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ARTICLE 2

Invasive Fungal Sinusitis

Ashok K Gupta, Sandeep Bansal, Rijuneeta, Bhumika Gupta

ABSTRACT

Invasive sinus *Aspergillus* infection has been reported in the last decade with increased frequency, most commonly in the setting of hematologic malignancy, neutropenia, HIV infection and other states of immunosuppression. Fungal rhinosinusitis can be broadly classified into two varieties—invasive and noninvasive on the basis of tissue invasion. Invasive fungal sinusitis are acute invasive, chronic invasive (both granulomatous and nongranulomatous forms), whereas noninvasive are fungus balls and allergic fungal sinusitis. Invasive fungal sinusitis is one of the most challenging forms of sinonasal pathology to manage, most commonly presenting in immunocompromised individuals. Chronic invasive being sinus aspergillosis (CISA) is being reported in immunocompetent patients at an increasing rate while most of these cases are being reported from the India subcontinent and middle east. Invasive fungal sinusitis is on the rise worldwide and especially in north India as it is endemic in this part of the country. It is affecting immunocompetent young and middle aged population causing a great morbidity and mortality. This entity needs to be picked up early by spreading awareness among the family physicians, internists, otolaryngologists, ophthalmologists, neurosurgeons, pulmonary physicians, critical care specialists so that an early management can initiated to achieve better control over the disease. This review is an attempt to initiate an interdisciplinary approach to achieve a better outcome.

Keywords: Rhinosinusitis, Fungal sinusitis, Invasive, Nose and paranasal sinuses.

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INTRODUCTION

Invasive sinus *Aspergillus* infection has been reported in the last decade with increased frequency, most commonly in the setting of hematologic malignancy, neutropenia, HIV infection and other states of immunosuppression.[1,2]

Fungal rhinosinusitis can be broadly classified into two varieties—invasive and noninvasive on the basis of tissue invasion. Invasive fungal sinusitis are acute invasive, chronic invasive (both granulomatous and nongranulomatous forms) whereas noninvasive are fungus balls and allergic fungal sinusitis. These manifestations may progress from a noninvasive form into an invasive form if the immunological status of patient changes.[3]

The increased numbers of immunocompromised patients, owing to improved survival from AIDS, malignancies and more intensive cytotoxic therapy, more transplantation (with immunosuppression) for organ dysfunctions has lead to a increased frequency of these infections developed countries.[4]

Invasive and noninvasive syndromes of fungal sinusitis share many features. They may occur in immunocompetent or immunocompromised persons, may have an acute or chronic course, and may extend beyond the thin walls of the sinuses into the orbit, structures of the eye and the brain. This fungal material is commonly associated with dense polyposis and calcification that results in areas of focal or diffuse radiodensity on computed tomographic (CT) imaging of the sinuses and decreased signal intensities on T_1 and T_2-weighted magnetic resonance imaging (MRI). Invasive fungal sinusitis can be distinguished from noninvasive disease with the use of clinical criteria that include radiologic diagnosis of sinusitis and histopathological examination of tissue from sinuses. Radiologic findings associated with fungal sinusitis include those also seen with isolated bacterial sinusitis, such as air fluid levels or more than 8 mm of mucoperiosteal thickening, and those more specific for fungal sinusitis, such as calcifications and loss of bony sinus margins. Fungal cultures of the nasal mucus are unreliable in the diagnosis of any form of fungal sinusitis. Stainable hyphae are not present in the mucosa of patients with chronic bacterial sinusitis; they are present solely in mucopurulent material within the sinus in noninvasive disease. Hyphae penetrate the sinus mucosa into submucosa, blood vessels or bone in invasive disease.[5]

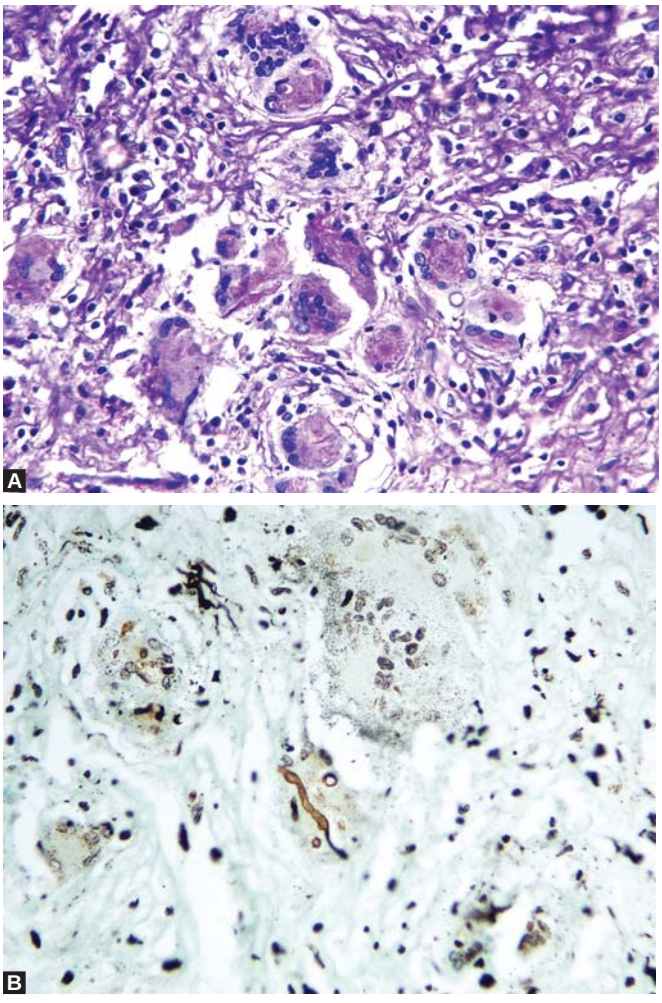
Invasive fungal sinusitis is one of the most challenging forms of sinonasal pathology to manage, most commonly presenting in immunocompromised individuals. Diagnosis of invasive fungal sinusitis requires histopathologic evidence of fungi invading nasal tissue: Hyphal forms within the sinus mucosa, submucosa, blood vessels or bone[6] (Figs 1A and B).

Invasive fungal sinusitis has been subclassified into three distinct forms: Acute fulminant invasive fungal sinusitis (AFIFS), chronic invasive fungal sinusitis and granulomatous invasive fungal sinusitis.[6-8]

For the treatment of invasive fungal sinusitis, three types of antifungals have been tried:

- Polyenes (amphotericin and its various formulations)
- Azoles (itraconazole, voriconazole, posaconazole, ravuconazole, saperconazole)
- Newer experimental classes, such as lipid complex nystatin and echinocandins—micafungin, caspofungin, anidulafungin.[9]

In India we find chronic invasive aspergillosis and the antifungals commonly used are amphotericin B, itraconazole and voriconazole.



Figs 1A and B: (A) PAS stain with septate hyphae within giant cell, (B) Grocott's stain showing septate fungal hyphae

Amphotericin B (AmB), was being used for a long time for invasive fungal sinusitis but the results have not been very good partly because of the substantial toxicities associated with the doses of AmB which leads to frequent stoppage of the treatment and partly because of the lack of efficacy of the agent in severely immunosuppressed hosts.[4,10]

Voriconazole is a novel wide-spectrum triazole antifungal agent active *in vitro* against *Aspergillus* species for which the geometric mean MIC is 0.4 mg/l, which compares favorably with that of AmB.[11-14] The drug is fungicidal *in vitro* for a majority of isolates. The drug can also be given orally and intravenously, making switch therapy easier. Voriconazole is rapidly absorbed after oral administration and exhibits nonlinear kinetics with disproportionate rises in plasma concentrations with increasing doses. Voriconazole accumulates up to 8-fold after multiple dosing as a result of saturation of its own metabolism.[15]

In a multicentric study, to evaluate the efficacy and safety of voriconazole in acute invasive aspergillosis (IA), Denning et al administered intravenously voriconazole 6 mg/kg twice a day (bid) twice and then 3 mg/kg bid for 6 to 27 days, followed by 200 mg bid administered orally for up to 24 weeks in 116 immunocompromised patients with acute IA. Response was assessed by clinical and radiographic change. IA was proven in 48 (41%) and probable in 68 patients. Voriconazole was given as primary therapy in 60 (52%). Good responses were seen in 56 (48%); 16 (14%) showed complete response and 40 (34%) partial response. A stable response was seen in 24 patients (21%), and 36 (31%) of the infections failed to respond to therapy. According to the underlying immunocompromised state they found good responses were seen in 60% of those with pulmonary or tracheobronchial IA, 16% with cerebral IA, 58% with hematologic disorders, and 26% of allogeneic stem cell transplant recipients.[16]

In another randomized unblinded study, Herbrecht et al compared voriconazole and amphotericin B as primary therapy for immunocompromised IA patients. A total of 144 patients in voriconazole group and 133 in amphotericin group with definite or probable aspergillosis. At week 12, there was a successful outcome in 52.8% of patients in voriconazole group and 31.6% of those in amphotericin B group. The survival rate at 12 weeks was 70.8% in voriconazole group and 57.9% in amphotericin group. Moreover, it was found that voriconazole-treated patients had significantly fewer severe drug-related adverse events.[17]

Perfect et al evaluated the efficacy, tolerability and safety of voriconazole as salvage treatment for 273 patients with refractory and intolerant-to-treatment fungal infections and as primary treatment for 28 patients with infections for which there is no approved therapy. Voriconazole was associated with satisfactory global responses in 50% of the overall cohort; specifically, successful outcomes were observed in 47% of patients whose infections failed to respond to previous antifungal therapy and in 68% of patients whose infections have no approved antifungal therapy. In this population at high-risk for treatment failure, the efficacy rates for voriconazole were 43.7% for aspergillosis.[18]

Acute Fulminant Invasive Fungal Sinusitis

The acute or fulminant invasive form was first described by McGill et al in 1980.[19] It is marked by vascular hyphal invasion, hemorrhage, and infarction, time course less than 4 weeks, and a predilection for the immunocompromised host.[20,21] AFIFS usually results in rapid progression and death if it is not diagnosed and treated promptly. AFIFS results from the rapid spread of fungi from the nasal and sinus mucosa by way of vascular invasion into the orbit, vessels and parenchyma of the brain. The time course of less than 4 weeks' duration separates acute from chronic disease.[3] Patients typically have ailments associated with impaired neutrophil function (hematologic malignancies, aplastic anemia, hemochromatosis, insulin-dependent

diabetes, AIDS, organ transplantation) or are undergoing iatrogenic immunosuppression with systemic steroids or chemotherapeutic agents.[3,6-8,22] Although rare, cases of AFIFS in otherwise healthy individuals have been documented in the literature.[22,23]

Several studies have investigated the signs and symptoms of AFIFS to determine the subset of patients who require a more aggressive diagnostic investigation. In the immunocompromised patient population, the presence of fever of unknown origin after 48 hours of appropriate broad-spectrum intravenous antibiotic or the presence of localizing sinonasal symptoms should prompt imaging studies and nasal endoscopy.[3,22,24] The physical findings in AFIFS can be subtle, but the most consistent finding is an alteration in the appearance of the nasal mucosa. Mucosal discoloration can be variable, and may be gray, green, white or black. Discoloration, granulation and ulceration typically replace the normal pale-pink mucosa. White discoloration indicates tissue ischemia secondary to angiocentric invasion, whereas black discoloration is a late finding of tissue necrosis. In a series by Gillespie et al[22] mucosal abnormalities were seen most commonly on the middle turbinate, followed by the septum, palate and inferior turbinate. Anesthetic regions of the face or oral cavity are features of early invasive process and may precede the development of objective changes in the mucosa. Decreased nasal mucosal bleeding or sensation should also be noted because they may be signs of fungal invasion. Park et al[24] discovered that bedside endoscopic findings did not correlate with intraoperative endoscopy because of a large amount of debris in the nasal cavity that was not removed during bedside examinations and the relative noncompliance of the pediatric patients. Examination under general anesthesia was recommended for nasal endoscopic examination and directed biopsies of suspicious lesions, the middle and inferior turbinate.

CT of paranasal sinuses is usually obtained during the workup of immunocompromised patients who have fever or sinonasal symptoms, usually before evaluation by an otolaryngologist. Severe unilateral thickening of the nasal cavity mucosa has been shown to be the most consistent finding on CT, suggestive of underlying invasive fungal sinusitis.[25] The earliest evidence of AFIFS on CT scan could be the infiltration of the periantral fat planes.[26] CT scans are helpful in defining individual variations in sinus architecture and possible periorbital and intracranial spread which helps to support the diagnosis of AFIFS.

MRI is superior to CT in delineating the intracranial extent of the disease and it may have a role in evaluating patients who demonstrate signs of intracranial invasion: Mental status changes, orbital apex syndrome, seizure or stroke. In patients with suspicion of AFIFS culture and microscopic examination of the specimen can be done. The potassium hydroxide—calcofluor white method can be used immediately on culture aspirate material to reach to an early diagnosis so that therapy can be started at the earliest. This highly sensitive technique uses potassium hydroxide to dissolve human material, and an optic brightener (calcofluor white) that binds to the cell wall of the hyphae. Fungal cell walls, including septations, fluoresce when viewed using a fluorescence microscope.[27] The fungal cultures may take days to weeks to grow but may be needed for antifungal susceptibility testing. Proper speciation also provides important clinical data, because certain species, such as *Pseudallescheria boydii*, do not respond to amphotericin.

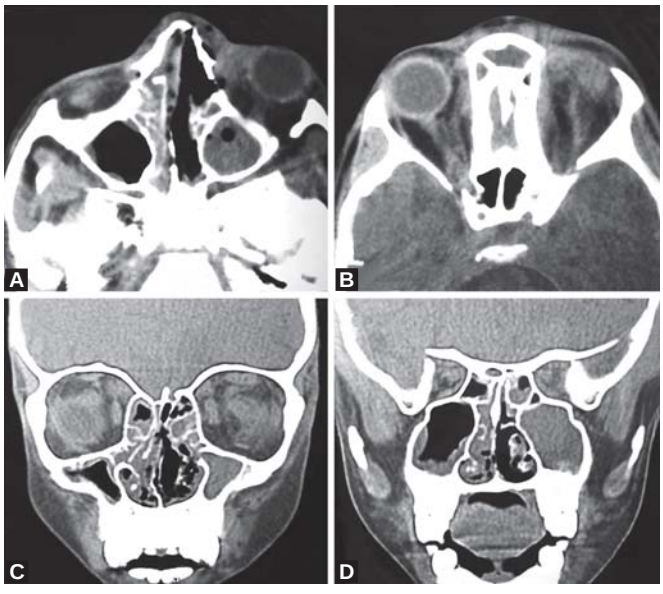
Histopathologic evaluation of the suspected tissue, however, is typically the most critical to making the diagnosis. Permanent section with the Gomori methenamine-silver stain uses deposition of silver onto the fungal cell wall and, because it can detect even a single cell, it undoubtedly is the most sensitive of the commonly used histologic stains. No histologic specimen should be considered to be negative for fungus unless a silver stain has been performed.[27]

Fungal disease is determined to be invasive if it meets the following criteria: (1) hyphal forms within the submucosa, with or without angiocentric invasion and (2) tissue necrosis with minimal host inflammatory cell infiltration.[7] Frozen section allows for a timely diagnosis, and, if positive, appropriate antifungal therapy and extended surgical resection can be initiated without delay.

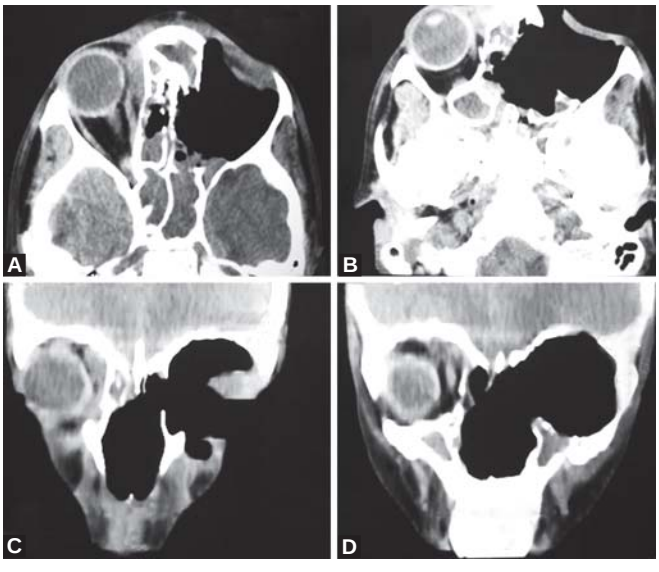
Mucormycosis fungal elements are broad, ribbon-like, irregular, and rarely septated, whereas the *Aspergillus* species demonstrate more narrow hyphae with regular septations and 45° branching.[3,22] *Aspergillus* species can be angioinvasive, but it is not the obliterative invasion seen with mucormycosis.

The treatment of AFIFS requires reversal of the underlying predisposing condition, surgical debridement and appropriate systemic antifungal therapy. Treatment of diabetic ketoacidosis or correction of neutropenia can be initiated concurrently with systemic antifungals. Medical antifungal therapy for most patients who have AFIFS consists of systemic amphotericin B at intravenous doses of 0.25 to 1.0 mg/kg/day to a total dose of 2 to 4 gm over 6 to 8 weeks. The use of amphotericin B is limited in some patients secondary to renal toxicity, and they may be candidates for liposomal amphotericin B at a concentration of 3 to 5 mg/kg/day. Liposomal amphotericin, secondary to high cost, is reserved for a clinically proven fungal infection in an immunocompromised host with an elevated serum creatinine (O2.5 mg/dl) or progression of fungal disease while on maximum dosage of standard amphotericin. Voriconazole is more effective than amphotericin B for invasive *Aspergillus*.[8]

Antifungals alone are not sufficient in the treatment of invasive fungal sinusitis. Early aggressive endoscopic sinonasal debridement should be performed on all patients who have biopsy-proven disease or on any patient suspected of having fungal invasion. Radical resections (radical maxillectomy, craniofacial resection and orbital exenteration) to remove disease outside the sinonasal cavity rarely achieve negative margins or improve long-term survival.[22,28] Endoscopic sinus debridement slows the progression of the disease, reduces the fungal load and provides a specimen for culture and histopathologic diagnosis.[22] Debridement of the involved sinuses or structures is extended until clear bleeding margins are exposed (Figs 2A to 3D).



Figs 2A to D: CT scans (A and B) axial sections, (C and D) coronal sections showing acute fulminant invasive fungal sinusitis (AFIFS)



Figs 3A to D: CT scans (A and B) axial sections, (C and D) coronal sections showing acute fulminant invasive fungal sinusitis (AFIFS) postdebridement and amphotericin B

Earlier studies have cited the mortality for AFIFS to be as high as 50 to 80%, more recent series have demonstrated a mortality rate of less than 20%.[29] In patients who have symptomatic intracranial involvement mortality rates are nearing 100%.[2,22,28] Thus, patients who have orbital apex involvement or intracranial spread are less likely to respond to radical surgery, and should be appropriately counseled when a radical surgical procedure is considered.[22] Identification of the fungal organism can also be an important predictor of survival.

In a large retrospective review by Parikh,[29] the overall mortality rate directly as a result of invasive fungal sinusitis was found to be 18%. When examining each specific disease subgroup, the mortality rate from invasive fungal sinusitis among diabetic patients (40%) was significantly higher than in patients who had hematologic malignancy (11%), chronic steroid users (33%), and solid organ transplant patients (0%). This disparity can be due to a greater incidence of Mucor over *Aspergillus* affecting diabetics and a delay in diagnosis resulting in more advanced disease at presentation in this subgroup of patients.[29]

Chronic Invasive Sinus Aspergillosis

Chronic invasive being sinus aspergillosis (CISA) is being reported in immunocompetent patients at an increasing rate while most of these cases are being reported from the India subcontinent and middle east but cases are being increasingly encountered from North America and elsewhere.[30] Less distinction, however, exists between the chronic invasive and granulomatous forms, calling into question the clinical relevance of the aforementioned classification.[8,31]

The granulomatous form has been described among immunocompetent patients in tropical regions in whom non-caseating granulomas are common and *A. flavus* is the predominant pathogen (Fig. 4).[1,32-34] But nongranulomatous aspergillosis invasion of the sinus wall in the absence of clinically significant immunodeficiency have also been reported.[30,35]

Several factors underlie the dichotomous geographic distribution of *Aspergillus* species. Although both species are considered ubiquitous saprophytic organisms,[36,37] *A. fumigatus* appears to be particularly tolerant to variations in temperature[38] and has been detected in greater concentration in cooler air samples of Europe and North America.[36,38-40] *A. flavus* is the most commonly isolated species from the environmental samples in areas where granulomatous fungal sinusitis predominates[41,42] probably due to the tropical climate which also promotes a microaerophilic sinus environment conducive to the growth of *A. flavus*.[1] In contrast, the chronic invasive form was

originally reported in association with diabetes mellitus or corticosteroid use, with a sparse inflammatory response.[7] In addition to geographic variations, significant differences based on *Aspergillus* species involved was also noted pertaining to host response, clinical course and perhaps prognosis. *A. flavus* was strongly associated with a granulomatous response, whereas infection with *A. fumigatus* elicited chronic inflammation or simple hyphal tissue invasion. Mechanisms of immunologic response to *Aspergillus* infection in the apparently immunocompetent host remain unclear[37] and may involve poorly characterized subcellular deficiencies.[1,43,44]

There are reports of nongranulomatous *Aspergillus* invasion of the sinus wall occurring in the absence of clinically significant immunodeficiency.[30,35] In North America, *A. fumigatus* is associated with a rapid invasion of adjacent tissues in older patients. Inflammatory response is nongranulomatous and patients tend to have a poor prognosis. *A. flavus*, however, was identified in the vast majority of worldwide cases; patients tend to be younger, with a protracted clinical course, and predominant granulomatous histology.[45]

The relapsing nature of invasive aspergillosis of the paranasal sinuses has been described previously.[30,46,47] The current report also identified the frequency of relapse after surgical evacuation and the mean time to the first relapse after first surgery. However, none of the evaluated variables was identified as a statistically significant risk factor predisposing to relapse. Factors investigated included duration of symptoms before diagnosis, extent of disease involvement, age, gender, geographic origin of the patient and mode of treatment.

The small number of cases may not be enough to evaluate the difference statistically. Nevertheless, the combination of complete surgical evacuation and Amphotericin B therapy postsurgery produced a trend toward fewer relapses and longer intervals between relapses. The role of complete surgical evacuation in reducing relapse was also noted previously, with the observation that 62% of patients treated by complete surgical resection either were cured or had stable disease compared to 31% of patients with incomplete resection.[30]

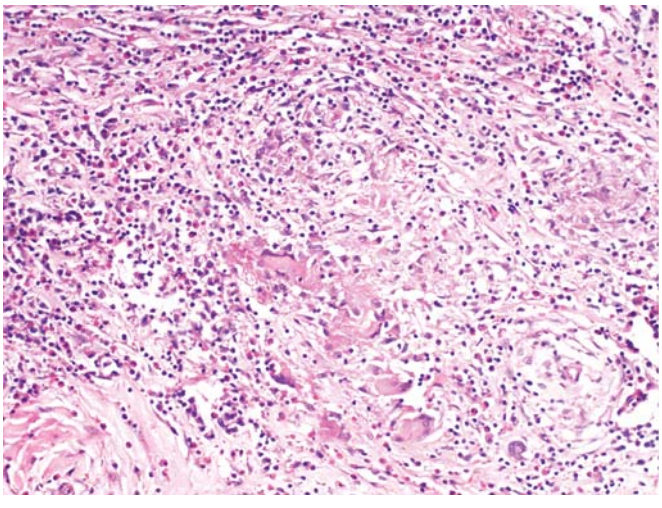


Fig. 4: H&E stain showing chronic invasive granulomatous fungal rhinosinusitis

Clancy and Nguyen[30] reviewed the literature for reports of invasive aspergillosis of the paranasal sinuses in apparently immunocompetent patients between 1987 and 1998. Their review identified 13 reports describing 29 patients, including three from their own institutions. The majority of cases identified were patients from the Sudan or Saudi Arabia who were infected with *A. flavus.* The delay in diagnosis was a peculiar finding, with a mean delay of 24 months.

The optimal treatment of invasive *Aspergillus* sinus disease in immunocompetent patients is not known. Partial, subtotal, staged or repeated debridement combined with antifungal treatment was associated with high failure rates.[30,35,46,48] There was a tendency for lower relapse rate (40%) in patients who had complete surgical evacuation compared to patients receiving incomplete evacuation (77%).

Amphotericin B therapy has been the gold standard treatment for invasive sinus aspergillosis in spite of a poor prognosis, partly because of strong side effects of amphotericin B which prevents its long-term administration. New antifungal agents have recently been developed with lesser side effects like voriconazole. Voriconazole is a second generation triazole with a broad spectrum of antifungal activity against *Candida*, aspergillosis, *Cryptococcus* and other species with superior effectiveness for invasive aspergillosis as compared to amphotericin B.[17] The optimum duration of antifungal drug administration for chronic invasive fungal sinusitis is controversial and reports very widely depending on the severity of the disease and institution from 2 months to more than 15 months.[49-51] In a review by Webb and Vikram on chronic invasive sinus aspergillosis in immunocompetent hosts, they found that treatment failure and mortality were not associated with degree of surgical intervention. But patients receiving azoles with activity against aspergillosis (i.e. vorinoazole) alone or in combination with amphotericin B survived more often, compared to patients receiving amphotericin B alone. A prospective, randomized unblinded study by Bansal and Gupta established the efficacy of voriconazole viz-a-viz amphotericin B. They administered oral voriconazole in loading dose of 400 mg 12 hourly in adults and 20 mg 12 hourly in children for two doses and then a maintenance dose of 200 mg 12 hourly in adults and 100 mg 12 hourly

in children to one group and conventional amphotericin B in the dose of 1 mg/kg/body weight once a day up to a maximum total dose of 2.5 mg or liposomal amphotericin B in the second group. They found comparable success rates with treatment with voriconazole, in fact having more success than amphotericin B in the extradural group and significantly lower adverse reactions with voriconazole. The results were not favorable with voriconazole in the intradural involvement probably due to the treatment duration of 14 weeks only (Figs 5 and 6).[52] A treatment of 6 to 12 months is being advocated in skull base aspergillosis these days.[15,16]

Rhinocerebral aspergillosis carries a high mortality, especially in immune-suppressed patients and after bone marrow transplantation.[53] The nose, paranasal sinuses and orbit are target organs in the head and neck. Intracranial extension of the infection is of major concern because this is usually a fatal complication. Presenting symptoms in these patients can be nonspecific initially. Fever is the most

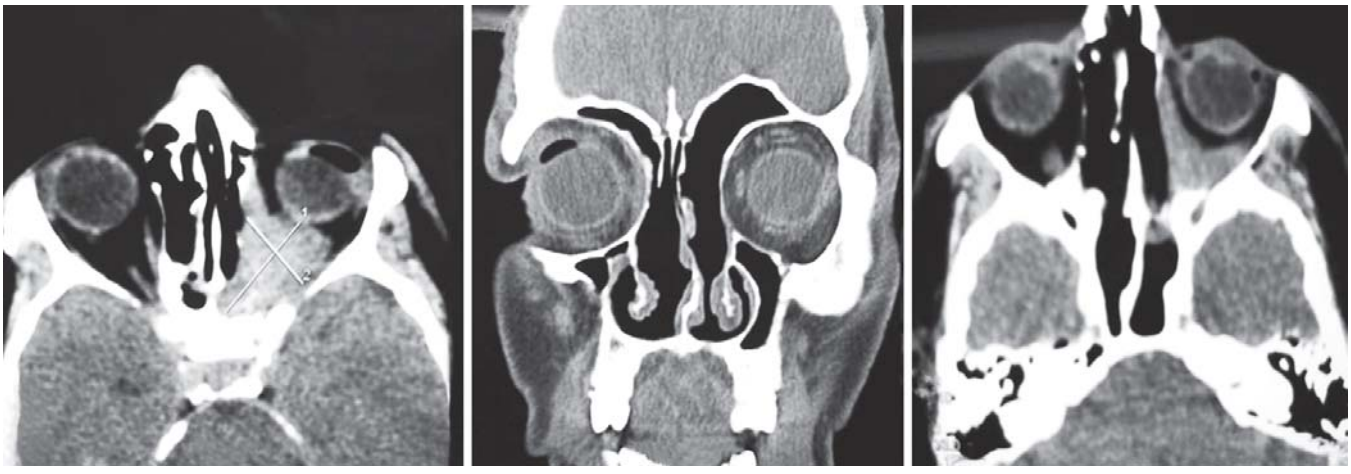


Fig. 5: CT scan nose, PNS, orbits (axial and coronal sections) showing chronic invasive sinus aspergillosis postdebridement and 3 months posttreatment with voriconazole

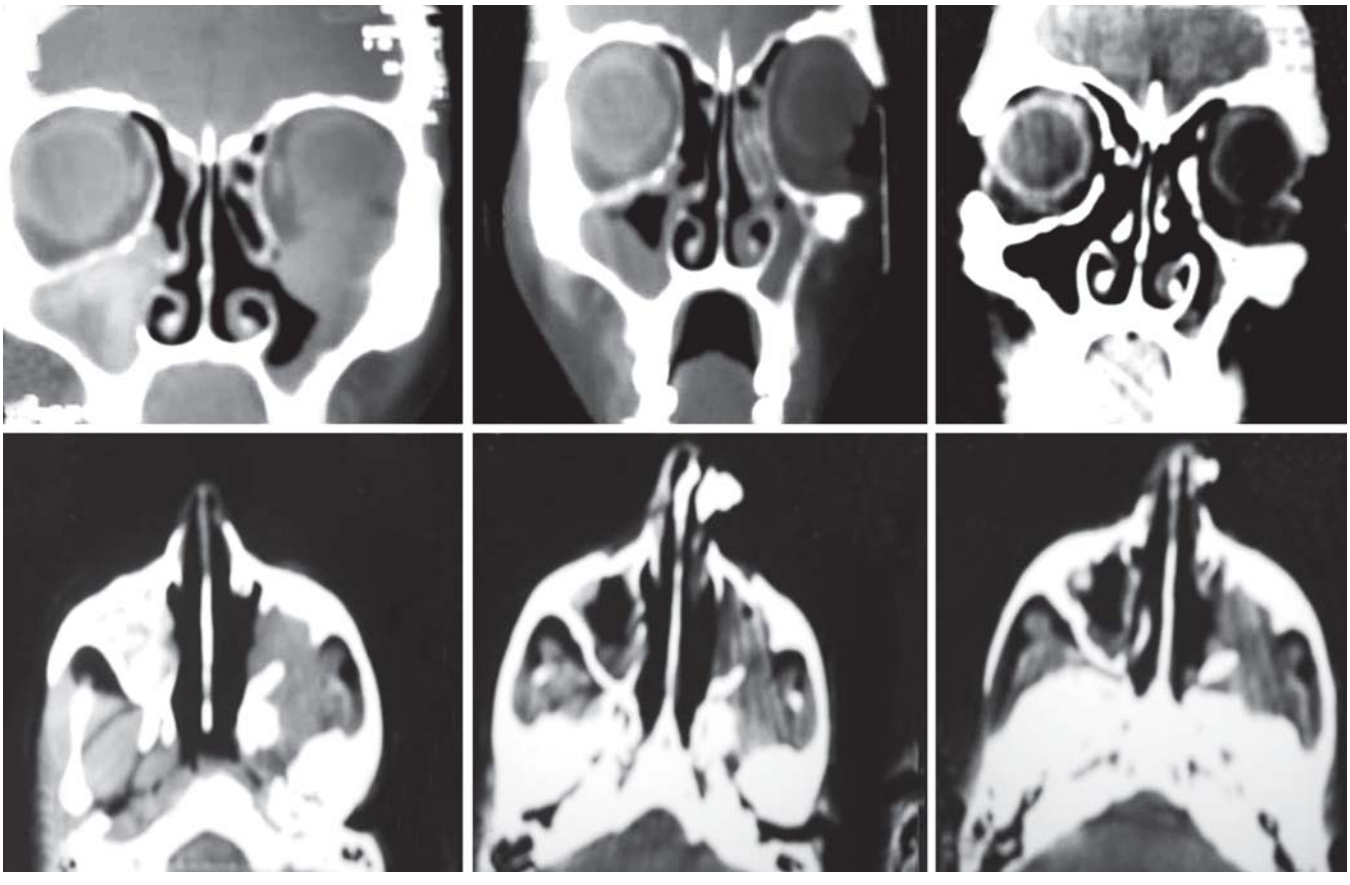


Fig. 6: CT scan nose, PNS, orbits (axial and coronal sections) showing response to treatment with voriconazole in chronic invasive sinus aspergillosis

common finding for which the patients are extensively investigated; this includes head and neck examination and CT of the head and sinuses. Other signs and symptoms include facial pain, swelling and tenderness over the involved sinuses, hyperesthesia and localized pallor of the nasal septum and/or turbinate. Necrosis of the septum and/or turbinate or palate manifesting as black crusts is a late finding and, when observed, indicates an already rapidly advancing infection. Periorbital swelling and redness, proptosis, and visual loss are grave signs. Facial necrosis, when it appears, progresses rapidly, leading to destruction of the face. Intracranial spread is manifested by disorientation, cavernous sinus thrombosis, orbital apex syndrome, hemiparesis seizures and coma. Death eventually ensues.[54]

Amphotericn B as well as voriconazole has been used in different studies as has been discussed before. In a study by Denning DW et al in 2,121 patients a mortality of 100% was noted in CNS aspergillosis,[55] Lin SJ et al[56] and Perfect JR et al[57] published in their series a case fatality rates for invasive aspergillosis: 58 to 62% of patients overall and 88% for patients with cerebral or disseminated aspergillosis.

Photosensitivity, raised SGOT/SGPT; ALP and rarely visual disturbances are few of the side effects of voriconazole. There were significantly increased number of adverse nephrotoxic and cardiotoxic events in patients on amphotericin as compared to voriconazole. In study by Denning DW et al 20 (14.8%) patients reported with abnormal LFT's; all requiring discontinuation of therapy; 12 (8.8%) had skin rashes; 4 (33.3%) requiring discontinuation of therapy and 15 (11%) reported visual disturbances; all temporary and none requiring discontinuation of therapy.[58] Perfect JR et al found photophobia in 11 (3%); abnormal vision in 85 (22.8%); rash in 28 (7.5%) and abnormal LFT's in >10% of patients but requiring discontinuation of therapy in 2.4% patients only.[18] In randomized trial of Herbrecht R et al hepatic abnormalities was seen in seven (3.6%) patients; rash in one (0.5%) and visual events in two (1.03%) patients. In their study with treatment with voriconazole, Bansal and Gupta reported that many patients developed skin rashes on voriconazole, but were transient and did not hamper the administration of voriconazole to the patients and disappeared after the stopping of the drug.[52]

Invasive fungal sinusitis is on the rise worldwide and especially in North India as it is endemic in this part of the country. It is affecting immunocompetent young and middle aged population causing a great morbidity and mortality. This entity needs to be picked up early by spreading awareness among the family physicians, internists, otolaryngologists, ophthalmologists, neurosurgeons, pulmonary physicians, critical care specialists so that an early management can initiated to achieve better control over the disease. An interdisciplinary approach is needed to achieve a better outcome.

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ABOUT THE AUTHORS

Ashok K Gupta

Professor and Head, Department of Otolaryngology and Head and Neck Surgery (Unit II), Postgraduate Institute of Medical Education and Research, Chandigarh, India, Phone: +91-9814198850, e-mail: drashokpgi@hotmail.com

Sandeep Bansal

Assistant Professor, Department of Otolaryngology and Head and Neck Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Rijuneeta

Associate Professor, Department of Otolaryngology and Head and Neck Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Bhumika Gupta

Senior Resident, Department of Otolaryngology and Head and Neck Surgery, Postgraduate Institute of Medical Education and Research Chandigarh, India