Breakthrough Penile Mucormycosis in a Patient With Acute Myelogenous Leukemia on Posaconazole Prophylaxis

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Abstract: In patients with acute myelogenous leukemia, posaconazole prophylaxis has been shown to prevent deep invasive fungal infections, including mucormycosis. In the present case, posaconazole prophylaxis was initiated in a 58-year-old man undergoing induction chemotherapy for acute myelogenous leukemia. Three weeks after initiating chemotherapy, he developed a tender violaceous macule on the shaft of his penis. The initial differential included fixed drug eruption versus pyoderma gangrenosum. However, punch biopsy ultimately showed mucormycosis, and cultures grew *Rhizopus* species, despite therapeutic posaconazole trough. He was treated with intravenous amphotericin B and required right orchiectomy, penectomy, and hyperbaric oxygen therapy. Oral posaconazole was reinstituted after completion of amphotericin B course, and at 4 months follow-up, his penectomy site was fully healed. As demonstrated by the present case, not all mucormycoses are prevented by posaconazole prophylaxis. A high index of suspicion and early biopsy for prompt diagnosis are of critical importance in improving outcomes.

Key Words: penile lesion, acute myelogenous leukemia, neutropenia, mucormycosis, posaconazole

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Posaconazole prophylaxis has been shown to prevent deep invasive fungal infections (IFIs), including invasive candidiasis, aspergillosis, and mucormycosis in patients with acute myelogenous leukemia (AML).[1–4] However, even with broad spectrum prophylaxis with posaconazole, immunocompromised patients are still susceptible to IFIs, including mucormycosis.[2,5–7] In this report, we present the case of a 58-year-old male patient with AML who developed a breakthrough mucormycosis of the penis after 2 rounds of induction chemotherapy despite receiving standard antifungal prophylaxis with posaconazole. The true incidence of mucormycosis in the United States is unknown; however, different estimates range from 1.7 to 3.0 cases per million.[8–10] Mucormycosis has a very high mortality rate, and many estimates near 100% for disseminated infection.[11–13] This high mortality rate may be in part due to missed or late diagnoses because signs and symptoms of mucormycosis are nonspecific. It is imperative for clinicians to have a high index of suspicion for mucormycosis in immunocompromised patients for prompt diagnosis and treatment.[2,13]

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CASE

A 58-year-old man with a past medical history of type 2 diabetes mellitus, hypertension, and hyperlipidemia presented to an outside facility with 3 weeks of worsening dyspnea and dizziness. Complete blood count revealed hemoglobin of 6.3 g/dL and white blood cell count of $10.4 \times 10^3/\mu L$ with 95% blasts. The patient was transferred to our university hospital where he was diagnosed with AML. He underwent induction chemotherapy with

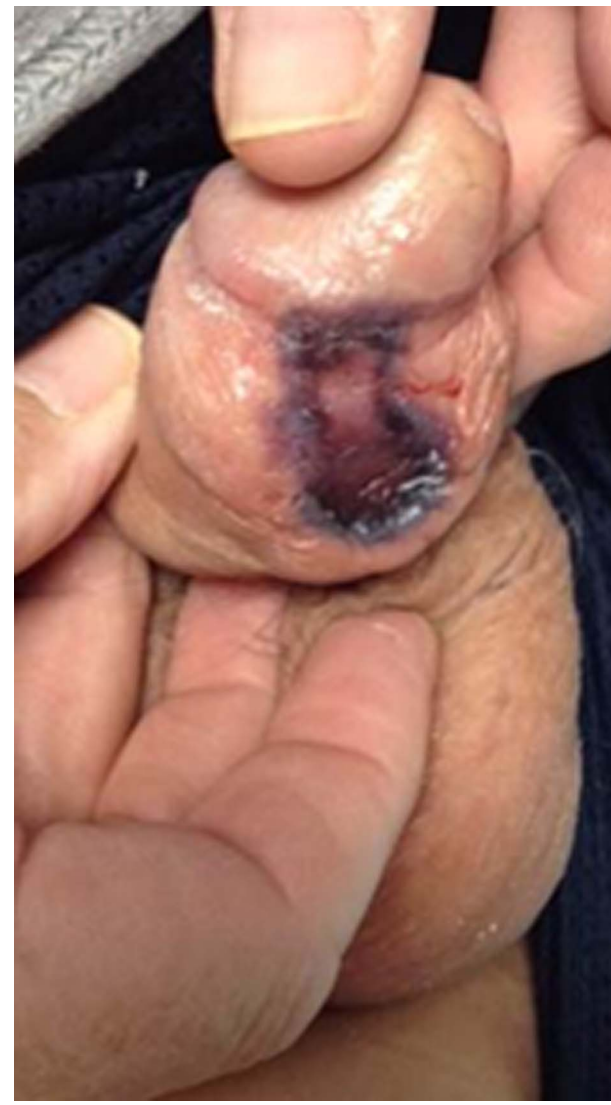

FIGURE 1. Penile lesion on day 3.

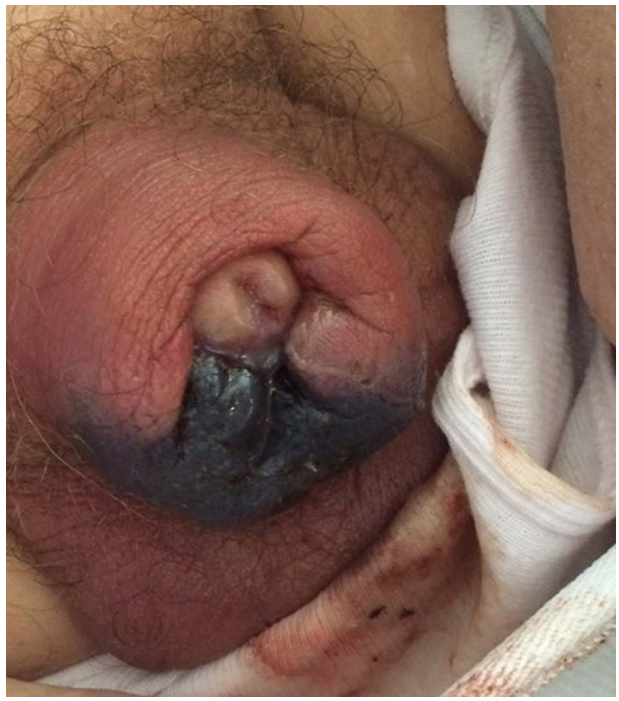

FIGURE 2. Penile lesion on day 7.

idarubicin and cytarabine as part of a clinical trial; however, because of persistent blasts (56%), he required reinduction with cladribine, cytarabine, and filgrastim with mitoxantrone. During chemotherapy, he developed profound and prolonged neutropenia (absolute neutrophil count of zero) and was placed on prophylactic acyclovir, 400 mg twice daily; ciprofloxacin, 500 mg daily; and posaconazole, 300 mg daily. Before reinduction, his course was complicated by development of a central line–associated coagulase-negative *Staphylococcus* bacteremia, requiring discontinuation of the line and initiation of treatment with nafcillin.

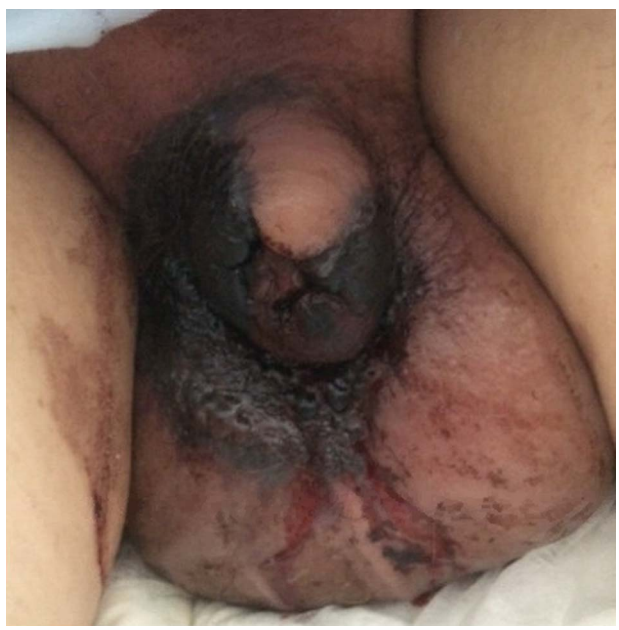

FIGURE 3. Penile lesion on day 13.

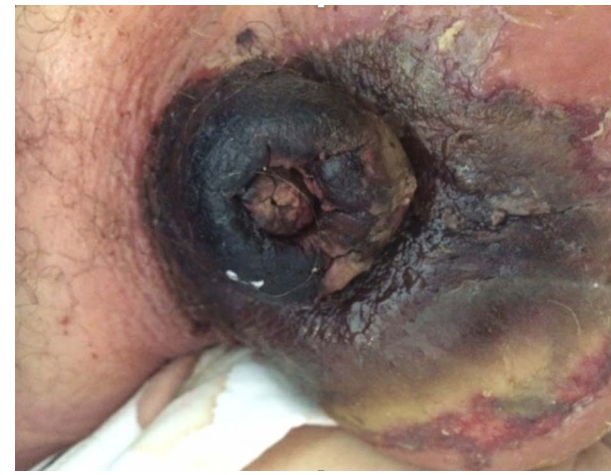

FIGURE 4. Penile lesion on day 21.

Approximately 3 days after completing reinduction with cladribine, cytarabine, and filgrastim with mitoxantrone, the patient developed a tender, pinpoint, violaceous lesion on the right penile shaft (day 1). On day 2, empiric topical docosonal 10% cream was started for viral eruption, and acyclovir was continued. By day 3, the lesion grew to the size of a half dollar (Fig. 1). At this point, Infectious Diseases, Urology, and Dermatology were consulted. He denied trauma, drainage from the lesion, or dysuria. On examination, his vital signs were normal, and there was no inguinal lymphadenopathy. His complete blood cell counts showed an absolute neutrophil count of zero, platelet count of $12 \times 10^3/\mu L$, and hemoglobin of 8.4 g/dL; serum chemistries were within normal limits; hemoglobin A1c was 7.1%. Fixed drug eruption (FDE) versus pyoderma gangrenosum was suspected, so topical docosonal cream was discontinued, and because of concern for FDE, nafcillin and ciprofloxacin were discontinued. Biopsy was deferred because of risk of bleeding from thrombocytopenia and poor healing. Topical clobetasol 0.05% ointment and topical lidocaine 5% ointment were initiated. Meanwhile, repeat blood cultures, drawn at the time of lesion progression, grew viridans group streptococci and vancomycin-resistant *Enterococcus* species. Treatment with daptomycin was initiated in addition to levofloxacin for gram-negative prophylaxis in context of neutropenia.

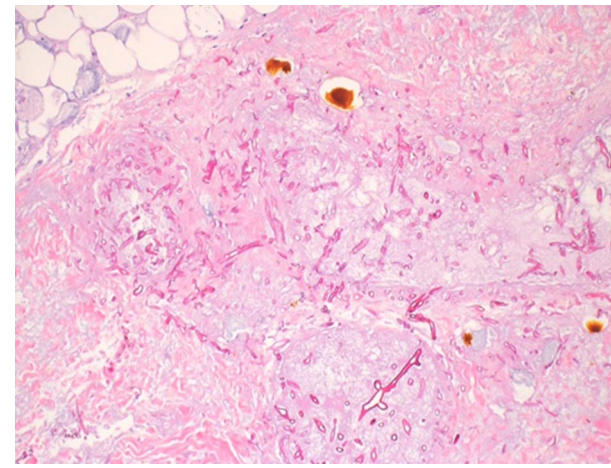

FIGURE 5. Hematoxylin and eosin–stained section from penile tissue biopsy.

TABLE 1. Published Case Reports of Mucormycosis Involving the Male Genitalia

Case Source	Patient Age, y	Risk Factor(s)	Source of Innoculation	PPX	Mucorales Species	Treatment	Survive
Lakshmi et al,[15] 1993	27	None	Surgical site contamination/ inguinal herniorrhaphy	—	*Apophysomyces elegans*	Surgical, AMB	No
Lai et al,[16] 2014	61	HCC s/p liver transplant	—	FLC	—	Surgical, discontinued immunosuppression, IV lip AMB, tt PO POS	Yes
Karam et al,[17] 2003	36	AML	—	ITZ	*Lichtheimia* (formerly, *Absidia*) *corymbifera*	Surgical; IV, inhaled, and topical AMB; HBOT	Yes
Grossklaus et al,[18] 1999	70	AML	—	—	*Rhizopus* species	Surgical, IV lip and topical AMB	—
Durand et al,[14] 2011	53	AML	Potentially related to urinary catheter	No	*Rhizopus microsporus*	Surgical, IV micafungin, IV lip AMB, PO POS, granulocyte infusion	No
Cohen-Ludmann et al,[19] 2006	52	DKA	—	—	*Rhizopus arrhizus*	Surgical, IV lip AMB, topical AMB	Yes
Williams et al,[20] 1995	27	T1DM DKA	Injury from masturbation device	—	*Rhizopus arrhizus*	Surgical, IV AMB	No
Bezzant et al,[21] 2019	80	T2DM A1c >20% No DKA	—	—	*Rhizopus arrhizus*	Surgical, IV lip AMB, tt PO isavuconazonium	Yes
Present case	58	AML	—	POS	*Rhizopus* species	Surgical, IV AMB, tt PO POS, HBOT	Yes

— indicates unknown, does not apply, or not mentioned by authors; HCC, hepatocellular carcinoma; DKA, diabetic ketoacidosis; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; ITZ, itraconazole; FLC, fluconazole; POS, posaconazole; lip, liposomal; AMB, amphotericin B; PPX, prophylaxis; PO, per os (eg, by mouth); s/p, status post; tt, transition to; A1c, hemoglobin A1c; HBOT, hyperbaric oxygen therapy.

By day 7, the lesion enlarged to involve the inferior aspect of the penile shaft with associated edema (Fig. 2). Because FDE was still in consideration, levofloxacin was discontinued. Surgical debridement was deferred because of continued severe thrombocytopenia and neutropenia. On day 9, computed tomography revealed large bilateral hydroceles and right epididymis hyperdensity, but no acute abdominopelvic findings or drainable abscesses. In the interim, fever, tachycardia, urinary incontinence, and altered mental status developed. Meropenem was added empirically, and he was transferred to the intensive care unit. By day 13, the increasingly edematous lesion involved the scrotum (Fig. 3) and was associated with cellulitis. Magnetic resonance imaging of the pelvis showed perineal fasciitis and spread into the pelvis via the right inguinal canal. On day 18, a posaconazole trough level was drawn, and the final result was 1.53 μg/mL (reference trough >0.7 μg/mL for prophylaxis in stem cell transplant recipients[1]). By 3 weeks, he had developed necrosis involving the entire penis and the anterior portion of the scrotum (Fig. 4). Profound neutropenia (absolute neutrophil count of 0.19×10^3/μL) and critical thrombocytopenia (platelet count of 11×10^3/μL) were still present. Punch biopsy performed on day 21 showed numerous broad hyphae throughout the full thickness of the skin and within vessel walls, with extensive dermal and epidermal necrosis, consistent with IFI (Fig. 5). Posaconazole was transitioned to intravenous (IV), nonliposomal, amphotericin B deoxycholate (Fungizone), 0.5 mg/kg daily, and the patient underwent surgical debridement and right orchiectomy. Cultures from biopsy and operative samples ultimately grew *Rhizopus* species and vancomycin-resistant *Enterococcus*.

Multiple additional debridements, hyperbaric oxygen therapy, penectomy, and suprapubic catheter placement were performed. The patient received 24 days of IV amphotericin B, and afterward, 300 mg daily posaconazole was reinstituted. In a follow-up visit 4 months later, he had complete healing of the perineal wound and had been referred for bone marrow transplantation.

DISCUSSION

Mucormycoses encompass a group of fungal infections caused by species in the order Mucorales, which include species of the genera *Rhizopus*, *Rhizomucor*, *Cunninghamella*, *Lichtheimia*, *Mucor*, and *Apophysomyces*. Among all the Mucorales, *Rhizopus arrhizus* (formerly, *Rhizopus oryzae*) is the most commonly implicated species in patients with mucormycosis.[12] These infections are capable of dissemination and severe disease in immunocompromised patients. Broad aseptate hyphae with wide branches and invasion of the blood vessels represent the histopathologic hallmark of mucormycosis.[2,13] The most typical forms of mucormycosis are rhinocerebral and pulmonary, but other forms include gastrointestinal, cutaneous, and disseminated mucormycosis.[11,13] Approximately 19% of all cases of mucormycosis have cutaneous involvement.[11] The differential diagnosis for cutaneous mucormycotic lesions is extensive and includes viral eruptions, tinea corporis, pressure necrosis, ecthyma gangrenosum, trauma, leukemic infiltration, erythema nodosum, panniculitis, FDE, and pyoderma gangrenosum.[11,13,14] After a review of the current literature, we found only 8 other published case reports of mucormycosis with male genitalia involvement (Table 1).[14–21]

Persistent neutropenia, immunosuppressive therapy, high-dose steroid therapy, diabetes mellitus, metabolic acidosis, illicit IV drug use, and trauma are commonly seen in patients with mucormycosis.[2,9–13] In our patient, the most important predisposing factor was severe neutropenia. Evidence from AIDS patients and severely neutropenic patients suggests that neutrophils, in particular, play a more crucial role in host defense against mucormycosis in contrast to T lymphocytes.[12] With regard to diabetes mellitus, hyperglycemia and low pH disrupt normal phagocyte function, and hyperglycemia is known to enhance expression of surface proteins that mediate endocytic entry of Mucorales.[12,13] However, our patient's hemoglobin A1c was 7.1%, and he did not have diabetic ketoacidosis.

Finally, states of increased serum iron (ie, diabetic ketoacidosis, transfusions) enhance the growth and pathogenesis of Mucorales, likely because of high-affinity iron permeases that facilitate iron uptake.[12,13] Given that our patient received several transfusions of packed red blood cells during his hospitalization, it is possible that the transfusions may have enhanced the infection by *Rhizopus*.

In 2018, the available literature on breakthrough invasive fungal diseases in patients with AML undergoing intensive chemotherapy and on antifungal prophylaxis was reviewed by a group of Italian experts.[22] They identified main causes for prophylaxis failure. Although our patient's serum posaconazole level should have been adequate for prophylaxis, other possible causes of failure they described include pathogen resistance, insufficient drug concentration in the affected body compartment, and colonization of a central venous catheter. Unfortunately, no susceptibility testing was done on the *Rhizopus* species identified in our patient, and additionally, literature on posaconazole concentrations in penile tissue was not found. Although our patient did require central venous catheters and experienced associated complications including bacteremia and deep vein thrombosis, we have no evidence of catheter colonization with *Rhizopus*. Nevertheless, it is still certainly possible that all the above may have contributed to his breakthrough mucormycosis.

From our case and other reports of breakthrough mucormycosis, it is evident that mucormycosis cannot be ruled out without a tissue biopsy and/or culture, even on posaconazole prophylaxis.[2,5–7] These cases signify that some *Rhizopus* species may lack adequate susceptibility to posaconazole.[6,7,23] With regard to treatment of mucormycosis, in addition to urgent surgical debridement, amphotericin B is the initial drug of choice.[13] Posaconazole is not approved by the US Food and Drug Administration for the treatment of mucormycosis.[13] However, it can been used off-label as sequential therapy after surgical debridement, amphotericin B, and clinical improvement, as in the present case.[13,24] Data from one study suggested that a delay of therapy by 6 days or more doubled mortality and was associated with a 12-week survival rate of less than 20%.[25] Early tissue biopsy is vital for prompt diagnosis and successful treatment.

In conclusion, mucormycosis must be considered in the differential diagnosis of necrotic penile lesions in neutropenic patients, even in those who receive posaconazole prophylaxis because it may not cover all agents of mucormycosis. Early diagnosis via biopsy followed by urgent surgical debridement, antifungal therapy with IV amphotericin B, and control of underlying risk factors improve outcomes.

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