



## Case Report

## MYH9 nephropathy



Taehoon Oh, Hyun Jung Seo, Kyu Taek Lee, Han Jo Kim, Hwi Jun Kim, Ji-Hye Lee, Hae Il Cheong, Eun Young Lee\*

Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Korea

## A B S T R A C T

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MYH9-related disorder is an autosomal dominant disease caused by a mutation in the *MYH9* gene, which encodes nonmuscle myosin heavy chain IIA (NMMHC-IIA). This disease is characterized by giant platelets, thrombocytopenia, granulocyte inclusion bodies, proteinuria, and high-pitch sensorineural deafness. Nephropathy has been observed in 30% of patients with MYH9-related disorder. The characteristic features are early onset proteinuria and rapidly progressing renal disorder. However, the prognosis of MYH9 nephropathy remains unclear. Herein, we describe a 36-year-old woman who presented with proteinuria and was diagnosed with MYH9 nephropathy via renal biopsy and gene analysis. Her proteinuria improved after administration of an angiotensin II receptor blocker, but was aggravated after changing to a calcium channel blocker.

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## Introduction

MYH9-related disorder has been known as May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome. Mutations in the *MYH9* gene encoding the nonmuscle myosin heavy chain IIA (NMMHC-IIA) have been identified in these syndromes. The clinical features include sensorineural hearing loss, cataract, and nephritis. The common laboratory findings are autosomal dominant macrothrombocytopenia, polymorphonuclear Döhle-like bodies, proteinuria, and elevated creatinine levels. However, our understanding of the clinical course and treatment of MYH9-related nephropathy is lacking, especially in adult patients, because this disorder is very rare and has been previously reported in young individuals [1,2].

## Case report

A 36-year-old Korean woman was referred to our clinic because of proteinuria that was incidentally detected at a local obstetrics

clinic 9 months previously. At the age of 28 years, the patient was diagnosed with thrombocytopenia, and she, along with her family members, underwent hematological examinations. All other family members were negative for thrombocytopenia. The patient had no history of bleeding tendency. Since that time, no further examination was performed.

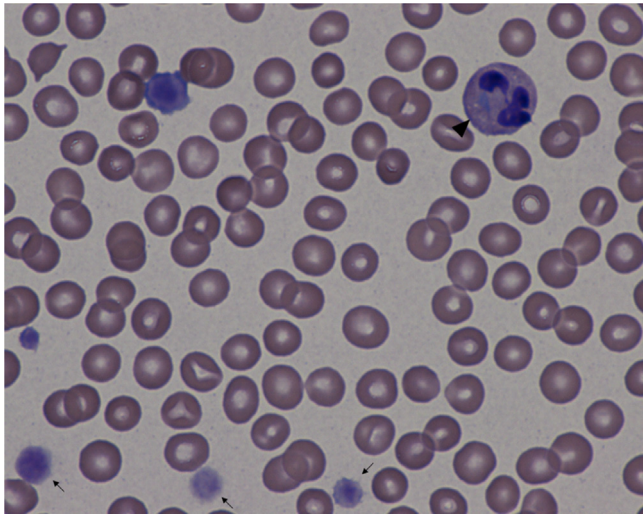
At her first visit to our clinic, her 24-hour urine analysis showed proteinuria (926.0 mg/day; creatinine, 1,018 mg/day). Blood chemistry findings revealed the following levels: blood urea nitrogen, 10.0 mg/dL; serum creatinine, 0.7 mg/dL; uric acid, 5.3 mg/dL; total protein, 6.7 g/dL; and albumin, 4.1 g/dL. The glomerular filtration rate was 99.70 mL/min/1.73 m<sup>2</sup>. Hematological examination showed thrombocytopenia (46,000/mm<sup>3</sup>), giant platelets, and Döhle bodies (Fig. 1). Ultrasonography did not reveal any abnormalities in either of the kidneys.

We performed a renal biopsy. Renal biopsy specimens were evaluated via light microscopy, immunofluorescence microscopy, and electron microscopy by using conventional techniques. On light microscopy, four out of 26 total glomeruli showed global sclerosis. Other glomeruli were unremarkable. Mild tubular atrophy and interstitial fibrosis were observed. On immunofluorescence microscopy, no glomerular immune deposits were detected. On electron microscopy, we observed severe podocyte

\* Corresponding author. Soonchunhyang University Cheonan Hospital, 23-20 Bongmyung-Dong, Cheonan 330-721, Korea.  
 E-mail address: eylee@sch.ac.kr (EY Lee).

foot process effacement. Immune complex-type electron-dense deposits were absent, and glomerular basement membranes (GBM) showed no structural abnormalities (Fig. 2). Before genetic diagnosis was performed, otolaryngologists and ophthalmologists conducted audiometry and eye examinations, respectively. No cataract was present, and the patient's audiometry showed high-pitch sensorineural hearing loss. Mutational analysis of the *MYH9* gene was performed for the patient and her sister. Entire coding regions of the *MYH9* gene were amplified via polymerase chain reaction and directly sequenced. The gene analysis showed a heterozygous c.5521G>A in exon 38 [p.Glu(GAG)1841Lys (AAG)] in the patient [3], but not in her sister. We then identified an *MYH9* mutation (Fig. 3).

The laboratory findings regarding glomerular disease were as follows: antinuclear antibody (-); antineutrophil cytoplasmic



**Figure 1. A peripheral blood smear.** Giant platelets (arrows) and Döhle bodies (arrow head) that appear as small, light blue/gray stained areas in the cytoplasm of the neutrophil are shown (Wright staining,  $\times 1,000$ ).

autoantibody (-); anti-dsDNA (-); anti-GBM antibody (-); hepatitis B surface antigen (-); antihepatitis B virus (-); antihepatitis C virus (-); IgG, 1,214.9 mg/dL; IgA, 284.2 mg/dL; IgM, 88.6 mg/dL; C3, 101.4 mg/dL; C4, 23.8 mg/dL; and CH50, 65.0 mg/dL. The pattern of urine protein electrophoresis showed selective proteinuria and was glomerular in origin. The result of serum protein electrophoresis was not remarkable.

The patient had two children, aged 16 years and 3 years; both were delivered by normal spontaneous vaginal delivery. Both children had thrombocytopenia. The first child was lost to follow-up, while the second continued to be followed up at our clinic with no proteinuria detected as of this publication.

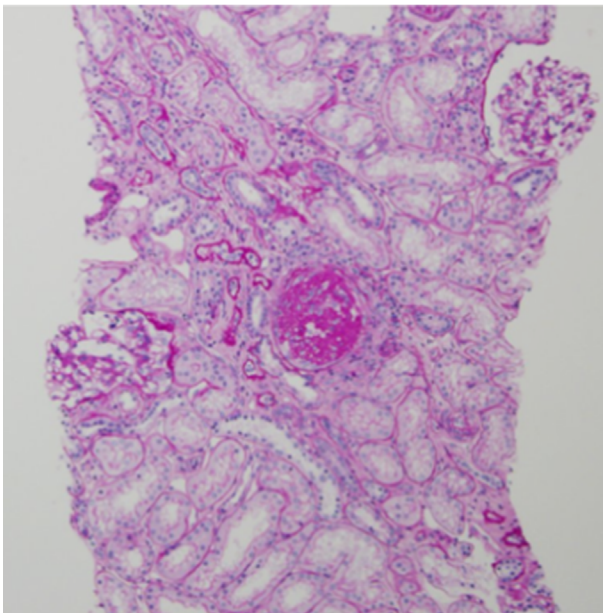
We followed up this patient for 2 years from her initial visit to our clinic. She was first administered an angiotensin II receptor blocker (ARB) for 1 year. Then, the medication was changed to amlodipine (calcium channel blocker; CCB) because she was planning a pregnancy. The patient's creatinine level remained in the 0.6–0.8 mg/dL range over 2 years. However, the patient's proteinuria decreased (224 mg/day) during ARB treatment and increased (1,149.5 mg/day) during CCB treatment (Fig. 4).

## Discussion

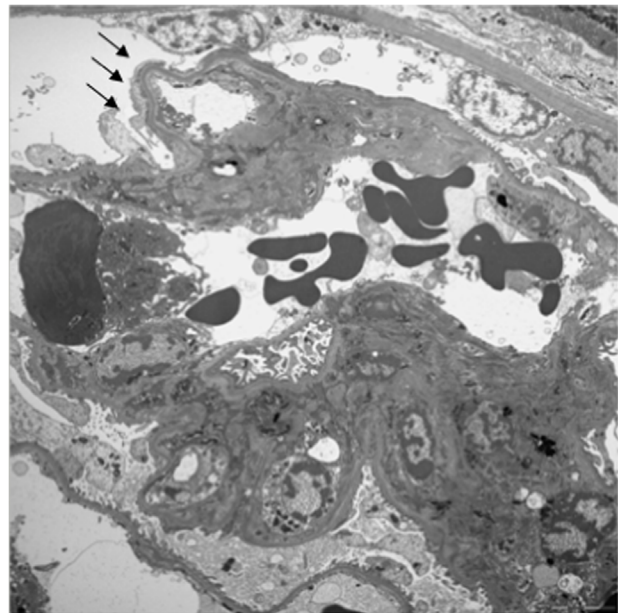
*MYH9*-related disorder is an autosomal dominant disease caused by a mutation in the *MYH9* gene. Nephropathy has been detected in 30% of *MYH9*-related disorder cases (Table 1). Its characteristic features are early onset proteinuria and rapidly progressing renal disorder. Extrarenal manifestations include hematological abnormalities (giant platelets, thrombocytopenia, and leukocyte inclusions), cataracts, and sensorineural deafness.

*MYH9*-related nephropathy usually progresses to end stage renal disease (ESRD) when a patient reaches his/her thirties. However, our patient was diagnosed with *MYH9*-related nephropathy when she was 36 years old, and she did not show the rapid aggravation of renal failure observed in

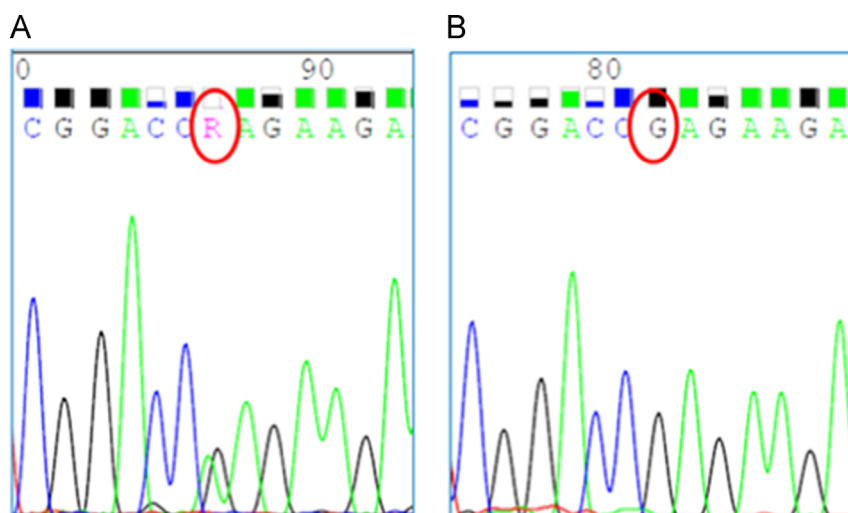
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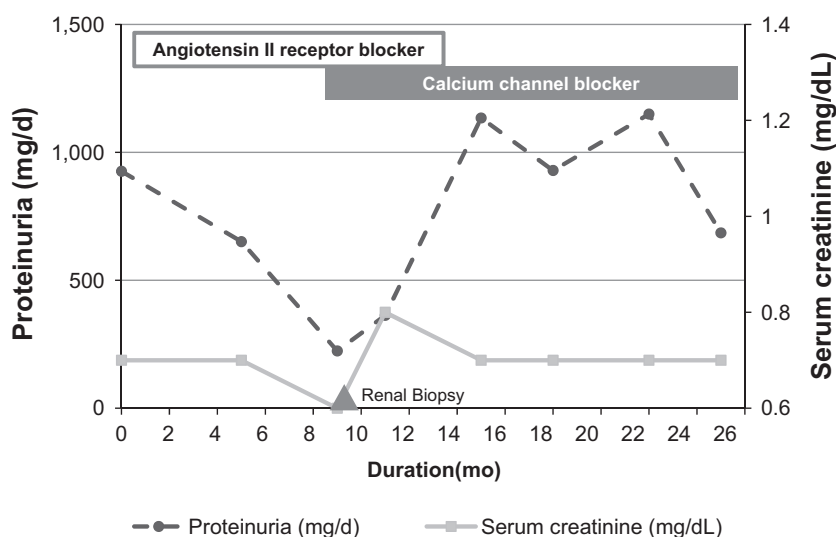
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**Figure 2. Renal biopsy findings.** (A) On light microscopy, global sclerosis is observed on four of 26 glomeruli. Mild tubular atrophy is also seen (periodic acid–Schiff,  $\times 100$ ). (B) On electron microscopy, partial podocyte foot process effacement (arrows) is observed ( $\times 2,500$ ).



**Figure 3. MYH9 mutational hot spot testing.** (A) A heterozygous c.G5521A in exon 38 [p.Glu(GAG)1841Lys(AAG)] is evident in the patient. (B) Her sister does not have the mutation.



**Figure 4. Proteinuria and serum creatinine over time.** Proteinuria decreased during angiotensin II receptor blocker treatment and increased during calcium channel blocker treatment. Serum creatinine remained stable during the follow-up.

**Table 1. Summary of previous cases of adult onset MYH9 nephropathy diagnosed via renal biopsy**

Age/sex	Family history	Proteinuria	Macrothrombocytopenia	Scr level at renal biopsy (mg/dL)	Renal biopsy findings
36/F*	–	+	+	0.6	Global glomerulosclerosis, foot process effacement
22/M [3]	+	+	+	0.8	Segmental glomerulosclerosis
49/M [4]	+	+	+	5.0	Glomerulosclerosis
24/F [4]	+	+	+	2.0	Foot process effacement
67/F [5]	–	+	N.D.	1.2	Focal global glomerulosclerosis
42/M [6]	–	+	N.D.	1.9	Segmental glomerulosclerosis, collapse of individual tuft lobules
42/F [6]	–	+	N.D.	2.4	Segmental glomerulosclerosis, collapse of individual tuft lobules

\* The present case.

N.D., no data; Scr, serum creatinine.

previous case reports. Because of her mild symptoms, this patient's diagnosis may have been delayed.

Proteinuria in MYH9-related nephropathy may be due to foot process effacement of the renal podocyte. Arrondel et al

[1] described a high expression of MYH9 in mature kidneys and showed that NMMHC IIA was mainly present on podocytes. Further analysis of the D1424N domain substitution in MYH9 revealed atypical distribution of NMMHC IIA in tubular

epithelia, focal and segmental effacement of podocytes, and cosegregation of a specific podocin haplotype [1,2].

Few studies have described patients with MYH9-related nephropathy that was detected while the patient was an adult. Pecci et al [7] reported that 61 of 247 evaluable patients (25%) developed proteinuric nephropathy, and the mean age at onset was 27 years; in addition, 72% of the patients were diagnosed prior to the age of 35 years. This study included consecutive patients enrolled in the Italian Registry for MYH9-RD as of March 2012. However, there are no data relating to renal biopsy findings in that article.

Han et al [3] described a case of MYH9 nephropathy proven via biopsy, with detected renal involvement, when the patient was 22 years old; he had persistent proteinuria, but no further deterioration was observed in renal function for > 16 years after the renal involvement was first detected. As previously mentioned, MYH9-related nephropathy usually progresses to ESRD when the patient reaches his/her thirties. Because rapid deterioration in renal failure was not observed in this patient, it is an interesting case.

MYH9-related disorder and MYH9 nephropathy are rare. Therefore, reliable data on the prevalence are lacking. However, MYH9 nephropathy may need to be considered if a patient shows thrombocytopenia, proteinuria, and megakaryocyte.

Historically, therapeutic options to slow the progression to ESRD in patients with MYH9-related nephropathy have been lacking. Regarding treatment, blockade of the renin-angiotensin system through the administration of angiotensin-converting enzyme inhibitors or ARBs seems to decrease proteinuria and preserve renal function, perhaps owing to the direct effects of these agents on podocytes [8,9]. In our case, a CCB did not seem to decrease proteinuria.

In summary, we describe a 36-year-old woman with proteinuria due to an MYH9 disorder who showed a mild disease course and whose proteinuria responded to treatment with an ARB but not a CCB. Further investigations regarding the role of the MYH9 gene in renal injury caused by MYH9 disorders are needed.

### Conflict of interest

All authors declare no conflict of interest.

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