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Paranasal sinus mycoses in north India

Nebenhöhlen-Mykosen in Nordinien

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Schlüsselwörter. *Aspergillus flavus*, Pilzinfektion, Nebenhöhlen-Mykose, Pilzgranulom, antimykotische Chemotherapie, Itraconazol.

Summary. Recognizing the high incidence of paranasal sinus mycoses in north India, we analysed retrospectively the clinical, mycological and management aspects of 178 patients with proven disease attending our institute. On the basis of clinical, radiological, histopathological and mycological findings, the patients could be categorized into those with allergic (8), non-invasive (92) and invasive (78) disease types. Bony erosion without mucosal invasion by fungi was seen in 16 patients with non-invasive disease. Young men from rural areas were the most commonly affected. Rhinorrhoea with nasal polyposis (45.8%) and proptosis (46.4%) was the most common presentation. Concurrent involvement of the maxillary and ethmoid sinuses was common in these patients, whereas isolated sphenoid and frontal sinuses were involved in the invasive variety only. Orbital and intracranial extensions were detected in 100% and 13.2%, respectively, of patients with the invasive type of disease. *Aspergillus flavus* (79.7%) was the most common isolate. Surgical debridement and sinus ventilation were adequate for the effective management of the non-invasive disease. However, adjuvant medical therapy was included in treatment of the semi-invasive and invasive varieties of the disease. Itraconazole was found to be most useful in prevention of recurrence in the invasive type. Mortality was highest (33.3%) among patients with zygomycotic infection. Invasive fungal granuloma with orbital and intracranial invasion is a distinct entity in terms of its clinical course and treatment compared with non-invasive fungal sinusitis, and it needs to be treated aggressively with surgical excision and post-operative itraconazole.

Zusammenfassung. Es wurden 178 Fälle von Mykosen der Nasennebenhöhlen in Nordindien retrospektiv analysiert. Nach klinischen, radiologischen, histologischen und mykologischen Befunden konnten diese in allergische (8), nicht-invasive (92) und invasive (78) eingeteilt werden. Knochenerosion ohne Schleimhautinvasion durch Pilze wurde bei 16 Patienten mit nicht-invasiver Mykose gesehen. Den größten Anteil der Patienten stellten junge Männer vom Lande. Rhinorrhoe mit Nasenpolyposis (45.8%) und Proptosis (46.4%) waren häufige Bilder. Gleichzeitige Beteiligung von Kiefern- und Siebbeinhöhle wurden nur bei invasiven Mykosen gefunden. Orbital- und Intrakranialbeteiligung wurde zu 100% bzw. 13.2% bei Patienten des invasiven Typs gefunden. *Aspergillus flavus* (79.7%) war das häufigste Isolat. Für die nicht-invasive Form genügte chirurgisches Debridement und Sinusventilation. Beim invasiven Mykosetyp war adjuvante Antimykotikatherapie notwendig; Itraconazol erwies sich als geeignet zur Rückfallprophylaxe. Die Mortalität war am höchsten bei Patienten mit Zygomyzeten-Infektion (33.3%). Das invasive Pilzgranulom mit orbitaler und intrakranialer Invasion stellt, verglichen mit nicht-invasiver Nebenhöhlenmykose, im klinischen Bild eine umschriebene Entität dar und muß aggressiv chirurgisch und antimykotisch therapiert werden.

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Introduction

Paranasal sinus mycoses have been described to be of four types: allergic, non-invasive, invasive and fulminant. Mucosal invasion has been seen in the last two varieties [1–3]. Recently, a possible fifth type, which is destructive, non-invasive and characterized by sinus expansion and bony erosion but with no histological evidence of tissue invasion, has also been recognized. Paranasal sinus mycoses is common in north India, northern Sudan and the south-western states of the USA. *Aspergillus flavus* is the commonest agent isolated from affected patients [4–6].

For effective management, surgical debridement and sinus ventilation are recommended for non-invasive disease, whereas the possible requirement of adjuvant medical therapy is stressed for the semi-invasive (non-invasive disease with bone destruction) and the invasive types to prevent recurrence and further extension [6, 7]. We diagnosed and treated 178 patients with paranasal sinus mycoses at our institute until December 1995. We have analysed these patients in the present study to understand the distinction between different varieties of fungal sinusitis and the outcome of management of these cases.

Materials and methods

Study population

One hundred and seventy-eight patients diagnosed with paranasal sinus mycoses in our institute during the period from January 1985 to December 1995 were included in this study.

Diagnostic criteria and categorization

The patients were diagnosed and categorized on the basis of the following clinical features and radiological, surgical, histopathological and microbiological findings.

1. Allergic. Patients with recurrent sinusitis, a definite history of atopy and the presence of fungi in eosinophilic mucus without mucosal invasion on histopathological examination—eight patients.
2. Non-invasive. Patients with symptoms of unilateral/bilateral nasal obstruction, pressure feelings and nasal discharge with the detection of a mass of mycelia embedded in mucus within the paranasal sinuses without mucosal invasion on histopathology—92 patients. In this group, 16 patients had associated bone erosion on computerized tomography (CT) scan. The disease in these patients was categorized as semi-invasive.
3. Invasive. Disease with involvement of multiple sinuses, orbit with or without intracranial extension and with evidence of mucosal invasion on histopathology—78 patients. This group also included 12 patients with invasive, rapidly progressive, gangrenous mucoperiostitis with the presence of broad aseptate hyphae in neutrophilic tissue reaction and isolation of zygomycetes.

Investigations

Radiology. CT of the paranasal sinuses, orbit and cranium as and when required in both axial and coronal planes was carried out to define the exact extent of the disease.

Histopathology. Histopathological examination of the excised fungal mass was performed for demonstration of tissue invasion by fungus using haematoxylin and eosin, periodic acid–Schiff and methanamine silver stains. The disease was categorized as invasive only when there was evidence of mucosal invasion.

Mycological studies. The study included direct microscopy on 10% potassium hydroxide wet mount of excised tissue, fungal culture by inoculating on Sabouraud glucose agar and fungal serology for demonstration of the precipitin band using sera against metabolic antigens of *A. flavus*, *A. fumigatus* and *A. niger* using Ochterlony's gel diffusion technique. Twenty-two patients who were suspected of having recurrence were tested again during follow-up for the presence of precipitating antibodies.

Treatment protocol

Surgical and medical management were performed according to the different categorizations of the disease.

Non-invasive. Total surgical extirpation with wide drainage was carried out using Moure's lateral rhinotomy or the Lynch Howarth incision. In 16 patients, in whom bony destruction in the region of the cribriform plate, the posterior table of the frontal sinus, the fovea ethmoidalis, the posterior wall of the maxillary sinus, the lamina papyracea or the sphenoid sinus was observed during radiology or at the time of surgery but with no mucosal invasion detected histopathologically, adjuvant medical therapy was given with oral ketoconazole (400 mg daily) for 3 weeks.

Invasive

Surgical treatment. Total surgical extirpation was performed after wide exposure using lateral rhinotomy or the Weber Fergusson approach whenever required. Total surgical extirpation included partial maxillectomy, ethmoidectomy, orbital exenteration and clearance from the infratemporal fossa. For intracranial extension in the anterior cranial fossa, craniofacial resection was performed. Subtotal resection was performed when invasive granuloma was found to involve the cavernous sinus, the internal carotid artery or the orbital apex with normal vision. These patients were subsequently treated with antifungal drugs. However, radical debridement of involved tissue was performed when zygomycetes were detected in the tissue.

Medical therapy. Until January 1993, in 45 patients with the invasive type of disease, adjuvant medical therapy constituted intravenous amphotericin B with a maximum dose of 1 mg kg^{-1} day^{-1} (total dose not more than 1.5 g) with or without 5-fluorocytosine (100 mg kg^{-1} day^{-1}) for the same period. From January 1993 onwards, 22 patients were treated with oral itraconazole (5 mg kg^{-1} day^{-1}) alone for 3–6 months.

Allergic. Surgical clearance was carried out either with open exploration or with nasal endoscopes for wide drainage of the sinuses with or without local steroid spray.

Results

Study patients

The patients diagnosed as having paranasal sinus mycoses could be categorized into three disease groups—allergic (8), non-invasive (92) and invasive (78)–on the basis of histopathological and mycological investigations. In the non-invasive group, 16 patients had the non-invasive destructive type of disease, as bone destruction was observed on radiology but no mucosal invasion was noticed on histology. The patients were aged 10–45 years and there were more men than women (M/F = 1.9 : 1). There were more patients from rural areas (115) than from urban areas (63). Rhinorrhoea with nasal polyposis (45.8%) and proptosis (46.4%) were the most common presentations, followed by headache (11.3%), cheek swelling (9.5%), diminished vision (8.9%), blindness (5.3%) and seizures, vomiting and altered sensorium (5.3%). Apart from 10 out of 12 patients with zygomycotic infection who had diabetes as the underlying disease, none had any predisposing illness. The maxillary (45.8%) and ethmoid sinuses (39.3%) were the most commonly involved paranasal sinuses. The frontal and sphenoid sinuses were involved in 16.7% and 11.3% patients. Intracranial extension was observed in 10 (5.6%) patients.

Fungi responsible

In all types of paranasal mycoses, *A. flavus* was the commonest isolate (79.7%). *A. fumigatus* was isolated from 11.1% patients. *Rhizopus arrhizus* (12 isolates) was detected in patients with the invasive type only. *Alternaria* spp. and *Candida albicans* were rare isolates (Table 1).

Fungal serology

Among the patients from whom aspergilli were isolated, precipitins against species of *Aspergillus* were detected in 63 (68.4%) patients with the non-invasive type of disease and 34 (51.6%) patients with the invasive type. No precipitating antibody against *Aspergillus* was detected in patients with allergic disease or in patients from whom species other than *Aspergillus* were isolated. Of 22 patients in whom repeat serology was performed after recurrence was suspected, the precipitating antibody was seen in 10 (45.4%) patients.

Outcome of management

Of the 178 patients, three were lost to follow-up (two non-invasive, one invasive). Therefore, the outcome of management of 175 patients is given in Table 2. Among the patients with non-invasive type disease, 16 had suspected bony erosion on radiology (categorized as semi-invasive). Adjuvant medical therapy with oral ketoconazole was administered in these patients. Thirteen patients responded well and three came back with recurrence.

Among the 10 patients with intracranial extension, seven had hydrocephalus with meningeal involvement. Two patients developed CSF rhinorrhoea after craniofacial resection. Two patients received amphotericin B alone as they were unfit for surgery because of extensive intracranial extension. Both of them succumbed because of the lesion. The other eight patients underwent craniofacial resection with chemotherapy, and seven of them responded well.

In patients with invasive type disease, changing medical therapy from amphotericin B to itraconazole resulted in an increase in the cure rate from 64.4% to 90%. The difference was statistically significant according to Student's *t*-test ($P<0.01$).

Table 1. Fungi isolated from different groups of paranasal sinuses

Species of fungi	Allergic	Non-invasive	Invasive	Total (%)
A. flavus	7	76	59	142 (79.7%)
A. fumigatus	—	13	6	19 (11.1%)
Aspergillus sp.	1	1	—	2 (1.2%)
Alternaria. sp.	—	2	—	2 (1.2%)
Rhizopus arrhizus	—	—	12	12 (7.1%)
Candida albicans	—	—	1	1 (0.6%)

Table 2. Outcome of management of patients with paranasal sinus mycosis

Types	Number of patients	Improved or cured	Recurrence	Died
Allergic	8	7	1	0
Non-invasive*	90	81	7	2
Invasive* (*Aspergillus*)				
Amphotericin B with or without 5-fluorocytosine	45	29	13	3
Itraconazole	20	18	2	—
Zygomycosis (amphotericin B)	12	8	—	4

*Two patients with the non-invasive disease and one patient with the invasive disease were lost to follow-up.

Mortality was highest (33.3%) in the patients with zygomycotic infection. Apart from two patients in the non-invasive group who died from unrelated causes, the other seven patients succumbed because of lesions produced by fungi.

Discussion

Paranasal sinus mycosis is being recognized more frequently in different parts of the world because of increased awareness. A significantly higher incidence is reported in the restricted zones of north Sudan, Saudi Arabia and in the south-western states of the USA, which have a warm and dry climate [4, 6, 8]. North India, including western Uttar Pradesh, north Rajasthan, Haryana, Punjab and Chandigarh, has a similar climate during the summer months. A plausible explanation for the endemicity of fungal granuloma in north India is not difficult to explain. Possibly the dust and frequent sand storms during the summer months contain large numbers of *Aspergillus* conidia that can easily settle on the injured mucosa of the sinuses of young men working outdoors who are exposed to the warm dry climate. In our study, the majority of patients were young men from a rural background (64.6%). In addition, the use of antibiotics (unwarranted at times), antihistamines and corticosteroids in the treatment of nasal allergy and sinusitis may play a role in the pathogenesis of the disease by suppressing bacterial flora and supporting fungal overgrowth. The maxillary and ethmoid sinuses were more commonly involved because drainage depends on mucociliary propagation in these sites.

Patients with non-invasive and invasive disease present differently. Our patients with the non-invasive form came to hospital with chronic sinusitis, unresponsive to conservative medical treatment and repeated sinus irrigations, and symptoms of rhinorrhoea and nasal obstruction. In contrast, patients with invasive disease had a firm, enlarging mass in the cheek, the orbit and the paranasal sinuses. Apart from 10 of the 12 patients with zygomycosis, none of the patients had any obvious immunodeficiency.

It is interesting to study the reasons why a particular fungus behaves in different ways in non-immunocompromised patients resulting in the non-invasive and invasive types of fungal sinusitis. Jahrsdoerfer *et al.* [9] have suggested that the distinction between the invasive and non-invasive forms of the disease is not clear. Rowe Jones and Moore-Gillon [10] have proposed that paranasal sinus mycoses have a wide spectrum of manifestations, and that the invasive disease may develop from the non-invasive type and progress to the destruction of bone. They felt that the duration of the disease might be important in determining the form of disease that develops. However, none of our 78 patients with the invasive form had any history of the non-invasive disease. Follow-up of the seven patients with the non-invasive form also did not show any transformation to the invasive form, even after multiple recurrences. The above

observations, in our opinion, suggest that invasive and non-invasive fungal sinusitis are two different disease processes.

The recently recognized non-invasive type of disease with bone destruction (semi-invasive) represents a clinical spectrum in which bone destruction could be an end result of a long-standing disease in the sphenoid and frontal sinuses, causing hyperaemic decalcification with the resultant exposure of dura [10]. Robb [11] has reported a case of locally destructive aspergillosis that on histological examination revealed tissue invasion only at the margins of the specimen. In our 16 possible patients in this group, bony erosion was observed on radiology in the region of the cribriform plate, the posterior table of the frontal sinuses, the posterior wall of the maxillary sinuses or the sphenoid sinuses. Proptosis was seen in 10 patients who had erosion of the lamina papyracea. However, histopathological examination suggested that none of the patients in this group had any mucosal invasion by fungus. Three of these patients had recurrence on follow-up. There was no progression of fungus across the mucous membrane during recurrence, which does not support the hypothesis that the different types of paranasal sinus mycosis are clinical spectra of a single disease. However, the entity of the non-invasive destructive form needs further study to understand its pathogenesis.

Aspergillus flavus is again the most frequent isolate (79.7%) in all types of paranasal sinus mycoses, as was observed in previous studies from north India [4, 12, 13]. *A. flavus* was isolated in most cases from Sudan [5, 14]. However, in the United States, *A. fumigatus* and *R. oryzae* have been found in an increasing number of cases [3, 6, 15]. In our study, *A. fumigatus* was isolated from 11.1% of patients. In allergic fungal sinusitis, the dematiceous fungi such as *Biopolaris* (*Drechslera*), *Curvularia* and *Alternaria* are the predominant aetiological agents in several studies [16–18]. However, in our limited experience of eight cases of allergic fungal sinusitis, *Aspergillus* was isolated from all cases.

The importance of detecting precipitating antibodies was highlighted in previous studies at this institute [4, 13]. In the present study, detection of antibodies was positive in 68.4% of patients with the non-invasive variety compared with 51.6% of patients with the invasive variety. The precipitin disappeared after surgery and medical treatment. However, it reappeared in 45.4% patients who experienced disease recurrence.

The effective management of paranasal mycoses requires early diagnosis, histological classification, surgery and, when appropriate, chemotherapy [7]. Our management protocol includes endoscopic examination, antral lavage and antroscopy as the first diagnostic steps that lead to debridement, wide aeration of the infected sinuses and the provision of specimens for histological and microbiological study. After confirmation of diagnosis, definitive surgery is planned. Histology is important to distinguish between the invasive and non-invasive disease, as possible adjuvant medical therapy is required in patients with invasive disease. We have changed our medical therapy over the years. Until 1991 we used only amphotericin B, then for 2 years 5-fluorocytosine was incorporated with amphotericin B, and finally from 1993 to 1995 itraconazole replaced both amphotericin B and 5-fluorocytosine.

Among patients with invasive disease, recurrence was observed in eight (36.4%) patients after using amphotericin B alone and in five (20%) patients using a combination of amphotericin B and 5-fluorocytosine. However, the recurrence rate dropped to 10% after using itraconazole. To reach a definite conclusion, more patients need to be evaluated. The newer azoles potentially offer improved efficacy and reduced toxicity [19]. Itraconazole has been shown to be an effective antifungal agent in human and experimental invasive aspergillosis [20], and unlike amphotericin B is active orally, well tolerated and non-toxic. Our patients tolerated itraconazole well, except for elevated liver enzymes and minor gastrointestinal disturbances in two patients.

Rowe Jones and Moore Gillon [10] have recommended oral itraconazole therapy in addition to surgery in patients with destructive non-invasive fungal sinusitis. We have used ketoconazole for 3 weeks in our 16 patients in this group, keeping itraconazole as an adjunct for invasive disease.

In patients with zygomycosis, aggressive radical surgery is required along with medical therapy [21]. Despite following this protocol, four (33.3%) of our patients with zygomycosis died.

In conclusion, this study highlights the importance of paranasal sinus mycosis in north India. Our observations suggest that invasive and non-invasive fungal sinusitis are two different disease processes. Further long-term prospective studies may help to unravel the mystery of whether the two entities are in fact spectra of the same disease.

References

1 Katzenstein, A. A., Sale, S. R. & Greenberger, P. A. (1983) Allergic *Aspergillus* sinusitis. A newly recognized form of sinusitis. *J. Allergy Clin. Immunol.* **72**, 82–93.

2 McGill, T. J., Simpson, G. & Healy, G. B. (1980) Fulminant aspergillosis of the nose and paranasal sinuses. a new clinical entity. *Laryngoscope* **90**, 748–754

3 Stammberger, H., Jakse, R. & Beanfort, F. (1984) Aspergillosis of the paranasal sinuses. *Ann. Otol. Rhinol. Laryngol.* **93**, 251–256.
4 Chakrabarti, A., Sharma, S. C. & Chander, J. (1992) Epidemiology and pathogenesis of paranasal sinus mycoses. *Otolaryngol. Head Neck Surg.* **107**, 745–750.
5 Milosev, B., Mahgoub, E. S., Aal, O. A. & El Hassan, A. M. (1969) Primary aspergilloma of paranasal sinuses in Sudan. *Br. J. Surg.* **56**, 132–137.
6 Washburn, R. G., Kennedy, D. W., Begley, M. G., Henderson, D. K. & Bennett, J. E. (1988) Chronic fungal sinusitis in apparently normal hosts. *Medicine* **67**, 231–247.
7 Denning, D. W. & Stevens, D. A. (1990) Antifungal and surgical treatment of invasive aspergillosis: review of 2121 published cases. *Rev. Infect. Dis.* **12**, 1147–1201.
8 McGuirt, W. F. & Harrill, J. A. (1979) Paranasal sinus aspergillosis. *Laryngoscope* **89**, 1563–1568.
9 Jahrsdoerfer, R. A., Ejercito, V. S. & Johns, M. E. (1979) Aspergillosis of the nose and paranasal sinuses. *Am. J. Otol.* **1**, 6–14.
10 Rowe Jones, J. M. & Moore Gillon, V. (1994) Destructive non invasive paranasal sinus aspergillosis. Component of a spectrum of disease. *J. Otolaryngol.* **23**, 92–96.
11 Robb, P. J. (1986) Aspergillosis of the paranasal sinus (a case report and histological perspective). *J. Laryngol. Otol.* **100**, 1071–1077.
12 Rao, G. S. P., Mann, S. B. S., Talwar, P. & Arora, M. M. L. (1983) Primary mycotic infection of paranasal sinuses. *Mycopathologia* **84**, 73–76.
13 Talwar, P., Sharma, M., Shell, S. C. & Ghost, K. K. (1982) Serology of *Aspergillus* granuloma. *Mycopathologia.* **79**, 79–85.
14 Veress, B., Malik, O. A., El Tayeb, A. A., El Daoud, S., El Mahgoub, S. & El Hassan, A. M. (1973) Further observations on the primary paranasal *Aspergillus* granuloma in Sudan. *Am. J. Trop. Med. Hyg.* **22**, 765–772.
15 Hora, J. F. (1965) Primary aspergillosis of the paransal sinuses and associated areas. *Laryngoscope.* **75**, 768–773.
16 Bartynski, J. M., McCaffrey, T. V. & Frigas, E. (1990) Allergic fungal sinusitis secondary to dematiceous fungi—*Curvularia lunata* and *Alternaria. Otolaryngol. Head Neck Surg.* **103**, 32–39.
17 Harpster, W. H., Gouzalez, C. & Opal, S. M. (1985) Pansinusitis caused by the fungus *Drechslera. Otolaryngol. Head Neck Surg.* **93**, 683–685.
18 Manning, S. C., Schaefer, S. D., Close, L. G. & Vuitch, F. (1991) Culture positive allergic fungal sinusitis. *Arch. Otolaryngol.* **117**, 174–178.
19 Denning, D. W., Tucker, R. M., Hansen, L. H. & Stevens, D. A. (1989) Treatment of invasive aspergillosis with itraconazole. *Am. J. Med.* **86**, 791–800.
20 Graybill, J. R. (1989) New antifungal agents. *Eur. J. Clin. Microbiol. Infect. Dis.* **5**, 402–412.
21 Parfrey, N. A. (1986) Improved diagnosis and prognosis of mucormycosis. *Medicine* **65**, 113–123.