CASE REPORT
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Mendelian Susceptibility to Mycobacterial Disease with Signal Peptide Peptidase-like 2A (*SPPL2A)* Deficiency: A Case Report

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ABSTRACT

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare genetic disorder characterized by immunodeficiency, leading to increased susceptibility to mycobacterial infections. Studies have identified several genes that are associated with MSMD in the interferon-gamma/interleukin (IL)-12/IL-23 signaling pathway.

One of these genes is signal peptide peptidase-like 2A (*SPPL2A),* which is very rare, and defects in this gene have been reported only in 3 patients with MSMD. This case report presents the rare *SPPL2A* deficiency with an abnormal presentation, which adds to the limited number of these genetic defects.

This report presents the case of a 1-year-old boy who developed Bacillus Calmette-Guerin infection (BCGitis), lymphadenopathy, and an arm abscess that required surgical drainage following BCG vaccination. The patient had hypogammaglobulinemia, normal B-cell counts, normal CD4 counts, low CD8 counts, and *SPPL2A* deficiency, which is related to MSMD. The patient received a second line of anti-tuberculosis agents.

SPPL2A deficiency is associated with MSMD and can cause severe BCGitis and disruption of immunoglobulin production.

Keywords: Bacillus calmette-guerin infection; Mendelian susceptibility to mycobacterial disease; Signal peptide peptidase-like 2A deficiency; Signal peptide peptidase

INTRODUCTION

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare genetic disorder with a prevalence of 1 in 50000 individuals, characterized by inborn errors of immunity which can cause immunodeficiency. These genetic defects make individuals more susceptible to infections caused by both less virulent mycobacteria,

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such as Bacille Calmette-Guérin (BCG),and environmental nontuberculous mycobacteria (NTM), as well as more virulent bacteria such as *Mycobacterium tuberculosis* (TB). In MSMD patients, the severity of BCG infections can be variable. Some patients develop localized infections that are relatively mild and limited to a specific area of the body. However, others may develop disseminated and life-threatening infections.[1,2] In Iran, the BCG vaccine is administered as a single dose after birth to give protection against TB.[3] Administration of BCG can develop into BCG infection (BCGitis) in certain patients and manifests as a regional or disseminated disease. The clinical characteristics include lymphadenopathy and skin involvement. However, infections of the lungs, central nervous system, bone, and gastrointestinal tracts have been reported. These manifestations can occur within the first year following the BCG vaccination.[4,5] The comorbid conditions and diseases associated with BCGitis and MSMD are recurrent pneumonia and chronic granulomatous disease (CGD).[6,7] Patients with CGD are more susceptible to MSMD. These diseases have an inborn error of immunity, such as leukocyte phagocytic dysfunction and natural killer gene defects, which are associated with interferon-gamma (IFN- γ).[8]

The pathogenesis of MSMD involves mutations in genes associated with the IFN-γ/interleukin (IL)-12/IL-23 signaling pathway, emphasizing the critical role of this signaling axis in antimycobacterial immunity. Phagocytes can detect mycobacterial infection by their receptors. This recognition triggers phagocytic uptake of the bacteria and leads to the production of essential cytokines, including IL-12, IL-23, and other immune mediators. These cytokines play an essential role in activating and modulating the immune response against mycobacterial pathogens. Studies have discovered defective genes in the MSMD. Several genes associated with MSMD are involved in the IFN/IL-12/IL-23 signaling pathways. More than 19 genes were identified in the genetic profile of the disease. It is important to note that the prevalence of the mutated genes can vary among MSMD patients. Different individuals may carry mutations in specific genes.[9,10]

Understanding the genetic basis of MSMD and its impact on the immune system is essential for early diagnosis and appropriate management for the affected individuals. By identifying and addressing these underlying genetic defects, healthcare providers can improve the prognosis and quality of life for patients with MSMD and reduce the risk of life-threatening mycobacterial infections.

CASE PRESENTATION

We present the case of a 1-year-old boy with a gestational age of 36 weeks and birth weight of 3200 grams with consanguineous parents (first cousins) in Iran. The patient is the second child, and there was a negative history of immunodeficiency, autoimmunity, and malignancy in the family members. At 4 months of age, he presented with irritability and swelling in the left axilla, shoulder, and arm along with tenderness at the site of the BCG vaccination were detected through physical examination. With the clinical impression of BCGitis, aspiration of the swelling area was done, and antibiotics (isoniazid and rifampin [all drugs manufactured in IR, Iran]) were started for the patient. The patient's symptoms progressed and did not resolve, and after a month, he presented with necrotic lymph nodes measuring 4×3 cm in the arm, multiple enlarged axillary lymph nodes, and splenomegaly. Also, the patient had signs and symptoms of acute otitis media. The patient was referred to our immunology clinic for immunodeficiency workup at 8 months of age. Due to the difficult treatment and poor response to the medications, an Initial immunodeficiency workup was performed for the patient. He had low CD8 T lymphocytes (initial absolute count: 479/μL; repeated absolute count: 320/μL; normal range: 500–1700/μL) and near the low limit of normal IgG level (initial: 2.11; repeated: 2.4 g/L; normal range: 2.32–1411). The patient had normal CD19 and CD20 counts (Table 1) and normal anti-tetanus IgG (2.09 IU/mL). The patient had hypogammaglobulinemia with normal B-cell counts and decreased CD8 counts. The whole exome sequencing was done for the patient due to suspected immunodeficiency. He had a homozygous deletion of exons 11 to 14 in the *SPPL2A* gene around the following region: Chr15-51012137 to 51018574. Mutations in this gene have been identified in patients with mycobacteriosis due to MSMD. In the following months, until the age of 10 months, despite being administered antibiotics for a mycobacterial soft tissue infection in the left arm and shoulder, the symptoms persisted without resolution. Consequently, the treatment regimen was altered from 2 anti-TB drugs to a 4-drug combination comprising isoniazid, rifampin, clarithromycin, and ethambutol (all manufactured in IR,

Iran). Despite this intensified medication regimen, the swelling in the arm continued to enlarge, eventually developing into an abscess. On examination, the patient had multiple lymphadenopathies in the axillary lesion, an abscess in the left arm, and redness of the clavicular area. The patient underwent surgery for excision and drainage of the abscess. The infected tissue was excised and sent to pathology. The pathological diagnosis revealed caseating granuloma consistent with BCG adenitis. After that, the second line 4-drug anti-TB regimen (ethambutol, isoniazid, rifampin, clarithromycin (All drugs are manufactured in IR, Iran)) was continued for 3 months with good clinical response and resolved lymphadenopathy and swelling. Then, the patient continued maintenance therapy of isoniazid, rifampin, and ethambutol. The patient had a good response to therapy. The patient has regular follow-ups every 3 months. In follow-up, The patient did not express any complaints and showed good adherence to the prescribed medication regimen. The complete initial and repeated lab work-ups are shown in Tables 1 and 2. The clinical timeline of the patient is shown in Figure 1.

Table 1. DHR-flowcytometry and immunoglobulin levels

Lab parameters	Initial test	Repeated test	Reference range
CD3 (Absolute count)	3486	-	1900-1500
CD4 (Absolute count)	2931	-	1400-4300
CD8 (Absolute count)	479	320	500-1700
CD4/CD8 ratio	6.11	-	1-3
CD19 (Absolute count)	3727	2291	610-2600
CD20 (Absolute count)	3726	228	610-2600
CD16/56 (Absolute count)	342	-	160-950
DHR (PMA)	99.83%	-	≥95%
DHR (MFI PMA)	288.01%	-	≥60%
IgM g/dL	0.29	0.27	0-1.45 g/dL
IgG g/dL	2.11	2.40	2.32-14.11 g/dL
Anti-tetanus (IgG) IU/mL	2.09	-	≥1.0 IU/ml has protection
Anti-diphtheria (IgG) IU/mL	0.01	-	≤0.01 IU/mL no protection
IgA g/dL	0.34	0.42	0.13-1.02 g/dL
IgE IU/mL	0.1	-	<15 IU/mL

CD: cluster of differentiation; DHR: dihydrorhodamine; PMA: phorbol myristate acetate; MFI: mean fluorescence intensity; Ig: immunoglobulin; IU: international unit

Table 2. Complete blood count

Lab parameters	Initial test	Repeated test
WBC	14.9 × 10^3/µL	10.2 × 10^3/µL
RBC	5.59× 10^6/µL	5.36 × 10^6/µL
Hb	11.2 g/dL	10.3 g/dL
MCV	67.1 fL	65.9 fL
Platelet	395× 10^3/µL	389× 10^3/µL
Neutrophil count	5.22 × 10^3/µL	3.16× 10^3/µL
Lymphocyte count	8.2 × 10^3/µL	5.81 × 10^3/µL
Monocyte count	0.74 × 10^3/µL	0.51 × 10^3/µL
Eosinophil Count	0.74 × 10^3/µL	0.71 × 10^3/µL
ESR	4 mm/h	-

ESR: erythrocyte sedimentation rate; Hb: hemoglobin, MCV: mean corpuscular volume; RBC: red blood cell; WBC: white blood cells

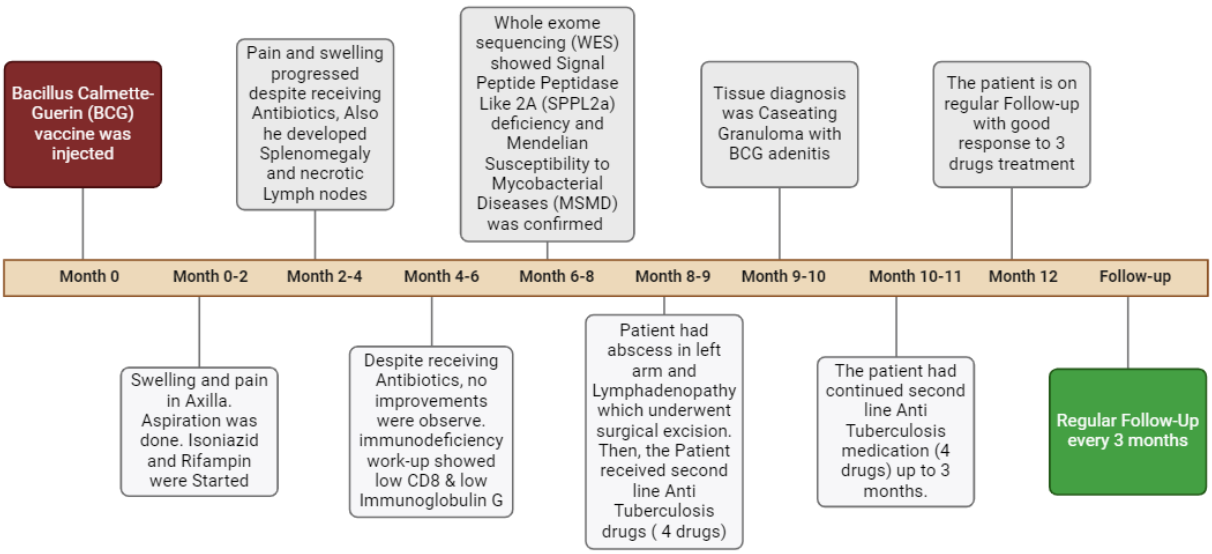

Figure 1. Clinical Timeline of the Disease

DISCUSSION

The occurrence of BCGitis and BCGosis following BCG vaccination indicates the presence of an underlying immunodeficiency. MSMD shows earlier and more severe BCG complications compared to other forms of immunodeficiency. Genetic factors, such as specific gene mutations and vaccine-related factors, can influence the outcome of BCG vaccination in patients with suspected immunodeficiency, such as MSMD.[11] To our knowledge, this is the fourth reported case of MSMD due to *SPPL2A* deficiency in the world and the

first reported case in Iran. In 2018, Kong et al, reported 3 cases of MSMD due to *SPPL2A* deficiency from Morocco and Turkey, which developed lymphadenopathy after BCG vaccination.[12] The reported patients from the Kong et al. study had decreased levels of IgG and normal B cells ($CD19^+$ and $CD20^+$ cells) and normal CD8 counts.[12] However, in our patient, a decreased CD8 count was found. In all cases, the levels of IgG were decreased. Transient hypogammaglobulinemia of infancy occurs at the age of 5 to 24 months. This condition is considered to be a primary immunodeficiency. The level of IgG may become normal from 2 to 6 years of age. The IgG level may be at the lower limit of the normal range until 2 years of age.[13] In the current case, the patient had a low IgG level and the repeated test shows a lower limit of normal IgG level.

The *SPPL2A* gene encodes a transmembrane protease called signal peptide peptidase-like 2A. This protease is present in various tissues of adult humans and is primarily located in late endosomal compartments and lysosomal membranes. The *SPPL2A* gene is on chromosome 15q21.2 and spans approximately 63 kilobases. In patients with a complete deficiency of *SPPL2A*, the reduction of $CD1c^+$ dendritic cells causes the decrease of IL-12 and IL-23. Additionally, memory T cells that do not have functional *SPPL2A* fail to secrete the immune response molecule IFN-γ when stimulated with mycobacterial antigens. These findings suggest that *SPPL2A* deficiency leads to impairments in immune responses and cytokines imbalance against mycobacterial infections, contributing to the susceptibility to mycobacterial disease.[9,14] Kong et al. in 2018 found that the defective genes for *SPPL2A* deficiency were homozygous c.733+1G>A and homozygous c.1328-1G>A mutations.[12] Despite the discoveries in molecular genetics and recent advances in recognizing MSMD, almost half of the cases do not have genetic profiles.[15] In a recent study in Iran, the genomic profile of 32 patients with MSMD was discovered. Sixteen genes were found to have an association with MSMD.[16] It is important to note that none of these patients were associated with *SPPL2A* deficiency. Recent cases of MSMD have been successfully treated with both first-line and second-line anti-TB agents. However, long-term complications like respiratory failure may occur due to the complications of the mycobacterial infection; IFN-γ therapy as adjuvant therapy for anti-TB agents can be used in the long-term management of MSMD. Also, the recommended therapy is second-line anti-TB agents.[17,18] Hematopoietic stem cell transplantation (HSCT) in cases of complete autosomal recessive IFN-γR1 deficiency should be used due to the high mortality of the disease.[19,20]

In Iran, BCG is routinely administered at birth without screening for underlying immunodeficiency. In countries where BCG is used, complete blood counts can detect lymphopenia and potential primary immunodeficiency at birth. Our case is the first in Iran of such gene defects, with unique laboratory abnormalities. Further genomic research is essential to understand the genetic basis of MSMD and explore therapeutic options like anti-TB agents, IFN-γ therapy, and HCST.

Primary immunodeficiencies such as MSMD are suspected in patients with persistent mycobacterial infection. This report adds to the limited number of cases of *SPPL2A* deficiency-related MSMD. The findings of the current case are BCGitis and arm abscess, which require surgical drainage, hypogammaglobulinemia, normal B-cell counts and function, and low CD8 counts.

STATEMENT OF ETHICS

This is a clinical case report; therefore, there was no need to obtain an ethics code from an ethics committee, however, informed written consent was obtained from the parents of the patient for the publication of their clinical data.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

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