CASE REPORT

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Bilateral allergic fungal rhinosinusitis caused by *Schizophillum commune* and *Aspergillus niger*. A case report*

Mohamed Khalifa Ahmed, Takashi Ishino, Sachio Takeno, Katsuhiro Hirakawa

Department of Otorhinolaryngology, Head & Neck Surgery, Division of Clinical Medical Science, Programs for Applied Biomedicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

SUMMARY

Schizophillum commune (S. commune) is a rare type of basidiomycetous fungus that has being reported as a cause of allergic fungal rhinosinusitis (AFRS), invasive type of fungal sinusitis and allergic bronchopulmonary mycosis (ABPM). However, it is believed that S. commune was often misdiagnosed to Aspergillus sp. We report a case of bilateral nasal polyps and maxillary, ethmoidal and sphenoidal involvement within the context of S. commune and Aspergillus niger associated AFRS. Our patient was suffering from a chronic disease with periods of remission and exacerbation and was treated successfully by a combination of surgical and antifungal treatment. In our experience, S. commune may be found frequently in patients with AFRS. AFRS, including the S. commune-associated type, usually runs a prolonged course and can affect any paranasal sinus. Surgical treatment alone is not sufficient and must be combined with medical treatment.

Key words: allergic fungal rhinosinusitis, Aspergillus sp., basidiomycetous fungi, Schizophillum commune, antifungul treatment

INTRODUCTION

Although bacteria have long been implicated as pathogens in most forms of chronic rhinosinusitis (CRS), it has been recognized that fungi may be responsible for some forms of CRS. Fungal spores, due to their ubiquitous nature, are continuously inhaled and deposited on the airways of healthy individuals; they may cause human diseases in some [(1)].

Fungi are ubiquitous saprophytes that reproduce by the formation of spores that are able to enter respiratory tract by means of inhalation [(1)]. There are several types of fungi that commonly induce mycosis in sinuses, mainly *Aspergillus, Penicillium, Cladosporium, Alternalia* and *Mucor*, although other types of fungi have also been recognized [(2,3)]. *Schizophillum commune* is a rare type of basidiomycetous fungus that has been reported as a cause of allergic fungal rhinosinusitis (AFRS), invasive type of fungal sinusitis and allergic bronchopulmonary mycosis (ABPM) [(4)]. It is suggested that *S. commune* has been often misdiagnosed as *Aspergillus* sp, as the histopathological findings are similar and also the fungus itself is difficult to identify in culture when atypical isolations are encountered [(4)]. However, in the absence of convincing immunological data and evidence of clinical improvement of CRS following therapy with antifungal agents, the case against the fungus remains unproven [(5)]. In this paper, we report a rare case of bilateral allergic fungal rhinosinusitis caused by *S. commune* and *A. niger* cured by surgical treatment and administration of antifungal drugs.

CASE STUDY

On January 2003, a 57-year-old women who had a history of aspirin sensitive asthma, myasthenia gravis and rheumatoid arthritis presented to the Department of Otolaryngology - Head and Neck Surgery, Hiroshima University hospital with a history of bilateral purulent nasal discharge associated with anosmia. There was a history of aspirin sensitive asthma, myasthenia gravis and rheumatoid arthritis and the patient had been receiving 25 mg of oral prednisolone daily for 3 years. On examination, bilateral purulent nasal discharge and bilateral nasal polypi were seen in nasal cavity (Figure 1A, 1B).

Olfaction testing showed almost total anosmia. On CT examination there was evidence of bilateral opacification of maxillary, ethmoidal and sphenoidal sinuses associated with bilateral obstruction of the osteomeatal complexes (Figure 2A, 2B). There was no evidence of bone destruction or calcification. We started treatment of the patient with betamethazone drops 1mg locally 2 times per day for 20 minutes and oral mucolytic (carbocysteine) and antibiotic (clarithromycin) for 1 month. However, there was no improvement and the patient refused surgical treatment. On June 2003, left otitis media resistant to medical treatment was noticed. We suspected that it was eosinophilic otitis media, based on the presence of systemic eosinophilia (30.7%) and the fact that the symptoms had not improved after 3 months of conventional therapy for sinusitis. The patient was then treated with intratympanic injections of

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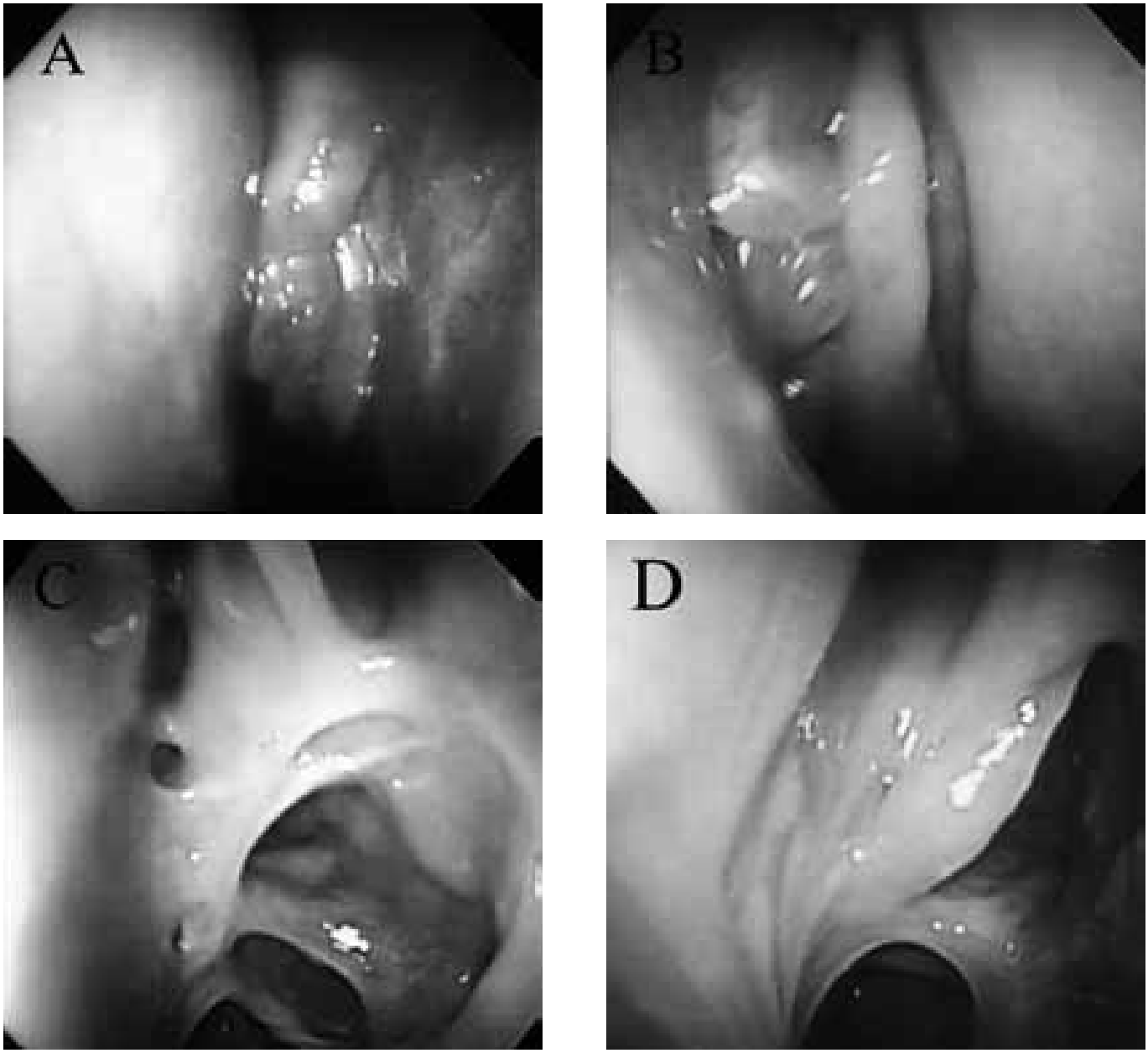

Figure 1. Endoscopic views of preoperative, preantifungal treatment (A: Lt, B: Rt) and post operative, post antifungul treatment (C: Lt, D: Rt).

steroids, but did not improve. At the end of June, the patient underwent myringotomy and insertion of a ventilation tube. Additionally, dexamethazone local drops were prescribed. Three months later, the same procedure was performed on the contralateral ear, with the same indication. However, chronic otorrhoea developed in both ears and a culture of left ear discharge proved to contain Methicillin-Resistant-*Staphyloccocus aureus* (MRSA). On April 2004, a blood test showed marked eosinophilia. As a result, we concluded that the patient was suffering from eosinophilic sinusitis that required surgical treatment. On July 2005, the patient finally underwent endoscopic sinus surgery in the form of bilateral ethmoidectomy, polyectomy, sphenoidotomy and bilateral middle meatal antrostomy. During the surgery, mucoid secretions were noticed in all sinuses, while eosinophilic infiltration was recognized in nasal polyps and sinus mucosa by histological examination (Figure 3).

After the operation, the patient noticed a marked improvement in all her nasal symptoms. However, four months later, she started to complain again of anosmia as a result of the recurrence of nasal polyps. On December 2005, the patient started to complain again of bilateral mucopurulent otorrhoea and nasal discharge. On August 2006, fungus was detected in her nasal discharge. At this time, many colonies of fungi were recognized in our laboratory following culture with sabouraud agar containing antibiotics (gentamycin and chloramphenicol) in culture dishes, but all of these colonies were proved to contain only *S. commune* (Figure 4).

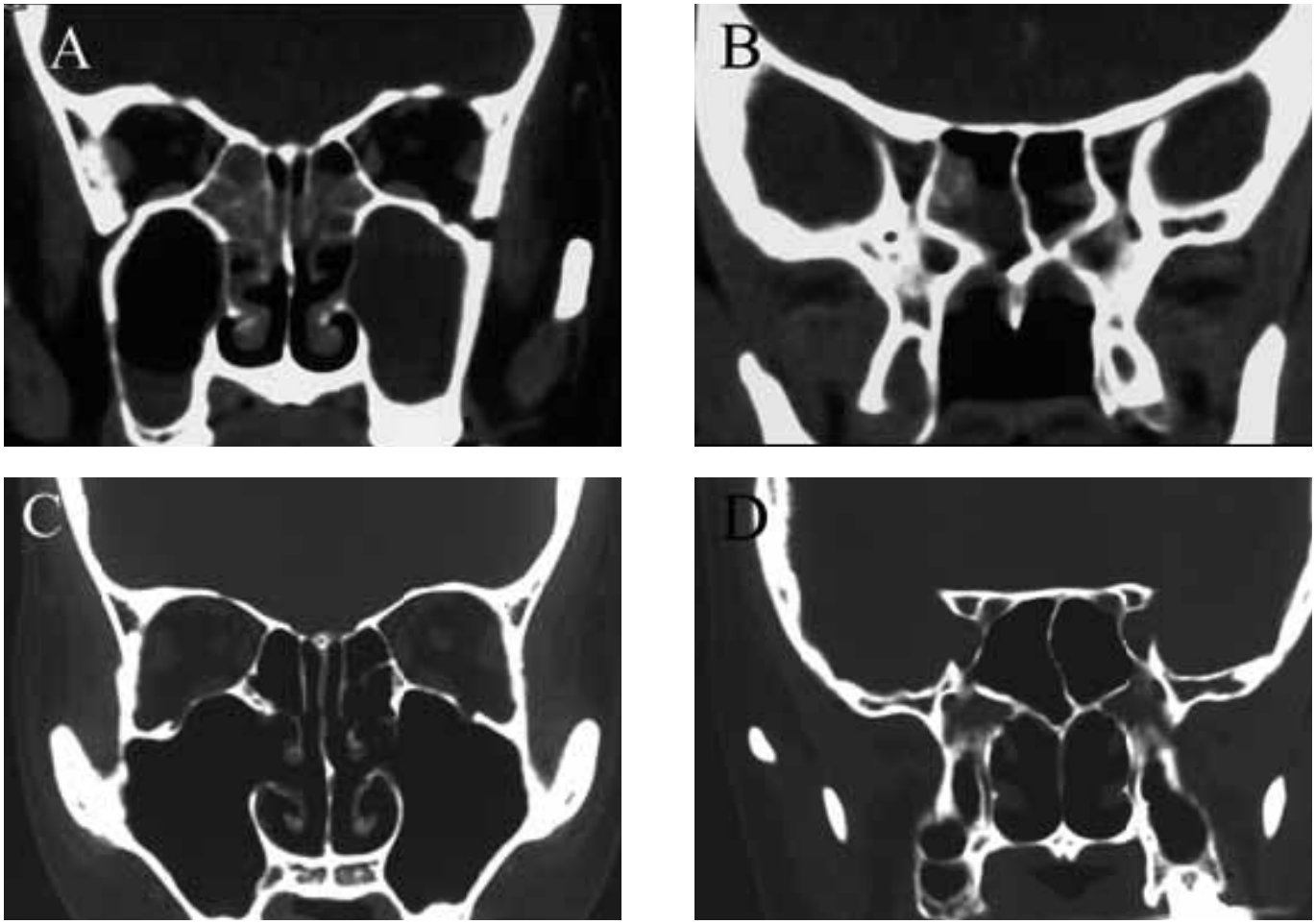

Figure 2. Coronal sinus CT before and following treatment A: Opacification of bilateral ethmoid and maxillary sinuses (Lt: complete, Rt: mild); before treatment B: Opacified sphenoid sinuses before treatment C and D: CT after endoscopic sinus surgery and anti-fungal treatment.

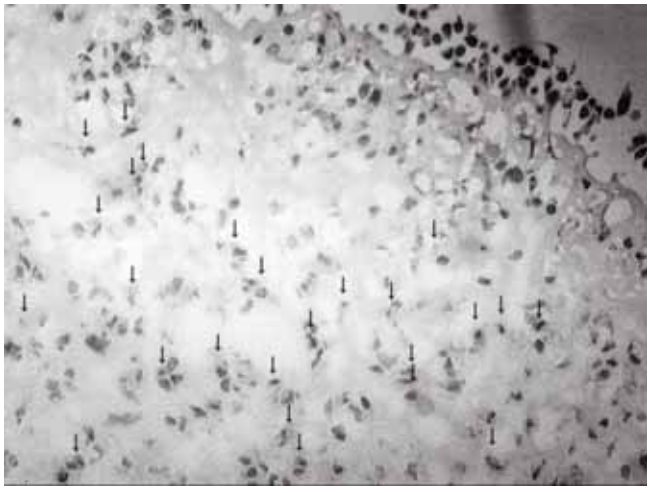

Figure 3. Eosinophilic infiltration in nasal polyps (arrow). Haematoxylin and eosin, original magnification x400.

Additionally, high levels of serum IgE (219-534 IU/ml) and systemic eosinophilia (2.0-23.0%) were also recognized. Therefore, we diagnosed this disease as AFRS, despite the negative skin prick test for *Aspergillus* and *Alternalia*. As the nasal symptoms did not improve following the use of prednisolone, we finally administrated oral anti-fungal treatment (itraconazole 200 mg daily) for three months. After that period, all nasal symptoms including anosmia, as well otitis media and nasal polyps improved significantly. However, after discontinuation of the anti-fungal medication, the patient's condition gradually worsened, and she started suffering from bronchial asthma attacks. Close regular follow-up of the patient using predonisolone for 4 days was done but the asthmatic attacks did not improve. Chest physicians suggested that these symptoms and CT findings in her lung were compatible with allergic bronchopulmonary aspergillosis (ABPA). The patient underwent bronchoscopy, which was negative for mucoid impaction of bronchi, bronchogranulomatosis, while culture of sputum did not produce *A. niger*. On July 2007, we detected *A. niger* within the nasal discharge. We also detected both high levels of serum IgE (3920.0 IU/ml) and systemic eosinophilia (31.4%) on August 2007. Therefore we administrated the anti-fungal treatment again. Following this second course of treatment (Figure 1C, 1D, 2C and 2D), the patient's condition including her asthma symptoms improved and remained in remission.

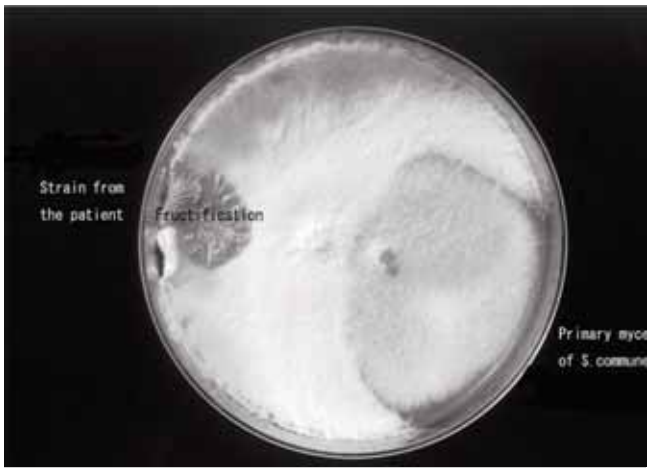

Figure 4. Culture of fungus, both the strain from the patient and primary mycelium of *S. commune* were mating and changed to dicaryotization, finally resulting in fructification.

DISCUSSION

Basidiomycete fungi are well-known widespread plant pathogens. They attack a wide range of host trees where mushroom-shaped basidiocarps can be easily identified [5]. Although *S. commune* is ubiquitous in nature, there are only rare reports of its association with human infections, including those of brain, lung and mouth [4]. They are whitish in colour when young and become darker shades of gray at maturity. They are identified by their characteristic hyphae and production of extra cellular oxidases [5]. Their pathogenic potential was studied by Greer and Bolanos, [8] who injected an inoculum of the fungus into the peritoneal cavity of white mice of various ages. Fifty percent of the youngest mice died, and mortality reached 75% within that group when they were pretreated with cortisone. However, in adult mice the mortality remained zero. Moreover, disease was induced in all age groups, with or without cortisone. The authors concluded that induced infection follows a course of opportunistic fungi. It is an infection of low virulence, but when aided by immunosuppression, it will lead to death in the younger host.

In the last fifty years, only 22 medical cases involving the basidiomycete fungus *S. commune* have been reported [9]. Invasive infection by basidiomycota (rusts, smuts, toadstools, mushrooms, and puffballs) is extremely rare. Rosenthal et al. [10] reported such an infection in a patient with human immunodeficiency virus disease who presented with chronic maxillary sinusitis associated with *S. commune.* The organism was isolated from the surgical drainage material, and the septate hyphae were seen invading the maxillary submucosa [10]. Clark et al. [11] described the first case of allergic fungal sinusitis associated with *S. commune.* Histological diagnosis was made on mucinous material from the sinus, which contained eosinophils, fungal hyphae and Charcot-Leyden crystals. The fungal isolate was identified as *S. commune* on the basis of its morphology and minute peg-like outgrowths from vegetative hyphae and clamp connections [11]. Sigler et al. [12] reported a case of sinusitis caused by *S. commune* in a 36-year-old female with a history of allergic rhinitis and dermatitis. The patient presented with sudden onset of 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 antrostomy showed hyaline, septate hyphae with rare spicules. Primary isolation yielded a white, woolly mould that demonstrated clamp connections and basidiocarp primordial but these characteristics were lost in subculture. Identification was confirmed by vegetative compatibility studies [12].

Another report by Sigler et al. [4] concerned a case of maxillary sinusitis in a diabetic female caused by *S. commune.* Identification of the isolate was hampered by its atypical features. Subcultures formed sterile medusoid structures from nonclamped mycelia until spontaneous dikaryotization resulted in the development of characteristic fan-shaped fruiting bodies. Identification was confirmed by the presence of spicules formed on the hyphae and by vegetative compatibility with known isolates [4]. Roh et al. [13] reported a 47-year-old diabetic man with chronic renal failure presenting with a 1-month history of complete ptosis of left upper eye lid, left proptosis and left sided headache; no association with orbital inflammatory syndrome, carotid- cavernous syndrome or cavernous sinus thrombosis was found. Neuroimaging revealed only minimal left sphenoid disease. Sphenoid biopsy revealed the presence of septate hyphae on gram staining and produced a fungal culture characteristic of *S. commune* and the patient was treated with intravenous liposomal amphotericin [13]. The basidiomycetous fungus has been recovered from cerebrospinal fluid of a patient with atypical meningitis from both sputum of a patient with chronic lung disease and ulcerating lesion on the hard palate of a 4-month girl [14]. However, most previously reported cases of sinusitis caused by basidiomycetous fungus affected maxillary sinus and it was unilateral with a reported case of involvement of the sphenoid sinus.

To our knowledge our present case is the first case in Japan of bilateral maxillary sinusitis, ethmoiditis, sphenoiditis and bilateral nasal polypis associated with *S. commune.* Our case was successfully treated by combination of surgical and medical treatment. In a previous report [15], criteria of diagnosis in AFRS were based on endoscopy documenting the presence of allergic mucin and inflammation, evidence of rhinosinusitis on CT or MRI, evidence of fungal specific IgE, and no histopathological evidence of fungal invasion. But recently, a broncholog-ical report *(16)* pointed out that ABPA was one of the types of ABPM and the mycosis could be occurred by several types of fungus such as *Aspergillus fumigatus, Aspergillus flavus, A. niger, Candida albicans, Penicillium, and S. commune.* As all fungal specific IgE cannot be detected by modern techniques, these findings suggest that it is impossible to detect an evi-

dence of fungal specific IgE in every case. In this case, we detected *S. commune* by culture. Previous reports documented that in selected groups of chronic rhinosinusitis patients fungi could play a role, when a positive middle meatal culture was associated with mucus eosinophilia [17]. So taking into account these symptoms and examinations, we suggested that this sinusitis was AFRS. This suggests that it may be necessary to change the criteria of diagnosis of allergic fungal rhinosinusitis. Previous reports [18] concluded that surgery and steroid therapy were main therapy strategy in AFRS and antifungal therapy was not effective. But in the research, terbinafine was used [18]. Antifungal drugs were commonly recognized as having poor bioavailability drugs in humans. In this case, we administrated itraconazole instead of terbinafine because of a better minimum inhibitory concentration (MIC) to several fungi compared to terbinafine. Previous reports also demonstrated the efficacy of itraconazole [19] in AFRS, therefore we feel that the use of itraconazole must be considered in AFRS therapy as it is similar histologically to ABPM [20].

CONCLUSION

We have shown that AFRS can sometimes be caused *S. commune* and a different fungus may cause it to relapse. We also recognized that it can affect any paranasal sinus and it usually runs a long chronic course with period of remission and exacerbation so close follow up is recommended. Surgical treatment alone is not sufficient and must be combined with antifungal medical treatment for at least 3 months. It is anticipated that *S. commune* may be found much more frequently in patients suffering from diseases of paranasal sinuses, especially in AFRS.

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Mohamed Khalifa Ahmed
Department of Otorhinolaryngology, Head & Neck Surgery
Division of Clinical Medical Science
Programs for Applied Biomedicine
Graduate School of Biomedical Sciences
Hiroshima University
1-2-3 Kasumi, Minami-ku
Hiroshima 734-8551 Japan

Tel: +81-82-257 5252 Fax: +81-82-257 5254
E-mail: khalifa369@yahoo.com or takashiishino@hotmail.com

Current address:
Mohamed Khalifa Ahmed
ENT Department
Assiut University
Assuit
Egypt

E-mail: khalifa369@yahoo.com