WHAT IS YOUR CALL?

Nonresponding osteomyelitis in a two-year-old boy

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A progressive limp and swelling of the heel developed in a previously healthy two-year-old boy over a two-week period. The child had been born in India and had lived in Canada since the age of seven months. There was no history of trauma.

On physical examination, the patient had no fever and appeared well, but he had swelling and tenderness at his right heel. A radiograph showed cortical destruction of the calcaneus, which was consistent with osteomyelitis or eosinophilic granuloma. Magnetic resonance imaging (MRI) showed bone marrow edema in the talus, in addition to calcification and T_2 hyperintensity in the calcaneus. Laboratory investigations showed an erythrocyte sedimentation rate (ESR) of 30 (normal 1–10) mm/h. Treatment was started empirically with cefazolin administered intravenously (150 mg/kg daily). After two weeks of therapy, however, the ESR showed little improvement (38 mm/h). C-reactive protein was less than 0.6 (normal 0–8) mg/L, and the leukocyte count was 8.2 (normal 5–12) $\times$ 10^9 cells/L. The patient's hemoglobin and platelet count remained normal.

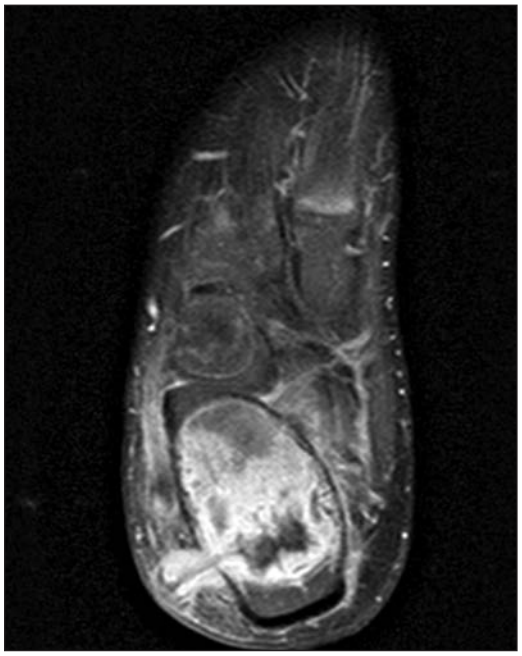

Figure 1: Axial postgadolinium T_1-weighted fat saturated magnetic resonance image of the right heel of a two-year-old boy showing a nonenhancing intraosseous abscess with sinus tract extending to the lateral soft tissues. Phlegmonous changes to the surrounding soft tissue were noted.

After one month of treatment, the patient was no longer able to weight-bear. An MRI showed necrotic areas with sinus tract formation in the posterior aspect of the calcaneus and subcutaneous abscess (Figure 1). The orthopedic service recommended reassessment after application of a stabilizing cast to minimize the risk of fracture and assist in weight-bearing.

After six weeks of treatment, the patient remained afebrile and was weight-bearing on the casted leg. The swelling had improved, but the patient remained tender to palpation over the calcaneus. On further history-taking, the patient had not travelled outside of Canada since his arrival at the age of seven months, had no contact with visitors from abroad and had no sick contacts. A tuberculosis skin test showed no induration at 48 hours.

What is the next step in managing this patient's condition?

a. Repeat laboratory investigations (ESR, C-reactive protein)
b. Repeat MRI or computed tomography
c. Surgical biopsy with débridement
d. Change antimicrobial therapy to target methicillin-resistant *Staphylococcus aureus*
e. Continue current treatment

The patient had not responded to a six-week course of antibiotic therapy directed against the most common cause of pediatric hematogenous osteomyelitis, *Staphylococcus aureus*. The presentation with two weeks of symptoms without fever suggests subacute osteomyelitis.[1] Although a delay in diagnosis can occur in acute calcaneal osteomyelitis, improvement should have occurred after six weeks of therapy.[2] Slight improvement in swelling and weight-bearing

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after cast immobilization is not reassuring because of the ongoing tenderness to palpation. At this point, surgical intervention (c) is required to assess for other pathogens, including community-acquired methicillin-resistant *Staphylococcus aureus*, and to rule out other disease processes such as eosinophilic granuloma or tumour. In addition, drainage of abscesses and débridement of dead bone may aid healing.[1]

The child underwent surgical débridement and curettage of the calcaneus. Intraoperatively, copious amounts of gelatinous tissue emanated from the calcaneus, atypical for pyogenic osteomyelitis. Pathology of the material showed chronic necrotizing granulomatous inflammation (Figures 2 and 3), which was negative for acid-fast bacilli on Ziehl–Neelsen staining.

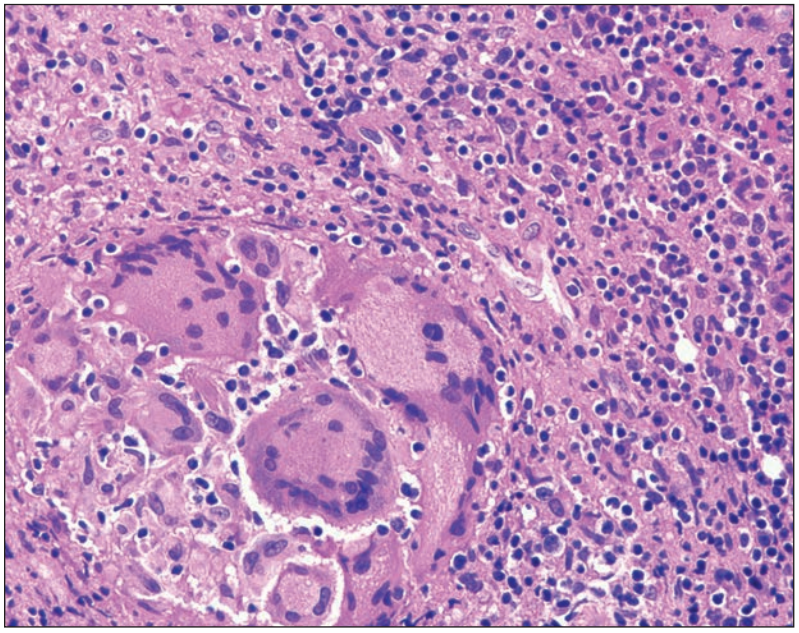

Figure 2: Bone biopsy sample shows an aggregate of Langhans giant cells (hematoxylin and eosin, original magnification × 100).

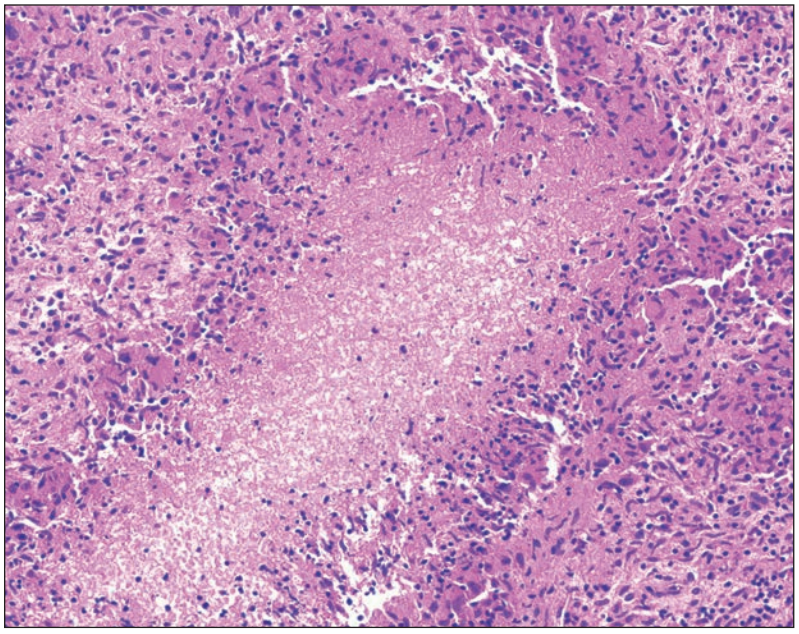

Figure 3: Bone biopsy sample showing a necrotizing granuloma (hematoxylin and eosin, original magnification × 50).

Which diagnosis can be ruled out with the most certainty?

a. *Mycobacterium tuberculosis* complex osteomyelitis
b. Fungal osteomyelitis
c. Langerhans cell histiocytosis
d. Sever disease (calcaneal traction apophysitis)
e. Chronic regional multifocal osteomyelitis

Granulomatous inflammation is seen with mycobacterial and fungal infection, but the differential diagnosis also includes noninfectious causes such as sarcoidosis and malignant growths (including Langerhans cell histiocytosis [c]).[3]

Chronic recurrent multifocal osteomyelitis, an autoinflammatory osteopathy, is characterized by the insidious onset of pain with swelling and tenderness. The metaphyses and epiphyses of long bones are often affected. Imaging shows bone edema, lytic areas and periosteal and soft tissue reaction. Biopsies show polymorphonuclear leukocytes with osteoclasts and necrosis in the early stages, followed by lymphocyte and plasma cell infiltration.[4]

Although a frequent cause of heel pain in children is Sever disease or calcaneal traction apophysitis (d), this condition can be ruled out. This condition usually presents in children 8–15 years of age, and the inflammation is mainly seen in soft tissue and tendons. Clinically important abnormal findings on radiography and MRI do not occur.[5]

In our patient, the gelatinous material from the calcaneus was negative for acid-fast bacilli on staining, but polymerase chain reaction testing and culture showed mycobacterial tuberculosis complex.

The child and his parents had normal chest radiographs and negative results on skin tests for tuberculosis. The parents reported that their son had received the bacille Calmette–Guerin (BCG) vaccine when he was three days old. The mycobacterial tuberculosis complex includes *Mycobacterium tuberculosis* and *Mycobacterium bovis*, from which BCG is derived. The BCG vaccine is used to reduce hematogenous spread of *M. tuberculosis* from the site of primary infection.[6] Because pediatric mycobacterial infections are typically paucibacillary, tissue samples can be acid-fast negative on staining.

The patient was started on empiric treatment

with isoniazid, rifampin, ethambutol and pyrazinamide until the antimicrobial sensitivities returned, which showed pyrazinamide resistance. *Mycobacterium bovis* is intrinsically resistant to pyrazinamide because the organism does not produce pyrazinamidase, the enzyme required to convert the compound to its active form.[7] Pyrazinamide resistance can often be an early clue of *Mycobacterium bovis* BCG infection.

The final speciation showed *Mycobacterium bovis* BCG. Treatment with pyrazinamide was stopped and levofloxacin was started. Our patient underwent testing for immunodeficiency with negative HIV serology, normal lymphocyte proliferation by mitogen stimulation and normal serum immunoglobulins, including vaccine-related antibody levels.

Treatment was continued with rifampin and isoniazid, and our patient continued to show a clinical response. Ethambutol was stopped after three months and levofloxacin after seven months. The patient completed 12 months of therapy, and radiography has shown resolution of his condition. At his last clinical visit, his physical examination was normal. A radiograph 14 months after the end of treatment shows stable bone density and evidence of healing of the calcaneus. The patient was followed for 18 months after completing therapy and remains well.

Discussion

The BCG vaccine was first used for immunization in 1921,[8] and about 100 million children receive it each year.[9] Complications related to the vaccine include local and disseminated abscesses, lymphadenitis and osteomyelitis. Such complications are estimated to occur in 3.3% of vaccine recipients and generally appear six to nine months after vaccination.[10]

Disseminated BCG infection is uncommon, occurring in one per million vaccinations, and is associated with severe abnormalities in cell-mediated immunity.[11] In Canada, BCG is given to infants in communities with an average annual rate of culture-positive pulmonary tuberculosis greater than 30 per 100 000; this has generally applied to some First Nations communities. Between 1993 and 2002, 21 BCG vaccine–related adverse events were reported in Canada. These included six patients with disseminated BCG, two patients with osteomyelitis, eight patients with BCG abscess and four patients with lymphadenitis.[8] The rate of disseminated BCG among First Nations children was much higher than the highest global rates, probably because of the high prevalence of severe combined immunodeficiency in this population.[8]

BCG osteomyelitis

The reported international frequency of BCG osteomyelitis is variable; the International Union Against Tuberculosis and Lung Disease reports 0.39 cases per million vaccinations.[12] Risk factors include strain and dose of BCG. Local reactogenicity differs between vaccines based on the strain and the number of viable bacilli. Pathogenesis has been attributed to local, hematogenous or lymphatic spread.[11]

As with our patient, the clinical presentation of BCG osteomyelitis is usually nonspecific and insidious. The diagnosis is often only entertained after failure of routine antibiotic therapy for bacterial osteomyelitis.

The condition usually affects the peripheral skeleton, but can involve the vertebrae, ribs, sternum and clavicle. The largest review of cases of BCG osteomyelitis from Finland found that a minority of cases were multifocal (4%), and these cases were more likely to be associated with an underlying immune defect.[11] The most common sites were the metaphysis and epiphysis of long bones. The leg was often implicated (58% of patients).[11] Musculoskeletal tuberculosis differs from BCG osteomyelitis; the former has a predilection for the spine and weight-bearing joints and occurs in school-aged children and adolescents.

The onset of symptoms is typically one year after vaccination (range 0.3–5 yr) (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140989/-/DC1). Kroger and colleagues described a longer incubation period (1.5 [range 0.25–5.7] yr) in children who received the vaccine at birth compared with those who received it at two years of age ($p < 0.05$).[11]

Diagnosis

Inflammatory markers (ESR, C-reactive protein) are usually mildly elevated, and radiographic changes are nonspecific. The "typical" radiographic picture of BCG osteomyelitis includes a well-demarcated destruction, usually located eccentrically in the metaphysis (sometimes in the epiphysis), a breakthrough of the cortex and no or slight spread of the lesion along the shaft, with scarce periosteal reaction.[13]

In seven published case series, surgical biopsy was performed in all but 1 of the 287 patients (Appendix 1). Substantial variability in investigations done to confirm the diagnosis occurred. Cultures were positive in 135 (47%) cases, and pathology was suggestive in 238 (83%) cases. Histopathology shows chronic inflammatory changes and caseating necrotizing granulomas, but does not discriminate between mycobacterial species. Skin tests for tuberculosis were positive in 120 (42%) cases (Appendix 1).

Culture, and more recently polymerase chain reaction testing, have been used to diagnose *M. bovis* BCG. The sensitivity pattern can provide an early clue to identify *Mycobacterium bovis,* because it is always pyrazinamide-resistant.

Immune status

The immune status of the patient must be considered. Our patient did not undergo testing for interferon γ receptor 1 (IFNGR1) and interleukin-12 specific defects, which are known risk factors for BCG osteomyelitis. A small case series from Japan described six children with BCG osteomyelitis, three of whom were found to have partial IFNGR1 mutations. The three children with partial mutations had multiple lesions, and two had recurrence of osteomyelitis.[14] Most patients with isolated BCG osteomyelitis do not have serious underlying immune deficiencies.

Treatment

Once initial pathologic and microbiologic results suggest mycobacterial infection, directed therapy can commence. We started four-drug combination therapy for presumed *Mycobacterium tuberculosis* infection. Given the sensitivity pattern of the organism, we opted to substitute levofloxacin for pyrazinamide.

We are aware of no randomized trials, and there is limited observational evidence, for an optimal treatment regimen in BCG osteomyelitis. Drug combinations have included isoniazid, rifampin and a third drug such as streptomycin or para-amino salicylic acid; 3 of the 287 cases described in the literature received fewer than three effective drugs (Appendix 1). A two-drug consolidation phase can be started later, after ongoing improvement is seen. The optimal duration of therapy is not clearly delineated; most series have used between 6 and 12 months of therapy (Appendix 1).

Most cases in the case series included surgical biopsy with débridement at diagnosis (Appendix 1). Surgical intervention allows for removal of necrotic tissue and drainage of abscess material, which improves antibiotic penetration.[13]

Complications

Complications are described in 3%–5% of cases, including fistulae, abscess formation and the need for further surgical intervention. Relapses have been described in 2% of cases.[11] No definite association between duration, drug regimen and complication rate has been determined.

Conclusion

Osteomyelitis is an uncommon complication of the BCG vaccine. Clinicians should consider the diagnosis when a child presents with osteomyelitis that does not respond to conventional antimicrobial therapy, especially within one to two years of receiving the BCG vaccine. A sensitivity pattern showing pyrazinamide resistance can provide a clue to the cause. Most BCG osteomyelitis shows favourable prognosis with orally administered antituberculosis chemotherapy, but surgical débridement may be necessary. Further study is required to identify the optimal therapy to prevent relapse and complications.

References

1. Peltola H, Paakkonen M. Acute osteomyelitis in children. *N Engl J Med* 2014;370:352-60.
2. Jaakkola J, Kehl D. Hematogenous calcaneal osteomyelitis in children. *J Pediatr Orthop* 1999;19:699-704.
3. Brackers de Hugo L, French M, Broussolle C, et al. Granulomatous lesions in bone marrow: clinicopathologic findings and significance in a study of 48 cases. *Eur J Intern Med* 2013;24:468-73.
4. Roderick MR, Ramanan AV. Chronic recurrent multifocal osteomyelitis. *Adv Exp Med Biol* 2013;764:99-107.
5. Hussain S, Hussain K, Hussain S, et al. Sever's disease: a common cause of paediatric heel pain. *BMJ Case Rep* 2013;2013.
6. Canada communicable disease report. Statement on Bacille Calmette Guérin (BCG) vaccine. Ottawa: Public Health Agency of Canada; 2004. Available: www.phac-aspc.gc.ca/publicat/ccdr-rmtc/04vol30/acs-dcc-5/index-eng.php (accessed 2014 July 3).
7. Raynaud C, Laneelle M, Senaratne RH, et al. Mechanisms of pyrazinamide resistance in mycobacteria: importance of lack of uptake in addition to lack of pyrazinamidase activity. *Microbiology* 1999;145:1359-67.
8. Deeks SL, Clark M, Scheifele DW, et al. Serious adverse events associated with Bacille Calmette–Guérin vaccine in Canada. *Pediatr Infect Dis J* 2005;24:538-41.
9. Trunz BB, Fine PEM, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and military tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006;367:1173-80.
10. Ahn HY, Kim YD, Jeon SE, et al. Parasternal mass revealing as a postvaccinal Bacillus Calmette–Guérin (BCG)-elicited sternal osteomyelitis. *Thorac Cardiovasc Surg* 2014;62:258-60.
11. Kröger L, Brander E, Korppi M, et al. Osteitis after newborn vaccination with three different Bacillus Calmette-Guerin vaccines: twenty-nine years of experience. *Pediatr Infect Dis J* 1994;13:113-6.
12. Lotte A, Wasz-Hockert O, Poisson N, et al. Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bull Int Union Tuberc Lung Dis* 1988;63:47-59.
13. 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.
14. Sasaki Y, Nomura A, Kusuhara K, et al. Genetic basis of patients with bacilli Calmette-Guerin osteomyelitis in Japan: identification of dominant partial interferon-gamma receptor 1 deficiency as a predominant type. *J Infect Dis* 2002;185:706-9.

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Contributors: Sarah Khan contributed substantially to the collection of data, review of the literature, analysis and interpretation of the results, drafted the article and contributed to revisions. Jennifer Stimec contributed to the radiologic component of the data and literature, analyzed and interpreted the radiologic findings from the case and acquired the images for publication. Ian Kitai contributed substantially to the conception and design of the manuscript and to the analysis and interpretation of data, helped draft the article and revised it critically for content. All of the authors agree to act as guarantors of the work and gave final approval of the version submitted for publication.

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