Primary paediatric TH1 immunodeficiency with BCG-osis

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ABSTRACT

Introduction: In tuberculosis (TB) endemic regions BCG vaccine is administered at birth in an effort to protect against neonatal tuberculous meningitis. However, this live vaccine facilitates overwhelming systemic infections by otherwise innocuous organisms in infants with cellular primary immunodeficiencies. Case Report: Our case is a seven month old infant who developed abscess at BCG vaccination site followed by disseminated BCG-osis and was diagnosed to have TH1 immunodeficiency. Conclusion: Dissemination following BCG vaccination warrants prompt investigation to diagnose primary immunodeficiency disorders in HIV seronegative individuals.

Keywords: BCG-itis, BCG-osis, NTM, Immunodeficiency

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INTRODUCTION

Bacille Calmette–Guerin (BCG) — a live attenuated vaccine — is routinely given to neonates in settings where tuberculosis is endemic [1]. Immunodeficient individuals are at high risk of developing BCG related complications like regional adenopathy i.e BCG-itis or disseminated disease i.e BCG-osis [2–4]. Primary immunodeficiencies are a diverse group of hereditary disorders leading to impaired immune response that creates high susceptibility to mycobacterial infections. Mycobacterium. tuberculosis, BCG and non-tuberculous mycobacterium (NTM) may cause a severe disease in patients with primary immunodeficiencies [5]. One such case is reported here.

CASE REPORT

A seven month old female child presented with an abscess at BCG vaccination site along with generalized lymphadenopathy. She was vaccinated with BCG one month after birth and there was no history of contact with tuberculosis. Family history suggested that her elder female sibling had developed BCG abscess following vaccination who later succumbed to cardiac disease and pneumonia at the age of eight years.

On examination the baby had normal developmental milestones, but was under weight. She had moderate pallor, generalized lymphadenopathy; the maximum
size of lymphnode being two cm. She also had hepatosplenomegaly (liver five cm and spleen seven cm palpable below the costal margin). Chest was clear to auscultation. Haemogram revealed Hb - 5.3 gm/dl, TLC - 18,400/mm³, DLC : neutrophils - 60%, lymphocytes - 36%, eosinophils - 04%, basophil - 0%, monocytes - 0%. platelet count - 2.2×10⁹/mm³, C-reactive protein (CRP) - 55 mg/L. Mantoux test was negative. Chest X-ray was normal. ELISA test for HIV was negative in the parents. CT scan of chest showed normal sized thymus. Aspiration cytology of the axillary lymph node revealed presence of large numbers of foamy histiocytes with negative imprints in the cytoplasm admixed with a paucicellular chronic inflammatory infiltrate dispersed in a necrotic background and raised the suspicion of a tubercular lesion. Ziehl-Neelsen stain confirmed presence of acid fast bacilli (Figure 1). Further the cytoaspirate was sent for mycobacterial culture and a resected node was subjected to histopathology examination. Lymphnode histopathology revealed poorly formed granulomas, good number of foamy histiocytes, along with neutrophils (Figure 2) Ziehl-Neelsen stain of tissue section revealed macrophages packed with AFB (acid fast bacilli) (Figure 3). Culture in Lowenstein-Jensen (LJ) medium showed growth of mycobacteria with flat, smooth, moist and white colonies in five weeks (Figure 4). The isolate was sent to a NABL (National accredited bacteriology laboratory) accredited referral laboratory for species identification and drugs susceptibility.

This baby was treated with first line antitubercular drugs. The baby was kept under follow-up. After three months she showed no response to antitubercular drugs, no weight gain and persistent lymphadenopathy. Rather she developed prolonged diarrhea and measles, hence leading to suspicion of immunodeficiency.

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Figure 1: Lymphnode cytoaspirate showing macrophages packed with AFB. (ZN stain, x400).

Figure 2: Lymphnode histomorphology showing poorly formed granuloma with foamy histiocytes (H&E stain, x400).

Figure 3: Lymphnode section showing macrophages packed with AFB (Z-N stain, x400).
DISCUSSION

BCG vaccines and environmental NTM are known to cause severe diseases in immunocompromised children. It is less well known that otherwise healthy children may also be affected. Unlike classic immunodeficiency they don’t have other associated symptomatic infections apart from salmonellosis in less than half of them [6]. Our patient had no other associated infection except BCG-osis. The prevalence of idiopathic disseminated BCG-itis in France has been estimated to be at least 0.59 cases per million children vaccinated6. While Chemli J et al. have reported a high frequency of severe adverse effects of BCG vaccination occurring in genetically immunodeficient children [7].

Immunological panel of our patient revealed hypergammaglobulinemia indicating hyper functioning B cells and thereby well functioning helper TH2 cells. There was persistence of AFB inside the macrophages as well as outside not responding to therapy. Thus there was a failure of activation of macrophages that is dependent on IFN-γ released by TH1 cells. Therefore, in our case possible defect was with TH1 cells resulting in lack of IFN-γ leading to inactivation of macrophages thereby facilitating persistence and multiplication of bacilli intracellularly. Further, lack of IFN-γ exerts no inhibitory effect on TH2 cells resulting in unopposed TH2 activity. This results in hypergammaglobulinemia. Further evaluation could not be done due to non-cooperation of the parents and ATT was extended with change of regimen.

Susceptibility to intracellular pathogens may develop from a range of different acquired or inborn defects in macrophage activation by IFN-γ [8]. Patients with inherited deficiency of interleukin (IL)-12/IL-23-IFN-γ axis show increased susceptibility to invasive diseases caused by the intra-macrophage pathogens such as Salmonellae and Mycobacteria. IL-12/IL-23/IFN-γ axis consists of two complementary components, first an IL-12/IL-23 component and second an IFN-γ component. Calman Mac Lennon et al. have reported in their study that mycobacterial disease occurred in 77% cases with IL-12/IL-23 component deficiency and in 94% cases with IFN-γ component deficiency [9].

Predisposition to mycobacterium is called mendelian susceptibility to poorly virulent mycobacteria such as BCG and NTM. It is thought to be due to impaired immunity, specifically altering host defenses against Mycobacteria. This syndrome is characterized by parental consanguinity, familial forms and an autosomal recessive pattern of inheritance. The rarity and heterogeneity of the syndrome make the diagnosis difficult. Different types of mutation have been detected in four genes (IFNγR1, IFNγR2, IL12B, IL12Rb1) resulting in eight different disorders whose common pathogenic mechanism is impaired IFN-γ mediated immunity. Severity of the clinical phenotype depends on IL-12 P40 the genotype. Complete IL-12 40, IL-12Rb1 IL-12Rb1 deficiency and partial IFN-γ R1 and IFN-γ R2 deficiencies generally lead to curable infections with antibiotics supplemented with IFN-γ.

The child was investigated for primary immunodeficiencies. Immunoglobulin profile revealed IgG - 1723 mg/dl, IgA - 129 mg/dl and Ig M - 297 mg/dl, serum ADA was 25 U/L. Lymphocyte enumeration test revealed lymphocyte - 47.01%, absolute T cell count - 2840/µl, CD3+ T cells - 50.24%, CD4+ T cells - 71.63% and absolute CD4+ T cells - 2064/µl, CD8+ T cells - 23.47 %, absolute CD8+ T cells - 676/µl. CD4+/CD8+ ratio was 1:3.05. Thus this panel of tests displayed a marked hypergammaglobulinemia, decreased absolute T cell count, CD3+ T cell count and absolute CD 4+ T cell count. Finally diagnosis of post vaccination BCG-osis in primary T cell (TH1) immunodeficiency was made and bacterial isolate from culture was sent for drug sensitivity test. Specific T cell function tests or cytokine and CK receptor assay could not be done. The infant was continuing antituberculosis drug treatment. Nitro blue-tetrazolium test was positive ruling out CDG (chronic granulomatous disease). The species was confirmed to be M. bovis (negative nitrate reductase activity and catalase positive) in a referral laboratory and drug sensitivity report revealed resistance to pyrazinamide. ATT was extended with modified regimen and the child is under follow up.

Figure 4: LJ medium showing flat, smooth, moist and white colonies of mycobacteria.
R1 and IFN-γ R2 deficiencies predispose to overwhelming infections in early childhood which respond poorly to antibiotics and are ineffective to IFN-γ treatment [5]. Bone marrow transplantation gives a possible hope while gene therapy is the treatment of choice.

Rapid diagnosis of complete IFN-γR deficiency is essential for the planning of clinical management by determining serum IFN-γ level by ELISA. High IFN-γ level suggests complete IFN-γR deficiency, where as low or undetectable level indicates IL-12, IL-12 R, partial IFN-γR deficiency or undetermined defects. IL-12 P40 deficiency can be diagnosed by ELISA, with low levels of IL-12 P40, IL-12 P70 and IFN-γ secretion by stimulated peripheral blood mononuclear cells (PBMC) [6].

Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-γ has been reported by Beata Kampmann et al. [7]. In three patients they detected high titres of auto antibodies in three patients that specifically bind to IFN-γ and inhibit its ability to activate macrophage function. All the cases had similar phenotype to that seen with mutation in the IFN-γR path way and all presented with severe progressive NTM infection.

In our case all possible causes, for secondary immune deficiency were excluded. Positive nitroblue tetrazolium test ruled out the possibility of CGD, which should be suspected in all cases of BCG-osis [3, 10, 11]. Other primary T-cell immunodeficiencies were excluded by absence of lymphocytosis, normal CD8+ T-cell counts, increased IgG (ZAP-70 deficiency), eczema & thrombocytopenia (Wiskott–Aldrich syndrome), complex congenital cardiac and cranio-facial defects. (Di George Syndrome), and hepatitis, haemophagocytic syndrome and aplastic anemia (X-linked lymphoproliferative disorder) [12]. Thus, with a similar history in the family primary immunodeficiency at the level of TH1 cell could be established.

CONCLUSION

Infection due to vaccination with BCG or non tuberculosis mycobacteria (NTM) may occur in patients with no hereditary or acquired immune deficiency. These idiopathic infections affect children or adults that are otherwise healthy thus make the diagnosis difficult. Clinicians should consider the possibility of defects at various levels of macrophage cell interaction and rapid diagnosis of complete IFN-γR deficiency is essential for the planning of clinical management. Ideally all live bacterial vaccines should be avoided in such immunodeficient cases.

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Author Contributions
Sitaram Mohapatra – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
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Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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