z, Wang L, et al. Tacrolimus monotherapy after intravenous methylprednisolone in adults with minimal change nephrotic syndrome. *J Am Soc Nephrol.* 2017;28:1286-95
16. Wang Y, Yu F, Song D, Wang SX, Zhao MH. Podocyte involvement in lupus nephritis based on the 2003 ISN/RPS system: A large cohort study from a single centre. *Rheumatology (Oxford).* 2014;53:1235-44

## Acknowledgments

The authors would like to thank ENAGO (<https://www.enago.jp/>) for their English proofreading.

## Department and Institution Where Work Was Done

Department of Comprehensive Medicine 1, Saitama Medical Center, Jichi Medical University, Saitama, Japan.

## Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.