Case report

Invasive *Aspergillus flavus* sinusitis in an immunocompetent patient using intranasal cocaine

Lauren Bougioukas\(^a\), Brendan Campbell\(^b\), Kyle Crooker\(^b\), Jason A. Freed\(^c\), Jonathan Wilcock\(^b\), Devika Singh\(^a,b\), Andrew J. Hale\(^a,b,\ast\)

\(^a\) Larner College of Medicine, University of Vermont, Burlington, VT, United States

\(^b\) University of Vermont Medical Center, Burlington, VT, United States

\(^c\) Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

**Abstract**

Invasive fungal sinusitis is a rare and potentially fatal infection that tends to occur in immunocompromised hosts. Presented is the case of a 33-year-old immunocompetent male with several months of recurrent facial and nasal pain refractory to several antibacterial courses before a diagnosis of invasive *Aspergillus* sinusitis was made. The patient's symptoms and infection were successfully treated with a combination of surgical debridement and voriconazole. The authors review the epidemiology, risk factors, diagnosis, and treatment of invasive fungal sinusitis due to *Aspergillus*.

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**Case presentation**

A 33-year-old male from New England presented to infectious diseases (ID) clinic with several months of chronic right facial and right nasal cavity pain. His medical history was significant for intranasal drug use (including cocaine, opioids, and crushed acetaminophen), asthma with occasional fluticasone inhaler use, and gastroesophageal reflux disease. He was a current tobacco smoker with an 18-pack year history, occasional marijuana use, and worked at a laundry cleaning service.

Symptoms began after a right maxillary canine extraction seven months prior to presentation. Three months after symptom onset, he had a computed tomography (CT) scan of the sinuses with contrast which demonstrated sinus drainage occlusion in the right maxillary and sphenoid sinuses. He was treated for acute sinusitis with multiple courses of antibiotics including penicillin, clindamycin, and amoxicillin-clavulananate, as well as nasal saline rinses and oxymetazoline spray, without significant improvement.

Two months prior to presentation, he was seen by an otolaryngologist for symptoms of fevers, chills, headache, nasal congestion, ear pain, blurred vision, and photophobia. On physical exam, he was in mild distress, had right-sided facial tenderness, and poor dentition. A nasal endoscopy showed right septal deflection, purulent discharge, and edema, thought to be consistent with right maxillary and ethmoid sinusitis with significant mucosal...
inflammation. Nasal cultures grew *Aspergillus flavus*, which was initially thought to be environmental contamination. Six weeks prior to presentation, he remained without improvement in symptoms despite ongoing amoxicillin-clavulanate therapy. Repeat nasal endoscopy at that time showed a right-sided septal spur, diffuse edema, purulent discharge, crusting, and an inferior synchiae on the right. Antibacterial coverage with amoxicillin-clavulanate was extended and surgery was recommended to clean the sinuses as well as to take tissue and cultures to aid in diagnosis. One month prior to presentation, he underwent right maxillary antrostomy without tissue removal, right anterior ethmoidectomy, debridement of the right nasal cavity, and removal of a right-sided septal spur. Diffuse white-gray necrotic tissue was debrided over the anterior portion of the right nasal cavity, and an inferior and middle turbinate, septum, nasal floor, and uncinate. Cultures from this grew *Aspergillus flavus* with colony morphology consistent with cultures from one month prior. Histopathology of the removed tissue showed tissue invasive branching septate fungal hyphae, consistent with invasive aspergillosis, as well as evidence of crushed pill material, which was thought to be due to snorting (Fig. 1).

One month after surgery (two days prior to ID presentation), his pain and swelling had improved. A third nasal endoscopy at that time showed anterior synechiae at the site of spur and debrided crust from the middle meatus with inflammation. His mucosa appeared to be healing well with no further evidence of pus or necrosis. He had not yet received any antifungals.

On presentation to ID clinic, he was asymptomatic without fevers, chills, right-sided facial pain, right eye pain, or visual changes. On examination, his right nare appeared inflamed, no sinus tenderness was appreciated, and his face and eyes were not swollen. No focal neurological deficits were evident. To rule-out possible intracranial invasion, magnetic resonance imaging (MRI) of the brain and orbits with and without contrast was performed and showed no abnormal intracranial finding and normal appearing orbits. Human immunodeficiency virus (HIV) fourth generation assay, hepatitis B and C serologies, and syphilis serologies were all negative. White blood cells (WBC) were 13,090/μL (4000–10,400/μL), absolute neutrophils 9380/μL (2200–8850/μL), and absolute eosinophils 390/μL (30–610/μL). Electrolytes and liver function tests (LFTs) were normal. His vision was found to be normal by ophthalmology evaluation. Given the histologic diagnosis of invasive aspergillosis sinusitis, antifungal therapy was offered to eliminate residual infection. He was started on voriconazole 200 mg by mouth two times a day for 12 weeks and fluticasone was stopped. He was advised to stop using all intranasal recreational drugs.

Two months after starting voriconazole, the patient reported doing well without any side effects such as visual changes or hallucinations. He had taken voriconazole as directed. Voriconazole level was normal at 1000 μg/mL (1000–5500 μg/mL). Electrolytes and LFTs remained within normal limits. Three months after presentation, he completed voriconazole, and remained without symptoms or side effects. On repeat nasal endoscopy, no polyps, secretions, or evidence of necrosis or fungal infection were present. The patient has remained asymptomatic with no evidence of recurrent clinical symptoms for two years since and has remained abstinent from intranasal drug use.

**Discussion**

*Aspergillus* is a ubiquitous environmental mold and is the most common fungus to infect the paranasal sinuses [2]. Invasive fungal sinusitis is a rare fungal disease characterized by tissue destruction, necrosis, and angioinvasion. Mortality rates are high, ranging from 28% to 80%, and is particularly high after the onset of neurological symptoms [1,5,10,16,20]. Although *Aspergillus fumigatus* is the most common species to cause invasive aspergillosis (80–90%), *A. flavus* is less common (5–10%) but more destructive due to toxin production [2–4,11].

Invasive fungal sinusitis generally occurs in the setting of neutropenia, immunosuppressive drugs, diabetes, HIV, trauma, or radiation therapy [2–5]. Other associated factors include male gender [3,10,20,21], asthma [11,12], use of inhalational steroids [11,12], marijuana use [12], heavy smoking [3], individuals in the 3rd or 4th decade of life [10,21], alcoholism [13,22], farming occupation [3,8,11,12], trauma or a surgical procedure such as implantation of prosthetic material [16], septal surgery [20], and endemic locations such as the Middle East, Indian sub-continent, and Southern United States [7–9] likely due to hot, dry climates [10].

The diagnosis of invasive fungal sinusitis can be challenging as illustrated in this case. Patients often present with several months of symptoms such as headache, nasal congestion, fever, and maxillary region facial pain, especially in the setting of refractory or recurrent sinusitis [2,5,7,10,12,14,21,23,24]. Neurological symptoms are associated with a greater risk of mortality [10,12,13,20,22]. Although the patient illustrated here was otherwise mostly healthy, he likely acquired the infection through his maxillary tooth extraction, intranasal drug use, or a combination of both. In the literature, we identified five prior case reports of invasive aspergillosis occurring after a maxillary tooth extraction [21,14], and two prior reports of *A. flavus* invasive sinusitis in the setting of intranasal cocaine use [5,15]. Cocaine is thought to cause vasconstriction, mucosal inflammation, and changes to the mucociliary clearance mechanism that can subsequently lead to local ulceration, tissue ischemia, and tissue necrosis enabling *Aspergillus* to thrive in the decomposing organic material, especially in the setting of nasal moisture [5,15,21].

The diagnosis of invasive fungal sinusitis is established with tissue histologic examination and fungal culture via tissue biopsy. It is important to note that surface cultures are often negative, and symptoms may precede radiological findings [8,13,16,17]. In one case series only 10 of 16 (63%) patients with invasive sinusitis from aspergillosis had a positive culture [21]. Another study found that as high as 75% of infected individuals had false negative surface cultures [23]. Further difficulties include poor accessibility to the sinus without procedural intervention [23]. A high index of suspicion for fungal invasive sinusitis must be maintained when a patient with risk-factors has sinusitis refractory to traditional antibacterial therapies. In addition to fungal sinusitis, other causes of antibacterial refractory sinusitis include malignancy and systemic vasculitis [25–27].

As illustrated here, surgery is of paramount importance for both diagnosis and treatment. Non-invasive disease (allergic aspergillosis or aspergilloma) can convert to semi-invasive (locally destructive disease without tissue invasion), or invasive disease without adequate debridement and antifungal treatment [4,9,12,13,28,29].
is illustrated in one case report where non-invasive disease converted to invasive disease in an elderly patient [29]. Longer duration of symptoms is associated with progression to intra-cranial disease and possible dural invasion, which carries a high risk of mortality [7–10]. Additionally, Aspergillus can occlude the vascular supply and inhibit anti-fungal treatment from reaching infected areas [22]. Lastly, as seen here, symptoms can significantly improve with surgery, prior to starting anti-fungal therapy.

In combination with surgery, a variety of anti-fungal agents have been used to successfully treat invasive sinusitis from aspergillosis. Historically, amphotericin B was used for treatment, though is associated with significant side effects such as renal and hepatic toxicities, anemia, fever, and electrolyte disturbances [2,3,12,21,28]. Itraconazole and echinocandin have also been used [11,12,15]. In 2016, the Infectious Diseases Society of America (IDSA) updated guidelines and recommended voriconazole to be the primary treatment of invasive syndromes of Aspergillus [18]. Voriconazole is more effective and poses fewer side effects than amphotericin B [19].

In summary, early diagnosis and treatment of invasive sinusitis from aspergillosis is critical to prevent disease progression. However, diagnosis can be difficult. Although invasive aspergillosis tends to infect immunocompromised patients, it should be included in the differential when patients with a history of recent intranasal drug use or maxillary tooth extraction present with refractory sinusitis.

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Lauren Bougioukas: conceptualization, writing: original draft; writing: review & editing, Brendan Campbell: conceptualization, writing: original draft; writing: review & editing, Kyle Crooker: conceptualization, writing: original draft; writing: review & editing, Jason A. Freed: conceptualization, writing: original draft; writing: review & editing, Jonathan Wilcock: conceptualization, writing: original draft; writing: review & editing, Devika Singh: conceptualization, writing: original draft; writing: review & editing, Andrew J. Hale: conceptualization, patient care, writing: original draft; writing: review & editing.

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