FUNGAL INFECTION OF THE NASAL CAVITY AND PARANASAL SINUSES: REVIEW OF 26 CASES

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Fungal infection of the nose and sinuses is an uncommon condition which is now being increasingly recognized. In this study, we review clinicopathologic features in a series of 26 cases encountered at King Faisal Specialist Hospital and Research Centre over a five-year period. The cases were divided into four categories according to the following histopathologic features: allergic fungal sinusitis (11 cases), aspergilloma (one case), chronic indolent fungal sinusitis (five cases), and acute fulminant fungal sinusitis (nine cases). In the cases of allergic fungal sinusitis and aspergilloma, the fungal hyphae were limited to the sinus cavity without any evidence of invasion. Invasion in the wall of the sinus, as well as the surrounding tissue, was noted in cases of chronic indolent fungal sinusitis and acute fulminant fungal sinusitis. All patients were treated surgically and those cases with evidence of tissue invasion on pathologic or radiologic examination were given antifungal therapy. The prognosis was excellent in the cases of allergic fungal sinusitis and aspergilloma. Most of the patients with acute fulminant fungal sinusitis died of uncontrolled fungus growth. In the cases of chronic indolent fungal sinusitis, all patients are still alive, but two patients had loss of vision due to fungal invasion. Fungal sinusitis with absence of tissue invasion is easily treated by surgery alone. However, in cases with tissue invasion, a combination of surgery with antifungal therapy may be successful. Acute fulminant fungal sinusitis, however, has a grave prognosis. *Ann Saudi Med 1996;16(6):615-621.*

Fungal infection of the paranasal sinuses is an increasingly recognized entity, both in normal and immunocompromised individuals. *Aspergillus* species are the most common causative agents of fungal sinusitis.[1-3] Other fungi which are implicated in causing fungal sinusitis are the mucormycoses.

The pattern of fungal infection of the sinuses has been traditionally divided into invasive and noninvasive, based on the presence of fungal hyphae in the tissue with associated granulomatous reaction or tissue necrosis. Hartwick and Batsakis (1991) classified sinus aspergillosis into four types: noninvasive extramucosal disease, which includes allergic fungal sinusitis and aspergilloma, and invasive mucosal disease, which includes indolent, chronic sinusitis and fulminant (acute) sinusitis.[4] This classification has provided a useful morphologic basis for diagnosis and has been found to have excellent prognostic and therapeutic correlations.

A few previously published studies from Saudi Arabia have documented the occurrence of fungal infections of the nasal cavity and paranasal sinuses in this region.[5,6] However, studies generally consist of only a few cases. The purpose of this study is to review our experience with this disease in order to highlight its clinicopathologic features and increase awareness among physicians.

Material and Methods

The medical records of all the patients diagnosed histologically to have any type of fungal sinusitis in the period from 1989 to 1995 at King Faisal Specialist Hospital and Research Centre (KSFH&RC) were reviewed. Information regarding age, sex, clinical presentation, radiologic appearance, geographic distribution, type of treatment and follow-up were recorded whenever available. A total of 26 patients were included in this study.

Histologic sections of all the biopsies of the patients included in the study were reviewed. All sections were stained with hematoxylin and eosin (H&E) and Gomori methenamine silver (GMS). Based on the histologic findings, the patients were classified into the four patterns of fungal infections of the nose and paranasal sinuses.[4]

Results

The distribution of cases in the various histologic subgroups was as follows: allergic fungal sinusitis (11),

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aspergilloma (one), indolent chronic sinusitis (five), and fulminant sinusitis (nine).

Pathologic Findings

Microscopic examination of 11 patients with allergic fungal sinusitis showed pale eosinophilic mucoid material in which were found eosinophils, sloughed epithelial cells, cellular debris and Charcot-Leyden crystals. The necrotic cellular debris was frequently arranged in multilayered rows. In all 11 cases of allergic fungal sinusitis, GMS stain showed septate fungal hyphae scattered singly or in small clusters, occurring exclusively within the mucin, and having morphology consistent with *Aspergillus* species. No evidence of tissue invasion was noted in any of these cases. Fungal cultures showed *Aspergillus* species in eight patients, two of which were classifiable as *Aspergillus flavus*. In three patients, the culture failed to grow any fungus.

One patient had pathologic findings of aspergilloma involving a single sinus. It was filled with friable greenish material which contained large numbers of fungal hyphae arranged in concentric growth layers.

In five cases with indolent chronic fungal sinusitis, there was a granulomatous tissue reaction and chronic inflammation with extension of the inflammation into the bone and beyond the bony confines of the sinus. There were Langhans' type giant cells containing fungal hyphae, which were surrounded by epithelioid histiocytes, plasma cells and eosinophils. Focal angioinvasion and tissue necrosis were noted in two cases. The morphology of these fungi was consistent with *Aspergillus* in two of the cases, and mucormycosis in three cases. Fungal cultures were negative in four patients; one patient had growths of *Aspergillus* species.

In the nine patients with acute fulminant sinusitis, there were large numbers of fungal hyphae with pronounced angioinvasion and tissue necrosis. There was little tissue reaction to the extensive invasion by the fungus and no granulomatous reaction was found. The morphology of the causative fungi in all of these cases was consistent with *Aspergillus*. Fungal culture showed *Aspergillus* species in three patients; one of these was *A. flavus*. In six patients, the cultures were negative.

Clinical Findings

The clinical features, including the geographic distribution of all the patients with allergic fungal sinusitis, are summarized in Table 1. The mean age of the patients was 17 years (range 12-27). Four patients had bronchial asthma and all had chronic nasal polyps with several polypectomies before the diagnosis of allergic fungal sinusitis. The clinical presentation of most of the patients was nasal obstruction of the corresponding side, with or without headache and nasal discharge. Four patients (4,7,8,10) complained of decreased visual acuity in the affected side. The duration of symptoms before diagnosis ranged from one month to 36 months, with a mean duration of 12.5 months. Radiographically, most of the patients showed opacification and soft tissue mass involving multiple paranasal sinuses either in one or both sides. Four cases (1,3,4,6) showed destruction and erosion of the bone and three of those (1,3,6) showed radiologic evidence of extension into the anterior cranial fossa. Eight patients were from the Western Provinces of the Kingdom, one was from the Central region, one from the South and the other was from the Eastern Province.

The patient with aspergilloma was a 65-year-old male from the Western Province, who complained of a right-sided headache of eight months' duration. He had no allergic or atopic symptoms. Radiographically, there was a soft tissue mass and opacification of the right sphenoid sinus.

The clinical features, including the geographic distribution of five patients with chronic indolent sinusitis, are summarized in Table 2. The age of the patients ranged from 20 to 64 years, with a mean age of 42 years. All of the patients were females, and three of them had diabetes mellitus. Three patients presented with proptosis, headache, and nasal obstruction. One patient (Table 2, Case 2) had loss of vision in the right eye. The duration of symptoms ranged from one month to 24 months, with a mean duration of seven months. Radiographically, Case 2 showed extensive soft tissue mass involving multiple sinuses with extension into the orbit and the middle cranial fossa. Other patients had opacification of multiple sinuses with bone destruction. The geographic distribution was inconsistent.

The clinical features of the patients with fulminant fungal sinusitis are summarized in Table 3. The mean age of these patients was 23 years (range 4-58 years). Four were male and five were female. All patients had some sort of immunodeficiency, either due to malignancies such as acute myeloid leukemia, chronic lymphocytic leukemia with or without bone marrow transplantation, or to other causes, such as aplastic anemia. The common clinical presentation was fever and painful sinuses or pharyngitis. The mean duration of symptoms was approximately 10 days. Radiographically, opacification and necrosis of multiple sinuses was the most consistent finding. Geographic distribution was inconsistent.

Treatment and Follow-Up

All patients with allergic fungal sinusitis were treated primarily with surgery to provide good drainage and

TABLE 1. *Clinical data of eleven patients with allergic fungal sinusitis.*

Case no.	Age (years) & sex	Clinical presentation	Duration of symptoms (months)	Geographic region	Underlying conditions (e.g., diabetes, immunosuppression, etc.)	Treatment	Clinical status and follow-up period
1	12-male	Headache, periorbital swelling, and nasal obstruction	12	Western Province, Medina	None	SR	ANED 3 months
2	14-male	Left nasal obstruction and proptosis	10	Western Province	Allergic rhinitis and mild bronchial asthma	SR	ANED 10 months
3	18-male	Right nasal obstruction, right nasal discharge	36	Western Province, Medina	None	SR, ATB	ANED 22 months
4	13-female	Left proptosis, loss of visual acuity of left eye	10	Central Area	None	SR, ATB	AWD 36 months
5	13-male	Right nasal obstruction, headache	11	Western Province	Bronchial asthma	SR	ANED 22 months
6	20-male	Right nasal obstruction, right nasal discharge	12	Western Province, Medina	None	SR, ATB	ANED 22 months
7	21-female	Loss of vision of left eye, right nasal obstruction	36	Southern Region	None	SR	ANED 7 months
8	25-female	Loss of visual acuity of left eye	4	Western Province, Medina	Mild bronchial asthma	SR, ATB	AWD 51 months
9	27-female	Headache	8	Western Province	Mild bronchial asthma	SR, ATB	ANED 48 months
10	24-female	Reduced vision of left eye, left nasal obstruction	1	Eastern Province	None	SR, ATB	ANED 4 months
11	18-female	Left nasal discharge, headache	10	Western Province	None	SR	ANED 2 months

ANED=alive with no evidence of disease; AWD=alive with disease; ATB=amphotericin B; SR=surgical resection.

aeration of the involved sinuses. Patients who had severe clinical symptoms or showed radiologic evidence of extension into the orbit or the anterior cranial fossa were treated postoperatively with a short course of amphotericin B. None of the patients was given postoperative steroids. The mean follow-up period of these patients was 20 months (range 2-51). Nine out of 11 (81.7%) were well, with no evidence of recurrence at the last follow-up. One patient (Table 1, Case 6) had recurrence. She was treated again with surgery and amphotericin B, after which she improved and had no further recurrences. The patient with aspergilloma was treated with surgery with evacuation of the sphenoid sinus. Patients with chronic indolent fungal sinusitis were treated with surgical exploration and evacuation, followed by amphotericin B in four out of five patients. At the follow-up period of 15 months (range 9-48), four (80%) were alive with no evidence of recurrence and one (Table 2, Case 5) had recurrence after a follow-up period of nine months. All patients with acute fulminant fungal sinusitis were treated with amphotericin B. At the follow-up period of five weeks (range 2-12), eight patients had died (88.8%), and one (Table 3, Case 9) is alive with no recurrence at the follow-up period of eight weeks.

Discussion

Aspergillus species is the most common fungal infection of the paranasal sinuses.[1] The causative organism is a spore-forming filamentous fungus which occurs as a saprophyte in soil and decaying vegetable matter and is spread by airborne transmission.[5-8] Transmission between humans is unknown.[5] *Aspergillus* is recognized histologically by its septate hyphae, which branch at a 45 ° angle and reproduce as a sexual conidia. The three species which are most commonly implicated in human pathogenicity are *A. fumigatus, A. flavus*, and *A. niger*. In most parts of the world, the organism usually isolated is *A. fumigatus*,[2,9] while in Sudan and southern Saudi Arabia, *A. flavus* is the more commonly isolated organism.[5,10] Another study from western parts of Saudi Arabia showed isolation of *A. fumigatus* in all five patients.[6] In our series, the most commonly isolated species is *A. flavus*.

Many factors have been implicated in the pathogenesis of fungal sinusitis. These may include environmental and host-related factors. Environmental factors which might explain the epidemiology of fungal sinusitis are the agricultural economy, which encourages proliferation of the *Aspergillus* organism, and the warm, moist climate

TABLE 2. *Clinical data of patients with chronic indolent fungal sinusitis.*

Case no.	Age (years) & sex	Clinical presentation	Duration of symptoms (months)	Geographic region	Underlying conditions (e.g., diabetes, immunosuppression, etc.)	Treatment	Clinical status and follow-up period
1	22-female	Bilateral nasal obstruction, bilateral proptosis	24	Eastern Province	None	SR, ATB	ANED 2 months
2	20-female	Left proptosis, loss of vision in right eye	2	Southern Province	None	SR, ATB	ANED 9 months
3	50-female	Swelling of left cheek	2	Western Province	Diabetes	SR	ANED 9 months
4	52-female	Right side headache, right proptosis, loss of vision in right eye	5	Western Province	Diabetes	SR, ATB	ANED 26 months
5	64-female	Fever, orbital cellulitis	1	Central Region	Diabetes	SR, ATB	AWD 9 months

ANED=alive with no evidence of disease; AWD=alive with disease; ATB=amphotericin-B; SR=surgical resection.

TABLE 3. *Clinical data of eleven patients with fulminant fungal sinusitis.*

Case no.	Age (years) & sex	Clinical presentation	Duration of symptoms (months)	Geographic region	Underlying conditions (e.g., diabetes, immunosuppression, etc.)	Treatment	Clinical status and follow-up period
1	58-male	Acute pharyngitis	14	Central Region	CLL	ATB	Died 1 month
2	17-male	Painful sinuses and pulmonary infiltrate	14	Central Region	Aplastic anemia	ATB	Died 2 weeks
3	14-female	Painful sinuses	7	Eastern Province	ALL, post-BMT	ATB	Died 1 month
4	4-female	Fever not responding to antibiotics	7	Central Region	ALL	ATB	Died 3 months
5	13-male	Fever not responding to antibiotics	14	Southern Province	Aplastic anemia, post-BMT	ATB	Died 2 months
6	20-male	Severe pharyngitis	21	Southern Province	Aplastic anemia, post-BMT	ATB	Died 1 month
7	50-female	Pain over maxillary sinus and fever	7	Central Region	Aplastic anemia	ATB	Died 1 month
8	5-female	Painful sinuses and fever	7	Central Region	Fanconi's anemia	ATB	Died 2 months
9	22-female	Sinusitis and fever	10	Central Region	Acute myeloid leukemia	ATB	ANED 1 month

ANED=alive with no evidence of disease; AWD=alive with disease; BMT=bone marrow transplantation; ATB=amphotericin B.

with its attendant high rate of allergic and infectious rhinosinusitis.[2] Genetic predisposition might also play a role in the pathogenesis of this disease. Immunosuppressive conditions such as chemotherapy, immunosuppressive therapy and congenital conditions such as Fanconi's or aplastic anemia might also predispose to fungal sinusitis, as seen on some of our patients with fulminant fungal sinusitis.[2]

There appears to be a clustering of patients with allergic fungal sinusitis in the Western Provinces of Saudi Arabia, especially in Medina, which is an agricultural city. Eight out of 11 patients with allergic fungal sinusitis were from the Western Province, and five of these patients (62.5%) were from Medina.

Allergic *Aspergillus* sinusitis (AAS) was first described as a form of fungal sinusitis by Katzenstein et al. in 1983. They stated that this type of fungal sinusitis showed a strong similarity to allergic bronchopulmonary aspergillosis.[9] Allergic *Aspergillus* sinusitis is considered to be the result of Type I (immunoglobulin) and Type III (immune-complex) hypersensitivity to fungal antigen.[11] Waxman et al. provided serological evidence of immune

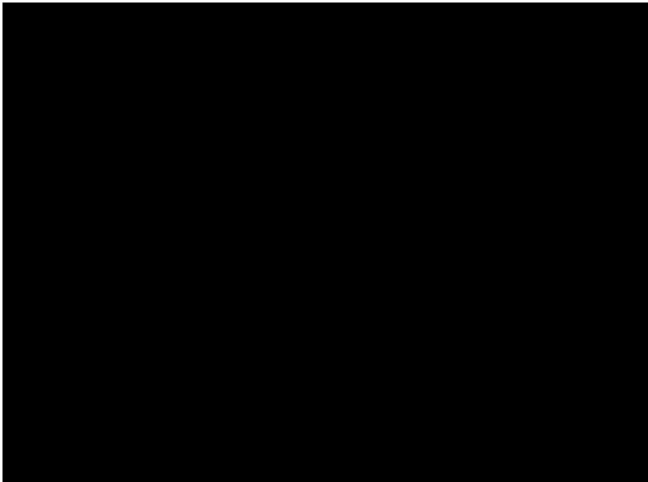

FIGURE 1. "Allergic" mucin showing clusters of darkly stained necrotic eosinophils and Charcot-Leyden crystals (H&E stain).

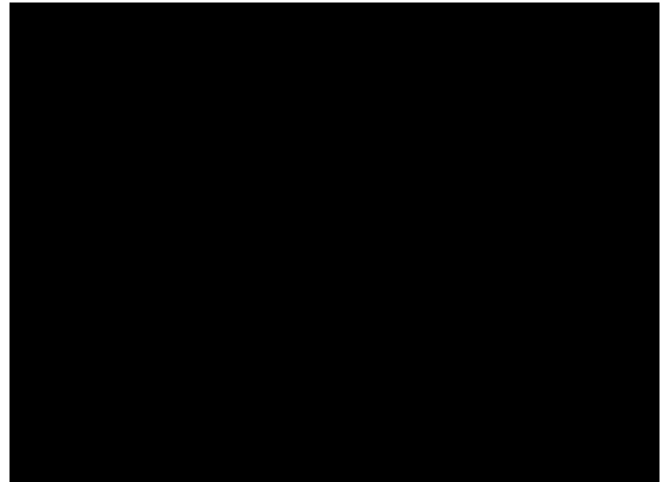

FIGURE 2. Septate fungal hyphae within the allergic mucin (GMS stain).

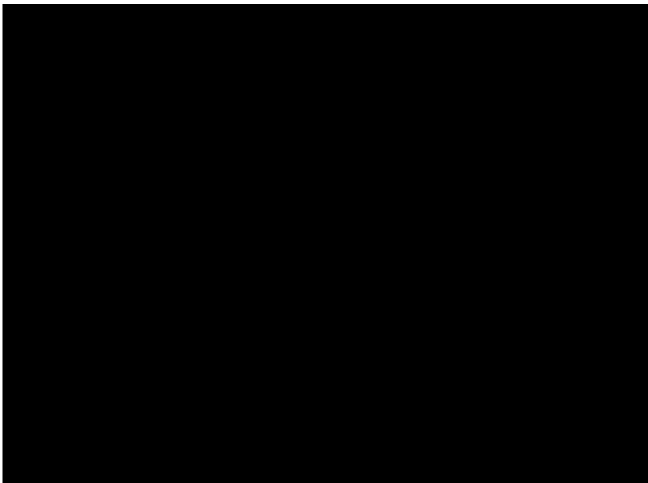

FIGURE 3. Aspergilloma showing numerous entangled septate fungal hyphae (H&E stain).

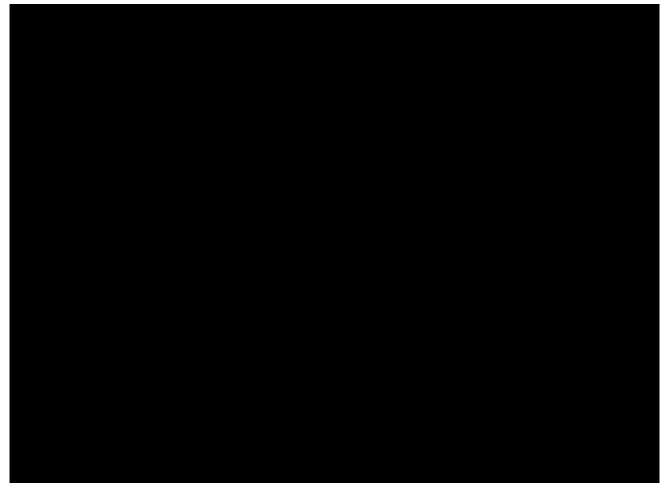

FIGURE 4. Chronic indolent fungal sinusitis, granulomatous reaction and giant cells around fungal hyphae (H&E stain).

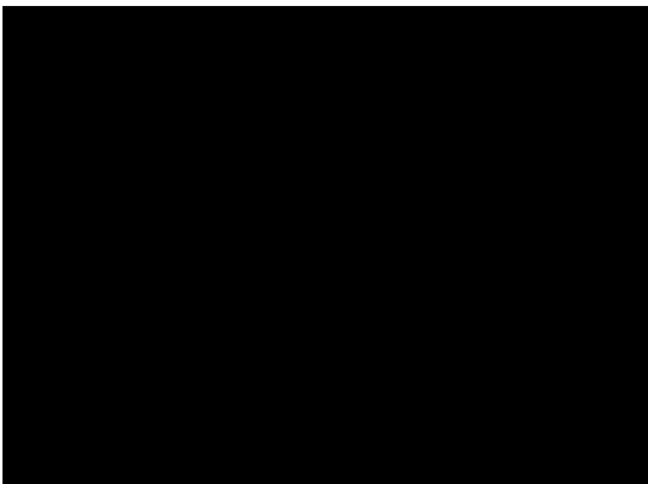

FIGURE 5. Broken fungal hyphae within giant cells (GMS stain).

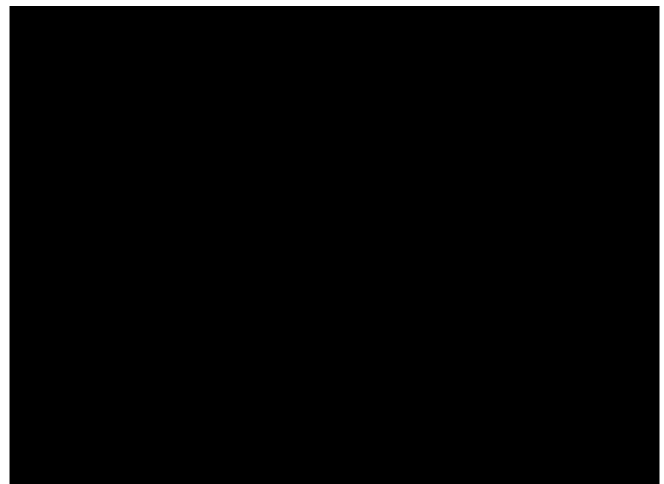

FIGURE 6. Fulminant fungal sinusitis, extensive tissue necrosis and angioinvasion by fungal hyphae (H&E stain).

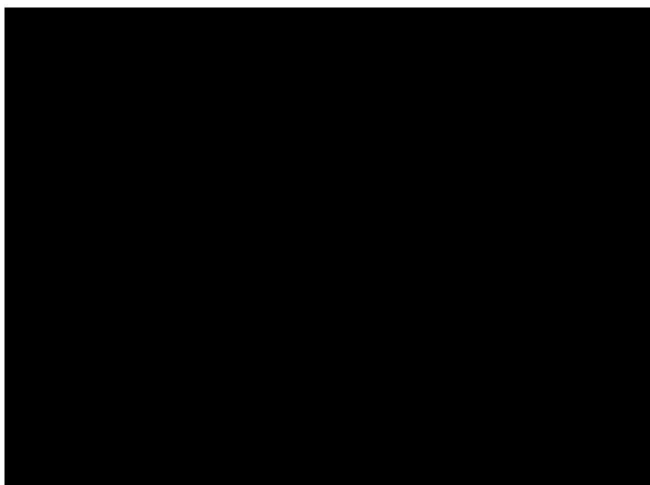

FIGURE 7. Numerous septate fungal hyphae within the tissue and in the blood vessels (GMS stain).

hypersensitivity to *Aspergillus* species as an etiologic factor. They found elevated levels of IgE in six out of 10 patients.[11] The histology is quite characteristic, with typical nasal polyps associated with thick "allergic mucin" which contains sloughed respiratory epithelial cells, chronic inflammatory cells, eosinophils, and Charcot-Leyden crystals. Fungal hyphae are scanty and limited to mucin, and are not easily recognized in H&E stained sections, but can be visualized with methenamine silver stain. Microbiologic culture may be negative in a considerable number of proven cases.[12]

The treatment of AAS is primarily surgical, which secures the drainage and aeration. Topical or systemic corticosteroids are advisable for certain groups of patients. A proportion of these cases, however, may recur within months or years. Three of our patients with allergic *Aspergillus* sinusitis showed radiologic evidence of extensive sinus involvement with orbital or intracranial extension, or showed serious symptoms (such as decreased visual acuity). These patients were treated postoperatively by a short course of amphoteracin-B. Also, those patients who had recurrence of their disease shortly after the first surgical intervention were put on a short course of antifungal chemotherapy, which gave good results in both circumstances. One patient (Table 1, Case 4), despite aggressive surgical intervention and postsurgical antifungal chemotherapy, had a recurrence of the disease after long-term follow-up (36 months). Postoperative systemic steroids and long-term topical steroids have also been used in the treatment of allergic *Aspergillus* sinusitis.[11,13,14]

Chronic indolent fungal sinusitis occurs in normal immunocompetent patients or in patients with altered immune response, such as diabetes mellitus, burns, trauma, and steroid therapy,[1,14] and was first described by Hora in 1965.[15] It is mostly invasive, and characterized histologically by a chronic granulomatous inflammation surrounding broken fungal hyphae. This type of fungal sinusitis extends beyond the bony confines of the sinuses to the orbit or even to the anterior cranial fossa.[4] Therefore, clinically it may mimic malignant neoplasm, Wagener's granulomatosis, osteomyelitis, tuberculosis and rhinoscleroma. The most logical approach to the management of these patients seems to be a combination of radical local surgery and antifungal chemotherapeutic agents.[5,16,17] However, some authors doubt the effectiveness of antifungal chemotherapy.[18] Four of our five patients with chronic indolent fungal sinusitis were treated by surgery followed by systemic antifungal therapy. At the mean follow-up period of 16 months,three of the patients were alive with no evidence of disease and one had recurrence, radiologically and clinically. One patient (Table 2, Case 3) was treated with surgery alone and he is well with no recurrence nine months after diagnosis.

Acute fulminant fungal sinusitis was first described by McGill et al. in 1980.[19] After that report, not much has been written about it in the literature. Fulminant aspergillosis in the paranasal sinuses represents an important cause of morbidity and mortality in patients whose host defense has been altered by primary disease or immunosuppressive therapy. Clinical manifestations include a rapidly progressive gangrenous necrosis of the mucoperiosteum advancing relentlessly to early destruction of the bony walls of the nose and paranasal sinuses.[19] Characteristically, the earliest lesion indicating involvement of the nose and sinuses is crusting of the anterior end of the inferior turbinate or adjacent part of the cartilaginous septum. This lesion may progress within days to involve the adjacent sinus wall or extend to the orbit and anterior cranial fossa, either by direct extension or along vascular channels, resulting in a fatal outcome.[19] The rapid progressive course of fulminant aspergillosis contrasts sharply with the chronic indolent fungal sinusitis. Control of fulminant fungal sinusitis requires early recognition, aggressive surgery, systemic antifungal therapy and correction of the immunological deficits.[19] All of our patients had a rapid clinical course and all but one died within one month of the diagnosis of fulminant *Aspergillus* sinusitis.

Although each type of fungal sinusitis discussed above represents a fairly distinct clinical entity, progression of allergic fungal sinusitis to the chronic indolent form might occur in long-standing, untreated cases. This view was supported by several authors.[4,20] Hartwick and Batsakis revealed that 28% of patients with AAS have radiographic evidence of bone erosion and sinus expansion. Two of our patients (Cases 1 and 4) with chronic indolent fungal sinusitis showed, in addition to the granulomatous inflammation, the typical allergic mucin-containing fungal hyphae, suggesting progression of allergic fungal sinusitis

to the chronic indolent form. Therefore, early diagnosis and recognition of allergic fungal sinusitis is very important, not only because it is curable in the early stages, but also to prevent progression of the disease into the more serious and destructive invasive forms.

Our recommendation to clinicians working in areas of high prevalence of allergic fungal sinusitis such as Saudi Arabia is that any sinus contents as well as polyps from all patients with a history of repeated polypectomies should be sent for histopathologic examination, and that the pathologist should examine the polypectomies and sinus contents very carefully, looking for the allergic mucin. Whenever there is allergic mucin, GMS must be done to rule out the presence of fungal hyphae.

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