Introduction

Fungal organisms are ubiquitous, and our exposure to these organisms occurs on a daily basis. A common location for these organisms to enter the human body is through the sinonasal cavity. Luckily, our immune system helps to prevent infection by these organisms. In those who do develop infection, a benign, noninvasive process usually occurs. However, in some patients, invasive disease does occur. As invasive fungal infections can lead to serious morbidity and mortality, it is important for the clinician to be able to recognize the difference between noninvasive and invasive fungal disease.

Basic Mycology

There is an estimated 20,000 to 1.5 million different fungal species. However, only a few dozen actually cause infectious disease in humans. There are two main forms of a fungus, yeasts and molds. The yeast is a unicellular organism roughly 3-15 µm in diameter. They reproduce asexually by budding. If these buds do not detach, a chain of fungal cells results. This chain is known as a pseudohyphae. The mold is a multicellular organism measuring 2-10 µm in diameter. These organisms grow by branching into structures termed hyphae.

Another important component of the fungal organism is the spore. The spore is a reproductive structure that can be produced in the presence of unfavorable conditions. These spores can withstand many adverse conditions, and are dispersed widely throughout the environment. Once these spores are exposed to a favorable environment, they begin to grow. Inhalation of spores is thought to be the primary means by which fungal organisms gain access to the sinonasal tract.

Classification of Fungal Sinus Disease

Fungal sinus disease can be broken into two categories, noninvasive and invasive. Noninvasive disease includes saprophytic fungal infestation, sinus fungal ball, and allergic fungal sinusitis. Invasive disease includes acute fulminant invasive fungal sinusitis, chronic invasive fungal sinusitis, and granulomatous invasive fungal sinusitis.

Saprophytic Fungal Infestation

Saprophytic fungal infestation within the sinonasal cavity occurs when fungus grows on mucus crusts without the involvement of the surrounding mucosa. Patients typically have minimal to no
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sinonasal symptoms. Diagnosis is done by direct examination, and the treatment involves removal of the crusting with sinonasal rinses. In addition, patients should undergo weekly endoscopy with removal of further crusting until the disease process resolves.

**Sinus Fungal Ball (Mycetoma)**

A fungus ball is the sequestration of fungal hyphal elements within a sinus without invasive or granulomatous changes. The disease begins with the inhalation of spores that then become sequestered in a specific location, usually the maxillary sinus (69-86% of cases). Growth of the fungus then occurs while evading the host immune system. In most cases, the offending agent is an Aspergillus species.

Signs and symptoms of the disease are the result of mass effect by the fungal ball and sinus obstruction. However, the symptoms are not specific as they mimic signs of chronic rhinosinusitis; facial pressure, pain, nasal congestion, rhinorrhea. Physical examination typically reveals mild to no mucosal inflammation, with 10% of patients having polyps. Diagnosis is done through physical examination, imaging, and biopsy. The most common imaging modality utilized is computed tomography. On CT scans, the disease involves a single sinus in 59-94% of cases with complete or subtotal opacification of the involved sinus. Bony sclerosis is usually seen, however, in 3.6-17% of cases bony destruction can be seen. On biopsy, the fungal component is noted. In the case of Aspergillus, one will see y-shaped, fungi with 45-degree branching.

The treatment of choice for a sinus fungal ball is complete surgical removal of the disease with creation of appropriate drainage pathways for the sinus. In addition, sinonasal irrigations should be instituted. Antifungal therapy is usually not required unless there is recurrence of disease or the patient is at high risk for invasive disease. Topical antifungals should be instituted first followed by the least toxic medications if they are required.

**Allergic Fungal Sinusitis**

Allergic fungal sinusitis occurs when a fungus colonizes a sinus cavity and then causes allergic mucosal inflammation through an IgE response to fungal protein. Patients present with nasal obstruction, rhinorrhea, facial pressure, sneezing, watery/itchy eyes, and periorbital edema. There are five major criteria used to make the diagnosis of AFS. These are the presence of eosinophilic mucin containing noninvasive fungal hyphae, nasal polyposis, allergy to the offending fungus, immunocompetence of the patient, and the classic radiographic findings associated with AFS.

Eosinophilic mucin is pathognomonic for AFS, and is described as a thick, tenacious and highly viscous material that is tan to brown or dark green in appearance. Under microscopic examination, the mucin contains branching fungal hyphae, sheets of eosinophils, and charcot-leyden crystals. Charcot-leyden crystals are slender and pointed crystals consisting of a pair of hexagonal pyramids joined at their bases. They result from the breakdown of cells by enzymes that are released by eosinophils.

The classic radiographic findings of AFS are best noted by CT imaging. The disease will usually be unilateral in 78% of cases. The involved sinuses are typically expanded, with rare cases of bony destruction. Bone destruction, if present, is usually seen in advanced or bilateral disease. Within the involved sinuses, one will see the presence of “double densities.” This is a heterogeneity of signal due to the increased presence of heavy metals (iron, manganese) and calcium salts. On MRI, there is a variable signal density noted on T1 weighted images. On T2 weight images, there is a hypointense central region within the affected sinus due to the low water content of the mucin. In addition, there is a peripheral enhancement due to tissue edema.
As stated previously, patients with AFS typically exhibit allergy to the fungus causing their disease. In a prospective study by Manning et al, 8 patients with proven culture positive Bipolaris AFS were compared to 10 controls with chronic rhinosinusitis. Both groups underwent RAST, ELISA, and skin testing. All 8 patients with AFS showed positive skin testing, RAST, and ELISA to Bipolaris. Eight of the ten controls were negative in their tests for Bipolaris. Authors concluded that AFS patients were more often likely to exhibit a fungal allergy. In addition to the positive allergy testing, patients also tend to exhibit higher levels of IgE.

The treatment of AFS begins with the surgical removal of all mucin while providing permanent drainage and ventilation of the affected sinuses. Following this, systemic steroids are utilized. Multiple studies have shown that the addition of systemic steroids helps to decrease the rate of recurrence of disease. There is no clear consensus on the length of treatment, but the usual length 2-3 months. Schubert examined steroid treatment for AFS looking at treatment lengths from 2-12 months. It was noted that longer treatment courses resulted in much fewer recurrences, but more side effects.

As AFS is an allergic response, immunotherapy has also been used as a treatment. One prospective study examined patients with AFS who were given immunotherapy consisting of all fungal and nonfungal antigens to which each patient was sensitive following surgical removal of the mucin. After one year, the patients did not require systemic steroids, and the recurrence rates were significantly better than patients who had not received immunotherapy. In a retrospective study by Folker et al, 22 patients with AFS were treated with surgery and steroids. Eleven were treated with immunotherapy while the other eleven were not. The results showed that the immunotherapy did not result in fewer recurrences. However, immunotherapy did result in better quality-of-life scores and decreased mucosal edema.

**Acute Fulminant Invasive Fungal Sinusitis**

Acute fulminant invasive fungal sinusitis (AFIFS) occurs when fungal infection begins to invade the mucosal tissues. Patients are typically immunocompromised with illnesses such as diabetes mellitus, AIDS, hematologic malignancies, aplastic anemia, organ transplantation, or on chemotherapy or steroids. The most common fungi involved are Aspergillus, Mucor, Rhizomucor, Absidia, and Rhizopus. Less common fungi are Candida, Bipolaris, and Fusarium.

In AFIFS, fungi gain access to the sinonasal cavity typically by way of spores that are inhaled. The fungi then grow and begin to invade neural and vascular structures. This leads to thrombosis of vessels with resultant mucosal necrosis and loss of sensation. Eventually, the fungi extend beyond the affected sinus via bony destruction, perineural and perivascular spread.

Fever is one of the most common signs of initial infection as it is seen in 90% of cases of AFIFS. Other signs and symptoms include rhinorrhea, nasal congestion, facial pain, facial numbness, diplopia, headaches, seizures, cranial nerve deficits, and ulcerations of the nasal, facial, or palatal mucosa. As the disease can result in mortality in days, it must be recognized early. Any immunocompromised patient with fever and one other sinonasal symptom should undergo evaluation for fungal sinusitis.

As part of a good examination, patients must undergo endoscopic examination of the sinonasal cavity. Changes in the appearance and anesthesia of the mucosa are the most consistent findings of AFIFS. In the early stages of the disease, the mucosa may just appear pale. In later stages, the mucosa will become ulcerative and black. Biopsies should be obtained whenever one suspects fungal disease or notes changes in mucosal appearance or sensation. If the biopsies return back normal, or there are no
changes noted with the mucosa, biopsies should be taken from the middle turbinate and nasal septum as both of these areas are the most common sites of involvement.

Imaging is an important part of the work-up, and should include CT and MRI. CT is better at detecting bony destruction while MRI is better at detecting mucosal/skin invasion as well as orbital or intracranial involvement. On CT scans, classically there is bony erosion and extrasinus extension. One may also note severe, unilateral mucosal thickening and thickening of periantral fat planes. MRI will also detect periantral fat obliteration, which should alert the clinician to the possibility of fungal invasion. Other findings include leptomeningeal enhancement with intracranial involvement and granuloma formation. Granulomas will appear hypointense on both T1 and T2 weighted images.

The treatment of AFIFS involves a combination of medical and surgical therapy. One of the most important aspects of medical management is the correction of the underlying immunocompromised state. In diabetics who are suffering from diabetic ketoacidosis (DKA), DKA should be corrected as soon as possible as this will improve survival by 80% if corrected promptly. Using white blood cell transfusions and granulocyte stimulating factor to maintain an absolute neutrophil count greater than 1000/mm$^3$ is important as counts less than this are associated with a much worse prognosis.

Systemic antifungals should also be started. Until mucormycosis is ruled out, amphotericin B at a dose of 1 mg/kg/day should be started. Close monitoring of renal function is imperative at this time as 80% of patients will suffer nephrotoxicity. A lipid-based form of amphotericin B is available, but is more expensive. However, it has less side effects, and higher concentrations of the drug can be maintained. If mucormycosis is not involved, less toxic antifungals such as voriconazole and itraconazole can be used; mucormycosis are resistant to these drugs. In addition to systemic antifungals, amphotericin B sinus rinses should be started as well. Results are mixed when it comes to the effectiveness of these rinses, but the potential benefits of such rinses greatly outweigh any risks.

Surgical therapy for AFIFS helps to decrease pathogen load, removes devitalized tissue, and establishes pathways for sinus drainage. Debridement should occur until clear, bleeding margins are obtained. In earlier stages of disease, endoscopic approaches should be utilized as they are less morbid, and survival rates are similar to open approaches. Advanced disease (orbital, skin, and palatal involvement) requires open approaches. The prognosis of the patient should be considered when extensive resection is going to be required. For instance, skull base/intracranial involvement results in mortality in greater than 70% of patient regardless of surgical treatment.

The overall mortality rate for AFIFS is 18-80% and depends on how early treatment can begin. Patients who are treated very early in their disease course do much better than those who present with advanced disease. The single most predictive indicator for mortality is intracranial involvement with a 70%+ mortality rate. An ANC < 1000/mm$^3$ is associated with a worse prognosis. Recovery from neutropenia is the most predictive indicator for survival. Mucor infection tends to worse than Aspergillus as Mucor tends to be more aggressive with earlier orbital and intracranial involvement. Diabetics do worse than those of other immunocompromised states. This is thought to be because mucormycosis is more often seen in diabetics.
Chronic Invasive Fungal Sinusitis

Chronic invasive fungal sinusitis (CIFS) has a very similar clinical appearance as AFIFS, but is much slower, occurring over months to years. Patients with this disease tend to be immunocompetent. The most common pathogen is Aspergillus, seen in about 80% of cases. Other fungi include Mucor, Rhizopus, Bipolaris, and Candida.

The signs and symptoms of CIFS are very similar to chronic rhinosinusitis, which makes it difficult to recognize until late in the disease course. Unresponsiveness to antibiotics, epistaxis, facial anesthesia, visual changes, altered mental status, and seizures should all increase suspicion for fungal infection. Once a detailed history has been obtained, a thorough head and neck examination with nasal endoscopy should be performed. Unlike AFIFS, nasal endoscopic findings in CIFS are very subtle and include mucosal edema, crusting, and the presence of polyps. Rarely will ulceration and eschar formation be noted. Imaging is a key to making the diagnosis of disease. This is done with the use of CT and MRI. CT scans will show hyperattenuating soft tissue within one or more sinuses with bony destruction and extrasinus spread. MRI findings are very similar to that found with AFIFS except there will be no granuloma formation. Biopsies should be obtained just as with AFIFS to assess for mucosal invasion. On microscopic evaluation, invasion of vascular and neural structures as well as mucosa is noted as is the case with AFIFS. However, with CIFS, there are few, if any, inflammatory cells. In addition, one will note the absence of granulomas, a key difference between CIFS and granulomatous invasive fungal sinusitis.

The treatment of CIFS is similar to AFIFS with a combination of surgical and medical treatments. Surgical resection should include all involved tissues until clear, bleeding margins are obtained. Systemic and topical amphotericin B should be started until cultures prove that the offending agent is not a Mucor species. If not a Mucor species, the clinician can use voriconazole or itraconazole to help limit side effects; Mucor species tend to be resistant to these drugs. Patients should be followed closely with examination and debridement. Biopsies should be taken from any suspicious areas as asymptomatic recurrence is not uncommon.

Granulomatous Invasive Fungal Sinusitis

Granulomatous invasive fungal sinusitis (GIFS) appears nearly identical to CIFS. The differences come in the pathogen involved, location that the disease is found, and the microscopic findings. GIFS is very rare, and is caused by Aspergillus flavus. The disease is almost exclusively found in North Africa and Southeast Asia. The workup for the disease is exactly like CIFS. On microscopic evaluation, one will note the presence of multinucleated giant cell granulomas.

The treatment of GIFS involves surgical resection of involved tissues to bleeding margins and the use of systemic and topical antifungals. As the disease is caused by Aspergillus flavus, one may start treatment with voriconazole. Close follow-up with debridement is mandatory. As with CIFS, one should biopsy any suspicious lesions.

Conclusion

Fungi are ubiquitous, and exposure to these organisms occurs on a daily basis. Our immune systems are usually able to clear the pathogens within the sinonasal cavity prior to the development of infection. When infection does occur, the process is typically benign. However, if treatment fails to resolve the disease process, an invasive infection should be suspected. Any immunocompromised patient with sinonasal symptoms and fever should be suspected of having invasive fungal disease, and a thorough workup should be performed with a low threshold for biopsy.
The mainstay of treatment of fungal sinus disease is surgical debridement. When the disease is invasive, the debridement should continue until one obtains clear, bleeding margins. However, one must weigh extensive surgical resection with the prognosis of the patient. In addition to surgical resection, systemic antifungals should be utilized when invasive disease is present. Once the disease has been cleared, close follow-up with debridement of crusts is mandatory to help with healing and to detect early recurrence. Biopsies of any suspicious lesions should be performed as asymptomatic recurrence may occur.

Discussion: Patricia Maeso, MD

Dr. Maeso:
Just a couple of points: Just remember that AFS is an allergic reaction. It has been defined as a Type 1 hypersensitivity reaction. I think it was first described at MCV and then UTHSC at Dallas they have the largest experience. You brought in some CT scans and you mentioned the pushing aspect. I wanted to bring in some scans that were a little bit different but are still AFS. Because this can be frequently confused with a tumor. You have to know what it looks like, both in soft tissue and bone windows. There are subtle differences, and they can be confused with a tumor. So, yes, there is expansion, absolutely. But there can also be erosion. Because of the expansion there can also be erosion, and I'll show you this. You can see how this side is completely displaced. That was the bone window and now you see the double density that Dr. Gleinser was describing. This is typical AFS. The Mecca for this is really in Georgia, where I trained and the first time they showed me an image like this I said "tumor!"
Sources


