

## Fungal Sinusitis in Patients with AIDS: Report of 4 Cases and Review of the Literature

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### Introduction

Fungal infection of the paranasal sinuses is a well-known manifestation of invasive aspergillosis and mucormycosis, antedating the era of recognition of human immunodeficiency virus (HIV). Fungal sinusitis due to these and other important agents has been increasingly recognized and reported in patients with and without immunocompromise. Washburn et al reviewed fungal infections of the paranasal sinuses and proposed a classification that includes acute invasive disease and chronic disease of invasive or noninvasive nature (66). They emphasized the diversity of etiologic agents and made recommendations for therapy of chronic fungal sinusitis (66). An additional type of sinusitis is allergic fungal sinusitis.

Sinusitis is a common problem in patients infected with HIV, in whom it is more severe than in non-HIV infected patients, and it may be persistent and difficult to treat. The usual etiology based upon routine cultures is bacterial (21, 43, 58, 72).

Opportunistic fungal infections were among the first opportunistic diseases described in HIV-infected patients, presumably due to multiple abnormalities in local host defenses, immunological functions, and phagocytic activity (10). In addition to the fungal infections in the revised Centers for Disease Control (CDC) definition for acquired immunodeficiency syndrome (AIDS), a series of other miscellaneous fungal infections has also been reported (7, 10). All reported cases of fungal sinusitis in patients with HIV or AIDS fit into this category (that is, not in the CDC definition), although other aspects of the cases may fit the definition (3, 6, 8, 9, 12, 41, 50, 64). Here we report 3 cases of aspergillus sinusitis in patients with AIDS and what we

believe to be the first fully described case of sinusitis associated with *Pseudallescheria boydii*, the teleomorph of *Scedosporium apiospermum*, in a patient with AIDS. We also review 8 cases of fungal sinusitis cases in patients with AIDS, discuss them in the context of infections in patients without HIV or AIDS, and comment on therapy of aspergillus and *P. boydii* infections in patients with HIV or AIDS.

### Methods

Infectious diseases subspecialty physicians performing consultations at Cedars-Sinai Medical Center were polled about cases of fungal sinusitis in patients with HIV or AIDS, and discharge diagnoses were searched for the period January 1981 to June 1993. Computer-based (MEDLARS, National Library of Medicine, Bethesda, MD) and other searches of the literature were performed. Cases were included if patients had clinical or laboratory evidence of sinusitis or both, as well as demonstration (culture and histopathologic or cytologic) of the fungal pathogen in material obtained from 1 or more paranasal sinuses. Histopathologic demonstration of invasion into the mucosa or beyond was not required. Several cases with limited clinical information (primarily in abstract form), lack of histopathologic confirmation of a culture result, or both are not included as definite cases (2, 19, 21, 26, 37, 44, 56, 60, 73).

### Case Reports: Cedars-Sinai Medical Center Series

#### Case 1: *P. boydii* sinusitis

A 44 year-old white man with AIDS (disseminated *Mycobacterium avium* complex infection and cytomegaloviral retinitis) and past oral candidiasis presented in June 1992 with a severe right periorbital headache radiating to the frontal area bilaterally and to the right mandible for 2 weeks. His medications included oral didanosine, fluconazole (200 mg/d), clarithromycin, rifampin, ganciclovir and monthly inhaled pentamidine.

On physical examination, the patient's oral temperature was 37.3°C. Pertinent findings included intact extraocular movements, normal pupillary responses, and otherwise normal neurological examination. Funduscopic examination revealed mild bilateral inactive retinitis. There was mild tenderness to percussion over the right frontal area without radiation. The oropharynx was free of thrush. Laboratory data showed a white blood cell count of  $3.2 \times 10^9/L$  with 78% segmented neutrophils and

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9% band forms, and CD4+ lymphocyte count was  $<50/\text{mm}^3$ . Blood cultures for bacteria, mycobacteria, and fungi were negative. Computed tomographic (CT) scan of the head and magnetic resonance image (MRI) scan with gadolinium enhancement revealed bilaterally opacified ethmoid and sphenoid sinuses.

The patient failed to improve despite therapy with phenylephrine and 6 days of intravenous cefuroxime and metronidazole. Sphenoidotomy, including aspiration and drainage, was performed. Smear of the aspirate from the sphenoid sinus showed no white cells and no bacteria but did show a mold; fungal culture yielded *P. boydii*. Histopathologic examination revealed no tissue or bony invasion of the fungal elements, which overlay the mucosal membrane in the sinus. Routine bacterial culture yielded a light growth of coagulase negative staphylococci; mycobacterial cultures remained negative.

The patient improved greatly after surgical drainage. Therapy with oral ketoconazole (400 mg/d) was given. Repeat MRI scan of the head after 1 week of therapy confirmed that there was no bony destruction and that the sphenoid sinuses remained impacted. Approximately 2 months postoperatively thrush occurred after an H-2 blocker was used to treat esophagitis; oral fluconazole (200 mg/d) was added. Right-sided headaches continued despite narcotic analgesics. Approximately 3 months postoperatively the patient was readmitted because of progressive right-sided headaches, facial numbness, and development of an ecchymotic erythematous lesion of the right lower eyelid. A repeat CT scan of the sinuses and orbit revealed pansinusitis and destruction of the right maxillary bone. Complaints of continued headaches led to an intranasal endoscopic debridement followed by irrigation; no cultures were taken. Ketoconazole was continued. The patient's course became very complicated with severe abdominal discomfort due to hepatosplenomegaly and spiking fevers despite broad spectrum antibacterial therapy. Despite supportive measures, he died of respiratory failure. Permission for autopsy was refused.

**Comment:** The patient appeared initially to have had a chronic noninvasive *P. boydii* sinusitis that likely occurred with or followed bacterial infection of the sinuses, diagnosis of which was obscured by prior antibacterial therapy. The chronic nature of the infection, which was mixed bacterial and fungal, may have accounted for the lack of fever, which, like the presence of headache, is one of the most common signs and symptoms of sinusitis in patients with HIV or AIDS (21).

Sinusitis may have been alleviated by surgical drainage although bony destruction was later documented. Alleviation or cure of noninvasive fungal sinusitis is routine in immunocompetent patients, but administration of systemic antifungal chemotherapy seemed to have been indicated, chiefly for 2 reasons. One is the propensity for extensive infection in cases of fungal sinusitis caused by other agents (see below).

The 2nd reason is the well-recognized ability of *P. boydii* to invade tissues and to spread outside the ambit of the paranasal sinuses. Various antifungal therapies against *P. boydii* have been used, and oral ketoconazole is 1 of the appropriate agents (32).

The occurrence of thrush during ketoconazole therapy was likely due to poor absorption and drug interaction with rifampin, and did not augur for the effectiveness of ketoconazole.

Culture of *P. boydii* from sinusitis in a patient with AIDS has been previously mentioned, but no clinical information and details of histopathologic examination are given (60).

#### Case 2: *A. fumigatus* sinusitis with local bony invasion

A 38-year-old white man with AIDS presented in June 1993 with 4 days of fevers, chills, and bitemporal headaches. He had a history of recurrent oral candidiasis (treated with fluconazole [100 mg/d]), disseminated cytomegaloviral infection with retinitis treated with foscarnet, and disseminated *M. avium* complex infection which had been treated and was stable, as well as a history of chronic left maxillary sinusitis and polyp. He frequently smoked marijuana. He noted recent increased phlegm production with mild purulence but no blood. Examination was remarkable for a temperature of 36.5°C, moderate retinitis bilaterally, and tenderness on percussion of the left maxillary and frontal sinuses. Abdominal examination showed an enlarged liver and a palpable spleen tip.

Laboratory findings included a white cell count of  $1.2 \times 10^9/\text{L}$  with 50% segmented neutrophils, platelet count of 80,000/L, and CD4+ lymphocyte count of  $8/\text{mm}^3$ . CT scan of the sinuses confirmed persistence of the left maxillary sinus opacification and ethmoid sinus disease without bony destruction. Bilateral ethmoidectomies, left Caldwell-Luc procedure, and placement of a left nasal antral window were performed. Culture of purulent material removed from the left maxillary sinus yielded *A. fumigatus*. Histopathologic examination demonstrated allergic polyposis, thick-walled blood vessels, and numerous stromal eosinophils; there were no viral inclusions or granulomata. Numerous fungal hyphae consistent with aspergillus were noted in the material without tissue invasion or bony destruction. Also of note was a sputum culture that yielded *Candida krusei*, although potassium hydroxide preparation of sputum did not show fungal elements. Imipenem and oral itraconazole therapy (200 mg twice daily) led to resolution of fevers on day 10 of therapy. Determination of serum IgE level was 371 U/mL ( $n < 180$ ) and aspergillus serum antibody titer by complement fixation was  $< 1:8$  (normal) after 7 days of itraconazole therapy.

Itraconazole was discontinued after 6 weeks of therapy. Four months after the initial presentation, the patient presented with fevers and tenderness over the left maxilla. MRI scan revealed bony destruction of the left maxillary wall and pansinusitis. Itraconazole (600 mg/d) was reinstated after extensive surgical debridement. The patient died 1 month later.

**Comment:** The patient likely developed atopy as part of HIV infection (58). The white blood cell count bordered on neutropenia. Some features are suggestive of sinus variant of allergic bronchopulmonary aspergillosis (ABPA) (33): allergic manifestations of recent onset, polyp, eosinophils in tissue, lack of hyphal invasion, and elevated serum level of IgE. Some of these features are also seen with fungal sinusitis in general (71), and this patient

initially had chronic noninvasive disease, as did patient #1. The patient also temporarily benefited from drainage and probably from antifungal therapy, given for the adverted reasons. Itraconazole is promising therapy for localized invasive aspergillus infection (see below) and has been used as an adjunct for therapy of ABPA (15). This case, however, illustrates that noninvasive infection may progress despite prior therapy and that suppressive therapy is essential.

#### Case 3: *A. fumigatus sinusitis with orbital and intracranial extension*

A 33-year-old white man with AIDS with extensive cutaneous Kaposi sarcoma presented in July 1993 with fevers of 38.8°C, chills, severe nausea, vomiting, chronic diarrhea, and left periorbital swelling. He took oral fluconazole (100 mg every other day) for recurrent oral candidiasis. Persistent swelling in the left periorbital area for more than 6 months had led to 3 courses of extended spectrum antibacterials. He previously used marijuana and had just completed his 12th cycle of chemotherapy 2 weeks prior to this admission (adriamycin, bleomycin, and vincristine). White cell count on admission was  $4.7 \times 10^9/L$  with 82% segmented neutrophils; neutropenia did not develop. CD4+ lymphocyte count was  $<10/mm^3$ . Initial physical examination showed mild swelling of the left superior palpebrum with impediment of upward gaze due to lid swelling. Cranial nerves were otherwise not affected. There was no sinus tenderness on percussion. The oropharynx revealed moderate thrush. MRI scan of the brain confirmed the presence of soft tissue swelling in the preseptal area as well as extensive disease in the sinuses.

Left fronto-ethmoidectomy with transorbital exploration of the left preseptal area was done. On day 3 neither biopsies nor cultures showed any bacteria, mycobacteria or fungi; histopathologic examination of ethmoid sinus biopsies revealed numerous cytomegaloviral inclusions in the glandular epithelium. Induction therapy with ganciclovir (5 mg/kg twice a day) was started. On day 10 worsening chemosis of the left orbit led to a repeat MRI scan, which showed a large abscess in the superior left orbit extending posteriorly and involving the frontal and ethmoid sinuses. A focus compatible with infection extended from the left frontal sinus into the cranium with subcortical edema and gadolinium contrast enhancement. On day 12 evacuation was performed with drainage of copious purulent material. Histopathologic examination showed invasive aspergillosis and culture showed *A. fumigatus*. Respiratory mucosa, the left optic nerve, the superior orbital bone, and both ethmoid and frontal sinuses were involved. Aggressive amphotericin B therapy was started on day 13 and repeat debridement performed on day 15. Local irrigation with amphotericin B was also given on days 18 through 20; the patient died on day 20. Autopsy was refused.

*Comment:* The patient initially may have had a bacterial cellulitis or a mixed bacterial, cytomegaloviral, and fungal infection. He also had polyps and presented with sinus disease, clinical features of an orbital apex syndrome and, in retrospect, a superior orbital abscess. Paranasal sinus drainage failed to alleviate the problem; this was later accomplished by an orbitotomy. Histopathologic exami-

nation showed paranasal sinus involvement, with significant spread into the area of the optic nerve. Follow-up MRI scan suggested invasion into meninges and brain parenchyma.

#### Case 4: *A. fumigatus sinusitis with intracranial extension*

A 50-year-old Chinese man with AIDS was admitted in January 1993 with complaints of blurred vision in the right eye and decreased visual acuity. Ophthalmologic evaluation confirmed the diagnosis of cytomegaloviral retinitis on day 2. Because of neutropenia, induction therapy with intravenous foscarnet was started on day 2 and filgrastim given. Mild untreated extensive Kaposi sarcoma had been present for about 1 year, as well as treated disseminated *M. avium* complex infection. Immunoblastic B-cell lymphoma (stage IV) had been diagnosed 7 days prior to admission by left inguinal mass biopsy. The patient had received 1 cycle of bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone 4 days prior to admission. White blood cell count on admission was  $0.4 \times 10^9/L$  with 30% segmented neutrophils. CD4+ lymphocyte count was  $30/mm^3$  approximately 9 months prior to admission. A subsequent course of chemotherapy on day 13 with etoposide and carboplatin resulted in another neutropenic episode with associated fevers to 38.8°C on day 24 through day 27. Fever continued despite extended spectrum antibacterial therapy. Fluconazole therapy (200 mg/d) was continued.

On day 24 the patient had a generalized tonic-clonic seizure and an MRI brain scan compared to a scan done 18 days earlier revealed a new mass in the frontal lobe adjoining the left frontal sinus, with no change in bilateral maxillary sinus disease including bilateral polyps. Surgical debridement and histopathologic examination on day 24 showed a mycetoma in the left frontal sinus and left frontal lobe abscess with tissue invasion by *A. fumigatus*. *M. avium* complex and *Candida glabrata* were also recovered by culture, but histopathologic examination did not show the latter. Of note was the finding of numerous cytomegaloviral inclusions in the respiratory mucosa of the left frontal sinus. Amphotericin B was given. Two days postoperatively the patient developed a large subdural hematoma, which, despite surgical drainage, led to left temporal lobe herniation. He received 370 mg of amphotericin B prior to terminal extubation because of permanent neurologic impairment. No autopsy was performed.

*Comment:* The patient had neutropenia and various features of late-stage AIDS in addition to polyps and sinusitis. While there were aspergillus hyphae in the frontal sinus without mucosal involvement, invasion and spread to the dura mater and brain likely occurred across the frontal sinus. The poor prognosis, even with a combined medical and surgical approach, was evident.

#### Cedars-Sinai Medical Center Series (Table 1)

All patients in the present series had late-stage AIDS with multiple opportunistic pathogens and,

TABLE 1. Fungal sinusitis in patients with HIV or AIDS: Present series

Case	Age (yr)/Sex	Isolate	Paranasal Sinuses Involved	Other Areas Involved	Treatment	Outcome/Follow-up
1	44/M	<i>Pseudallescheria boydii</i>	Pansinusitis ( <i>P. boydii</i> documented in sphenoid sinus)	None	Sphenoidotomy, aspiration, drainage, ketoconazole	Partially controlled; death probably due to other causes
2	38/M	<i>Aspergillus fumigatus</i>	Left maxillary and bilateral ethmoid	None	Bilateral ethmoidectomies, left Caldwell-Luc procedure, left antral window placement, itraconazole	Improvement; relapse after 4 mo and death at 5 mo
3	33/M	<i>A. fumigatus</i>	Left frontal, bilateral maxillary, and ethmoid	Left frontal lobe of brain, left orbital apex and optic nerve	Left frontoethmoidectomy, transorbital exploration of left preseptal area and drainage, left superior orbitectomy, amphotericin B	Death within 1 wk
4	50/M	<i>A. fumigatus</i>	Left frontal, bilateral maxillary, and ethmoid	Left frontal lobe of brain	Left frontotemporal craniotomy, resection left frontal lobe abscess, duraplasty with pericranium graft, amphotericin B	Death within 48 h secondary to herniation

in 2 cases, lymphoma. All had, concomitantly, received fluconazole therapy which would not be active against fungal pathogens later found. All causative agents were fungi with hyphal forms, with 1 member of the Ascomycota and 3 of the same species within Fungi Imperfecti. Most if not all the paranasal sinuses were involved in our patients.

Two of the 3 patients with aspergillus sinusitis are known to have smoked marijuana, which is known to be associated with aspergillosis. Two (Table 1, patients #2 and 3) had chronic sinusitis, and 1 (Table 1, patient #1) had subacute sinusitis. Two (Table 1, patients #3 and 4) had received chemotherapy, 1 (Table 1, patient #4) had neutropenia, and another (Table 1, patient #2) of the patients with aspergillus sinusitis had marginal neutropenia. Two patients, 1 of whom had ganciclovir therapy, even had cytomegalovirus inclusions demonstrated in sinus respiratory mucosa, a condition we were unable to find in the literature, although culture of cytomegalovirus from sinuses has been noted (21).

Therapy with an appropriate systemic antifungal agent and drainage procedures appeared to have temporarily benefited 2 patients (Table 1, patients #1 and 2), but was of no avail in the other 2 patients with advanced invasive aspergillus sinusitis.

The findings of *C. krusei* (Table 1, patient #2) and *C. glabrata* (Table 1, patient #4) on cultures likely were consequences of prior fluconazole use. Emergence of strains of candida resistant to fluconazole, including *C. krusei* and *C. glabrata*, has been noted with prolonged use in therapy of oropharyngeal (1, 18, 59, 67) and esophageal candidiasis in

patients with AIDS (16, 18, 28). Failure has also been noted with fluconazole treatment of fungemia due to both genera in patients without AIDS (23, 36, 38, 57).

#### Case Reports: Literature Review (Table 2)

A computer-based and other searches of the literature yielded 8 cases of fungal sinusitis. In previously reported cases of sinusitis in patients with HIV or AIDS, none had any additional important predisposing factors, except for patient #4 with neutropenia and corticosteroid use (Table 2). Fungi with hyphal forms predominate over yeast forms in previously reported cases, but members of the Fungi Imperfecti (Table 2, patients #1, 2, 5, 6, 7, 8) predominated over members of the Zygomycota (Table 2, patient #3), and Basidiomycota (Table 2, patient #4) classes. CD4+ lymphocyte counts are stated in the 2 cases available; in the other 6 cases all patients had the diagnosis of AIDS. The reported cases are summarized in Table 2 and as follows with comments.

#### Case 1

A 31-year-old man presented with 2 weeks of fever, headache, nausea, and vomiting. Physical examination showed thrush, shotty adenopathy, and hepatosplenomegaly. A CT scan of the head was normal except for air-fluid levels in the maxillary sinuses. Cerebrospinal fluid (CSF) examination showed a positive India ink preparation; serum and CSF cryptococcal antigens were strongly positive. Culture of the CSF grew *Cryptococcus neoformans*. Amphotericin B was given with flucytosine, but the

TABLE 2. Fungal sinusitis in patients with HIV or AIDS: Previously reported cases

Case (Ref)	Age (yr)/Sex	Isolate	Paranasal Sinuses Involved	Other Areas Involved	Treatment	Outcome/Follow-up
1 (8)	31/M	<i>Cryptococcus neoformans</i>	Right frontal, bilateral maxillary, and sphenoid	Meninges	Bilateral sphenoidectomy and antrostomies, right frontal sinus trephination, amphotericin B, flucytosine	Successfully treated
2 (9)	20/M	<i>Candida albicans</i>	Bilateral maxillary and ethmoid	Left subdural empyema	Amphotericin B, fluconazole	Successfully treated
3 (3)	30/M	<i>Rhizopus arrhizus</i>	Right maxillary, ethmoid, and sphenoid	Orbital bone, ocular muscle, and internal capsule of cerebrum	Open surgical drainage, right Caldwell-Luc procedure with anterior ethmoidectomy, amphotericin B; later right external ethmoidectomy and sphenoidectomy	Amphotericin B therapy until death from progressive CMV infection 6 mo later
4 (50)	62/F	<i>Schizophyllum commune</i>	Left maxillary		Left maxillary sinus drainage, Caldwell-Luc procedure with antrostomy, amphotericin B	Repeat sinus biopsy 2 y later, negative; patient died with PCP, non-Hodgkin lymphoma and herpes zoster
5 (12)	NA/M	<i>Aspergillus</i> sp.	Maxillary*	Bronchi (obstructing type)—preceding, trachea and lung	Caldwell-Luc procedure, amphotericin B, preterminal intracranial amphotericin B	Death (probable cerebral involvement)
6 (41, case no. 25)	32/M	<i>Aspergillus fumigatus</i>	Maxillary		"Surgery," amphotericin B	Death due to disseminated isosporosis; sepsis
7 (64)	32/F	<i>A. fumigatus</i>	Ethmoid	Left superomedial orbit	Intranasal transorbital ethmoidectomy, amphotericin B	Successfully treated
8 (6)	44/M	<i>A. fumigatus</i>	Left sphenoid	Basilar meningitis with pontine and suprasellar infection	Antibacterials due to CSF findings, no antifungals	Neurologic deterioration leading to right hemiparesis, seizure, coma, and death

Abbreviations: CMV = cytomegaloviral, PCP = *Pneumocystis carinii* pneumonia, NA = not available, CSF = cerebrospinal fluid.  
\* Uncertain.

patient did not improve. He then underwent sphenoidectomy, bilateral antrostomies, and a right frontal sinus trephination, which yielded *C. neoformans* on India ink and culture. He improved postoperatively (8).

**Comment:** Although the authors did not comment on the patient's HIV status or immune function, the clinical presentation and course fulfill the criteria for AIDS definition. Here the sinus infection acted as a closed-space abscess, for which medical therapy was insufficient.

#### Case 2

A 20-year-old male intravenous drug user with HIV infection and 5 CD4+ lymphocytes/mm<sup>3</sup> was hospitalized with high fever, palpebral edema, and temporal-maxillary headache. Despite intravenous antibiotics, the patient became confused and lethargic, and developed proptosis, increasing facial edema, and meningismus. CT scan showed left cerebral edema and ethmoid and maxillary sinus opacification. A lumbar puncture demonstrated elevated leukocyte count and protein concentrations; no organisms were seen on gram stain. The patient underwent bilateral Caldwell-Luc procedures. Bone erosion was noted, and a few days later the patient developed a right hemiparesis and focal seizures. The patient underwent an emergency craniotomy for drainage of a left subdural empyema. Cultures of blood, sinus tissue, and the empyema all yielded *Candida albicans*. The patient was treated with amphotericin B initially, and later with fluconazole. He recovered, although he was left with significant residual neurologic deficits (9).

**Comment:** This patient (who did not have mucocutaneous candidiasis) developed a subdural empyema because of direct invasion of the candida in his sinus through bone. The occurrence of palpebral and facial edema (similar to case #3 in the Cedars-Sinai Medical Center series reported above) is a strong clinical suggestion that urgent surgical drainage be attempted.

#### Case 3

A 30-year-old man with AIDS and a history of neutropenia presented with right maxillary sinusitis. Culture of a needle aspirate of the sinus grew only normal respiratory flora. The patient was treated with ciprofloxacin, but developed progressive fevers and facial edema over the next 2 weeks. CT scan of the head and sinuses showed right maxillary sinusitis with some bone erosion. Five weeks of parenteral antibiotics led to no improvement. A repeat sinus needle aspirate showed no growth. Facial edema and proptosis led to a Caldwell-Luc procedure. Cultures of the biopsy material grew *Rhizopus arrhizus*; hematoxylin-eosin stain of the biopsy showed invasion by nonseptate hyphal elements. Amphotericin B therapy resulted in slow improvement, with resolution of the proptosis and edema (3).

**Comment:** Rhinocerebral zygomycosis is most often reported in the context of diabetic ketoacidosis, where it is suspected that a defect in neutrophil function from acidosis increases risk. This

patient had had several prior episodes of neutropenia, which likely predisposed him to zygomycete infection.

#### Case 4

A 62-year-old woman with diabetes mellitus and transfusion-acquired HIV infection presented with 2 months of nasal obstruction and facial pain, unresponsive to amoxicillin and decongestants. Physical examination revealed thrush and left maxillary sinus tenderness. CD4+ lymphocyte count was 150/mm<sup>3</sup>. She underwent a left Caldwell-Luc procedure; routine culture of the drained material grew diphtheroids and *Staphylococcus epidermidis*. Microscopic examination of the sinus mucosal biopsy showed chronic inflammation and invasion of the submucosa with narrow septate hyphal elements. Fungal culture of the sinus material yielded mushrooms, later identified as *Schizophyllum commune*. She was treated with amphotericin B and responded; 2 years later she developed a left maxillary sinus non-Hodgkin lymphoma (50).

**Comment:** The only member of the phylum Basidiomycota that is an important human pathogen is *C. neoformans*. *Schizophyllum commune* belongs to the class Holobasidiomycetae, subclass Hymenomycetes (32). The Hymenomycetes include common toadstools and mushrooms. Case reports of human infection with *S. commune* are extremely rare and have not been reported to be associated with immune suppression. One of the 3 cases reported in the literature occurred in a person with diabetes (50).

#### Case 5

A man (age not stated) with a diagnosis of *P. carinii* pneumonia 33 months earlier presented with productive cough, hemoptysis and chest pain. The patient underwent bronchoscopy and *A. fumigatus* was recovered from culture. This patient was not treated aggressively with antifungal therapy and developed aspergillus infection of his sinuses and subsequent cerebral involvement, which proved fatal (12).

**Comment:** This case, and a series from France (34), suggest that the traditional distinction between invasive and noninvasive aspergillosis is not meaningful in the context of HIV infection. Aggressive aspergillosis is found even in patients who do not initially have biopsy-proved tissue invasion.

#### Case 6

A 32-year-old man with AIDS-related wasting syndrome presented with sinusitis and concurrent isosporiasis. He underwent sinus biopsy which demonstrated tissue invasion with *A. fumigatus*. He was treated with amphotericin B, but died of sepsis and disseminated isosporiasis (41).

**Comment:** Minamoto et al (41) reviewed aspergillosis in patients with AIDS and showed that the most common site of infection is the lungs, followed

by the brain and the heart. The sinuses were involved in only 1 of their 37 patients. Additional risk factors for aspergillosis proposed were leukopenia, corticosteroid use, alcoholism, and treatment with broad-spectrum antibiotics or chemotherapeutic agents. Some or all of these risk factors were present in the 3 patients with aspergillus sinusitis from the Cedars-Sinai Medical Center series reported above.

#### Case 7

A 32-year-old woman with AIDS presented with mild edema, erythema, and pruritis of the left eyelid. Two weeks later she complained of left orbital pain and was seen to have mild exophthalmos. A CT scan showed an enhancing mass in the left superomedial orbit consistent with abscess. A fine-needle aspirate contained hyphae. The cavity was drained, and the patient had subsequent ethmoidectomy. Culture of the sinus material grew *A. fumigatus*, and she was treated with amphotericin B, both locally and systemically, and improved (64).

*Comment:* Vitale et al (64) make the point that the clinical presentation of aspergillus orbital infection may differ in the immunosuppressed patient from that in the immunocompetent. In the latter, the disease is more frequently low-grade, with a fibrotic and granulomatous tissue response rather than abscess formation. In this patient (and in the patients with aspergillosis in the Cedars-Sinai Medical Center series reported above), the presentation was suggestive of abscess formation.

#### Case 8

A 44-year-old man with AIDS presented with chronic headache, fever, and ataxia. Examination showed nuchal rigidity and a subtle right hemiparesis. A CT scan of the head and sinuses showed only left sphenoid sinus clouding. CSF examination disclosed 196 white blood cells/mm<sup>3</sup>, increased protein and decreased glucose concentrations; cultures were initially sterile. Despite treatment with broad-spectrum antibiotics, the patient's neurologic status worsened, and a repeat CT scan showed rupture of the left sphenoid sinus into the suprasellar area. The patient died shortly thereafter. Autopsy examination showed abundant aspergilli invading the walls of the sinuses, with associated fungal arteritis and basilar meningitis (6).

*Comment:* The rapid progression of this patient's aspergillus infection underlines the need for aggressive surgical and medical management in the immunosuppressed. In retrospect, it appears that this patient might have benefited from early sphenoidectomy.

### Discussion

Sinusitis is now recognized as a frequent complication of infection with HIV. Review of the medical

literature shows isolated case reports began to appear as early as 1984, followed more recently by several review articles. These reviews have shown that the frequency of sinus disease is strikingly high: retrospective analyses have placed its incidence at 10% to 20% of all HIV patients, and 1 prospective study reported an incidence of 68% (39, 51).

Given that the major immune defect in patients with HIV is in cellular immunity, it is perhaps surprising that bacterial infection of the sinuses is so prevalent and fungal infections are so rare. It is speculated that deficiencies of the IgG2 and IgG4 subclasses of immunoglobulins, together with an elevation of IgE levels, may predispose these patients to rhinocerebral infection (51).

In patients with HIV and sinusitis, the pathogens reported are similar to those seen in patients without HIV who have sinusitis: commonly *Streptococcus pneumoniae*, *Haemophilus influenzae*, and less commonly *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Cytomegalovirus and *P. carinii* have also been reported to cause sinusitis (39, 51).

Bacterial sinusitis in HIV-infected patients occurs at any time during the course of HIV disease, but fungal sinusitis appears to be associated with late-stage AIDS, including CD4+ lymphocyte counts < 150/mm<sup>3</sup>. A difference between fungal sinusitis in HIV-infected patients and that in non-immunocompromised patients is that histopathologic demonstration of the organism appears to indicate adequately the need for therapy in the face of signs and symptoms in the former, whereas demonstration of invasion is necessary in the latter (66). Lortholary et al state "it does not seem useful to differentiate invasion from non-invasive tracheobronchial aspergillosis" in patients with AIDS because of the propensity for later dissemination (34). It is also likely not useful to differentiate invasive from noninvasive—the usual division—in fungal sinusitis when it occurs in patients with HIV or AIDS. The tempo and course of the disease in patients with HIV or AIDS also appear to be closer to cases seen in heavily immunocompromised neutropenic patients (63).

Therapy of fungal sinusitis in patients with AIDS should include both drainage procedures and administration of antifungal agents. In the small number of cases reported it appears that such management can be curative or at least suppressive, whereas infection has progressed when no therapy was given (Tables 1 and 2). That a combined approach is necessary is likely due to the propensity for mucosal, submucosal, and even more extensive invasion in reported cases involving *C. albicans* (9), *R. arrhizus* (3), *S. commune* (50), and *Aspergillus* species (Table 2; 6, 12, 41, 64). Much less common

in patients with AIDS is the situation of initially noninvasive disease, as exemplified by patients #1 and 2 in the Cedars-Sinai Medical Center series, where histopathologic examinations and cultures of purulent material from maxillary sinuses in patients with sinusitis showed, respectively, *P. boydii* and *A. fumigatus*.

Immediate institution of systemic antifungal therapy is indicated in leukemic or immunosuppressed patients with fungal sinusitis (63). In immunocompetent patients, it was traditionally considered important to distinguish between noninvasive and invasive fungal sinusitis in order to select therapy, with the choice of either surgical or surgical plus antifungal chemotherapy, respectively. Recently, however, a combined approach has been favored in many of these immunocompetent patients (66, 71). Zieske et al found that with dematiaceous fungal sinusitis, surgical treatment alone led to less favorable results (e.g. recurrence, persistence) than surgical treatment combined with systemic antifungal chemotherapy, even in immunocompetent patients (71). There appears to be a spectrum of severity of fungal sinusitis in patients with AIDS, and at least some cases seem to be closer to the type seen in classically immunosuppressed patients than to types seen in immunocompetent patients.

#### *P. boydii* infections

*P. boydii*, found in soil and decaying vegetation worldwide, is an occasional human pathogen. It commonly enters the body either by penetrating injury (causing mycetoma, a chronic suppurative cutaneous infection) or via the respiratory tree. The most severe cases, with invasive sinusitis and meningitis, occur in immunosuppressed patients.

The hyphae of *P. boydii* may be difficult to distinguish from those of aspergillus on histopathologic sections. The hyphae of *P. boydii* are somewhat narrower (2–5  $\mu\text{m}$ ) and do not branch regularly compared to those of aspergillus, but the hyphae of both may contain thin-walled vesicles. Both organisms frequently show angioinvasion. Differentiation with conjugated antibodies and direct immunofluorescence can be made, but culture is the most reliable method of identification.

A number of cases of *P. boydii* sinusitis in patients without AIDS has been reported (5, 20, 32, 35, 42, 53, 55, 68). These range from the chronic noninvasive form (32, 66) to those with superficial invasion (35) or to intracranial extension (5). *P. boydii* has rarely been isolated from cultures of sinus punctures in patients with acute community-acquired sinusitis (24). Sphenoidal or maxillary

sinusitis predominates (32) and management is primarily surgical (66, 68).

Only 2 cases of *P. boydii* infection in patients with AIDS have been reported and both were fatal. The 1st was a patient with rapidly progressive and fatal native-valve endocarditis initially diagnosed by blood culture as the anamorph form *S. apiospermum* (48). The other, in a patient with renal and pulmonary involvement, was found at autopsy and ascribed to *P. boydii*. In the latter case *Candida albicans*, *Torulopsis glabrata*, and *Aspergillus* sp. had also been cultured antemortem (54). Colonization of the respiratory tract with *S. apiospermum* and *Scedosporium inflatum* has also been reported (69).

Antifungal therapy of *P. boydii* infections has been either ketoconazole or miconazole (32). Itraconazole also has been successful alone or with gamma-interferon in treatment of 2 cases of *S. apiospermum* infection after other antifungal therapy, and alone against pulmonary *P. boydii* (22, 46, 47). It has been less successful in treatment of some cases of keratitis due to *P. boydii* (4).

#### Aspergillosis

Aspergillosis was initially included in the CDC AIDS definition but was removed in 1987 because of low incidence. When it does occur it is usually late in the course, perhaps as a nosocomial complication, but initial presentation of HIV disease with aspergillosis has also been seen. The incidence in patients with AIDS appears to be rising (12), and a recent large, multicenter series of 33 cases over a 3-year period suggests that it is an "emerging complication of AIDS" (34). Almost half the patients with aspergillosis had none of the classic risk factors of neutropenia or corticosteroid therapy, and all cases occurred in patients in the late stages of AIDS with CD4+ lymphocyte counts of  $<50/\text{mm}^3$  (34), similar to the 3 patients with aspergillus sinusitis in the present series. Neutropenia in 1 and borderline neutropenia in another of our 3 patients with aspergillus sinusitis were associations.

The spectrum of pulmonary infection, the most common manifestation of aspergillosis in patients with AIDS, includes extensive nodular and cavitary disease, aspergilloma with fatal hemoptysis but no further tissue invasion, necrotizing bronchial invasion, and empyema thoracis (12, 34, 41, 44, 70). Localized pulmonary or disseminated disease may not be diagnosed until autopsy (12, 41, 70). Abscesses in the brain or spinal cord cause focal neurologic deficits and are visualized on scans (70) but likewise may not be diagnosed until autopsy examination. Unusual manifestations include infections at numerous metastatic sites. Those reported in the head and neck area in addition to sinusitis



are oral ulcer following chemotherapy (52), invasive external otitis in patients with remote history of mastoidectomy (49), and mastoiditis (25, 61).

Amphotericin B at high doses (> 1.0 mg/kg per day) has been the primary antifungal agent employed against aspergillus sinusitis and other infections (40, 63). Response rates to amphotericin B therapy of aspergillus infections in patients with AIDS have not been impressive (12, 34).

Itraconazole has been reported effective in open studies of selected cases of aspergillosis described as invasive, primarily in immunosuppressed patients. Unfortunately, no intention-to-treat analyses have been presented, some patients had prior or concomitant therapy, and histopathologic documentation of invasion was not made in most cases (14, 17, 27, 29, 31, 65). Despite these and other shortcomings of the trials, itraconazole is an alternative to amphotericin B therapy of invasive aspergillosis in certain situations, particularly in transplantation recipients receiving cyclosporine A, in patients with chronic granulomatous disease; and in milder invasive forms (11, 13, 30, 45, 62). Some cases of sinusitis in patients with AIDS may fit this last category. Doses of itraconazole in adults need to be at least 400 mg/d and serum levels > 5 µg/mL or perhaps > 9 µg/mL. Despite the attractiveness of itraconazole, results of its use in patients with AIDS and aspergillosis (primarily pulmonary) have been limited and variable (12, 73), with generally negative results in primary or salvage therapy in 1 series (34). The lack of clear effectiveness of either amphotericin B or itraconazole indicates the likely importance of surgical therapy, if feasible.

### Summary

We report here 3 cases of aspergillus sinusitis in patients with AIDS and the 1st fully described case, to our knowledge, of sinusitis associated with *Pseudallescheria boydii* in a patient with AIDS. We review the microbiology and pathology of fungal sinusitis in patients with AIDS and the morphologic and clinical features and treatment of *P. boydii* infection and aspergillus sinusitis.

Fungal sinusitis in patients with HIV or AIDS generally occurs later in the course of primary disease with low CD4+ lymphocyte counts (< 50/mm<sup>3</sup>), unlike bacterial sinusitis which may occur at any time. Differentiation between invasive and noninvasive forms is likely not important, in contrast to fungal sinusitis in noncompromised patients. The number of cases is likely to increase as the number of patients with AIDS increases, patients survive longer, and other opportunistic infections are prevented or treated. Causative agents are

likely to be resistant to fluconazole, which is in widespread use. Aspergillus sinusitis in patients with HIV or AIDS occurs in both those with and without traditional risk factors. Fungal sinusitis may present vexing management problems and be relentlessly progressive in the face of therapy. Ideal therapy has yet to be defined but an early combined surgical and medical approach in these compromised patients is preferred.

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