Protective immunity to bacteriae that can multiply intracellularly such as mycobacterium and salmonella is known to depend on cell-mediated immunity (1). The major effector mechanism of cell-mediated immunity is thought to be the activation of infected macrophages by type-1 cytokines, particularly interferon-γ (IFN-γ). IFN-γ is produced by natural killer and Th1 cells and its production is up-regulated by interleukine-12 (IL-12), which is released by macrophages as well as dendritic cells. It has been reported that IL-12 dependent interferon-γ secretion is essential in the control of mycobacterial infections (2-6). In addition, studies of patients with severe infections arising from poorly pathogenic mycobacterium and salmonella species have revealed genetic mutations in type-1 cytokine (IL-12p40) or type-1 cytokine receptor (IFN-γR1, IFN-γR2, IL-12Rb1) genes (1).

A 101/2-year-old boy was referred to our hospital for chronic diarrhoea, abdominal pain and weight loss. Weight loss of 6 kg had occurred in the 6 weeks prior to his admission. He had been hospitalised in another hospital for 15 days with diagnoses of giardiasis and anemia and had been given metronidazol and iron treatment. No improvement had been observed in his symptoms after treatment.

According to his medical history, he had suffered from chickenpox and mumps in early childhood. His immunisation status was up to date at the time of admission, and he had been given BCG vaccines twice (at birth and at 7 years of age) and a live measles vaccine. The patient was healthy until 7 years of age, when he was diagnosed with pulmonary tuberculosis in another hospital and was treated with isoniazid, rifampicine and streptomycine.

The parents were found to be first cousins, with 3 healthy daughters. The third child of the family (female) died at the age of 11/2 years because of severe persistent diarrhoea.

His weight was 24 kg (3rd-10th centile), and his height was 137 cm (50th-75th centile). He had two BCG scars. The physical examination was otherwise normal except for hepatomegaly, 5 cm below the costal margin.

Laboratory studies revealed a WBC count of 7200/µL with 54% neutrophils, 40% lymphocytes, and 6% monocytes; the hemoglobin level was 8.3 g/dL; MCV, 69 fl; platelet count, 490,000/mL; erythrocyte sedimentation rate, 56 mm/hour; C-reactive protein, 5.1 mg/dL; total protein, 5.3 g/dL; albumin, 2.7 g/dL; ALT, 39 IU/L; AST, 73 IU/L; LDH, 470 IU/L; prothrombin time, 13 sec; APTT, 30 sec; and blood urea, 31 mg/dL. ANA, antigliadin antibody, and anti-endomysium antibodies were all negative. Stool and blood cultures were also negative. Anti-EBV, CMV and Herpes simplex 1 virus antibodies (IgG) were found to be negative. The anti-HIV antibody was negative. A tuberculin skin test was negative. His chest x-ray was normal. Cultures for three consecutive early morning gastric aspirates for acidoresistant bacteriae (ARB) were negative. A computed tomography scan of the abdomen demonstrated hepatomegaly, multiple paraaortic and
mesenteric lymphadenopathies, and dilatations and a mild mucosal thickening of the wall of the ileum, caecum and ascending colon.

For differential diagnoses of lymphoma or intestinal tuberculosis, excisional biopsy samples from lymph nodes and a needle biopsy sample from the liver obtained by exploratory laparotomy demonstrated well-organized granulomata with large numbers of ARB inside macrophages. The patient’s family history revealed no known cases of tuberculosis. Both parents underwent Mantoux tests with negative results. Since the pathological findings were suggestive of an atypical mycobacterial infection, the patient was administered antimycobacterial treatment consisting of rifampin (15 mg/kg per day), ethambutol (15 mg/kg per day), clarithromycin (25 mg/kg per day) and ciprofloxacin (40 mg/kg per day). The results of lymphocyte phenotyping and a burst test by flow cytometry and serum immunoglobulins were normal in the patient, ruling out classical immunodeficiencies such as severe combined immunodeficiency and chronic granulomatous disease. Peripheral blood mononuclear cells in the patient did not express IL-12 receptor β1 (IL-12Rβ1) on the cell surface (Dr. Jean-Laurent Casanova, Paris, France). IFN-γ receptor (IFN-γR) expression was normal. He was shown to have IL-12Rβ1 deficiency. Our patient did not exhibit any susceptibility to other viral, bacterial, or fungal pathogens. However, the mycobacterial infection diagnosed after the second BCG vaccine might have been disseminated BCG infection. It has been reported that milder forms of BCG infections are observed in IL-12Rβ1-deficiencies (1).

Two weeks after the onset of antimycobacterial therapy, the diarrhoea and abdominal pain disappeared. One month after the onset of therapy, rifampin and then ciprofloxacin were withdrawn because of the elevation of transaminases, and streptomycin was added to the treatment. Although the general clinical status of the patient was clinically stable, multiple cervical, axillary and inguinal lymphadenopathies (the largest one was 1.5 x 1.5 cm in diameter) appeared during the end of the second month of the treatment. Lymph node biopsies also demonstrated ARB and granulomata. Although mycobacteria was grown from the sample obtained from lymph nodes, microbiological identification was not possible until appropriate gene probes were available. When clofazimine became available, the therapy was changed to clarithromycin, ethambutol and clofazimine and recombinant IFN-γ treatment (50 µg/m², SC, three times a week) was started.

Despite this aggressive treatment, the lymph nodes remained enlarged and the spleen enlarged progressively. The WBC (2,000/mm³) and platelet (68,000/mm³) counts decreased. With the diagnosis of hypersplenism, a total splenectomy was carried out. The pathological examination of the spleen showed well-developed granulomata with large numbers of ARB inside macrophages. The WBC and platelet counts rapidly increased after the splenectomy. Six months after hospitalisation, the causative agent was identified as mycobacterium fortuitum-chelonae complex, and treatment was arranged according to an antibiotic sensitivity test (to amikacin, doxycycline and clofazimine). The microorganism was resistant to streptomycin, rifampicin, isoniazid and ethambutol. One month after this treatment, the patient gained weight (about 8 kg), and the hepatomegaly and lymphadenomegalies disappeared. Liver function tests, CRP and ESR were normal. The paraaortic and mesenteric lymphadenopathies also disappeared. Amikacin (after it had been used for a total of 2 months) and IFN-γ (after it had been used for a total of 6 months) were stopped. It was decided that the doxycycline and clofazimine treatments should be continued for a total of 6 months.

IL-12Rβ1 deficiency has recently been reported in a total of 7 individuals with mycobacterial infections (2, 3). Insufficient IFN-γ production appears to be the main pathogenic mechanism in IL-12Rβ1- deficient patients. IFN-γR receptor deficiencies can also lead to infection with mycobacteria of low-grade virulence (7-9). In contrast to complete IFN-γR deficiencies, in which the onset of infection is before three years of age and affected children develop severe and mostly fatal infections, patients with complete IL-12Rβ1- deficiency often develop milder, although still severe, infections. These patients resemble children with partial IFN-γR deficiency. Children with complete IL-12Rβ1- deficiency and partial IFN-γR deficiency have mature granulomas, unlike children with complete IFN-γR deficiency. The milder phenotype is probably attributable to IL-12 independent pathways of IFN-γ production.

In conclusion, patients with disseminated atypical mycobacterial infections must be examined for IL-12 or IFN-γ receptor deficiencies unless they have other well-known immunodeficiencies.
References


