Journal of Clinical Immunology (2019) 39:127–130
https://doi.org/10.1007/s10875-019-00595-7

LETTER TO EDITOR

A Novel Recessive Mutation of Interferon-γ Receptor 1 in a Patient with *Mycobacterium tuberculosis* in Bone Marrow Aspirate

Mahsima Shabani[1,2] · Soheila Aleyasin[3] · Sara Kashef[3] · Samaneh Zoghi[4,5,6] · Caroline Deswarte[7,8] · Jean-Laurent Casanova[7,8,9,10,11] · Jacinta Bustamante[7,8,11,12] · Nima Rezaei[1,2,13]

Received: 13 October 2018 / Accepted: 21 January 2019 / Published online: 5 February 2019

To the Editor

In this letter, we report a case of IFN-γR1 deficiency with a novel bi-allelic mutation in exon 6 of *IFNGR1* gene and multiple bacterial, viral, and fungal infections, who had positive PCR for *Mycobacterium tuberculosis* in bone marrow aspirate. To the best of our knowledge, recessive complete IFN-γR1 deficiency is seldom manifested by disseminated *M. tuberculosis* infection.

Case Presentation

The patient was a 2-year-old boy from consanguineous parents from Iran. He had a normal development and was healthy until 2 months prior to his first admission. At first, he was admitted due to fever, diarrhea, and abdominal distention. Despite starting antibiotic therapy with Ceftriaxone, he had developed decreased appetite and malaise. Ultrasonography (US) revealed intussusception which was reduced via enema. Additional findings in US were multiple mildly enlarged paraaortic and mesenteric lymph nodes. The patient's symptoms gradually subsided following add-on treatment with Metronidazole and Vancomycin. This patient was not vaccinated with Bacillus Calmette–Guérin (BCG), since his sibling had died at the age of 2 months due to severe sepsis.

One week later, he was admitted with fever, cough, abdominal distention, and oral aphthous lesions. Laboratory studies reported leukocytosis (WBC 30,500/mm^3) and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels of 140 mm/h and 96 mg/L, respectively. In physical examination, hepatomegaly was not palpable since the abdomen was severely distended. According to unilateral patchy infiltrations observed in chest x-ray and worsening of the febrile and ill

✉ Soheila Aleyasin
alyasins@sums.ac.ir

✉ Nima Rezaei
rezaei_nima@tums.ac.ir

1 Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Dr Qarib St, Keshavarz Blvd, Tehran 14194, Iran

2 Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

3 Department of Immunology and Allergy, Shiraz University of Medical Sciences, Shiraz, Iran

4 Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Vienna, Austria

5 CeMM Research Centre for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

6 Primary Immunodeficiency Diseases Network (PIDNet), Universal Scientific Education and Research Network (USERN), Vienna, Austria

7 Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Institut National de la Santé et de la Recherche Médicale, Paris, France

8 Paris Descartes University, Paris, France

9 St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA

10 Howard Hughes Medical Institute, New York, NY, USA

11 Pediatric Hematology-Immunology Unit, Assistance Publique-Hôpitaux de Paris AP-HP, Necker Hospital for Sick Children, Paris, France

12 Center for the Study of Primary Immunodeficiencies, Assistance Publique-Hôpitaux de Paris AP-HP, Necker Hospital for Sick Children, Paris, France

13 Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

condition of the patient Vancomycin was administered. The patient also suffered from anemia with a hemoglobin level of 6 g/dL (reference level, 11–14 g/dL) without reticulocytosis and with normal hemoglobin electrophoresis, which was treated with irradiated packed-cell transfusion. Further immunological studies showed normal lymphocyte by flow cytometry, low dihydrorhodamine (DHR) activity (80 and 60%), and low levels of immunoglobulins (IgG 14 mg/Dl (reference level, 216–1010), IgA 1.86 mg/dL (9–148), IgM 4.8 mg/dL (17–223), IgE 1.54 IU/mL (2–373)); Thus, intravenous immune globulin (IVIG) was prescribed due to the impression of primary immunodeficiency (PID). Unexpectedly, the patient's febrile condition became even worse. Total protein level was within normal limits (7.6 g/Dl), whereas albumin levels were decreased to 2.9 g/dL.

The abdominal US showed prominent liver size (about 11 cm) and upper normal limit spleen size, both with normal parenchymal echo and without coarseness or space-occupying lesion. Diffused lymphadenopathy in pancreatic, celiac, and porta hepatis regions and the root of mesentery in right lower quadrant of the abdomen was observed. Fine-needle aspiration of mesenteric lymph nodes did not reveal any malignant cells; just a polymorphous population of lymphocytes with groups of epithelial cells in a bloody background was observed.

On the 12th day of admission, vesiculobullous eruptions throughout the body developed which were suggestive of chicken pox and were healed after IV Acyclovir injection. Positive VZV PCR of the skin lesions confirmed the diagnosis. Additionally, the patient developed resistant oral thrush and napkin dermatitis with positive *Candida albicans* culture in urine and sputum. Due to the resistance of lesions to oral Nystatin drop, local clotrimazole ointment, and oral fluconazole, IV amphotericin-B infusion was started. Once again, the patient was transfused with irradiated packed cells due to severe anemia (hemoglobin, 7.2 g/dL).

In laboratory findings, he had a negative PPD (purified protein derivative) test compared with age-adjusted healthy control reference level and a positive Widal test with 1/1280 titer (OA and OB antigens) of *Salmonella paratyphi*. Indirect immunofluorescent assay for Leishmania was negative. Serum PCR results were negative for *M. tuberculosis*, CMV, and *Aspergillus* but positive for HSV. Serum antibodies against HIV, HCV, HBV, and EBV were negative. Autoantibody and serum complement levels were within normal limits. Additional laboratory findings noted triglyceride level of 440 mg/dL (reference level, < 125 mg/dL), fibrinogen level of 225 mg/dL (150–400 mg/dL), ferritin level of 303 ng/mL (7–140 ng/mL), and normal liver transaminase levels and alkaline phosphatase of 2240 U/L (100–350 U/L). Once again, normal total protein level (6.1 g/dL) and decreased albumin level (2.4 g/Dl) were detected. Prolonged fever, hypertriglyceridemia, splenomegaly, elevated inflammatory markers, and anemia led us to investigate further hemophagocytic lymphohistiocytosis (HLH) findings. However, later bone marrow analysis reported normocellular marrow with mild myeloid hyperplasia and no evidence of macrophage activation. The patient's complaints subsided within 48 h after IV hydrocortisone administration and he was afebrile.

Once again, the patient developed fever, abdominal distention, and ileus, which was treated with meropenem. This time, a thorough cardiac, neurologic, and eye examination was done for the patient by associated specialists. There were no abnormalities in examinations. In order to investigate evidence of malignancies, the patient underwent a whole body scan which was normal. Abdominal sonography reported hepatomegaly without splenomegaly and moderate free fluid in the pelvic and abdominal cavity. Another bone marrow aspiration was done for the patient with a positive PCR report for *M. tuberculosis* and negative for leishmaniasis. Of note, there was no evidence of mycobacterial infections until his third admission which was about 4 months after his initial symptoms. Thereby, anti-mycobacterial treatment with rifampin, isoniazid, and ethambutol was started. At first, the patient's conditions improved and he was a candidate of HSCT. But unfortunately, he died 5 months later due to sepsis, disseminated intravascular coagulation, and alveolar hemorrhage.

Whole-exome sequencing (WES) analysis of the patient revealed a homozygous c.745delA mutation in exon 6 of the *IFNGR1* gene leading to a predicted frameshift mutation (p.Ile249Phe fs*11). This mutation was confirmed by Sanger sequencing in the patient. In addition, both parents were heterozygous for the mutation (Fig. 1). No cellular samples were available from the patient to study in vitro the impact of the mutation in term of protein expression and IFN-γ signaling. This is the first bi-allelic mutation in 6th exon of *IFNGR1* gene. This variant is predicted to lead to a frameshift, p. Ile249Phefs*11. Even though no data is available about the expression level of IFN-γR1 in this patient, we assume this mutation may have brought about complete deficiency of functional IFN-γR (without protein expression), since almost the entire part of the docking site of this protein to membrane is affected. Unfortunately, level of IFN-γ on plasma was not measured. As the patient had various criteria of HLH, we analyzed also the loci of the genes involved in HLH but no mutation was observed.

Discussion

Mendelian susceptibility to mycobacterial diseases (MSMD) is caused by inborn errors in pathways of

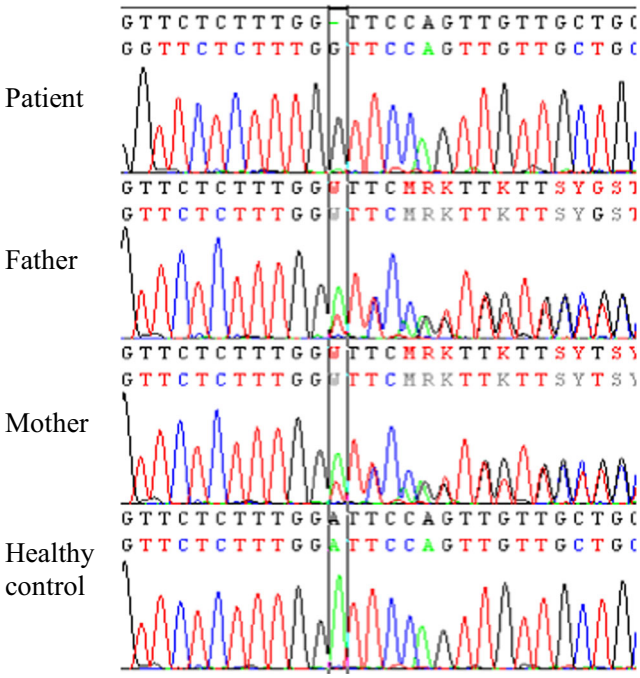

Fig. 1 Complete IFN-γ R1 deficiency. Genetic analysis of *IFNGR1* gene in patient c.745delA/745delA, patient's father c.745delA/WT, patient's mother c.745delA/WT, and healthy control WT/WT. The c.745delA is a predicted frameshift mutation leading to p.Ile249Phefs*11

IFN-γ mediated immunity [1]. Mutations in IFN-γ receptor 1 (IFN-γR1), the ligand-binding domain of IFN-γR, have been associated with defective macrophage response to various mycobacterial infections and increased the vulnerability of patients to BCG vaccine and environmental mycobacterial infectious diseases [2]. IFN-γR1 deficiency (OMIM: 107470) is caused by bi-allelic or mono-allelic mutations in *IFNGR1* responsible for autosomal recessive (AR) complete or partial; and dominant (AD) disease, respectively. To date, six AD mono-allelic mutations have been identified in exon 6 of *IFNGR1* gene which cause partial deficiency of *IFNGR1* [3], whereas multiple bi-allelic AR mutations with partial or complete deficiency of IFN-γR1 are documented in other exons [3]. The genetic pattern and IFN-γR expression level define the severity of symptoms and age at the onset [3]. Clinical manifestations in AR complete IFN-γR1 deficiency patients, as in this case, are more severe than in AD patients.

AR complete IFN-γR1 deficiency is characterized by an impaired response to IFN-γ, despite high levels of serum IFN-γ [4]. Patients with AR complete IFN-γR1 deficiency mostly present with early-onset infections with BCG vaccine, environmental *Mycobacterium* (such as *M. bovis*, *M. avium*, *M. avium complex*, *M. scrofulaceum*, *M. chelonae*, *M. mageritense*, *M. peregrinum*, *M. fortuitum*, *M. smegmatis*, *M. abcessus*, *M. szulgai*) and less common reports of *M. tuberculosis*, *M. bovis*, *Listeria*, *Salmonella*, *Haemophilus*, *Klebsiella*, *Legionella*, *Shigella*, *Mycoplasma*, and viral infections [3, 5]. Rarely, patients with AR complete IFN-γR1 deficiency have been reported to be accompanied by manifestations of hemophagocytosis [1]. In addition to prolonged antibiotic therapy, which is the only accepted method for controlling the susceptibility to resistant infections, hematopoietic stem cell transplantation (HSCT) is the single curative treatment for these patients. However, a high rate of rejection has been observed due to high serum IFN-γ levels [6].

We report a novel homozygous mutation in *IFNGR1* gene due to a deletion and a frameshift mutation in c.745delA (predicted p.Ile249Phefs*11). This is the first reported bi-allelic mutation in 6th exon of *IFNGR1* gene affecting the transmembrane domain of IFN-γR1 protein conferring probably a loss-of-protein and loss-of-function IFN-γR1 deficiency.

The unusual pattern of common infections like VZV, *M. tuberculosis*, Salmonellosis, diffuse Candidiasis, and the resistance of pathogens to first-line treatments is in accordance with previously reported complete forms of IFN-γR1. However, disseminated *M. tuberculosis* is not commonly expected in AR IFN-γR1 deficiency patients. On the other hand, negative serum PCR for *Mycobacteria* was a remarkable feature, regarding the patient's life-threatening *Mycobacterium tuberculosis* infection.

Likewise a few reported MSMD patients, this patient had also developed hemophagocytosis [1, 7]. In fact, IFN-γ-associated pathways are pivotal in driving HLH or macrophage activating syndrome. Thus, studies suggest that macrophage activation in MSMD patients with defective IFN-γ pathways depends on TLR overstimulation by severe *Mycobacteria* infections; however, this association is still a controversy [8].

Interestingly, the patient developed hypogammaglobulinemia which is not expected in this group of PID. The latter may have developed either due to a secondary immunodeficiency driven by recurrent infections, the patient's malnourished hypoalbuminemic status or protein loosing enteropathy accompanied by mesenteric lymphadenopathy, or an additional unidentified mutation.

Although AR complete IFN-γR1 deficiency is a rare disease and there is yet to be elucidated about the clinical presentation and pathophysiology of the disease, the unexpected manifestations in this patient may suggest the bi- or polygenetic nature of his disease. In this regard, whole exome sequencing of the patient excluded other associated genes, in particular, known genes of HLH.

In conclusion, the vast range of microbial pathogens and infected sites in patients with MSMD indicates the importance of pathogen identification in prescribing specific timely treatment in these PID. We assume an earlier definite diagnosis of this patient followed by earlier anti-mycobacterial therapy and HSCT could have improved his survival.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Staines-Boone AT, Deswarte C, Venegas Montoya E, Sánchez-Sánchez LM, García Campos JA, Muñiz-Ronquillo T, et al. Multifocal recurrent osteomyelitis and hemophagocytic lymphohistiocytosis in a boy with partial dominant IFN-gammaR1 deficiency: case report and review of the literature. Front Pediatr. 2017;5:75.
2. Rezaei N, Aghamohammadi A, Notarangelo L.D. Primary immunodeficiency diseases; definition, diagnosis, and management. Springer-Verlag Berlin Heidelberg; 2017.
3. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol. 2014;26(6):454–70.
4. Fieschi C, Dupuis S, Picard C, Smith CI, Holland SM, Casanova JL. High levels of interferon gamma in the plasma of children with complete interferon gamma receptor deficiency. Pediatrics. 2001;107(4):E48.
5. Dorman SE, Picard C, Lammas D, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. *Lancet (London,* England) 2004; 364(9451): 2113–2121.
6. Rottman M, Soudais C, Vogt G, Renia L, Emile JF, Decaluwe H, et al. IFN-gamma mediates the rejection of haematopoietic stem cells in IFN-gammaR1-deficient hosts. PLoS Med. 2008;5(1):e26.
7. Tesi B, Sieni E, Neves C, Romano F, Cetica V, Cordeiro AI, et al. Hemophagocytic lymphohistiocytosis in 2 patients with underlying IFN-gamma receptor deficiency. J Allergy Clin Immunol. 2015;135(6):1638–41.
8. Ishii E. Hemophagocytic lymphohistiocytosis in children: pathogenesis and treatment. Front Pediatr. 2016;4:47.