Mycobacterium haemophilum and Histoplasma capsulatum Coinfection in a Renal Transplant Patient

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We report the case of a 22-year-old man who presented with a Mycobacterium haemophilum and Histoplasma capsulatum coinfection occurring 21 years after a living-donor-related renal transplant.

CASE REPORT

The patient is a 22-year-old male native of Corpus Christi, TX, who had undergone a living-donor-related kidney transplant from his mother when he was 15 months old, due to dysplastic kidneys. His immunosuppressive treatment consisted of mycophenolate mofetil, cyclosporine, and prednisone. Four months before admission to our hospital, he was in his usual state of health, working as a manager of an athletic team, when he experienced some discomfort in his right distal forearm near his wrist. A progressive swelling and erythema developed in that region and extended to his palm. He experienced no weakness, numbness, tingling, fever, chills, rigor, or night sweats. Within the month prior to admission, the swelling of his right forearm worsened and became painful. He developed difficulty in closing his fingers, along with boils on the left elbow and left shoulder. There was no history of trauma, insect bite, fish tank water exposure, or gardening. The patient did, however, report a history of travel to Arkansas, Houston, TX, and Austin, TX, during the 4 months prior to admission. Before the onset of the skin lesions, there was a deterioration of the patient's renal function, with an elevation of creatinine levels. This development required an increase in his immunosuppressive regimen. At our hospital, examination revealed a swollen and slightly tender and warm right distal forearm and palm, compared to the adjacent skin, as well as an abscess formation in the left arm and pustular lesions close to the left shoulder. The patient underwent surgical exploration, which revealed abscesses on the right forearm and left arm that were drained, along with extensive soft tissue debridement. Tissue samples were submitted to the surgical pathology department for histopathologic examination. Comitantly, tissue specimens of the right arm fascia were sent to the surgical pathology department for histopathologic examination. Gomori methenamine silver staining revealed necrotizing granulomas with histiocytes containing budding yeasts, consistent with H. capsulatum (Fig. 1A).

Auramine O staining on tissue samples obtained from the left arm revealed + bacilli (>9 acid-fast bacilli per field at a magnification of ×1,000) on direct smear. Liquid medium mycobacterial growth indicator tubes (Bectec MGIT 960; BD Diagnostic Systems, Sparks, MD) and a Middlebrook 7H11/Middlebrook 7H11 selective agar biplate (BBL; BD Diagnostic Systems) were inoculated and incubated at 37°C. Per our laboratory protocol for mycobacterial isolation from tissue recovered from external sites, an additional Middlebrook 7H11 biplate and a chocolate agar plate (BBL; BD Diagnostic Systems) were inoculated and incubated at 30°C. This protocol has been incorporated to enhance recovery of fastidious mycobacterial organisms such as Mycobacterium haemophilum and Mycobacterium marinum, if present. After 3 days, growth was observed on the chocolate agar plate at 30°C, and a positive signal was detected in the MGIT tube after 9 days of incubation. A Kinyoun stain prepared from MGIT growth demonstrated acid-fast bacilli (AFB)-positive beaded bacilli exhibiting cording (Fig. 1B). The isolate was sent to our reference laboratory, ARUP Laboratories, and was later identified as M. haemophilum by 16S rRNA gene sequencing.

Abdominal and chest computed tomography (CT) scans were negative for systemic dissemination of both H. capsulatum and M. haemophilum infection. Several blood cultures were also negative. However, following a magnetic resonance imaging (MRI) for pansinusitis, a nasal mucosa biopsy on the right middle turbinate revealed a granulomatous inflammation, with AFB-positive bacilli, consistent with atypical mycobacterium infection. Treatment was started with itraconazole, clarithromycin, linezolid, and trimethoprim-sulfamethoxazole. Due to an elevation in the patient's creatinine levels, trimethoprim-sulfamethoxazole was discontinued. Within 5 weeks, new erythematous papules appeared on his left arm, abdomen, and right leg. Subsequent KOH direct preparations and fungal cultures of these lesions were all negative. AFB staining re-
vealed 4+ bacilli on direct smear, and histopathologic examination revealed sheets of dermal acid-fast bacillus-filled histiocytes, but no acid-fast bacilli were isolated after 6 weeks. Total nucleic acids were extracted from 100 μl of fresh ground tissue resuspended in phosphate-buffered saline (PBS), obtained from one of the lesions, and were tested by a MycoID assay, which combines mycobacterial broad-range PCR amplification and liquid array detection and identification as previously described (13). The tissue tested positive for a Mycobacterium species, which was specifically identified to the species level as M. haemophilum. Therapy was subsequently changed, with addition of ethambutol and moxifloxacin and discontinuation of linezolid. After 7 months with this regimen, all the patient’s skin lesions significantly improved, and there was no evidence of H. capsulatum by histological examination or by culture. M. haemophilum cultures were all negative; however, histological examination of a skin biopsy specimen from the left arm continued to show occasional acid-fast bacilli. Therefore, it was decided that the treatment regimen would continue to complete 1 year.

To our knowledge, this is the first report of M. haemophilum and H. capsulatum coinfection occurring after more than 20 years of immunosuppressive therapy for renal transplantation. Although not a case of coinfection, there is a previous report of a patient with a history of cutaneous Mycobacterium kansasi who was responsive to treatment. However, 7 years later the patient developed similar new cutaneous lesions that were sampled, which were positive for H. capsulatum, and there was no evidence of M. kansasi (6). Histoplasmosis is the most common endemic mycosis in the United States, considered endemic in the Ohio and Mississippi river valleys, and there are also high incidences of this mycosis in Illinois, Indiana, Missouri, Kentucky, Tennessee, and Arkansas. In areas of endemicity, more than 50% of the population shows positive skin test results, demonstrating prior exposure to histoplasmosis (19). Histoplasmosis among renal-transplant recipients has been reported from as early as 5 days to as late as 20 years after transplantation. Immunosuppressive therapy makes these patients susceptible to a variety of infections, including histoplasmosis. According to Jha et al., the intensity of the immunosuppressive therapy does not appear to be an important risk factor in the development of this infection (9). However, Peddi et al. reported 4 cases of renal transplant recipients that received intense immunosuppressive therapy in the 3 months prior to the onset of the infection (19). There are very low incidences of histoplasmosis among allogeneic-bone-marrow and solid-organ-transplant recipients, even in areas of hyperendemicity, and the risk of reactivation is also very low (23). This infection is very rare in our population. There were only two additional isolates found within the same year as the isolate from our patient, with these occurring more than 3 months after our patient’s isolate was identified.

Cutaneous histoplasmosis can be either primary, from direct inoculation, or secondary, from hematogenous dissemination (6, 24, 25). These cutaneous lesions can manifest as papules, nodules, plaques, abscesses, or cellulitis-like manifestations. Although the majority of cutaneous presentations have been reported for immunocompromised patients, cutaneous histoplasmosis is very uncommon among patients who have received solid-organ transplantation, and such an infection is usually associated with pulmonary or chronic disseminated infection (15, 17). Cutaneous histoplasmosis by direct inoculation of the fungus is very rare (1, 15, 22, 24). Our patient had visited an area of endemicity in the last 4 months prior to admission. However, since his histoplasmosis manifested as a cutaneous-subcutaneous infection with no evidence of systemic involvement, and with no history of any local trauma, we could speculate that this infection represented reactivation of a subcutaneous focus that had been latent since a previous hematogenous spread from an undetected mild pulmonary disease. Moreover, deterioration of his renal function, which required

![Image](https://example.com/image1.png)

**FIG. 1.** (A) Skin biopsy specimen from right arm showing histiocytes containing budding yeasts consistent with H. capsulatum (GMS stain; magnification, ×400). (B) Smear prepared from M. haemophilum growth in MGIT broth showing strongly AFB-positive bacilli, single and forming cords (Kinyoun stain; magnification, ×1,000).
an increase in his immunosuppressive regimen prior to the onset of the cutaneous lesions, could have favored this reactivation. Cutaneous lesions may be the only sign of serious systemic disease in posttransplant immunosuppressed patients (1). Because the cutaneous manifestations are nonspecific, there must be a high clinical index of suspicion for timely diagnosis and treatment.

On the other hand, *M. haemophilum* has mainly been identified as a cause of cutaneous or subcutaneous lesions, possibly as a reflection of the propensity of this organism to grow at lower temperatures (8, 12). Painful nodules, swellings, and ulcers that can progress into abscesses are common clinical presentations. Most of the *M. haemophilum* infections reported for renal transplant patients receiving immunosuppressive therapy involved skin lesions (2, 3, 4, 7, 12, 16, 18, 20), although infections at extracutaneous sites have also been described (8, 11). Several reports indicate that there are still many questions regarding the transmission of *M. haemophilum* to the human host. This mycobacterium appears to be ubiquitous; however, no environmental reservoir has been identified. Water has been suggested as a possible reservoir because cases have occurred in persons residing near the ocean or large lakes (2, 5, 11, 14, 21). The frequency of *M. haemophilum* disease in the United States appears to be very low, but most cases have been found in the southern region of the country (5). *M. haemophilum* in our population is extremely rare; no isolates of this organism were found in other patients within the same year as the isolate from the patient that we report here. Therefore, we can only speculate that this patient could have become infected with this organism in his area of residence.

*M. haemophilum* is a slowly growing nontuberculous mycobacterium with special growth requirements. It grows optimally at 30°C to 32°C, which may explain the predilection of this organism for infection of cooler areas of the body, such as the extremities, similar to what is observed for *Mycobacterium ulcerans* and *Mycobacterium marinum*. Also, for optimal growth, culture medium must be supplemented with iron-containing compounds, such as ferric ammonium citrate of hemin, and the addition of 10% CO2 to the atmosphere (13, 23). In our laboratory, an additional Middlebrook 7H11 biplate and a chocolate agar plate are incubated at 30°C, with addition of 10% CO2 for mycobacterial isolation from tissues taken from external sites (e.g., skin biopsy specimens, abscesses, or ulcers). This ensures the recovery of these fastidious growth species, which otherwise may have been missed or delayed in diagnosis. Two to three weeks is usually required for confluent growth to be evidenced. However, we were able to identify small mycobacterial colonies 3 days after incubation on chocolate agar plates, probably due to a very heavy inoculum. On microscopic examination, *M. haemophilum* usually appears as a short, beaded bacillus that may exhibit cording similar to that observed with *Mycobacterium tuberculosis* (13, 19, 23). Cord formation, or cording, is considered a virulence factor, first identified in *M. tuberculosis*. Scanning electron microscopy has demonstrated that nontuberculous mycobacteria can also show cording (10). However, the correct interpretation of cording morphology and the way that cord formation occurs remain unknown and are beyond the scope of this report.

Treatment of the *H. capsulatum* lesion on the patient’s right forearm with itraconazole was rapidly effective, as has previously been reported for cutaneous lesions (15). However, there are less data and consensus on treatment of *M. haemophilum* infections. There is no consensus on the duration of therapy, but it is recommended that therapy continue for at least 1 year and perhaps for as long as 2 years (8, 21). There are no standardized antimicrobial susceptibility tests for *M. haemophilum*, and it is not clear how these in vitro test results predict clinical response (21). Published results show discrepancies, and this remarks on the need for standardization of methods for testing antibiotic sensitivity of *M. haemophilum* (2). During the early treatment of our patient, there was a worsening of his condition, which resulted in the appearance of new lesions. However, cultures on these specimens were all repeatedly negative, which supports the conclusion that the treatment was efficacious. This may have been an effect of an immune reconstitution syndrome, a phenomenon that involves newly competent T cells causing acute inflammatory reactions, which can take place with initiation of treatment. Lesions may become worse in the first months before improvement is evidenced (21). As previously mentioned, after 7 months of treatment almost all lesions were completely resolved and the patient was scheduled to complete at least 1 year of treatment.

This case report illustrates the importance of processing specimens for *M. haemophilum*, which remains an important pathogen among transplant patients. In contrast, although cutaneous infection with *H. capsulatum* appears to be uncommon among patients receiving solid-organ transplantation, this infection should be rapidly identified and treated due to potentially fatal dissemination.

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REFERENCES