LETTER TO THE EDITOR

Turk J Hematol [Epub Ahead of Print]

Sitosterolemia with Compound Heterozygous Variants in the *ABCG5* Gene: A Rare Cause of Non-Immune Hemolysis and Macrothrombocytopenia

ABCG5 Geninde Bileşik Heterozigot Varyantlar ile Sitosterolemi: İmmün Olmayan Hemoliz ve Makrotrombositopeninin Nadir Bir Nedeni

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To the Editor,

Sitosterolemia (OMIM #210250 and #618666) is a rare disorder of lipid metabolism and is frequently underdiagnosed. It is an autosomal recessive disease caused by pathogenic variants in the ATP-binding cassette subfamily G member 5 (*ABCG5*) or member 8 (*ABCG8*) genes, resulting in the accumulation of plant sterols [1,2].

An 18-year-old female patient was referred to the hematology department due to bicytopenia. The patient also had anemia and thrombocytopenia in laboratory tests 4 years ago. There was no hepatosplenomegaly or limb abnormality on physical examination. In the laboratory results of the patient, hemoglobin of 9.5 g/dL, mean corpuscular volume of 96 fL, white blood cells of $7.1x10^9$/L, absolute neutrophil count of $5.4x10^9$/L, platelets of $72x10^9$/L, reticulocyte count of $313x10^9$/L (9.2%), and normal nutritional anemia parameters were detected. Lactate dehydrogenase was 282 U/L, alkaline phosphatase was 150 U/L, and bilirubin and renal function tests were normal in the biochemical analysis. A peripheral blood smear showed polychromasia, stomatocytosis, anisocytosis of erythrocytes, and macrothrombocytopenia (Figure 1A). The patient was evaluated for hemolysis. A direct Coombs test was negative; 5′-nucleotidase, pyruvate kinase, glucose 6-phosphate dehydrogenase, an osmotic fragility test, and hemoglobin electrophoresis were normal. C-reactive protein was 10.0 mg/L, sedimentation was 24 mm/hour, an anti-nuclear antibody test was negative, and thyroid function tests were normal. The patient's routine lipid panel was found to be normal. Since no laboratory measured plant sterols, genetic analysis was initially performed. c.1217G>A (p.Arg406Gln) and c.161G>A (p.Trp54*) compound heterozygous variants were detected in the *ABCG5* gene (Figures 1B and 1C). Segregation analysis revealed that the father had the heterozygous c.1217G>A (p.Arg406Gln) and the mother had the heterozygous c.161G>A (p.Trp54*) variant. The c.161G>A (p.Trp54*) variant is known to be pathogenic and c.1217G>A (p.Arg406Gln) is a variant of uncertain significance according to the ClinVar database.

There was no improvement in the patient's hemoglobin level after 3 months of a diet low in plant sterols. Ezetimibe treatment was then started. At the end of 2 months of treatment, the patient's hemoglobin level increased to 11.8 g/dL and her platelet count increased to $135x10^9$/L.

Our patient had biallelic variants in the *ABCG5* gene. The c.161G>A (p.Trp54*) variant of the *ABCG5* gene was previously detected in a Turkish boy with a homozygous state [3]. The c.1217G>A (p.Arg406Gln) variant of the *ABCG5* gene was previously detected in a Korean boy with another frameshift variant [2]. Cutaneous/tendon xanthomas, premature coronary artery disease, high serum sitosterol level (≥1 mg/dL), pathogenic variants in *ABCG5/ABCG8*, and exclusion of familial hypercholesterolemia/cerebrotendinous xanthomatosis were defined as diagnostic criteria in Tada's et al. [1] review. In our case, only hematological findings were present. The diagnostic process was managed by accurate evaluation of peripheral blood smear findings. Although not mentioned among Tada's diagnostic criteria, sitosterolemia should be considered in cases of unexplained hemolysis with stomatocytosis and macrothrombocytopenia, as shown in previously published studies similar to our case [3,4,5,6]. Patients have been misdiagnosed with idiopathic thrombocytopenic purpura and Evans syndrome, and inappropriate therapy has also been documented [7,8]. Our experience suggests that plant sterol measurement is required if all tests imply sitosterolemia.

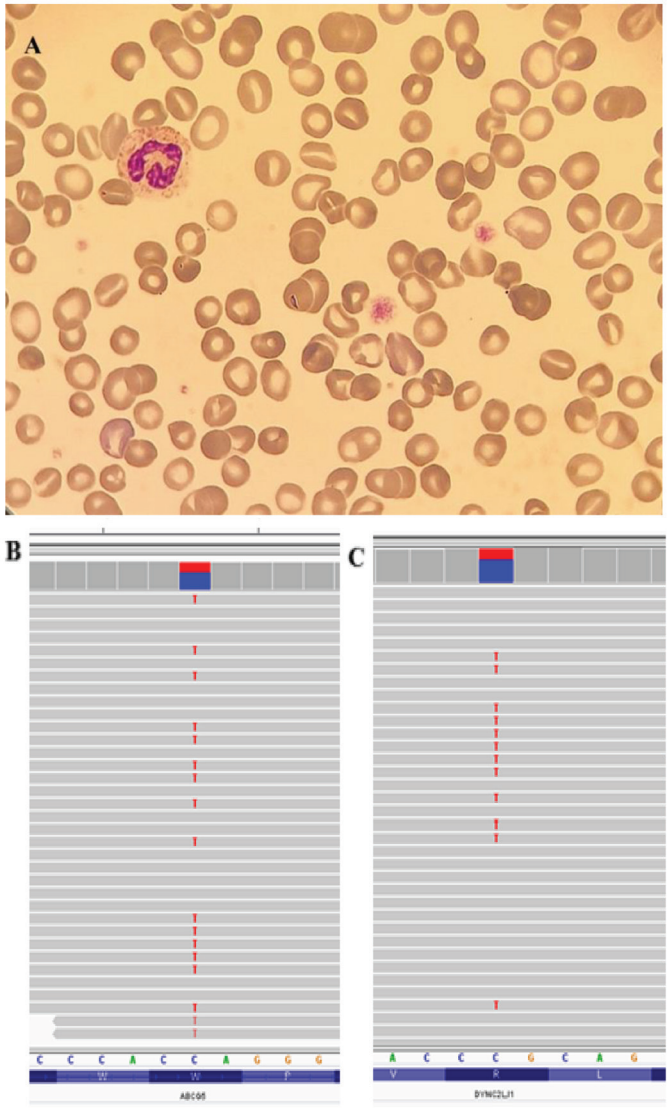

Figure 1. A) Peripheral blood smears showing stomatocytosis, anisocytosis of erythrocytes, and macrothrombocytopenia (Wright-Giemsa stain, 100^{x} magnification). B) Integrative Genomics Viewer visualization of c.161G>A (p.Trp54*) variant in the *ABCG5* gene. C) Integrative Genomics Viewer visualization of c.1217G>A (p.Arg406Gln) variant in the *ABCG5* gene.

Keywords: Sitosterolemia, Hemolysis, *ABCG5*, Macrothrombocytopenia

Anahtar Sözcükler: Sitosterolemi, Hemoliz, *ABCG5*, Makrotrombositopeni

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of the case.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B.D.; Concept: B.B.D.; Design: B.B.D.; Data Collection or Processing: B.B.D., H.P.; Analysis or Interpretation: B.B.D., H.P.; Literature Search: B.B.D., H.P.; Writing: B.B.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Received/Geliş tarihi: March 11, 2025
Accepted/Kabul tarihi: April 29, 2025
Epub: April 29, 2025
DOI: 10.4274/tjh.galenos.2025.2025.0093