Mycobacterial Disease in a Child with Surface-Expressed Non-functional Interleukin-12Rβ1 Chains

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Key words: atypical mycobacteria, interleukin-12, interferon gamma, salmonella, deficiency

IMAJ 2007;9:560-561

Defects in the interleukin-12/interferon-gamma axis may cause selective susceptibility to intracellular pathogens such as atypical mycobacteria, bacillus Calmette-Guérin and salmonella [1]. Contrary to most other immunodeficient patients, these patients are usually not susceptible to other pathogens.

We describe a child in whom recurrent salmonella infection and chronic mycobacterial cervical lymphadenitis was found to be due to a defect in IL-12Rβ1.

Patient Description

A 6 year old boy was admitted because of massive cervical lymphadenopathy of 2 months duration. Past medical history included two episodes of aspiration-confirmed *Salmonella typhimurium* cervical lymphadenitis before age 2, and one event of *Salmonella typhimurium* bacteremia. His parents are first-degree cousins of Arab descent, and he has two healthy sisters. Pregnancy and delivery were normal.

Physical examination revealed bilateral massive cervical lymphadenopathy with firm, non-tender lymph nodes of 5–6 cm diameter. Enlarged lymph nodes were also palpated in the axillae and groin. Abdominal examination yielded hepatosplenomegaly and several large firm masses in the right lower quadrant.

Laboratory findings were remarkable for high levels of C-reactive protein and erythrocyte sedimentation rate, numerous atypical lymphocytes without blasts on blood smear, and positive rheumatoid factor. Serology for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus and toxoplasma were negative. Cervical and abdominal ultrasonography demonstrated large lymphadenopathy without liquefaction.

Fine-needle biopsy from the cervical nodes showed granuloma formulation, and culture yielded *Mycobacterium avium*. Immunological workup revealed IgG 2910 mg/dl, IgM 470 mg/dl and IgA 220 mg/dl. Complement, B lymphocytes, T lymphocytes, number of natural killer cells, lymphocyte stimulation tests, NK cell function tests and neutrophil function tests were normal. However, on the basis of the clinical findings, a defect in the IL-12/IFNγ axis was suspected.

Incubation of the patient's lymphocytes with bacillus Calmette-Guérin did not yield the expected INFγ production, nor did the addition of IL-12. Genetic analysis revealed a large defect in the cDNA of the IL-12Rβ1 gene (caused by a deletion of exons 8 to 13 on chromosome 1), establishing the diagnosis.

Following treatment with clarithromycin and rifampicin or rifabutin and IFNγ (50–100 µg/day) for 1 year, the abdominal masses disappeared but the cervical lymph nodes remained enlarged; repeated aspiration from the cervical lymph nodes again yielded *Mycobacterium avium* complex. Based on the *in vitro* susceptibility tests, treatment was changed to clarithromycin, rifabutin, and cycloserin, and IFNγ 150 µg/day.

One year later, apparently as a consequence of discontinuation of treatment, the patient presented with weight loss, hepatomegaly, enormous spleen and left pleural effusion. Blood, bone marrow, and pleural fluid cultures yielded multiresistant *Mycobacterium avium* complex. The patient was treated with five anti-mycobacterial medications, corticosteroids and a high dose of IFNγ (200 mg/day), and was fed by nasogastric tube. Splenectomy was performed for the non-functional spleen and histology revealed numerous acid-fast bacilli in multiple granulomata and abscesses. The patient's clinical condition improved and he was discharged home on the same medications.

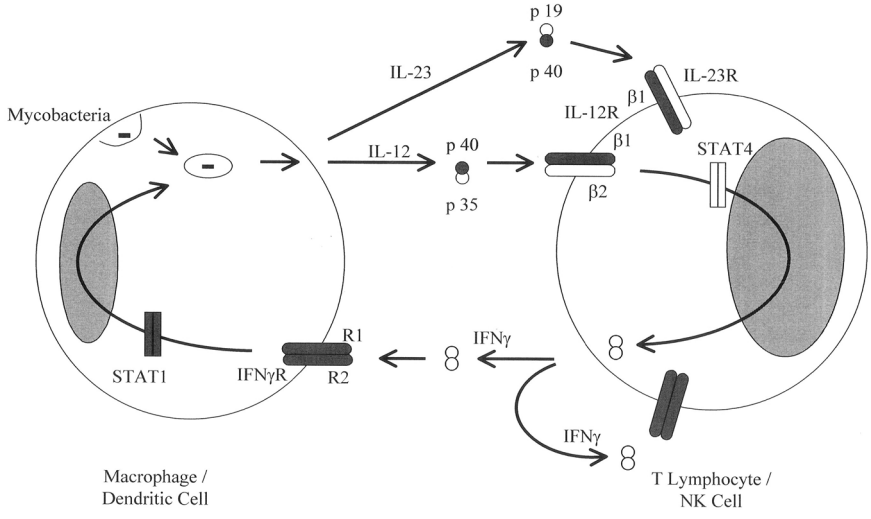
Comment

In the normal mechanism of defense against intracellular mycobacteria [Figure], IL-12 released from infected macrophages activates specific receptors on natural killer cells/T lymphocytes. In response, these cells secrete IFNγ which interacts with its specific receptors on the macrophages, starting a metabolic cascade of enhanced killing of the intracellular pathogen and further activation of the macrophages and T cells [2]. Five disease-causing autosomal genes of this axis have been identified, accounting for least 12 disorders that result in impaired IFNγ-mediated immunity.

IL-12Rβ1 deficiency, first described in 1996 [3,4], is the most frequent genetic defect of Mendelian susceptibility to mycobacterial disease. Inheritance is usually autosomal recessive [2]. Clinical features range from chronic lymphadenopathy to disseminated disease, and death. Over 80 patients have been reported worldwide

IL = interleukin

NK = natural killer
IFN = interferon



IL-12 and INFγ axis in mycobacteria immunity: Infected macrophages release IL-12 which binds to a high affinity receptor on natural killer cells (NK) or T helper cells (TH1), or cytotoxic T cells. The receptor has two subunits (β1+β2). The activation of the receptor results in secretion of IFNγ that adheres to a receptor on the macrophage, which also consists of two subunits. This binding to the IFNγ receptor induces intracellular events via IFNγ-responsive signal transducers and activators. Defects in any of the five genes: namely, IL-12 heterodimer (IL-12p40), IL-12-receptor (IL-12Rβ1), IFNγ receptor (IFNγR1 and IFNγR2), or STAT-1 can cause susceptibility to intracellular pathogens, especially mycobacteria.

(our unpublished data). In most cases, the IL-12Rβ1 is not found on the cell surface, because of a premature stop codon or misfolding and intracellular retention of the mutant proteins [2]. Our patient exhibited a mutation similar to that in another Israeli patient reported by Fieschi et al. [5], also of Arab/Bedouin descent. Both had a large deletion (12165 nucleotides), encompassing exons 8 to 13 of the IL-12Rβ1 gene which encode the proximal NH2-terminal half of the extracellular domain that led to the surface expression of the internally truncated receptor and its consequent inability to bind IL-12 or IL-23. Although, to the best of our knowledge, the families of these two patients were not directly related, the same mutation in the two Arab kindreds in Israel may reflect a founder effect.

In conclusion, IFNγ axis defects should be suspected in the clinical setting of chronic BCG or atypical mycobacterial infection or recurrent salmonella infection. The present report indicates that IL-12Rβ1 deficiency due to the surface-expression of non-functional receptors is not limited to a single family. Our evaluation also highlighted the importance of broad cellular assays and in-depth molecular investigations in certain unusual infections. The accurate diagnosis of genetic defects of the IL-12/IFNγ axis may have therapeutic implications as exemplified by the addition of IFNγ treatment to the anti-mycobacterial agents in our patient.

BCG = bacillus Calmette-Guérin

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