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

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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

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IgM, IgA, IgE, serum C3, and C4 levels were normal. Anti-neutrophil cytoplasmic antibodies and antinuclear antibodies were not detected. KBx results are shown in Fig. 1. 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. 22), 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 (EURO-IMMUNE). 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 reac-
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

tions (8, 9, 10, 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). However, in this case, no malignancy, allergic disease, or eosinophilia was detected.

To our knowledge, this is the first case report of THSD7
A–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 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). 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). In these reports, however, levels of THSD7A antibodies were not followed in remission.

In conclusion, we reported a case of self-limited THSD7A-associated membranous nephropathy 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.

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

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