

# Osteitis secondary to BCG vaccine in immunocompetent patients

## Three case reports

Napoleón González Saldaña, MD<sup>a</sup>, Agustín Rafael De Colsa Ranero, MD<sup>a</sup>, Diego Mauricio Galvis Trujillo, MD<sup>b</sup>, Eduardo Arias De la Garza, MD<sup>a</sup>, Ana Isabel Quesada Tortoriello, MD<sup>a</sup>, Bárbara Varela Ruiz, MD<sup>c</sup>, Rodolfo Rodríguez Jurado, MD<sup>d</sup>, Hugo Juárez Olguín, PhD<sup>e,\*</sup>, Miroslava Lindoro Silva, MD<sup>e</sup>

### Abstract

**Rationale:** Osteitis corresponds to a rare but potentially serious complication reported in pediatric population after the application of the Bacillus Calmette-Guerin (BCG) vaccine. In the present study, 3 clinical cases associated with this entity are reported.

**Patient concerns:** The 1st case corresponds to a 1-year-old female patient who presented an increase in the volume of the right pelvic limb after BCG application. The second case is a 2-year-old male who began with an increase in volume, overactive gait and pain at the level of the left knee on walking that began after a trauma in the left low limb. The 3rd case corresponds to a 3-year-old patient who started with intense pain and limitation for ambulation.

**Diagnosis:** Both the radiographical and histological studies presented data suggestive of infection by *Mycobacterium tuberculosis* complex, corroborated through biopsy and genotyping analysis with the isolation of *Mycobacterium bovis* as the causal agent.

**Interventions:** The basic treatment scheme was based on Ethambutol, Rifampicin, Pyrazinamide, and Isoniazid. When *M. bovis* was typified, clarithromycin was added in the treatment.

**Outcomes:** Osteitis secondary to BCG vaccine usually has a favorable evolution, especially in immunocompetent patients.

**Lessons:** It was possible to confirm the association of BCG vaccine with the clinical picture of the patients who presented improvement after the start of antimicrobial management. Osteitis secondary to BCG vaccine usually presents a favorable evolution, especially in immunocompetent patients; however, the involvement of joint, growth discs and vertebrae increases the risk of presenting long-term sequels.

**Abbreviations:** BCG = Bacillus Calmette-Guérin, CRP = C reactive protein, GSR = globular sedimentation rate, IDP = inflammatory demyelinating polyneuropathy, MRI = magnetic resonance imaging, NBT = nitroblue tetrazolium, PPD = purified peptide derivative, TB = tuberculosis.

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(ORCID 0000-0002-1405-1728)

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<sup>a</sup> Service of Infectology, National Institute of Pediatrics (NIP), Mexico City, <sup>b</sup> Pediatric Infectious Disease Clinic, Cafam, Colombia, <sup>c</sup> Laboratory of Microbiology, National Institute of Nutrition and Medical Science, <sup>d</sup> Department of Anatomical Pathology, NIP, <sup>e</sup> Faculty of Medicine, Department of Pharmacology, NIP, National Autonomous University of Mexico, Mexico.

\* Correspondence: Hugo Juárez Olguín, Laboratorio de Farmacología, Instituto Nacional de Pediatría, Avenida Imán N° 1, 3rd piso Colonia Cuicuilco CP 04530, Mexico City, Mexico (e-mails: juarezol@yahoo.com, adrianos27@hotmail.com).

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## 1. Introduction

Bacillus Calmette-Guerin (BCG) corresponds to the live attenuated vaccine used in the prevention of disseminated Tuberculosis in the pediatric population.<sup>[1]</sup> Despite being considered as a safe vaccine, it has been associated with complications both at local and systemic levels.<sup>[2]</sup> These complications include ulceration on the site of application, circular adenopathies, osteitis, and dissemination of the disease, which usually occurs in immunocompromised patients.<sup>[3]</sup> The appearance of the adverse effects depends on multiple factors such as dose, strain, method of application and the immunological status of the vaccinated individual.<sup>[4]</sup>

Post-BCG osteitis is a complication that has been reported in pediatric population, with greater incidence in male than in female population. It can progress through contiguous dissemination, as in the case of humeral osteitis or through hematogenous dissemination with primary extension to epiphysis of long bones due to its wide vascularization. The site of the injury may be independent of the region of application of the vaccine. It usually has a unilateral condition, which suggests a local increase in the vasculature due to a probable traumatic antecedent in the area before the dissemination of the bacillus.<sup>[3]</sup> At the radiological level, it is characterized by presenting lytic lesions which predominate in the metaphyseal region of the long bones with the presence of periosteal reaction. With regard to the paraclinical tests, it usually shows low response of inflammatory markers, as opposed to the marked elevation of the same in “classic” cases of septic or osteomyelitis arthritis.<sup>[5]</sup>

Post-vaccinal osteitis is a condition rarely detected in pediatric practice due to the limited diffusion and knowledge of this pathological entity, which is why it is usually difficult to establish the diagnosis. It is estimated that only 25% is diagnosed. The clinical manifestations usually occur after 18 months of the application of the vaccine; nevertheless, the range of clinical appearance varies from few months to 5 years after the application. The lack of response to antimicrobial management, atypical biochemistry, as well as the clinical presentation in a patient suggests the presence of this entity.<sup>[2]</sup> There are criteria proposed by Foucard & Hjelmsted in 1971 to facilitate the diagnosis of the cases of osteitis associated with the BCG vaccine.<sup>[6]</sup>

1. Vaccination with BCG in neonatal period.
2. Period less than 4 years between the vaccination and the onset of symptoms.
3. Lack of contact between the child and any person with Tuberculosis.
4. Compatible clinical picture.
5. Histopathology suggestive of Tuberculosis.

The gold standard to establish the diagnosis corresponds to the biopsy of the lesion through the detection of histopathological changes characterized by the presence of granulomatous reaction and caseous necrosis. Once the diagnosis is established, antituberculosis treatment should be initiated, taking into consideration the results of resistance and susceptibility of the etiological strain.<sup>[5]</sup>

## 2. Report of cases

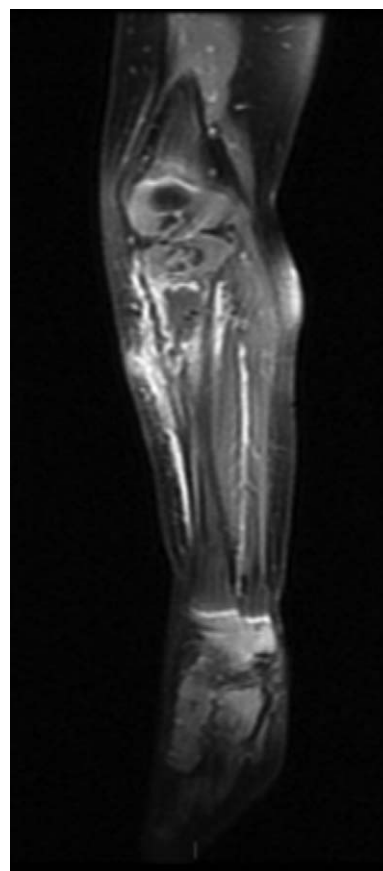
This study describes the cases of osteitis secondary to BCG vaccine in immunocompetent patients in a tertiary hospital. Post-vaccination osteitis is a condition that is rarely detected in

pediatric practice. So, it is fundamental the study of this pathology, its clinical presentation and appropriately diagnosis.

### 2.1. Case 1

The case is a female patient of 21 months old, who presented an increase in volume in the right pelvic limb. The patient has a complete vaccination for her age with application of BCG on April 30<sup>th</sup>, 2015. The mother reported a clinical picture of approximately 2 months of evolution, characterized by pain in the bone at the traction of pelvic limb with subsequent claudication to walk. She denies the presence of fever, weight loss, hyporexia or any other symptom.

The patient was then referred to the Oncology Service to begin a procedure of bone tumor management in the anterior tibia of the right leg after denial of the above symptoms, traumatic antecedent or recurrent infection of the airways. Paraclinical studies reported 11.3 g/dL of hemoglobin, 33.8% of hematocrit,  $9.5 (10^3/\text{mm}^3)$  of leucocytes,  $1.3 (10^3/\text{mm}^3)$  of neutrophils,  $6.9 (10^3/\text{mm}^3)$  lymphocytes,  $1 (10^3/\text{mm}^3)$  of monocyte,  $319 (10^3/\text{mm}^3)$  of platelets, 16 (mm/h) of globular sedimentation rate (GSR) and  $<0.316 (\text{mg/dL})$  of C reactive protein (CRP). The X-ray of the right pelvic limb depicted a delimited metaphyseal lytic lesion of the proximal right tibia with periosteal reaction and geographical pattern, and increased volume of the soft tissues, as well as metastatic bone series without evidence of other lesions. In magnetic resonance imaging (MRI), compatible chronic granulomatous osteomyelitis lesion was detected, (Fig. 1). Based on

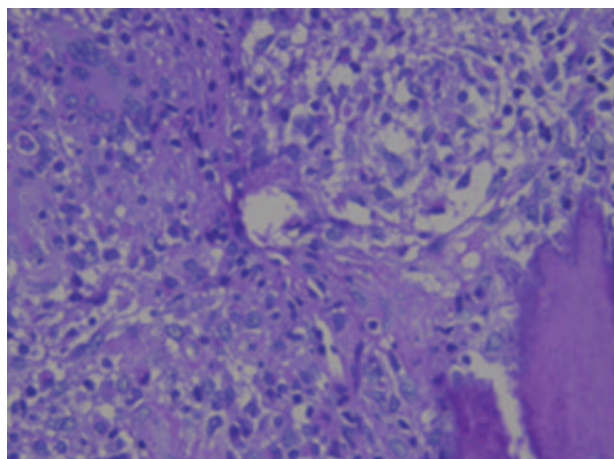


**Figure 1.** Magnetic resonance imaging (MRI) showing the destruction of the tibial bone in the proximal region. MRI = magnetic resonance imaging.



**Figure 2.** Antero-posterior of thorax of the patient with images suggestive of bronchial wing thickening secondary to inflammatory process.

these evidences, the patient was transferred to Infectious Disease Service to continue his management procedures. The patient was subjected to Purified Peptide Derivative (PPD) test and resulted to be negative with a value of 3x3 mm. Chest X-ray was performed and it ruled out lung compromise (Fig. 2). High resolution tomography of the lung carried out in search of mediastinal adenopathies suggestive of Tuberculosis was without apparent aggregated lesions. Curettage was done with subsequent application of cryotherapy and graft placement at the site of the lesion. Biopsy of the bone was performed obtaining a culture with histopathological characteristics suggestive of *Mycobacterium tuberculosis* (Fig. 3). In genotype analysis of the sample, *Mycobacterium bovis* (BCG) was identified as the causative



**Figure 3.** Photomicrograph showing fragments of destroyed residual bone and giant Langerhans-type cell within granuloma.

agent; thus confirming the association of the lesion with the application of the vaccine in this patient. Sensitivity test performed confirmed the susceptibility of the agent to Isoniazid, Rifampicin, Ethambutol, and Streptomycin. In view of this, antimicrobial scheme based on Clarithromycin 80 mg/kg/day, Ethambutol 20 mg/kg/day, Rifampicin 10 mg/kg/day, and Isoniazid 10 mg/kg/day was started and then began to improve favorably.

## 2.2. Case 2

The 2nd patient is a boy of 2 years and 1 month old, who was referred by the local health center to rule out neoplastic process for presenting a lytic lesion in the epiphysis of left distal femur. His vaccination scheme was completed except the 3rd dose of rotavirus vaccine. The BCG immunization antecedent was recorded at birth, in July 2015. He had a history of low extremity trauma due to a fall from the bed of approximately 50 cm that provoked contusion in the left lower limb with increase in volume, limitation of gait and pain predominantly at the level of the left knee.

He was 1st admitted in the Emergency Service of National Institute of Pediatrics (INP- Spanish acronym) in regular general conditions but with an increased volume of the medial anterior face of the left knee, manifesting pain of mild intensity on flexion extension of the knee, claudication of gait (walking impairment) and pain on bipedal. On admission, reported 12 g/dL of hemoglobin, 37.9% of hematocrit,  $6.6 (10^3/\text{mm}^3)$  of leucocytes,  $2.5 (10^3/\text{mm}^3)$  of neutrophils,  $3 (10^3/\text{mm}^3)$  of lymphocytes, and  $465 (10^3/\text{mm}^3)$  of platelets. He was subjected to oncological evaluation by the Service of Oncology who ruled out neoplastic processes based on incompatible radiological data. Probable infectious osteomyelitis was suspected and in view of that, empirical treatment based on 200 mg/kg/day of dicloxacillin was started. The patient was later sent to the ward of Pediatric infectious Diseases to continue his treatment procedure. The X-ray of the left low limb depicted a large lytic lesion, compromising the internal condyle of the distal epiphysis of the left femur, with conserved cortical edges in the border of the lesion (Fig. 4). The MRI showed data suggestive of chronic osteomyelitis; hence, bone surgery and curettage were performed and subsequently, graft placement with bioactive bone was undertaken. During the trans-surgical scan, bone tissue biopsy was obtained which reported chronic granulomatous arthritis with caseous necrosis, histopathological data suggestive of *M tuberculosis*. The staining and polymerase chain reaction of the positive sample for *M tuberculosis* are reported. On suspecting osteitis secondary to Tuberculosis, it was decided to start a comprehensive approach or procedure based on the following: lumbar radiography without apparent alterations; lung radiography with the presence of 2 bilateral radiopaque lesions in pulmonary hila, suggestive of calcified nodule without another apparent alteration of the pulmonary parenchyma (Fig. 5); the parent's radiographies were normal; high resolution computed tomography (CT) of lung of the patient with report of left perihilar ganglionic growth of 13 to 8 mm and presence of a 2 mm nodular lesion on the left lower lobe at the basal level, suggestive of calcified granuloma. Antituberculous treatment based on isoniazid, 10 mg/kg/day; rifampicin, 15 mg/kg/day; pyrazinamide, 25 mg/kg/day and ethambutol, 27 mg/kg/day was started. When *M bovis* was typified, clarithromycin at 15 mg/kg/day was added in the treatment scheme. Presently, the evolution of the patient is favorable. He is still subjected to procedures to rule out primary immunodeficiency



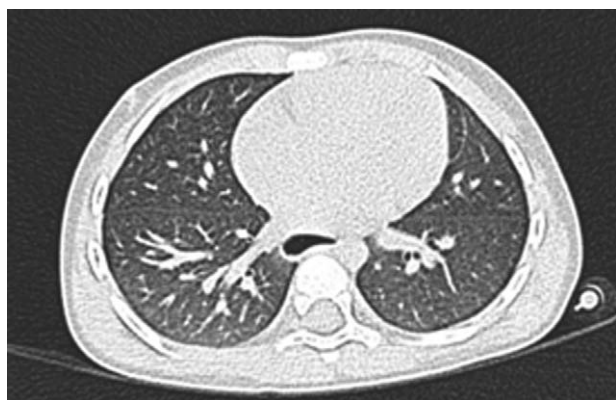


**Figure 4.** X-ray of the left lower extremity with the presence of a large lytic lesion involving the internal condyle of distal epiphysis of the left femur with preserved cortical edges in the border of the lesion.

with report of nitroblue tetrazolium negative for chronic granulomatous disease.

### 2.3. Case 3

Case 3 is a female of 3 years and 7 months old. She was admitted in the hospital for presenting intense pain and walking limitation of approximately 5 months of evolution. Analysis of her referral studies consisting on tomographic evidence depicted a lytic lesion on the acetabulum in the iliopectic eminence and anterior-inferior iliac spine with thinning and rupture of the cortical bone.



**Figure 5.** High resolution computed tomography (CT) of left parahilar ganglionic growth of 13 to 8mm and the presence of a 2mm nodular lesion located in the left lower lobe at the basal level suggestive of calcified granuloma. CT = computed tomography.

Moreover, a referral biopsy performed in February, 2016, showed hemorrhagic material with few groups of histiocytes and giant multinucleated Langerhans cells and chronic granulomatous inflammation compatible with Tuberculosis. In view of the above, she was referred to NIP by the National Institute of Rehabilitation for comprehensive evaluation. The BCG immunization record depicted the application of the vaccine at birth in July, 2015.

On being referred to the institute for presenting intense pain with walking limitation, she was attended in the outpatient service of the Orthopedic Department. Extension studies performed before her admission in the institute consisted of bone gammagraphy done on 19<sup>th</sup> January, 2016, with report of normal metabolic activity; and bone biopsy, performed on 18 February, 2016, where chronic granulomatous inflammation was appreciated. Upon admission, the approach was complemented with pelvic radiography, performed on 23<sup>rd</sup> March, 2016, which showed the presence of lytic lesion on the right acetabulum. Based on the biopsy report, the Infectious Disease Service decided to start treatment based on isoniazid, 10 mg/kg/day; rifampicin, 15 mg/kg/day; pyrazinamide, 20 mg/kg/day; and ethambutol, 25 mg/kg/day. She was also assessed by the Immunology Service with report of good clinical evolution. The laboratory exams of 6<sup>th</sup> April, 2016, of the patient reported hemoglobin of 13.3(g/dL), hematocrit of 39.9 (%), Leucocytes of 10.4 ( $10^3/\text{mm}^3$ ), neutrophils of 5.7 ( $10^3/\text{mm}^3$ ), lymphocytes of 3.4 ( $10^3/\text{mm}^3$ ), platelets of 404 ( $10^3/\text{mm}^3$ ), and normal nitroblue tetrazolium test, without significant hereditary family history or other infectious events suggestive of inflammatory demyelinating polyneuropathy (IDP).

### 3. Discussion

The BCG vaccine, obtained from the attenuation of *M Bovis* bacillus, is routinely applied in pediatric population in our country. It is considered a safe vaccine; nevertheless, cases of local and systemic complications including Osteitis have been reported following its application. Some publications, especially in developed countries, have suggested suspending the routine application of the vaccine. However, since Mexico is considered endemic country of Tuberculosis based on the records of World Health Organization (WHO), the rare complications, which have an incidence of approximately 0.39 per 1.000.000 vaccines applied, should not contraindicate its use.<sup>[7]</sup>

The key points in these cases are based on the presence of osteitis associated with the BCG vaccine in 3 immunocompetent patients. Based on literature reported, most patients with osteitis associated with BCG have some type of deficiency at the immunological level that predisposes them to develop this pathological entity.

The importance of this study and the dissemination of these cases consists on identifying the risk factors and clinical characteristics that are associated with them, since they could differ from those seen in immune-compromised patients, taking into account its clinical variability in pediatric population where currently only 25% of the cases are diagnosed.<sup>[7]</sup>

Osteitis due to BCG should be suspected in any child who presents limb edema without evidence of fracture and in cases with compatible radiological characteristics such as metaphyseal lytic lesions and periosteal reaction structures, or histological features associated with *M tuberculosis* complex.

Medications are the 1st line of treatments for bone Tuberculosis, and the duration of treatment can go between 6 and 18 months.<sup>[8]</sup> Osteitis secondary to BCG vaccine usually has a favorable evolution, especially in immunocompetent patients; however, the involvement of joints, growth discs, and vertebrae

increases the risk of presenting long-term sequelae.<sup>[9]</sup> The lack of response to antimicrobial management as well as the absence of contact with any positive case of tuberculosis and the history of BCG vaccination supports the diagnostic suspicion.

The difficulty of diagnosing this pathological entity in the pediatric population in immunocompetent patients lies on its low incidence (<1%) when compared with the general population. Taking this into account, it is of paramount importance to disseminate the basic aspects and diagnoses of this entity, especially the clinical variability of osteitis by BCG in the pediatric population, with the objective of promoting early detection and timely management so as to reduce morbidity, mortality and the incidence of sequelae or complications associated with it in affected patients.

#### 4. Conclusion

The adverse effects of BCG vaccination are well documented and are presented in a very low frequency; thus, depicting the benefit in circumstances of an endemic country. Given the large scale application, it should be suspected as the etiological cause of osteitis when this immunization is applied during the neonatal life, with latency period of up to 5 years. Its diagnosis and treatment as well as the identification of early immunocompromise would guarantee the reduction of long-term sequels of the disease.

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#### Author contributions

**Conceptualization:** Napoleon Gonzalez Saldaña.

**Formal analysis:** Napoleon Gonzalez Saldaña, Agustin Rafael Decolsa Ranero, Diego Mauricio Galvis Trujillo, Eduardo Arias de la Garza, Ana Isabel Quezada Tortoriello, Barbara Varela Ruiz, Rodolfo Rodriguez Jurado, Hugo Juárez Olguín, Miroslava Lindoro Silva.

**Investigation:** Napoleon Gonzalez Saldaña, Agustin Rafael Decolsa Ranero, Diego Mauricio Galvis Trujillo, Eduardo Arias de la Garza, Ana Isabel Quezada Tortoriello, Barbara Varela Ruiz, Rodolfo Rodriguez Jurado, Hugo Juárez Olguín, Miroslava Lindoro Silva.

**Methodology:** Napoleon Gonzalez Saldaña, Agustin Rafael Decolsa Ranero, Diego Mauricio Galvis Trujillo, Eduardo Arias de la Garza, Ana Isabel Quezada Tortoriello, Barbara Varela Ruiz, Rodolfo Rodriguez Jurado.

**Project administration:** Hugo Juárez Olguín.

**Writing – original draft:** Napoleon Gonzalez Saldaña, Agustin Rafael Decolsa Ranero, Diego Mauricio Galvis Trujillo, Eduardo Arias de la Garza, Ana Isabel Quezada Tortoriello, Barbara Varela Ruiz, Rodolfo Rodriguez Jurado, Hugo Juárez Olguín, Miroslava Lindoro Silva.

**Writing – review & editing:** Napoleon Gonzalez Saldaña, Diego Mauricio Galvis Trujillo, Eduardo Arias de la Garza, Ana Isabel Quezada Tortoriello, Barbara Varela Ruiz, Rodolfo Rodriguez Jurado, Hugo Juárez Olguín, Miroslava Lindoro Silva.

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