

Clinical case

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Osteomyelitis of the talus in infants following *Bacillus Calmette-Guérin* (BCG) vaccination

Osteomielitis del astrágalo en lactantes tras la vacunación con bacilo de Calmette-Guérin (BCG)

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ABSTRACT. Osteomyelitis caused by *Bacillus Calmette-Guérin* (BCG) is a rare complication of *Mycobacterium bovis* vaccination. Lesions are usually localized in the metaphysis or epiphysis of long bones, but rarely affect the foot. This report describes two cases of BCG osteomyelitis involving the talus in infants of 13 months and eight months old. BCG-osteomyelitis should be suspected in children under two years of age with insidious osteomyelitis, accompanied with characteristic imaging findings.

Keywords: BCG osteomyelitis, Mendelian susceptibility to mycobacterial diseases, *Mycobacterium bovis*, children.

RESUMEN. La osteomielitis causada por el bacilo de Calmette-Guérin (BCG) es una complicación poco frecuente de la vacunación con *Mycobacterium bovis*. Las lesiones suelen localizarse en la metafisis o epífisis de los huesos largos, pero rara vez afectan el pie. En este informe se describen dos casos de osteomielitis por BCG que afectaban el astrágalo en lactantes de 13 y ocho meses de edad. La osteomielitis por BCG debe sospecharse en niños menores de dos años con osteomielitis insidiosa, acompañada de hallazgos característicos en las imágenes.

Palabras clave: osteomielitis por BCG, susceptibilidad mendeliana a enfermedades micobacterianas, *Mycobacterium bovis*, niños.

Introduction

Infection caused by *Mycobacterium tuberculosis* (CMT) remains a public health challenge despite vaccination efforts.^{1,2} In Argentina, a live attenuated *Mycobacterium bovis* vaccine (*Bacillus Calmette-Guérin* Danish strain 1331) is universally administered to all newborns before they leave the maternity ward as part of a national immunization program aimed at preventing invasive forms of tuberculosis.³ Although administration is generally safe, lymphadenitis, abscesses, and osteomyelitis have been described. The incidence of BCG

osteomyelitis is 0.2 cases per 100,000 vaccinations.⁴ Lesions are usually localized in the metaphysis or epiphysis of long bones and rarely affect the foot.^{5,6} We reported two cases of BCG osteomyelitis involving the talus in infants.

Clinical case

Case 1

A healthy 13-month-old female with an up-to-date vaccination schedule presented to the emergency department

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with swelling, pain and restricted mobility of the right ankle without history of trauma. She had no fever. X-ray imaging of the foot revealed an osteolytic lesion in the talus, accompanied by rupture of the dorsal cortex (*Figure 1*). Magnetic resonance imaging (MRI) showed compromise and rupture of the dorsal cortex of the talus, along with

ankle joint effusion (*Figure 2*). Blood tests were normal and blood cultures results negative (*Table 1*). Cultures results and the pathology report of samples obtained through a CT-scan guided biopsy were inconclusive. Therefore, new samples were obtained by surgical debridement revealing necrotic bone tissue negative for Ziehl-Neelsen staining. Based on the suspicion of osteomyelitis, empirical antibiotic treatment with clindamycin was provided. One month after the initial surgery, persistent ankle swelling was observed, leading to another debridement procedure. The second biopsy sample showed no growth of atypical organisms but revealed chronic granulomatous osteomyelitis suggestive of a mycobacterial process (*Figure 3*). Antibiotic therapy for *Mycobacterium tuberculosis* was initiated including isoniazid (H), rifampicin (R), pyrazinamide (P), and ethambutol (E) and continued orally for an additional 60 days, followed by a second phase of HR for 120 days. After antibiotic treatment, the patient was asymptomatic. Radiographic follow-up showed improvement of the bone defect (*Figure 4*).



Figure 1: A) Anteroposterior and lateral radiographs of the right ankle, B) magnetic resonance imaging T2 STIR of Case 1.

Case 2

An eight-month-old male patient attended the emergency department with persistent fever lasting four days and right lower limb pain. He presented a slight swelling and tenderness around the right medial malleolus, without erythema or localized temperature elevation. Blood tests showed altered values and negative blood cultures (*Table 1*). Ultrasonography and plain radiography of the ankle and foot were performed, revealing alterations in the shape of the talus (*Figure 5*). An MRI revealed heterogeneous signal intensity in the talus consistently with an intraosseous abscess, along with rupture of the dorsal cortex and edema of the subcutaneous tissue around the ankle and foot (*Figure 6*). Suspected osteomyelitis was treated with intravenous empiric antibiotics with clindamycin. 10 days later, the pathology report of a guided biopsy showed a caseous granuloma suggestive of mycobacterial infection. Although cultures were negative,



Figure 2:

Intraoperative images of the approach and debridement.

Table 1: Blood test results.

	White blood cell count	C-reactive protein	Erythrocyte sedimentation
Case 1	10,500/mm ³ (5,000-10,000/mm ³)*	0.32 mg/dl (0.5 mg/dl)*	16 mm/h (2-20 mm/h)*
Case 2	11,000/mm ³ (16,000-17,500/mm ³)*	16 mg/dl (0.97 mg/dl)*	30 mm/h (2-20 mm/h)*

* Reference ranges for each test according to the local laboratory.

Figure 3:

Histological findings: small red arrows point to multinucleated giant cells, and large red arrows indicate bone fragments with multinucleated giant cells and granulomas.

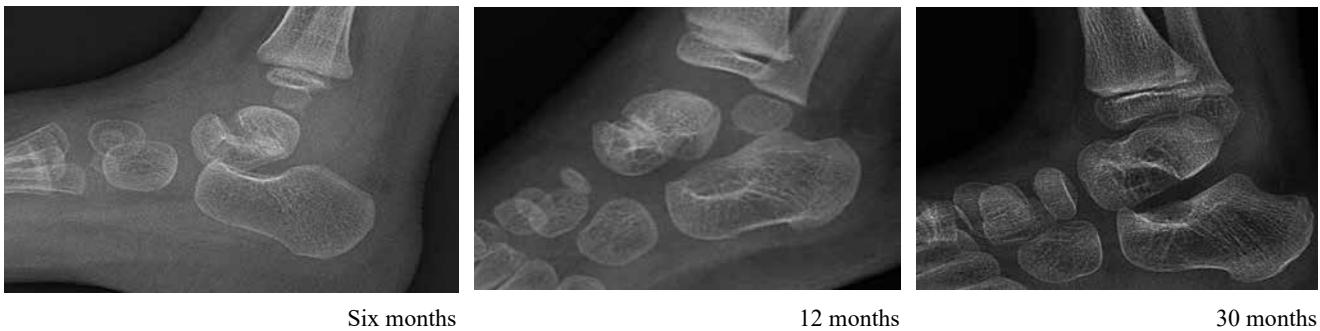
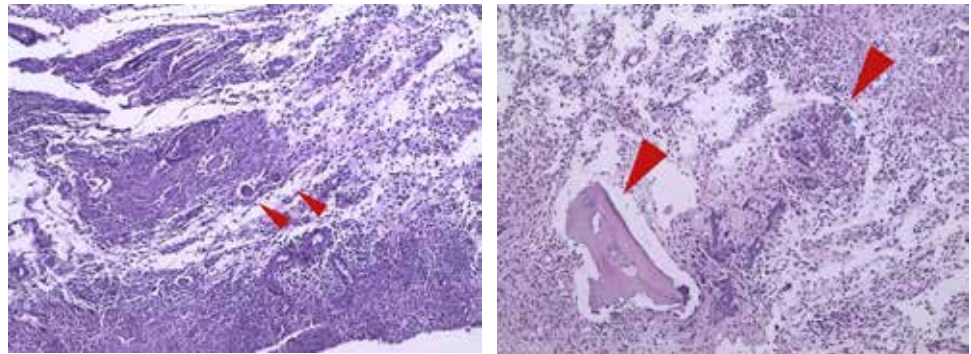


Figure 4: Lateral radiographs at six, 12 and 30-months after treatment, showing restoration of the talus with minimal residual deformity.

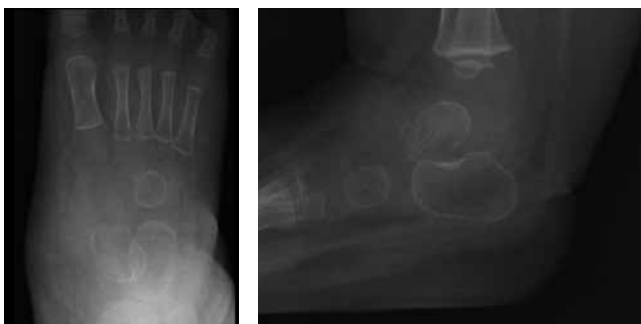


Figure 5: Radiographs of Case 2 obtained at admission.

the Ziehl-Neelsen stain showed positivity. The patient underwent the intensive phase of the anti-tuberculosis regime for *Mycobacterium tuberculosis* for two months. Within the second antibiotic phase the patient showed clinical signs of relapse. A subsequent MRI revealed an

abscess involving the talus. After surgical debridement, new samples confirmed an infection caused by *Mycobacterium bovis*. The time from initial presentation to final BCG osteomyelitis diagnosis was four months. An immunology test revealed a mendelian susceptibility to mycobacterial disease (MSMD). Seven months after completing specific antibiotic treatment, plain radiographs showed improvement of the bone defect (Figure 7). Sixteen months after diagnosis, the patient remained asymptomatic.

Discussion

The administration of 0.5 ml to 1 ml dose of BCG vaccine is generally safe, nevertheless it can be associated with adverse events and complications. Choi et al.⁷ reported twenty-one cases of BCG osteitis with several strains and methods of administration. 16 children (76.2%) received

Tokyo-172 vaccine by percutaneous multiple puncture method, four (19.0%) received intradermal Tokyo-172 strain, and only one child received the Danish strain 1331 by intradermal method. In our case, both patients received the BCG Danish strain 1331 intradermally at birth.

Host immunity, particularly interferon-gamma receptor 1 and interleukin-12 receptor genetic mutations, may also contribute to the development of infection.^{2,4,8} Although Case 1 was considered immunocompetent, Case 2 presented with MSMD. MSMD is a Primary Immunodeficiency Disease (PID) caused by genetic mutations that affect IFN- γ immunity and the IL12/23 axis. This condition leads to an incomplete response to mycobacterial infections, resulting in high susceptibility to BCG vaccines, *Mycobacterium tuberculosis*, *Candida*, and *Salmonella*.⁹ Symptoms of

MSMD often manifest later, with an incubation period of 1.5 years (range 0.25-5.7 years) described by Kroger et al. in children vaccinated at birth.¹⁰

BCG osteomyelitis involves the spread of the pathogen through hematogenous, lymphatic, or local routes. Foot and ankle osteomyelitis in infants account for only 1-4% of CMT infections.⁴ Clinical manifestations of osteoarticular infections caused by CMT and *Mycobacterium bovis* are similar, including pain, edema, erythema, mild fever (absent in some patients), decreased joint mobility, and intolerance to weight-bearing.^{1,2} Although, *M. tuberculosis* infection is commonly located in the spine and affects children and adolescents, while *M. bovis* osteomyelitis is associated with BCG vaccination in infants and commonly affects the epiphysis of long bones.^{7,11,12} Under suspicion of BCG osteomyelitis differential diagnoses such as deep mycosis, atypical mycobacteriosis, tumor lesions, sarcoidosis, and secondary or primary amyloidosis should be considered in the presence of granulomas without pathogen isolation.^{2,13,14}

Consistently with our cases, laboratory tests may show either elevated or normal erythrocyte sedimentation rate,⁴ C-reactive protein, and white blood cell count.^{2,4} Polymerase chain reaction testing is useful in distinguishing between *M. tuberculosis* and *M. bovis* species.¹⁴ Images from our patients did not show the typical BCG osteomyelitis large intraosseous abscess extending through the growth plate because of the infrequent localization in the talus.¹⁵ Histopathological studies may reveal the presence of caseum and granulomas, although bacilli are not always evident under Ziehl-Neelsen stain.²

The World Health Organization guidelines¹⁶ recommend treating extrapulmonary tuberculosis in children with the same regimens as pulmonary disease (an initial phase of two months with Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E) administered daily followed by a continuation phase of four months with HR). However, the duration of the continuation phase should be extended from four to 10 months of HR if osteoarticular tuberculosis is confirmed or suspected. In some Latin American countries, the initial regimen for children does not include Ethambutol.¹⁷ In Argentina, the recommended regimen by the Health department is 2HRZE followed by a second phase of 7-10 months with HR.³ Because *M. bovis* exhibits intrinsic resistance to pyrazinamide, it is crucial to identify the species for appropriate treatment.^{1,4} In cases where isolation is not possible, the complete drug regime is employed (2HRZE/10HR), as was in Case 1. Curettage is recommended to eliminate necrotic tissue areas that are inaccessible to antibiotic therapy and to eradicate mycobacteria sequestered in osteolytic regions.¹

Conclusion

BCG osteomyelitis of the talus is a rare condition but should be considered in infants presenting insidious and progressive ankle pain and swelling following recent vaccination. Our report aims to raise awareness about this

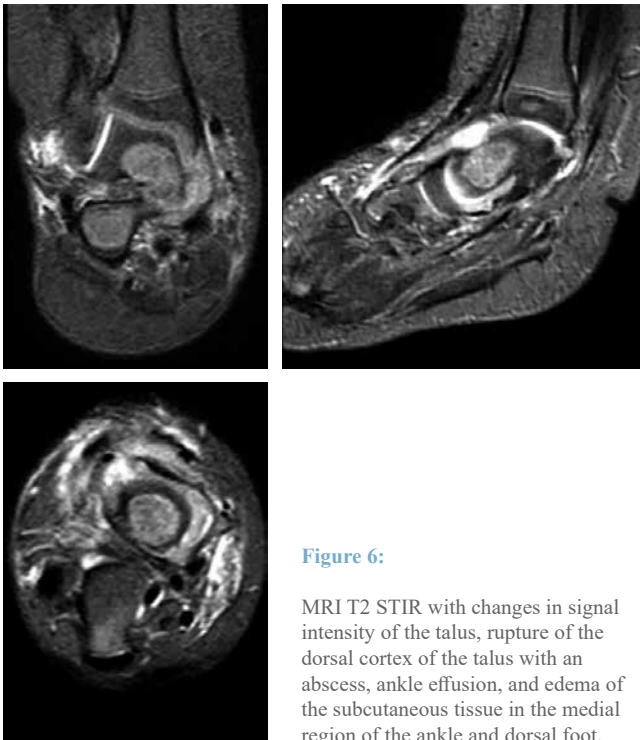


Figure 6:

MRI T2 STIR with changes in signal intensity of the talus, rupture of the dorsal cortex of the talus with an abscess, ankle effusion, and edema of the subcutaneous tissue in the medial region of the ankle and dorsal foot.



Figure 7: Radiographs after seven months of antituberculosis treatment and four months of surgery, showing improvement of the bone defect.

uncommon condition. Evaluation and treatment require a multidisciplinary approach. Bone biopsy is recommended to confirm the diagnosis. Genetic analysis should be conducted to rule out PIDs. Timely therapeutic intervention, including surgery and prolonged specific antituberculous chemotherapy, is crucial in preventing bone sequelae.

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