BCG OSTEITIS

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Abstract- The only available vaccine against tuberculosis is BCG which has been found to protect children against disseminated tuberculosis and tuberculous meningitis. BCG is one of the safest vaccines being used, and osteitis is a rare complication of it. During a period of eight years, we had eleven cases of osteitis occuring in infants following BCG vaccination. Eight cases were female. Defect in immune response was not found in any of the patients and all got cured with simple curretage of the lesion and appropriate drug therapy without any sequelae.

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INTRODUCTION

Immunization against tuberculosis (TB) theoretic-cally would be a tremendous boon to humanity, but in practice it has been fraught with great difficulties (1). The only available vaccine against tuberculosis is the bacille Calmette–Guerin (BCG). The only people who might benefit from BCG vaccination are those who are repeatedly exposed to TB (2). The BCG vaccine is extremely safe in immunocompetent hosts (3) and untoward reactions to BCG have rarely been a problem (1). Focal tuberculosis–like bone lesions have been reported in a few infants inoculated with BCG vaccine (4).We present 11 cases of osteitis following BCG vaccination.

Report of cases

From January 1995 to February 2003 eleven patients with the final diagnosis of BCG osteitis were admitted in the pediatric ward. They comprised of eight females and three males. The age of the patients at the onset of the disease in our study varied from 4 to 36 months. The mean incubation period in the male patients was 4 months , whereas in the girls was 14 months. All patients had been inoculated intradermally with BCG vaccine during the first week of life. As a rule the symptoms and signs were vague.

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Symptoms became evident between 4 and 36 months of age (average 6.3 months). They comprised of a tender swelling usually located near a joint, decreased motion of the nearby joint, slight to moderate elevation of ESR and in some cases a slight fever. The general condition was not affected in any patient.

The most common radiological feature, present in 10 cases, was a well demarcated, eccentrically located destruction in the metaphysis of one of the long bones and breakthrough of the cortex with an inflammatory process extending into the surrounding soft tissues. The most common sites of osteitis were metaphyses of the long bones of the lower extremities (6/11 cases, 54.5%) (Fig. 1 and 2), three cases were in the proximal humerus (27.2%) (Fig. 3), one case was in the proximal radius, and osteitis was found to be in the thoracic vertebra in one case (Fig. 4).Chest X–ray was normal in all cases. Mantoux test was performed with a mean induration of 13.2 mm (range 0–21). The average sedimentation rate in our patients was 61 mm (range 23–119).All patients had normal humeral and cellular immune function.

All patients underwent simple curettage of the lesion after opening an elliptical cortical window. Bone grafting was not performed in any case. Biopsy specimen obtained from the bone lesion revealed epithelioid cell granulomas with caseous necrosis or necrosis without cassation and Langhans giant cells, compatible with the histological diagnosis of ‘‘tuberculous-like lesion”. Direct smear and culture of the specimen were negative for tuberculous bacilli in all cases. All patients had typical histopathological lesions.The criteria for diagnosis of BCG osteitis as in other studies (5) were lack of florid systemic

reactions, a good general condition and normal chest x-ray in the presence of typical radiological and histopathological findigs of tuberculous–like bone involvement. All patients received a course of anti-tuberculosis chemotherapy consisting of isoniazid plus rifampin and pyrazinamide for 6-8 weeks. The mean follow-up period was 36 months (range 3 months to 7 years). During the last follow up all patients were symptom free with complete healing of the bony lesions (Fig. 2B and 3B).

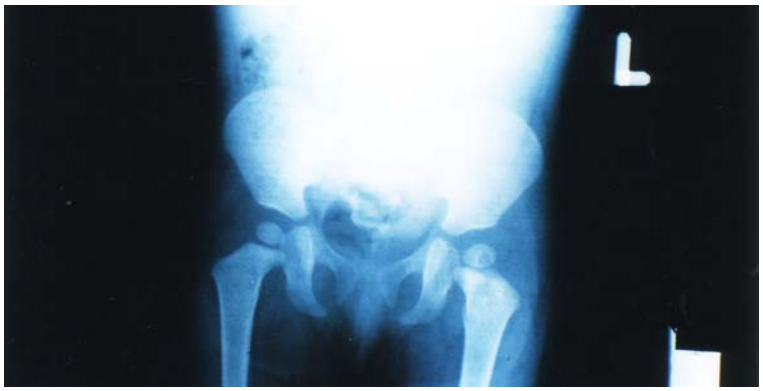
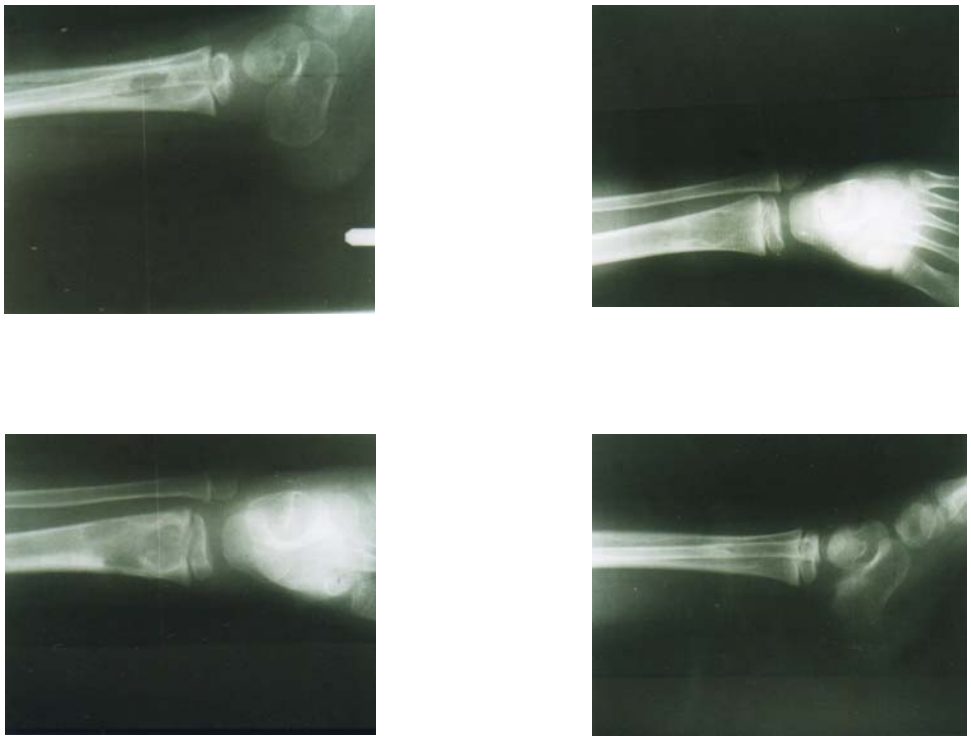
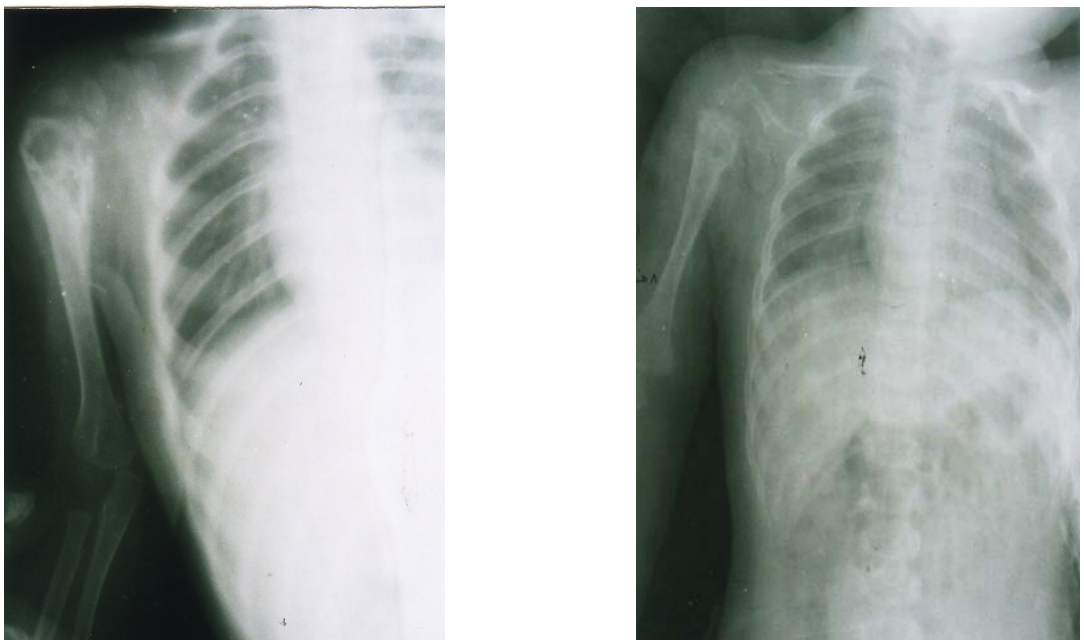


Fig.1. Female patient aged 12 months with fever and irritability for 8 days. She was not able to move the left lower limb. A large destructive lesion is noted in the femur near the hip joint



2-A **2-B**

Fig.2. Three-year-old girl with swelling of left ankle of 2 months duration. Large destruction in distal end of tibia. A: before treatment, B: Three months after treatment



A **B**

Fig.3. Five-month-old girl who was unable to move right upper limb since 30 days. Low grade fever was present. A: before treatment, B: eight weeks after treatment

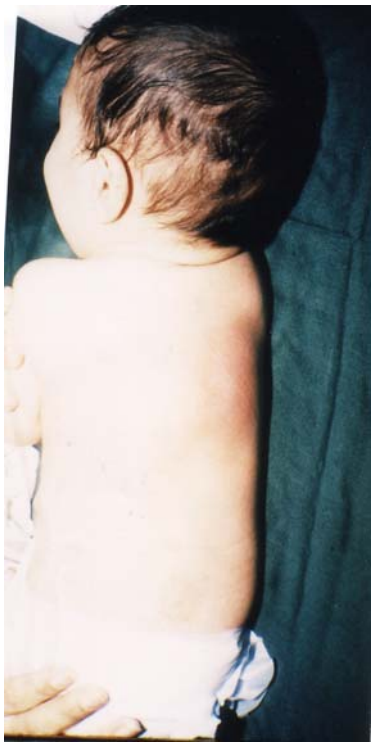


Fig. 4. Four-month-old boy. Swelling over the thoracic spine

DISCUSSION

BCG was discovered at the Pasteur institute in Paris by Calmette and Guerin, who, starting in 1908 made 231 passages of a strain of *M. bovis* on a beef bile medium , thereby producing marked attenuation (1). BCG vaccine attempts to replace the potentially dangerous primary infection due to *M. tuberculosis* with an innocuous primary infection due to bacillus of Calmette and Guerin, thus activating host cell–mediated immunity with minimal chance of progressive disease, so that an infection with *M. tuberculosis* will be of the "reinfection" type. New interest in the use of tuberculosis vaccines has cropped up because of its beneficial effect in certain types of malignancies (1). The best use of BCG vaccination appears to be prevention of life-threatening forms of tuberculosis in infants and young children (3), and protection of children against disseminated tuberculosis and tuberculous meningitis (6). BCG is 50% effective in preventing pulmonary tuberculosis in adults and children. The protective effect for disseminated and meningeal tuberculosis appear to be 50-80% (3). However, BCG vaccination

may contribute to tuberculosis control in selected population groups. BCG is recommended for tuberculin skin test-negative infants and children who are:

1- At high risk of intimate and prolonged exposure to persistently untreated or ineffectively treated adults with infectious pulmonary tuberculosis and who can not be removed from the source of infection or placed on long-term preventive therapy.

2- Continuously exposed to persons with tuberculosis who have bacilli that are resistant to isoniazide and rifampin (3).

Untoward reactions to BCG have rarely been a problem (1). Adverse effects of BCG which occur in 1-10% of cases include prolonged ulceration at the site of injection, regional lymphadenopathy, lupus vulgaris, osteomyelitis or disseminated infection. These complications are very rare and are typically found in immunocompromised patients (6). Vitkova and associates studied post-vaccination adverse reactions in the period from 1981 to 1993 and demonstrated an elevated incidence of local and regional lymph node complications (0.08% of the vaccinated children were affected) .In addition, bone and joint involvement in children vaccinated at birth was reported as a new phenomenon (7). Systemic complaints such as fever, convulsions, loss of appetite, and irritability are extraordinarily rare after BCG vaccination. Local ulceration and regional suppurative adenitis occur in 0.1-1% of vaccine recipients (3). Local lesions do not suggest underlying host immune defects and do not affect the level of protection afforded by the vaccine (3). In some studies lymphadenopathy has been reported in up to 1- 10% of the vaccine recipients (8). This usually resolves spontaneously and surgical excision of the affected nodes should be avoided if possible. Profound immunocompromised patients may develop disseminated BCG infection after vaccination (3). Complications occurring in healthy children long time after BCG vaccination have been occasionally reported.

Osteitis is a rare complication of BCG vaccination that appears to be related to certain strains of the vaccine that are no longer in wide use (3,7). There are few reports in the literature of focal tuberculosis-like bone lesions in infants inoculated with BCG vaccine and the attenuated organism has been recovered from some of these lesions. These children were not seriously ill and their recovery was complete, unlike immunodeficient children who usually develop a generalized and fatal disease (4). Osteomyelitis especially of the long bones occurs in 1 per 1 million vaccines. The rate may be higher in newborns (8). In one study it was diagnosed in 5 per 100,000 neonates. It usually becomes manifested between 5 and 33 months of age when a tender swelling is noted near a joint. Bone destruction is well localized and response to conservative treatment is very good (1).In differential diagnosis, tuberculous osteitis should be excluded in infants with undiagnosed bony lesions, even if they have been vaccinated with BCG (9). Bone lesions produced by atypical tuberculous bacilli are indistinguishable from those of tuberculosis. Nevertheless, they are characterized clinically by chronicity and recurrent breakdown of tissue, healing usually occurs with short course chemotherapy. Frequent association with skin and lymph node lesions is a helpful clue to recognize this form of infection (4).

Despite its rarity, osteitis seems to be the most frequent one of these complications (10). In the period between 1980 to 1985 only 6 cases of osteitis were recorded in the literature (11). In another study between the years of 1981 to 1986 , 26 cases had been presented (12) and in 1997 Castro– Rodriguez from University of Santiago, Chile, reported 10 cases, six of whom were male (5).However, there have been two reports with large number of cases (13,14).

The age of onset of BCG osteitis in our study varied from 4 to 36 months. In the study from Finland in 222 children, Kroger and associates showed an age range of 0.25 to 5.7 years (13). In another study the mean age was 11 months (range 6.5– 21) (5). The most common sites of osteitis in our series were metaphyses of the long bones of lower extremity (6/11 cases, 54.5%, five cases in femur and one case in tibia) and upper extremity (4/11cases, 36.3%, three cases in humerus), while the study from Finland, showed involvement of lower extremity in 58% and the upper extremities in 14% of the cases (13). In the experiences in Sweden, out of a total of 152 known cases, the epiphyses of the long bones of the extremities were the most frequent sites of involvement (109 lesions). In that study spinal involvement was seen only in 6 patients whereas in classic tuberculosis of the skeletal system spine is the commonest site of involvement (14). In our study osteitis was situated in the thoracic vertebra in one case. In our study the mean size of skin induration with Mantoux test was 13.2 mm (range 0–21). In the study from Chile the mean size of induration was 21.5 mm (range 16–28 mm) (5). The mean incubation period in our series was 4 months in the boys and 14

months in the girls, while in the study from Sweden this time was 23 months for girls and 14 months for boys (14).

In conclusion, BCG vaccination very rarely produces adverse reaction and therefore must be considered as a safe method for tuberculosis prevention (15) but osteitis is a recognized complication of it. Most of the times, unfortunately, the orthopaedic surgeon and the pediatrician do not consider such a diagnosis in mind, and as such the final diagnosis is delayed. Initial diagnosis in most of the cases is not correct. For instance one of the cases had been erroneously suspected to have a bone tumor for a long time. Even despite correct diagnosis, the appropriate and correct treatment is not being instituted most of the times.

With adequate treatment, the prognosis of BCG osteitis is good (13). On the whole, BCG is one of the safest vaccines in use.

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