

Diffuse bony involvement in disseminated BCG disease in a patient with possible severe combined immune deficiency (SCID)

Nausheen Khan, MB BS, FC (Rad) (D) SA

Irma van de Werke, FRCR

Department of Radiology, Kalafong Hospital and University of Pretoria

Farzanah Ismail, FC Rad (D) SA, MMed Rad (D)

Department of Radiology, Steve Biko Academic Hospital and University of Pretoria

Corresponding author: N Khan (nausheenkhan5@yahoo.com)

BCG (bacille Calmette-Guérin) vaccination is carried out worldwide to prevent tuberculosis. It is considered to be very effective and has an excellent safety profile, but complications do occur. These may range from erythema and abscess at the site of inoculation to extensive disseminated disease including regional and distant lymphadenopathy, lymphadenitis, musculoskeletal lesions and non-fatal and fatal disseminated infections, depending upon the immune status of the patient. Osteomyelitis is a rare but serious complication that may have a fatal outcome. We report a case of severe tuberculous osteomyelitis secondary to BCG vaccination in a child with possible severe combined immune deficiency.

Case report

A 4-month-old white baby was brought to Kalafong Hospital by his parents, who reported that he had been ill for 3 weeks. He had received all his vaccinations to date, including BCG. An uncle had died of severe septicaemia at the age of 7 months. On clinical examination the child was severely ill with swollen, tender limbs. He was afebrile with a pulse rate of 202/min and a respiratory rate of 70/min. He had a gallop heart rhythm and hepatosplenomegaly. On further work-up he was found to have anaemia, thrombocytopenia and neutropenia. The haemoglobin concentration was 9.2 g/dl (normal 10 - 15), the platelet count $39 \times 10^9/l$ (normal 140 - 350), the white cell count $2.92 \times 10^9/l$ (normal 5.50 - 18), and the C-reactive protein level 182 g/l. Both total protein (36 g/l, normal 48 - 76) and albumin (13 g/l, normal 28 - 46) were low, as were immunoglobulin levels (IgG 2.56 g/l, normal 3 - 10; IgA 0.33 g/l, normal 0.10 - 0.70; and IgM 0.26 g/l, normal 0.20 - 1.10). The total IgE was 4 kU/l (<7.3). He was HIV negative with a CD4 count of 1 cell/ μ l (normal 500 - 2 010), a CD8 count of 2 cells/ μ l (normal 250 - 990), a CD3 count of 3 cells/ μ l (normal 699 - 3 001) and a CD4/CD8 ratio of 0.500. His complement classical pathway was 325 CH100 U/l (normal 488 - 1 200). A diagnosis of severe combined immune deficiency (SCID) was postulated, but since only the CD4 and CD8 counts were done, and not the entire lymphocyte spectrum and genetic testing, the diagnosis of SCID was not proven.

A chest radiograph showed no signs of tuberculosis. A skeletal survey demonstrated diffuse involvement with lytic lesions in the metadiaphysis of the long bones and diffuse soft-tissue swelling (Fig. 1, a - d). There was an undisplaced metaphyseal fracture of the right humerus with callus formation. An ultrasound scan showed hepatosplenomegaly and multiple small hypo-echoic lesions in the spleen (Fig. 2, a). The extensiveness of the disease was demonstrated by computed tomography (CT), which showed lytic lesions throughout the skeleton, including the ribs, spine, scapula and pelvis along with the long bones (Fig. 3, a - c). There were hypodense

lesions in the spleen (Fig. 2, b). The differential diagnosis at this stage was metastatic neuroblastoma or osteomyelitis with abscesses in the spleen.

A tibial bone biopsy was done. Direct microscopy revealed acid-fast bacilli (AFB), and culture for AFB was positive after 7 days of incubation. Polymerase chain reaction (PCR) for mycobacteria was positive and DNA belonging to *Mycobacterium bovis* was detected in the specimen. The BCG strain was not specified. A final diagnosis of disseminated BCG disease in a patient with possible SCID was made. Despite immediate treatment with antibiotics and antituberculosis drugs, the child's condition deteriorated and he died.

Discussion

The original BCG strain was derived from *M. bovis* and was first used as a tuberculosis vaccine in 1921.¹ Although it is considered safe in general, complications do occur even in normal infants.^{2,3} It should be noted that dissemination of BCG as a sequel to BCG vaccination was confirmed on autopsies in 1956 and reproduced in 1982 in asymptomatic patients who died of unrelated causes.¹ When dissemination occurs, an underlying immune deficiency state must be excluded.³ The World Health Organization (WHO) currently recommends giving BCG, a live attenuated *M. bovis* vaccine strain, to all neonates in areas with a high prevalence of tuberculosis, irrespective of HIV exposure, unless the child has symptomatic HIV disease or suspected congenital immune deficiency.¹

Systemic or disseminated BCG disease may be clinically and radiologically indistinguishable from tuberculosis and disseminated malignancy, and can only be confirmed through PCR.⁴ Apart from metastatic disease, disseminated bone lesions in an infant should raise a suspicion of possible infective process and an underlying immune deficiency.

If disseminated BCG disease is suspected, the standard investigations should include fine-needle aspiration of the



Fig. 1. a: chest radiograph, anteroposterior view with no radiological signs of pulmonary TB; **b:** anteroposterior radiograph of the right humerus with pathological fracture through the lytic lesion in proximal metaphysis with callus formation; **c:** the right radius and ulna show metadiaphyseal involvement with lytic lesions; **d:** radiograph of the pelvis including the right femur showing similar metaphyseal involvement.

regional and/or distant lesions, a chest radiograph, sputum specimen microscopy, mycobacterial blood culture, bone marrow biopsy, urine culture and other systemic investigations as clinically indicated.^{1,5}

Osteomyelitis is a rare but very serious complication of BCG immunisation that results from generalised haematogenous dissemination.⁶ The lesions are localised to the metaphysis or epiphysis of long bones. In our patient the involvement was widespread. Timely diagnosis of BCG osteomyelitis is important, since antituberculosis therapy is effective when initiated early in the course of the disease.⁶

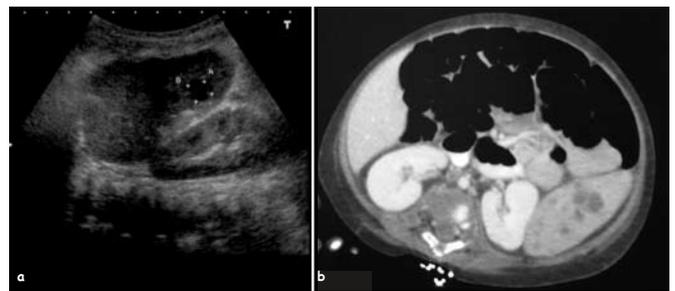


Fig. 2. Ultrasound (a) and CT scans (b) of the spleen with intravenous contrast showing multiple hypo-echoic and hypodense lesions in keeping with TB abscesses.

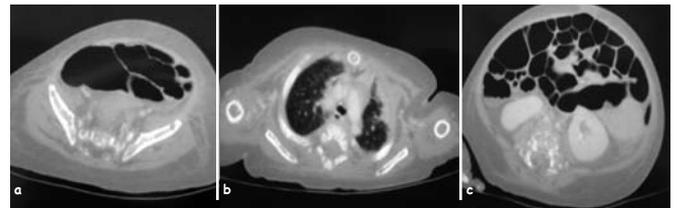


Fig. 3, a - c. Selected CT images (in bone window) through chest, abdomen and pelvis showing extensive bony involvement.

Immune deficiency diseases are a heterogeneous group of disorders characterised by an increased risk of infection. HIV infection is now the most common of these, but the inherited disorders such as SCID or chronic granulomatous disease, mendelian susceptibility to mycobacterial infection and Di George anomaly must not be forgotten.^{2,3}

SCID is a heterogeneous group of diseases that affect cellular and humoral immune functions and can be categorised into various groups with different underlying genetic defects.² In patients with SCID, as was probable in our case, there is also increased susceptibility to severe mycobacterial disease following vaccination.² The underlying genetic defects in SCID are not always reported, as in our case, but it appears that all types of SCID are susceptible to BCG dissemination.² The risk of disseminated BCG in HIV-positive patients is also considerably higher than was previously estimated.²

The most important factor in improving the prognosis of an infant with SCID is to diagnose and treat the disease with bone marrow transplantation before overwhelming infections occur, but this is not always possible as BCG is usually given within days of birth and no high-throughput screening test for SCID is currently available.⁷ Better prevention of maternal and infant HIV infection and more rapid access to HAART for those infected is likely to reduce the infant population at risk of disseminated BCG disease.³

Conclusion

Vaccination strategies attempt to balance risk and benefits. The benefit of BCG immunisation against mycobacterium infection has been the subject of much controversy.¹ Owing to the risk of disseminated BCG disease in immune deficiency, the WHO advises increasing caution on the use of BCG in affected children, or those in whom immune deficiency is suspected.

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