

Asthma and Allergic Rhinitis in a Patient with BTK Deficiency

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■ Abstract

BTK deficiency is a primary immunodeficiency disease characterized by the absence of circulating B cells and agammaglobulinemia. While recurrent bacterial infections are the most common manifestations, symptoms of allergy and asthma are rare.

We present the case of a 7-year-old boy who presented with asthma symptoms, allergic rhinitis, and severe papular urticaria. He had a positive skin prick test to aeroallergens and food allergens. However, further laboratory tests revealed a low number of B cells and decreased serum levels of all immunoglobulin isotypes. Molecular analysis revealed a mutation in the *BTK* gene.

Although patients with BTK deficiency seem to be protected from atopy, our patient had allergic symptoms suggesting a bias toward a type 2 helper T cell pattern in this case. Primary antibody deficiency should be considered in the differential diagnosis of pediatric allergy and asthma when respiratory infection persists despite appropriate treatment.

Key words: Allergy. Asthma. BTK. X-linked agammaglobulinemia.

■ Resumen

La insuficiencia de Btk es una enfermedad de inmunodeficiencia primaria caracterizada por la ausencia de linfocitos B circulantes y agammaglobulinemia. Las infecciones bacterianas recurrentes son las manifestaciones más comunes, mientras que los síntomas de alergia y asma son poco frecuentes.

Presentamos el caso de un niño de 7 años que debutó con síntomas de asma, rinitis alérgica y urticaria papular grave. Las pruebas cutáneas con los aeroalérgenos y los alérgenos de los alimentos fueron positivas. No obstante, las pruebas de laboratorio adicionales mostraron un número reducido de linfocitos B y unas concentraciones séricas de todos los isotipos de inmunoglobulina bajas. El análisis molecular reveló que existía una mutación en el gen Btk.

Aunque los pacientes con insuficiencia de Btk parecen estar protegidos de la atopia, nuestro paciente presentaba síntomas alérgicos que sugerían que existía una tendencia hacia un patrón de linfocitos T cooperadores de tipo 2. La insuficiencia de anticuerpos primaria debe considerarse en el diagnóstico diferencial de la alergia y el asma pediátricas, cuando la infección respiratoria persiste a pesar de los tratamientos específicos.

Palabras clave: Alergia. Asma. Btk. Agammaglobulinemia ligada a X.

Introduction

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency disease characterized by the absence of circulating B lymphocytes, severe reduction in all serum immunoglobulin (Ig) levels, and early onset of recurrent pyogenic infection [1-3]. Described more than 50 years ago, XLA was one of the first primary immunodeficiency diseases [4]. In 1993, defects in the Bruton tyrosine kinase (BTK) gene were discovered as the underlying genetic defect of

XLA [5,6]. Since then, several mutations in the *BTK* gene have been identified and the term BTK deficiency has been included in the latest classification of primary immunodeficiency diseases [7].

Recurrent bacterial infections are the most common manifestations of BTK deficiency. They start in early infancy and are associated with hypoplasia or atrophy of lymphoid tissues and the tonsils [1-3,8]. Although respiratory and gastrointestinal tract infections—especially recurrent pneumonia, sinusitis, otitis media, and gastroenteritis—are the

most common infections, other sites may be involved [1,2,8]. Manifestations such as arthritis and neutropenia are also frequent in these patients; however, allergic symptoms are rare and asthma has not been reported.

We describe a patient who presented with asthma symptoms, but for whom laboratory tests and mutation analysis revealed *BTK* deficiency.

Case Description

The patient was a 7-year-old boy with an immediate family history of allergy, recurrent infections, and infection-related death (Figure 1). He was well until the age of 1 year, when he experienced recurrent common colds and upper respiratory tract infections. He developed a chronic cough and continued to suffer from recurrent upper respiratory tract infections until he was 3 and a half years old, when he was referred to a children's hospital, where he was diagnosed with asthma. At that time, he had difficulty breathing, chest tightness, wheezing, and the chronic cough became worse at night. A chest X-ray revealed air trapping and interstitial pneumonia and a sinus X-ray indicated maxillary sinusitis. His complete blood count, erythrocyte sedimentation rate, and C-reactive protein level were normal. Antibiotics were administered, and testing for cystic fibrosis and infection by *Mycobacterium tuberculosis* was negative. The patient was discharged in good health. Despite the diagnosis of moderate asthma and appropriate asthma treatment, he presented 1 month later with acute abdominal pain and severe infectious diarrhea.

Because of the recurrent infections, an immunodeficiency disease was suspected. Immunological studies revealed decreased serum levels of all Ig isotypes: IgG, 150 mg/dL (normal range: 345-1236); IgA, 14 mg/dL (normal range: 15-159); IgM, 35 mg/dL (normal range: 43-207); and IgE 0.1 IU/mL (normal range: 0-230). Flow cytometry revealed a low number of B lymphocytes (CD19⁺ B cells, < 1%; CD20⁺ B cells, < 1%; CD3⁺ T cells, 90%; CD3⁺CD4⁺ T cells, 28%; and CD3⁺ CD8⁺ T cells, 55%). Although the patient's blood group was O-positive, the isohemagglutinin test was negative for anti-A and anti-B antibodies. As the palatine tonsils could not be observed by direct examination of the pharynx, a lateral view neck X-ray was requested and revealed atrophic adenoids. Therefore, XLA was diagnosed and intravenous immunoglobulin (IVIG) therapy was started at the age of 4 years. While taking IVIG therapy, the patient did not experience infection, although he continued to suffer from chronic cough, wheezing, allergic rhinitis, and episodes of severe papular urticaria.

To confirm the diagnosis of XLA, *BTK* expression was examined by intracellular staining of Btk in monocytes. Very low *BTK* expression (0.70%) was observed in the patient (Figure 2a), whereas a mosaic pattern of *BTK* expression (30.4%) was found in his mother (Figure 2b). In addition, Western blotting showed that the *BTK* protein was truncated (Figure 3). Deletion of 1351-1353 GAG (Del E 407) in the TK domain of *BTK* was detected by direct sequencing of genomic DNA [2].

As for his allergic symptoms, a skin prick test was performed at the age of 6 years; this proved to be positive for

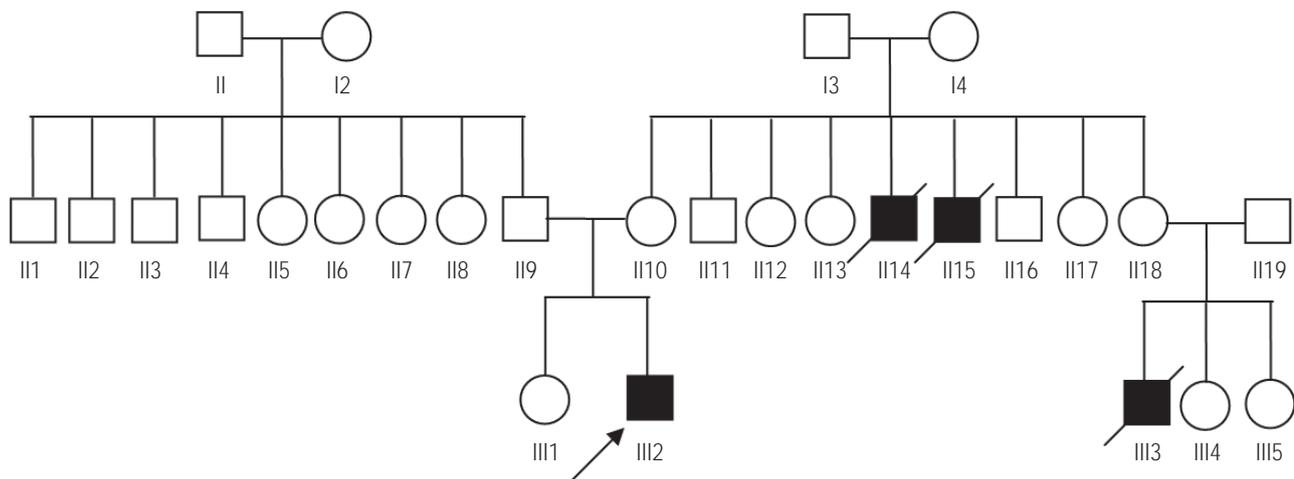


Figure 1. The pedigrees of the patient with XLA (III2). Open shapes represent healthy individuals, solid shapes represent affected patients, and shapes with slashes represent deceased individuals. Boxes represent men and circles women.

II10 (patient's mother): Perineal allergic rhinitis, contact dermatitis, urticaria

II11 (patient's uncle): Seasonal allergic rhinitis

II12 (patient's aunt): Seasonal allergic rhinitis, contact dermatitis

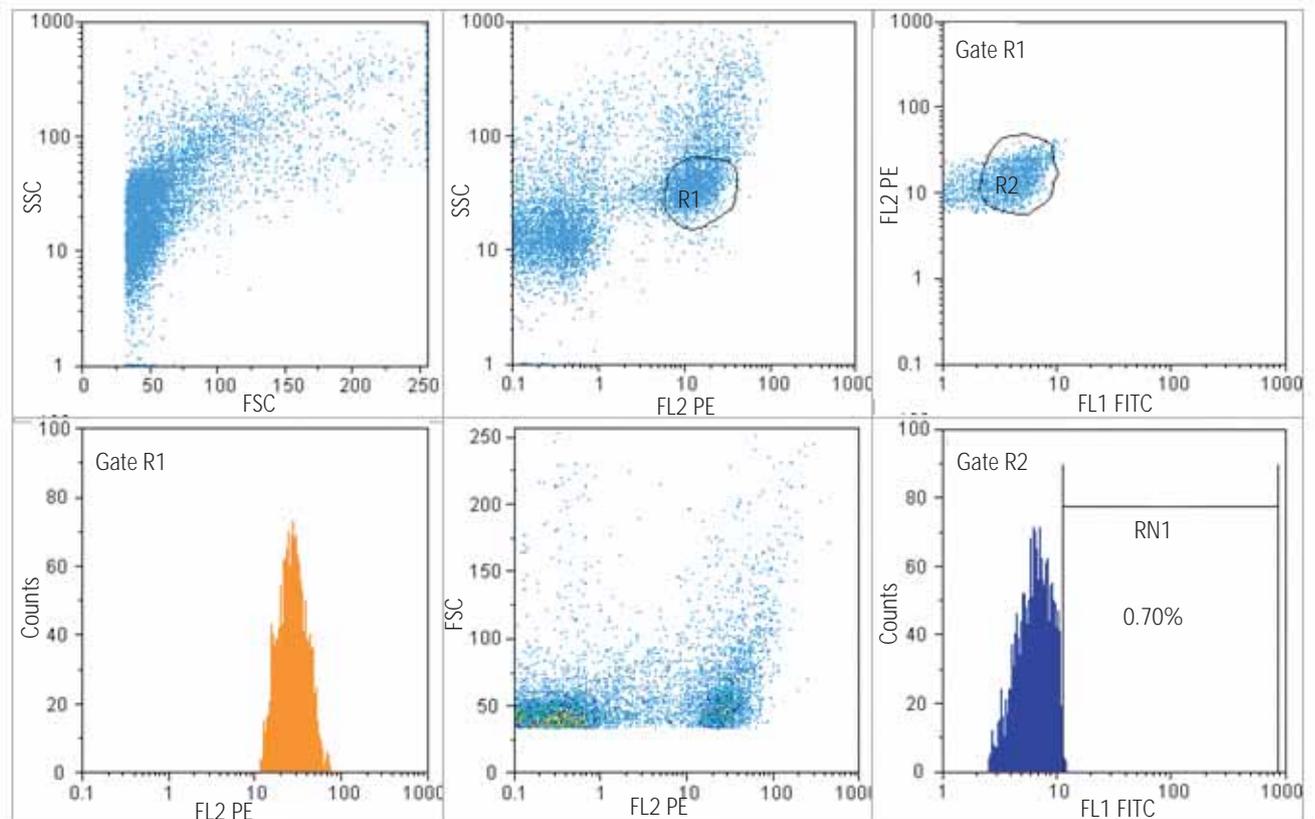
II14 (patient's uncle): Died at the age of 4, history of recurrent infections

II15 (patient's uncle): Died at the age of 6, history of recurrent infections

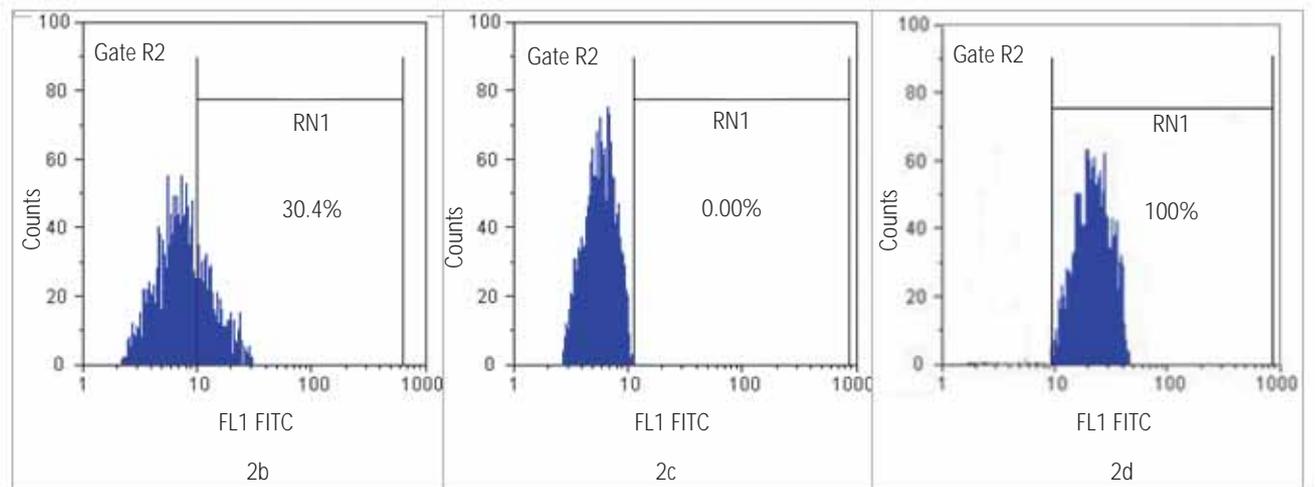
III1 (patient's sister): Seasonal allergic rhinitis, contact dermatitis

III3: (patient's cousin): Died at the age of 4, history of recurrent infections

III4: (patient's cousin): Hyperreactive airway disease



2a



2b

2c

2d

Figure 2. Flow cytometric analysis of cellular *BTK* expression in the patient and his mother. Expression of *BTK* in monocytes was evaluated by gating on the CD14⁺ population (FL1 FITC, *BTK*; FL2 PE, CD14⁺; R1, monocytes; R2, monocytes expressing *BTK*).



Figure 3. Western blotting in the patient with XLA.

trees, cat, almond, and mosquito. Pulmonary function tests revealed exercise-induced bronchospasm.

Bronchodilators and corticosteroids were prescribed in addition to monthly IVIG. His cough has improved dramatically and he has not had an infection for 1 year.

Discussion

BTK is an important cytoplasmic enzyme for B-cell differentiation. Its defect in XLA does not allow differentiation of B cells from plasma cells and, consequently, serum levels of all immunoglobulin isotypes fall [1,5, 6]. Although low numbers of B cells are a frequent finding in BTK-deficient patients, the number of circulating T cells and their subsets is usually normal, as *BTK* is not expressed in mature T cells [9].

We describe an unusual case of BTK deficiency in which the patient presented with symptoms of allergy and asthma. Although we did not suspect an association between immunodeficiency and allergy, the co-occurrence of such conditions is very rare [8].

The fact that the serum IgE level and other Ig levels of our patient were low did not allow us to rule out allergy. The cytokines secreted by T lymphocytes in response to allergens can play a crucial role in the induction and maintenance of airway allergic inflammation and airway hyperresponsiveness, which may occur in the absence of B lymphocytes and IgE [10]. There are reports of a bias toward helper T type 1 responses in patients with XLA [9]. Consequently, increased prevalence of T_H1 -dominated diseases (such as autoimmune disorders) and a decreased prevalence of T_H2 -dominated diseases (such as allergic disorders) in XLA could be explained [9]. Even though XLA patients seem to be protected from atopy, our patient

had atopic manifestations, thus suggesting a bias toward a type 2 helper T cell pattern. Nevertheless, further studies on the T cells of this type of patient are necessary to establish the pathophysiology of conditions such as that experienced by our patient.

Primary antibody deficiency should be considered in the differential diagnosis of pediatric allergy and asthma, especially when the patient is susceptible to recurrent infection. If fact, if symptoms and respiratory infection persist in a child diagnosed with asthma despite appropriate treatment, further immunological studies are necessary to rule out other causes. A delay in diagnosis can lead to chronic infection, irretrievable organ damage, or even death.

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