

Painful Necrotic Ulcer on the Vulva

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A 48-year-old woman with relapsed T-cell acute lymphoblastic leukemia was admitted to the oncology service for salvage chemotherapy and allogeneic stem cell transplant. Her admission was complicated by extended-spectrum β -lactamase-producing *Escherichia coli* sepsis

and persistent pancytopenia, which required transfer to the intensive care unit. After 2 weeks and while still in the intensive care unit, she developed a painful necrotic vulvar ulcer over the right labia and clitoris that progressed and formed an overlying black eschar.

What's the diagnosis?

- a. ecthyma gangrenosum
- b. Fournier gangrene
- c. herpes simplex infection
- d. leukemia cutis
- e. mucormycosis

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The Diagnosis: Mucormycosis

Skin biopsy and histology revealed broad, wide-angle, branched, nonseptate hyphae suggestive of mucormycosis infection (Figure 1). Computed tomography of the abdomen and pelvis revealed marked stranding in the vulvar region and urothelial thickening and enhancement suggestive of infection (Figure 2). Computed tomography of the chest demonstrated multiple irregular nodules in the bilateral upper lobes consistent with disseminated mucormycosis (Figure 3). The patient was started on intravenous amphotericin B and posaconazole. Surgery was not pursued given the poor prognosis of her refractory acute lymphoblastic leukemia, pancytopenia, and disseminated fungal infection. The patient was discharged home with hospice care.

Mucormycosis is an infection caused by fungi that belong to the order Mucorales. The most common genera responsible for human disease are *Rhizopus*, *Mucor*, and *Rhizomucor*, which are organisms ubiquitous in nature and found in soil.¹ Mucorales hyphae are widely branched and primarily nonseptate, which distinguishes them from hyphae of ascomycetous molds such as *Aspergillus*, which are narrowly branched and septate.

Mucormycosis primarily affects immunocompromised individuals. The overall incidence of mucormycosis is difficult to estimate, and the risk for infection varies based on the patient population. For example, the incidence of mucormycosis in hematologic malignancy ranges from 1% to 8% and from 0.4% to 16.0% in solid organ transplant recipients.² One large series of 929 cases noted that the most common risk factors were associated with impaired immune function including diabetes mellitus and diabetic ketoacidosis (36% of cases), hematologic malignancy (17%), and solid organ (7%) or bone marrow transplantation (5%). Other risk factors include neutropenia, steroid therapy, and other immunocompromising conditions.³ Healthy individuals have a strong natural immunity to mucormycosis and rarely are affected by the disease.²

The host response to Mucorales is primarily driven by phagocyte-mediated killing via oxidative metabolites and cationic peptides called defensins.¹ Thus, severely neutropenic patients are at high risk for developing mucormycosis.¹ In contrast, it appears as though AIDS patients are not at increased risk for mucormycosis, supporting the theory that T lymphocytes are not involved in the host response.¹ The conditions of diabetic ketoacidosis leave patients

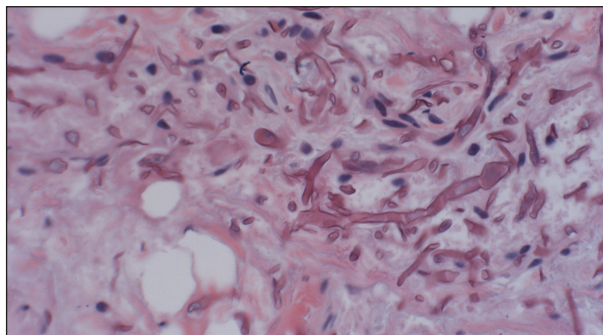


Figure 1. Histology demonstrated broad, wide-angle, branched, nonseptate hyphae suggestive of mucormycosis (H&E, original magnification $\times 400$).

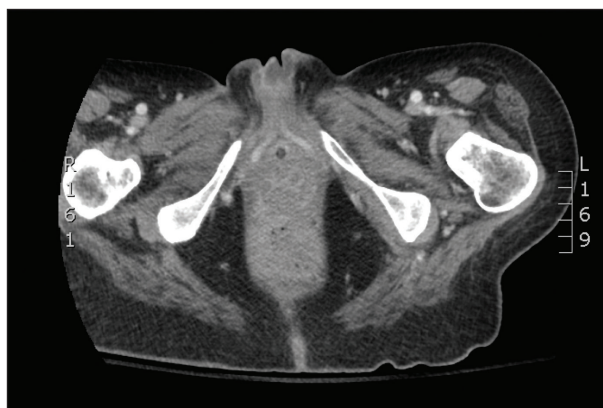


Figure 2. Computed tomography of the abdomen and pelvis demonstrated marked stranding in the vulvar region and urothelial thickening and enhancement suggestive of mucormycosis.

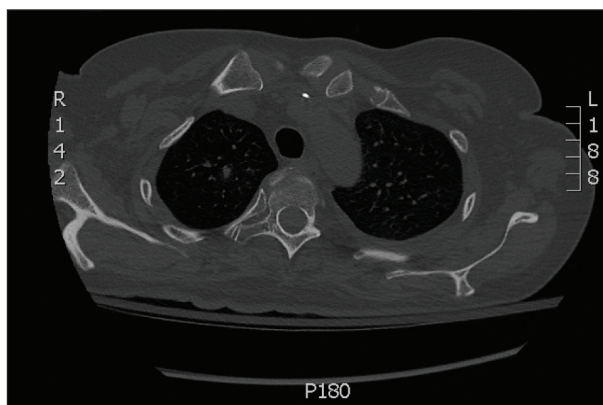


Figure 3. Computed tomography of the chest demonstrated multiple irregular nodules in the bilateral upper lobes consistent with disseminated mucormycosis.

susceptible to mucormycosis for several reasons. First, hyperglycemia and low pH induce phagocyte dysfunction and thus inhibit the host response to Mucorales.⁴ Second, these organisms have an active ketone reductase system that may allow them to grow more readily in high glucose, acidic conditions.¹ Third, diabetic ketoacidosis conditions increase serum free iron, and Mucorales utilizes host iron for cell growth and development.¹ Individuals such as hemodialysis patients receiving the iron chelator deferoxamine also are at risk for mucormycosis, as *Rhizopus* can bind to this molecule and transport the bound iron intracellularly for growth utilization.¹

Mucormycosis infection is characterized by infarction and rapid necrosis of host tissues resulting from vascular infiltration by fungal hyphae. The most common site of infection is rhino-orbital-cerebral (39%), followed by lungs (24%) and skin (19%).³ Dissemination occurs in 23% of cases.³ Inoculation most commonly occurs via inhalation of airborne fungal spores by an immunocompromised host with resultant fungal proliferation in the paranasal sinuses, bronchioles, or alveoli. Gastrointestinal tract infection is presumed to occur via ingestion of spores.⁵

Cutaneous infection, as in our patient, occurs via the inoculation of spores into the dermis through breaks in the skin such as from intravenous lines, urinary catheters, injection sites, surgical sites, and traumatic wounds. Cutaneous infections typically present as a single erythematous, painful, indurated papule that rapidly progresses to a necrotic ulcer with overlying black eschar. In some cases, the progression may be more indolent over the course of several weeks.² There are few reported cases of primary vulvar mucormycosis, as in our patient.^{6,7} The previously reported cases involved severely immunocompromised patients who developed large necrotic lesions over the vulva that demonstrated widely branching, nonseptate hyphae on histologic examination. Each patient required extensive surgical debridement with systemic antifungal treatment.^{6,7}

A timely diagnosis of mucormycosis often hinges on a high index of suspicion on behalf of the clinician. A fungal etiology always should be considered for an infection in an immunocompromised patient. Furthermore, nonresponse to antibiotic treatment should be an important diagnostic clue that the infection could be fungal in origin. The definitive diagnosis of mucormycosis is confirmed by tissue biopsy and

the presence of broad, widely branching, nonseptate hyphae seen on histopathologic examination.

Treatment involves aggressive surgical debridement of all necrotic tissues and elimination of predisposing factors for infection such as hyperglycemia, metabolic acidosis, deferoxamine administration, and immunosuppressive medications. Early initiation of antifungal therapy with the lipid formulation of amphotericin B is recommended. Oral posaconazole or isavuconazole typically are used as step-down therapy after a favorable clinical response with initial amphotericin B treatment. Deferasirox, in contrast to deferoxamine, is an iron chelator that may reduce the pathogenicity of Mucorales and may help as an adjunctive therapy.⁸ In addition, hyperbaric oxygen therapy may have limited benefit in some cases.⁹ In spite of these treatments, the overall mortality of mucormycosis is 50% or higher and approaches nearly 100% in cases of disseminated disease, such as in our patient.^{1,3}

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