

Pathology of Fungal Rhinosinusitis: A Review

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Abstract Fungal rhinosinusitis (FRS) comprises a spectrum of disease processes that vary in clinical presentation, histologic appearances, and biological significance. FRS can be acute or chronic and is most commonly classified as non-invasive or invasive based on whether fungi have invaded into tissue. This manuscript will review the pathologic classification of FRS.

Keywords Rhinosinusitis · Fungal ball · Allergic fungal rhinosinusitis · Acute invasive fungal rhinosinusitis · *Aspergillus* · Allergic mucin

Introduction

Fungal rhinosinusitis (FRS) comprises a spectrum of disease processes, which vary in clinical presentation, histologic appearances, and biological significance. FRS can be acute (aggressive; symptoms <30 days), subacute (symptoms 30–90 days), and chronic (indolent; symptoms >90 days) [1–7]. FRS is most commonly classified as non-invasive or invasive based on whether fungi have invaded into tissue. While FRS has been medically known for decades, it has been more recently that FRS terminology and pathologic classification has been further defined and reviewed [1, 2].

Fungal Rhinosinusitis: Classification

As noted above, FRS is classified as either non-invasive or invasive. Non-invasive sinonasal fungal diseases include: saprophytic fungal infestation, fungal ball, and allergic fungal rhinosinusitis. The invasive forms of FRS include: acute, chronic, and chronic granulomatous. While non-invasive FRS is a serious condition requiring surgical and medical intervention, invasive forms of disease more often result in significant morbidity and mortality, particularly if left untreated.

Non-invasive Fungal Rhinosinusitis

Saprophytic Fungal Infestation

The recently proposed FRS guidelines added an additional category for non-invasive FRS referred to as saprophytic fungal infestation [1, 2]. This category was proposed to classify fungal colonization of the sinonasal tract usually following a surgical procedure or traumatic event that results in inflamed and ulcerated/crusted sinonasal mucosa with the presence of surface fungal infection without tissue invasion. While this form of FRS has been least described in the literature, it is felt that this form of FRS may precede the development of a “fungus” ball.

Fungal Ball

A second form of non-invasive FRS is the fungal ball, an extramucosal, entangled mass of fungi usually associated with minimal mucosal inflammation [1–7]. The most recent FRS guidelines consider fungal ball to be the most appropriate term for this entity as opposed to

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previously used terms, such as “mycetoma” (a term used to describe a chronic, soft tissue granulomatous fungal infection) and “aspergilloma” (fungal organisms other than *Aspergillus* sp. can cause a fungal ball) [1, 2]. For unknown reasons, fungal balls are more commonly identified unilaterally in the maxillary sinus in middle aged to elderly females [6, 8, 9]. Histologically, fungal balls are characterized by entangled masses of fungal organisms or masses of fungi embedded in fibrinous, necrotic exudate, with minimal mucosal inflammatory reaction (Fig. 1). By definition, no tissue invasion or granulomatous reaction is present in the surrounding tissue [1, 2]. On low power, microscopic examination of a fungal ball may be confused with the eosinophilic (allergic) mucin seen in allergic fungal rhinosinusitis, particularly since both have a “layered” appearance. However, this confusion is lost on high power which reveals abundant fungal organisms. While prior surgery has been considered a risk factor for fungal ball development, in a recent large study, only one patient had sinonasal surgery prior to the fungal ball development; however an association with prior dental procedures has been proposed [8]. In addition, fungal balls may develop

when there are blockages of the sinonasal passages such as the presence of an obstructing neoplasm. Fungal cultures are often negative; however the most commonly isolated pathogen is *Aspergillus* sp. [3–6, 8–12]. Treatment consists of surgical removal of the fungal material without the need for antifungal therapy.

Allergic Fungal Rhinosinusitis

Allergic FRS is not considered to represent a true fungal infection but is rather a result of an inflammatory reaction toward fungi in the sinonasal tract [13–18]. Interestingly, fungi begin to inhabit the sinonasal tract during the first few months of life [19]; however only a fraction of individuals develop allergic FRS. Allergic FRS occurs in immunocompetent, atopic patients who present with symptoms of chronic rhinosinusitis (CRS) not responsive to standard conservative medical therapy. Allergic FRS is seen more commonly in warm humid climates such as in the southern and southeastern United States, India, and the Middle East, although a high incidence has also been reported in large urban areas in the Midwest and north-eastern United States [3–6, 10–12].

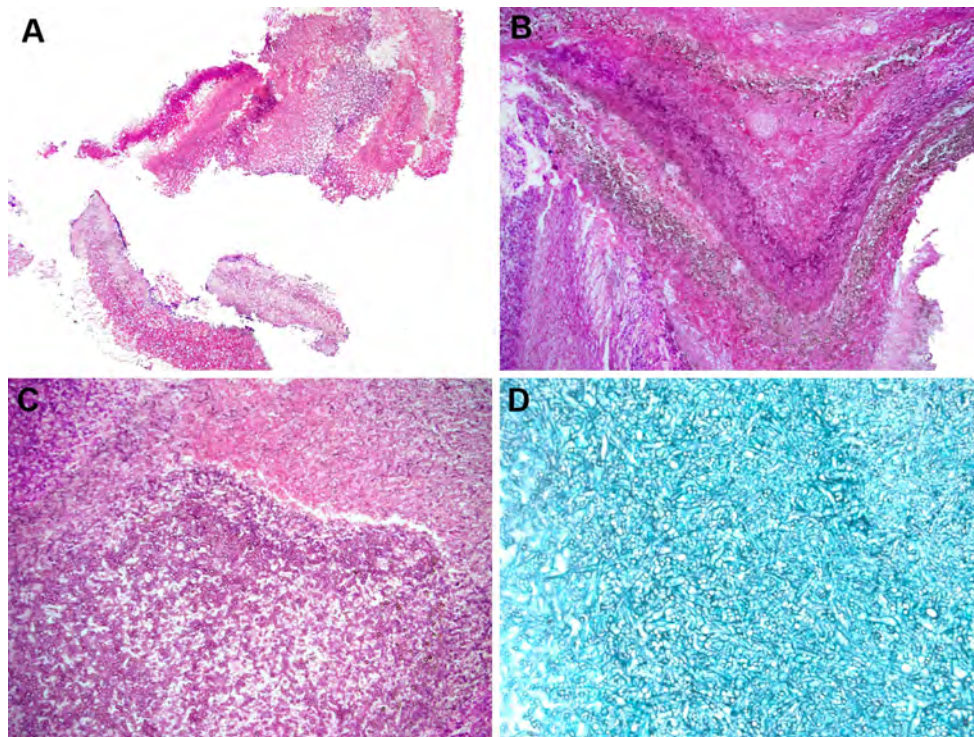


Fig. 1 Fungal ball **a** low power appearance of a maxillary sinus fungal ball from a 60 yo female. Fungal ball is composed of an entangled mass of fungal organisms (Hematoxylin and eosin; original magnification $\times 10$). **b** Low power of a fungal ball showing a lamellated appearance, which can be confused with eosinophilic (allergic) mucin (EM). This fungal ball shows a layered appearance

and pigmented fungal forms. Cultures grew *Aspergillus niger* (Hematoxylin and eosin; original magnification $\times 25$). **c** Higher power of fungal ball showing an entangled mass of fungal organisms with very little inflammation (Hematoxylin and eosin; original magnification $\times 50$). **d** Silver stain highlighting fungal organisms in a fungal ball (Grocott stain; original magnification $\times 100$)

Grossly, the sinus contents from allergic FRS patients are described as inspissated, clay-like, mucin which is green, brown, or grayish in color. Microscopic examination shows eosinophilic (“allergic”) mucin that contains mucin admixed with sloughed epithelial cells, eosinophils, Charcot–Leyden crystals, eosinophilic debris, and other inflammatory cells arranged in a laminar pattern and associated with rare, scattered fungal hyphae (Figs. 2, 3). Eosinophilic mucin is now the preferred term instead of allergic mucin since there is debate regarding whether the etiology of this mucinous material, as well as allergic FRS, is allergic at all [1, 2, 17, 18, 20–29]. Fungal hyphae are occasionally seen on H and E stain but are best highlighted by histochemical stains such as silver or periodic acid Schiff (PAS) (Fig. 3). All of the material received from sinus contents of suspected allergic FRS patients should be histologically examined since fungal hyphae are often scarce. When positive, cultures from allergic FRS patients most commonly grow Dematiaceous fungi such as *Alternaria* sp., *Bipolaris* sp., *Curvularia* sp., etc. or *Aspergillus* sp. depending on geography [3, 4, 6, 10–12]. In India as well as Saudi Arabia, *Aspergillus flavus* appears to be the most common fungal organism cultured in allergic FRS; however, in the US, particularly in the South and

Southeast, the majority of allergic FRS cases (70–90 %) are associated with dematiaceous fungi [10–16, 30]. Alternatively, in the Midwest and Northeastern US, equal incidences of dematiaceous fungi as well as *Aspergillus* sp. have been identified in allergic FRS patients [3–7]. Multiple fungi cultured in the same patient are not uncommon. A limited study using in situ hybridization found that about 50 % of allergic FRS patients contained *Aspergillus* or *Penicillium* rRNA in the eosinophilic mucin [31] (Fig. 3). Recent in situ hybridization (ISH) assays have also been developed to detect dematiaceous fungi in allergic FRS [32].

Eosinophilic mucin has also been described in patients without identifiable evidence of fungal infection by histology or conventional culture, particularly those with aspirin sensitivity syndrome. Ferguson coined the term eosinophilic mucinous rhinosinusitis to describe patients with eosinophilic mucin but without the presence of fungal organisms [33]. In Ferguson’s experience, patients with eosinophilic mucinous rhinosinusitis were clinically different from allergic FRS patients including presentation at an older age, an association with asthma and a significantly higher risk of aspirin sensitivity syndrome. However, eosinophilic mucinous rhinosinusitis as a distinct entity has

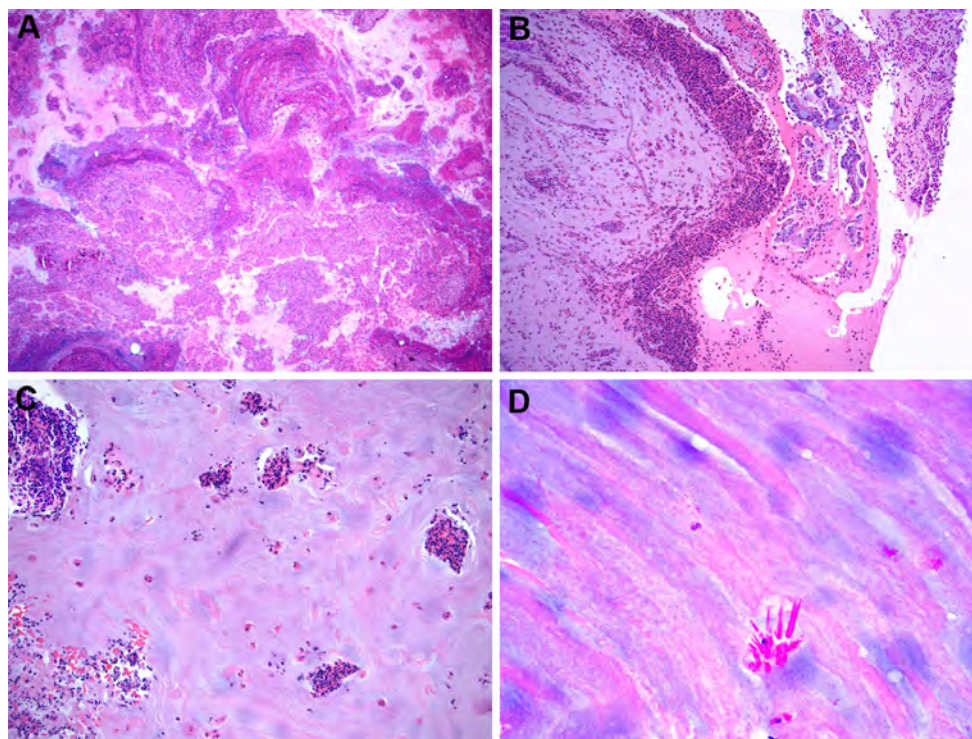
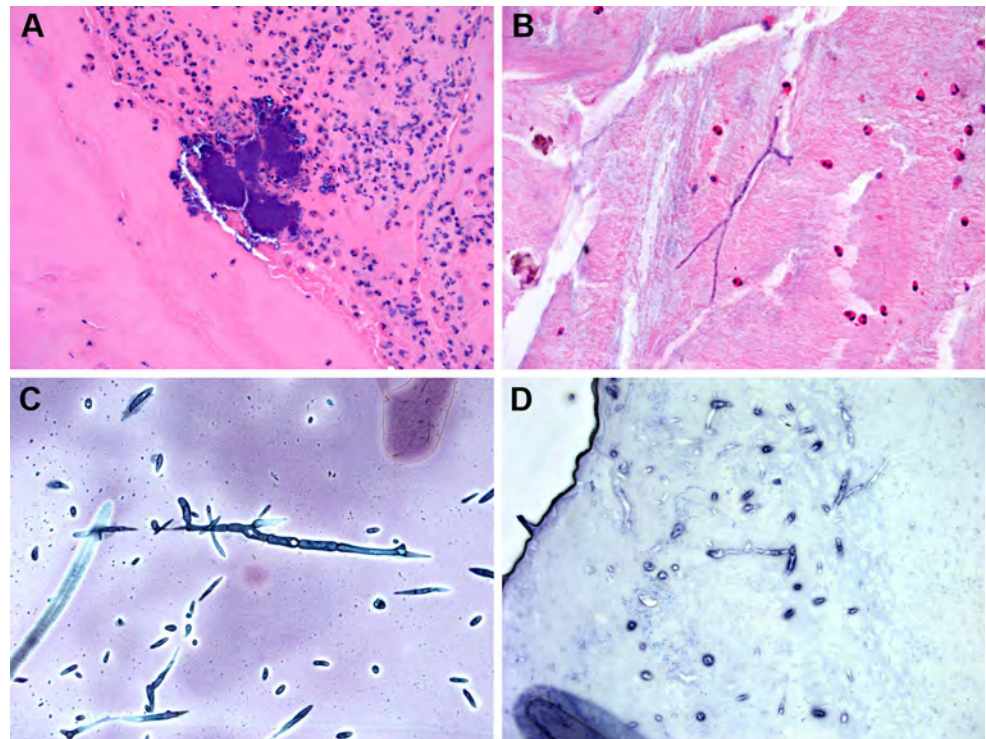


Fig. 2 Allergic fungal rhinosinusitis **a** low power of eosinophilic (allergic) mucin showing a layered appearance of mucin admixed with inflammatory cells and debris (Hematoxylin and eosin; original magnification $\times 10$). **b** Eosinophilic mucin showing collections of eosinophils and sloughed epithelial cells (Hematoxylin and eosin;

original magnification $\times 50$). **c** Eosinophilic mucin showing eosinophils singly and in cluster (Hematoxylin and eosin; original magnification $\times 50$). **d** Eosinophilic mucin showing Charcot–Leyden crystals (Hematoxylin and eosin; original magnification $\times 200$)

Fig. 3 **a** Eosinophilic mucin often contains bacterial colonies (Hematoxylin and eosin; original magnification $\times 100$). **b** Rarely, fungal organisms may be seen in eosinophilic mucin without use of special stains. Cultures grew *Curvularia* sp. (Hematoxylin and eosin; original magnification $\times 100$). **c** Silver stain of fungal organisms in eosinophilic mucin. Cultures grew *Alternaria alternata* (Grocott stain; original magnification $\times 200$). **d** In situ hybridization for *Aspergillus* ribosomal RNA in eosinophilic mucin. Cultures confirmed *A. fumigatus*. (Nitroblue tetrazolium violet; original magnification $\times 100$)



been called into question by those that feel that sensitive methods to evaluate for fungus have not been applied fully to these patients [20, 21, 26, 29]. Guo et al. [34] using conventional Gomori methenamine silver stain (GMS) on eosinophilic mucin observed fungal organisms in only 27 % of specimens; however with trypsin pre-digestion followed by GMS, the yield was increased to 91 % of specimens. In addition, using antibodies targeting chitinase and *Alternaria* sp. antigens, fungi have been reported in 90–100 % of eosinophilic mucin samples, even those negative for histochemical stains [34].

The pathogenesis of allergic FRS is not completely understood. It is believed that allergic FRS is a host reaction to fungal proteins and not an actual fungal infection. Initially allergic FRS was considered a type I hypersensitivity reaction to fungi. In fact, using the diagnostic criteria of Bent and Kuhn [35], hypersensitivity to fungi is essential to the diagnosis. However, not all patients with the pathologic diagnosis of allergic FRS have systemic (or even local) hypersensitivity to fungi. More recent studies indicate that fungi induce production of eosinophil attracting T_H2 cytokines and the subsequent inflammatory reaction produced results in the formation of allergic mucin [7, 17, 18, 20, 29]. Fungal proteases can induce the production of cytokines attract an influx of inflammatory cells including eosinophils which migrate through the barrier epithelial cells in response to fungi present. Interestingly, a recent review of FRS observed that a marked eosinophilic

sinonasal mucosal infiltrate preceded the observed presence of fungi (either by histology or by culture) in over 30 % of allergic FRS patients [6]. Treatment of allergic FRS remains controversial but mostly the disease is treated with surgical removal of the eosinophilic mucin and steroids, although some advocate utilization of antifungal therapy.

Invasive Fungal Rhinosinusitis

Acute Invasive Fungal Rhinosinusitis

Acute invasive FRS is a devastating form of sinonasal fungal disease, which is characterized by rapid onset (<4 weeks' duration) and an aggressive clinical course, particularly if untreated [1–7, 36–38]. Acute invasive FRS is seen in immunocompromised patients, particularly those with hematologic malignancies with low absolute neutrophil counts. Grossly, the mucosa appears pale and necrotic due to vascular thrombosis from fungal invasion. Histologically, the mucosa shows infarction vascular thrombosis and usually scant inflammatory cells. Close review shows angioinvasion of fungal forms resulting in luminal thrombosis. While the fungi are usually seen on routine H and E stains, silver and PAS stains are often useful at highlighting the organisms particularly in vessel walls and vascular space lumens where they are often

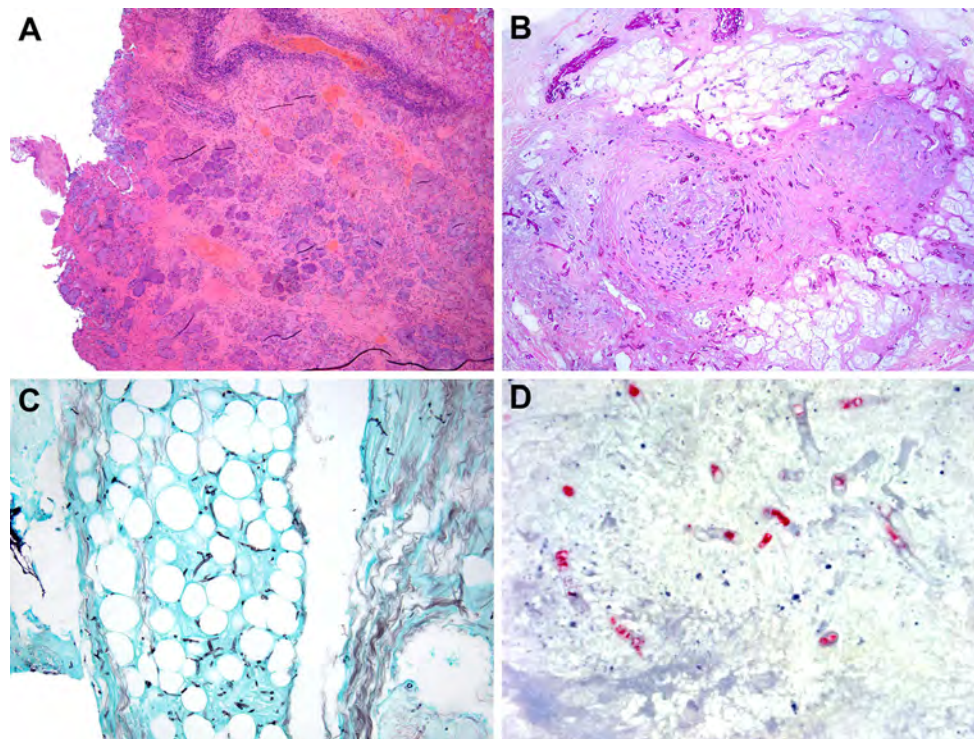


Fig. 4 Acute invasive fungal rhinosinusitis **a** low power view of infarcted sinonasal without significant inflammatory reaction in immunosuppressed patient with acute leukemia with acute invasive fungal rhinosinusitis Culture grew *Rhizopus* sp. (Hematoxylin and eosin; original magnification $\times 12.5$). **b** Acute invasive FRS showing fungal organisms invading blood vessels and soft tissue. Cultures grew *Aspergillus fumigatus* (Hematoxylin and eosin; original

magnification $\times 100$). **c** Silver staining highlighting fungal hyphae in soft tissue in acute invasive FRS. Cultures grew *A. fumigatus* (Hematoxylin and eosin; original magnification $\times 100$). **d** In situ hybridization (ISH) for *Aspergillus* ribosomal RNA. Note the extensive necrosis and only rare positive organisms. rRNA ISH is not always reliable on necrotic tissues (*Fast red tetrazolium violet*; original magnification $\times 100$)

mixed with fibrin (Fig. 4). Rapid diagnosis is critical since fungal forms may grow into vital structures including the orbit and cranial cavity and patients with involvement of these structures have a significantly high morbidity and mortality rate.

The diagnosis of acute invasive FRS includes histopathologic identification of tissue-invasive fungal forms, which is often performed during intraoperative consultation (frozen section) [39, 40]. Frozen section is almost always required since this technique can be performed in a rapid fashion and provide the surgeon with immediate results for treatment planning, which is usually debridement surgery followed by IV antifungals. Most cases grow either *Aspergillus* sp. or *Rhizopus* sp. Other rare pathogens such as *Fusarium* sp. and dematiaceous species may also cause acute invasive FRS; however, in approximately 30 % of acute invasive FRS patients, fungal cultures are negative [6, 41, 42]. Rapid ISH for rRNA targets has become a useful means for identifying fungal species in patients with acute invasive FRS (Fig. 3). In one study,

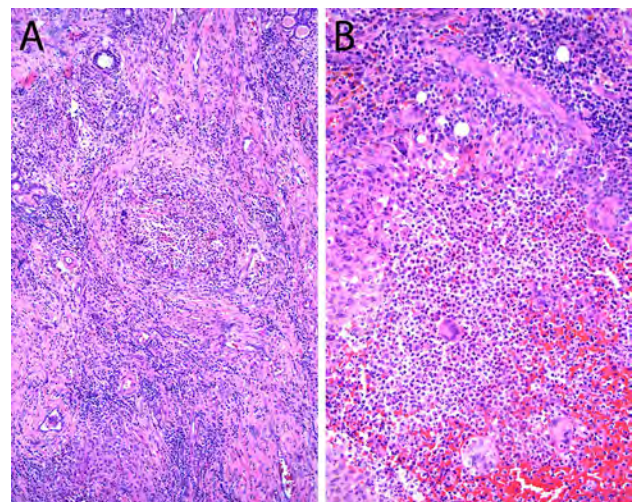


Fig. 5 Chronic invasive granulomatous fungal rhinosinusitis **a**, **b** Granulomatous reaction toward *Aspergillus flavus* in patients with chronic invasive granulomatous fungal rhinosinusitis (Hematoxylin and eosin; original magnification $\times 25$ for **a** and $\times 100$ for **b**)

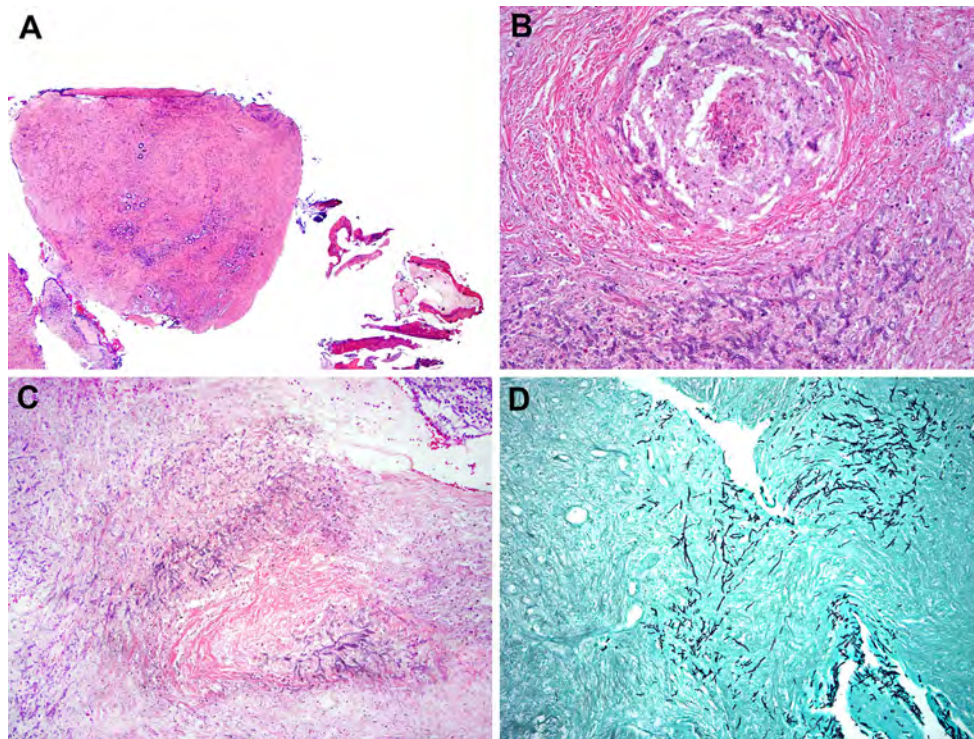


Fig. 6 Chronic invasive fungal rhinosinusitis **a** low power of inflamed and fibrotic sinonasal mucosa in liver transplant patient with chronic invasive fungal rhinosinusitis (Hematoxylin and eosin; original magnification $\times 12.5$). **b, c** Chronic invasive FRS with extensive sinonasal mucosal necrosis/infarction with visible fungal

organisms in liver transplant patient with symptoms greater than 3 months duration. **b** Fungi within blood vessels (Hematoxylin and eosin; original magnification $\times 100$). **d** Silver stain shows fungal hyphae infiltrating sinonasal mucosa in chronic invasive FRS (Hematoxylin and eosin; original magnification $\times 50$)

ISH confirmed the fungal pathogen in culture positive cases and also identified the pathogens in culture negative cases [43]. A drawback of the procedure was the limited utility of ISH in extensively necrotic tissues such as can be seen in acute invasive FRS (Fig. 4).

Chronic Invasive and Chronic Granulomatous Fungal Rhinosinusitis

Chronic forms of invasive FRS are rare in the United States but more common in India and the Middle East [10–12]. In fact, the recently published guidelines considered whether to separate these two entities; however, it was considered that these two forms of invasive FRS had enough clinical and pathological differences to keep them as separate entities [1, 2]. By definition, patients presenting with CRS have had symptoms for greater than 12 weeks duration. Despite the fact that they are chronic in nature and slower to progress than AIFRS, they do require aggressive therapy for adequate cure.

Chronic granulomatous invasive FRS is seen in immunocompetent patients, in contrast to the immunosuppressed patients in acute invasive FRS, and is endemic to India, Sudan, and Africa [1, 2]. The infection is characterized the presence of submucosal granulomatous inflammation, rare fungal

hyphae, and extensive fibrosis [10–12, 44] (Fig. 5). The most common associated fungal organism is *A. flavus*.

Chronic invasive FRS is a slowly growing invasive fungal infection characterized by invasion of numerous fungal organisms into the sinonasal mucosa with rare angioinvasion. This entity occurs in the background of acquired immunodeficiency syndrome, solid organ transplantation, diabetes, and in patients undergoing treatment with corticosteroids. *A. fumigatus* is the most common fungus isolated in these patients [1, 2, 44]. In contrast to granulomatous fungal sinusitis, fungal organisms are more numerous, there is a sparse inflammatory infiltrate, and occasionally angioinvasion (Fig. 6). Both of these forms of fungal sinusitis should be treated by surgical debridement and systemic antifungal therapy.

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