Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6413-20
Intern Med 60: 3125-3128, 2021
http://internmed.jp

【 CASE REPORT 】

Spontaneous Remission of Thrombospondin Type-1 Domain-Containing-Associated Membranous Nephropathy

Shiika Watanabe[1], Tomo Suzuki[1,2], Wei Han[1], Mayumi Nakata[1], Kenichiro Koitabashi[1], Daisuke Ichikawa[1], Atsuko Kamijo-Ikemori[3], Junki Koike[4] and Yugo Shibagaki[1]

Abstract:

Membranous nephropathy often achieves spontaneous remission. However, there are scarce reports of spontaneous remission of thrombospondin type-1 domain-containing 7A (THSD7A)-associated membranous nephropathy. A 64-year-old female presented with nephrotic syndrome and edema of the lower extremities. We diagnosed membranous nephropathy by kidney biopsy and confirmed positive THSD7A on immunofluorescence using frozen sections; serum THSD7A antibodies were also detected. Thirty-four months after the initial diagnosis, she achieved a spontaneous complete remission without immunosuppressive therapy. With the complete remission, no serum THSD7A levels were detected. In this study, we describe serial examinations of kidney biopsies and serum THSD7A antibodies.

Key words: membranous nephropathy, THSD7A, spontaneous remission, nephrotic syndrome

(Intern Med 60: 3125-3128, 2021)
(DOI: 10.2169/internalmedicine.6413-20)

Introduction

Primary membranous nephropathy (MN) is associated with antibodies to phospholipase A2 receptor 1 (PLA2R) or thrombospondin type-1 domain-containing 7A (THSD7A) present in podocytes (1). It is usually treated with various immunosuppressive agents, including glucocorticoid; (2) however, spontaneous remission can occur in as many as 30% of primary MN cases (3). In PLA2R-MN, spontaneous remissions significantly occurred less frequently among patients with high antibody titers (4). Reports of THSD7A-associated MN and of THSD7A-MN spontaneous remission are scarce.

We report a case of self-limited THSD7A-associated MN that received no treatment from immunosuppressive agents, including glucocorticoid. Moreover, we analyzed serial kidney biopsies and serum antibodies and confirmed that serum antibodies decreased alongside a complete remission of proteinuria.

Case Report

A 64-year-old female presented to our hospital with a 3-week history of lower-extremity edema. She was admitted to our department for a kidney biopsy (KBx) and further treatment. Her medical history was significant for a cerebral hemorrhage and hypertension, and she had no known drug allergies. On physical examination, her blood pressure was not elevated (115/80 mmHg).

She had remarkable bilateral pitting edema of the lower extremities. Laboratory test results showed white blood cells (eosinophils 1.5%), low serum total protein (4.3 g/dL), low serum albumin (2.1 g/dL), high LDL cholesterol (301 mg/dL), and normal serum creatinine (1.0 mg/dL) and C-reactive protein (0.03 mg/dL). Urinalysis revealed a protein content of 7.9 g/day without hematuria. Serological tests showed low immunoglobulin (Ig) G levels (270 mg/dL), and IgM, IgA, IgE, serum C3, and C4 levels were normal. Antineutrophil cytoplasmic antibodies and antinuclear antibodies were not detected. KBx results are shown in Fig. 1.

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, Japan, [2]Department of Nephrology, Kameda Medical Center, Japan, [3]Department of Anatomy, St. Marianna University School of Medicine, Japan and [4]Department of Diagnostic Pathology, St. Marianna University School of Medicine, Japan
Received: October 1, 2020; Accepted: January 26, 2021; Advance Publication by J-STAGE: April 12, 2021
Correspondence to Dr. Tomo Suzuki, suzuki.tomo@kameda.jp

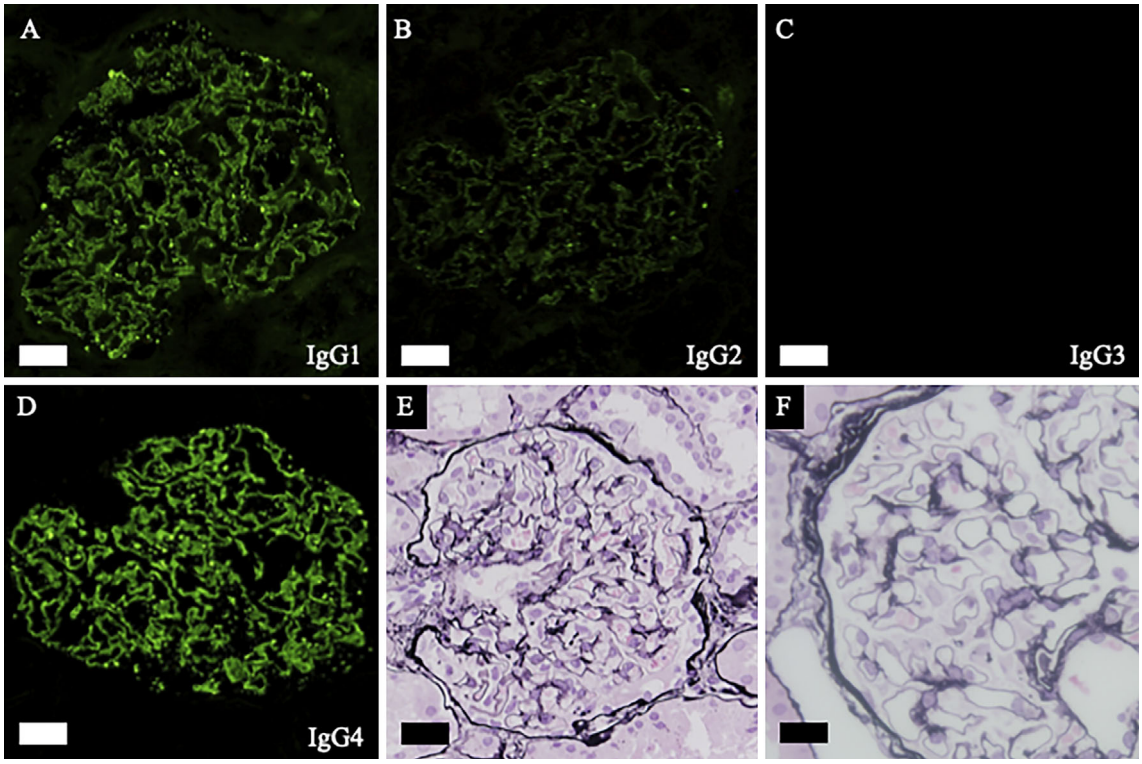

Figure 1. **First kidney biopsy. Immunofluorescence of IgG1 (A), IgG2 (B), IgG3 (C), IgG4 (D), and PAM (E) and high-power field of PAM (F) are shown. IgG2 (B) and IgG3 (C) staining show a negative pattern. (E, F) PAM staining shows that there are no spikes on the glomerular basement membrane. (A-E) scale bars=20 μm, (F) scale bars=40 μm. PAM: Periodic acid methenamine silver**

The glomeruli showed no spike formations, endothelial proliferation, or crescents under light microscopy. Moderate arteriolosclerosis was present. Immunofluorescence (IF) staining revealed diffuse positive results for IgG at the periphery and negative results for IgA, IgM, C3, and C1q. IgG subclass-staining results were strongly positive for IgG4, slightly positive for IgG1, and negative for IgG2 and IgG3.

IF examination of PLA2R and THSD7A (Atlas Antibodies, Bromma, Sweden), using frozen sections of kidney biopsy samples, showed strong positive staining for THSD7A and negative staining for PLA2R (Fig. 2A, B). Electron microscopy (EM) revealed subepithelial electron-dense deposits in the glomeruli (Fig. 2C), suggesting a diagnosis of MN, stage II.

Given the patient's age, stable lower edema, and kidney function, we did not use immunosuppressive agents, and the level of proteinuria did not change. One year later, the patient was again admitted to our department for enteritis due to *Yersinia enterocolitica*; her proteinuria had slightly increased, and we performed a second KBx. Under light microscopy, proliferation lesions and spike formation were still inconspicuous, as in the first KBx. IF examination was again strongly positive for IgG4 and THSD7A, slightly positive for IgG1, and negative for PLA2R (Fig. 2D, E). EM suggested MN, stage III, with intramembranous dense and lucent deposits (Fig. 2F).

We again did not use immunosuppressive therapy due to the confirmed histology of second KBx and stable kidney function, and her proteinuria gradually decreased. The patient's clinical course is shown in Fig. 3.

Thirty four months after the onset of symptoms, the patient has achieved complete remission, with proteinuria under 0.3 g/gCr. For further investigation, we examined serum THSD7A antibody levels at first KBx, second KBx, and 34 months after the first KBx using an ELISA assay (EUROIMMUNE). Her serum THSD7A antibody levels decreased, and proteinuria levels are now undetectable (Fig. 3). Throughout the clinical course, we searched for possible malignancies, but none were detected.

Discussion

We reported a case of THSD7A-associated MN that achieved spontaneous remission 34 months after the onset of symptoms. We observed signs of MN mitigation during serial KBx and reduction of serum THSD7A antibody levels and proteinuria.

The prevalence of THSD7A-MN is as low as 10% among cases of primary MN in a Japanese sample (5, 6), which makes management of this disease still undetermined. A relationship between THSD7A-MN and malignancy has been reported in various populations (6, 7). In addition, THSD7 A-MN has recently been associated with allergic reactions (8-11). In our previous study, allergic disease was significantly more prevalent in a group exhibiting THSD7A-MN than in one exhibiting PLA2R-MN group (12). How-

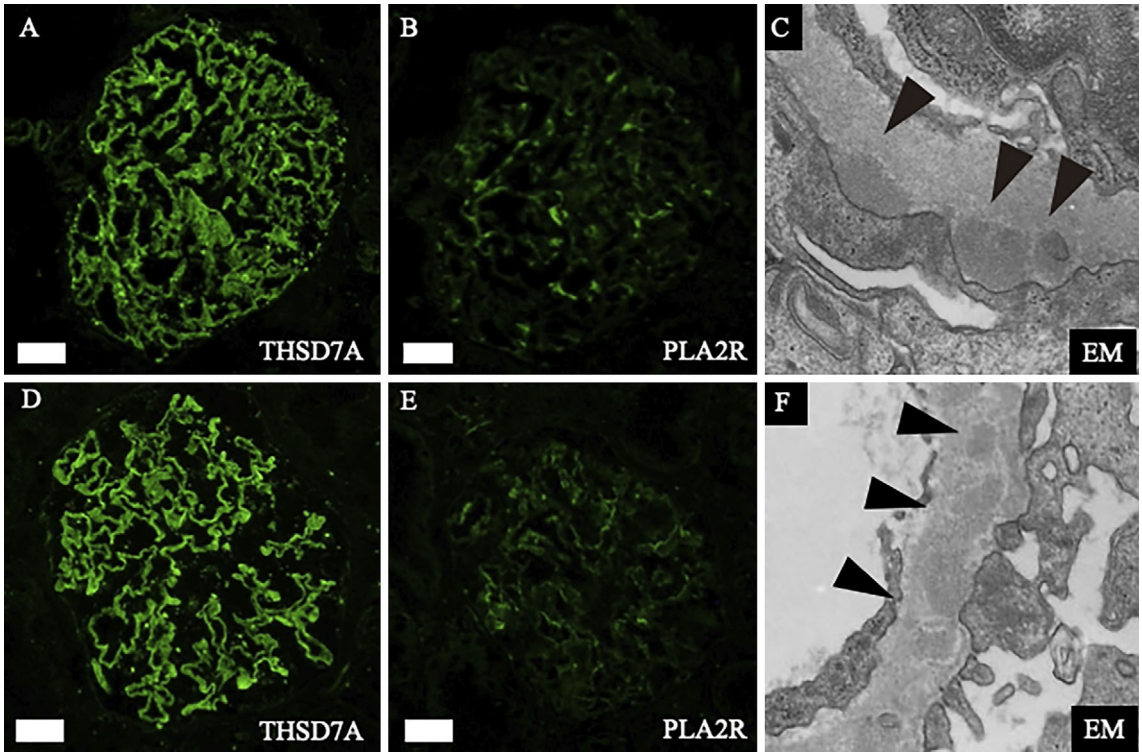

Figure 2. **THSD7A, PLA2R, and electron microscopy (EM) of first and second kidney biopsy. (A) THSD7A, (B) PLA2R, and (C) EM of first biopsy. (D) THSD7A, (E) PLA2R, and (F) EM of second biopsy. (C, F) EM shows that there are subepithelial electron-dense deposits (arrows). THSD7A: thrombospondin type-1 domain-containing 7A, PLA2R: phospholipase A2 receptor 1**

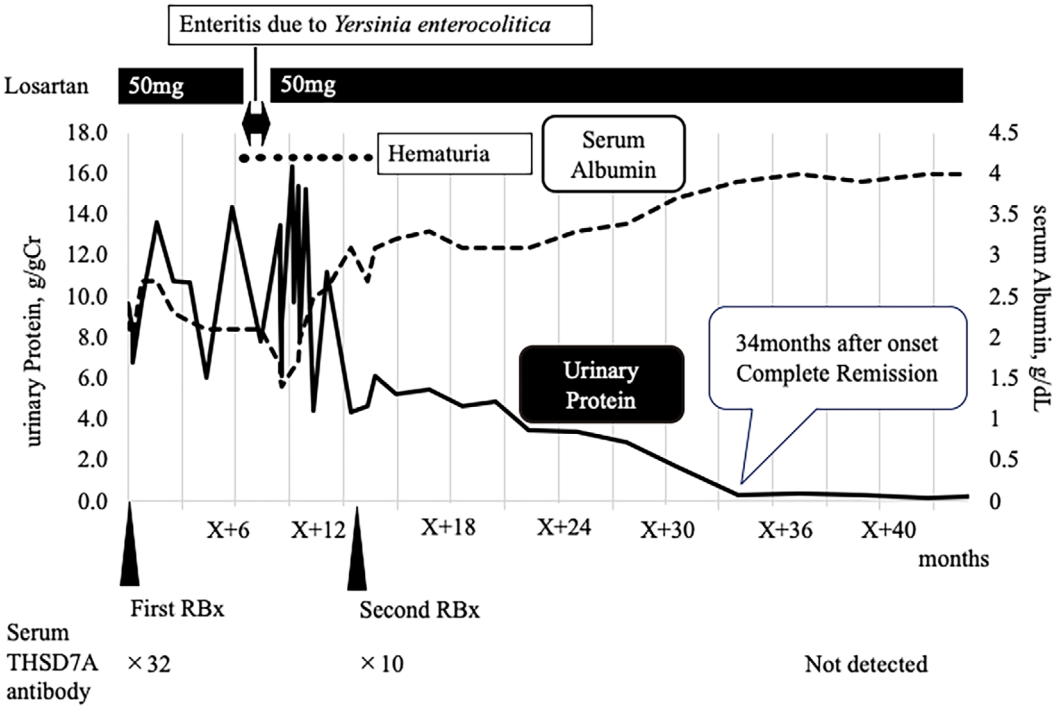

Figure 3. **Patient's clinical course. THSD7A: thrombospondin type-1 domain-containing 7A, RBx: renal biopsy**

ever, in this case, no malignancy, allergic disease, or eosinophilia was detected.

To our knowledge, this is the first case report of THSD7A-MN that shows complete remission of proteinuria (after 34 months), with a parallel reduction in the level of serum THSD7A antibody titers. EM of the second KBx confirmed

lucent deposits, which indicates the remission of MN.

In PLA2R-MN, there is a correlation between serum albumin and serum PLA2R antibodies (13); furthermore, a decrease in PLA2R antibody levels is associated with a decrease in proteinuria (14). In the first report of THSD7A-MN treated with glucocorticoid and cyclosporine, and in a case report of malignancy-associated THSD7A-MN, the remission of proteinuria paralleled a decrease in serum antibodies (7, 15). Hoxha et al. reported that serum antibody titers and proteinuria did not correlate (16). However, we observed both an improved clinical course and decreased serial serum antibodies. Serum PLA2R antibodies in patients exhibiting PLA2R-MN can initially be negative but become positive after prolonged follow-up, leading to the concepts of "kidney as a sink hypothesis" (17, 18). In our case, we considered a discrepancy between proteinuria and serum THSD7A antibodies, similar to PLA2R-MN.

There are few reports of THSD7A-MN without immunosuppressive therapy, and only two previous case series of THSD7A-MN with spontaneous remission have been reported (7, 19). In the report by Sharma et al., 6 out of 24 patients had no immunosuppressive therapy, but these 6 patients did not achieve complete remission (partial remission, 1 of 6; no response, 5 of 6) (19). On the other hand, Wang et al. reported that four out of six patients who did not receive immunosuppressive therapy achieved complete remission (partial remission, one of six; non-response, one of six) (7). In these reports, however, levels of THSD7A antibodies were not followed in remission.

In conclusion, we reported a case of self-limited THSD7 A-associated MN without the use of therapeutic immunosuppressive agents, including glucocorticoid; levels of proteinuria were reduced in tandem with reductions of serum antibodies. Serial measurements of serum antibodies may help to predict spontaneous remission in the cases of THSD7A-MN.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank Mami Ohori, Yoshiko Ono, and Mie Tagaya for the technical support of IF.

References

1. Couser WG. Primary membranous nephropathy. Clin J Am Soc Nephrol **12**: 983-997, 2017.
2. Ponticelli C, Glassock RJ. Glomerular diseases: membranous nephropathy--a modern view. Clin J Am Soc Nephrol **9**: 609-616, 2014.
3. Polanco N, Gutiérrez E, Covarsí A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol **21**: 697-704, 2010.
4. Hofstra JM, Debiec H, Short CD, et al. Antiphospholipase A2 receptor antibody titer and subclass in idiopathic membranous nephropathy. J Am Soc Nephrol **23**: 1735-1743, 2012.
5. Iwakura T, Ohashi N, Kato A, Baba S, Yasuda H. Prevalence of enhanced granular expression of thrombospondin type-1 domain-containing 7A in the glomeruli of Japanese patients with idiopathic membranous nephropathy. PLoS One **10**: e0138841, 2015.
6. Hoxha E, Wiech T, Stahl PR, et al. A mechanism for cancer-associated membranous nephropathy. N Engl J Med **374**: 1995-1996, 2016.
7. Wang J, Cui Z, Lu J, et al. Circulating antibodies against thrombospondin type-I domain-containing 7A in Chinese patients with idiopathic membranous nephropathy. Clin J Am Soc Nephrol **12**: 1642-1651, 2017.
8. Matsumoto A, Matsui I, Namba T, et al. VEGF-A links angiolymphoid hyperplasia with eosinophilia (ALHE) to THSD7A membranous nephropathy: a report of 2 cases. Am J Kidney Dis **73**: 880-885, 2019.
9. Hara S, Tsuji T, Fukasawa Y, et al. Clinicopathological characteristics of thrombospondin type 1 domain-containing 7A-associated membranous nephropathy. Virchows Archiv **474**: 735-743, 2019.
10. Shirai S, Akiyama S, Kamijo-Ikemori A, et al. Membranous nephropathy associated with thrombospondin type-1 domain-containing 7A (THSD7A) in an adult woman with eosinophilia. CEN Case Rep **9**: 65-73, 2020.
11. Suzuki T, Ushimaru S, Uchida D, et al. Refractory THSD7A membranous nephropathy with severe asthma related to eosinophilia. Clin Nephrol **92**: 103-108, 2019.
12. Suzuki T, Han W, Watanabe S, et al. Clinical characteristics of thrombospondin type-1 domain-containing 7A-associated membranous nephropathy. Ren Fail **42**: 966-968, 2020.
13. Hihara K, Iyoda M, Tachibana S, et al. Anti-phospholipase A2 receptor (PLA2R) antibody and glomerular PLA2R expression in Japanese patients with membranous nephropathy. PLoS One **11**: e 0158154, 2016.
14. Hoxha E, Thiele I, Zahner G, Panzer U, Harendza S, Stahl RA. Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. J Am Soc Nephrol **25**: 1357-1366, 2014.
15. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med **371**: 2277-2287, 2014.
16. Hoxha E, Beck LH Jr, Wiech T, et al. An indirect immunofluorescence method facilitates detection of thrombospondin type 1 domain-containing 7A-specific antibodies in membranous nephropathy. J Am Soc Nephrol **28**: 520-531, 2017.
17. Van de Logt AE, Hofstra JM, Wetzels JF. Serum anti-PLA2R antibodies can be initially absent in idiopathic membranous nephropathy: seroconversion after prolonged follow-up. Kidney Int **87**: 1263-1264, 2015.
18. Ramachandran R, Kumar V, Nada R, et al. Serial monitoring of anti-PLA2R in initial PLA2R-negative patients with primary membranous nephropathy. Kidney Int **88**: 1198-1199, 2015.
19. Sharma SG, Larsen CP. Tissue staining for THSD7A in glomeruli correlates with serum antibodies in primary membranous nephropathy: a clinicopathological study. Mod Pathol **31**: 616-622, 2018.