ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.122
Asthma Allergy Immunol 2023;21:156-159

CASE REPORT

Received: 01.10.2022 • Accepted: 04.01.2023
Online Published: 31.01.2023

A Rare Cause of Congenital Neutropenia: SRP54 Variant

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ABSTRACT

Severe congenital neutropenia (SCN) is a heterogeneous disease characterized by maturation arrest in the granulopoiesis stage of the myelocytic lineage, accompanied by early-onset bacterial infections. Absolute neutrophil count in the peripheral blood in SCN patients is typically below 500/mm^3. In humans, the signal recognition particle (SRP) complex consists of six proteins located on the 7S ribonucleoprotein (RNA) molecule. The signal recognition particle 54 (SRP54) protein forms the basic element of this complex with its guanosine triphosphatase (GTPase) activity, regulating this whole physiological process. This case report features a three-year-old girl with isolated severe congenital neutropenia with a heterozygous mutation in the SRP54 gene.

Keywords: Congenital neutropenia, SRP54 mutation, primary immunodeficiency

INTRODUCTION

Congenital neutropenia (CN) is a family of genetic disorders associated with low neutrophil count, susceptibility to infection, various organ dysfunction, and high risk for leukemic transformation (1). Some CN forms are limited to hematologic disorders, while others are syndromic and associated with dysfunction of extrahematopoietic organs including the pancreas, brain, heart, bone, and skin (2). To date, 24 genes that play a role in the pathogenesis of severe congenital neutropenia (SCN) have been identified (2). In 2017, Carapito et al. reported that SCN patients with a heterozygous mutation in the signal recognition particle 54 (SRP54) gene had Shwachman-Diamond syndrome (SDS)-like features (3). In this context, this case report features a three-year-old female SCN patient with a pathological heterozygous mutation in the SRP54 gene but without syndromic features.

CASE REPORT

A three-year-old girl presented to the pediatric immunology and allergy clinic of our hospital because of recurrent soft tissue abscesses and gingivitis. Her medical history indicated that the abscess that had formed on her right leg was drained for the first time when she was one year old, after which she received antibiotic treatment and had recurrent skin abscesses. Her 28-year-old mother had given her birth spontaneously as a result of her second pregnancy. It was learned that there were no problems in the mother's prenatal follow-up examinations but the patient had undergone surgery for intussusception when she was four months old. There was no consanguineous marriage between the parents. There was no patient with primary immunodeficiency in the patient's familial history. At admission, the patient's temperature was 36 °C, pulse 90/min, respiratory rate 20/min, blood pressure 95/60 mm Hg, oxygen saturation 96% in room air, body weight 16.2 kg (78th percentile), height 99 cm (71st percentile), and head circumference 50.0 cm (74th percentile). On physical examination, the gingiva was hyperemic and edematous and the enamel was hypoplastic. Her abdominal examination did not reveal anything abnormal except for the scar that remained from the previous surgery. Additionally, there were scars on her extremities and

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trunk originating from the soft tissue infections she previously had. Her neurologic examination did not reveal anything abnormal. At her first admission to the hospital, her leukocyte count was 10900/mm^3, neutrophil count 30/mm^3, hemoglobin (Hgb) level 11.3 g/dL, and platelet count 393000/µl. Repeated blood count measurements revealed neutrophil counts of less than 200/mm^3. Her serum immunoglobulin G (IgG) and immunoglobulin A (IgA) levels were normal [IgG 750 (879.9 ± 157.2) mg/dL, IgA 71 (68.8 ± 22.2) mg/dL], whereas her total serum immunoglobulin M (IgM) and immunoglobulin E (IgE) levels were slightly high [IgM 199 (86.1 ± 35.3) mg/dL, IgE 166 (0-100) mg/dL] (Normal values are based on reference 4). Her total T cells (CD3+), helper T cells (CD4+), and cytotoxic T cells (CD8+) levels were within an age appropriate range [CD3+ 61.35% (55% - 79%), CD4+ 38.99% (26% - 49%), CD8+ 21.03% (9% - 35%)] , whereas her total B cells level (CD 19+) was slightly high [(CD19+ 33.51 (11-31)] and natural killer (CD16+56+) cells level was slightly low [(CD16+56+ 2,59 (5-28)] (Normal values are based on reference 5). Her laboratory test results are summarized in Table I. No virus infections, including Hepatitis A, B and C, Human Immunodeficiency Virus (HIV), Human Herpes Virus 6, Cytomegalovirus or Epstein–Barr virus, were confirmed. Her abdominal ultrasonography (USG) examination did not indicate hepatosplenomegaly. She was then started on trimethoprim-sulfamethoxazole prophylaxis. No mutation was detected in the analysis of *ELANE (Elastase, Neutrophil Expressed)* and *HAX1 ((haematopoietic cell-specific protein 1 (HS1)-associated protein X-1))* gene sequences. Afterward, whole-exome sequencing was performed. Genes identified in Human Phenotype Ontology (HPO) associated with neutropenia were filtered and analyzed. Consequently, a heterozygous c.349_351del (p. Thr117del) variant was detected in the *SRP54* gene (Figure 1). In light of these findings, bone marrow trans-

Table I: Laboratory test results of the patient with SRP54 mutation.

Parameter, unit value	Patient value (Normal range)
Hemoglobin, g/ dL	11.3 (10.2- 12.7)
Leukocyte, mm^3	10900 (4860- 13380)
Absolute neutrophil count, mm^3	30 (1540- 8290)
Absolute lymphocyte count, mm^3	7170 (1250- 5770)
Absolute eosinophil count, mm^3	500 (30-530)
Absolute monocyte count, mm^3	3130 (190- 940)
Platelet, mm^3	393.000 (189.000- 403.000)
IgG, mg/dL	750 (879.9 ± 157.2) *
IgA, mg/dL	71 (68.8 ± 22.2) *
IgM, mg/dL	199 (86.1 ± 35.3) *
IgE, mg/dL	166 (0-100)*
CD3 (%)	61.35 (55- 79) †
CD4 (%)	38.99 (26- 49) †
CD8 (%)	21.03 (9- 35) †
CD16+56 (%)	2.59 (5- 28) †
CD19 (%)	33.51 (11-31) †
Molecular analysis	c.349_351del (p.Thr117del) at SRP54 gene

*; Based on reference number 4, †; Based on reference number 5.

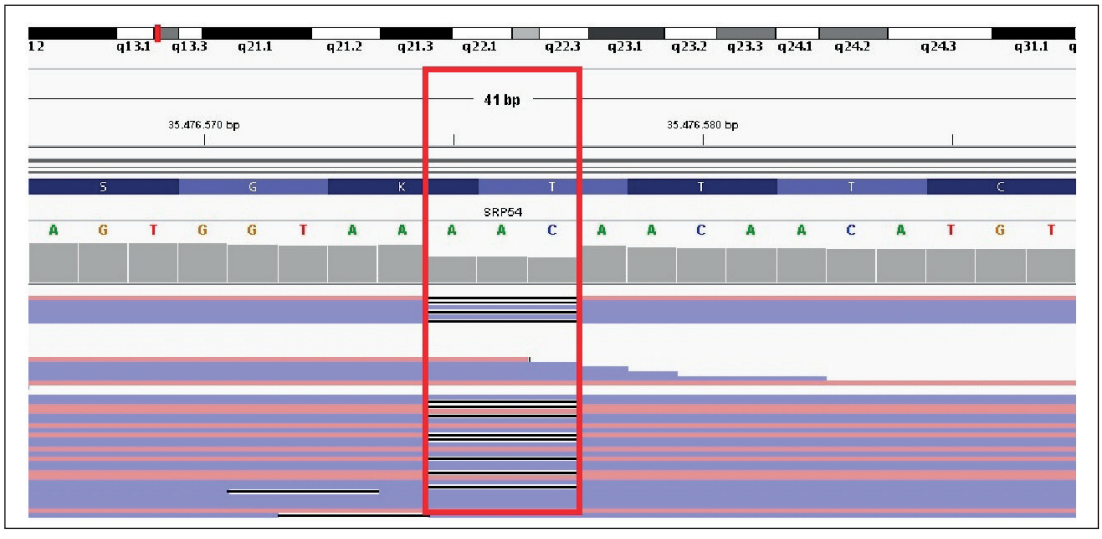

Figure 1. IGV (Integrative Genomics Viewer) image of the patient showed a c.349_351del (p.Thr117del) heterozygous variant in the SRP54 gene.

plantation was planned for the patient. However, given that the patient's maternal and paternal tissue groups are not compatible, the search for a suitable donor continues.

DISCUSSION

The signal recognition particle (SRP) recognizes the signal sequence of the newly formed polypeptide on the ribosome, blocks translation, and initiates translocation. The SRP is composed of 7SL ribonucleoprotein (RNA) and six proteins (SRP9, SRP14, SRP19, SRP54, SRP68, and SRP72) (6). The SRP54, a guanosine triphosphatase (GTPase) protein, is a key component of the RNA complex. It controls cotranslational targeting and translocation of secretory and membrane proteins to the endoplasmic reticulum, and also plays a role in granulocytic differentiation of myeloid progenitor cells (7,8).

SCN is a rare genetic disorder characterized by a low neutrophil count and classified as a primary immunodeficiency disease (9). While some CN forms are limited to hematologic disorders, other forms can be syndromic and accompanied by extrahematologic organ dysfunction (2). In 2017, Carapito et al. identified the SRP54 gene mutation in three unrelated SDS patients who tested negative for the Shwachman-Bodian-Diamond Syndrome (SBDS) gene mutation. All of these patients had CN and different clinical phenotypes of SDS (3). In 2018, Bellanné-Chantelot et al. detected the SRP54 gene mutation in a total of 23 CN patients, of which 16 were sporadic and 7 were familial (2). There are currently 28 cases of SRP54 gene mutations reported in the literature. The absolute neutrophil count was below 200/mm^3 in all but two of these cases (2,3,10). In comparison, the neutrophil count of the patient presented herein was below 500/mm^3, consistent with most cases reported in the literature.

In Carapito's case series, one of the patients had mild neurodevelopmental delay, while the other two had autism (3). Eight patients in Bellanné-Chantelot et al.'s cohort had neurological problems such as neurodevelopmental delay, language delay, learning disability, and autism spectrum disorder (2). Neurodevelopmental problems occurred in both cases of Goldberg et al. (10). In contrast, the neurological and cognitive development of the patient presented in this case report was consistent with her age.

In the case series by Carapito et al., two of the three patients had pancreatic insufficiency requiring enzyme therapy (3). Similarly, the three patients in the cohort of Bellanné-Chantelot et al. had pancreatic insufficiency (2). Along these lines, one of the two patients in Goldberg et al. cohort had pancreatic insufficiency (10). In comparison, the patient presented herein did not have steatorrhea, the pancreatic enzyme levels were normal, the USG did not reveal anything abnormal in the pancreatic anatomy, and she did not have lipomatosis. In light of these findings, pancreatic insufficiency was ruled out.

In the case series by Carapito et al., only one of the three patients responded to granulocyte-colony stimulating factor (G-CSF) treatment and only mildly (3). Similarly, nearly none of the patients in the cohort of Bellanné-Chantelot et al. responded to G-CSF treatment (2). In view of these literature data, G-CSF treatment was not administered to the patient subject to this case report.

Of the 28 case reports published to date featuring SRP54 gene mutations, four had bone dysplasia, six had short stature, two had bone mineralization disorder, and one had osteopetrosis (2,3,10). In addition, one patient had a low ear line and ear asymmetry, a frontal angioma, microretrognathism, a high palate, and premature adrenarche (3). In comparison, height, weight, and head circumference percentiles of the patient featured in this case report were normal, and bone radiographs did not indicate any metaphyseal dysplasia. In addition, unlike the other cases reported in the literature, she also did not have any dysmorphic features such as high palate, microretrognathia, or thin and weak hair.

Twelve patients in the Bellanné-Chantelot et al.'s cohort had the same mutation (c.349_351del, p.Thr117del) as the patient presented herein. One of these patients had autism, another had osteopetrosis and type 2 diabetes mellitus, and one other had short stature with growth hormone deficiency (2). In comparison, the patient presented herein had none of these features even though she had the same gene mutation.

In conclusion, this case report demonstrated that not every patient with an SRP54 gene mutation may have SDS-like features. Therefore, a mutation of the SRP54 gene should be considered in all SCN patients, regardless of whether there is dysmorphism, and the corresponding genetic analysis should include the SRP54 mutation.

Authorship Contributions

Concept: **Mehmet Halil Çeliksoy, Çiğdem Aydoğmuş, Alper Gezdirici, Işılay Turan,** Design: **Mehmet Halil Çeliksoy, Çiğdem**

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