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First Report of an *SH2D1A* Mutation Associated with X-Linked Lymphoproliferative Disease in Turkey

Türkiye'den Bildirilen İlk X'e Bağlı Lenfoproliferatif Hastalık İlişkili *SH2D1A* Mutasyonu Olgusu

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To the Editor,

X-linked lymphoproliferative disease (XLP) is a rare disorder characterized by an extreme vulnerability to Epstein-Barr virus (EBV) infection, frequently resulting in hemophagocytic lymphohistiocytosis (HLH) [1]. XLP-1, its more common subtype, is caused by defects in the *SH2D1A* gene that encodes the signaling lymphocyte activation molecule-associated protein (SAP), which regulates the activation of T lymphocytes [2], whereas XLP-2 is caused by mutations in the *XIAP* gene, also known as *BIRC4* [3].

We present here an XLP-1 patient with a family history of the death of multiple male children, who presented with EBV-triggered fatal HLH. To our knowledge, this is the first report of an *SH2D1A* mutation from Turkey.

Case: The 19-month-old male patient, admitted with the complaints of fever and abdominal distention, had pale appearance, fever (body temperature: 39.5 °C), dyspnea, tachycardia, abdominal distention, and hepatosplenomegaly. Laboratory findings are summarized in Table 1.

In the family history, the death of a 2-year-old male sibling with the clinical diagnosis of HLH and of five young male children of unknown etiology among maternal relatives was noted (Figure 1).

The patient received intravenous immunoglobulin. However, in the follow-up, fever recurred and his general condition worsened. Bone marrow aspiration revealed hemophagocytosis. Therefore, the patient fulfilled the HLH diagnostic criteria. Plasma exchange was performed. Blood products, antimicrobials, and supportive therapeutic agents were used as indicated.

The results of EBV serologic testing and polymerase chain reaction were both reported as positive. On the 6th hospitalization day, the HLH-2004 protocol treatment was initiated, and rituximab therapy was planned. Continuous veno-venous hemodialysis was performed. However, the vital signs of the patient deteriorated further and active gastrointestinal bleeding was observed. The patient died on the 10th day of hospitalization.

In the cytotoxic lymphocyte activity analysis, low SAP expression in addition to signs of severe immunoactivation was detected (Figure 1). In the genetic analysis performed in the Clinical Genetics Unit of Karolinska University Hospital, Stockholm, Sweden, the c.163C>T (p.Arg55Ter) mutation in the *SH2D1A* gene, described previously as pathologic [4], was identified (Figure 1). Genetic counseling was provided to the family. This letter was written after receiving informed consent from the parents.

We report here an XLP-1 case in which the patient presented with EBV-associated HLH. Although no genetic analysis was performed among the male relatives of the patient lost previously in childhood, XLP-1 seems to be the underlying cause in those children as well.

In XLP cases, the most common clinical manifestation is fulminant infectious mononucleosis (frequency: 58%, survival: 4%). Death is generally attributable to liver failure with hepatic

Table 1. Laboratory findings of the patient.	
Hemoglobin (g/L)	76 (NR: 98-134)
White blood cells (10^3 /µL)	23.04 (NR: 5-14.8)
Platelets (10^3/µL)	169 (NR: 150-400)
Direct Coombs	Negative
Ferritin (ng/mL)	841* (NR: 12-150)
Lactate dehydrogenase (IU/L)	757 (NR: 140-304)
Albumin (g/dL)	2.6 (NR: 3.1-4.8)
Serum sodium (mEq/L)	128 (NR: 135-143)
Aspartate aminotransferase (IU/L)	354 (NR: <48)
Alanine aminotransferase (IU/L)	178 (NR: 0-39)
Bilirubin (total/direct) (mg/dL)	2.0/1.1 (NR: 0-2.0/0-0.5)
Triglyceride (mg/dL)	320 (NR: 30-100)
Prothrombin time (s)	20.3 (NR: 10.0-14.7)
Activated partial thromboplastin time (s)	38.7 (NR: 22.0-34.0)
Fibrinogen (mg/dL)	130 (NR: 170-350)
D-dimer (ng/mL)	4,658 (NR: 0-550)
Immunoglobulin M (mg/dL)	455 (NR: 72-212)
Immunoglobulin G (mg/dL)	1,620 (NR: 658-1,460)
Immunoglobulin A (mg/dL)	347 (34-89)
C-reactive protein (mg/L)	60 (NR: 0-4)
EBV VCA IgM	Positive
EBV PCR	Positive (526,736 copies/mL)

*Serum ferritin rose to 28,321 ng/mL on the 5th hospitalization day.

NR: Normal range, EBV: Epstein-Barr virus, PCR: polymerase chain reaction, VCA: viral capsid antigen, IgM: immunoglobulin M.

encephalopathy or bone marrow failure with fatal hemorrhages in various organs [5]. The only curative treatment of XLP is hematopoietic stem cell transplantation [6].

In our case, the HLH-2004 protocol, initiated on the 6th hospitalization day, did not prevent the deterioration of the patient's clinical status. Rituximab therapy has been reported to successfully induce remission in some cases of XLP [7,8]. Unfortunately, our patient was lost before we could start rituximab therapy.

Establishment of the genetic diagnosis in male children suspected to have XLP will enable valuable genetic counseling.

Keywords: Lymphoproliferative disease, Hemophagocytosis, Epstein-Barr virus

Anahtar Sözcükler: Lenfoproliferatif hastalık, Hemofagositoz, Epstein-Barr virüsü

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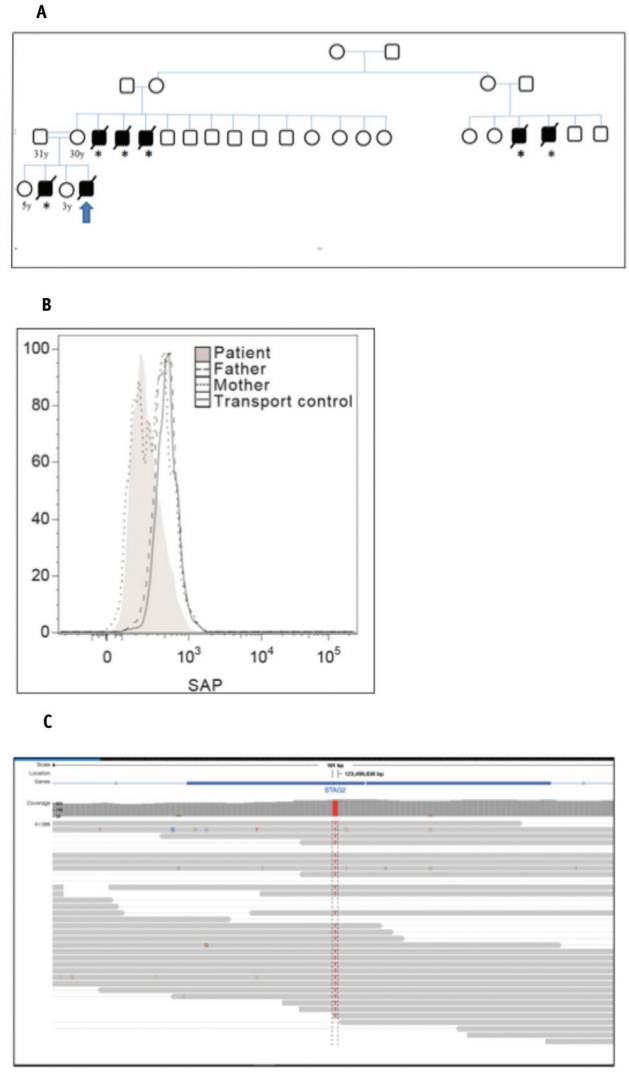

Figure 1. A) Pedigree of the family demonstrating loss of six male children, compatible with X-linked recessive inheritance of disease. *All of the designated deaths occurred between 1 and 3 years of age. The propositus is indicated with an arrow; B) The levels of signaling lymphocyte activation molecule-associated protein (SAP) expression on dim natural killer cells of the patient and the parents by intracellular SAP analysis; C) Identification of the c.163C>T (p.Arg55Ter) mutation in the *SH2D1A* gene by sequencing analysis in the index case.

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Intracranial Bleeding in a Female Hemophilia Patient: Molecular Analysis of the *Factor 8* Gene and Determination of a Novel Mutation

İntrakraniyal Kanama ile Başvuran Hemofili A Olgusu: Yeni Bir Mutasyonun Moleküler Olarak Tanımlanması

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To the Editor,

An 11-month-old female patient was admitted to the emergency department with right occipital fracture and epidural hematoma. The father had severe hemophilia A and the parents were cousins. Laboratory tests revealed normal complete blood count and prolonged activated partial thromboplastin time. Mixing test results were normalized after mixing with normal plasma. After plasma samples were collected for further diagnostic tests, fresh frozen plasma and dexamethasone were administered. The factor VIII level was 0.1%, 35%, and 0.5% for the patient, mother, and father, respectively. The patient's von Willebrand factor (VWF) level was 128 IU/mL, VWF:Ricof was 110 IU/mL, collagen ADP was 110 (reference: 71-118) s, and collagen epinephrine was 98 (reference: 85-165) s. Intron 22 inversion was investigated with the IS-PCR method and was found to be normal. Whole-genome analysis including all exonic regions of the *F8* gene (NM_000132.3) was conducted and the homozygous c.608T>C (L203P) mutation was found. This mutation was not previously reported. As this variant was not reported in any exome databases (ExAC, EVS) and as it was shown to be the cause of the disease in at least three in silico protein modeling programs, the mutation was considered as a novel mutation causing hemophilia A ("probably damaging" with 0.987 PolyPhen2 score, "disease causing" with 0.999 MutationTaster score, and "damaging" with 0 SIFT score). The mutation was also confirmed by Sanger sequencing (Figure 1). Plasma-derived FVIII at 2x500 IU/day was administered for 14 days followed by 300 IU/week prophylaxis. Inhibitor screening at the 5th and 10th exposure days was negative.

Hemophilia A is rarely seen in female patients due to skewed inactivation of the X chromosome leading to inactivation of the wild-type X chromosome, anomalies like Turner syndrome, or translocations, as well as homozygous/compound heterozygous mutations for hemophilia A [1,2,3,4,5]. The karyotype analysis of our patient revealed 46,XX. The patient and the father were hemizygous and mother was heterozygous for the c.608T>C