Published in final edited form as:

Transpl Infect Dis. 2018 February ; 20(1): . doi:10.1111/tid.12804.

***Scedosporium apiospermum* infection of the urinary system with a review of treatment options and cases in the literature**

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Abstract

Infection with *Scedosporium* species is associated with a significant morbidity and mortality and is becoming increasingly common, especially in immunocompromised patients. We describe the presentation and successful management of an immunocompromised patient with *Scedosporium apiospermum* infection of the upper urinary tract system, a rare disease manifestation. The current literature on urinary tract scedosporiosis is further reviewed with emphasis on treatment options and limitations of current antifungal therapy.

Keywords

bone marrow transplant; genitourinary; kidney; opportunistic infection; *Scedosporium*; transplantation; urinary

1 | INTRODUCTION

Scedosporium species is a ubiquitous, saprophytic, filamentous mold found in soil, sewage, polluted water, and compost.¹ It is an increasingly prevalent and devastating cause of infection in immunocompromised patients.² In the transplant population, *Scedosporium* species accounts for 25% of non-*Aspergillus* mold infections, the third most common after Mucorales and *Fusarium* species.³ *Scedosporium* infections are caused mainly by *Scedosporium apiospermum* and *Lomentospora prolificans* (formerly known as

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AUTHOR CONTRIBUTIONS

E.B. involved in drafting of the article, literature review, and critical revisions of the article; A.T.Y. involved in drafting of the article, literature review, and critical revisions of the article; L.X. involved in drafting of the article; S.F.-P. involved in acquisition and interpretation of pathology figures; A.Y.L. performed the critical revisions of the article and approval of article; D.Y.H. performed the critical revisions of the article and approval of article.

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Scedosporium prolificans). Disseminated infection is the most common form of disease, often involving the central nervous system or pulmonary or integumentary systems.^{2,4} Invasion of the urinary system has rarely been described and is usually a late manifestation of otherwise disseminated disease.

Infection with *Scedosporium* species often requires prolonged antifungal therapy as well as surgical intervention, but outcomes remain poor, with mortality rates as high as 71% in disseminated cases.⁴ Treatment is challenging in part owing to the organism's resistance profile, difficulties in achieving adequate antifungal drug levels in infected tissues, and toxicities associated with antifungal therapies.

We describe below an unusual case of *S. apiospermum* infection in an immunocompromised patient with primary manifestation in the urinary system, treated successfully using a combination of antifungal and surgical therapy. We review the available literature on *Scedosporium* infections of the urinary system and discuss the clinically relevant question of antifungal penetration into renal parenchyma and urine.

2 | CASE DESCRIPTION

A previously healthy 27-year-old male was diagnosed in August 2015 with precursor B-cell acute lymphoid leukemia and underwent induction chemotherapy with CALBG protocol 10403.⁵ Two months later, during his first week of consolidation therapy, he developed back pain requiring admission. A renal ultrasound demonstrated the right-sided hydronephrosis caused by a soft tissue mass at the right ureterovesical junction, confirmed on computed tomography (CT) of the abdomen and pelvis. Several small nodules <3 mm were also incidentally noted in the lower lung parenchyma. The patient had no prior history of urinary instrumentation. Cystoscopy with retrograde pyelogram and ureteroscopy revealed soft white sediment in the distal ureter, which was removed and sent for culture and pathology. A ureteral stent was placed, with subsequent resolution of hydronephrosis and back pain. Cultures from the ureteroscopy did not yield any growth. Fungal elements were, however, seen on pathology, and targeted fungal sequencing was done on paraffin-embedded tissue collected from the distal ureteral mass. Polymerase chain reaction (PCR) targeting the ITS2 and D2 regions of ribosomal RNA locus revealed *S. apiospermum*. Testing was performed at Stanford Diagnostic Microbiology laboratory.⁶ Voriconazole (VRC) was started at 400 mg twice daily by mouth (PO). Unfortunately, his acute lymphoid leukemia later relapsed in November 2015 and he underwent reinduction with blinatumomab.

A month into VRC therapy, in December 2015, surveillance CT pyelogram showed a new 3 × 1.6 cm complex cyst in the inferior pole of the right kidney. Thoracic CT showed multiple pulmonary nodules of <3 mm, unchanged from prior abdomen and pelvis CT done a month earlier. Sinus CT and magnetic resonance imaging of the brain were performed for screening purposes and were normal. Repeat cystoscopy and ureteroscopy revealed debris that was again positive for *S. apiospermum* by PCR, but without growth on culture. The ureteral stent was exchanged and subsequently removed 3 weeks later, and no debris was seen at that point. The patient remained on VRC with therapeutic trough levels between 1.9 and 3.2 µg/mL.

A month after stent removal, the patient was readmitted for consolidation chemotherapy with blinatumomab, with plan to proceed with hematopoietic stem cell transplant (HSCT). He remained asymptomatic, but CT scan showed an enhancing soft tissue irregularity in the right kidney, now exophytic, increased in size from a month prior, and newly abutting the right psoas and iliacus muscles (Figure 1). Given the high likelihood of a fungal etiology that might cause significant morbidity or mortality during HSCT, a decision was made to surgically resect the kidney while optimizing systemic antifungal therapy. The patient underwent laparoscopic radical right nephrectomy on January 21, 2016. The lower pole of the kidney was found to be necrotic (Figure 2) and pathology showed necrotizing inflammation with fungal elements (Figure 3), although cultures and PCR were negative.

For antifungal therapy, micafungin 150 mg intravenously daily and terbinafine 250 mg PO daily were added to VRC. The latter was subsequently changed to posaconazole 300 mg PO daily owing to decreasing trough levels to subtherapeutic despite dose adjustments. A month later, ultrasound follow-up showed no lesions in the nephrectomy bed. However, a 1.8-cm prostate lesion was noted, with magnetic resonance imaging showing rim-enhancing fluid collections consistent with phlegmonous prostatitis. A positron emission tomography CT was performed, showing fluorodeoxyglucose-avid fluid collections in the prostate as well as the left shoulder. Joint aspirate from the left shoulder was noninflammatory and negative for bacteria and fungi by cultures and PCR. Given clinical stability, surgical intervention was deferred with close monitoring.

The patient remained asymptomatic on combination antifungal therapy. He underwent total body irradiation and etoposide conditioning followed by successful allogeneic matched-related donor HSCT in March of 2016. Terbinafine and micafungin were discontinued in the summer of 2016. Oral therapy with posaconazole was maintained through the first year following HSCT. At last follow-up, 16 months post HSCT in April 2017, the patient was asymptomatic and doing well.

3 | DISCUSSION

In immunocompromised hosts, angioinvasion with *Scedosporium* species is more frequent and can result in fungemia with hematogenous dissemination. While dissemination likely occurred in our patient, the only symptomatic manifestation and confirmed area of involvement were in the urinary system.

3.1 | A review of the literature on urinary scedosporiosis

Scedosporiosis of the urinary tract has been rarely described. Review of cases' search criteria were "scedosporium" and "genitourinary" or "urine" or "urinary" or "kidney." Among the nine cases found in the literature, all involved disseminated *Scedosporium* infection in immunocompromised hosts (Table 1).^{1,7-13} In seven of these cases, urinary involvement was asymptomatic, and in five cases, urinary involvement was only discovered postmortem. Five patients grew *Scedosporium* species in blood cultures. Six cases involved *L. prolificans*, and the remaining three involved *S. apiospermum*. All but one patient had a fatal outcome; six died within a month of presentation, with five deaths occurring prior to the initiation of appropriate antifungal therapy.

Only two cases had symptomatic involvement of the urinary system by *Scedosporium* species, manifested as ureteral obstruction. The first was a 63-year-old male who underwent bilateral lung transplantation for interstitial pneumonitis.¹² The patient was diagnosed with fungal retinitis caused by *S. apiospermum* 93 days post transplant. Initial therapy with amphotericin (AmB) intravenously and VRC PO was later changed to VRC 200 mg PO twice per day and terbinafine 250 mg daily combined with intraocular injection of VRC. Four months later, while still on PO VRC, the patient presented with the left-sided renal colic and urethral discharge. Abdominal CT demonstrated a filling defect in the left ureter. *S. apiospermum* was identified on biopsy of the ureteral mass and in urine cultures. The patient received VRC PO and by irrigation via ureteric catheter, which led to resolution of his symptoms, but urine cultures remained positive. At the time of the case report publication, the patient continued to be asymptomatic with a plan for continued serial ureteric irrigations.¹²

Sahi et al¹³ reported a case of ureteral scedosporiosis as a late manifestation of disseminated infection. That case involved a 19-year-old bilateral lung transplant recipient who was taking VRC prophylaxis (200 mg PO every 12 hours) for pulmonary colonization with *S. apiospermum* before and immediately post transplant. A month after transplantation, she presented with chorioretinitis, and *S. apiospermum* was detected in vitreal aspirate. Caspofungin, terbinafine, and intravitreal VRC were added to PO VRC, but she eventually required enucleation. In addition to chorioretinitis, she further developed skin nodules, pansinusitis, chest wall cellulitis, mediastinitis, vertebral osteomyelitis, and septic arthritis secondary to disseminated *S. apiospermum* infection. VRC was switched to posaconazole (solution form) 200 mg every 6 hours. Despite initial improvement, she presented 6 months later with worsening respiratory symptoms and new ureteral obstruction that required stenting. Cultures from the endobronchial plaques found during bronchoscopy at the anastomotic site and from the ureter grew *S. apiospermum*. Posaconazole was increased to a daily dose of 1200 mg combined with liposomal AmB and aerosolized pentamidine. She continued to have urinary and pulmonary symptoms as well as recurrent bacterial infections and died 15 months later.¹³

3.2 | Antifungal therapeutic options for *S. apiospermum* and urinary penetration of antifungals

VRC is considered the treatment of choice for *S. apiospermum*. This recommendation is based partially on in vitro data showing lower minimum inhibitory concentration (MIC) with VRC (MICs 0.03-0.5 µg/mL) compared to AmB as well as other azoles including posaconazole and itraconazole.¹⁴ Limited in vivo data also support the clinical utility of VRC. A 2007 retrospective review of 107 patients with *S. apiospermum* and *L. prolificans* infection from the Pfizer VRC global clinical trials database treated with VRC as primary or salvage therapy showed overall successful therapy in 57%, with success rate varying widely by sites of infection; central nervous system infections and disseminated infections had a 43% and 48% response rate, respectively, whereas skin and subcutaneous infections had a 91% response rate.¹⁵ Combination therapy with VRC plus terbinafine or micafungin for synergy has also been used based on in vitro data suggesting 20–60-fold decrease in MIC,^{14,16} and at least a few successful case reports.^{17,18}

Treatment of fungal infections of the urinary tract presents additional challenges given variable penetration of antifungals into urine and kidney tissue. Echinocandins readily penetrate and accumulate in renal tissue, reaching levels multiple times that of plasma. However, <2% is excreted into urine and has questionable efficacy for treatment of fungal or candidal cystitis.^{19,20}

Of the azoles, only fluconazole reaches therapeutic levels in the urine and kidney. It penetrates renal tissue with levels up to 4× serum plasma levels and with ~80% excreted unchanged in the urine. VRC is also excreted in the urine; however, unlike fluconazole, VRC is excreted mostly as inactive metabolites and thus unlikely to be effective for urinary infections. Kidney tissue concentration of VRC appears to be adequate, with detectable levels in postmortem human kidney tissue and good efficacy for treating renal candidal infection in an animal model.^{20–22} The pharmacokinetics of itraconazole and posaconazole regarding the urinary system are similar to VRC, with good renal parenchymal levels but minimal urinary excretion of the active drug.^{20,21}

Also like VRC, terbinafine is mostly excreted in the urine as an inactive metabolite, possibly rendering it ineffective for urinary tract infection. Although a study in rats demonstrated detectable levels of terbinafine in kidney tissue, the majority of drug accumulation was in adipose and skin, with kidney levels falling below the level of detection 4 hours after administration.²³

AmB deoxycholate is not used for the treatment of *Scedosporium* species owing to a lack of efficacy. However, it also readily accumulates in the kidneys and has good urinary excretion. The lipid formulations of AmB are preferred because of their decreased renal toxicity as compared to deoxycholate, but have significantly lower levels of concentration in the kidney and urine, and failures in treating candiduria have been reported.^{20,21} Flucytosine is excreted almost completely unchanged in the urine and able to reach very high concentrations in the urine and high levels in renal parenchyma.²¹

4 | CONCLUSION

We have described a unique case of primary urinary scedosporiosis in an immunocompromised host successfully managed using combination antifungal therapy and surgical intervention. We chose a combination of VRC (and subsequently posaconazole) with micafungin and terbinafine for synergy, but it remains unclear which of these antifungals or their combinations were most effective. Surgical intervention has been previously shown to improve survival in patients with disseminated *Scedosporium* infections.⁴ Given the patient's impending immunosuppression and the high morbidity and mortality associated with *Scedosporium* infections, we opted for an aggressive approach with good outcomes. At last follow-up in April 2017, 16 months post HSCT, the patient had no symptoms of infection relapse and was off all antifungal therapy.

As the number of transplant patients continues to grow and the threat of morbidity and mortality from fungal infections increases, it is important to recognize the ability of

Scedosporium species to cause invasive disease including in the urinary system, the therapeutic options available, and the limitations of antifungal pharmacokinetics.

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FIGURE 1.

Progression of renal abscess (arrows) as seen on computed tomography scan of the abdomen and pelvis over time, starting from (A) initial discovery, (B) at week 8, and (C) at week 10

FIGURE 2.

Gross specimen of surgically resected right kidney, bisected. Arrows point to a $4.2 \times 3.7 \times 1.5$ cm area of abscess with tissue necrosis at the inferior pole

FIGURE 3.

Hematoxylin and eosin-stained section of the necrotic area of the kidney showing fungal elements with surrounding necrotizing inflammation (400× magnification photo). The fungal elements are characterized by entangled septate hyphae with 45° angle branching. The oval highlights a 45° angle branch point. The arrowheads indicate septa

TABLE 1

Review of cases with evidence of urinary scedosporiosis

Author (Ref)	Age (years), gender	Underlying condition	Antifungal prophylaxis	Primary urinary tract disease	Culture results/specimen ^a	Affected sites/postmortem findings ^b	Antifungal	Surgical management	Outcome
Marin et al ⁷	66, M	AML, ChT	None	No	<i>L. prolificans</i> Skin, blood, urine	Lung, skin, eye postmortem: heart, lung, kidneys, liver, thyroid, spleen, brain	AMB	No	Died
Salesa et al ⁸	56, F	AML, Auto-SCT	FLC	No	<i>L. prolificans</i> Blood	Skin postmortem; jugular vein; fungal abscesses in lungs, kidneys, esophagus, pancreas, brain, thyroid	AMB	No	Died
Nenoff et al ¹⁰	60, M	Burkitt Lymphoma HIV, ChT	FLC	No	<i>L. prolificans</i> Lung tissue	Skin postmortem: lungs, kidney, spleen, myocardium, brain	FLC, AP	No	Died
Westerman et al ⁹	65, M	AML, ChT	FLC	No	<i>L. prolificans</i> Blood, sputum, feces	Catheter insertion site postmortem: lungs, kidneys, spleen, liver, adrenals, mediastinal nodes, myocardium, brain	AMB	No	Died
Idigoras et al ¹¹	28, M 28, M	HIV ALL, ChT	None FLC	No No	<i>L. prolificans</i> BAL, blood, urine, feces <i>L. prolificans</i> surgical wound, abscess fluid, blood	Lung Wound, skin postmortem: septic emboli to lungs, liver, heart, diaphragm and right kidney	None AMB + ITR +TER; VRC (iv)	No No	Died Died
Musk et al ¹²	63, M	Lung transplant	AMB	No	<i>S. apiospermum</i> retinal, vitreal, ureteral tissue	Retina followed by ureter	VRC (iv) + LAMB; VRC (po + ivi + pelvic irrigation) + TER	Yes: ureteral debridement + stent	Survived
Sahi et al ¹³	19, F	Lung transplant	VRC	No	<i>S. apiospermum</i> vitreal, synovial fluid; urine; lung, skin	Lungs, eye, skin, mediastinum, sinus, bone, joints; followed by ureter	VRC (po+ivi) + CSP + TER; POS (po) + AP + LAMB	Yes: enucleation, ureteral stent	Died
Campa-Thompson et al ¹	62, M	Lung transplant	None	No	<i>S. apiospermum</i> pleura, ETA	Brain, lung, pleura, surgical wound postmortem: abscesses in kidneys, aortic wall, thyroid gland, brain, heart	AMB	No	Died

^a *Scedosporium* species identified and specimens from which cultures resulted.

^b Sites involved at presentation and sites where infection was detected postmortem by autopsy.

L. prolificans: *Lomentospora prolificans* (formerly known as *Scedosporium prolificans*); M, male; F, female; AML, acute myeloid leukemia; ChT, chemotherapy; Auto-SCT, autologous stem cell transplant; HIV, human immunodeficiency virus; ALL, acute leukoblastic leukemia; FLC, fluconazole; AMB, amphotericin B; VRC, voriconazole; AP, aerosolized pentamidine; ITR, itraconazole; LAMB, liposomal amphotericin B; iv, intravenous; po, oral; ivi, intravitreal; TER, terbinafine; CSP, caspofungin; POS, posaconazole; BAL, bronchoalveolar lavage fluid; ETA, endotracheal aspirate.