Case Report

Disseminated BCG in primary immunodeficiency

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ABSTRACT

Bacillus Calmette–Guerin (BCG) vaccination is administered at birth in all tuberculosis (TB)-endemic countries as part of the immunization schedule. Usually, only local complications are seen with this vaccine; however, disseminated mycobacterial infection is possible in the immunocompromised. Our case is a 6-month-old girl who presented with pneumonia, loose stools, oral candidiasis, and failure to thrive. Blood counts showed leukopenia and chest X-ray showed the absence of thymus. Flow cytometry and immunoglobulin profile were suggestive of primary immunodeficiency (PID), possibly severe combined immunodeficiency (SCID), and hence, the child was started on cotrimoxazole and monthly immunoglobulin prophylaxis. A month later, the child presented with apathy, loss of acquired development milestones, indurated BCG site with local lymph node enlargement, multiple subcutaneous nodules, and hyperintensities in the ulna in the magnetic resonance imaging bone screen. Acid–fast bacilli were isolated from both BCG sites and subcutaneous nodules on the trunk. Disseminated BCG should be suspected in any case of PID if they have received the BCG vaccine at birth. This case also highlights the need for neonatal screening for SCID.

Key words: Bacillus Calmette–Guerin, Immunodeficiency, Severe combined immunodeficiency

Immunization of children with Bacillus Calmette–Guerin (BCG), a live-attenuated bacterial vaccine derived from *Mycobacterium bovis*, is recommended by the World Health Organization (WHO) in tuberculosis (TB)-endemic countries with the highest incidence of TB being in the South East Asian region (234/1 lakh) with India constituting 28% cases as compared to Indonesia (9%), China (7%), and Pakistan (5%) (WHO 2021). BCG vaccine is safe in immunocompetent but complications ranging from local inflammatory reactions (lymphadenitis, abscess, fistula formation) to disseminated diseases (osteomyelitis, bacteremia, meningitis) and death are reported in immunocompromised individuals, especially primary immunodeficiency (PID) [1]. The incidence of disseminated BCG is <1 in a million population. Several PID syndromes have been associated with disseminated BCG disease, such as Mendelian susceptibility to mycobacterial disease, hyper-IgM syndrome, DiGeorge syndrome, chronic granulomatous disease (CGD), severe combined immunodeficiency (SCID), interleukin (IL)-12/23 receptor β1 chain deficiency, IL-12p40 deficiency, signal transducer and activator of transcription 1 deficiency, and nuclear factor kappa-beta essential modulator deficiency [2]. Out of these, SCID is the most common disease associated with disseminated BCG.

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We report the case of a 6-month-old girl with SCID who presented with disseminated BCG. BCGosis or disseminated BCG although rare is fatal and therefore early detection and initiation of treatment is of utmost importance and hence such clinical scenarios help in alerting paediatricians to think beyond the common aetiologies.

CASE REPORT

A 6-month-old female baby, the third child of a third-degree consanguineous marriage with previous sibling death at 6 months, who had an uneventful antenatal and postnatal period, normal development, and immunized for age presented with fever, cough, oral ulcers, and loose stools.

On examination, she had marked failure to thrive, tachypnea, increased work of breathing, and compensated shock. Pneumonia was managed with intravenous antibiotics and non-invasive ventilation. The child was noted to have oral candidiasis, absence of tonsils and lymph nodes, absent thymic shadow on chest X-ray, and leukopenia (Table 1).

Considering the possibility of immunodeficiency, flow cytometry and immunoglobulin profile (Table 1) were sent which were suggestive of PID, and the child was discharged on cotrimoxazole prophylaxis and monthly intravenous immunoglobulin.

After 2 months, the baby presented with pneumonia and extensive oral candidiasis. She was managed with intravenous

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Table 1: Laboratory investigations of the patient

Hemoglobin (g/dL)	11.5	
Total count (cells/mm^3)	3900	
Differential count	P68 L41. ANC 2652 ALC 1599	
Platelet (cells/mm^3)	6.28	
Flow cytometry		
Total leukocyte count (cells/mm^3)	4100	4000–10000
CD45%	20.6	20–40
CD45 absolute (cells/mL)	848.3	1000–3000
CD3%	9.2	59–83
CD3 absolute	78.1	677–2383
CD4%	26	31–59
CD4 Absolute	221.2	424–1509
CD8%	2	12–38
CD8 absolute	16.9	169–955
CD4/CD8 ratio	13	>0.7
CD19%	3.62	4.6–22.1
CD19 absolute	39.6	56.6–417.4
CD20%	3.96	5–22.3
CD20 absolute	42.5	74.4–441.1
Immunoglobulin profile (mg/dL)		
IgA	0.09	0–0.85
IgM	0.31	0.4–1.45
IgG	3.36	7–14.8
IgE	125.3	

Ig: Immunoglobulin

antibiotics including cotrimoxazole and fluconazole. On examination, the child was noted to have hyperpigmentation and extensive BCG site induration of size 6×4 mm with left axillary lymph node enlargement 0.5×0.5 cm and few subcutaneous nodules on the forearm, trunk, and head (Fig. 1). Based on the European Society for Immunodeficiencies (ESID) criteria, we considered the possibility of disseminated BCG.

A cerebrospinal fluid study was done which was normal; acid–fast bacilli (AFB) were negative; and India ink stain was negative. Ultrasound abdomen showed hepatosplenomegaly. CECT brain showed cortical volume loss and magnetic resonance imaging (MRI) brain showed no evidence of TB. MRI chest and abdomen screen were done which did not show any radiological evidence of intra-abdominal TB but subcutaneous nodules were noted over the trunk and right arm. MRI bone screen showed hyperintensities in the ulna. Gastric aspirate cartridge-based nucleic acid amplification test (CBNAAT) was negative. BCG site biopsy was sent for CBNAAT which was positive for *Mycobacterium tuberculosis* complex. A biopsy from the subcutaneous nodule on the trunk was sent for histopathology and it revealed a dense inflammatory infiltrate with predominantly neutrophils and histiocytes with a small degree of suppuration. Acid–fast staining shows plenty of acid–fast bacilli and poor granuloma formation consistent with disseminated BCG (Fig. 2).

The child was started on standard antitubercular treatment (ATT) with four drugs. Clinical Exome results came which revealed DCLRE1C gene deletion associated with SCID, and hence, the child was advised hematopoietic stem cell transplant and discharged on ATT.

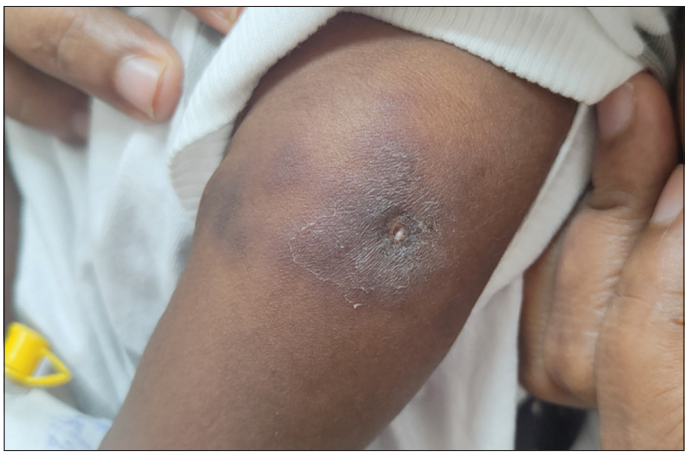

Figure 1: Indurated Bacillus Calmette–Guerin site

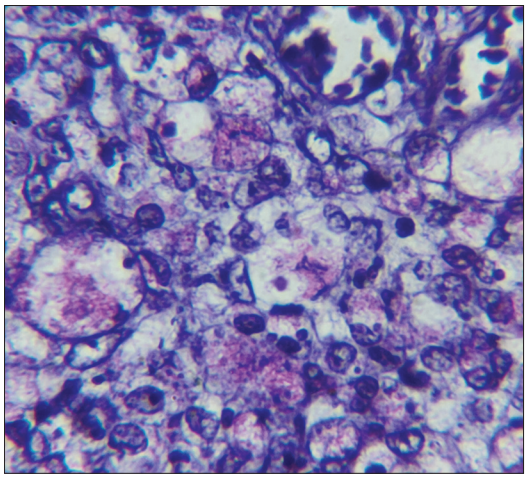

Figure 2: Histopathology specimen (from subcutaneous nodule on the trunk) showing acid–fast bacilli (red in color)

DISCUSSION

Case definitions of BCGosis were in accord with the ESID diagnostic criteria. Probable BCGosis is diagnosed by the presence of systemic symptoms, with at least two areas of involvement beyond the site of a BCG vaccination (lymph nodes, skin, soft-tissues, lungs, spleen, liver, and bones), identification of *M. tuberculosis* complex by polymerase chain reaction (without differentiation of *M. bovis* subspecies), negative mycobacterial cultures, and with the presence of typical histopathological changes with granulomatous inflammation. Disseminated BCG must be presumed in all BCG-vaccinated patients with SCID until proven otherwise [3]. In our case, the child had SCID with BCG site induration, and hence, the possibility of disseminated BCG was considered. Conversely, disseminated BCG could be the first presentation of an immunodeficiency.

The median age of clinical diagnosis of PID is 5.5 (range: 0.8–35.5) months old, and the median age at presentation of symptoms of BCG infection is 3.8 (0.8–7.4) months [4]. In

our case, although PID presented at 6 months, disseminated BCG presented only at 8 months.

Bone changes generally appear between 3 months and 5 years after vaccination [1]. BCG osteomyelitis involves the hand, foot, long bone, spine, rib, sternum, and clavicle, the tubular bones of the fingers and toes being the most common sites of involvement [1]. In our case, hyperintensities in the ulna were noted on MRI but X-rays were normal.

Disseminated BCG infection in patients with SCID may also involve other organs. In our patient, subcutaneous nodules were noted which on biopsy revealed inflammatory infiltrate with plenty of AFB. The absence of granulomas was attributed to immunodeficiency. Typing of the Mycobacteria subspecies could not be done as we do not have facilities at our center. Skin biopsy has been shown to be a critical investigation in the diagnosis of BCG as skin manifestations have always been an interesting way of presentation in disseminated BCG [2]. Data on 349 BCG-vaccinated patients with SCID from 17 countries were analyzed which showed that 51% had complications (17% were localized and 34% were disseminated). 46 BCG-associated deaths were reported among 160 patients treated with antimycobacterial therapy for a symptomatic BCG infection [5].

ESID recommends that anti-mycobacterial treatment, consisting of a combination of four anti-mycobacterial agents, should be given to patients with BCGosis and PID until full recovery. After that, a prophylactic regimen with two anti-mycobacterial agents should be continued until complete immunological reconstitution after a hematopoietic stem cell transplant. Early hematopoietic stem cell transplant (HSCT) with appropriate empiric anti-mycobacterial therapy is essential [4]. Overall mortality has been reported to be 50%.

In a review of adverse events following immunization (AEFI), in cases of immunodeficiency, SCID and CGD had the greatest percentage of serious AEFI with BCG being the most commonly associated vaccine [6]. Delaying the BCG vaccine beyond the 1st month of age may decrease BCG-associated morbidity and mortality in SCID patients [5]. However, delaying vaccination may also lead to less vaccination coverage which is detrimental in countries like ours where there is such a high burden of TB. Newborn screening (NBS) with the T cell receptor excision circle analysis can detect genetic causes of SCID [7]. Our patient was vaccinated before the diagnosis of PID. Hence, the importance of NBS for SCID in cases with a family history is emphasized so that live vaccines can be avoided. For infants who have received BCG immunization before diagnosis, isoniazid and rifampicin prophylaxis is needed [8].

Prenatal diagnosis of SCID can be obtained by Sanger sequencing for the well-characterized mutation in the index case (sibling) by chorionic villus sampling or amniocentesis and termination can be planned according to the parent's discretion [9].

DCLRE1C gene encodes a protein called Artemis which is responsible for DNA repair and early development of B and T cells and its deletion results in T-B-NK + SCID) associated with radiosensitivity. Other clinical features were painful ulcers in the mouth and genital area, chronic or recurrent diarrhea, growth failure, frequent opportunistic infections, recurrent respiratory infections, and candidiasis. All these features were seen in our patient. Most of the patients in a study conducted in Iran on a cohort of patients with DCLRE1C gene defect [10] had consanguineous parents and so does our case. HSCT is the treatment for children with DCLRE1C defect but the application of alkylator agents for conditioning regimens is limited due to their toxic effects in radio-sensitive SCID patients such as poor growth, short stature, dental, and dermatological problems [10].

CONCLUSION

In any case of PID, keep a high index of suspicion and watch for complications of live vaccines as they can be lethal.

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