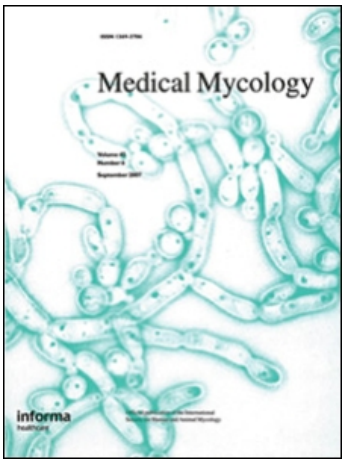

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Case report

Maxillary sinusitis caused by *Schizophyllum commune* and experience with treatment

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A case of sinusitis caused by the basidiomycete *Schizophyllum commune* is reported in a 36-year-old female with a history of allergic rhinitis and dermatitis. The patient presented with sudden nasal obstruction, purulent nasal discharge, headache and general discomfort. Computer tomography revealed extensive opacity of the left maxillary sinus as well as erosion of the nasal wall and maxillary bone. Mycological examinations of nasal discharges and material aspirated during anthrostomy showed hyaline, septate hyphae with rare spicules. Primary isolation yielded a white, woolly mould which demonstrated clamp connections and basidiocarp primordia but these characteristics were lost in subculture. Identification was confirmed by vegetative compatibility studies. The patient was treated with itraconazole to avoid possible postsurgical dissemination. Three months after cessation of therapy, no recurrence of infection had occurred.

Keywords basidiomycetes, sinusitis, *Schizophyllum commune*, allergy, intraconazole

Introduction

Reports of infection caused by *Schizophyllum commune* now include local or disseminated disease involving the brain [1,2], lung [2–4], hard and soft palate [5] and possibly nail [6] in both immunocompetent and immunosuppressed patients. Since 1985, there have been five cases of maxillary sinusitis in which individuals were healthy or had underlying diabetes or HIV infection [7–10]. The role of *S. commune* in allergic disorders of the lung has also been indicated [11,12]. The diagnosis of the various clinical conditions attributed to this fungus is hampered by the lack of awareness of its pathogenic role and by the difficulties encountered in the laboratory to properly identify an organism usually recognized by the presence of clamp connections and fruiting bodies, both of which may be lacking in a particular isolate [4,12,13]. We describe a case of maxillary sinusitis caused by an atypical isolate of *S. commune* in a female patient with a history of allergic rhinitis and dermatitis. The fungus was observed and isolated several times from nasal secretions and once from an aspirate taken during anthrostomy. Treatment with itraconazole halted symptoms and resulted in eradication of the agent from pathological specimens.

Case report

A 36-year-old otherwise healthy female physician consulted in August 1995 due to sudden nasal obstruction, accompanied by fatigue, weakness, headache and fever of a month's duration. The nasal obstruction was followed by mucopurulent nasal discharge that increased in intensity and hindered the patient's ability to sleep in a horizontal position. Examination revealed inflammation of the mucosa, bilateral nasal obstruction, hypertrophy of the left inferior and central turbinates and pain at palpation over the maxillar and frontal regions. With the clinical diagnosis of sinusitis, the patient was prescribed analgesics, anti-inflammatory drugs and antibiotics,

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initially trimethoprim-sulfamethoxazole and garamicin. When the symptoms exacerbated, medication was changed to chlaritromycin, methronidazole and lincomycin. The patient complained of constant rhinorrheae; the nasal secretions were mucopurulent, dark-olive in colour and had a granular appearance. The patient reported that she had been diagnosed as atopic in early childhood based on presentation of Dennie-Morgan double folds below the eyes, depigmentation of the elbow folds, alimentary intolerance and some other dermatological signs. Past medical records indicated a history of nasal allergies and dermatitis and food allergy to milk-derived products.

A month after the initial consultation, direct examination of the nasal discharge was reported as having abundant polymorphonuclear cells which were shown to be eosinophils (Hanssel's stain); there were no bacteria. Blood and chocolate agar cultures were also negative. A week later, a KOH preparation of a new sample revealed that the granular material was formed by intertwined hyaline, septate hyphae. Cultures were done on Sabouraud glucose agar and Mycosel agar plates (BBL); a few days later, the former exhibited growth of a white, rather fluffy mould without sporulation. Microscopic examination and cultures of nasal discharges were done in three separate samples and each showed the presence of hyaline, septate hyphae as well as growth of a white, woolly mould. Classification was pending at the time.

Computer tomography scan also taken a month after the initial consultation indicated the presence of an extensive opacity especially over the left maxillary sinus which, in addition, covered the ostiomeatal ipsilateral complex; the ethmoidal sinus was deviated towards the central line structures (Fig. 1a). Also, there was destruction of the nasal wall and of the maxillary bone (Fig. 1b); the lesion involved the draining ostium but formed no hydroaerial line. These findings suggested the presence of dry sinusal secretions, a polyp, a mass or haemorrhage.

A left maxillary anthrostomy was performed in order to clarify the diagnosis and obtain more representative samples for mycological studies. The only abnormal finding was the inflammation of the mucous membranes with involvement of the central turbinate. Samples were taken by aspiration and once the fungal nature of the sinusitis was confirmed, antifungal therapy was initiated with itraconazole, 200 mg day^{-1} for 3 months. This was done mainly to avoid possible postsurgical dissemination. Symptoms improved and control cultures taken 3 months after end of treatment proved negative.

In the aspirated material, there were hyaline, septate hyphae which showed irregular walls and scarce spicules. Cultures on Sabouraud glucose and potato glucose agars (PGA) (BBL) yielded the same mould. Microscopic examination of the colonies revealed the presence of

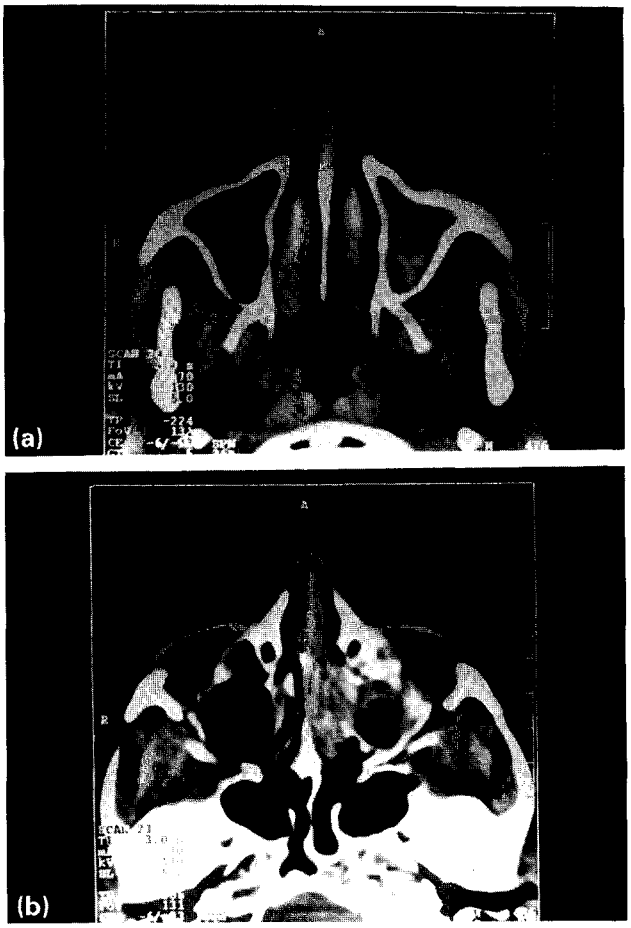

Fig. 1 Computer tomography of the orbit and maxillary sinuses. (a) Observe extensive opacity especially over the left maxillary sinusis; there is no osseous erosion. (b) Ethmoidal sinus is deviated towards the central line structures. There is destruction of the nasal wall and of the maxillary bone.

clamp connections. After 4 weeks of growth on PGA, colonies developed primordia indicative of basidiocarp formation (Fig. 2); however, these primordia failed to develop into the mature fan-shaped gilled basidiocarps characteristic of *S. commune*, and could not be reproduced upon subculture. The culture was sent as presumptive *S. commune* via the University of Texas Health Science Center, San Antonio, to the University of Alberta Microfungus Collection and Herbarium (UAMH), Edmonton, Alberta, Canada (strain UAMH 8365).

At UAMH, the isolate was tested for growth on a variety of media at 25 and 37 °C and for tolerance to benomyl as reported previously [4]. The isolate was sterile under all conditions and failed to develop clamps, spicules or abortive fruiting bodies. However, the isolate demonstrated features consistent with *S. commune*, including fast growing, dense woolly colonies, tolerance to benomyl, good growth at 37 °C, presence of narrow and broad

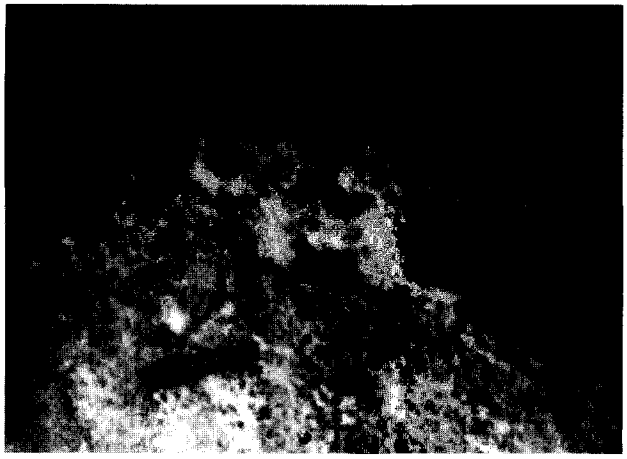

Fig. 2 Potato glucose agar culture exhibiting abortive fruiting body after 4 weeks of growth at 25 °C.

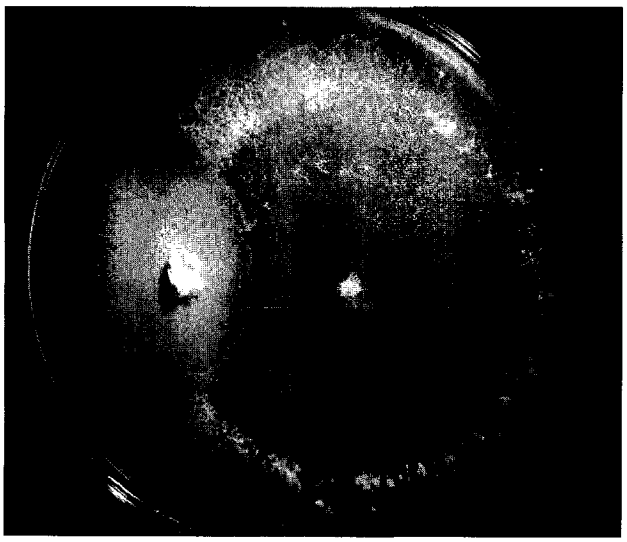

Fig. 3 Compatibility between case isolate (UAMH 8365-left) paired with single basidiospore isolate (UAMH 7694-right) on potato glucose agar.

hyphae, and the production of a strong odour [4]. An explanation for the different findings between the two laboratories is that upon initial isolation from the patient, the fungus consisted of a dikaryotic genotype formed by partially compatible homokaryons [14]. This could demonstrate clamps and primordia, but fail to develop sexual fruiting bodies and could be genetically unstable. Subculture may have selected a homokaryon (monokaryon). Compatibility between the case isolate and single basidiospore isolates of *S. commune* (UAMH 7694 and 7695) was tested following the procedures outlined previously [4] (Fig. 3). The mycelium in the contact zone between the advancing mycelium was examined microscopically for presence of clamp connections

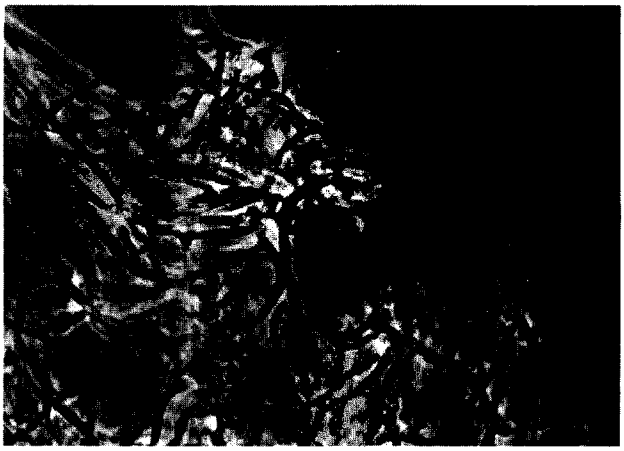

Fig. 4 Microscopic examination of contact zone between paired mycelial case isolate (UAMH 8365) with single basidiospore isolate (UAMH 7694) shows clamp connections (dikaryotization). (× 580)

(dikaryotization). Clamps were demonstrated when the case isolate, was paired with either UAMH 7694 or 7695 (Fig. 4).

Discussion

Sinonasal disease caused by a wide variety of fungi is being increasingly reported and several clinical entities have been recognized (Table 1). The acute fulminant form with fungal vascular invasion and thrombotic ischaemia usually occurs in immunosuppressed patients while chronic invasive (profuse fungal growth with regional tissue invasion and inciting a chronic inflammatory reaction), non-invasive colonization ('fungal ball' with minimum inflammatory response), or allergic sinusitis (chronic infection occurring in atopic individuals) is usually associated with immunocompetent patients [15–18]. Chronic non-invasive sinusitis is recognized as presence for a prolonged period of a mycelial mass confined to the lumen usually without bony erosion but with local inflammatory response being common [19]. The clinical and pathologic findings of allergic fungal sinusitis include chronic and refractory sinusitis occurring in patients with allergic histories, polyposis, bony erosion, histologic features including distinct mucinous material containing eosinophils, Charcot-Leyden crystals, presence of fungal hyphae but without invasion, and immunologic findings of elevated IgE, precipitating antibodies and/or positive skin tests [16,18,20–22]. Initially considered to be incited primarily by species of *Aspergillus* [20], evidence from culture of many patients with this condition suggests that various dark coloured moulds are more often involved [15,21–23]. Although the findings in our patient's case are suggestive of an allergic pathology including a history of

Table 1 Fungal sinus conditions

Sinus condition	Main histopathological characteristics	Patient's background
Acute fulminating	Fungal vascular invasion Thrombotic ischemia	Immunosuppressed
Chronic invasive	Profuse fungal growth Regional tissue invasion Chronic inflammation	Usually immunocompetent
Chronic, non-invasive	Fungal mass in lumin spaces Minimal inflammation Bony erosion infrequent	Usually immunocompetent
Allergic sinusitis	No tissue invasion Chronic infection Recurrent or perennial symptoms Bony erosion Mucinous material usually containing eosinophils and Charcot–Leyden crystals Hyphae present	Atopic

allergies, the presence of eosinophils in mucopurulent discharge, bony erosion and presence of hyphae, confirmatory immunological and skin tests were not performed. However, some authors have suggested that in cases of sinusitis caused by dark fungi, the distinctions between the clinical pathology of allergic sinusitis and chronic invasive sinusitis are not clear [15,23]. Five of six immunocompetent patients studied by Ziesk *et al.* [15] demonstrated histories of allergic rhinitis. Examinations of tissues revealed invasion of hyphae into submucosa or bone (four of six cases) and presence of eosinophilic mucin (six of six) resembling the allergic mucin considered a characteristic finding of allergic fungal sinusitis. Based on these findings and literature review of 33 other cases, they considered most cases of sinusitis caused by dark fungi to be invasive. Adam *et al.* [24] also expressed reservations about the distinction between invasive and non-invasive disease as radiological and histological evidence of bone destruction could be present even if fungal invasion were not demonstrated.

With this report, six cases of chronic infection of the maxillary sinus caused by *S. commune* are known. The average age of the patient (including our patient) is 46·6 years with a female to male predominance of 5 to 1. In contrast for culture-proven cases of allergic sinusitis caused by dark fungi, the average age of the patient was 26·5 years with a male to female predominance of 13 to 5 [22]. In two patients with *S. commune*, sinusitis was a complication of HIV infection [9,10]; hyphae were detected in the sinus submucosa of one of these patients [9]. Therapy for these patients consisted of debridement in combination with amphotericin B therapy [9] or drainage and fluconazole therapy [10]. Both individuals died of other complications. Two cases involved immunocompetent but unhealthy hosts one of whom had underlying diabetes [7]. These patients were cured by surgical debridement using the Caldwell-Luc procedure alone.

The importance of basidiomycetous fungi in allergy is widely recognized [25]. The present report and prior reports of chronic sinus infection in an allergic female [8], bronchial mucoid impaction, a type of hypersensitivity reaction to the mycelium of *S. commune* [12] and allergic bronchopulmonary mycosis [11] indicate the emerging role of *S. commune* in allergic pathology. Antibodies to *S. commune* in patient's sera supported the diagnosis in both latter cases. Although there are many similarities between our patient's condition and that of the patient described by Catalano *et al.* [8], CT imaging clearly revealed tissue damage in our patient while bone erosion was absent in the other. Debridement and drainage are often adequate treatment. The role of antifungal therapy for the treatment of allergic fungal sinusitis is not resolved [15,26]. Evidence of tissue invasion is the main criterion supporting the use of adjunctive therapy but some have argued that bone erosion alone is not sufficient ground [26]. Adjunctive antifungal therapy is recommended in cases of dematiaceous fungal sinusitis [15]. With the finding of bone erosion in our patient and evidence of the invasive potential of *S. commune* [2,5,27], our patient was given itraconazole with the aim of avoiding postsurgical dissemination. Itraconazole was effective in eradicating symptoms in our patient after 3 months and has been used

in combination with amphotericin B for treating a patient with a cerebral abscess who later died of bacterial sepsis [2]. The role of steroid therapy in management of *S. commune* allergic disease also is not clear as it has not been tested in the other recently described cases [11,12].

Despite increasing awareness of allergic and invasive potential of *S. commune*, there remain difficulties in laboratory recognition of the fungus especially when atypical forms are encountered as in this and prior cases [4,12]. The possibility of misidentification of the hyphae in tissue as representative of the genus *Aspergillus* is also likely, especially if the mycelium fails to produce clamp connections or their presence is overlooked. Clamp connections are an important marker for recognition of a basidiomycete but they are produced only if the mycelium is dikaryotic [2,5,12,13,28]. The presence of spicules (also called tubercles, pegs) on hyphae is highly characteristic of *S. commune* but monokaryons may fail to produce these structures [4,13]. The isolate from our patient demonstrated clamps and spicules upon primary isolation but these were lost upon subculture. *S. commune* characteristically produces fan-shaped basidiocarps that are visible to the naked eye. These fruiting bodies are produced under conditions of light, only if the constituent mycelium are dikaryotic and formed from fully compatible homokaryons. If the genotype is formed from incompatible or partially compatible homokaryons [14], identification is more difficult. Mating studies between test isolates and single basidiospore isolates can provide definitive results [4,12]. Because the outbreeding potential of the progeny of *S. commune* basidiocarps reaches almost 100%, it is not difficult to demonstrate compatibility between strains derived from different fruiting bodies. Partial compatibility is expressed in the formation of clamps as was seen in the pairings between the case isolate and two stains derived from single basidiospores. For the dikaryon to be fully compatible, the fusing homokaryons must differ at four mating-type loci on two chromosomes [14]. Tolerance to benomyl at $10\,\mu g\,ml^{-1}$ is also an indicator of basidiomycetous affinity [13], but some isolates of *Aspergillus* can demonstrate comparable levels of tolerance to lower levels [29] and may appear as white, non-sporulating forms especially from patients with chronic respiratory problems [30].

Rihs *et al.* [2] have noted an increase in the number of *S. commune* isolates referred for identification most of which could be readily confirmed. They suggested that serological procedures such as antibody and antigen tests and *Aspergillus*-specific fluorescent antibody staining of the hyphae in tissue are useful in the differential diagnosis. As antibodies specific to *S. commune* can be demonstrated in the patient's serum [11,12], the possibility of establishing a serological diagnosis in patients in whom repeated samples have revealed the presence of hyaline mycelium and whose cultures have shown growth of a white, rapid growing non-easily identifiable mould, would be an asset.

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