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Left hand necrosis as the initial presentation of disseminated mucormycosis: A case report and literature review

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ABSTRACT

Cutaneous mucormycosis typically occurs as a primary infection following traumatic inoculation or as a secondary disseminated disease in immunocompromised patients with hematologic malignancy or organ transplantation. We describe an unusual case of a poorly controlled type 1 diabetic patient presenting with wet gangrene of the hand due to angioinvasive dissemination from a primary pulmonary infection, with additional suspected foci of cardiac and central nervous system involvement. Despite combined medical and surgical treatment, the patient ultimately died due to complications of her infection. This case and the associated literature review of secondary cutaneous mucormycosis highlight that invasive fungal infections can present peripherally, and identifying the primary source is important in order to promptly pursue aggressive combined medical and surgical treatment for this highly fatal disease.

Case Presentation

A 47-year-old female with a medical history significant for poorly controlled type 1 diabetes mellitus (T1DM), heart failure with a mildly reduced ejection fraction of 47%, mild severe acute coronavirus respiratory virus-2 (SARS-COV-2) two months prior (did not receive steroids), and left lower extremity deep vein thrombosis, presented with altered mental status and a burning sensation of her left hand. On examination she was cachectic, only alert to self, and appeared comfortable. She had a blood pressure of 104/65 mm/Hg, pulse of 88 beats/min, respiratory rate of 20 breaths/min, and oxygen saturation of 99% on room air. Exam revealed wet gangrene of the left fourth digit. The remainder of her physical exam was unremarkable. Pertinent laboratory results included leukocytosis (white blood cell count of 15 ×10(9)/L), acute kidney injury with a creatinine of 6.63 mg/dl, and diabetic ketoacidosis (DKA) with a glucose of 746 mg/dl and anion gap of 30. X-ray of the left hand revealed atrophy of the fourth digit with subcutaneous gas. Computerized tomographic (CT) scan of the brain was unremarkable while CT scan of the abdomen and pelvis revealed consolidative and reticular opacities in the right lower lung. Subsequent CT scan of the chest showed a cavitary right lower lobe lesion with possible reversed halo sign. She was started on vancomycin, piperacillin-tazobactam, and clindamycin for empiric antimicrobial coverage and admitted to the intensive care unit (ICU) for management of DKA and sepsis from suspected pulmonary and skin/soft tissue infections.

After resolution of DKA on hospital day 2, the patient was taken to the operating room for amputation of her left fourth digit given concern for a necrotizing hand infection from a gas-producing organism. No viable tissue was observed throughout the hand; therefore, left wrist disarticulation was performed. Given worsening leukocytosis which peaked at a white blood cell count (WBC) of 54,320, antimicrobial coverage was broadened to vancomycin, meropenem, and doxycycline with the addition of liposomal amphotericin B on hospital day 3 due to concern for underlying invasive fungal infection (IFI). At this point, initial diagnostic work-up was pending which included surgical pathology results, infectious studies (bacterial, fungal, and mycobacterial cultures), and an autoimmune laboratory panel.

Bronchoscopy was performed which revealed infiltrates of the right middle and lower lobe with diffuse necrotic tissue past the

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Fig. 1. *Rhizopus*, lactophenol cotton blue prep, 10x (left hand surgical specimen).

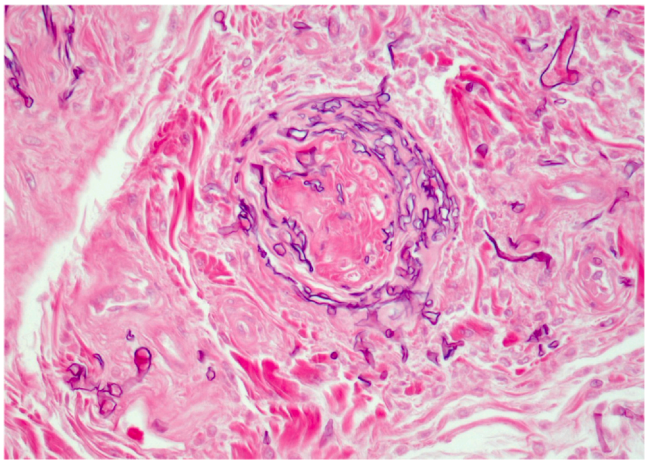

Fig. 3. Hyphae within a nerve, H&E, 20x (left hand surgical specimen).

right lower lobe bronchus with fibrinous clot, findings which were concerning for IFI. Thoracic surgery was consulted for operative management and a right lower lobectomy was performed for surgical source control through a posterolateral thoracotomy. Posaconazole was added to her anti-fungal regimen. Further evaluation for dissemination of IFI revealed bilateral frontal lobe punctate infarcts on magnetic resonance imaging (MRI) of the brain and a 1.6 centimeter right atrial vegetation with a patent foramen ovale (PFO) on transesophageal echocardiography (TEE). The patient was taken for urgent AngioVac extraction of the right atrial vegetation given her elevated risk of right-to-left embolization through her PFO. Intraoperatively, a small vegetation was noted that was not the same vegetation seen on pre-operative TEE, which was suspected to have embolized. No tissue was obtained for culture or pathology.

Outcome

The bronchoalveolar lavage cytologic specimen, right lower lobe surgical specimen, and left hand surgical specimen all demonstrated pauciseptate hyphae of a zygomycete and the associated cultures grew a *Rhizopus* species (Fig. 1). Notably, the hand surgical pathology noted hyphae present within vessels and around nerves (Figs. 2 and 3), suggestive of vascular spread rather than cutaneous inoculation. The patient remained stable post-operatively and was transferred to the general medicine floor. However, she was re-admitted to the ICU for hypothermia and hypotension requiring vasopressor support and had a prolonged hospital course complicated by acute metabolic encephalopathy, bilateral pleural effusions (managed with percutaneous drains), acute kidney injury, and mixed transaminitis thought secondary to antifungal medications. Eventually, given the poor prognosis of disseminated mucormycosis and the patient's progressive renal and hepatic dysfunction, the patient's family decided to discontinue further treatment. The patient was transitioned to comfort care and passed away a few days later.

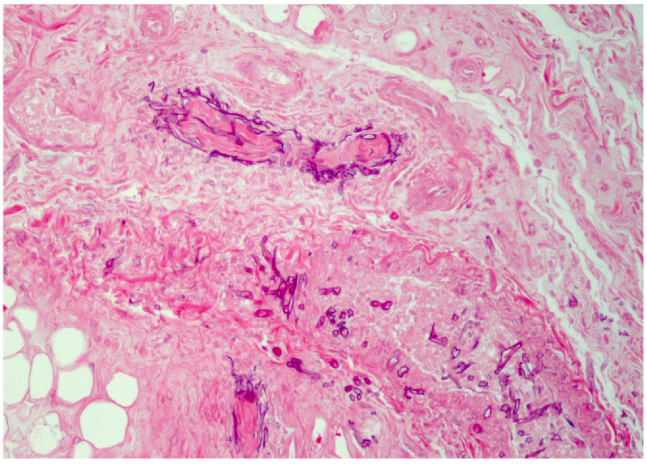

Fig. 2. Intravascular and perineural hyphae, H&E, 10x (left hand surgical specimen).

Discussion

In this report, we present a case of pulmonary mucormycosis with hematogenous dissemination causing cutaneous disease in the hand. Most cases of cutaneous mucormycosis are primary in nature, arising from direct inoculation of fungal spores in the skin. However, a minority of cutaneous cases are secondary to hematogenous dissemination, most commonly from a primary lung source as evidenced in our case [1]. Seeding of peripheral organs from primary pulmonary mucormycosis is a rare finding and raises several key questions: How exactly does this happen and why is there such heterogeneity in the tropism and degree of skin involvement in disseminated disease? Are certain patients more prone to developing this disease pattern and are there factors which are predictive of death?

The largest review of 929 mucormycosis cases by Roden et al. [2] found that secondary cutaneous infections are extremely rare, occurring in only 6 (3%) of the cutaneous mucormycosis cases analyzed. To better understand the manifestations, management, and outcomes of secondary cutaneous mucormycosis due to primary pulmonary involvement, a MEDLINE literature review was performed.

A search string comprised of "mucormycosis AND cutaneous," "zygomycosis AND cutaneous," "mucormycosis AND skin," "zygomycosis AND skin," was performed. Five hundred and ten (510) articles were identified. Each article was reviewed for secondary disseminated cutaneous mucormycosis from a primary pulmonary source. Seventeen case-based studies were identified and selected. Relevant data concerning number of affected patients, causative organism, cutaneous location, organ involvement, treatment intervention, and mortality outcomes from these case studies were extracted and tabulated in Table 1.

The mean age of the patients was 47.9 ± 15.0 years (range: 20–69). All fifteen patients were immunocompromised as their risk factor for mucormycosis; however, none of the patients had poorly controlled T1DM as their sole immunocompromising condition, as was seen in our case. Fourteen patients (93.3%) had an underlying

Table 1
Cases of secondary disseminated cutaneous mucormycosis from a primary pulmonary source.

Author	Year	Age/Gender	Organism	Immunocompromised State	Cutaneous Location	Other Organs Involved	Antimicrobials, (Dosage)	Clinical Course
Ding[3]	2020	52/M	Mucor spp.	Acute Lymphoblastic Leukemia	Thigh (Present 10 Days Prior to Hospital Admission)	Lungs	Amphotericin B (50 mg/d), Posaconazole (800 mg/d)	Resolution 4 weeks after treatment
Menzinger[4]	2019	27/W	Rhizomucor pusillus	Acute Myelomonocytic Leukemia with Immunosuppressive Therapy	Palm	Lungs	Not Specified	Not Specified
Taj-Aldeen[6]	2017	55/M	Mucor indicus	Diabetes, Liver Transplant with Tacrolimus and Mycophenolate Therapy, High-Dose Prednisolone Therapy for Pneumocystis jirovecii Infection	Knee, Thigh	Right Lung	Liposomal Amphotericin B (5 mg/kg/d) and Piperacillin/Tazobactam followed by R. Anterolateral 5th Intercostal Thoracotomy for Removal of Fungus Ball	Discharge after 3 months of antifungal therapy and surgical intervention
Iyengar[7]	2017	60/M	Rhizopus spp	Chronic Lymphocytic Leukemia	Thigh, Chest	Lungs	Liposomal Amphotericin B (2 doses of 3 mg/kg/day followed by 500 mg IV daily)	Death due to acute left cerebellar infarct related to fungal emboli and acute respiratory failure 5 days after admission
Kanemaru[8]	2016	62/W	Rhizopus oryzae	Treatment-Related Myelodysplastic Syndrome with Bone Marrow Transplant	Right Lower Limb	Lungs	Liposomal Amphotericin B (3 mg/kg/d)	Death 2 weeks after admission for cutaneous lesions
Peixoto[9]	2014	59/M	Rhizomucor pusillus and miehei	Acute Myelogenous Leukemia	Face, Scalp, Neck, Back	Right Lung, Brain	Liposomal Amphotericin B (5 mg/kg) later switched to Posaconazole (200 mg qid), Isavuconazole (600 mg/d loading dose followed by 200 mg/d)	Improved status, Death due to refractory leukemia after 29 weeks of Isavuconazole treatment
Hsieh[10]	2013	69/M	Cunninghamella bertholletiae	Acute Myeloid Leukemia, Neutropenia	Forehead, R. Index Finger, R. 1st, 5th toe, and L 1st toe	Lungs	Amphotericin B (0.5 mg/kg/d)	Death 11 days after admission
Sugui[11]	2011	57/F	Mucor velutinosus	Acute Myelogenous Leukemia	Forehead, Back	Right Lung	Liposomal Amphotericin B (7.5 mg/kg/d), Fluconazole (for Candida parapsilosis)	Death due to multiorgan failure 31 days after the onset of infection
Hocker[13]	2010	45/M	Rhizomucor sp.	Acute Myeloid Leukemia, Neutropenia	Abdomen	Lung	Liposomal Amphotericin B, G-CSF, Partial Lung Resection and Excision of Subcutaneous Abscesses on Abdominal Wall	Resolution, Time frame not specified
Darrisaw[14]	2000	46/F	Cunninghamella spp.	Chronic Myelogenous Leukemia with Bone Marrow Transplant and Prednisone Use	Lower Extremity	Lungs	Liposomal Amphotericin B (5 mg/kg)	Death due to multi-system organ failure 20 days after admission
Cuvelier[15]	1998	35/F	Mucor spp.	T-Cell Large Granular Lymphocytic Leukemia	Whole Body Surface	Lungs, Heart, Liver, Brain, Kidneys	Cotrimoxazole, Erythromycin, Anti-Cytomegalovirus globulin, Fluconazole (400 mg/d)	Death due to refractory septic shock and respiratory failure 10 days after admission
Peñas[16]	1995	54/F	Unknown Mucorales	Acute Myelogenous Leukemia, Neutropenia	Thigh, Trunk, Abdominal Flank, Nose, Finger	Lungs, Liver, Brain, Heart, Stomach, Large and Small Intestine, Kidneys	Amphotericin B	Death due to brainstem compression by intracerebral hemorrhage 13 days after admission
Myskowski[17]	1983	20/F	Rhizpus rhizopodiformis	Idiopathic Aplastic Anemia with Prednisone Treatment and Bone Marrow Transplant	Thigh	Lungs	Amphotericin B (1 mg/kg)	Death due to respiratory failure 38 days after admission
Kramer[18]	1977	20/F	Mucor pusillus	Acute Lymphoblastic Leukemia	Abdomen	Lungs, Liver, Kidney, Brain	None, due to rapid progression	Death due to cavitary pneumonia and cerebral infarction 120 days after admission
Meyer[19]	1973	58/M	Mucor pusillus	Acute Granulocytic Leukemia	Chest, Heel	Lungs, Heart, Small bowel, Liver, Pancreas, Spleen, Kidneys, Thyroid, Bone Marrow	Rifampin (900 mg/d), Isoniazid (300 mg/d), Carbenicillin Disodium (5 g q4h), Oxacillin (1.5 g q6h), Gentamicin (40 mg q6h for suspected Pseudomonas; no antifungals due to post-mortem diagnosis of Mucor)	Death due to cardiorespiratory arrest 11 days after admission

hematologic malignancy/bone marrow transplant (BMT) while one patient had diabetes mellitus, a liver transplant and treatment with high-dose prednisolone for *Pneumocystis jirovecii* infection. Five patients (33.3%) were noted to have additional multiorgan dissemination aside from the skin and lung, four of whom succumbed to their disease. Only two of the five patients with multiorgan involvement beyond the lung and skin received amphotericin B, and only one of those patients survived. Five patients (33.3%) experienced cutaneous lesion(s) of the upper limb, five patients (33.3%) experienced cutaneous lesion(s) of the lower limb, and five patients (33.3%) experienced cutaneous lesion(s) in both areas. For treatment, eleven patients (73.3%) received amphotericin B and four of those survived. Two patients underwent surgery for source control and administration of amphotericin B, and both patients experienced clinical resolution of their illness. Among the fourteen cases with specified outcomes, ten patients succumbed to complications due to their disseminated mucormycosis (71.4%).

Multi-organ involvement outside of the lungs and skin affected one-third of the patients with secondary cutaneous mucormycosis and 80% of these patients succumbed to their illness. Unfortunately, due to the absence of tissue biopsies in our patient, we were unable to determine whether the right atrial vegetation or frontal lobe infarct represented further sites of disseminated mucormycosis. However, based on the extent of disease, we believe this was likely the case. Data is limited in delineating the true natural history of this disease, particularly with rates and sites of dissemination. However, given the angioinvasive nature of Mucorales infections, we can assume that progressive multi-organ involvement leads to increased mortality and that early diagnosis, perhaps due to more effective surgical control, may improve outcomes in affected patients.

Based on our literature review, it seems that the major predisposing risk factors for development of disseminated mucormycosis are underlying hematologic malignancy or an organ transplant/BMT. Notably, there were no patients with poorly controlled T1DM as their sole risk factor for development of secondary cutaneous mucormycosis. To our knowledge, in this report, we describe the first patient to have developed this condition with T1DM as their only risk factor. Despite expeditious surgical resection of pulmonary and cutaneous disease and appropriate medical therapy, the patient presented in this paper unfortunately died within six weeks of surgical resection, highlighting the extremely aggressive and fatal natural history of this disease process. Therefore, it is prudent to include disseminated mucormycosis on the differential diagnosis when encountering a patient with poorly controlled T1DM presenting with a suspected fungal respiratory infection and skin necrosis. Peripheral signs of an invasive fungal infection should raise suspicion for disseminated disease and prompt a search for a primary source.

Finally, it is worth mentioning that administration of high dose corticosteroids is a major risk factor for developing mucormycosis, as evidenced by one of the patients studied as well as emerging cases being described associated with treatment of severe SARS-CoV-2 infections. [20] However, our patient had only mild SARS-CoV-2 infection that was not treated with corticosteroids and had resolved, so the contribution of this infection to her disseminated mucormycosis is less clear.

Conclusions

Members of the order Mucorales cause devastating infections in immunocompromised individuals, including those with poorly controlled T1DM. Mucormycosis has variable presentations, most commonly presenting as rhino-orbital-cerebral or pulmonary infections. However, it is important to recognize that there may be atypical manifestations related to the angioinvasive nature of these organisms and their ability to cause tissue infarction at secondary sites. Thus, in patients with peripheral signs of IFI, it is critical to consider the presence of disseminated disease and search for a possible primary source in order to pursue early surgical debridement. In our patient with uncontrolled T1DM found to have pulmonary mucormycosis, cutaneous necrosis served as an early clue to an IFI. Early recognition of disseminated mucormycosis and prompt treatment with antifungal medications and surgical source control are key to improving outcomes for this fatal disease.

CRediT authorship contribution statement

Phen, Ali, Hoff, Yagnik: Roles, Writing – original draft, Writing – review & editing, Formal analysis; **Cutrell, Waters**, **Odedosu**: Supervision, Writing – review & editing, Formal analysis; **Phen, Ali**: Investigation, Formal analysis, Writing – review & editing.

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Declarations of Interest

None.

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Patient Consent Statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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