A Case of Disseminated *Mycobacterium Haemophilum* in a Kidney Transplant Recipient Presenting With Subcutaneous Nodules

Xin Ran Li, MD; Devesh Kumar, MD; Amber Y. Bo, MD; Jenna T. Le, BS; Ariana Ellis, MD; Kara Young, MD; Karolyn A. Wanat, MD; Mohan Dhariwal, DO; Pinky Jha, MD; Jaime Green, MD; Sol Aldrete, MD

ABSTRACT

Introduction: Dermatologic manifestations of diseases in solid organ transplant recipients are common due to long-term immunosuppression.

Case Presentation: We present the case of a 63-year-old man with a kidney transplant who exhibited subcutaneous nodules on lower extremities, cytopenia, and asymptomatic pulmonary infiltrate. Through a skin biopsy and 16S ribosomal RNA (rRNA) sequencing, *Mycobacterium haemophilum* was identified. His clinical course was complicated by empyema, septic arthritis, and recurrence of his skin manifestations, despite ongoing antimicrobial treatment.

Discussion: This case emphasizes the challenges and potential complications associated with *M haemophilum* infections in solid organ transplant recipients receiving long-term immunosuppressive therapy. It highlights the importance of employing advanced diagnostic techniques when evaluating dermatologic manifestations in these patients. The patient's complex clinical course also underscores the difficulties involved in effectively addressing and managing complications that may arise even after initiating therapy.

INTRODUCTION

Lifelong immunosuppression to prevent rejection in solid organ transplant recipients increases the risk of disseminated infections, including viral, bacterial, fungal, and mycobacterial infections. Nontuberculous mycobacteria, such as *Mycobacterium haemophilum*, are emerging infections affecting transplant recipients.[1] We present a case of disseminated infection by *M haemophilum* in a kidney transplant recipient.

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Author Affiliations: School of Medicine, Medical College of Wisconsin (MCW), Milwaukee, Wisconsin (Li, Kumar, Bo, Le); Department of Dermatology, MCW, Milwaukee, Wisconsin (Ellis, Young, Wanat); Department of General Internal Medicine, MCW, Milwaukee, Wisconsin (Dhariwal, Jha); Department of Medicine, Division of Infectious Diseases, MCW, Milwaukee, Wisconsin (Green, Aldrete).

Corresponding Author: Xin Ran Li, MD; email xili@mcw.edu; ORCID ID 0000-0001-9505-2134

CASE PRESENTATION

A 63-year-old White man with a history of end-stage renal disease due to contrast-induced nephropathy received a kidney transplant from a living relative in 2019. The donor and recipient had matching human leukocyte antigen 4/8, with the donor being cytomegalovirus IgG+ and the recipient IgG-. Additionally, the donor was Epstein-Barr virus IgG+ and the recipient IgG+. The patient was initially treated with basiliximab for induction and was maintained on mycophenolate mofetil 1000 mg twice daily, prednisone 5 mg daily, and belatacept 350 mg intravenously every 28 days. He recovered well from the transplant, with stable kidney function and no post-transplant issues, prior infections, or rejection episodes..

Hospitalization 1

The patient was admitted with 2 months of polyarthralgia, malaise, painful subcutaneous nodules, and erythematous rash over the lower extremities. Two weeks prior, he had returned from Hawaii with symptoms of a viral upper respiratory infection, including congestion, nonproductive cough, fatigue, chills, shortness of breath, and diarrhea. He tested negative for COVID-19. He was preparing for a triathlon and had a career in automotive restoration. Physical exam was notable for bilateral hand swelling, bilateral lower extremity pitting edema with erythematous, indurated plaques, and subcutaneous nodules on the lower extremities (Figure 1A, B). Initially, he had been evaluated by rheumatology as an outpatient for his arthralgias with concerns for inflammatory arthritis. His steroids were increased, and his immunosuppression was changed from belatacept to everolimus and a lower dose of

mycophenolate mofetil 500 mg twice a day to avoid over immunosuppression.

At the time of admission, he remained afebrile, comfortable on room air, and hemodynamically stable. Right lower extremity skin biopsies demonstrated suppurative dermatitis and panniculitis with neutrophilic inflammation within the dermis and subcutaneous fat with areas of necrosis, concerning for an infectious process (Figure 2A, B). Acid-fast bacilli (AFB) stain demonstrated numerous organisms (Figure 2C). The skin biopsy was submitted for 16S ribosomal RNA (rRNA) polymerase chain reaction (PCR) to the University of Washington. Concomitantly, computed tomography (CT) chest was notable for ground glass opacities with a respiratory viral panel positive for respiratory syncytial virus. A 5-day course of oral ribavirin was initiated, and everolimus was changed to tacrolimus 1 mg twice daily. Further antimicrobial therapy targeting mycobacteria was held pending further organism identification.

Hospitalization 2

Twenty days after hospital discharge, the patient was readmitted with anemia and concerns for gastrointestinal bleeding. Physical exam revealed extension of subcutaneous nodules to the back, chest, and face (Figure 1C). At this time, the 16S rDNA PCR analysis of the initial biopsy identified *Mycobacterium haemophilum*. Antimicrobial therapy of azithromycin 500 mg daily, ciprofloxacin 500 mg twice daily, and rifabutin 300 mg daily was initiated. Due to worsening thrombocytopenia, a bone marrow biopsy was performed, which revealed a 10% to 20% hypocellular bone marrow, erythroid hypoplasia, and thrombocytopenia, with focal mycobacterial organisms seen on AFB stain and anemia of chronic inflammation on iron stain. Clinically, he was tolerating his antimicrobial therapy and was discharged to a rehabilitation facility in stable condition.

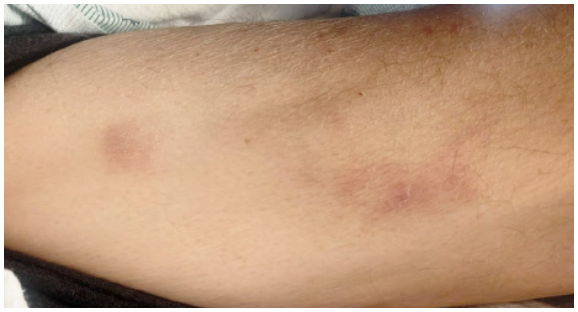
Hospitalization 3

One month after hospital discharge, the patient was readmitted with ongoing generalized weakness and leukocytosis. Further evaluation of a chest x-ray and CT chest revealed a moderate to large right pleural effusion with associated atelectasis, small left effusion, and a rounded opacity in the right lower lobe, although he remained comfortable on room air without hypoxemia, cough, or dyspnea on exertion. Bilateral thoracentesis demonstrated empyema with thoracentesis culture positive for AFBs. Given that he remained asymptomatic from a respiratory standpoint with only 1 month of targeted therapy, the initial 3-drug regimen with conservative management without chest tube placement ensued. Repeat imaging did not demonstrate reaccumulation of the pleural effusion.

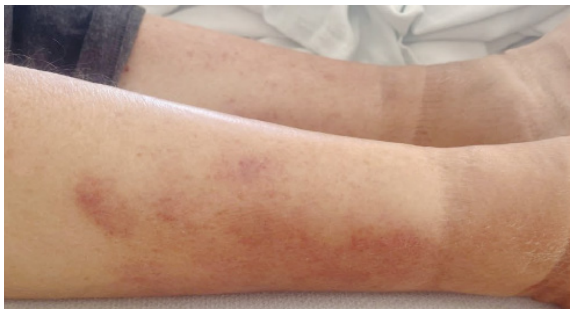
Hospitalization 4

Two months following hospital discharge and after 3 months of targeted antimycobacterial treatment, the patient presented with 1 month of right knee pain and swelling. Synovial fluid stain and culture was positive for AFB, *M haemophilium*, consistent with septic arthritis. Management included arthroscopy with wash out, and clofazimine 100 mg daily was added to his multidrug regimen. Around this time, his initial antimicrobial susceptibilities became available and demonstrated susceptibility to rifabutin, ciprofloxacin, clarithromycin, moxifloxacin, and rifampin, resistance to

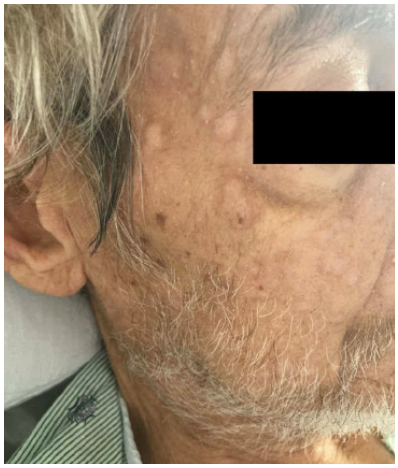
Figure 1. Subcutaneous Nodule Findings



A) Tender, nonulcerated, erythematous, firm subcutaneous nodules (1-2 cm) on right lateral upper thigh. These lesions are localized to the thighs and lower legs, with 1 lesion on the left forearm.



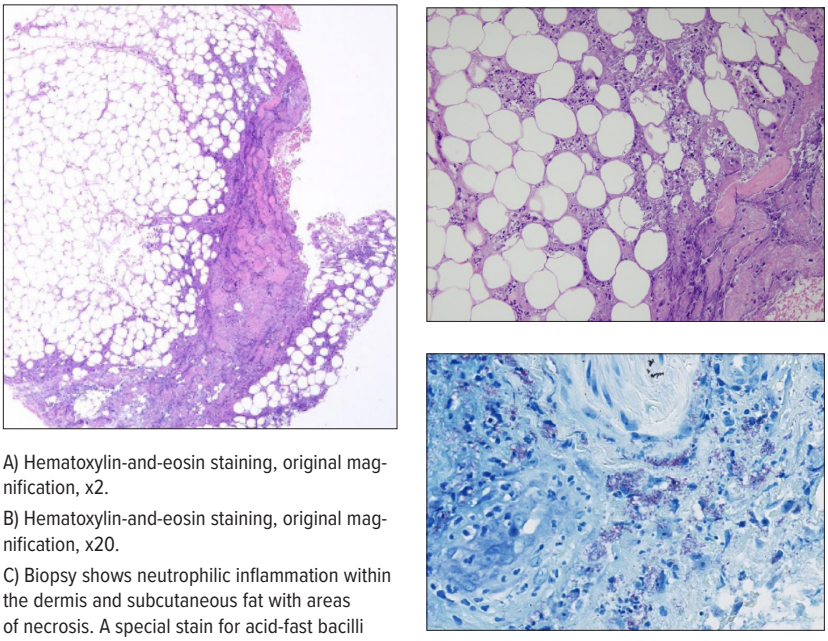
B) Mildly erythematous, firm, indurated nodules, and plaques on the right lateral leg.



C) Subcutaneous nontender nodules found on the face 2 months after the appearance of bilateral lower extremity lesions. The lesions also spread to the chest and back (not pictured).

ethambutol and streptomycin, and intermediate to amikacin. His septic arthritis improved, and he was discharged on a regimen of ciprofloxacin 500 mg twice daily, rifabutin 300 mg daily, azithromycin 500 mg daily, and clofazimine 100 mg daily.

Figure 2. Punch Biopsy From the Right Lower Leg



A) Hematoxylin-and-eosin staining, original magnification, x2.

B) Hematoxylin-and-eosin staining, original magnification, x20.

C) Biopsy shows neutrophilic inflammation within the dermis and subcutaneous fat with areas of necrosis. A special stain for acid-fast bacilli highlights numerous organisms within zones of inflammation.

Hospitalization 5

One month after hospital discharge, the patient presented with a recurrence of skin nodules on bilateral upper extremities consistent with persistent *M haemophilum* infection. To address this, linezolid 600 mg daily was added to his current medication regimen, while mycophenolate mofetil was discontinued. His most recent immunosuppressive regimen included prednisone 5 mg daily and tacrolimus 7 mg twice daily.

Hospitalization 6

One month after being discharged, the patient returned with a 1-week history of numbness and tingling in bilateral upper and lower extremities. This peripheral neuropathy was determined to be a side effect of linezolid, and the medication was discontinued. During his hospital stay, there was a continuous decline in his renal function, which was likely caused by acute cellular rejection due to reduced immunosuppression. Unfortunately, increasing his immunosuppression would potentially exacerbate his infection. He was very clear that he did not wish to go back on hemodialysis and, following multiple multidisciplinary discussions, he expressed willingness to explore end-of-life care options and learn about palliative and hospice services. Upon discharge, he made the decision to transition to home hospice care with the provision of psychological support.

DISCUSSION

Mycobacterium haemophilum, as an emerging pathogen presenting with disseminated disease in immunosuppressed patients, poses challenges in identification and management. Given the immunosuppression experienced by kidney transplant recipients, these patients are particularly vulnerable to illness and infection. Since skin nodules can be caused by various infections, making an accurate diagnosis is crucial for implementing appropriate treatment. This case highlights the challenges in diagnosing nontuberculous mycobacteria infections in immunosuppressed kidney transplant recipients due to limitations of AFB stain and mycobacterial culture methods and the need for more advanced molecular diagnostics.

M haemophilum, or "blood-loving," is a slow-growing AFB with unique preferences for lower growth temperatures and the need for iron supplementation.[2] When AFB-positive smears are unable to identify the organism through AFB stain and mycobacterial cultures, suspicion should arise for *M haemophilum*.[3,4] First described as a pathogen causing skin infections in immunocompromised individuals in 1978 with cases reported worldwide, *M haemophilum*'s habitat and transmission modes remain unknown.[5] It predominantly causes skin and soft tissue infections, septic arthritis, osteomyelitis, and pneumonitis in immunocompromised recipients.[4,6-8] However, these skin lesions often start as painless papules that progress to pustules, deep ulcers, or abscesses, presenting similarly to other nontuberculous mycobacteria.

Disseminated infections caused by nontuberculous mycobacteria, such as *M haemophilum,* often present with nonspecific cutaneous or systemic findings. Our patient presented with polyarthralgias and skin nodules. His joint pain initially was thought to be due to inflammatory arthritis, and his immunosuppression was increased prior to his initial presentation to the hospital. Joint pains and swelling often are misdiagnosed for inflammatory disorders, such as rheumatoid arthritis and bursitis. These symptoms often are seen in an ambulatory setting and are difficult to recognize as potentially due to infectious causes, especially if patients are afebrile and clinically stable. Under these circumstances, recipients may receive steroids for treatment, which can further exacerbate their immunosuppression and promote the spread of infection.

Similarly, the differential of subcutaneous nodules in immuno-

compromised recipients is broad, including noninfectious and infectious etiologies, such as erythema nodosum, panniculitis, medium-vessel vasculitis, and mycobacterial and fungal infections. Skin biopsies and more advanced diagnostic methods might be needed for diagnosis. In this case, testing with 16S rRNA PCR identified *M haemophilum* after 3 weeks, while AFB cultures took 8 weeks. The acquisition of nucleic acid testing helped accelerate diagnosis and treatment from 8 to 3 weeks,[9] highlighting the importance of rapid diagnosis to guide appropriate empiric treatment, while avoiding unnecessary antibiotic interactions and toxicity.

Starting empiric therapy right after diagnosis was considered in this case, but the patient was hemodynamically stable and mostly asymptomatic. Discussions to start empiric therapies, such as azithromycin and ciprofloxacin, were made while waiting for culture results, but ultimately the decision was made to wait for further identification as we weighed treatment side effects and potential toxicities. Once the 16sRNA identification resulted, the patient was started immediately on the recommended regimen according to guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, which suggested a combination of azithromycin (a macrolide), rifabutin, and ciprofloxacin (a fluoroquinolone).[9]

Our patient had a unique presentation of initial joint and skin findings and, on subsequent hospitalization, was found to have bone marrow involvement as well as pulmonary findings that evolved into pleural effusions. Despite starting on the recommended regimen, he developed bilateral empyemas a month into his therapy and, later on, septic arthritis. This led to lengthy multidisciplinary discussions between nephrology, infectious disease, and pulmonology on management of his effusions and whether he would require some form of tube thoracostomy, including potential tunneled indwelling pleural catheter, or to start more aggressive therapy and/or decrease his immunosuppression. As pleural involvement of disseminated mycobacteria is quite uncommon, there is no clear guidance.[10] Relatively uncomplicated cases eventually can resolve with antimicrobial therapy alone. More serious cases have been documented as requiring surgical intervention--particularly when there is concern for diffuse cavitary disease abruption into the pleural space and when complicated by secondary coinfection.[11] During the patient's third hospital stay, he was mostly asymptomatic from a respiratory standpoint and his leukocytosis improved after drainage of his effusions with very slow reaccumulation. At that time, the thought was that antimicrobial therapy alone was the safest option. However, when he presented with septic arthritis due to *M haemophilum* after 3 months of therapy, clofazimine 100 mg daily was added to his antimicrobial regimen. Furthermore, to provide broader coverage for his disseminated disease and recurrence of skin nodules, linezolid 600 mg daily was added. As part of the treatment plan to allow for immune system recovery and effective treatment of *M haemophilum*, mycophenolate mofetil was discontinued during his fifth hospital stay due to recurrence of skin lesions. These modifications resulted in improvements of his skin lesions, but they led to worsening of his renal function.

When initiating therapy, it is important to consider various factors, including the use of multiple medications over an extended period, overall immunosuppression, the potential toxicity of medications, and the possibility of drug interactions. Significant drug interactions exist when using rifamycins and antibiotics with immunosuppressants (Table). Rifamycins are potent inducers of cytochrome P450 3A4, and macrolides inhibit these enzymes.[9] In this particular case, rifabutin was chosen instead of rifampin to minimize the risk of significant interactions with the patient's immunosuppressive regimen. Another drug that has significant interactions is clofazimine, which inhibits CYP3A4 and increases immunosuppression levels, therefore requiring close monitoring of weekly tacrolimus FK506 levels in this patient to adjust doses as needed. His corrected QT (QTc) interval slowly uptrended and maintained between 416 and 445. During his last clinical hospitalization, he had shown clinical improvement with decreases in skin lesion sizes; however, his kidney function was noted to be declining, which was attributed to graft rejection.

There is currently limited data on the management of progressive infections in patients with a solid organ transplant. Existing literature focuses heavily on prophylaxis against bacterial infection

Table. Drug Interactions

Drug Combinations	Drug Interactions	Effects on Patient
Rifabutin and tacrolimus	Rifamycins (rifabutin) induce CYP3A4, increasing the metabolism of calcineurin inhibitors (tacrolimus).	Tacrolimus levels were decreased. FK506 was checked weekly, and doses were adjusted to maintain appropriate levels.
Rifabutin, ciprofloxacin, and tacrolimus	Rifabutin can increase the metabolism of ciprofloxacin, reducing the antibiotic effects of ciprofloxacin. Ciprofloxacin can prolong QTc.	Patient's QTc slowly increased while on the drug regimen and is monitored closely
Rifabutin, azithromycin, and tacrolimus	Rifabutin induces CYP3A4 and macrolides (azithromycin) inhibit CYP3A4, causing the drugs to offset each other with less effects on tacrolimus. Azithromycin can prolong QTc.	Azithromycin is preferred, causing less rifabutin effects on tacrolimus. QTc is monitored.
Clofazimine and tacrolimus	Clofazimine inhibits CYP3A4 substrates, which can increase the level of tacrolimus toxicity and increase immunosuppression. Clofazimine can prolong QTc.	Tacrolimus levels are monitored closely since starting clofazimine for dose lowering. QTc is monitored.

Abbreviations: QTc, corrected QT interval.

Significant drug interactions exist between rifabutin, antibiotics (fluoroquinolone and macrolides), and tacrolimus. Side effects and immunosuppression levels are monitored closely.

in transplant patients, with minimal recommendations on how to proceed after infection has occurred.[12] Despite our patient's suspected graft rejection and declining kidney function, increasing his immunosuppression risked worsening his existing infection. In these instances, it is important to weigh the pros and cons of preserving immune function at the expense of graft function. Along with this, it is important to have open communication with patients about their goals of care and quality of life, as that will ultimately guide further care decisions.

This case highlights the challenges associated with selecting treatments to effectively manage an immunosuppressed transplant recipient with disseminated mycobacterial infections.

CONCLUSIONS

Transplant recipients are highly susceptible to infections due to their significant immunosuppression. Mycobacterium haemophilum is a slow-growing mycobacteria in culture, and techniques like 16S rRNA PCR are crucial for early treatment. This case demonstrates the importance of conducting an extensive infectious workup in immunosuppressed individuals, emphasizing the potential complications that can arise despite starting appropriate treatments. It also aims to increase awareness among clinicians about challenges in managing infections in this specific patient population.

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Data Availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Patient Consent: The patient's written informed consent was obtained before publication of this case report. All patient-specific information has been anonymized, including illustrations. This study has been exempted from the Institutional Review Board and does not involve experiments conducted on human subjects.

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