Case Report

Two Cases of the MYH9 Disorder Fechtner Syndrome Diagnosed from Observation of Peripheral Blood Cells before End-Stage Renal Failure

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As a MYH9 disorder, Fechtner syndrome is characterized by nephritis, giant platelets, granulocyte inclusion bodies (Döhle-like bodies), cataract, and sensorineural deafness. Observation of peripheral blood smear for the presence of thrombocytopenia, giant platelets, and granulocyte inclusion bodies (Döhle-like bodies) is highly important for the early diagnosis of MYH9 disorders. In our two cases, sequencing analysis of the MYH9 gene indicated mutations in exon 24. Both cases were diagnosed as the MYH9 disorders Fechtner syndrome before end-stage renal failure on the basis of the observation of peripheral blood smear.

1. Introduction

MYH9 mutations cause the autosomal dominant macrothrombocytopenic syndrome of May-Hegglin anomaly, Fechtner syndrome, Sebastian syndrome, and Epstein syndrome. Recently, these diseases are being referred to as MYH9 disorders. The MYH9 gene encodes the nonmuscle myosin heavy chain –IIA (NMMHC-IIA). MYH9 disorders are characterized by giant platelets, thrombocytopenia, and characteristic Döhle-like bodies in granulocytes. Among these diseases, the involvement of Alport syndrome symptoms, namely nephritis, cataract, and sensorineural deafness, is associated with the mutation site of the MYH9 gene. Fechtner syndrome, a MYH9 disorder, develops nephritis and end-stage renal failure. In most previous reports of MYH9 disorders in Japan, Fechtner syndrome was diagnosed after end-stage renal failure. Here, our two cases were diagnosed before end-stage renal failure on the basis of the observation of peripheral blood smear, neutrophil inclusion bodies (Döhle-like bodies), and giant platelets.

In the management of chronic kidney disease, the findings from peripheral blood smear, presence of the Döhle-like bodies in neutrophils, and giant platelets are important for the early diagnosis of MYH9 disorders, especially if the symptoms are not evident.

2. Case Presentation

2.1. Case 1. A 56-year-old male was referred to our hospital for the management of chronic kidney disease. At the age of 17 years, hematuria and proteinuria were observed. At the age of 30 years, he presented with thrombocytopenia, sensorineural deafness, and cataract. At the age of 56 years, he was referred to our hospital for the management of hypertension and elevated serum creatinine level. His blood and urinary analysis results are shown in Table 1. In the peripheral blood smear, thrombocytopenia, giant platelets, and neutrophil inclusion bodies (Döhle-like bodies) were observed with May-Giemsa staining (Figure 1). We identified a relevant family history.
His son had thrombocytopenia. His mother died of subarachnoid hemorrhage at the age of 61 years, and his younger brother had thrombocytopenia and renal dysfunction. From these findings, we considered the possibility of \( \text{MYH9} \) disorders and performed immunofluorescence analysis for neutrophil NMMHC-IIA localization [1, 2]. We found a few large NMMHC-IIA aggregates in the neutrophils (Figure 1).

Mutational analysis of the \( \text{MYH9} \) gene revealed a heterozygous duplication of 21 nucleotides in exon 24 (p.E1066_A1072dup, c.3195_3215dup; Figure 2(a)).

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**2.2. Case 2.** A 59-year-old male was referred to our hospital because elevated serum creatinine level was indicated in his medical examinations. Renal dysfunction was only recognized at the age of 59 years, when he presented with cataract and sensorineural deafness. In his family history, his father had sensorineural deafness from the age of 20 years and died of cerebral infarction at the age of 84 years. His mother had hypertension from the age of 50 years (Figure 2(b)). Blood and urinary analysis results are shown in Table 1. In the peripheral blood smear, thrombocytopenia, giant platelets, and neutrophil inclusion bodies (Döhle-like bodies) were observed using May-Giemsa staining (Figure 1). We suspected the possibility of a \( \text{MYH9} \) gene abnormality. Immunofluorescence micrographs of neutrophils showed granular accumulation of NMMHC-IIA in the neutrophils (Figure 1). Subsequent genetic mutation analysis revealed p.E1084del mutation (c.3250_3252delGAG) in \( \text{MYH9} \) exon 24 (Figure 2(b)). To determine other factors of renal dysfunction, we performed renal biopsy by percutaneous needle aspiration. In the histological analysis, no significant changes were observed in the mesangium and tubulointerstitial lesions on light microscopy. However, on electron microscopy, focal effacement of podocytes and loss of the interpodocyte slit diaphragm were observed (Figure 3). From these findings, he was diagnosed with Fechtner syndrome, a \( \text{MYH9} \) disorder. Hypertension and additional risk factors of renal failure had been managed mainly with dietary intervention. Even at 5 years after the diagnosis, his creatinine level remained at 1.3 mg/dL.

The institutional review boards of Sumitomo Hospital and Nagoya Medical Center approved this study. Written informed consent was obtained from all the patients in accordance with the principles of the Declaration of Helsinki.

### Table 1: Clinical characteristics, blood and urinary analysis of these cases.

|                     | Case 1 | Case 2 | Reference range |
|---------------------|--------|--------|----------------|
| **Height (cm)**     | 173    | 164    |                 |
| **Weight (kg)**     | 79.2   | 64.1   |                 |
| **BMI (kg/m²)**     | 26.5   | 23.8   |                 |
| **Urinary analysis**|        |        |                 |
| pH                  | 6.0    | 5.0    | 5.0–7.5         |
| Specific gravity    | 1.003  | 1.019  | 1.005–1.030     |
| Protein (g/day)     | 1.5    | 0.02   | negative        |
| Urine occult blood reaction Cast | 1+ fatty cast, epithelial cast and granular cast | Negative hyaline cast, epithelial cast and granular cast | Negative negative |
| **Blood analysis**  |        |        |                 |
| White blood cell (/μL) | 4,300  | 4,000  | 3,300–8,600     |
| Red blood cell (×10⁶/μL) | 3.00   | 4.38   | 4.30–5.60       |
| Hemoglobin (g/dL)   | 9.8    | 13.6   | 13.5–17.0       |
| Hematocrit (%)      | 29.9   | 40.9   | 40.0–51.0       |
| Platelet counts (×10⁹/μL) | 8.2  | 8.7    | 15.0–35.0       |
| Mean platelet volume (fL) | 11.5 | 13.2   | 6.8–9.4         |
| Bleeding time (minutes) | 1       | 1      | 1–5            |
| Sodium (mEq/L)      | 141    | 143    | 143            |
| Potassium (mEq/L)   | 4.7    | 4.2    | 3.6–5.0        |
| Chloride (mEq/L)    | 109    | 109    | 98–108         |
| Calcium (mg/dL)     | 8.7    | 8.9    | 8.2–10.2       |
| Phosphorus (mg/dL)  | 6.2    | 2.8    | 2.7–4.4        |
| Total protein (g/dL)| 7.0    | 6.4    | 6.7–8.3        |
| Albumin (g/dL)      | 4.1    | 4.4    | 3.8–5.3        |
| Blood urea nitrogen (mg/dL) | 78    | 17     | 8–20           |
| Creatinine (mg/dL)  | 5.91   | 1.24   | 0.36–1.06      |
| estimate glomerular filtration rate (eGFR) (mL/min/1.73m²) | 8.8 | 47.6   |                 |
| Hemoglobin A1c (NGSP) (%) | 5.7 | 5.3    | 4.6–6.2        |
| Antinuclear antibody | ×40    | <×40   | <<×40          |

(Figure 2(a)). His son had thrombocytopenia. His mother died of subarachnoid hemorrhage at the age of 61 years, and his younger brother had thrombocytopenia and renal dysfunction.
MYH9 disorders include May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome. These are classified according to the presence of giant platelets, granulocyte inclusion bodies (Döhle-like bodies), nephritis, sensorineural deafness, and cataract [1–3] (Table 2). Here, we describe two cases of Fechtner syndrome before end-stage renal failure. In case 1, a large amount of proteinuria was observed. Owing to renal atrophy, we did not perform a renal biopsy. In contrast, in case 2, mild proteinuria was observed. However, electron microscopy revealed focal and segmental effacement of podocytes and loss of the interpodocyte slit diaphragm. The MYH9 gene encodes the nonmuscle myosin heavy chain –IIA (NMMHC-IIA). NMMHC-II A is an actin-binding protein that also plays an important role in cell adhesion and maintenance of tissue architecture [4]. It forms myosin II A with myosin light chain and is responsible for the contractile mechanism in the foot process of podocytes [5]. In previous studies, these changes were reported to be associated with the loss of NMMHC-II A expression [6]. This falling out of the foot process is responsible for proteinuria [7]. In many previous reports of MYH9 disorders, cases of Fechtner syndrome complicated with renal failure were diagnosed after end-stage renal failure [8, 9]. Here, our two cases could be diagnosed before end-stage renal failure on the basis of the main findings, including giant platelets and granulocyte inclusion bodies (Döhle-like bodies). As an advantage of diagnosis before end-stage renal failure, erroneous treatment such as immunosuppressive therapy can be prevented. In addition, antihypertensive therapy can be started early, as done in our cases. In previous studies, administration of an angiotensin II receptor blocker or an angiotensin-converting enzyme inhibitor for renal injury associated with MYH9 disorders was

3. Discussion

MYH9 disorders include May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome. These are classified according to the presence of giant platelets, granulocyte inclusion bodies (Döhle-like bodies), nephritis, sensorineural deafness, and cataract [1–3] (Table 2). Here, we describe two cases of Fechtner syndrome before end-stage renal failure. In case 1, a large amount of proteinuria was observed. Owing to renal atrophy, we did not perform a renal biopsy. In contrast, in case 2, mild proteinuria was observed. However, electron microscopy revealed focal and segmental effacement of podocytes and loss of the interpodocyte slit diaphragm. The MYH9 gene encodes the nonmuscle myosin heavy chain –IIA (NMMHC-IIA). NMMHC-II A is an actin-binding protein that also plays an important role in cell adhesion and maintenance of tissue architecture [4]. It forms myosin II A with myosin light chain and is responsible for the contractile mechanism in the foot process of podocytes [5]. In previous studies, these changes were reported to be associated with the loss of NMMHC-II A expression [6]. This falling out of the foot process is responsible for proteinuria [7]. In many previous reports of MYH9 disorders, cases of Fechtner syndrome complicated with renal failure were diagnosed after end-stage renal failure [8, 9]. Here, our two cases could be diagnosed before end-stage renal failure on the basis of the main findings, including giant platelets and granulocyte inclusion bodies (Döhle-like bodies). As an advantage of diagnosis before end-stage renal failure, erroneous treatment such as immunosuppressive therapy can be prevented. In addition, antihypertensive therapy can be started early, as done in our cases. In previous studies, administration of an angiotensin II receptor blocker or an angiotensin-converting enzyme inhibitor for renal injury associated with MYH9 disorders was

![Figure 1: Upper panels present the control samples; middle panels, case 1 samples; and lower panels, case 2 samples. The May-Giemsa-stained platelets (in the left: original magnification ×1000) show giant platelets from the case 1 and 2 samples. In the May-Giemsa-stained neutrophils (in the middle: original magnification ×1000), the cytoplasmic inclusion bodies (Döhle-like bodies) in the case 1 and case 2 samples are indicated with arrowheads. The nonmuscle myosin heavy chain-II A (NMMHC-II A) distribution in neutrophils is shown in the immunofluorescence micrographs of the neutrophils (in the right). NMMHC-II A is diffusely distributed in the control neutrophils. Arrowheads represent the accumulation of granular NMMHC-II A in neutrophils of cases 1 and 2.](image_url)
Because MYH9 disorders are genetic diseases, early detection of patients based on family history is also important. We can offer a genetic consultation to patients' families and other relatives. In fact, in the younger brother of case 1, therapeutic intervention started to suppress the identified to be effective to reduce proteinuria and suppress the development of renal dysfunction [10]. Diagnosis before end-stage renal failure is necessary for the management around the perioperative period, such as hemostasis during maintenance hemodialysis or tube insertion for peritoneal dialysis. Finally, because MYH9 disorders are genetic diseases, early detection of patients based on family history is also important. We can offer a genetic consultation to patients' families and other relatives. In fact, in the younger brother of case 1, therapeutic intervention started to suppress the identified to be effective to reduce proteinuria and suppress the development of renal dysfunction [10]. Diagnosis before end-stage renal failure is necessary for the management around the perioperative period, such as hemostasis during maintenance hemodialysis or tube insertion for peritoneal dialysis. Finally, because MYH9 disorders are genetic diseases, early detection of patients based on family history is also important. We can offer a genetic consultation to patients' families and other relatives. In fact, in the younger brother of case 1, therapeutic intervention started to suppress the identified to be effective to reduce proteinuria and suppress the development of renal dysfunction [10].
development of renal failure. As mentioned earlier, the diagnosis of MYH9 disorders before end-stage renal failure is meaningful; therefore, careful observation of giant platelets and Döhle-like bodies in patients with chronic kidney disease (CKD) is important. However, in Epstein syndrome, inclusion bodies are difficult to recognize in granulocytes. Cases with MYH9 mutations in exon 24 might clearly show Döhle-like bodies and giant platelets. Previously, about 30 mutations of the MYH9 gene were reported. However, among the 40 exons in the MYH9 gene, mutations are concentrated in the specific codons of exons 1, 16, 26, 30, 38, and 40 [11]. Both our cases had mutations in exon 24. In previous studies, cases with mutations in exon 24 were very rare [12–14]. Even among the same genetic mutations, the phenotype can vary [15]. Kidney damage occurs in approximately 25% of patients with MYH9 disorders as progressive protein-uric nephropathy. In most cases, nephropathy occurs before the age of 35 years and presents an aggressive course. In some cases, proteinuria may appear later and/or show a slower progression [16]. Hearing loss occurred in approximately 50% of cases at a mean age of 33 years [17]. As indicated in Table 2, thrombocytopenia is common, but the occurrence of symptoms such as renal disorder, deafness, and cataract differed from each other even in the same genetic mutation. These findings indicate that other factors such as age or sex might be required for the onset and progression of symptoms. Therefore, in cases with thrombocytopenia, attention should be paid to the possibility of MYH9 disorders.

Table 2: MYH9 disorders; May-Hegglin syndrome, Sebastian syndrome, Epstein syndrome and Fechtner syndrome and clinical features.

| MYH9 disorders                          | Giant platelets | Granulocyte inclusion bodies | Nephritis | Sensorineural deafness | Cataract |
|-----------------------------------------|-----------------|------------------------------|-----------|------------------------|----------|
| May-Hegglin syndrome                    | +               | + (large)                    | −         | −                      | −        |
| Sebastian syndrome                      | +               | + (small)                    | −         | −                      | −        |
| Epstein syndrome                        | +               | −                            | +         | +                      | −        |
| Fechtner syndrome                       | +               | +                            | +         | +                      | +        |

| MYH9 gene mutations | Age and sex | Giant platelets and platelet count (reference range: 15.0−35.0×10⁴/μL) | Granulocyte inclusion bodies | Nephritis | Sensorineural deafness | Cataract |
|---------------------|-------------|-----------------------------------------------------------------------|-----------------------------|-----------|------------------------|----------|
| Case 1              | p.E1066_A1072dup Male | 56 | + | + | + | + | + | + |
| N. Pujol-Moix et al. [12], De Rocco D et al. [13] | 50 | + | + | − | − | − | − | − |
| Case 2              | p.E1084del Male | 59 | + | + | + | + | − | + |
| Miyazaki et al. [14] | 21 | + | + | + | − | − | − | − |

Disclosure
Shinji Kunishima, Department of Medical Technology, School of Health Sciences, Gifu University of Medical Science, Seki, Gifu, Japan.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Shin Teshirogi and Jun Muratsu contributed equally to this work.

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