

Case report

Invasive sino-orbital aspergillosis with brain invasion in an immunocompetent pregnant patient

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ABSTRACT

Purpose: Invasive Fungal Sinusitis (IFS) is a potentially life-threatening condition that can progress rapidly to the orbit and the brain, especially if it goes on undetected for a long period. We report a case of a 28-year-old pregnant woman in her second trimester with sino-orbital *Aspergillosis* and subsequent brain involvement who tragically developed deterioration of her neurological status and a spontaneous abortion.

Observations: The patient presented to the ophthalmology emergency department, King Khaled Eye Specialist Hospital, Riyadh, complaining of left upper eyelid fullness with a palpable eyelid mass and chronic relapsing remitting dull pain for 4 months. Clinical examination was significant for reduced colour vision in the left eye, limited left supraduction, left upper eyelid firm palpable mass, inferior dystopia and proptosis of 4 mm. Magnetic Resonance Imaging (MRI) done without contrast-enhancement due to her pregnancy revealed aggressive infiltrative sinonasal, nasal septum, cribriform plate, orbital, intracranial infiltration with extensive brain edema and midline falcine herniation patterns. Endoscopic endonasal biopsy of the lesions showed septate hyphae branching at acute angles, suggestive of *Aspergillosis*. Her neurological status deteriorated with a spontaneous abortion during admission.

Conclusions and Importance: This case demonstrates that IFS could present only with proptosis, eyelid fullness, chronic pain without external inflammatory signs and should be considered in such presentation even in immunocompetent patients. Early detection and management are crucial. Whether pregnancy presents a relative immune susceptibility to IFS is an issue that needs further in-depth investigation.

1. Introduction

Aspergillus is a pathogenic fungus found in a wide range of organisms and exists in soils, water, and decaying plants. Inhalation of *Aspergillus* spores released into the atmosphere is the typical route of infection.¹ *Aspergillus* infections are broadly divided into non-invasive and invasive categories. Invasive *Aspergillosis* can penetrate the blood vessels and the central nervous system (CNS) and is often found in immunocompromised patients with long-term corticosteroid use, hematologic malignancy, and/or HIV infection.^{1,2,3} Invasive fungal sinusitis (IFS) is an uncommon fatal disease with an aggressive clinical course.^{4,5} Although this entity usually occurs in immunocompromised patients, it has also been reported in immunocompetent individuals.⁵ In this paper, we

report a unique case of invasive fungal *Aspergillosis* of the sinuses, orbit and brain in a 28-year-old pregnant, though apparently healthy woman. The reported case adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013. To the best of our knowledge, this case has not been reported previously in the medical literature and it presents a challenge in radiological diagnosis and the role of pregnancy.

2. Case presentation

A 28-year-old pregnant woman in her 21st week of gestation presented with left upper eyelid swelling with 4-months duration. This condition was accompanied with chronic relapsing remitting dull pain,

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but there was no deterioration, loss or change in vision or diplopia. She denied having any history of trauma, nasal symptoms, fever, or any other constitutional symptoms. Her past medical history showed that she had undergone sinus surgery two years earlier, further inquiry on the nature and reason of surgery was not successful as the details of which were not known to the patient. She was a non-smoker, with no drug abuse or relevant family history. On close examination, her vision was found to be 20/20 in both eyes; her intraocular pressure was within normal limits bilaterally. Colour vision chart done by Ishihara test showed 10/10 in the right eye and 2/10 in the left eye. Her extra ocular motility was full horizontally and inferiorly in the right eye and significant for 30-degree limited supraduction movement in the left eye. There was no relative afferent pupillary defect visible. External examination of her eyes revealed inferior dystopia in her left eye, and 4 mm of relative proptosis in the left eye measured using Hertel exophthalmometer (Fig. 1). Left eyelid examination showed palpable firm mobile mass in the superolateral third of the eyelid measuring 1.5 cm in diameter. There were no palpable head and neck lymph nodes. Her visual field test was normal. MRI without contrast media injection (Fig. 2A–C) revealed an extensive heterogeneously T1W and T2W hypointense solid mass lesion of the entire left nasal cavity, ethmoid and frontal sinuses with left orbital and intracranial extension through the cribriform plate of ethmoid bone and lamina papyracea. The lesion invaded the apex and medial wall of the left orbit, cavernous sinus, basifrontal cortex, and frontal lobes above cribriform plates with marked edema and mass effect. Based on the imaging findings, the diagnosis of invasive fungal sinusitis versus olfactory neuroblastoma (esthesioneuroblastoma) was anticipated.

The patient subsequently underwent endonasal surgery for biopsy of the lesion. The pathological findings showed septate hyphae with acute angle branching, highly suggestive of *Aspergillus*. We decided to opt for aggressive surgical and medical management to try to save the patient's life disregarding foetus safety. She was immediately administered Intravenous Vfend (Voriconazole) 300 mg bid for ten months. Specialists from the otorhinolaryngology, oculoplastic surgery, and neurosurgery departments were consulted, and combined/joint debulking surgery was performed on the patient. Despite that, the patient's eyelid swelling continued to progress, and her neurological status worsened. A spontaneous abortion occurred during admission. Her status eventually stabilized with prolonged antifungal treatment that lasted for 10 months. However, she ended up in a bedridden state and was subsequently transferred to a long stay/rehab centre with no report of progression of her disease.

3. Discussion

Opportunistic fungi are ubiquitous.⁶ They enter the body primarily through respiratory tract, and intracranial infection results directly through nasal sinuses or via spread of infection in the systemic circulation.⁷ Intracranial *Aspergillus* from direct infection of the adjacent paranasal sinus tissue accounts for 76% of CNS *Aspergillus* cases. Early



Fig. 1. External photography showing palpable firm mobile mass in the superolateral third of the left upper eyelid with apparent left proptosis and hypoglobus.

sinus infections are often confined to the maxillary and sphenoid sinuses.⁸ Intracranial *Aspergillus* can cause chronic meningitis or brain abscesses (mucormycosis, earlier called zygomycosis); can penetrate the blood vessels, causing vasculitis, thrombosis, microaneurysms, and cerebral ischemia and necrosis.² Fungal paranasal sinusitis can be broadly categorized based on the histopathological evidence of tissue invasion into non-invasive and invasive forms based on the absence or presence of microscopic evidence of fungal hyphae within the tissues.^{4,5} Invasive variant in mildly immunocompromised host is a rare occurrence and is often caused by spores of *Aspergillus* spp. (*Aspergillus fumigatus* and/or *Aspergillus flavus*) from zygomycetes order. IFS caused by *Aspergillus* spp. is often encountered in patients with neutropenia, HIV/AIDS, patients receiving chemotherapy, and those with haematological malignancies.⁴ Such infection carries a high mortality rate up to 50% despite receiving aggressive treatment.⁹ IFS also appear to occur in immunocompetent patients.^{10,11} Some case reports have also demonstrated intracranial complications of *Aspergillus* in immunocompetent patients.⁷ IFS tends to follow a more chronic course ranging from months to years. Despite its chronicity, the disease can progress to the orbits and the brain with many cases leading to mortality or significant morbidity as in our case; and some cases leading to relapse too.¹² In this case, the patient presented with an upper eyelid palpable mass, proptosis, and recurrent pain without any external signs of inflammation, fever, or nasal symptoms. Alrajhi et al.¹² analysed 23 cases of IFS in immunocompetent patients, 16 (69%) of which presented with proptosis. For this, an ophthalmologist could be the first diagnosing physician. In this present case, there was a delay in the diagnosis, despite the presence of symptoms for 4 months. Similarly, Clancy and Nguyen reported in their review mean delay of 24 months in diagnosis¹³ while Alrajhi et al.¹² reported mean duration of symptoms for 18 months before diagnosis.

CT scan is frequently used as the preferred method for the initial diagnosis of the sinonasal fungal lesion including hyperattenuating material in the sinus cavities and osseous destruction followed by postcontrast MRI. However, in the current case, due to the safety issues related to CT radiation and the gadolinium-based contrast media risk during pregnancy, plain MRI was done to assess the intracranial and intra-orbital extension associated with invasive fungal sinusitis involving the anterior skull base that may overlap with esthesioneuroblastoma, as both may exhibit osseous destruction. Esthesioneuroblastoma is hypointense to gray matter on T1-weighted images and isointense or hyperintense to gray matter on T2-weighted images.¹⁴ with characteristics cystic areas between the tumor and the adjacent normal brain tissue.

A study of 21 patients with CNS *Aspergillus* infection in South India revealed that 76% of patients had intracranial invasion by contiguous spread from paranasal sinus, with over 50% of the patients presenting with skull base syndromes.⁸ One Ukrainian patient presented with left retro-orbital pain and ipsilateral monocular visual loss, with rapid progression to the contralateral temporal visual field, proptosis, and reduced eye movements; secondary to an acute chiasmal abscess caused by *Aspergillus fumigatus*, highlighted invasive sino-orbital *Aspergillus* in an immunocompetent patient.¹⁵ The presence of pregnancy state adds to the complexity of such case in terms of diagnosis, management and prognosis for the mother and the foetus. Some reports described invasive fungal sinus infection by *Aspergillus* spp. and dematiaceous fungi in immunocompromised pregnant women.¹⁶ The major limitation faced in treatment is toxicity and teratogenicity. Two other reports described invasive *Aspergillus* infection in other parts of the body in previously healthy pregnant women with no history of immunocompromise. One with pulmonary *Aspergillus* and brain involvement and the second with disseminated invasive *Aspergillus*.^{17,18} Both reports indicated the increased rate of invasive *Aspergillus* infection in pregnant women. Voriconazole, a relatively new azole approved by the FDA for treatment for invasive fungal *Aspergillus*, is now considered to be the first line of treatment in such cases. However, Voriconazole is labelled category D (fetal risk that in certain situations can be outweighed by maternal

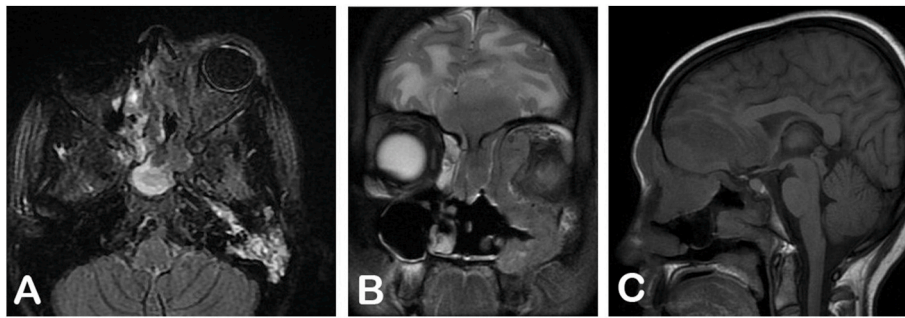


Fig. 2. A-C. Plain MRI in axial and coronal T2WI and sagittal T1WI demonstrating an extensive solid mass lesion of the entire left nasal cavity, ethmoid and frontal sinuses, with intracranial extension through the cribriform plate and lamina papyracea, invading basifrontal cortex, frontal lobes, with marked edema and mass effect.

benefit) treatment in pregnancy, given its strong association with teratogenicity in animals in low doses compared to human doses.¹⁹ A case report described administering voriconazole to an immunocompromised 28-year-old lady with invasive fungal *Aspergillus* during the second and third trimester of pregnancy without subsequent harm to foetus.²⁰ This report to our knowledge is not supported by other data in the literature yet. Our case report presents a rare but serious complication of invasive orbital *Aspergillus*. The patient's clinical manifestations, signs and imaging examinations led to the diagnosis of invasive orbital *Aspergillus* with brain invasion; the final pathological biopsy confirmed *Aspergillus*. The prognosis was poor, and early diagnosis and aggressive management, with surgical debridement and adjuvant anti-fungal therapy, could help reduce mortality and morbidity. In conclusion, the diagnosis of IFS should be considered even in immunocompetent patients, especially if the signs and symptoms chart a chronic course. Pregnancy represents a major challenge in terms of diagnosis and management. MRI without contrast is the first imaging choice in such presentation. This paper illustrates the clinical features and radiographic findings in pregnant patient with sino-orbital *Aspergillus*, presenting with proptosis, upper eyelid swellings, and chronic relapsing-remitting dull pain. The topic of pregnancy presenting a relative immune susceptibility to invasive fungal infection needs further investigation to arrive at definitive diagnosis and reduce mortality.

Patient consent

Consent to publish this case report has been obtained from patient(s) in writing.

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