Necrosis of Nasal Cartilage due to Mucormycosis in a Patient With Severe Congenital Neutropenia due to *HAX1* Deficiency

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Abstract

Severe congenital neutropenia (SCN) is a primary immunodeficiency disease characterized by early onset of severe bacterial infection and persistent severe neutropenia. We describe an SCN patient with a history of recurrent infections. The clinical course was complicated by necrosis of the nasal cartilage due to mucormycosis. Molecular studies revealed a homozygous germline *HAX1* mutation.
Fungal infections may lead to serious complications in immunodeficient patients. Recurrent and severe infections should alert physicians to possible immunodeficiency disease. Early diagnosis and appropriate treatment are the most important keys to preventing irreversible organ damage.

Key words: Fungal infection. *HAX1.* Mucormycosis. Severe congenital neutropenia.

Resumen

La neutropenia congénita grave (NCG) es una inmunodeficiencia primaria caracterizada por la aparición precoz de infecciones bacterianas severas y neutropenia severa persistente. Describimos un paciente con NCG con historia de infecciones recurrentes. El curso clínico se complicó con la necrosis del cartílago nasal por mucormicosis. Los estudios moleculares revelaron una mutación homocigota en la línea germinal.
Las infecciones por hongos pueden derivar en serias complicaciones en pacientes con inmunodeficiencias. Las infecciones recurrentes y graves deben alertar a los médicos de posibles inmunodeficiencias. Un diagnóstico precoz y un tratamiento adecuado son las claves más importantes para prevenir los daños orgánicos irreversibles.

Palabras clave: Infección por hongos. HAX1. Mucormicosis. Neutropenia congénita grave.

Introduction

Severe congenital neutropenia (SCN) is a rare primary immunodeficiency disease characterized by the early onset of severe bacterial infection and persistent severe neutropenia [1-5]. SCN comprises a heterogeneous group of disorders. Patients with an autosomal dominant pattern frequently have heterozygous mutations in *ELA2* [6], and many patients with the autosomal-recessive variant have mutations in *HAX1* [6-8].

While superficial or systemic bacterial infections in infancy are the hallmark of SCN, fungal infections may also occur [1]. Zygomycosis is a group of uncommon fatal mycoses caused by fungi of the class Zygomycetes [9] and categorized into Mucorales and Entomophthorales. Mucormycosis is one

of the most serious invasive fungal infections caused by Mucorales [10], and may lead to severe complications and even death in children with underlying risk factors such as neutropenia, malignancy, diabetes mellitus, hematopoietic stem cell transplantation, and prematurity [9,10]. Rhino-orbito-cerebral involvement is one of the most common forms of mucormycosis with high morbidity and mortality [10].

We present the clinical details of a *HAX1*-deficient patient who developed necrosis of the nasal cartilage as a result of mucormycosis. To our knowledge, this is the first time that this complication has been observed in a patient with *HAX1* deficiency.

Case History

The patient was a 12-year-old girl, the daughter of consanguineous parents with no family history of immunodeficiency or recurrent infections (Figure 1a). She had received all the relevant vaccinations with no complications and was well until the age of 1 year, when she developed an upper respiratory tract infection and otitis media. She subsequently experienced recurrent episodes of otitis media and 1 episode of pneumonia that required antibiotic treatment (Figure 1b). However, no laboratory tests were performed at that time and no underlying conditions were diagnosed.

At the age of 3 and a half, her clinical course was complicated by an extensive fungal infection involving the ear, nose, and mastoid process and leading to necrosis of the nasal cartilage (Figure 1c). Cultures from the nasal cavity and mastoid process confirmed mucormycosis and aspergillosis. Therapeutic measures included surgical debridement (mastoidectomy) and intravenous amphotericin B.

A complete blood count revealed severe neutropenia with an absolute neutrophil count of 468/μL (Table). Further blood

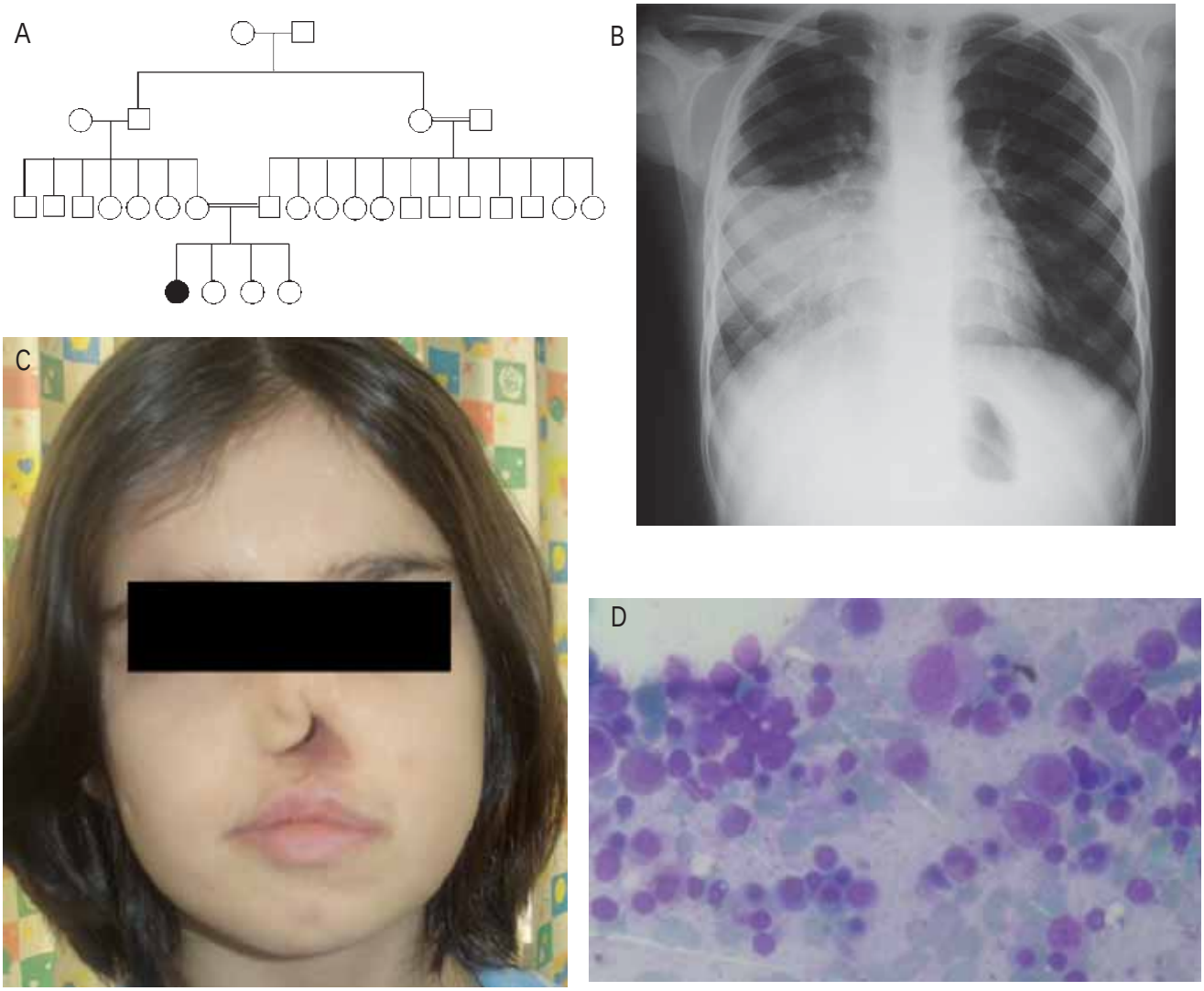

Figure 1. Clinical and bone marrow characteristics. A, The pedigree of the patient. Open symbols indicate healthy individuals; the solid symbol denotes the affected patient (rectangle, male; circle, female). B, Chest radiograph showing pneumonia. C, Necrosis of the nasal cartilage due to mucormycosis (photograph taken at the age of 10 years). D, Maturation arrest in myelopoiesis at the promyelocytic-myelocytic stage in the bone marrow.

Table. Patient Laboratory Data

Test	Age, y	Results					
		White blood cells (cells/μL)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Absolute neutrophil count (cells/μL)
Complete blood count	3.5	2600	18%	76%	4%	2%	468
	11	2000	10%º	89%	1%	–	200
Serum immunoglobulin levels, mg/dL		IgE (patient)	IgG (normal range)	IgM (patient)	IgM (normal range)	IgA (patient)	IgA (normal range)
	11	2380	608-1572	194	52-242	290	33-236
Differential count (number fraction)		CD19 (patient)	CD19 (normal range)	CD3 (patient)	CD3 (normal range)	CD4 (patient)	CD4 (normal) range)
	11	10.5%	8-24%	75.03%	52-78%	31.92%	25-48%
		CD8 (patient)	CD8 (normal range)	CD4/CD8 (patient)	CD4/CD8 (normal range)		
	11	43.35%	9-35%	0.73	0.9-3.4		

testing revealed absolute neutrophil counts of 184, 200, and 96/μL, thus confirming persistent severe neutropenia. Bone marrow examination revealed maturation arrest during myeloid differentiation (at the promyelocyte-myelocyte stage) with the presence of rare forms of mature neutrophils. There was also a preponderance of eosinophils (Figure 1d).

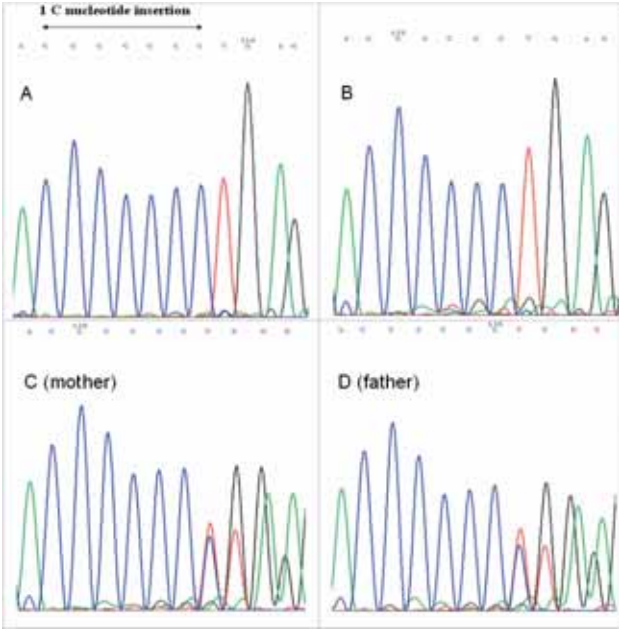

Figure 2. Chromatograms of the patient (A), her sister (B), and her parents (C and D). A single base pair (C) insertion in a repetitive C sequence in exon 2 (at nucleotide 167), which leads to a stop codon after amino acid number 58.

The patient was started on recombinant granulocyte colony-stimulating factor and her neutrophil count improved. Poor adherence to treatment meant that she occasionally experienced cutaneous and oral manifestations such as skin ulcers and gingivitis, but she did not develop any serious infections. At the age of 11 years, her absolute neutrophil count fell again and recurrent upper respiratory tract infection was noted (Table). Immunological studies revealed high serum immunoglobulin levels and slightly increased $CD3^+CD8^+$ T-cell titers (Table). To determine the genetic basis of SCN, *HAX1* was sequenced. A homozygous single base pair (C) insertion in a repetitive C sequence in exon 2 was detected, leading to a premature stop codon (c.174_175insC/ .Glu59X) (Figure 2). This case was listed as patient number 4 in a recent survey of novel *HAX1* mutations [8]. As expected, the parents were heterozygous for this mutation.

Discussion

We report a patient with a history of recurrent upper and lower respiratory tract infection whose clinical course was complicated by mucormycosis, a rare fungal infection usually seen in the presence of underlying risk factors such as immunodeficiency. Subsequent rhino-orbital-cerebral involvement in the form of necrosis of the nasal cartilage as a result of the infection is common [9,10].

Unfortunately, a delay in diagnosis aggravated the clinical condition, thus stressing the need to raise awareness of this condition among health care professionals [11,12].

Most patients with SCN suffer from recurrent and invasive

bacterial infections, although fungal infections are fairly uncommon. This unusual case should alert clinicians to the possibility that fungal infections may be the first symptom of a primary immunodeficiency disorder such as SCN. Granulocyte-colony stimulating factor and antibiotic therapy remain the most important therapeutic strategies for patients with SCN. For invasive fungal infections such as mucormycosis, however, surgical debridement is necessary.

Timely diagnosis and management of the underlying disease and infectious complications is the key to preventing irreversible end-organ damage or even death [2,9].

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