
Gene A. Krishingner
Mahtab Forouzandeh
José A. Rodríguez
Kenan Ashouri
Kiran Motaparthi
Bristol B. Whiles

Corresponding Author: Bristol B. Whiles, e-mail: bristolwhiles@gmail.com

Financial support: None declared
Conflict of interest: None declared

Patient: Male, 55-year-old
Final Diagnosis: Angioinvasive deep fungal infection of the penis
Symptoms: Violaceous macule on the corona of glans penis
Clinical Procedure: —
Specialty: Dermatology • Infectious Diseases • Pathology • Urology

Objective: Rare disease
Background: Mucormycosis, a cause of opportunistic infections in immunocompromised patients, is rarely identified in the penis. The literature often describes drastic surgical interventions or rapid patient demise, with scant mention of surgical management specifics. The objective of this report is to detail our experience with this unique infection and highlight the utility of intraoperative frozen margins during surgical management.

Case Report: Herein, we describe successful treatment of a 55-year-old man with biopsy-proven B-cell acute lymphoblastic leukemia (B-ALL) undergoing Hyper-CVAD (Cyclophosphamide, Vincristine, Adriamycin, and Dexamethasone) therapy who initially presented with an asymptomatic violaceous lesion of the penis. Differential diagnoses ranged from infectious, vasculogenic, and pharmacologic in nature. Ultimately, a punch biopsy tissue culture confirmed angioinvasive fungal infection with Rhizopus and Fusarium species. Initial debridement combined with intravenous antifungal therapy was unsuccessful. However, partial penectomy with use of intraoperative frozen margins, a 5-week course of antifungal therapy, and continued B-ALL treatment allowed effective and lasting resolution of the infection, with partial penile preservation.

Conclusions: This case supports a multidisciplinary approach as the primary treatment for penile angioinvasive fungal infections. This includes treatment of the underlying immunocompromising condition, appropriate intravenous antifungal therapy, and urgent operative debridement. This report highlights the importance of utilizing intraoperative frozen sections to ensure negative margins and to optimize overall tissue sparing in this anatomically sensitive area.

Keywords: Frozen Sections • Fusarium • Mucormycosis • Penile Diseases

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/939971

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
Background

Mucormycosis is a severe opportunistic fungal infection caused by environmental fungi from the Zygomycetes class, typically harmless to individuals with healthy immune systems [1]. It exhibits several clinical forms, including pulmonary, gastrointestinal, cutaneous, encephalic, and rhinocerebral sites, which largely depend on the route of entry of the fungi and the host’s underlying conditions. However, in immunocompromised individuals, such as patients with leukemia, uncontrolled diabetes, or those undergoing immunosuppressive therapy, these fungi can trigger rapidly progressive, necrotizing infections [1]. The diagnosis is primarily based on histopathological evaluation, with non-septate or minimally septated broad, ribbon-like hyphae characteristic of the disease. Treatment typically requires early and aggressive surgical intervention coupled with high-dose intravenous antifungal therapy [1,2].

Angioinvasive deep fungal infections of the penis are exceedingly rare, with only a handful of cases reported in the literature [3]. Despite various medical and surgical approaches described, nearly every reported case resulted in severe morbidity if not fatality [3]. This report is of a 55-year-old man with B-cell acute lymphoblastic leukemia (ALL) and penile ulceration due to opportunistic angioinvasive mucormycosis treated with amphotericin B and surgical debridement. Herein, we describe our experience with this rare condition with specific emphasis on the technical medical and surgical aspects of our management strategy, including the use of intraoperative frozen section margin analysis.

Case Report

A 55-year-old white man with a past medical history of myocardial infarction, heart failure, diverticulitis, and hypertension who works in the mining industry was admitted to the hospital with newly diagnosed B-cell acute lymphoblastic leukemia (B-ALL). Diagnosis of B-ALL was based upon external bone marrow biopsy, revealing markedly hypercellular bone marrow (>95%) diffusely involved by a blast population expressing terminal deoxynucleotidyl transferase (TdT), cluster of differentiate (CD) 20, paired box 5 (PAX-5), CD79a, CD10, CD43, B-cell lymphoma 2 (BCL2), and BCL6 (80-90% of marrow elements). Computed tomography (CT) scans of patient’s chest, abdomen, and pelvis revealed numerous areas of lymphadenopathy and splenomegaly. Bone marrow biopsy was repeated, with 80% B-cell lymphoblasts, confirming B-cell ALL. The patient was placed on Hyper-CVAD (Cyclophosphamide, Vincristine, Adriamycin, and Dexamethasone) therapy. The patient provided signed and informed consent for this case report.

After several weeks undergoing inpatient treatment, he reported new onset of an asymptomatic deeply violaceous macule on the corona of his glans penis (Figure 1A). The patient stated that the location of the lesion was precisely the area that routinely contacted his bedside urinal during urinary voiding. The patient’s oncology team subsequently consulted Infectious Disease, Dermatology, and Urology, resulting in the initial diagnosis of fixed-dug eruption secondary to fluconazole therapy. Despite cessation of the presumed offending medication, the patient’s exam results worsened with progressive edema and penile tenderness (Figure 1B). Given these new findings, fixed-drug eruption became less likely and deep fungal infection was suspected. Empiric intravenous (IV) liposomal B amphotericin was promptly initiated, and Dermatology performed an urgent biopsy of the lesion. The biopsy was processed as a frozen section and revealed strong suspicion for angioinvasive deep fungal infection, and tissue cultures grew Rhizopus and Fusarium species. The multidisciplinary team performed an extensive physical exam, reviewed recent CT imaging, and obtained CT imaging of the maxillary sinuses, to rule out disseminated fungal infection. When the only clinical site identified was the penile lesion, this prompted the need for further urgent surgical intervention by Urology in conjunction with ongoing IV antifungal therapy with amphotericin.

On day 6 after lesion presentation, the patient underwent surgery with superficial debridement, including removal of involved dartos fascia of the penis, down to grossly viable and well-perfused tissue. The macule overlying the glans penis was spared intraoperatively after demonstrating brisk bleeding with incision of the lesion in an effort to obviate the need for partial penectomy (Figure 1C). Close postoperative observation revealed persistent and progressive infection. Therefore, the decision was made to perform partial penectomy on day 8 (Figure 2A, 2B). Despite grossly negative margins intraoperatively during the partial penectomy at both the corpora cavernosa and urethra, repeat margins were initially both positive. This required the surgical team to re-resect and re-send margins to pathology until negative margins were obtained. Importantly, this use of intraoperative frozen specimens ensured pathology-confirmed negative margins (Figure 3A-3D). This gave assurance that the infected tissue was adequately resected while avoiding a more aggressive debridement, which would have resulted in a total penectomy (Figure 2C-2E). Wound cultures again grew Rhizopus and Fusarium species. IV amphotericin was continued, and IV voriconazole was added with incision of the lesion in an effort to obviate the need for partial penectomy (Figure 1A). Close postoperative observation revealed persistent and progressive infection. Therefore, the decision was made to perform partial penectomy on day 8 (Figure 2A, 2B). Despite grossly negative margins intraoperatively during the partial penectomy at both the corpora cavernosa and urethra, repeat margins were initially both positive. This required the surgical team to re-resect and re-send margins to pathology until negative margins were obtained. Importantly, this use of intraoperative frozen specimens ensured pathology-confirmed negative margins (Figure 3A-3D). This gave assurance that the infected tissue was adequately resected while avoiding a more aggressive debridement, which would have resulted in a total penectomy (Figure 2C-2E). Wound cultures again grew Rhizopus and Fusarium species, IV amphotericin was continued, and IV voriconazole was added to the regimen, pending tissue culture susceptibilities. Blood fungal cultures continued to be negative throughout the remainder of his hospitalization. On outpatient follow-up, susceptibilities were notable for voriconazole resistance, at which point voriconazole was discontinued, with the continued administration of IV amphotericin for a total course of 5 weeks.

Eight weeks postoperatively, the patient had no evidence of persistent infection, was voiding spontaneously per urethra.
Figure 1. Evolution of the deeply violaceous macule on the corona of glans penis. (A) First encounter. (B) Day 3 and (C) Day 6 following debridement to bleeding, well-vascularized tissue.

Figure 2. Intraoperative findings and postoperative exams. (A) Resected distal penis. (B) Cross-sectional corporal margin sent for frozen sectioning (urethra sent separately). (C) Penile stump with healthy margin prior to closure. (D) Penile stump at time of partial penectomy. (E) Penile stump 8 weeks postoperatively.
without difficulty, and was in good spirits. The patient continued to have a good surgical outcome and was continuing to do well at 8 months postoperatively.

Discussion

This case not only emphasizes the importance of multidisciplinary care when presented with angioinvasive fungal infection of the penis, but particularly underlines the need for intraoperative frozen margin analysis when attempting penile-sparing surgery, as grossly negative margins were inadequate.

Despite aggressive treatment, mortality rates of angioinvasive deep fungal infections of the penis involving aggressive fungal species, such as Rhizopus and Fusarium, are exceedingly high, ranging from 50% to 100%; whereas mortality rates for angioinvasive candidiasis and aspergillosis range from 20% to 50% and 35% to 45%, respectively [4]. Mortality approaches 90% once these infections become disseminated; however, mortality for localized cutaneous infections is approximately 30%. This rapid rise in mortality rate with disseminated infection narrows the therapeutic window for early intervention and source control in well-vascularized tissues such as the penis [1].

The initial onset of invasive fungal infections of the penis can be subtle, with differential diagnosis including ecthyma gangrenosum, pyoderma gangrenosum, fixed-drug eruption, cutaneous anthrax, necrotizing fasciitis, heparin- or warfarin-induced necrosis, cocaine-induced skin necrosis, embolic phenomenon, and necrosis secondary to the use of vasoactive drugs [5,6].

We hope that others find our case useful, as appropriate surgical management for penile angioinvasive deep fungal infections is scarcely reported in the literature. To the best of our knowledge, this is the first case describing the implementation of organ-sparing surgery with successful partial penectomy, facilitated primarily by the use of intraoperative frozen sections, in the context of angioinvasive Rhizopus and Fusarium species of the penis [3]. This example reiterates the importance of prompt surgical and medical management, with the unique incorporation of intraoperative frozen sections to facilitate optimal organ-sparing in a timely manner.

In the literature, all documented instances of mucormycosis affecting the male genitalia outline a multimodal treatment regimen, involving a combination of surgical resection and systemic antifungal medication [3], but survival is not unequivocally ensured by this approach. A number of case reports, including those from Lakshmi et al, Durand et al, and Williams et al, recount patient deaths despite such combined treatment. Notably, treatment of these cases did not employ the use of intraoperative frozen margins [7-9].

Grossklaus et al delineated a scenario involving a 70-year-old man with acute myeloblastic leukemia who developed isolated...
angioinvasive mucormycosis of the penis. The management required repeated surgical debridements with the aim of achieving ‘adequate margins’. However, the explicit use of intraoperative frozen margins was absent from the report, and no data were provided regarding the patient’s survival outcome [10].

Other studies that reported patient survival, including Lai et al and Shayan et al, documented more radical surgical resections involving complete penectomy [3,11]. The potential for a more penile-preserving strategy could have been explored had intraoperative frozen margins been utilized. Mirroring our case, Bezzant et al detailed the necessity of 2 surgeries to achieve source control, a scenario potentially avoidable with the incorporation of intraoperative frozen sections [12].

In a case documented by Karam et al, a 36-year-old farmer with acute myeloblastic leukemia presented with a shallow necrotic ulceration of the glans penis due to *Absidia corymbifera*. This was successfully managed with superficial surgical debridement, intravenous, and topical amphotericin B. This case serves as a testament to the critical role of early detection in disease management [13]. Langford et al first described the use of intraoperative frozen sections for angioinvasive deep fungal infection in 1997 in the context of rhino-orbital debridement [14]. To the best of our knowledge, the use of intraoperative frozen margin sections for penile angioinvasive fungal infections has not been previously described [3]. This case report also emphasizes the importance of multidisciplinary care in complex fungal infections of the penis, as the collaboration by the Hematology, Dermatology, Infectious Disease, and Urology teams was directly responsible for the good outcome in this patient.

Early recognition and prompt surgical intervention along with appropriate initial empiric antifungal treatment are critical aspects of the management of this infection [15]. The choice of empiric antifungal therapy depends on the clinical scenario, drug-drug interactions, adverse effect profile, and patient tolerance. It should be noted that IV amphotericin B in either liposomal or lipid complex have a lower adverse effect profile compared to the amphotericin B colloidal formulation. If amphotericin cannot be tolerated, triazoles such as voriconazole, posaconazole, or isavuconazole can be helpful alternatives. Lastly, topical antifungal ointments were not used in this patient, but can be a reasonable addition to IV therapy in the immediate postoperative period.

Conclusions

Our presented case of penile mucormycosis, in conjunction with an evaluation of existing literature on the management of deep-seated fungal infections in anatomically critical regions, underscores the importance of prompt surgical intervention as the primary treatment strategy. Specifically, urgent operative debridement, guided by intraoperative frozen specimens, can maximize the preservation of healthy tissue while assuring clear margins. In emphasizing this approach, we highlight the potential for an organ-sparing procedure.

Department and Institution Where Work Was Done

Department of Urology, University of Florida, Gainesville, FL, USA.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References: