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CHRONIC INVASIVE ASPERGILLOSIS OF THE PARANASAL SINUSES IN IMMUNOCOMPETENT HOSTS FROM SAUDI ARABIA

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Abstract. In immunocompetent patients, paranasal invasive aspergillosis is rare and has a high recurrence rate. Twenty-three cases of paranasal invasive aspergillosis, involving 14 male and nine female immunocompetent patients were reviewed. All patients were cancer-free, HIV-negative, with normal WBC, and none of the patients had received immunosuppressive therapy or corticosteroids. Mean duration of symptoms before diagnosis was 18 months. *Aspergillus flavus* was the species most frequently isolated. Surgical debridement was performed in all patients followed by antifungal therapy in 18 patients. Mean follow-up duration was 30 months. Fourteen patients relapsed after a mean of 13 months and required an average of 4.3 admissions for repeat surgical evacuation. In a logistic regression model, relapse was not associated with age, duration of symptoms, clinical findings, extent of disease, or mode of therapy. However, patients who were relapse-free tended to have had complete surgical evacuation followed by antifungal therapy.

INTRODUCTION

Invasive aspergillosis has been increasing over the last several years[1,2] and has been associated with an increase in the number of patients with some form of immunodeficiency.[3] However, several reports have described invasive aspergillosis in patients who had no obvious immunocompromise including patients who had disseminated aspergillosis, pulmonary aspergillosis, or invasive aspergillosis of the paranasal sinuses.[4–11] The spectrum of fungal diseases of the paranasal sinuses ranges from allergic sinusitis to acute invasive disease. Case reports and series have not always provided sufficient details necessary to distinguish various forms of fungal sinusitis. These reports used variable definitions, had small numbers, incomplete clinical descriptions, and short-term follow-up.[12] For these reasons, attempts were made to classify fungal disease of the paranasal sinuses.[13–17]

Invasive aspergillosis of the paranasal sinuses was reported in immunocompetent hosts for the first time by Milosev and others in 1966.[18] Since then, this condition was reported mainly from the Sudan but also from other tropical areas, including the Indian subcontinent.[10,19–23] Therapy for chronic invasive *Aspergillus* sinusitis includes surgical evacuation and antifungal chemotherapy. Nevertheless, outcome is poor and the disease frequently relapses.[12,24–26] Risk factors for relapse in spite of complete surgical evacuation have not been previously evaluated.

We have reviewed our experience with chronic invasive *Aspergillus* sinusitis in apparently immunocompetent hosts, aiming to identify risk factors associated with relapses after primary surgical evacuation. Our database represents the largest clinical series of a fairly homogenous group, as we adopted newly proposed classifications of invasive fungal sinusitis.

PATIENTS AND METHODS

Patient selection. Cases (N = 43) involving positive isolates of *Aspergillus* from paranasal sinus material between 1991 and 1997 at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) were reviewed retrospectively. Histopathology findings of paranasal sinus material were also reviewed for invasive fungal elements. In defining invasive fungal disease of the paranasal sinuses, criteria suggested by Denning[3] and DeShazo and others[13,14] were used.

We identified patients who had invasive fungal elements, with paranasal sinus surgical specimens that grew *Aspergillus* and had histopathology showing fungi breaching mucosal barriers and causing tissue necrosis. Patients were included only if they had no documented evidence of compromised immunity. Patients were presumed to be immunocompetent if they had not received chemotherapy, steroids, or other immunosuppressive agents, and if they had not received a diagnosis of cancer, chronic liver disease, end-stage renal failure, diabetes mellitus, HIV infection, or congenital immunodeficiency before the isolation of *Aspergillus* or during the follow-up period. Additional tests were performed on some patients, including lymphocyte subset count, respiratory burst activity, chemotaxis of polymorphonuclear cells, nitroblue tetrazolium dye reduction test for polymorphonuclear cell function, and quantitation of immunoglobulin levels. If the results of any of these or other immune function tests were abnormal, patients were excluded.

Demographic data including age, sex, and place of origin were collected on all patients. Data concerning clinical presentation, medical history, physical, radiological findings, and therapies were collected on all patients from initial and follow-up visits. Patients who had at least one episode of culture-proven relapse were compared to relapse-free patients to identify relapse risk factors.

Mycology. Tissue material from paranasal sinuses was plated onto Sabouraud dextrose agar plates with and without cycloheximide (Saudi Prepared Media Laboratory, Riyadh, Saudi Arabia). Plates were incubated at 30°C for four weeks. Czapek Dox agar (Remel Inc., Lenexa, KS) was used to observe pigmentation.

Data collection and analysis. Epi Info Version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA, and World Health Organization, Geneva) was used for data collection. Statistical analysis was performed using Statistica Software package Version 5.0 (StatSoft, Tulsa, OK). The Student's *t* test was used to calculate continuous variables, and the χ^2 or Fisher's exact test was used for proportions.

TABLE 1
Summary of patient characteristics and clinical and radiological findings

Characteristic		No. of Patients (%) no. (%)
Gender	Male	14 (61)
Geographic origin in Saudi Arabia	Southwest	15 (65)
	East	5 (22)
	Central/North	3 (13)
Clinical findings	Nasal blockage	20 (87)
	Proptosis	16 (69)
	Nasal discharge	14 (61)
	Headache	11 (48)
Radiological findings	Bone erosion	14 (61)
	Pansinusitis	14 (61)
	Intraorbital extension	13 (57)
	Intracranial extension	8 (35)

All reported P values are two-tailed and a value of ≤ 0.05 was considered significant.

RESULTS

Thirty-eight patients had histopathological evidence of invasive fungal disease in the paranasal sinuses. Twenty-three patients met the study criteria. Nine patients were excluded because they had neutropenia related to hematological malignancy and chemotherapy, and six patients were excluded because *Aspergillus* was not isolated.

Table 1 summarizes patient demographics and clinical findings. The mean age was 25 years (median, 20; range, 9–61 years). The mean duration of symptoms before diagnosis was 18 months (median, 16; range, 2–46 months). Fifteen patients (65%) came from southwest Saudi Arabia. All patients had normal WBC count and differential and had normal renal and hepatic profiles. No patient had fever. Four patients had diabetes that was controlled by diet only.

On histopathological examination, granulomata in paranasal sinus material were noted in six patients. Radiologically, opacification of all sinuses was noted in 14 patients (61%). The ethmoid sinus was the sinus most frequently affected, and was spared only in two patients. By comparison, maxillary sinuses were spared in four patients, while frontal and sphenoid sinuses were spared in five patients each. Fifteen patients had bilateral involvement.

The *Aspergillus* species was identified as *A. flavus* in 15 cases and as *A. fumigatus* in two cases. In the remaining six cases, species identification was not attempted. Surgical evacuation was performed on all patients. Complete evacuation was achieved in ten patients, partial in 13 patients. No preoperative antifungal therapy was given because diagnosis was not available. Five patients did not receive postoperative antifungal therapy; all five relapsed. Table 2 summarizes the type of antifungal therapy given postoperatively and the number of patients who relapsed. There was no significant difference in relapse rates between the various groups. Five patients developed renal impairment on amphotericin B and were switched to liposomal amphotericin B.

Relapse was noted in 14 patients (61%) who required multiple admissions, with a per-patient average of 4.3 admissions (range, 2–9 admissions). The first relapse after surgery occurred after a mean of 13 months (median, 6 months; range, 2–62 months). Repeated surgical evacuation was required in those patients, three times on average (range, 1–7 times). Nine patients (39%) were relapse-free and considered cured.

TABLE 2
Relapse rates of patients receiving antifungal therapy

Therapy	Total Number N = 23	Relapse N = 14 (%)
No antifungal therapy	5	5 (100)
Itraconazole alone	4	2 (50)
Amphotericin B alone	3	1 (33)
Amphotericin B followed by itraconazole	6	3 (50)
Amphotericin B followed by liposomal amphotericin B then itraconazole	5	3 (60)

Complete surgical evacuation followed by amphotericin B therapy was performed on seven patients. Three other patients had complete surgical drainage without chemotherapy. Relapse was noted in four of ten patients (40%) who had complete evacuation, compared to ten of 13 (77%) who had partial evacuation (Fisher's exact test, $P = 0.1$). In a logistic regression model, risk factors associated with relapse were evaluated. There was no association between relapse and age, sex, geographic origin, duration of symptoms, clinical or radiological findings, extent of disease, or therapy offered. Table 3 compares patients who were cured with patients who had relapse. No patient relapsed while receiving antifungal therapy.

Mean duration of follow-up was 30 months (median, 21; range, 1–103 months). Two patients experienced loss of vision. One patient was lost to follow-up and one patient died from complications of ischemic heart disease.

DISCUSSION

This is the largest clinical series of a fairly homogeneous group of patients from a single institution using recently-published classification of fungal sinusitis.[3,13,14] Cases of *Aspergillus* invasive disease of the paranasal sinuses in immunocompetent patients have frequently been reported from the Sudan, the Indian subcontinent, and other tropical areas. The syndrome has also been noted in Saudi Arabia.[26–30] Our center receives cases referred from all over the country. Most cases in this series came from the southwestern region of Saudi Arabia. The geography and climate in this area are similar to that of the Sudan. However, these data should not

TABLE 3
Comparison of relapsing and non-relapsing patients

Characteristic	Relapse Groups (N = 14)	Relapse-free Group (N = 9)
Mean age (SE), yr	21 (2.8)	31 (5.9)
Complete evacuation, no. (%)	4 (29%)	6 (67%)
Mean duration of symptoms before diagnosis (SE), mo.	19 (11.7)	17 (10.6)
Mean total amphotericin-B dose (SE), mg	4,300 (538)	4,200 (170)
Mean duration of follow-up (SE), mo	32 (7.6)	29 (6.2)

SE = standard error.

be considered reflective of true prevalence rates, due to the possibility of referral bias.

The relapsing nature of invasive aspergillosis of the paranasal sinuses has been described previously.[12,24–26] The current report also identified the frequency of relapse after surgical evacuation and the mean time to the first relapse after first surgery. However, none of the evaluated variables was identified as a statistically significant risk factor predisposing to relapse. Factors investigated included duration of symptoms before diagnosis, extent of disease involvement, age, gender, geographic origin of the patient, and mode of treatment. The small number of cases may not be enough to evaluate the difference statistically. Nevertheless, the combination of complete surgical evacuation and amphotericin B therapy post-surgery produced a trend towards fewer relapses and longer intervals between relapses. The role of complete surgical evacuation in reducing relapse was also noted previously, with the observation that 62% of patients treated by complete surgical resection either were cured or had stable disease compared to 31% of patients with incomplete resection.[12]

Clancy and Nguyen[12] reviewed the literature for reports of invasive aspergillosis of the paranasal sinuses in apparently immunocompetent patients between 1987 and 1998. Their review identified 13 reports describing 29 patients, including three from their own institutions. The majority of cases identified were patients from the Sudan or Saudi Arabia who were infected with *A. flavus.* The delay in diagnosis was a peculiar finding, with a mean delay of 24 months. Similarly, in our patients the mean duration of symptoms before diagnosing *Aspergillus* paranasal sinus disease was 18 months. In their review of the literature, Clancy and Nguyen observed a 31% mortality rate with cure in only 24%.[12] However, this high mortality rate and low cure rate may be due to bias related to reporting of individual cases in the various reports reviewed.

The clinical findings in our patients were different from those previously reported. The most common presenting symptom was nasal obstruction, which was noted in 87% of our patients compared to 45% described previously.[12] Proptosis was the second most common finding in our patients and in the patients described by Clancy and Nguyen, occurring in 69% and 52% of patients, respectively.[12] Proptosis is a well-known complication of fungal sinusitis[31–33] and can be the presenting symptom.[34] Abnormalities of paranasal sinuses were noted on CT scan in all patients: all sinuses were involved in 61% of our patients as well as in 61% of patients described earlier.[12] In our patients the ethmoid sinus was the most frequently involved, affecting 91% of our patients, followed by the maxillary sinus in 83%, and sphenoid or frontal sinuses, each affecting 78%. Clancy and Nguyen[12] found the maxillary and frontal sinuses less frequently affected, affecting 48% and 10% of patients, respectively. In general, our patients had less extensive disease than those reported previously.[12] Sixty-one percent of our patients had extension beyond the sinus walls and nasal cavity, compared to 90% of patients described by Clancy and Nguyen.[12] In contrast to these earlier reports, none of our patients died. The potential bias of reporting more severe cases in the review of Clancy and Nguyen[12] may have influenced the reported disease severity and outcome.

The optimal treatment of invasive *Aspergillus* sinus disease in immunocompetent patients is not known. Our results make clear that complete surgical evacuation is important. Partial, subtotal, staged, or repeated debridement combined with antifungal treatment was associated with high failure rates.[12,21,24,26,35] There was a tendency for lower relapse rate (40%) in patients who had complete surgical evacuation compared to patients receiving incomplete evacuation (77%).

The role of antifungal chemotherapy is not well established. As an adjuvant to surgery, antifungal agents may reduce the chance of recurrence. However, it has not been determined which antifungal agent is most effective, or what the optimal duration of therapy should be. Amphotericin B or one of its lipid formulations may be needed for some undefined period after surgery. Amphotericin B lipid formulation has been successful in invasive *Aspergillus* sinusitis where therapy with conventional amphotericin B has failed.[36]

As an adjunct to surgery, long-term itraconazole therapy has been reported to reduce relapse.[24,37] Itraconazole has the advantage of oral administration and it is safe. A dose of 200–400 mg daily, accompanied by measurement of blood levels, might be sufficient.

Invasive sinus aspergillosis in non-immunocompromised hosts is rare and has primarily been reported in tropical and subtropical areas. *Aspergillus flavus* seems to be the most common causative species. Diagnosis may be delayed because symptoms are indistinguishable from those of bacterial or viral causes, the syndrome is rare, and imaging studies at disease onset are often uninformative. Unidentified, the condition may become complicated, with extension to the orbit, the cranium, and cerebral tissue. Prompt recognition of the disease is very important for effective therapy. Radiological imaging is essential to determine the degree of extension. Complete surgical evacuation followed by antifungal therapy for a few months should be considered to reduce relapse rates.

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