CASE REPORT

Isolated Growth Hormone Deficiency in a Patient with Immunoglobulin Class Switch Recombination Deficiency

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Abstract

Growth hormone deficiency (GHD) may be associated with a number of immunodeficiency diseases, but its association with immunoglobulin class switch recombination (Ig CSR) deficiencies is very rare.
We report the case of a patient with a history of recurrent diarrhea and respiratory infections diagnosed with hyper IgM syndrome on the basis of immunological findings (low serum levels of IgG and IgA and an elevated serum level of IgM). In view of the patient's short stature, growth hormone evaluation was performed and growth hormone deficiency confirmed. The patient received growth hormone therapy in addition to Ig replacement therapy and antibiotics and responded well.
As the coding regions of the genes known to be responsible for Ig CSR (*CD40L, CD40, AICDA*, and *UNG*) were intact in our patient, this might be a new form of Ig CSR deficiency.

Key words: Class switch recombination. Growth hormone deficiency. Hyper-IgM syndrome.

Resumen

La deficiencia de hormona de crecimiento (DHC) puede estar asociada a un número de inmunoeficiencias, pero su asociación con la deficiencia en la recombinación del cambio de clase de inmunoglobulinas (DRCC Ig) es muy rara.
Notificamos el caso de un paciente con historia de diarrea recurrente e infecciones respiratorias diagnosticado de síndrome hiper-IgM en base a los hallazgos inmunológicos (bajos niveles séricos de IgG e IgA y unos elevados niveles de IgM). A la vista de la corta estatura del paciente, se realizó una evaluación de la hormona de crecimiento, y se confirmó una deficiencia de hormona de crecimiento. El paciente recibió terapia con hormona de crecimiento además de terapia de sustitución con inmunoglobulinas y antibióticos y respondió bien a la terapia.
Dado que las regiones codificantes de los genes conocidos responsables de la DRCC Ig (*CD40L, CD40, AICDA*, and *UNG*) estaban intactas en nuestro paciente, esta podría ser una nueva forma de DRCC Ig.

Palabras clave: Recombinación del cambio de clase. Déficit de hormona de crecimiento. Síndrome hiper-IgM.

Introduction

Immunoglobulin class switch recombination (Ig CSR) deficiencies, previously known as hyper-IgM (HIGM) syndromes, comprise a group of primary immunodeficiency diseases characterized by decreased serum levels of IgG and IgA and normal or elevated levels of IgM [1-3]. Mutations of the CD40 ligand (CD40L) lead to the X-linked form of disease, which is the most common form of Ig CSR deficiency, whereas mutations in CD40, activation-induced cytidine deaminase (*AICDA*), and uracil glycosylase (*UNG*) cause autosomal recessive forms of the disease [2]. The molecular basis for at least 50% of patients with an Ig CSR deficiency phenotype, however, is still unknown [4,5]. Recurrent infections in the respiratory tract, involving encapsulated bacteria and *Pneumocystis jiroveci* in particular, are the most common clinical manifestations in affected patients. Nevertheless, gastrointestinal problems, hematologic abnormalities, and neurologic manifestations may also occur [6].

Growth hormone deficiency (GHD), which leads to short stature, is associated with a number of immunodeficiency states [7]. Its association with Ig CSR deficiencies, however, is very rare, and to the best of our knowledge has only been reported in 1 patient (Japanese) to date [8]. Growth retardation has also been reported in 2 female patients with an undefined HIGM syndrome but without GHD [9].

Here we report a case of GHD with an Ig CSR deficiency phenotype where all the genes known to be responsible for HIGM syndrome were intact.

Case Report

The patient was a 23-year-old man born in 1985 via a normal vaginal delivery following a full-term pregnancy without perinatal problems. The only sibling of the patient is a healthy boy of normal stature. The mother had a stillbirth delivery in her first pregnancy at the gestational age of 9 months due to an unknown cause. There was no history of immunodeficiency disease or recurrent infections in the family, although malignancies were common (Figure). The patient remained in good health until the age of 2 years, when he developed chronic diarrhea that continued until 6 years of age. During these years, he also experienced repeated respiratory infections that were treated with antibiotics. At 6 years of age, he was admitted to a local hospital with acute abdominal pain and underwent laparotomy due to sigmoid perforation. After discharge, he continued to have recurrent diarrhea, developed sinopulmonary infections and chronic otitis media, and failed to thrive. Consequently, he was referred to the immunology department at Namazi Hospital in Shiraz, Iran with suspected immunodeficiency at the age of 7 years.

The patient was pale at the time of admission and weighed 16.3 kg (below third percentile). He had bilateral ear discharge, recurrent cough, and perforation of both tympanic membranes confirmed by otoscopy. There were also fine basilar rales. Mild splenomegaly was detected in abdominal sonography. Chest radiography did not show any abnormal findings, but radiographic studies revealed chronic mastoiditis. Laboratory analysis showed iron deficiency

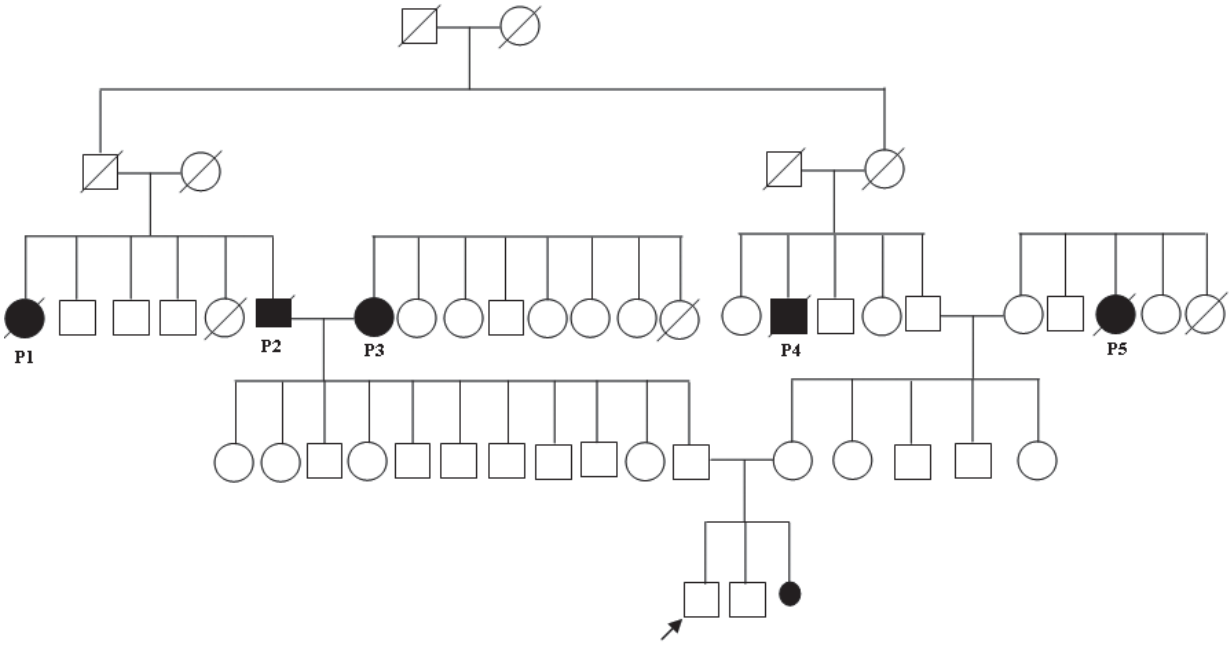

Figure. Family pedigree. Boxes represent males; circles, females; open shapes, healthy individuals; filled shapes, patients with malignancies; shapes with slashes, deceased individuals; small filled circles, abortion. P1, P3, and P5, gastrointestinal cancer; P2, lung cancer; P4, cancer of the bladder. P indicates patient.

anemia (hemoglobulin, 9.8 g/dL; serum iron, 32 µg/dL, total iron binding capacity, 219 µg/dL, all results below normal range for age) and normal counts for white blood cells (WBC) (WBC, 8100/mm^3; neutrophils, 68%; lymphocytes, 28%) and red blood cells (4.81×106/mm^3). Bone marrow aspiration demonstrated normocellular marrow with decreased iron storage and incorporation. Serum total protein, albumin, and globulin were decreased (3.9 g/dL, 2.3 g/dL, and 1.6 g/dL, respectively), but liver enzymes were within the normal range. Immunological studies revealed low serum IgG and IgA levels but elevated serum IgM levels in repeated measurements (Table). On the basis of the above results, a diagnosis of HIGM syndrome was made and immunoglobulin replacement therapy and antibiotics were started.

Table. Laboratory Test Results

Serum Immunoglobulins (Ig)						
IgG: 300 mg/dL (normal range, 660-1520)						
IgA: 15 mg/dL (normal range, 39-143)						
IgM: 700 mg/dL (normal range, 69-201)						
Hormone Tests						
Triiodothyronine: 184 ng/dL (normal range, 94-241)						
Thyroxine: 13.7 µg/dL (normal range, 6.4-13.3)						
Tyroid stimulating hormone: 3.6 mIU/mL (normal range, 0.6-6.3)						
Cortisol: 23.8 µg/dL (normal range, 5-25)						
Growth Hormone Stimulation Tests[a]						
Time, min	0	20	40	60	90	120
Growth hormone, ng/mL	5.5	<1	<1	<1	1.06	6.7

[a] Stimulated with a combination of L-dopa and propranolol.

Although the patient improved clinically with treatment, his growth retardation continued. At the age of 13 years, growth hormone evaluation confirmed growth hormone deficiency. Growth hormone levels measured using a combination of L-dopa and propranolol were low. Other hormone tests yielded results within normal ranges (Table). The patient was given growth hormone therapy and responded well. He also had 1 episode of severe fungal lung infection that was well controlled by regular intravenous Ig and antifungal therapy.

Further immunological work-up showed normal numbers for CD3$^+$ T cells, CD4$^+$, and CD8$^+$ T cells (measured by flow cytometry), and CD19$^+$ B cells (7.5% of total lymphocytes). The lymphocyte transformation test was normal. Genetic studies showed that the coding regions of *CD40L, CD40, AICDA,* and *UNG* were all normal.

Discussion

Although drastic growth retardation has been reported in HIGM deficiencies, the association with HIGM is very rare, having been first described by Ohzeki et al [8] in 1993. Here, we describe the association in a second patient in whom all 4 known genes responsible for Ig CSR deficiencies were intact.

Although an autosomal dominant pattern was suggested in the first case by the presence of immunodeficiency in the paternal pedigree of the patient [8], we cannot confirm such a transmission in our patient. Nonetheless, the presence of malignancies in the family suggests that further linkage analysis would be worthwhile as these might be the result of genome instability in Ig CSR deficiency. DNA cleavage or DNA repair defects can lead to impaired CSR and somatic hypermutation [10], which, in turn, can lead to different Ig CSR deficiency phenotypes depending on whether the defect is located upstream or downstream of the DNA breaks [11]. There are a number of candidate genes that might be affected, including ataxia-telangiectasia mutated (*ATM*), the *MRE11/Rad50/NBS1* complex, phosphorylated histone H2AFX, the repair protein p53 binding protein 1 (53BP1) and nonhomologous end-joining (NHEJ) DNA repair enzymes [12,13].

The fact that the coding regions of the genes known to be responsible for HIGM syndrome (*CD40L, CD40, AID* and *UNG*) were intact in our patient suggests that this might be a new form of Ig CSR deficiency.

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