Case Study

Paranasal Sinus Aspergillosis: A Case Report and Review of Literature

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A B S T R A C T

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The author presents a case report and review of literature of paranasal sinus aspergillosis. An 11 year old immunocompetent male patient presented with bilateral nasal obstruction due to paranasal sinus aspergillosis. The biopsy tissue was sent for histopathological examination which revealed features of allergic rhinosinusitis. Wet mount preparation revealed septate fungal hyphae about 4-8 μm in diameter with branching at acute angles. A diagnosis of *A. flavus* was made from wet mount and repeated isolation in culture. The patient responded to surgical excision of the nasal polyps and oral itraconazole post operatively. Paranasal sinus aspergillosis (PSA) is a common disease with significant morbidity and health care cost, although the medical and surgical treatments for PSA have improved markedly over the past few decades. The aim of this study is to increase awareness among clinicians and provide more accurate treatment option to patients.

Introduction

The fungal agents isolated from paranasal sinuses include *Aspergillus, Mucor, Histoplasma, Coccidiodies, Candida, Acremonium, Curvularia, Fonsecaea* and *Penicillum* (Marple and Mabry, 2002*). Aspergillus species* are the most common colonizers of the sinuses. There are four categories of paranasal sinus aspergillosis, classified based on the host's immune response to the fungus: chronic indolent sinusitis (invasive), fulminant sinusitis (invasive), fungal balls (noninvasive), and allergic sinusitis (noninvasive) (Ryan and Marple, 2010). In paranasal sinus the most common *Aspergillus species* that produce this illness are *Aspergillus fumigatus,*

Aspergillus flavus and *Aspergillus niger*. In India, *Aspergillus flavus* is isolated in more than 80% of the cases of acute fungal rhinosinusitis (Chatterjee and Chakrabarti, 2009).

Aspergillus as a pathogen cannot actively penetrate undamaged and intact mucus membrane or skin as it lacks keratolytic enzymes. They adhere to dust particles and are inhaled and deposited on the nasal and paranasal sinus mucosa. The warm, moist environment of the upper respiratory tract is an ideal environment for the proliferation of these organisms. However, they are rarely pathogenic because host resistance is high except under favorable growth conditions in

highly susceptible individuals. The pathology caused by *Aspergillus species* depends on the immunologic state of the patients (Benoliel, 2001).

Diagnosis of paranasal sinus aspergillosis can be made by history, clinical examination, radiography, nasal endoscopy and additional tests for allergy, aspirin sensitivity, bacteriology, and pulmonary function tests Prerequisites for diagnosis are sinonasal polyps, infiltrative or non-infiltrative fungal hyphae on microscopy with Potassium Hydroxide (KOH) and histopathological examination of the resected polyps and positive fungal culture of the tissue following surgery. A close clinical, endoscopic, and radiographic follow-up of paranasal sinus aspergillosis is important. Successful treatment includes early diagnosis, pre and post operative steroids and antifungal therapy, surgical debridement of the polyps and caseous material with adequate drainage and ventilation along with control of the underlying disease (Singh and Bholodia, 2005).

With the objective of understanding better pathogenesis of the disease, the author presents a case report and literature review of paranasal sinus aspergillosis.

Case Report

A 31 year old female presented with history of nasal obstruction, mouth breathing and snoring since two years. The patient gave history of scanty seropurulent, odourless nasal discharge from nasal cavity. Onset was insidious starting on left side and gradual progression to bilateral total nasal blockage. Patient subsequently developed breathing through mouth. She denied epistaxis, excessive sneezing, headache or trauma to nose. History of recurrent upper respiratory

infections including fever, cough, sputum production, ear discharge, earache, tinnitus, vertigo, ataxia and asymmetry of face or facial pain were negative. She had no history of tuberculosis, diabetes mellitus, asthma, use of corticosteroids, other immunosuppressants or prolonged antibiotic therapy. On general physical examination, she was a febrile with a blood pressure of 120/80 mm of Hg and pulse rate of 90 per minute. All other vital parameters were normal. Anterior rhinoscopy revealed bilateral pale white nasal polyps. Polyps were non- tender and probe could be moved all around the growth. Nasal mucosa was normal with no bleed on touch. Bilateral nares blockage was assessed by patency test. There was no abnormal finding on posterior rhinoscopy. Clinical examination of ears and throat was normal. Computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed bilateral pale white nasal polyps. Fiber-optic endoscopic sinus surgery (FESS) was done and biopsy tissue sent for histopathological and microbiological studies. Hematological parameters were not suggestive of inflammatory pathology. Kidney function test and liver function tests were normal. Urine did not show any protein or glucose and culture did not show any growth. Blood culture was sterile. Chest X-ray was normal. The patient was presumed to be immunocompetent as the patient was not reactive for HIV and had no diabetes mellitus, neutropenia, evidence of hematologic or any other malignancy in the body, or any concurrent infections.

Culture of the nasal secretions on Sabouraud dextrose agar (SDA) with chloramphenicol was incubated at 37°C and 25°C. On day three of incubation, yellowish growth suggestive of *Aspergillus flavus* was observed on SDA (Fig. 1). Lactophenol Cotton blue preparation (LPCB) from colony on SDA showed head of *Aspergillus*

flavus surrounded by sterigmata and conidia all over the surface (Fig. 2). The features were consistent with the diagnosis of *Aspergillus flavus.* Histopathological examination of the biopsy polyp tissue revealed abundant septate fungal hyphae and features of allergic rhinosinusitis. Patient was treated with oral itraconazole. She was reviewed for endoscopic examination after one month. Assessment revealed few bilateral small nasal polyps which were excised by sphenoidectomy, uninectomy and posterior ethmoidectomy. Biopsy was taken from these samples and sent for histopathogical and microbiological studies which yielded *Aspergillus flavus*.

Discussion

With increasing numbers of immunocompromised patients (Diabetics, patients with chronic renal failure, chronic malnutrition and the persons on prolonged corticosteroid and antibiotic treatment) the fungal infections of nose and paranasal sinuses has been on rise. Plaignaud was the first one to report fungal sinusitis in 1791 AD (Fergusson**,** 2000). The combination of nasal polyps, crust formation and sinus cultures yielding the *Aspergillus* was first noted in 1976 by Safirsteinand by Katzenstein and her colleagues in 1983.

It was rarely noticed before eighties but the condition is now diagnosed easily with the introduction of endosinuscopy and the better diagnostic facilities and the incidence of fungal infections has increased dramatically in recent years. Fungi have been reported in 96% of chronic sinusitis. *Aspergillus* is the commonest isolate (95.8%) from paranasal sinuses (Joshi, 2007). *Aspergillus spp* growing commonly in soil, in decaying vegetation and organic debris are ubiquitous in our plant. About 18 groups and 600 species of the genus *Aspergillus* are known,

but only eight species are pathogenic for man. *Alternaria, Penicillium, Cladosporium, Candida*, *Dreshlera*, *Fusarium* are the other fungi reported from paranasal sinuses. Mixed infection is also reported. Maxillary sinus and ethmoidal sinuses are commonly involved. Mixed infection due to *Schizophillum commune* and *A. niger, Aspergillus* and *Curvularia*, *Candida albicans* and *C. tropicalis* was reported as a cause of allergic fungal rhinosinusitis (Sumangala, 2007). In studies performed in India as well as Saudi Arabia, *A. flavus* appears to be the most common fungal organism cultured from paranasal sinuses. A higher incidence of *Aspergillus* disease has been reported in areas that have a hot, dry climate-especially of *A. flavus* (Fadl A. Fadl *et al.,* 2000), *A. flavus* was the pathogen isolated inour case report. However, rare isolates of *Aspergillus* causing fungal sinusitis is also on the rise such as *A. tamari* (Rahul Kamble, 2015), *A. versicolor* and A. *sydowii* (Chadiesh Nagarajan, 2014). The population more commonly exposed to the irritant pollutants of traffic, dust, factories residuals in compare to the population in the other region often suffer from chronic sinusitis. The disease is more common in warmer and humid climate.

The pattern of organism varies from place to place and depends upon age, habitual of the inhabitants, their immune status and the clinical factor (Rupa, 2001). Chronic indolent invasive sinonasal infections occur in immunocompetent hosts in regions with high levels of environmental spores, such as the Sudan, Saudi Arabia, and other tropical or desert areas, and occasionally in patients with diabetes in other locales. These infections have a progressive clinical course over months to years, with invasion of the surrounding tissues: the ethmoid sinuses, orbit, and subsequent cranial bone osteomyelitis and intracranial extension.

Aspergillus sinus infections may also present as a fungus ball or mycetoma. These lesions usually remain confined to a single sinus cavity for months to years, with little tissue reaction and no invasive features.

Aspergillus allergic fungal sinusitis, typically occurs in immunocompetent, atopic young adults, with a long antecedent history of allergic rhinitis, nasal congestion, headache, nasal polyposis, asthma, and/or recurrent sinusitis. Primary symptoms of paranasal sinus aspergillosis are nasal blockage, nasal congestion, hyposmia or anosmia and if associated with chronic sinusitis a purulent nasal discharge. Secondary symptoms comprise post nasal drip, rhinorrhea, facial pain, headache and sleep disturbance (Panda, 1998). Aggressive nasal polyposis and multisinus involvement is a hallmark of fungal sinusitis. Thick brown to green cheesy material with concretions, from the sinuses is very pathognomonic of allergic *aspergillus* sinusitis. Most theories consider polyps to be ultimate manifestation of chronic inflammation. Therefore, conditions leading to chronic inflammation in the nasal cavity can lead to nasal polyps.

The underlying mechanisms of paranasal sinus *aspergillosis* are still largely unknown. Several hypotheses have been put forward including chronic infection, aspirin intolerance, alteration in aerodynamics with trapping of pollutants, epithelial disruptions, epithelial cell defects/ gene deletions, inhalant or food allergies. According to Corey research, persistence of allergic fungal sinusitis with recurrence of sinonasal symptoms (with or without polyposis) is common, particularly when there has been incomplete eradication of allergic fungal mucin. Even when the patient is clinically disease free, recurrence can occur presumably from reexposure to fungal antigens (Corey, 1995).

Immune mechanism (Blanco and Garcia, 2008)**:**

Host defence against *Aspergillus* comprises the following sequence of events: (1) recognition of the pathogen; (2) a rapidly deployed and highly effective innate effector phase (non-specific or innate immunity); and (3) a delayed but robust adaptive effector phase characterized by immunologic memory (adaptive immunity). There are three different mechanisms of defence: (a) physical barriers; (b) phagocytosis; and (c) humoral compounds.

Physical barriers:

Include mucous membranes, mucociliary clearance and local secretion of inflammatory mediators by innate immunity cells. *Aspergillus species* synthesizes toxins, such as gliotoxin, fumagillin and helvolic acid, that are able to inhibit this ciliary movement. Also, the endothelial and epithelial cells are capable of internalizing conidia, which can facilitate the infection.

Phagocytosis:

In spite of the enormous capacity of the macrophages to kill conidia, their effectiveness is not 100%. Polymorphonuclear neutrophils are responsible for the destruction of the hyphae of *A. fumigatus*, and they are able to kill the conidia that escape destruction by the macrophages. The hyphae are too large for the phagocytes to internalize for destruction; however, monocytes and macrophages have extracellular antifungal activity that is able to damage the fungi in an important way

Humoral compounds:

The immune response against an *Aspergillus species* infection is usually a mixed response

that is as much humoral as cellular, but it is effective only if it is associated with a cellular answer, with increase of CD4 lymphocytes, and elevation of the levels of IL-2, IFN-g and IL-12. If the response is largely humoral, with an increase in the production of antibodies, IL-4, IL-5 and IL-10, it is usually associated with progression of the disease.

Disseminated aspergillosis:

It is intimately related to the ability of members of the genus *Aspergillus* to synthesize substances, such as elastase, that are able to invade non-necrotic tissues and penetrate into the bloodstream. This capacity is associated with the production of certain types of lateral spores, named aleuriospores, which are usually observed when the fungus grows *in vivo*. Once the fungus has penetrated into the bloodstream, it spread to the organs. Development begins upon arrival at the capillary vessels, causing an inflammatory local reaction by the host, in which neutrophils and monocytes participate. Therefore, because the entrance is not through mucous membranes, but directly into the bloodstream, the first line of defence that is so effective in immunocompetent individuals and it raises the possibility that the disease occurs in immunocompetent individuals.

Definitive diagnosis of paranasal sinus aspergillosis requires both histopathologic evidence of acute-angle branching, septated non pigmented hyphae measuring 2–4 m in width, and culture(s) yielding *Aspergillus* species from specimens obtained by biopsy from the involved site (Chrostowski and Pongracic, 2002). The septated hyphae of *Aspergillus* are best detected by Gomorimethenamine silver and Periodic acid–Schiff stains and it would be desirable to include these stains in the initial tissue evaluation if invasive fungal disease is suspected. *Aspergillus* hyphae are difficult to distinguish from those of *Fusarium* species, *Pseudallescheria boydii,* agents of phaeohyphomycosis, and some other molds. *Aspergillus* species recovered from cultures of the respiratory tract (e.g., sputum and nasal cultures) are usually a result of colonization in the immunocompetent host but may indicate invasive disease in the immunocompromised host. *Aspergillus* sinonasal infections may or may not be invasive and can follow a fulminant or an indolent course. The disease manifestations and the subsequent treatment approach may also vary, depending on the degree of immunocompetence of the host. Biopsy and subsequent fungal culture of suspicious lesions are important not only to demonstrate mucosal invasion but also to differentiate *Aspergillus* infections from those caused by other isolates, such as those due to *Mucorales* or *Alternaria* species. Nasal endoscopy may be normal or show mucosal oedema, or polyps with or without allergic mucin (thick yellow–green mucus plugs) on one or both sides. Sinus CT scan may reveal heterogeneous and serpiginous sinus opacities, with or without pseudocalcifications and bone lysis on one or both sides. Serum hyper-eosinophilia may be present. Type I hypersensitivity to fungal species is frequent.

Bone destruction from erosion is seen in 30%–50% of cases, especially in the cribriform plate, posterior wall of the frontal sinus, ethmoid septa, lamina papyracea, and medial antral wall. Intracranial spread of the infection occurs due to close proximity of the sinuses with cranial cavity. It is a dreaded complication, as it is usually fatal if not treated promptly. Orbital involvement occurs by contiguous spread of the disease from paranasal sinuses, by expansion or bone erosion due to pressure effect of the polyps or fungal tissue invasion.

Table.1 Case reports of paranasal sinus by *Aspergillus* species with description of patients' symptoms

Sr no	References	Country	Number of cases	Fungal isolate	Symptoms
1	Jayant Deshmukh *et al.,* 2014	India	21	*A. flavus(15), A. fumigatus(4), A. niger(2)*	Nasal discharge, headache, nasal blockage either bilaterally or unilaterally, halitosis, hyposmia or anosmia, facial pain or fullness and dental pain.
2	Chadiesh Nagarajan *et al.,* 2014	India	3	*A. versicolor A. sydowii*	*A versicolor*:nasal blockage *A sydowii*:headache, nasal discharge and frequent sneezing
3	Rahul Kamble, 2015	India	1	*A. tamarii*	Nasal obstruction, mouth breathing and snoring
4	Sumangala *et al.,* 2014	India	1	*A. fumigatus*and *A. niger*	Nasal obstruction and foul-smelling nasal discharge
5	Satyanarayana, 2015	India	30	*A. flavus(18)* and *A. fumigatus(12)*	Nasal polyps
6	Elgylani Hind and Wafa, Elhag, 2014	Sudan	13	*A. flavus(5), A. fumigatus(2), A. niger(6)*	Nasal polyps
7	Fadl A. Fadl *et al.,* 2009	Saudi Arabia	4	*A. flavus*	Nasal polyps, asthma, or both with radiographical evidence of pansinusitis
8	Kordbacheh *et al.,* 2006	Iran	9	*A. flavus(7), A. fumigatus(2), Rhizopus* (1)	Nasal polyps
9	Maroof Aziz Khan *et al.,* 2010	Pakistan	19	*Aspergillus species*	Proptosis, nasal obstruction and multiple nasal polyps
10	Isabel Cristina Espíndola Cardoso *et al.,* 2015	Brazil	32	*A. flavus(6), A. fumigatus(14), A. niger(2), A. terreus*(1), *A. fischeri*(1), and *Aspergillus* sp.*,* (3)	Chronic sinusitis refractory to medial management
11	Present study	India	1	*A. flavus*	Nasal obstruction, mouth breathing and snoring, scanty seropurulent, odourless nasal discharge

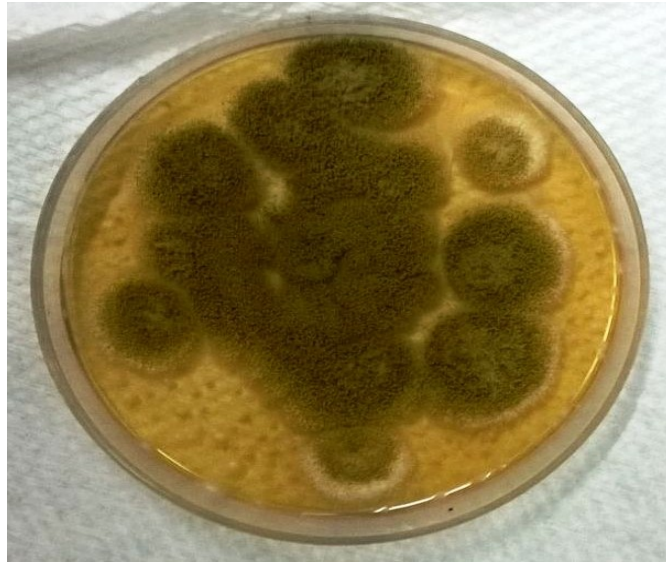**Figure.1** *Aspergillus flavus* growth on Sabouraud dextrose agar

Figure.2 Lactophenol Cotton Blue preparation (LPCB) showing head of *Aspergillus flavus* surrounded by sterigmata and conidia all over the surface

It is considered to worsen the prognosis of sinonasal *Aspergillosis.* Moreover, the superior orbital fissure and optic canal directly open into the middle cranial fossa, and are ready pathways for further intracranial spread of the infection.

Medical treatment includes postoperative oral corticosteroids, antiallergic inflammation therapy, surgical debridement, aeration, oral itraconazole and steroids (Agarwal, 2005). Postoperative Itraconazole is necessary in all the cases where the fungal

culture is positive. Local amphotericin B sinonasal lavage or spray after debridement has been used by some clinicians. The role of antifungal therapy is secondary Systemic and topical steroid play an important role in prevention of recurrence. Although surgical debridement alone may be curative in immunocompetent hosts, it may increase mortality among patients with neutropenia. Endoscopic surgery has been used for ethmoid sinus disease, in which an ethmoidectomy is performed in an anterior to posterior direction, with debridement continued as far posteriorly as abnormal tissue is encountered; more extensive surgery is indicated when there is widespread involvement of the paranasal sinuses or lateral nasal wall, or when orbital, facial, or intracranial involvement is present. Despite this approaches, multiple recurrences are common.

Conclusion and recommendations

There is a need to develop a greater understanding of the pathogenesis of the disease, formulate better and more sensitive diagnostic techniques, develop superior antifungal agents and increase an awareness of the disease among clinicians. The final specimen obtained during surgery should be submitted for histopathological examination to detect invasion of the tissues as this has effects on further management of disease. The use of follow-up measurements of total serum IgE during treatment of allergic fungal sinusitis can help to monitor disease activity. More important is the need to develop antifungal susceptibility testing for *Aspergillus species* and means to prevent occurrence of the disease especially in immunocompromised individuals. Knowledge of local patterns of infection and antifungal susceptibility would prove useful in selecting empirical therapy and formulating prophylactic strategies.

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