FUNGAL RHINOSINUSITIS: A RETROSPECTIVE ANALYSIS OF CLINICOPATHOLOGIC FEATURES AND TREATMENT OUTCOMES AT RAMATHIBODI HOSPITAL

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Abstract. The objective of this study was to determine the clinicopathologic findings of invasive and non-invasive fungal rhinosinusitis and to compare the features of the two diseases. The medical records of patients with invasive and non-invasive fungal rhinosinusitis at Ramathibodi Hospital between July 1999 and June 2009 were analyzed. The criterion for the diagnosis of fungal rhinosinusitis was the evidence of fungal elements from histopathologic section on sinonasal specimens. The age, gender, clinical manifestations, duration of symptoms, associated diseases, laboratory data, results of mycotic culture and treatment outcomes were analyzed. The relationship between fungal rhinosinusitis and patient characteristics as well as clinical presentations were assessed. The fungus-attributable mortality rate was determined. The study included 43 cases of invasive fungal rhinosinusitis and 68 cases of non-invasive fungal rhinosinusitis. There were 44 male, and 67 female patients. The mean age at diagnosis was 54.6 years (range: 5 to 86 years). A total of 70 (63.1%) were attributed to aspergillosis, 8 (7.2%) to candidiasis, 6 (5.4%) to zygomycosis, 4 (3.6%) to phaeohyphomycosis, 1 (0.9%) to pseudallescheriasis, 1 (0.9%) to entomophthoromycosis and 21 (18.9%) to non-specific fungi. Cultures from sinonasal tissues were positive for fungus in 37 of 87 cases (42.5%). The clinical presentations of fungal rhinosinusitis included nasal stuffiness (27.9%), nasal discharge (27.9%), facial pain (27.9%), fever (24.3%) and headache (19.8%). One-fifth of cases had an underlying hematologic malignancy. Invasive fungal rhinosinusitis was significantly associated with hematologic malignancy and neutropenia. Fungus-attributable mortality rate was 44.2% in invasive fungal rhinosinusitis. Early antifungal therapy and surgical drainage were associated with a survival advantage.

Key words: fungal rhinosinusitis, invasive, non-invasive, clinicopathologic findings

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INTRODUCTION

Fungal rhinosinusitis is broadly defined as a spectrum of conditions caused by fungal infection of the nose and paranasal sinuses. On the basis of clinico-

pathologic evidence of tissue invasion, fungal rhinosinusitis has two major classifications: noninvasive and invasive fungal rhinosinusitis (deShazo *et al*, 1997a; Granville *et al*, 2004; Das *et al*, 2009). There are three forms of noninvasive fungal rhinosinusitis: superficial sinonasal mycosis, allergic fungal rhinosinusitis and fungal ball (deShazo *et al*, 1997a; Ferreiro *et al*, 1997; Granville *et al*, 2004; Das *et al*, 2009). Invasive fungal rhinosinusitis has the following subgroups: acute or fulminant, invasive, and chronic invasive (deShazo *et al*, 1997b; Granville *et al*, 2004; Das *et al*, 2009). Patient symptoms with invasive fungal rhinosinusitis include nasal stuffiness, nasal discharge, facial pain, fever, and headache (deShazo *et al*, 1997b). Invasive lesions may develop on the hard palate or skull base. The infection can spread directly into the orbits or brain, causing thrombosis, infarction and hemorrhage. Invasive fungal rhinosinusitis has emerged as a catastrophic condition with high morbidity and mortality. The incidence rate of invasive fungal rhinosinusitis has been increasing, with a rising incidence in immunosuppressed patients. The purpose of the present study was to determine the clinicopathologic findings of invasive and non-invasive fungal rhinosinusitis and to compare the features of both diseases.

MATERIALS AND METHODS

This was a retrospective study of invasive and non-invasive fungal rhinosinusitis diagnosed by surgical material from the Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, over the period of 10 years (July 1999 - June 2009). The histopathological diagnosis of fungal rhinosinusitis was reviewed. Information obtained from the otolaryngologist records, including age, gender, clinical manifestations, duration of symptoms, associated diseases, laboratory data, results of the mycotic culture, and treatment outcomes, were analyzed. Patients were grouped based on the invasiveness of fungal organisms. A two-tailed Fisher's exact test was used to evaluate statistical significance between the groups. This study was approved by the committee on human research at the Faculty of Medicine, Ramathibodi Hospital (ID02-52-65).

RESULTS

One hundred eleven cases, affecting patients between 5 and 86 years old, with a mean age of 54.8 years, met the inclusion criteria. There were 44 male and 67 female patients with fungal rhinosinusitis. There were 43 cases of invasive fungal rhinosinusitis, and 68 cases of non-invasive fungal rhinosinusitis. The mean age of patients with invasive fungal rhinosinusitis was 52.14 years (range 5-79 years), which was somewhat younger than the patients with non-invasive fungal rhinosinusitis (56.19; 18-86 years). Patients presented with a variety of symptoms and physical findings. The duration of symptoms ranged from one day to twenty years, 33.3% of the cases being shorter than one month and 37.8% being longer than three months. Acute rhinosinusitis was more frequent in invasive than in non-invasive fungal rhinosinusitis. The mode and median intervals between the onset of the initial symptoms and admission were more than three months in non-invasive fungal rhinosinusitis. The body temperature (on admission) varied from 36ºC to 40ºC. The mean body temperature was 37.3ºC. Twenty-four percent had a body temperature > 37.8ºC. Details of the

Table 1
Patient characteristics with invasive and non-invasive fungal rhinosinusitis (n =111).

Detail	Invasive fungal rhinosinusitis (n = 43)		Non-invasive fungal rhinosinusitis (n = 68)		p-value
	No. of patients	Range	No. of patients	Range	
Age, years, mean	52.14	5-79	56.19	18-86	-
Gender					
Male	16		28		0.696
Female	27		40		
Duration of chief complaint	-		-		0.002
<1 month	22		15		
1 month to 3 months	11		13		
≥ 3 months	8		34		
Temperature on admission, ºC, mean	37.9	36.5-40.0	36.9	36.0-39.1	-
≥ 37.8ºC	22		5		<0.001
Post-antibiotic treatment	18		14		0.019
Hematologic malignancy	18		4		<0.001
Chemotherapy	13		3		<0.001
Neutropenia	13		0		<0.001
Corticosteroid treatment	7		5		0.209
Mortality	19		2		<0.001

patients' characteristics are shown in Table 1. The clinical manifestations of fungal rhinosinusitis, which included nasal stuffiness (27.9%), nasal discharge (27.9%), facial pain (27.9%), fever (24.3%), and headache (19.8%), are listed in Table 2. Fever and proptosis were found significantly more often in invasive fungal rhinosinusitis.

Underlying predisposing condition

Diabetic mellitus was the most common underlying disease, found in 33 (29.7%) patients. Other underlying diseases included hematological malignancy (22 cases, 19.8%), nasal polyps (14 cases, 12.6%), solid tumors (7 cases, 6.3%) and systemic lupus erythematosus (4 cases, 3.6%) (Table 3).

Neutropenia (defined as an absolute neutrophil count in peripheral blood <1,000 cells/mm^3) was found in 30.2% of patients with invasive fungal rhinosinusitis. Another factor in the occurrence of invasive fungal rhinosinusitis was immunosuppression due to chemotherapy, found in 30.2%. Seven cases (16%) of invasive fungal rhinosinusitis were on long-term corticosteroids. Eighteen cases had a history of taken broad-spectrum antibiotics for acute rhinosinusitis. Associated bacterial infection found on hemoculture with *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and methicillin-resistant *Staphylococcus aureus* (MRSA) were found in 6, 2 and 1 cases, respectively.

Mycology

Many different species of fungi cause fungal rhinosinusitis. It is important to note

Table 2
Clinical presentations in 111 patients with invasive and non-invasive fungal rhinosinusitis.

Symptoms	Invasive fungal rhinosinusitis[a] (*n* = 43)		Non-invasive fungal rhinosinusitis[a] (*n* = 68)		*p*-value
	No. of patients	%	No. of patients	%	
Fever	22	51.2	5	7.4	<0.001
Facial pain	14	32.6	17	25.0	0.515
Headache	11	25.6	11	16.2	0.329
Nasal stuffiness	10	23.3	21	30.9	0.393
Nasal discharge	7	16.3	24	35.3	0.031
Blurred vision	7	16.3	6	8.8	0.364
Face swelling	7	16.3	4	5.9	0.105
Proptosis	7	16.3	3	4.4	0.048
Productive sputum	5	11.6	16	23.5	0.139
Periorbital pain	5	11.6	5	7.4	0.509
Bloody sputum	4	9.3	5	7.4	0.735
Cough	3	7.0	8	11.8	0.523
Numbness	3	7.0	2	2.9	0.375
Hearing loss	2	4.7	2	2.9	0.643
Halitosis	1	2.3	8	11.8	0.087
Epistaxis	1	2.3	7	10.3	0.146
Post-nasal drip	1	2.3	5	7.4	0.401
Chemosis	1	2.3	2	2.9	1.000
Incidental finding	1	2.3	10	14.7	0.048

[a] The patient may have one or more symptoms.

that hyphal organisms are responsible for the vast majority of cases. Cultures were positive for fungal organisms in 37 out of 87 cases (42.5%). The common fungal organisms isolated were: *Aspergillus fumigatus* (14 cases), *Aspergillus flavus* (9 cases), *Aspergillus niger* (1 case), and *Aspergillus* spp (5 cases) were implicated as causative agents. Other causes included *Candida albicans* (6 cases), *Candida tropicalis* (2 cases), *Candida krusei* (1 case), *Rhizopus* spp (1 case), *Pseudallescheria boydii* (1 case), and *Curvularia* spp (1 case). The details of the mycologic characteristics are presented in Table 4. Positive fungal culture occurred more often in invasive fungal rhinosinusitis than in non-invasive fungal rhinosinusitis.

Treatment

All cases of invasive fungal rhinosinusitis received both surgical and medical treatments. Twenty-seven patients received intravenous amphotericin B as soon as the diagnosis of invasive fungal rhinosinusitis was established. Ten and 6 patients were treated with itraconazole, and voriconazole, respectively. Treatment success was seen in 24 patients; the fungus-attributable mortality rate was 44.2%. Most patients died due to extensive fungal infection involving multiple organs, especially pulmonary infection causing respiratory distress and pulmonary hemorrhage. Direct invasion of adjacent vital organs, such as cerebral involvement, was also noted.

Table 3
Underlying predisposing conditions in 111 patients with invasive and non-invasive fungal rhinosinusitis.

Underlying diseases	Invasive fungal rhinosinusitis[a] (n = 43)		Non-invasive fungal rhinosinusitis[a] (n = 68)		p-value
	No. of patients	%	No. of patients	%	
Diabetes mellitus	13	30.2	20	29.4	1.000
Myeloproliferative disorders	11	25.6	3	4.4	0.002
Lymphoproliferative disorders	7	16.3	1	1.5	0.005
Other hematologic diseases[b]	3	7.0	1	1.5	0.297
Solid tumor	3	7.0	4	5.9	1.000
Nasal polyp	3	7.0	11	16.2	0.240
Systemic lupus erythematosus	2	4.7	2	2.9	0.640
Nutrition deficiency	2	4.7	1	1.5	0.558
End state renal disease	1	2.3	3	4.4	1.000
Allergic rhinitis	1	2.3	5	7.4	0.402
Rheumatoid arthritis	1	2.3	0	0	0.387

[a] The patients may have one or more underlying diseases.
[b] Including aplastic anemia in 3 cases, and autoimmune hemolytic anemia in 1 case.

DISCUSSION

Invasive fungal rhinosinusitis is a common opportunistic infection in immunosuppressed and debilitated hosts. It is an aggressive, destructive process that is frequently fatal. The overall incidence of invasive fungal rhinosinusitis is increasing due to the increase in immunocompromised patients who are at risk and the increased use of broad-spectrum antibiotics (Singh, 2001). The proportion of invasive fungal rhinosinusitis among fungal rhinosinusitis in the authors' series was unexpectedly high (38.7%), whereas the proportion ranges from 4.3 to 8.3% in the reports from Western countries (Granville *et al*, 2004; Taxy, 2006) and 34% in a report from India (Michael *et al*, 2008). The overall incidence of invasive fungal rhinosinusitis in the autopsy cases is 3.2% (Larbcharoensub *et al*, 2007). These findings and the authors' data suggest invasive fungal rhinosinusitis is not uncommon in developing countries in tropical regions.

An important finding from the data is hematologic malignancy was a major disease associated with invasive fungal rhinosinusitis (41.9%). Other predisposing factors include post-antibiotic treatment (41.9%), neutropenia (30.2%), and post-chemotherapy treatment (30.2%). The authors' findings were concordant with a previous observation regarding the association between invasive fungal rhinosinusitis and hematologic malignancy and neutropenia (deShazo *et al*, 1997b). The common clinical manifestation in the present study were nasal stuffiness, nasal discharge and facial pain, followed by fever, headache, productive sputum and blurred vision. The duration of these presenting symptoms was highly variable ranging from days to years. However, 11 cases were incidentally detected with

Table 4
Fungal organisms in the 87 patients with mycologic culture in invasive and non-invasive fungal rhinosinusitis.

Fungal species	Invasive fungal rhinosinusitis[a]	Non-invasive fungal rhinosinusitis[a]	*p*-value
Positive fungal culture	21	16	0.007
Aspergillus fumigatus	9	5	0.044
Aspergillus flavus	5	4	0.305
Aspergillus niger	0	1	1.000
Aspergillus spp	3	2	0.374
Candida albicans	2	4	1.000
Candida tropicalis	1	1	1.000
Candida krusei	1	0	0.387
Rhizopus spp	1	0	0.387
Pseudallescheria boydii	1	0	0.387
Curvularia spp	0	1	1.000
Hyaline fungi	1	1	1.000

[a] The patients may have one or more fungal species.

radiography, one of them was invasive fungal rhinosinusitis. Hence, the diagnosis of fungal rhinosinusitis cannot be made clinically. A high index of suspicion is therefore very essential, especially in immune depressed patients.

In the present study, the predominant laboratory finding was the presence of acute angle dichotomous branching narrow septate hyphae, morphologically consistent with *Aspergillus* spp. The species which accounted for the majority of culture-positive cases was *Aspergillus fumigatus*. *Aspergillus* spp typically cause fungal rhinosinusitis and can directly invade the skull and the central nervous system. However, some fungi, such as *Pseudallescheria boydii*, are indistinguishable morphologically from *Aspergillus* spp, therefore culture is required for a definite identification. This is an important distinction because the choice of antifungal agents is guided in part by the fungal species identified.

Candida spp are commensal of the oropharyngeal mucosa. Invasive candidiasis needs overgrowth of a mucosal surface and translocation occurs by hematogenous route. *Candida albicans* is the most common fungi, accounting for 66.7% of yeasts isolated from patients with sinonasal candidiasis. However, *Candida albicans* can be found in 53.4% of oral mucosal swabs taken from middle-aged and elderly subjects (Zaremba *et al*, 2006). Only clinical and radiologic correlations, and repeated tissue cultures yielding heavy growth of these fungi suggest a true *Candida* spp-associated invasive fungal rhinosinusitis.

Mucormycosis is commonly seen in acidotic individuals, particularly those with uncontrolled diabetes mellitus, but it also occurs in neutropenic patients. The clinical presentation of rhinofacial mucormycosis includes headache, sinonasal congestion, pain, and serosanguinous nasal discharge. *Mucor* spp typically have right

angle branching, broad, non-septate hyphae and often spread into the surrounding tissue resulting in a black necrotic lesion. Nasal septum or palatal perforation is frequent. Periorbital swelling, ptosis, proptosis, and cranial nerve involvement may occur. Orbital infection may spread into the brain leading to frontal lobe necrosis and abscess formation. The patients' data support the fact that *Mucor*-associated invasive fungal rhinosinusitis is more likely to show orbital and neurological symptoms at presentation and long-term morbidity and mortality than *Aspergillus* spp associated invasive fungal rhinosinusitis (Ingley *et al*, 2008).

Recent technology has not improved the overall accuracy of diagnosis of invasive fungal rhinosinusitis. Therefore, histopathology and culture of specimens remain the gold standard of diagnosis and may reveal major unexpected findings that are of clinical importance. There is evidence suggesting histopathology of invasive fungal rhinosinusitis is one of the most powerful predictors of clinical outcome and one of the most influential factors used to determine treatment of fungal rhinosinusitis (Leopairut *et al*, 1992). However, a superficial sinonasal biopsy cannot determine the invasiveness of fungal infection. In the present study, there were 21 patients (48.8%) who were histologically unable to be diagnosed with invasive fungal infection on first biopsy. Follow-up endoscopic examination with biopsy and/or resection of the sinus were mandatory to determine invasion with fungi. This may reflect an increased difficulty in making a diagnosis, especially with a limited sinonasal biopsy. A frozen section for evaluating invasion should be performed in suspected cases of invasive fungal rhinosinusitis (Ghadiali *et al*, 2007; Taxy *et al*, 2009). Computed tomography or magnetic resonance imaging is very helpful in assessing the extent of rhinosinusitis. Therefore, a correlation of all factors, including clinical, radiologic, and pathologic, is most important in detecting invasive fungal rhinosinusitis and determining of treatment.

The clinical outcome of invasive fungal rhinosinusitis depends on prompt awareness of the diagnosis and early effective treatment (DelGaudio and Clemson, 2009). Surgical debridement and surveillance remains the cornerstone of treatment in invasive fungal rhinosinusitis. Subsequent antifungal agents are based on the results of histopathology and mycology. Liposomal amphotericin B is the agent typically initiated (Sungkanuparph *et al*, 2001; Roongrotwattanasiri *et al*, 2007). Itraconazole or voriconazole are indicated for initial treatment of invasive *Candida* spp or *Aspergillus* spp-associated invasive fungal rhinosinusitis, but are of no value for *Mucor* spp-associated fungal rhinosinusitis (Bennett, 2005). The duration of therapy depends on the location of residual disease, the possible reversal of any underlying sources of immunosuppression, and the response to treatment. Recurrence is not uncommon, despite systemic antifungal treatment following surgical debridement.

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