

A male infant with recurrent opportunistic infections and fulminant BCG-osis

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Trabajo recibido: 17-VI-2008; aceptado: 25-VI-2008
Conflicto de intereses: Ninguno

ABSTRACT

In this section, devoted to the discussion of case histories with an immunological interest, we now review the case of a 2-month-old male infant with recurrent opportunistic respiratory infections and fulminant BCG-osis. Although the diagnosis could not be pursued to the molecular level, his history of recurrent infections at a very young age, with a catastrophic evolution and profound CD8+ lymphopenia led us to think of ZAP-70 deficiency.

Key words: CD8 lymphopenia, primary immunodeficiency, case history, ZAP-70, severe combined immunodeficiency disease.

Palabras clave: Linfopenia de CD8, caso clínico, inmunodeficiencia primaria, inmunodeficiencia combinada grave, ZAP-70.

THE PATIENT

A two-month-old eutrophic male infant was referred to the Ismael Cosío Villegas National Institute of Respiratory Diseases with a complicated lower respiratory infection and a previous history of recurrent pneumonia. He came from an urban very-low-income area with crowded conditions, where he lived with young, unrelated parents who smoked, and a 2-year-old sister, all in apparent good health.

His gestation was complicated by maternal recurrent genitourinary infections. Full-term spontaneous vaginal delivery was prolonged and re-

RESUMEN

En esta sección, dedicada a la discusión de historias clínicas con un interés inmunológico, presentamos el caso de un lactante varón de dos meses de edad con infecciones respiratorias oportunistas recurrentes, y un cuadro de BCG-osis fulminante que lo llevó a la muerte por sepsis y falla sistémica múltiple en el 29° día de hospitalización en el INER. Aunque el diagnóstico no se pudo perseguir hasta el nivel molecular, la historia con infecciones recurrentes a una edad muy temprana, con una evolución catastrófica y linfopenia CD8+ severa, nos llevó a pensar en deficiencia de ZAP-70.

quired the use of forceps. An Apgar score of 7/8 was given, and he was administered oral live-polio (OPV) and bacillus Calmette-Guérin (BCG) vaccines before discharge. He was breastfed for 1 month. Oral H2 agonists and a prokinetic were started early because of feeding difficulties (choking and regurgitation).

At 18 days after birth the patient was hospitalized for respiratory distress and a high-grade fever, with a diagnosis of pneumonia and sepsis, for (ampicillin and amikacin) which he was given two endovenous antibiotics and discharged after 12 days, but nineteen days later he was hospitalized again with respiratory distress, leucocytosis

and a pulmonary micronodular diffuse infiltrate. He was transferred to our institution, where he was started on IV antibiotics but deteriorated quickly due to severe septicemia, requiring mechanical ventilation at the Intensive Care Unit, where he nevertheless died of severe sepsis and multiple organ failure, on his 29th day of hospital stay.

The diagnostic workup

Blood cultures grew *Burkholderia cepacia* and *Staphylococcus aureus*. A lung biopsy showed incompletely formed granulomas with acid-fast bacilli. Lymphocyte subpopulation counts were: 1,335 CD3+, 1,245 CD4+, and only 86 CD8+ (3%). Serum immunoglobulins: IgG 1,287, IgA 112, IgE 12, IgM 113. CD19, CD20, CD56 and CD16 were all within normal range.

Severe combined immunodeficiency (CD4+, CD8-, NK+, B+) was diagnosed. The almost complete absence of CD8 T cells and catastrophic

evolution strongly suggest ZAP-70 deficiency as the molecular substrate. This diagnosis, however, could not be confirmed. The patient underwent an autopsy that confirmed miliary tuberculosis caused by *Mycobacterium bovis* from the BCG vaccination. To definitely prove ZAP-70 deficiency, mutation genetic analysis is necessary but it could not be done.

In endemic regions the BCG vaccine is administered at birth in an effort to protect against neonatal tuberculous meningitis; however, the nature of the vaccine (live bacilli) facilitates overwhelming systemic infections by otherwise innocuous organisms in infants with cellular primary immunodeficiencies, like our patient.

The disease

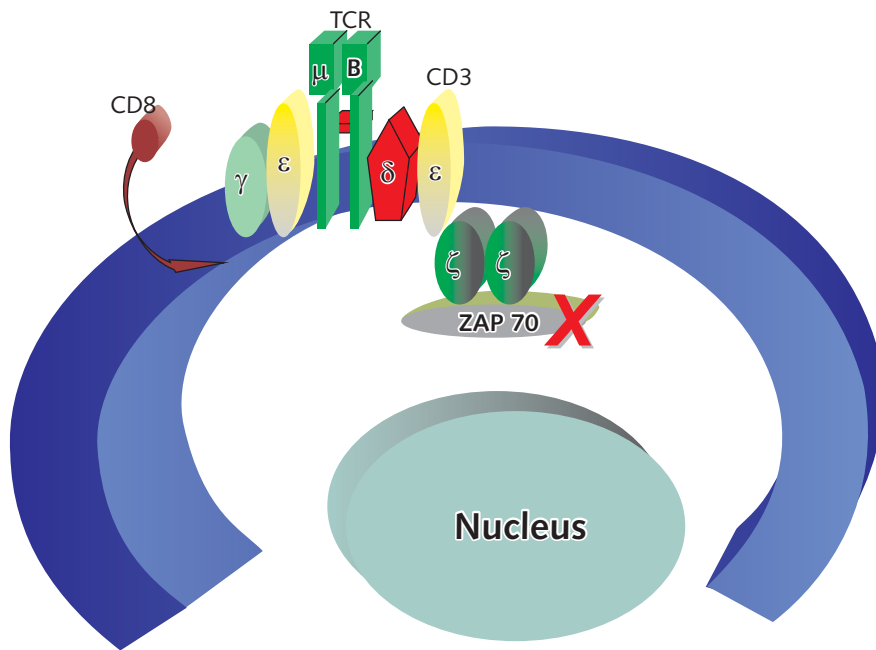
Severe combined immunodeficiency disease (SCID) is a syndrome of diverse genetic origin characterized by profound deficiencies of T- and

Table I. Types of molecular defects associated with SCID.

Disease or syndrome	Mutant genes	Clinical characteristics
<i>Deficiencies of cytokine receptor chains</i>		
X-linked SCID T-cell (-), B-cell (+), NK cell (+)	Common cytokine-receptor γ -chain gene on Xq13.1	Occurs in the first few months of life. Affected infants have diarrhea and show failure to thrive. Infections with opportunistic organisms. Usually, infants with SCID are lymphopenic. Thymuses are quite small.
Autosomal recessive SCID T-cell (-), B-cell (+), NK cell (+)	Interleukin-7 receptor α -chain gene on 5p13	
<i>Deficiencies of signaling molecules</i>		
Autosomal recessive SCID		Patients may have palpable lymph nodes. Normal size thymus. Clinical heterogeneity: Patients with ZAP-70 deficiency present with mild infections or infections as severe as those in patients with other types of SCID
T-cell (+), B-cell (+), NK cell (+)	56lckgene	
T-cell (-), B-cell (+), NK cell (-)	Jak3 gene on 19p13.1	
T-cell (+), B-cell (+), NK cell (+)	Gene for CD45 tyrosine phosphatase	
T-cell (-), B-cell (-), NK cell (+)	RAG1 or RAG2 gene on 6q21.3	
CD8 lymphopenia ZAP-70	ZAP-70 gene on 2q12	

Table II. Overview of ZAP-70 deficiency.

- **Category:** Primary immunodeficiency disease due to defects in lymphocytes
- **Incidence:** Very rare. First described in 1992. By the year 2000, only eight patients had been described, the majority of whom were Mennonites
- **Heritability:** Autosomal recessive
- **Defect:** Mutations in a gene at chromosome 2q12 that encodes ZAP-70, a tyrosine kinase important in T-cell signalling
- **Invading pathogens:** Opportunistic organisms such as *C. albicans*, *P. jirovecchi*, varicella, adenovirus, respiratory syncytial virus, parainfluenza, cytomegalovirus, Epstein-Barr virus, and bacillus Calmette-Guérin (BCG)
- **Key features:** Recurrent opportunistic infections before 6 months of age, and low CD8+ lymphocyte count



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Figure 1. T-cell diagram depicting the molecular defect in ZAP-70 deficiency. TCR=T cell receptor

B-cells functions. In some molecular types, there is also a deficiency of NK-cells. SCID occurs at a rate of 1 per 75,000 births.¹ During the first few months of life, affected infants have diarrhea and show failure to thrive. Persistent infections with opportunistic organisms such as *C. albicans*, *P. jirovecchi*, varicella, adenovirus, respiratory syncytial virus, parainfluenza, cytomegalovirus, Epstein-Barr virus, and bacillus Calmette-Guérin (BCG) lead to death. This condition is uniformly fatal in the first two years of life, unless immune reconstitution can be accomplished, especially by means of allogeneic bone marrow transplant.²

Usually, infants with SCID are lymphopenic, and their thymuses are quite small. Flow cytometric studies have shown that there are unique lymphocyte phenotypes for the various genetic forms of the disease. Some have B cells and no NK cells (so called T⁻ B⁺ NK⁻ SCID), others have no B cells but many NK cells (T⁻ B⁻ NK⁺ SCID), and still others have extremely low numbers of all lymphocytes (T⁻ B⁻ NK⁻ SCID) (Table I).^{2,3}

In this report, the patient had normal levels of total lymphocytes, but profound CD8 lymphopenia. This is due to mutations in a gene at chromosome 2q12 that encodes zeta-associated protein

70 (ZAP-70), a tyrosine kinase important in T-cell signalling (Figure 1).

ZAP-70 has an essential role in the positive and negative selection of maturing T cells in the thymus. The defect is presumably due to defects in signaling pathways that are essential for the development of CD8+ cells within the thymus. Circulating CD4+ T cells fail to respond normally to mitogens or to allogeneic cells *in vitro*, or to become cytotoxic cells. By contrast, the activity of natural killer cells, the number of B cells, and serum immunoglobulin levels are normal, as they were in our patient.²

ZAP-70 deficiency is clinically different from most other types of SCID, in that ZAP-70 deficient patients usually have palpable lymph nodes, especially in the axillary and groin areas. The other major clinical distinction of ZAP-70 deficiency is the presence of a normal size thymus.⁴

Patients with this condition may present with moderate infections or infections as severe as those seen in patients with severe combined immunodeficiency; this clinical heterogeneity can hamper the diagnosis of patients with ZAP-70 deficiency. Recently, two cases of ZAP-70 deficiency with an unusual presentation were described; the first patient presented as a healthy looking wheezy infant, whereas the second patient came to clinical attention because of eczematous skin lesions simulating atopic dermatitis with eosinophilia and elevated immunoglobulin E (IgE), similar to the Omenn syndrome.⁵

The curative treatment is allogeneic hematopoietic stem-cell transplantation. Gene therapy in mice with ZAP-70 deficiency has been successfully used by investigators in France. This process applied to the thymus could represent a simplified and effective alternative therapy for T cell immunodeficiencies.⁶

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