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Research Article

POST VACCINATION BCG-OSIS: AN EXPRESSION OF PRIMARY T- CELL IMMUNODEFICIENCY

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ABSTRACT

Introduction: BCG (BacilleCalmette-Guerin) – a live attenuated vaccine is routinely given to neonates where tuberculosis is endemic. Immunodeficient individuals are at a high risk of developing BCG related complications like BCG-itis or BCG-osis.
Case summary: A six month old baby who was vaccinated with BCG at birth developed an abscess at the vaccination site with regional adenopathy with disseminated BCG-osis. He was found to have T-cell immunedeficiency after thorough investigation.
Conclusion: Dissemination following BCG vaccination warrants prompt investigation to rule out primary immunodeficiency in HIV seronegative individuals.

INTRODUCTION

In tuberculosis endemic regions BCG vaccine is routinely given to neonates at birth. This live attenuated vaccine causes overwhelming systemic infection and BCG related complications in immunodeficient individuals who develop regional adenopathy i.e BCG-it is or disseminated form i.e BCG-osis (1). Primary immunodeficiencies are a diverse group of hereditary disorders leading to impaired immune response that creates high susceptibility to mycobacterial infection thus, causing severe disease by M. tuberculosis, BCG and non-tuberculous mycobacteria (NTM) (2).

Case Report

A six month old infant presented with low grade irregular fever and swelling of abdomen for one and half month . He was vaccinated with BCG at birth and there was no history of contact with tuberculosis. On general examination baby was underweight and had normal developmental milestones. He had moderate pallor, ipsilateral matted axillary lymphadenopathy (4x3) cm with enlarged bilateral cervical lymph nodes 2.5 cm in maximum dimension. He also had hepatosplenomegaly (liver 6 cm and spleen 8 cm palpable below the costal margin) and clinically suspected as leukaemia. Chest X-ray was clear and BCG vaccination site revealed partially healed abscess (fig-1). Haemogram showed Hb-6.5 gm/dl, TLC-16,000/cmm DC: Neutrophils-80%, Lymphocytes-20%, TPC-1.8 lakh/cmm. FNAC of left axillary lymph node revealed good number of polymorphs admixed with macrophages that were stuffed with acid fast bacilli (AFB) in Ziehl-Neelsen stain (fig-2). Cytoaspirate from liver also showed the similar picture (fig-3). Bone marrow aspiration revealed myeloid acceleration and no AFB.

Antitubercular drugs were started and culture in Lowensten-Jensen medium showed growth of mycobacteria with flat, smooth, moist and white colonies. With no clinical improvement, no weight gain and persistent lymphadenopathy baby was investigated for primary immunodeficiency. Serum ADA was 36 U/L. Immunoglobulin profile showed IgG-1389 mg/dl, IgA-177 mg/dl, IgM-338 mg/dl. Lymphocyte enumeration test revealed lymphocyte-20%, absolute T cell count-1249/µl, CD3+ T cells- 40.2%, CD4+ T cells-58.6%, absolute CD 4+ cell count-1364/µl, CD 8+ T cells-23%, absolute CD 8+ cell count-568/µl, CD4+: CD 8+ ratio- 2.4.

Fig-1 Partially healed BCG abscess with axillary lymphadenopathy

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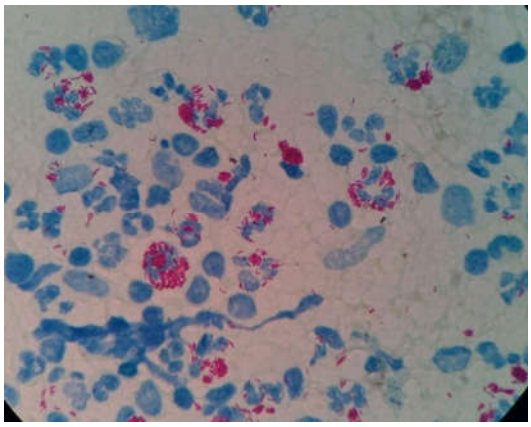

Fig-2 FNAC of LN shows macrophages packed with AFB with polymorphs (Z.N. stain X1000)

CT scan of thorax showed normal sized thymus. Mantoux was negative and ELISA for HIV was negative in both the parents. These panel of tests reflected marked hypergammaglobulinemia, decreased absolute T cell count, CD3+ and CD4+ T cell count. Species was confirmed to be M. bovies (nitrate reductase negative, catalase positive) thus, pointing to a diagnosis of post vaccination BCG-osis in a primary T cell immunodeficiency. Nitro blue tetrazolium test (NBT) was positive that ruled out chronic granulomatous disease (CGD). Other specific tests like T cell function tests, cytokine and cytokine receptor assay could not be done. No response to ATT was noted and baby succumbed.

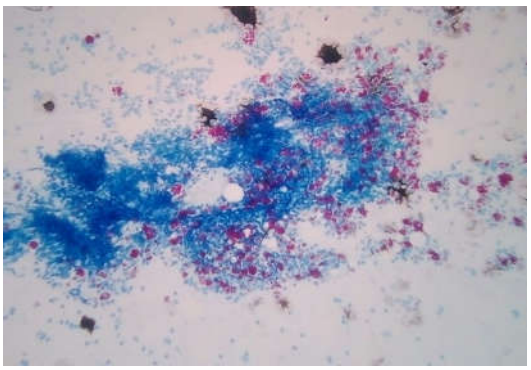

Fig-3 FNAC of liver shows persistent AFB inside the macrophages (Z.N.stain X400)

DISCUSSION

The prevalence of idiopathic disseminated BCG-it is in France has been estimated to be at least 0.59 cases per million children vaccinated (3). While Chemili J *et al* have reported a high frequency of severe adverse effects of BCG vaccination in genetically immunodeficient children(4). Unlike classic immunodeficiency our patient had no other associated infection except BCG-osis.

Persistence of AFB inside and outside the macrophages not responding to therapy indicates macrophage inactivation. This may be due to lack of INF-Ɣ release from Th1 cells responsible for macrophage activation. Furthermore, no inhibitory effect of INF-Ɣ on Th2 cells leads to unopposed help to B cells causing hyperfunction leading to hypergammaglobulinemia. No further evaluation of immune system could be done due to non-cooperation of the parents.

Patients with inherited defects in interleukin (IL)-12/IL-23-INF-Ɣ axis show increased susceptibility to intracellular pathogen such as mycobacteria and salmonellae. Calman Mac Lennon *et al* have reported in there study 77% cases having IL-12/IL-23 component deficiency while 94% of cases having INF-Ɣ component deficiency had mycobacterial disease (5).

Mendelian susceptibility to mycobacterial disease (MSMD) is characterized by parental consanguinity, familial forms and an autosomal recessive pattern of inheritance. It is thought to be due to impaired immunity, specifically altering host defenses against mycobacteria. The rarity and heterogeneity of the syndrome makes the diagnosis difficult. Impaired INF-Ɣ mediated immunity has been related to mutations in four different genes (INFGR1, INFGR2, IL-12β, IL-12Rβ1). Severity of the clinical phenotype depends on the genotype. Complete IL-12, P40, IL-12Rβ1 deficiency and partial INF-ƔR1 & INF-ƔR2 deficiencies generally lead to curable infections with antibiotics supplemented with INF-Ɣ. Complete INFyR1 & INFyR2 deficiencies predispose to overwhelming infections in early childhood which respond poorly to antibiotics and ineffective to INF-Ɣ treatment (2). Gene therapy is the treatment of choice while bone marrow transplant gives a possible hope in such cases.

Detection of INF-Ɣ level by ELISA is essential for management. High INF-Ɣ level suggests complete INF-ƔR deficiency, whereas low or undetectable level indicates IL-12, IL-12R, partial INF-ƔR or undetermined defects. IL-12 P40 deficiency can be diagnosed by ELISA, with low levels of IL-12 P40, IL-12 P70 and INF-Ɣ secretion by stimulated peripheral blood mononuclear cells (PBMC) (5).

Beata Kampmann *et al* have reported auto antibodies to INF-Ɣ in high titres in three cases that specifically bind to INF-Ɣ and inhibit its ability to activate the macrophages. All presented with severe progressive NTM infection (6).

In the present case all possible causes for secondary immune deficiency were excluded. Positive NBT test ruled out CGD which should be suspected in all cases of BCG-osis (7). Other primary T cell immunodeficiencies like Zap-70 deficiency, Wiscot-Aldrich syndrome, Di George syndrome, haemophagocyticlymphohistiocytosis (HLH) and X-linked lymphoproliferative disorder were excluded (8). Thus a primary immunodeficiency at Th1 level could be established.

CONCLUSION

Dissemination following BCG vaccination warrants prompt investigation to diagnose primary immunodeficiency disorder in HIV seronegative children. Possibilities of defects at various levels of macrophage cell interaction should be considered for planning of management. Ideally all live bacterial vaccines should be avoided in such immunodeficient cases.

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