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Case report

# A child with acute myeloid leukemia complicated by calcaneal osteomyelitis due to *Mycobacterium abscessus* infection after induction chemotherapy successfully salvaged with bedaquiline and clofazimine☆

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ABSTRACT

Our patient was a 4-year-old female with acute myeloid leukemia complicated with right calcaneal osteomyelitis due to *Mycobacterium abscessus* with subcutaneous abscesses extending to the popliteal and groin regions after two courses of induction chemotherapy according to NOPHO-AML 2012 protocol. She required multiple operations and prolonged anti-mycobacterial therapy. A high index of suspicion for mycobacterial infection is required for immunocompromised patients with prolonged fever or unusual presentation. Mycobacterial osteomyelitis is rare, difficult to diagnose and treat, and may necessitate prolonged interruption of anti-leukemic therapy. Multidisciplinary collaboration in patient management is crucial. Long-term toxicity of antimicrobials with uncertain efficacy should not be overlooked.


## Introduction

Infection is often encountered during induction chemotherapy for acute leukemia. Severe bone and soft tissue infection due to non-tuberculous mycobacteria (NTM) is possible but rare. Here we report a case of acute myeloid leukemia (AML) complicated with right calcaneal osteomyelitis due to *Mycobacterium abscessus* with subcutaneous abscesses extending to popliteal and groin regions requiring multiple operations and prolonged anti-mycobacterial therapy.

## Case report

Our case was a 4-year old female with t(8;21) AML and central nervous system involvement was treated with NOPHO-AML 2012 protocol (Jonas, 2020). Four days after completion of a second-course of induction chemotherapy, she developed neutropenic fever and experienced fluctuating right knee, hip, and ankle pain for 4 weeks (Graphical abstract). Magnetic resonance imaging (MRI) of the right lower limb revealed multiple abscesses over the right groin and popliteal region with calcaneal osteomyelitis and subcutaneous edema (Figure 1A and B). Ultrasound-guided aspiration and biopsy yielded granulomas with surrounding suppurative inflammation (Figure 1C). A smear of joint fluid was positive for acid-fast bacilli (AFB), while polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* was negative. The patient was treated with intravenous (IV) daptomycin, meropenem, levofloxacin, and amikacin while awaiting identity and sensitivity testing

*Abbreviations:* AFB, Acid-fast bacilli; AML, Acute myeloid leukemia; CT, Computed tomography; HSCT, Hematopoietic stem cell transplantation; I&D, Incision and drainage; IFN-γ, Interferon-gamma; IV, Intravenous; LN, Lymph node; MRD, Minimal residual disease; MRI, Magnetic resonance imaging; MTBC, *Mycobacterium tuberculosis* complex; NTM, Non-tuberculous mycobacteria; PET, Positive emission tomography.

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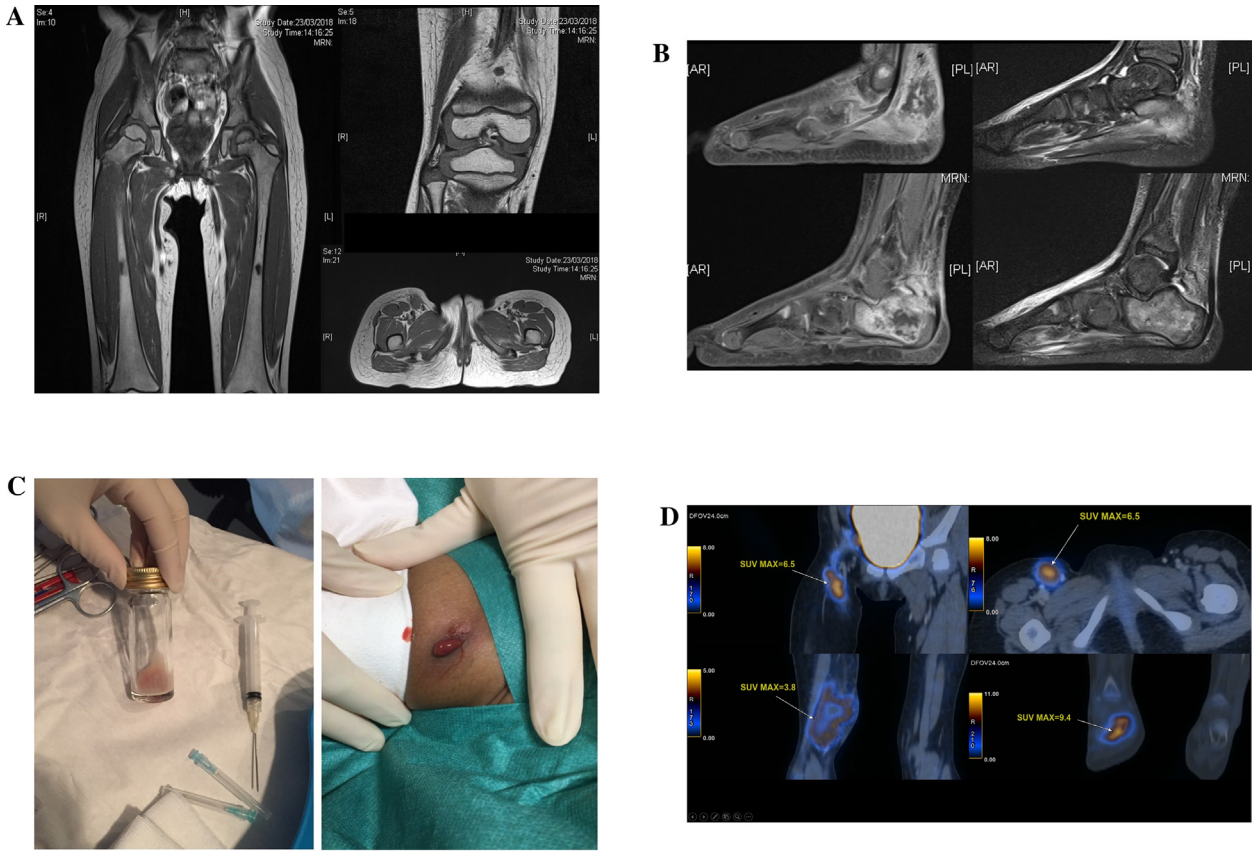


**Figure 1.** (A) MRI of bilateral hips and thigh showing bilateral shotty groin LNs accompanied with subcutaneous edema over right upper medial thigh and posterior distal thigh. (B) MRI of right ankle showing T1 hypointense and T2 hyperintense signals at right talus, right distal tibia, right third proximal metatarsal, right distal fibula, right calcaneus, and right posterior ankle. (C) Suppurative aspirate obtained by ultrasound-guided aspiration of the right groin abscess. (D) PET-CT 12 days after the first operation showing abscesses in the right posterior thigh and popliteal fossa ($SUV_{max}$ 3.8), right calcaneal osteomyelitis ($SUV_{max}$ 9.4), as well as multiple hypermetabolic LN at the right groin ($SUV_{max}$ 6.5) extending to the right internal iliac LN.

of mycobacteria. Incision and drainage (I&D), calcaneal bone excision, and right ankle debridement were performed followed by IV amikacin, oral clarithromycin, oral levofloxacin, and oral ethambutol (given 1 week and then stopped after the identity of the NTM was revealed). Histology of excised calcaneum confirmed osteomyelitis, while culture of bone and pus grew *M. abscessus*. Susceptibility testing of the *M. abscessus* isolate was determined using the broth microdilution method. The results were interpreted according to the Clinical and Laboratory Standards Institute. The isolate was susceptible to amikacin and trimethoprim-sulfamethoxazole, intermediate to cefoxitin, imipenem, linezolid, and resistant to ciprofloxacin, doxycycline, and moxifloxacin. The isolate was susceptible to clarithromycin on initial testing but inducible resistance was demonstrated after incubation for 14 days. Antimicrobials were thus switched to oral trimethoprim-sulfamethoxazole (with trimethoprim dosage 10 mg/kg/day), oral clarithromycin, IV imipenem-cilastatin (later switched to IV cefoxitin), IV amikacin, and thrice weekly interferon-gamma (IFN-γ). Retrospectively, the mother suspected that the child might have sustained an external injury to the foot due to a tight-fitting shoe.

Despite the initial clinical response, the patient developed another abscess at the right posterior thigh 12 days after the first operation as confirmed by positive emission tomography-computed tomography (PET-CT) (Figure 1D). A second operation was performed 3 weeks after the first operation, and I&D of the right groin and popliteal abscesses along with debridement of the right ankle soft tissue were achieved. Pus from the posterior thigh grew *M. abscessus*. When fever subsided for 48 hours with absolute neutrophil count (ANC) normalized ($2.54 \times 10^9$/L), a single dose of intrathecal cytarabine 40 mg was administered, followed by daily oral thioguanine 120 mg/m$^2$/day and IV cytarabine 75 mg/m$^2$/dose daily on Days 1–4 and 15–18 of the 4-weekly cycle. Chemotherapy was prematurely stopped on Day 18 due to worsening of the infection, which necessitated a third operation 4 weeks after the second operation, involving sequestrectomy of right calcaneus and insertion of antibiotic-infused cement (vancomycin, amikacin, and gentamycin). Subsequent consolidation chemotherapy could not be given due to a high risk of infection-related death. Disease status was then monitored with 4-weekly quantitative PCR and an 8-weekly marrow exam. The child then developed a drug-related rash and hepatitis with highest alanine aminotransferase and aspartate aminotransferase above 1500 IU/L. The rash subsided and liver function improved after stopping all antimicrobials. Bedaquiline (100 mg thrice weekly) and clofazimine (50 mg twice weekly) were introduced as salvage therapy for NTM infection at 18 days after the third operation. Antibiotic-infused cement was kept for 7 months before removal and bone graft insertion. Perioperatively, the patient was covered with a 1-week course of IV amikacin and imipenem-cilastatin. Intra-operative cultures did not yield any aerobic, anaerobic bacteria, fungi, or AFB. Histology showed granulomatous inflammation with no evidence of AFB or fungi. The bone graft donor site and right calcaneal wounds healed well with stitches removed on post-operative Day 11 and non-weight bearing for 6 weeks post-operatively. Bedaquiline and clofazimine were continued for 4 more weeks post-operatively and then stopped. Total duration of usage of bedaquiline and clofazimine was 8 months. Apart from a mild prolongation of

corrected QT interval from 450 to 470 ms during initiation of medication, the patient did not suffer any adverse effects. Serial electrocardiograms and echocardiograms showed normal cardiac anatomy and function. Serial audiograms also reported normal hearing despite courses of prolonged amikacin. At that stage it had been 22 months since the removal of the antibiotic-infused cement. Limb function was preserved with no problem in walking and daily activities. For disease control, the patient was followed up for 29 months since the last chemotherapy given (33 months from initial diagnosis) and remained in clinical and hematological remission. Minimal residual disease (MRD) was persistently negative <0.1%. There has been no relapse so far for 2 years.

## Discussion

### *Predisposition to NTM infections*

*Mycobacterium abscessus* is an environmental rapidly-growing mycobacteria pathogenic to humans. Clinical manifestations include pneumonia (Martinez et al., 2007; Wolfe et al., 2000), lymphadenitis (Chetchotisakd et al., 2000; Springer et al., 1993), skin and soft tissue infections (Wallace et al., 1992), intra-vascular catheter-related infections, systemic bacteremia, and peritonitis (Vera and Lew, 1999). Hemic malignancy and cytotoxic therapy impair cell-mediated immunity (Wallace et al., 1992; Snydman et al., 2010), which is the major protective immune response against intracellular bacteria (Griffith et al., 2015; Tortoli et al., 2016), and thus predisposes patients to NTM infections. Because NTM infection post-induction is possible but rare, and a local single-institution retrospective review demonstrated nearly all pediatric patients with NTM infection had an underlying congenital or acquired immunodeficiency (Chan et al., 2020), it was postulated that the child reported here might have an underlying congenital immune defect along the macrophage/interleukin-12/IFN-γ pathway apart from acquired immunodeficiency due to hemic malignancy and cytotoxic therapy (Chan et al., 2020).

### *Dilemma between disease and infection control*

The outcome of pediatric AML is generally fair with an overall survival around 70% and a relapse rate of 30–40% after primary treatment. Premature termination of chemotherapy without consolidation presumably increases relapse risk but further administration of high dose chemotherapy might result in uncontrolled disseminated NTM infection, limb amputation, or even death. Hence the option of allogeneic hematopoietic stem cell transplantation (HSCT) had been explored and discussed. Potential benefits of HSCT include graft-versus-leukemia effect which lowers the risk of disease relapse and allows reconstitution of healthy cellular immunity against mycobacterial infection. A major drawback is an ultra-high infection and mortality risk even with non-myeloablative reduced intensity conditioning or a mini-transplant. After multidisciplinary discussion among pediatric oncologists, microbiologists, and orthopedic surgeons together with the parents and the child, it was finally decided to control the infection first and consider HSCT in the case of disease relapse.

### *Challenges in management of NTM infection*

Surgical debridement is the mainstay for the treatment for bone and soft tissue infection (Sizaire et al., 2006) followed by prolonged anti-mycobacterial treatment for at least 6–12 months (Bermudez et al., 2003). Drug-related toxicities and development of drug resistance may be encountered. In the case of our patient, antibiotics had to be stopped due to a drug-related rash and liver toxicity. In view of the need to continue treatment for months, administration of drugs (e.g. trimethoprim-sulfamethoxazole) with good oral bioavailability by the oral route is required (Daley et al., 2020). Because experience with usage, efficacy, and the safety profile of bedaquiline and clofazimine as salvage therapy in the pediatric population is limited in the literature (Harausz et al., 2017), close monitoring of the potential side effects and drug interactions is crucial.

## Conclusion

A high index of suspicion for mycobacterial infection is required for immunocompromised patients with prolonged fever or unusual presentation. Mycobacterial osteomyelitis is rare, difficult to diagnose and treat, and may necessitate prolonged interruption of anti-leukemic therapy. Multidisciplinary collaboration in patient management is crucial. Toxicity due to long-term use of antimicrobials should not be overlooked.

## Conflict of interest

The authors report no conflict of interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Ethical approval

Informed consent had been properly obtained and documented for clinical photographs and radiological imaging used for demonstration in this manuscript. Identifiers on patient identity had been obscured prior to review.

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