**CASE REPORT**
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# Disseminated *Mycobacterium simiae* Infection in a Patient with Complete IL-12p40 Deficiency

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## ABSTRACT

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare group of genetic disorders characterized by infections with weakly virulent environmental mycobacteria (EM) or *Mycobacterium bovis* bacillus Calmette-Guérin (BCG). Herein, we described the case of a 4.5-year-old boy with protein-losing enteropathy, lymphoproliferation, and candidiasis, who was found to have disseminated *Mycobacterium simiae* infection. A homozygous mutation in the *IL12B* gene, c.527_528delCT (p.S176Cfs*12) was identified, responsible for the complete IL-12p40 deficiency. He was resistant to anti-mycobacterial treatment and finally died due to sepsis-related complications.

**Keywords:** Mycobacterium simiae; Primary immunodeficiency

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## INTRODUCTION

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare group of genetic disorders characterized by infections with weakly virulent environmental mycobacteria (EM)or *Mycobacterium bovis* bacillus Calmette-Guérin (BCG). Genetic etiologies of MSMD affect the pathways involved in the production of and/or response to the interferon-gamma (IFN-ɣ).[1] Various EM can infect patients with MSMD, such as *M. abscessus, M. asiaticum, M. avium*, *M. bohemicum, M. chelonae, M. elephantis*, *M. fortuitum M. genevense*, *M. gordonae, M. kansasii, M. mageritense, M. peregrinum, M. porcium, M. scrofulaceum, M. smegmatis*, *M. simiae*, *M. szulgai, M. triplex,* and *M. tilburgii*. The more virulent *M. tuberculosis* has also been implicated in some patients. Herein, we report a 4.5-year-old Iranian patient with disseminated *Mycobacterium simiae* and a homozygous frameshift mutation in the*IL12B* gene, c.527_528delCT (p. S176Cfs*12).

## CASE PRESENTATION

The present study was conducted according to the principles expressed in the Helsinki Declaration and ethical standards of the National Research Institute of Tuberculosis and Lung Diseases (NRITLD) committee. Informed consent was obtained from the parents of the patient before being included in the study.

The patient was an Iranian male born to consanguineous parents. The family history was unremarkable for unusual infections or early death. He received the BCG vaccine at birth without any complications. At the age of 2.5 years, he was initially presented with abdominal pain and distension. Further evaluation showed hepatosplenomegaly and abnormal liver function tests. Due to the direct hyperbilirubinemia and findings of the biliary tract obstruction on the abdominal computed tomography (CT) scan, he underwent diagnostic laparotomy which revealed gallbladder hydrops, a retroperitoneal tumor-like lesion near the pancreas head, as well as celiac and para-aortic lymphadenopathies. The histopathologic findings were consistent with the non-necrotizing granulomatous inflammation in lymph nodes and focal centers of narrow septate mycelia within the gallbladder wall and pancreatic stroma with no microorganism found in the special staining performed for the detection of fungi and bacteria. He was empirically treated with a combination of antibiotics and antifungal agents (voriconazole and then itraconazole), which resulted in complete resolution of fever but the abdomen was still distended.

One year later, he presented with complaints of fever and abdominal pain. He was also suffering from recurrent episodes of oral thrush in the last few months. He received packed cells and albumin infusion due to the evidence of anemia and malabsorption. The purified protein derivative (PPD) skin test was negative but gastric washing culture was positive for acid-fast bacilli (AFB), of which the subspecies were not identified. The colonoscopy at the time revealed severe nodularity, fragile mucosa, and multiple pseudo-polyps in all parts of the colon. The colon biopsy was negative for different bacterial and fungal microorganisms by polymerase chain reaction (PCR) method but reported to be positive for mycobacteria species (unknown species). With suspicion of EM infection, the patient had been treated with isoniazid, rifampin, ethambutol, and clarithromycin.

At the age of 4.5 years, he was referred to our center as he had not responded to anti-mycobacterial treatment. He suffered from protracted diarrhea, fever, growth failure, and recurrent oral herpetic lesions.

In the physical examination, oral candidiasis, abdominal distension, hydrocele, and cervically lymphadenopathy were found. The complete laboratory survey including immunologic workup was in the normal range except for elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (Table 1).

The gastric lavage PCR was positive for *M. simiae*, later confirmed by culture. In the bacterial susceptibility profile, the pathogen was sensitive to amikacin, kanamycin, and resistant to ciprofloxacin and ofloxacin. He received fluconazole for oral candidiasis and was placed on imipenem, amikacin, levofloxacin, clarithromycin, and trimethoprim/sulfamethoxazole (TMP/SMX).

We enrolled his genomic DNA in the whole exome-sequencing (WES) program and identified a frameshift homozygous mutation in exon 5 of the *IL12B* gene, c.527_528delCT (p. S176Cfs*12), verified by the Sanger sequencing method. This mutation has been already reported in other MSMD patients and the diagnosis of complete autosomal recessive (AR) IL-12p40 deficiency was established.[2] Both parents were

**Table 1. Summary of immunologic work-up**

| Laboratory test | Patient | Normal Range |
|---|---|---|
| **Complete blood count** | | |
| White blood cells ($\times 10^3$cells/mm$^3$) | 8.3 | 3.98-10.2 |
| Neutrophils (%) | 66% | - |
| Lymphocytes (%) | 31% | - |
| MXD (%) | 3% | - |
| Hemoglobin (gr/dL) | 7.5 | - |
| Platelets ($\times 10^3$cells/mm$^3$) | 725 | 150-450 |
| **Lymphocytes subsets (% of lymphocytes)** | | |
| CD3+ | 46.8% | 35-78 |
| CD4+ | 31% | 22-62 |
| CD8+ | 15% | 12-36 |
| CD19+ | 33% | 3-14 |
| CD16+ | 5.1% | 4.5-25 |
| CD56+ | 5.1% | 5-29 |
| CD4+/CD8+ ratio | 2.0 | 1.0-4.0 |
| **Serum immunoglobulins** | | |
| IgG (g/L) | 15.6 | 7.0-16.0 |
| IgM (g/L) | 1.0 | 0.4-2.3 |
| IgA (g/L) | 0.9 | 0.4-3.9 |
| IgE (IU/mL) | 85 | <144 |
| **Specific antibodies** | | |
| Anti-tetanus antibody(IU/mL) | 0.7 | >0.1 |
| Anti-diphtheria antibody(IU/mL) | 0.2 | >0.01 |
| Anti-A Isohemagglutinin | 1/32 | |
| Anti-B Isohemagglutinin | 1/16 | |
| **Others** | | |
| NBT test (%) | 99 | >95 |
| PPD skin test | Negative | |
| ESR | 81 | 0-22 |
| CRP | 50 | <10 |
| Wright and Widal test | Negative | |
| PCR for HIV | Negative | |
| Gamma-GT | Normal | |

MXD; Mixed Cell Count, NBT; Nitro blue tetrazolium test, PPD; purified protein derivative

**Table 2. A summary of demographic and clinical features of Mendelian susceptibility to mycobacterial disease (MSMD) patients with Mycobacterium simiae infection**

| Patient | Mutated gene | Age (years) | Sex | Parental consanguinity | Study country (Patient's origin) | Clinical manifestations | The site of M. Simiae isolation | First treatment | Second treatment | Life status | Reference, Year |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P1 | IL12B | 4.5 | Male | Yes | Iran (Iranian) | Protracted diarrhea, Fever, growth failure, Hepatosplenomegaly, Lymphadenopathy, Oral candidiasis and herpetic lesions, Colon pseudo-polyps | Gastric lavage | Isoniazid, Rifampin, Ethambutol, Clarithromycin | Amikacin, Levofloxacin, Clarithromycin, Cotrimoxazole | Deceased | The present case, 2020 |
| P2 | NEMO | 37.0 | Female | N/A | USA (Caucasian) | Chronic granulomatous skin lesions, Recurrent sinusitis, Fever, Pancytopenia, *Mycobacterium avium-intracellulare infection,* Lymphadenopathy | Skin biopsy | Rifampin, Clarithromycin, Minocycline | Clarithromycin, Ethambutol, Rifampin, Corticosteroids, Gamma interferon | Alive | (14), 2015 |
| P3 | IFNGR2 | 4.5 | Male | Yes | USA (Israeli) | Pneumonia, Pleural effusion, Lymphadenopathy, Hepatosplenomegaly, | Lymph node | Rifampin, Ethambutol, Cycloserine | Cycloserine, Clarithromycin, Moxifloxacin, Trimethoprim-sulfamethoxazole | Deceased | (13), 2014 |
| P4 | IFNGR2 | 5.0 | Female | Yes | USA (Palestinian) | Severe diarrhea, Anemia, Lymphadenopathy, *Mycobacterium fortuitum* infection | Liver biopsy, Brain abscess | Isoniazid, Rifampin, Ethambutol | Massive antimycobacterial treatment, Cycloserine, Umbilical cord blood transplantation | Deceased | (13), 2014 |
| P5 | IL12RB1 | 5.1 | Male | N/A | France (Saudi Arabian) | Disseminated BCG disease | N/A | N/A | N/A | Alive | (12), 2010 |

heterozygous concerning the mutation. The exogenous recombinant human IFN-ɣ treatment was added to the regimen of antibiotics.

At the age of 6, while receiving the above-mentioned medications, he was hospitalized again due to refractory diarrhea, malabsorption, abdominal distension, and muscle atrophy. In the ultrasound examination, he was found to have abdominal wall thickening and ascites. The colonoscopy was repeated with almost the same results mentioned before and in the histopathologic examination, histiocytic infiltration, and focal granuloma in rectosigmoid and villous blunting by an infiltrate of foamy macrophages with numerous AFB were observed. His clinical condition gradually deteriorated and he developed protein-losing enteropathy. His condition was complicated by candida septicemia, hyponatremia, hypokalemia, hypocalcemia, and respiratory distress. He was admitted to the intensive care unit (ICU) and eventually died following acidosis, electrolyte imbalance, and septicemia. To our knowledge, this is the first AR complete IL-12p40 deficiency case with disseminated *M. simiae* infection.

## DISCUSSION

*M. simiae* is a slowly-growing EM that was first isolated from Indian Rhesus monkeys in 1965.[3] *M. simiae* infection seems to be restricted to certain geographical regions, including southwestern United States, Cuba, Western Europe, and Middle East countries.[4] In Iran, it is estimated to have a pooled prevalence of 25% among NTMs.[5,6]

It usually affects immunocompromised patients, such as those with acquired immunodeficiency syndrome (AIDS).[7] However, particular underlying risk factors, including the history of pulmonary tuberculosis, chronic obstructive pulmonary disease, cystic fibrosis, diabetes mellitus, cardiovascular disorder, and malignancy, can also impose immunocompetent individuals to *M. simiae* infection.[8] The most common symptoms include productive cough, dyspnea, fever, weight loss, and hemoptysis, mostly associated with micronodular or cavitary lesions and bronchiectasis in radiological studies.[9] Furthermore, rare involvements of extra-pulmonary organs such as the parotid gland, skin, genitourinary tract, lymph nodes, and vertebral column are reported in the literature.[10,11]

In this study, we reported disseminated *M. simiae* infection in an MSMD patient with *IL12B* defect. Among patients with MSMD, four other patients have been reported to be complicated with *M. simiae* infection (Table 2). De Beaucoudrey et al in a cohort of 141 MSMD patients with AR IL-12Rβ1 deficiency, reported a 5-year-old male from Saudi Arabia with disseminated BCG disease and mutation in the *IL12RB1* gene (Y88*), who was found to have *M. simiae* infection.[12]

In 2014, *M. simiae* infection was reported in two patients with AR IFN-γ receptor 2 (IFN-γR2) deficiency.[13] One of them initially presented with pneumonia and pleural effusion and later complicated with abdominal lymphadenopathy and hepatosplenomegaly. *M. simiae* was found in the lymph node culture. The other patient suffered from severe diarrhea, anemia, and peripheral lymphadenopathy. *M. simiae* was cultured from liver tissue and brain abscess. Both patients died despite early anti-mycobacterial treatments. Later, Braueet al described another Caucasian patient with granulomatous skin lesions, lymphadenopathy, persistent fever, and disseminated *Mycobacterium avium*-intracellulare infection. The *M. simiae* was also cultured from his skin biopsy and he was finally found to have a mutation in the *NEMO* gene (c.1-16G>C).[14] The treatment of *M. simiae* infection is challenging as most isolates show resistance to first-line antituberculosis agents, no therapeutic protocol has been defined yet, and the in vitro susceptibility test may not reflect the in vivo susceptibility. However, the most frequent drug regimens applied included clarithromycin in different combinations with trimethoprim/ sulfamethoxazole, moxifloxacin (or ofloxacin), and amikacin.[10] Our case exemplifies the importance of considering *M. simiae* infections in patients with genetic defects in the IFN-γ mediated immunity, due to its difficult to treat nature.

## CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

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