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Systemic aspergillosis in a patient with interferon gamma receptor 1 deficiency; a case report

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Abstract

Background Interferon-gamma receptor deficiency is a heterogeneous spectrum of disease which involves mutations in *IFNGR1*, *IFNGR2* genes, and the downstream signaling proteins such as STAT1. These mutations are associated with immunodeficiency 27 A and 27B, making the patient prone to mycobacterial infections. Patients with this condition are also at increased risk for affliction with viral and bacterial infections, such as with the Herpesviridae family, Listeria, and Salmonella. Moreover, SH2B3 mutation is associated with autoimmune and lymphoproliferative conditions.

Case presentation the patient was a 19-month-old infant girl who presented with a two-week history of fever. She had near-normal flowcytometry with high IgM and IgE. She had pneumonic infiltration in her chest and right hilar and para-aortic lymphadenopathy. PCR of whole blood for Aspergillus fumigatus came back positive. In her Whole Exome Sequencing she had *IFNGR1* and *SH2B3* mutations.

Conclusion systemic fungal infections such as Aspergillosis can occur in patients with interferon-gamma receptor one deficiency. This type of immunodeficiency should be considered in treating patients with systemic Aspergillosis.

Keywords IFNGR1D, SH2B3, Aspergillosis

Introduction

Interferon-gamma receptor deficiency is a heterogeneous spectrum of disease which involves mutations in *IFNGR1*, *IFNGR2* genes, and the downstream signaling proteins such as *STAT1* [1]. These mutations are associated with immunodeficiency 27 A and 27B, making the patient prone to mycobacterial infections [1–3]. Patients with this condition are also at increased risk for affliction with viral and bacterial infections, such as with the Herpesviridae family, Listeria, and Salmonella [4, 5].

Lack of cytokine production after interferon addition and high serum levels of interferon-gamma are the diagnostic hallmarks of the disease [6]. The inheritance of these conditions might follow autosomal recessive

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Table 1 Clinical lab data of the patient at 19 months old

Lab data	result	Reference range
WBC (/mm^3)	26,100	4000–11,000
Neutrophils (%)	57	-
Lymphocytes (%)	24	-
Eosinophils (%)	**16**	-
Monocytes (%)	2	-
Basophils (%)	1	-
ESR (mm/hr)	85 (H)	< 20
CRP (?)	122 (H)	< 6
Serum IgM (g/L)	4.10 (H)	0.19–1.5
Serum IgG (g/L)	10.1	4.53–9.16
Serum IgA (g/L)	0.70	0.22–1.18
Serum IgE (IU/mL)	133.0 (H)	< 50
Fibrinogen (mg/dL)	375	200–550
Uric acid (mg/dL)	5.1	3.6–7.7
Triglycerides (mg/dL)	265 (H)	< 150
Total cholesterol (mg/dL)	137	< 200
LDH (IU/L)	388	120–300
Ferritin (ng/mL)	473.5 (H)	10.9–117
CH50 (U/mL)	72.0	50–150
DHR (%)	95	≥ 95
CD3 (%) (absolute count)	71.96 (5617.71)	53–84 (2500–5500)
CD4 (%) (absolute count)	49.21 (3841.68)	35–61 (1600–4000)
CD8 (%) (absolute count)	17.70 (1381.78)	12–28 (560–1700)
CD4/CD8 ratio	2.78	1–3
CD7 (%) (absolute count)	77.78 (6073.62)	57–87 (2670–6100)
CD19 (%) (absolute count)	17.38 (1356.80)	6–32 (300–2000)
CD20 (%) (absolute count)	17.40 (1358.36)	6–32 (300–2000)
CD16 (%)	11.49	5–19
CD56 (%)	6.54	5–19
CD16/56 (%) (absolute count)	5.99 (467.62)	4–18 (170–1100)
Interferon gamma (pg/mL)	65	< 18

Table 2 Follow-up lab data of the patient at 20 months old

Lab data	result	Reference range
WBC (/mm^3)	20,400	4000–11,000
Neutrophils (%)	24	-
Lymphocytes (%)	50	-
Eosinophils (%)	24	-
Monocytes (%)	1	-
Basophils (%)	1	-
Hb (g/dL)	11.1	12–14
Platelets (/mm^3)	682,000	150,000-450,000
ESR (mm/hr)	13	< 20
CRP (mg/dL)	20	< 6

or autosomal dominant modes with complete or partial penetrance [7]. Complete autosomal recessive type of Interferon-gamma receptor one deficiency carries the worst prognosis, while the partial autosomal dominant form has the best prognosis [8, 9]. Hematopoietic Stem Cell Transplantation (HSCT) is the mainstay of treatment in these patients [9].

In this study, we report a case of Interferon gamma receptor deficiency with aspergillosis who has presented with generalized lymphadenopathy.

Case presentation

The patient was a 19-month-old infant girl who presented with a two-week history of fever. with no sign of cough, respiratory distress, or abdominal tenderness. The patient did not have any history of recurrent infections; however, since the patient's sibling had passed away at two months old following vaccination with BCG, oral poliovirus vaccine, and hepatitis B vaccine, the possibility of immunodeficiency was considered. The consanguinity history of her parents was positive and the patient's grandmother suffered from systemic lupus erythematous. She had hepatosplenomegaly and generalized lymphadenopathy in her physical examination. The patient had not received BCG vaccine due to the possibility of hemophagocytic lymphohistiocytosis (HLH). HLH was then ruled out by bone marrow aspiration and biopsy which showed essentially cellular marrow with mild shift to the left and no evidence of hemophagocytosis. Chest and abdominopelvic CT scans were taken which showed multiple lymphadenopathies in hilar and para-aortic regions as well as ground-glass opacities suggestive of pneumonic infiltration in the lower lobes of both lungs. Immunodeficiency workup was done for the patient and the results of her laboratory studies are summarized in Table 1. She had near-normal flowcytometry with high IgM and IgE. Moreover, since she had eosinophilia in her complete blood count, fungal infections were considered. PCR of whole blood for Aspergillus fumigatus came back positive and the whole blood PCR for Mycobacterium came back negative. The Whole Exome Sequencing of the patient showed autosomal recessive *IFNGR1* (NM_000416:exon6) mutation of Chr6-137522134 T-c.745delA:p.1249Ffs*11 which was confirmed by Sanger sequencing method. Also, the parents of the patient underwent whole exome sequencing and they were heterozygote for the same mutation; thus, showing the autosomal recessive nature of this disease.

The patient also had a homozygote mutation in *SH2B3* mutation; however, this mutation was not confirmed by Sanger sequencing method due to financial constraints.

The patient then received two weeks of intravenous Voriconazole 4 mg/Kg every 12 h, Vancomycin 10 mg/Kg every six hours, and Meropenem 40 mg/Kg every eight hours. She was discharged with oral Voriconazole 4 mg/Kg every 12 h for three months. In her follow up session after one month she had no signs and symptoms and her lab data was as follows in Table 2.

She was planned to have hematopoietic stem cell transplantation and HLA typing was done for her and her family members; however, no matched donor was found. Prophylactic antibacterial, antiviral, and

antifungal antibiotics were started for her. Moreover, due to the mutation in *SH2B3* she was put on Rituximab 375 mg/m^2/dose once every two weeks; however, after three doses of Rituximab, she developed severe bloody diarrhea which in further follow up turned out to be Salmonellosis which she was previously prone to due to IFNGRD. Rituximab was discontinued for the patient but she developed septic shock and is currently under treatment for this condition.

Discussion

In this article, we described a case with interferon gamma receptor 1 deficiency who came with generalized lymphadenopathy and had systemic aspergillosis.

IFNGR1 gene mutations lead to autosomal recessive immunodeficiency type 27 A and autosomal dominant immunodeficiency type 27B as a part of a heterogenous group of diseases called Mendelian Susceptibility to Mycobacterial Disease (MSMD) [10]. The patients are also susceptible to low-virulence intracellular pathogens such as viruses, Histoplasma, and Toxoplasma [11].

Upon connection of interferon gamma to its receptors, various cytokines are released from macrophages and dendritic cells to induce the microbicidal effects of the leukocytes [1]. Multiple case reports have described systemic infections with non-tuberculous mycobacteria and intracellular microorganisms in patients with IFNGR1D [12–16]. However, no systemic infection with Aspergillus fumigatus in this context had been reported.

SH2B3 is another gene that was mutated in this patient. This gene is responsible for stages in the process of negative regulation of hematopoiesis [17]. Consequently, mutated SH2B3 can result in hypercellularity of lymph nodes and spleen. This phenomenon can predispose the patients to hematologic malignancies such as lymphoma this mechanism of action explains the reason behind the patient's generalized lymphadenopathy. Due to this reason, the patients with this condition better undergo routine investigations to rule out malignancies.

Mutations in *SH2B3* gene have also been associated with autoimmune diseases such as type 1 diabetes mellitus, celiac disease, systemic lupus erythematous, rheumatoid arthritis, and multiple sclerosis [18–21]. Consequently, the probability of autoimmunity should also be considered in this patient.

Conclusion

systemic fungal infections such as Aspergillosis can occur in patients with interferon-gamma receptor one deficiency. This type of immunodeficiency should be considered in treating patients with systemic Aspergillosis.

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Authors' contributions
The authors are members of the team responsible for providing medical care to the patient in Shiraz and Tehran. AA wrote the first manuscript and all of the authors have read te manuscript and revised it as necessary.

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Not applicable.

Declarations

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Not applicable.

Consent for publication
The patient's parents signed an informed consent form for publication of their child's clinical data if she remained anonymous.

Competing interests
The authors declare no competing interests.

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