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Case Report

Genetic susceptibility to Tuberculosis in an infant with BCG-osis

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ABSTRACT

Mendelian susceptibility to mycobacterial diseases (MSMD) is a group of innate immunity defects characterized by inborn susceptibility to intracellular pathogens. These are due to defects in the interleukin 12-23-interferon gamma γ axis. Twenty-three genetic mutations have been identified in this axis, of which mutation in the *IL12RB1* gene is the most common genetic defect of MSMD identified. An 11-month-old infant presented with features of axillary lymphadenitis and skin lesions both of which were positive for acid-fast bacilli on Ziehl-Neelsen stain and GeneXpert. Keeping a high index of suspicion of primary immunodeficiency, the child was evaluated further and was diagnosed as a case of MSMD with *IL12RB1* gene mutation.

Keywords: Bacillus Calmette Guerin, Genetic susceptibility to tuberculosis, Interferon gamma, Mendelian susceptibility to mycobacterial diseases

INTRODUCTION

Mendelian susceptibility to mycobacterial diseases (MSMD) is a group of innate immune defects localized to 23 genes and 37 clinical phenotypes. Interleukin (IL)-12/23/interferon-stimulated gene 15 (ISG15)-interferon gamma (IFN- γ) axis is the principal immunological pathway for intra-macrophagic pathogens. Defects in this pathway lead to an inborn susceptibility to intracellular pathogens such as Mycobacteria (including Bacillus Calmette Guerin (BCG) vaccine strains and Non Tuberculous Mycobacteria), *Salmonella*, Fungi (*Candida*, *Histoplasma*), parasites like *Leishmania*, and some viruses like Cytomegalovirus (CMV). Mutations in the *IL12RB1* gene are the most common genetic defect identified in MSMD.

CASE REPORT

An 11-month-old male infant, first born of the non-consanguineous union, with normal birth, developmentally normal, and completely immunized, was referred to our institute with a swelling at the BCG injection site since 5 months of age. At 10.5 months of age, he developed a painful swelling in the left axilla with fever, which later developed into an abscess. There was history of

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tuberculosis in the mother at 8 years of age and in the father at 10 years of age; however, no microbiological confirmation was available for the same. No history of early-onset tuberculosis (TB) in other extended family members was present.

On examination, he was well-grown with length (75 cm), weight (9.5 kg), and head circumference (45 cm) between -1 standard deviation to the median. On local examination, the left deltoid had a non-tender erythematous papule with no discharge [Figure 1]. The left axillary node was enlarged (2×2.5 cm), fluctuant and tender [Figure 2]. Systemic examination was otherwise unremarkable.

Chest X-ray was normal. Ultrasonography (USG) of the left axilla showed 4 to 5 lymph nodes with abscess formation. Incision and drainage of the abscess was done and pus was Ziehl Neelsen stain and GeneXpert, positive. Pus culture isolated the MTB complex. The child was started on isoniazid,



Figure 1: Erythematous indurated non-tender papule.



Figure 2: Left axillary node, fluctuant and tender 2×2.5 cm in dimensions.

rifampicin, pyrazinamide (PZA), and ethambutol, as per Revised National Tuberculosis Control Program (RNTCP) protocol.

On follow-up 15 days later, the left axillary node continued to drain pus and there were new-onset skin lesions papulo-macular in nature with central crusting [Figure 3]. Punch biopsy of the skin lesion was also found to be acid-fast bacilli and GeneXpert positive. As two sites i.e., axillary nodes and skin were involved a diagnosis of BCG-osis was made and an attempt was made to look for dissemination. USG abdomen, repeat chest X-ray, and gastric lavage GeneXpert performed was normal. Meanwhile, drug sensitivity revealed PZA resistance confirming disseminated *Mycobacterium bovis* infection [Figure 4]. On Isoniazid, Rifampicin, Ethambutol (HRE)+Ofloxacin there was good clinical response.

As BCG-osis can be a presenting feature of the phagocytic defect chronic granulomatous disease (CGD) and defects in innate immunity (MSMD), primary immunodeficiency was suspected and an immunological workup was done. Lymphocyte subset assay and immunoglobulin levels were normal. CGD was ruled out as the nitroblue tetrazolium test and dihydrorhodamine test were normal. MSMD was suspected in view of BCG-osis. Flow-cytometric expression of CD212 (IL12RB1) on activated T cells was 27% against the control of 75%. Hence, Whole Exome Sequencing was done to identify the genetic defect driving MSMD, which identified a homozygous deletion in the *IL12RB1* gene.

DISCUSSION

MSMD is a rare condition secondary to mutations in at least one of the genes encoding cytokines, receptors, and/or their relative essential modulators of the IL12/23-IFN- γ axis.^[1] If this pathway is defective, the individual becomes more vulnerable to intracellular pathogens such as mycobacteria, including



Figure 3: Skin lesions papulo-macular with central crusting.



Figure 4: Genome sequencing of mycobacterial tuberculosis complex from culture showed 95.2% of the markers for the lineage tool mapped to *Mycobacterium bovis*.

attenuated *M. bovis*-BCG vaccine strains, non-tuberculous environmental mycobacteria, salmonella, fungi, parasites like *Leishmania*, and some viruses like CMV. The identified mutations were reported to be in IFNGR1, IFNGR2, IL12B, IL12R γ 1, signal transducer and activator of transcription 1 (STAT1), IKBKG, CYBB, RORc, IRF8, ISG15, TYK2, JAK1, and NEMO resulting in impaired cellular responses and susceptibility to mycobacterial infections.^[2]

Mutations in *IL12RB1* (with 191 variants reported in 17 exons) are the most affected gene among MSMD patients.^[3] *IL12RB1* deficiency results in the absence of a functioning receptor for both IL12 and IL23 cytokines.^[4] The production of IFN- γ by T cells and NK cells in response to intracellular infections is greatly aided by IL12.^[5] IL23 is a key mediator in employing different components of innate immunity through the induction of IL17 production. IL17 stimulates the production of pro-inflammatory cytokines, chemokines, and prostaglandins.^[6] Therefore, any IL-12 receptor dysfunction may be associated with a greater propensity to become infected with non-typhoidal Salmonellae, poorly pathogenic Non-Tuberculous Mycobacterial infections, and fungal infections.^[7] Therefore, patients with *IL12RB1* mutation along with susceptibility to Mycobacteria are also known to have reported infections with *Candida*, *Histoplasma*, *Giardia*, *Staphylococcus*, *Proteus*, *Enterococcus*, and *Clostridium difficile*. Defects in the TH17 pathway caused by *IL12RB1* are also linked to autoimmunity and autoinflammatory disease. Autoimmune manifestations in the form of inflammatory bowel disease and autoimmune hemolytic anemia with leukocytoclastic vasculitis have been reported.^[8] IL-12 signaling pathway also regulates Fas ligand expression, defect of this regulation in patients with *IL12RB1* mutations

may be a potential cause of presentation with autoimmune lymphoproliferative syndrome-like disease.^[9] These unusual presentations with autoimmunity are not reported in the world literature and need further evaluation.

Different mutations cause heterogeneity in the clinical manifestations and prognosis of the disease. MSMD increases the risk of infection by a particular intracellular pathogens. About 4–80% of MSMD patients may present with BCG-related problems (the practice of immunizing all newborns shortly after delivery may be the cause of this). According to the largest cohort study of MSMD patients conducted in India,^[8] the most common clinical presentation was disseminated BCG-osis (82% of patients). Furthermore, all patients in the cohort had Mycobacterial disease with MTB complex (96%), and non-tuberculous mycobacteria in (4%). Multisystem involvement with Mycobacteria was the most common followed by lymph node involvement, tubercular osteomyelitis, pulmonary, skin, and central nervous system. Moreover, around one-third of patients were infected with more than one organism.

Cytokine production assay, flow cytometry-based tests targeting surface receptors/cytokines/phosphorylated STAT molecules, molecular detection, and other tests are widely used for the evaluation of MSMD.

Treatment options constitute antitubercular treatment (ATT) modified on the basis of drug sensitivity usually given for the duration of 6 months to 2 years based on the site of involvement. ATT may have to be continued for longer periods possibly even for life, and other anti-infective and anti-viral drugs can be selected according to the type of infection. IFN- γ therapy is also available. Hematopoietic stem cell transplant is the definitive treatment. Our patient was continued on ATT for a period of 18 months and currently is on regular follow-up and is clinically well.

CONCLUSION

A high index of suspicion for MSMD should be kept in patients presenting with adverse effects of BCG vaccination and should be investigated for the same.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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