Title: Fungal Frontal Sinusitis - Allergic and Non-Allergic

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Introduction

Fungal sinusitis can be a significant disorder in any of the sinuses and may prove problematic in the frontal sinus when severe. This chapter will delineate the different forms of fungal sinusitis and their discerning features as well as consider how the management of these conditions in the frontal sinus specifically may require additional challenges. To help illustrate this, a specific case example is included, that highlights these challenges.

Classification

Based on the clinical picture, imaging and histology, fungal sinusitis can be broadly classified into invasive and non-invasive fungal rhinosinusitis.

Invasive

Acute Invasive Fungal Rhinosinusitis (AIFRS)

Acute Fulminant Invasive Fungal Rhinosinusitis (AIFRS) is a potentially lethal disease entity with low survival rate (49.7%)[1]. It primarily affects patients with conditions associated with severe neutropenia (absolute neutrophil count [ANC] < 500/μL)[2] and/or impaired neutrophil function; i.e. patient undergoing transplantation, leukemia, uncontrolled diabetic ketoacidosis, patients receiving chemotherapy and hæmochromatosis[3 4] and especially those in receipt of bone marrow transplantation[5 6]. Although nonspecific, red flags for AIFRS include pyrexia and symptoms of localization to the paranasal sinus area (e.g. facial pain and pressure, nasal congestion, orbital swelling). Symptoms of greater concern include visual disturbances, paraesthesia and cranial neuropathy, indicating late presentation and more advanced disease. On endoscopic examination, the findings can range from oedema to dry or pale mucosa in the early stages to frank necrosis in the advance stages. The middle turbinate (67%) and the nasal septum (24%) are the most common sites to show clinical findings[4]. The genera of Aspergillus and Mucor are the most common organisms that have been associated with AIFRS[2 7],

hence why the condition is also sometimes known as mucormycosis. Histopathological features include fungi invading the mucosal barriers and tissue necrosis[8] [9]. Management requires an attempt at reversal of the underlying immunocompromised state and multidisciplinary approach is needed with both medical and surgical interventions. It is therefore important to have high index of suspicion in patients who are considered to be high-risk populations. This is accomplished by prompt biopsies being taken and pathologic evaluation in such patients. High-resolution, non-contrasted CT scan is crucial part for the work-up and MRI is recommended in patients who present with orbital or intracranial involvement signs or symptoms. Thickening of the peri-antral fat plane has been reported as an early indicator of AIFRS[10].

Chronic Invasive Fungal Rhinosinusitis (CIFRS)

CIFRS is encountered in patients who are not or with limited immunocompromised status such as diabetic or patients on long term corticosteroids[9]. It is slowly destructive disease over a time course of more than 12 weeks and can reach up to 12 months duration. Granulomatous Invasive Fungal Rhinosinusitis (GIFRS) is a subtype of CIFRS that is more commonly encountered in healthy and immune competent patients at the Middle East, North Africa and India[3]. Orbital and CNS involvement is less common than in AIFRS, although orbital apex syndrome is possible. Radiological findings include hyperdense soft tissue and bony involvement on CT scanning and very hypointense T2 signal on MRI with possible evidence of intracranial involvement.

CIFRS is distinguished histologically by the formation of non-caseating granuloma in which giant cells contain the hyphae reside[11]. Aspergillus flavus, Aspergillus fumigatus, Alternaria, P. boydii, Sporothrix schenckii are reported to be the organisms associated with CIFRS. The presentation does not differ from AIFRS but it is suspected when the symptoms of CRS are refractory to medical management and progressing in severity, especially persistent headache, visual disturbance or development of cranial nerve deficits. Tissue biopsy is the only definitive tool to diagnose CIFS[12] but radiological imaging will help and with surgical planning. Urgent endoscopic sinus surgery to debride the affected areas is needed along with

systemic antifungals and once controlled they should continue on itraconazole for up to 1 year. Recurrence is common and thus long-term follow up is needed to ensure the disease remains controlled.

Granulomatous Invasive Fungal Sinusitis (GIFS)

This form of invasive fungal sinusitis is attributed to infection with Aspergillus flavus and is principally seen in North Africa, India and Pakistan. The infection manifests as a locally invasive disease over at least 3 months duration but usually in immunocompetent patients. Typical presenting symptoms include those of CRS and possibly of proptosis or an enlarging mass in the affected sinus. Histological examination of material will show a pattern of non-caseating granulomas and of foreign body/Langhans giant cells with central necrosis. These cases need surgical debridement followed by systemic antifungal medication. Disease recurrence is uncommon and GIFS has a good prognosis.

Noninvasive

Eosinophilic fungal sinus disease

Eosinophilic fungal sinus disease, secondary to an over-responsiveness to fungus with or without fungal hypersensitivity, can be subdivided into:

- Allergic fungal rhinosinusitis (AFRS)
- Eosinophilic mucinous/fungal rhinosinusitis (EMRS/EFRS)

Allergic Fungal Rhinosinusitis (AFRS)

Allergic fungal rhinosinusitis (AFRS) may be considered a form of chronic rhinosinusitis (CRS) and accounts for 7-10% of CRS. In the late 1970's AFRS was recognized as an upper airway manifestation of allergic bronchopulmonary aspergillosis (ABPA)[13] [14]. It was in 1994 that Bent & Kuhn defined the 5 diagnostic criteria for AFRS (table 1)[15] [16]. The name itself may indeed be a misnomer as a type I hypersensitivity reaction is not always proven despite the evidence of the other key clinical features and a modified version has been proposed whereby immunocompetence replaces type I hypersensitivity, reflecting the group of

characteristic patients seen in rhinologic practice[17]. The constant features in these patients are a distinct clinical pattern of recurrent nasal poylposis and accumulation of fungal mucin. AFRS classically involves all sinus cavities with impacted thick mucin, polyps and chronic inflammation with pushing bony margins. Radiological changes include double densities with a railtrack pattern in the sinus, sinus expansion, remodeling of the sinus wall and bony erosion on CT imaging and hypointense areas on T1 and signal voids on T2 on MRI[18].

Isolated fungal frontal sinusitis is rare and only few case reports are available in the literature[19]. Their consistent clinical pattern is the key factor in their management as, unlike the management of classical CRS, the cornerstone for treatment of AFRS is surgery. They require meticulous and complete endoscopic sinus surgery (see below), along with careful and regular follow-up in the outpatient clinic in order to try and prevent the polyp reformation and accumulation of mucin and a comprehensive postoperative medical regimen is almost always a necessity[20].

Eosinophilic Mucinous Rhinosinusitis (EMRS)

In a study conducted by Ponikau et al. on CRS patients, 93% of the patients undergoing sinus surgery had both eosinophilic mucin and fungus[21]. However less than half of their sample of almost 100 patients in whom eosinophilic mucin and fungus were present were allergic. They demonstrated the movement of eosinophils out of blood vessels and into the sinus cavity to engulf fungal hyphae. They proposed that a cell-mediated response provoked by fungi in susceptible hosts was responsible and coined the term EMRS. Some studies attempted to differentiate EMRS and AFRS patients based on demographics. They suggested EMRS patients to be relatively younger, less likely to have asthma and aspirin sensitivity and more likely to have bilateral disease when compared with AFRS patients[22]. However, in reality, there is overlap in the clinical pictures between EMRS and ARFS[23]. Orbital involvement and higher IgE levels have been found to be more common in AFRS patients. This may be due to variations in climate, genetic susceptibility and socioeconomic factors. Orlandi et al carried out a microarray gene analysis between these two subgroups[24]. They showed 38 genes or potential

genes were differentially expressed in AFRS patients, while 10 genes were differentially expressed in EMRS patients.

Sinus mycelia

Sinus mycelia, also known as fungal balls, represent an accumultation of fungal material in which the immune system is neither over- nor under-responsive. They are mainly caused by Aspergillus species e.g. Aspergillus fumigatus in immunocompetent patients. Demographics include being more common in middle-aged and elderly females, in contrast to all forms of invasive and chronic aspergillosis, which are more common in males. Typical presentation is with symptoms relating to chronic sinusitis of one sinus, which is usually the maxillary and less commonly the sphenoid sinus, but they can be incidental findings on CT scans requested for non-sinugenic causes/symptoms. Typical symptoms, if present, include nasal discharge, nasal obstruction, headache, facial pain and cacosmia, the latter of which may be a predominant symptom. Occasionally they can be associated with unilateral proptosis and facial hypoaesthesia.

Radiological imaging (CT scan) will demonstrate a unilateral, single sinus disease with heterogeneous opacification (Figure 2). Fungal cultures are positive in less than one third of patients despite fungal elements on histopathology in more than 90% of those affected. There is no predominance of eosinophils or granulomata or allergic mucin, and no histopathological evidence of fungal invasion of mucosa. Treatment is surgical, invariable an endoscopic approach to remove fungal ball and open affected sinus; however in an asymptomatic patient a discussion about watchful waiting may be needed depending on the age and co-morbidities of the patient. At surgery the sinus full of dense brown/green material which requires irrigation to help dislodge (Figure 3). Following removal of the fungal ball, no antifungal treatment is required and no long-term follow-up required once patency and healing of sinus is confirmed endoscopically in clinic.

Special considerations in frontal sinus fungal disease

The frontal sinus is the least susceptible to fungal infection due to the location of the ostium. Acute fulminant and chronic invasive fungal sinusitis therefore rarely

involve the frontal sinus with only 14.8% of cases being reported to involve the frontal sinus in a large case series[25]; other series have reported slightly higher levels of involvement (17-21%)[26 27]. Fungal ball involvement of the frontal sinus is also rare[19 28]. There are few case reports in the English literature describing primary sinus mycelia in the frontal sinus, with several authors advocating an external approach for its management[19 29 30] .

In contrast, it is estimated that 71% of AFRS cases have frontal sinus involvement [31]. The relatively thin bones that are in close proximity to the frontal sinus (lamina papyracia, cribriform plate) are more susceptible to changes in a manner equivalent to pressure necrosis secondary of the accumulation of dense eosinophilic fungal mucin. This may result in erosion and extension of the disease to the orbit and intracranial space[32], but is a more indolent process than is seen in the invasive forms of fungal disease.

Medical Management

Acute Invasive Fungal Rhinosinusitis is routinely managed both medically with systematic antifungal therapy in conjunction with surgical intervention. Amphotericin-B in liposomal formulation is the mainstay therapy for the past 50 years[4 33]. Topical antifungal therapy should be considered as well[34]. A patient who recovers their neutrophil count and function has a better prognosis[35].

Surgical and Post-operative Management in the Frontal Sinus

Acute Invasive Fungal Rhinosinusitis depends highly on surgical debridement. Resection of gross necrotic tissue is required and sometimes requires stages approach. Aggressive debridement and early diagnosis are associated with positive prognostic factors[36].

Fungal balls involving the frontal sinuses have been treated traditionally with external approaches. However, with the advancement in surgical techniques and instrumentation, endoscopic eradication is achievable with or without external trephination in an “above and below” fashion[37]. The surgical management of CIFRS does not differ from that of AIFRS and radical surgical resection and intravenous

amphotericin B is recommended [38-41].

In AFRS, the surgery aims to eradicate all eosinophilic mucin and fungal debris, provide adequate ventilation and drainage to the sinus, and facilitate postoperative access for debridement and monitoring of disease[32]. In cases with extensive fungal disease that is difficult to control post-operatively in the clinic, revision surgery with Draf IIb or III may be required. Frontal sinus obliteration must not be used if frontal osteoplastic flap is considered as it is almost impossible to eradicate all mucosal disease and recurrence is high[42]. Monitoring of disease status requires a combination of symptom reporting with patient reported outcome measures such as the SNOT-22 and endoscopic examination and staging systems can help to track fluctuations between visits[17]. Table 2 shows the Philpott-Javer staging system devised as a more specific method of tracking all sinus cavities and the olfactory cleft in AFRS. Patients with AFRS appear to show good correlation between subjective and objective measures of disease, especially with reference to olfaction[43].

Case example

A 24-year-old male presented with severe allergic fungal rhinosinusitis (AFRS). Initial assessment revealed grade 4 polyposis bilaterally with evidence of allergic mucin. IgE levels were consistently over 5000 throughout the course of medical and surgical management. He underwent primary complete bilateral computer-assisted sinus surgery (BiCASS) in 2012 where he was identified to have left-sided orbital and intracranial extension. Despite aggressive topical and oral therapies and appropriate medical management, he continued to have severe allergic mucin and development of polyposis, 3 months post-surgical intervention. He underwent revision surgery one year later, where he was identified to have significant fungus with extensive disease in the left supra-orbital ethmoid cells, lateral left frontal recess and extending into the crista galli. There was evidence of dehiscence of the anterior and posterior tables of the left frontal sinus. A frontal trephine and wide frontal sinostomy was required to access the deep and lateral cavities. Post-operative maintenance therapy included a low dose daily oral Prednisone (5mg), topical pulmicort via MAD syringe, and oral itraconazole. Unfortunately the patient

was lost to follow-up for 1 year and upon presentation, he was identified to have severe recurrence of AFRS. He was commenced on oral and topical therapy but was again lost to follow-up. He presented in 2015 with left frontal facial swelling and significant left frontal headache. He was subsequently taken to the operating room for revision BiCASS and left frontal resection of mucocoele and fungal mucin. The frontal sinus recess was resected and marsupialized bilaterally and the lateral recess was debrided bilaterally and cleared of inflammatory disease. Despite the use of angled 70 and 90-degree scopes and accompanying angled instrumentation specifically designed for use in the frontal sinus, it was challenging to visualize and completely remove all fungal debris due to its extension laterally within the frontal sinus, as well as the presence of deep cavities harbouring disease. In such cases, it is prudent to utilize angled instrumentation and scopes to visualize and reach such extensive frontal sinus disease in order to ensure complete removal of fungal debris. Post-operatively the patient did well and at his last visit 6 months post-operatively, he was identified to have completely clear sinus cavities bilaterally, with no evidence of mucin or polyposis.

Figure 1: Frontal sinus filled with dense fungal mucin

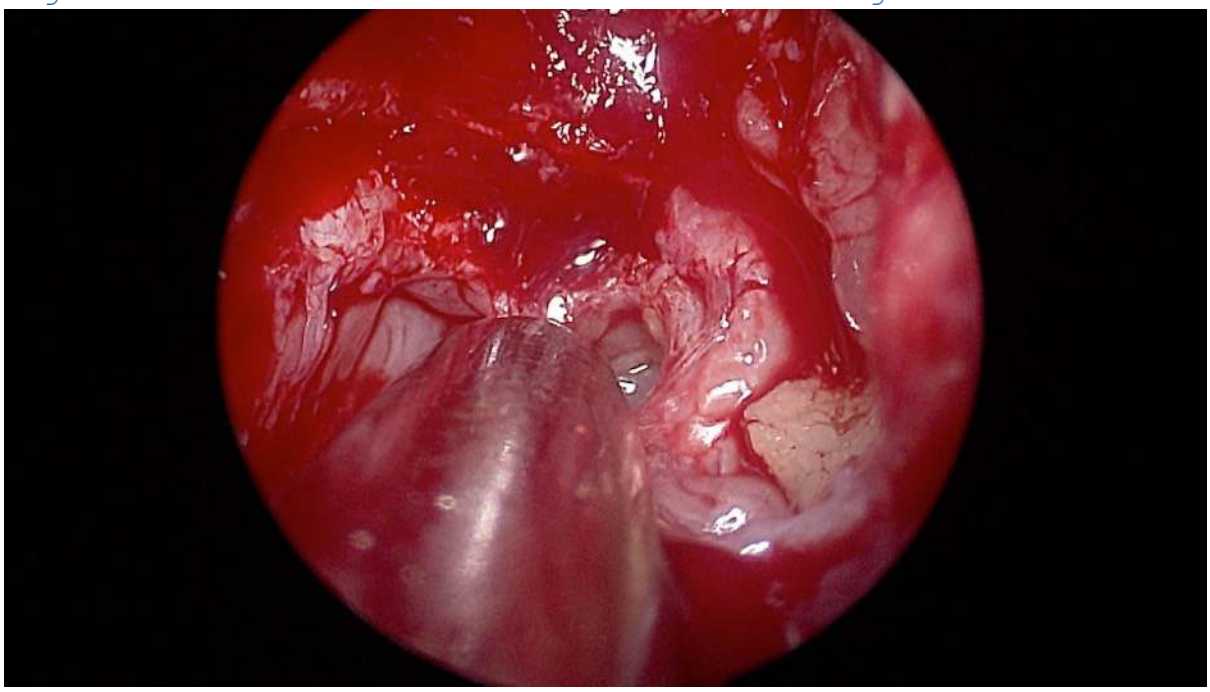


Figure 2: Bony expansion around left frontal sinus

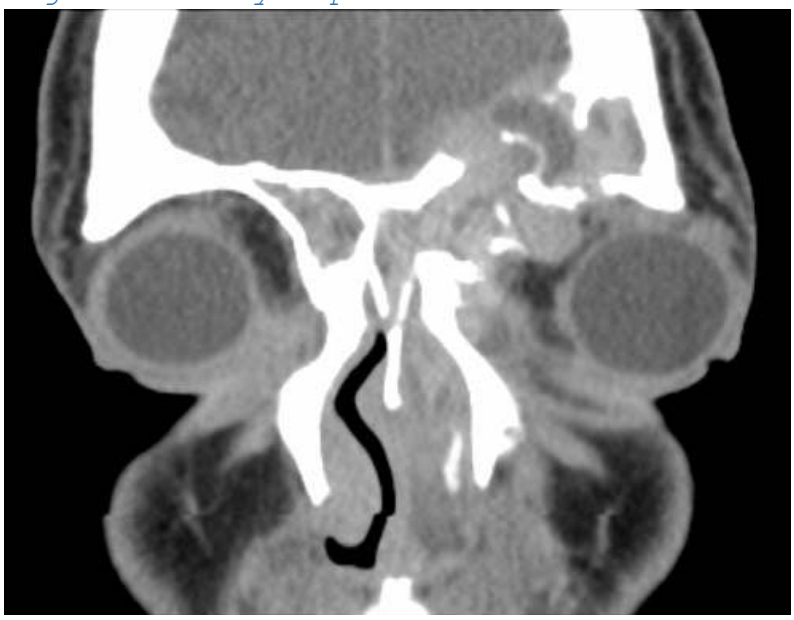
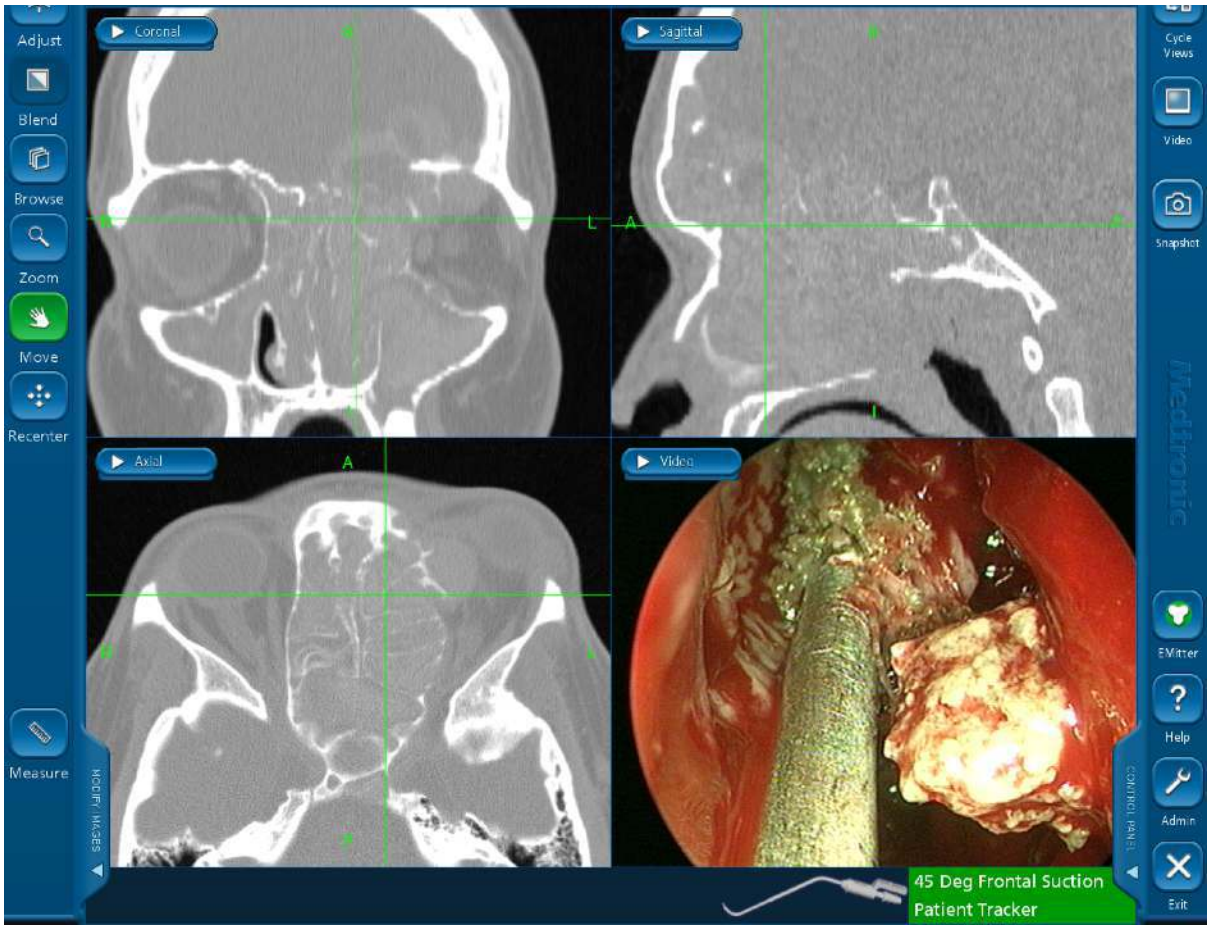
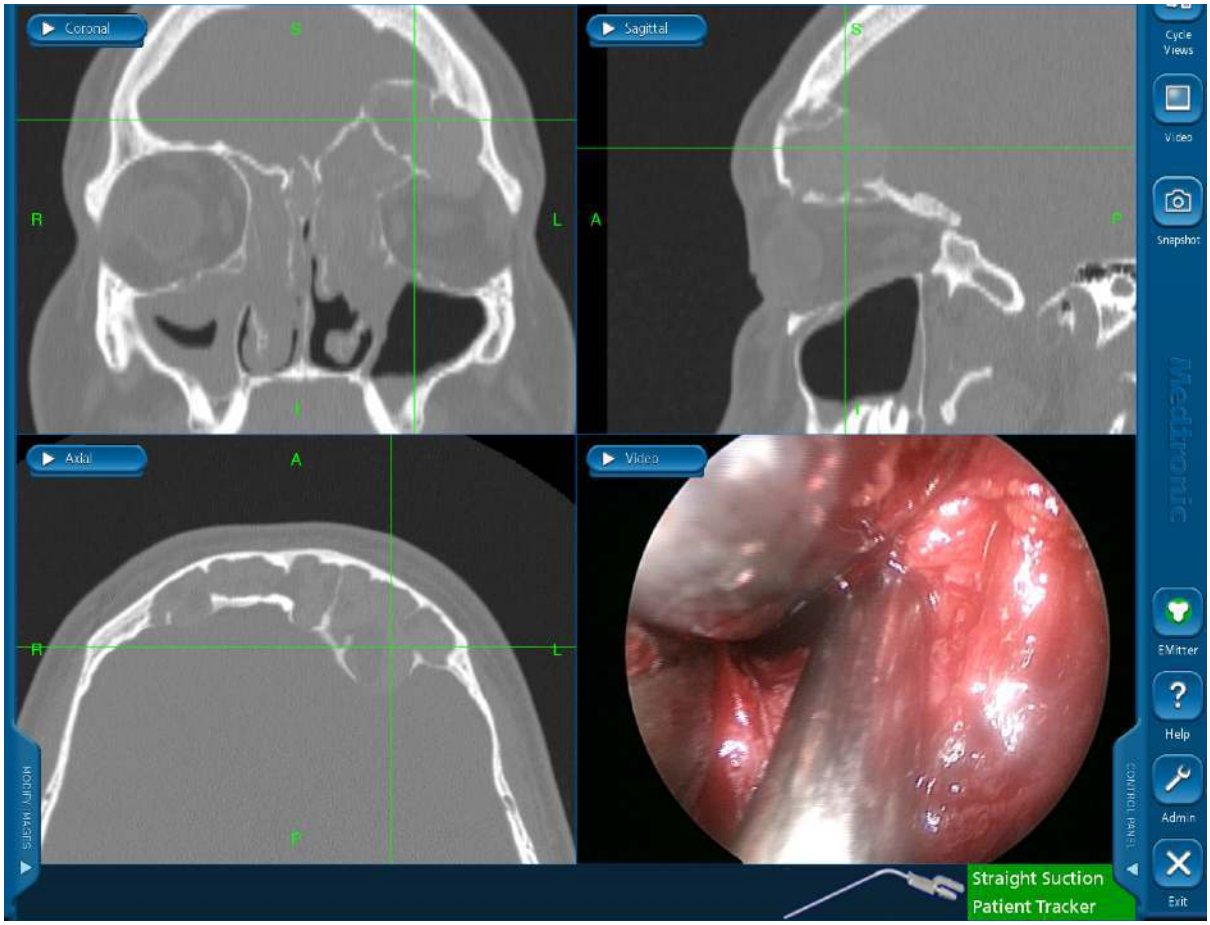


Figure 3a and b: Image guidance views at the back of the left frontal recess and in the left frontal sinus





Conclusion

Fungal sinus disease involves a spectrum of severity from invasive and potentially fatal infection to benign affectation with poor quality of life and high rates of potential relapse. Ultimately most scenarios involve the need for some form of surgical debridement; in the frontal sinus this will bring specific challenges for access and the surgeon tasked with these cases must have the skills and equipment to be able to tackle the varying scenarios to ensure success. In the case of AFRS, long-term follow up of patients will be needed to maintain control of the disease with an emphasis on compliance for the patients. With increasing understanding of disease endotypes, perhaps in the future we will see more focused treatment from the outset in such patients.

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Table 1: Diagnostic Criteria for AFRS – Bent & Kuhn¥/ Vancouver*

Major	Minor
Type 1 hypersensitivity¥/ Immunocompetence*	Asthma
Nasal polyposis	Unilateral disease
Characteristic CT findings	Bone erosion
Eosinophilic mucin without invasion	Fungal cultures
Positive fungal stain	Charcot-Leyden crystals
	Serum eosinophilia

Table 2a and 2b: Philpott-Javer Endoscopic Staging system for AFRS

Grading	State of mucosa
0	No oedema
1-3	Mucosal oedema (mild/moderate/ severe)
4-6	Polypoid oedema (mild/moderate/ severe)
7-9	Frank polyps (mild/moderate/severe)

Sinus cavity	Right	Mucin	Left	Mucin
Olfactory cleft	0-9	1	0-9	1
Frontal	0-9	1	0-9	1
Ethmoid	0-9	1	0-9	1
Maxillary	0-9	1	0-9	1
Sphenoid	0-9	1	0-9	1
Total (maximum score)		50		50

Bilateral total	100