

Fungal Sinusitis



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KEYWORDS

- Invasive fungal sinusitis • Noninvasive fungal sinusitis • Granulomatous fungal sinusitis
- Allergic fungal sinusitis

KEY POINTS

- Fungal sinusitis is classified into invasive and noninvasive forms based on histopathologic evidence of tissue invasion by fungi.
- The invasive category includes acute invasive, chronic invasive, and granulomatous forms.
- The noninvasive category includes allergic fungal sinusitis and mycetoma.
- Each of the subtypes of fungal sinusitis has a different clinical presentation, distinct from the other forms, is associated with unique radiologic features, and a specific treatment plan.

INTRODUCTION

Among causes of sinonasal inflammatory disease, fungal sinusitis is a relatively uncommon but well-established clinical entity. Fungi are ubiquitous in the environment, and can colonize the upper respiratory tract mucosa when fungal spores are inhaled. In people with normal immune function, the fungal growth is kept in check. With impaired host immunity, fungi can invade host mucosa and cause invasive disease. Clinicians should therefore maintain a high index of suspicion of fungal sinusitis in immunocompromised patients with sinusitis, and those with chronic sinusitis. Fungal sinusitis consists of a heterogeneous group of disorders, with diversity in the affected patient population, offending agents, mechanism of disease, clinical presentation, histopathology, imaging appearances, treatment, and overall prognosis.¹

Fungal sinusitis is broadly classified into two major groups: invasive and noninvasive forms. Although fungal sinusitis can be caused by any fungus, most result from *Aspergillus* infection. The invasive form is distinguished from the noninvasive variety depending on the presence of fungal elements outside the paranasal sinuses. It should be noted that although the distinction between invasive and noninvasive forms is suggested

based on the clinical presentation, imaging evidence and/or histopathologic confirmation is required. Patients with noninvasive form typically present with chronic sinusitis that fails to respond to repeated courses of antibiotics and surgeries.² Invasive fungal sinusitis usually occurs with an acute onset characterized by fever, cough, and occasionally nasal mucosal ulceration. Usually this invasive form is seen in immunocompromised patients. There are chronic forms of invasive disease that can have an innocuous presentation, but usually demonstrate progressive worsening of symptoms suggestive of involvement of adjacent structures, such as associated visual disturbance suggesting orbital invasion.

This article first explains the classification of fungal sinusitis, and then evaluates separately the different entities with a particular focus on the radiologic appearance, and the information that the clinician needs to know to institute an appropriate therapy.

CLASSIFICATION OF FUNGAL SINUSITIS

The first attempt to classify fungal sinusitis was made in 1965, when two subtypes were recognized: a noninvasive form, clinically similar to chronic bacterial sinusitis; and an invasive form,

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where the infection mimicked a disease similar to a tumor with bone erosion with invasion into adjacent tissues.³ The most commonly accepted classification system, based on International Society for Human and Animal Mycology Group, February 2008, categorizes fungal sinusitis into invasive and noninvasive types based on histopathologic evidence of tissue invasion by fungi.⁴ The noninvasive subtypes include allergic fungal sinusitis (AFS) and mycetoma; the invasive subtypes include acute invasive fungal sinusitis, chronic invasive fungal sinusitis, and granulomatous invasive fungal sinusitis.⁴

GENERAL IMAGING CONSIDERATIONS

There are certain characteristic computed tomography (CT) and MR imaging findings that are highly suggestive of fungal sinusitis.^{5,6} Imaging overall therefore plays a key role in evaluating patients with suspected fungal sinusitis. Noncontrast CT remains the initial imaging study of choice in the work-up of fungal sinusitis.^{7,8} In cases of complicated especially invasive fungal sinusitis, MR imaging can be performed for a more definitive evaluation.⁷ CT in general is better in assessing for hyperattenuation within the opacified sinus, which in an appropriate clinical setting can suggest fungal infection. MR imaging is better at evaluating disease extension into adjacent soft tissues, including soft tissues of the neck, such as pterygomaxillary fissure, orbit, intracranial compartment, and vasculature.⁶

On CT, inflammatory watery secretions are seen as low-attenuation. As the inflammatory sinus disease persists, the secretions become inspissated and demonstrate a higher attenuation than muscle. In cases of fungal sinusitis, calcium and magnesium salts become deposited in areas of fungus growth and fungus-infected mucin.⁶ These fungal concretions appear hyperdense on noncontrast CT.

MR imaging appearance of secretions depends on their protein content, viscosity, and presence of calcifications. Watery secretions usually contain less than 5% protein content; they appear as low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. As they become inspissated, the secretions contain higher percentage of protein content (between 5% and 25%). Increasing T1 signal intensity is noted on T1-weighted images and a variable signal is seen on T2-weighted images. Within sludge or mycetoma where protein content can be between 25% and 40%, low signal intensity on T1-weighted images, and low signal or signal void on T2-weighted images are seen. This last pattern has been described to be highly suggestive of fungal sinusitis.⁶

NONINVASIVE FUNGAL SINUSITIS *Allergic Fungal Sinusitis*

AFS is the most common form of fungal sinusitis, and is common in humid climates.⁹ The overall incidence of AFS is estimated at 5% to 10% of all hypertrophic sinus disease cases going to surgery.¹⁰ It was first reported as allergic aspergillosis by Millar and colleagues in 1981¹¹ who noted the similarity of the fungal-containing sinus exudate characteristic of this condition to the one found in the bronchi of patients affected by allergic bronchopulmonary aspergillosis.

AFS refers to noninvasive collection of impacted mucus and cellular debris, resulting from an allergic response to fungal colonization within the sinus cavity.⁴ It should be noted that the amount of fungal elements within the opacified sinus is variable, often times scanty. The secondary inflammatory process that results does not depend on the quantity of fungus present. Hence, the role of fungi in initiating or promoting this disease is controversial and by some, thought to be circumstantial.⁴

The typical patient with AFS is young, atopic, immunocompetent, and presents clinically with hypertrophic sinus disease experiencing chronic headaches, nasal congestion, and chronic sinusitis for several years.⁹ Fungal-specific IgE as detected by type I hypersensitivity skin testing is a constant feature. Total serum IgE is elevated, up to 5000 IU/mL, with a mean of 600 IU/mL commonly seen.¹² Originally considered to be caused solely by *Aspergillus* species, other causative fungi commonly reported include dematiaceous fungi, such as *Bipolaris*, *Curvularia*, *Alternaria*, and *Fusarium*.

Within affected sinuses, "allergic mucin" is found, characterized by a purulent, yellow-green and sometimes black mucus, which at histopathologic analysis reveals the presence of eosinophil granulocytes and Charcot-Leyden crystals, which are eosinophil degradation products.^{13–15} Fungal hyphae are sparse and noninvasive, and may be identifiable by special stains, such as Gomori methenamine silver stain. Given the specific histopathologic findings, the presence of allergic mucin is virtually diagnostic for AFS, sometimes even in the absence of fungal identification.

Imaging features

On imaging, there is unilateral or asymmetric involvement of the sinuses. Characteristically, multiple sinuses are involved. Maxillary and ethmoid sinuses are most commonly involved. Noncontrast CT shows hyperdense areas within the sinus cavities outlined by hypodense-appearing thickened

and inflamed mucosa (**Fig. 1**).^{16,17} Depending on the contents of the material, the MR imaging signal is variable, ranging from isointense to hypointense signal to signal void on T1- and T2-weighted images. This signal heterogeneity is related to the presence of deposited heavy metals, such as iron and manganese. On contrast-enhanced studies, the intrasinus contents usually demonstrate no masslike enhancement. Because of the expansive nature of allergic mucin, and its propensity to incite local inflammatory response, sinus expansion along with osseous remodeling and erosive changes of the sinus walls are seen.¹⁸

Treatment

Endoscopic removal of polyps and inflammatory material, including mucin, to re-establish aeration and drainage of involved sinuses is essential for successful treatment.¹⁹ Following surgery, additional measures including the use of topical steroids for immune response suppression is important to prevent recurrences; this concept was actually derived from experience with allergic bronchopulmonary aspergillosis. Other therapies, such as immunotherapy, antihistamines, oral anti-leukotrienes, oral steroids, and nasal irrigation, are helpful in certain clinical situations.^{12,20}

Fungus Ball

Fungus ball, also referred to as a fungal mycetoma or aspergilloma, is reported as a distinct clinical entity and a discrete form of noninvasive fungal sinus disease.⁶ It refers to an indolent growth of fungal hyphae in a sinus cavity until a masslike

lesion is formed. Affected patients are immuno-competent, nonatopic, and otherwise healthy. Some studies have reported the disease to be more common in older women. However, patients of all ages are affected. The maxillary sinus by far is the most common site of occurrence. It has been postulated that the host's deficient mucociliary clearance mechanism is accountable for the disease. This allows the uncleared fungal elements to colonize and proliferate in the retained secretions within the sinonasal cavity, inciting an inflammatory response. Previous endodontic treatment and radiotherapy are sometimes implicated in the development of a mycetoma. *Aspergillus fumigatus* is the most commonly implicated pathogen.²¹

Clinical diagnosis

Typically, medical attention is sought for mild sinus pressure. In some cases, patients are asymptomatic and the diagnosis is made incidentally on imaging. A surgical specimen of a fungal mycetoma has been described as a thick, semisolid mass with "claylike" consistency. Histopathologic examination reveals tightly packed fungal hyphae without allergic mucin, a feature distinct from AFS.² Calcium oxalate deposition often accompanies the growth of *Aspergillus*, and appears as radiating clusters of birefringent crystals on histochemistry.

Imaging features

Characteristic imaging findings are critical to the diagnosis. Typically, a single sinus cavity is affected, a distinct feature from other forms of

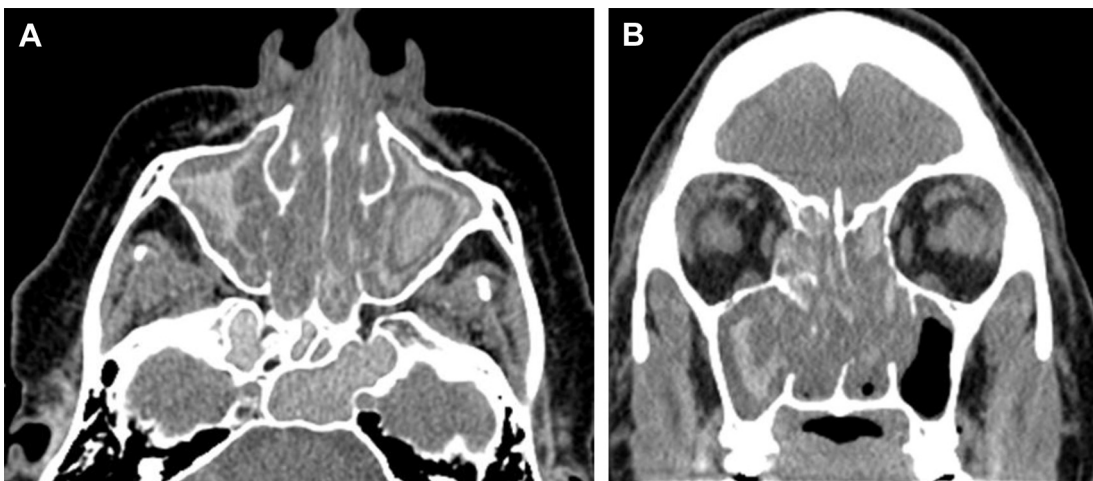


Fig. 1. Allergic fungal sinusitis in a 72-year-old woman with history of nasal polyposis. Noncontrast (A) axial and (B) coronal CT scans demonstrate opacified paranasal sinuses and nasal cavity relatively sparing the left maxillary sinus. Hyperdensity seen within opacified sinuses suggests a mixture of inspissated secretions and fungal concretions.

fungal sinusitis.^{5,8} Maxillary sinuses are most commonly affected, followed by sphenoid, frontal, and ethmoid sinuses. Another unique feature is the lack of sinus expansion. Because of its chronic nature, osseous remodeling of the sinus wall can be seen, noted as thickening and sclerosis. There is opacification of the involved sinus with central areas of high density and fine, round-to-linear matrix calcifications (**Fig. 2**). T1-weighted images demonstrate low signal intensity of the thick, solid, mycetomatous mass, although the signal can be heterogeneous depending on the content.^{5,8} Because of the presence of calcifications and paramagnetic metals, such as magnesium, iron, and manganese, low T2 signal intensity is also observed. Contrast-enhanced studies demonstrate thickening and enhancement of the surrounding inflamed mucosa. There is no involvement of the soft tissues surrounding the involved sinus cavity.⁵

Treatment and prognosis

Good prognosis is noted following surgical excision and reestablishing adequate sinus aeration.²

INVASIVE FUNGAL SINUSITIS

Acute Invasive Fungal Sinusitis

Acute invasive fungal sinusitis is a fungal infection of nasal cavity and paranasal sinuses with a rapid progressive time course (<4 weeks).^{22,23} There is associated invasion of fungal elements into vessels and adjacent soft tissues. Affected patients tend to be critically ill, and demonstrate some degree of compromised immune function. Such

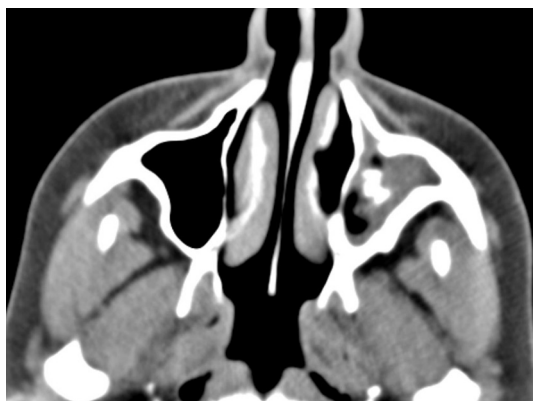


Fig. 2. Fungal mycetoma in a 41-year-old woman presenting with sinus pressure. Noncontrast axial CT scan demonstrates an opacified left maxillary sinus. Central hyperdensity seen within is suggestive of fungal concretions. Note the circumferential thickening of the osseous walls of the left maxillary sinus, a finding consistent with a chronic inflammatory process.

patients typically include those with decreased host cell-mediated immunity, specifically with impaired neutrophil function, hematologic malignancies, aplastic anemia, hemochromatosis, poorly controlled diabetes, acquired immunodeficiency syndrome, or organ transplantation; or are undergoing immunosuppressive treatments, such as systemic steroids or chemotherapeutic agents. Infrequently, acute invasive disease has been reported in patients with normal immune function.²⁴

Aspergillus sp and members of the family *Mucoraceae* (*Mucor*, *Rhizopus*, and *Absidia*) are implicated in most cases of acute invasive fungal sinusitis. In poorly controlled diabetics, *Mucor*, *Rhizopus*, and *Absidia* predominate, and in neutropenic patients, *Aspergillus* sp account for most cases.²²

As expected in this patient population, the disease course is rapidly progressive and can prove to be fatal within days to weeks. Therefore, it is important for clinicians to maintain a high level of awareness, and for radiologists to proactively look for subtle changes that can be identified in the early stages of the disease.

Clinical features

The presenting symptoms are nonspecific and include fever, headache, rhinorrhea, facial pain, and diplopia, which can also be seen with acute bacterial sinusitis. Therefore, when sinusitis is considered in patients with impaired immune function, appropriate diagnostic work-up, including imaging studies and nasal endoscopy with possible biopsy, must be initiated in a timely manner.

Involvement of the nasal cavity is common, with the middle turbinate being the most commonly affected site, thus a high-yield target for nasal biopsy. On nasal endoscopy, the infected mucosa appears pale, progressing to ulceration and tissue necrosis with worsening disease. The affected area is commonly painless. Definitive diagnosis is made with microscopic identification of invasive fungi in the biopsy samples of mucosa, submucosa, vessels (angioinvasion), and bone. Infarcted tissue and inflammatory cellular infiltrates are also seen.

Imaging features

Maxillary and ethmoid sinuses are most commonly affected. On CT, mucosal thickening with partial or complete opacification of the affected sinus is a typical imaging feature.^{8,23} Hyperattenuation areas within the opacified sinuses are commonly seen, and in an immunocompromised state should raise a red flag for an underlying fungal cause. This is especially concerning when associated soft tissue/vascular invasion, as suggested of effacement

of fat, beyond intact sinus walls is seen (**Fig. 3**). In such cases, disease spread is thought to occur through microvascular channels present within the bone. The areas to be particularly mindful of to evaluate for such soft tissue infiltration are spaces adjacent to maxillary sinuses, such as premaxillary and retroantral fat, and pterygopalatine fossa. Occasionally, focal areas of bone erosion can be seen.²³ On MR imaging, opacified sinuses are seen. Within these opacified sinuses are areas of signal drop-out suggestive of fungal concretion. It should therefore be noted that appreciation of such fungal concretion is therefore best made on noncontrast CT, and can be a limitation of MR imaging. However, invasion of adjacent soft tissues is best assessed on MR imaging. With involvement of the spaces around the sinuses, there is T1 signal intensity similar to soft tissue replacing normal fat signal intensity. Edematous change on T2-weighted images, and enhancement within these soft tissues is commonly seen. A unique feature on imaging suggestive of invasive fungal sinusitis is the lack of enhancement in areas that should typically enhance following contrast administration, such as the nasal mucosa and the turbinates. Lack of enhancement of the affected mucosa of the turbinates, described as the black-turbinate sign on imaging, is highly suggestive of tissue necrosis, and is consistent with the angioinvasive nature of fungal sinusitis (**Fig. 4**).²³ For radiologists, it is also crucial to identify and alert clinicians of the extension of the disease, especially to the orbits and intracranial compartment. In addition, the angioinvasive nature of some of the fungi makes it important to assess adjacent intracranial vessels,

such as the cavernous segment of internal carotid arteries for thrombosis, dissection, and pseudoaneurysm formation (**Fig. 5**).

Treatment

Treatment consists of emergency surgical debridement and systemic antifungal agents. Aggressive management of any inciting factor, such as diabetic ketoacidosis, is crucial in the management. The mortality associated with acute invasive fungal sinusitis has been traditionally cited up to 50% to 80%.²⁵ Despite a recent downward trend, likely caused by better understanding of the disease and timely diagnosis and initiation of treatment, the mortality remains high, with some studies reporting up to 18%.²⁶ Studies have shown that overall mortality is higher in patients infected with *Mucor* compared with those infected with *Aspergillus* sp.

Chronic Invasive Fungal Sinusitis

Chronic invasive fungal sinusitis is characterized by an indolent course of the disease (>4–12 weeks), in contrast to the rapidly progressive course of its acute counterpart.^{2,21} As with acute invasive disease, patients in immunocompromised states, such as poorly controlled diabetes mellitus or undergoing immunosuppressive treatments, show predisposition to the disease. Patients with normal immune function are uncommonly affected.

Clinical diagnosis

Patients usually seek medical attention for symptoms of chronic sinusitis, for which findings of



Fig. 3. Acute invasive fungal sinusitis in a 58-year-old man with neutropenia and right maxillary pain. (A) Non-contrast axial CT scan demonstrates complete opacification of the right maxillary sinus with mixed attenuation material. (B) At a level slightly cranial, CT scan demonstrates ill-defined soft tissue infiltration in the region of the right pterygomaxillary fissure and soft tissues of the cheek. Also, note edematous change involving the right masseter, temporalis, and pterygoid muscles suggestive of masticator space invasion.

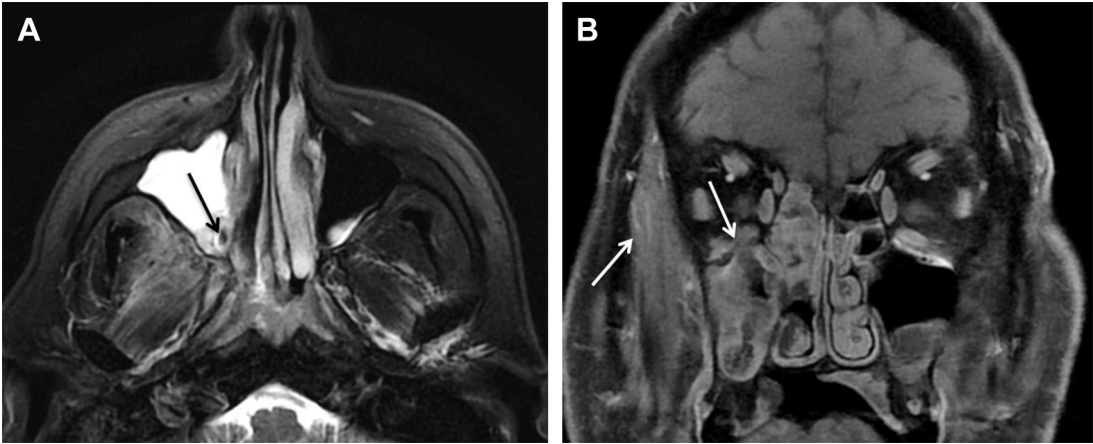


Fig. 4. Acute invasive fungal sinusitis in a 33-year-old man with immunosuppression and acute right facial pain and swelling. (A) Axial T2-weighted image demonstrates an opacified right maxillary sinus. Focus of hypointensity (arrow) is likely suggestive of fungal concretion. There is a suggestion of soft tissue infiltration within the right pterygomaxillary fissure and edematous change within the right pterygoid muscles. (B) Contrast-enhanced fat-suppressed coronal MR imaging demonstrates lack of “normal” enhancement of the right middle and inferior turbinates suggestive of black turbinate sign. There is a suggestion of right orbital invasion and masticator space invasion (arrows).

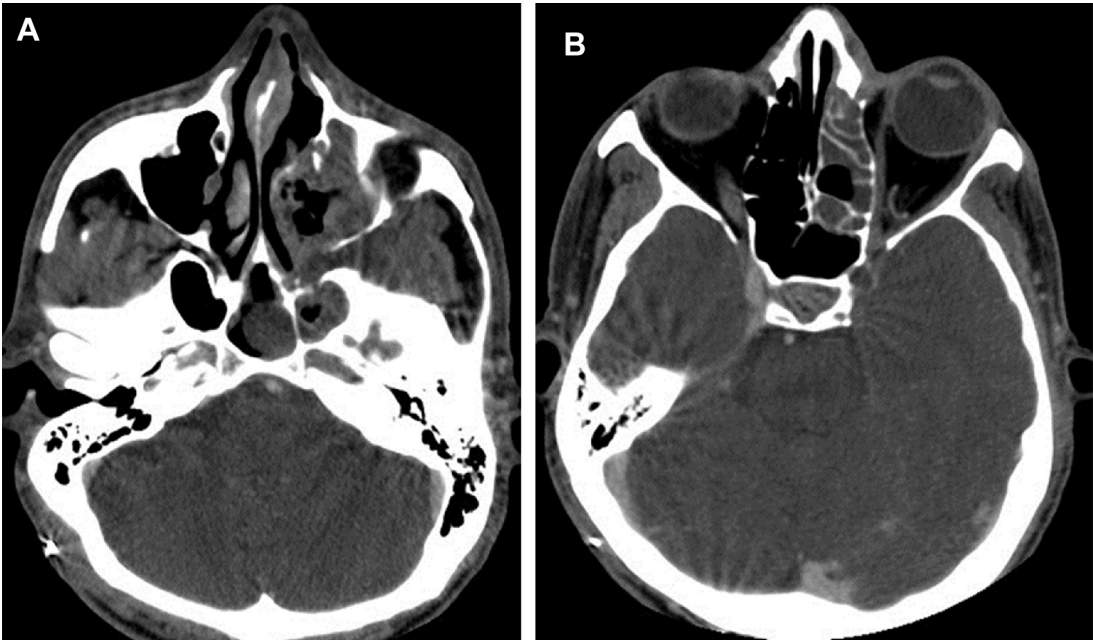


Fig. 5. Acute invasive fungal sinusitis in a 61-year-old woman with headache and change in mental status. (A) Contrast-enhanced axial CT scan demonstrates nonvisualization of the medial wall of the left maxillary sinus suggestive of recent surgical intervention. Opacified left sphenoid sinus is also seen. There is a suggestion of effacement of the fat in the left pterygomaxillary fissure and edema within the left infratemporal fossa suggestive of tissue invasion. (B) At a slightly more cranial level, there is no enhancement of the cavernous segment of the left internal carotid artery suggestive of thrombosis and reflecting vascular invasion secondary to the angioinvasive nature of fungal infection.

protracted disease course, slow progression, and refractoriness to standard antibiotic treatment are common. In some cases, patients report decreased vision and ocular immobility, known as orbital apex syndrome. This has been reported to be associated with disease extension to the orbital apex in patients with chronic invasive fungal sinusitis. The causative agent is known to be of *Aspergillus* genus with *A. fumigatus* being the most common species. Except for the difference in time course compared with the acute disease, the clinical and imaging work-up should be identical. Clinical examination reveals evidence of nasal congestion and nasal polyposis. On histology, the specimen includes material containing densely packed hyphae, mixed with scattered, chronic, inflammatory infiltrates. Evidence of fungal invasion into the paranasal mucosa and adjacent tissues is often seen.

Imaging features

Intranasal and extrasinus imaging features are mostly similar to the acute counterpart. However, there is a difference in the pattern of calcifications between acute and more chronic diseases. On CT, intranasal calcifications in an acute stage show fine punctate appearance. With a protracted course of the disease, more calcium metabolites are deposited in the fungal mass, taking on a more dense and coarse appearance.²⁷ Otherwise, in keeping with its invasive nature, localized erosive changes in the sinus walls are seen with extension into adjacent tissues (Fig. 6). Extension to the orbits and intracranial compartments is seen.



Fig. 6. Suspected chronic fungal sinusitis in a 61-year-old man with symptoms of chronic sinusitis. Axial non-contrast CT scan demonstrates mixed-attenuation material filling the right sphenoid sinus. Note the focal dehiscence of the right carotid canal.

Treatment and prognosis

Treatment typically includes surgical debridement, followed by systemic antifungal agents, a strategy similar to acute invasive fungal sinusitis. Although the overall mortality is lower than the acute disease, when there is invasion into adjacent structures, such as cavernous sinus or intracranial compartment, a high mortality rate is reported.²

Granulomatous Invasive Fungal Sinusitis

Similar to chronic invasive fungal sinusitis, the disease course is slowly progressive. The affected patients are usually immunocompetent and report a history of chronic sinusitis.² This disease is prevalent in Africa and Southeast Asia, with rare reported cases in the United States. The causative agents are of *Aspergillus* genus, with *Aspergillus flavus* being most commonly implicated.

Clinical diagnosis

Microscopic features include evidence of fungal invasion, noncaseating granulomas with giant cells, plasma cells, central small granulomas containing eosinophils, fibrinoid necrosis, fibrosis, and vasculitic changes.

Imaging features

The imaging features are nonspecific and similar to other invasive fungal sinusitis. There is soft tissue opacification of the involved sinus, and evidence of surrounding tissue invasion. Extension to soft tissues around the sinuses and the orbits and intracranial compartment is also seen. Typically, only one or two sinuses are involved. Sinus expansion is uncommon. Bone erosion is localized to the area of extrasinus extension and extrasinus component of the disease tends to be more extensive than intrasinus component.²⁸

Treatment and prognosis

Surgical resection is the mainstay of treatment. If surgical intervention is not initiated in a timely manner, the disease can invade adjacent structures, resulting in worse prognosis. Concurrent antifungal agents are usually used to lower relapse rate.²

SUMMARY

Fungal sinusitis is classified into the noninvasive (AFS, fungal ball) and invasive (acute invasive, chronic invasive, and chronic granulomatous) forms. These different types and subtypes of fungal sinusitis present with clinical features similar to the viral and bacterial forms of sinusitis. However, the associated morbidity and mortality of fungal sinusitis is worse when compared with the other pathogens. The radiologist based on

imaging features can help suggest the diagnosis of fungal sinusitis in an appropriate clinical setting. Such accurate assessment by the radiologist, especially when assessing invasive forms, is crucial with regards to further management, and therefore the overall prognosis of the patient.

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