NASOSINUSAL FUNGAL GRANULOMA - CLINICAL PROFILE

G Andrews, M Kurien, V Anandi, B Ramakrishna, R Raman

ABSTRACT

Fifty cases of nasosinusal fungal granuloma were admitted under the ENT Department in a teaching tertiary care hospital in India during a thirteen-year period. Aspergillus species was found to be the most common causative fungus (29) followed by Mucorales (14), Entomophthorales (5) and Fusarium (2) species. There were 13 cases of non-invasive and 16 cases of invasive variants of Aspergillosis. In spite of intravenous amphotericin B therapy and radical surgical debridement, 81% in the invasive group showed relapse and required prolonged oral antifungal drugs and multiple surgical procedures. Among the 14 cases of Mucormycosis, all of the 10 cases who received intravenous amphotericin B and radical surgery showed complete recovery with no relapse over a period of 2 to 10 years. This is contrary to earlier published reports which suggest poor prognosis. The entomophthoromycosis received oral steroids and cotrimoxazole, and oral potassium iodide or intravenous amphotericin in case of relapse. Both the cases of Fusariosis recovered completely with oral ketoconazole.

Keywords: *nasosinusal fungal granuloma, relapse, long-term therapy*

SINGAPORE MED J 1996; Vol 37: 470-474

INTRODUCTION

Fungal infections of the nose and paranasal sinuses can occur in a spectrum of diseases varying from acute fulminant to chronic invasive/non-invasive and allergic variants[1]. The acute fulminant variant (or fungal vascular invasion) occurs more commonly in debilitated and immunocompromised patients[2-6]. The chronic variant[1] can be invasive where there is profuse fungal growth with tissue invasion[7-10] or non-invasive which is characterised by colonisation or fungal ball[11]. The chronic and allergic variants occur more commonly in immunocompetent hosts[10,11]. The purpose of this study was to evaluate the clinical presentation and outcome of patients who were diagnosed to have fungal granuloma of the nose and paranasal sinuses.

MATERIALS AND METHOD

The study included patients admitted in Christian Medical Hospital, Vellore from March 1981 to February 1994 who were diagnosed to have fungal granuloma of the nose and paranasal sinuses. The criteria for inclusion in the study were those who had histopathological evidence of fungal hyphae and/or positive culture of fungus from the tissue taken from the nose or sinuses. Patients with evidence of generalised mycotic infection and rhinosporidiosis were excluded from the study.

They were then classified for the various clinical types, aetiological agents and patient status (Fig 1, Tables I and II). The clinical presentation are shown in Fig 2, treatment instituted and outcome are given in Tables III and IV.

Department of ENT
Christian Medical College and Hospital
IDA Scudder Road
P O Box 3, Vellore - 632 004
South India

G Andrews, MS
Registrar

M Kurien, MS
Professor

Department of Microbiology
Christian Medical College

V Anandi, PhD
Reader

Department of Pathology
Christian Medical College

B Ramakrishna, MD
Reader

R Raman, MS
Professor

Correspondence to: A/Prof M Kurien

RESULTS

This series comprised 50 patients, 40 males and 10 females, with a median age of 37 years (range 15-91 years).

Aspergillosis was the most common among the fungal infections with granuloma formation involving nasosinusal areas (58%), followed by Mucormycosis (28%). Entomophthoromycosis and Fusariosis were relatively uncommon (Table I, Fig 1).

Among the 50 patients, 32 cases (63%) were found to be healthy immunocompetent hosts. Eighty-nine percent of aspergillosis and 80% of entomophthoromycosis were immunocompetent while 100% cases of Mucormycosis were immunocompromised (Table II).

Patients were followed-up every two months. Clinical and endoscopic examination were done to determine the disease status. Tissues from the involved areas were sent for both histopathological and microbiological examination.

Aspergillosis

There were 29 cases of aspergillosis, of which 26 were healthy adults, 2 were diabetics and one had hypothyroidism. All the cases had history of symptoms varying from 3 to 24 months. We encountered the chronic variant only which was either non-invasive or invasive.

1) Non-invasive form – the disease was limited to the mucosa and the bony walls were intact.
2) Invasive form – there was involvement of multiple sinuses with or without extra sinusal spread (orbit/infratemporal fossa/cranial cavity).

Thirteen (44%) cases were in the non-invasive form with 10 males and 3 females ranging from age 25-50 years. Sixteen (54%) cases were in the invasive form with 9 males and 7 females, age range being 15-91 years. The symptomatology in the two major forms of nasosinusal aspergillosis is given in Fig 2. Nasal obstruction and discharge were present in all the patients of the non-invasive single sinus form but none of them had epistaxis,

Fig 1 – Nasosinusal Fungal Granuloma

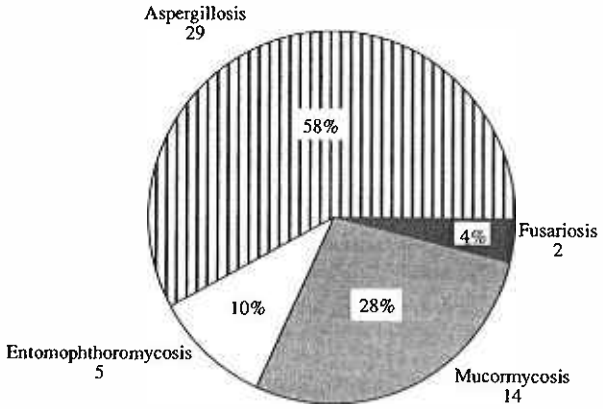


Table I

Clinical types	No. of cases	Aetiological Agents	No.
Aspergillosis (Chronic variant)	29		
1. Non-invasive single sinus)	13	Asp. species	1
		Asp. fumigatus	8
		Asp. flavus	4
2. Invasive (multiple/extra sinusal spread)	16	Asp. species	2
		Asp. fumigatus	8
		Asp. flavus	6
Mucormycosis*		Mucorales	
Acute (nasal with multiple/extra sinusal spread)	14	Mucor	7
		Rhizopus	5
		Absidia	2
Entomophthoromycosis* (subcutaneous)	5	*Conidiobolus coronata*	5
Fusariosis (invasive naso-maxillary sinus)	2	*Fusarium solani*	2

* Zygomycosis

Table II

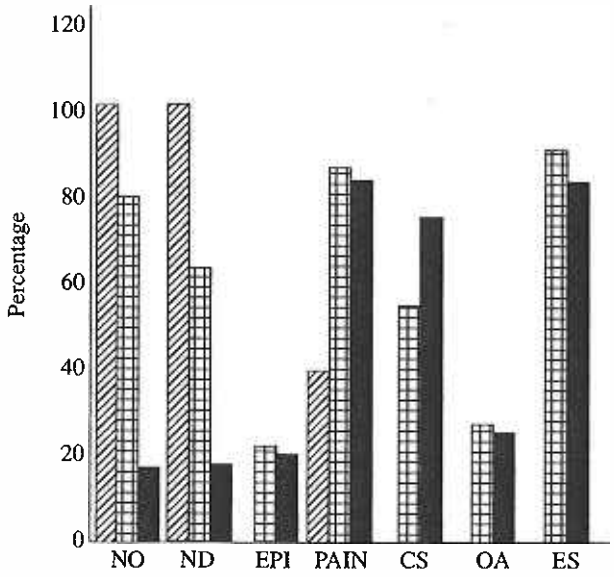
Clinical Entity	Patient status			Other medical illness (hypothyroidism)	Total
	Healthy	Immunocompromised D*	S*		
Aspergillosis	26	2	–	1	29
Mucormycosis	–	11	3	–	14
Entomophtho-romycosis	4	1	–	–	5
Fusariosis	2	–	–	–	2
Total	32	14	3	1	50

*D: Diabetic, *S: On Steroids

cheek swelling or eye symptoms. In the invasive form, the commonest symptoms were headache and proptosis followed by nasal symptoms including epistaxis. Other eye symptoms were diplopia, epiphora and/or total ophthalmoplegia.

The treatment instituted and the outcome in Aspergillosis are shown in Table III. The antifungal agents were either oral 100% solution of potassium iodide (9 g/day); intravenous amphotericin B cumulative dose being 30 mg/kg[11] followed by cap. itraconazole 200 mg once a day. However, in case of itraconazole toxicity cap. rifampicin 450 mg with tab ketoconazole 200 mg twice a day were given[13]. Among the 9

Fig 2 – Clinical Presentation



NO - Nasal obstruction, ND-Nasal discharge, EPI-Epistaxis, HA-Headache/ facial pain, CS-Cheek swelling, OA-Oroantral fistula, ES-Eye symptoms.

Aspergillosis (Non-In) Aspergillosis (In) Mucormycosis

Table III - Aspergillosis

Clinical types	Treatment	No. of patients	Outcome	
Chronic non-invasive Aspergillosis (maxillary sinus)	Caldwell-Luc + removal of the nasal mass/polyp +			
	1. oral potassium iodide solution	7	All cured	
	2. I/V amphotericin B.	2	All cured	
	3. Beclate nasal spray	4	Cured	1
			Lost to follow-up	3
Chronic invasive Aspergillosis (with multi extra sinus spread)	I/V amphotericin B + Caldwell - Luc	2	Died	1
			Lost to follow-up	1
	Caldwell - Luc + Palatoalveolar resection	1	Lost to follow-up	1
	Transantral ethmoidectomy + septoplasty + lateral rhinotomy and excision + itraconazole.	2	Cured	2
	Contralateral external ethmoidectomy + medial maxillectomy for recurrence + itraconazole.	4	Cured	2
			On treat-ment*	2
	Transantral ethmoidectomy + medial maxillectomy + itraconazole for recurrence.	5	Cured	4
			On treat-ment*	1
	Medial maxillectomy + itraconazole	2	Cured	2

*Rifampicin + ketoconazole

patients (31%) who were not cured of the disease, 3 were in the non-invasive group and they were lost to follow-up. The other 6 patients belonged to the invasive group. Three of them had only intravenous anti-fungal therapy and Caldwell-Luc surgery. One expired of extensive local and intracranial spread, the other 2 refused radical surgery and were lost to follow-up. The other 13 patients in the invasive group, though they had full course of I/V amphotericin and radical surgeries, showed evidence of relapse.

Table IV – Mucormycosis

Clinical types	No. of patients	Treatment	Outcome
Acute (multi/extra sinus spread).		I/V amphotericin B +	
Unilateral nasal cavity, maxillary and ethmoidal sinus with orbital apex syndrome.	3	Medial maxillectomy	Recovery of eye movements. Vision not recovered. Free of disease 6, 3 and 2 years.
Unilateral nasal cavity, maxillary, ethmoidal, and sphenoidal sinuses with orbital and cavernous sinus involvement.	3	Total maxillectomy + orbital exenteration	Free of disease 6, 5 and 3 years.
Unilateral maxillary and ethmoidal sinuses and orbit.	2 1	Refused surgery. Not fit for amphotericin/ surgery as gross renal failure.	Lost to follow-up. Died within 1 week.
Unilateral maxillary and ethmoidal sinuses.	4	Medial maxillectomy.	Free of disease 3, 2 years, 20 and 18 months.
Bilateral ethmoidal and maxillary sinuses and both orbits.	1	Terminally ill. Not fit for amphotericin surgery.	Died within 24 hours of diagnosis.

They were on oral itraconazole 200 mg once a day for 4-6 months along with multiple surgical debridements after which 10 of them are disease-free (Table III). These patients were on oral anti-fungal therapy till a month after the biopsy of the areas involved were histopathologically and microbiologically negative. The duration of therapy varied from 3 to 9 months. Three patients developed hypersensitivity to itraconazole and are still on rifampicin and ketoconazole (>10 months), long-term response to which is awaited[13].

Mucormycosis

There were 14 cases of nasosinusal mucormycosis in our series, all were males, with ages ranging from 19-55 years. There were nasal and multi-sinusal involvement with or without extra sinusal spread. There were 4 rhino-sinusal, 8 rhino-orbital, 2 rhino-cerebral involvement. Eleven of them were uncontrolled diabetics (9 had ketoacidosis at the time of admission), 2 were renal transplant patients on immunosuppressant therapy and one had acute renal failure and was on steroids. The history of illness ranged from one to three weeks. The clinical features are shown in Fig 2.

The treatment given and the outcome of these patients are shown in Table IV. Of the 14 patients diagnosed, 10 are disease-free to-date (71%). All of them had intravenous amphotericin B (cumulative dose of 30 mg/kg) and radical surgery of the areas involved. The 4 patients who were not disease-free did not have amphotericin therapy. Two of them could not afford the drug, refused surgery and were lost to follow-up. The other 2 patients expired within 24 hours and a week of diagnosis respectively.

Entomophthoromycosis

This disease was diagnosed in 5 cases, all being males, aged from 17-35 years. One was a diabetic, the others were healthy and presented with the features consistent with earlier description of the clinical entity[8,14]. Four were treated with oral steroids and cotrimoxazole for a period of 3-4 months[14]. Two of them had recurrence within three months of the above treatment and were on oral potassium iodide 9 gms daily for 3 months and 6 months respectively[12]. However, these patients showed evidence of relapse 3 and 2 years later and had to be on intravenous amphotericin. The diabetic patient was cured with oral potassium iodide 9 gms daily for 4 months. Four of them are disease-free to-date (80%).

Fusariosis

There were two cases of fusariosis of maxillary sinus. Both these patients were otherwise healthy adults. They underwent Caldwell-Luc operation followed by oral ketoconazole 100 mg once a day for two months and are free of disease to-date[15].

PATHOLOGY

Histopathological examination in Aspergillosis showed fragments of fibrocollagenous and adipose tissue, containing a dense inflammatory cell infiltrate composed predominantly of eosinophils, lymphocytes and some plasma cells. Several granulomas were seen composed of epitheloid histiocytes and multinucleated foreign body type giant cells. Sparse fungal hyphae of uniform width were demonstrated by silver impregnation within giant cells (Fig 3).

In mucormycosis, there was dense infiltrate of neutrophilic and eosinophilic leukocytes with lymphocytes and plasma cells. Several granulomas composed of epitheloid histiocytes and multinucleate giant cells were seen with a central necrotic zone containing broad, non septate and haphazardly branched and some partially collapsed and distorted fungal hyphae. The hyphae stained well with hematoxylin and also by silver impregnation (Fig 4 and 5).

MYCOLOGY

A 10% potassium hydroxide preparation of the infected tissue revealed a few to many septate, narrow dichotomously branched fungal hyphae suggestive of aspergillus species. Zygomyces was identified as broad, aseptate or occasionally septate, haphazardly branched fungal hyphae. The identification of the fungus was carried out based on the colony morphology on Sabouraud dextrose agar and czapek agar and microscopic morphology in lactophenol cotton blue preparation of slide cultures[16,17].

DISCUSSION

In our study of nasosinusal fungal granuloma, the commonest class of fungus causing the above was found to be *Ascomyces* (species Aspergillus) followed by the class *Phycomyces* (order Mucorales and Entomophtherales) and very rarely Fusarium species.

Aspergillosis has been reported as the commonest fungal infection of the sinuses. Two variants have been described:

Fig 3 – Fungal hyphae within a poorly staining giant cell (Gomori methenamine-Silver x400).

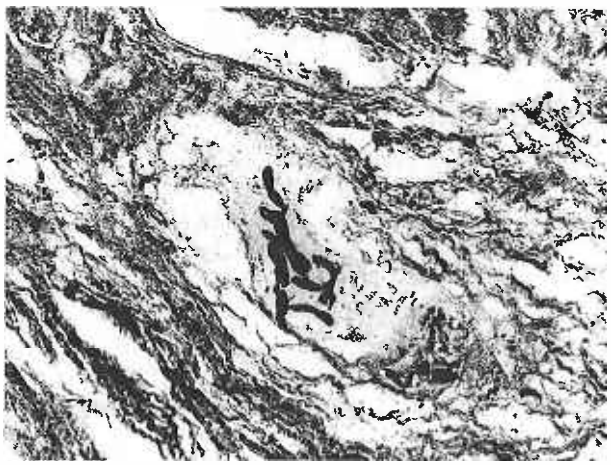


Fig 4 – Mucosal granuloma showing central necrosis, fungal hyphae and giant cells. (Hematoxylin - eosin x200).

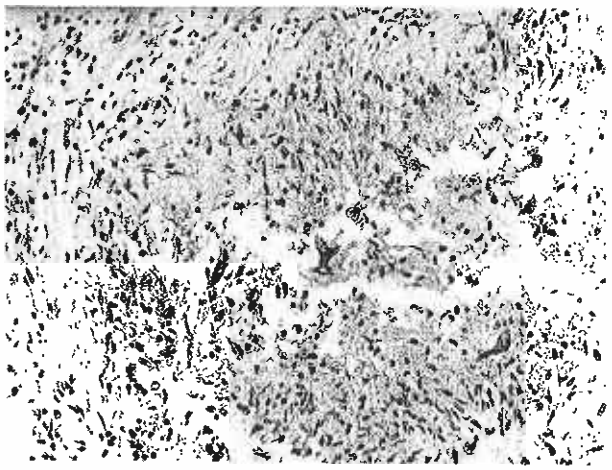
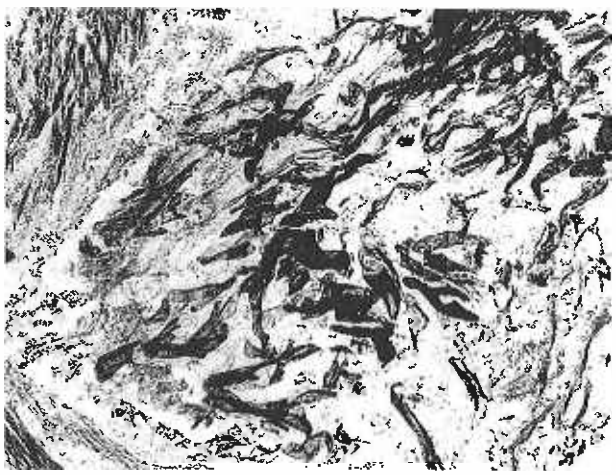


Fig 5 – Necrotic tissue containing fungal hyphae of variable width. (Gomori methenamine - Silver x400)



chronic indolent and fulminant: the former occurring more commonly in healthy adults and the latter occurring more commonly in immunocompromised hosts[1,2,11]. In our study, we have noted two major groups of the chronic indolent variants: non-invasive (single sinus) and invasive (multiple sinuses with or without extra sinus involvement). The treatment and survival rates reported are varied. Milosev et al[7] have mentioned a survival rate of 94% with local debridement and establishing the drainage of the involved sinuses into the nose. However, Sudhir Bahadur et al[9] in their review of 9 cases have reported a cure rate of 56% with local surgery and amphotericin B therapy. In our study, 13 belonged to the non-invasive group and 85% of them were cured with local surgery and antifungal therapy. In the invasive group, only 60% of the patients were cured. Relapses occurred in 40% of cases in spite of repeated debridements, radical surgeries and intravenous amphotericin B therapy.

Nasal and paranasal sinus mucormycosis with or without orbital or intracranial involvement has been reported by various authors. Immunocompromised state with facial and ocular pain occurred in all the patients[4,16] and in 40% of patients[6] respectively. Amphotericin B and surgical debridement have been the treatment followed by all with a survival rate of 54%, 75% and 60% respectively. However in our study of 14 patients, 10 had definitive therapy and all of them have survived.

CONCLUSION

Nasosinusal aspergillosis, entomophthoromycosis and fusariosis occur more commonly in immunocompetent patients unlike mucormycosis which occurs only in immunocompromised hosts. The symptoms of invasive aspergillosis and mucormycosis are similar except in the former, the illness is of a long duration in a relatively immunocompetent patient in contrast to the latter. Surgical debridement and ventilation was noted to be an essential factor in the successful treatment of all these nasosinusal fungal granuloma. In addition to the above, intravenous amphotericin B was given in invasive aspergillosis and mucormycosis. In fusariosis and entomophthoromycosis oral anti-fungal agents were given and amphotericin was reserved for relapse only. In invasive aspergillosis and entomophthoromycosis, in spite of the non-immunocompromised state, the relapse rates were high, requiring prolonged oral anti-fungal drugs and long-term follow-up. Mucormycosis, in contrast, though acute in onset in immunocompromised individuals and potentially fatal, responded well to specific therapy with no evidence of relapse if treatment was instituted early.

REFERENCES

1. Bradwin M. Histopathology of sinunasal fungal disease. The fungal infections of the head and neck. Otolaryngol Clin North Am 1993; 26: 949-66.
2. Blitzer A. Lawson W. Fungal infections of nose and paranasal sinuses. Otolaryngol Clin North Am 1993; 26: 1007-35.
3. Anaisse E. Opportunistic mycosis in the immunocompromised host: Experience at a cancer centre and review. Clin Infect Dis 1992; 14 (Suppl 1): S43-53.
4. Parfiey NA. Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. Medicine 1986; 65: 113-25.
5. Kaczmarski R. Pagliuca A. Pullon H. Philpott-Howarth J. Salisbury J. Muftii G. Fulminant fungal sinusitis following intensive chemotherapy. Q J Med 1990; 276: 365-70.
6. Ishida M. Toya N. Noiri T. Toshiko K. Hatta C. Matsumoto T. et al. Five cases of mucormycosis in paranasal sinuses. Acta Otolaryngol Suppl (Stockh) 1993; 501: 92-6.
7. Milosev B. Mahgoub El S. Abdal Aal. El Hassan AM. Primary aspergilloma of paranasal sinuses in the Sudan. A review of seventeen cases. Br J Surg 1969; 56(2): 132-8.
8. Martinson FD. Chronic phycomycosis of the upper respiratory tract. Rhinophycomycosis entomophthorae. Am J Trop Med Hyg 1971; 20: 449-55.
9. Sudhir, Bahadhur, Kacker SK. Paranasal sinus aspergillosis. J Laryngol Otol 1983; 97: 863-5.

10. Ronald GW, David WK, Martin GB, David KH, John EB. Chronic fungal sinusitis in apparently normal hosts. Medicine 1988; 67: 231-47.
11. Hartwick RW, Batsakias JG. Sinus aspergillosis and allergic fungal sinusitis. Ann Otol Rhinol Laryngol 1991; 100: 427-30.
12. Meyer RD. Current role of therapy with amphotericin B. Clin Infect Dis 1992; 14 (Suppl 1): S154-60.
13. Haran RP, Chandy MJ. Intracranial aspergillus granuloma. Br J Neurosurg 1993; 7: 383-8.
14. Balraj A, Anandi V, Raman R. Nasofacial conidiobolomycosis. Ear Nose Throat J 1991; 70 (10): 737-9.
15. Kurien M, Anandi V, Raman R, Brahmadathan KN. Maxillary sinus fusariosis in immunocompetent host. J Laryngol Otol 1992; 106: 733-6.
16. Austwick PKC, Longbottom JL. Medically important aspergillus species. In: Lennette EH, Balows A, Hausler Jr WJ, Traunt JP, eds. Manual of clinical microbiology, 3rd edition. A S M 1980: 620-7.
17. Green DL. Agents of zygomycosis. In: Lennette EH, Balows A, Hausler Jr WJ, Traunt JP, eds. Manual of clinical microbiology. 3rd edition. A S M 1980: 611-9.