

## Brain Abscess Caused by *Schizophyllum commune*: an Emerging Basidiomycete Pathogen

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**Despite the worldwide distribution and prevalence of *Schizophyllum commune*, an emerging basidiomycetous pathogen, human infections occur only rarely. We describe the first well-documented pulmonary infection caused by *S. commune* which disseminated to the brain of a 58-year-old patient undergoing empiric corticosteroid therapy. Magnetic resonance imaging scans revealed ring-enhancing masses. Histologic examination of biopsy tissue from lungs and brain showed hyaline, septate, branched hyphae with clamp connections. Cultures of the lung tissue grew *S. commune*, which produced numerous, characteristic flabelliform and medusoid fruiting bodies on Czapek's agar. The isolate was susceptible to amphotericin B (MIC, <0.03 µg/ml) and fluconazole (MIC, 8 µg/ml). Despite treatment with antifungal and antibacterial agents, the patient developed progressive pulmonary failure and bacterial sepsis and died.**

The basidiomycetous fungus *Schizophyllum commune* is emerging as one of the important agents of sinusitis (2, 6, 8, 10). In addition, well-documented cases of *S. commune* infections include allergic bronchopulmonary disease (4), fungus ball in the lung (12), repeated isolation from the sputum of a patient with chronic lung disease (3), ulcerative lesions of the hard palate (9), and a nail infection (7). The isolation of *S. commune* from cerebrospinal fluid in a patient manifesting signs of atypical meningitis has been reported (1). However, definite pathogenicity and its etiologic role were not supported by histologic evidence of the fungus in tissue, and the patient recovered completely without treatment. We describe the first well-documented infection caused by *S. commune* initially involving the lungs with subsequent dissemination to the brain.

### CASE REPORT

A 58-year-old male was admitted to the Pittsburgh Veterans Affairs Medical Center on 9 August 1994 with progressive muscle weakness and multiple lung and brain lesions. The patient had a history of hypertension and coronary artery disease but was well until approximately 2 months previously, when he presented with left-sided facial numbness and tinnitus. At that time, the patient had no respiratory tract symptoms and physical examination of the thorax was normal. A magnetic resonance imaging scan (MRI) done on 15 June 1994 revealed an enhancing mass in the left pons, and a chest radiograph showed a 1-cm right upper lobe nodule. Bronchoscopy with biopsies failed to yield adequate tissue for diagnosis. Cerebrospinal fluid was acellular, but cytologic examination revealed lymphoid aggregates; the protein concentration was 54 mg/dl, and cultures for bacteria and fungi were negative. A presumptive diagnosis of lymphoma was made. Because biopsy of the pontine lesion was felt to be too risky, an empiric trial of dexamethasone (4 mg twice daily) was begun on 28 June 1994.

Over the next several weeks diffuse muscle weakness developed. A repeat MRI on 21 July 1994 showed complete resolution of the pontine lesion. The weakness was attributed to corticosteroids, and the dexamethasone dosage was tapered.

After 5 weeks on dexamethasone (total dose, 330 mg), the patient was admitted to an outlying hospital for progressive muscle weakness and steroid-induced hyperglycemia. Physical examination showed marked diffuse weakness (proximal greater than distal) and muscle wasting. He was transferred to the Pittsburgh Veterans Administration Medical Center hospital on 9 August 1994. Computed tomographic examinations of the head and thorax showed a new ring-enhancing lesion within the right frontal lobe and multiple bilateral lung masses. Abdominal and pelvic computed tomographic scans were unremarkable.

A wedge resection of a lung mass revealed necrotizing granulomatous inflammation with hyphae consistent with an *Aspergillus* sp. A tentative diagnosis of disseminated aspergillosis was made, and treatment with amphotericin B and itraconazole was begun. In 4 days cultures showed a white, floccose mold which did not sporulate.

On 8 August 1994, an MRI of the brain showed enlargement of the right frontal lobe lesion, measuring 3 by 3 cm. Two smaller lesions were noted in the right frontal lobe and the left parietal lobe, respectively. A stereotactic biopsy produced 5 ml of reddish fluid which showed fungal elements again suggestive of an *Aspergillus* sp. on frozen section. This culture attempt was not revealing.

The isolate was sent to the Audie L. Murphy Memorial Veterans Hospital Mycology Reference Laboratory in San Antonio, Tex. The MIC of amphotericin B for the fungus was <0.03 µg/ml (susceptible), and that of fluconazole was 8 µg/ml (susceptible). Testing of susceptibility to itraconazole could not be done because of the failure of the isolate to grow on the control medium. On 1 October 1994, fluconazole (600 mg twice daily) was substituted for itraconazole. After the patient had received 1,754 mg of amphotericin B over 36 days, a repeat MRI showed a decrease in the size of the largest lesion, although the smaller lesions remained unchanged (Fig. 1). The

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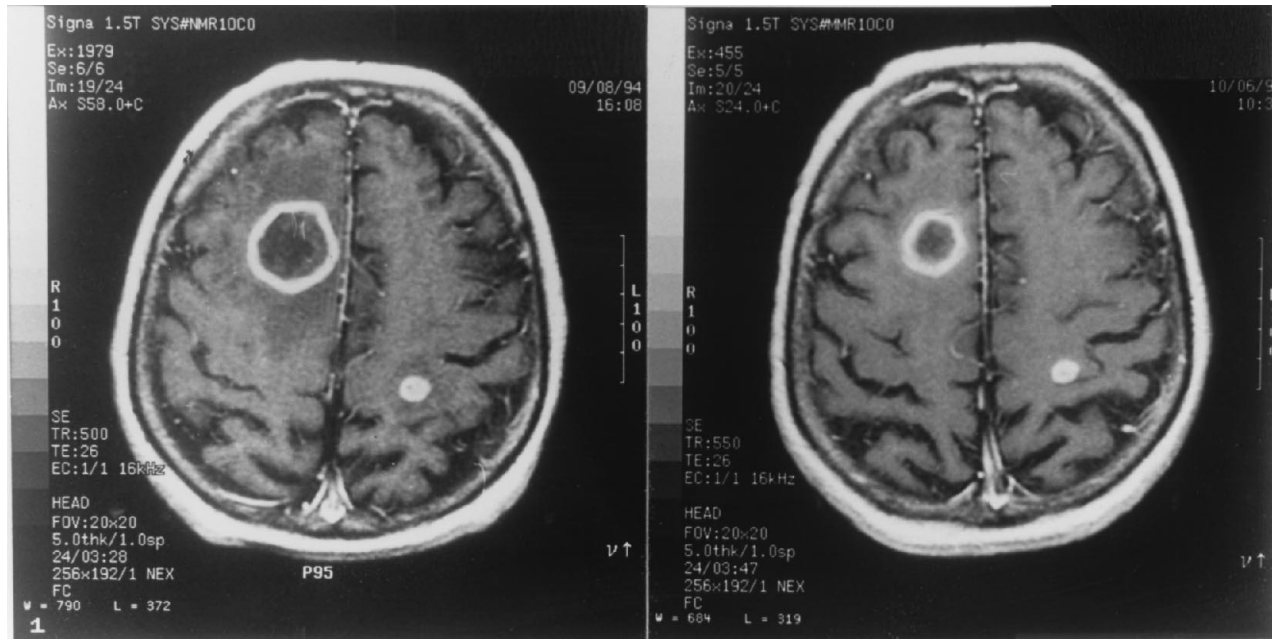


FIG. 1. MRI of the frontal lobe lesion before and after amphotericin B therapy.

patient developed progressive bacterial pneumonia with respiratory failure and sepsis and died on 18 October 1994, despite antibacterial and antifungal therapy.

#### MATERIALS AND METHODS

**Mycology studies.** Numerous septate, hyaline, hyphal elements of various widths, measuring 2.5 to 5.5  $\mu\text{m}$  in diameter, were seen in lung and brain sections stained with hematoxylin and eosin and with Grocott-Gomori methenamine silver stain. Many hyphae branched at acute as well as right angles but did not exhibit dichotomous branching. Many hyphal elements seen in the tissue slides of both the lung and brain showed clamp connections (Fig. 2).

Sabouraud dextrose agar (Sab) containing chloramphenicol (Difco Laboratories, Detroit, Mich.) (Sab+C) and Sab+C containing cycloheximide (0.5 mg/ml; Sab+C+C) were used for fungal cultures. The thermotolerance was studied with Sab+C at 25, 37, and 42°C. Because of the preliminary diagnosis of *Aspergillus* sp., the isolate was subcultured onto Czapek's agar. Slide cultures were made on Czapek's agar, and the cultures were incubated at 25°C in the dark for 14 days. Benomyl tolerance was determined by using Sab containing 10  $\mu\text{g}$  of benomyl per ml (13).

#### RESULTS

Growth on Sab+C was rapid, cottony, and white and raised in the center, becoming slightly powdery and tan after 2 weeks at 25°C. Growth was inhibited on Sab+C+C. The isolate grew well on Sab containing benomyl. It grew well at 25, 37, and 42°C. After 2 weeks at 25°C, colonies on Czapek's agar showed white mycelial growth with several flabelliform (fan-shaped) basidiocarps with split gills and some medusoid fruiting bodies (Fig. 3). Slide cultures showed hyaline, septate, branched hyphae of 2.0 to 4.5  $\mu\text{m}$  in diameter with clamp connections. Many hyphae developed lateral, short, thin, truncate tubercles diagnostic of *S. commune* (Fig. 4). On the bases of the production of characteristic basidiocarps, hyphae with clamp connections, and the susceptibility of the isolate to cycloheximide and its tolerance to 10  $\mu\text{g}$  of benomyl per ml, the fungus was identified as *S. commune* (CDC B-5575). Subcultures of the isolate were deposited in the American Type Culture Collection (ATCC 96279) and in the University of Alberta Micro-

fungus Collection and Herbarium (UAMH 7796), where its identity was confirmed by Lynne Sigler.

#### DISCUSSION

We have observed a steady increase in the numbers of non-sporulating basidiomycete isolates referred to the Fungus Reference Laboratory of the Centers for Disease Control and Prevention (35 isolates in 2 years). The majority of such isolates produce woolly, white to tan colonies without sporulation or clamp connections. Some produce only fission arthroconidia

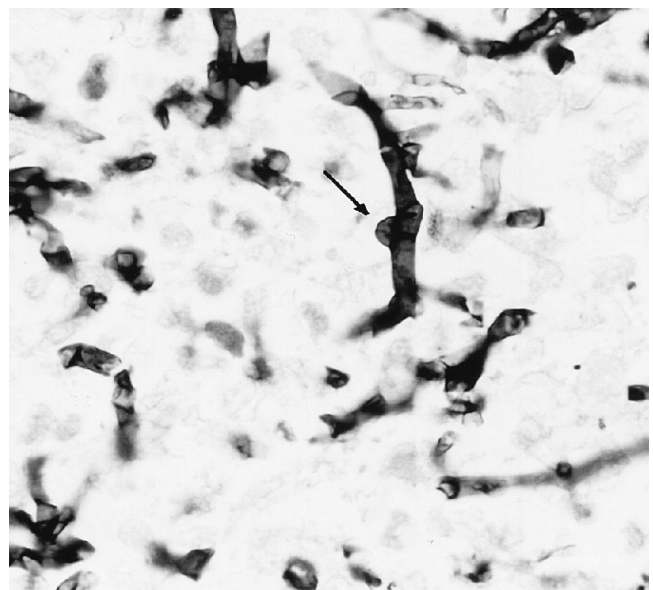


FIG. 2. *S. commune* in brain tissue. Septate hyphae with clamp connection (arrow) are shown. Grocott-Gomori methenamine silver stain was used. Magnification,  $\times 875$ .



FIG. 3. *S. commune* CDC B-5575 colony on Czapek's agar after 14 days at 25°C showing fruiting bodies.

(11), often leading to their initial misidentification as *Coccidioides immitis*. Most of these specimens are from the respiratory tract. Their clinical significance as pathogens could not be determined because of the lack of histologic evidence. The availability of the benomyl test (13) has provided a useful presumptive criterion that can be used to recognize monokaryotic basidiomycetes which do not form clamp connections or fruiting bodies. Such monokaryons are presumptively identified on the bases of their colony morphology, inhibition of growth by cycloheximide, and noninhibition of growth by benomyl. Equally important is the increase in the number of cultures identified as *S. commune* (16 isolates in 2 years). Most isolates readily produce basidiocarps and clamp connections on Czapek's, potato dextrose, or corn meal agars and lateral

tubercles on their hyphae. In tissue sections, the hyphae did not always exhibit clamp connections. Their differentiation from hyphal elements of *Aspergillus* spp. could be readily achieved by the use of fluorescent-antibody staining with genus-specific conjugate against *Aspergillus* spp. and by the use of serologic tests for the detection of *Aspergillus* antibodies and antigens (5).

We suspect that *S. commune* is emerging as an important agent of sinusitis. Clinicians should include this fungus in the differential diagnosis of patients with chronic sinusitis refractory to standard therapy. It is likely that infections caused by *S. commune* are misdiagnosed or are not recognized because of clinicians' lack of familiarity with this fungus and the inability of many laboratories to identify this basidiomycete. Neverthe-

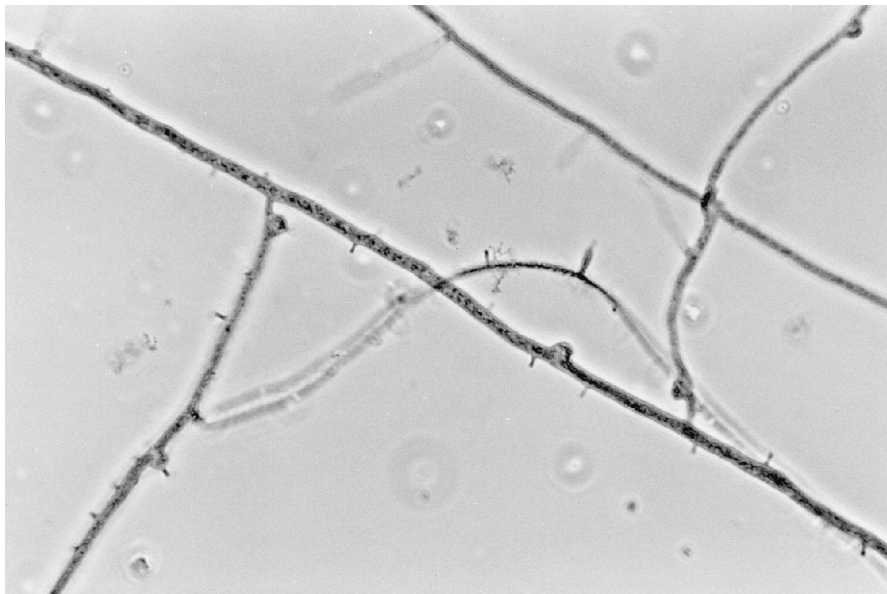


FIG. 4. Slide culture of *S. commune* CDC B-5575 with clamp connections and tubercles. Magnification,  $\times 450$ .

TABLE 1. *S. commune* infections in humans<sup>a</sup>

Investigator(s) (yr)	Age, Sex <sup>a</sup>	Underlying disease	Infection	Source of isolate	Histologic findings	Treatment	Outcome	Reference
Kligman (1950)	33 yr, M		Onychomycosis	Toe nails	Nail scrapings revealed hyphae	Nails avulsed, matrices destroyed	Recovered	7
Batista et al. (1955)	24 yr, M		Atypical meningitis	CSF		None	Recovered	1
Ciferri et al. (1956)	M		Chronic lung disorder	Sputum				3
Restrepo et al. (1973)	4 mo, F	Dehydration	Ulceration	Soft and hard palate	Chronic inflammation Hyphae infiltration of submucosa	Ampho (200 mg)	Recovered	9
Kern and Uecker (1986)	30 yr, F		Sinusitis	Maxillary sinus		Caldwell-Luc procedure	Recovered	6
	75 yr, F	Diabetes	Sinusitis	Maxillary sinus	Acute and chronic inflammation, hyphae present	Caldwell-Luc procedure	Recovered	
Catalano et al. (1990)	35 yr, F		Sinusitis	Maxillary sinus	Acute and chronic inflammation	Caldwell-Luc procedure	Recovered	2
Rosenthal et al. (1992)	62 yr, F	Diabetes, HIV	Sinusitis	Maxillary sinus	Chronic inflammation, hyphal infiltration of submucosa	Caldwell-Luc procedure; Ampho (750 mg)	Probable cure death due to lymphoma	10
Marlier et al. (1993)	42 yr, M	HIV	Sinusitis	Maxillary sinus		Drainage; fluconazole, 400 mg/day	Possible recovery death due to meningoencephalitis	8
Kamei et al. (1994)	57 yr, F		Allergic broncho-pulmonary mycosis	BAL fluid brushings	Hyphae present	Itraconazole, 50/100 mg/day	Failure	4
Sigler et al. (1995)	53 yr, F	Diabetes, tuberculosis	Fungus ball	Lung RUL	Necrotizing granuloma, hyphae present	Lobectomy		12
This report	58 yr, M		Lung and brain abscess	Lung RUL brain	Chronic inflammation, hyphae present	Ampho, 2.4 g; itraconazole, 16.8 g; fluconazole, 20.4 g	Recovering but death due to bacterial pneumonia	

<sup>a</sup> Abbreviations: CSF, cerebrospinal fluid; BAL, bronchoalveolar lavage; RUL, right upper lobe; HIV, human immunodeficiency virus; Ampho, amphotericin B.

less, there are increasing numbers of reports of infections caused by *S. commune* in both immunocompetent and immunocompromised hosts. Our patient represents the first with a documented fatal case of invasive *S. commune* disease occurring in the setting of immunosuppression caused by corticosteroids. The known human infections caused by *S. commune* are summarized in Table 1.

The optimal approach to the management of infections caused by *S. commune* is uncertain. Five of the 11 cases appearing in the literature have been chronic infections of the maxillary sinus (2, 6, 8, 10). A Caldwell-Luc surgical procedure without antifungal therapy was curative for three patients (2, 6); two of these patients were young healthy adults, and the third was an elderly patient with type II diabetes mellitus. The other two sinus infections occurred in AIDS patients. One patient with a CD4 lymphocyte count of 150/mm<sup>3</sup> was cured with a Caldwell-Luc procedure and amphotericin B (10). The other patient with a CD4 lymphocyte count of 1/mm<sup>3</sup> underwent a right maxillary sinus aspiration and drain placement (8). The patient was treated with fluconazole (400 mg/day) but died from meningoencephalitis 1 year later. The investigators did not comment on whether the patient responded to therapy.

The utility of the azoles in treating *S. commune* infections is not known. One patient with allergic bronchopulmonary infection was treated with itraconazole for 10 months without clinical or radiological improvement (4). In our patient with a

cerebral abscess, itraconazole was used in combination with amphotericin B during the first month, with clinical and radiological improvement.

Amphotericin B is active in vitro against *S. commune*. A child with ulceration of the hard and soft palates was cured by amphotericin B therapy alone (9). With sinusitis or invasive disease, surgical drainage or debridement and antifungal therapy would seem to be the approach of choice. The type, dose, and duration of antifungal therapy remain uncertain.

Clinical laboratories are familiar with the diagnostic features of the common fungal pathogens; however, the presence of clamp connections and hyphal tubercles may be overlooked, resulting in misidentification. Any white, nonsporulating mold that grows on routine mycologic media and that is inhibited by cycloheximide should be carefully studied as a possible *S. commune* isolate before being discarded as a sterile contaminant.

#### REFERENCES

- Batista, A. C., J. A. Maia, and R. Singer. 1955. Basidiomycetous infection of the maxillary sinus. *An. Soc. Pernambuco* 13:52-60.
- Catalano, P., W. Lawson, E. Bottone, and J. Lebenger. 1990. Basidiomycetous (mushroom) infection of the maxillary sinus. *Otolaryngol. Head Neck Surg.* 102:183-185.
- Ciferri, R., A. C. Batista, and S. Campos. 1956. Isolation of *Schizophyllum commune* from a sputum. *Atti Inst. Bot. Lab. Crittogam. Univ. Pavia* 14:3-5.
- Kamei, K., H. Unno, K. Nagao, T. Kuriyama, K. Nishimura, and M. Miyaji. 1994. Allergic bronchopulmonary mycosis caused by basidiomycetous fungus *Schizophyllum commune*. *Clin. Infect. Dis.* 18:305-309.

5. **Kaufman, L.** 1992. Immunohistologic diagnosis of systemic mycoses: an update. *Eur. J. Epidemiol.* **8**:377-382.
6. **Kern, M. E., and F. A. Uecker.** 1986. Maxillary sinus infection caused by the homobasidiomycetous fungus *Schizophyllum commune*. *J. Clin. Microbiol.* **23**:1001-1005.
7. **Kligman, A. M.** 1950. A basidiomycete probably causing onychomycosis. *J. Invest. Dermatol.* **14**:67-70.
8. **Marlier, S., J. P. de Jaureguiberry, P. Aguilon, E. Carloz, J. L. Duval, and D. Jaubert.** 1993. Sinusite chronique due a *Schizophyllum commune* au cours du SIDA. *Presse Med.* **22**:1107.
9. **Restrepo, A., D. L. Greer, M. Robledo, O. Osorio, and H. Mondragon.** 1973. Ulceration of the palate caused by a basidiomycete *Schizophyllum commune*. *Sabouraudia* **9**:201-204.
10. **Rosenthal, J., R. Katz, D. B. DuBois, A. Morrissey, and A. Machicao.** 1992. Chronic maxillary sinusitis associated with the mushroom *Schizophyllum commune* in a patient with AIDS. *Clin. Infect. Dis.* **14**:46-48.
11. **Sigler, L., and J. W. Carmichael.** 1976. Taxonomy of *Malbranchea* and some other hyphomycetes with arthroconidia. *Mycotaxon* **4**:349-488.
12. **Sigler, L., L. M. de la Maza, G. Tan, K. N. Egger, and R. K. Sherburne.** 1995. Diagnostic difficulties caused by nonclamped *Schizophyllum commune* isolate in a case of fungus ball of the lung. *J. Clin. Microbiol.* **33**:1979-1983.
13. **Summerbell, R. C.** 1993. The benomyl test as a fundamental diagnostic method for medical mycology. *J. Clin. Microbiol.* **31**:572-577.