

# **Invasive fungal sinusitis caused by *Pseudallescheria boydii*: case report and literature review**

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## **Abstract**

Fungal sinusitis secondary to *Pseudallescheria boydii* is rare, as only 25 cases have been previously reported in the literature. Although *P boydii* resembles *Aspergillus* on pathologic examination, it is typically resistant to amphotericin B. Therefore, culture is necessary to differentiate the two. Patients with *P boydii* sinusitis should generally be treated with a combination of surgery and antifungal therapy. Combination treatment is particularly important for immunocompromised patients with fungal invasion because mortality among these patients is high. The prognosis is better for immunocompetent patients, even those with fungal invasion. We describe a new case of invasive fungal sinusitis secondary to *P boydii* infection, and we review the literature on this emerging pathogen.

## **Introduction**

*Pseudallescheria boydii*--a ubiquitous, saprophytic fungus in the class Ascomycetes--is an emerging pathogen found worldwide. It is commonly isolated in soil, in polluted and coastal waters, and in animal manure. (1) Siebenmann first isolated the organism in the 1880s as a pathogen in the ear of a child with chronic otitis externa. (2) The first complete description of the organism was published in 1922 by Shear. (3)

*P boydii* is associated with Madura foot (maduromycosis), a cutaneous and subcutaneous suppurative disease that affects farmers in tropical and subtropical countries. (4) Historically, Madura foot has accounted for 99% of all *P boydii* infections. (1) The organism has also been identified in specimens obtained from pulmonary cavities and pulmonary infiltrates. It has been shown to cause sinusitis, corneal infections, endophthalmitis, parotitis, skin infections, arthritis, osteomyelitis, brain and thyroid abscesses, endocarditis, chronic prostatitis, and disseminated infection?

In this article, we describe a case of *P boydii* invasive fungal sinusitis in a diabetic patient who died before the pathogen was identified. As we discuss, this organism can be mistaken for *Aspergillus* on fungal smear, but it is typically resistant to amphotericin B, the antifungal medication that is commonly started empirically for patients with invasive fungal sinusitis. Thus, in cases of invasive fungal sinusitis, proper identification via culture is imperative to ensure effective pharmacotherapy.

## **Case report**

A 76-year-old man with non-insulin-dependent (type 2) diabetes mellitus presented with a 4-month history of intractable temporal and occipital headaches. Since the onset of the headaches, he had been diagnosed with sinusitis and treated twice with a penicillin derivative, but his headaches did not resolve. Two subsequent courses of a steroid taper provided no relief. At that point, the patient was admitted to our hospital for a further workup.

Upon admission, the patient was dehydrated and hyperglycemic; a finger-stick blood test revealed that his glucose level was 477 mg/dl. He had discontinued his oral hypoglycemic medication prior to admission, despite being on a steroid course. The early part of his hospitalization was complicated by the medical and later surgical treatment of diverticulitis. After one of his abdominal surgeries, he awoke from surgery confused and combative and complaining of blindness in both eyes. Prior to the onset of the blindness, the patient's visual acuity had been 20/60 in the right eye and 6/200 in the left eye; he had also had a left relative afferent pupillary defect. However, after the onset of the blindness, he was found to have a disconjugate gaze with poor extraocular motility (worse in the left eye), and he was not able to perceive hand movements in front of his eyes.

The laboratory workup revealed an elevated white blood cell (WBC) count of  $12.6 \times 10^9$ /L (normal: 4.8 to 10.8), an elevated erythrocyte sedimentation rate of 81 mm/hr (normal: 0 to 20), and an elevated glycosylated hemoglobin concentration of 11.2% (normal: 4.5 to 6.4%). The rapid plasma reagin test was nonreactive, and the vitamin [B.sub.12] level was elevated at 1,143 pg/ml (normal: 210 to 705). Lumbar puncture revealed a low cerebrospinal fluid (CSF) glucose concentration of 104 mg/dl (normal: 239 to 358 for a blood glucose level of 477 mg/dl) and an elevated CSF protein level of 49.2 mg/dl (normal: 15 to 45); no WBCs were found in the CSF.

Noncontrast computed tomography (CT) of the head showed partial opacification at the sphenoid sinus. Contrast-enhanced magnetic resonance imaging (MRI) of the brain demonstrated enhancement of the dura along the planum sphenoidale, the anterior frontal lobes bilaterally, and the orbital apices bilaterally (figure 1). Enhancement was also noted along the anterior clinoid. Bilateral engorgement of the superior orbital veins was noted.

[FIGURE 1 OMITTED]

Nasal endoscopy detected no necrosis of any turbinate or of the rostra of the sphenoid sinuses (figure 2). Contrast-enhanced CT of the sinuses revealed mucoperiosteal thickening of the right sphenoid and frontal sinuses and opacification of the left sphenoid sinus (figure 3). Enhancing soft tissue was seen at the posterior wall of the frontal sinus, and it extended along the planum sphenoidale and through the fovea ethmoidalis; intracranial extension was seen along the dura at the anterior cranial fossa and the anterior aspect of the

interhemispheric falx (figure 4). Additionally, the process extended anteriorly through the optic nerve foramina and superior orbital fissures and was associated with a loss of normal fat planes bilaterally in the pterygopalatine fossae. Bone erosion accompanied the abnormal soft-tissue extension from the ethmoid air cells and frontal sinuses through the adjacent anterior cranial floor and cribriform plate.

[FIGURES 2-4 OMITTED]

In light of these findings, the patient was placed on empiric piperacillin/tazobactam and amphotericin B lipid complex to cover bacterial skull base osteomyelitis and invasive fungal sinusitis. He was then taken to the operating room for image-guided bilateral endoscopic sphenoidotomy with biopsy. Operative findings included minimally inflamed mucosa within the nasal cavity. No necrotic tissue was present on the right or left sphenoid rostrum, and no purulent or necrotic debris was present in either sphenoid sinus (figure 5). A frozen-section biopsy of the right sphenoid sinus was reported as only inflamed mucosa with no evidence of invasive fungal disease. A Gram's stain of the sinus contents identified gram-positive cocci and yeast. Final pathology identified a mass of fungal hyphae in 1 of 5 specimens that were morphologically consistent with the presence of *Aspergillus* spp. Culture grew 2+ coagulase-negative staphylococci and 1+ multidrug-resistant *Klebsiella pneumoniae*. Based on these findings, the antibacterial coverage was changed to vancomycin and meropenem.

[FIGURE 5 OMITTED]

Over the next several days, the patient's mental status worsened. A cerebral angiogram showed an area of opacification within the anterior aspect of the left cavernous sinus consistent with thrombosis. Hence, the patient was started on heparin anticoagulation. However, his mental status continued to worsen, and he developed epistaxis that required packing of the left nasal cavity. The heparin drip was discontinued, but soon thereafter, he developed worsening respiratory distress and died. Of note, he had been switched from amphotericin B lipid complex to voriconazole approximately 3 days prior to his death because the maximum amphotericin B dosage had been reached.

At autopsy, the dura of the anterior falx cerebri was indurated and thickened (as much as 0.5 cm). Microscopic examination of this area detected acute and chronic inflammation associated with necrosis and a granulomatous component. Silver stains showed septate fungal hyphae. Fungal cultures from the sphenoid biopsies performed at surgery grew *P. boydii* in the postmortem period.

#### Literature review

For our literature review, we searched the PubMed database, using the keywords *Pseudallescheria*, *boydii*, *Verticillium graphii*, *Allescheria*, *Glenospora*, *Indiella*

americanus, *Acremonium lusii*, *Petriellidium*, *Scedosporium apiospermum*, *monosporium*, and sinusitis. We found 25 reported cases of sinusitis that were caused by *P. boydii*. (5-29) The case described in this article brings to 26 the total number of cases documented in the literature (table). These patients included 17 women and 9 men, aged 20 to 85 years (mean: 48.3). The first case was reported by Gluckman et al in 1977; their patient was a 58-year-old diabetic man on hemodialysis who ultimately died of a cause unrelated to his *P. boydii* infection. (6)

Of the 26 cases, mucosal invasion by fungal organisms was proven or suspected in 12 patients, excluded or not suspected in 9 patients, and unknown in the remaining 5 patients. Of the 12 patients with proven or suspected invasive disease, 9 were immunocompromised; 4 patients had leukemia, 3 were diabetics, and 2 had acquired immunodeficiency syndrome (AIDS). All 9 of these patients either died of infection or another cause or had persistent or recurrent infection at the time the case was reported. Six of these 9 immunocompromised patients were treated with surgery and antifungal therapy, 1 was treated with surgery and antibacterial therapy, and 2 were treated with antifungal therapy alone. Of the 3 immunocompetent patients with proven or suspected invasive disease, 1 experienced a complete resolution of disease after undergoing combined surgery and antifungal therapy, 1 responded completely to surgery alone, and 1 died of infection after being treated with combined surgery and antifungal therapy.

Five of the 9 patients without evidence or suspicion of invasion were immunocompetent, and all 5 experienced a complete resolution of their infection; 4 patients had been treated with surgery alone and the other with combined surgery and antifungal therapy. Of the 4 patients without signs of invasion who were immunocompromised (1 case each of adrenocortical insufficiency, sickle cell anemia, diabetes, and organ transplantation), 1 patient experienced a full resolution with combined surgery and antifungal therapy, 1 recovered completely with surgery alone, 1 died of squamous cell carcinoma of the sinuses following surgery, and the outcome of the other patient, who had undergone surgery, was not reported.

Among the 5 patients in whom the presence or absence of fungal invasion was not reported, 2 were immunosuppressed (1 case of diabetes and 1 case of bone marrow transplantation); the diabetic patient was treated with surgery alone and his outcome was not reported, and the post-transplant patient was treated with combined surgery and antifungal therapy but died of a related cause. Of the 3 immunocompetent patients in whom the presence or absence of fungal invasion was not reported, all experienced a complete resolution of symptoms; 2 had been treated with surgery alone, and 1 had been treated with combined surgery and antifungal therapy.

Among the 26 cases, the maxillary sinuses were involved in 15 cases, the sphenoid sinuses in 14, the ethmoid sinuses in 9, the frontal sinuses in 2, and the nasal

cavity only in 1. Seven of the 14 patients with sphenoid sinus involvement had isolated sphenoid disease.

Of the 26 patients, 13 had concomitant bacterial infections; these pathogens included *K pneumoniae* (n = 3), *Staphylococcus aureus* (3), *Citrobacter freundii* (3), *Staphylococcus epidermidis* (3), *Proteus mirabilis* (2), *Enterobacter cloacae* (2), anaerobic gram-positive rods (1), *Serratia liquefaciens* (1), and *Klebsiella oxytoca* (1). Fungal coinfection (*Candida albicans*) was seen in 1 patient.

## Discussion

Fungal infection of the paranasal sinuses includes a broad spectrum of disease processes. At one end of the spectrum is allergic fungal sinusitis, which represents an immune reaction to noninvading fungal colonizers that was first associated with *Aspergillus*. (30) At the other end of the spectrum is acute invasive fungal sinusitis, which is usually caused by *Mucor* or *Aspergillus* spp. Intermediate disease processes include chronic invasive fungal sinusitis and chronic noninvasive fungal sinusitis (fungus ball). In 1997, deShazo et al proposed that invasive fungal sinusitis be classified into three categories: granulomatous, acute fulminant, and chronic. (31) They described 2 cases of chronic invasive sinusitis in middle-aged adults with well-controlled non-insulin-dependent diabetes mellitus and apical orbital syndrome. The 2 patients had a similar course: protracted disease for more than 6 months with proptosis, vision changes, and late neurologic symptoms reflecting cavernous sinus invasion. Both patients died of their infection. Our patient followed a similar course with several months of protracted headache.

*Aspergillus*, *Mucor*, and *Candida* spp. are responsible for most pathologic fungal sinus infections. (32) However, improvements in the medical management of immunosuppressed patients and the wider use of immunosuppressive therapies has led to the identification of a long list of unusual fungal pathogens, some of which were previously thought to be solely commensal. Specifically, rare fungal pathogens have been isolated in AIDS patients, (22) in cancer patients (particularly those being treated for leukemia (33)), and in transplant recipients. (34) One of these emerging pathogens is *P boydii*.

*P boydii* has undergone many name changes over the years. In his original report, Siebenmann called it *Verticillium graphii*. (2) It has since been referred to as *Allescheria boydii*, *Glenospora boydii*, *Indiella americanus*, and *Acremoniella lusii*. (14) In 1970, Malloch suggested that the species be transferred from the genus *Allescheria* to *Petriellidium*. (35) This change was later thought to be an error, and the organism was placed in the valid and previously described genus *Pseudallescheria*. (1) The anamorph (imperfect) form of the organism is called *Scedosporium apiospermum* (formerly *Monosporium apiospermum*), and was shown by Emmons (36) in 1944 to be the same organism as *P boydii*. Both forms have been implicated as pathogens.

Of the 26 cases (5-29) of fungal sinusitis secondary to *P boydii* infection that have now been reported in the literature, fungal invasion was proven or suspected in 12 patients, 9 of whom were immunocompromised. It is interesting that the other 3 patients with invasive disease were immunocompetent: 2 experienced a full resolution of infection (1 with combination surgery and antifungal therapy and the other with surgery alone). Among the 13 patients with immunosuppression whose outcome was reported, 1 either died or had persistent or recurrent infection by the time the case was reported. Two patients with immunosuppression experienced a complete resolution of the infection, but neither had evidence of invasion: 1 of these patients had been treated with combined surgery and antifungal therapy and the other had been treated with surgery alone. These data suggest that our patient's prognosis probably would have been poor even if he had been diagnosed sooner.

Identification of *P boydii* by fungal culture is essential to selecting effective pharmacotherapy. The hyphae of *P boydii* can resemble those of *Aspergillus* on fungal stains, and their tropism for blood vessels is similar. (15) But unlike *Aspergillus*, *P boydii* is typically resistant to amphotericin B. (37) This can be problematic because amphotericin B is often the first-line pharmacologic therapy for suspected invasive fungal sinusitis. Miconazole is the antifungal of choice for *P boydii*, (38) and several authors have reported successful treatment with ketoconazole. (12,14,17,19) In 1978, Cosgrove et al theorized that combining amphotericin B with an imidazole antifungal might result in antagonism because the two agents competed for the same binding sites on cell membranes. (39) However, Walsh et al challenged that theory in 1995 when they reported that in vitro studies specific for *P boydii* showed that the two compounds actually might have a synergistic relationship. (40) More recently, the results of other in vitro studies have supported the use of voriconazole, a new triazole antifungal agent, in the treatment of *P boydii* infections. (41-43)

Our patient presented with a 4-month history of vague headaches, which are often characteristic of chronic sphenoid sinusitis. (28) He underwent an extensive workup, but the diagnosis was elusive. Only after orbital apex syndrome had developed was the diagnosis of chronic sinusitis with skull base osteomyelitis made. Even then, the organisms responsible were not known. Pathologic specimens from sphenoid sinus biopsies yielded a mass of fungal hyphae that resembled *Aspergillus*. It was for this reason that amphotericin B was started. It was not until after the patient had died that *P boydii* was grown in cultures of the sphenoid sinus. As discussed, *P boydii* is typically resistant to amphotericin B, so this patient received inadequate pharmacologic therapy. As for surgical therapy, by the time this patient had been diagnosed, imaging had already demonstrated erosion of a significant part of his anterior skull base and enhancement of the dura of the anterior cranial fossa. An earlier diagnosis and the use of miconazole or voriconazole as the initial therapy might have changed this patient's outcome.

However, the literature suggests that patients with invasive *P boydii* who are immunocompromised have a high mortality rate regardless of therapy.

In conclusion, fungal sinusitis secondary to *P boydii* infection is rare. When it does occur, it can appear in both immunosuppressed and immunocompetent patients. Although the organism resembles *Aspergillus* on pathologic examination, *P boydii* is typically resistant to amphotericin B. Therefore, culture and a definitive identification of the organism are crucial to selecting adequate pharmacologic therapy. Sensitivity testing will help direct antifungal therapy. In general, patients should be treated with a combination of surgery and antifungal therapy, particularly those patients with immunosuppression and fungal invasion. Immunocompetent patients with *P boydii* fungal sinusitis have a better prognosis, even when invasion is present.

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Table. Summary of the 26 cases of sinonasal infection with *P boydii* reported in literature

Sinus(es)	Immune status	Fungal
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Author	Age/sex	involved	(cause)	invasion
Gluckman et al, (6) 1977	58/M	Maxillary, ethmoid, sphenoid	Compromised (diabetes)	Proven
Winston et al, 1977	57/F	None (nasal cavity)	Compromised (leukemia)	Proven
Hecht and Montgomerie, (8) 1978	20/M	Maxillary	Compromised (leukemia)	Proven
Mader et al, (9) 1978	33/F	Sphenoid	Competent	Proven
Bark et al, (10) 1978	28/F	Maxillary	Compromised (diabetes)	Unknown
Bryan et al, (11) 1980	47/F	Sphenoid	Competent	Proven
Bloom et al, (12) 1982	57/F	Maxillary	Compromised (adrenocortical Insufficiency)	Excluded
Winn et al, (13) 1983	43/F	Maxillary	Competent	Unknown
Schiess et al, (14) 1984	61/F	Maxillary, ethmoid, frontal, sphenoid	Compromised (diabetes)	Proven
Morgan et al, (15) 1984	45/M	Maxillary	Competent	Proven
Travis et al, (5) 1985	47/M	Maxillary	Competent	Unknown
Washburn	77/F	Maxillary	Competent	Excluded

et al, (16) 1988

Salitan et al, (17) 1990	28/F	Ethmoid, sphenoid	Competent	Unknown
Terris and Steiniger, (18) 1992	69/F	Sphenoid	Competent	Excluded
Stamm and Frable, (19) 1992	23/F	Maxillary, ethmoid, sphenoid	Competent	Excluded
Watters and Milford, (20) 1993	52/F	Ethmoid, sphenoid	Competent	Excluded
Grigg et al, (21) 1993	35/F	Maxillary, ethmoid	Compromised (leukemia)	Proven
Meyer et al, (22) 1994	44/M	Maxillary, ethmoid, frontal, sphenoid	Compromised (AIDS)	Suspected, after initially excluded
Fiero et al, (23) 1995	28/F	Ethmoid, sphenoid	Competent	Excluded
Machado et al, (24) 1998	40/M	Maxillary	Compromised (bone marrow transplant)	Unknown
Tadros et al, (25) 1998	33/F	Maxillary	Compromised (sickle cell anemia)	Excluded
Jones et al, (26) 1999	68/M	Maxillary, ethmoid	Compromised (leukemia)	Suspected
Horton et al, (27)	44/M	Sphenoid	Compromised (AIDS)	Suspected

1999

Shaw et al, (28) 2000	85/F	Sphenoid	Compromised (diabetes)	Excluded
Castiglioni et al, (29) 2002	58/F	Sphenoid	Compromised (post- transplant)	Not suspected
Bates and Mims, ([dagger]) 2006	76/M	Sphenoid	Compromised (diabetes)	Proven

Author	Concomitant bacteria	Treatment	Outcome
Gluckman et al, (6) 1977	Staphylococcus aureus, Proteus mirabilis	Surgery, * antifungal therapy (amphotericin B)	Died of an unrelated cause
Winston et al, 1977	S aureus, P mirabilis	Surgery, antibacterial therapy	Died of disease
Hecht and Montgomerie, (8) 1978	Staphylococcus epidermidis, Enterobacter cloacae	Surgery, antifungal therapy (5-fluorocytosine, amphotericin B)	Died of disease
Mader et al, (9) 1978	Citrobacter freundii	Surgery, antifungal therapy (miconazole)	Infection resolved
Bark et al, (10) 1978	Klebsiella pneumoniae, E cloacae, anaerobic gram- positive rods	Surgery	Unknown
Bryan et al, (11) 1980	None	Surgery, antifungal therapy (amphotericin B, then miconazole)	Died of disease

Bloom et al, (12) 1982	Klebsiella oxytoca	Surgery	Infection resolved
Winn et al, (13) 1983	None	Surgery	Infection resolved
Schiess et al, (14) 1984	K pneumoniae, S epidermidis (also Candida albicans)	Surgery, antifungal therapy (miconazole, then ketoconazole)	Died of an unknown cause
Morgan et al, (15) 1984	C freundii	Surgery	Infection resolved
Travis et al, (5) 1985	C freundii	Surgery	Infection resolved
Washburn et al, (16) 1988	No	Surgery	Infection resolved
Salitan et al, (17) 1990	S aureus	Surgery, antifungal therapy (amphotericin B, switched to miconazole then ketoconazole)	Infection resolved
Terris and Steiniger, (18) 1992	Serratia liquefasciens	Surgery	Infection resolved
Stamm and Frable, (19) 1992	None	Surgery, antifungal therapy (amphotericin B, switched to ketoconazole)	Infection resolved
Watters and Milford, (20) 1993	None	Surgery	Infection resolved
Grigg	None	Surgery,	Infection

et al, (21) 1993		antifungal therapy (amphotericin B, switched to miconazole, rifampin)	persisted a the most recent follow-up
Meyer et al, (22) 1994	S epidermidis	Surgery, antifungal therapy (ketoconazole)	Infection recurred; died of a related cause
Fiero et al, (23) 1995	None	Surgery	Infection resolved
Machado et al, (24) 1998	None	Surgery, antifungal therapy (itraconazole)	Died of a related cause
Tadros et al, (25) 1998	None	Surgery	Unknown
Jones et al, (26) 1999	None	Antifungal therapy (amphotericin B, itraconazole)	Died of leukemia
Horton et al, (27) 1999	None	Surgery, antifungal therapy (amphotericin B, switched to itraconazole)	Died of an unknown cause
Shaw et al, (28) 2000	None	Surgery	Died, probably of squamous cell carcinoma
Castiglioni et al, (29) 2002	None	Surgery, antifungal therapy (miconazole, then itraconazole)	Infection resolved

Bates and Mims, ([dagger]) 2006 K pneumoniae Antifungal therapy (amphotericin B) Died of disease

\* Surgical drainage and/or debridement.

([dagger]) Present report.

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