Osteomyelitis following Bacille Calmette-Guérin vaccination

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ABSTRACT

يعد حدوث المضاعفات الثانوية بعد التلقيح بلقاح الدرن من الأمور النادرة. نصف في هذا المقال حالة 3 أطفال ذو مناعة سليمة قد أُصيبوا بالتهاب العظم والنقي بعد التلقيح بهذا اللقاح. لقد كانت دورة المرض طبيعية وخالية من الأمور الخطيرة، إلا أنه قد تمت ملاحظة تغيرات واضحة في صور الأشعة العادية وصور الرنين المغناطيسي. لقد كان للتفاعل التسلسلي المبلمر ذو الوقت الفعلي دور أساسي في تأكيد تشخيص هذا المرض بعد التلقيح بلقاح الدرن، وعادة ما تكون النتائج جيدة بعد إجراء التدخل الجراحي المناسب والعلاج الكيميائي المُضاد للدرن.

Secondary complications after Bacille Calmette-Guérin (BCG) vaccination are unusual. We describe 3 immunocompetent children who developed osteomyelitis after BCG vaccination. The course of the disease is not dramatic, but marked changes are frequently visible in plain radiograph and MRI. The real-time polymerase chain reaction has an essential role to confirm the diagnosis of BCG osteomyelitis. With proper surgical intervention and chemotherapy, the prognosis is usually good.

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Although vaccination against tuberculosis by means of Bacillus Calmette-Guérin (BCG; strain of *Mycobacterium bovis*) is widespread all over the world and is generally considered to be safe, some serious adverse reactions can occur.[1-3] The BCG vaccination could also be associated with minor complications at the site of vaccination such as abscess formation or skin ulceration. Fatal disseminated infection has been reported in patients with immune insufficiency. The complications after BCG vaccination were assumed to be related to the strain of the vaccine, vaccine over dosage, or faulty technique of vaccination.[1,4,5] Osteomyelitis is a rare complication of BCG vaccination in immunocompetent hosts, and its incidence varies between countries.[6-8] A meta-analysis of previous reports indicated the frequency of BCG osteomyelitis as one in 80,000 in some European countries.[1] Risk of osteomyelitis due to BCG in immunodeficient patients is much higher and is associated with fatal disseminated infections.[5] This late complication may occur in children within a few months to a few years after the vaccination. The lesions are localized in the metaphysis or epiphysis of long bones.[3,9,10] In Saudi Arabia, although most of the newborns are vaccinated with BCG within the first year of life, the diagnosis of culture-proven BCG osteomyelitis has not been reported previously. Herein, we report culture proven BCG osteomyelitis in 3 immunocompetent infants that were confirmed by the real-time polymerase chain reaction (PCR). The aim of this report is to add 3 more cases to the previously published series of the same condition, and to discuss the management and prognosis for this complication.

Case Report. ***Patient 1.*** An 11-month-old boy presented with pseudoparalysis of his right upper limb and tenderness over the proximal arm for a period of 2 weeks. There was no history of trauma, fever, or constitutional symptoms. He had received the BCG vaccination 7 months prior to presentation. On examination, there was decreased range of motion

Disclosure. This study was conducted by the Orthopedic Surgery Research Chair Group, King Saud University, Riyadh, Kingdom of Saudi Arabia

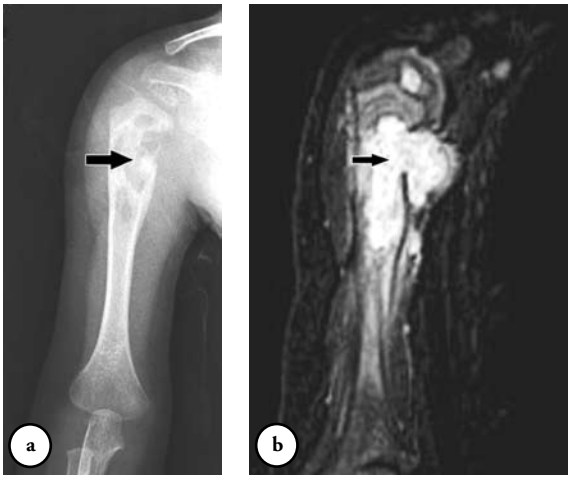

Figure 1 - Radiological assessment of the first patient showing: **a**) plain radiograph, and **b**) MRI showing destructive lesion (black arrows) upper metaphysis of the right humerus.

at the right shoulder with obvious swelling, but no skin changes. Blood work up was carried out and showed normal parameters except for high erythrocyte sedimentation rate (ESR). Plain radiograph and MRI showed a destructive lesion at the proximal humerus near the growth plate with cortical disruption (**Figures 1a and 1b**). The first impression was Ewing's sarcoma versus infection. Bone biopsy showed caseating granulomatous inflammatory tissue consistent with TB osteomyelitis. The BCG osteomyelitis was confirmed later by tissue PCR.

Patient 2. A 13-month-girl presented with painful limping and swelling in her left knee. The family denied any history of trauma or fever. The BCG vaccination was given 10 months prior to presentation. On examination, there was tenderness, and complete limitation of left knee motion. Blood work up was carried out and showed normal parameters, but was high for ESR. Plain x-rays showed a well-demarcated lesion at the proximal left tibia. An MRI showed a lytic lesion within the proximal tibial metaphysis of inflammatory character. Bone biopsy showed necrotizing granulomatous tissue. Tissue PCR was positive after 8 weeks, which confirmed the diagnosis of BCG osteomyelitis.

Patient 3. A 2-year-old boy presented with painful limping and swelling in his right knee. He had received BCG vaccination at the age of 6 months. Examination and blood work were similar to patient 2. Radiological imaging showed a lytic lesion in the right distal femur with large soft tissue mass suspicious of sarcoma. An MRI showed an aggressive lesion within the distal right femoral metaphysis with cortical disruption (**Figures 2a, 2b, and 2c**). Tissue biopsy showed caseating granulomatous inflammation, and tissue PCR was positive for BCG osteomyelitis.

A chest radiograph was normal in all patients in our series. All patients were treated with surgical irrigation, extensive curettage, and debridement followed by a full course of anti TB medications according to the treatment protocol of the Infectious Disease Division in our Institute (triple drug treatment including rifampicin, para-amino salicylic acid [PAS], and isoniazid [INH]). The third case had revision surgery. All 3 patients had

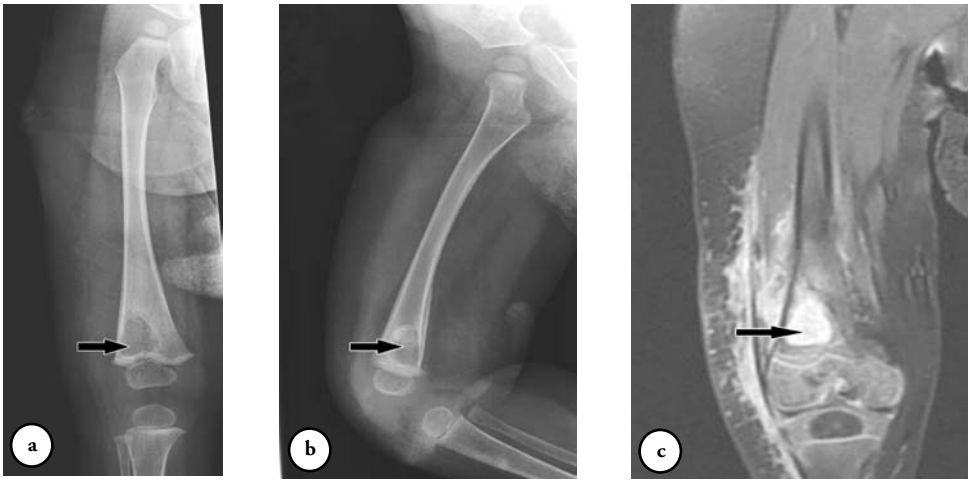

Figure 2 - Radiological assessment of the third patient **a**) AP, **b**) lateral x-ray views, and **c**) MRI showing a lytic lesion (b arrows) in the distal right femur with soft tissue extension.

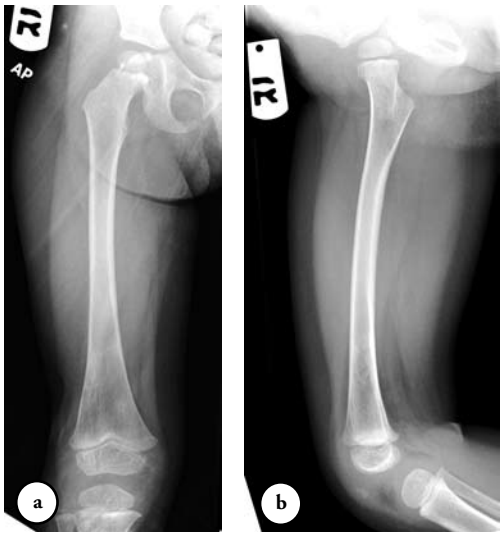

Figure 3 - Final follow up radiographs of the third patient: **a)** AP, and **b)** lateral x-ray views showing complete resolution of the lesion.

regular follow up for 2 years, and they showed complete clinical and radiological resolution (**Figures 3a and 3b**). At the final follow up all patients were normal.

Discussion. The BCG is used worldwide as a vaccine against tuberculosis. Currently, the BCG coverage rate exceeds 95% of newborns in Saudi Arabia, and it is usually given soon after birth. The vaccine is not entirely harmless. Many authors have reported osteomyelitis and infectious arthritis following vaccination with BCG in children who have normal immunity as well as in those who have immune defects.[2,9,10] The BCG bacteria spread rapidly throughout the body if deposited in or under the skin. The bacteria could be traced to several internal organs less than one hour after their introduction. Hematogenous spread of the BCG vaccine may result in osteomyelitis, but this is a rare complication. The lesion may be distant to the site of injection or on the same side of vaccination,[1,5] a fact that was supported by our findings.

The incubation period for BCG osteomyelitis is usually more than 6 months after vaccination, and in most cases the metaphysis or epiphysis of long bones are affected. This differs from disease caused by *Mycobacterium tuberculosis*, which more commonly occurs in the spine and weight bearing joints in older children and adults.[4,8] Many authors reported that the symptoms might appear over a wide time-period (range, 3 months to 5 years). The clinical signs of BCG osteomyelitis generally include limited motion; otherwise, the affected child appears constitutionally and generally well, but may have a low-grade fever and high ESR.[3,8-10] All the patients of the current series showed the same behavior of BCG osteomyelitis as previously reported including incubation period, site of affection, and clinical picture.

As serious complications of BCG infection are thought to occur more frequently in patients with immunological deficiencies,[1,5,7] we thoroughly investigated the immunological status of all patients. All children have shown no greater susceptibility to infection and no deficiency of immunoglobulin or leukocytes. Infections seem to have occurred in otherwise healthy individuals. Also, there was no evidence that the vaccines used were defective, as no complications have been reported in other children. Accordingly, the findings of the present study support the hypothesis that BCG osteomyelitis could occur in immunocompetent hosts.[6,9,10]

The management of BCG disease is difficult in the absence of standard treatment guidelines, which is complicated by the inherent resistance of *Mycobacterium bovis* strains to pyrazinamide. The BCG osteomyelitis is generally highly susceptible to antituberculous drugs; nevertheless, the most effective chemotherapy regimen for the treatment of this condition is not well established. However, a combination of INH and rifampicin is the preferred regimen by most authors.[6,7,10] Although the literature recommends treatment for 12 months, Yamada et al[9] opted for discontinuing both drugs after 8 months, due to the rapid clinical and radiological improvement of their patient. In the cases of our series, the favorable clinical and serological response to initial anti-TB drug regimen, which included rifampicin, PAS, and INH, and the absence of side-effects influenced the Infectious Disease Group in our institute to continue this drug regimen for a total of 12 months. If the BCG osteomyelitis were confirmed before commencing the chemotherapy, PAS may have not been included.

Treatment for a period of 9-12 months together with surgical evacuation usually results in good outcome. Our findings agree with previous reports, stated that operative treatment is indicated to obtain specimens for biopsy for definitive diagnosis and to facilitate the healing process.[1,4,8] It is important to diagnose BCG osteomyelitis as early as possible, since management is very effective when started at the beginning of the disease. Problems of early diagnosis include unawareness of the condition by most primary physicians and the slow progress of symptoms, which looks relatively benign.[1,6] Another essential problem is the complexity in confirming the diagnosis. Conventionally, the diagnosis depends mainly on tissue culture by identification of the BCG strain of *Mycobacterium bovis*. Recent reports have highlighted the potential role of PCR for the rapid and specific identification of *Mycobacterium bovis* BCG, which provides a definitive diagnosis of BCG osteomyelitis after suspicious history and laboratory data. A single nucleotide difference distinguishing *Mycobacterium*

bovis from *Mycobacterium tuberculosis* can be used to differentiate BCG osteomyelitis from tuberculous osteomyelitis.[3,4,6] It was reported that the PCR method is 100% sensitive and specific for the identification of BCG among strains of the *Mycobacterium tuberculosis* complex.[11] This was true in all patients of this series, where BCG osteomyelitis was confirmed rapidly with the use of a recently developed diagnostic protocol of molecular analysis in which the real-time PCR was used. Rapid diagnosis positively affected the prognosis of all patients in our series.

The 3 patients of the present study were reported at a single institute during a relative short period. This may indicate that BCG osteomyelitis is probably underestimated in Saudi Arabia, and it is conceivable that some children who were previously diagnosed as tuberculous osteomyelitis might have been suffering from BCG osteomyelitis.

In conclusion, BCG osteomyelitis, although rare, should be kept in mind when assessing a child presenting with apparent tuberculous osteomyelitis without evidence of pulmonary tuberculosis or a tuberculosis contact history. Clinical suspicion, early diagnosis using tissue biopsy and PCR studies, surgical drainage, and early commencement of chemotherapy are necessary for good outcome.

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