Bécégite disséminée révélatrice d'un déficit immunitaire combiné sévère: à propos d'un cas

Disseminated BCG infection revealing a severe combined immunodeficiency: A case report

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Résumé

Introduction: Le vaccin Bacillus Calmette Guerin (BCG), administré à tous les nouveau-nés en Tunisie, pourrait entraîner des complications sérieuses allant d'une maladie locale à une maladie disséminée chez les patients atteints d'un deficit immunitaire primitif.

Cas clinique: un garçon de 3 mois avait présenté une fièvre persistante, une hépato-splénomégalie et de multiples lesions ostéolytiques. Il a été diagnostiqué d'un deficit immunitaire combine sévère et une bécégite disséminée. Malgré un traitement antituberculeux associé à des veinoglobulines intraveineuses, l'évolution a été fatale.

Conclusion: Notre observation met en évidence le risque possible d'une complication rare qui peut être mortelle du vaccin BCG. En cas de suspicion d'un deficit immunitaire primitif, l'inoculation du BCG doit être reportée jusqu'à ce que des tests de dépistage appropriés excluent ce diagnostic afin d'éviter cette complication.

Mots clé: Déficit immunitaire primitif; Mycobacterium Bovis; Vaccin BCG.

Abstract

Introduction: Bacillus Calmette Guerin (BCG) vaccine, which is administered to all newborns in Tunisia, can lead to serious complications ranging from local disease to disseminated disease in a group of patients with primary immunodeficiency diseases.

Case report: A 3-month-old boy presented with persistent fever, hepato-splenomegaly and multiple osteolytic lesions. He was diagnosed with severe combined immunodeficiency disease and disseminated BCG infection. Despite anti-tubercular therapy combined with intravenous immunoglobulin, the evolution was fatal.

Conclusion: The case highlights the possible risk of such rare yet lethal complication of BCG vaccine. In suspected cases of primary immunodeficiency disease, inoculation of BCG should be postponed until appropriate screening tests exclude such diagnosis to prevent serious complications.

Key Words: Primary immunodeficiency, Mycobacterium Bovis; BCG vaccine

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INTRODUCTION

Bacillus Calmette Guerin vaccine (BCG), made from an attenuated strain of Mycobacterium Bovis, is administered routinely to all newborns in tuberculosis endemic countries including Tunisia (1). It has an excellent safety profile, but a wide range of complications can occur (2). Disseminated BCG infection following BCG vaccination is a rare complication that only occurs in patients with immunodeficiency (3). The case highlights the possible risk of such rare yet lethal complication of BCG especially when it is given routinely at birth or in the neonatal period, and also emphasizes the need for neonatal screening for severe combined immunodeficiency disease (SCID) in Tunisia.

CASE REPORT

The present case was reported according to the CARE guidelines (4).

A 3-month-old boy was admitted to hospital for persistent fever with intermittent diarrhea lasting for 3 weeks before admission. He received multiple courses of oral antibiotics with no response. He was the second child of non-consanguineous parents. There was no family history of tuberculosis. There were no perinatal concerns and he remained asymptomatic and well thriving. On examination, he had stable vital parameters with mild pallor but no icterus or lymphadenopathy. Systemic examination was remarkable with spleno-hepatomegaly, but no other abnormalities. Initial laboratory investigation showed lymphopenia at 54 cells/mm3, microcytic anemia (hemoglobin at 9 g/dL and mean corpuscular volume at 75 fl) and a high level of C-Reactive-Protein (111 mg/L). The infectious investigations were negative. Cyto-bacteriological urine test, lumbar puncture cultures and blood cultures were all negative. Virological and bacteriological examinations of stools were negative. The Chest X-ray revealed no abnormality of lung parenchyma or hilar lymphadenopathy. Viral serology, leishmaniasis serology and wright test were also negative. The gastric aspiration was negative on acid-fast bacilli microscopy. Abdominal ultrasonography revealed a multi-nodular diffuse liver and homogeneous splenomegaly. Contrast enhanced computed tomography of the abdomen showed enlarged liver and spleen with multiple hypodense lesions (Figure 1). Tumor markers (Alpha-fetoprotein, human chorionic gonadotropin) were negative. Urinary Vanillylmandelic Acid level was normal. Myelogram showed a normal rich marrow with presence of some histiocytic cells.

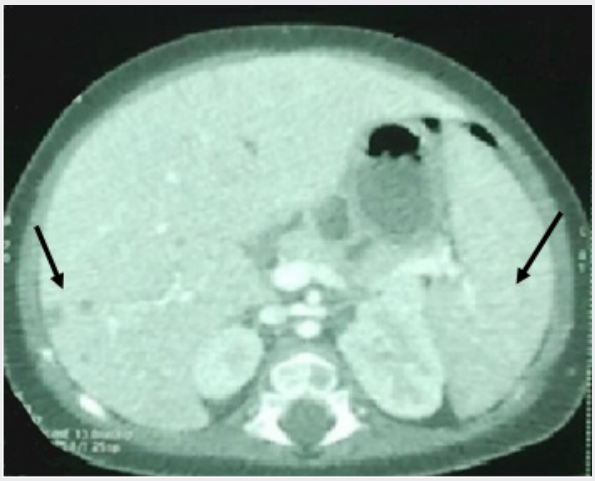

Figure 1. Abdominal computed tomography scan: Enlarged liver and spleen with multiple hypodense lesions.

Despite broad-spectrum antibiotic, the patient remained febrile. On the 10th day of admission, the child developed generalized maculopapular rash and the mobilization of the lower limb was painful, especially in the right leg. Bone X-rays revealed multiple, round, osteolytic lesions in the femora and tibiae (Figure 2).

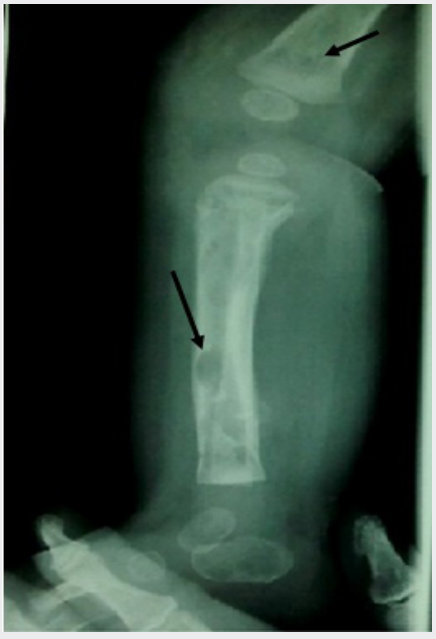

Figure 2. Bone X-ray of lower limbs: multiple, round, osteolytic lesions in the femora and tibiae.

Skeletal scintigraphy showed a radiotracer hyperfixation in lower third of the tibias and femurs and moderate and heterogeneous hyperfixation in the right iliac wing (Figure3). On the 12th day of admission, the child developed neurological deterioration and became hyporeactive and drowsy. Brain scan showed multiple lacunae in the cranial vault (Figure 4a). A liver biopsy showed a granulomatous inflammation with the presence of acid-fast bacilli resistant by Ziehl-Nielsen staining. Moreover, the bone biopsy showed the presence of numerous acid-fast bacilli in the cytoplasm of histiocytic cells. The immunohistochemical study carried out using the Cluster of Differentiation CD1a marker did not show any labeling on the histiocytic cells. Skin biopsy showed no abnormalities. He was started on anti-tubercular therapy including isoniazid, rifampicin, ethambutol and clarithromycin with analgesic treatment. Actually, these severe and widespread clinical manifestations have led us to perform an immunological investigation. It showed negative human immunodeficiency virus serology, low serum immunoglobulin G (Ig G), absence of T lymphocyte, Natural killer cells and 69% of B lymphocyte via lymphocyte phenotyping and a poor lymphocytic response to mitogen stimulation; these signs are suggestive of SCID. Based on clinical findings, immunological work-up and a positive culture to Mycobacterium Bovis identified later on bone biopsy, the patient was diagnosed as having disseminated BCG infection.

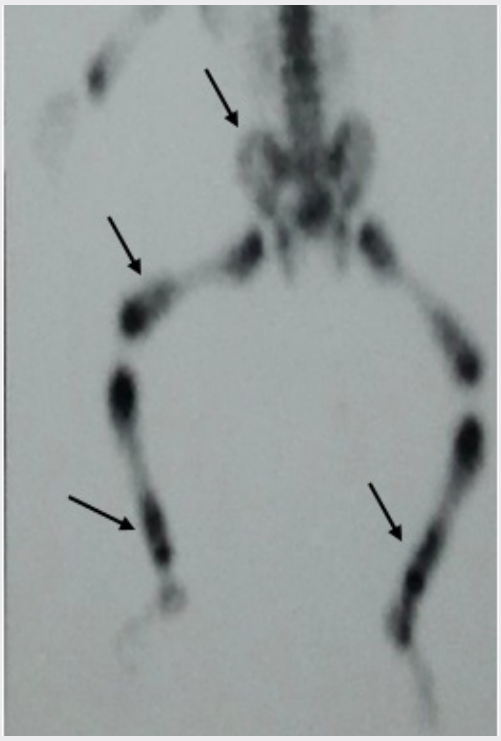

Figure 3. Skeletal scintigraphyhyperfixation in lower third of the tibias and femurs and moderate and heterogeneous hyperfixation in the right iliac wing

Gradually, the child's clinical condition has deteriorated with persistent fever, worsening of general condition and enlargement of the liver and spleen. The child developed seizures and a coma after one month of anti-tubercular therapy. Cerebral computed tomography scan showed an intra-axial lesion in the right temporal lobe suggestive of tuberculoma (Figure 4b).

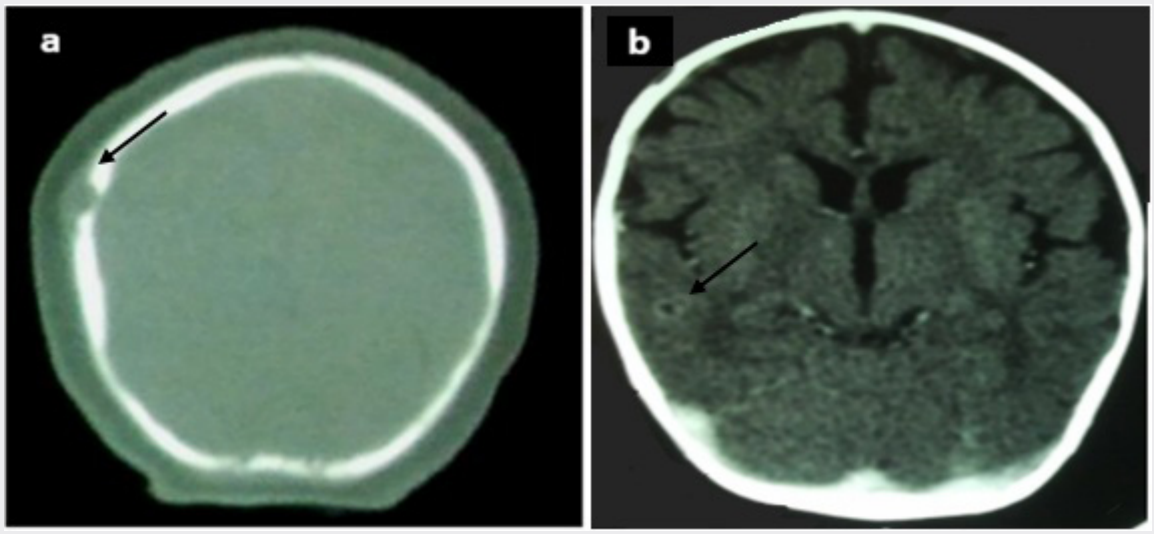

Figure 4. Cerebral computed tomography scan: (a) multiple lacunae in the cranial vault. (b) Intra-axial lesion in the right temporal lobe, measuring 6,5mm hypodense, with peripheral enhancement and no perilesionaledema: Tuberculoma.

The anti-tubercular therapy was enhanced by the addition of Levofloxacin. He was given intravenous immunoglobulin and was also started on antifungal (Fluconazole) and antibacterial (Cotrimoxazole) prophylaxis. Typing of histo-compatibility antigens for marrow transplantation was performed for the sister and parents. However, the child developed septic shock with disseminated intravascular coagulation and respiratory failure. He died due to severe disseminated BCG infection.

DISCUSSION

Our patient presented a devastating complication of BCG vaccination. BCG is administered in many developing countries to prevent severe tuberculosis, particularly in children. Disseminated BCG infection is a severe complication of this vaccine and can be seen in patients with an underlying immunodeficiency, particularly in those with SCID (5,6). SCID is a heterogeneous group of diseases that affects cellular and humoral immune function. The molecular defect prevents T-cell function. SCID immuno-phenotypes can be classified according to the presence (T– B+ SCID) or absence (T–B– SCID) of B cells in the peripheral blood. Both main groups of SCID include forms with or without natural killer (NK) lymphocytes (5,7). BCG complications including disseminated BCG infection, as the adverse reaction to BCG vaccination, could be seen in all underlying genetic types of SCID (7).

The most commonly reported symptoms in disseminated BCG disease are fever, lymphadenopathy, weight loss, failure to thrive, hepatosplenomegaly and osteomyelitis (5,8). Skeletal involvement may affect the hands, arms, legs, vertebrae and orbit. BCG osteomyelitis usually occurs in the epiphysis and metaphysis (9). Skin manifestations are rare in disseminated BCG disease with a wide range of lesions being described ranging from macula-papules, subcutaneous nodules and ulcers (10). Our child had most of the frequently described manifestations of disseminated BCG infection, i.e., fever, anemia, skin rash and organomegaly, but lymphadenopathy was conspicuously absent.

The diagnostic criteria for disseminated BCG were defined by the European Society for Immunodeficiency (11). Definitive disseminated BCG infection is diagnosed basing on the existence of systemic symptoms and two or more areas of involvement beyond the BCG vaccination site, in addition to identification of Mycobacterium Bovis BCG strain by culture and/or standard polymerase chain reaction (PCR), as well as histopathologic changes with granulomatous inflammation (9,11). Non invasive investigations were non-contributory in our patient. Liver and bone biopsy confirmed the diagnosis of mycobacterial infection by a positive acid-fast bacilli and the presence of granulomas on histological examination. In the immunocompromised patient, the lesions in histology usually consist of ill-defined and poorly differentiated granulomas, with few if any giant cells and lymphocytes but widespread histiocytes loaded with acid-fast bacilli (12). These patients can be misdiagnosed as having Langerhans' histiocytosis (13). As a matter of fact,the use of conventional techniques to identify Mycobacterium Bovis is fastidious and slow. Genotypic methods can be used to accelerate the bacteriological diagnosis. They provide rapid results of susceptibility of Mycobacterium Bovis to antituberculosis drugs simultaneously with diagnosis, improving therapeutic management (14,15).

The diagnosis of disseminated BCG infection, often unrecognized or late, generally reveals severe immunodeficiency diseases in infants. Several genetic defects that correlate with BCG disease have now been identified, such as Mendelian susceptibility to Mycobacterial disease, chronic granulomatous disease, and SCID (7,10). SCID is the most severe form of inherited primary immunodeficiency (5,9). Disseminated BCG infection in infants with SCID is associated with high mortality (5,11). Inheritance can be X-linked, autosomal recessive, or sporadic. The most common form is X-linked T cell-negative (T-), B cell-positive (B+), natural killer cell-negative (NK-) SCID caused by mutations in the X-linked gene IL2Rγ, which encodes the common gamma chain of the leukocyte receptors for interleukin-2 and multiple other cytokines (12). Our patient had such phenotypic form of SCID but it had not been genetically confirmed.

Actually, there are no clear guidelines on the most suitable treatment for disseminated BCG disease (9,11). Aggressive therapy involving at least four antituberculous drugs is usually needed (8,16). Commonly used anti-BCG regimen consists in a backbone of 3 first-line anti-tuberculous drugs (isoniazid, rifampicin and ethambutol), plus an additional agent to which BCG is also susceptible, such as quinolone (e.g. ciprofloxacin, levofloxacin), aminoglycoside (e.g. amikacin, streptomycin) and clarithromycin (9,16). Because of the BCG resistance to pyrazinamide, there is no place for this drug in the treatment protocol of these children (17). Treatment with

gamma interferon may be associated with antibiotherapy to activate bactericidal activity in neutrophils and macrophages (18). A patients with compatible clinical signs and symptoms, suspected of primary immunodeficiencies, positive acid-fast bacilli smear is sufficient to start specific anti-tubercular treatment. It should not be delayed till the results of PCR or cultures are available (9,14).

SCID should be considered a pediatric emergency, and hematopoietic stem cell transplantation should be performed on an urgent basis (7,10). To avoid delayed diagnosis of SCID and the organ damage secondary to disseminated BCG infection, neonatal screening to identify lymphopenia should be taken into account. T cell receptor excision circle assay is commonly used in western countries as part of newborn blood spot screening program as the assay has high sensitivity and specificity to identify SCID infants, allowing early intervention (19). On the other hand, patients who already received BCG before diagnosis of SCID may be started on antitubercular therapy along with standard management guidelines even before symptom onset (19,20).Altogether, precise control and measures aiming to avoid administration of BCG at birth in those with family history of recurrent infections and immunodeficiency are highly recommended(7). BCG vaccination can be administered later once screening tests rule out underlying immune-deficiencies (21). In 2020,the BCG Moreau vaccine produced in Poland, with well-documented genetic characteristics, seems to be safer than other BCG substrains used in other parts of the world (22).

Disseminated BCG disease is rare and should be considered in the appropriate clinical setting. Our case highlights the difficulty of diagnosis and management of this severe disease. Unfortunately, the prognosis for children with SCID is very poor in Tunisia. Stem cell transplantation is the only curative treatment in this group of patients; however, there is only one center for stem cell transplantation in Tunisia.

CONCLUSION

Disseminated BCG infection may be the preliminary sign of an unidentified immunodeficiency. Family history of early death due to recurrent infections in some patients should be considered an alarm for primary immunodeficiency diseases. Delaying BCG vaccination for a few months could be suggested in those families.

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