DISSEMINATED BACILLE CALMETTE - GUERIN (BCG) DISEASE IN AN INFANT WITH SEVERE COMBINED IMMUNODEFICIENCY

Shagufta Sohail, Muhammad Afzal, Vaqas Anwar and Quratulain Shama

ABSTRACT

Bacille Calmette-Guerin (BCG) vaccine is administered to all newborns in countries where tuberculosis is still endemic. It is a live attenuated vaccine and considered quite safe in immunocompetent children. Disseminated BCG disease is the most serious complication seen only in individuals with underlying primary or secondary immunodeficiencies. We report a case of disseminated BCG disease in an infant with Severe Combined Immunodeficiency (SCID) who received BCG administration prior to diagnosis of SCID.

Key Words: BCG. Disseminated BCG infection. Severe Combined Immunodeficiency (SCID). Meningitis. Seizures.

INTRODUCTION

Bacille Calmette-Guerin (BCG) is live attenuated isolate of Mycobacterium bovis. It is one of the oldest vaccines used since 1921 in humans. It is considered to be a vaccine with excellent safety profile. Complications are rare and range from local ulceration, regional suppurative adenitis to disseminated BCG infection in only 1.5 - 4 per million infants vaccinated.1 Patients who develop disseminated disease have most likely underlying immunodeficiency.2 Severe combined immunodeficiency is characterized by early onset of infection, defects in both T and B-cells system with underlying lymphoid aplasia and thymic dysplasia.3 As clinical manifestation of immunodeficiency states are not evident in new born period, these new borns are likely to develop disseminated disease later on in infancy. Initially clinical characteristics are likely to be masked and attributed to immunodeficiency state. However, careful history of immunodeficiency state in family, especially siblings can alert the attending physician and one can skip administration of BCG in these cases. Secondly, suspicion of disseminated disease in patients refractory to conventional antibiotics treatment can lead to early diagnosis and appropriate management.

This report describes the occurrence of disseminated post-BCG.

CASE REPORT

An eleven months old male infant presented in our hospital with complaints of lethargy and breathing difficulty for 7 days. He was also failing to thrive. He was born at 31 weeks of gestation by caesarean section to consanguineous parents. There was history of death of 2 male siblings in neonatal age probably due to sepsis and had only one alive, healthy male sibling (pedigree in Figure 1). He received BCG at one and half months of age on right deltoid and within 6 weeks developed a swelling in right axilla that started oozing after 2 weeks. Lymph node biopsy from right axilla was done after 4 months that was suggestive of BCG lymphadenitis. He was started on three antituberculous drugs, isoniazid, rifampicin and pyrazinamide. As no improvement was noted after 4 months of therapy so serum immunoglobulin levels were done which showed decreased levels of IgG, IgM and IgA. A single dose of intravenous (IV) immunoglobulin was infused before referral to our hospital.

At the time of admission, he was lethargic, pale and tachypneic but was vitally stable. His height and weight were less than 5th centile. He had an ulcerated, wet lesion in right axilla and over BCG administration site on right arm. There was no lymphadenopathy elsewhere. Chest examination revealed bilateral coarse crepitations. Anterior fontanelle was tense and full. Rest of systemic examination was unremarkable. Preliminary diagnosis of septicaemia, severe pneumonia and meningitis was made with underlying possibility of disseminated BCG disease and severe combined immunodeficiency. He was continued with isoniazid and rifampicin. Pyrazinamide was discontinued whereas oral ethambutol, co-trimoxazole and intravenous meropenum were started. His complete blood count revealed leukopenia (WBC 4.27 x 10, neutrophils 43.6%, lymphocytes 23%, monocytes 21%, eosinophils 11% and basophils 1.4%). Cerebrospinal Fluid (CSF) routine examination was normal. Blood and CSF cultures revealed no bacterial or fungal growth. Chest X-ray showed right middle and lower lobe consolidation. Lymphocyte subsets were also sent.
He was discharged after 3 days on same treatment but he was readmitted after 2 days with continuous seizures. Clinical examination was unremarkable. Random blood sugar level was normal. CT scan brain with contrast was suggestive of tuberculous meningitis (Figures 2 A,B). Considering drug resistant tuberculosis, fluoroquinolone (ofloxacin) and aminoglycocides (amikacin) along with intravenous dexamethasone were also started. His condition gradually worsened and he became oxygen dependant. Lymphocyte subsets report revealed decreased T-lymphocytes, decreased B-lymphocytes and increased NK-cells, suggestive of cellular immunodeficiency. Based on low serum immunoglobulins levels, lymphocyte subsets analysis (T-B-NK+) final diagnosis of severe combined immunodeficiency along with disseminated BCG disease was made (Table I). Parents were counselled about the nature of disease, its complications, prognosis and possibility of bone marrow transplant. However, despite all supportive and specific measures the baby expired within a week of diagnosis.

**DISCUSSION**

Disseminated BCG disease is extremely rare complication of BCG vaccination. Any patient (who has received BCG) with systemic symptoms of fever, weight loss or stunted growth and at least two areas of involvement beyond the site of BCG vaccination like lymph node, skin, soft tissues, lungs, spleen, liver, bones or meninges is said to have disseminated BCG disease. Laboratory evidences include identification of *Mycobacterium bovis* BCG substrain from patient organ by culture or standard polymerase chain reaction along with a typical histopathological findings of granulomatous inflammation.4

Severe Combined Immunodeficiency (SCID) is a life threatening illness. It is the prototype of primary immune disorders and is caused by numerous molecular defects that cause defects in function and number of T-cells,
B-cells and occasionally natural killer cells. Infants with SCID have lymphopenia (less than 2500/mm³) and lack lymphocyte proliferative response to mitogens, antigens and allogenic cells in vitro. Serum immunoglobulin concentration is low or absent and no antibodies are formed after immunization. T-cells are extremely low or absent and analysis of lymphocytes subsets reveal distinctive phenotype (T-B+NK+SCID), (T-B-NK+SCID), (T-B-NK-SCID), (T-B+NK-SCID) based on gene defects. In this case, it was T-B-NK+SCID. Treatment is bone marrow transplantation. Without intervention it results in recurrent severe infections and death in children in first year of life. Live vaccines are contraindicated in these children, however, BCG vaccine is inoculated prior to diagnosis due to its timing in vaccination schedule as in this case.

Treatment of patient having disseminated BCG disease with underlying severe combined immunodeficiency is complex and includes four or more antituberculous drugs until the patient fully recovers from tuberculosis. Then prophylaxis with 2-drugs should be continued until complete immunological reconstitution after Hematopoietic Stem Cell Transplantation (HSCT) is achieved. Prognosis is poor with mortality rate of more than 80% as literature reports. Talbot et al. reviewed 28 definite cases of disseminated BCG disease from more than 5000 reports through 1980 - 1995. They noticed predilection of disseminated BCG infection in immunocompromised patients. Out of 28 cases, 5 had underlying SCID and all were less than 2 years of age. Antimicrobial therapy was not documented in these patients and only one of these patients survived with mortality rate of 80%. Only one of these 5 children had involvement of meninges. Paiman et al. reviewed 17 cases of disseminated BCG disease retrospectively. Eight patients had underlying SCID who were treated with first line antituberculous therapy in different combinations. Again mortality rate was 87% as 7 out of 8 patients died. None out of these 8 patients was reported to have meningeal involvement.

The literature describes more than 200 cases of disseminated BCG infection in patients with primary immunodeficiency with very few cases reported with meningeal involvement. To authors’ knowledge this is the first report of disseminated BCG infection with meningeal involvement in a patient with underlying SCID in this region.

REFERENCES