

Letter to the Editor

A novel mutation in IFN- γ receptor 1 presenting as multisystem *Mycobacterium intracellulare* infection

To the Editor:

We report the case of a 15-month-old boy with disseminated *Mycobacterium intracellulare* infection causing multifocal osteomyelitis and pneumonia. A novel heterozygous frameshift mutation (805delT) encoding the IFN- γ receptor 1 (IFNGR1) was identified. Cell surface receptor expression was upregulated, consistent with dominant negative effect. After antimycobacterial treatment, the infection resolved and he has remained healthy on antimycobacterial prophylaxis with the exception of a diarrheal illness.

A 15-month-old white boy was hospitalized after a workup for fever of unknown origin revealed right upper-lobe pneumonia. His history was significant for being unimmunized and failure to thrive, and his primary diet was a homemade formula consisting of unpasteurized goat's milk, cooking oil, and probiotics. Lytic lesions were seen on chest x-ray, and a bone scan revealed a total of 9 bone lesions involving the ribs, long bones, and skull. Family history was negative for mycobacterial infections or other unusual infectious disease. Both parents as well as 6 full siblings and 2 half siblings are in good health. The diagnostic workup included a bronchoalveolar lavage (BAL) and lung biopsy, biopsy of lytic lesion in the tibia, bone marrow aspirate, purified protein derivative skin test, complete blood cell count, C-reactive protein, and cultures of blood, stool, and BAL fluid. *Mycobacterium intracellulare* was isolated from BAL fluid, and other infectious etiologies were ruled out. His purified protein derivative skin test result was positive at 12 mm, and serum IFN- γ release assay for *Mycobacterium tuberculosis* was negative. He was started on isoniazid, rifampin, ethambutol, and azithromycin. His fevers rapidly resolved with treatment, and he was released from the hospital after 3 weeks.

Further immunologic workup revealed normal T/B/natural killer cell numbers by flow cytometry. IFNGR1 (CD119) was detected in high levels on his monocytes by flow cytometry. IL-12 levels were slightly elevated at 8 pg/mL. Genetic analysis for IFN- γ receptor mutation indicated a heterozygous deletion (c.805delT) leading to a frameshift and a stop codon. Flow cytometric analysis of parental monocytes showed normal IFNGR1 expression, indicating that the patient most likely had de novo autosomal-dominant IFNGR1 deficiency.

Autosomal-dominant IFNGR1 deficiency is a rare primary immunodeficiency disease that renders the affected individual susceptible to nontuberculous environmental mycobacterial infection. Nontuberculous mycobacteria are ubiquitous organisms in our environment but are poorly pathogenic in immunocompetent persons. Infection with other intracellular bacterial (most frequently *Salmonella*), fungal (*Histoplasma* and *Coccidioides*), and viral (varicella-zoster virus and cytomegalovirus) pathogens has been described in the conditions that are in the cluster of disorders known as Mendelian susceptibility to mycobacterial disease (MSMD).^{1,2} MSMD is a heterogeneous collection of disorders that share susceptibility to bacillus Calmette-Guerin (BCG) and nontuberculous mycobacteria as well as the other pathogens noted. To date, mutations in 9 genes

(*IFNGR1*, *IFNGR2*, *STAT1*, *IL-12 β p40* [IL12B], *IL12RB1*, *NEMO*, *ISG15*, *IRF8*, and *GATA2*) have been associated with nontuberculous mycobacterial infections.³ IFNGR1 deficiency is an unusual immunodeficiency in that it exhibits both recessive and dominant inheritance patterns. Recessive IFNGR1 deficiency is usually complete as the biallelic mutations usually result in loss of the receptor from the cell surface and complete loss of IFN- γ response.⁴ Partial recessive forms of IFNGR1 deficiency have also been described.^{5,6} Dominant negative heterozygous mutations cause partial deficiencies due to the function of the wild-type allele being inhibited by the mutant IFNGR1 receptor allele. The mutant allele is nonfunctional but is unable to be removed from the cell surface, leading to the accumulation of nonfunctional receptors on the cell surface. Patients with recessive complete mutations develop mycobacterial disease at an earlier age, are less responsive to antibiotics, relapse more frequently, and have a higher mortality rate than do those with dominant disease.⁷ Patients with dominant partial mutations develop *Mycobacterium avium* complex (MAC) or BCG osteomyelitis more frequently.⁷

In conclusion, the syndromes referred to as MSMD are a heterogeneous group of primary immunodeficiencies. In addition to recessive or dominant inheritance, MSMD can be classified as partial or complete deficiencies on the basis of retained cellular responsiveness to IFN- γ . MSMD causes increased susceptibility to nontuberculous mycobacterial species. After excluding HIV, or cystic fibrosis in the case of isolated pulmonary nontuberculous mycobacterial infections, clinicians should consider defects in the IFN- γ -IL-12 immune pathway in patients with severe or recurrent mycobacterial infections. Numerous countries still use the BCG vaccine, and MSMD may present as a localized, regional, or disseminated post-BCG mycobacterial infection. Our patient presented with nonspecific symptoms of fever and lymphadenopathy and was eventually diagnosed with MAC pneumonia and multifocal osteomyelitis. MAC osteomyelitis is a common presentation of autosomal-dominant IFNGR1 defects.^{3,8} These patients respond well to antibiotics, and our patient has done well on prophylactic antibiotics and is infection free 7 months after presentation. In patients with partial disease and poor response to antibiotics, IFN- γ may be helpful because they retain some IFN- γ responsiveness.

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