Mycobacterium haemophilum: A Challenging Treatment Dilemma in an Immunocompromised Patient

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PRACTICE **POINTS**

- *Mycobacterium haemophilum* is a slow-growing acid-fast bacillus that requires iron-supplemented media and incubation temperatures of 30°C to 32°C for culture. Because these requirements for growth are not standard for acid-fast bacteria cultures, *M haemophilum* infection may be underrecognized and underreported.
- There are no species-specific treatment guidelines, but extended course of treatment with multiple active antibacterials typically is recommended.

To the Editor:

The increase in nontuberculous mycobacteria (NTM) infections over the last 3 decades likely is multifaceted, including increased clinical awareness, improved laboratory diagnostics, growing numbers of immunocompromised patients, and an aging population.[1,2] Historically, the majority of mycobacteria-related diseases are due to *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium leprae*.[3]

Mycobacterium haemophilum is a slow-growing acid-fast bacillus (AFB) that differs from other *Mycobacterium* species in that it requires iron-supplemented media and incubation temperatures of 30°C to 32°C for culture. As these requirements for growth are not standard for AFB cultures, *M haemophilum* infection may be underrecognized and underreported.[3] *Mycobacterium haemophilum* infections largely are cutaneous and generally are seen in AIDS patients and bone marrow transplant recipients who are iatrogenically immunosuppressed.[4,5] No species-specific treatment guidelines exist[2]; however, triple-drug therapy combining a macrolide, rifamycin, and a quinolone for a minimum of 12 months often is recommended.

A 64-year-old man with a history of coronary artery disease, hypertension, hyperlipidemia, and acute myelogenous leukemia (AML) underwent allogenic stem cell transplantation. His posttransplant course was complicated by multiple deep vein thromboses, hypogammaglobulinemia, and graft-vs-host disease (GVHD) of the skin and gastrointestinal tract that manifested as chronic diarrhea, which was managed with chronic prednisone. Thirteen months after the transplant, the patient presented to his outpatient oncologist (M.K.) for evaluation of painless, nonpruritic, erythematous papules and nodules that had emerged on the right side of the chest, right arm, and left leg of approximately 2 weeks' duration.

On review of systems by oncology, the patient denied any fevers, chills, or night sweats but noted chronic loose nonbloody stools without abdominal pain, likely related to the GVHD. The patient's medications included prednisone 20 mg once daily, fluconazole, amitriptyline, atovaquone, budesonide, dabigatran, metoprolol, pantoprazole, rosuvastatin, senna glycoside, spironolactone, tramadol, and valacyclovir.

Physical examination revealed multiple singular erythematous nodules on the right side of the chest (Figure 1A), right arm (Figure 1B), and left leg. There was no regional

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lymphadenopathy. The patient was afebrile and hemodynamically stable. A biopsy of the arm performed to rule out leukemia cutis revealed a granulomatous dermatitis with numerous AFB (Figures 2A and 2B), which were confirmed on Ziehl-Neelsen staining (Figures 2C and 2D). The presence of AFB raised concern for a disseminated mycobacterial infection. The patient was admitted to our institution approximately 1 week after the outpatient biopsy was performed. He was evaluated by infectious diseases (B.H.) and was recommended for repeat biopsy with AFB culture and for initiation of intravenous antibiotics.

FIGURE 1. A, Erythematous nodule on the right chest wall. B, Multiple, discrete, erythematous papules and nodules in a sporotrichoid pattern on the right arm.

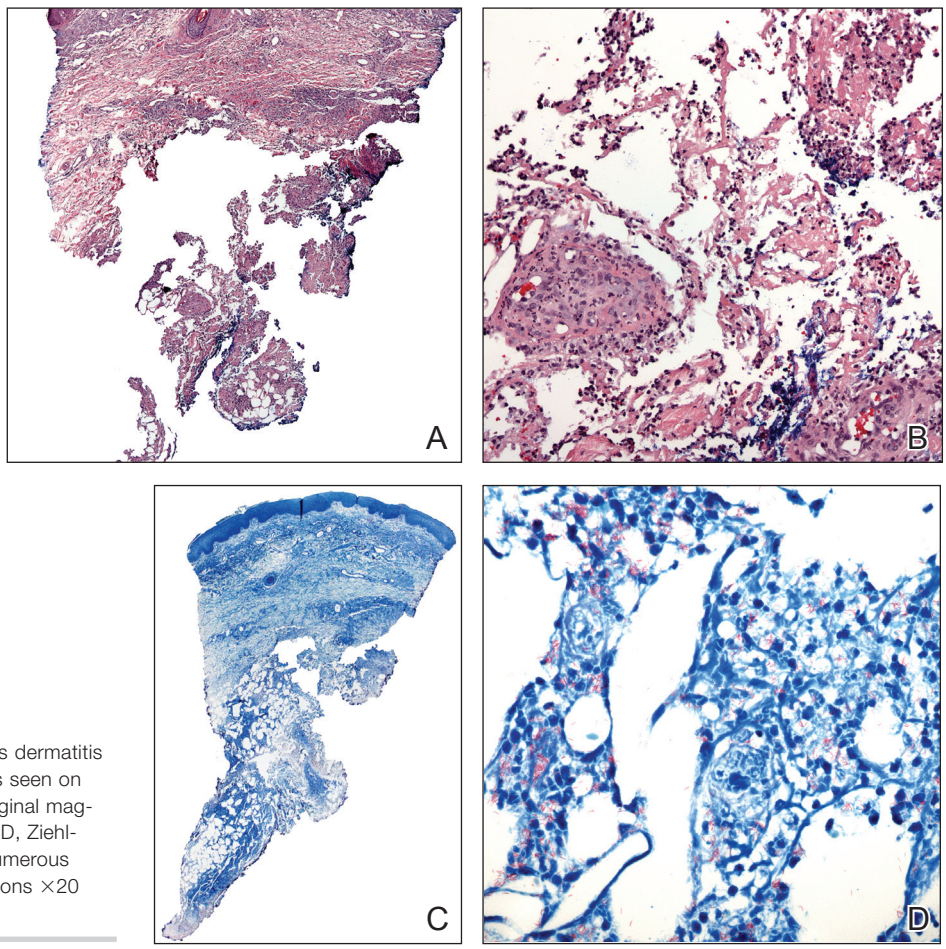

FIGURE 2. A and B, Granulomatous dermatitis with numerous acid-fast bacilli was seen on hematoxylin and eosin staining (original magnifications ×40 and ×200). C and D, Ziehl-Neelsen staining also confirmed numerous acid-fast bacilli (original magnifications ×20 and ×600).

The patient was evaluated by the dermatology consultation service on hospital day 1. At the time of consultation, the lesions were still painless but had enlarged. Two new satellite lesions were noted on his other extremities. Due to the widespread distribution of the lesions, there was concern for disseminated disease. The relatively rapid onset of new lesions increased concern for infection with rapid-growing mycobacteria, including *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae*. A detailed history revealed that the patient's wife had a fish tank, which supported the inclusion of *Mycobacterium marinum* in the differential; however, further questioning revealed that the patient never came in contact with the aquarium water. The initial outpatient biopsy had not been sent for culture. Following inpatient biopsy, the patient was initiated on empiric antimycobacterials, including imipenem, amikacin, clarithromycin, and levofloxacin. Computed tomography of the head was negative for cerebral involvement.

Acid-fast bacilli blood cultures were drawn per the recommendation from infectious diseases in an attempt to confirm disseminated disease; however, blood cultures remained negative. Tissue biopsy from the right arm was sent for AFB staining and culture. Many AFB were identified on microscopy, and growth was observed in the mycobacterial growth indicator tube after 6 days of incubation. The DNA probe was negative for *M tuberculosis* complex or *Mycobacterium avium* complex.

The patient was discharged on hospital day 6 on empiric therapy for rapid-growing mycobacteria while cultures were pending. The empiric regimen included intravenous imipenem 1 g every 6 hours, intravenous amikacin 1 g once daily, clarithromycin 500 mg every 12 hours, and levofloxacin 750 mg once daily. All solid media cultures were negative at the time of discharge.

The biopsy specimen proved difficult to culture on solid media using traditional methods. Three weeks after the inpatient biopsy, the microbiology laboratory reported that growth was observed on solid media that was incubated at 30°C and supplemented with iron. These findings were not characteristic of a rapidly growing mycobacteria (eg, *M fortuitum*, *M chelonae*, *M abscessus)* or *M marinum* but raised concern for infection with *M haemophilum*. Antimycobacterial treatment was adjusted to amikacin, clarithromycin, levofloxacin, and rifabutin.

Six weeks after the inpatient skin biopsy, final speciation confirmed infection with *M haemophilum*. The isolate proved susceptible to amikacin (minimal inhibitory concentration [MIC], 16), clarithromycin (MIC, 0.12), linezolid (MIC, <1), moxifloxacin (MIC, 0.5), rifabutin (MIC, <0.25), and trimethoprim-sulfamethoxazole (MIC, 0.5/9.5). The isolate was resistant to ciprofloxacin (MIC, 4), ethambutol (MIC, >16), and rifampin (MIC, 2). Based on these findings, an infectious disease specialist modified the treatment regimen to azithromycin 600 mg once daily, moxifloxacin 400 mg once daily, and rifabutin 300 mg once daily. Azithromycin was substituted for clarithromycin in an attempt to minimize the gastrointestinal side effects of the antibiotics. The infectious disease specialist was concerned that the clarithromycin could exacerbate the patient's chronic GVHD-associated diarrhea, which posed a challenge to the oncologist, who was attempting to manage the patient's GVHD and minimize the use of additional prednisone. At the time of this change, the patient was doing well clinically and denied any active skin lesions.

Four months later, he developed new left-sided neck swelling. Computed tomography revealed nonspecific enhancement involving the skin and superficial subcutaneous tissues in the left anterior neck. He was referred to otolaryngology given concern for recurrent infection vs leukemia cutis. He underwent excisional biopsy. Pathology was negative for malignancy but demonstrated subcutaneous necrotizing granulomatous inflammation with a positive AFB stain. Tissue AFB cultures revealed moderate AFB on direct stain, but there was no AFB growth at 12 weeks. Clarithromycin was restarted in place of azithromycin to increase the potency of the antimycobacterial regimen. Cultures from this neck biopsy were negative after 12 weeks of incubation.

In addition to this change in antibiotic coverage, the patient's medical oncologist tapered the patient's immunosuppression considerably. The patient subsequently completed 12 months of therapy with clarithromycin, moxifloxacin, and rifabutin starting from the time of the neck biopsy. He remained free of recurrence of mycobacterial infection for nearly 2 years until he died from an unrelated illness.

Nontuberculous mycobacteria are an ubiquitous environmental group.[2] Sources include soil and natural water (*M avium*), fish tanks and swimming pools (*M marinum*), and tap water and occasionally domestic animals (*Mycobacterium kansasii*). Additionally, rapidly growing NTM such as *M abscessus*, *M chelonae, and M fortuitum* have been isolated from soil and natural water supplies.[3]

Mycobacterium haemophilum is a fastidious organism with a predilection for skin of the chest and extremities. Iatrogenically or inherently immunocompromised patients are most commonly affected[6-11]; however, there also have been reports in healthy patients.[12,13] Infections typically present as painless erythematous papules or nodules that eventually suppurate, ulcerate, and become painful. Presentations involving Fitz-Hugh–Curtis syndrome,[13] new B-cell lymphoma,[10] and lymphadenitis[12] also have been described. Beyond cutaneous involvement, *M haemophilum* has been cultured from bone, the synovium, the lungs, and the central nervous system.[4,9] The majority of morbidities occur in patients with lung involvement.[4] Therefore, even patients presenting with isolated cutaneous disease require close follow-up.

Mycobacterium haemophilum is a slowly proliferating organism that is unable to grow in standard egg-potato

(Lowenstein-Jensen) medium or agar base (Middlebrook 7H10 or 7H11 agar) without iron supplementation (ferric ammonium citrate, hemin, or hemoglobin). It also requires temperatures of 30°C to 32°C for growth. Its iron requisite is unique, but species such as *M marinum* and *Mycobacterium ulcerans* also share reduced temperature requirements. Without a high index of suspicion, growth often is absent because standard *Mycobacterium* culture techniques will not foster organism growth. Our case demonstrated that special culture instructions must be relayed to the laboratory, even in the face of positive AFB smears. Failure to request hemin and modified incubation temperatures may have contributed to the negative AFB blood culture in our patient.

Due to the relatively rare incidence of *M haemophilum* infection, there are no known randomized controlled trials guiding antibiotic regimens. Infectious disease specialists often treat empirically with triple-drug therapy derived from locally reported species susceptibilities. The largest case series to date did not identify resistance to amikacin, ciprofloxacin, or clarithromycin.[4] Our case identified a novel finding of ciprofloxacin and rifampin resistance, which may highlight the emergence of a newly resistant strain of *M haemophilum*. Of note, one case of rifampin resistance has been reported, but the culture was drawn from a postmortem specimen in the setting of previously rifampin-sensitive isolates.[4] Empiric therapies should be guided by hospital susceptibility reports and expert consultation.

Coinfection with 2 or more NTM—including *M tuberculosis*, *M leprae,* and *M fortuitum*—has been reported.[8,14] Temporally distinct coinfections with *M leprae* and *M haemophilum* also have been described.[15] Thus, practitioners should have a low threshold for repeat cultures in the context of new cutaneous nodules or granulomas, not only to detect concomitant infections but also to identify resistance patterns that might explain recurrent or recalcitrant disease. Immune reconstitution inflammatory syndrome also must be considered with new or worsening lesions, especially in the first months of therapy, as this is a common occurrence when immunosuppressive regimens are tapered to help manage infections.

In conclusion, *M haemophilum* is an underrecognized infection that presents as cutaneous nodules or lymphadenitis in immunocompromised or healthy individuals. Diagnosis requires a high index of suspicion because its unique growth requirements necessitate special laboratory techniques. Our case represents a classic presentation of this NTM infection in a patient with AML following allogenic stem cell transplantation. Repeat cultures, workup of potentially disseminated infections, and close follow-up are requisite to minimizing morbidity and mortality. A multidisciplinary approach involving infectious disease, medical oncology, radiology, and dermatology best manages this type of infection.

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