Deadly Sphenoid Fungus—Isolated Sphenoid Invasive Fungal Rhinosinusitis: A Case Report

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ABSTRACT

Introduction: Acute invasive fungal rhinosinusitis (AIFRS) is a potentially fatal infection, usually affecting immunocompromised patients. Isolated sphenoid sinus involvement is rare and has been reported in only a few cases. We discuss the clinical characteristics, histopathologic features, and differential diagnosis of AIFRS of the sphenoid sinus.

Case Presentation: A 57-year-old man with a history of refractory non-Hodgkin lymphoma and neutropenia presented with a 1-week duration of left-sided headache and ipsilateral cheek paresthesia. Nasal endoscopy showed mucoid drainage from the sphenoethmoidal recess. Magnetic resonance imaging demonstrated left sphenoid mucosal thickening and enhancement along the adjacent skull base. The patient underwent endoscopic sinus surgery with extended sphenoidotomy and débridement. The lateral wall and recess of the left sphenoid sinus demonstrated pale mucosa and fungal debris. Pathologic analysis demonstrated necrotic tissue and fungal hyphae with angioinvasion. Microbiology studies isolated *Aspergillus fumigatus*. The right maxillary sinus contained a synchronous fungal ball, which was removed during surgery; there was no evidence of tissue necrosis or invasive fungus in the maxillary sinus. He was treated with long-term voriconazole therapy, and 6-month follow-up showed disease resolution.

Discussion: AIFRS should be considered in the differential diagnosis of immunocompromised patients with nonspecific sinonasal symptoms. Usually, AIFRS is diffuse with multiple sinus involvement; however, isolated sphenoid AIFRS can occur. This is one of the few cases of AIFRS demonstrating isolated sphenoid involvement and is thought to be the first case showing a synchronous noninvasive fungal ball of another sinus cavity. Prompt recognition and surgical treatment may be curative and lifesaving.

INTRODUCTION

Acute invasive fungal rhinosinusitis (AIFRS) is a rare and often deadly infection that occurs primarily in immunocompromised patients. The incidence of AIFRS reported in the literature in immunocompromised patients is about 2%, with the most susceptible group being patients with hematologic diseases.[1] Other frequently affected patient groups are those with immunosuppression related to hematologic malignancy, bone marrow transplantation, poorly controlled diabetes, acquired immunodeficiency syndrome, immunosuppressive medications, and chemotherapy.[2]

AIFRS is most frequently caused by the *Aspergillus* and *Mucor* species. Studies have found a higher predisposition to aspergilli among patients with hematologic malignancies and to Mucoraceae among patients with diabetes mellitus.[2-5] Patients typically present with acute onset of signs and symptoms of sinusitis, with the most frequent symptoms reported being fever, nasal obstruction, headache, and purulent rhinorrhea with nasal crusting.[3] Pathophysiologically, the disease is characterized by fungal invasion into sinus tissue with frequent extension into adjacent structures. Treatment involves timely medical and surgical therapy. Surgical débridement of necrotic tissues is important in patients with AIFRS to reduce the fungal burden and to potentiate antifungal therapy. Short-term mortality ranges from approximately 20% to 80% across studies, largely dependent on extent of disease and recovery of immunologic function.[2,4,6,7]

CASE PRESENTATION

Presenting Concerns

A 57-year-old man presented initially to the Emergency Department with a medical history of chemotherapy-refractory diffuse large B-cell lymphoma, neutropenia, prior myocardial infarction after coronary artery bypass grafting in 2007, congestive heart failure, cardiomyopathy, and coronary artery disease with approximately a 1-week duration of left-sided headache centered along the left cheek and extending to the temple. The patient was then referred for a computed tomography (CT) scan that was initially read as sphenoid opacification without bony erosion. At the Head and Neck Surgery Clinic visit 2 days later, he affirmed he had numbness and swelling of his left cheek. He denied having nasal congestion, rhinorrhea, vision changes, fevers, chills, weight loss, and fatigue. His surgical history included laser trabeculoplasty in 2009 but no prior sinonasal procedures.

Examination revealed asymmetric pupils, larger on the left eye, with the rest of the ocular examination findings within normal limits. Nasal endoscopy in the clinic revealed bilateral inferior turbinate bogginess without lesions or erythema, no nasal polyps, and mild translucent white mucous drainage from the sphenoethmoidal recesses bilaterally.

Prompt CT and magnetic resonance imaging (MRI) were completed. Notable CT findings included mucosal thickening of the left sphenoid sinus and right osteomeatal unit obstruction by a soft-tissue density (Figure 1). Notable MRI findings included T2-weighted hypointense

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material in the left sphenoid sinus with abnormal thickening and enhancement along the foramen rotundum and the medial aspect of the left middle cranial fossa, eliciting concern for invasive fungal sinusitis with mild perineural/intracranial extension. Apparent T2 prolongation and enhancement of the left inferior rectus muscle and surrounding fat was favored to be artifactual (Figure 2). Chronic mucoperiosteal thickening of the right maxillary sinus with T2 hypointense and T1 hyperintense material, which was unchanged from a prior image in 2011, was thought to be compatible with proteinaceous/inspissated secretions.

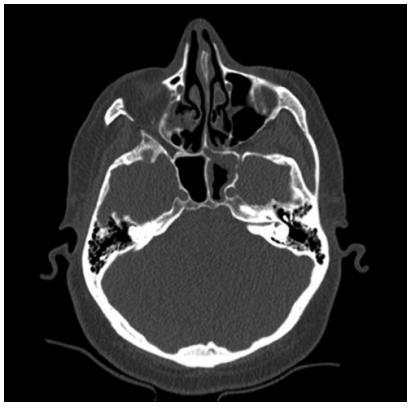

Figure 1. Computed tomography scan, axial view, without contrast enhancement. Mucosal thickening of the left sphenoid sinus is apparent. Possible dehiscence is demonstrated along the lateral wall of left sphenoid sinus.

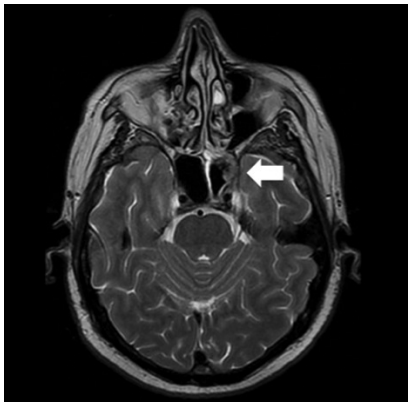

Figure 2. Magnetic resonance image, T2 weighted, axial view, with intravenous contrast enhancement. Hypointense signal is seen in the left sphenoid sinus with abnormal enhancement and thickening along the foramen rotundum and medial left middle cranial fossa (arrow).

Therapeutic Intervention and Treatment

The patient was admitted to the hospital that evening for intravenous (IV) antifungal therapy. Initial laboratory study results were remarkable only for neutropenia.

Endoscopic sinus surgery was performed the next morning. Procedures included left extended endoscopic sphenoidotomy, right endoscopic maxillary antrostomy, and right endoscopic anterior ethmoidectomy. Notable operative findings included left sphenoid with evidence of yellow-white necrotic tissue and fungal debris in the lateral wall and lateral recess of the sphenoid sinus (Figure 3). Intraoperative frozen section revealed fungal debris and necrotic tissue with submucosal presence of hyphae, consistent with invasive fungal sinusitis. On the right side, there was no evidence of invasive fungal sinusitis; well-perfused tissue was seen around a fungal ball in the right maxillary sinus, which was completely removed.

Final histopathologic analysis revealed sphenoid sinus contents consistent with acute invasive fungal sinusitis and numerous hyphae in the mucosal tissue, confirmed by positive Gomori methenamine silver nitrate stain, as well as necrosis (Figures 4A and 4B). Later, final microbiology culture isolated *Aspergillus fumigatus*. On postoperative day 1, filgrastim (Neupogen, Amgen, Thousand Oaks, CA) was started to address neutropenia after clearance by an oncologist.

Follow-up and Outcomes

On postoperative day 6, the patient was taken back to the operating room for a second look after follow-up MRI revealed possible residual left sphenoid sinus opacification. During the operative procedure, the left sphenoid lateral wall showed improved appearance of the mucosa and lacked eschar. The right maxillary sinus demonstrated a widened opening, with a thick granular appearance of the mucosa on the posterior wall. The maxillary sinus tested negative for fungal invasion on frozen sections.

The patient was discharged on hospital day 10. As an outpatient, he received IV voriconazole, 200 mg every 8 hours for 30 days, and then voriconazole orally, 200 mg every 12 hours for an additional 2 months. During the course of the next 3 months, he returned to clinic for repeated examinations and débridements.

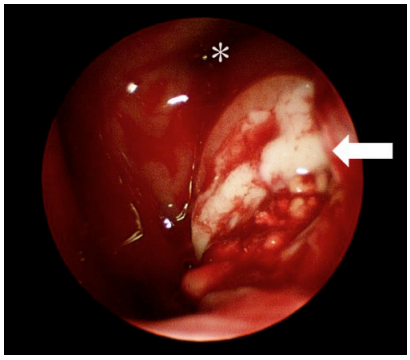

Figure 3. Intraoperative view of left sphenoid sinus, showing lateral wall (arrow) and opticocarotid recess (asterisk) with mucopurulence and tissue necrosis.

Follow-up MRI 1 month after discharge revealed substantial interval improvement with resolution of T2 hypointense fungal material in the left sphenoid sinus and in the region of foramen rotundum and bilateral maxillary and resolution of T1 hyperintensity in the right maxillary sinus.

At his six-month outpatient follow-up examination, nasal endoscopy revealed a healthy sphenoid sinus with a patent os and no evidence of recurrent sinus disease. The case timeline appears in Figure 5.

DISCUSSION

AIFRS is a rare disease, occurring in only about 2% of immunocompromised patients. The most susceptible group reported in the literature has been patients with hematologic malignancies. Valera et al[3] reported neutropenia, either caused by aplastic anemia or secondary to chemotherapy for hematologic malignancy, as the main cause of AIFRS (62%), a finding in agreement with other studies.[8,9] Regarding isolated sphenoid disease, as demonstrated in our patient, the rarity is increased. Of all sinus infections, the estimated incidence of sphenoid sinusitis is 2.7%. Isolated sphenoid sinusitis can be bacterial or fungal. Fungal sinusitis represents approximately 15% to 20% in all cases and is classified as noninvasive, invasive indolent, and fulminant. Only a few cases of sphenoid sinus aspergillosis have been reported in the published literature. Lee et al,[10] in 2009, reported that

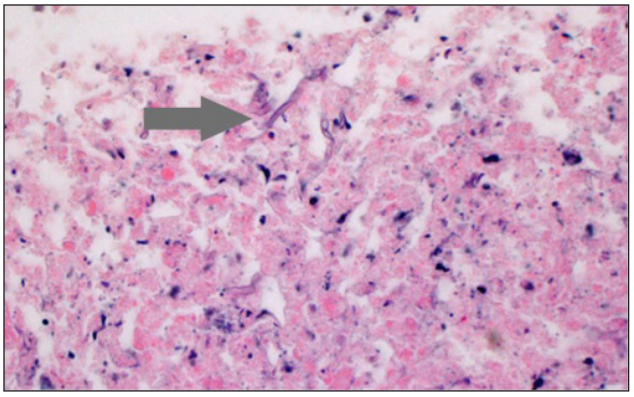

Figure 4A. Histopathologic specimen, hematoxylin-eosin stain, showing fungal hyphae (arrow) and necrotic tissue with submucosal presence.

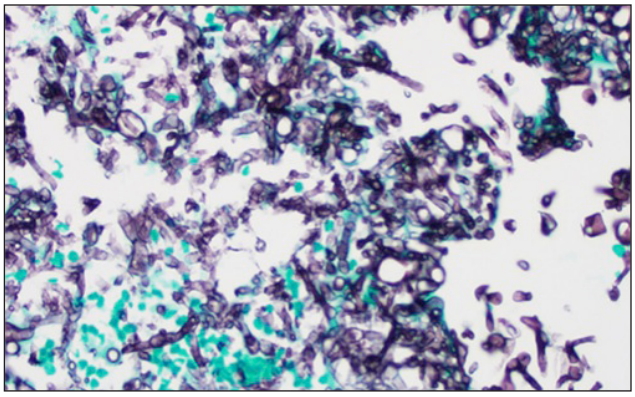

Figure 4B. Histopathologic specimen, Gomori methenamine silver nitrate stain, showing fungal elements stained black with sharp margins and a cleared center, against a light-green tissue background.

50 cases of noninvasive sphenoid aspergilloma were published since 1950. However, only a few cases of AIFRS of the sphenoid have been reported.[6,10]

The causative organism in our patient was *Aspergillus,* which, along with Mucoraceae, are the cause in most cases of AIFRS. *Aspergillus* has a predisposition for patients with hematologic malignancies, whereas Mucoraceae species tend to occur more often in patients with uncontrolled diabetes.[2,3,5] Both fungi are saprophytes, found worldwide in dust, decomposed substances, soil, and fruits, as well as in the throats, nasal cavities, and feces of healthy individuals. In immunocompromised patients, these fungi can be angioinvasive, resulting in thrombosis and ischemia of the nasal mucosa. The fungi can rapidly spread and invade paranasal structures, including the orbit and brain. Mucormycosis-causing species primarily invade the nose, lungs, and gastrointestinal tract, whereas *Aspergillus* species primarily invade the lungs and later spread to other organs.[4] *Rhizopus* has also been identified as a common causative organism in some cases, although its prevalence ranges greatly, between 0% and 26% in the series in the literature,[3,11,12] and was not reported in a 2013 meta-analysis of 398 patients by Turner et al.[13] Recently, dematiaceous fungi have now been recognized as causal organisms of AIFRS. Dematiaceous fungi are environmental pathogens, characterized by melanin in their cell wall. In 2010, Derber et al[14] reported that since 1987, there have been 14 published cases of invasive sinonasal infection caused by dematiaceous fungi in immunocompromised individuals.

For identification of patients with AIFRS, the history and physical examination findings are of paramount importance. Demographically, AIFRS tends to occur in the fifth decade of life and in female patients.[2,6,10,15] Patients traditionally present with signs and symptoms of sinusitis but may also display orbital and central nervous system signs and symptoms. For example, in the series of 32 patients described by Valera et al,[3] the most frequent symptoms reported were fever, nasal obstruction, headache, and purulent rhinorrhea with nasal crusting. Of these symptoms, headache has been cited as the most common presenting factor.[6,10,16,17] Clinical signs may include nasal discharge, epistaxis, orbital disorders (including oculomotor restriction and decreased visual acuity), and dysesthesia of the maxillary division of the trigeminal nerve. Posterior nasal discharge, although nonspecific, is frequently described. Be wary, however, of blood-streaked nasal discharge because this is considered a more specific indicator of AIFRS. Bleeding is related to either irritation of the sinus mucosa by the fungal infection or, at a more advanced stage, bone destruction of the sinus wall.[6] On nasal endoscopy, the most common signs seen are characteristic necrotic avascular and black crusts, granular serosanguinous rhinorrhea, septal perforation, and occasionally, visible hyphae.[4]

Additionally, the medical history will nearly always include an immunocompromised state, because it is the greatest risk factor for AIFRS. Monroe et al[2] reported that approximately one-fourth of the patients with AIFRS had more than one cause of immunosuppression.[2] AIFRS of a nonimmunocompromised patient is exceedingly rare. Lee et al[10] examined four cases of acute invasive sphenoid sinusitis and found one patient without a history of immunosuppression, and the others having either diabetes or multiple myeloma. In addition, any factor inducing decreased aeration of the sphenoid sinus has been classically described to constitute a risk factor for the development of fungal disease. For example, the presence of polyps on nasal endoscopy may contribute to obstruction of the ostium of the sphenoid sinus.

Our patient presented with headache but, interestingly, did not report other sinus complaints. Salient clinical findings included ipsilateral cheek paresthesia and pupil dilation, suggesting dysfunction of the maxillary division of the trigeminal nerve and oculomotor nerve, respectively. Nasal endoscopy revealed only mild, partially clear, white drainage from the sphenoethmoidal recess but no characteristic necrosis. The history of refractory diffuse large B-cell lymphoma aroused our suspicion for AIFRS, particularly when we considered the cranial nerve deficits and the risk of intracranial extension with AIFRS. It is critical, therefore, to keep AIFRS on the differential in immunosuppressed patients with both specific and nonspecific findings.

The distribution of disease in our patient was relatively unique. Valera et al[3] found a predominance of unilateral disease with bone erosion, with diffuse sinus involvement less common, orbital involvement being uncommon, and only a single case of intracranial extension. Sphenoid sinus involvement is less common than maxillary or ethmoid involvement, and isolated sphenoid disease is even rarer.[3] Moreover, simultaneous mycetoma has not been reported in the prior literature. The presence of the mycetoma does suggest the transformation of noninvasive to invasive fungal rhinosinusitis. Lee et al[10] found only 25% of their isolated invasive sphenoid fungal sinusitis to be acute, and only 4 cases over 12 years, highlighting the rarity of this distribution. Furthermore, all the patients in that situation presented with visual disturbances, which were absent in our patient.

In treatment of AIFRS, timely recognition of the underlying disease that caused the immunodeficiency and its correction, if possible, are essential to improve the survival rate in these patients. The goals of treatment in AIFRS are the reestablishment of the immune response in combination with systemic antifungal therapy and surgical débridement of necrotic sites. Surgical débridement of necrotic tissues is crucial to increase the delivery of antifungal drugs to affected tissues, reducing the fungal burden, and slowing the progression of disease. Additionally, débridement reduces stress on neutrophil development and helps bone marrow recovery.[3] In our patient, the source of his immunosuppression was known, and the patient was started on a regimen of filgrastim, but in the acute setting, the course of action left to us was surgical débridement and IV antifungal therapy.

Interestingly, there is no well-defined course for voriconazole therapy, given the rarity of AIFRS. Traditionally, amphotericin B has been used, but it also comes with substantial side effects. A 2002 randomized comparative study of voriconazole and amphotericin B in invasive aspergillosis found better outcomes and fewer side effects with voriconazole.[7] Additionally, the Global Comparative Aspergillosis Study found a similar result in a randomized controlled trial. This study had a median course of 7 days for IV voriconazole, followed by 76 days of oral voriconazole.[7,18] The Infectious Diseases Society of America guidelines for invasive aspergillosis now recommend voriconazole use.[19] As such, our decision was to use voriconazole as the primary antifungal therapy in our patient. He received IV voriconazole for 30 days, followed by oral voriconazole for 60 days after an infectious disease consult, with complete recovery and minimal side effects.

The outcome for our patient was good, with resolution of AIFRS. Success was attributed to early detection and treatment of a relatively limited extent of disease. In most cases of AIFRS, the morbidity and mortality are substantial. A meta-analysis by Turner et al[13] in 2013 examining survival in AIFRS found an overall survival rate of 49.7%, with intracranial involvement and advanced age being negative prognostic factors on multivariate analysis. In an analysis by Foshee et al[20] of 27 patients, patients with sphenoid involvement had a mortality rate of 56.3%. In a series of 29 cases reported by Monroe et al,[2] the median survival of this group was 3 months, with only 17% overall survival at 6 months. The study notes that a large proportion of patients in whom AIFRS develops will die of their disease or of other causes within 6 months of diagnosis. Extension beyond the sinuses portends worse prognosis. Recovery of immune function is believed to be vital to disease clearance. However, little other prognostic data are known regarding this rare patient population, specifically as it relates to long-term survival.[2] Treatment does relate to mortality. Before the advent of amphotericin B, mortality rates were as high as 90%. Mortality rates were reduced to 15% to 50% with combined use of surgery and newer antifungal medication.[2-4] The cause of immunosuppression may also have an effect on survival. Valera et al[3] found the mortality rate in patients with aplastic anemia and diabetes mellitus was high (near 100% when considering both groups together), whereas those with acquired immunodeficiency syndrome/human immunodeficiency virus (AIDS/

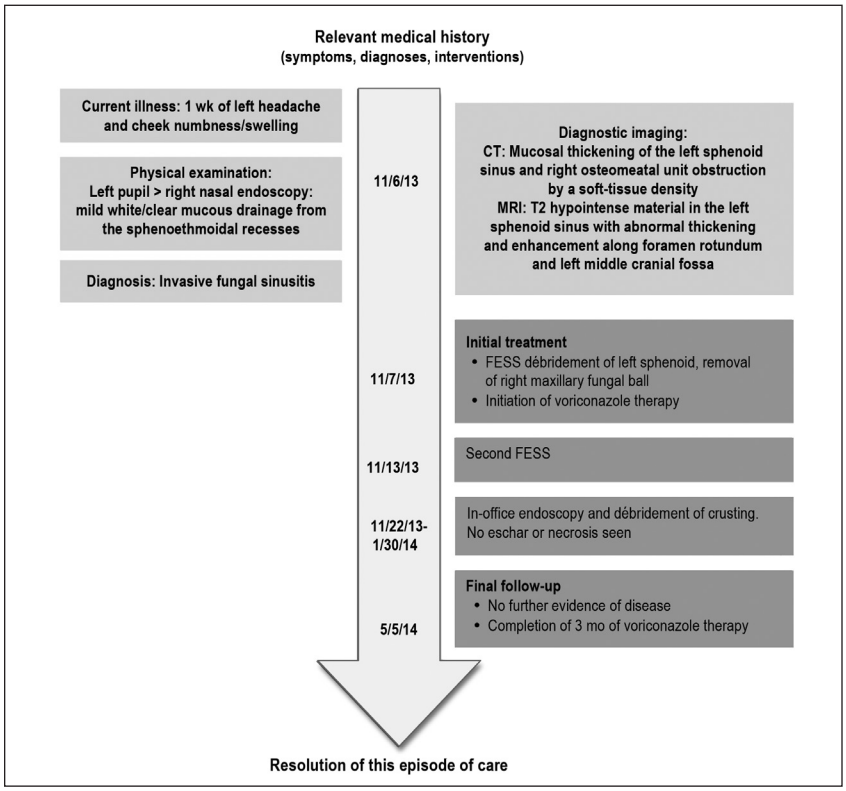

Figure 5. Timeline of the case. Dates are month/day/year.

CT = computed tomography; FESS = functional endoscopic sinus surgery; MRI = magnetic resonance imaging; > = larger than.

HIV) all had a good outcome. Patients with hematologic malignancies showed an intermediate prognosis; one-third of these patients died of AIFRS.[3]

CONCLUSION

AIFRS is a rare but deadly disease. Clinical suspicion must be high in the immunocompromised patient, because clinical signs and symptoms may be subtle. Prompt ancillary testing, including imaging and laboratory testing, can aid in diagnosis, but histopathologic evaluation is fundamental. The pattern of involvement is usually diffuse sinus disease, but it is often unilateral. Isolated sphenoid involvement is rare. Effective treatment relies on both addressing the underlying cause of immunosuppression and treating the fungal disease with surgical débridement and antifungal therapy. Morbidity and mortality are high, with orbital and intracranial extension signifying worse prognosis. Ultimately, timely diagnosis and treatment are critical to achieving satisfactory outcomes. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Fundamental Activity

The fundamental activity of medical science is to determine the ultimate causation of disease.

— Wilfred Batten Lewis Trotter, FRS, 1872-1939, English surgeon and pioneer in neurosurgery