Interleukin-12 Receptor \( \beta1 \) Chain Deficiency in a Child with Disseminated Tuberculosis

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An 11-year-old girl who presented with disseminated tuberculosis associated with secondary hemophagocytosis received a diagnosis of interleukin–12 receptor \( \beta1 \) chain deficiency. This diagnosis of immunodeficiency should, therefore, be considered for children with disseminated tuberculosis, even in the absence of any personal or familial history of prior infection by weakly pathogenic *Salmonella* and *Mycobacterium* species.

Mendelian susceptibility to mycobacterial disease (MIM 209950) is a rare syndrome that predisposes patients to clinical disease caused by weakly virulent mycobacterial species, such as bacille Calmette-Guérin (BCG) vaccines and nontuberculous environmental mycobacteria [1–4]. Patients are also susceptible to the more virulent species *Mycobacterium tuberculosis*, the agent of tuberculosis [5–8]. Other infectious diseases rarely occur in these patients, with the exception of nontyphoid salmonellosis. Five disease-causing autosomal genes (*IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1*) have been identified, and allelic heterogeneity accounts for the existence of 10 defined disorders that result in impaired IFN-\( \gamma \)-mediated immunity [3, 4]. Defects in the *IFNGR1, IFNGR2*, and *STAT1* genes are associated with impaired cellular responses to IFN-\( \gamma \), and defects in *IL12B* and *IL12RB1* are associated with impaired IL-12–dependent and IL-23–dependent production of IFN-\( \gamma \). Complete deficiencies of the 2 IFN-\( \gamma \) receptor components (IFN-\( \gamma \)R1 and IFN-\( \gamma \)R2) are associated with severe mycobacterial diseases that have an early onset. Partial IFN-\( \gamma \)R1, IFN-\( \gamma \)R2, and signal transducer and activator of transcription (STAT)–1 molecule deficiencies, like complete IL-12p40 and IL-12R\( \beta1 \) deficiencies, are associated with a later onset and a better prognosis [3, 4].

IL-12R\( \beta1 \) deficiency is the most common genetic etiology of Mendelian susceptibility to mycobacterial disease, with 54 patients with this syndrome in the literature [6, 8, 9–19]. The known mutations in the *IL12RB1* gene are recessive and are associated with the abolition of the response to both IL-12 and IL-23 [18, 19]. In all patients except one, no IL-12R\( \beta1 \) was detectable on the cell surface. In that one patient, the mutation was associated with the surface expression of nonfunctional, internally truncated receptors [19]. Patients with IL-12R\( \beta1 \) deficiency classically experience clinical disease caused by BCG, environmental mycobacteria, and nontyphoid *Salmonella* species. One patient from Morocco had abdominal tuberculosis at 18 years of age, and she received a diagnosis of IL-12R\( \beta1 \) deficiency after the deficiency had been diagnosed in her younger brother, an index case patient with BCG disease and nontyphoid, extraintestinal salmonellosis [6]. In a family from Spain, a diagnosis of IL-12R\( \beta1 \) deficiency was considered for a 6-year-old girl with disseminated tuberculosis, because her sister had a history of extraintestinal nontyphoid salmonellosis [8]. The patient’s sister also developed pulmonary tuberculosis, despite receipt of isoniazid prophylaxis. To date, IL-12R\( \beta1 \) deficiency has thus been diagnosed in a few children and teenagers with tuberculosis, on the basis of a personal or familial history of clinical disease that was caused by weakly virulent mycobacteria or *Salmonella* species. We describe a child with IL-12R\( \beta1 \) deficiency and disseminated tuberculosis who had no relevant personal or familial history.

Case report. An 11-year-old girl was admitted to the hospital (Department of Pediatrics, Baskent University, Ankara, Turkey) with fever, a cervical mass with purulent discharge, abdominal pain, weakness, and night sweats. The patient was the fourth child of healthy, consanguineous parents. The patient and her parents and siblings had been vaccinated with BCG vaccine, with no adverse effect. One of the patient’s sisters had died of an infection of unknown origin at the age of 1 year. An analysis of the family’s medical history revealed no cases of tuberculosis, and the patient’s mother and siblings had negative tuberculin skin test results. The patient’s illness began 3 months before admission, with fever, anorexia, fatigue, and night sweats. Her weight and height were below the third per-
Figure 1. Frontal (A) and horizontal (B) views of MRI of the abdomen showing a large abscess (black arrow) with a thick wall (white arrow) and septum in close contact with the left hemipelvis.

centile. The patient’s diphtheria-tetanus-pertussis and attenuated poliovirus vaccinations were up to date. The patient had been revaccinated with BCG vaccine after she had received a negative tuberculin skin test result at 7 years of age; no complications occurred.

Physical examination revealed fever, hepatomegaly, and bilateral packed cervical and supraclavicular lymphadenopathies—some of which were fistulized—that measured 3 cm in diameter. An intra-abdominal mass measuring 4 cm in diameter was palpable in the periumbilical area. Laboratory test results were as follows: hemoglobin concentration, 9.9 g/dL; WBC count, 21.5 × 10³ cells/L; platelet count, 933 × 10⁹ platelets/L; and serum C-reactive protein concentration, 96 mg/L. Serum levels of electrolytes, glucose, and creatinine, as well as the results of renal and liver function tests, were within normal ranges. No bacterial pathogens were detected in blood or stool cultures. No serum antibodies to herpes simplex virus, Epstein-Barr virus, cytomegalovirus, Toxoplasma gondii, and human herpes virus 8 were detected.

Ultrasonography of the abdomen showed multiple enlarged lymph nodes of 3 cm in diameter on the periportal, celiac, mesenteric, para-aortic, and pericaval areas. CT of the cervix, thorax, abdomen, and pelvis demonstrated multiple cervical, mediastinal, and abdominal lymphadenopathies with no detectable sign of primary infection of the lungs. MRI of the abdomen revealed the formation of an abscess in the left psoas muscle (figure 1). An increase in activity for the left hemipelvis and the lateral condyl of the femur was detected by technetium Tc 99m methyldiphosphonate scintigraphy of the skeletal system. The findings of thoracic and lumbar MRI were normal.

Biopsy of an abdominal lymph node showed tuberculoid granulomas and numerous visible acid-fast bacilli within histiocytes (figure 2). Bone marrow aspiration and biopsy showed the marrow to be hypercellular, with numerous macrophages and marked hemophagocytosis. Liver biopsy revealed granulomatous hepatitis, with granulomas consisting of epitheloid histiocytes and multinucleated giant cells, some of which displayed emperiploides. A culture of pus obtained from the abscess in the psoas muscle revealed M. tuberculosis, which was resistant to isoniazid and ethambutol. The tuberculin skin test result was positive (18 × 15 mm). The patient received a diagnosis of disseminated drug-resistant tuberculosis and secondary hemophagocytosis. Because the initial microbiological and pathologic findings suggested an atypical, multidrug-resistant mycobacterial infection, a daily regimen of rifampin, clarithromycin, ciprofloxacin, and streptomycin was initiated. The patient’s fever subsided 13 days after the initiation of treatment, with improvement of the other symptoms noted. The findings of subsequently performed physical examinations were

Figure 2. A well-circumscribed tuberculous granuloma in a biopsy sample of the abdominal mass (hematoxylin-eosin stain).
normal, and laboratory test results gradually returned to normal. Treatment with streptomycin was ended after 30 days. However, the patient developed a relapse of tuberculosis in the abdominal lymph nodes 8 months after treatment initiation, as was shown by signs of abdominal lymph node enlargement on an ultrasound scan and by the results of a lymph node biopsy, which revealed epitheloid histiocytes and multinucleated giant cells without acid-fast bacilli. The culture result for this biopsy specimen was negative for acid-fast bacilli and mycobacteria. Amikacin and cycloserine were added to the regimen, and the patient responded well to treatment during the 5 months after treatment initiation.

Whole blood samples were diluted, plated, and stored at 37°C, either unstimulated, stimulated with BCG alone, or stimulated with BCG and IL-12. IFN-γ was quantified in the supernatant after 48 h, as described elsewhere [20]. IFN-γ production did not increase in response to the addition of IL-12 to the test well, whereas a 1.5-log increase was observed for the wells corresponding to the control specimen and the specimen from the patient’s mother (not shown). The Epstein-Barr virus–transformed B cells of the patient lacked IL-12Rβ1, as shown by flow cytometry performed with 2 different antibodies (24E6 and 2B10; Pharmingen). The exon and flanking intron regions of the IL12RB1 gene (encoding IL-12Rβ1) were amplified by PCR. Direct sequencing of the PCR products revealed a homozygous mutation affecting a consensus splice site (1021+1G>C). This mutation results in the skipping of exon 9, as shown by cDNA-PCR. Despite the residual expression of a wild-type IL12RB1 mRNA, blood cells and T cell blasts failed to respond to IL-12 in vitro, in terms of IFN-γ production. The patient’s parents, brother, and sister were heterozygous for the mutant allele and for the wild-type allele. The patient therefore received a diagnosis of IL-12Rβ1 deficiency due to a homozygous mutation in the IL12RB1 gene. The present study was conducted according to the principles expressed in the Helsinki Declaration, and informed consent was obtained from the patient’s family.

Discussion. In the present report, we describe a child with disseminated tuberculosis and inherited IL-12Rβ1 deficiency. Tuberculosis in children with IL-12Rβ1 deficiency appears to run a relatively unusual course, because the children described in previous reports had abdominal tuberculosis [6], disseminated tuberculosis [8, 15], or pulmonary tuberculosis, despite receipt of isoniazid prophylaxis [8]. The case reported here lends weight to the argument that a diagnosis of inherited IL-12Rβ1 deficiency should be considered for children with severe, extrapulmonary tuberculosis. These children probably develop a severe form of tuberculosis soon after infection. Children with other disorders of the IL-12/IFN-γ axis are probably also prone to such severe forms of tuberculosis with early onset, as suggested by our previous description of tuberculosis in children with partial IFN-γR1 deficiency [5] and IL-12p40 deficiency [7].

The prevalence of tuberculosis in IL-12p40–deficient and IL-12Rβ1–deficient patients is lower than that of disease due to BCG or nontuberculosis mycobacteria infection [21]. To date, only 4 of 73 patients with IL-12p40 or IL-12Rβ1 deficiency have been reported to experience tuberculosis (3 [5.6%] of 54 patients with complete IL-12Rβ1 deficiency and 1 [5.3%] of 19 patients with complete IL-12p40 deficiency) [21]. This may be because patients are less frequently exposed to M. tuberculosis than to the BCG vaccines (which have 85% coverage worldwide) and to the almost ubiquitous environmental mycobacteria. This, in turn, probably accounts for the fact that all 4 previously described case patients had a personal or familial history of clinical disease caused by weakly virulent mycobacteria or Salmonella species.

The patient described here is the first patient with an inherited disorder of the IL-12/IFN-γ axis and tuberculosis to be identified in the absence of any relevant personal or familial history. The 2 previous BCG inoculations had possibly protected the patient from subsequent nontuberculosis mycobacteria disease [15]. In keeping with the low penetrance of complete IL-12Rβ1 deficiency for the case definition phenotype of BCG/ environmental mycobacteria clinical disease, the present report thus suggests that there may be other patients with IL-12Rβ1 deficiency and tuberculosis as the sole clinical manifestation. Together with our previous reports [5–8], the present report provides strong evidence that the development of tuberculosis in the general population may be favored by a Mendelian predisposition. A diagnosis of IL-12Rβ1 deficiency or of another related genetic defect [4] should thus be considered for select children with unusually severe tuberculosis, even if they have no personal or familial history of infection with weakly virulent Mycobacterium or Salmonella species.

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