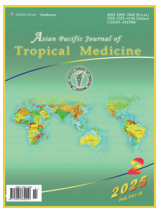

Case Report

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Disseminated BCGosis in an infant with mendelian susceptibility to mycobacterial diseases: A case report

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ABSTRACT

Rationale: Primary immunodeficiency disorders can be fatal especially in infants. Prompt recognition with a comprehensive medical history, genetic evaluation, and appropriate treatment can be lifesaving in a few subtypes.

Patient concerns: A 4-month-old male infant presented with axillary swelling, fever, and ulcerative lesions. Despite care at multiple facilities, symptoms persisted, raising concern for an underlying immunodeficiency. The patient's sibling had similar symptoms and died at six months, suggesting a genetic predisposition.

Diagnosis: Mendelian susceptibility to mycobacterial disease, IFNGR2 deficiency.

Interventions: The patient was treated with tailored anti-tubercular therapy and azithromycin prophylaxis.

Outcomes: Following treatment, the patient's symptoms have resolved. At 20 months, he is thriving with normal development.

Lessons: This case highlights the importance of a thorough medical history and genetic testing in infants with recurrent or unusual infections. Early diagnosis of mendelian susceptibility to mycobacterial disease can lead to effective treatment and better outcomes.

KEYWORDS: Mendelian susceptibility to mycobacterial disease; Interferon-gamma; Tuberculosis; *Mycobacterium bovis*; Case report

1. Introduction

Tuberculosis poses a significant public health challenge in India, with an estimated 2.1 million cases in 2021[1]. Mendelian susceptibility to mycobacterial diseases (MSMD) is a genetic condition that leads to increased susceptibility to infections by mycobacteria, even weakly virulent mycobacteria, including *Mycobacterium bovis*, causing disseminated Bacillus Calmette-Guérin (BCG) infection[2]. This susceptibility is due to defects in genes critical for the immune response against these pathogens[2,3]. The pathogenesis in MSMD revolves around Interferon-γ and its receptor's action on macrophages. The current standard of care involves aggressive antimycobacterial antibiotics against non-tubercular mycobacteria but with greater intensity and duration and azithromycin prophylaxis. Cytokine replacement therapy with interferon gamma is an option in selected patients[4]. Our case highlights the successful management of a child with a tailored regimen.

2. Case report

A 4-month-old male infant presented with recurrent episodes of fever, left axillary swelling, and ulcerative lesion on the left deltoid and cervical region for one month. The child received care at multiple facilities and sought our expertise for a second opinion. The child was healthy till the age of 3 months but later developed numerous episodes of fever, loose stools, left axillary swelling and generalised erythematous rash starting from extremities and progressing to involve the oral cavity and the entire body. The baby had normocytic normochromic anaemia with neutrophilic leukocytosis and received antibiotics for the

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same. However, blood and urine cultures were negative. In view of anemia, packed red blood cell transfusion was given. Persistent fever, despite adequate antibiotics added with elevated lactate dehydrogenase in the presence of hepatosplenomegaly with ascites, prompted a workup for malignancy. Bone marrow aspiration revealed reactive marrow with infection related changes and the culture was sterile. In order to rule out possibility of underlying inborn errors of immunity, lymphocyte subset analysis was done and the result was normal. Nitroblue tetrazolium test to rule out possible chronic granulomatous disease was done and the result was also normal. However, dihydrorhodamine test was positive, the interpretation of the same weren't available. To look for other infections associated with Primary Immunodeficiency, serology was sent for Beta galactomannan (to rule out Aspergillosis infection), which was negative. Skin rash was attributed to drugs and managed conservatively with the application of liquid paraffin.

The child then presented to our hospital with the above-mentioned complaints. After probing the history, it was found that the child was born to a 2nd degree consanguineously married couple with the birth order 3. The elder male sibling experienced a similar disseminated infection following BCG vaccination and subsequently succumbed at six months, likely due to tuberculosis; however, medical records are not available. The current child was outborn, who received the BCG vaccine, but the specific strain used was not documented by the outborn delivery facility. The Danish 1 331 strain, the most commonly used BCG vaccine strain in India, could have been administered to the current child. Both the history and clinical examination suggested disseminated BCGosis. This prompted us to do a lymph node fine needle aspiration cytology, which showed acid-fast bacilli and features consistent with granulomatous tubercular lymphadenitis.

Considering the above presentation, a possibility of MSMD was thought, and whole exome sequencing was done, which revealed IFNGR2 deficiency on exon 4 of variant c.397C>T of Autosomal Recessive Inheritance. However, a limitation was that the functional assessment to evaluate surface expression of the gene could not be performed due to financial constraints. Considering the organism to be likely *Mycobacterium bovis*, the child was started with anti-tubercular therapy of isoniazid (H), rifampicin (R), ethambutol (E) for two months, followed by a seven-month two drugs course (H) (R), which was supplemented with azithromycin prophylaxis, however, pyrazinamide was excluded in our case due to the BCG strain's inherent resistance. Rigorous monitoring showed that the child was thriving well at the age of 20 months with complete resolution of ulceration, lymphadenopathy and organomegaly.

3. Discussion

BCG disease is characterized by severe infections caused by the Bacillus Calmette-Guérin vaccine strain of *Mycobacterium bovis*. This condition is especially prevalent in individuals with inborn errors of immunity, particularly those with defects in the IL-12/interferon-gamma (IFN-γ) signaling pathway. The disease manifests as disseminated infections affecting multiple sites, including lymph nodes, lungs, and skin[5].

MSMD is a congenital disorder characterised by severe infections from weakly virulent mycobacteria, typically emerging around six months of age. MSMD has three inheritance patterns: autosomal recessive, autosomal dominant, and X-linked recessive, each with varying functional impairments in immune response. Over 17 genes and 32 clinical phenotypes have been linked to MSMD[5]. The most common genetic defects include mutations in *IL12RB1* and deficiencies in *IFNGR1* and *IFNGR2*, which impair the immune response to mycobacteria. IFN-γ and its receptor trigger immune responses, including nitric oxide production and T cell activation, critical for fighting infections[3,5]. *IFNGR2* mutations disrupt the IFN-γ receptor's function, leading to reduced or absent IFN-γ response, compromising immunity against mycobacteria[2,6]. The genetic analysis of our case identified a complete *IFNGR2* deficiency. Notably, there have been only eight reported cases of *IFNGR2* mutation in India. Among the 8 cases of *IFNGR2* mutations reported in India, ages at presentation ranged from 3 to 11 months. Three of these patients were infected with CytoMegaloVirus. Of these cases, 4 patients died, 1 was lost to follow-up, and 3 are currently alive. Additional details were not available[7].

These cases respond to first- and second-line anti-Tubercular Therapy, thus necessitating an individualized approach[8]. The duration of the proposed treatment is six months to 2 years[7]. Apart from receiving definitive treatment, individuals with MSMD necessitate Azithromycin prevention, as in other immunodeficiency, to prevent secondary infections; the same was given to our child[8,9].

In cases of AR complete IFN-γ receptor 1 or 2 deficiency, allogenic HSCT is considered a curative option[8]. This option was not possible due to financial limitations. Interferon-gamma therapy, effective in *IL12RB1* defects, has no role in complete *IFNGR2*, as no residual functional receptor exists[9].

The cases in the literature with MSMD typically present in infancy or early childhood with recurrent and severe infections, failure to thrive, and developmental delays. Common features include chronic mucocutaneous candidiasis, pneumonia, sepsis, and opportunistic infections, often leading to early death if untreated. Hematopoietic stem cell transplant (HSCT) has been the primary treatment approach for these patients, showing promise in managing these life-threatening conditions. The majority of cases reported mutations in the *IFNGR2* gene[5].

In conclusion, with an unprecedented presentation of disseminated BCGosis in a four-month-old infant, linked to an IFN-γ axis defect,

our approach underscores the importance of early identification for optimal intervention. This case report emphasizes the significant role of clinical history, coupled with a high index of suspicion and timely direct whole-exome sequencing, not only facilitated an accurate diagnosis but also guided the implementation of timely and effective treatment strategies. This case underscores the broader implications of genetic defects in immune responses, urging a multidisciplinary approach for improved outcomes in MSMD cases.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethical approval and the patient´s consent

According to institutional policy, case reports do not require approval from the Ethics Committee. However, the Institute Ethics Committee (Subbaiah Research Centre) was informed of this report's submission. Informed consent was obtained from the patient's guardian.

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Authors′ contributions

DRR and NK were involved in the patient's care. DRR, NK, and VSK conceptualised the work. DRR, GSM, and NRR acquired the data and drafted the manuscript. DRR, GSM, NK, and VSK made critical revisions to the manuscript. All the authors approved the manuscript for publication.

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