Chapter 8
Fungus in Sinus Disease

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Introduction

Fungal rhinosinusitis appears to be more common than in decades past. This apparent increase may be due to greater awareness among healthcare practitioners, an excessive use of antibiotics for upper respiratory symptoms, and a greater population of immunocompromised individuals. Many aspects of fungal rhinosinusitis remain poorly understood, and diagnostic distinction between fungal rhinosinusitis and other forms of rhinosinusitis can be a challenge. However, a revised nomenclature and a clearer understanding of the risk factors, natural history, and prognosis of fungal sinus disease have simplified the diagnosis and treatment approach. The aim of this chapter is to give an overview of the diagnosis and treatment of fungal disease in the sinuses.

Classification of Fungal Sinus Disease

Fungal disease was reported as early as 1791 by Plaignaud. Since that time descriptions of fungal disease focused on the causative organism, leading to terms such as "aspergillosis," "mucormycosis," and "zygomycosis." *Aspergillus* is the most common organism to cause fungal sinusitis. However, it is now clear that aside from selecting an appropriate antifungal agent, the particular organism involved is not salient in the diagnosis or classification of fungal rhinosinusitis. As a result, terms such as "mucormycosis" are not recommended for describing fungal sinus disease.

In 1965 Hora [1] described the clinical and histopathological distinction between invasive and noninvasive fungal infections of the sinuses, highlighting for the first time the importance of differentiating invasion as an indicator of prognosis and need for emergent treatment. We now recognize tissue invasion to be one of the most important factors for determining the appropriate treatment for fungal rhinosinusitis. The host's immunologic response to the fungus is an additional factor in determining the manifestation of fungal rhinosinusitis in a particular patient. Katzenstein et al. [2] described "allergic *Aspergillus* sinusitis," a clinical presentation of fungal disease characterized by type 1 hypersensitivity, polypoid rhinosinusitis, and sinus mucus that resembled the bronchial aspirates of patients with allergic bronchopulmonary aspergillosis (ABPA).

Fungal disease of the sinuses has been classified into five distinct categories [3]. The forms of noninvasive fungal disease are *saprophytic colonization*, *fungus ball*, and *allergic fungal rhinosinusitis* (AFRS). Saprophytic colonization with the growth of fungus on dried mucus secretions is usually asymptomatic, and the condition is detected as an incidental finding.

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Hence, it is not usually considered in the classification of fungal rhinosinusitis. A fungus ball is a collection of dense debris usually found in a single sinus. Histologically, a fungus ball is noninvasive and appears under the microscope as a collection of fungal hyphae. In comparison, allergic fungal rhinosinusitis (AFRS) usually occurs in atopic patients and involves multiple sinuses, and multiple sinuses contain mucus that is filled with eosinophils and fungal elements. Invasive fungal rhinosinusitis can be divided into acute and chronic forms. Acute invasive fungal rhinosinusitis (AIFRS) usually occurs in the immunocompromised host and is associated with rapid progression and poor prognosis. Chronic invasive fungal rhinosinusitis (CIFRS) on the other hand usually occurs in the immune-competent patient. As its name suggests, the clinical course is less aggressive. CIFRS has been further divided into a granulomatous and nongranulomatous form, although they both seem to follow the same clinical course [4].

Fungal rhinosinusitis is relatively uncommon, with a majority of cases being noninvasive. Studies have shown up to 7 % [5] of chronic rhinosinusitis cases taken to surgery have a noninvasive fungal pathology. In comparison, invasive forms of fungal rhinosinusitis are rarer. AIFRS is largely a disease of the immunocompromised and has classically been described in immunocompromised patients with neutropenia or diabetic ketoacidosis. The annual incidence in patients with leukemia has been reported to approach up to 3.4 % [6] in this immunocompromised population. Chronic invasive fungal rhinosinusitis is extremely rare in the United States [4] and is more common in dry desert regions in Sudan and Saudi Arabia [7].

Role of Fungi in Chronic Rhinosinusitis

Chronic rhinosinusitis is a heterogeneous group of disorders with similar symptomatic presentation but without a single unifying etiology. Fungi have traditionally been accorded a small role in causing chronic sinus disease. However, a report in 1999 [8] suggested that most cases of chronic rhinosinusitis are caused by environmental fungi. This report described the presence of fungi in 96 % of patients with CRS (though also in 100 % of "normal" controls) utilizing a novel method of specimen collection and culture to identifying fungi in nasal mucus. Further publications postulated that ubiquitous fungi in the environment evoke an eosinophilic inflammatory response that results in the chronic inflammation of CRS [9]. Subsequent investigation focused on eradicating the fungus in an attempt to treat CRS. In a small randomized double-blind placebo-controlled trial published in 2005 [10], topical treatment with amphotericin B led to a small improvement in CT and endoscopic findings in patients with CRS. Multiple randomized trials of antifungal therapy have now been performed, and reviews [11, 12] from the various subsequent trials showed no benefit of systemic or topical antifungal therapy on patients with CRS. In particular, a Cochrane review [12] of 6 trials on 380 patients showed that patients treated with antifungal therapy actually had worse symptom scores and a higher rate of adverse effects than those treated with placebo.

Limited laboratory data exist to provide support for the "fungal hypothesis" of CRS pathogenesis. Shin et al. [9] showed that exposure of peripheral blood mononuclear cells (PBMCs) of patients with CRS to fungal antigens (especially *Alternaria*) resulted in an increase in IL-5 and IL-13 production, while normal control PBMCs did not. These results lend support to the notion that fungal exposure in CRS patients incites an eosinophilic response that is not seen in normal individuals. However, these results were not replicated in a later study by Orlandi et al. [13] who found both IL-5 and IL-13 production increased in both CRS and normal patients following *Alternaria* exposure. Recent studies have also focused on the presence of fungal biofilms in patients with CRS [14]. In a study of 50 patients with CRS and 10 controls, fungal biofilms were found to be present in 11 of the 50 study subjects and none of the controls. Of the 11 subjects with fungal biofilms, 9 had concomitant bacterial biofilms present. Although the data suggests that biofilms are more prevalent in patients with CRS than controls, there is a lack of definitive evidence suggesting that the presence of the fungal biofilm contributes to the disease process of CRS. Furthermore, there is no evidence that the removal of such these fungal biofilms result in a resolution of CRS. Without a clearly defined pathophysiology and a clear demonstration of cause and effect, the hypothesis that fungi is the cause of CRS has been widely rejected, putting an end to more than a decade of controversy.

Microbiology of Fungi

Fungal classification can be confusing due to the large number of terms and different classification systems that have been developed. On a microscopic level, fungi can appear as a mold or yeast. A mold is distinguished by its multicellular colony with filaments or hyphae (which may appear septated). In comparison, yeast appears as a spherical or ellipsoid unicellular form. Certain fungi are able to grow as yeast or as a mold depending on physical conditions. Fungi are also able to exist in both sexual and asexual forms, each having its own name. The asexual name is most commonly used in the medical

Table 8.1 Common fungal pathogens

Category	Genera
Mucoraceae	*Mucor*
	Rhizopus
	Rhizomucor
	Absidia
Hyaline molds	*Aspergillus*
	Fusarium
	Pseudallescheria
Dematiaceous molds	*Alternaria*
	Bipolaris
	Curvularia
	Exserohilum

literature. Depending on the presence of septations and pigment and branching patterns, these fungi can be broadly classified as mucoraceae, hyaline molds, or dematiaceous molds (Table 8.1). Although the specific genera may cause more than one pathology, certain pathologies are more likely associated with specific fungi. For example, acute invasive fungal rhinosinusitis is commonly associated with *Mucor* or *Aspergillus*, fungus balls are almost commonly caused by A*spergillus*, and allergic fungal rhinosinusitis is commonly associated with *Alternaria*, *Bipolaris*, and other dematiaceous molds.

Diagnostic Tests

The diagnosis of fungal rhinosinusitis requires the demonstration of fungus in tissue or sinus contents. Identification of fungal elements in surgical specimens can be difficult even with special stains. While some molds may stain with the Gram or hematoxylin–eosin stains, special stains like Gomori methenamine silver (GMS) or periodic acid–Schiff (PAS) demonstrate fungi better. Often, potassium hydroxide may be added to dissolve away human cells so that the fungi can be better seen. Fungal cultures may take weeks for results to return, may be affected by bacterial contamination, and are hard to interpret due to their variable yield [15]. Recently, attention has been turned to polymerase chain reaction techniques as well as ELISA identification of fungal specific antigen for rapid diagnosis of invasive fungal conditions [16, 17]. However, these advanced diagnostic tools have not been adequately studied in sinus disease.

Fungus Ball

A fungus ball is the common term used to describe a gross collection of fungal elements within a sinus. The previous terms "mycetoma" or "aspergilloma" have given way to this preferred terminology. A more precise description would also include the site as well as the causative organism [18], for example, "maxillary sinus fungus ball due to *Aspergillus*." A fungus ball may be an incidental finding in patients undergoing endoscopic surgery for chronic rhinosinusitis or incidentally noted on head and neck imaging. When symptomatic, the clinical presentation is similar to other forms of chronic rhinosinusitis with patients reporting symptoms such as nasal obstruction, postnasal drainage, facial pain, and a foul-smelling discharge. These symptoms may wax and wane with associated bacterial infection of the diseased sinus. Patients who develop fungus balls are typically not atopic or immunocompromised and usually belong to the older age group [19]. Fungus balls are usually found in the maxillary or sphenoid sinus but may also occur in the ethmoid and frontal sinuses. Some even involve multiple adjacent sinuses [20].

Computed tomography (CT) imaging usually shows an isolated sinus with heterogeneous opacification due to the presence of fungal debris within the sinus with surrounding mucosal inflammation. In about 65 % of cases, the fungus ball may show apparent calcifications [21] (Fig. 8.1a–c). In chronic cases, there may be thickening of the surrounding bone or bony erosion [22].

Grossly, fungus balls are composed of thick yellowish green, cheesy material. Histological examination of the fungus ball reveals tangles of fungal hyphae that are extramucosal and noninvasive into the sinus tissue (Fig. 8.2). Calcifications and oxalate crystals may also be found within the sinus contents [20]. Despite the gross presence of many apparently viable fungal elements, negative fungal cultures are common [19]. *Aspergillus* is the most common causative organism.
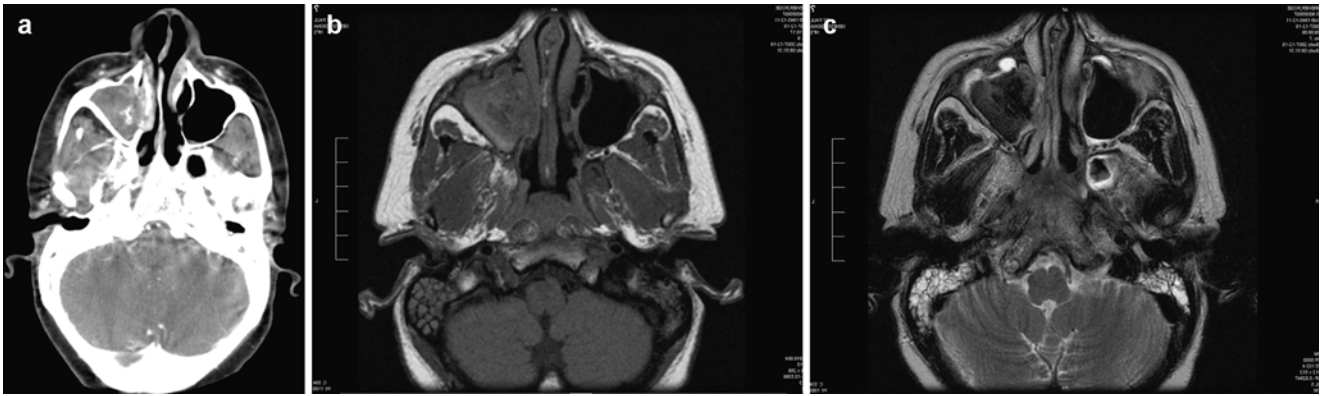
Fig. 8.1 (**a**) CT scan of fungus ball. Axial CT demonstrating the presence of a fungal ball in the maxillary sinus. Note the heterogeneous opacification and presence of calcification. (**b**, **c**) MRI of fungus ball. Corresponding axial MRI T1 (**b**) and T2 images (**c**) of the same patient. Note the presence of surrounding mucosal inflammation and the hypodense appearance of the fungus ball

Fig. 8.2 Histopathology of a fungus ball. Large masses of densely packed fungal hyphae with feathered borders. The hyphae are densely packed, and the branching septate hyphae are readily identified under high magnification
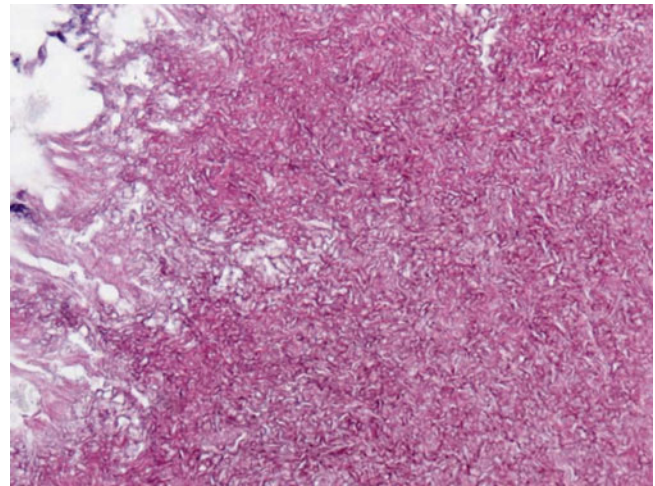
The pathogenesis of a fungal ball requires trapping of fungal spores within a sinus followed by proliferation and associated impairment of the normal clearance of mucus from the sinus. Fungus balls grow slowly and if they do not evoke a significant inflammatory response may remain asymptomatic for months to years. If the fungus ball expands in the presence of sinus outflow tract obstruction, a mucocele may form (an expanded opacified sinus). The diseased sinus is susceptible to acute or chronic bacterial infection.

Treatment for a fungus ball aims to remove the fungus and restore normal drainage and aeration of the involved sinus. This is usually achieved through an endoscopic approach [22]. Postoperative management usually consists of saline irrigation. Although microbiological cultures of the extracted fungus ball may harbor aerobic and anaerobic bacteria [23], their significance is not well understood, and symptoms generally resolve without the use of antibiotics or antifungal medications. Recurrences of a fungus ball are rare [19], and these are quite easily managed with endoscopic removal through the surgical sinusotomy.

Allergic Fungal Rhinosinusitis

Allergic fungal rhinusinusitis was first described as a distinct clinical entity when it was noticed that the thick, dark, sticky nasal mucus in these patients was similar to the inspissated bronchial mucus of patients with bronchopulmonary aspergillosis. Microscopically, this "eosinophilic mucin" contains eosinophils, lysophospholipase crystals (Charcot–Leyden crystals), and occasional fungal elements. *Aspergillus* was initially thought to be the causative organism giving rise to the term "allergic *Aspergillus* sinusitis." However, as studies showed that dematiaceous fungi [24] were more commonly isolated, the

Table 8.2 Bent and Kuhn criteria

1	Type I hypersensitivity
2	Nasal polyps
3	Characteristic CT features
4	Eosinophilic mucin
5	Positive fungal stain

terminology has shifted to allergic fungal rhinosinusitis (AFRS). Although the type of fungi isolated does not affect the clinical presentation or course of the disease, its presence is important to fulfill the diagnostic criteria of AFRS. AFRS is the commonest form of fungal sinus disease, though epidemiologic data is lacking. This disease usually occurs in the immune-competent, young patient with a history of atopy. It has a particular geographical distribution and seems to be more prevalent in the southern United States [25]. The pathogenesis, while still not resolved, is believed to include a combination of a Gell and Coombs type I and III sensitivity to fungal antigens. This theory is supported by elevated levels of fungi specific IgE and IgG [26] in patients with AFRS. Changes of these levels seem to correspond with symptoms [27], and there is evidence suggesting improved outcomes with fungal desensitization [28].

The original diagnostic criteria for AFRS were described by Bent and Kuhn [29], who based their description on a series of 15 patients. Their criteria included (1) type 1 hypersensitivity as evidenced by serum IgE, skin testing, or clinical history; (2) nasal polyps; (3) characteristic computed tomographic findings of serpiginous areas of high attenuation in affected sinuses; (4) presence of eosinophilic mucus without fungal tissue invasion; and (5) positive fungal smear in the mucus (see Table 8.2). Although alternative diagnostic criteria exist, these are the most widely accepted.

In some patients, fungal elements cannot be identified in the allergic mucin, giving rise to the term "AFS-like syndrome" [30] and "eosinophilic mucin rhinosinusitis" (EMRS) [31]. Yet another group of patients have identifiable fungi but do not show the characteristic IgE-mediated allergy to the fungi [32]. The relationship of these groups of patient with the originally described AFRS is now controversial. These inconsistencies have raised doubts about the role of fungi and allergy in the development of AFRS and demonstrate that the exact pathogenesis of AFRS remains elusive.

Patients with AFRS are typically adolescents or young adults. Older patients with similar presentations are more likely to have "eosinophilic mucin rhinosinusitis." A previous history of allergic rhinitis or asthma is common and the clinical evolution of sinus symptoms usually gradual. Patients commonly present with the typical symptoms of polypoid sinonasal inflammation, often with unilateral symptoms of nasal obstruction, anosmia, postnasal drip, and the production of characteristic thick, dark mucus (Fig. 8.3). In severe cases, there may be diplopia, proptosis, or telecanthus resulting from mucocele impingement on the orbital contents [33]. Such late presentations are not uncommon due to the insidious nature of the disease.

Physical examination in these patients may reveal external physical deformity caused by the expanding mass, raising concern for a neoplastic process. However, sinonasal endoscopic examination reveals typical nasal polyps, often with an asymmetric distribution, and loculations of "eosinophilic mucin." Entrapped by the polyps, the inspissated mucus often appears as thick yellowish, brown collections.

Diagnostic testing is required to establish the diagnosis of AFRS. Skin prick testing or serum antigen specific IgE tests are required to establish the presence of fungal type 1 hypersensitivity. As these patients often demonstrate allergy to both fungal and non-fungal antigens [34], it is common practice to test for region-specific seasonal and perennial allergens together with the fungal allergens. While not necessary from a diagnostic standpoint, total serum IgE levels are dramatically elevated and peripheral eosinophilia is common.

CT imaging is necessary for diagnosis and surgical treatment. The classic findings in AFRS include asymmetric disease with multiple inflamed or opacified sinuses, hyperdense sinus contents, bony erosion, and mucocele formation (Fig. 8.4). Compared to other forms of polypoid chronic rhinosinusitis, there is a greater propensity for bony erosion with up to half of CT scans showing some evidence of skull base or orbital erosion [35]. Magnetic resonance imaging is reserved for cases where there are orbital or intracranial complications. On T2-weighted images, there are central areas of signal void corresponding to the thick eosinophilic mucin, while surrounding inflamed mucosa has a high intensity signal [36]. The T1 signal is often hypo or isotense relative to the brain.

Treatment of AFRS includes a combination of surgical and medical approaches. Due to physical obstruction and the distortion of normal anatomy and sinus drainage pathways, surgery is required to effectively treat this disease. The primary aim is to improve drainage by removing obstructing polyps and sinus septations and to remove the eosinophilic mucin [34]. This is usually accomplished with an endoscopic surgical approach. Due to the distortion of normal bony landmarks and dehiscence of bony barriers to the brain and orbit, the risk of surgery is potentially increased. The consequence of incomplete surgery is often the recurrence of the disease [37], as retained bony lamella may harbor pockets of the eosinophilic mucin
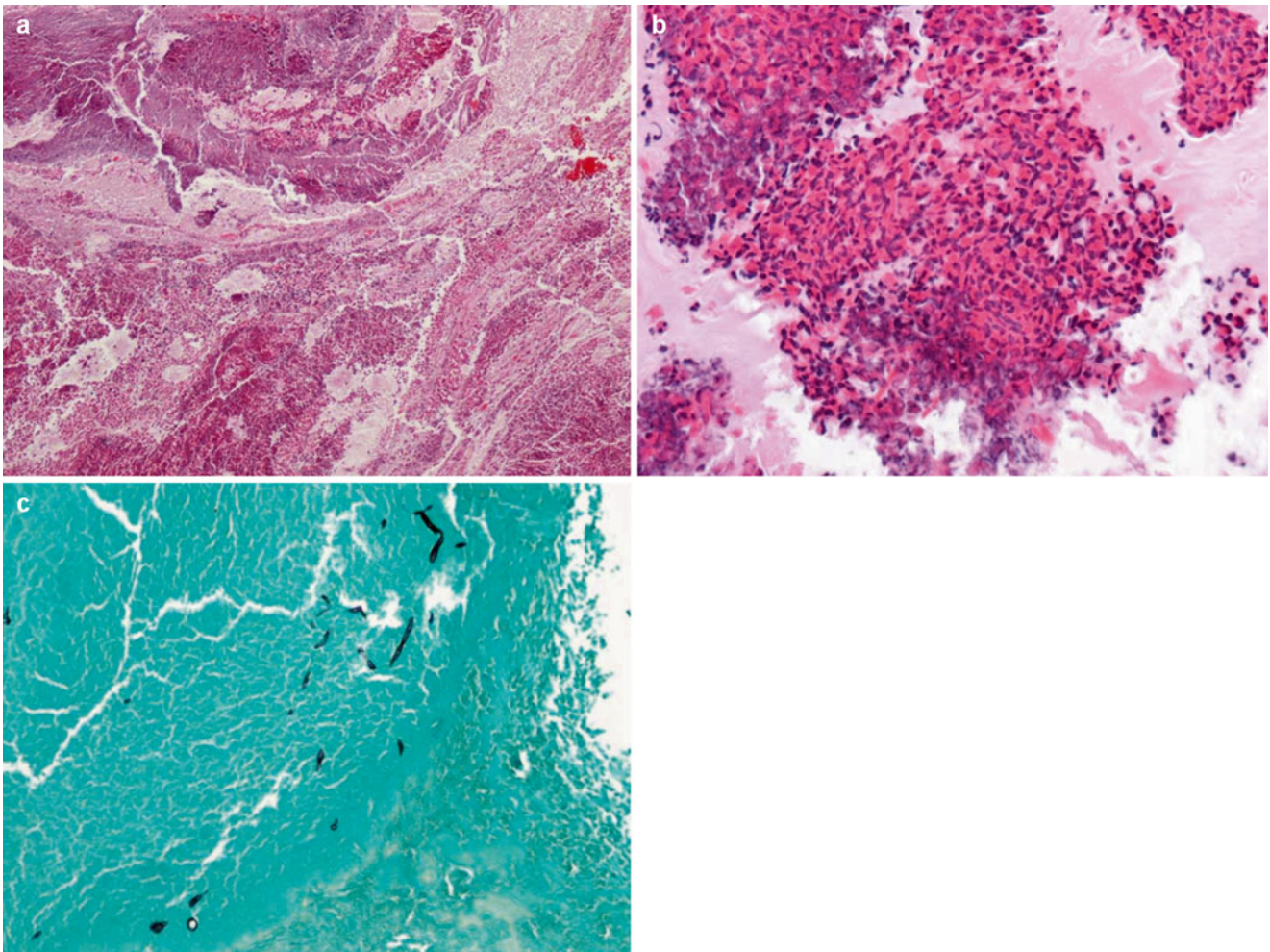
Fig. 8.3 Histopathology of allergic fungal rhinosinusitis. (**a**) Eosinophilic mucin under 40× magnification showing inspissated mucus with eosinophilic material and admixed inflammatory cells (so-called eosinophilic mucus). (**b**) 100× magnification showing amorphous eosinophilic material with eosinophils and scattered neutrophils. (**c**) GMS stain identifies occasional branching septate fungal hyphae

that function as a stimulus for further inflammation. Over the course of the disease, revision surgery is commonly required for recurrences that are resistant to medical therapy or when massive polyposis results in entrapment of mucin within the sinuses. Minimally invasive approaches such as balloon dilation are not appropriate in this disease process.

Comprehensive medical therapy is a crucial component in the long-term management of this disease process [38]. AFRS is an inflammatory disease, not a fungal infection. Systemic and topical corticosteroids are the main forms of medical therapy [39]. Steroids are used perioperatively and for long-term maintenance therapy. The use of steroids has been shown to improve symptoms and increase the time interval between relapses [40]. In severe cases, prolonged treatment with systemic corticosteroids may be necessary to maintain control of inflammation. Due to the potential side effects of prolonged systemic steroid use, it is common practice to confine steroid usage to the immediate postoperative period and in short bursts to treat acute exacerbations or polyp recurrences. Topical steroids have the advantage of targeted delivery of the medication without the side effects of systemic steroids. Topical steroids have demonstrated efficacy for nasal polyps [41], and they are often used at higher doses to improve their efficacy [39]. While high-dose topical steroids have not been adequately studied in polypoid CRS, there is considerable interest in the use of these agents as a means to reduce the use of systemic corticosteroids. In a previous operated patient without a significant polyp burden, topical agents are able to reach the sinus mucosa directly. Budesonide respules, for example, may be applied directly as drops, mixed with a nasal irrigation or sprayed via an atomizer device. Inverted head positioning is required to insure distribution into the frontal, ethmoid, and sphenoid regions. Although these agents are anecdotally effective, topical steroid alone is often insufficient to completely eliminate the need for systemic steroids. Other anti-inflammatory agents such as leukotriene receptor antagonists [42], macrolides, and itraconazole have been recommended; however, none of these agents has been adequately studied. The use of systemic and topical antifungal
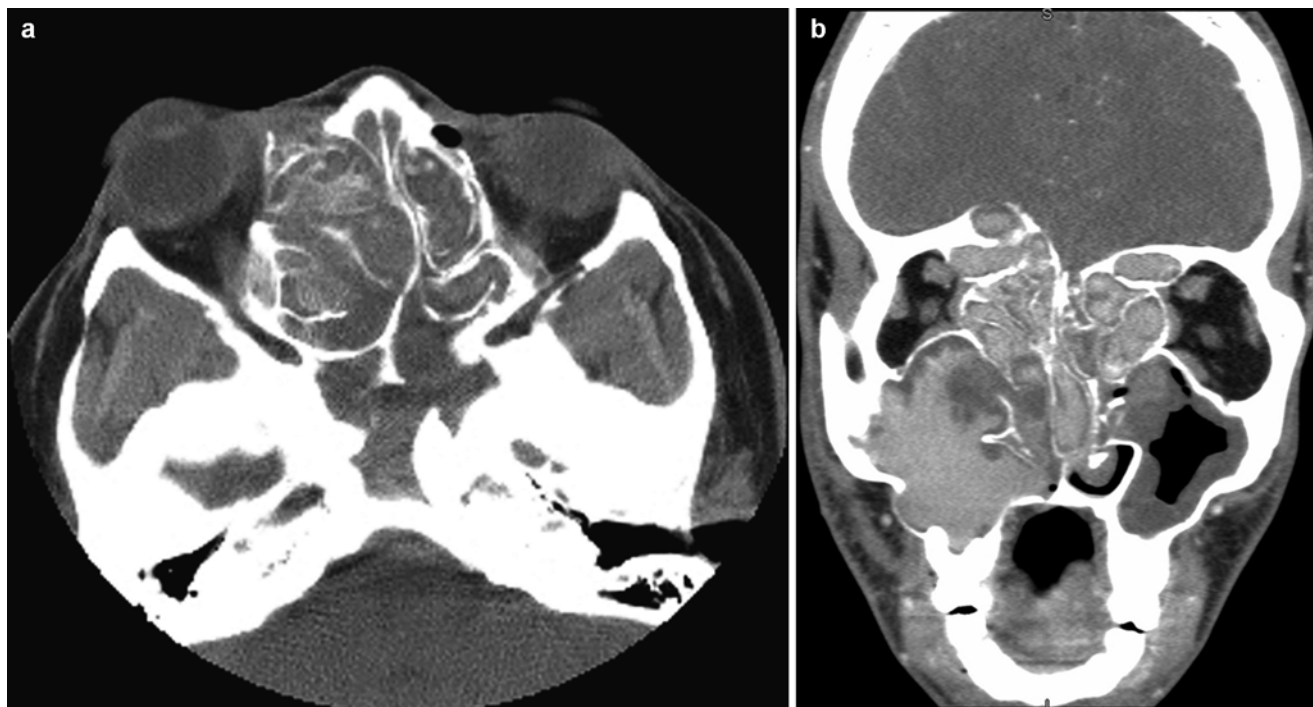
Fig. 8.4 Axial and coronal CT of a patient with AFRS. Axial (**a**) and coronal (**b**) images of a patient with severe allergic fungal rhinosinusitis with extensive mucocele formation. Note the extension into the anterior cranial fossa and right orbit causing proptosis. Eosinophilic mucin has a heterogeneous appearance within the sinuses

therapy has also been described, with the aim to reduce the antigenic load contributed by the fungus [43]; however, these are not commonly employed.

Immunotherapy is another treatment option in the management of AFRS, based on the theory that AFRS is due to allergen-specific IgE-mediated inflammation. Although the role of the type 1 hypersensitivity in AFRS is still unclear, studies have shown that immunotherapy is well tolerated and may be effective in the management of AFRS, reducing recurrences after surgery and decreasing the need for corticosteroids [44]. In a study of 22 patients treated with immunotherapy for AFRS, results at a mean treatment time of 33 months showed better symptoms scores and endoscopic appearance and less reliance on corticosteroids [45]. Given that all of these patients are allergic, it seems reasonable to include immunotherapy as one of the immunomodulating treatment modalities for AFRS.

Despite initial treatment success, some patients with AFRS continue to relapse and may do so at variable times. In a study spanning 7 years, patients with AFRS required an average of two surgeries and three course of systemic steroids per year [46]. It was also noted that serum IgE in these patients also remained high despite resolution of symptoms, suggesting a chronic process with a high propensity for recurrence. Hence, the need for regular endoscopic examination and follow-up of these patients cannot be overemphasized.

Chronic Invasive Fungal Rhinosinusitis

Chronic invasive fungal rhinosinusitis (CIFRS) is a slowly progressing fungal infection of the sinuses that evolves over a time course of >12 weeks. When there is the presence of a granulomatous reaction, the term "granulomatous invasive fungal rhinosinusitis" is used. The latter is differentiated by the presence of noncaseating granulomas with giant cell formation and fewer fungal hyphae. The granulomatous form seems to have a distinct geographical distribution and is more commonly found in the dry desert areas of Sudan [47]. In contrast, the histology of the nongranulomatous variant shows a larger number of fungal hyphae with tissue invasion. Both are largely caused by *Aspergillus*, and due to their similarities in terms of presentation, prognosis, and management, for the purposes of this chapter, they will be discussed as a single entity.

Chronic invasive fungal rhinosinusitis typically manifests in the healthy patient without demonstrable immune defect. However, some may have a mild immune impairment in the form of diabetes mellitus [4]. Symptoms develop slowly and

Fig. 8.5 Histopathology of acute invasive fungal
rhinosinusitis. 400× magnification image showing broad-based,
"ribbonlike" hyphae, consistent with mucoraceae, in a
background of necrosis
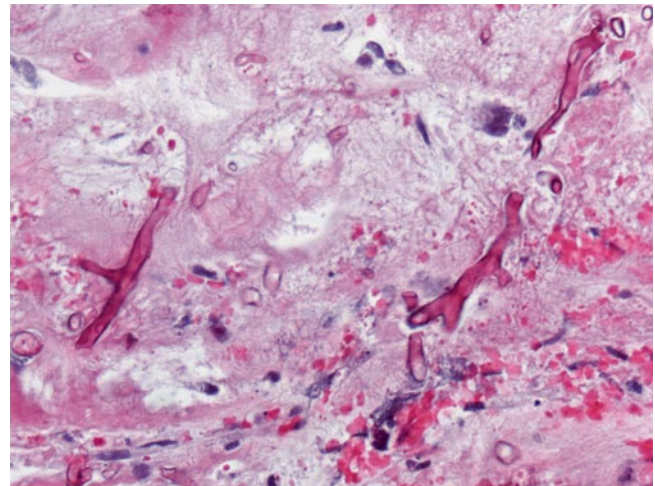
may evolve over months to years. The clinical presentation may resemble a sinonasal neoplasm. The most common presentation is proptosis resulting from erosion into the orbit. Extensions to other areas may lead to palatal fistulas and neurological deficits. Fatal complications may result from erosions into the internal carotid artery and cavernous sinus thrombosis [48].

Physical examination findings are quite variable depending upon the location and extent of disease. Endoscopic examination shows nasal congestion with occasional nasal polyps. There may be a soft tissue mass or evidence of mucosal ulcerations. A faint yellowish hue of the tissue has also been described [4].

The imaging modality of choice for chronic invasive rhinosinusitis is the CT scan. However, in view of the potential for dural extension and a differential diagnosis of malignancy, MRI is also employed to rule out these processes. Characteristic imaging findings include a homogeneous opacity that is iso- or slightly hyperdense compared to muscle, intermediate signal intensity on T1-weighted MRI, and low signal intensity on T2. Contrasted scans may show extensive tissue involvement outside of the sinuses [49]. Definitive diagnosis, however, relies on histological examination showing fungal invasion (Fig. 8.5).

Management of chronic invasive fungal rhinosinusitis is accomplished with a combination of surgical resection and antifungal therapy. The treatment is based on the principles of management of acute invasive fungal rhinosinusitis. Surgical resection secures tissue for the diagnosis of invasion as well as identification of the offending organism. The second role of surgery is debridement; the extent of surgical resection required is not well defined, but this may range from simple debridement to radical resection of all tissue that is involved with fungus. Most authors would favor an individualized approach with the extent of surgery dependent on the initial extent of disease and response to medical therapy [4].

The antifungal armamentarium for chronic invasive fungal disease includes the use of amphotericin B and the oral triazoles. As with surgical therapy, the intensity and duration of antifungal therapy should be tailored to the patient's circumstances. Some advocate a course of intravenous amphotericin B of up to 2 g followed by a long-term course of oral antifungal therapy [50], while others advocate a more conservative treatment with monitoring of response [51]. The wide variability of treatments, potential side effects of treatment, and variable response highlight the need for individualized treatment and long-term follow-up of this condition.

Acute Invasive Fungal Rhinosinusitis

Acute invasive fungal rhinosinusitis (AIFRS) or fulminant invasive fungal rhinosinusitis is defined as an invasive fungal infection of less than 4 weeks [18]. Left untreated, this condition is rapidly fatal. AIFRS affects mainly the immunocompromised, with prolonged neutropenia being the most important risk factor. Patients with hematological malignancies are especially at risk for developing AIFRS with *Aspergillus* species. The other classic risk factor for AIFRS is diabetic ketoacidosis, and these cases usually involve the mucoraceae. Other risk factors include end-stage AIDS, systemic corticosteroid therapy, and chronic renal failure. Restoration of immune function is considered vital in the treatment of AIFRS.

The initial clinical symptoms of AIFRS may be mild and appear innocuous. However, symptoms such as clear rhinorrhea and nasal congestion may rapidly progress to other more ominous signs and symptoms such as fever, severe facial pain, visual disturbances, facial swelling, palatal and facial necrosis, and cranial nerve palsies [52]. Erosion of the skull base with direct invasion into the brain may lead to altered mental status.

Fig. 8.6 CT Scan of acute invasive fungal rhinosinusitis.
Coronal CT scan of acute invasive fungal rhinosinusitis with
nonspecific changes of mild opacification of the left ethmoid
and bilateral maxillary sinuses. Imaging findings are not benign
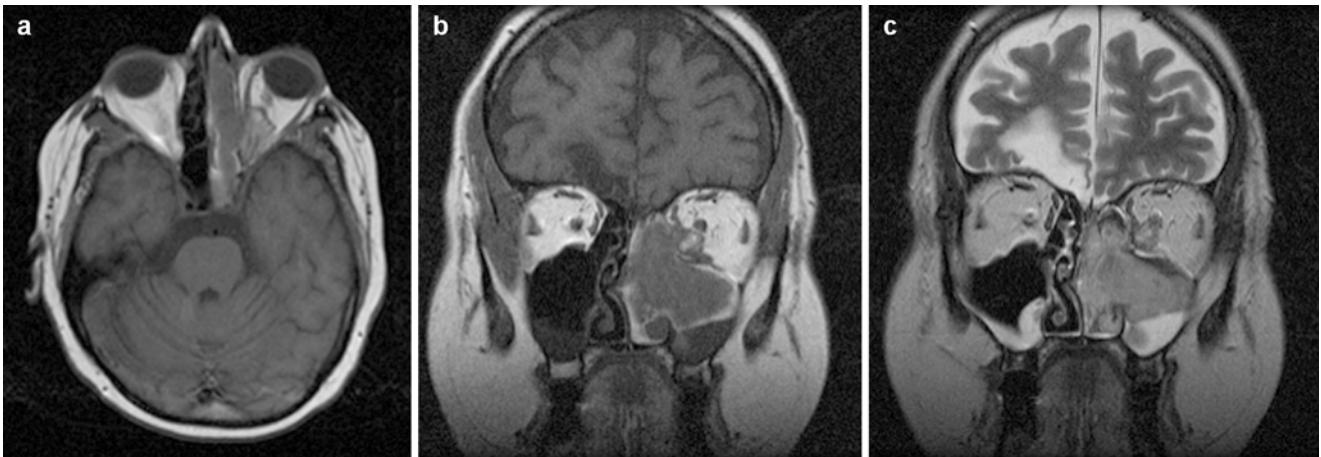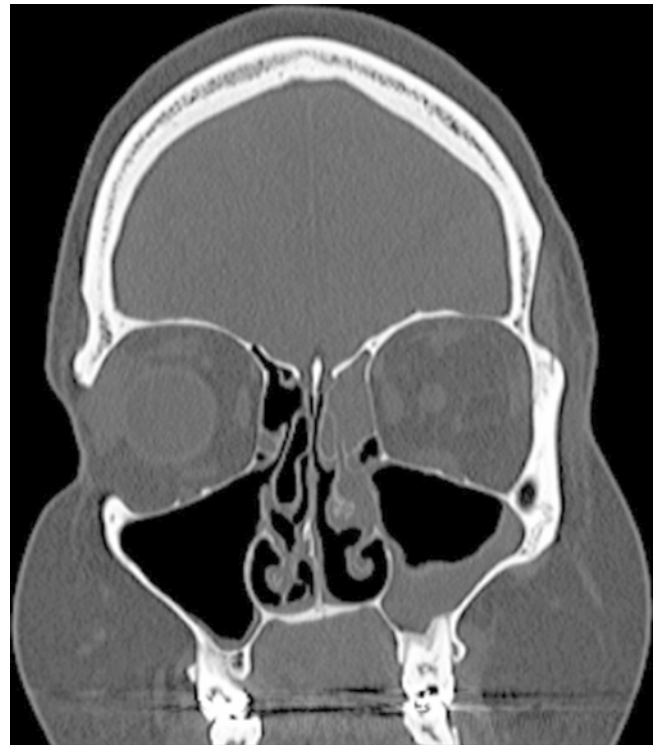appearing in the early course of this disease

Fig. 8.7 MRI images of acute invasive fungal rhinosinusitis. MRI axial T1 (**a**) and coronal T1(**b**) and T2 (**c**) images. Showing invasive fungal
rhinosinusitis with left inferomedial orbital involvement

External physical examination findings are not present until the disease has extended out of the sinonasal cavities. Early
diagnosis therefore requires nasal endoscopy. Acute invasive fungal rhinosinusitis causes tissue necrosis that is initially
manifest as erythematous or pale mucosa that is insensate to touch. As the disease progresses, these areas become necrotic
and the mucosa may take on a dark, dusky appearance. Although these changes may occur anywhere along the nasal mucosa,
the most common areas is the mucosa of the middle turbinate [53]. As progression may occur in a matter of hours, it is
important to repeat an endoscopic examination if initial findings are inconclusive and there is diagnostic uncertainty.

Imaging of the patient with AIFRS is important for diagnosis as well as to delineate the extent of the disease. A CT scan is the
initial imaging study. Early findings may be nonspecific with areas of mucosal thickening or sinus opacification (Fig. 8.6). One
large series showed that severe unilateral nasal soft tissue swelling [54] was a common feature of early AIFRS. Late radiological
signs include bony erosion and orbital or facial soft tissue invasion. If extra-sinus involvement is suspected, an MRI (Fig. 8.7) may
be used to delineate the extent of tissue involvement and may be helpful in guiding the extent of surgical resection.

AIFRS is a disease that is better prevented than treated. By identifying patients that are at risk for immune suppression, for example, as a result of chemotherapeutic drugs or in posttransplant patients, measures to reduce exposure to fungal spores, screening for sinus disease, or even prophylactic antifungal therapy [55] may be implemented to reduce the rate of AIFRS.

Due to a paucity of trials, the ideal treatment regimen for treating AIFRS is unknown. The principles of therapy include reversal of the immunocompromised state, surgical debridement, and the use of antifungal therapy.

Reversal of the immunocompromised state is vital for survival in AIFRS. Depending on the cause, this may necessitate stopping chemotherapeutic agents, aggressively reversing hyperglycemia and ketoacidosis, or the administration of granulocyte-stimulating factors [56]. If the underlying immunocompromise cannot be reversed, the prognosis for survival is poor.

Surgical debridement of patients with AIFRS has been a mainstay of therapy [57]. Surgery also secures a specimen for proper identification of the offending organism, confirms the diagnosis, and clears necrotic tissue [58]. With advancements in surgical techniques, there is a trend toward endoscopic resection of the necrotic tissue as it entails a lower surgical morbidity. Additionally, it is increasingly recognized that AIFRS is primarily a "medical" disease and that surgery is at best an adjunct to antifungal medications and the restoration of immune function. Traditional open surgery is reserved for advanced cases where there is significant orbital or intracranial involvement, and radical facial resections are not common. The contemporary approach to surgical treatment is to remove all tissue that is obviously involved with fungus. Frozen section examination of the resected specimen has been used for the initial diagnosis and to guide the extent of debridement. However, this should be used with care as one study [59] showed that up to 37 % of intraoperative specimens sent for frozen section had false-negative results. Surgery in cases of AIFRS is often fraught with difficulties as these patients are often thrombocytopenic and coagulopathic. As a result, there is significant intraoperative hemorrhage and potential for morbidity.

Antifungal therapy is a critical component of the treatment of AIFRS. It can be administered systemically or in combination with topical therapy, although evidence for the latter is lacking. As most invasive fungal infections are caused by *Aspergillus* or the mucoraceae, amphotericin B is commonly used for empiric therapy. Amphotericin B deoxycholate causes significant infusion related and systemic toxicities that limit its dosing. However, newer lipid formulations have fewer side effects that permit more aggressive dosing [60]. Other antifungal agents include voriconazole or itraconazole, which are effective against *Aspergillus*, and posaconazole, which is typically used as an oral therapy for mucoraceae after initial therapy with amphotericin B. The duration of antifungal therapy required once the disease process is arrested is unclear. Ultimately the duration of therapy should be dependent on the immune status of the patient and clinical evidence of disease recurrence and should be decided in conjunction with an infectious disease specialist.

Conclusions

Fungal rhinosinusitis has a wide variety of clinical presentations. These range from the minimally symptomatic fungus ball to the lethal acute invasive fungal rhinosinusitis (Table 8.3). It appears that the host immune response to the fungus plays an important role in determining the manifestation of the disease. While most rhinosinusitis can be adequately managed with medical therapy alone, all of the subtypes of fungal rhinosinusitis require surgery for diagnosis and treatment. Antifungal medications are only indicated for tissue invasive forms of fungal sinusitis. In allergic fungal rhinosinusitis, long-term

Table 8.3 Summary table of fungal rhinosinusitis

	Fungus ball	AFRS	CIFRS	AIFRS
Pathogen	*Aspergillus*	*Alternaria*, *Bipolaris*, dematiaceous molds	*Aspergillus*	*Mucoraceae*, *Aspergillus*
Patient profile	Normal immunity elderly	History of atopy or allergic rhinitis	Older age group	Immune compromised
		Adolescent, young adult	Diabetes mellitus	
Presentation	Nasal obstruction	Gradual onset	Proptosis	Medical emergency
	Purulent nasal discharge, facial pain	Unilateral symptoms	Facial pain	Nasal congestion, rhinorrhea, facial pain, fever
		Characteristic dark colored mucus		Visual disturbance
		Proptosis		
Treatment	Surgical removal of fungus ball	Surgical drainage	Surgical resection of affected areas	Restore immune function
		Systemic corticosteroids		
	No antifungals needed	Topical steroids	Systemic antifungal therapy	Surgical debridement
		Immunotherapy		Systemic antifungal therapy

anti-inflammatory medication in the form of topical and systemic corticosteroids is required to prevent the recurrence of polyps and the reaccumulation of eosinophilic mucin.

References

1. Hora JF. Primary aspergillosis of the paranasal sinuses and associated areas. Laryngoscope. 1965;75:768–73.
2. Katzenstein AL, Sale SR, Greenberger PA. Allergic Aspergillus rhinosinusitis: a newly recognized form of rhinosinusitis. J Allergy Clin Immunol. 1983;72:89–93.
3. Ferguson BJ. Definitions of fungal rhinosinusitis. Otolaryngol Clin North Am. 2000;33:227–35.
4. Stringer SP, Ryan MW. Chronic invasive fungal rhinosinusitis. Otolaryngol Clin North Am. 2000;33:375–87.
5. Schwietz LA, Gourley DS. Allergic fungal rhinosinusitis. Allergy Proc. 1992;13:3–6.
6. Talbot GH, Huang A, Provencher M. Invasive aspergillus rhinosinusitis in patients with acute leukemia. Rev Infect Dis. 1991;13:219–32.
7. Milosev B, el-Mahgoub S, Aal OA, et al. Primary aspergilloma of paranasal sinuses in the Sudan. A review of seventeen cases. Br J Surg. 1969;56:132–7.
8. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal rhinosinusitis. Mayo Clin Proc. 1999;74:877–84.
9. Shin SH, Ponikau JU, Sherris DA, et al. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. J Allergy Clin Immunol. 2004;114:1369–75.
10. Ponikau JU, Sherris DA, Weaver A, et al. Treatment of chronic rhinosinusitis with intranasal amphotericin B: a randomized, placebo-controlled, double-blind pilot trial. J Allergy Clin Immunol. 2005;115:125–31.
11. Fokkens WJ, van Drunen C, Georgalas C, et al. Role of fungi in pathogenesis of chronic rhinosinusitis: the hypothesis rejected. Curr Opin Otolaryngol Head Neck Surg. 2012;20(1):19–23.
12. Sacks PL, Harvey RJ, Rimmer J, et al. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Cochrane Database Syst Rev. 2011;8:CD008263.
13. Orlandi RR, Marple BF, Georgelas A, et al. Immunologic response to fungus is not universally associated with rhinosinusitis. Otolaryngol Head Neck Surg. 2009;141:750–6.e1–2.
14. Foreman A, Psaltis AJ, Tan LW, et al. Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. Am J Rhinol Allergy. 2009; 23:556–61.
15. Glass D, Amedee RG. Allergic fungal rhinosinusitis: a review. Ochsner J. 2011;11:271–5.
16. Buchheidt D, Hummel M, Schleiermacher D, et al. Current molecular diagnostic approaches to systemic infections with aspergillus species in patients with hematological malignancies. Leuk Lymphoma. 2004;45:463–8.
17. Lass-Florl C, Gunsilius E, Gastl G, et al. Clinical evaluation of Aspergillus-PCR for detection of invasive aspergillosis in immunosuppressed patients. Mycoses. 2005;48 Suppl 1:12–7.
18. Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. Laryngoscope. 2009;119:1809–18.
19. Klossek JM, Serrano E, Peloquin L, et al. Functional endoscopic sinus surgery and 109 mycetomas of paranasal sinuses. Laryngoscope. 1997;107:112–7.
20. Ferreiro JA, Carlson BA, Cody 3rd DT. Paranasal sinus fungus balls. Head Neck. 1997;19:481–6.
21. Seo YJ, Kim J, Kim K, et al. Radiologic characteristics of sinonasal fungus ball: an analysis of 119 cases. Acta Radiol. 2011;52:790–5.
22. Ferguson BJ. Fungus balls of the paranasal sinuses. Otolaryngol Clin North Am. 2000;33:389–98.
23. Brook I. Recovery of aerobic and anaerobic bacteria in sinus fungal ball. Otolaryngol Head Neck Surg. 2011;145:851–2.
24. Manning SC, Schaefer SD, Close LG, et al. Culture-positive allergic fungal rhinosinusitis. Arch Otolaryngol Head Neck Surg. 1991;117:174–8.
25. Ferguson BJ, Barnes L, Bernstein JM, et al. Geographic variation in allergic fungal rhinosinusitis. Otolaryngol Clin North Am. 2000;33:441–9.
26. Stewart AE, Hunsaker DH. Fungus-specific IgG and IgE in allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg. 2002;127:324–32.
27. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal rhinosinusitis. II. Treatment and follow-up. J Allergy Clin Immunol. 1998;102:395–402.
28. Horst M, Hejjaoui A, Horst V, et al. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. J Allergy Clin Immunol. 1990;85:460–72.
29. Bent 3rd JP, Kuhn FA. Diagnosis of allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg. 1994;111:580–8.
30. Allphin AL, Strauss M, Abdul-Karim FW. Allergic fungal rhinosinusitis: problems in diagnosis and treatment. Laryngoscope. 1991;101:815–20.
31. Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. Laryngoscope. 2000;110:799–813.
32. Pant H, Kette FE, Smith WB, et al. Eosinophilic mucus chronic rhinosinusitis: clinical subgroups or a homogeneous pathogenic entity? Laryngoscope. 2006;116:1241–7.
33. McClay JE, Marple B, Kapadia L, et al. Clinical presentation of allergic fungal rhinosinusitis in children. Laryngoscope. 2002;112:565–9.
34. Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. Laryngoscope. 2001;111:1006–19.
35. Ghegan MD, Lee FS, Schlosser RJ. Incidence of skull base and orbital erosion in allergic fungal rhinosinusitis (AFRS) and non-AFRS. Otolaryngol Head Neck Surg. 2006;134:592–5.
36. Manning SC, Merkel M, Kriesel K, et al. Computed tomography and magnetic resonance diagnosis of allergic fungal rhinosinusitis. Laryngoscope. 1997;107:170–6.

37. Marple BF, Mabry RL. Allergic fungal rhinosinusitis: learning from our failures. Am J Rhinol. 2000;14:223–6.

38. Rupa V, Jacob M, Mathews MS, et al. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal rhinosinusitis. Eur Arch Otorhinolaryngol. 2010;267:233–8.

39. Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: a four-year follow-up. Am J Rhinol. 2000;14:149–56.

40. Ryan MW, Marple BF. Allergic fungal rhinosinusitis: diagnosis and management. Curr Opin Otolaryngol Head Neck Surg. 2007;15:18–22.

41. Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2008;139:340–7.

42. Schubert MS. Antileukotriene therapy for allergic fungal rhinosinusitis. J Allergy Clin Immunol. 2001;108:466–7.

43. Jen A, Kacker A, Huang C, et al. Fluconazole nasal spray in the treatment of allergic fungal rhinosinusitis: a pilot study. Ear Nose Throat J. 2004;83(692):94–5.

44. Mabry RL, Marple BF, Folker RJ, et al. Immunotherapy for allergic fungal rhinosinusitis: three years' experience. Otolaryngol Head Neck Surg. 1998;119:648–51.

45. Folker RJ, Marple BF, Mabry RL, et al. Treatment of allergic fungal rhinosinusitis: a comparison trial of postoperative immunotherapy with specific fungal antigens. Laryngoscope. 1998;108:1623–7.

46. Marple B, Newcomer M, Schwade N, et al. Natural history of allergic fungal rhinosinusitis: a 4- to 10-year follow-up. Otolaryngol Head Neck Surg. 2002;127:361–6.

47. Veress B, Malik OA, el-Tayeb AA, et al. Further observations on the primary paranasal aspergillus granuloma in the Sudan: a morphological study of 46 cases. Am J Trop Med Hyg. 1973;22:765–72.

48. Chakrabarti A, Sharma SC, Chandler J. Epidemiology and pathogenesis of paranasal sinus mycoses. Otolaryngol Head Neck Surg. 1992;107:745–50.

49. Reddy CE, Gupta AK, Singh P, et al. Imaging of granulomatous and chronic invasive fungal rhinosinusitis: comparison with allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg. 2010;143:294–300.

50. Washburn RG, Kennedy DW, Begley MG, et al. Chronic fungal rhinosinusitis in apparently normal hosts. Medicine (Baltimore). 1988;67:231–47.

51. Gumaa SA, Mahgoub ES, Hay RJ. Post-operative responses of paranasal Aspergillus granuloma to itraconazole. Trans R Soc Trop Med Hyg. 1992;86:93–4.

52. Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am. 2000;33:349–65.

53. Gillespie MB, Huchton DM, O'Malley BW. Role of middle turbinate biopsy in the diagnosis of fulminant invasive fungal rhinosinusitis. Laryngoscope. 2000;110:1832–6.

54. DelGaudio JM, Swain Jr RE, Kingdom TT, et al. Computed tomographic findings in patients with invasive fungal rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2003;129:236–40.

55. Malani PN, Kauffman CA. Prevention and prophylaxis of invasive fungal rhinosinusitis in the immunocompromised patient. Otolaryngol Clin North Am. 2000;33:301–12.

56. Goering P, Berlinger NT, Weisdorf DJ. Aggressive combined modality treatment of progressive sinonasal fungal infections in immunocompromised patients. Am J Med. 1988;85:619–23.

57. Blitzer A, Lawson W, Meyers BR, et al. Patient survival factors in paranasal sinus mucormycosis. Laryngoscope. 1980;90:635–48.

58. Gillespie MB, O'Malley Jr BW, Francis HW. An approach to fulminant invasive fungal rhinosinusitis in the immunocompromised host. Arch Otolaryngol Head Neck Surg. 1998;124:520–6.

59. Taxy JB, El-Zayaty S, Langerman A. Acute fungal rhinosinusitis: natural history and the role of frozen section. Am J Clin Pathol. 2009;132:86–93.

60. Patterson TS, Barton LL, Shehab ZM, et al. Amphotericin B lipid complex treatment of a leukemic child with disseminated Fusarium solani infection. Clin Pediatr (Phila). 1996;35:257–60.