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Case Report

Osteomyelitis as a late complication of Bacille Calmette-Guérin vaccination

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Bacille Calmette-Guérin (BCG) osteomyelitis is a very rare complication of BCG vaccination. We report a 14-month-old boy who received BCG vaccination at birth. He developed pain and swelling in his left calf at 11 months of age. BCG osteomyelitis was diagnosed in right femur and left tibia. He had no evidence of immunodeficiency. After antituberculous therapy and surgical treatment, the bone lesions disappeared and he was discharged from hospital without any sequela during 11 months of follow-up.

Key words: BCG vaccine, complications, Osteomyelitis

Introduction

Mycobacterial disease (tuberculosis [TB]) caused by infection with *Mycobacterium tuberculosis* or *Mycobacterium bovis*, remains a serious medical problem worldwide. Bacille Calmette-Guérin (BCG) vaccine contains a live attenuated strain of *M. bovis* which is widely used to protect against TB [1]. This vaccine was named after the 2 French investigators responsible for its original development in 1923 and has now been used for nearly 100 years in the prevention of TB [2,3].

Vaccination against TB by means of intracutaneous inoculation of BCG is associated with a low rate of complications. However, some unfavorable adverse reactions may develop after immunization with BCG. These vary in incidence with age and vaccine strain and include: local subcutaneous abscess, regional lymphadenopathy, musculoskeletal lesions, multiple lymphadenitis, non-fatal disseminated infection and fatal disseminated lesions [3]. Osteomyelitis is a very rare but serious late complication of BCG-immunization in immunocompetent individuals and results from generalized dissemination of BCG [1,4,5]. The risk of osteomyelitis of the long bones following BCG immunization was estimated in the range from 1 in a million to 5 per 100,000 neonates and infants [2,6-8]. However, a meta-analyses of the published literature during the period 1950 to 1970 by Colditz et al indicated the frequency of BCG osteitis was equal to 1 in 80,000 in some European countries [2]. This late complication may occur in children within a few months to a few years after the vaccination. The lesions are localized to the metaphysis or epiphysis of long bones [4,6,8]. Risk of osteomyelitis due to BCG in immunodeficient patients is much higher than in the normal population and is associated with fatal disseminated infection [2].

We report a rare case of culture-proven osteomyelitis in a 14-month-old boy who had no underlying immunodeficiency disorders.

Case Report

A 14-month-old boy was referred to the Children Medical Center in November 2004 due to progressive pain and swelling in his left calf. The patient had been well until 8 months prior to referral, when a mass appeared in his left axillary region. Three months later, painful inflammation in his left calf and ankle developed with limitation in active movement and inability to stand.

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The patient was the product of healthy parents and was born by normal vaginal delivery with normal Apgar scores. He received BCG vaccination intracutaneously immediately after birth. He had received routine immunizations up to date including hepatitis B, diphtheria-pertussis-tetanus, oral poliovirus, and measles, mumps, and rubella in accordance with the national vaccination program guidelines. The patient had no previous history of illness and no known tuberculous history in his family.

Physical examination revealed a febrile (temperature: 38.2°C) boy weighing 9 kg, with a mobile firm lymph node of 2×2 cm in the left axillary region. Tenderness, erythema and marked swelling were noted in the left calf and the range of foot movement was restricted. A scar from local fistulization was noted over the lower part of the left calf. Other physical examinations were normal.

The laboratory results at admission revealed leukocytosis (white blood cell count, 14,000/mm^3 with neutrophil dominance), hemoglobin 10.4 g/dL, erythrocyte sedimentation rate 50 mm^3 and C-reactive protein 1+.

Radiological study suggested the presence of lesions in the distal left tibia (Fig. 1A). Radiological examination of other bones revealed a lytic lesion in the distal right femur (Fig. 1B). Repeated radiological examinations of the thorax revealed no abnormalities. Whole body bone scan revealed increased radiotracer activity at the distal end of the left tibia, and the proximal and distal end of the right femur. No other significant abnormal radiotracer activity was noted in the rest of the skeleton. Osteomyelitis was diagnosed and antibiotic therapy was started with cephazolin (which had been changed to vancomycin and then ceftriaxone) after obtaining negative results in 3 consecutive blood cultures.

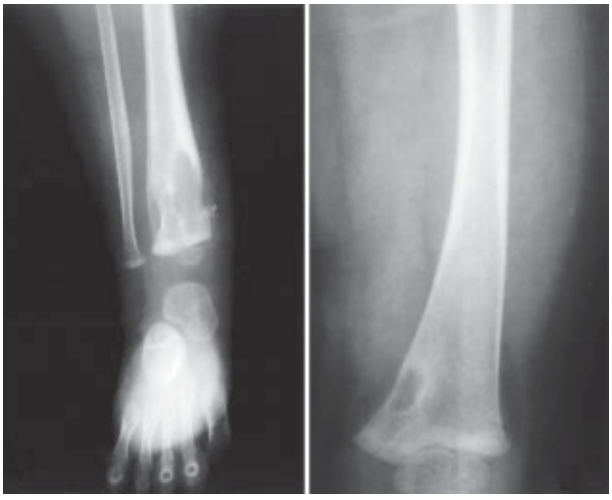

Fig. 1. A) Anteroposterior roentgenogram of the left tibial bone shows multiple osteolytic lesions in distal parts. B) Anteroposterior roentgenogram of the right femur shows multiple rounded osteolyic lesions in the distal parts.

Surgery was performed to treat the chronic osteomyelitis of tibia and revealed concentrated purulent yellow to green material which was drained. A lesion biopsy specimen was sent for pathology. Histopathological examination of the biopsy specimen revealed chronic granulomatous inflammatory reaction. Microscopy of the pus with Ziehl-Neelsen staining showed no acid and alcohol-fast bacillus but tissue culture from the biopsy specimen confirmed the diagnosis of osteomyelitis due to *M. bovis*. Purified protein derivative test was 8 mm in size on the forearm. Based on these findings, the diagnosis of osteomyelitis due to BCG vaccination was confirmed.

Immunological investigations for the evaluation of cellular and humoral immunity were performed, including complement CH50, C3 and C4, immunoglobulins, chemotaxis assay, and intracellular oxidation (nitro blue tetrazolium, dihydrorhodamine), and revealed normal findings. Therefore, immunodeficiency disorders were ruled out and a good prognosis for the patient was assumed. Evaluation for extrapulmonary TB was negative. Treatment with antituberculous medications (isoniazid 10 mg/kg/day; ethambutol 15 mg/kg/day; streptomycin 20 mg/kg/day; rifampin 15 mg/kg/day) was started and surgical intervention was performed soon after tissue diagnosis was made. The patient's condition improved with several curettages and continued treatment with anti-TB drugs and he was discharged after 6 weeks of hospitalization.

At follow-up examinations during the 11 months after discharge from hospital (at first every month for 3 consecutive months and then every other month, the patient gained weight progressively and at the last visit his weight was 12 kg. He could stand and walk. Radiological examination showed healing of the process in the tibia and femur. Continued antituberculous treatment for 1 year was planned. He had normal gait at last follow-up on June 2005.

Discussion

Effective immunization against TB would be a tremendous advance for medicine, but in practice this goal has been fraught with enormous difficulties.

The World Health Organization Expanded Program on Immunization recommends universal immunization of newborn infants with a single dose of BCG only in developing countries. Hematological spread of BCG and the formation of epitheloid cell granulomas at different locations is an ordinary consequence of BCG vaccination. The granulomas resolve spontaneously within 40 months of the vaccination without causing clinically obvious signs [9].

Hematogenous spread of BCG vaccine may result in osteomyelitis, but this is a rare complication [6-8]. Osteomeyelitis usually becomes manifest when the child is between 5 and 33 months of age [10]. The lesions tend to appear on the same side of the body as the vaccination [6]. In our patient, the lesions were located on both sides of the body. Lotte et al extensively reviewed all reported BCG complications up to 1977, including 272 lesions of bones and joints. 160 patients (58.8%) were smear- or culture-positive, and 90% of those with histological study showed tuberculous-like lesions [9].

In 1988, the frequency of BCG osteomyelitis was reported to be 0.03% in Europe [1]. Since then, only rare cases of BCG osteomyelitis have been reported worldwide [1,6,8]. As serious complications to BCG infection are thought to occur more frequently in patients with immunological deficiencies [2], we thoroughly investigated the immunological status of our patient but found no evidence of immunodeficiency. Tests for humoral or cell-mediated immunity yielded normal results. The diagnosis of BCG osteomyelitis in this case was made based on clinical history and positive smear for acid-fast bacillus and then positive culture for *M. bovis*. There was no record of exposure to Koch bacillus, chest radiograph was normal and the patient recovered quickly recovery after tuberculostatic therapy and surgical treatment.

Timely diagnosis of diagnosis of BCG osteomyelitis is important since antituberculostatic therapy is effective when initiated early in the course of disease. But several factors may delay prompt diagnosis. The lesions may be overlooked due to their rarity. The symptoms tend to develop slowly, and the primary course is fairly benign. The chest radiological changes (when detectable) are not diagnostic, and erythrocyte sedimentation rate and C-reactive protein (as in this case) are only moderately elevated if at all [6].

Treatment of BCG osteomyelitis usually consists of both surgical intervention and tuberculostatic medication, but pyrazinamide cannot be used because BCG is resistant to it [6]. Operative treatment is recommended for 2 reasons: 1) specimens can be obtained for definitive diagnosis; and 2) the healing process will be quicker. The course of the disease seems to be fairly benign [3,8]. However, in spite of the favorable prognosis, this disease is not without consequences to the patient.

The patients are generally hospitalized during treatment for several months; many of them undergo repeated operations before the correct diagnosis is established. Virtually all patients had primarily received antimicrobial treatment without tuberculostatic activity [4,6]. Our patient also had received antimicrobial therapy after the initial diagnosis of common osteomyelitis and before an etiological diagnosis was made.

In conclusion, osteomyelitis running a fairly benign course in children should arouse suspicion of a tuberculous origin, particularly if the disease does not respond favorably to treatment with recommended antibiotics. It is important that an exact etiological diagnosis be established as early as possible so that adequate antituberculostatic therapy can be instituted.

References

1. Hotokezaka H, Kitamura A, Matsumoto S, Hanazawa S, Amono S, Yamada T. Internalization of *Mycobacterium bovis* Bacillus Calmette-Guérin into osteoblast-like MC3T3-E1 cells and bone resorptive responses of the cells against the infection. Scand J Immunol 1998;47:453-8.
2. Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, et al. The efficacy of bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. Pediatrics 1995;96:29-35.
3. Besnard M, Sauvion S, Offredo C, Gaudelus J, Gaillard JL, Veber F, et al. Bacillus Calmette-Guérin infection after vaccination of human immunodeficiency virus-infected children. Pediatr Infect Dis J 1993;12:993-7.
4. Bergdahl S, Fellander M, Robertson B. BCG osteomyelitis: experience in the Stockholm region over the years 1961-1974. J Bone Joint Surg Br 1976;58:212-6
5. Mortensson W, Eklof O, Jorulf H. Radiologic aspects of BCG-osteomyelitis in infants and children. Acta Radiologica Diagn 1976;17:845-55.
6. Peltola H, Salmi I, Vahvanen V, Ahlqvist J. BCG vaccination as a cause of osteomyelitis and subcutaneous abscess. Arch Dis Child 1984;59:157-61.
7. Vallejo JG, Ong LT, Starke JR. Tuberculous osteomyelitis of the long bones in children. Pediatr Infect Dis J 1995;14:

542-6.
8. Hoppe JE, Orlikowsky T, Klingebiel T, Niethammer D. Costal BCG osteomyelitis presenting as a tumor. Infection 1992;2: 94-6.
9. Lotte A, Wasz-Hockert O, Poisson N, Dumitrescu N, Verron M, Couvet E. BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. Adv Tuberc Res 1984;21:107-93.
10. Sirinavin S, Chotpitayasunondh T, Suwanjutha S, Sunakorn P, Chantarojansiri T. Protective efficacy of neonatal Bacillus Calmette-Guérin vaccination against tuberculosis. Pediatr Infect Dis J 1991;10:359-65.