MYH9 유전자 변이가 확인된 May-Hegglin Anomaly 증례
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A Case of Myosin-heavy-chain-9 (MYH9) Gene Mutation Confirmed May-Hegglin Anomaly: 11-year Follow-up
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May-Hegglin anomaly (MHA) is a myosin-heavy-chain-9 (MYH9)-related disorder characterized by thrombocytopenia with giant platelets and inclusion bodies in leukocytes. MHA does not require treatment, but it may be misdiagnosed as immune thrombocytopenic purpura (ITP) and inappropriately managed. Reported herein is a case of a 12 year old female patient diagnosed as MHA with laboratory findings of severe thrombocytopenia and giant platelets in peripheral blood morphology, and followed up until 23 years of age. The patient had been diagnosed with ITP and treated with intravenous gamma-globulin therapy at another hospital, and showed no improvements in platelet count. She was then referred to our hospital for further diagnostic workup and followed up for 11 years, showing platelet count of 6,000-20,000/μL and prolonged platelet function test. She was occasionally treated with iron therapy due to iron-deficiency anemia. In 2014, we conducted a DNA analysis that revealed c.4339G>T(p.Asp1447Tyr), a known mutation of MYH9 gene.

Key Words: May-Hegglin anomaly, MYH9-related disorders, MYH9 gene, Thrombocytopenia, Asp1447Tyr

Introduction
Myosin-heavy-chain-9 (MYH9)-related disorders, including May-Hegglin anomaly (MHA) and the Sebastian, Fechtner, and Epstein syndromes, are rare autosomal dominant disorders characterized by thrombocytopenia with giant platelets (megathrombocytopenia) and basophilic cytoplasmic inclusion bodies (resembling Döhle bodies) in the leukocytes [1]. The MYH9-related disorders are caused by mutation in the MYH9 gene located on chromosome 22q13.1, which encodes the non-muscular myosin heavy-chain IIA (NMMHC-IIA) protein but are differentiated by some clinical manifestations and findings (Table 1) [1,2].
Table 1. Myosin-heavy-chain-9 (MYH9)-related disorder

<table>
<thead>
<tr>
<th>MYH9-related disorder</th>
<th>Characteristics</th>
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<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Giant platelet</td>
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<tr>
<td>May Hegglin anomaly</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fechtner syndrome</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Epstein syndrome</td>
<td>+</td>
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<td>Sebastian syndrome</td>
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MHA may manifest as a mild bleeding tendency, epistaxis, and bruising, but most patients are asymptomatic. MHA does not require treatment but may be misdiagnosed as acute immune thrombocytopenic purpura (ITP) and treated. We report a case of a patient confirmed as MHA through gene analysis, which showed heterozygous mutation of the known MYH9 gene, c.4339G>T (p.Asp1447Tyr).

Case Report

A 12-year-old girl was referred and admitted to the Pediatric Department of Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine in 2003 due to severe thrombocytopenia with platelet count 6,000/μL on her blood test for routine checkup. She had been diagnosed with acute ITP and had been treated with intravenous high-dose gamma-globulin therapy twice, without any response in platelet count, in another hospital. She did not have a family history of coagulopathy or history of preceding viral infection. She did not manifest symptoms and signs of ITP such as easy bruising, petechiae, ecchymosis, purpura or gum and mucous membrane bleeding. On physical examination, she did not show hepatomegaly, splenomegaly or lymphadenopathy. Her initial complete blood count (CBC) in 2003 showed WBC 3,700/μL, with absolute neutrophil count (ANC) 1,988/μL, hemoglobin (Hb) 12.6 g/dL, platelet count 3,000/μL and the other laboratory data including the RBC index, PT/aPTT, and bone marrow biopsy results were normal. The patient went to United States for overseas studies, and she was diagnosed as MHA at the Philadelphia Children’s Hospital, with the laboratory findings of severe thrombocytopenia and giant platelets observed in her peripheral blood (PB) morphology.

The patient came back to South Korea in 2006, and since then, she had been regularly followed up at the outpatient clinic of the authors’ Pediatric Department, without medication. Her laboratory test in 2006 showed WBC 3,300/μL, with ANC 1,712/μL, Hb 8.9 g/dL, mean corpuscular volume (MCV) 76.9 fl, corrected reticulocyte 1.06%, ferritin 3.6 ng/mL, and platelet 13,000/μL. She was treated with iron for 3 months due to iron-deficiency anemia, after which her Hb normalized. Her platelet count was in the range of 6,000-20,000/μL. During the past 11 years, she lived her usual life with frequent epistaxis and menorrhagia, but without other bleeding symptoms such as easy bruising, petechiae, purpura, gum bleeding or hematuria. She was occasionally treated with iron due to relapse of iron-deficiency anemia.

In 2014, at 23 years of age, the patient was again admitted to the authors’ Pediatric Department for laboratory test follow-up and for platelet transfusion for third-molar-tooth extraction. Her CBC showed Hb 12.6 g/dL, Hct 37.6%, and WBC 2,800/μL, with ANC 1,456/μL and platelet count 12,000/μL. Her PB smear showed giant platelets and hypersegmented neutrophil (Fig. 1). The platelet function measured by platelet function analyzer (PFA-100) showed collagen/epinephrine 238 seconds and collagen/ADP 158 seconds, which was severely prolonged. The bone marrow study showed normocellular marrow for her age with normal erythropoiesis, increased granulopoiesis and megakaryopoiesis. The other laboratory studies including electrolyte, liver enzyme, BUN/creatinine, PT, aPTT, von Willebrand factor (VWF) antigen and activity, VWF multimer assay and plasma mixing test were normal. The paroxysmal nocturnal hemoglobinuria (PNH) study result was negative. Mutational analysis was performed using a poly-
Fig. 1. Peripheral blood smear of the May-Hegglin anomaly patient: giant platelet (red arrow) and hypersegmented neutrophil (green arrow) (Wright Giemsa, ×400).

Fig. 2. MYH9 gene sequence analysis (exon 2, 11, 17, 26, 27, 31, 39, 41) showing c.4339G>T (p.Asp1447Tyr), known mutation on MYH9 gene is found.

Discussion

MYH9-related disorders result from mutations in MYH9 gene, which is located on chromosome 22q12-13, encoding for the heavy-chain A of class II non-muscle myosin (NMMHC-IIA), a cytoskeletal contractile protein [3]. NMMHC-IIA proteins, which are expressed in many cells, including the platelets, leukocytes, kidneys, and cochleae, are associated with cell motility, cell phagocytosis, cell adhesion, cytokinesis, and cell architecture and development [4]. Therefore, the mutation of NMMHC-IIA may change the platelet cytoskeletal architecture, which may cause thrombocytopenia and the emergence of giant platelets. Moreover, the abnormal changes in the podocytes cytoskeleton due to the mutation of NMMHC-IIA can damage the glomerulus, which can cause hematuria or renal injury. The mechanisms of hearing loss and cataracts are still poorly understood [1,4]. There are four related syndromes of MYH9-related disorders (i.e., MHA, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome), and three common characteristics in these disorders are thrombocytopenia, giant platelets and Döhle bodies in leukocytes. All of which can be distinguished by different clinical manifestations and signs (Table 1).

MHA was first described by May in 1909 and by Hegglin in 1945 [5]. Since then, some cases have been reported worldwide, but the accurate number of incidences to date is unknown [6]. In South Korea, since the case reported by Lee et al. in 1992, eight cases have been reported [7-11]. MHA patients are usually asymptomatic and do not require transfusion or other specific treatments, but some MHA patients may present a mild bleeding tendency, such as epistaxis, bruising, and menorrhagia. In asymptomatic patients with severe thrombocytopenia, history-taking to determine
if there is a family history of thrombocytopenia, and examination of the PB morphology for giant platelets and Döhle bodies in the leukocytes, are necessary when there is a suspicion of MHA [6]. MHA must be in the differential diagnosis of ITP to avoid unnecessary treatment with intravenous high-dose gamma-globulin. Finally, MHA gene mutation analysis is required for the confirmatory diagnosis of MHA.

The MHA patient in the case reported herein was a symptomatic patient presenting mild bleeding symptoms such as frequent epistaxis and menorrhagia, but serious enough to cause recurrent iron-deficiency anemia due to blood loss, and required repeated iron therapy. The patient also showed severe platelet dysfunction measured by the platelet function analyzer, which could be corrected by platelet transfusion. Her CBC showed leukopenia in repeated blood test, but we thought that it was not significant because repeated her bone marrow examination results showed normocellular marrow for her age with normal erythropoiesis, increased granulopoiesis and megakaryopoiesis. In this regard, the patient was different from the general MHA patients. It is suspected that giant platelets lower the platelet count in the automated blood cell counter, causing severe thrombocytopenia, and may not function normally in platelet aggregation. Mutational analysis was performed using a PCR, by amplifying 5'UTR, coding region and flanking region of exons 2, 11, 17, 26, 27, 31, 39, and 41 followed by the direct DNA sequencing of the MYH9 gene in the patient. c.4339G>T (p.Asp1447Tyr), a known mutation of the MYH9 gene, was found, and the MHA diagnosis was confirmed. As far as we know, the patient in the case reported herein is the fourth MHA patient confirmed through gene analysis and reported in the literature in South Korea [10-12]. As MHA and other MYH9-related disorders are very rare diseases, multicenter collaborative studies are required to determine the incidence and function of the giant platelets presented in the MYH9-related disorders. The MYH9-related disorders also need long-term follow-up by hematologists as some of them are quite symptomatic.

References