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Research Paper

Evidence for a 'preinvasive' variant of fungal sinusitis: Tissue invasion without angioinvasion

Hassan Paknezhad, Nicole A. Borchard, Greg W. Charville, Noel F. Ayoub, Garret W. Choby, Andrew Thamboo, Jayakar V. Nayak*

Division of Rhinology, Department of Otolaryngology — Head and Neck Surgery, Stanford University School of Medicine, USA

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Immunosuppressed;
Antifungal therapy

Abstract Clinical experience has suggested the existence of an intermediate form of fungal sinusitis between the categories of non-invasive fungal sinusitis (non-IFS) and invasive fungal sinusitis (IFS). This fungal sinusitis variant demonstrates unhealthy mucosa by endoscopy with fungal invasion, but lacks angioinvasion microscopically, representing what clinically behaves as a 'pre-invasive' subtype of fungal sinusitis. Unlike non-IFS disease, patients with pre-invasive fungal sinusitis were still felt to require anti-fungal medications due to histologic presence of invasive fungus. While sharing some clinical features of IFS, these 'intermediate' patients were successfully spared extended and repeated surgical debridements given the microscopic findings, and have been successfully treated with shorter courses of antifungal therapy. These select patients have had favorable outcomes when managed in a judicious and semi-aggressive manner, in an undefined zone between the treatments for routine fungal ball and aggressive IFS.

* Corresponding author. Division of Rhinology, Department of Otolaryngology — Head and Neck Surgery, Stanford University School of Medicine, 801 Welch Road, Stanford, CA 94305, USA.
E-mail address: jnayak@stanford.edu (J.V. Nayak).
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Introduction

Fungal sinusitis is classically divided into non-invasive (fungal ball, allergic fungal sinusitis, saprophytic fungal growth) and invasive forms (acute invasive fungal sinusitis, chronic IFS, chronic granulomatous fungal sinusitis) (Table 1).[1–6] Invasive fungal sinusitis (IFS) is a life-threatening entity involving fungal species such as *Mucor* and *Aspergillus* that, in the immunosuppressed host, become invasive, and extend beyond the bony boundaries of the sinuses and skull base.[1,2,6] The morbidity and mortality associated with IFS are high, especially for acute IFS.[3]

Histopathologic studies of IFS demonstrate both mucosal and submucosal invasion with angiovasion.[4] When successfully treated, patients with IFS require urgent surgical interventions, repeated surgical debridements, long-term antifungal therapy, and critically, reversal of the inciting cause of immunosuppression where possible.[1,2,5]

We share our experience with patients presenting with intermediate conditions of fungal sinusitis not entirely consistent with IFS nor non-invasive fungal sinusitis (non-IFS). While these patients demonstrate dusky tissue and intra-mucosal fungal infiltration characteristic of IFS, they failed to show direct angioinvasion and wide extension beyond the submucosa.[1,2] Although presenting clinically as IFS, these patients were managed successfully with limited surgical debridement and, in one case, short-term antifungal therapy. These data suggest the existence of an undescribed category of 'preinvasive' fungal sinusitis, supported by histologic analysis, which may be treated using distinct surgical and medical options.

Case series

Case 1

A 37-year-old male with acute lymphocytic leukemia presented shortly after bone marrow transplantation (BMT) with low-grade fever and sphenoid sinus opacification on a CT scan of the paranasal sinuses (Fig. 1A). Further examination revealed no abnormal findings on nasal endoscopy. MRI demonstrated left sphenoid opacification with heterogeneous material showing central hyperdensity and peripheral mucosal thickening, and signal loss on T2 MRI (Fig. 1B and C). Endoscopic sinus surgery (ESS) revealed purulence and central fungal debris surrounded by edematous, devitalized left sphenoid sinus mucosa. Frozen histology of the debrided tissue showed acellular tissue mixed with septated fungal hyphae without angioinvasion (Fig. 2).

A limited 'second look' operation was performed four days later which showed no new necrotic mucosa. Because of immunosuppression following BMT, the patient was prophylactically placed on longer term intravenous and oral antifungals postoperatively despite the resolution of symptoms and pathology findings. The patient has recovered well, without recurrence of fungal sinusitis over the past six years.

Case 2

A 70-year-old immunocompetent male presented with headaches and progressive vision loss OS over five days. No

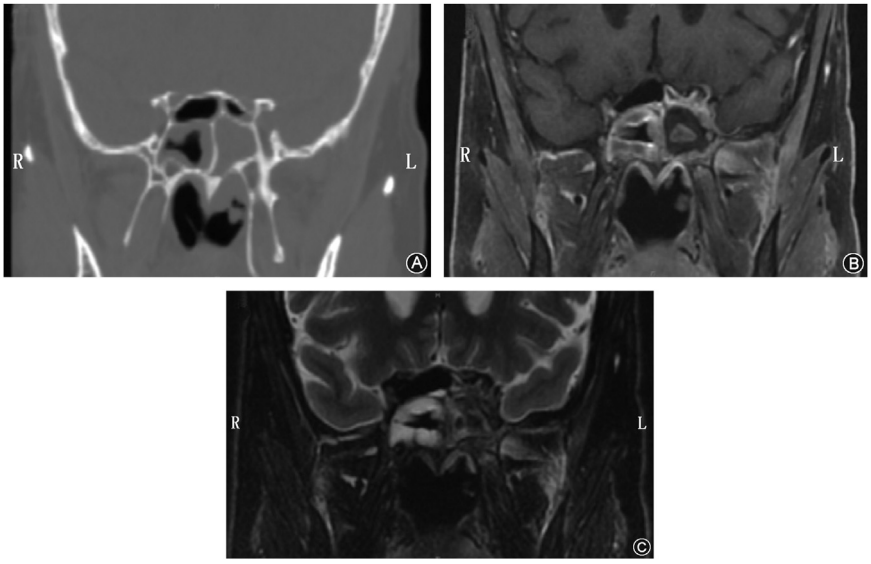

Fig. 1 CT and MRI imaging for Case #1. A: CT-scan coronal view without contrast demonstrating complete opacification of the left sphenoid sinus; no speckled calcifications noted; B: Coronal MRI T1 with contrast demonstrating left sphenoid central signal hyperintensity with surrounding rim of hypointensity; C: MRI T2 coronal view demonstrating loss of signal intensity within the left sphenoid, suggestive of fungal sinusitis and possible IFS.

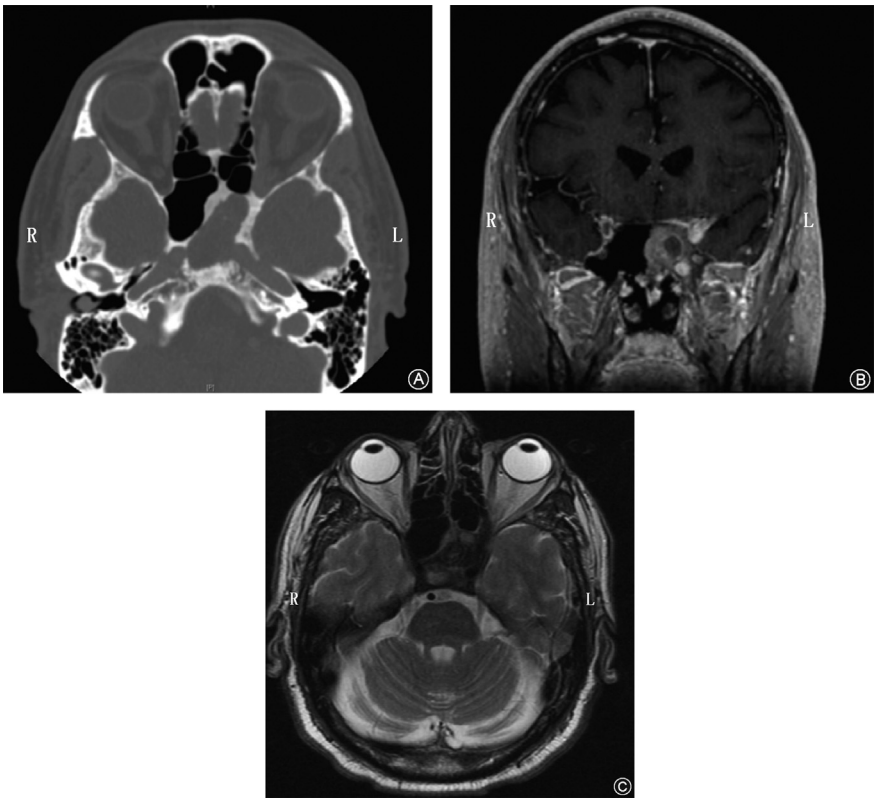

Fig. 2 CT and MRI imaging for Case #2. A: Axial CT scan without contrast demonstrating left sphenoid opacification and bony erosion over the carotid. 1—2 spots of calcification can be seen; B: MRI T1 with contrast coronal view demonstrating left sphenoid opacification with heterogeneous signal pattern; C: MRI T2 axial view demonstrating complete signal drop out within left sphenoid, suggestive of dense left sphenoid fungal sinusitis and possible IFS given crescendo in symptoms.

mucosal abnormalities were noted on nasal endoscopy. CT imaging demonstrated left sphenoid opacification with skull base dehiscence (Fig. 3A), and MRI demonstrated centrally hypointense material on T1 sequences, and complete signal dropout on T2 (Fig. 3B and C).

ESS was urgently undertaken, and bilateral sphenoidotomies revealed devitalized sites of left sphenoid mucosa with admixed fungal debris. Frozen section analysis revealed areas of necrotic tissue and fungal hyphae within tissue without angioinvasion (Fig. 2). The patient was treated with five days of intravenous, and one month of oral, antifungals. His vision markedly improved post-operatively and he has remained disease-free for seven months.

Discussion

Defining the subtype of fungal sinusitis is essential in determining the appropriate management and outcome. We present two related cases of fungal sinusitis outside of the traditional classification system (Table 1).[1—6] Both cases presented acutely in both immunocompromised and immunocompetent individuals. The fungal disease was circumscribed to the sphenoid sinus, and the affected mucosa was locally devitalized/abnormal in quality. Frozen section confirmed the presence of septated fungal elements in tissue, specifically devoid of angioinvasion. Given the unexpected, intermediate scenario of fungal tissue invasion, with specific absence of vascular invasion by microscopy, ESS was selectively redirected to resection of only devitalized mucosal epithelium without extensive debridement or mucosal stripping. Adjuvant treatment was also limited to one month of antifungal use in the immunocompetent case, but a longer antifungal course in the setting of immunosuppression following BMT. Repeated rounds of sinus debridement (required for IFS) were avoided, and collectively this limited management strategy was sufficient to treat both patients.

Despite the concerning clinical presentations, the absence of widespread mucosal necrosis and partially-aggressive pathology features led us to pursue intermediate courses of treatment between traditional IFS and non-IFS. The major discriminator for the pathology and surgery teams was the absence of angioinvasion on pathology and the lack of extension of fungal disease beyond the (sphenoid) sinus boundaries. This also dictated reduced primary surgical intervention, negated the need for serial operative debridements, and reduced overall anti-fungal dosing in the setting of immunocompetence. These unique features represented an early invasive, or 'pre-invasive', form of fungal sinusitis, and suggest that angioinvasion is a required threshold to define IFS.

IFS reports from other institutions illustrate patients with features resembling pre-invasive fungal sinusitis, but

Table 1 Fungal sinusitis definitions/categories.

	Subtype	Commonly affected sinuses	Immune system characterization	Common causative fungus	Histopathology	Classic Imaging Findings	Symptoms	Management	Outcome
Non-Invasive	Fungal Ball	Maxillary and sphenoid sinus	Immuno-competent	Aspergillus species	Sinus contents: dense tangles of hyphae with calcification and oxalate crystals	CT: Single opacified sinus w/o erosion MRI: hypointense sinus content T1, T2	Asymptomatic, Or symptomatic as nonspecific chronic rhinosinusitis	1) Endoscopic debridement 2) Repeated topical irrigations	Excellent; rare local recurrence
	Allergic Fungal Sinusitis	Bilateral sinuses affected, one side often more severe	Immuno-competent, Hx of allergic rhinosinusitis and/or asthma, Type 1 hypersensitivity to fungi	Aspergillus fumigatus, Dematiaceous species	Hyphae present but scarce, eosinophilic mucin without fungal invasion into sinus tissue; Charcot-Leyden crystals present	CT: hyperattenuated mucin with in sinuses, thinning of sinus walls MRI: T1 variable, T2 hypointense sinus content	Symptomatic as nonspecific chronic rhinosinusitis	1) Endoscopic debridement 2) Repeated topical irrigation 3) Topical and/or oral steroids	Favorable, common loco-regional recurrence
	Saprophytic Fungal Growth	Non-specific	Immuno-competent	Aspergillus	N/A	N/A	Not symptomatic	None, removal during nasal endoscopy	Excellent
Pre-Invasive	Pre-invasive Fungal Sinusitis[a]	Sphenoid	Immuno-compromised and immuno-competent	Culture negative	**Submucosal presence of septated hyphae without angioinvasion**	CT: sphenoid sinus opacity w/or w/o erosion MRI: variable in T1, T2	- Fever - Headache - Visualloss	1) **Limited endoscopic debridement without serial re-inspection** 2) **Short term antifungal use possible**	Favorable
Invasive	Acute Invasive Fungal Sinusitis	Non-specific; middle turbinate mucosa is frequently involved	Almost always immuno-compromised	Aspergillus, Rhizopus and Mucor species	Fungal hyphae in mucosa that invades blood vessels or bones with tissue necrosis and neutrophilic infiltration	CT: mucosal thickening, bone erosion, soft tissue infiltration MRI: variable on T1, T2; lack of mucosal enhancement with contrast	- Fever - Facial swelling - Nasal congestion - Diplopia - Decreased vision - Nasal discharge - Facial pain - Headache	1) Aggressive surgical debridement 2) Immune restoration therapy 3) High dose anti-fungal therapy	High mortality, possibility of recurrence

	Chronic Invasive Fungal Sinusitis	Ethmoid, sphenoid	Immuno-competent and immuno-compromised secondary to numerous causes of immune dysfunction	Aspergillus fumigatus, mucor	Presence of a dense fungal element, infiltration of mucosa and angioinvasion with a nonspecific inflammatory response, and necrosis of adjacent tissue	CT: hyperattenuating intranasal soft tissue mass $\pm$ calcification within $\geq$ one sinus and $\pm$ bone erosion or sinus expansion MRI: decreased signal on T1 and T2	- Rhinosinusitis symptoms - Proptosis - Diplopia - Visualloss - Cranial nerve deficit - Cavernous sinus syndrome - Orbital apex syndrome	1) Aggressive surgical debridement 2) Immune restoration therapy 3) Antifungal therapy	Moderate, variable
	Granulo-matous Invasive Fungal Sinusitis	Non-specific	Immuno-competent	Aspergillus flavus	Noncaseating granulomas with giant cells and plasma cells with surrounding vasculitis and perivascular fibrosis	Overlaps with imaging findings from chronic invasive fungal sinusitis (above)	- Enlarging mass in the sinonasal cavity - Proptosis	1) $\pm$ antifungal therapy 2) $\pm$ surgical debridement	Uncertain

[a] Candidate category.

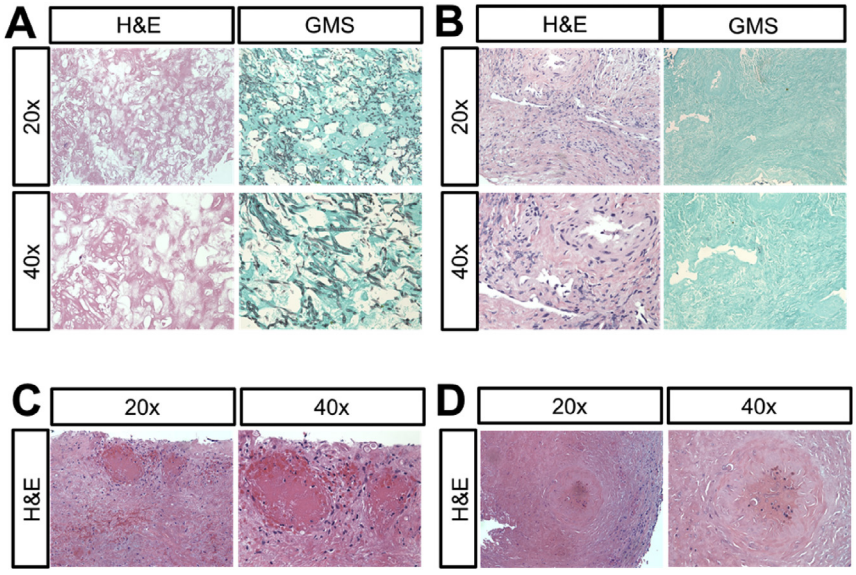

Fig. 3 Histologic assessment of fungal invasion. A: Hematoxylin/eosin (H&E) and Grocott-Gomori methenamine silver (GMS) stained histologic sections demonstrating presence of submucosal fungal species without angioinvasion; B: Additional H&E and GMS stained sections as A with small blood vessels included and without evidence of fungal angioinvasion; C and D: For comparison, H&E stained histologic sections from 2 different patients with 'classic' invasive fungal sinusitis, demonstrating histologic angioinvasion. Representative images at 20- and 40-fold magnification are shown.

Table 2 Comparison to invasive fungal sinusitis.

Syndrome	Affects immunocompetent individuals	Angio invasion on pathology	Submucosal fungal elements on pathology	Presence of expansive tissue necrosis	Aggressive surgical management	Long-term antifungal therapy
Pre-invasive Fungal Sinusitis[a]	+	−	+	−	−	−[b]
Acute Invasive Fungal Sinusitis	−	+	+	+	+	+
Chronic Invasive Fungal Sinusitis	−	+	+	+	+	+
Granulomatous Invasive Fungal Sinusitis	+	+	+	+	+	+

[a] Candidate category.
[b] For immunocompetent host; role unclear in immunosuppression.

complete treatment details are lacking to verify parallels.[7,8] The subtle but germane distinctions described here between fungal sinusitis subtypes, summarized in Table 2, provide for a measured, semi-aggressive treatment algorithm for the patients reported, and may need to be considered in the spectrum of management of fungal sinusitis (Table 1). Early experience suggests that limited surgery and antifungal therapy are realistic options, especially in immunocompetent patients. Additional reports will be informative for assessing the incidence and relevance of this proposed category of fungal sinusitis.

Conflicts of interest

The authors have no relevant conflicts of interest to declare.

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