Inherited IL-12Rβ1 Deficiency in a Child With BCG Adenitis and Oral Candidiasis: A Case Report

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Tuberculosis is a major worldwide problem, and protection from it is achieved mainly by live attenuated bacille Calmette–Guérin vaccine, which is capable of causing disease in immunocompromised hosts. Oral thrush is abnormal in healthy children, which suggests an underlying immunodeficiency. Mendelian susceptibility to mycobacterial disease is a rare primary immunodeficiency characterized by a selective predisposition to weakly virulent Mycobacteria and Salmonella and also predisposition to chronic mucocutaneous candidiasis. Interleukin 12 receptor β1 (IL-12Rβ1) deficiency is the most common disease of Mendelian susceptibility to mycobacterial disease, and to date only 50 IL-12Rβ1 deficient patients with clinical signs of chronic mucocutaneous candidiasis have been reported. We report a 2.5-year-old daughter of consanguineous parents with both regional bacille Calmette–Guérin lymphadenitis and recurrent oral candidiasis carrying biallelic R175W mutation in the IL12RB1 gene, resulting in complete loss of expression of IL-12Rβ1. To our knowledge, this is the first report of bacille Calmette–Guérin lymphadenitis with concurrent oral candidiasis displaying such a mutation. New mutations and wide clinical diversities are the indisputable fact of populations with a high rate of consanguineous marriages.

Tuberculosis (TB) remains a major worldwide problem, and, although it is only partially effective, protection from it has been achieved mainly by bacille Calmette–Guérin (BCG) vaccine in many countries, including Turkey. 1 BCG vaccines are live attenuated substrains of Mycobacterium bovis, which are capable of causing regional or disseminated disease in immunocompromised infants. 2 Chronic or recurrent oral thrush is also abnormal in healthy children and suggests an underlying immunodeficiency. Mendelian susceptibility to mycobacterial disease (MSMD) is a rare primary immunodeficiency (PID) characterized by a selective predisposition to intramacrophagic pathogens, such as weakly virulent Mycobacteria and Salmonella. 2 The first genetic disorder was described in 1996. 3 Mutations in 8 autosomal genes (IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, IRF8, TYK2, and ISG15) and in 2 X-linked genes (NEMO and CYBB) have been identified as responsible for MSMD. 2 The immunologic defects are all related to interferon γ (IFN-γ). Interleukin 12 receptor β1 (IL-12Rβ1) deficiency is the most common disease of MSMD, and to date only 50 IL-12Rβ1–deficient patients with clinical signs of chronic mucocutaneous candidiasis (CMC) out of 187 have been reported. 2, 4, 5

abstract

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This feature of CMC is seen also in IL-12p40 deficiency but not in other genetic etiologies of MSMD because it is related to impaired IL-17 immunity (presumably through impaired IL-23 immunity in IL-12p40 or IL-12Rβ1 deficiency). We report here a patient with both regional BCG lymphadenitis (BCG-itis) and recurrent oral candidiasis carrying biallelic R175W mutation in the IL12RB1 gene, resulting in complete loss of expression and function of IL-12Rβ1.

**CASE REPORT**

A 2.5-year-old girl from Turkey was referred with a painless, draining mass 4 x 4 cm in diameter under her left armpit and recurrent thrush (Fig 1). She received BCG vaccine at 2 months of age. The left axillary lump first appeared when the patient was 1 year old; it continued to enlarge and resisted improvement despite successive courses of oral amoxicillin, intravenous cefuroxime sodium, and then clindamycin therapy. Her first tuberculin skin test was negative. Because she had a BCG vaccine in early infancy, isoniazid (INH) was initially given for 6 months, when at 14 months old she received a diagnosis of presumptive enlarged reactive lymphadenopathy (LAP) secondary to BCG vaccine at a medical center. However, the LAP failed to regress. Thrush in the oral cavity had been present since early infancy; it became prominent and persistent during recurrent antibiotic treatment periods covering LAP. White plaques of oral mycosis resolved with but recurred soon after cessation of topical antifungal medication. Fortunately, axillary LAP and recurrent thrush did not affect her growth. The assays for other infectious and oncological etiologies were all within normal range, including culture from draining LAP, aspiration of bone marrow, and extensive immunologic workup.

On admission to the hospital, she had normal development. A BCG scar on the same side as the aforementioned LAP and moniliasis over the tongue and hard palate were observed. The rest of her physical examination was unremarkable, with no lymph node enlargement or hepatosplenomegaly. Her repeated tuberculosis skin test was 20 mm indurated. An enlarged left axillary lymph node was seen on chest radiograph (Fig 1), and no other cervical or abdominal lymphadenomegaly was visualized by ultrasonography. The mass was excised totally under general anesthesia, with successful repair of the degenerated skin (Fig 1). Pathologic examination disclosed chronic granulomatous inflammation, and acid-fast bacilli were seen under fluorescent microscope (Fig 2). Spoligotyping performed directly from the lymph node biopsy specimen revealed the spoligopattern of ST 482, which is specific to *M bovis* BCG (Fig 2). No growth could be obtained in regular mycobacteria growth indicator tubes (MGITs) and Lowenstein–Jensen slants, which are enriched with oleic albumin dextrose catalase–containing growth supplement (Becton-Dickinson, Sparks, MD) and glycerol, respectively. Culture from oral plaques grew *Candida albicans*. Her immunoglobulin (Ig) levels (IgG, IgA, IgM, and IgE), lymphocyte subsets (T, B, and NK cells), and nitroblue tetrazolium test were also repeated and were normal, excluding the diagnosis of combined immunodeficiency and chronic granulomatous disease; HIV, cytomegalovirus, Epstein–Barr virus, *Toxoplasma gondii*, and *Brucella* spp. serologies and Widal test were also negative. Flow cytometry showed an absence of IL-12Rβ1 expression on surface of phytohemagglutinin T cell blasts from the patient (data not shown). By Sanger method, we identified a biallelic mutation in the *IL12RB1* gene, R175W. Her parents were first-degree cousins, and all 4 of her siblings were healthy. Familial segregation was also analyzed: Both parents and siblings are heterozygous for the mutant allele except 1 sister, who is homozygous wild type (Fig 3). There were no physical and radiologic signs of bone involvement, and therefore the patient received a diagnosis of local BCG-itis without dissemination. Antituberculous therapy for BCG-itis with INH, rifampin, and ethambutol was started; ethambutol was discontinued after 2 months, and the therapy was completed at 1 year with no recurrence. Oral candidiasis disappeared after a 7-day-course of fluconazole treatment. The patient was also put on adjuvant subcutaneous IFN-γ. Trimethoprim/sulfamethoxazole and antifungal prophylaxis to prevent recurrence of opportunistic infections were prescribed. At present, she is
We report here a new patient with R175W mutation in the IL12RB1 gene, leading to autosomal recessive complete IL-12Rβ1 deficiency, which is the most common genetic etiology of MSMD.5,7 Clinical manifestations of the patient consist in both BCG-itis and recurrent oral candidiasis. Although R175W type of defect has been reported in 3 IL-12Rβ1-deficient patients with unresolved BCG-itis from Turkey,8 this is the first report of such a case with concurrent oral candidiasis. Deficiency in IL-12Rβ1 leads to a heterogeneous spectrum of clinical presentation ranging from early death in infancy to an asymptomatic adult life. Patients usually experience mycobacterial infections,8 half of them had salmonellosis, and CMC disease was reported only in 50 of 187 of them. Activated T and NK cells carry functional IL-12 receptors over their surfaces, which are necessary for IFN-γ production. The distribution and function of the IL-23 receptor are less clear, although it seems to be key for the production of IL-17 cytokines by T cells.

The diagnosis of M bovis BCG in this case was based on spoligotyping, which was done directly from the biopsy sample. The reason for no growth in MGITs and on Lowenstein–Jensen slants remained unclear, because M bovis BCG strains are known to be adapted to grow in glycerol-containing media and MGITs. Biopsy material showed visible bacilli and relevant DNA structure detected by polymerase chain reaction. However, presumably because of 6 months of INH treatment, the mycobacterial culture was negative. BCG disease in patients with this PID is usually disseminated and may be difficult to control. The lack of disseminated BCG disease in this patient may have been favored by early INH administration. Recent meta-analyses have shown the effectiveness of BCG vaccination against severe Mycobacterium tuberculosis disease and infection also.9,10 BCG vaccination is recommended in developing countries, taking into account the HIV status of the host.11 Turkey is 1 of the countries routinely doing BCG vaccine at 2 months of age. Based on the moderate incidence of TB in Turkey (18 per 100 000 population),12 this vaccine seems necessary. Apart from protection against TB, some protective effect on other types of mycobacterial diseases is observed with BCG vaccination in this type of PID.2,6,8

The most recent case series of candidiasis in patients with IL-12Rβ1 deficiency evaluated 36 patients and reported oropharyngeal Candida infection as the predominant type, with recurring infection in 70% of 76 episodes.4,13 The genetic features of these patients were also reported, and only 2 of 36 patients received a diagnosis based on clinical phenotype. Twenty children, who received a diagnosis between 3 months and 2 years of age, experienced BCG-related disease after vaccination. It is interesting that this patient received her diagnosis at a later age (2.5 years). BCG disease was initially diagnosed at 1 year of age. However, proper treatment was delayed an additional year and a half because of expectations of spontaneous resolution over time and physicians’ reluctance to operate.14

IL-12Rβ1 deficiency is not rare in Turkey, and most patients reported as having this type of PID presenting as Candida infection were from Turkey.4,15 CMC infection worsens the prognosis in patients with IL-12Rβ1 deficiency; and it seems that mortality is remarkably higher than in those without Candida infection (P = .00004).4,6 This difference might
be caused by delays in diagnosis and therapeutic intervention. Our case illustrated good collaboration during follow-up, and no recurrence of lymphadenitis or thrush was observed.

**CONCLUSIONS**

In the presence of a persistent axillary lymphadenitis in a previously BCG-vaccinated child with concomitant recurrent oral candidiasis, PID affecting production of IL-17 and IFN-γ, especially IL-12Rβ1, IL12 p40, and RORγT deficiencies, should be tested if first-line immunologic tests are normal (immunoglobulins, lymphocyte subsets, and dihydrorhodamine test).

In populations with high rates of consanguineous marriages, prospective disclosure of wide clinical diversities and unidentified possible mutations will not be surprising.

**ACKNOWLEDGMENTS**

We thank the patient and her family. We also thank Yelena Nemirovskaya, Lahouari Amar, Cécile Patissier, Canan Hasbal Akkus, Lida Bulbul, and Sami Hatipoglu for their assistance.

**ABBREVIATIONS**

- **BCG**: bacille Calmette–Guérin
- **BCG-itis**: BCG lymphadenitis
- **CMC**: chronic mucocutaneous candidiasis
- **IFN-γ**: interferon γ
- **IL-12Rβ1**: interleukin 12 receptor β1
- **INH**: isoniazid
- **LAP**: lymphadenopathy
- **MGIT**: mycobacteria growth indicator tube
- **MSMD**: Mendelian susceptibility to mycobacterial disease
- **PID**: primary immunodeficiency
- **TB**: tuberculosis

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**FUNDING:** The Laboratory of Human Genetics of Infectious Diseases is supported by institutional grants from INSERM, Paris Descartes University, The Rockefeller University, and the St Giles Foundation, grants from the French National Research Agency (ANR) under the “Investments for the Future” program (grant ANR-10-IAU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-BEID) and the GENMSMD project (grant ANR-16-CE17-0005-01) and a grant from the National Institute of Allergy and Infectious Diseases (grant R37AI095983). Funded by the National Institutes of Health (NIH).

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.
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Pediatrics 2017;140;
DOI: 10.1542/peds.2016-1668 originally published online October 12, 2017;

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