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Fatal disseminated *Mycobacterium haemophilum* infection involving the central nervous system in a renal transplant recipient

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ABSTRACT

Mycobacterium haemophilum is a slow growing nontuberculous mycobacterium which prefers cooler temperatures and requires iron for growth. It usually causes skin and soft tissue infections in immunocompromised hosts and cervical lymphadenitis in healthy children. We present the case of fatal disseminated M. haemophilum in an immunocompromised host with central nervous system (CNS) involvement. Our case is a 65-year-old Hispanic male with history of end-stage renal disease status post renal transplantation six years prior (on maintenance immunosuppression with mycophenolate, tacrolimus and prednisone), diabetes mellitus type 2, coronary artery disease, ventricular arrhythmias with implantable cardioverter defibrillator, prior stroke and cochlear implant. In the four months preceding admission to our institution he had frequent hospitalizations for altered mental status (AMS), sepsis syndromes and failure to thrive. Two months prior to presentation he developed progressive swelling and redness of the wrists, right third and left fifth digits. Computed tomography (CT) showed extensive cellulitis in distal right forearm and hand with chronic osteomyelitis. Serial incision and drainage (I&D) of right wrist yielded positive AFB stain and growth on AFB culture. PCR was negative for Mycobacterium tuberculosis. Patient was started on rifampin, clarithromycin and ethambutol. Two days later patient developed AMS and severe septic shock requiring transfer to our facility. CT head revealed indeterminate lesion in the left frontal lobe along with nonspecific hypodensities in the pons and thalamus. Repeat CT upper extremities showed osteomyelitis of distal radius and small hand bones with adjacent abscesses. I&D also revealed bilateral tenosynovitis. Cultures were resent. With suspicion for rapidly growing mycobacterial infection, the regimen was changed to linezolid, imipenem and azithromycin. Several changes in antimicrobials were necessary throughout hospitalization due to complicated hospital course. Unfortunately, despite aggressive measures, patient developed multiorgan failure culminating in death 10 days after starting anti-mycobacterial drugs. On the day of death, the organism was identified as M. haemophilum. Susceptibilities were not done as patient had died. On autopsy the brain was noted to have multiple abscesses containing AFB. The organism also grew from the wrists and right finger cultures. M. haemophilum of the CNS is extremely rare and has been reported in HIV or AIDS patients. To our knowledge this is the first reported case of M. haemophilum brain abscesses in a patient without HIV/AIDS. Because of its fastidious growth requirements, M. haemophilum usually shows on acid fast stains but does not grow on routine AFB cultures. Although it prefers lower temperatures for growth and is usually limited to skin and soft tissues, disseminated disease occurs in immunocompromised patients and has high mortality. It is usually treated with a multi drug regimen including clarithromycin, rifampin, ciprofloxacin and amikacin.

1. Introduction

Mycobacterium haemophilum (*M. haemophilum*) is an acid-fast bacillus (AFB) belonging to the nontuberculous mycobacteria (NTM). It is a slow growing mycobacterium that prefers cooler temperatures and requires iron supplementation for growth [1,2]. It is an emerging pathogen that primarily causes infection in severely immunocompromised hosts and rarely, lymphadenitis in healthy children [2–4]. Central nervous system (CNS) infection with *M. haemophilum* is very rare and to date has been reported in individuals with human immunodeficiency virus (HIV)

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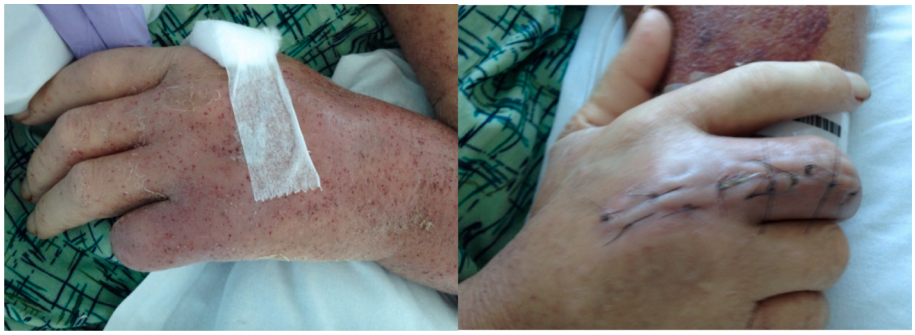

Fig. 1. The patients left and right hand on transfer to our institution. Left hand: demonstrates the excoriated rash as well as swelling and erythema involving the left wrist and fifth digit. Right hand: swelling and erythema of the right third digit with retained sutures from recent incision and drainage.

infection [5], and acquired immune deficiency syndrome (AIDS) [6–10]. Endophthalmitis however, has been reported in a cardiac transplant [11], and two diabetic patients [10,12]. We present the case of a 65-year-old renal transplant recipient diagnosed with *M. haemophilum* tenosynovitis, osteomyelitis and brain abscesses. To our knowledge this is the first reported case of *M. haemophilum* with CNS abscesses in a patient without HIV/AIDS.

2. Case presentation

A 65-year-old male was admitted in transfer to our institution with altered mental status and septic shock. His past medical history was significant for end-stage renal disease and a deceased-donor renal transplantation (DDRT) six years prior to presentation. He was on maintenance immunosuppression with mycophenolate 250 mg twice daily, tacrolimus 2 mg twice daily, and prednisone 5 mg daily. Additional comorbidities included type 2 diabetes mellitus, coronary artery disease, ventricular tachycardia/ fibrillation with implantable cardioverter defibrillator (ICD) in place, history of peptic ulcer disease, cerebrovascular accident (CVA) and cochlear implant. He was originally from Mexico but had not visited there in ten years. At the age of eleven he immigrated to Texas. In the last year of life, his overall health decline prompted a move to live with his daughter in Missouri. He was a retired truck driver. He had no recent close animal exposures. He had no history of exposure to persons with tuberculosis. He was a former smoker with a remote alcohol and cocaine use.

In the four months prior to his presentation, his health had continued to gradually deteriorate leading to multiple complicated hospitalizations at an outside facility primarily for repeated episodes of altered mental status, lethargy, failure to thrive and sepsis syndromes. Infectious diagnoses during these hospitalizations included *Escherichia coli* urosepsis and *Clostridiodes difficile* colitis.

Following each hospitalization, he would improve but never returned to his prior baseline. About two months prior to presentation at our facility, he was noted to have a swollen, red right third digit and wrist. Detailed history did not reveal any inciting injury or relevant water exposures, although it was noted that decline in health resulted in inability to care for self and unsanitary living conditions prior to recent move. A small amount of clear fluid was aspirated from the wrist, but no cultures were sent. On subsequent admission he had progression of redness and swelling of the right third digit and wrist as well as development of new swelling and redness of his left wrist and fifth digit. He was also noted to have a diffuse pruritic, excoriated rash on his chest, back, and extremities. Computed tomography (CT) scan of bilateral wrists and hands revealed extensive cellulitis on the right distal forearm with tiny collections of air, and soft tissue swelling of the right third digit with possible osteomyelitis. There was diffuse bony demineralization and extensive arterio-vascular calcification on the left. Magnetic Resonance Imaging (MRI) could not be done due to his cochlear implant. An incision and drainage (I&D) of his right wrist revealed purulent fluid. Routine cultures showed no growth. A few days later, I&D of his right third digit revealed a deep abscess. The metacarpophalangeal (MCP) joint was opened and irrigated. DNA probe on the purulent fluid for *Mycobacterium tuberculosis* complex was negative. Routine cultures remained negative. However, five days after collection, the AFB culture showed growth at the outside facility. He was started on rifampin 600 mg daily, clarithromycin 500 mg twice daily, and ethambutol 800 mg daily for a presumptive diagnosis of non-tuberculous mycobacterial

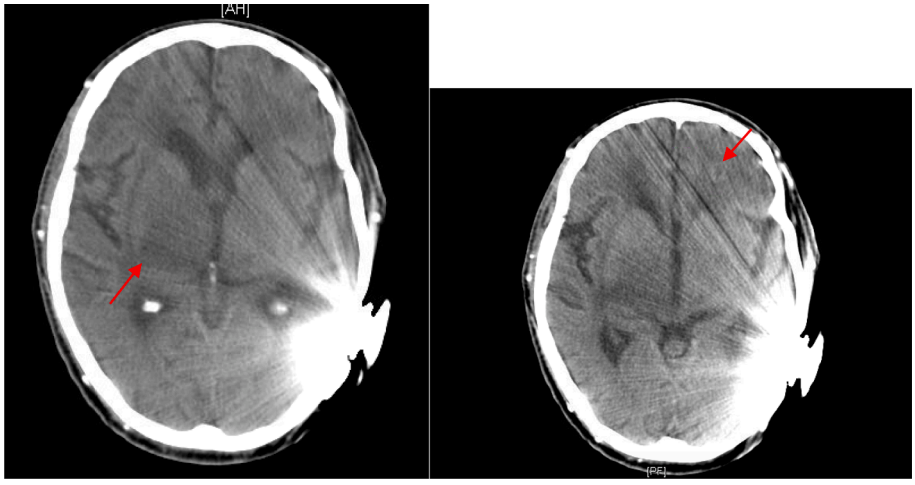

Fig. 2. Computed tomography (CT) head on transfer to our facility demonstrates lesion in the left frontal lobe and hypodensity in the thalamus (red arrows). Metallic artifact is due to the cochlear implant.

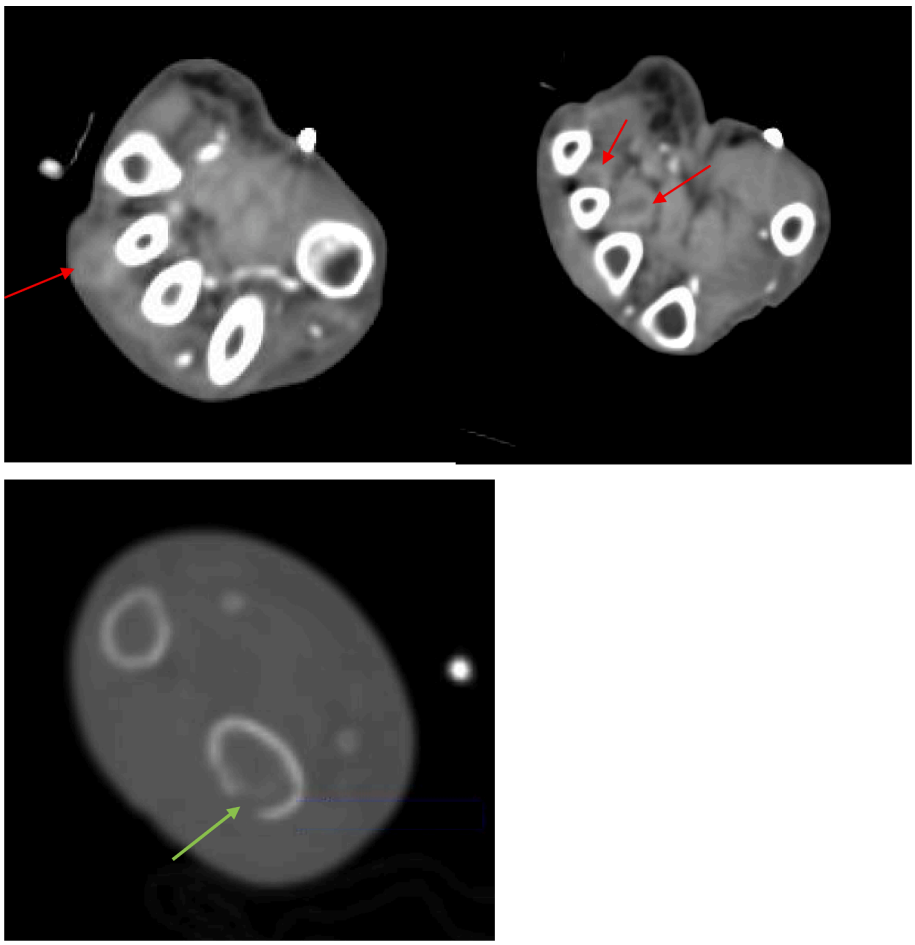

Fig. 3. CT right upper extremity demonstrates abscesses along the dorsal and volar aspects of the third and fourth metacarpals (red arrows), and focal cortical destruction of the right radial metaphysis (green arrow) concerning for osteomyelitis.

(NTM) infection. He was discharged to a skilled nursing facility.

A few days after discharge, his mental status worsened, and he was emergently taken to an outside hospital. On presentation, his vital signs were significant for temperature 32.1 °C, blood pressure 89/68 mmHg, heart rate 74 beats per minute, respiratory rate of 22 breaths per minute and oxygen saturation 90% on room air. Labs revealed severe hypoglycemia with glucose 10 mg/dL, white blood cells (WBC) 12.7k cells/mm^3, lactic acid 5.1 mmol/L, and creatinine 1.4 mg/dL. CT scan of the head revealed progression of the nonspecific right thalamic and basal ganglia lesions previously seen on CT scan four months earlier. He was treated with intravenous (IV) dextrose and fluids and started on IV vancomycin, piperacillin-tazobactam for sepsis. Enteral vancomycin,

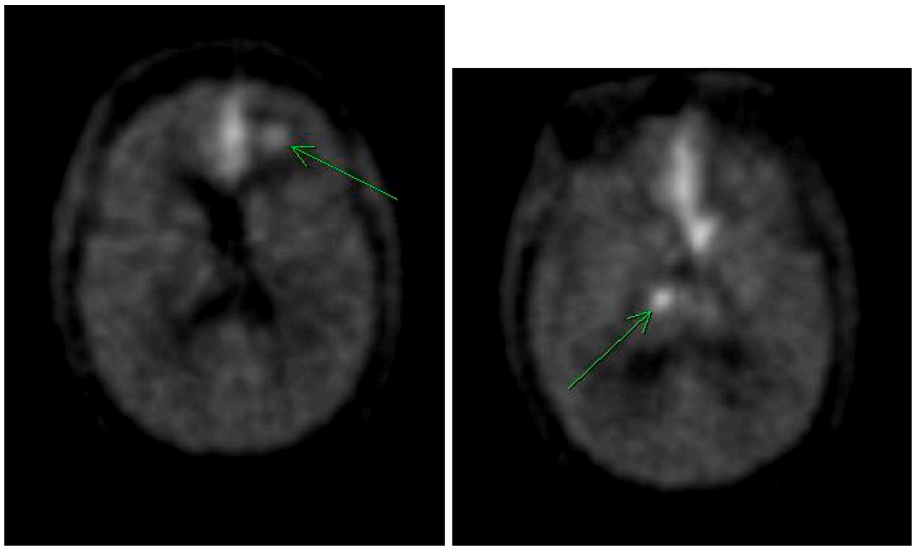

Fig. 4. PET scan of the head demonstrates increased FDG uptake along the medial left frontal lobe lesion and hypodense right thalamic lesion.

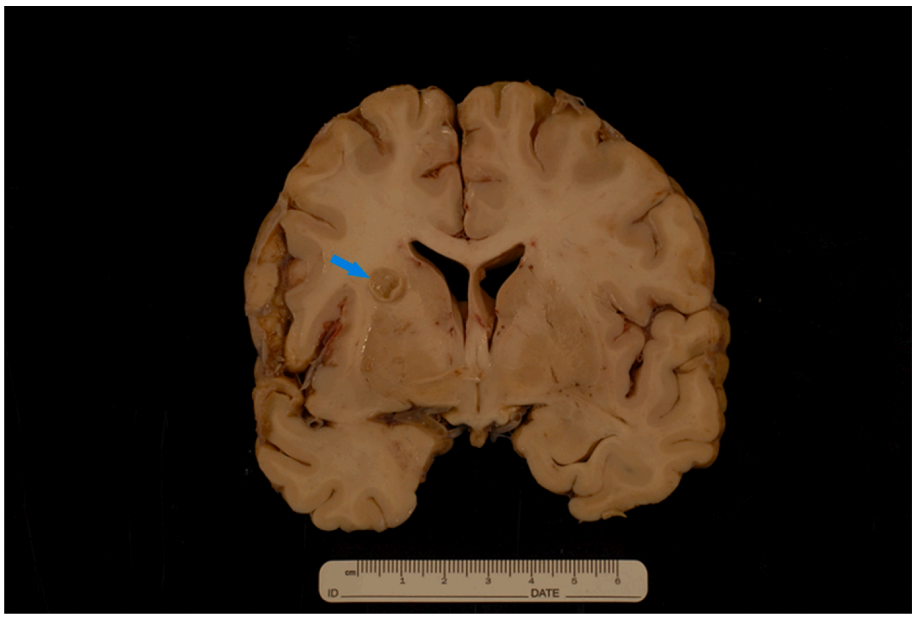

Fig. 5. Brain autopsy gross section. Multiple tan-yellow circumscribed abscesses, ranging from 4 to 10 mm in size, were identified in the brain, including one in the left internal capsule (arrow). Similar lesions were present in the right caudate nucleus, right thalamus, and the left inferior frontal lobe white matter.

rifampin, clarithromycin and ethambutol were continued.

He was then transferred to our facility. Upon examination he was noted to be lethargic, acute and chronically ill appearing. He did not verbalize or follow commands; he would moan in response to pain. There was absence of nuchal rigidity, a well healed ICD surgical scar, benign abdominal exam and diffuse excoriated rash on his chest, abdomen, back and extremities. Right wrist and third digit were swollen, warm, erythematous, tender, and had limited range of motion and retained sutures from recent I&D. The left upper extremity had erythema, warmth, swelling, tenderness and limited range of motion of his fifth digit and wrist [Fig. 1]. A repeat CT head revealed a left frontal lobe indeterminate lesion of possible infectious or neoplastic etiology, and small hypodensities in the pons and thalamus were interpreted as edema or old infarction [Fig. 2]. A lumbar puncture showed an opening pressure of 11.5 cm H_2O, and cerebrospinal fluid (CSF) analysis showed WBC 3 cells/μL, red blood cells (RBC) 2 cells/μL, glucose 40 mg/dL, protein 227 mg/dL and Gram stain was negative. CSF routine, fungal and mycobacterial cultures remained negative. The day of arrival to our institution, a skin biopsy of the diffuse excoriated rash obtained by the referring facility resulted and was consistent with severe scabies.

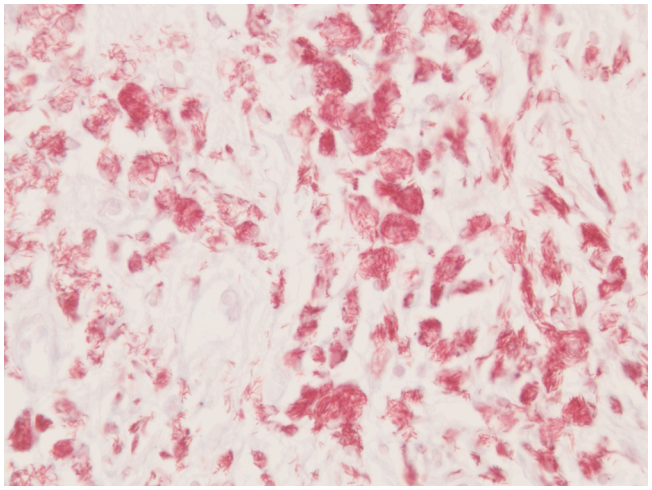

Fig. 6. Acid-fast stain, 40× original magnification. Numerous, short needle-shaped acid-fast organisms packed the cytoplasm of macrophages within the cerebral abscesses.

Ultrasound of his ICD pocket was unremarkable and transesophageal echocardiogram (TEE) showed no evidence of endocarditis. CT of the abdomen and pelvis had of mural thickening of rectosigmoid colon with hypo-enhancing irregular mucosal margin consistent with fulminant rectosigmoid colitis, bilateral pleural effusions, anasarca, and mesenteric stranding. Repeat CT imaging of the right upper extremity showed focal cortical destruction of the right radial metaphysis concerning for osteomyelitis and two small abscesses in the right hand along volar and dorsal aspects of the third and fourth metacarpals [Fig. 3]. CT of the left upper extremity showed findings consistent with osteomyelitis of the distal third metacarpal, adjacent small abscesses in the left hand, and additional abscesses at the ulnar aspect of the wrist within the flexor carpi radialis brevis. Debridement of the infected tissue revealed bilateral extensor tenosynovitis and left fifth digit dorsal infection. Bilateral wrist arthrotomy was without gross evidence of infection. Cultures were sent.

With suspected rapidly growing NTM infection, his antimycobacterial coverage was changed to linezolid and imipenem. The use of a macrolide was limited by a corrected QT interval greater than 600 ms on electrocardiogram. He was continued on enteral vancomycin for C. difficile coverage and empiric IV vancomycin. His immunosuppression was reduced to only prednisone. Scabies was treated with ivermectin and topical permethrin.

Additional infectious workup was negative and included blood and CSF cultures, T-spot, serum cryptococcal antigen, serum Histoplasma antigen and antibody, serum Epstein-Barr virus (EBV) polymerase chain reaction (PCR), serum BK virus PCR, serum Cytomegalovirus (CMV) PCR, cysticercosis IgG. CSF had a negative cryptococcal antigen and CMV PCR. Serum Toxoplasma gondii IgG was positive with a negative IgM. Serum beta-D-glucan was 147 pg/mL. Ferritin was 2,380 ng/mL. Thoracentesis revealed transudative fluid with negative cultures. Positron Emission Tomography (PET) scan revealed increased fluorodeoxyglucose (FDG) uptake along the medial left frontal lobe lesion and hypodense right thalamic lesion [Fig. 4]. Findings did not differentiate infectious versus neoplastic etiology of these cerebral lesions.

Despite aggressive medical care, over the next seven days the

Table 1
Cases of central nervous system *Mycobacterium haemophilum* infection reported in the literature.

Reference	Age, y/ sex	Disease or condition, CD4 cell count/mm^3	Clinical Manifestation	Site of positive culture	Treatment	Duration of treatment (months)	Surgical treatment	Outcome
Pinitpuwadol et al. 2018 [12]	66/ M	DM, HbA1C 8.2%	Endophthalmitis	Vitreous fluid	Imipenem, Levofloxacin, Amikacin with: Levofloxacin eye ggt, Tobramycin eye ointment Local injections Amikacin Imipenem THEN Azithromycin, Doxycycline, Rifampicin	0.5 Intermittent 12	Pars plana vitrectomy and iris membranectomy	Loss of vision no recurrence at the five-year follow-up
Barr et al. 2015 [5]	41/ M	HIV+, 404	CNS intraventricular granuloma	Brain tissue by PCR analysis	Clarithromycin, Rifabutin, Ciprofloxacin	NA	Surgical resection	Resolution of hydrocephalous and control of seizures no radiographic reoccurrence at 10 months follow up
Merkler et al. 2014 [6] Sogani et al. 2014 [7]	44/ M	AIDS, 4	Chiasmitis Hypothalamus Leptomeninges	Optic chiasm by PCR analysis	Azithromycin, Rifabutin Moxifloxacin	2	None	Initial improvement in vision when on treatment but in setting of non-compliance had worsening visual acuity and radiographic progression
Buppajarntham et al. 2015 [8]	35/F	AIDS, 12	Brain abscesses	Brain tissue	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol THEN Ciprofloxacin, Azithromycin Rifampicin. Amikacin	1.5 0.75	None	Died
Phowthongkum et al. 2008 [9]	40/ M	AIDS, 26 DM	Spindle cell pseudotumor of the brain Skin papules	Blood culture *M. haemophilum* Brain culture *M. simiae*	Isoniazid, Rifampin Pyrazinamide Ethambutol, Clarithromycin	3	Partial surgical removal	Clinical improvement with some neurologic deficits Last follow up was 3 months after presentation
Modi et al. 2007 [11]	66/ M	Cardiac transplant DM	Endophthalmitis Skin nodules	Vitreous fluid Skin lesions enucleated eye	Ethambutol, Rifampin Isoniazid, Pyridoxine Pyrimethamine THEN Azithromycin, Gatifloxacin Doxycycline, Rifabutin	1.5 10	Enucleation – 1 year after presentation due to perforation	Progression that resulted in enucleation of the eye Eventual improvement on antimicrobials and with reduction in immunosuppression; no recurrence at 2 year follow up
Nookeu et al. 2019 [10]	25/F	AIDS, 17	Brain abscesses Septicemia	Blood	Azithromycin, Ethambutol Levofloxacin	1	None	Died
Nookeu et al. 2019 [10]	35/F	AIDS, 12	Brain abscesses	Brain tissue	NA	NA	None	Lost to follow up
Nookeu et al. 2019 [10]	35/F	AIDS, 40	Myelitis	Spinal cord tissue	Isoniazid, Rifampin Pyrazinamide, Ethambutol Clarithromycin, Amikacin	2	None	Treatment failure
Nookeu et al. 2019 [10]	65/ M	DM, HbA1C 13.3%	Endophthalmitis	Vitreous fluid	Imipenem, Levofloxacin, Amikacin THEN Azithromycin, Rifampin, Doxycycline	0.5 11.5	None	Cured
Pacholec et al. [current report]	65/ M	Renal transplant DM, HbA1c 6.5%	Brain abscesses Tenosynovitis Osteomyelitis	Wrist and finger tissue/pus	Rifampin , Clarithromycin Ethambutol THEN Linezolid, Imipenem	0.25 0.25	Debridement wrists/hands	Died

* HbA1C, hemoglobin A1C; DM, diabetes mellitus; NA, not available; PCR, polymerase chain reaction.

patient's mental status deteriorated. He developed septic shock requiring multiple vasopressors and mechanical ventilation. His clinical status further declined leading to renal failure with acidosis necessitating renal replacement therapy. With his grim prognosis, the family elected for palliative extubation. The patient died shortly thereafter. After his death, and twenty-five days after the initial I&D at the outside facility, the acid-fast organism was identified as *M. haemophilum*. Additionally, AFB cultures also grew *M. haemophilum* from right third digit and bilateral dorsal wrists collected at our facility. Autopsy revealed multiple brain abscesses containing AFB involving the right caudate nucleus, left frontal white matter, and thalamus [Figs. 5-6]. Acid-fast organisms were also seen in the postmortem skin samples from his wrists along with findings of acute and chronic osteomyelitis.

3. Discussion

We report a fatal case of multifocal brain abscesses and concurrent tenosynovitis and osteomyelitis due to *M. haemophilum.* This case underscores several of the unusual characteristics of *M. haemophilum*; the preference for cooler temperatures for growth and usual involvement of the extensor surfaces of extremities, fastidious nature and difficulty to culture impacting timely identification and treatment, and generally poor outcome in reported cases of *M. haemophilum* with CNS involvement. To our knowledge, this is the first reported case of *M. haemophilum* with CNS abscesses without concurrent HIV infection.

M. haemophilum is an opportunistic organism reported to cause a variety of clinical syndromes in patients with marked suppression of cell-mediated immunity like those with lymphoma, HIV, solid organ or bone marrow transplant recipients [2–4]. Rarely, in healthy children *M. haemophilum* can cause cervicofacial lymphadenitis [2–4]. It most commonly presents as cutaneous infection and can vary in appearance manifesting as papules, nodules, plaques, abscesses or chronic ulcers. As in our patient, skin lesions are most frequently seen in the extremities overlying joints. Other less common manifestations include disseminated infection, pneumonia, septic arthritis, osteomyelitis, pyomyositis, central venous catheter tunnel infections, endophthalmitis, and epididymitis [2].

Our patient's disseminated infection probably started as skin/soft tissue infection over the extensor surfaces of his hands and wrists that later progressed to tenosynovitis, osteomyelitis, and brain abscesses. Extensor surfaces are some of most commonly involved areas of skin and soft tissue likely due to minor injuries and this organism's predilection for body areas with a lower temperature [2]. No reported inciting injury or unusual water exposures could be elicited on history. The natural reservoir(s) of *M. haemophilum* and mode(s) of transmission remain(s) unknown but when *M. haemophilum* has been recovered from the environment it has been in association to water distribution systems and biofilms [13,14]. We suspect that scabies skin infection could have provided a portal of entry. Surgical drainage is not related to dissemination of the infection as a CT scan obtained four months prior to arrival to our institution showed a nonspecific right thalamic lesion which while indeterminate at the time retrospectively correlated with the location of CNS mycobacterial abscesses and developed prior to any surgical intervention. This delay in diagnosis highlights the fastidious nature and difficulty culturing this organism impacting timely diagnosis and treatment.

Diagnosis of *M. haemophilum* can be challenging and the number of cases may be higher than what is reported in the literature. This may be partly because the organism is fastidious with special growth requirements including a lower incubation temperature of 28–30 °C and need for hemin or iron supplementation [1,2,15]. To date, eleveneleven eleven other cases [Table 1] with CNS involvement have been reported in the literature [5–12] including an intraventricular granulomatous mass [5], a spindle cell pseudotumor of the brainstem [9], infection of the optic apparatus and hypothalamus [6,7], lesions involving the brainstem, basal ganglia, and thalamus [8], brain abscesses [10], myelitis [10], and endophthalmitis [10–12]. The outcome for patients with CNS *M. haemophilum* is generally poor. Of the eleven cases mortality and morbidity was high. One patient was lost to follow up. Out of the ten remaining cases, five (50%) experienced treatment failure or death at last follow up. If the cases of endophthalmitis are excluded, 5 out of 7 cases (71%) experienced treatment failure or death at last follow up. The cases that improved with treatment presented as CNS masses; an intraventricular granulomatous mass [5] and a spindle cell pseudotumor of the brainstem [9]. Patients that presented with CNS mass either underwent surgical resection [5] or partial surgical resection [9] in addition to antimicrobials suggesting either that surgical resection or presenting with CNS mass resulted in improved outcome compared to brain abscesses, though both had residual neurologic deficits [5,9]. The poor outcomes could be related to the poor penetration of antimicrobials to the CNS, the fastidious nature and difficulty in culturing and identifying *M. haemophilum* leading to delay in treatment, and the profoundly immunocompromised state of those who are infected. The cases of endophthalmitis had better outcomes with no loss of life. Morbidity was high with enucleation required in 1/3 (33%) [11], loss of vision in 1/3 (33%) [12] and cure in 1/3 (33%) [10]. No patients with endophthalmitis had evidence of relapse or reinfection at follow up.

Clinicians should have a high index of suspicion for *M. haemophilum* in immunocompromised patients with skin lesions and typical NTM manifestations. To optimize chances of detection, evaluation for *M. haemophilum* should be carried out simultaneously along with standard mycobacterial detection methods. Evaluation for *M. haemophilum* should include special culture conditions and if available, use of molecular detection methods with mycobacterial DNA by PCR [16,17]. Additionally, suspicion should be raised for *M. haemophilum* when there is failure to isolate a pathogen using standard mycobacterial culture from a clinical specimen that reveals acid-fast organisms on pathology. Currently, there is no standardized treatment for disseminated *M. haemophilum* infection according to ATS/IDSA guidelines, but multidrug regimens including a macrolide (clarithromycin or azithromycin), a rifamycin (rifampin or rifabutin), and a fluroquinolone (ciprofloxacin or moxifloxacin) have been reported to be successful [15]. Amikacin appears active in vitro, but all isolates are resistant to ethambutol. Most experts would agree that two to four active antibiotics should be used for a prolonged course of at least 12–24 months [2,5]. If possible, immunosuppression should be reduced during acute infection.

4. Ethical guidelines statement

All ethical guidelines have been met according to the standards of the journal in the production and submission of this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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