Disseminated BCG as a unique feature of an infant with severe combined immunodeficiency

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Severe combined immunodeficiency (SCID) is a rare primary immunodeficiency disease, which renders patients prone to recurrent severe infections in early childhood.

Herein, we present a five-month-old boy with SCID who was referred to our center with recurrent diarrhea, respiratory infection and lymphadenopathy. Immunological studies showed hypogammaglobulinemia and low number of T-cells, which was compatible with the diagnosis of T- B+ SCID. An advanced cytomegalovirus pneumonitis was detected based on the results of lung necropsy. Cultures and polymerase chain reaction studies of bone marrow aspirates and spleen specimen were indicative of *Mycobacterium bovis*.

This report emphasizes the importance of lymphadenopathy as a sentinel sign of immunological disorders. Underlying immunodeficiency diseases such as SCID should be considered in the differential diagnosis of an infant with infections and lymphadenopathy, particularly in the regions with routine national Bacillus Calmette-Guérin (BCG) vaccination.

Key words: severe combined immunodeficiency, Bacillus Calmette-Guérin, disseminated BCG.

Severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiency disease, characterized by an arrest in T cell development, which could be variably associated with an abnormal differentiation of B and NK cells[1]. SCID is considered as a heterogeneous group of diseases with different forms of inheritance.

Generally, most patients suffer from various infections in their early months of life, presenting with episodes of diarrhea, pneumonia and cutaneous infections, all of which would contribute to failure to thrive. Unfortunately, the ultimate uniform destination of a substantial proportion of patients would be an overwhelming sepsis and the consequent death in the first year of life[1,2]. Variable presentations of SCID have been described in the literature[1,3,4].

Here, a unique feature of SCID is presented in a five-month-old boy, primarily affected with disseminated Bacillus Calmette-Guérin (BCG) after routine vaccination for BCG under a national vaccination program.

Case Report

A five-month-old boy, born of a second-degree consanguineous marriage, was referred to our center with complaints of recurrent diarrhea and fever, which started almost simultaneously two weeks before admission. The infant was the second child of the family from a full-term normal vaginal delivery, with a birth weight

of 3.25 kg. The first child was healthy, with no significant problem in his medical history. The parents did not mention a positive family history of early infant death or immunological diseases among their relatives.

The parents also complained of poor feeding of the infant during the last week, which led them to present to a pediatrician as the frequency of diarrhea increased and the total well-being of the infant worsened. At the time of admission, the frequency of diarrhea was as high as 7-8 times a day, green in color, and did not cease with fasting. The infant looked noticeably ill and pale. He was underweight but not toxic; he was febrile and mildly dehydrated with a normal skin turgor.

The patient underwent a thorough physical examination in which no lymphadenopathy was present in the head and neck, but a firm well-defined (5×5 cm) mass was detected in his left axillary region, upon which the skin was mildly warm and erythematous. The mass seemed to be tender in palpation. A coarse sound was heard over the lungs. Mild hepatosplenomegaly was detected while examining the abdomen. The liver was palpated about 1 cm below the lower costal margin at the midaxillary line, and the same size enlargement was detected for the spleen on the left side. No other problems were evident on the rest of the physical examination.

The febrile child with diarrhea and coarse pulmonary sounds with an enlarging axillary mass was admitted for further evaluation. The laboratory tests and imaging results were as follows: white blood cell count: 11,100/mm^3 (neutrophil: 57.6% and lymphocyte: 41%), hemoglobin concentration: 5.2 g/dl, platelet count: 537,000/mm^3, erythrocyte sedimentation rate: 21 mm/h, and C-reactive *protein: > 3+*. Urine culture showed colonies of the germ *Citrobacter freundii* with a colony count of more than 100,000 colonies per mm^3. Chest roentgenogram defined a small thymus, a heart with upper limit size and disseminated radiolucencies in both lungs.

Subsequent laboratory studies revealed a significant low serum iron concentration of 13 μg/dl (normal: 59-158 μg/dl), total iron binding capacity of 249 μg/dl (normal: 250-450 μg/dl), and a high serum ferritin of 738.8 (normal: 10-400). Liver function tests revealed aspartate aminotransferase (AST) of 87 U/L (normal: up to 40 U/L), alanine aminotransferase (ALT) of 36 U/L (normal: up to 40 U/L), and serum alkaline phosphatase of 131 U/L (normal: 180-1200) U/L.

The presence of BCG lymphadenitis and respiratory infection, in addition to gastroenteritis and the underweight condition of the infant raised suspicion regarding the competency of the immune system. Assessment of the humoral arms of the immune system led to detection of low serum immunoglobulin levels: IgG: 46 mg/dl (normal: 196-558 mg/dl), IgM: 22 mg/dl (normal: 27-110 mg/dl) and IgA: 9 mg/dl (normal: 10-73 mg/dl). Human immunodeficiency virus (HIV) antibody ELISA test was non-reactive. Blood flow cytometry counted the following T cell markers: CD4+ T cell: 0.3% (normal: 22-58), CD8+ T cells: 0.2% (normal: 10-37), CD56+ T cells: 3% (normal: 4-15) and CD19+ B cells: 40.6% (normal: 9-38), which was compatible with a diagnosis of T- B+ NK- SCID.

The presence of unusual BCG adenitis in conjunction with findings on chest X-ray and diagnosis of SCID predicted diagnosis of disseminated BCG. Anti-tuberculosis (TB) regimen, co-trimoxazole, anti-fungal, and immunoglobulin replacement therapy were started; however, bone marrow aspiration was performed in order to document this prediction. Aspirated bone marrow specimens underwent acid-fast bacilli (AFB) staining and culture. In acid-fast staining of bone marrow aspiration, an acid-fast bacillus was detected (Fig. 1). Unfortunately, the patient did not respond to the treatment and experienced a fatal sudden respiratory distress followed by cardiac arrest, which was not reversed with resuscitation attempts.

Lung necropsy revealed the presence of disseminated intra-nuclear inclusion bodies within owl-eye-like pneumocytes with a generalized hyaline membrane formation inside the alveolus (Fig. 2), suggestive of a full-blown cytomegalovirus (CMV) pneumonitis in an immunocompromised host.

Liver and spleen necropsies were performed, which showed disseminated small parenchymal granuloma microscopically upon hematoxylin and eosin (H&E) staining (Fig. 3). Cultures and polymerase chain reaction (PCR) studies

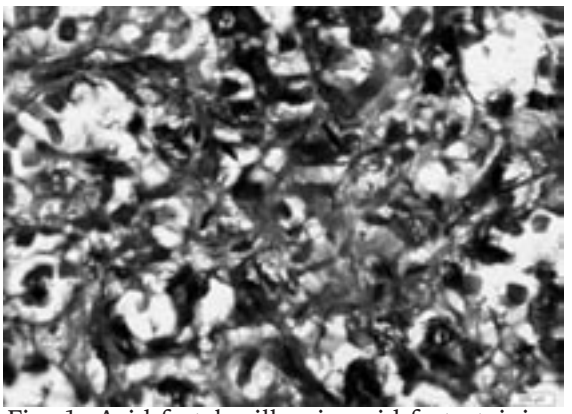

Fig. 1. Acid-fast bacillus in acid-fast staining of bone marrow aspiration.

of bone marrow aspirates and spleen specimen were both indicative of Mycobacterium bovis.

Discussion

In this case study, we introduced an atypical feature of SCID, an infant presenting with a reactional lymph node as a result of BCG vaccination, which dramatically progressed and became a generalized infection. SCID is a rare disease of the immune system, with an estimated occurrence rate of 1 per 75,000 births[5]. Nevertheless, enough reports have been published describing the early clinical presentations of the disease.

Based on reports, fundamental clues that raise suspicion about the inheritance of SCID include positive family history of early infant death, paucity of tonsil and lymphoid tissues on physical examination, presence of cutaneous fungal infection, and detection of lymphopenia on laboratory assessments[6]. Our report, albeit, describes an atypical feature of SCID. Based on this experience, SCID can also present only with a BCG lymphadenitis. In this case, the patient manifested his immunity defect with a mass which, in fact, was the only outward expression of what was occurring inside his body, a defective immune system that led to a disseminated infectious disease and finally caused the debilitating feature of the infant.

BCGosis, as a herald of immunodeficiency, has been described previously in reports originating from countries in which BCG vaccine accounts for a major component of the routine national vaccination program[7].

In a developing country like ours, due to the alarming rates of new infections with TB every year, an approximate number of 24 per 100,000 in the population countrywide or even higher in eastern Iran, vaccination for BCG at the time of birth is necessitated in the national vaccination program[8].

It seems that reporting such cases could provide convincing rationales for a more precise nationwide registry and surveillance tracing of vaccination side effects. However, early establishment of the simplest tests for evaluating the immune system, like quantifying immunoglobulin levels, seems mandatory in such cases. Surely cost-effectiveness studies are needed to assess the cost and benefit of these claims.

An important point that is necessary for further declaration is the method used for the diagnosis of SCID in this report. Although SCID has been proven incurable in many cases, early diagnosis would be promising, as it might provide the opportunity to find an appropriate donor, if any, for bone marrow transplantation, a method that is the only definite cure for the condition. Patients should receive supportive therapy until the transplantation and should be promptly protected from possible infections. As for this case, the late diagnosis precluded even the smallest hope for the parents as the infant became infected with a disseminated multi-organ disease. The result of lung necropsy of the presented patient was indicative for CMV infection, whilst liver and spleen necropsies

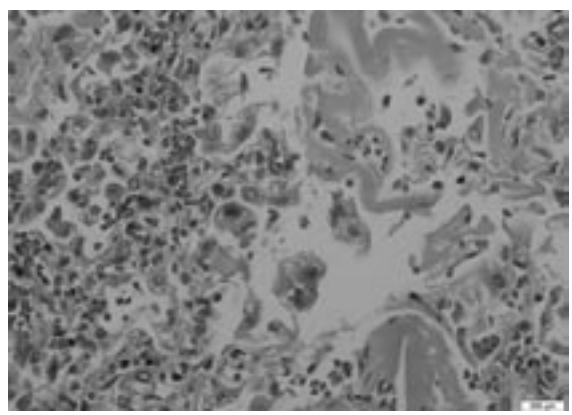

Fig. 2. Lung necropsy: the presence of disseminated intra-nuclear inclusion bodies within owl-eye-like pneumocytes with a generalized hyaline membrane formation inside the alveolus.

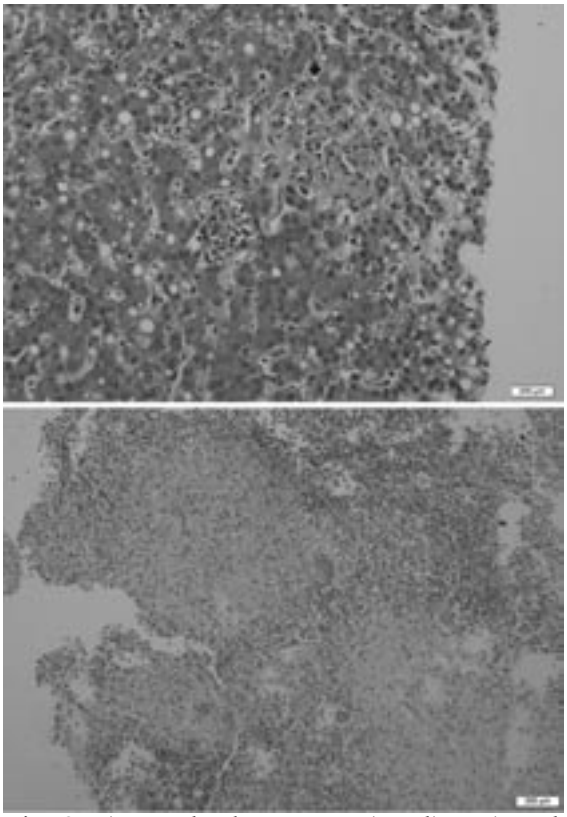

Fig. 3. Liver and spleen necropsies: disseminated small parenchymal granulomas upon H&E staining.

showed disseminated small parenchymal granuloma, which was indicative of *M. bovis* by PCR. As an immunodeficiency condition, both complications are expected. Although the pattern of CMV pneumonitis, which was seen in this case, could be the main cause of death, the role of M. bovis should not be neglected.

For SCID, as previously mentioned, the diagnosis is suspected mainly based on clinical presentation, a point that again highlights the importance of paying more attention to the enlarging axillary masses in infancy. An immune system profile is also mandatory for prompt diagnosis. It should be noted that in some immunocompromised patients, the enlarged lymph node could be seen just after bone marrow transplantation. Hence, the presence of lymphadenopathy in this case shows that the immune system had not been completely shut down.

It should be noted that there are a number of primary immunodeficiency diseases that are vulnerable to BCG. For instance, in addition to SCID, other primary immunodeficiencies that could lead to widespread disease due to BCG include chronic granulomatous disease, ZAP70 deficiency, and Mendelian susceptibility to mycobacterial diseases (including interferon [IFN]-γ receptor 1/2 deficiencies, interleukin [IL]-12/23 receptor β1 chain deficiency, IL-12p40 deficiency, STAT1 deficiency, and LZ-NEMO deficiency)[7,9].

Here, the infant showed a generalized decrease in all types of immunoglobulins and also the number of T cells. Hence, the disease was diagnosed by means of clinical presentation and immunological surveys. On the other hand, regarding his flow cytometry, it was likely to be T-B+NK- SCID type, and the most common subtype in this group is γc deficiency (mutation in IL2RG gene) with X-linked inheritance; however, as the case was born of consanguineous parents, it could be the Janus-Associated Kinase 3 (JAK3) deficiency subtype as a non-common form of SCID in the world[1].

Ultimately, this report can emphasize the importance of a persistent axillary lymph node as a sentinel sign of immunological diseases. Ignoring such a finding in an infant, even without apparent family history of immunological disease, would be disastrous, particularly in countries like ours in which, according to unofficial reports, immunological diseases like SCID account for a higher rate than the reported numbers from developed countries[10-13]. On the other hand, since the routine national vaccination program in Iran includes BCG, an epidemiological survey on disseminated BCG and SCID could be beneficial to achieve a more appropriate national guideline on this topic.

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