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Disseminated BCG Disease and *Aspergillus* Pneumonia Presenting Feature for Chronic Granulomatous Disease Patient Case Report

Hanan Elsalhein[1], Yousif Sulaiman[2], Huda Kutrani[3], Salah Alamroni[4]
[1,2] *(Pediatric Department, Faculty of Medicine, University of Benghazi, Libya)*
[1] *(Hematology Unit, Pediatric Department, Benghazi Medical Center, Libya)*
[3] *(Health Informatics Department, Faculty of Public Health, University of Benghazi, Libya)*
[2,4] *(Infectious and immunology Department, Benghazi Children's Hospital, Libya)*
Corresponding Author: Hanan Elsalhein

Abstract: *In many countries, BCG vaccine is scheduled in the national vaccination program to be given at birth. However, It may lead to local BCG disease, regional axillary lymphadenitis. Moreover, it may lead to a serious complication with disseminated BCG disease in some immune compromised groups. This case report of a 10-month-old male Libyan infant presented with disseminated BCG disease; as well as Aspergillus pneumonia as a presenting feature for the chronic granulomatous disease.*

Keywords: *BCG vaccine, Mycobacterium bovis, Aspergillus pneumonia, chronic granulomatous disease, Libya.*

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I. Introduction

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disease. It is characterized by the inability of neutrophils and monocytes to kill catalase positive microorganisms; because of the total absence or low levels of reactive oxygen species production. It is caused by a deficiency of the NADPH oxidase complex in phagocytes [1,2], and the inheritance of the defect can be X-linked or autosomal recessive [3,4]. The affected patient prone to recurrent bacterial and fungal infection [5]; with a predisposition to disease caused by weakly mycobacteria in BCG vaccine [6]. As well as invasive Aspergillosis [7-9] which is the leading cause of mortality in CGD [10]. We report a case of a 10-month-old male infant presented with disseminated BCG disease and Aspergillus pneumonia as a presenting feature for (CGD).

II. Case Presentation

A 10-month-old male Libyan infant from Ejdabia (west of Benghazi) was born to nonconsanguineous parent. He was admitted with a history of a cough and anorexia for more than one month. As well as a previous history of inguinal lymphadenitis from one month and needed incision and drainage. However, he had no history of fever; he has one healthy sister and no family history of any chronic disease. At the time of admission, he was pale, tachypneic with mild respiratory distress. His left axillary lymph node measuring about 3cm firm non-tender and not hot. Chest examination revealed a reduced air entry in the left infraclavicular area with bronchial breathing and fine crepitation. Abdominal examination revealed hepatosplenomegaly.

Initial investigation done; WBC: 17 x 10^9/ L (Lymphocytes 7.5 x 10^9/ L, Neutrophils 7.7 x 10^9/ L). HB: 7.9 g/dL. Platelets: 773 x 10^9/ L.

Peripheral blood film showed hypochromic microcytic RBC with anisocytosis, thrombocytosis, and neutrolymphocytosis with atypical lymphocyte. CRP was positive, and ESR was 75 mm/hr, RFT and LFT were normal.

Chest x-ray showed homogenous opacity in the left upper lobe (Figure 1). CT scan chest revealed collapsed left upper lung lobe with the obstructed left upper bronchus and patch of consolidation with air bronchogram.

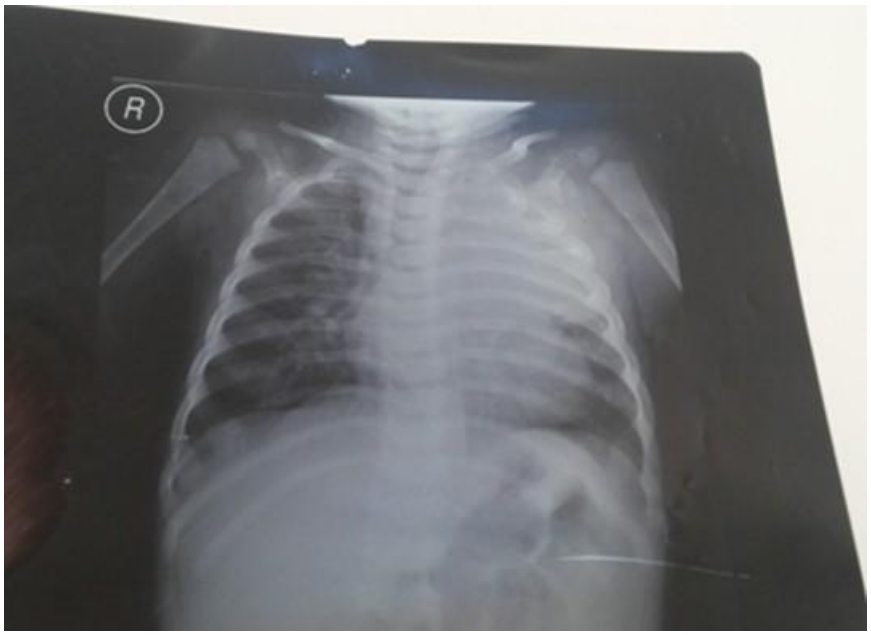

Figure (1)

The patient received intravenous (IV) ceftriaxone and cloxacillin for three weeks without any clinical or laboratory improvement. CBC showed an increase in leukocytosis, anemia, thrombocytosis, and ESR. The WBCs were 28 x 109/ L, HB was 8g/dL, platelets were 945 x 109/L, and ESR was 105 mm/hr.

He developed a firm ill-defined non-tender mass in the left upper chest wall at the same site of the persistent lung opacity, as shown in Figure 2.

Ultrasound (USS) for the chest swelling showed 4.6x2 cm thick walled mixed echo collection deep to the left breast. Evidence of continuation to the thoracic cavity through the intercostal space was shown. Multiple enlarged lymph nodes were seen at the left axilla measured about 3cm with an area of liquefaction.

The case was referred to the infectious and immunology department and further evaluation was done for some specific investigations:

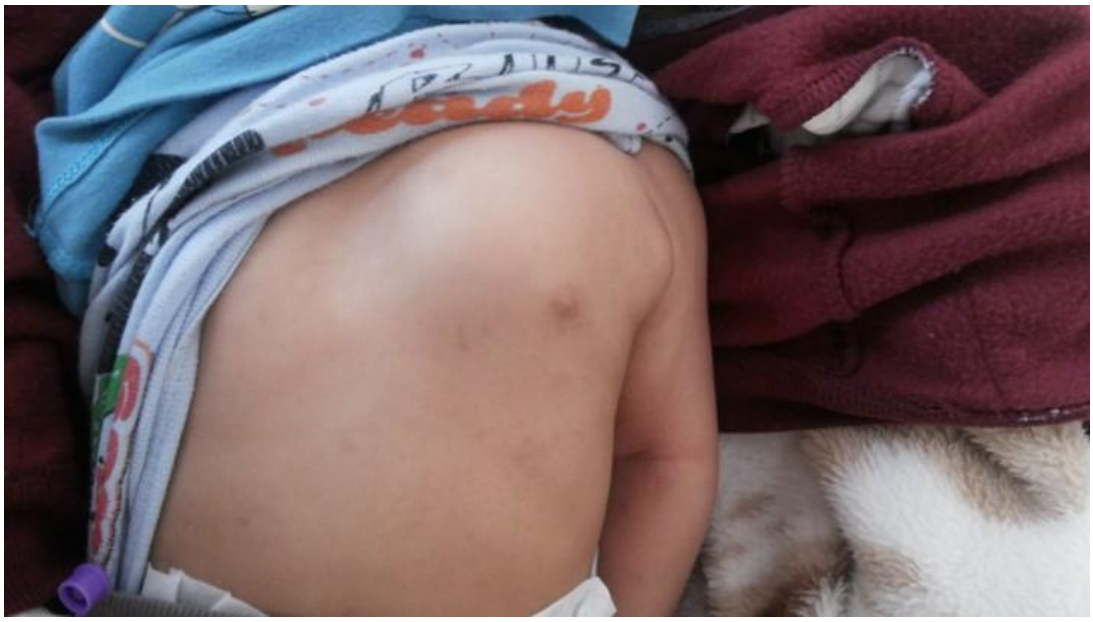

Figure (2)

Tuberculin test was positive (15mm), and three early morning samples of the gastric aspirate (GA); for acid-fast bacilli (AFB) and mycobacterial culture were negative. Testing for HIV was negative too.

Aspiration of collection from the chest wall swelling was negative for AFB, and no growth of Mycobacterium and other bacterial cultures were shown. Cytology study for the collection revealed colonies of fungal organisms and hyphae consistent with Aspergillus infection.

The cardiac echo and abdominal USS were normal. CT guided biopsy from the left apical lung showed granuloma with positive PCR for Mycobacterium tuberculosis complex (MTC). Positive PCR for MTC and no family history of tuberculosis (TB), with opportunistic Aspergillus infection; suggesting that primary immunodeficiency disease with disseminated BCG disease may exist. Hence, investigations for primary immunodeficiency were carried out.

Laboratory values were as follows: IgA, 53mg/dL (normal); IgG,1309 mg/dL(high for age); IgM, 148 mg/dL (high for age); IgE, 34 mg/dL (normal). C3 and C4 were normal. T and B lymphocytes subsets were normal with low CD4/CD8 ratio and slightly increased NK cell.

Nitrobluetetrazoliumtest was negative which suggest that CGD may exist, and the dihydro-rhodamine test proved the diagnosis of CGD.

Conventional anti-TB regimen (INH, rifampicin, and ethambutol) was started.

The patient has received IV amikacin for 10 days, IV ciprofloxacin for 26 days and IV amphotericin B deoxycholate for 21 days. CBC, ESR, RFT, and LFT were conducted weekly to follow the case improvement.

Table (1): shows CBC before and after starting anti-TB and antifungal treatment

Blood test	Before treatment	After 10 days	After 2weeks	After 3weeks
WBC	25 $x10^9$/L	22.3 $x10^9$/L	14.9 $x10^9$/L	10 $x10^9$/L
HB	8.6 g/dL	7 g/dL	7.7 g/dL	7.5 g/dL
Platelets	908 $x10^9$/L	472 $x10^9$/L	647 $x10^9$/L	444 $x10^9$/L
ESR	105 mm/hr		58 mm/hr	45 mm/hr

Patient general condition improved concerning breathlessness and appetite, but there was no change of radiological finding in a chest x-ray. The plan was to continue on anti TB drugs and to give further courses of amphotericin B deoxycholate.

III. Discussion

CGD is a rare primary immunodeficiency disease characterized by recurrent infections. The most frequently determined agents are microorganisms that produce catalase such as Staphylococcus aureus and Aspergillus types. In addition, the infection can develop with serratiamarcescens, Burkholderia cepacia complex and Nocardia types [11].

The patient presented with non-resolving pneumonia which must raise the suspicion for the possibility of primary immunodeficiency existence even in a case of negative family history. His pneumonia was due to two serious pathogens Mycobacterium and Aspergillus which is rarely reported as simultaneously causing pneumonia. The mycobacterium infection was most properly due to disseminated BCG infection.

The BCG vaccine has a protective effect against meningitis and disseminated tuberculosis (TB) in children [12]. The World Health Organization (WHO) recommends that all infants in endemic countries receive a single dose of the BCG vaccine [13]. In Libya, BCG vaccine is given immediately after birth, and it is contraindicated in CGD. However, the problem we are facing is most of the patients who diagnosed with primary immunodeficiency diseases, had already given BCG vaccine. Hence, we advise the family to delay BCG vaccination for the next baby until he/she was investigated for primary immunodeficiency disease.

Complications that arise from BCG vaccination are uncommon. Less than one in a thousand vaccinated individuals develop severe local reactions. The serious disseminated disease develops in less than one in a million cases [14].

Disseminated BCG disease is characterized by failure to thrive, skin rash, anemia, lymphadenopathy and hepatosplenomegaly [15]. The patient presented with anorexia, underweight, left axillary lymph node enlargement, hepatosplenomegaly, and anemia with atypical lymphocytosis.

The availability of the new polymerase chain reaction primers that allow the distinction between Mycobacterium tuberculosis and bovis can be a useful tool in the management of these patients; allowing for quicker diagnosis. Thus preventing the use of inappropriate drugs.

Mycobacterium bovis strains are naturally resistant to PZA [16], hence treating the patient with INH, rifampicin, and ethambutol was administered.

Previous studies showed an association between TB and CD4+ T-lymphocytes depletion [17,18], as noted in this case since the HIV serology was negative, his CD4/CD8 ratio was low.

Invasive aspergillosis is characterized by an impaired ability to damage hyphae, dysregulated inflammation, and local extension to the pleura and the chest wall among one-third of patients [19, 20]. The patient developed chest wall mass extended from the lung lesion with the destruction of ribs at the same site of

extension; it was proved as Aspergillus infection by histopathology. Henriet et al. found that fine needle lung biopsies in CGD patients with invasive fungal infection were all positive; in either microscopy or culture [21].

IV. Conclusion

Unresolved infection or unusual aggressive infection existence must always raise the question about the competency of the immune system of a child.

Patient Consent

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

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