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Bacille Calmette-Guérin Vaccine–Induced Tuberculous Elbow Osteomyelitis in an Infant

A Case Report

Shigeki Ishibashi, MD, Akira Kodama, MD, PhD, Natsuki Maruyama, MD, Teruyasu Tanaka, MD, Yuta Hayashi, MD, Rikuo Shinomiya, MD, PhD, Satoshi Okada, MD, PhD, and Nobuo Adachi, MD, PhD

Investigation performed at the Department of Orthopaedic Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University Kasumi, Hiroshima, Japan

Abstract

Case: We report a case of Bacillus Calmette-Guérin (BCG) vaccine–induced osteomyelitis of the distal end of the right humerus in a 1-year and 8-month–old girl. The patient was treated with debridement and a 12-month antituberculosis drug. After 3 years of follow-up, no growth disturbances or sequelae were observed.

Conclusion: BCG osteomyelitis is difficult to diagnose because of its rarity. It is important to suspect BCG osteomyelitis based on symptoms and blood tests and to perform PCR testing. Long-term follow-up after treatment is necessary to monitor for recurrence and avoid growth disturbances until epiphyseal line closure occurs.

The Bacillus Calmette-Guérin (BCG) vaccine is used worldwide as immunization against tuberculosis, especially against tuberculosis-related meningitis and disseminated tuberculosis in children. Osteomyelitis is one of the complications of the BCG vaccine, but the incidence reported in Japan is rare, at 0.2 per 100,000[1,2]. BCG osteomyelitis occurs in the metaphyseal ends of long bones such as the femur and humerus[2,3]. Delayed diagnosis of BCG osteomyelitis results in growth retardation as the infection spills over to the epiphyseal line. Early diagnosis and early initiation of treatment are, therefore, important[3]. However, BCG osteomyelitis is difficult to diagnose and takes 1 to 2 months to diagnose[4-6]. This is because it takes 13.9 months from the time of vaccination to the onset of disease, and local fever and warmth are lacking[3].

We report the case of a 1-year and 8-month–old girl who developed BCG osteomyelitis involving the distal end of her right humerus. In this case, we suspected BCG osteomyelitis early and quickly made a diagnosis by performing polymerase chain reaction (PCR) and other tests. We were then able to treat BCG osteomyelitis that reached the epiphyseal line without sequelae by early initiation of appropriate debridement and antituberculosis drugs.

The parents were informed that data concerning the case would be submitted for publication, and they provided consent.

Case Report

The parents noticed a mass over the right elbow of their 1-year and 8-month–old girl who was healthy by nature, with no history of prior illness. There was no history of trauma to the right elbow, or it was not noted at the 1-year well-baby examination. She did not complain of pain, so the parents observed for 2 weeks. However, the mass gradually grew more significantly, so she visited a local orthopaedic doctor. Owing to a suspected tumor diagnosis, she was referred to our hospital.

Physical examination revealed an approximately 3-cm mass over the posterolateral side of the right elbow joint. There was no associated fever, warmth, or redness. The elbow joint was limited to flexion contracture, 20° and 90° of flexion.

Radiographs showed no abnormal findings involving the bones or joint but noted enhanced soft-tissue shadows (Fig. 1). Laboratory results showed White Blood Cell 12,230/μL and C-reactive Protein 0.23 mg/dL. A magnetic resonance imaging (MRI) T2-weighted Short Tau Inversion Recovery image showed signal changes in the distal humerus from the metaphysis to the epiphysis and a cyst formation from the physis to the lateral aspect of the right elbow joint (Fig. 2). Based on these findings, we suspected infectious lesions, including tuberculosis infection, and submitted the abscess fluid to bacterial culture testing, Ziehl-Neelsen staining, and Mycobacterium tuberculosis PCR.

Ziehl-Neelsen staining and Mycobacterium tuberculosis PCR of the abscess fluid were positive. Because of the possibility of tuberculosis, we consulted the pediatric department in our hospital. Additional T-spot and interferon-γ test results were

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSCC/B958).
Keywords complication; osteomyelitis; elbow; Bacillus Calmette-Guérin vaccine; pediatric

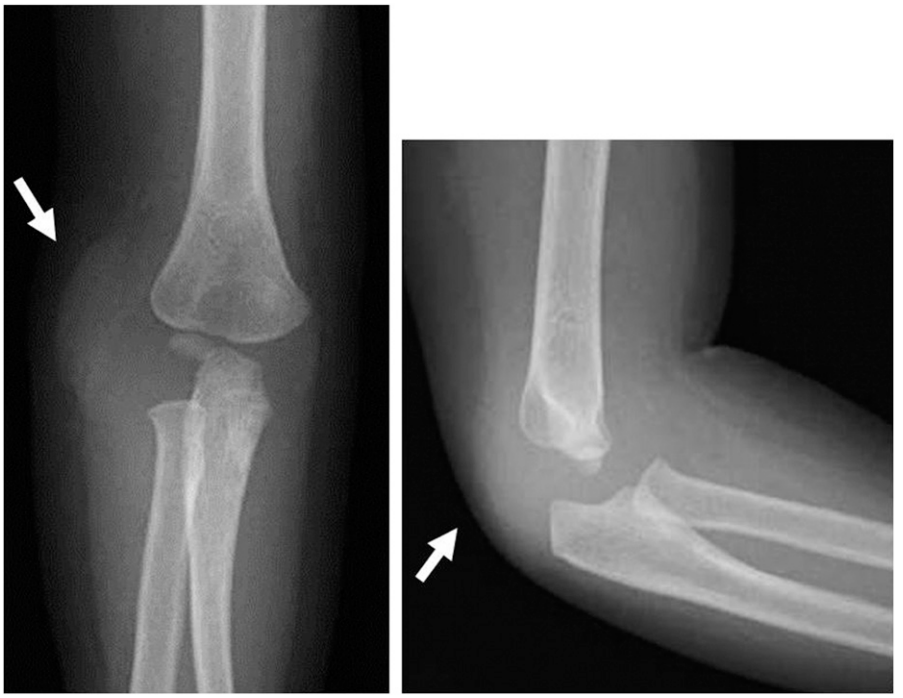

Fig. 1

Radiograph of the right elbow obtained during the initial examination. There were no abnormal findings involving the bones or joints, although soft-tissue enhanced shadowing was appreciated (white arrow).

negative, and there was no close contact with a person with a history of tuberculosis. In addition, computed tomography showed no abnormal lung findings suggestive of tuberculosis. Therefore, we suspected that osteomyelitis was caused by the BCG vaccine. We initiated a drug regimen consisting of isoniazid (Isoniazid: 10 mg/kg/day) and rifampicin (RFP: 10 mg/kg/day). Ga scintigraphy showed no accumulation, except in the right elbow (Fig. 3).

She was vaccinated with the BCG Tokyo-172 strain over her left upper arm at age 5 months using the multipuncture method. No adverse reactions associated with BCG vaccination, such as vaccination site reactions or swollen lymph nodes in the affiliation, were observed. She received standard Japanese vaccinations according to the National Immunization Program guidelines[7].

Immunological examination showed no decrease in immunoglobulins. Lymphocyte subsets were within reference values, including CD3, CD4, and CD8. The lymphocyte stimulation test and phagocyte reactive oxygen species production capacity showed no abnormalities. Immunodeficiency disorders were ruled out.

Surgery was performed for surgical debridement and definitive diagnosis. The mass was an uncoated granulation-like tissue contiguous to the distal humeral epiphysis through a fistula,

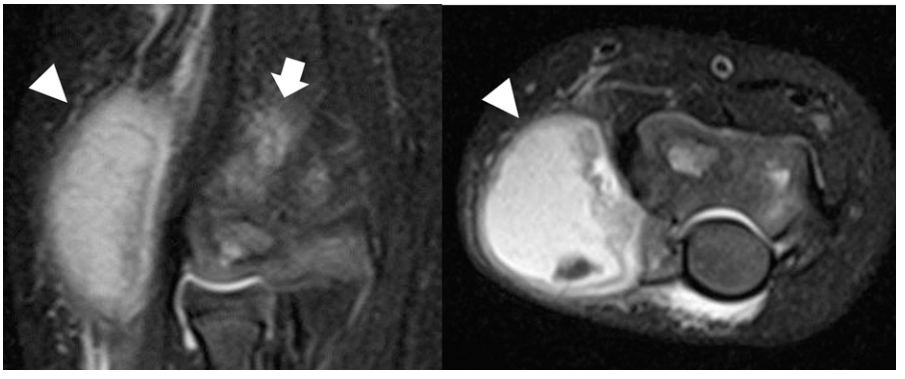

Fig. 2

Magnetic resonance imaging (MRI) T2-weighted Short Tau Inversion Recovery image showed signal changes in the distal humerus from the metaphysis to the epiphysis (white arrow) and a cyst from the physis to the lateral aspect of the right elbow joint (white arrowhead).

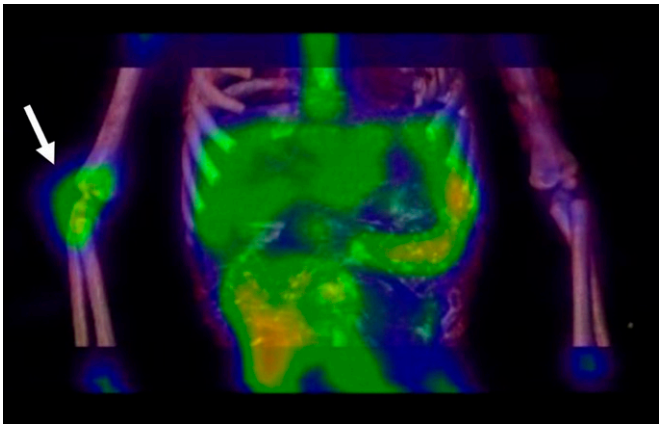

Fig. 3

Ga scintigraphy showed accumulation only within the right elbow (white arrow). There were no findings indicative of multiple lesions.

with spread around the epiphyseal line (Fig. 4). We performed debridement with as little injury to the growth plates as possible. The pathological results showed an epithelioid granuloma with Langhans giant cells, suggesting Mycobacterium infection (Fig. 5). Multiplex PCR revealed that the Mycobacterium cultures in the biopsy samples amplified the same as the BCG Tokyo-172 strain (Fig. 6). Based on these findings, a definitive diagnosis of osteomyelitis caused by Tokyo-172 BCG vaccination was confirmed.

Isoniazid and RFP therapy was continued for 12 months. She was followed up for 3 years and showed no signs of growth disturbance or dysfunction of the adjacent joints. The function of her right elbow was comparable with that of her left elbow for range of motion and activity. The radiographs revealed residual irregularity in the epiphyseal nucleus of the humeral capitellum (Fig. 7). MRI at one and a half years postoperatively showed a residual high signal at the distal humerus, but MRI at 3 years postoperatively showed normalization of the bone marrow signal at the distal end of the humerus (Fig. 8).

Discussion

Although BCG osteomyelitis is considered to carry a good prognosis, early treatment is desirable because recurrence and sequelae occur if the infection extends across the growth plate[3,8]. The reported positivity of tests is 70% for culture, 85% for antimicrobials, and 93% for PCR[9]. Based on the symptoms, blood tests, imaging findings, and other general findings, the diagnosis can be made by adding BCG osteomyelitis to the differential.

On suspicious findings for BCG osteomyelitis, the most common symptoms were swelling (77.5%), tenderness (54.9%), palpable mass (51.4%), fever (21.1%), redness (33.8%), and local warmth (22.5%) in a review of 71 cases of BCG osteomyelitis from Taiwan[4]. Another study showed that fever and pain were significantly less prevalent in BCG osteomyelitis vs. bacterial osteomyelitis[9]. Regarding laboratory characteristics, C-reactive Protein and Erythrocyte Sedimentation Rate were reportedly significantly lower than those in bacterial osteomyelitis[4]. Radiographic imaging is characterized by osteolytic lesions and mild periosteal reactions[2,10-12]. It has been reported that demarcated bone destruction was found in 78% of 182 cases in Finland[5]. However, there are reports that radiographs demonstrate nonspecific findings, as most do not show osteolytic lesions[4,13]. Osteolytic lesions are similar to bacterial osteomyelitis and should not be considered a characteristic finding[14].

BCG osteomyelitis occurs most often in the metaphyseal ends of long bones such as the femur and humerus but is a hematogenous infection and can occur anywhere in the body. Incidence involving the upper extremities has been reported at 15.4%, with most cases occurring at the proximal end of the

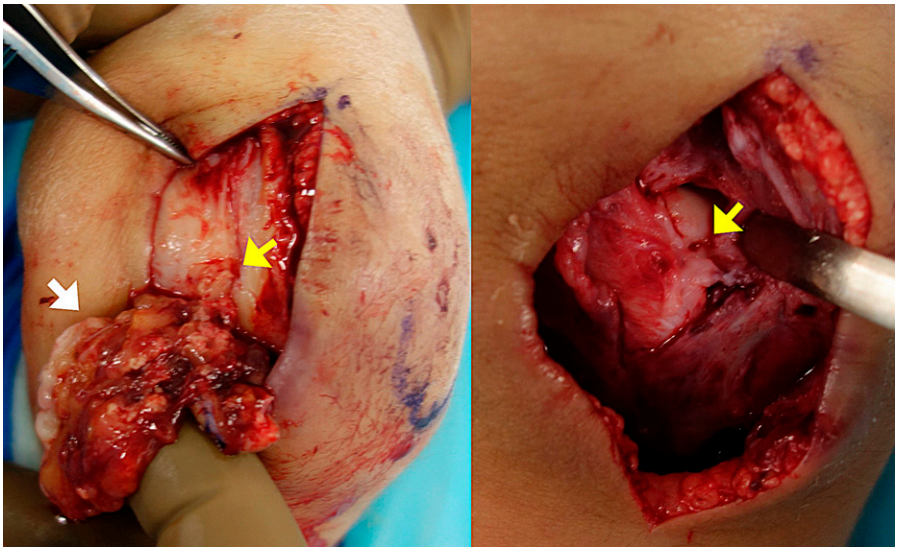

Fig. 4

Intraoperative photograph. Granulation-like tissue (white arrow) was continuous with the distal metaphysis of the humerus through small fistula (yellow arrow). We performed debridement to avoid damaging the growth plate.

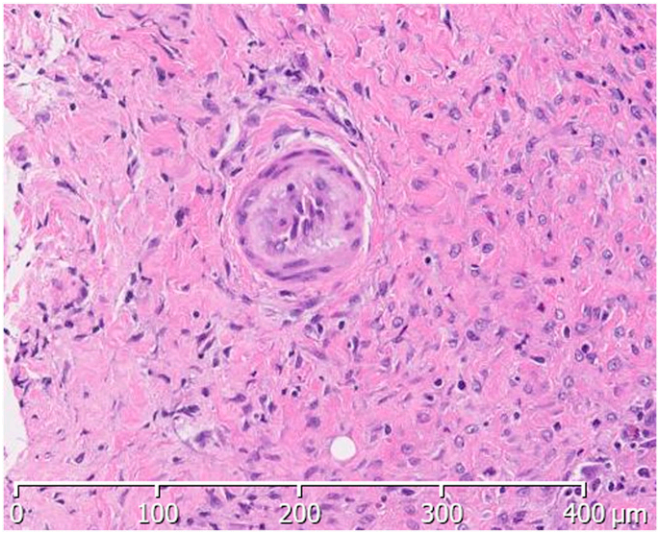

Fig. 5

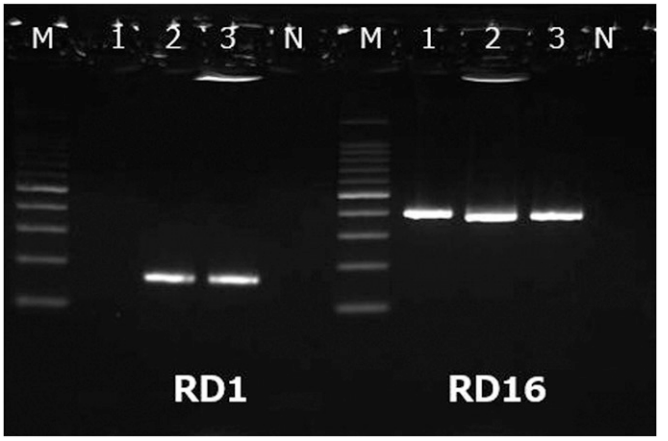

Fig. 6

Fig. 5 Pathology showed Langhans giant cells and epithelioid cell granulomas with caseous necrosis, suggesting a Mycobacterium infection. **Fig. 6** Multiplex polymerase chain reaction: M, marker; 1, *Mycobacteriumtuberculosis*; 2, *Mycobacterium bovis* (BCG Tokyo-172 strain); 3, the colony of the patient specimen; and N, negative control. Multiplex PCR showed the same amplification as that of the BCG Tokyo-172 strain. BCG = Bacillus Calmette-Guérin, and PCR = polymerase chain reaction.

humerus and the main complaint being difficulty in shoulder elevation[3]. Onset involving the distal end of the humerus is rare, to the best of our knowledge, with only one other reported case similar to ours[13].

In this case, a large subcutaneous abscess was formed. BCG-associated regional lymphadenitis and injection site abscess are known complications of BCG vaccination, but these are known to occur early after injection[1]. There have been no reports of isolated soft-tissue granulomas occurring late at a site distant from the injection site. However, in immunocompromised patients, multiple abscesses may occur throughout the whole body[3]. We have confirmed the absence of immunodeficiency disorders and performed scintigraphy to confirm the absence of multiple lesions[15].

Fig. 7

Three-year postoperative radiograph shows residual irregularity in the epiphyseal nucleus of the humeral capitellum.

Fig. 8

Fig. 8-A Eighteen-month postoperative magnetic resonance imaging shows high signal intensity with T2 fat suppression within the bone marrow.
Fig. 8-B Magnetic resonance imaging at 3 years postoperatively shows recovery to normal appearance.

We suspected tuberculosis or BCG osteomyelitis based on age and an abscess without redness or warmth, and subsequently, we performed a PCR test. Since the PCR was positive, there was no family history of tuberculosis, and the interferon-γ test was negative, we considered the diagnosis of BCG osteomyelitis and started treatment with antituberculosis drugs. Our patient had swelling in the elbow joint due to an abscess, but despite this, she had little pain and warmth, and her C-reactive Protein was barely elevated. These are characteristic features of BCG osteomyelitis. The multiplex PCR method enabled the definitive diagnosis by identification of *Mycobacterium bovis*, a BCG bacterium[16,17]. Since *M. bovis* is resistant to pyrazinamide, distinguishing it from other mycobacteria can reduce unnecessary drug use[18]. It also eliminates the differential of tuberculosis.

The mainstay of treatment is the antituberculosis drugs RFP and Isoniazid, continued for 6 to 12 months[3]. Because the most important thing is to avoid serious complications, surgery should be performed as minimally as possible[3,8]. In this case, we avoided damaging the growth plate as much as possible during surgery.

A long-term follow-up report stated that a similar case developed growth arrest and overgrowth during their recovery process[10]. In our patient, 3 years after surgery, the irregularity in the epiphyseal nucleus of the humeral capitellum was still present on radiographs. MRI revealed 3 years for the normalization of bone marrow signals. This suggests that long follow-up after

BCG osteomyelitis treatment is necessary not only to monitor for recurrence but also to avoid growth disturbance until the closure of the epiphyseal line.

BCG osteomyelitis is difficult to diagnose. Moreover, its rarity prevents the development of good evidence-based guidelines. We have presented a multifaceted examination of the clinical picture of BCG osteomyelitis. Sharing our experience and key diagnostic points can help initiate treatment early and prevent growth retardation in children. ■

Shigeki Ishibashi, MD[1]
Akira Kodama, MD, PhD[1]
Natsuki Maruyama, MD[2]
Teruyasu Tanaka, MD[1]
Yuta Hayashi, MD[3]
Rikuo Shinomiya, MD, PhD[3]
Satoshi Okada, MD, PhD[2]
Nobuo Adachi, MD, PhD[1]

[1]Department of Orthopaedic Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University Kasumi, Hiroshima, Japan

[2]Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, Kasumi, Hiroshima, Japan

[3]Department of Musculoskeletal Traumatology and Reconstructive Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University Kasumi, Hiroshima, Japan

E-mail address for A. Kodama: akirakodama@hiroshima-u.ac.jp

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