Abstract

Objective: to present a case report of a child who developed sepsis by *Salmonella enteritidis* associated with the diagnosis of primary immunodeficiency, and compare two groups of school age girls from different social strata were compared in terms of their perception and knowledge about breastfeeding.

Description: a twenty-one months old boy presenting fever and skin lesions, bilateral pneumonia with pleural effusion and septic shock. *Salmonella enteritidis* was isolated in blood cultures and pleural fluid. The identification of the bacteria suggested the presence of the MIM syndrome. The diagnosis of IL-12R β1 was confirmed after IL-12 and IFN-γ levels were measured using patient cells in a culture medium. The results showed absence of IL-12 and the IFN-γ post stimulation using BCG.

Comments: a severe infection by *Salmonella enteritidis* is strongly suggestive of an immune system dysfunction. Laboratory tests for humoral, cellular and innate immunity were performed. Interleukin 12 receptor β1 (IL-12 Rβ1) deficiency was confirmed after specific laboratory evaluation. The use of INF-γ is recommended in severe cases.


Introduction

Primary Immunodeficiency Diseases (PID) are characterized by genetically determined, qualitative and/or quantitative defects in one or more of the systems responsible for the protection of the organism. The prevalence of PID is 1:10,000 excluding IgA deficiency. More than 95 different types of PID have been described varying according to the part of the immune system affected and with the gravity of clinical status. At one extreme we have severe combined immunodeficiency (SCID), considered a pediatric emergency and at the other we have IgA deficiency, which is asymptomatic in the majority of cases. Primary Immunodeficiency Diseases are classified into four large groups: defects of B-cell (antibody), T-Cell (cellular), phagocyte and complement immunity.

*Mycobacteria* which are *non-tuberculous* are microorganisms with a low level; of virulence commonly present in the environment. Disease caused by these agents is highly suggestive of defective immunity in the host. Recently a new syndrome has been described, designated “Mendelian Susceptibility to Mycobacterial Infection” (MIM 209950) in which patients present increased susceptibility to infections by BCG, *non-tuberculous mycobacteria* and *Salmonella*. 
Infections caused by *non-typhus salmonella* in healthy children are usually confined to the gastrointestinal tract, characterized by acute diarrhea, fever and are generally auto-limiting. However, the clinical course may be affected by factors such as age, base disease and immunosupression which may favor an invasion of the bloodstream with complications. *Salmonella* is a rod-shaped Gram-negative, nonencapsulated, nonsporeforming, facultative anaerobe. The immunoresponse to *Salmonella* and other intracellular organisms depends upon cell-mediated immunity (CMI). The most important CMI effector mechanism is the activation of macrophages infected by cytokines, particularly the interferon (IFN)-γ.8

The objective of this work is to relate the clinical case of a child who developed septicemia due to *Salmonella enteritidis* and having as base disease a primary immunodeficiency.

**Case Description**

A one year, nine month old patient of mixed race with a history of fever and skin lesions over 50 days: generalized cutaneous hyperemia, vesicles and crusts on the hands, feet and the perioral region, having used ampicillin for 14 days with improvements to the skin condition, but persistence of fever. Four days after the treatment was discontinued there was a deterioration of the cutaneous lesions, and he was interned at this unit with an ulcerated perilabial lesion, with purulent secretions, disintegrating, ulcerated lesion of the tongue, oral moniliasis, purulent secretions from the oropharynx. Ulcerous, crusting lesions on the palms of the hands and the dorsal regions of both hands and feet (Figures 1 and 2). Upon physical examination he further presented: pallor ++/4, tachydyspnea, discrete edema of the cervical region with engorgement of the superficial veins of the neck and the presence of collateral circulation in the upper thorax. Liver 1.5 cm from the right costal margin; edema 3+/4 of upper left limb; petechiae on anterior surface of lower right limb; weight = 7835; stature = 77 cm; heart rate = 140bpm; aspiratory pressure = 100 X 70 mmHg; respiratory frequency = 36bpm.

**Personal antecedents**: at three months presented laryngitis and acute otitis media and, at 12 months of age presented vesicles and crusts on the hands and feet, treated with ampicillin.

**Family antecedents**: parents healthy, one healthy brother and one healthy sister. Mother had had one stillborn child.

**Neuro Psychomotor Development**: normal.

**Vaccinations**: up to date - including for BCG.

Interned with HD: malnutrition, pyoderma, cellulitis of upper left limb, deep vein thrombosis of upper left limb, thrombosis of upper vena cava and pneumonia. Evolved pleural effusion on the right and septic shock.

Remained interned for 51 days. During this period the following antibiotics were used Vancomycin, Fortaz (Ceftazidine), amikacin, Chloramphenicol and Ceftriaxone (Cephalosporins).

One week after discharge the patient was re-interned with respiratory insufficiency and bilateral pneumonia remaining in ICU for 10 days. On the 14th day of hospitalization, new skin lesions similar to those at first admission appeared.

**Laboratory tests**

During internment hemoglobin levels varied from 5.3 to 11.1g/dl. The total number leukocytes varied from 9,200 to 12,300/mm³ with com neutrophil predominance. Sixteen blood tests were performed with 14 revealing lymphopenia (3 to 23% reference value for age: 38-53%).9 Thrombocytopenia during the first days of internment; HIV negative; three blood cultures positive for *Salmonella enteritidis*; pleural liquids culture positive for *Salmonella*; fecal culture produced no pathogen growth; T lymphocytes and subpopulations: CD3 = 503/mm³ (normal:1,800-3,000), CD4 = 343/mm³ (normal:1,000-1,800), CD8 = 138/mm³ (normal: 800-1,500); immunoglobulins in serum: IgA = 367 mg/dl (normal= 7-149); IgG= 1,300 mg/dl (normal= 526-951); IgM = 35.2 mg/dl (normal= 40-154); IgE = 1090.7 IU/ml; NBT test (nitroblue tetrazolium) normal; hemoglobin electrophoresis normal.

**Cytokine assay**

– IL-12: in BCG + IFN-γ stimulated medium;  
– control: 2,068 pg/ml;  
– patient: 63 pg/ml;  
– IFN-γ in BCG + IL12 stimulated medium;  
– control: 19,408 pg/ml;  
– patient: 12 pg/ml.

**Imaging examinations**: superior vena cava thrombosis and cephalic vein blockage extending to the jugular.
Discussion

With this patient, what attracts attention is an extremely serious infection by *Salmonella enteritidis*, with no intestinal involvement suggesting a dysfunction of the immune system. The hypothesis initially raised was of severe combined immunodeficiency (SCID) due to the lymphopenia presented during the acute phase which reversed after the infection. Infants and children present an absolute number of lymphocytes (3,000 to 5,000/mm³) greater than that of adults (1,500 to 2,500/mm³) and a significant reduction of the number of these cells can be the cause of serious infections with fatal evolution if not adequately treated. 10

The identification of the etiologic agent was crucial to guiding the investigation towards the MIM 209950 syndrome. Molecular studies of this syndrome reveal varying types of mutations resulting in different conditions: recessive absolute deficiency of the gamma interferon ligand-binding chain (IFN-γR1); absolute deficiency of the gamma interferon signal-transducing chain (IFN-γR2); recessive partial IFN-γR1 deficiency; recessive partial IFN-γR2 deficiency; dominant partial IFN-γR1 deficiency; absolute deficiency of the p40 subunit of IL-12 (IL-12p40); absolute deficiency of the IL-12 receptor 1 chain encoding gene (IL-12Rβ1). 5,6,11 The common characteristic among these deficiencies is the reduction or absence of IFN-γ during an infectious process.

Mononuclear phagocytes are critical to defense against both virulent and non-virulent pathogens. When mycobacteria infects the macrophages they are stimulated to produce IL-12. This cytokine, joining to its receptor (IL-12R) stimulates T and NK cells to produce IFN-γ. IFN-γ acts, by means of its receptor, on the macrophages stimulating greater IL-12 production, production of tumor necrosis factor (TNF-α) and macrophage and granulocyte colony-stimulating factor. 12-14

IL-12 is a heterodimer composed of two distinct components: p35 and p40, which, together, constitute the biologically active form p70. This, joins to its receptor (IL-12R) which is a complex heterodimer composed of two chains 1 and 2 (IL-12Rβ1 and IL-12Rβ2) which are expressed on activated T and NK cells. 5,11 (Figure 2).

IFN-γ is primarily produced by T and NK cells in response to inflammatory stimuli, stimulating the development and function of activator cells. Together with tumor necrosis factor (TNFα)- it activates the microbicidal mechanisms of the macrophages activating genes which regulate apoptosis and antiviral activity, increasing the expression of MHC class I and class II molecules, modulates the expression of other molecules involved in the signaling of antigens which results in an increase in T cell function. 12

Patients with IL-12R defects do not stimulate the production of IFN-γ by T and NK cells. 5 The study of cytokine production revealed that our patient produces an extremely small quantity of IFN-γ even after stimulation with IL-12, leading to a diagnosis of IL12RB1 deficiency. Infections disseminated by mycobacteria and septicemia by *Salmonella enteritidis* constitute the predominant clinical features of this disease. 15 Although BCG dissemination with evolution to death may also occur in this syndrome, 11 patients with an IL-12R deficiency generally form a granuloma in response to this vaccine with no further complications. 11 Our patient received BCG during the first month of life, and has also received all the other vaccines on the official calendar, but, to date, has not presented any reaction to this vaccine. The formation of the granuloma may not be sufficient at many levels, depending upon the pathogen involved. Generally such patients do not present problems with encapsulated bacteria as they produce adequate antibodies.
The diagnosis of these patients should be realized as quickly as possible in order to plan appropriate treatment. Measurement of serum IFN-γ levels by the ELISA method is highly useful to the identification of this disease. Elevated serum levels of this cytokine suggest an absolute deficiency of the IFN-γ receptor (IFN-γR), while low or undetectable levels suggest an IL-12 or IL-12R deficiency. An IL-12RB1 deficiency can be diagnosed in cases of very low IFN-γ production with analysis by flow cytometry of the presence of the IL-12RB1 chain in activated T cells.11

The number of non-tuberculosis mycobacteria identified has been reducing continually. Although etiologic diagnosis has advanced greatly, treatment remains prolonged, expensive and difficult. Many of these mycobacteria present resistance to treatment making it almost impossible in patients with MIM syndrome. The establishment of therapy specific to the etiologic agent identified is crucial to the recovery of the patient. In cases of IL-12 and IL-12R deficiency and of partial IFN-γR deficiency, additional therapy with IFN-γ has proved effective. This cytokine has been used with success in patients with infections by mycobacteria and its use for prolonged periods with patients with chronic granulomatosis has shown it to be a safe and well tolerated drug.5 The importance of this case history is the fact that certain patients in our environment develop an adverse reaction to BCG or to mycobacteria infection, sometimes evolving fatally, and a diagnosis of immunodeficiency is not established. The identification of these cases would result in more appropriate treatment with higher survival rates for the patients.

References