Disseminated atypical mycobacterial infection in an allogeneic stem cell transplant recipient

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Abstract

Nontuberculous mycobacteria are pathogens with diverse manifestations in immunocompromised hosts. The lesser-known *Mycobacterium haemophilum* usually causes cutaneous infection. Diagnosis is challenging but is aided by molecular testing and multidisciplinary communication. We present an immunocompromised patient with disseminated cutaneous mycobacterial infection with digital tenosynovitis.

Keywords: cutaneous disease, Mycobacterium haemophilum, nontuberculous mycobacteria, stem cell transplant

Introduction

Beyond *Mycobacterium tuberculosis* complex and *Mycobacterium leprae,* nontuberculous mycobacteria (also called atypical mycobacteria) are ubiquitous in the environment. They are a diverse group of acid-fast organisms that cause a broad range of disease in immunocompromised patients. Nontuberculous mycobacteria can be stratified into rapidly or slowly growing mycobacteria based on the time required to form mature colonies on appropriate media. Although this information is insufficient for pathogen diagnosis, it is helpful in narrowing down possible organisms.

Mycobacterium haemophilum is a slow-growing mycobacterium that can cause a variety of localized or disseminated infections in immunocompromised hosts and rarely does so in immunocompetent individuals. Presentations include cutaneous infection, arthritis, and with less frequency, pneumonitis [1]. As with *Mycobacterium marinum* and *Mycobacterium ulcerans*, cutaneous lesions are the most common manifestation of *Mycobacterium haemophilum* infection [2]. Two groups of patients reportedly contract *Mycobacterium haemophilum*: immunocompetent children with lymphadenitis and patients with underlying immunodeficiency, such as those with human immunodeficiency virus, recipients of solid organ or hematopoietic stem cell transplants, or those undergoing immunosuppressive therapy [1,3–11]. The true prevalence of *Mycobacterium haemophilum* is not known as it is likely under-recognized owing to the difficulty of diagnosis.

An acid-fast stain is incapable of differentiating *Mycobacterium haemophilum* (or any nontuberculous mycobacteria) from *Mycobacterium tuberculosis* and additional steps are needed to identify the specific pathogen. Skin cultures for nontuberculous mycobacteria are less frequently performed as they are rarely suspected pathogens and there are unique conditions for recovery of *Mycobacterium haemophilum* [1]. Owing to its special growth requirements, *Mycobacterium haemophilum*

is difficult to diagnose, necessitating the use of novel diagnostic methods (such as molecular diagnostic testing) in collaboration with Mayo Clinic Laboratories [1]. We present a multidisciplinary effort to diagnose and treat a protracted course of presumed *Mycobacterium haemophilum* cutaneous infection in a patient with T cell prolymphocytic leukemia who had been treated with alemtuzumab and allogeneic matched unrelated donor stem cell transplant.

Case Synopsis

A 55-year-old woman presented for dermatology consultation with persistent severe lymphocytopenia 6 months after treatment for The cell prolymphocytic leukemia. She had been treated with alemtuzumab (30mg every four weeks; 19 doses) followed by allogeneic matched unrelated donor stem cell transplantation. She had received a conditioning regimen of fludarabine, melphalan, and post-transplant cyclophosphamide. Graft-versus-host disease prophylaxis was with mycophenolate mofetil (through post-transplant day 35) and tacrolimus. She did not develop graft-versus-host disease and was successfully tapered off tacrolimus 6 months after transplantation, just after her initial presentation to the dermatology department. While on immunosuppressive therapy, she received posaconazole (300mg once daily), valacyclovir (500mg twice daily), and atovaquone (1500mg once daily) for infection prophylaxis. Additionally, she started maintenance venetoclax (100mg daily for 14 days + 14 days off) beginning two months after transplantation, but it was discontinued after one 28-day cycle while the skin nodules were further investigated.

Five months after transplantation, the patient had first noted a nodule on her left thigh, with nodules then progressing to her abdomen, arms, and back. The patient's oncology provider consulted the department of dermatology when unremitting nodules started to ulcerate. On presentation to the dermatology clinic one month after the initial nodule was noted, the patient had persistent indurated erythematous papules on both lower extremities. The right lower leg had a deep and minimally mobile nodule in addition to indurated erythematous papules on the right heel. The lesion on her left thigh was a firm deep-set nodule with new superficial ulceration and purulent exudate (**Figure 1**). The patient also complained of pain in her right hand. She did not report fevers, weakness, or fatigue. The differential diagnosis included bacterial abscess, atypical mycobacteria infection, deep fungal infection, herpes folliculitis, and leukemia cutis.

At her initial visit, punch biopsies were obtained from the nodule on her right thigh (specimen A) and an ulcerated lesion on her left thigh (specimen B). Specimen A was sent for routine pathology and tissue culture, and specimen B was sent for routine pathology only. Specimen A showed focal acute inflammatory infiltrate in the deep dermis and superficial subcutis, whereas specimen B revealed ruptured folliculitis and associated acute and chronic granulomatous inflammation, including numerous acid-fast bacilli on Fite stain (**Figure 1C-E**). Bacterial, acid-fast bacillus, and fungal cultures of specimen A, however, revealed no growth. An ultrasound of the right lower leg showed an inflammatory nodule. Infectious disease evaluation revealed tenosynovitis of the palmar flexor tendons of the patient's right hand on magnetic resonance imaging and no evidence of mycobacterial lung infection on chest X-ray. Given her progressive disease and high suspicion of infectious etiology, identification of the causative pathogen became imperative to developing a specific therapeutic regimen.

After multidisciplinary discussions between dermatology, infectious diseases, clinical microbiology, pathology, and oncology specialists, a plan was made to collect new tissue samples for 16S ribosomal RNA broad-range polymerase chain reaction followed by sequencing. Biopsy of the right lower leg nodule, which had since started to ulcerate, was performed at one-month dermatology follow up and the sample was sent for acid-fast bacilli culture at MD Anderson (Houston, TX) and 16S ribosomal RNA broad-range polymerase chain reaction at Mayo Clinic Laboratories (Rochester, MN). After these samples were collected, the patient was started on

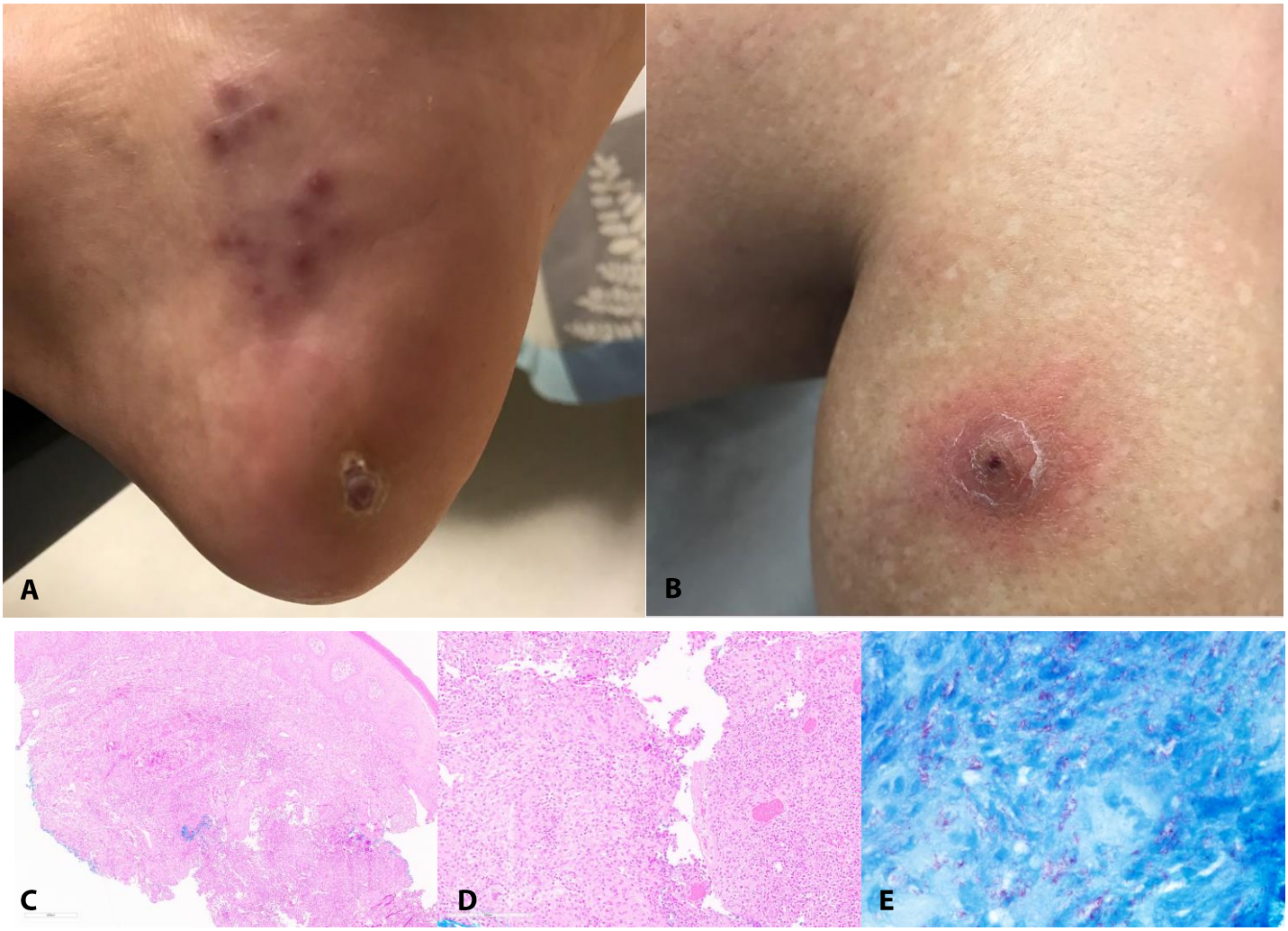

Figure 1. ***A)*** *Erythematous indurated papules on medial aspect of right heel.* ***B)*** *Inflammatory nodule on right calf.* ***C)*** *Skin biopsy from left thigh. Notice the residual ruptured folliculitis in the superficial dermis, associated with acute inflammation (hematoxylin and eosin. H&E, 40×.* ***D)*** *Deep portions of the biopsy revealed granulomatous and acute inflammation. H&E, 200×.* ***E)*** *Numerous acid-fast bacilli in the biopsy are highlighted by Fite stain, 600×.*

an empiric course of azithromycin (500mg daily), ethambutol (1000mg daily), and rifampin (600mg daily) for coverage of disseminated nontuberculous mycobacteria infection. Drugs were started sequentially to avoid gastrointestinal intolerability. Venetoclax was not restarted owing to its potential to aggravate the patient's lymphocytopenia to which the antimicrobials contribute and there was no evidence of leukemia recurrence.

The 16S rRNA polymerase chain reaction sequencing results identified a *Mycobacterium* species but RNA analysis showed almost equal probabilities for *Mycobacterium riyadhense* and *Mycobacterium haemophilum*. As *Mycobacterium riyadhense* is typically associated with pulmonary infections and is very rare, the suspected diagnosis was *Mycobacterium haemophilum*. The patient's acid-fast bacilli cultures were finalized as no growth after 8 weeks. The empiric therapy was continued after definitive diagnosis as it was appropriate for *Mycobacterium haemophilum*. A 12-month course of triple therapy is clinically suggested. Although no new lesions developed after four weeks of therapy, triple therapy was continued despite our patient's sustained lymphocytopenia at 5 months because the tenosynovitis persisted. Treatment was discontinued after 8 months of therapy when tenosynovitis had resolved. The patient's pancytopenia improved after three months of discontinuing therapy. The medication regimen necessitated strictly monitoring

for medication toxicity, including lymphocytopenia because of the patient's severely compromised immune system. She remains in complete remission from her T cell prolymphocytic leukemia.

Case Discussion

This report features a unique case of disseminated cutaneous mycobacterial disease in a patient after stem cell transplantation, which necessitated persistent workup and multidisciplinary collaboration to yield a diagnosis and appropriate treatment plan. Our patient presented with severe immunosuppression from treatment of T cell prolymphocytic leukemia with alemtuzumab and allogeneic stem cell transplantation.

Mycobacterium haemophilum is an opportunistic atypical mycobacterium and has been reported worldwide [1]. It is most often associated with immunocompromised individuals and has been reported once following alemtuzumab treatment [13]. The organism has distinct growth requirements consisting of a strict temperature window of 30-32C and heme-supplemented growth medium [1,12]. *Mycobacterium haemophilum* is difficult to diagnose because it is infrequently suspected and difficult to isolate in traditional acid-fast bacilli cultures. In addition to its unique growth requirements, *Mycobacterium haemophilum* is a slow growing mycobacterium, requiring several weeks to grow on culture media, potentiating complications by delaying diagnosis. These characteristics could explain the repeated negative acid-fast bacilli cultures in our patient.

Lesions typically begin on the extremities, possibly related to the pathogen's propensity to thrive in cooler temperatures and migrate to the torso. Skin lesions are described as tender papules or nodules that evolve to be suppurative or to ulcerate, which is consistent with our patient's presentation [1]. The ruptured folliculitis present in her left thigh biopsy is consistent with previously reported histologic and clinical manifestations of *Mycobacterium haemophilum* infection [14]. Existing literature also associates *Mycobacterium haemophilum* with tenosynovitis, similar to our patient's experience [2,15].

Although *Mycobacterium haemophilum's* nonspecific histopathologic presentation and stringent growth requirements make diagnosis difficult and time consuming, molecular testing has proven a rapid and accurate method of discerning the most likely offending pathogen [16,17]. The disadvantage of molecular testing is that it provides probabilities of the most plausible organisms and not a confirmed diagnosis, making clinical correlation necessary, as in this case. Patients who have acid-fast bacilli visible in the tissue but negative culture results should be encouraged to undergo molecular diagnostic testing. Incidence of *Mycobacterium haemophilum* is climbing, possibly related to improved testing by laboratories, increased awareness, and increased number of individuals undergoing immunosuppressive therapies [8]. Appropriate methods for detection are crucial for timely diagnosis and early appropriate therapy in patients with rapid progression of symptoms. Although molecular testing is not definitive for the pathogenic organism, it provides valuable information, allowing clinicians to target antimicrobial therapy to the most likely organism.

A standardized treatment for disseminated *Mycobacterium haemophilum* in immunocompromised hosts has not been established, but 12-24 month multidrug regimen is recommended; such regimens can include a macrolide, ciprofloxacin, ethambutol, and rifabutin or rifampin, depending on individual antimicrobial susceptibility [2,8]. A study in Thailand found that patients with cutaneous nontuberculous mycobacterial infections being treated with less than three agents were more susceptible to relapse (odds ratio 65.86; P=0.02), [18]. When antimicrobial susceptibility testing is unavailable, in vitro susceptibility data can help tailor management [2]. In a retrospective study examining *Mycobacterium haemophilum* infections, patients with strictly skin involvement had favorable outcomes, but 5 of 7 patients with lung infection died, making early diagnosis before disseminated disease imperative [8].

Conclusion

Mycobacterium haemophilum is uncommon but presents in immunocompromised individuals at an increased incidence. Polymerase chain reaction testing should be pursued in the case of inconclusive diagnostics because of the patients' susceptible state in addition to the slow-growing nature of the bacterium. This case highlights the importance of early diagnosis and intervention to minimize extracutaneous involvement and potentially fatal complications. It also reaffirms the need for persistent and effective multidisciplinary communication to ensure diagnosis and treatment are not delayed. Dermatologists and oncology care teams should be aware of *Mycobacterium haemophilum* as a cause of chronic erythematous and ulcerating nodules appearing on the body in high-infectious-risk groups such as stem cell transplant patients.

Potential conflicts of interest

The authors declare no conflicts of interest.

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