Chapter 11
The Role of Fungus in Diseases of the Frontal Sinus

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Contents

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Introduction

The nose and paranasal sinuses can be hosts to a variety of disease states, of which fungal species are an increasingly well-understood etiologic agent. Over the past 35 years, enhanced understanding of the role of fungus in sinus disease and the complex interactions between host and pathogen have allowed for a logical classification of fungal rhinosinusitis facilitating proper prognostic information and therapeutic intervention. Coincident with this same time period is the introduction and popularization of minimally invasive endoscopic techniques to better understand frontal sinus anatomy and address pathologic conditions. As such, fungal rhinosinusitis involving the frontal sinus is now more amenable to appropriate treatment with endoscopic approaches.

Basic Mycology

Fungi are eukaryotic organisms ubiquitous to our environment and the human body. Scientists estimate the total number of different fungal species ranges between 20,000 and 1.5 million, of which approximately 400 are responsible for human illnesses, perhaps with only a few dozen species responsible for over 90 % of infections [26, 39, 48]. Fungi can exist either as yeast or molds.

Characteristically, molds produce *hyphae*, multicellular, branching tubular extensions (2–10 μm in diameter), which coalesce as a colony known as a *mycelium* [40]. Yeasts are unicellular, from 3 to 15 μm in diameter, and reproduce asexually via budding; though failure of buds to detach can result in a characteristic chain of fungal cells known as *pseudohyphae* [40]. The spore is fungi's evolutionary solution to the survival problems posed by unfavorable conditions. These derivatives of sexual or asexual fungal reproduction disperse readily into the environment, can withstand adverse surroundings, and retain their germinative abilities until more receptive surroundings are encountered. Inhalation of spores is the most common route by which fungal rhinosinusitis is initiated. Once the nasal mucosa has been accessed, development of a pathologic condition is determined not only by the inherent characteristics of the fungus, but by the host's immune system and the complex interplay between the two.

Classification of Fungal Rhinosinusitis

Fungal disease of the nose and paranasal sinuses can be classified based on the clinical, radiologic, and histologic manifestations of the host-pathogen relationship. Most commonly accepted classification schemes divide fungal rhinosinusitis into invasive and non-invasive diseases based solely on histopathologic evidence of fungus penetrating host tissue (Table 11.1) [11].

Table 11.1 Classification of fungal rhinosinusitis

Invasive fungal sinusitis
Acute fulminant invasive fungal sinusitis
Granulomatous invasive fungal sinusitis
Chronic invasive fungal sinusitis
Non-invasive fungal sinusitis
Saprophytic fugal infestation
Fungal ball
Allergic fungal rhinosinusitis

Ferguson [13]

Acute Fulminant Invasive Fungal Sinusitis

The characteristics of acute fulminant invasive fungal sinusitis (AFIFS) are as follows:

- A clinical time course of less than 4 weeks duration.
- Prominent pathologic evidence of vascular invasion, which may include hyphal invasion of blood vessels, such as the carotid artery and cavernous sinus, vasculitis with thrombosis, and tissue infarction [6, 13].
- The genus *Aspergillus* and the class zygomycetes are responsible for most cases of AFIFS [6].
- AFIFS is almost always seen in immunocompromised patients, though it has been occasionally been reported in patients with normal immune function [4].
- Conditions associated with impaired neutrophil function or neutropenia, such as hemochromatosis, uncontrolled diabetes mellitus, AIDS, hematologic malignancies, or those undergoing iatrogenic immunosuppression from anti-neoplastic chemotherapy or following transplantation, are particularly prone to development of AFIFS [10, 18].
- A high index of suspicion for invasive disease must be maintained in the immunocompromised patient with symptoms of rhinosinusitis, as early findings are often subtle.

Clinical Presentation

Patients may present with:

- Facial swelling is the most commonly reported finding according to a recent systematic review [54].
- Fever of unknown origin, present in 50–90 % of patients in the 3 days prior to diagnosis [18, 57].
- Rhinorrhea
- Double vision
- Ophthalmoplegia

- Headache or facial pain
- Hypoesthesia or anesthesia of the face or oral cavity. This is a particularly concerning sign for early invasive disease and can precede mucosal changes. Patients should be questioned specifically and facial sensation must be tested accurately to identify neurologic deficits [14].

Timely endoscopic exam and directed biopsies are indicated in any immunocompromised patient with facial anesthesia or above signs and symptoms that fail to improve despite appropriate medical therapy [14, 18, 19]. Endoscopic findings will change drastically as the disease progresses. Alterations in the visualized nasal mucosa may be subtle early in the course of AFIFS; however, nasal mucosa changes are the most consistent physical finding and should always be investigated carefully with nasal endoscopy. Mucosal abnormalities are most commonly noted at the middle turbinate (67 %), followed by the nasal septum (24 %) [18]. Pale mucosa with evidence of decreased bleeding or sensation may be reflective of tissue ischemia and incipient fungal angioinvasion [9, 18, 19]. The natural history of AFIFS leads to extrasinus involvement and more obvious findings in later stages of the disease.

Findings seen in later stages of the disease include:

- Necrotic nasal and/or palate mucosa
- Densely anesthetic regions of the face
- Proptosis
- Ophthalmoplegia
- Decreased vision
- Mental status changes

Radiology

Diagnostic imaging of the paranasal sinuses is often performed in the work-up of patients with presumed or proven AFIFS. High-resolution, non-contrasted CT scan of the sinuses in axial and coronal planes is required to adequately evaluate sinus anatomy and the extent of disease. MRI is recommended in patients who present with signs or symptoms of orbital or intracranial involvement, or in those with skull base or lamina papyracea erosion noted on CT scan. Although bone erosion and extrasinus extension are historically cited as classic findings of AFIFS, recent investigations have shown severe unilateral thickening of nasal cavity mucosa to be the most consistent CT finding suggestive of early IFS; yet this is a non-specific finding [9]. Others have suggested thickening of peri-antral fat planes as another early indicator of AFIFS; however, most authors have found this finding to be either non-specific or too uncommonly encountered in AFIFS to assist in providing diagnostic assistance [9].

Treatment of Acute Fulminant Invasive Fungal Sinusitis

The most important treatment for AFIFS is reversal of the patient's underlying immunocompromised state if possible. Otherwise, treatment of AFIFS relies on medical and surgical therapy directed against the offending fungal pathogen. Operative

debridement decreases the fungal load and removes necrotic tissue. Endoscopic techniques directed to completely address the sinonasal disease process, are favored to aggressive radical resections of disease beyond the confines of the sinonasal cavity [18, 24]. Systemic antifungal therapy is routinely employed in AFIFS as an adjunct to surgery. Liposomal formulations of amphotericin-B, the mainstay of antifungal therapy for over 50 years, have improved safety profiles, less renal toxicity, and are effective in treating AFIFS [18, 55]. The topical route of administration via nasal irrigations or nebulizer may enhance delivery of drug within the sinonasal cavity and should be considered in AFIFS patients [14]. Azole antifungal medications, echinocandins, and iron chelating agents may be used as alternative medications in select patients [7].

The prognosis of AFIFS is heavily dependent on the patient's immune status, as those who recover neutrophil function have the greatest chance of survival [24]. Patients with hematologic malignancies have typically been thought to have lower survival (20–50 %), as their immune deficiency is not amenable to rapid improvement [14, 18]. However, in a recent systematic review, survival of patients with hematologic malignancies was virtually identical to that of the entire patient cohort, with overall survival for all AFIFS patients was 46.1 %. Diabetics, in general, did continue to do better than non-diabetics with a survival rate of 50.75 % ($p<0.003$, OR 0.492), presumably due to the potential reversibility of their underlying disorder, while the lowest survival rates were seen in patients with altered mental status (9.1 %), aplastic anemia (20 %), and renal/liver failure (23.8 %) [54].

Acute Fulminant Invasive Fungal Sinusitis and the Frontal Sinus

The frontal sinus is the most unlikely site of involvement in AFIFS, as only 4.8 % of cases in a large series demonstrated definitive histopathologic changes, and never in isolation from the other paranasal sinuses [19]. Though outcomes specifically for frontal sinus AFIFS are not reported in the literature, its proximity to the intracranial space would give AFIFS significant potential for untoward outcomes. Extended endoscopic techniques, such as the endoscopic modified Lothrop or Draf IIb, provide wide exposure of the frontal sinus to facilitate adequate biopsies and thorough debridement. Open frontal approaches, such as an osteoplastic flap, may be considered for wide exposure of the frontal sinus; however, this approach should be considered as a fallback option and the sinus must never be obliterated when addressing AFIFS. Wide access to the frontal sinus allows the surgeon clear access to both perform postoperative surveillance with routine office endoscopy as well as deliver topical antifungal medication via irrigations or nebulizer.

Chronic Invasive Fungal Sinusitis

Chronic invasive fungal sinusitis (CIFS) is a slowly progressive fungal infection with a typical time course over 12 months. This is further subdivided into granulomatous invasive fungal sinusitis (GIFS) and chronic invasive fungal sinusitis (CIFS) based on histopathology [10].

GIFS is a rare entity that is largely reported in Sudan, Saudi Arabia, and the Indian subcontinent. *Aspergillus flavus* is the most common fungus isolated in these patients [6]. It typically presents with an enlarging mass in the cheek, orbit, nose, and paranasal sinuses in immunocompetent hosts, with proptosis being a prominent feature. Histopathologically, a granulomatous response is seen with considerable fibrosis.

In contrast, CIFS is a slowly destructive process that most commonly affects the ethmoid and sphenoid sinuses, but may involve any of the paranasal sinuses. Histologically, it is characterized by dense accumulation of hyphae, occasional presence of vascular invasion, and sparse inflammatory reaction. The process is usually seen in the context of AIDS, diabetes mellitus, and corticosteroid treatment. Tissue cultures are positive in >50 % of cases, and *Aspergillus fumigatus* is the most commonly isolated agent [11, 41]. Most authors regard GIFS and CIFS as identical with respect to the, diagnostic evaluation, treatment options, and clinical course [6, 11, 53].

Typical patient presentation includes symptoms of chronic rhinosinusitis (CRS), made remarkable by their long duration, slow progression, and refractoriness to standard therapy. Patients are usually immunocompetent and, therefore, it is not until the development of associated ophthalmologic or neurologic findings, such as facial paresthesias, seizures, altered mental status, proptosis, or vision changes, that alternate diagnostic possibilities like GIFS or CIFS are explored [53].

Because of the chronicity of CIFS, coupled with concerning neurologic or ophthalmologic deficits, the differential diagnosis should include [47, 53]:

- Malignant processes
- Benign neoplasms
- Autoimmune disease
- Intracranial pathology
- Orbital neoplasms
- Unusual sinonasal infectious agents

Diagnosis

Diagnostic evaluation should begin with a complete head and neck exam, including nasal endoscopy and biopsy, as well as careful neurologic evaluation with cranial nerve testing to determine the extent of imaging that will be required initially. Neurologic or ophthalmologic deficits warrant a contrast enhanced MRI of the brain, orbit, and sinuses to evaluate for intracranial and orbital extension in addition to high-resolution coronal and axial CT scan of the sinuses to delineate the extent of paranasal sinus disease (Fig. 11.1a, b). Mucosal thickening and bone erosion may be noted and can mimic neoplastic lesions. MRI is useful in assessing dural and intracranial extension [22, 53]. However, a diagnosis of invasive fungal disease can only be established on histopathologic grounds, though imaging may shorten the differential diagnosis and guide directed biopsies [53].

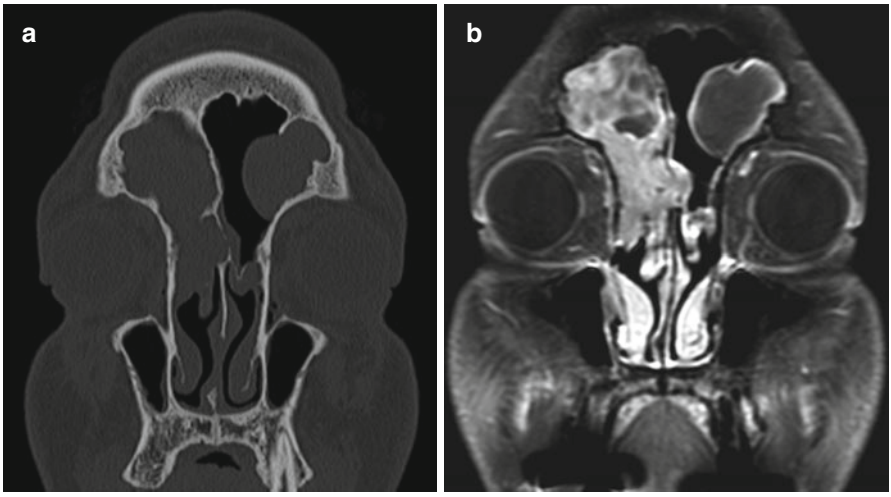

Fig. 11.1 (**a**) Coronal bone window CT scan demonstrates complete right frontal opacification in patient with known chronic granulomatous fungal rhinosinusitis (**b**). T1- weighted MRI with contrast demonstrates enhancing lesion in the *right* frontal sinus. In contrast, the *left* frontal sinus has a mucous retention cyst

Treatment of Chronic Invasive Fungal Sinusitis

The extent of surgery necessary to control CIFS is a point of controversy, as is the need for and duration of concomitant antifungals. A minority of authors draw a distinction between granulomatous and non-granulomatous CIFS, treating the non-granulomatous variety with aggressive surgery and antifungals as for AFIFS, with surgery alone being reserved for GIFS [11, 41]. The majority opinion favors debridement of all non-viable sinus tissue, preservation of as much normal anatomy as possible, and allowing prolonged culture-guided systemic antifungal medications to eliminate the remaining fungal infection [53]. Though the literature lacks definitive recommendations for duration of systemic antifungal therapy in CIFS, it may be possible to transition some postoperative patients to topical antifungal irrigations in an effort to avoid the renal toxicity of long-term amphotericin B.

Chronic Invasive Fungal Sinusitis and the Frontal Sinus

CIFS of the frontal sinus is not a well-documented entity, thus it is not clear that diagnostic or treatment strategies would vary significantly from those described for the other paranasal sinuses. Patients with symptoms of CRS refractory to medical therapy, especially persistent headache, visual changes or development of neurologic deficits require expeditious physical evaluation and appropriate imaging. Invasive infections of the frontal sinus have a predilection for early involvement of the intracranial space, either directly via bone erosion or angioinvasion of vessels

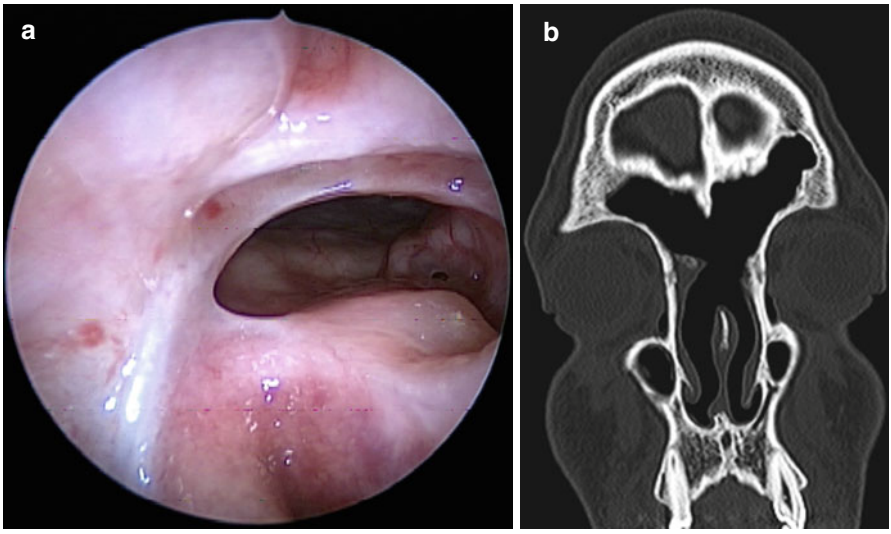

Fig. 11.2 (**a**, **b**) Endoscopic view at 1-year demonstrates patent frontal neo-ostium after Lothrop procedure. Corresponding coronal bone window CT demonstrates excellent frontal aeration

that traverse the posterior table. Aggressive surgical therapy is recommended to resect all visible frontal sinus disease and establish healthy tissue margins. An endoscopic approach is favored, with careful consideration of an osteoplastic flap to ensure clearance of all disease (Fig. 11.2a, b). Postoperative antifungal medication is initiated systemically, with conversion to topical irrigations as dictated by clinical response and follow-up endoscopy.

Paranasal Sinus Fungal Ball

Fungal ball (FB) best typifies non-invasive fungal disease of the paranasal sinuses, a condition resulting from sequestration of densely tangled, concentrically arranged masses of fungal hyphal elements within a sinus in the absence of mucosal invasion [12]. FB (formerly, and inaccurately, referred to as "mycetoma") has been reported since the late nineteenth century, though most early case series have been small owing to the relative infrequency of this condition. One series estimates FB represents 3.7 % of inflammatory sinus conditions [17]. Patients with FB are typically females (2.97:1, female:male ratio) with mean age of 52.7 years (range 19–85 years). The maxillary sinus is the most frequently affected (84.4 %), followed by the sphenoid sinus (14.4 %) [42]. Ethmoid and, especially, frontal sinus involvement is rare.

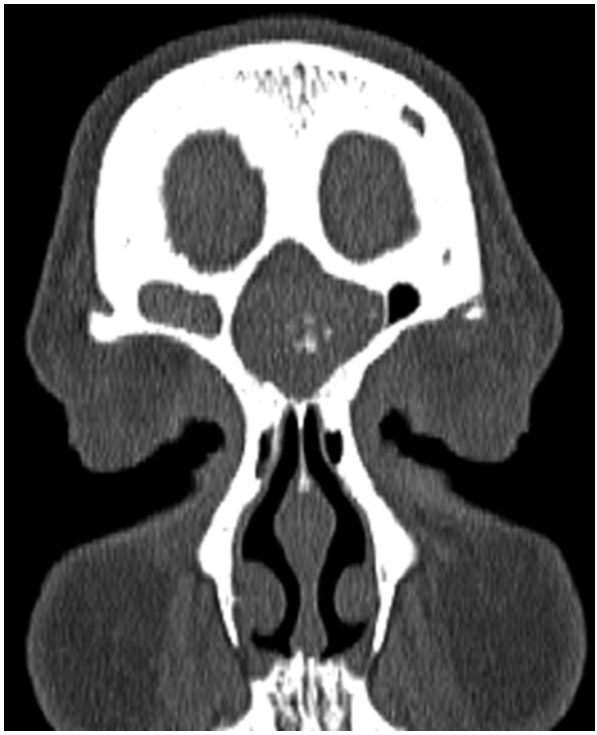

Fig. 11.3 Coronal CT scan demonstrates right frontal fungal ball with multiple areas of hyperdensity. This was cleared via endoscopic frontal sinusotomy

Clinical Presentation

Medical attention is typically sought for symptoms suggestive of CRS, with symptoms including facial pain or headache, nasal airway obstruction, or purulent rhinorrhea localizing to the side of the fungal ball [13, 15]. Patients with maxillary FB may present with facial or dental pain, initially being misdiagnosed as an odontogenic process. Sphenoid FB may present with vertex headaches and non-specific postnasal drainage, highlighting the need for imaging to elucidate proper diagnosis. Nasal endoscopy may demonstrate polyp disease in only 10 % of patients, and is more likely to show normal to mild mucosal inflammation without evidence of fungus or other revealing characteristics [25].

Radiology

CT scan of the paranasal sinuses is the study of choice for diagnosis of FBs, though imaging is certainly not diagnostic. Single sinus involvement is reported in 59–94 % of FB cases, almost always with near complete opacification of the involved sinus, and frequently demonstrating hyperdensity within the opacification (41 %) (Fig. 11.3) [17, 25]. Bony sclerosis of the involved sinus is common, as radiographic

evidence of this bony thickening is noted in 33–62 % in different case series [17]. In contrast, bony erosion, commonly seen in AFRS, is noted in only 3.6–17 % of CT scans of FB patients [17, 25].

Treatment of the Paranasal Sinus Fungal Ball

Complete surgical removal of the FB, with thorough irrigation of involved sinus and establishment of sinus ventilation, constitutes treatment of choice for this non-invasive fungal disease. Endoscopic techniques are usually sufficient to achieve these surgical objectives. Recent studies report recurrence rates of 3.7–6.8 % in those patients treated endoscopically [17, 25]. Postoperative antifungal therapy is not necessary unless the patient suffers from comorbid conditions with predisposition to compromised immune function. Progression from FB to AFIFS has been reported in patients with blood dyscrasias, diabetes mellitus, systemic corticosteroids, or other similar conditions associated with immunodeficiency [15]. In these patients, antifungal selection should be guided by fungal histology and culture results to identify the least toxic, most cost-effective agent available. Amphotericin B formulations should be restricted to cases in which culture results suggest resistance to imidazole antifungals [15].

Paranasal Sinus Fungal Ball and the Frontal Sinus

Frontal sinus involvement with FB is distinctly unusual. The first case of FB isolated to the frontal sinus was reported in 1978, successfully treated solely by removal via an osteoplastic flap approach [52]. Other studies attest to the relative rarity of this condition. Ferreiro reported an incidence of 21 % for FB involving the frontal sinus, with only 7 % of patients having disease isolated to this site alone [17]. Klossek et al. noted frontal sinus location in only 1.8 % of 109 patients with FB [25]. Difficult locations within the frontal sinus were addressed via a complete endoscopic anterior ethmoidectomy combined with irrigations through the anterior wall of the frontal sinus, successfully treating both cases of frontal sinus FB [25]. Indeed, the frontal sinus poses a significant surgical challenge for successful evacuation of a FB. Endoscopic frontal sinusotomy may be sufficient for successful extirpation of frontal sinus FB. This can be extended to a Draf IIb or III procedure based on the amount of frontal access required to achieve the surgical goals. Endoscopic frontal trephination may also serve as an additional porthole for irrigation of fungus in a difficult to reach frontal location. Osteoplastic frontal flap should be used as an absolute last resort for frontal FB; obliteration is contraindicated given it precludes the ability to monitor recurrent disease.

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) was initially described by Safirstein in 1976 who reported on a 24-year-old woman with recurrent nasal obstruction, mucosal ulcerations, thick secretions within the nose, and culture evidence of *Aspergillus* that resembled the clinico-pathologic findings of allergic bronchopulmonary Aspergillosis (ABPA) [46]. Several early authors further reported on these findings helping clarify this as a distinct disease entity [23, 39, 45]. Millar and colleagues reported on similarities between material obtained from the maxillary sinuses of five patients and pathologically diagnosed specimens of ABPA [39]. Katzenstein et al. retrospectively reviewed 113 consecutive cases, identifying seven young adults with asthma and nasal polyposis with similar findings and termed the condition allergic *Aspergillus* sinusitis [23]. Though *Aspergillus* was almost exclusively associated with the disorder in early descriptions, later studies have demonstrated that the dematiaceous family of fungus is present in a majority of cases of AFRS, giving credence to a more generalized term [30].

Pathogenesis

Despite improved understanding of the disease process and advances in treatment of AFRS, no single unifying explanation exists for the pathogenesis of AFRS. A popular theory, referred to as "the AFRS cycle," offers a preliminary construct through which the multifactorial process can be better understood. The theory posits AFRS as the sinonasal correlate of ABPA and depicts a cascading inflammatory cycle resulting in the diagnostic characteristics of AFRS [33, 34, 36, 37]. Disease initiation requires fungal antigens inhaled by an atopic host to generate Gel and Coombs type I (IgE) and, possibly, type III (immune-complex) reactions, which induce an intense eosinophilic inflammatory response. Increased IgE levels can be seen both systemically and within the eosinophilic mucin [8]. Patency of sinus ostia is compromised and resultant stasis facilitates fungal proliferation and production of viscid fungal mucin. This mucin accumulates within sinuses producing further obstruction perpetuating the AFRS cycle [21, 33, 36, 37].

Sequestered collections of mucin, the hallmark of AFRS, provoke changes in the effected sinuses consistent with those usually attributed to mucoceles [5, 36, 44]:

- Bony remodeling
- Bony erosion
- Extension into contiguous anatomic spaces

Persistence of the disease state allows inflammatory mediators to slowly damage the sinonasal mucosa [26]. These inflammatory mediators are:

- Major basic protein
- Eosinophil cationic protein

- Eosinophil peroxidase
- Eosinophil derived neurotoxin
- Tumor-necrosis factor-beta
- Interleukins 4, 5, 10, and 13

Epidemiology

AFRS is more commonly diagnosed in younger populations (average age 21.9–42.4 years) and may represent 5–10 % of all patients undergoing surgery for CRS [30, 36, 37]. Manning has suggested a slight male preponderance (1.6:1), though this is not borne out in other reviews [30]. AFRS also appears to disproportionately affect African Americans and patients of low socioeconomic class [56]. Multiple studies have depicted AFRS to have a geographic variability favoring temperate regions with relatively high humidity, especially Texas, the Mississippi River basin, and portions of the American southeast and southwest where AFRS may represent upwards of 20 % of all patients undergoing surgery for CRS [16].

Clinical Features

The unrelenting inflammation of AFRS can result in a host of patient signs and symptoms. Typical presentation includes unilateral symptoms suggestive of underlying CRS. Unchecked AFRS may lead to [5, 32, 34, 44]:

- Diplopia
- Proptosis
- Blindness
- Facial dysmorphia (hypertelorism, malar flattening)
- Intracranial extension
- Complete nasal airway obstruction

AFRS patients are atopic (>90 %) and frequently report history of allergic rhinitis and asthma; yet classic aspirin sensitive triad is not part of the disease constellation [36]. Typically, these patients have symptoms of sinusitis refractory to antibiotics, intranasal corticosteroids, immunotherapy, as well as attempts at prior surgery if eosinophilic mucin was not noted or collected at the time of operation; thereby failing to establish the correct diagnosis [21, 34, 36].

Diagnosis

The Bent and Kuhn criteria are generally regarded as the most well accepted diagnostic criteria for AFRS (Table 11.2) [2]. However, a positive fungal stain suffices for their requirement of a positive fungal culture. Fungal morphology is sufficient to establish the presence of fungi, and often specific enough to identify the responsible

Table 11.2 Bent and Kuhn diagnostic criteria for allergic fungal rhinosinusitis

1. Gel and Coombs type I (IgE-mediated) hypersensitivity
2. Nasal polyposis
3. Characteristic radiologic findings
4. Positive fungal stain and/or fungal culture
5. Eosinophilic mucin without fungal invasion into sinus tissue

Bent and Kuhn [2]

organism at the genus level [48]. Reliance on fungal cultures for diagnosis is hindered by the variable yield of such cultures (64–100 %) as well as techniques which may merely identify a saprophytic organism within the nose and not the fungus responsible for the patient's clinical findings [30, 36].

Eosinophilic mucin, a diagnostic criterion of AFRS, is perhaps the most specific finding of the disease and occupies a central role in the understanding of the pathogenesis, histology, diagnosis and treatment of the disease process. Eosinophilic mucin is thick, highly viscous, tan to dark green or brown material that may be removed from the sinuses with some difficulty. Extra-mucosal fungi are identified microscopically with various silver stains, while hematoxylin and eosin stains illustrate the sheets of eosinophils and Charcot-Leyden crystals within a mucinous background [21, 36].

Radiology

Diagnostic imaging findings in AFRS have been delineated in a number of retrospective reviews including both CT and MRI modalities. AFRS patients demonstrate bilateral disease in 51 % of cases, with asymmetric involvement in 78 % of reviewed cases [41]. Complete opacification of at least one sinus was noted in 98 % of reviewed cases.

Complete sinus cavity opacification is associated with the following signs that have become suggestive of AFRS (Fig. 11.4):

- Sinus expansion (98 %)
- Remodeling of the sinus walls (95 %)
- Bony erosion (91 %)

AFRS can also be characterized by the nature of CT scan attenuation and MRI signal intensities. Opacified paranasal sinuses have increased central signal attenuation on non-contrast CT, which correspond with hypointense areas on T1-weighted MRI and signal voids on T2-weighted MRI [31, 41].

These heterogeneous areas of signal intensity within opacified sinuses on soft-tissue CT algorithms are thought to result from heavy metal accumulations and calcium salt precipitation within inspissated mucin and debris [41]. The presence of hyperdensities on CT, corresponding to areas of signal dropout on T2-weighted MRI, can be highly suggestive, though not confirmatory, for the diagnosis of AFRS.

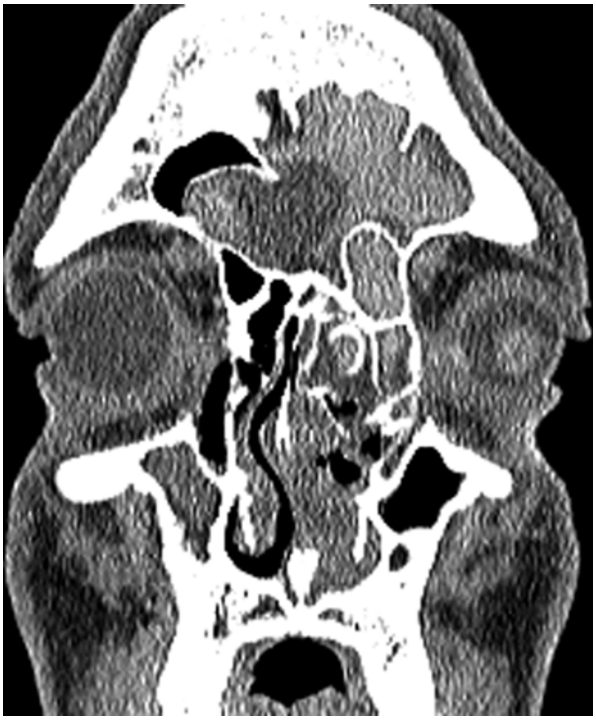

Fig. 11.4 Coronal CT scan with AFRS demonstrates expansion of the left frontal sinus with bowing of the intersinus septum. Complex pneumatization pattern, including an expansile type III cell, is noted in the left frontal recess

Surgical Treatment

Though the ideal treatment strategy for AFRS remains open for debate, comprehensive endoscopic sinus surgery forms the basic foundation for any successful intervention in this disease process. Functional endoscopic sinus surgery (FESS) techniques are employed to interrupt the "AFRS cycle" and set the stage for postoperative immune modulation.

The goals of sinus surgery are [35, 36]

- Complete removal of all eosinophilic mucin and fungal debris.
- Achievement of permanent drainage and ventilation of the affected sinuses while preserving underlying mucosa.
- Provide postoperative access to the diseased areas, such that adequate adjunctive topical care can be performed.

Preoperative antibiotics and corticosteroids (equivalent to 0.5–1.0 mg/kg/day of prednisone) are utilized to decrease generalized sinonasal inflammation and polyp volume, thereby improving visualization and decreasing bleeding at the time of surgery [36]. Meticulous postoperative care with serial endoscopic debridement is

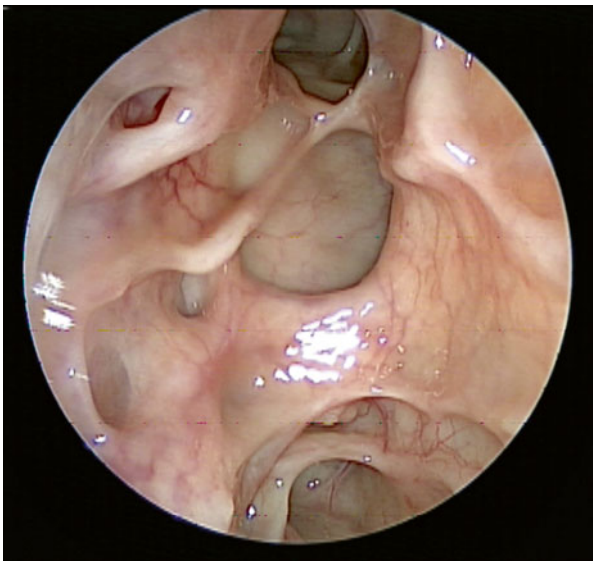

Fig. 11.5 Postoperative endoscopy demonstrates healed frontal internal ostium after comprehensive FESS in patient demonstrated in Fig. 11.4

imperative to achieve functional sinonasal cavities (Fig. 11.5). Patients are tapered from oral steroids over the ensuing weeks and transitioned to innovative topical therapies to minimize risk of relapse of AFRS.

Medical Treatment

The similarities between ABPA and AFRS play a large role in much of the current concepts of medical therapy for AFRS. Successful application of steroids in ABPA patients led to their introduction in AFRS cases. Decreased recurrence rates in those treated with steroids, and marked recidivism in those who discontinue treatment, have made systemic steroids an integral therapy for AFRS, though no consensus has been reached on the ideal dose or duration [3, 26, 49]. The addition of topical steroids within the newly ventilated sinonasal cavity is expected to assist in alleviating local inflammation, whereas preoperatively, this route is limited by obstructive nasal polyps [36]. A pilot study of CRS patients in 2009 suggested that the addition of budesonide suspension to nasal saline irrigations produces significant improvement in subjective patient symptoms based on a visual analog scale, as well as objective findings on CT and endoscopy [51]. This was followed by a trial of 111 patients who were randomized to receive daily irrigations of budesonide (1 mg) or betamethasone (1 mg) diluted in 240 mL saline. Improvements were noted in patient symptom scores, SNOT-22 scores, and endoscopy scores when compared to baseline ($p < 0.001$). In addition, patients with high tissue eosinophilia or nasal polyps

had greater improvement [50]. This technique allows for improved steroid contact with sinus mucosa but with less than 5 % residual of the total drug within the sinus, which is equivalent to that of standard nasal steroid sprays [20].

Institution of immunotherapy directed against fungal antigens should be considered in the postoperative period in order to modulate the patient's exuberant inflammatory reaction to fungi [28]. Retrospective data has shown that patients receiving immunotherapy have significantly better overall outcomes than those postoperative patients who declined or discontinued immunotherapy. Potential benefits include symptom control, decrease in the use of topical and systemic steroid use, reduction in revision surgery, and improvement in both subjective quality of life scores and objective assessments of the postoperative inflammatory state of the sinuses [1, 27, 29]. However, immunotherapy failed to show a significant impact on long term control of disease when patients are followed beyond the first 5 years as the disease may enter a quiescent state after successful initial control of the disease [38].

Additional adjunctive measures in the management of AFRS directly target the fungi that initiate the "AFRS cycle." Systemic antifungals have not clearly demonstrated their value in treating AFRS, and all are fraught with poor therapeutic indices, risks of serious medical complications, increased costs and uncertain duration of drug therapy [36]. Generally, systemic antifungal therapy is reserved for cases that are refractory to traditional treatment. Given that patients may inhale up to 5.7×10^7 spores of various fungi each day, it seems more efficacious to alter the host's immune response rather than expose the patient to chronic antifungal therapy [43]. Topical antifungals likely have lower risks of complications; however, their efficacy, as in systemic therapy, is limited to conjecture.

AFRS and the Frontal Sinus

The exact frequency with which the frontal sinus is involved in cases of AFRS is unknown, though one radiographic study puts the estimate as high as 71 % [41]. Proximity of the frontal sinus to both the anterior cranial fossa and orbit increases the precision required to address disease in this location. Accumulation of dense eosinophilic mucin, in a manner very similar to the pressure necrosis exerted by mucoceles, can cause dissolution and erosion of already delicate bone and extension of the process into the orbit or intracranial space [36]. Complete evacuation of eosinophilic mucin and fungal debris from the frontal sinus coupled with establishment of permanent ventilation and drainage is a requisite to successfully manage AFRS involving the frontal sinus. Preservation of the mucosa at the internal ostium is key to achieving long-term frontal recess patency. Typically, the fungal process will widen the frontal outflow drainage pathway, thus endoscopic frontal sinusotomy should be sufficient to achieve the surgical objectives [26, 36]. However, in cases with extensive fungal involvement or complex pneumatization patterns, Draf IIb or III may be required. If a frontal osteoplastic flap is required, Kuhn and Swain caution against frontal sinus obliteration in treating fungal disease, especially in complicated cases with erosion through the posterior table or orbital roof, as frontal

sinus mucosa cannot be removed completely from the underlying periorbita or dura [26]. Surgery should allow for postoperative visualization of the frontal sinus though the frontal internal ostium during clinic endoscopy to evaluate for recurrence of disease (Fig. 11.5). If re-stenosis of the frontal ostium is noted or there is significant recurrence of polyp disease, CT imaging may be warranted in monitoring for recurrent disease or frontal ostial stenosis with mucocele formation.

Conclusion

The accrued body of literature attests to the improved understanding of the role of fungus in paranasal sinus disease over the past 35 years. The frontal sinus is not a common location for fungal disease, and as such, most otorhinolaryngologists have limited experience in treating fungal pathology in this location. Indeed, the close proximity to critical structures and narrow confines of the frontal recess add to the surgical dilemma. Nonetheless, endoscopic frontal approaches, either through standard endoscopic frontal sinusotomy or extended drill-out procedures, allows for management of majority of fungal disease involving the frontal sinus. Further, a careful understanding of fungal sinus disease states, appropriate diagnostic investigation, and perioperative medical therapy, coupled with sound knowledge of the surgical anatomy of the frontal sinus, will provide patients the best opportunity for an optimal outcome.

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