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Original Article

Bacillus Calmette-Guérin (BCG) osteomyelitis among children: Experience in a single tertiary center in central Taiwan

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KEYWORDS
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Abstract *Background:* The insidious nature of BCG-osteomyelitis makes it challenging for clinicians to detect it early on.
Methods: This 12-year retrospective analysis was conducted at a single tertiary hospital in central Taiwan. Electronic medical records of pediatric patients treated for BCG-osteomyelitis were reviewed. Demographics, clinical features, and laboratory findings were compared with patients diagnosed with culture-proven pyogenic osteomyelitis.
Results: In total, eight patients fulfilled our inclusion criteria. Their median age was 16 months, and no obvious gender prevalence was found. Six of the eight patients had lesions involving the lower extremities. When compared with the pyogenic osteomyelitis group, age of disease onset was found to be significantly younger in the BCG osteomyelitis group ($p=0.038$). Absence of fever and pain in the BCG osteomyelitis group was found to be statistically significant when compared with the pyogenic group ($p=0.002$ and $p=0.026$ respectively). CRP and ESR were found to be significantly higher in the pyogenic osteomyelitis group ($p=0.000$ and $p=0.004$ respectively).
Conclusion: BCG-related osteomyelitis must be considered when evaluating an afebrile child presenting with an unexplainable swelling or limp, and especially when the lesion is located on a lower limb. Laboratory studies may reveal normal WBC and CRP, with a normal to modest elevation of ESR. Imaging studies, including plain radiographs, magnetic resonance imaging

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(MRI), or computed tomography (CT) should be employed to rule out BCG-related osteomyelitis. Early diagnosis help minimize inappropriate antibiotics use, and may lead to a better outcome.

Introduction

The Bacillus Calmette—Guérin (BCG) vaccine has been incorporated into Taiwan's National Immunization Program for children since 1965 in accordance to the recommendations of the International Union Against Tuberculosis and Lung Disease.[1,2] In areas with high prevalence of tuberculosis, BCG vaccination plays a vital role in minimizing mortality caused by tuberculosis meningitis and disseminated tuberculosis disease.[3] Although rare, tuberculosis meningitis has been reported to have a mortality rate of 19.3% in children and a neurological sequelae rate of 53.9%.[4] Numerous trials and epidemiological studies reported that BCG has 60%—80% protective efficacy against serious forms of tuberculosis diseases, particularly tuberculosis meningitis, in children.[5] However, adverse events with this vaccination may occur. Common but minor side effects include local abscess formation and/or lymphadenitis, which is usually managed with watchful waiting where most of the lesions resolve with time.[6] If the lesion persists or progresses, it can be treated with needle aspiration or excisional surgery, sometimes with the addition of anti-tuberculosis medications, often leaving the patient with nothing more than a minor scar.[7] The more severe complication, namely, BCG-associated osteitis or osteomyelitis, is uncommon but could sometimes leave the patient with long-term sequelae, including limb length discrepancy, especially if the lesion is located at a lower extremity, or kyphosis, when vertebral bone is involved.[8] According to literature, these adverse effects may be associated with vaccine strain, inoculation methods, age when receiving the vaccine, and/or recipient's immune status.[9] To minimize these adverse effects, the government changed the BCG vaccine in Taiwan from Pasteur strain 1173 P2 to Tokyo strain 172 on March of 1979.[10] This change in inoculation strain has dramatically decreased the incidence of BCG-induced lymphadenopathy from 1.7%—17.1% to 0.1%—1.1%.[10] To improve the surveillance of BCG-related complications, a laboratory program to distinguish *Mycobacterium bovis* from other species of *Mycobacterium tuberculosis* complex was established in 2004.[1,8] By 2008, this testing was made available to all clinicians and they were encouraged to send specimens collected from children under five years of age for further identification of *M. bovis*.[1,8] In the same year, Taiwan began active surveillance of adverse events caused by BCG. According to data collected from Taiwan's vaccine injury compensation program (VICP) between 2008 and 2012, the incidence of BCG-associated osteitis/osteomyelitis is estimated to be 30.1 cases per million vaccinations.[8] Given this rare but serious complication of BCG vaccine, Taiwan changed its recommended vaccination age from within 24 h of birth to 5—8 months of age on January 1, 2016.

BCG-associated osteomyelitis remains a diagnostic challenge, as evident in the delay of diagnosis for 1—2 months from the onset of symptoms.[11] It is often diagnosed at a more advanced stage due to its rarity and subtle nature,[12] but sometimes, as a result of under-recognition by clinicians. Moreover, some of its clinical similarities with pyogenic osteomyelitis also make it difficult for BCG-associated osteomyelitis to be considered in an earlier stage. This late diagnosis could in turn have a negative effect on the patient's outcome. Although there have been several studies discussing BCG-associated osteomyelitis in Taiwan, there is no literature discussing the differences in the clinical findings of pyogenic osteomyelitis from osteomyelitis caused by *M. bovis*. This study aims to analyze the demographics, clinical manifestations, and laboratory results of BCG-related osteomyelitis and compare them with culture-proven pyogenic osteomyelitis. Results provide significant basis to aid clinicians in early diagnosis of this insidious disease.

Methods

Study design

This retrospective study was conducted at a single medical center, China Medical University Children's Hospital (CMUCH), in Taichung, Taiwan. Electronic medical records of patients under the age of 18 years who were discharged under the diagnosis of osteomyelitis from January 2008 to February 2020 were carefully reviewed. Only patients with confirmed cases of *M. bovis* infection as determined by Taiwan Centers for Disease Control (CDC) National Reference Mycobacterial Laboratory for BCG detection were included in our study. A multiplex PCR test is used to amplify specific DNA fragments of our sample. The PCR products are analyzed using gel electrophoresis. Targeted DNA fragments are then isolated and purified from gel electrophoresis and sent for further sequencing to confirm *M. bovis*.[13] Patients with clinical manifestations and/or pathohistological reports that were highly suggestive of BCG-related osteomyelitis but not confirmed by Taiwan CDC were excluded from our study. Data including demographic characteristics, clinical presentations, laboratory parameters on admission, lesion sites, management, and outcomes were collected and analyzed. The results of BCG-associated osteomyelitis from our study were cross analyzed with those of culture-positive pyogenic osteomyelitis from the previous study of Chen et al.[14] In addition, we searched PubMed for published works that discussed BCG-associated osteomyelitis in Taiwan. We found four relevant articles and compared their findings with our study.

Ethics

This study was approved by the Research Ethics Committee of the China Medical University and Hospital (CMUH109-REC1-018).

Statistical analysis

SPSS Version 25 (Chicago, IL, USA) was used for all statistical analyses. Continuous variables were presented as median and interquartile range and compared by Mann—Whitney *U* test. Categorical variables were presented as absolute numbers and proportions (%) and compared by Fisher's exact test. All statistical tests were two-tailed, and a p value of ≤ 0.05 was considered statistically significant.

Results

Eight patients satisfied our inclusion criteria. Two cases were excluded from our study; they were born after the vaccination policy change in 2016 and thus assumed to have received their BCG vaccination between 5 and 8 months of age. Both cases presented with symptoms at 2 years and 1 month of age, and were afebrile on presentation. Their imaging studies revealed osteolytic lesions located at right proximal tibia, and pus culture obtained during surgery showed positive findings for *M. tuberculosis* (MTB) complex at our hospital's MTB quantitative PCR test. However, further testing at Taiwan CDC revealed negative results for *M. bovis*. Thus, both cases were excluded from our study.

The age of the eight patients ranged from 8 months to 1 year and 10 months, with a median age of 16 months (Table 1). Six patients were born before January 1, 2016 and received their BCG vaccine within 24 h of birth, and two patients were born after January 1, 2016 and received their BCG vaccine between 5 and 8 months of age. No obvious gender prevalence was detected, and the most common presenting symptom was swelling of the affected region, followed by limping gait if the lesion occurred in the lower extremities. Fever was uncommon, unless concurrent infections, such as upper respiratory tract infections (URI), similar to two of our patients, occurred. The two patients had the shortest time to diagnosis of osteomyelitis from the onset of symptoms compared with the other patients (diagnosed within 1 week of presentation versus the median of 2 months). The mean time from symptom onset to initial X-ray evaluation was 13.8 days, with only three of the eight patients revealing osteolytic lesions.

Six of the eight patients had lesions involving lower extremities: tibia (37.5%) and talus (37.5%). Only one case reported involvement of multiple bones (distal femur and proximal tibia), and one case reported involvement of adjacent joint (left talus with septic arthritis of left ankle joint). None of the participants reported previous history of trauma. The laboratory tests revealed that all patients had white blood cell (WBC) counts within the normal range, and all but one patient had C-reactive protein (CRP) below 1 mg/dL. The one exception was a patient with concurrent febrile URI. The erythrocyte sedimentation rate (ESR) ranged from 10 mm/h to 77 mm/h, with a median of 23 mm/h. All patients received surgery including debridement and/or sequestrectomy, and all except one patient received inappropriate empiric antibiotic treatment prior to anti-tuberculosis medications. The mean duration of inappropriate antibiotics was 14 days. Upon confirmation of BCG-associated osteomyelitis, all but one patient have been treated with a one year course of TB regimen that includes a combination of rifampin and isoniazid. No patients had significant sequelae on follow up.

Comparison among studies of BCG-related osteomyelitis in Taiwan

A search on PubMed for literature that discussed BCG-related osteomyelitis in Taiwan yielded four relevant articles.[8,11,15,16] Table 2 shows the comparison among the studies. Although our sample size is small, similar results were found across the studies with regard to the lack of gender prevalence, young age of disease onset (average of 16 months), and a 1—1.5-year interval between BCG vaccination to onset of symptoms. Swelling is the most common presenting symptom. Similar to findings from previous works,[17,18] BCG-related osteomyelitis appears to have an inclination for lower limbs; if the lesion occurs on lower limbs, many patients would also present with limp, unsteady gait, inability to bear weight, or weakness. Most patients received some form of surgical intervention partly for the sake of obtaining specimens but also for excision and debridement. Upon diagnosis, many patients were placed on 1-year treatment protocol of oral anti-tuberculosis medications, including isoniazid and rifampin. In our study, all eight patients recovered well without obvious signs of sequelae. However, one patient in Yang's study suffered from disease recurrence,[16] while patients in other studies survived with major sequelae including limb length discrepancy in three patients[11,15] and severe kyphosis in four patients.[8,11]

Discussion

BCG vaccination remains a major strategy in combating tuberculosis especially in countries with a high prevalence of the disease.[19] According to the data collected from Taiwan CDC, an estimated 7900 cases were diagnosed with tuberculosis in 2020,[20] and the incidence rate was 34 cases per 100,000 persons. With much of its population densely inhabiting the major cities of Taiwan, BCG vaccination is important to keep children safe. Since its implementation in the early 1950s, several changes have been made to the administration of this vaccine, including the removal of Tween 80 in 1971,[10] the change in vaccine strain from Pasteur strain 1173 P2 to Tokyo strain 172 in 1979, and the change in the immunization schedule from within 24 h of birth to 5—8 months old. These changes were implemented to minimize the adverse effects of the vaccine. However, according to statistics from Taiwan Vaccine Injury Compensation Program (VICP), BCG remains the highest compensated vaccine from 1989 to 2021, with 500 claims being made and 455 approved claims since the beginning of the program.[21] Similar to previous studies,[11,15,16] our present research showed that BCG-related osteomyelitis

Table 1 Clinical data of patients included in our study.

Patient/age[a]/sex	1/14/F	2/8/M	3/17/F	4/14/F	5/17/M	6/19/F	7/20/M	8/22/M
Age at BCG vaccination[b]	24 h	24 h	24 h	24 h	24 h	1 mon	5—8 mons	5—8 mons
Interval from vaccination to symptom onset, mo	12	7	15	12	16	17	15	15
Medical visits before diagnosis	8	3	3	4	3	1	1	3
Time to diagnosis of osteomyelitis, mo	2	1	2.5	2	2	0.13	0.10	2
Presenting symptoms	Poor weight bearing, progressive left ankle swelling	Right thumb painless swelling	Progressive limping gait	Right ankle swelling with local heat and tenderness	Left medial ankle swelling with local heat	Right knee swelling, limping gait, fever, URI symptoms	Unsteady gait, right leg ROM limitation, fever, URI symptoms	Painful swelling and redness of right index finger
Time from symptom onset to initial x-ray in days; Evident osteolytic change	28; No	1; No	7; No	15; No[d]	32; No[e]	4; Yes	2; Yes	21; Yes
Laboratory test								
WBC, k/μL	6.92	14	11.62	11.12	8.92	10.4	15.8	10.6
CRP, mg/dL	0.69	—	0.1	0.6	<0.02	0.25	1.42	0.02
ESR, mm/hr	13	—	26	23	15	34	77	10
Lesion site	Left talus, with septic arthritis of left ankle joint	Right thumb, 1st metacarpal	Left distal femur and proximal tibia	Right talus	Left talus	Right tibia	Right tibia	Right index finger, proximal phalanx
Surgery	Arthroscopy, arthrotomy of left ankle joint	Tumor excision, debridement	Debridement, sequestrectomy	Arthroscopic debridement, sequestrectomy	Arthroscopic sequestrectomy	Sequestrectomy	Debridement, sequestrectomy	Debridement, saucerization
Empiric antibiotics prior to TB regimen, duration in days	Yes, 24	Yes, 9	Yes, 9	No	Yes, 6	Yes, 5	Yes, 17	Yes, 28
Duration of anti-TB medications	INH + PZA + RIF 2 mons → INH + RIF 10 mons	INH + PZA + RIF 2 mons → INH + RIF 10 mons	INH + RIF 12 mons	INH + RIF 12 mons	INH + RIF 12 mons	INH + RIF 12 mons	INH + RIF 12 mons	INH + PZA + RIF 25 days → INH + RIF 7 mons[f]
Follow-up duration[c]	10.5 years	1 year	1.2 years	6 years	4.5 years	5.5 years	3 years	6 months
Sequelae	Left ankle pain on dorsiflexion and ROM limitation → resolved on f/u	Nil	Nil	Nil	Nil	Nil	Nil	No complications on last f/u

[a] Age in months.

[b] Age of BCG vaccination was recorded according to medical records or based on the assumption that patients born before January 1, 2016 were vaccinated within 24 h after birth and patients born on or after January 1, 2016 were vaccinated between 5 and 8 months of age.

[c] Shown in time since surgery.

[d] Osteolytic change noted on x-ray 29 days after symptom onset.

[e] Osteolytic change noted on x-ray 39 days after symptom onset.

[f] Non-adherence and lost to follow up.

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; F: female; f/u: follow up; INH: isoniazid; M: male; PZA: pyrazinamide; RIF: rifampin; ROM: range of motion; TB: tuberculosis; URI: upper respiratory infection; WBC: white blood cell.

Table 2 Clinical features of BCG-related osteitis/osteomyelitis studies reported to date in Taiwan.

Report	Chiu et al.[8]	Huang et al.[11]	Tsai et al.[15]	Yang et al.[16]	Current study
Study Period	1989–2012	1998–2014	2001–2019	2008–2019	2008–2020
Number of cases (M:F)	38 (18:20)	71 (37:34)	4 (3:1)	13 (N/A)	8 (4:4)
Median age in months (range)	N/A	14.4 (3.2–38.8)	13.5 (9–20)	19.2 (14.4–20.4)	17 (8–22)
Median interval from BCG vaccination[a] to symptom onset in months (range)	Average: 12.4 ± 6.1 (3–32)	13.9 (3–36)	11 (6.5–19)	16.4[c] (15.0–20.2)	15 (7–17)
Medical visits before diagnosis, median	N/A	3.0 (1–20)	N/A	N/A	3.0 (1–8)
Most common presentation	1. Swelling (66%) 2. Tenderness (58%) 3. Limp[b] (50%)	1. Swelling (77.5%) 2. Limp[b] (64.6%) 3. Tenderness (54.9%)	1. Swelling (75%) 2. Limp[b] (75%)	N/A	1. Swelling (75%) 2. Limp[b] (100%), n = 6
Laboratory results, median	All within normal ranges (except for 1 child with rib erosion)	Mean ± SD	All within normal ranges		
WBC, k/μL (range)		13 ± 8.8		9.81 (8.54–13.21)	10.86 (6.92–15.8)
CRP, mg/dL (range)		1.78 ± 3.12		0.38 (0.10–0.65)	0.25 (<0.02–1.42), n = 7
ESR, mm/hr (range)		29.9 ± 25.0		N/A	23 (10–77), n = 7
Most common lesion site	Lower extremities (55%; 21/38) →Tibia 9/38 →Ankle 8/38 →Femur 4/38	1. Lower long bones (36.6%) 2. Foot (23.9%) 3. Ribs or sternum (15.5%)	1. Lower long bones (75%) 2. Ulnar (25%)	1. Femur (38%) 2. Tibia (23%) 3. Sternum (23%)	1. Lower extremities (75%; 6/8) →Talus 3/8 →Tibia 3/8 2. Hand bones (25%)
Management: Surgical intervention (including excision, open biopsy, or debridement)	84%	98.6% (7 received extensive debridement, 3 developed major sequelae)	100%	N/A	100%
Medication	100%: INH + RIF	98.6%; median duration of 12 months	100%: INH + RIF for 10–12 months	12 months	100%: INH + RIF for 7–12 months
Sequelae	Severe kyphosis in 2 patients with involvement of thoracic spine	Severe kyphosis in 2 patients; 1 patient with limb length discrepancy	2 patients with minimal limb length discrepancy	Disease recurrence in 1 patient	None

[a] Interval from BCG vaccination to symptom onset was calculated according to medical records, or based on the assumption that patients born before January 1st 2016 were vaccinated within 24 h after birth and patients born on or after January 1st 2016 were vaccinated between 5 and 8 months of age.

[b] Includes limp, abnormal/unsteady gait, inability to bear weight, or weakness.

[c] Median interval from BCG vaccination to diagnosis (interquartile range).

Abbreviations: BCG: Bacillus Calmette-Guérin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; F: female; INH: isoniazid; M: male; N/A: not available; RIF: rifampin; SD: standard deviation; WBC: white blood cell.

occurred in patients of younger age, with a high prevalence in children in the 1—2 year age group. Many lesions were found in lower limb; scholars previously hypothesized that the increase in physical activity among children of this age group could have resulted in microtrauma in the long bones of their lower limbs, increasing the risk for the hematogenous seeding of the BCG strain.[11,16] Fever is not a common feature of BCG-related osteomyelitis unless other concurrent infections occur. However, a spiking fever up to 39 °C was reported in a child with BCG-related osteomyelitis who received the Tokyo 172 vaccine strain in Japan.[22]

In our study, one of the shortest time to diagnosis was found in a girl aged 1 year and 7 months (case no. 6 in Table 1), who presented to our Pediatric Orthopedics out-patient department with complaints of right knee painful swelling and limping gait for 4 days. She also had fever with productive cough and rhinorrhea for 3 days. Plain radiograph of her right knee revealed a shadow over proximal tibia (Fig. 1A). Osteomyelitis was suspected, and she was immediately admitted. Laboratory tests revealed WBC 10400/μL, neutrophilic segment 26%, lymphocytes 59.1%, monocytes 10.6%, CRP 0.25 mg/dL, and ESR 34 mm/h. Magnetic resonance imaging (MRI) of the right knee (Fig. 1B) showed increased signal intensity in right proximal tibia, involving epiphysis to metaphysis, with a small intraosseous abscess in epiphysis; these features were compatible with osteomyelitis. Surgery was performed the next day, and specimens obtained during surgery were sent to Taiwan CDC to confirm the diagnosis of BCG-related osteomyelitis. This case demonstrates the atypical presentation of BCG-related osteomyelitis, where fever and early osteolytic changes in radiologic examinations aided to speedy diagnosis and treatment of this otherwise slow onset disease. However, in most cases, it is not uncommon for patients to go through several medical visits before getting the right diagnosis. In our study, we conducted an average of 3.3 medical visits, and about 1 month from the onset of symptoms before the diagnosis of osteomyelitis was made. This disease is often missed by clinicians on first encounter with an otherwise well-appearing child presenting with localized symptoms such as swelling, limping, or mild tenderness of the affected region and is often being passed off as muscle sprain or cellulitis. The diagnosis of osteomyelitis was only made when the patient exhibited poor responses to several courses of empiric antibiotics or pain relievers. Even when the diagnosis of osteomyelitis is considered, patients are often treated initially with antibiotics targeting pyogenic osteomyelitis. Depending on the site of the lesion, the delay in diagnosis could potentially have a negative effect on the treatment outcome, thereby increasing the patient's risk of sequelae.

Osteolytic lesions on radiologic examination provides a clue to the differential diagnosis of osteomyelitis. However, in our study, five of the eight children had negative findings on initial X-ray examination. When combined with an afebrile condition, the diagnosis of osteomyelitis is easily missed by unwary clinicians. To help identify key hints that may aid clinicians to an earlier diagnosis of BCG osteomyelitis, we compared the demographics of our BCG-related osteomyelitis group with culture-proven pyogenic osteomyelitis group (Table 3) as described in the previous study of Chen et al.[13] The age of disease onset was significantly younger in the BCG-osteomyelitis group, with an age difference of about 26 months (1.41 vs. 3.64 years, $p = 0.038$). The pyogenic group had shorter time to diagnosis than the BCG-osteomyelitis group (6 days vs. 30 days, $p = 0.002$). Although swelling and limp ranked high in the presenting symptoms of BCG osteomyelitis, these phenomena were also common in the pyogenic osteomyelitis group. The absence of fever or pain in the BCG-osteomyelitis group was found to be statistically significant when compared with that of the pyogenic group ($p = 0.002$ and $p = 0.026$ respectively). The occurrence of concurrent septic arthritis or the involvement of multiple bones were found to be similar between the two groups. In terms of laboratory parameters, CRP and ESR were significantly higher in the pyogenic group. When we applied cut-off values of CRP >2 mg/dL and ESR >20 mm/h, the statistical significance remained.

In conclusion, an unexplainable swelling or limp in an afebrile toddler without previous history of trauma and who had received the BCG vaccine should prompt clinicians to further survey the possibility of osteomyelitis. If laboratory tests reveal a normal WBC count and a normal to modest elevation of ESR, further imaging studies, including plain radiographs or the more sensitive magnetic resonance imaging (MRI) or computed tomography (CT), should be employed to rule out BCG-related osteomyelitis. Inappropriate use of empiric antibiotics may be minimized in children diagnosed with osteomyelitis but with normal laboratory findings.

Although no standard treatment for BCG-related osteomyelitis has been established, minimally invasive surgery for biopsy and debridement in combination with an adequate course of anti-tuberculosis therapy seem to obtain good results. In our study, all patients received open biopsy with conservative debridement and/or sequestrectomy. Extensive debridement was avoided for fear of further damage to epiphyseal plates. All our patients recovered well, exhibited good response to oral medications with isoniazid and rifampin, and healed without obvious limb length discrepancy. Major sequelae after extensive debridement were reported in other studies, especially in patients whose lesions were located in the vertebrae.[8,11] In Huang's study, two patients suffered from lesions located in the thoracic vertebrae: one received laminotomy and transpedicular corpectomy, while the other patient received partial excision of abscess on one vertebrae, along with extensive debridement of the paraspinal area. Both patients survived but had major sequelae of severe kyphosis. A previous study on spinal tuberculosis reported that children are more likely to develop severe kyphosis because progress in deformity continues even after the disease is cured.[23]

This study has several limitations. First, we may have missed some cases due to the strict inclusion criteria of *M. bovis* as confirmed by the National Reference Mycobacterial Laboratory because both of our excluded cases had positive PCR results for MTB complex and compatible pathological findings. Second, our sample size is small. However, this limitation is somewhat compensated by similar findings when compared with previous works in Taiwan.

Although patients in our study achieved good recovery, some patients with BCG-related osteomyelitis survived the disease with long-term sequelae.[8,11,15,16] Future studies are

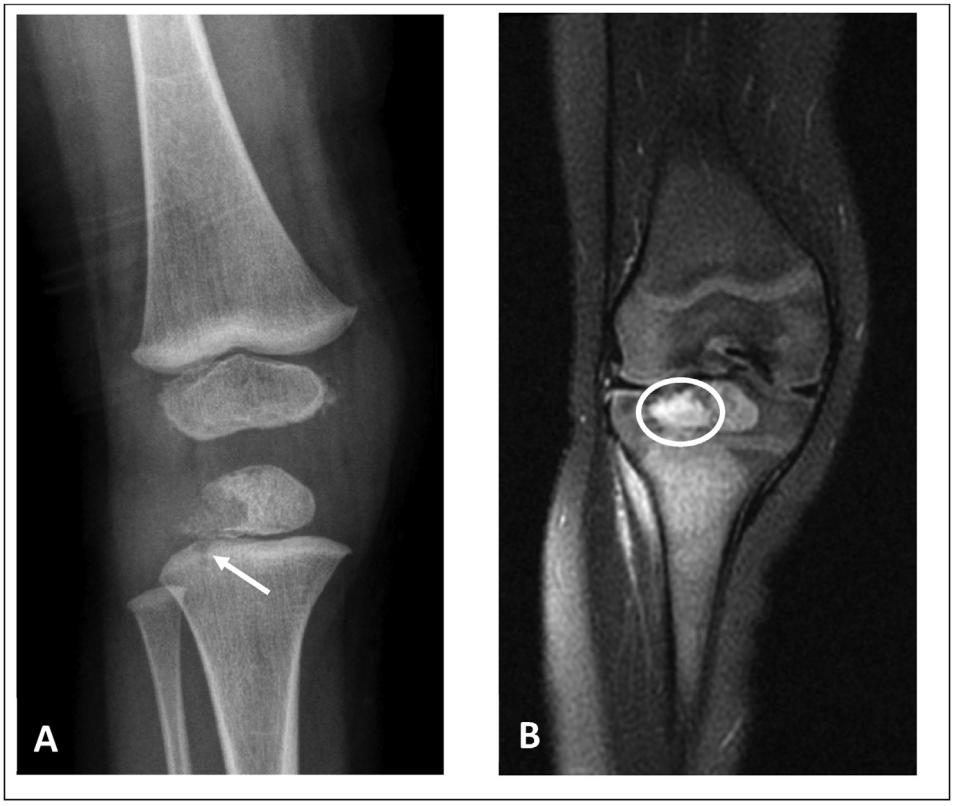

Figure 1. (A) X ray of the patient's right knee taken upon initial out-patient visit showing soft tissue swelling around knee, with demineralization in lateral portion of epiphysis of right tibia (B) T2 weighted MRI image of right knee showing small intraosseous abscess in epiphysis (circled area), and abnormal bone marrow signal with heterogenous enhancement in the epiphysis and metaphysis of right proximal tibia.

Table 3 Comparison of demographics, clinical presentations, and laboratory findings between BCG osteomyelitis and pyogenic osteomyelitis (culture positive).

	Present study BCG osteomyelitis (n = 8)	Chen et al.[14] Pyogenic osteomyelitis (n = 37)	*p* value
Gender, male	4 (50)	25 (67.6)	0.427
Median age in years	1.4 (1.2–1.7)	3.6 (0.9–11.6)	**0.038**
Days from onset of symptoms until diagnosis	30 (23.3–51)	6 (3–10.5)	**0.002**
Symptoms			
Fever	1[a] (12.5)	28 (75.7)	**0.002**
Swelling	6 (75)	31 (83.8)	0.618
Limp[b]	6 (100), n = 6	16 (53.3), n = 30	0.062
Pain or tenderness	4 (50)	32 (88.9)	**0.026**
Osteomyelitis with concomitant septic arthritis	1 (12.5)	15 (40.5)	0.226
Multifocal bone involvement	1 (12.5)	5 (13.5)	1.00
Initial laboratory data			
WBC count × 10^3/mm^3	10.86 (9.29–13.41)	14.09 (9.84–17.80)	0.191
WBC count >15,000/mm^3	1 (12.5)	17 (45.9)	0.119
C-reactive protein mg/dL	0.25 (0.02–0.69), n = 7	10.68 (3.11–15.97)	**0.000**
C-reactive protein >2 mg/dL	0 (0), n = 7	30 (81.1)	**0.000**
ESR mm/hour	23 (13–34), n = 7	60 (33–82), n = 34	**0.004**
ESR >20 mm/h	4 (57.1), n = 7	33 (97.1), n = 34	**0.012**

[a] With concomitant febrile upper respiratory infection.
[b] Includes limp, abnormal/unsteady gait, inability to bear weight or weakness.
Abbreviation: ESR = erythrocyte sedimentation rate; SD = standard deviation; WBC = white blood cell.
Data are presented as case number (percentages) or median (interquartile range) unless otherwise indicated.
Statistically significant results are indicated in bold print.

needed to reach a consensus on optimal management of this rare but sometimes aggravating side effect of the BCG vaccine. Early identification of the disease could lead to better outcomes.

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Declaration of competing interest

All authors have no conflicts of interest or financial relationships relevant to this article to disclose.

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