Case report of penile Rhizopus arrhizus infection in an unexpected patient

Matthew Bezzant*a, Kathryn Lago*b, Tatjana Calvanob

*a Internal Medicine Service, Brooke Army Medical Center, 3551 Roger Brooke Dr, Fort Sam Houston, TX, 78234, USA
*b Infectious Disease Service, Brooke Army Medical Center, 3551 Roger Brooke Dr, Fort Sam Houston, TX, 78234, USA

A R T I C L E   I N F O

Keywords:
Rhizopus arrhizus
Cutaneous mucormycosis
Isavuconazonium
Diabetes
Penile

A B S T R A C T

There are few reports of penile mucormycosis and even fewer in the absence of overt immune suppression. An eighty year old male with diabetes presents with penile mass. The pathology and culture demonstrated Rhizopus arrhizus. He was treated with surgery and liposomal amphotericin B. His therapy was stopped after pathology demonstrated clear surgical margins. His good outcome provides evidence that stopping antifungal therapy after achieving clear surgical margins is acceptable in patients without ongoing immunosuppression.

1. Introduction

Mucormycoses are rare and exceptionally lethal fungal infections that spread rapidly through angioinvasion. When appropriate antifungals are combined with surgery the average mortality rate is 30% [1]. Cutaneous mucormycosis is the third most common cause of mucormycosis [2] and is associated with a significant mortality rate of 10% [3]. The keys to successful treatment of mucormycosis are early diagnosis, immune restoration, surgical debridement and anti-fungal therapy [3].

However, past studies have indicated that the location of a mucormycosis infection heavily influences the physician’s ability to make the diagnosis [4]. There are few case reports of penile mucormycosis found in current literature and even fewer in the absence of diabetic ketoacidosis or overt immune suppression. Furthermore, there is not a consensus on treatment with anti-fungal therapy after source control has been achieved. In this case report, we describe a case of penile Rhizopus arrhizus (formerly known as Rhizopus oryzae) in a patient with uncontrolled diabetes and no evidence of ketoacidosis. He was successfully treated with surgical debridement and liposomal amphotericin transition to isavuconazonium and subsequent cessation of anti-fungal treatment after obtaining clear surgical margins.

2. Case

An eighty year old male with poorly controlled type II diabetes mellitus due to medication non-adherence presented to his primary care doctor with penile pain for one week (day −7). Three weeks (day −21) prior he noticed a white area on the glans of his penis which enlarged over the following several weeks and developed a hyper pigmented area in the center of the lesion. A 2 × 3 cm white lesion with central necrosis was noted on exam (Fig. 1). Due to concern for malignancy, he was sent to the emergency department (day 0) for urgent evaluation and debridement by Urology. Rapid plasma reagin, human immunodeficiency virus antibody and urine culture were all negative. His hemoglobin A1C obtained on admission was > 20%. Wound, fungal and acid fast cultures, along with histopathology, were obtained on the specimen. Shortly after discharge (day 3) the preliminary pathology demonstrated fungal elements with non-septate hyphae involving the necrotic tissue with evidence of angioinvasion. The following day (day 4), the calcofluor white prep had evidence of non-septate hyphae, which eventually revealed growth of rhizoids from tissue culture (Fig. 2) and was later confirmed by gene sequencing to be Rhizopus arrhizus.

After multiple attempts to reach the patient, he returned to the hospital for re-admission and treatment over a week after initial discharge (day 7). At that time, he had paraphimosis with worsening penile pain and evidence of new fevers, chills, night sweats, tachycardia, and dysuria. The wound bed showed necrosis and the foreskin could not be manually retracted. Immediately upon admission (day 7) he was started on liposomal amphotericin B at 5 mg/kg every 24 hours, given an insulin regimen, and underwent surgical debridement by Urology. Histopathology revealed focal fungal elements in necrotic tissue without fungal elements in viable tissue and the fungal culture grew rhizopus (Fig. 3). On day 11, Urology noted necrosis on the patient’s penis at the previous area of debridement so he underwent a partial penectomy in an effort to gain adequate source control. Amphotericin was continued while awaiting pathological review of surgical margins. However, in the setting of worsening kidney function, electrolyte losses,
and elevation in alkaline phosphatase, amphotericin was discontinued on hospital day 15. Patient was transitioned to oral isavuconazonium with a loading dose of 372 mg every 8 h for six doses and then a maintenance dose of 372 mg daily. His isavuconazonium was continued until the pathology from the penectomy demonstrated 2.5 cm of clear surgical margins on day 18. With clear surgical margins, absence of any systemic symptoms concerning for disseminated infection, or any additional metastatic foci of infection, it was determined that the source control was achieved and isavuconazonium. At a follow up appointment eighteen months after his definitive surgical debridement (day 547), he did not show any signs of recurrent infection.

3. Discussion

While diabetics make up around 36% of patients in a large set of case series of mucormycosis infection, only 10% of diabetic patients had a localized cutaneous lesion as compared with 50% in patients with no underlying conditions. The majority of diabetic patients present with sinus or rhino-cerebral involvement [1]. Most patients who develop localized cutaneous lesions have a penetrating trauma, burn, or contaminated dressing leading to the infection without an underlying immunosuppressive condition [4,5]. In the absence of a penetrating trauma or preceding wound, it appears that hyperglycemia was the isolated risk factor for the infection. The largest case series showed that only 34–48% of patients with diabetes had documented ketoacidosis at the same time as their mucormycosis infections [1]. Therefore the absence of diabetic ketoacidosis should not rule out the possibility of mucormycosis infection.

Cutaneous infections involving the penis are very rare and mucormycosis is often not considered as a possible diagnosis leading to delays in recognition of the condition and delay in appropriate care [1,4]. Multiple reports describe mucormycosis presenting as Fournier's gangrene or solitary lesions in solid organ transplant patients or patients with active hematologic malignancies [6–8]. A similar case of mucormycosis of the penis was reported in a patient with diabetic ketoacidosis. He responded to topical amphotericin B and surgery [9]. Our case appears to be unique as the patient was not in ketoacidosis and had no clear evidence of immunosuppression.

Duration of therapy is a complex and challenging decision due to the lack of consensus on duration of antifungal therapy after surgical source control. Duration of therapy in the VITAL trial for the FDA approval of isavuconazonium was highly variable. The patients in this study were treated with isavuconazonium for a median of 84 days [10]. Some studies recommend a total of 6–8 weeks of therapy even after surgical resection in cancer patients [11]. Case studies of other cutaneous mucormycoses used subsequent antifungal therapy after surgical resection, but either involved severe penetrating wounds with no long-term outcomes or duration of therapy provided [5] or used topical amphotericin [9] with limited follow up. Since there is general paucity of long-term outcomes data, we considered multiple factors when determining duration of therapy. His improved glycemic control, large surgical margins, absence of metastatic foci of infection and history of poor medication adherence were all considered when deciding to stop isavuconazonium following successful resection. He appears to have done well at 18 months with no recurrence of disease. While treatment decisions in cutaneous mucormycosis remain difficult due to a lack of evidence based guidelines or consistent findings, this case provides some evidence that stopping antifungal therapy after achieving clear surgical margins may be an acceptable option in patients without ongoing immunosuppression.

Conflict of interest

The authors have no conflicts of interests to disclose.

Disclaimer

The contents of this publication are the sole responsibility of the author(s) and do not necessarily reflect the views, opinions or policies of the Department of Defense (DoD), the Departments of the Army, Navy, or Air Force, or Brooke Army Medical Center, the U.S. Army Medical Department, and/or the U.S. Army Office of the Surgeon General. The views expressed in this manuscript are those of the author(s) and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.
Acknowledgements

Pictures taken by the Brooke Army Medical Center Medical Photography service.

References

[1] M.M. Roden, T.E. Zaoutis, W.L. Buchanan, T.A. Knudsen, T.A. Sarkisova, R.L. Schaufele, et al., Epidemiology and outcome of zygomycosis: a review of 929 reported cases, Clin. Infect. Dis. 44 (2005) 634–653.
[2] D. Farmakiotis, D. Konoyiannis, Mucormycoses, Infect. Dis. Clin. N. Am. 30 (2016) 143–163.
[3] H.Y. Sun, N. Singh, Mucormycosis: its contemporary face and management strategies, Lancet 11 (2011) 301–311.
[4] B.M. Prabhu, R. Patel, Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment, Clin. Microbiol. Infect. 10 (Suppl 1) (2004) 31–47.
[5] R.N. Fanfair, K. Benedict, J. Bos, S.D. Bennett, Y.C. Lo, T. Adebanjo, et al., Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011, N. Engl. J. Med. 3 (2012) 2214–2225.
[6] M.C. Lai, W. Zhang, Z. Yang, W. Zhang, K.G. Owusu-Ansah, S.F. Yu, et al., First case report of isolated penile mucormycosis in a liver transplantation recipient, Int. J. Infect. Dis. 29 (2014) 208–210.
[7] W. Crowell, R. Roberts, S. Tarry, Fungal fournier’s gangrene in an immuno-compromised patient, Urol. Case Rep. 4 (2016) 1–3.
[8] C.M. Durand, C.D. Alonso, A.P. Subhaswong, N.P. Kwiatkowski, M. Showel, K.C. Carroll, et al., Rapidly progressive cutaneous Rhizopus microspores infection presenting as Fournier’s gangrene in a patient with acute myelogenous leukemia, Transpl. Infect. Dis. 13 (2011) 392–396.
[9] C. Cohen-Ludmann, D. Kerob, M. Feuilhade, B. Chaine, A. Guermazi, M. Janier, et al., Zygomycosis of the penis due to Rhizopus oryzae successfully treated with surgical debridement and a combination of high-dose liposomal and topical amphotericin B, Arch. Dermatol. 142 (2006) 1657–1658.
[10] F.M. Marty, L. Ostrosky-Zeichner, O.A. Cornely, K.M. Mullane, J.R. Perfect, G.R. Thompson Illet et al., Isavuconazole treatment for mucormycosis: a single arm open-label trial and case-control analysis, Lancet Infect. Dis. 16 (2016) 828–837.
[11] A. Skiada, F. Lanternier, A.H. Groll, L. Pagano, S. Zimmerli, R. Herbrecht, et al., Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia, Haematologica (2012), https://doi.org/10.3324/haematol.2012.065110.