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.

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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) 2 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 which peaked at a white blood cell count (WBC) of 15 ×10(9)/L, acute kidney injury with a creatinine of 6.63 mg/dl, and diabetic ketoacidosisis (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...
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 paucisepitate 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.

**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

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

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

**Fig. 3.** Hyphae within a nerve, H&E, 20x (left hand surgical specimen).
| 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-Akleen[6] | 2017 | 55/M       | Mucor indicus             | Diabetes, Liver Transplant with Tacrolimus and Mycophenolate Therapy, High-Dose Prednisolone Therapy for Pneumocystis jiroveci Infection | Knee, Thigh                         | Right Lung                                                                           | Liposomal Amphotericin B (5 mg/kg/day) 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/day)                                               | Death due to cutaneous lesions                                                  |
| Peixoto[9]   | 2014 | 59/M       | Rhizomucor pusillus and miehei | Acute Myelogenous Leukemia                                                          | Face, Scalp, Neck, Back             | Right Lung                                                                           | Liposomal Amphotericin B (5 mg/kg) later switched to Posaconazole (200 mg qid), Itraconazole (600 mg/d loading dose followed by 200 mg/d) | Death due to refractory leukemia after 29 weeks of Itraconazole 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                                                                                 | Liposomal Amphotericin B (7.5 mg/kg/d), Fluconazole (for Candida parapsilosis)         | Death due to multiorgan failure 31 days after the onset of infection              |
| Sugui[11]    | 2011 | 57/F       | Mucor velutinosus         | Acute Myelogenous Leukemia                                                            | Forehead, Back                      | Right Lung                                                                           | Liposomal Amphotericin B, G-CSF, Partial Lung Resection and Excision of Subcutaneous Abscesses on Abdominal Wall | Death due to refractory septic shock and respiratory failure 10 days after admission |
| Hocket[13]   | 2010 | 45/M       | Rhizomucor sp.            | Acute Myeloid Leukemia, Neutropenia                                                   | Abdomen                             | Lung                                                                                  | Liposomal Amphotericin B (5 mg/kg)                                                  | 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 Granulat 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       | Rhizopus 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 cavitory pneumonia and cerebral infarction 120 days after admission |
| Meyer[19]    | 1973 | 58/M       | Mucor pusillus            | Acute Granulocytic Leukemia                                                           | Chest, Heel                         | Lungs                                                                                 | Rifampin (900 mg/d), Isoniazid (300 mg/d), Carbencillin Disodium (5 g q4h), Oxacillin (1.5 g q6h), Gentamycin (40 mg q6h for suspected Pseudomonas) | Death due to cardiopulmonary 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 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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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 IFl, 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.
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