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Refractory THSD7A membranous nephropathy with severe asthma related to eosinophilia

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Key words

membranous nephropathy – THSD7A – severe asthma – eosinophilia – nephrotic syndrome

Abstract. We report a case of a 50-year-old Japanese man with a history of pediatric asthma diagnosed with nephrotic syndrome after 4 years of relapsing asthma with severe eosinophilia. Thrombospondin type-1 domain-containing 7A membranous nephropathy (THSD7A-MN) was diagnosed based on histological evaluation. We started a course of steroid semi-pulse therapy, high-dose oral prednisolone, mizoribine, and cyclosporine. Frequent relapse of asthma was observed after gradual tapering of prednisolone dose to 10 mg/day. After improvement of asthma symptoms and eosinophilia, his serum albumin level increased gradually. Considering the clinical course of refractory MN and asthma, we suggest that THSD7A-MN may be associated with severe asthma and eosinophilia.

was detected in the glomeruli, using frozen sections of kidney biopsy samples.

Case presentation

A 50-year-old Japanese man presented with lower extremity edema. He had a history of pediatric asthma with a relapse at the age of 46 years and then developed severe eosinophilia (3,605 cells/ μ L). A course of both inhaled and oral glucocorticoids was started at that time (prednisolone, 5 – 20 mg/day). The oral glucocorticoid dose could not be reduced to < 15 mg/day of prednisolone due to frequent relapsing asthma. The patient also had steroid-induced diabetes and was diagnosed with nephrotic syndrome. Given his condition, history, and asthma relapses, he was admitted to our department. Past history was unremarkable except for diabetes and asthma. Smoking history was 20 cigarettes per day until the age of 46. He had no known drug allergy. On physical examination, his height was 168.5 cm and body weight was 102 kg. His blood pressure was 152/100 mmHg. He had remarkable edema of the lower extremities. Laboratory test results were as follows: serum albumin, 1.6 g/dL (low); serum creatinine, 1.0 mg/dL (normal); total cholesterol, 420 mg/dL (high); and C-reactive protein, 0.37 mg/dL (slight high). A urine test revealed a protein content of 7.9 g/day with no hematuria. On serological testing, antinuclear antibody and anti-dsDNA anti-

Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. In ~ 70% of the cases, primary MN is associated with phospholipase A2 receptor 1 (PLA2R) in the podocyte membrane. [1] In addition to PLA2R, thrombospondin type-1 domain-containing 7A (THSD7A) is occasionally detected. [2] The prevalence of THSD7A-MN was 9.1% among cases of primary MN in a Japanese sample [3], making it a rare condition. Recently, THSD7A-MN was reported to be associated with complicated malignancy including gallbladder tumors. [4] However, other features of THSD7A-MN are still unclear.

We report a case of MN with severe asthma related to eosinophilia where THSD7A

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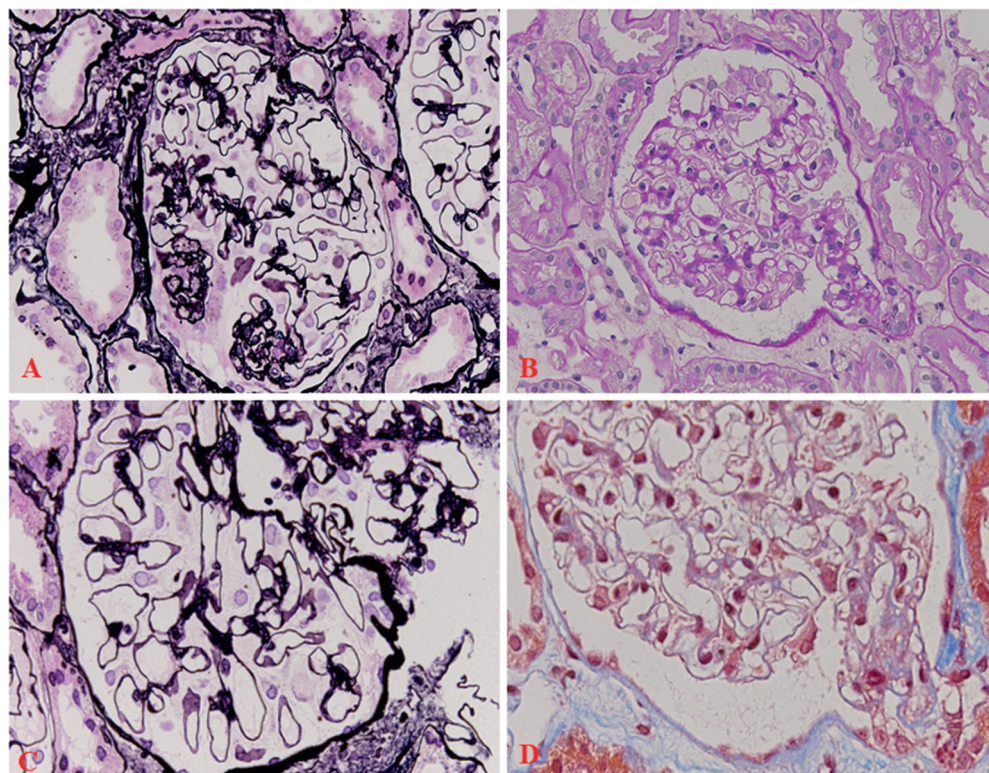


Figure 1. Kidney biopsy specimen. A: Periodic acid-Schiff-methenamine silver (PAM) staining of the glomeruli shows focal glomerulosclerosis with mild epithelial cell hyperplasia. B: PAS staining of the glomeruli shows epithelial hyperplasia at the tubular pole. C: PAM staining of the glomeruli shows no spike formation and bubbly appearance. D: Masson trichrome staining of the glomeruli shows epithelial deposit.

body results were negative. IgG level was low at 270 mg/dL. IgM, IgA, IgE, serum C3 and C4 levels were normal at 114 mg/dL, 143 mg/dL, 51 mg/dL, 133 mg/dL, and 33 mg/dL, respectively. Anti-neutrophil cytoplasmic antibody was not detected.

Kidney biopsy results are shown in Figure 1. One core of kidney tissue was present, containing 9 glomeruli, 1 of which was globally sclerosed and 1 was collapsed. Two glomeruli showed focal segmental sclerotic lesions with epithelial cell hyperplasia in the tubular poles (Figure 1A, B). Spike formation and bubbly appearance of glomerular basement membrane were not present (Figure 1C). Conversely, subepithelial deposit was observed by Masson trichrome staining (Figure 1D). Endothelial proliferation, necrosis and eosinophil infiltration were absent. In addition, mild intimal thickening was present in the arcuate artery. Hyaline arteriosclerosis was not observed. Immunofluorescence (IF) staining yielded diffuse positive results for IgG and C3 at the periphery and negative results for IgA, IgM, and C1q. IgG subclass staining result was

predominantly positive for IgG4, slightly positive for IgG1 and IgG2, and negative for IgG3 (Figure 2E, F, G, H). Electron microscopy revealed diffuse massive subepithelial electron-dense deposits and a small quantity of deposit in the mesangial area. Structural deposit was absent. Further, foot process effacement was mainly observed around the deposit site (Figure 2A). The histologic diagnosis was MN with focal segmental glomerulosclerosis (FSGS). IF examination of glomerular PLA2R and THSD7A (Atlas Antibodies, Bromma, Sweden) using frozen sections of kidney biopsy samples showed positive staining for THSD7A and negative staining for PLA2R (Figure 2C, D). We did not note any abnormalities on examination for malignant tumors.

The patient's clinical course is shown in Figure 3. We started a course of steroid semi-pulse therapy (500 mg of methylprednisolone) and 50 mg/day of oral prednisolone because he was diagnosed with MN with nephrotic syndrome. In addition, we prescribed combined cyclosporine and anti-coagulation therapy for inferior vena cava thrombosis.

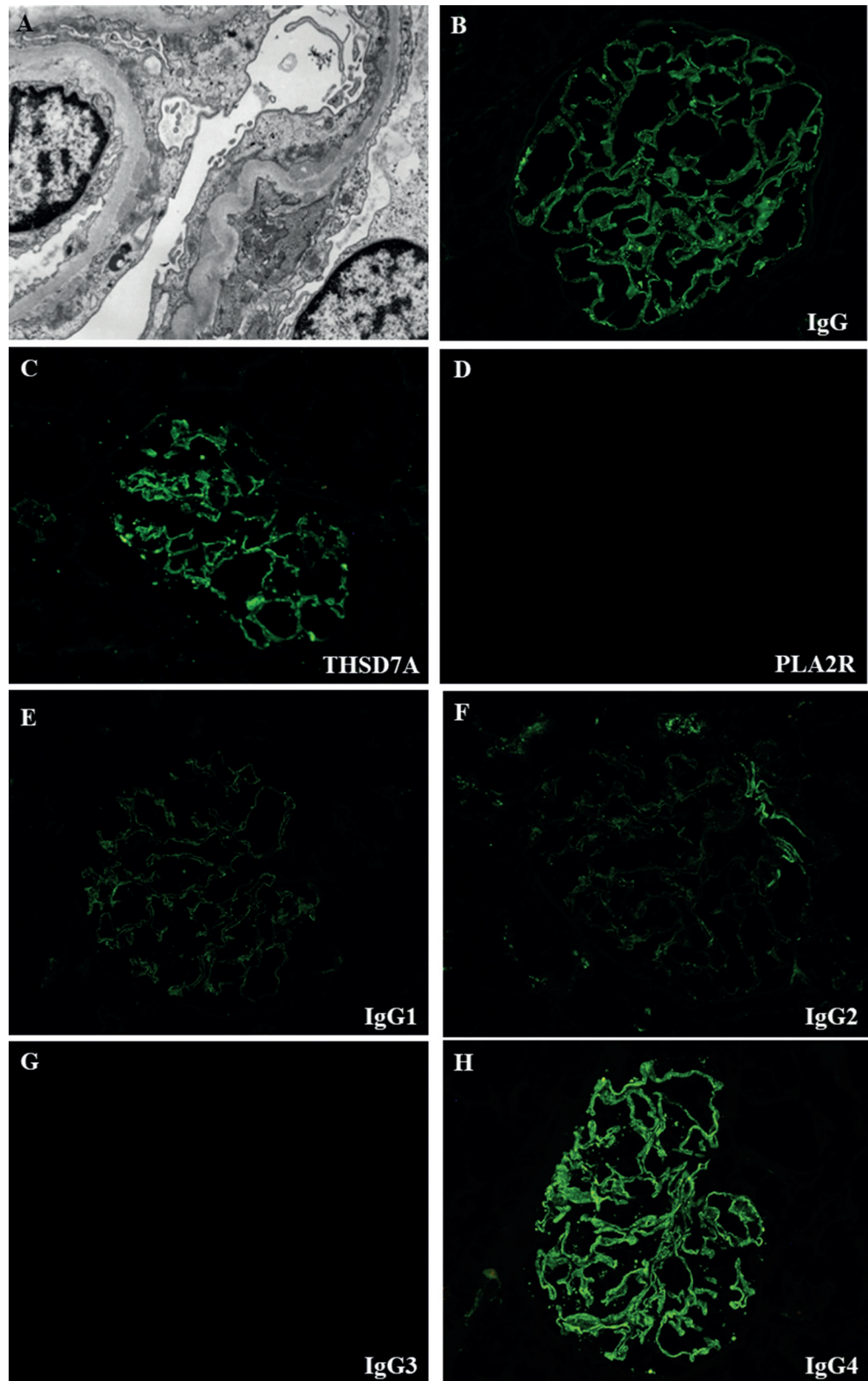


Figure 2. Electron microscopy and immunofluorescence of kidney biopsy. A: Electron microscopy shows epithelial electron-dense deposit and no thickening of glomerular basement membrane. Immunofluorescence shows glomerular (B) IgG, (C) THSD7A, (D) PLA2R, (E) IgG1, (F) IgG2, (G) IgG3, and (H) IgG4.

Thereafter, his proteinuria decreased to half the amount after ~ 6 months. However, his asthma relapsed frequently after reducing

prednisolone dosage to 10 mg/day gradually. In addition, we added on mizoribine 150 mg/day. However, his proteinuria increased with

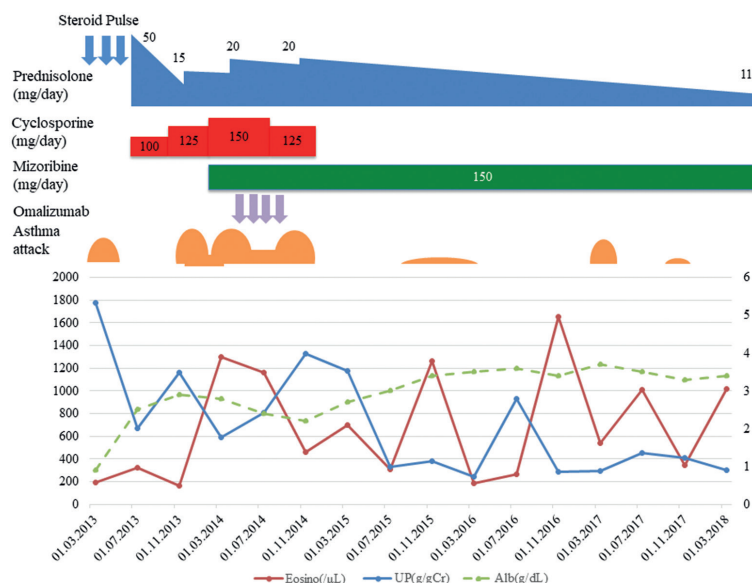


Figure 3. Patient's clinical course.

episodes of asthma recurrence. Therefore, we used omalizumab (monoclonal anti-IgE antibody) for severe asthma with IgE radio-immunosorbent test (240 IU/mL). However, his asthma relapsed in a steroid-dependent manner despite the use of omalizumab. Therefore, we increased prednisolone dose again for severe asthma. At that time, we stopped cyclosporine because of the increased prednisolone dosage. After an improvement in asthma symptoms using oral glucocorticoid, his serum albumin level increased gradually. He is currently in partial remission with proteinuria of ~ 1 g/gCr. Blood pressure control is adequate, and his body weight is stabilized between 77 and 80 kg. His renal function is stable as serum creatinine is ~ 0.8 mg/dL.

Discussion

We present a case of THSD7A-MN after relapsing asthma with severe eosinophilia. The prevalence of THSD7A-MN is low [3]. A relationship between THSD7A-MN and malignancy has been reported; however, this case did not show any malignancy. The other characteristics of THSD7A-MN are still unknown due to the rarity of the condition. A study in a Chinese sample found a mixed renal prognosis in 12 patients with THSD7A-MN [5]. We considered the association between THSD7A-MN and severe asthma and eosinophilia from the clinical course. The

proteinuria in our case was refractory, which, coupled with the severe asthma, warranted the use of omalizumab. After the improvement of asthma control and eosinophilia, the patient's proteinuria decreased until incomplete remission. Based on the clinical course, we consider that THSD7A-MN was associated with severe asthma. However, we could not suppress eosinophilia without using oral glucocorticoid as well as asthma despite using omalizumab.

Asthma and MN in nephrotic syndrome are common diseases. However, the relationship between MN and asthma has not been clearly established. On the other hand, kidney biopsy in a series of 8 cases of Kimura's disease, which is an inflammatory disease endemic in Asia, associated with allergic disease and eosinophilia revealed 2 cases of MN [6]. In addition, Okura et al. [7] reported Kimura's disease associated with MN in which a kidney biopsy specimen revealed positive staining for IgG4 and PLA2R. However, these cases did not examine glomerular THSD7A. In fact, serum PLA2R antibody in Okura et al.'s [8] case could not be detected. Unlike THSD7A-MN, PLA2R-MN could not be reproduced in a mouse model. Therefore, the association between MN with Kimura's disease and PLA2R is not clear. On the other hand, MN with hypereosinophilic syndrome has been reported [9]. Matsumoto et al. [10] reported recently that a substantial number of eosinophils in the patient of THSD7A-MN with angiolymphoid hyperplasia with eosinophilia unregulated vascular endothelial growth factor A (VEGF-A) and VEGF-A-induced THSD7A expression for vascular endothelial growth factor A (VEGF-A) and VEGF-A-induced THSD7A expression, especially under the TH2-prone condition in cultured human umbilical vein endothelial cells (HUVEC). It is possible that MN is related to allergic disease and eosinophilia.

As for other histological features of the present case, FSGS lesion was present. Glomerular endothelial injury in cases of MN with FSGS lesion is less frequent than in cases of MN without FSGS lesion [11]. A previous study showed that eosinophils induced the proliferation of smooth muscle cells [12]. In the previous Banff criteria, tissue eosinophilia is associated with vascular

rejection [13]. In our case, both eosinophilia and proteinuria persisted, albeit in partial remission. Consequently, FSGS lesion may be associated with eosinophilia. On the other hand, it was reported that overexpression of a THSD7A carboxyl-terminal fragment in human umbilical vein endothelial cells inhibited cell migration and that THSD7A is a placenta endothelial protein that mediates endothelial cell migration [14]. In addition, Matsumoto et al. showed that VEGF-A induced THSD7A expression, especially under the TH2-prone condition in cultured HUVEC [10]. Therefore, we speculate that one of the mechanisms in THSD7A-MN was endothelial injury due to VEGF-A from eosinophilia.

In conclusion, we presented a case of THSD7A-MN with refractory asthma and eosinophilia. Considering the clinical course in this patient, we suggest that THSD7A-MN may be associated with severe asthma and eosinophilia.

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Conflict of interest

The authors declare that they have no relevant financial interests.

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