



CASE STUDY

A UNIQUE CASE OF ASPERGILLOSIS INVOLVING THE MAXILLARY ANTRUM

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ABSTRACT

Fungal infections are common globally with varied clinical presentations. Among them, Aspergillosis is the second most common opportunistic fungal disease and is difficult to diagnose. Immunocompromised patients are mostly affected by invasive aspergillosis. Spores of the aspergilli are inhaled or ingested which if left untreated will disseminate in the lungs, paranasal sinuses, cranium and orbit, leading to cough, dyspnoea, ulceration, loss of vision, fever, meningitis etc. Early diagnosis and prompt treatment is therefore necessary for improvement of the survival rate. We present a case of invasive aspergillosis involving the maxillary sinus in an uncontrolled diabetic patient with the emphasis on early diagnosis, as delay in the initiation of treatment could be detrimental due to the dissemination of the disease process.

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INTRODUCTION

Aspergillosis is a fungal disease caused by sensitization, colonization and tissue invasion by the species of genus aspergillus (Prabhu *et al.*, 1993). There are several species of Aspergillus of which *A. Fumigatus* and *A. Flavus* are responsible for most of the cases of Aspergillosis (Neville *et al.*, 2015). Sluyter, first identified this infection in the year 1847 (Hinson *et al.*, 1952). The aspergillus species which tolerate a temperature of 37 degrees centigrade, have the potentiality of replication and tissue invasion while others cause allergic syndromes (Harrison's Principle of Internal Medicine, 17th edition). Hora, initially classified this infection as invasive and non-invasive based on bony invasion, in 1965 (Hora, 1965). After that, in the year of 1994, Rowe Jones and Moore Gillon, classified aspergillosis into three types, invasive, non-invasive and non-invasive destructive (Rowe Jones and Moore Gillon, 1994). It can affect both healthy and immuno compromised individuals depending on the immune status of the patient (Neville *et al.*, 2015). The clinical manifestations of invasive Aspergillosis are swelling, ulceration, crusting and necrosis of the anterior turbinates, nasal septum and lateral nasal wall (Prabhu *et al.*, 1993). In immunocompromised patients, marginal gingiva and gingival sulcus are the port of entry for this infectious disease (Neville *et al.*, 2015). Intraoral manifestations begin as painful gingival ulcerations with a diffuse swelling which develops peripherally in the mucosa and soft tissues with a grey or violaceous hue which later turns into a black

or yellow ulcer due to necrosis if left untreated (Neville *et al.*, 2015). Neurological and ocular signs such as blurred vision, chemosis, proptosis, ptosis, diplopia, gradual loss of vision and facial nerve palsy were also reported by various authors (Sarti *et al.*, 1988; Arora *et al.*, 2011). Radiological evaluation with MRI and CT scan are of great help in diagnosing invasive cases of Aspergillosis. CT scan reveals focal radiodense shadows with homogeneous opacification of the sinus (Preeti Sethi *et al.*, 2012). In advanced stages, bony erosion or destruction and extrasinus extension may be elicited (Del Gaudio *et al.*, 2003). Biopsy is the only procedure in conjunction with or without culture to confirm the diagnosis. The histopathological features of invasive Aspergillosis reveals the presence of septate hyphae measuring 3-4 µm in diameter, flat, broad, refractile with dichotomous branching at acute angles and invade the blood vessels resulting in necrosis (Neville *et al.*, 2015; Tarun Taneja *et al.*, 2010). Extensive tissue destruction with weak inflammatory response may be noted in the immunocompromised host (Neville *et al.*, 2015). For confirmation of the diagnosis, the section stained with PAS revealed the presence of magenta coloured septate dichotomously branched hyphae while with Grocott Gomori Methanamine Silver stain (GGMS), it showed the presence of black septate hyphae along with spores of Aspergillus species (Tarun Taneja *et al.*, 2010). The line of treatment for invasive aspergillosis involves aggressive surgical debridement of the necrotic devascularized tissue with administration of systemic medications like Amphotericin B, Voriconazole and Posaconazole etc. (George Rallis *et al.*, 2014). The prognosis of invasive Aspergillosis is potentially fatal, with an extremely high mortality rate, particularly in immuno-compromised patients (Beatriz Peral –Cagigal *et al.*, 2014).

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Case report: A 48 year old male patient from rural area reported to our department with a chief complaint of persistent headache, pain and discomfort involving both jaws along with difficulties in opening his mouth since two and half months. Patient was suffering from uncontrolled diabetes since ten years with irregular medication. In conjunction with this, he gave a history of generalized weakness, weight loss and occasional fever. He had consulted a neurosurgeon for persistent headache and was advised for MRI and CT scan of PNS and PA view of chest. Patient also gave a history of multiple sexual partners. Extraoral examination revealed the presence of an ulceration involving the margin of right external nares and a pus discharging sinus involving the left middle 1/3 of face (Figure 1b). Unilateral proptosis of the left eye and yellowish appearance of the sclera was also noted with left submandibular lymphadenopathy (Figure 1a). Intraorally, pus discharging sinus was noted in the maxillary alveolar mucosa in relation to left canine and premolars along with the presence of an ulceration over the incisive papilla, being covered by slough (Figure 2c & 2b). Oral hygiene of the patient was very poor with a yellowish white coated tongue (Figure 2a). Curdy white flecks of plaque type lesion was also noted over the labial and buccal mucosa. Based on clinical findings patient was advised for OPG and PNS view radiograph. Chest radiograph showed accentuated bronchovascular markings of the lung field which were non-contributory in terms of diagnosis (Figure 3a). Paranasal sinus view showed diffuse radio-opacity involving the left maxillary sinus region (Figure 3b). MRI of PNS showed the presence of a hyperintense mass in the left maxillary sinus region while CT scan revealed the presence of a hyperdense mass in relation to left maxillary sinus (Figure 4a & 4b). Based on the clinical and radiological presentation, our first provisional diagnosis was any sexually transmitted disease or any type of fungal infection. Routine haematological investigations were performed which revealed an increase in the neutrophil count, decrease in the lymphocyte count and raised blood sugar levels. Preoperative serology for HIV and HCV were found to be non-reactive and a negative VDRL test ruled out the possibility of Syphilis. Cytological smear taken from the labial, buccal mucosa and dorsal surface of the tongue for PAS staining was negative, thereby excluding the presence of Candidal infection. Patient was referred to Nilratan Sarkar Medical College and Hospital. The exploration and debridement of left maxillary sinus was done under general anaesthesia and yielded necrotic tissue was sent for histopathological evaluation. The section stained with H&E revealed the presence of pseudostratified ciliated columnar epithelium with underlying fibrovascular connective tissue stroma which consists of non-specific inflammatory cell infiltrate and blood vascular channels. The most striking feature is the presence of multiple elongated, ovoid darkly staining areas within the collagen fibres (Figure 5a). The overall histopathological features are suggestive of fungal infection involving the maxillary sinus. To confirm the diagnosis, the sections were sent for PAS and Grocott Gomori Methanamine Silver (GGMS) staining which revealed the presence of branched septate hyphae and spores of *Aspergillus* species (Figure 5b & 5c). Our final diagnosis was "Invasive Aspergillosis" involving the left maxillary antrum. Patient was sent to The School of Tropical Medicine, Kolkata for further evaluation and treatment.

DISCUSSION

Mycotic infections are on the verge of rise globally in the recent years and since 1968, there has been a three fold increase of all fungal infections (Mandel GL, 1985). Aspergillosis is the second most common fungal infection to affect the immune-compromised patients after Candidiasis (Allphin AL, 1991). In 1729, a priest botanist Michelli first described Aspergillosis (Neville, 2015).



Fig. 1a. Extraoral photograph of the patient. Fig 1 b Extraoral photograph of the patient showing ulceration and crusting of the left external nares along with presence of extraoral discharging sinus over the left cheek



Fig. 2a. Intraoral photograph of the patient showing poor oral hygiene with white coated tongue. Fig 2b. Intraoral photograph of the patient showing an ulceration over the incisive papilla region associated with pseudo-membranous slough. Fig 2c. Intraoral photograph of the patient showing discharge of pus from the mucogingival fold in relation to 23 and 24

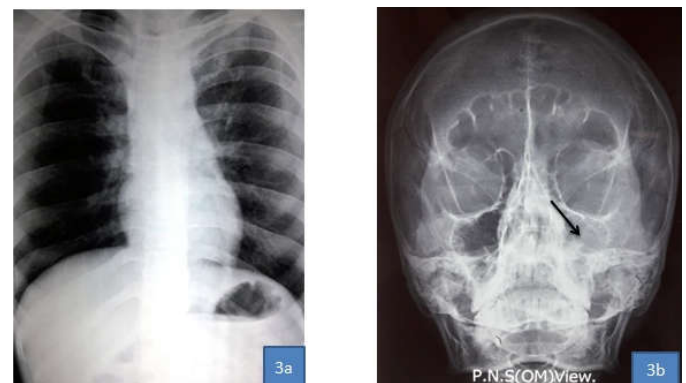


Fig. 3a. Chest radiograph showing accentuated bronchovascular markings of the lung field. Fig. 3b. PNS view showing diffuse radio-opacity involving the left maxillary sinus region

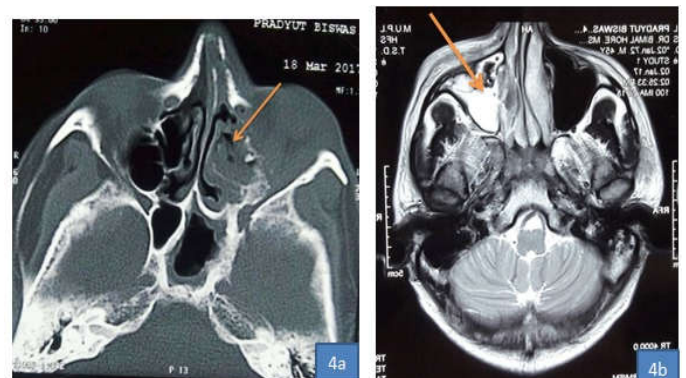


Fig. 4a. CT scan axial view showing a hyperdense mass occupying the left maxillary antrum. Fig 4b MRI of PNS revealed the presence of an hyperintense mass involving the left maxillary sinus region

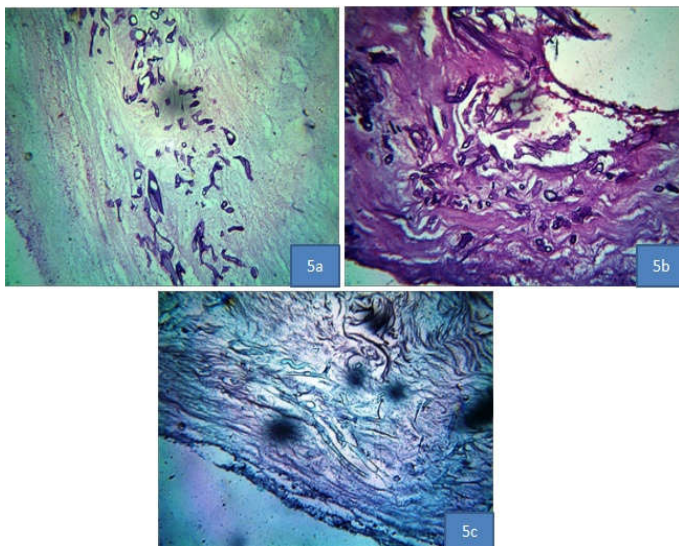


Fig 5a Photomicrograph of H& E (40x) stained section showing septate hyphae of aspergillus species. Fig 5b Photomicrograph of PAS (40x) stained section showing magenta coloured septate hyphae with conidia. Fig 5c Photomicrograph of GGMS (40x) stained section showing greyish- black coloured septate hyphae of aspergillus species

It has been reported that Aspergillosis is more prevalent in tropical and sub-tropical regions of Asia, Africa, South and Central America where fungus thrive well in hot and humid climate (Prabhu, 1993). There are about 35 pathogenic and allergic species of Aspergillosis associated with human disease. *A. fumigatus* is the commonest aspergillus species to affect the immunocompromised individuals (Beatriz Peral, 2014). *A. flavus* is the second most common agent to affect the oral cavity, causing destruction due to its toxins (Preeti Sethi, 2012; Robb PJ, 1986). It is a filamentous fungus, ubiquitous in nature growing in plant materials and in bedding (Beatriz Peral, 2014). Non-invasive form affects the normal host, usually presenting as an allergic reaction without any tissue invasion (Neville *et al.*, 2015). The prevalence of invasive Aspergillosis has increased in the past 20 years with the advent of intensive chemotherapeutic agents, use of corticosteroids, AIDS, improper use of antibiotics, organ or bone marrow transplantation, leukemia, lymphoma, uncontrolled diabetes, chronic granulomatous diseases, aplastic anaemia, burn and radiation therapy (Neville *et al.*, 2015). The patients suffering from long-standing diabetes mellitus are at increased risk as it alters the immune status of patients to infections with decreased granulocyte phagocytic activity and altered polymorphonuclear leukocyte response (Auluck, 2007). The patient under discussion was a 48 year old male, a quack practitioner from a rural area who was suffering from uncontrolled diabetes since ten years, with irregular medication. The primary route of infection is via inhalation of the air-borne spores which colonizes in the bronchopulmonary tract and paranasal sinuses (Mandell *et al.*, 1985; Allphin *et al.*, 1991). Maxillary sinus is the most commonly affected site and the spores enter via the oro-antral communication formed during dental procedures (Beatriz Peral –Cagigal *et al.*, 2014). First report of Aspergillosis involving the maxillary sinus was published in 1893 by Morel Mackenzie (Rudaqi *et al.*, 2010). The mass of fungus enters the blood vessels resulting in formation of thrombi and ultimately leading to tissue necrosis due to infarction (Kim *et al.*, 1993). Local factors such as sinus obstruction, hypoxia and anaerobic conditions favour the growth of Aspergillus species (Rossouw and Swart, 1988). The clinical manifestations of invasive Aspergillosis are pain, headache, fever, cellulitis, ptosis, proptosis, facial swelling, nasal congestion, rhinorrhoea (Kim *et al.*, 1993). The patient presented with severe left hemifacial pain, persistent headache, generalized weakness, weight loss, occasional fever, unilateral proptosis, restricted mouth opening and left submandibular

lymphadenopathy. These clinical findings are consistent with the observations reported by the authors of various studies. Radiological evaluation with MRI and CT scans are helpful in diagnosing the invasive case of Aspergillosis (Tugsel *et al.*, 2004). CT scan of the present case revealed the presence of a hyperdense mass occupying the left maxillary sinus, which was thus very characteristic of the said disease. Histopathologically aspergillus lesions show varying numbers of branching, septate hyphae, 2-4µm in diameter (Del Gaudio *et al.*, 2003). These hyphae show a tendency to branch at an acute angle and to invade adjacent small blood vessels (Neville *et al.*, 2015). Special fungal stains like PAS and Grocott Gomori Methanamine Silver (GGMS) are very helpful to reach a confirmatory diagnosis (Preeti Sethi *et al.*, 2012). The nature of tissue and the characteristic staining pattern of the fungi in the present case was strongly mimicking the features of invasive aspergillosis. The line of treatment for invasive Aspergillosis is surgical debridement followed by systemic administration of antifungal therapy comprising of Amphotericin B, Voriconazole, Posaconazole, Caspofungin (George Rallis *et al.*, 2014). The prognosis of Aspergillosis is directly related to the severity and extent of the disease when treatment begins and the aggressiveness of the treatment (Tarun Taneja *et al.*, 2010). Even with appropriate therapy only about 1/3 rd of the immunocompromised patients can survive (Neville *et al.*, 2015)

Conclusion

The recognition and prevention of invasive Aspergillosis involving the maxillary antrum in immunocompromised patients is very deceptive and misleading, making the clinicians aware of the disease process through radiological and histopathological findings to emphasize an early diagnosis and prompt treatment to prevent patient demise.

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