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Case report

Infective intracardiac lesion in the setting of Mycobacterium franklinii bacteremia identified by cell-free DNA sequencing in a child with acute lymphoblastic leukemia: A potential new foe in intracardiac infections

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ABSTRACT

Mycobacterium franklinii (Mfra) is a recently identified member of the Mycobacterium chelonae-abscessus complex (MCAC), a rapidly growing, acid-fast bacilli that have the potential to cause invasive human infections. Identification of Mfra is crucial for selecting the appropriate antimicrobial therapy, as Mfra displays a unique susceptibility profile compared to other MCAC members. The literature on Mfra is limited, with a few studies focusing on respiratory and skin infections. To our knowledge, we describe the first reported case of cardiac involvement associated with Mfra bacteremia in a patient with acute lymphoblastic leukemia. The isolation of Mfra through a next-generation sequencing test allowed for prompt identification and subsequent implementation of tailored antimicrobial agents, ultimately resulting in positive clinical outcomes. This case also emphasizes the significance of next-generation testing in managing immunocompromised patients with persistent fever.

Case description

We report a 3-year-old female with a history of high-risk pre-B cell acute lymphoblastic leukemia (ALL) who was admitted for management of low-grade fever, cough, and shoulder pain. The patient had been recently admitted for Haemophilus influenzae sepsis, candidemia detected through a Karius (microbial cell-free DNA sequencing test), and mucositis with oral cultures positive for Streptococcus mitis and Prevotella. After completion of intravenous (IV) antibiotics, the patient was discharged home on fluconazole and continued consolidation chemotherapy. During the current admission, there were no concerning findings on the physical exam. Labs were significant for normal absolute neutrophil count and elevated C-reactive protein (CRP) of 24.9 mg/dl (normal reference range: 0–1 mg/dl).

Given the patient's medical history, broad coverage with cefepime and fluconazole was initiated. A chest CT scan with contrast revealed worsening nodular opacities and lesions in the spleen and liver, raising concern for disseminated disease. These findings prompted a transition in antifungal coverage to voriconazole and amphotericin. Cultures obtained from Bronchoalveolar Lavage (BAL) grew 10,000 colony-forming units (CFUs) of Streptococcus mitis and 1000 CFUs of Rothia spp. Karius revealed a decrease in Candida albicans from 8370–288 molecules per microliter (MPMs) but also demonstrated Mycobacteriodes franklinii at 102 MPMs. While awaiting further classification of cultures, antimicrobial coverage was shifted to include micafungin for coverage of Candida albicans and linezolid, azithromycin, and amikacin for atypical mycobacteria coverage. Linezolid also provided coverage for streptococcus mitis. Due to the presence of a Mediport and disseminated infection, an echocardiogram was obtained that showed a right atrial mass measuring 10 × 13 mm without valvular involvement (Image 1). Notably, a baseline echocardiogram performed one month prior did not detect any intracardiac masses. As the source of the right atrial mass was unclear, the port was removed. The patient was started on therapeutic enoxaparin for anticoagulation.

The BAL mycobacterial and acid-fast bacilli (AFB) stain results were positive, but sensitivities were unavailable before discharge. To decrease

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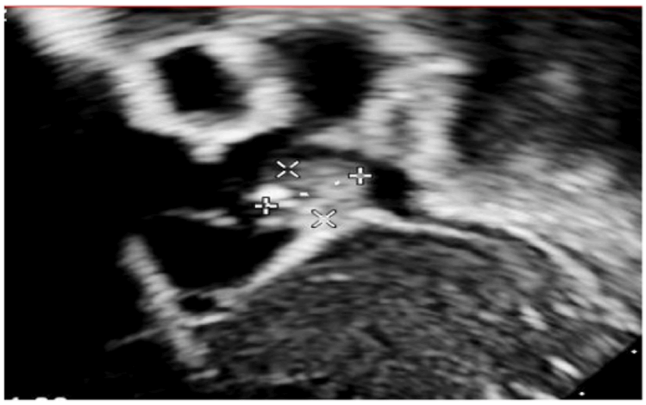

Image 1. Pre-treatment subcostal view of transthoracic echocardiography showing a 10 × 13 mm mass in the right atrium at the time of the diagnosis.

incidence of severe myelosuppression in light of the multiple systemic infections, the leukemia therapy was transitioned to immunotherapy with Blinatumomab for continued treatment of Pre-B ALL. A repeat chest CT prior to discharge was remarkable for improved pulmonary opacities and improved number, and size of hepatic and splenic lesions. After 36 days of hospitalization, the patient was discharged home on IV amikacin, oral fluconazole, oral linezolid, oral azithromycin, and rivaroxaban. Three months later, the patient underwent a repeat echocardiogram, which showed a decrease in mass size to 8.19 × 8.14 mm (Image 2).

The patient has been closely followed by the infectious disease outpatient team and has been noted to be doing well clinically, with some fluctuations in inflammatory markers but overall improving. The AFB test from the BAL specimen was positive for Mycobacterium abscessus complex, and the sensitivities, as shown in Table 1, allowed for the transition to sulfamethoxazole-trimethoprim. Currently, the patient continues on sulfamethoxazole-trimethoprim, azithromycin, fluconazole, and Blinatumomab, with plans for interval echocardiogram and CT to monitor the resolution of the disease and determine the eventual duration of treatment.

Discussion, literature review

The Mycobacterium cheloanae-abscessus complex (MCAC) is a group of non-tuberculous mycobacterium known to cause serious infections. A newly characterized member of this group, Mycobacterium franklinii (Mfra), was described in 2011 by Simmon et al. [1]. This organism was named after Benjamin Franklin, the founder of the University of Pennsylvania. Mfra is considered difficult to isolate due to its indistinguishable features from other MCAC members, including rapidly growing acid-fast bacilli and similar 16 S rRNA gene sequences at the molecular levels [2]. Simmon et al. isolated Mfra using DNA-DNA hybridization analysis due to higher divergence than other MCAC [1]. Further, Mfra can be differentiated from other MCAC by its susceptibility or intermediate susceptibility to cefoxitin. Therefore, it is crucial to recognize Mfra as a distinct pathogen in order to choose antimicrobial agents correctly. Clinically, Mfra has been reported to cause invasive infection in patients with chronic lung disease, catheter-associated infection, and chronic rhinosinusitis [1]. It has also been associated with skin and soft tissue infections, particularly those secondary to tattoos [3]. A recent study isolated Mfra in five Taiwanese patients with lung cancer; although it was not reported to cause invasive infection, it was instead considered a potential lung cancerogenic [4]. In our patient, Mfra was identified using a new-commercially available microbial cell-free DNA sequencing test known as Karius. This test utilizes next-generation sequencing technology of plasma samples to detect 1250 different types of bacteria, viruses, and fungi, making it a valuable diagnostic modality of invasive infection [5]. Karius utilization in our case resulted in faster Mfra detection compared to conventional acid-fast culture, which typically requires weeks to produce results.

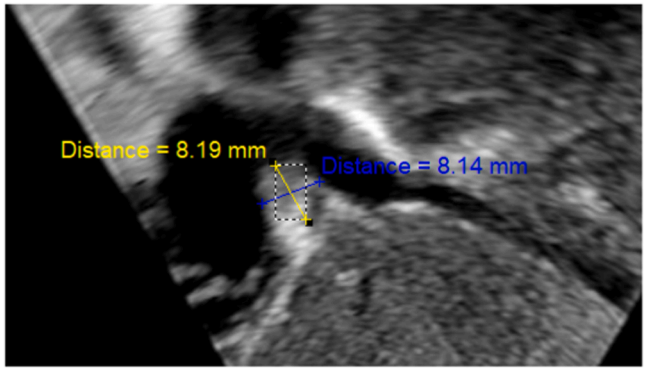

Image 2. Subcostal view of Transthoracic echocardiography showing an 8.19 × 8.14 mm right atrial mass after three months of treatment.

Table 1
Antibiotic sensitivity panel for Mycobacterium franklinii.

Antibiotics	Sensitivity	MIC
Cefoxitin	Intermediate	= 32
Imipenem	Intermediate	= 8
Clofazimine	NA	= 0.06
Ciprofloxacin	Resistant	> 4
Moxifloxacin	Susceptible	= 1
Tobramycin	Resistant	> 16
Doxycycline	Resistant	= 8
Tigecycline	NA	0.12
TMP/SMX	Susceptible	= 2/38
Linezolid	Susceptible	< =1
Clarithromycin	Susceptible	1

Echocardiography was obtained to evaluate the persistent fever, revealing the presence of a non-mobile broad-based mass in the right atrium. This finding raised suspicion for infective endocarditis but did not meet the modified Duke criteria [6].

There are no dedicated guidelines for managing patients with this particular mass. Therefore, a multidisciplinary discussion was conducted that included oncology, infectious disease, cardiology, and cardiothoracic surgery teams. The agreement was to pursue medical management as the mass was not causing hemodynamic instability. The regimen included Amikacin and Azithromycin to cover for Mfra and Linezolid to cover the Streptococcus mitis oralis. Part of the reasoning for the antibiotic choice included two case reports demonstrating a good clinical response to macrolides, Clarithromycin combined with Doxycycline for treating soft-tissue infections [3] [7].

The mass intermittently touched the tip of the central catheter (Mediport), raising concerns about thrombus formation. The mass remained unchanged following the central catheter removal, raising suspicion of infective intracardiac thrombus. Therefore, anticoagulation with Enoxaparin was initiated at a therapeutic level.

Despite being on appropriate antimicrobial coverage for Streptococcus mitis oralis and Candida albicans, the patient remained febrile until amikacin and azithromycin were added to the treatment regimen, resulting in fever resolution and improvement in the inflammatory markers. Additionally, the two-week follow-up echocardiography showed an interval decrease in mass size. This further supports the theory that Mfra was likely the causative organism, although this could not be confirmed without a biopsy of the mass.

We conducted a literature review to identify published studies on Mfra as a causative organism of human infection. The search was performed using PubMed and Google Scholar, with the time frame from the databases' inception to January 2023. Four studies were identified, comprising a total of 33 patients, as presented in Table 2. Few case

Table 2
Summary of the published literature on patients with Mycobacterium franklinii (N = 33).

Ref	Journal	No pts	Diagnostic tool	Clinical presentation	Antibiotic used
[7]	International Journal of Dermatology	1	RNA Polymerase B gene sequencing	Skin rash associated with Tattoos	Clarithromycin and Doxycycline
[3]	Clinical Research in Dermatology	1	RNA Polymerase B gene sequencing	Skin rash associated with Tattoos	Clarithromycin and Doxycycline
[1]	Emerging infectious Diseases	26	Sequencing: ITS region (between 16 S and 23 S rRNA genes), *hsp65*, *rpoB*, and *sodA* genes complete 16 S rRNA gene sequence analysis in conjunction with cefoxitin and minocycline susceptibility patterns.	20: patients with lower respiratory tract disease[ABC] 2: patients with skin infection 1: patient with granulomatous liver lesion[D] 2: patients with central line infection and sinusitis[E]	[A] Cefepime [B] Fluoroquinolones [c] Azithromycin, ethambutol and rifampin [D] Clindamycin, ceftazidime [E]Levofloxacin, cefoxitin, clarithromycin
[4]	Genes	5	By the following: SAMSA2 and Kraken2, SAMSA2 and 16 S rRNA sequencing, or the by Kraken2 and 16 S rRNA	Lung cancer	Not reported

reports have been published on the clinical presentation of Mfra, with most focusing on respiratory illness. To our knowledge, this is the first report of Mfra with cardiac involvement. Additionally, our case highlights the clinical utility of Karius for identifying Mfra.

Conclusion

The present case report describes a child with acute lymphoblastic leukemia who developed a persistent fever and was subsequently found to have Mfra in the setting of an intracardiac lesion. We highlighted the utility of next-generation sequencing testing to promptly identify Mfra and its positive impact on managing an immunocompromised patient.

Ethical approval

None.

Consent

Written informed consent was obtainedfrom the patient for publication of this case report andaccompanying images.

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CRediT authorship contribution statement

Khalifah A. Aldawsari: Literature review, consent obtaining, manuscript writing and submission. **Evelina Dedic:** Literature review, manuscript writing. **Braden Olsen:** Literature review, manuscript writing. **Haneen Y Abdella:** Manuscript review and editing. **Manuel R Cotilla:** Manuscript review and editing. **Danyal M Khan:** Obtaining figures, manuscript review, writing and editing.

Declaration of Competing Interest

All authors disclose no conflicts of interest.

Acknowledgments

Not applicable.

Consent

The consent from the patient's legal guardian was obtained.

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