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Case report

Allergic fungal sinusitis complicated by fungal brain mass

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SUMMARY

A 36-year-old African American female with a 14-year history of allergic fungal sinusitis (AFS) presented with progressive worsening headache, fevers, proptosis, and a large frontal lobe brain mass. After excisional biopsy, the non-invasive, dematiaceous mold, *Bipolaris australiensis*, was identified. We review the epidemiology, etiology, pathophysiology, and clinical presentations of fungal sinusitis, as well as the complex management and multifaceted therapeutic modalities of AFS.

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1. Introduction

Allergic fungal sinusitis (AFS) is most commonly caused by the dematiaceous molds, *Bipolaris*, *Curvularia* and *Pseudallescheria*. AFS is historically considered to be a non-invasive form of fungal sinusitis, although it is well known to be associated with significant recurrence and morbidity, necessitating frequent endoscopic and aggressive medical management. We report a rare case of an invasive form of AFS to the central nervous system. We review the epidemiology, etiology, pathophysiology, and clinical presentations of fungal sinusitis. Additionally, in order to decrease the elevated morbidity and recurrence rate, we discuss the complex management and multifaceted therapeutic modalities of AFS.

2. The case

A 36-year-old African American female with a history of mild intermittent childhood asthma and chronic allergic rhinosinusitis presented with one-day severe headaches. Symptoms of allergic rhinosinusitis began at age 22, for which she had undergone five endoscopic nasal surgical procedures to remove multiple recurring nasal polyps, at intervals of approximately 2 years. After each procedure she developed nasal congestion, rhinorrhea, and facial pain within a few months. At no time did she have fever or

systemic symptoms. Intermittently, she used twice daily sinus irrigation with warm isotonic saline via a bulb irrigator, along with intranasal corticosteroids. Symptoms were almost continuous. She had lived in New Orleans, Louisiana all her life and had moved to Houston, Texas after Hurricane Katrina in late summer 2005.

In October 2004 she developed a subacute headache without fever. Computed tomography revealed a large left frontal lobe mass, which was resected and the cranium closed without any organic or other material occupying the residual space. Cultures revealed a mold. However, medical records from New Orleans were unavailable, due to flooding. She was discharged without any complications after 3 weeks with instructions to take an unknown oral antifungal medication for several more weeks as an outpatient.

Symptoms of mild allergic sinusitis recurred, and in March 2007 she began to have progressive worsening headache, subjective fevers, and sinus pain. Seven months later she began to lose her vision. She continued using intranasal corticosteroids, 10 mg oral prednisone daily for 4 weeks, and isotonic saline irrigations to remove nasal secretions. She was seen in the emergency department in December 2007 with severe headache and left proptosis.

On admission her vital signs were within normal limits. She had total loss of visual perception bilaterally and a sluggish pupillary reaction to light. Mild nasal edema but no necrotic tissue or mass was visualized. Her strength, sensation, and gait were intact. A complete blood count and differential were normal. Total serum IgE was 183 IU/ml and HIV testing was negative. Computed tomography of the head and facial bones revealed pansinusitis

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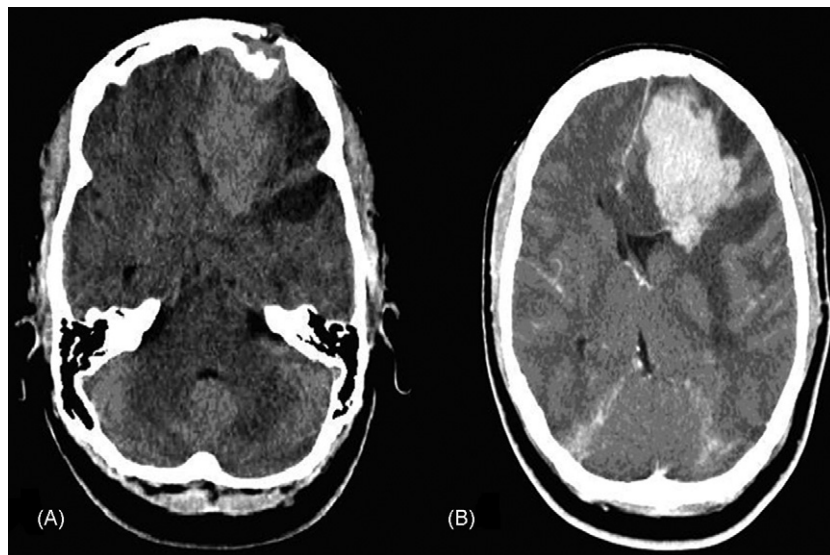


Figure 1. Computed tomography of the head with and without contrast: (A) frontal sinusitis with invasion to the frontal lobe and (B) extensive vasogenic edema resulting in left-to-right subfalcine herniation.

with diffuse mucosal thickening and a hyperdense mass, 4.2×6.7 cm, extending from the left frontal sinus into the left supraorbital frontal lobe (Figure 1). The mass was associated with extensive vasogenic edema resulting in left-to-right subfalcine herniation of approximately 6 mm.

She underwent emergent resection of the frontal lobe mass and ablation of the sinuses. Immediately, she was started on amphotericin B deoxycholate, vancomycin, ceftriaxone, and metronidazole. On subsequent days her symptoms greatly improved with no neurological deficits except for unchanged bilateral visual loss and papilledema observed on fundoscopic exam. Operative cultures grew a black mold on Sabouraud dextrose agar plates, which was eventually identified as *Bipolaris australiensis* (Figure 2). The diagnosis of allergic fungal sinusitis complicated with central nervous system invasion was made. Unfortunately, on the 14th day of admission, the patient had a cardiac arrest and died, most likely from a massive saddle pulmonary embolism.

3. Discussion

Recent studies suggest that fungi appear to play a major role in the pathogenesis of chronic rhinosinusitis.¹ Approximately 300

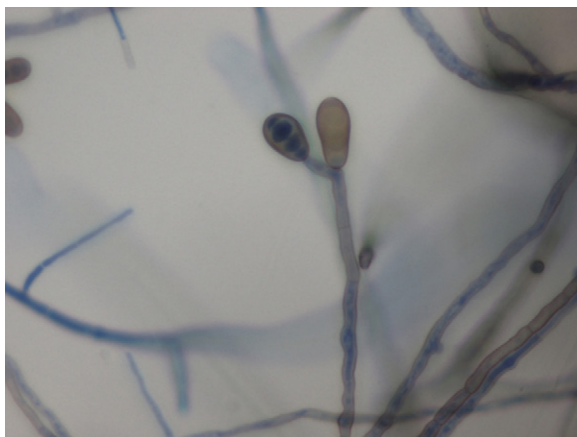


Figure 2. Microscopic view of *Bipolaris australiensis* $\times 100$.

fungal species are known to cause mycotic disease in humans and other animals. More than 50 of these species are documented as agents of rhinosinusitis. Most such infections are caused by species of *Aspergillus*, *Fusarium*, *Rhizopus*, *Alternaria*, *Bipolaris*, *Pseudallescheria* and *Curvularia*.²

The dematiaceous (brown-pigmented) fungi are a large and heterogeneous group of molds that cause a wide range of diseases, including phaeohyphomycosis, chromoblastomycosis, and eumycotic mycetoma. These organisms are widespread in the environment, being found in soil, wood, and decomposing plant debris. Disease occurs worldwide, but is more common in tropical and subtropical climates.³ These dematiaceous fungi are unique, owing to the presence of melanin in their cell walls, which imparts the characteristic dark color to their spores and hyphae. Fontana–Masson stains of tissue sections may be useful in confirming the diagnosis if culture results are negative.⁴

Interestingly, many of these cases have been encountered in Texas, South Carolina, Arizona, and Georgia in the USA, Brisbane in Australia, and in Pakistan and India.⁵ Schubert made similar observations and reported *Bipolaris spicifera* to be the most common cause of allergic fungal sinusitis in the southwestern USA.⁶

It is crucial to recognize the different entities of fungal sinusitis, which span the gamut from the most benign and non-invasive to most malignant and invasive. These include AFS, sinus mycetoma, granulomatous invasive fungal sinusitis, and chronic and acute invasive fungal sinusitis.⁷ The invasive forms are usually caused by hyaline molds (zygomycetes, *Aspergillus* and *Fusarium*), with few caused by dematiaceous molds. Patients usually present with fever, headache, epistaxis, cough, nasal mucosal ulcers or eschar, and proptosis. In the majority of cases, patients are immunocompromised, with uncontrolled diabetes, hemochromatosis, or severe malnutrition.⁸ Such patients should undergo immediate endoscopic evaluation of the sinuses and any excised mucosa or bone stained using silver-impregnated stains. Surgical debridement of all necrotic tissue and initiation of high-dose amphotericin B are mandatory.⁸ Immunosuppressive agents should be discontinued, if possible.

The most common organisms of the non-invasive forms, as in our patient with a history of AFS, are the dematiaceous molds (*Bipolaris*, *Curvularia* and *Pseudallescheria*) and the hyaline molds (*Aspergillus* and *Fusarium*).^{7,8} The overall incidence of AFS is

believed to be underestimated. However of all patients with rhinosinusitis requiring surgery, Schubert estimated the incidence to be from 6% to 9%.⁹ Usually, AFS presents in immunocompetent patients. A suspicion of AFS should arise in patients with atopy, chronic sinusitis, nasal polyps, and intractable symptoms, despite adequate treatment for bacterial sinusitis. In one case series, 100% of patients had a history of polyps, 54% had asthma, 27% had aspirin sensitivity, 65% had eosinophilia, and 69% had increased total IgE levels.¹⁰

The diagnostic criteria for AFS consist of: (1) the presence of 'allergic mucin' (laminated accumulations of intact and degenerating eosinophils, Charcot–Leyden crystals, cellular debris, and sparse hyphae rarely visualized without fungal stains), (2) demonstration of fungal hyphae in the allergic mucin, (3) radiologically confirmed sinusitis, and (4) no evidence of fungal invasion of submucosa, blood vessels, or bone.⁸

In AFS, the adjacent sinus mucosa has a mixed cellular infiltrate of eosinophils, plasma cells, and lymphocytes. Buzina et al. questioned whether an inappropriate response of eosinophilic granulocytes to the mold rather than allergy (IgE mediated) may be the mechanism of the chronic inflammation.⁵ However, others believe that type I and III hypersensitivity reactions underlie the pathogenesis of this disease.⁴ Furthermore the allergic mucin and polyps may form a partially calcified expansile mass that obstructs sinus drainage and perpetuates the bacterial sinusitis often associated with AFS. Growth of the mass may lead to pressure-induced erosions of the bone, rupture of sinus walls, and occasional sinus leakage into the orbits and brain.⁸ Therefore, as in our patient, suspicion of invasive disease should arise if the patient presents with fevers, worsening sinus pain, or headaches.

There are no universally accepted treatment protocols for AFS, however AFS requires frequent sinus irrigation with warm isotonic saline to prevent impaction of mucus, and recurrent endoscopic nasal polyp resection. Postoperative changes in total serum IgE mirror the clinical status and should be followed as they can predict disease recurrence.^{7,11} Additionally, postoperative oral and intranasal corticosteroids should be administered. Oral corticosteroid reduces disease activity and forestalls the need for recurrent sinus surgery.⁷ Furthermore, aggressive allergy management including allergen immunotherapy may be useful. However despite aggressive surgical debridement, sinus aeration, and medical management, which clearly improves patient symptoms, AFS recurrence rates remain high.¹²

In the past years, AFS has been found to be analogous in several ways to allergic bronchopulmonary aspergillosis (ABPA). Both are chronic inflammatory respiratory tract disorders that are driven by hypersensitivity responses to the presence of small numbers of extramucosal fungi found growing within airway-impacting allergic mucin. Medical treatment of AFS has been modeled to an extent after treatment approaches for ABPA, which includes the use of postoperative oral corticosteroids and aggressive anti-allergic inflammation therapy.⁹ Stevens et al., in a multicenter randomized control trial, found that high-dose itraconazole therapy was effective in managing ABPA without added toxicity.¹³ The underlying mechanism of systemic itraconazole therapy is thought to be a decreased pulmonary antigenic fungal load,

thereby decreasing immunologic responses. Therefore, due to the pathological, clinical, and therapeutic similarity of AFS to ABPA, itraconazole has been increasingly used for AFS. Chan et al. performed an uncontrolled pilot study utilizing itraconazole for >3 months in 32 patients with AFS who were refractory to conventional therapy; 37% had endoscopic improvement.¹⁴ Additionally, Rains and Mineck reviewed the use of their high-dose itraconazole protocol, with short-burst low-dose oral corticosteroids, topical corticosteroids, and endoscopic surgery, and also concluded that it is a safe and clinically effective regimen in the management of AFS.¹⁵ Therefore, itraconazole should be considered as a reasonable adjunct in the management of AFS.

In summary, AFS should be strongly suspected in patients who present with recurrent episodes of sinusitis requiring multiple polyp resections, and failed medical responses. In order to achieve the best clinical outcome and decrease disease recurrence and progression, patients should undergo early endoscopic sinus surgery and aggressive medical management, including frequent sinus irrigation with warm isotonic saline, steroids, immunotherapy where necessary, and prolonged itraconazole therapy in refractory cases. Close follow-up and coordination of treatment by both medical and surgical physicians as a team leads to the best clinical outcomes.¹¹ Even though AFS is historically considered non-invasive, there have been reports of invasion into paranasal structures. Furthermore, there are no studies evaluating the early red flags and risk factors to suspect when AFS may progress towards an invasive form. Consequently, a high clinical suspicion is warranted.

Conflict of interest: No conflict of interest to declare.

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