HAX1 mutation in an infant with severe congenital neutropenia

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Severe congenital neutropenia (SCN) is a rare primary myelopoiesis disorder, characterized by persistent severe neutropenia and early-onset bacterial infections.

Herein, we describe an 11-month-old male who was referred with recurrent cutaneous infections and chronic diarrhea. Serial complete blood counts indicated persistent neutropenia. Bone marrow aspiration of the patient demonstrated maturation arrest of myeloid series at promyelocyte-myelocyte stages. W44X mutation in the *HAX1* gene confirmed the diagnosis of SCN. The patient was successfully treated with granulocyte colony-stimulating factor.

Severe congenital neutropenia should be considered in children with early-onset recurrent infections and neutropenia, since early diagnosis and appropriate treatment can prevent further complications.

Key words: severe congenital neutropenia, HAX1 mutation, granulocyte colony-stimulating factor.

Severe congenital neutropenia (SCN), also named as Kostmann syndrome, was firstly described by Rolf Kostmann in 1956[1]. It is a rare primary myelopoiesis disorder, characterized by persistent severe neutropenia and severe bacterial infections in childhood[2-4]. Maturation arrest in the myeloid differentiation at promyelocyte-myelocyte stages is a typical finding in the bone marrow examination of patients with SCN[2,5].

Severe congenital neutropenia can be inherited in different forms, including autosomal recessive, autosomal dominant, and X-linked, which could show involvement of several distinct genes[2,6,7]. Mutations of the gene encoding neutrophil elastase (*ELA2*) were identified in a number of SCN patients[5,8,9]. Recent studies indicated that mutations in the gene encoding the antiapoptotic HCLS1-associated protein X1 (*HAX1*) are responsible for autosomal recessive form of SCN[10,11]. According to the report from the Severe Chronic Neutropenia European Registry, almost 60% of SCN patients have *ELA2* mutations, while about 10% of them have *HAX1* mutations[12]. Mutations of some other genes, such as growth factor-independent 1 (*GFI1*), Wiskott-Aldrich syndrome gene (*WAS*) and glucose-6-phosphatase catalytic subunit 3 (*G6PC3*), could also lead to SCN[13,15].

In this report, we present a patient with SCN who had mutation in the *HAX1* gene.

Case Report

An 11-month-old boy was referred to our center with complaints of recurrent pyogenic skin infections and diarrhea. He was the first child of a consanguineous family with family history of stillbirth and early death of four maternal uncles in the first month of life due to severe infections (Fig. 1). The patient had a history of pyogenic infections since the first month of his life. He experienced cutaneous infections and superficial abscesses in early

infancy, which were treated with appropriate antibiotics. The patient also had a history of inguinal hernia and chronic diarrhea, leading to four hospital admissions in the first year of his life.

At the time of admission to our hospital, his body temperature was 38°C, pulse rate 140/min, and respiratory rate 30/min. No hepatosplenomegaly or lymphadenopathy was detected. Laboratory studies revealed neutropenia: leukocytes of 7000/µl (88% lymphocytes, 10% neutrophils, 2% monocytes), hemoglobin 10.1 g/dl, and thrombocytes of 437,000/µl. Serial complete blood counts were performed over one month, which indicated persistent neutropenia in this patient (Fig. 2).

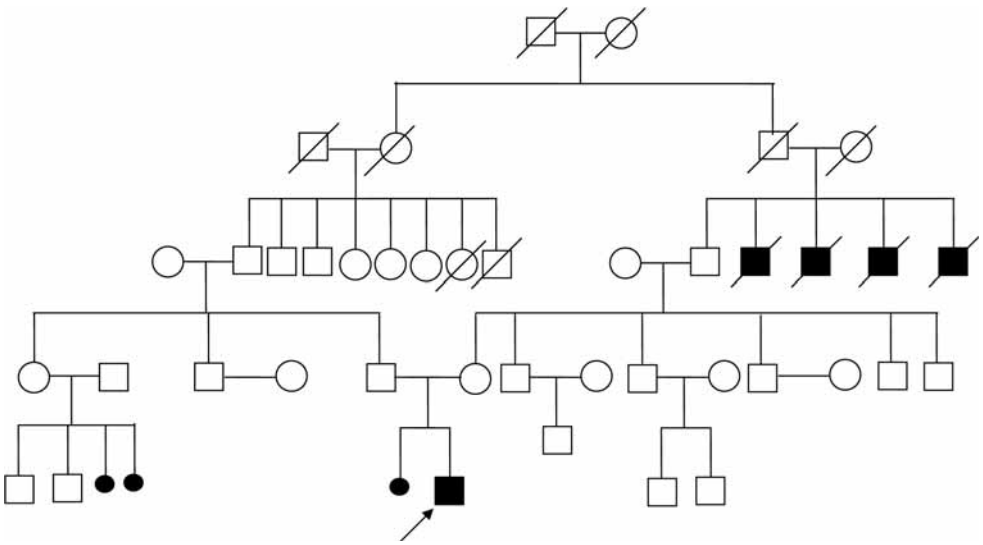

Fig. 1. The pedigree of the patient with severe congenital neutropenia. (Open symbols represent healthy individuals, filled symbols represent affected patients, small filled symbols represent stillbirth, and symbols with slashes represent deceased individuals. Boxes: males, Circles: females).

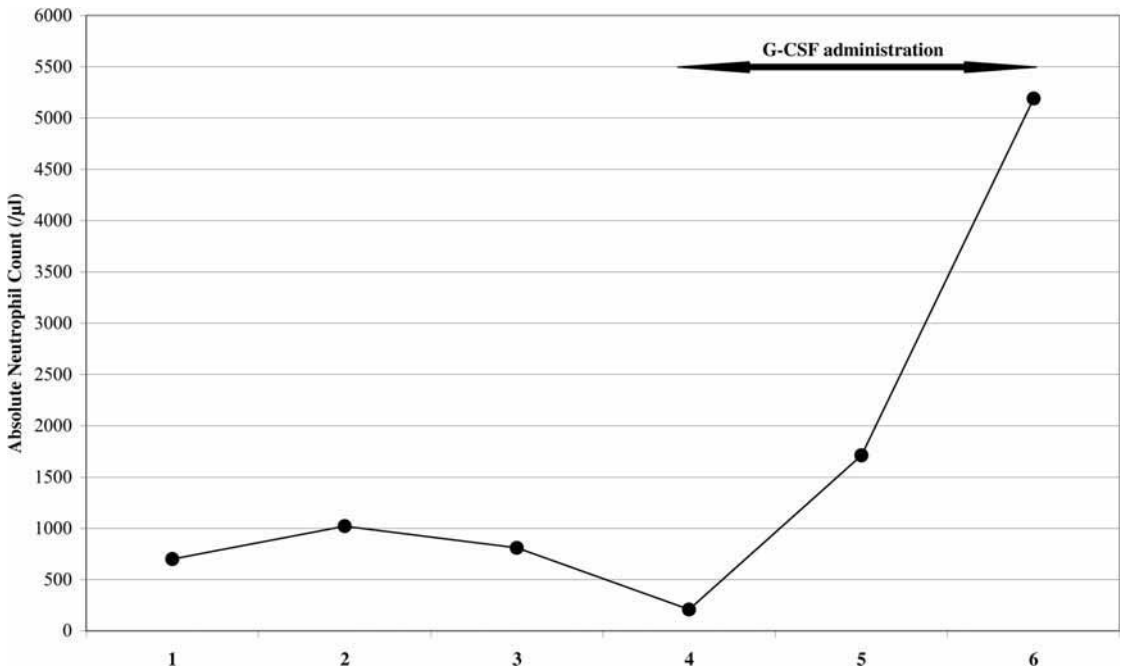

Fig. 2. Absolute neutrophil count (cells/µl) of the patient before and after G-CSF therapy.

The patient had an increased serum level of IgG (1290 mg/dl, normal: 350-1180 mg/dl), but serum levels of IgM and IgA were within normal ranges. The bone marrow aspiration of the patient demonstrated maturation arrest of myeloid series at promyelocyte-myelocyte stages, but megakaryocytic and erythroid series were normal.

Considering the clinical and laboratory findings, the diagnosis of SCN was considered. Molecular study revealed a homozygous single-nucleotide insertion (position 130-131insA) leading to a premature stop codon (W44X) in the *HAX1* gene.

Upon the diagnosis, granulocyte colony-stimulating factor (G-CSF) 5 µg/kg/day was started. Absolute neutrophil count of the patient increased (Fig. 2), and the patient was discharged in good condition. He is currently two years old and is under regular G-CSF therapy.

Discussion

HAX1 deficiency or autosomal recessive form of SCN is a rare primary immunodeficiency disease[2,16], and there have been only a few reports of such patients since discovering the mutated gene in 2007[10]. Since consanguineous marriages are common in our region[17], frequency of autosomal recessive diseases, such as SCN, due to homozygous mutations of *HAX1*, should be more common than previously expected.

The patient had experienced recurrent infections from the first month of his life. Early-onset bacterial infections as well as fungal infections is a characteristic finding in patients with SCN, while almost all patients suffer the first episode of infection during early infancy [3-5,18]. The most common manifestations of disease are superficial abscesses, oropharyngeal ulcers, mucocutaneous lesions, periodontitis, omphalitis, pneumonia, otitis media, and diarrhea[2-4]. Our patient presented with recurrent cutaneous infections, superficial abscesses, and chronic diarrhea. He had also suffered from inguinal hernia, which is a rare finding in SCN, albeit common in the general population[19]. Although it could be considered as a coincidental finding, in view of the different phenotypes with SCN, it should be kept in mind for further studies. On the other hand, although there is insufficient evidence of connective tissue disorder in patients with *HAX1* mutations, it could be hypothesized that a significant HAX1 deficiency can cause sheath weakness and connective tissue and ligament exposure[19]. While it could lead to inguinal hernia, further studies are needed to show the function of the HAX1 molecule in this regard.

Severe congenital neutropenia patients typically have absolute neutrophil count of less than 500/µl[2]. Although the neutrophil count of our patient ranged from 208/µl (severe) to 1020/µl (mild) before G-CSF therapy, his neutropenia was persistent. Mild anemia and increased IgG serum level were also seen in this case. Such findings, in addition to other hematological findings, can often occur in association with neutropenia[2,4].

Severe congenital neutropenia should be considered in any child with early-onset recurrent infections and neutropenia, since early diagnosis and appropriate treatment with G-CSF can prevent further complications.

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