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CASE REPORT PEER REVIEWED | OPEN ACCESS

Aspergillus brain abscess presents as sinusitis in immunosuppressed and hyperglycemic patient

Sarah C Kurkowski, Michael J Thimmesch, Pinky Jha, Yasir H Abdelgadir

ABSTRACT

Introduction: There are currently very few documented case reports of *Aspergillus* brain abscesses in the setting of persistent sinusitis symptoms and comorbid conditions of Type II Diabetes Mellitus and steroid treatment. Many cases of intracranial aspergillosis are secondary to a disseminated invasive *Aspergillus* infection or primary pulmonary aspergillosis. This case illustrates the importance and vitality of considering the rare but potentially lethal diagnosis of *Aspergillus fumigatus* brain abscess in the differential of persistent sinusitis, even in the absence of systemic symptoms.

Case Report: A 73-year-old female with risk factors of Type II Diabetes Mellitus (T2DM) and steroid treatment presented to the hospital with persistent sinusitis symptoms lasting three months. She subsequently was diagnosed with *Aspergillus* brain abscess after bicoronal bifrontal craniotomy with pericranial flap. The patient was treated with voriconazole and amphotericin B for 3–6 months post-resection and follow-up with neurosurgery to monitor abscess reduction. She was admitted five more times after initial diagnosis for sequelae related to the brain abscess. The initial abscess did decrease in size but then began to worsen. The patient unfortunately passed away six months after initial presentation and diagnosis.

Conclusion: Few cases of invasive rhino-orbito-cerebral *Aspergillus* brain abscesses secondary to *Aspergillus* sinus infections have been documented. If missed it can be lethal. Therefore, when a patient presents with persistent sinusitis, in the relevant context, *Aspergillus* brain abscesses are an important differential diagnosis that warrant consideration.

Keywords: *Aspergillus* brain abscess, *Aspergillus fumigatus*, *Aspergillus* sinusitis, Immunocompromised

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INTRODUCTION

Aspergillus, a moniliaceous mold found in soil and decaying vegetation is an opportunistic fungus that demonstrates septate hyphae with acute angle branching, which often take advantage of immunocompromised states [1, 2]. Neurologic infectivity is majorly affected by immune status of the patient and virulence of the specific strain of the culprit fungus. Fungal neuroinfections cause significant morbidity. In a meta-analysis reviewing 135 articles from 2000 to 2018, the main presentations of fungal neuroinfections documented were meningitis, encephalitis, hydrocephalus, cerebral abscesses, and stroke symptoms [2].

The most common causes of fungal brain abscesses in immunocompromised patients are *Candida*, *Aspergillus*, *Cryptococcus*, and *Mucor*. *A. fumigatus*, *Aspergillus*

flavus, *Aspergillus amstelodami*, *Aspergillus sjdowi*, *Aspergillus candidus* are the subspecies of *Aspergillus* that have been shown to be most likely to cause central nervous system (CNS) infections. Of these subtypes, *A. fumigatus* is most often the culprit [3]. A brain abscess due to *Aspergillus* can be due to direct or hematogenous spread from a local or distant site of infection. Direct extension is often through the paranasal sinuses, ear, nose, or eye [1]. *Aspergillus* spores have a preference for the anterior and middle cranial fossa [4]. In this case specifically, a frontal and ethmoidal sinus *Aspergillus* infection likely led to direct invasion of the frontal lobes.

The patient presented here had a significant immunocompromised state due to uncontrolled Type II Diabetes Mellitus and steroid treatment, putting the patient at increased risk for opportunistic infections such as *Aspergillus*. Diagnosis of *Aspergillus* brain abscess, although rare, should always be included on differential when evaluating hyperglycemic and immunosuppressed patients with sinusitis symptoms. *Aspergillus* brain abscesses are severe and can progress to frontal bone erosion (or the cranial bone closest to the abscess), subsequent neurological sequelae, and therefore should not be overlooked or disregarded from the differential. Our objective is to highlight the importance of including *Aspergillus* brain abscesses in the differential diagnosis in individuals presenting with sinusitis symptoms whose medical history showcases immunosuppression and hyperglycemia.

CASE REPORT

A 73-year-old female with a past medical history of poorly controlled Type II Diabetes Mellitus and arthritis treated with steroids presented to the emergency department with sinusitis symptoms. Three months prior to presentation, she developed a copious, thick, yellow-green nasal discharge, and headaches. She traveled from Mexico to Milwaukee since these symptoms persisted, and upon arrival to the emergency department was admitted. Computed tomography (CT) head scan without contrast showed a likely 5.7 cm brain abscess located in the anterior cranial fossa associated with bilateral frontal bones and ethmoid plate; imaging also demonstrated opacification of both frontal sinuses (Figure 1A–C). To remove the abscess, a bicoronal bifrontal craniotomy with pericranial flap was performed by neurosurgery. CALCOs (Calcofluor White fungal stain) from the surgical abscess were 1/4 positive for septate hyphae concerning *Aspergillus*; fungal cultures of resected tissue showed *A. fumigatus*. Blood cultures were negative for fungi. The patient was treated with antifungals—amphotericin and voriconazole—which she would continue for 3–6 months post-surgery.

Subsequently, over the following five months, the patient returned to the emergency department on five separate occasions. Most of these hospitalizations were secondary to the brain abscess. She developed seizures confirmed by electroencephalogram (EEG), subdural hematoma, and right eye blindness.

Two and a half months post-op, outpatient magnetic resonance imaging (MRI) showed marked reduction in frontal lobe abscess, approximately 2.2×2.5×4.2 cm residual intraparenchymal abscess compared to 5.7 cm diameter abscess at presentation. Also appreciated was a reduction in midline shift, but new extension of right ethmoid sinus infection into medial right orbit (Figure 1D and E).

The last hospitalization (five months post-craniotomy/initial hospital admission), the patient was admitted for right eye blindness. This blindness had persisted for three days prior to the patient arriving at the hospital. At that time, the patient underwent endoscopic sinus surgery and right orbitotomy. Cultures from the right orbit showed *A. fumigatus*, while blood cultures were still negative.

One month after being discharged for right eye blindness (six months after initial diagnosis), the patient followed up outpatient for a subsequent postoperative MRI. This imaging showed overall stable postoperative findings, however noted improvement in some regions and worsening in others. Her right frontal lobe abscess, first noted on CT six months prior, and paranasal sinus infection had improved dramatically. Nodular enhancement in the periphery of the left frontal lobe still persisted while left frontal lobe vasogenic edema had increased. In addition, there was notable dural and subdural thickening over the right frontal convexity. This increased concern for progression of the abscess (Figure 2A–C).

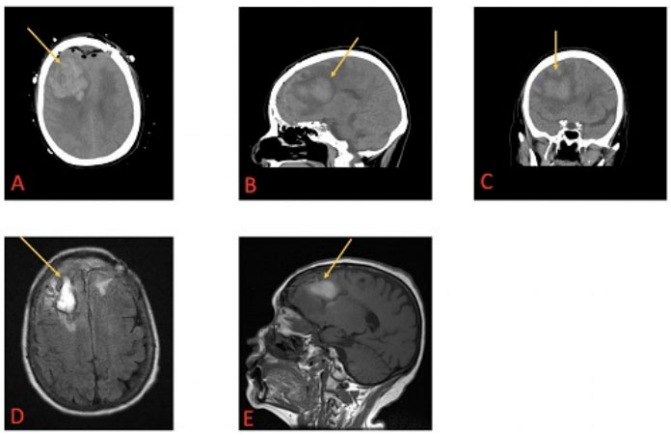

Figure 1: (A) Date of admission transverse CT image of brain abscess with mass effect and vasogenic edema; arrow denotes abscess. (B) Date of admission sagittal CT image of brain abscess with mass effect and vasogenic edema; arrow denotes abscess. (C) Date of admission coronal CT images of brain abscess with mass effect and vasogenic edema; arrow denotes abscess. (D) 2.5 months postoperative craniotomy and resection, MRI transverse image; arrow denotes abscess. (E) 2.5 months postoperative craniotomy and resection, MRI sagittal image; arrow denotes abscess.

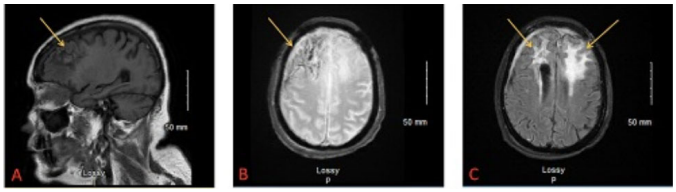

Figure 2: (A) T1 MRI image in sagittal plane, six months post-resection/craniotomy and initial diagnosis. Arrow denotes right front lobe abscess reduction from initial CT scan. (B) Gradient recalled echo (GRE) T2-weighted MRI image in transverse plane, six months post-resection. Arrow denotes reduction in right frontal lobe abscess. (C) Flair T2-weighted MRI image in transverse plane, six months post-resection. Arrows denote the nodular enhancement in periphery of left frontal lobe, persisting from original CT scan, and notable dural/subdural thickening over right frontal convexity. Concern for progression of abscess.

Unfortunately, one week after the above findings were noted on MRI, the patient passed away. The total time from initial presentation and diagnosis to death was approximately six months.

DISCUSSION

Here we report a case of a bilateral frontal brain abscess due to *A. fumigatus*. The abscess likely developed due to the longstanding history of sinusitis and immunosuppression from steroid use and poorly controlled Type II Diabetes Mellitus. The patient's presentation first was thought to be solely due to sinusitis (three months of nasal drainage and headache), however, subsequent imaging elucidated brain involvement. *Aspergillus fumigatus* brain abscesses that present with symptoms of sinusitis have been characterized as an easily missed diagnosis [5]. Cerebral abscesses secondary to *Aspergillus* sinusitis may be rare but are often lethal to patients [6].

It is often assumed that an *Aspergillus* brain abscess represents underlying disseminated invasive *Aspergillus* infection [1]. For example, case reports have been published with immunocompromised patients developing an intracranial *Aspergillus* abscess secondary to a pulmonary *Aspergillus* abscess [3, 7]. Additionally, other documented cases describe intracranial aspergillosis in organ transplant patients and intensive care unit (ICU) patients who were hospitalized prior to developing the infection [8, 9].

Multiple studies have listed the most common presentations of intracranial aspergillosis as mental status changes, seizures, focal neurological deficits, sudden headache, loss of consciousness, proptosis, vision changes, nasal discharge, cranial nerve palsies, etc. [9–12]. One study reported altered mental statuses as accounting for the largest percentage of presentations [9]. Our patient's presentation was much more insidious and could have been easily missed and passed off as just sinusitis.

However, our patient did not have disseminated or pulmonary aspergillosis at presentation or when an abscess was found on imaging. She also was not hospitalized prior to the development of her symptoms, and her presenting symptom of sinusitis was not among the most common presentations of an *Aspergillus* brain abscess.

As our patient's CT scan showed, an infection in the frontal/ethmoidal sinuses can spread to the frontal lobes, either by direct or hematogenous spread. Brain abscesses due to *Aspergillus* are rare and an example of an opportunistic infection. This cause should be included in the differential diagnoses in patients presenting with longstanding severe sinusitis symptoms, especially in those with current or past medical history of immunosuppression (which is a well-known risk factor for opportunistic infections). It has also been reported that patients with hyperglycemia (such as from poorly controlled diabetes) show increased rates of mortality due to brain abscesses [13]. This highlights another important reason to keep *Aspergillus* brain abscesses on the differential in a patient with a history of poorly controlled Type II Diabetes Mellitus, as seen here. This case demonstrates a unique intertwining of the risk factors of immunosuppression and hyperglycemia in the development of an *Aspergillus* brain abscess, and the importance of not ruling out potential diagnoses simply because of their rarity.

One article listed vulnerable individuals for CNS fungal infections as those who had hematological malignancies, transplant recipients, and HIV [14]. However, our patient did not have any of these diagnoses. It is important to mention that our patient clearly had a predisposition to opportunistic infections due to steroid treatment and uncontrolled T2DM.

As done in our patient, the pillar of cerebral aspergillosis treatment is surgical resection followed by systemic antifungal therapy [15]. Sole antifungal therapy was shown to have over 90% mortality rate in CNS aspergillosis, but surgical resection reduced the rate from 64% to 39%. The combination of both decreases mortality rate further, particularly when the orbit is involved in addition to brain parenchyma [10, 16]. After surgical resection of abscess, a combination of voriconazole and amphotericin B was used to treat this patient. Voriconazole is a moderately lipophilic compound with good CNS penetration, making it a well-established first-line treatment for CNS aspergillosis. Another well-identified treatment for fungal neuroinfections is the use of amphotericin B and flucytosine for cryptococcal meningitis [2]. Prior to voriconazole, amphotericin B was the mainstay for cerebral aspergillosis. In a randomized controlled study, voriconazole was compared to amphotericin B for invasive aspergillosis. Voriconazole was found to be better than amphotericin B, specifically having a 21.2% greater response than amphotericin B.

This study also found that voriconazole led to greater survival rates. Voriconazole reaches concentrations in the brain parenchyma that are effective for treatment of CNS aspergillosis [17]. Within fungal abscesses in the brain parenchyma, voriconazole has been found to penetrate both brain tissue and the abscess material itself. Its peak concentration within the brain is higher than that achieved within the plasma [18].

However, there have been cases documented of failed voriconazole treatment in the instance of invasive CNS aspergillosis. In a previous case report, a patient on corticosteroid and immunomodulator therapy was diagnosed with invasive cerebral aspergillosis and subsequently failed treatment with voriconazole alone. However, when treated with a combination of voriconazole and amphotericin B, the patient recovered well [19]. The concern arose that *A. fumigatus* exhibits increasing rates of azole resistance. Recently, Dutch guidelines for antibiotic use recommended that a combination of voriconazole and liposomal amphotericin B or echinocandin should be used to treat *A. fumigatus* (at this time, 12.9% of *A. fumigatus* were azole-resistant) until strain sensitivity resulted [17]. Therefore, as it was determined that the tissue sample from our patient's resection was positive for *A. fumigatus*, treatment with voriconazole and amphotericin B was chosen.

Following initial imaging with CT, MRI was chosen for the rest of the patient's imaging. Magnetic resonance imaging (MRI) seems to be a better tool for diagnostic purposes and involvement of important neural parenchymal structures. One article outlined specific MRI characteristics that should heighten suspicion for an intracranial fungal granuloma: "faintly enhancing intracranial masses, poorly defined margins, central hypodensities, and disproportionate cerebral edema" [12].

An interesting mechanism of *Aspergillus* extension into the brain was proposed as being through a perineural pathway by Safdar et al. where *Aspergillus* may travel via nerves from sinuses to the brain to establish intracranial infection [20]. It is well-established that viral respiratory infection can be complicated by superimposed bacterial pneumonia. Our patient presented here did not have pneumonia, but did have three months of persistent sinusitis. It is reasonable to wonder if she had a primary viral sinus infection that led to the development of a secondary fungal infection (such as *Aspergillus*). Her assumed *Aspergillus* infection of the frontal and ethmoid sinuses allowed for erosion of bone and infiltration into brain parenchyma. Potentially, her sinusitis began as viral in nature and *Aspergillus* was a superimposed fungal infection, to which she was susceptible due to her immunocompromised state. A very recent article, "Invasive Aspergillosis of nose and paranasal sinus in COVID-19 convalescents: Mold goes viral?," was published in January 2022 on post-COVID fungal infections of the nose and paranasal sinuses. The study stated that during the first wave of COVID-19, most post-COVID fungal infections seemed to be due to mucormycosis, however, invasive *Aspergillus* infections seemed to be rising in number during the second wave of COVID-19 [21]. Our patient tested negative for COVID-19 at presentation to the emergency department. However, this does not rule out a previously resolved COVID-19 infection that could have predisposed our patient to an invasive *Aspergillus* sinus infection. The previously mentioned article stated that 46% of their patients who had COVID-19 infection followed by an invasive fungal infection were young and did not have predisposing comorbidities. Compared to their study's patients, our patient did have underlying comorbidities (steroid treatment and uncontrolled T2DM) and therefore was significantly more predisposed to develop an invasive *Aspergillus* sinus infection after infection with COVID-19. COVID-19 virus is known to decrease CD8+ and CD4+ T cells which would further increase the susceptibility of post-COVID patients to developing fungal infections [21]. In addition, glucocorticoid treatment (our patient was taking for arthritis) inhibits inflammatory molecules like adhesion molecules, cytokines, and chemokines that aid in the immune system's response to pathogens [22]. Shetty et al. also made clear that there are few case reports of rhino-orbito-cerebral aspergillosis compared to the many documented cases of rhino-orbito-cerebral mucormycosis. Two of these cases did involve the primary site of infection being the ethmoid sinuses and subsequent extension of infection to frontal lobes, similar to our patient [23, 24]. One case postulated that primary sinus *Aspergillus* infection could be a chronic infective process, similar to the chronicity of aspergilloma of the lung [24]. This further validates the importance of our patient's case as it is one of few on invasive rhino-orbito-cerebral *Aspergillus* abscesses presumably secondary to *Aspergillus* sinus infection.

CONCLUSION

Diagnosis of *Aspergillus* brain abscess should always be included on differential when evaluating hyperglycemic and immunosuppressed patients with sinusitis symptoms. *Aspergillus* brain abscesses are severe and can progress to frontal bone erosion (or cranial bone closest to abscess) and significant neurologic sequelae (seizures, right eye blindness, etc.). This diagnosis has a high mortality rate, poor prognosis, and is an easily missed diagnosis when the presenting symptom is persistent sinusitis. Proper treatment with surgical resection of abscess and subsequent combination therapy with voriconazole and amphotericin B can increase the likelihood of survival, but does not eliminate the significant risk of patient death, as in our patient. It is plausible that previous and resolved COVID-19 infection (not confirmed in our patient) could predispose to fungal sinus infections, *A. fumigatus* in particular. Few cases of invasive rhino-orbito-cerebral *Aspergillus* brain abscesses secondary to *Aspergillus*

sinus infections have been documented. If missed it can be lethal. Therefore, when a patient presents with persistent sinusitis, in the relevant context, *Aspergillus* brain abscesses are an important differential diagnosis that warrants consideration.

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Sarah C Kurkowski – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Michael J Thimmesch – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Pinky Jha – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yasir H Abdelgadir – Conception of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.