Disseminated Mycobacterium simiae infection in a patient with complete IL-12p40 deficiency

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To the Editor:

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). 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. Genetic etiologies of MSMD affect the pathways involved in the production of and/or response to the interferon-gamma (IFN-γ) (1). 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).

The patient was an Iranian male born to consanguineous parents. The family history was unremarkable for unusual infections or early death. Patient received BCG vaccine at birth without any complication. At the age of 2 years, he presented with abdominal distension. Further evaluation showed hepatosplenomegaly and abnormal liver function tests. 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 pathologic 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 without any microorganism found in special staining. He had been empirically treated with a combination of antibiotics and antifungal agents with partial improvement.

One year later, he presented with fever and abdominal pain. He was also suffering from recurrent episodes of oral thrush. 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 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 cervical lymphadenopathy were found. The complete laboratory survey including immunologic workup was in 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. He received fluconazole for oral candidiasis and was placed on amikacin, levofloxacin, clarithromycin, and cotrimoxazole, which offered moderate improvement.

We enrolled his genomic DNA to 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 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 heterozygous with respect to the mutation. The exogenous recombinant human IFN-g 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, abdominal distension, and malabsorption. 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 hyponatremia, acid-base disturbance, and hypoxia. He was admitted to the intensive care unit (ICU) and eventually died.

To our knowledge, this is the first AR complete IL-12p40 deficiency case with disseminated *M. simiae*infection.

M. simiae is a slowly-growing EM that usually affects immunocompromised individuals (3). 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 (4). 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 (5, 6).

M. simiae infection seems to be restricted to certain ethnic groups, particularly those from the Middle East countries (7). Among patients with MSMD, four patients have been reported to be complicated with *M. simiae* infection. 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 (8). In 2014, *M. simiae* infection was reported in two patients with AR IFN-γ receptor 2 (IFN-γR2) deficiency (9). 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, Braue*et 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) (10).

The treatment of *M. simiae* infection is challenging and no therapeutic protocol has been defined yet. However, the most frequent drug regimens applied included clarithromycin in different combinations with trimethoprim/sulfamethoxazole, moxifloxacin (or ofloxacin), and amikacin (5). 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.

Ethics statement

Informed consent was obtained from the parents of the patient prior to being included in the study.

Disclosure of potential conflict of interest

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

REFERENCES

1. Bustamante J. Mendelian susceptibility to mycobacterial disease: recent discoveries. Hum Genet. 2020.

2. Alodayani AN, Al-Otaibi AM, Deswarte C, Frayha HH, Bouaziz M, AlHelale M, et al. Mendelian Susceptibility to Mycobacterial Disease Caused by a Novel Founder IL12B Mutation in Saudi Arabia. J Clin Immunol. 2018;38(3):278-82.

3. Patel NC, Minifee PK, Dishop MK, Munoz FM. Mycobacterium simiae cervical lymphadenitis. Pediatr Infect Dis J. 2007;26(4):362-3.

4. Coolen-Allou N, Touron T, Belmonte O, Gazaille V, Andre M, Allyn J, et al. Clinical, Radiological, and Microbiological Characteristics of Mycobacterium simiae Infection in 97 Patients. Antimicrob Agents Chemother. 2018;62(7).

5. Hamieh A, Tayyar R, Tabaja H, S ELZ, Bou Khalil P, Kara N, et al. Emergence of Mycobacterium simiae: A retrospective study from a tertiary care center in Lebanon. PLoS One. 2018;13(4):e0195390.

6. Varghese B, Enani M, Shoukri M, AlJohani S, AlThawadi S, Al-Hajoj S. Burden of non-tuberculous mycobacterial diseases in Saudi Arabian children: The first nationwide experience. J Infect Public Health. 2019;12(6):803-8.

7. Hashemi-Shahraki A, Darban-Sarokhalil D, Heidarieh P, Feizabadi MM, Deshmir-Salameh S, Khazaee S, et al. Mycobacterium simiae: a possible emerging pathogen in Iran. Jpn J Infect Dis. 2013;66(6):475-9.

8. de Beaucoudrey L, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, et al. Revisiting human IL-12Rbeta1 deficiency: a survey of 141 patients from 30 countries. Medicine (Baltimore). 2010;89(6):381-402.

9. Martinez-Barricarte R, Megged O, Stepensky P, Casimir P, Moncada-Velez M, Averbuch D, et al. Mycobacterium simiae infection in two unrelated patients with different forms of inherited IFN-gammaR2 deficiency. J Clin Immunol. 2014;34(8):904-9.

10. Braue J, Murugesan V, Holland S, Patel N, Naik E, Leiding J, et al. NF-kappaB Essential Modulator Deficiency Leading to Disseminated Cutaneous Atypical Mycobacteria. Mediterr J Hematol Infect Dis. 2015;7(1):e2015010.

Table 1: Summary of immunologic work-up	Table 1: Summary of immun
Laboratory test	**Patient**
Complete blood count	Complete blood count
White blood cells ($\times 10^3$ cells/mm^3)	8.3
Neutrophils (%)	66%
Lymphocytes (%)	31%
MXD (%)	3%
Hemoglobin (gr/dl)	**7.5**
Platelets ($\times 10^3$ cells/mm^3)	**725**
Lymphocytes subsets (% of lymphocytes)	Lymphocytes subsets (% of l
CD3+	46.8%
CD4+	31%
CD8+	15%
CD19+	**33%**
CD16+	5.1%
CD56+	5.1%
CD4+/CD8+ ratio	2.0
Serum immunoglobulins	Serum immunoglobulins
IgG (g/L)	15.6
IgM (g/L)	1.0
IgA (g/L)	0.9
IgE (IU/ml)	85
Specific antibodies	Specific antibodies
Anti-tetanus antibody (IU/ml)	0.7
Anti-diphtheria antibody (IU/ml)	0.2
Anti-A Isohemagglutinin	1/32
Anti-B Isohemagglutinin	1/16
Others	Others
NBT test (%)	99
PPD skin test	Negative
ESR	**81**

Table 1: Summary of immunologic work-up	Table 1: Summary of immun
CRP	**50**
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	*MXD; Mixed Cell Count, NI*