

# Disseminated BCG Disease in a Child with Interferon Gamma Receptor Deficiency: Case Report from Libya

Hanan Elsalhein<sup>1</sup>, Idriss Matoug<sup>2</sup>, Huda Kutrani<sup>3</sup>, Yousif Sulaiman<sup>4</sup>

<sup>1,2,4</sup> (Pediatric Department, Faculty of Medicine, University of Benghazi, Libya)

<sup>1</sup> (Hematology Unit, Pediatric Department, Benghazi Medical Center, Libya)

<sup>3</sup> (Health Informatics Department, Faculty of Public Health, University of Benghazi, Libya)

<sup>2,4</sup> (Infectious and immunology Department, Benghazi Children's Hospital, Libya)

Corresponding Author: Hanan Elsalhein

**Abstract:** Although in the last two decades, the World Health Organization (WHO) has introduced tuberculosis as "a global threat". The vaccination with the Mycobacterium bovis Bacillus Calmette-Guerin (BCG) is the only way to prevent this fatal infectious disease. The WHO has recommended developing countries to give BCG at birth to every newborn. Despite the efficacy of BCG vaccine especially against infants' miliary and meningeal TB, it has still some limitations due to a variety of adverse effects. Complications of BCG vaccination especially disseminated infection is rare. The most severe forms of this infection are known to occur to immunodeficient patients; such as Mendelian susceptibility to mycobacterial disease (MSMD) which could be due to defects in some elements of IL-12/IFN- $\gamma$  axis. This is the first case report from Benghazi for a male infant presented with disseminated BCG infection due to interferon gamma receptor deficiency.

**Keywords:** Disseminated BCG infection, MSMD, interferon gamma receptor deficiency

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## I. Introduction

Bacillus Calmette Guérin (BCG) is an attenuated strain of Mycobacterium bovis that is currently used to prevent early life infections of Mycobacterium tuberculosis [1,2]. Although BCG vaccination is safe for most children [3], in rare cases vaccination causes disseminated BCG infection, which may be lethal. Impaired immunity of the host is generally thought to be the pathogenic mechanism. Disseminated BCG infection has been reported in children with inherited immune disorders. Most of these children had severe combined immunodeficiency (SCID), cellular immune defect, chronic granulomatous disease [4,5]. And Mendelian susceptibility to mycobacterial disease (MSMD) [6]. This is the first case report from Benghazi; for a 5-month male Libyan infant presented with disseminated BCG infection with a history of three siblings died with the same problem; because of interferon gamma receptor deficiency.

## II. Case Presentation

A 5-month male Libyan infant a product of a consanguine parent. He was admitted to peripheral hospital with fever, skin rash and left axillary lymph node swelling with ulceration at the site of BCG from two months. He has two brothers with good health; one sister and two brothers died in early infancy (around three months) without a diagnosis. They had the same complaints with the left axillary lymph node swelling, anemia, and recurrent blood transfusion tell they died from bronchopneumonia and huge hepatosplenomegaly. He was pale and underweight all his measurements were below the third centile. He has left axillary lymph node swelling and hepatosplenomegaly. His WBC was high  $58 \times 10^9$ , Hb 7g/dl, platelet  $269 \times 10^9$ , ESR 157/hr, CRP 102mg/dl, PBF showed neutrophilia with atypical lymphocyte. Regarding the family history of other siblings' death with the same problem Disseminated BCG disease; as a result, the primary immune deficiency disease was the initial diagnosis. The patient received a blood transfusion, and he was started on anti - (TB) drugs with INH and rifampicin. The mother was advised to see immunologist, but she did not.

The mother stopped both the follow-ups and the anti -TB drugs after two months without consulting the physician. At the age of 11 months, the patient returned to our immunology unit; after three months of stopping anti-TB. He has left axillary and right inguinal lymph nodes swelling. He suffered from a cough for the last month and fever for the last 20 days.

He was febrile, pale, tachypnic and distressed. His measurement was below the third centile with maculopapular, skin rash involved the trunk. The chest examination revealed a reduction of air entry with

crepitation, abdomen distended with huge hepatosplenomegaly. The left axillary and the right inguinal lymph node swelling.

CBC: WBC  $33,5 \times 10^9$ /L (Neut  $24 \times 10^9$ /L, lymph  $8 \times 10^9$ ), HB 4.6g/dl, plat  $12 \times 10^9$ , ESR 47/hr, CRP 285mg/dl. RFT, LFT normal apart from reversed of albumin to globulin ratio, total protein 6.4 g/dl (albumin 2.2g/dl, globulin 4.2g/dl).

Blood PCR for Tuberculosis was positive for Mycobacterium complex including (*M. Tuberculosis*, *M. africanum*, *M. bovis*, *M. bovis* BCG, *M. microti*) and no molecular detection of rifampicin resistance. Histopathology study of Excisional biopsy from the right inguinal lymph node swelling was consistent with TB granuloma.

Chest x-ray revealed homogenous opacity involving the right lung (figure 1)



Immunological investigation immunoglobulin level, number of peripheral T cells and CD4/CD8 subsets were normal, NBT and DHR were normal too.

Flow cytometry analysis failed to detect the IFN- $\gamma$  receptor on peripheral lymphocytes. He had no other severe infectious illnesses, and no other opportunistic pathogens were isolated at any time.

Broad-spectrum antibiotics started with anti -TB- drugs INH, Rifampicin, and ethambutol. Interferon was unavailable for therapeutic trial. The patient condition was getting worse and later he died.

### III. Discussion

BCG vaccine a live attenuated strain of *M. bovis* is currently the only licensed vaccine against TB [7]. It is a part of the Libyan national childhood immunization program given on the first day of life for all newborns.

The adverse reactions of BCG have been described thoroughly. The normal local reaction following intradermal BCG vaccination is swelling and redness which appears at the site of injection after a few weeks. This develops into a small pustule or an ulcer that heals and leaves a small scar after weeks or months. Local lymphadenopathy < 1 cm is also part of normal reactions [8]. Risk of BCG-induced suppurative lymphadenitis is often present, but it is benign and well-responsive to conservative treatment [9-11]

BCG vaccine can cause very serious life-threatening disseminated BCG infection. It has especially been observed in children with primary immunodeficiency (PID). The Mendelian susceptibility to mycobacterial diseases (MSMD) are examples of PID [12].

BCG vaccination results in disseminated infection involving lymph nodes, lungs, kidney, bone marrow, skin, spleen and other organs with high mortality rates (71%) [13].

IFN- $\gamma$ R1 deficiency causes selective susceptibility to early onset and severe mycobacterial infection. Also, it is associated with severe, often fatal infection with BCG and environmental mycobacteria (EM); as the leading cause of the disease in all IFN- $\gamma$ R1 deficient patients in early childhood [14-15].

The overwhelming infections manifested by fever, loss of weight, lymphadenopathy, and hepatosplenomegaly [16]. Our patient presented with fever, anemia probably due to the involvement of bone marrow by *Mycobacterium bovis*, also he had huge hepatosplenomegaly and died due to lung infiltration.

Forty-four Iranian patients with disseminated BCG had a decrease in blood cells including anemia, leucopenia, neutropenia and thrombocytopenia which were associated with more severe diseases and even deaths. Moreover, 70% to 80% of patients who died had a high level of C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [17]; as found in our patient, the anemia and thrombocytopenia with high ESR and CRP associated with a fatal outcome.

Blood PCR is not used frequently in the diagnosis of disseminated BCG infection. It seems helpful especially in cases where the PCR sample is difficult to take from a suspected organ involved.

The prognosis of patients with IFN- $\gamma$ R1 deficiency is poor, and IFN- $\gamma$  therapy would not be effective because of the absence of functional receptors. Haematopoietic stem cell transplantation (HSCT) has been used in a few patients [18-19]. IFN- $\gamma$  therapy is ineffective because of the lack of specific receptors and overwhelming mycobacterial infections [20].

It is important for pediatricians to be aware of BCG-related complications and recognize the disseminated BCG infection. Because this might be the first manifestation in immunodeficiency disease patient, as in our case. Despite seeking medical attention for the previous siblings, the general pediatricians lacked the experience to diagnosis such a case.

We highly recommend that in a country with a high incidence of tuberculosis and high mortality in patients with primary immunodeficiency; inoculation of BCG vaccine should be postponed to a newborn in families with a history of inherited immunodeficiency. Also any unexplained death or infection of previous siblings related to immunodeficiency diseases.

#### IV. Conclusion

Carefully taken family history before BCG injection as well as delaying vaccination if PID is suspected. It could be a simple and effective method to avoid vaccination of an immunodeficient child in some cases until the full immunological screen is done.

#### Patient Consent

Written informed consent was obtained from the patient's parent for the publication of this manuscript.

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