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Rapidly progressive cutaneous *Rhizopus microsporus* infection presenting as Fournier's gangrene in a patient with acutemyelogenous leukemia

C.M. Durand[1], **C.D. Alonso**[1], **A.P. Subhawong**[2], **N.P. Kwiatkowski**[3], **M. Showel**[4], **K.C. Carroll**[3], and **K.A. Marr**[1,4]

[1]Division of Infectious Diseases, Johns Hopkins University, Baltimore, Maryland, USA

[2]Department of Pathology, Johns Hopkins University, Baltimore, Maryland, USA

[3]Division of Medical Microbiology, Johns Hopkins University, Baltimore, Maryland, USA

[4]Department of Oncology, The Sidney Kimmel Cancer Center, Johns Hopkins, Baltimore, Maryland, USA

Abstract

Members of the genus *Rhizopus* within the class Zygomycetes can cause devastating opportunistic infections. Cutaneous disease arising from direct inoculation of fungal spores has the potential to disseminate widely. Here, we describe a dramatic case of cutaneous *Rhizopus* infection involving the penis in a patient with acute myelogenous leukemia. Despite aggressive surgical debridement, systemic antifungal therapy, and donor lymphocyte infusion, the infection was ultimately fatal. This case illustrates the unique diagnostic and therapeutic challenges in the clinical management of cutaneous *Rhizopus* infection.

Keywords

Rhizopus; Zygomycetes; zygomycosis; mucormycosis; Fournier's gangrene; penile infection

Zygomycetes are ubiquitous in nature and can cause fulminant infections in the immunocompromised host. Known risk factors include hematologic malignancy, neutropenia, diabetes mellitus, steroid use, and trauma (1). A recent increase in the incidence of zygomycosis compared with candidiasis or aspergillosis may be explained by increasing use of antifungal agents lacking activity against Zygomycetes, in addition to the increasing numbers of higher risk bone marrow transplants (2). Organisms in the genus *Rhizopus* cause the majority of human infections. They typically manifest as cutaneous, rhino-cerebral, pulmonary, or gastrointestinal infection and may progress to disseminated disease.

Cutaneous disease may arise either from direct inoculation of the skin, or less commonly, from hematogenous dissemination. Genital infection is exceedingly uncommon and only 4 cases involving the penis have been reported in the medical literature (3–6). Our case illustrates the diagnostic challenge of penile infection caused by *Rhizopus*. One of the key diagnostic dilemmas is that the appearance of skin lesions secondary to *Rhizopus* may be

Correspondence to: Kieren A. Marr, MD, Transplant and Oncology Infectious Diseases, Johns Hopkins University School of Medicine, 720, Rutland Ave., Ross 1064, Baltimore, MD 21205, USA, Tel: 410-614-9141, Fax: 410-614-0714, kmarr4@jhmi.edu.

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confused with viral eruptions, cutaneous leukemia, and bacterial necrotizing infection. The anatomy, physiology, and lymphatic drainage of the penis and perineum may predispose to rapid dissemination into the deep tissues of the pelvis with nearly universally fatal results. Current management strategies including novel adjuvant therapies are discussed.

Case report

A 53-year-old male with acute myelogenous leukemia (AML) was admitted to the hospital with one day of fever. He reported several months of malaise but no additional localizing symptoms. His past medical history was significant for diffuse large B-cell lymphoma, treated with chemotherapy and autologous bone marrow transplantation 9 years earlier. One month before admission, he was diagnosed with AML with trilineage dysplasia, presumably secondary to his prior chemotherapy.

Medications on admission included norfloxacin and val-acyclovir. He was not receiving antifungal prophylaxis. Before his admission, he had not started any chemotherapy for his AML. On physical exam, his temperature was 38.5°C, heart rate was 106 beats/min, blood pressure was 105/63 mm Hg, respiratory rate was 18 breaths/min, and oxygen saturation was 100% on room air. Physical examination including evaluation of the sinuses, chest, and skin was unremarkable. Laboratory data were significant for a white blood cell count of 3010 cells/mm^3 with 33% polymorphonuclear cells (absolute neutrophil count of 1447 cells/mm^3), 7% blasts, and 5% young unidentified cells. His hematocrit was 25% and platelet count was 7 K/mm^3. Computed tomography of the sinuses and chest were unrevealing. The patient was started on intravenous (IV) broad-spectrum antimicrobial agents including piperacillin-tazobactam (4.5 g IV every 6 h), vancomycin (1 g IV every 12 h), and micafungin (100 mg IV every 24 h).

His fevers abated within the first week without determination of a clear infectious etiology. Micafungin was discontinued but broad-spectrum antibacterial coverage with piperacillin–tazobactam and vancomycin was continued. On hospital day 7, he was initiated on chemotherapy with cytarabine, daunorubicin, and etoposide. On hospital day 10, the patient had new onset chest pain with diffuse ST elevations seen on electrocardiogram, elevated cardiac enzymes (peak troponin I 19.9 ng/mL; normal <0.06 ng/mL), and a depressed cardiac ejection fraction of 45%. He was diagnosed with myopericarditis and was treated with methyl-prednisolone sodium succinate 125 mg IV every 6 h. Blood sugars ranged from 200 to 300 mg/dL and subcutaneous insulin was initiated for steroid-induced diabetes mellitus.

By the second week of hospitalization, the patient had progressive renal dysfunction secondary to acute tubular necrosis. Piperacillin–tazobactam was switched to meropenem out of concern for nephrotoxity. A Foley catheter was placed for documentation of the urinary output. The patient was obese and had a retracted penis, making catheter placement difficult. Within days of catheter placement, the patient complained of dysuria and penile pain. The Foley catheter was removed and a condom catheter was placed for patient comfort. Frequent dislodgement of the catheter occurred because of scrotal edema, and a heating pad and barrier cream were applied to promote adhesion. Four days after placement of the condom catheter, the patient was noted to have 2 purpuric bullae on the glans of the penis and at the coronal sulcus.

Initial urologic consultation suggested that the patient had pressure necrosis secondary to catheter placement and conservative management was recommended. Despite scrotal elevation, the patient developed a blackened eschar extending from the base of the penis to the scrotum within 72 h. Initial bedside impression suggested Fournier’s gangrene. He was brought emergently to the operating room for escharotomy and debridement of the scrotum

and perineum. Intraoperatively, necrotic skin was noted in the penis, the scrotum, and the perineum below the scrotum, which was debrided. Adjacent lymph nodes demonstrated black stippling without gross purulence. Postoperatively, liposomal amphotercin B (AmB) (5 mg/kg IV daily) was added to his medications.

Within 48 h, tissue cultures from the penis and deep tissue grew a presumptive Zygomycete, based on macroscopic and microscopic morphology, growth characteristics, and temperature studies. The organism was further speciated as *Rhizopus microsporus* by nucleic acid sequencing using two targets, the Internal Transcribed Spacer region and the D1/D2 region of the large-subunit of the 28S rRNA gene. Histopathologic examination of surgical specimens from skin, adipose tissue, penis, and lymph nodes revealed broad, branching, non-septated fungal elements (Fig. 1A). Extensive tissue vascular infiltration and necrosis were noted (Fig. 1B).

Further expansion of the skin necrosis was observed and the patient was taken back to the operating room for penectomy, scrotectomy, and bilateral orchiectomy (Fig. 2). Liposomal AmB was increased to 8 mg/kg IV daily and micafungin (100 mg IV daily) and posaconazole (400 mg by mouth twice daily) were added. The patient remained neutropenic (total white blood cell count 60 cells/mm^3) and granulocyte infusion was attempted to restore immune function.

Despite 3 sequential extensive surgical debridements, the patient developed a non-contiguous necrotic skin lesion in the right gluteal area, potentially indicative of new hematogenous dissemination. Further surgical intervention was declined by the patient and his family. He died in hospice 2 weeks after his last debridement.

Discussion

This dramatic case of rapidly progressive and fatal cutaneous *Rhizopus* infection of the penis illustrates the diagnostic and therapeutic challenges of cutaneous Zygomycosis in the immunocompromised host.

From a clinical perspective, the differential diagnosis of cutaneous genital lesions in a leukemic patient is broad. On physical examination, the ulcerative lesions of early zygomycosis have a non-specific appearance and may be mistaken for mechanical trauma, viral eruptions (herpes simplex, varicella zoster), echythema gangrenosum, or tumor infiltration (3). In addition to Zygomycetes, other fungi such as *Fusarium* and *Aspergillus* can mimic the clinical presentation of cutaneous *Rhizopus*. In the case of our patient, the purpuric bullous lesions were initially thought to be the result of pressure necrosis due to a condom catheter. As the lesion progressed and developed a visible eschar, Fournier's gangrene due to a classical bacterial pathogen was suspected.

In retrospect, several characteristics of the penis and perineum may have predisposed this patient to an invasive fungal infection. Ideal growth conditions for fungi include acidity, a temperature at or above 37°C, high moisture levels, and a glucose source. His blood glucose had been markedly elevated at times, presumably as a result of exogenous steroid administration. The use of barrier cream and local heat pad application may have further altered the penile/perineal milieu in favor of mycotic seeding and growth. Finally, the patient had significant general risk factors for *Rhizopus* including hematologic malignancy, chemotherapy-related neutropenia, and renal failure.

Cutaneous zygomycosis can be primary, due to inoculation at sites of local trauma, or less commonly, due to hematogenous spread from a primary pulmonary, rhinocerebral, or gastrointestinal source. In our patient, the most likely portal of entry was the breakdown of

the normal epidermal barrier related to urinary catheter placement. Although prior institutional outbreaks of *Rhizopus* have been linked to ostomy bags, adhesive bandages, wooden tongue depressors, and contaminated air ventilation systems (7–11), no definitive link between a contaminated source and our patient could be established.

Once local infection is established, it is not uncommon for cutaneous lesions to progress to disseminated disease. The largest review of zygomycosis in the literature of 929 cases includes 176 cutaneous infections. Of these, 56% of cases remained localized, 24% progressed to involve deeper structures, and 20% spread hematogenously to involvement of a remote site. Conversely, hematogenous spread leading to secondary skin lesions was exceedingly rare with only 6/176 cases in this review (12).

With genital lesions in particular, the proximity of the inguinal lymph nodes makes the perineum a dangerous site of infection. The lymphatic drainage of the penis is particularly complex, as the more superficial tissues drain to the deep and superficial inguinal nodes, whereas the deeper tissues drain to the external iliac chain nodes within the pelvis. Invasion of the deep soft tissues of the penis, therefore, provides an anatomic gateway for pelvic invasion.

In our patient, surgical pathology from the initial debridement demonstrated lymphovascular invasion, although deeper lymphadenectomy was never attempted. Despite systemic antifungal therapy and multiple surgeries, the subsequent development of a non-contiguous necrotic lesion on the patient's buttocks area suggested spread through the pelvic lymphatic system and/or hematogenous dissemination. A plausible source for these secondary lesions was the penile site, as both the physical exam and imaging revealed no other typical primary source, such as lungs or sinuses.

Treatment of zygomycosis requires surgical debridement in addition to systemic antifungal therapy with the deoxycholate or lipid formulation of AmB (13), as voriconazole has little or no activity against *Rhizopus* species. While *in vitro* data suggest that posaconazole may also be effective (14, 15), breakthrough has been described in leukemic patients who are already receiving posaconazole for antifungal prophylaxis (16, 17). Drugs of the echinocandin class have been demonstrated to enhance the activity of AmB in animal models (18). Clinical data to demonstrate benefit of combination therapy are currently limited to small retrospective studies (19). Immune function is critical in controlling the infection (20, 21). Innovative therapies such as granulocyte-colony stimulating factor and donor lymphocyte infusions have been used. Other therapeutic strategies, such as hyperbaric oxygen and iron chelation, have been tried based on *in vitro* evidence of efficacy, despite a lack of clinical evidence (22). Despite aggressive surgical debridement; systemic antifungal therapy with liposomal AmB, micafungin, and posaconazole; and adjuvant therapy with granulocyte infusions, our patient developed progressive cutaneous lesions. Mortality rates of 10% have been reported for localized cutaneous zygomycosis, 26% with extension to deeper structures, and 94% with disseminated disease (12). Given his extremely poor prognosis, our patient chose hospice care.

This case illustrates the development of a rapidly progressive, angioinvasive, and ultimately fatal cutaneous *Rhizopus* infection of the penis in a patient with AML. A high index of suspicion for invasive mycoses is critical in any immunosuppressed patient with necrotizing cutaneous lesions. Practitioners should be aware that cutaneous mold infections may manifest as Fournier's gangrene. Penile lesions, in particular, may have a unique propensity to disseminate rapidly because of the lymphatic drainage of the perineum, at which point they become nearly uniformly fatal. Prompt diagnosis and aggressive therapy combining

early skin biopsy, surgical management, systemic antifungals, immune therapy, and other innovative approaches are critical.

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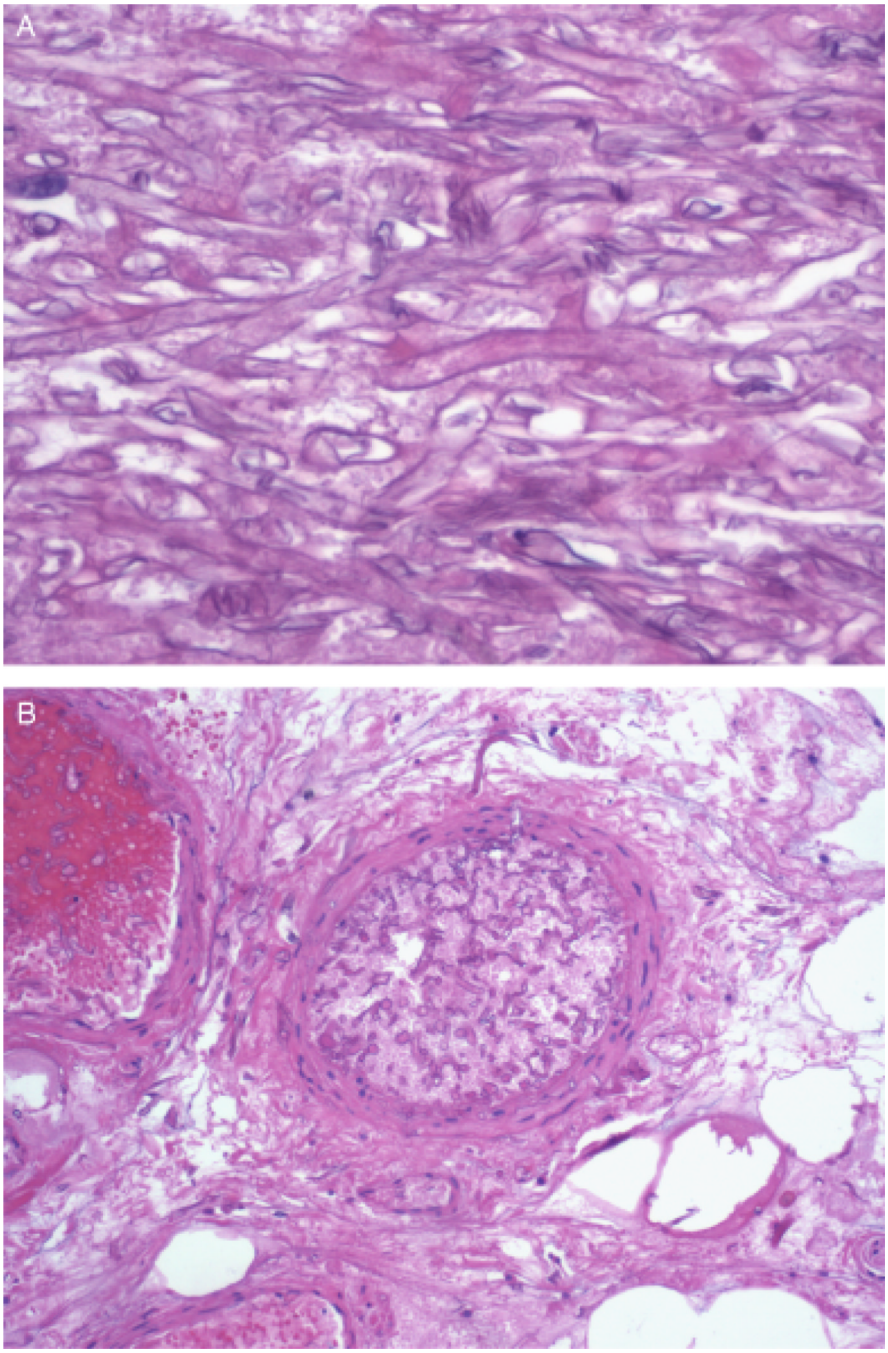

Fig. 1.

(A) Methenamine silver stain of the necrotic tissue at × 400 magnification within the surgical specimen revealed broad, branching, non-septated fungal elements characteristic of *Rhizopus* growth at 37°C. (B) Methenamine silver stain of the necrotic tissue at × 100 magnification shows a thrombosed arteriole infiltrated with non-septated fungal elements, establishing the diagnosis of angioinvasive *Rhizopus*.

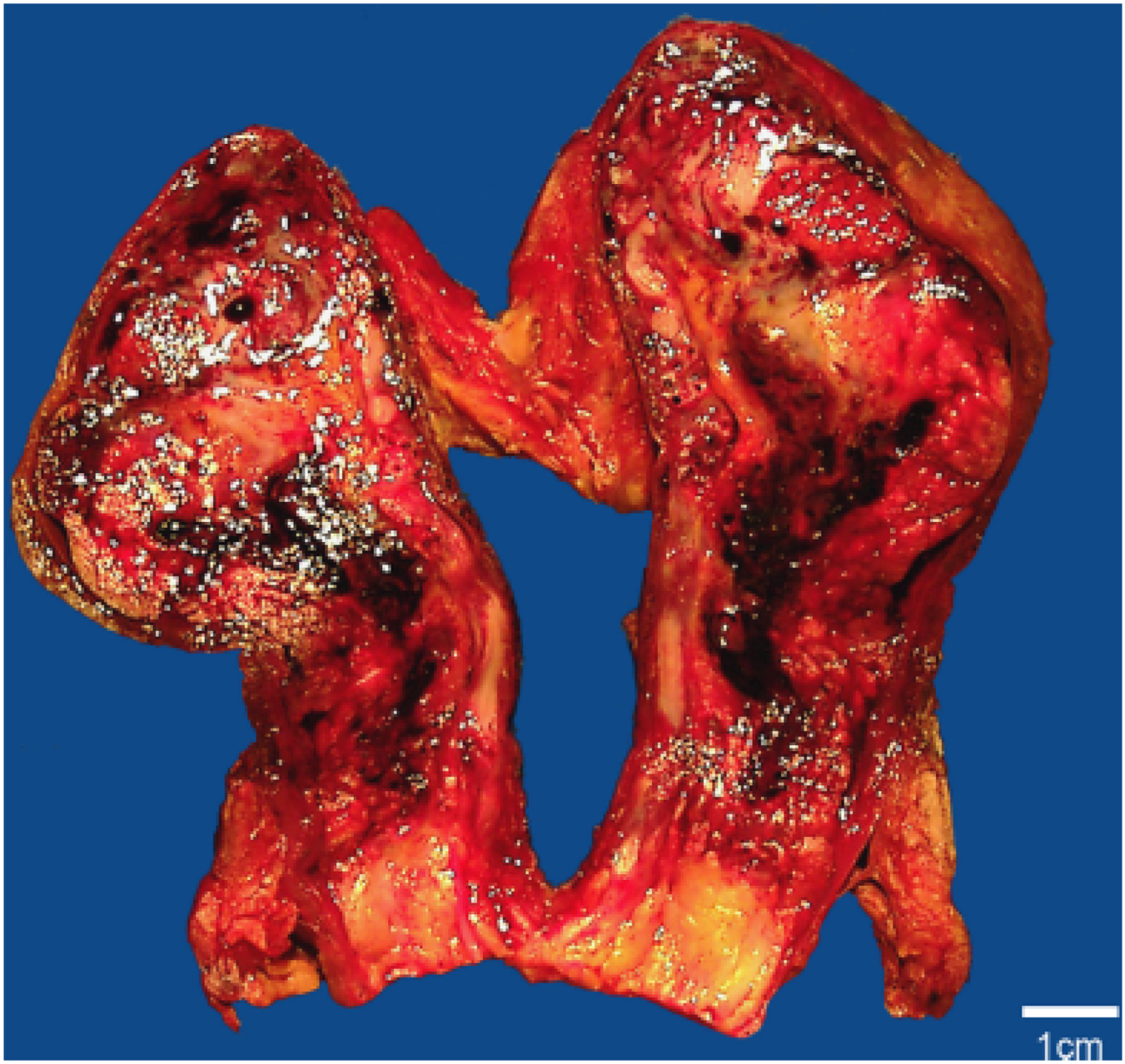

Fig. 2.
Photograph of the bivalved testes shows multiple dusky, necrotic, and hemorrhagic foci of tissue, with prominent involvement of the deep tissues of the spermatic cord and testes.