

Curing the “Incurable”: First Successful Hematopoietic Stem Cell Transplantation in Severe Hereditary Spherocytosis with Homozygous *SPTA1* Variant and Hepatic Fibrosis

“Tedavi Edilemez” Hastalığı Tedavi Etmek: Homozigot *SPTA1* Varyantı ve Karaciğer Fibrozu Olan Şiddetli Kalıtsal Sferositozda İlk Başarılı Hematopoetik Kök Hücre Nakli

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To the Editor,

Recently, Doğru et al. [1] emphasized the critical role of molecular diagnosis in Turkish patients with hereditary spherocytosis, noting that pathogenic variants in the *SPTA1* and *SPTB* genes are frequently associated with severe clinical phenotypes. Our case, involving a severe phenotype linked to a homozygous *SPTA1* c.7134G>A variant successfully treated with hematopoietic stem cell transplantation (HSCT), adds a vital therapeutic dimension to the molecular landscape discussed in their study.

Hereditary spherocytosis is a genetic hemolytic disorder caused by defects in the erythroid membrane cytoskeleton, leading to the formation of spherocytes and subsequent splenic destruction. The disease predominantly follows an autosomal dominant (75%) or recessive (25%) inheritance, with mutations in *ANK1*, *SLC4A1*, *SPTB*, *EPB42*, and *SPTA1* identified as primary pathogenic drivers [2,3].

A 14-year-old girl with a history of severe anemia that began in the intrauterine period was referred to our clinic. The clinical course of this case had begun in the prenatal period. Due to fetal anemia, intrauterine transfusions were administered. After delivery, the patient required two plasma exchange procedures and intensive phototherapy for refractory anemia and indirect hyperbilirubinemia. Hepatosplenomegaly and recurrent hemolytic crises were observed during childhood.

Reticulocytosis, direct Coombs positivity, and the presence of normoblasts observed in peripheral blood smears from the neonatal period supported the diagnosis of hemolysis; however, osmotic fragility and eosin-5'-maleimide binding tests initially performed to determine the cause of hemolysis were

not diagnostic. This was attributed to the masking of the host erythrocyte profile by intensive red blood cell transfusions received from a very early age. Elevated transaminases (aspartate transaminase: 502 U/L, alanine transaminase: 302 U/L) detected in the neonatal period initially indicated neonatal hepatitis or primary hemochromatosis, requiring chelation and early intervention with antioxidants. In accordance with this preliminary diagnosis, deferoxamine, N-acetylcysteine, vitamin E, and selenium were given. Evaluations performed during the neonatal period further showed that the hemoglobin F level was below 0.5, the HbA2 level was 2.1, and the HbA level was 97.4.

Initial genetic analysis (Cd2 T>C, IVS II-16 G>C) failed to explain the clinical severity of the case. Complications included mild left ventricular non-compaction and transfusion-related grade IV hepatic iron accumulation with focal perisinusoidal/periportal fibrosis, confirmed via liver biopsy. Despite prior splenectomy, the patient remained transfusion-dependent every 2-3 weeks. Consequently, clinical exome sequencing identified a homozygous splice-site variant (c.7134G>A) in the *SPTA1* gene [4]. Absent from the gnomAD database, the variant's deleterious effect was supported by in silico tools (SpliceAI, dbSNV). Segregation analysis confirmed heterozygous parental carriers, and the variant was classified as “likely pathogenic” according to the guidelines of the American College of Medical Genetics, which link it to hereditary spherocytosis type 3 (Figure 1).

Despite splenectomy and cholecystectomy, transfusion independence could not be achieved. Due to transfusion-related stage 4 iron accumulation and focal perisinusoidal fibrosis in the liver, allogeneic HSCT from a human leukocyte antigen-matched sibling was performed. Due to liver fibrosis, “Protocol 26,” a combination of busulfan, cyclophosphamide, and anti-

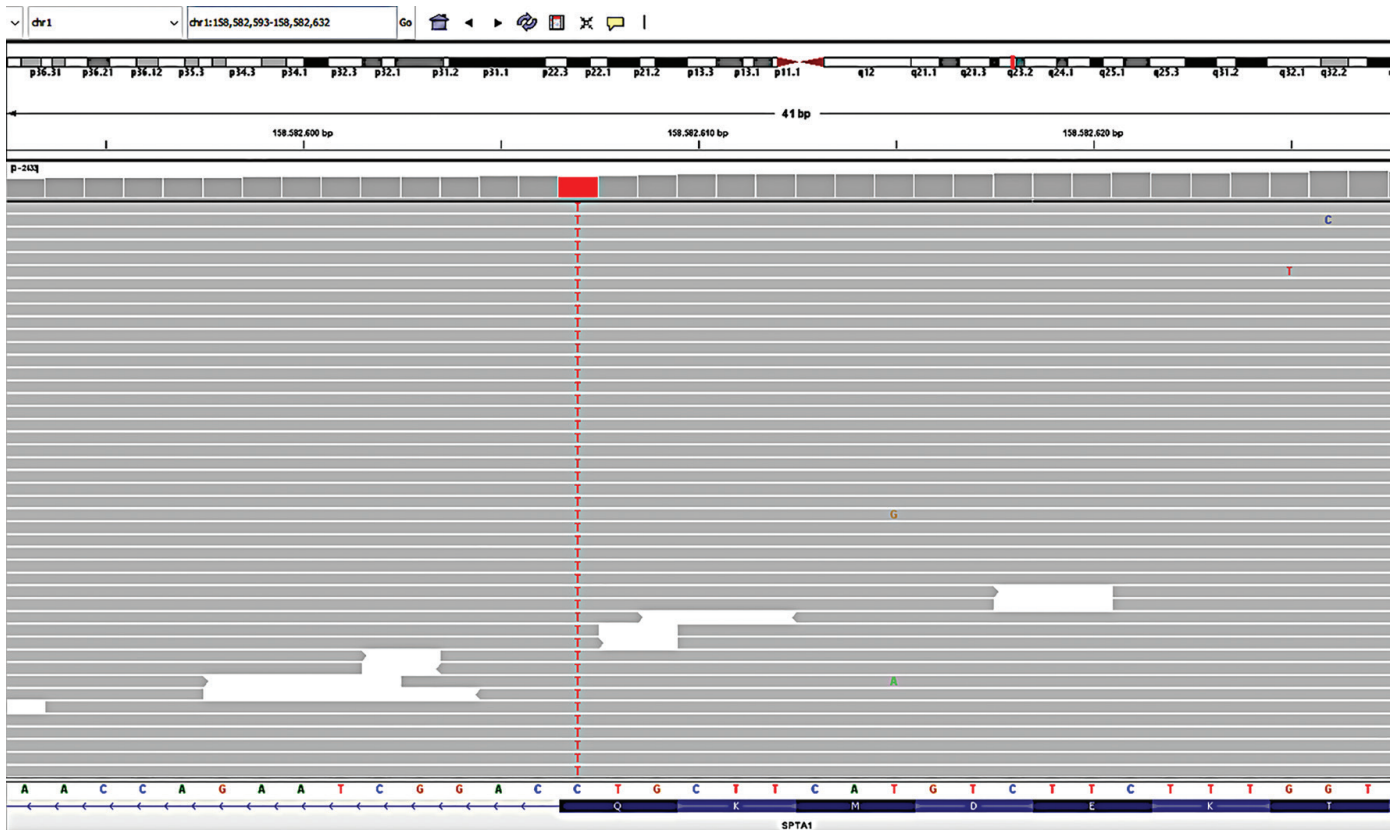


Figure 1. Homozygous *SPTA1* c.7134G>A variant visualized using the Integrative Genomics Viewer Program.

thymocyte globulin, was chosen as the preparation regimen, which minimizes liver toxicity. Antifungal prophylaxis and strict infection control measures were administered as supportive care. The post-transplant period did not involve complications such as acute or chronic graft-versus-host disease, severe infection, or organ damage. The patient is now in the fourth year following transplantation, has gained complete transfusion independence, and continues outpatient treatment with full chimerism.

Hereditary spherocytosis is a hemolytic disorder caused by disruption of the erythroid membrane cytoskeleton [5]. Its pathogenesis is primarily attributed to genetic mutations that lead to the production of abnormal erythrocyte membrane proteins [6,7]. Mutations in alpha-spectrin (*SPTA1*), band 3 (*SCL4A1*), ankyrin (*ANK1*), beta-spectrin (*SPTB*), and protein 4.2 (*EPB42*) have been identified as causes of membrane protein deficiency in hereditary spherocytosis patients [8,9]. Clinical exome sequencing for our patient revealed that there was a homozygous variant in the *SPTA1* gene.

While the treatment of hereditary spherocytosis often focuses on transfusions, spleen surgery, and folic acid, bone marrow transplantation has emerged as a viable treatment option for severe cases. The literature includes examples of successful

HSCTs performed for patients with hereditary spherocytosis and comorbidities such as chronic myeloid leukemia or different mutations such as homozygous *SPTA1* c.2671C>T [10,11,12]. However, this report is the first to demonstrate the success of allogeneic HSCT in a patient with severe hereditary spherocytosis who specifically carried the *SPTA1* c.7134G>A variant, maintained transfusion dependence despite splenectomy, and did not have comorbidities.

One of the most striking findings from our case is that despite advanced liver fibrosis secondary to chronic transfusions, the complete chimerism provided by an appropriate priming regimen (i.e., Protocol 26) offered a permanent and curative solution for this rare genetic phenotype.

In conclusion, our case strongly underscores that HSCT should be included as a life-saving option in standard treatment algorithms for refractory hereditary spherocytosis cases with a high risk of secondary complications, regardless of the genetic profile.

Keywords: Hemolytic anemia, Hereditary spherocytosis, Stem cell transplantation, *SPTA1* gene

Anahtar Kelimeler: Hemolitik anemi, Herediter sferositoz, Kök hücre nakli, *SPTA1* geni

Ethics

Informed Consent: Informed consent was obtained from the individual participant included in the study or the parents.

Authorship Contributions

Surgical and Medical Practices: D.K.G., E.I., V.G., A.Ö., E.Y., E.Ü., M.K.; Concept: D.K.G., E.I., A.Ö.; Design: D.K.G., A.Ö., V.G., E.Y., E.Ü.; Data Collection or Processing: D.K.G., E.I., A.Ö., E.Y.; Analysis or Interpretation: D.K.G., V.G., A.Ö., E.Y., M.K.; Literature Search: D.K.G., V.G., A.Ö., E.Y., E.Ü., M.K.; Writing: D.K.G., V.G., A.Ö., E.Y.

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Reply from the Authors:

We read with great interest this letter by Koçak Göl et al. regarding our recently published study, “Multigene Panel Testing Reveals Novel Variants in Hereditary Spherocytosis Patients in Türkiye” [1]. We appreciate these authors sharing their successful clinical experience with allogeneic hematopoietic stem cell transplantation (HSCT) in a pediatric patient harboring a homozygous *SPTA1* c.7134G>A variant. Their report provides significant “proof-of-concept” for the curative potential of HSCT in the most extreme phenotypes of hereditary spherocytosis.

As emphasized in our original cohort analysis, the molecular landscape of hereditary spherocytosis in Türkiye is characterized by significant allelic heterogeneity. We particularly highlighted that biallelic mutations in the *SPTA1* gene often culminate in severe spectrin deficiency, leading to transfusion dependency and a suboptimal clinical response to splenectomy [1]. The case presented here by Koçak Göl et al. underscores the therapeutic challenge posed by these recessive forms, where conventional management may fail to prevent progressive iron overload and secondary end-organ damage, such as the hepatic fibrosis that they describe.

From a clinical perspective, while splenectomy remains the gold standard for mitigating hemolysis in the majority of hereditary spherocytosis cases, the “incurable” subset, specifically including cases with severe autosomal recessive hereditary spherocytosis (type 3), necessitates nuanced risk stratification. The successful outcome achieved by Koçak Göl et al. with “Protocol 26” is encouraging; however, the transition of HSCT from an “exceptional intervention” to a “standard treatment algorithm” requires caution. In non-malignant hematology, the decision for HSCT must be rigorously balanced against possible transplant-related mortality and significant long-term morbidities. These include not only chronic graft-versus-host disease but also late effects such as infertility, growth retardation, and the potential risk of secondary malignancies [2]. These risks must be carefully weighed against the relatively favorable life expectancy afforded by modern chelation and transfusion support.

We agree that molecular characterization should serve as more than a diagnostic tool; it should be a prognostic indicator that identifies high-risk patients early in the disease course. The contribution by Koçak Göl et al. reinforces our conclusion that comprehensive genetic screening is indispensable. Identifying a homozygous or compound heterozygous *SPTA1* mutation at infancy may indeed delineate a distinct subgroup where HSCT could be considered as a proactive salvage therapy before irreversible complications occur.

In conclusion, we believe that integrating precise molecular data with longitudinal clinical findings is the key to personalizing the management of hereditary spherocytosis. We thank the authors

for extending the discussion from molecular diagnosis to definitive therapeutic outcomes, further enriching the literature on the management of severe hereditary hemolytic anemias.

Sincerely,

Ömer Dođru, Ceren Alavanda, Őenol Demir, Ahmet Koç, Pınar Ata

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