Chronic Invasive Sinus Aspergillosis in an Immunocompetent Patient

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When this fungal infection, which most frequently strikes patients with compromised immune systems, eludes diagnosis and prompt intervention, it can have devastating consequences.

Aspergillosis, one of the most common causes of fungal sinus infections, is acquired through inhalation of airborne *Aspergillus* spores.[1] It can involve the ear canal, eyes, nose, sinus cavities, and lungs.

Sinus aspergillosis may be either invasive or noninvasive. Noninvasive aspergillosis remains confined to the sinus cavity[2] and may present as allergic sinusitis or sinus mycetoma. Invasive sinus aspergillosis takes one of three forms: (1) acute fulminant, (2) granulomatous, or (3) chronic invasive.[3,4] Differentiation between noninvasive and invasive fungal sinusitis relies on the patient's clinical presentation and histopathologic examination. In noninvasive disease, hyphae are present solely in the mucopurulent material within the sinus, whereas invasive cases show hyphae penetration into the submucosa, blood vessels, or bone.[3,4] While invasive fungal infections occur frequently in immunocompromised hosts, they are extremely rare in otherwise healthy individuals.

In this article, we present the case of a patient who developed chronic invasive sinus aspergillosis, despite a generally healthy immune system. In this case, the fungal etiology was recognized only after the patient had been hospitalized multiple times and had experienced substantial deterioration and disease progression. Through the description of this case and a review of the presentation, diagnosis, and treatment of the infection, we aim to help clinicians avoid such delays and optimize care of patients with this potentially destructive disease.

INITIAL EXAM

An 83-year-old, Ukrainian man was brought to the emergency department (ED) because he had headaches of increasing severity and had displayed lethargy and combative behavior over the previous three weeks. His presentation also included right-sided facial droop and right-sided weakness.

Prior to the development of the present symptoms, the patient had been leading an active life, despite chronic headaches. He had undergone evaluation of his headaches at another hospital six months earlier, and these investigations had revealed a sinus mass in the right ethmoid region. A biopsy of this mass showed necrotic tissue with no malignancy. No cultures had been performed at that time.

For a period of approximately five months after these investigations, the patient's symptoms remained in spontaneous remission. Eventually, however, they recurred and the patient's right-sided visual acuity began to deteriorate.

Three weeks prior to the current ED visit, the patient had presented to our ED reporting severe right-sided frontal headaches and orbital pain. Because of an elevated erythrocyte sedimentation rate of 87 mm/hour, jaw claudication, right-sided headache, and fatigue, his clinicians considered a diagnosis of temporal arteritis and initiated empiric, high dose steroid therapy (prednisone 60 mg daily for two weeks). A temporal artery biopsy was scheduled, but the patient subsequently postponed this test. Although his headaches initially resolved, they soon returned at a more severe intensity, accompanied by mental status changes—his condition at the present ED visit.

A medical history interview conducted during the current ED visit

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and admission revealed coronary artery disease, hypertension, hypercholesterolemia, hypothyroidism, degenerative joint disease, and chronic sinusitis. His surgical history was significant for percutaneous coronary intervention with stent placement and sinus surgery. Specifically, he had undergone a right endoscopic ethmoidectomy, maxillary sinus antrostomy, and sphenoidotomy six months earlier due to the frequent headaches and chronic sinusitis.

On physical examination, the patient appeared ill and lethargic. He had proptosis in his right eye and was unable to count fingers with the right eye uncovered. He had right-sided weakness in his upper and lower extremities with a right-sided facial droop. His other cranial nerves were intact. The patient was not cooperative enough to allow assessment of sensory function. His reflexes were increased in the right extremities, and both of his plantar reflexes were extensor.

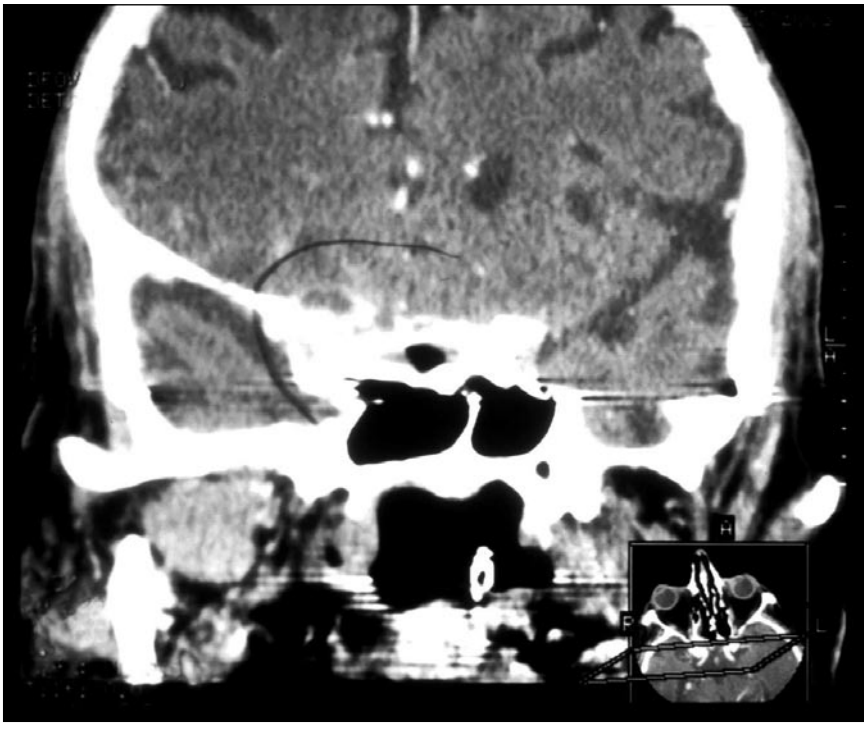

Figure 1. The patient's computed tomography scan with contrast, showing a soft tissue density with erosion within the right posterior ethmoid sinuses.

Results of blood investigations were normal, except for an elevated white blood cell count of 15.4 x 10^9 cells/L (normal, 4 to 11 x 10^9 cells/L). A lumbar puncture revealed 40 nucleated cells (76% polymorphonuclear cells), a cerebrospinal fluid (CSF) protein level of 106 mg/dL, and a CSF glucose level of 37 mg/dL.

Because the differential diagnosis included bacterial infection, the patient was treated empirically with ceftriaxone sodium 2 g IV every 12 hours and ampicillin 2 g IV every six hours. His lack of response to this treatment, however, suggested a nonbacterial etiology, which was supported by the results of the CSF Gram stain and cultures (which grew neither bacteria nor fungus).

A computed tomography (CT) scan of the sinuses with contrast confirmed the presence of a soft tissue density within the right posterior ethmoid sinuses (Figure 1). This scan also showed an osseous dehiscence and erosion in the same area, entering the region of the cavernous sinuses and the right optic canal. A mild, extra-axial enhancement inferior to the right frontal lobe also was noted. At this point, the differential diagnosis included infection, neoplasm, and granulomatous disease.

Magnetic resonance imaging of the brain with contrast showed an acute infarct in the left thalamus (Figure 2). It also revealed edema in the posteroinferior right frontal lobe with meningeal enhancement overlying this region extending into the anterior roof of the sphenoid sinus.

Biopsy of the soft mass at the base of the skull superolateral to the right sphenoid sinus was sent for pathologic testing. These tests showed septated hyphae branching at sharp angles, consistent with *Aspergillus* invading the submucosa (Figure 3). Ultimately, these findings were reviewed by several pathologists—from the University of Rochester School of Medicine and Dentistry and Rochester General Hospital in Rochester, NY and from State University of New York Upstate Medical University in Syracuse—all of whom concurred with the diagnosis of invasive sinus aspergillosis. Unfortunately, culture of the specimen was not performed.

TREATMENT COURSE

The patient was evaluated by the otolaryngology department and deemed not to be a surgical candidate due to his impaired neurologic status. He was treated with combination antifungal therapy, consisting of voriconazole (6 mg/kg IV twice a day on day

one, followed by 4 mg/kg twice daily for 30 days) and caspofungin acetate (70 mg IV once on day one, followed by 50 mg IV once a day for 30 days).

Despite this treatment, a repeat CT scan of the head four weeks later revealed progression of the sinus disease and multiple new infarcts. His neurologic condition continued to deteriorate until, ultimately, he was determined to be brain dead. At this point, the family asked that his care be withdrawn.

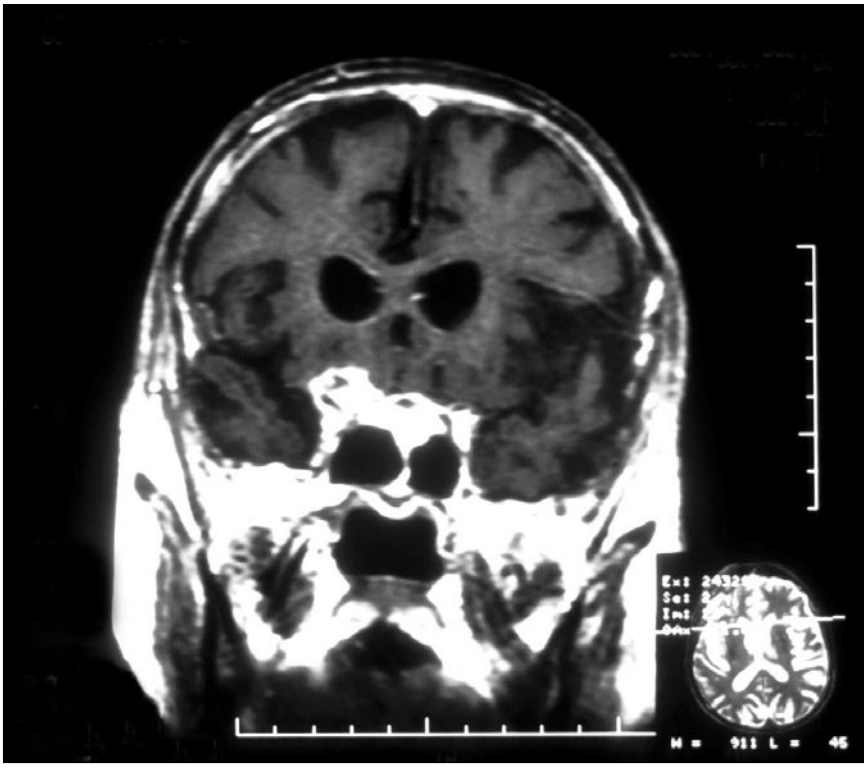

Figure 2. The patient's magnetic resonance imaging scan, showing edema in the posteroinferior right frontal lobe and a left thalamic infarct.

ABOUT THE CONDITION

Aspergillus is a ubiquitous, spore forming saprophyte found primarily in soil and decaying organic matter. The spores may be inhaled and frequently inhabit the human upper respiratory tract. When they are inoculated into the sinuses, they may become pathogenic.[5]

Certain occupations, such as milling and farming, have been suggested as predisposing factors for aspergillosis.[6] In these contexts, *Aspergillus* spores may be encountered while working with soil, water, compost, stored grain, or ventilation systems. Our patient was an avid gardener, which may have put him at a higher risk for *Aspergillus* exposure.

Invasive fungal sinusitis usually is seen in immunocompromised patients but can occur in apparently immunocompetent individuals.[2] While our patient was not immunocompromised, he had been receiving high dose steroid therapy for two weeks at the time of diagnosis, which may have contributed to the progression of his condition.

A challenging diagnosis

There are two diagnostic criteria for invasive fungal sinusitis: (1) sinusitis confirmed by radiologic imaging and (2) histopathologic evidence of hyphal forms within the sinus mucosa, submucosa, blood vessels, or bone.[3] Our case study met both criteria.

Initially, aspergillosis presents with mild symptoms of sinusitis, but eventually the infection causes tissue destruction of the sinuses and adjacent structures.[7] Difficulties in diagnosing this condition arise because of the similarity of its presentation to bacterial sinusitis in the initial stage and to malignant disease in later stages.[7] Clinical suspicion should be aroused when any patient with chronic sinusitis fails to respond to antibiotics. Our patient's symptoms did not improve with empiric antibiotic therapy, which led to further investigation that ultimately confirmed fungal infection. His initial lumbar puncture results also were consistent with fungal meningitis: Although his CSF cultures did not grow fungus, it is well known that fungal meningitis can present with no fungal growth.[8]

Treatment strategies

Aggressive surgical debridement and antifungal therapy constitute the mainstay of treatment for invasive fungal sinusitis in both immunocompromised and immunocompetent patients.[9,10] While antifungal medication alone may cure 24% of patients, Clancey and Nguyen showed that the addition of surgery to antifungal therapy can cut mortality rates in half (from about 50% to 24%).[2] Our patient, unfortunately, was not a surgical candidate, which necessitated a therapeutic approach of antifungal medication alone.

Voriconazole is a triazole antifungal agent that acts by inhibiting fungal cytochrome P-450, which is essential

in fungal ergosterol biosynthesis. The subsequent loss of ergosterol in the fungal cell membrane causes destruction of the cell wall and fungal death. In a direct comparative, international, multicenter, randomized, open-label trial of initial therapy in patients with confirmed and probable aspergillosis, a satisfactory global response was observed at 12 weeks in 53% of patients taking voriconazole, compared to 32% of those taking amphotericin B.[11]

Caspofungin acetate's mode of action is inhibition of fungal cell wall synthesis. Thus, with a different mechanism of action, the drug offers theoretical benefit in combination treatment. Unfortunately, our patient did not appear to benefit from the dual therapy of voriconazole and caspofungin acetate he received. Contributing factors to his lack of response likely include the progression of his invasive disease, with spread to the right posterior ethmoid sinuses and edema in the posteroinferior right frontal lobe, and his ineligibility for surgery.

Even when aggressive surgical and medical intervention are possible, chronic invasive sinus aspergillosis is associated with high morbidity and mortality. This was the case with our patient, though we were unable to verify whether his brain infarcts were, in fact, caused by his aspergillosis since an autopsy was not performed. It is likely, however, that they occurred secondary to his infection through either associated vasculitis or multiple mycotic aneurysms.

As a general rule, the best way to avoid such devastating complications is to keep a high index of suspicion for aspergillosis in patients who present with signs and symptoms of a sinusitis that is refractory to antibiotic therapy. In this way, early diagnosis and intervention may optimize outcomes. Whenever possible, patients with invasive disease should be treated with a combination of antifungal therapy and aggresive surgical debridement. ●

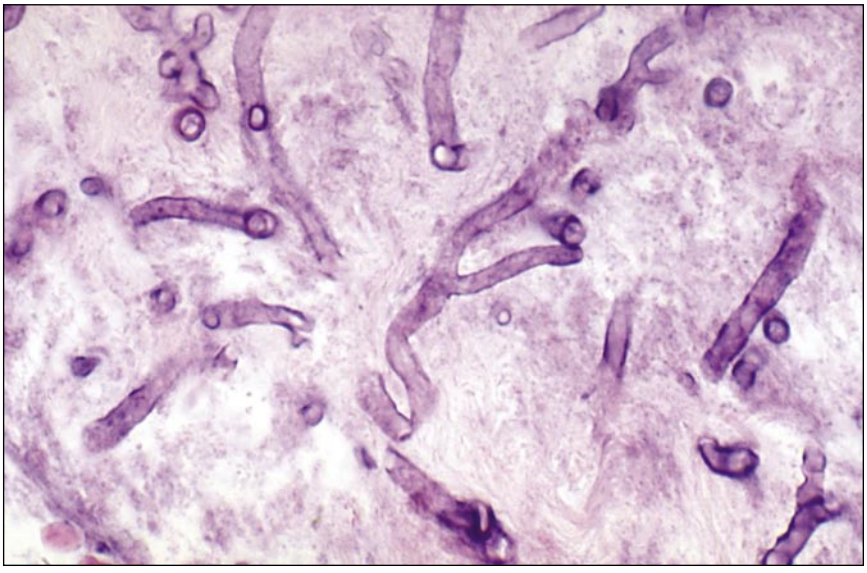

Figure 3. The patient's histopathologic image, showing septated fungal hyphae that appear to branch at sharp angles, characteristic of invasive aspergillosis.

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