IL12Rβ1 defect presenting with massive intra-abdominal lymphadenopathy due to Mycobacterium intracellularare infection

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Abstract

Infections due to non-tuberculous mycobacteria species are problematic for immunodeficient individuals. Mendelian susceptibility to mycobacterial diseases (MSMD) defines a group of genetic defects affecting cellular interactions and the interferon (IFN)-γ pathway. Patients with MSMD may present with a disseminated infection resulting from the Bacillus Calmette-Guerin vaccine, Mycobacterium tuberculosis complex, environmental nontuberculous mycobacteria or Salmonella species. Atypical mycobacterial infections and deficient granuloma or giant cell formation are important indicators for MSMD, especially in patients with a family history of parental consanguineous marriage.

Herein we report the case of a boy with an IL-12Rβ1 defect who presented with massive intraabdominal lymphadenopathy due to Mycobacterium intracellularare infection. The patient was born to consanguineous parents, both heterozygous for the IL-12Rβ1 defect mutation. Debulking surgery was planned in order to decrease the abdominal mass, but could not be performed due to a high risk of fatal outcomes. He has been receiving linezolid, levofloxacin, azithromycin, rifabutin and IFN-γ therapy for the past 14 months. At follow-up, the patient showed significant clinical improvement and weight gain.

Keywords: Atypical mycobacteria; Child; Immune deficiency; Mycobacterium intracellularare; IL-12Rβ1 defect

Introduction

Nontuberculous mycobacteria (NTM) species, otherwise known as atypical mycobacteria, are defined as species of the Mycobacterium genus excluding Mycobacterium tuberculosis complex and M. leprae. NTM are ubiquitous in the environment, and while they can cause disease in immunocompetent individuals, NTM infection is particularly problematic for immunodeficient individuals or those with a chronic lung disease.1,2 The most common forms of NTM infection in children involve the cervical lymphadenitis, skin and soft tissue, and can cause disseminated disease in immunocompromised patients.1

Interactions between macrophages, T cells, natural killer (NK) cells and the interferon (IFN)-γ pathway are critical for the control of mycobacterial infections.3-5 Mendelian susceptibility to mycobacterial diseases (MSMD) are defined by a group of genetic defects involving cellular interactions and the IFN-γ pathway, important for the control of intracellular infections.6 Patients with MSMD typically present with disseminated infection due to the Bacillus Calmette-Guerin (BCG) vaccine or infection with environmental NTM species. Disease severity and age of onset depends on both the part of the IFN-γ pathway affected and the severity of the genetic defect.5,8 Consanguineous marriage is a risk factor for a subgroup of MSMD patients due to its autosomal recessive (AR) inheritance pattern.
Herein we present a case report of a 3-year-old boy with an IL-12Rβ1 defect who presented with massive intraabdominal lymphadenopathy due to *Mycobacterium intracellulare* infection.

**Case report**

A 3-year-old boy, born to consanguineous Azerbaijani parents, was admitted to a hospital in Azerbaijan with abdominal distention, fever, night sweats, anorexia and weight loss. Multiple intra-abdominal lymphadenopathies were detected by ultrasonography. The patient was transferred for treatment in Iran with the presumed diagnosis of Histiocytosis X, after histopathological examination of the abdominal lymph nodes. Chemotherapy for Histiocytosis X was given for 2 months. He was then transferred to Turkey due to poor response to chemotherapy. The physical examination revealed a fever (39ºC), abdominal distention and cachexia. Laboratory evaluation of the patient was as follows: hemoglobin 11.6 g/dL, white blood cell count 15 × 10^3/µL, absolute neutrophil count 10.7 × 10^3/µL, absolute lymphocyte count 2.5 × 10^3/µL, erythrocyte sedimentation rate (ESR) 95 mm/hour, C-reactive protein 112 g/dL (range 0–5 g/dL). Liver transaminases were found to be within the normal range. Multiple massive diffuse intraabdominal lymph nodes were found during his abdominal ultrasonography, the largest of which was 4 × 5 cm in size. The positron emission computerized tomography (PET-CT) showed multiple, intensely hypermetabolic lymph nodes at cervical, mediastinal and abdominal sites, consistent with lymphoproliferative disorders (**Figure 1**). To strengthen the diagnosis, another biopsy was taken from the mesenteric lymph nodes, and this second biopsy showed multiple irregular histiocytes that were filled with acid-fast bacilli (AFB) (**Figure 2**). The thorax CT scan showed pneumonic consolidation on the lower lobe of the left lung and paratracheal lymphadenomegaly (1.2 × 0.8 cm). Direct microscopy for AFB was negative, in addition to negative results for a PCR analysis of *M. tuberculous* in the gastric lavage fluid, anti-HIV serology and the T-spot-TB test. Isoniazid, rifampicin, ethambutol, pyrazinamid (HRZE) and clarithromycin therapies were given for 2 months. The anti-mycobacterial combination regimen was changed to linezolid, levofloxacin, azithromycin, rifabutin and amikacin when the lymph node mycobacterial PCR analysis revealed *M. intracellulare* infection. His lymphocyte subset (T, B and NK cells) analysis, immunoglobulin level and dihydrorhodamine tests were normal, excluding the most frequent classical primary immunodeficiencies. Debulking surgery to decrease the abdominal mass could not be performed due to a high possibility of fatal outcomes. His lymph node biopsy revealed histiocyte irregularities and the absence of an organized giant cell structure, indicating defects in the IFN-γ pathway. A homozygous mutation in the *IL12RB1* gene (c.1073G>C), p.Trp358X, was detected by the molecular genetic analysis, which was performed by a research laboratory in France. Both parents were also found to be heterozygous for this mutation. In addition, staining of the IL-12Rβ1 protein in the patient's T lymphocytes was negative.

IFN-γ therapy (0.05 mg/day, subcutaneously three times a week) began following the MSMD diagnosis. Fever and chills were observed in the boy during IFN therapy. The diameter of the abdominal lymph nodes and the ESR was found to have decreased after 6 months of antimicrobial therapy. Amikacin therapy was discontinued due to parental concerns about its autotoxic side effects. The patient has been receiving linezolid, levofloxacin, azithromycin and rifabutin for the past 14 months. The most recent laboratory evaluation of the patient was as follows: hemoglobin 12.6 g/dL, white blood cell count 6×10^3/µL, ESR 8 mm/hour, C-reactive protein 4 g/dL (range 0–5 g/dL). The size of the largest abdominal lymph node has decreased from 4 × 5 cm to 1.5 × 1 cm. The clinical condition of the patient has improved substantially, with weight gain and no fever. Furthermore, no persistent infection was present at follow-up. The two healthy siblings of the patient were invited for genetic analysis and genetic counseling.
Discussion

*Mycobacterium avium-intracellulare* complex (MAC) is ubiquitous in soil and water. *Mycobacterium avium* complex and MAC include two mycobacterial species, *M. avium* and *M. intracellulare*. These two species cannot be differentiated based on traditional physical and biochemical tests. While *M. avium* usually causes disseminated disease, *M. intracellulare* acts as a respiratory pathogen.3-9 Cervical lymphadenitis resulting from MAC can be observed in immunocompetent children. Patients should be screened for HIV infection if they present with abdominal or mediastinal lymphadenitis due to MAC.10 Most first-line antituberculosis drugs have poor activity against MAC, however, macrolide drugs have demonstrated clinical activities against MAC.

Interleukin (IL)-12 and IFN-γ are responsible for providing an activation loop between macrophages and T cells/NK cells in order to amplify the immune response against mycobacteria, in addition to the formation of granuloma or giant cells.11 To date, 18 different genetic disorders have been associated with a mutation in the IFN-γ pathway, most of which have an AR inheritance pattern. The genetic disorders underlying MSMD can be differentiated based on their mode of transmission, expression of the mutant protein or its function.12-14 Clinical phenotypes of these diseases are heterogeneous, ranging from localized to severe infection, and dissemination can cause potentially fatal infections.5

In the literature, only few case reports have described patients with MSMD and intra-abdominal mycobacterial infections. Özbek et al. reported the case of an 11-year-old girl who presented with disseminated tuberculosis and an intra-abdominal abscess, who was found to have an *IL12Rβ1* defect. She was treated with rifampin, clarithromycin, ciprofloxacin and streptomycin.12 Law et al. reported a 13-year-old girl with defective mitogen-induced IL-12 production, who developed intestinal tuberculosis with wide dissemination, including the lungs and urinary tract. Similar to our case, histological examination of the intestinal tissue revealed several ill-formed granulomas with numerous AFB, however, caseous necrosis was absent. The patient described by Law et al. remained well following 18 months of anti-tuberculous therapy, which included isoniazid, pyrazinamide, ethambutol, amikacin, levofloxacin and moxifloxacin.13

The patient reported here had a family history of consanguineous marriage, and presented with NTM infection, isolated from the abdominal lymph nodes, in addition to the existence of numerous AFBs, irregular histiocytes, and an absence of well-organized giant cell structures in lymph node specimens, which lead to the MSMD diagnosis. Therefore, genetic analysis was performed, and a mutation in the *IL12Rβ1* gene was identified, conferring complete *IL-12Rβ1* deficiency, characterized by no expression of the receptor. Similar to the aforementioned case reports, our patient responded well to anti-tuberculous therapy including both first- and second-line drugs with high bactericidal activity. The patient was also started on IFN-γ therapy, which is recommended for patients with an *IL-12Rβ1* deficiency.

Patients with an *IL-12Rβ1* deficiency usually have relatively mild clinical symptoms and good prognosis,14 and hematopoietic stem cell transplantation is not required. Management consists of anti-mycobacterial drugs and recombinant IFN-γ treatment. In the literature, children with an *IL-12Rβ1* deficiency have been reported to present with nocardiosis, recurrent salmonellosis, cryptococcal osteomyelitis, multifocal tuberculous osteomyelitis, BCG-osis and disseminated *M. tuberug* infection.15-19 Differential MSMD diagnosis requires the exclusion of other granulomatous (infectious or noninfectious) inflammation according to the clinical and biological manifestations. Other diseases can be misdiagnosed, such as Langerhans cell histiocytosis or bone metastasis.20 Therefore, a detailed summary of the clinical and histological features should facilitate accurate diagnosis and treatment in order to avoid unnecessary cytotoxic chemotherapy. In our patient, the therapy was altered to a different anti-mycobacterial regimen following MAC isolation, which included a macrolide drug. The therapy also included second-line parenteral anti-tuberculosis drugs with high bactericidal activity (linezolid, amikacin and levofloxacin), in addition to rifabutin and IFN-γ, due to the patient’s poor clinical condition.

Atypical mycobacterial infections and deficient granuloma or giant-cell formation are important indicators of MSMD, especially if there is a family history of consanguineous marriage of parents.

Conflict of interest

All authors declare no conflicts of interest.

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References


