Disseminated Bacillus Calmette-Guerin (BCG) Infection in Severe Combined Immunodeficiency (SCID) Patients

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Published on 15th April 2024

ABSTRACT

Disseminated Bacille Calmette-Guerin (BCG) infection is a rare and life-threatening complication of BCG vaccination. It is mainly seen in cases of severe immune deficiency. We report two cases of disseminated BCG infection in genetically proven cases of Severe Combined Immunodeficiency (SCID) from our institution. The first case is that of a one-year-old child who presented with fever, cough, yellowish discoloration of eyes, multiple skin nodules all over the body, and ulcer over the BCG vaccination site. Biopsy from the skin nodules showed multiple granulomas with plenty of Acid-fast bacilli; hence, anti-tubercular treatment was started for the child. The second case is that of a five-month-old child who presented with a lower respiratory tract infection, multiple episodes of loose stools, vomiting, poor feeding, poor activity, and a deranged Liver Function Test. Gastric aspirate Gene expert study was done and Mycobacterium tuberculosis was detected. Hence the patient was started on anti-tubercular treatment. Subsequent liver biopsy revealed a focus of granuloma. Genetic study was done in both cases and SCID was proved. Because of the rarity, we are presenting the cases.

Keywords: SCID, BCG, Granuloma

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BACKGROUND

Immunization of children with BCG, a live attenuated vaccine derived from Mycobacterium bovis, is recommended by the World Health Organisation in communities with a high prevalence of tuberculosis. BCG vaccines are extremely safe in immunocompetent hosts, but possible complications range from local inflammatory reactions to disseminated disease and death. The disseminated form of tuberculosis which has a high mortality rate, develops mostly in patients with immunologic deficiency.[1] We report two cases of disseminated BCG infection (BCGitis) in genetically proven cases of SCID.

CASE 1

1 year and 1-month-old girl child was brought to our institution by her parents with chief complaints of multiple skin nodules and ulceration at the BCG site.

A detailed clinical history was elicited. At the age of 5 months, the child had a fever, cough, and persistent oral thrush, for which she was admitted to a local hospital and treated for the same. She was referred to our institution because of persistent symptoms. A genetic study was done and this confirmed a defect in her immunity, Severe Combined Immunodeficiency. Since then she has been taking monthly IV injections for the same and the child has had multiple hospital admissions for similar complaints.

Family history revealed that she was the 3rd child of a 3rd-degree consanguineous marriage. One elder sister, a 9-year-old girl was alive and healthy. A sibling died at 6 months of age, he had a developmental delay and skin lesions.

A biopsy was taken from a skin nodule.

Macroscopy showed a skin-attached nodular tissue measuring 1.5 x 1 x 0.6 cm cut section which was grey-white to yellowish.

Microscopy showed skin with dense inflammatory infiltrates composed of predominantly neutrophils and histiocytes with a small degree of suppuration **[Figure 1, Figure 2, Figure 3].**

Cite this article as: Jose RM, Priya VS, Raji NL, Bindhu GS, Bindhu S, Sankar VH. Disseminated Bacillus Calmette-Guerin (BCG) Infection in Severe Combined Immunodeficiency (SCID) Patients. Kerala Medical Journal. 2024 Apr 15;17(1):45–8.
| DOI: https://doi.org/10.52314/kmj.2024.v17i1.632

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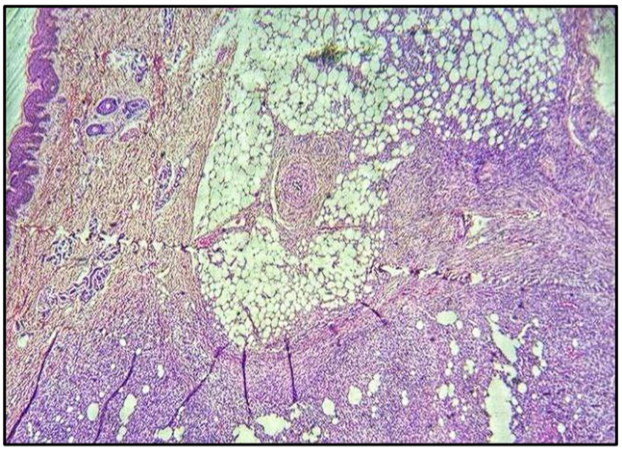

Figure 1. **Scanner view**

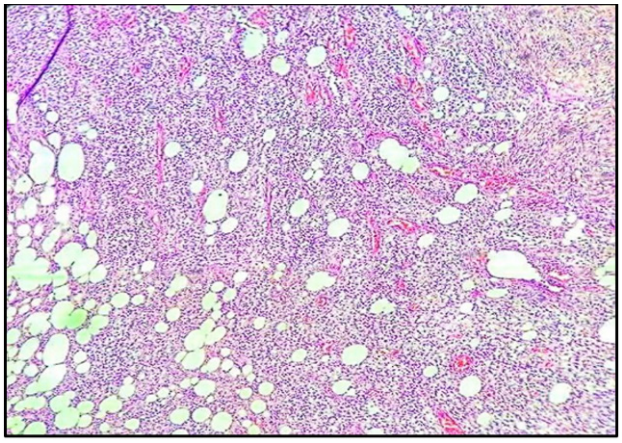

Figure 2. **Low power view**

DIAGNOSIS

Skin Biopsy: Consistent with Disseminated BCG infection.

Genetic Testing was done which revealed Clinical Exome **DCLRE1C gene deletion,** consistent with Severe combined Immunodeficiency.

CASE 2

A 5-month-old male child was brought to our institution by the parents with chief complaints of cough for 2 months, fever for 1 month, weight loss, breathlessness for 10 days, multiple episodes of loose stools, vomiting poor feeding, and poor activity for 1 day.

At 3 months of age, the child had recurrent bouts of cough was on treatment, and a month later was diagnosed with right-sided pneumonia. Suspecting tuberculosis, a gastric aspirate gene expert was done and Mycobacterium tuberculosis was detected. He was started on anti-tubercular treatment. AFB staining was done and showed plenty of Acid fast bacilli **(Figure 4)**

A diagnostic liver biopsy was done and sent to the department of Pathology.

Microscopy:

Microscopy showed fragmented linear cores of liver tissue with 2 to 3 portal tracts showing architectural disarray. Hepatocytes showed predominantly macrovesicular steatosis admixed with scattered microvesicular steatosis. Focal small aggregates of epithelioid histiocytes were seen. Sinusoidal congestion and focal neutrophil collection were present. Portal areas showed mild ductular proliferation as shown in **Figure 5 and 6**. Reticulin was done and there was no increase in reticulin fibrosis. AFB staining was done and did not show any bacilli.

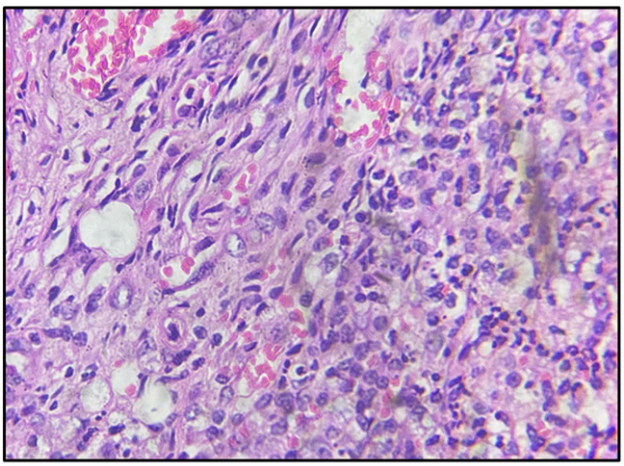

Figure 3. **High power view Skin Biopsy: Consistent with Disseminated BCG infection**

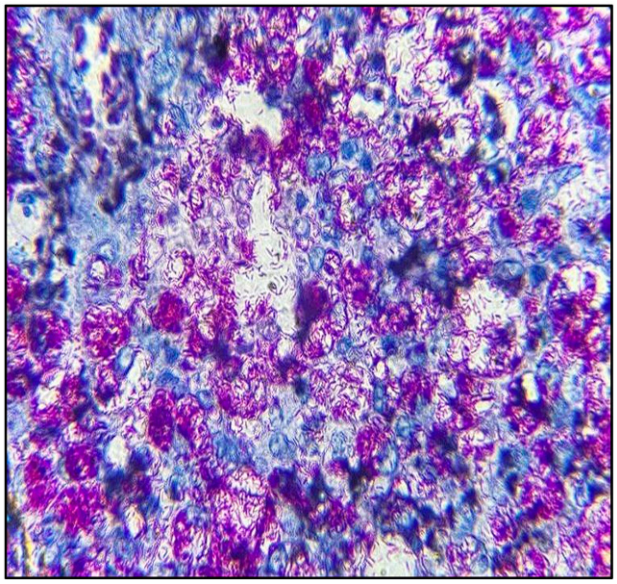

Figure 4. **AFB staining was done and showed plenty of Acid-Fast Bacilli**

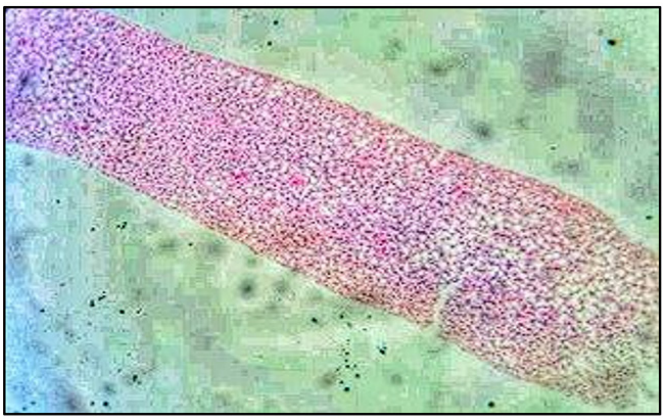
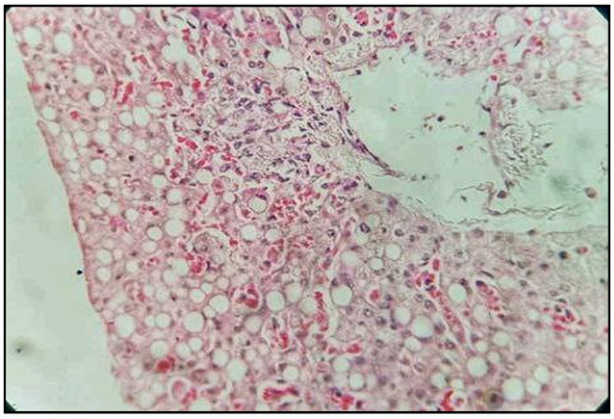

Figure 5&6. **Core of liver tissue with 2 to 3 portal tracts showing architectural disarray.**

DIAGNOSIS

Liver Biopsy: Cores of liver tissue showing steatosis (>66%) with a focus on small aggregates of epithelioid histiocytes suspicious of granuloma.

Despite all treatment measures, both the children succumbed to death. The 2nd child was diagnosed with SCID postmortem by Genetic Testing. A hemizygous missense variant in exon 2 of IL2RG was detected confirming the diagnosis of Severe Combined Immunodeficiency.

DISCUSSION

BCG is a live attenuated bacterial vaccine that is normally given at birth in countries with a high incidence of Mycobacterium tuberculosis.[2] The most frequent complications are local inflammatory reactions.

Disseminated BCG infection, the most serious complication of this vaccination develops in less than one case in a million. Disseminated BCG infections have occurred following vaccination of children with immunodeficiency disorders such as severe combined immunodeficiency, chronic granulomatous disease, complete Di George syndrome, AIDS, HIV infection or idiopathic immunodeficiency of genetic origin, but only rarely in normal individuals.[1] It is a rare complication with an estimated incidence of 0.1 to 4.3 per one million vaccinated children but is lethal in 50 to 71 % of the cases. The death rate is especially higher in cases of immunodeficiency (83%) and it is important to note that a temporary or permanent immune deficiency is observed in 86% of all cases.[3]

Severe combined immunodeficiency, as in these cases, usually presents in infancy, with severe infections, and is characterized clinically and immunologically by profound abnormalities of cell-mediated and humoral immunity. Infants with immunodeficiency should not receive BCG vaccination but they are usually vaccinated before the diagnosis is made. In other cases, immunodeficiency may be diagnosed after the development of BCG complications.[1]

Severe combined immunodeficiency disease (SCID) includes a heterogeneous group of genetic conditions characterized by profound deficiencies of T (and in some types, B and/or NK cell) numbers and function. If untreated, infants with typical SCID succumb early in life from severe and recurrent infections. Mutations in different genes affecting cytokine signalling (e.g., IL2RG, and IL7RA), antigen receptor processing (e.g., RAG1, RAG2, and CD3δ) or nucleotide processing (e.g., adenosine deaminase –ADA-) cause this fatal childhood condition, unless immune reconstitution can be accomplished. However, it should be noted that individuals with severe manifestations of other syndromic conditions may have clinical signs and symptoms consistent with SCID.[4]

The prognosis for SCID is typically grim, with the majority of patients succumbing before reaching the age of one. Essential interventions involve the prevention and treatment of infections through IV Immunoglobulin substitution and cotrimoxazole for Pneumocystis carini, though these measures only marginally extend survival. Additional necessary steps include irradiating blood products with 25 Gy to prevent fatal GVHD and abstaining from live vaccines like BCG.[5]

END NOTE

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Conflict of Interest: None declared

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