A noninvasive renal fungus ball caused by *Rhizopus* – a previously unreported manifestation of zygomycosis

FEDERICO PALACIO-BEDOYA,‡§, JOSE A. CADENA‡§, GEORGE R. THOMPSON III†§#, DEANNA A. SUTTON‡, AARON D. OWENS†§, THOMAS F. PATTERSON†§

Departments of Internal Medicine *Division of Hospital Medicine, †Division of Infectious Diseases, ‡Department of Microbiology, Fungus Testing Laboratory University of Texas Health Science Center at San Antonio, San Antonio Texas, §South Texas Veterans Health Care System, San Antonio Texas, and #University of California – Davis, Sacramento California, USA

We describe the first reported case of renal zygomycosis presenting as an isolated fungus ball (bezoar) without renal parenchymal invasion. Since all previous descriptions of renal involvement have discussed tissue invasion, our case is unique in that the infection was confined solely in the renal pelvis and extended to the distal ureter without signs of contiguous renal infection. Our patient later developed renal insufficiency while receiving amphotericin B Lipid Complex (ABLC). The therapy was changed to posaconazole with subsequent clinical, mycologic, and radiographic improvement and the patient has remained free of recurrence 5 years after diagnosis.

**Keywords**  zygomycetes, *Rhizopus*, fungus ball, renal, mucormycosis

**Introduction**

Zygomycosis is an uncommon infection that may cause a variety of manifestations particularly in immunocompromised patients and those with diabetes mellitus. Although invasive fungal infections caused by zygomycetes are rare, recent publications have suggested an increasing incidence over the last decade [1]. Traditional risk factors for zygomycosis include metabolic acidosis, corticosteroid use, hematologic malignancies, organ transplantation, iron overload, diabetes mellitus (DM), intravenous drug use (IVDU) and acquired immunodeficiency syndrome (AIDS) – all comorbid conditions that may have also increased in frequency over the past 10 years [2]. However, DM is the most common predisposing etiology described in a recent review [3]. The most frequent clinical presentations of infection include; rhinocerebral, pulmonary, disseminated, gastrointestinal, or cutaneous disease [4]. Renal zygomycosis remains rare and is generally a complication of disseminated disease with evidence of extensive tissue invasion [5,6]. The case described in this paper differs from those reports of renal zygomycosis in the literature by the agent’s location strictly within the renal collecting system with no evidence of parenchymal invasion.

Renal fungus balls are typically due to *Candida* spp. and occur most commonly among neonates and patients with immune dysfunction such as those with DM, AIDS, or solid organ transplant recipients. moulds, including *Aspergillus* spp., have also been shown to cause renal fungus balls and the management of these lesions typically includes a combined surgical and medical approach with systemic antifungal agents [7–9]. To our knowledge, a renal fungus ball secondary to zygomycosis without concurrent tissue invasion has not been previously reported.

Infection with one of the mucormycetes (formerly zygomycetes) is typically managed with an amphotericin B formulation and surgical resection, if feasible, of involved tissue. However, these infections often require prolonged antifungal therapy placing patients at risk for medication-induced side effects. Posaconazole is a new extended-spectrum azole antifungal that has demonstrated *in vitro* and *in vivo* activity against the mucormycetes [10]. It may have lower MICs when tested against *Rhizopus* spp. than amphotericin B but has been used successfully in the past as salvage...
therapy during infection with these difficult pathogens [11]. Posaconazole is an attractive regimen due to its; (1) favorable safety profile even with long-term therapy, (2) typically low MICs against Rhizopus spp., and (3) availability of an oral formulation [12].

Herein we report the novel presentation of an isolated Rhizopus oryzae fungus ball, and highlight the successful use of posaconazole as salvage therapy in combination with surgical drainage to avoid nephrectomy.

**Case report**

A 32-year-old male with a history of diabetes mellitus and IVDU presented with a two-month history of hematuria associated with right flank pain, oliguria, and 45 kg weight loss. He denied fevers, chills, night sweats, or dysuria. He described the inability to urinate although with continued straining he was able to pass multiple fragments of tan-brown necrotic tissue followed by gross hematuria. The patient described these as 4–5 inch long pieces of tissue that resembled ‘cigarettes’. Samples were collected and sent to pathology, and were later found to be consistent with a fungus ball (Fig. 1).

On admission the patient had a temperature of 98.6°F, pulse of 96 per minute and a blood pressure of 128/80 mmHg. He was in no distress, and his nasal mucosa and oropharynx appeared normal. Cardiac, pulmonary and abdominal examinations were unremarkable. However he exhibited mild pain to palpation over his right iliac fossa without evidence of peritoneal irritation, and no costovertebral angle tenderness. His admission laboratory values included; white blood cell count 5,000 cells/ul, hemoglobin 6.8 gm/dl, hematocrit 19.8% (MVC 79.9), platelet count 132,000 cells/ul. His renal function and anion gap were normal. His serum glucose and creatinine increased to 1.9 mg/dL after 4 weeks of therapy. The mean inhibitory concentration for posaconazole and amphotericin B deoxycholate were 2.0 and 0.25 μg/ml, respectively.

Fluconazole was stopped and amphotericin B lipid complex 350 mg (5mg/kg) and amphotericin B deoxycholate 50 mg/l of water were instilled through the nephrostomy tube every 8 h. The patient tolerated this treatment well and on day 9 of hospitalization amphotericin B instillation through his nephrostomy tube was discontinued as he left against medical advice. The patient did, however, continue amphotericin B lipid complex 350 mg IV daily. His creatinine increased to 1.9 mg/dL after 4 weeks of therapy. MRI at this time showed only indeterminate non-enhancing punctate foci in the inferior pole, without evidence of abscess or pyelonephritis. His therapy was changed to posaconazole 400 mg orally twice daily to complete six months of therapy. The patient has had no signs or symptoms of recurrence and has been free of antifungal medications for 5 years.
and negative urine cultures. However this diagnosis is not often clinically suspected prior to surgical resection or postmortem examinations due to the rarity of this manifestation of disease. Our case differs significantly from those in the literature due to the presence of an isolated fungal bezoar (fungus ball) without evidence of invasive disease. This manifestation has not been previously reported with respect to the mucormycetes.

Renal fungus balls are almost uniformly secondary to Candida spp. infections and are most commonly observed in neonates [14]. These cases are presumed to occur through hematogenous seeding or via ascending infection from the lower genitourinary tract [8,9]. However, Candida fungus balls have also been described in diabetics, transplant patients, those with HIV, or more rarely in the elderly without obvious underlying immunosuppression. Aspergillus spp. have also been implicated as a cause of renal fungal balls although these cases are quite uncommon [15,16].

The pathologic findings within a renal fungus ball differ significantly from those in pulmonary fungus balls caused by the mucormycetes or Aspergillus spp. Fruiting bodies develop from mycelia in areas of high oxygen tension, such as lung/or sinus cavities, and consequently, do not develop in tissues. Thus, the pathologic findings associated with a renal mycetoma are considerably different from those found with a mycetoma within the lung, even though both may be caused by the same fungus.

Therapy advocated for bezoars caused by these pathogens usually involves a combined medical and surgical approach [14]. The majority of existing data relates to fungal balls caused by Candida spp. and previous publications suggest the early initiation of systemic antifungal therapy prior to surgical manipulation of the genitourinary tract so as to avoid hematogenous dissemination. Irrigation of amphotericin B deoxycholate (50mg/l of sterile water) via the catheter or

Discussion

Mucormycetes (formerly zygomycetes) include the genera Rhizopus, Lichtheimia (formerly Absidia), Apophysomyces, Cunninghamella, Saksenaea, Rhizomucor, and Mucor amongst others [2]. These pathogens have a worldwide distribution and infection can be acquired through inhalation, ingestion, cutaneous exposure, contamination of wounds, trauma, or injection [2]. Renal zygomycosis is presumed to occur via seeding of the kidneys during an episode of fungemia. Isolated renal zygomycosis is rare and patients usually have well recognized risk factors for fungemia, including an intravenous catheter, intravenous drug use, alcoholism, corticosteroid therapy, or infection with the human immunodeficiency virus [13].

Patients with renal zygomycosis typically present with fever, flank pain (may be unilateral or bilateral depending upon the extent of disease), hematuria, urinary obstruction,

Fig. 2 (A) IVP of our patient’s right kidney showing a large filling defect within the renal pelvis. This filling defect was found secondary to a Rhizopus oryzae fungus ball. (B) Normal intravenous pyelogram (IVP) of a right kidney for comparison.

Fig. 3 Fungal bezoar (white fluffy material) seen during percutaneous renal endoscopy. This lesion is seen within the renal pelvis.
nephrostomy tube has also been recommended [14]. Balloon dilatation of inflammatory strictures may be required to reestablish drainage through the ureters and some infections will need open pyelotomy for debridement. Percutaneous resection of the fungus ball has also been suggested during the treatment of Candida associated bezoars. Although there are no previous reports of the mucormycetes causing renal fungus balls without renal parenchymal involvement, infections caused by these agents at other sites typically mandates debridement given their high mortality (up to 50%) and frequent poor response to antifungal therapy [3].

Our patient was asymptomatic aside from his intermittent urinary obstruction and his laboratory and radiographic findings were not suggestive of an invasive infection. For this reason we opted to avoid nephrectomy and attempted systemic antifungal therapy and resection of the fungus ball through percutaneous endoscopy. The mechanism of infection was presumed to be the result of his intravenous drug abuse. Inoculation via this mechanism seems feasible and heroin abuse has been associated with transient but significant leukopenia which may have further predisposed our patient [17]. However with an otherwise intact immune system direct tissue invasion did not occur, although this remains hypothetical.

The patient tolerated 4 weeks of ABLC and at that time his therapy was changed to posaconazole. Oral posaconazole has been used as salvage therapy for patients with zygomycosis who are unresponsive or intolerant of amphotericin B and has a reported success rate of 79% in one recent study [18]. Another similar investigation evaluating posaconazole as salvage therapy in 91 patients with zygomycosis reported a success rate of 60% at 12 weeks and 21% of patients had stable disease [19]. Despite the lack of tissue invasion a longer course of an amphotericin B formulation was chosen given the relatively low renal clearance of posaconazole (13% of total drug is excreted in the urine) [20].

In conclusion although fungal bezoars caused by non-Candida spp. remain rare, a similar approach as used in the treatment of Candida fungus balls may yield satisfactory results in patients without evidence of tissue invasion. In this case we have shown that a combined minimally invasive surgical approach and an amphotericin B formulation followed by long-term posaconazole may provide effective and curative therapy.

Acknowledgments
This report was unfunded.

Declaration of interest: G.R.T. has served as a consultant for Basilea. T.F.P. has received research support from Basilea, Merck, Pfizer, and Schering-Plough, has received speaking fees from Merck and Pfizer, and as a consultant for Basilea, Merck, Nektar, Pfizer, and Toyama.

References
20 Posaconazole [package insert]. Kenilworth NSC.