ORIGINAL ARTICLE

# Invasive Sino-aspergillosis in Immunocompetent Individuals: Atypical Presentations

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**Abstract**

*Aims:* To describe the demographic, clinical and radiological findings of invasive aspergillosis of the orbit and paranasal sinuses in immunocompetent individuals that presented without any nasal symptoms and to review the role of voriconazole in such cases.

*Materials and methods:* A series of 13 cases is being reported with review of literature. All these cases except one underwent complete surgical debridement of the disease at the time of biopsy. On histopathological confirmation of invasive aspergillosis, the cases with sphenoid sinus involvement were given 2.5 gm of intravenous Amphotericin B (1 mg/kg/day) followed by oral itraconazole in a dose of 10 mg/kg/day for 6 months. The cases where there were lesser chances of intracranial involvement or the cases that refused for intravenous Amphotericin B were started on voriconazole 200 mg twice a day for six to twelve months. All these cases were followed up with the help of radiology, clinical improvement in symptoms and signs and fungal serology.

*Results:* We found isolated sphenoid sinus involvement in 10 (76.92%) cases, isolated maxillary sinus involvement 2 (15.38%) cases and isolated orbital involvement 1 (7.69%). Our protocol was successful in 11 (84.61%) cases, one patient was lost to follow-up while one died due to intracranial complications during the third week of therapy.

*Conclusion:* This study showcased the atypical presentations of invasive aspergillosis in immunocompetent individuals and the high degree of suspicion required to diagnose this entity. An aggressive, effective and optimal management protocol has been suggested and the role of voriconazole has been highlighted.

**Keywords:** Invasive aspergillosis, isolated sinus involvement, Voriconazole.

## INTRODUCTION

Invasive aspergillosis of the paranasal sinuses was reported in immunocompetent hosts for the first time by Milosev and others in 1966.[1] Since then, this condition has been reported mainly from tropical areas and is endemic in the Northern parts of India.[2] Therapy for chronic invasive *Aspergillus sinusitis* includes surgical evacuation of the sinus followed by antifungal chemotherapy. Nevertheless, outcome is poor and the disease frequently relapses.[3-5] Hence, newer antifungals are being tried.

The incidence of invasive aspergillosis has been increasing over the last several years in view of an increase in the number of patients with immunodeficiency but in cases of immunocompetent individuals the diagnosis may be delayed especially when there are no nasal complaints. Hence, although these cases are rare, the disease carries a high morbidity and mortality.[6] Here we report our experience of thirteen immunocompetent patients with atypical presentations of invasive fungal sinusitis.

## MATERIALS AND METHODS

This prospective study was carried in the department of Otolaryngology, Head and Neck Surgery, Postgraduate Institute of Medical Education Research, Chandigarh from January, 2000 to June, 2008 wherein all the cases with a final diagnosis of invasive aspergillosis involving paranasal sinuses and/or orbit without any nasal complaints were enrolled. These cases were evaluated for immunocompetence using total leukocyte count (TLC), Nitrozolium blue, blood sugar, HIV serology, HBsAg and other viral markers for hepatitis B and C, serum immunoglobulin levels, CD4 and CD8 counts. The cases that were found to be immuno-compromised were excluded from the study. These cases were analyzed for clinical profile; radiological extent of the disease using contrast enhanced computed tomography (CECT) or magnetic resonance imaging (MRI). All theses cases underwent debridement of the disease endoscopically endonasally. The cases which had sphenoid sinus involvement or had intracranial extension of the disease were

started on intravenous Amphotericin B formulation with a dose of 1 mg/kg/day and a cumulative dose of 2.5 gm was given. It was followed by Itraconazole in a dose of 10 mg/kg/day for a period of 6 months. The cases with no intracranial extension, cases that refused for intravenous Amphotericin B therapy and cases with no involvement of sphenoid sinus were started on oral Voriconazole in a dose of 7.5 mg/kg/day for a period of 6-12 months. The cases that had no improvement with Amphotericin B or had shown poor response to Itraconazole after 3 months of therapy were also given Voriconazole in the same dosage. Regular monitoring RFT (Renal Function Test) and serum electrolytes was ensured for the cases receiving Amphotericin B. Hepatic profile was regularly monitored during azole therapy. The cases were followed up by symptomatology, radiology at 6 monthly interval for first year and then at yearly interval for next 2 years and fungal serology at the time of radiology.

## RESULTS

A total of 13 cases were included in this study. The average age was 30.5 years (range 10-46 years). There were ten males (76.92%) and 3 females (23.08%) in our study. There were 10 cases (76.92%) presenting with headache which was temporal in 5, retro-orbital and frontal in 2 cases each and diffuse in 3 patients. Fundus examination showed papilloedema in 4 patients and all of these had diminished vision. In rest of the cases fundus examination was normal. All these cases had isolated sphenoid sinus involvement on radiology with erosion of the lateral wall. There were two cases that presented with cheek swelling and these had isolated maxillary sinus involvement with erosion of the anterolateral wall of the maxilla with the lesion extending onto cheek. There was one patient that presented with proptosis with no visual symptoms and had radiological lesion seen intraconally in the orbit just reaching the orbital apex. This case underwent lateral orbitotomy and biopsy and was given Voriconazole as he refused for Amphotericin B. The clinical presentations have been summarized in Figure 1. The radiological findings have been summarized in Table 1.

During endoscopic clearance, we encountered grayish white, soft to firm cheesy material in the sinuses. In cases of sphenoid sinus involvement there was associated destruction of the lateral wall (Fig. 2) while the maxillary sinus disease destroyed the anterior wall to present in the cheek. Debridement was done in all cases of sinus involvement to achieve proper ventilation. The histopathological examination of the fungus debris showed 45° branching septate hyphae with mucosal invasion and

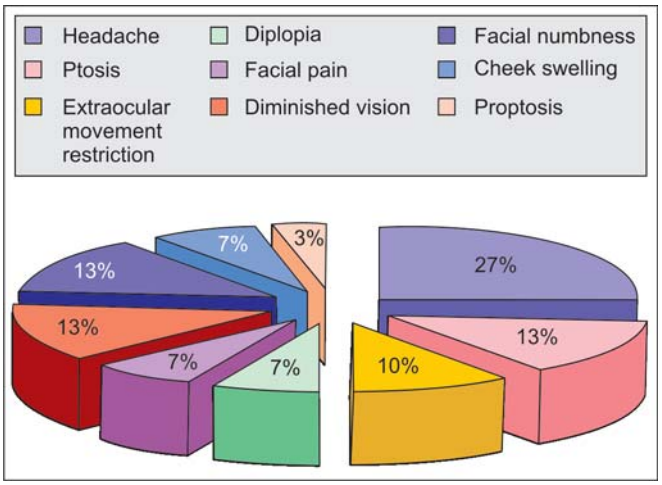



**Figure 1:** Clinical presentation of the patients

**Table 1:** Radiological findings

| *Radiological findings* | *No of patients* |
|---|---|
| Isolated sphenoid sinus involvement | 10 (76.92%) |
| Isolated maxillary sinus involvement | 2 (15.38%) |
| Isolated orbital involvement | 1(7.69%) |

the presence of giant cell granulomas. In cases of sphenoid sinus involvement, 7 of these responded to Amphotericin B and Itraconazole but two had to be given voriconazole and they responded to it. One patient died due to intracranial complications during the third week of therapy. Autopsy revealed angioinvasive pathology. Reversal of ptosis was seen as the first sign of improvement, which was followed by disappearance of headache. Extraocular muscle affections

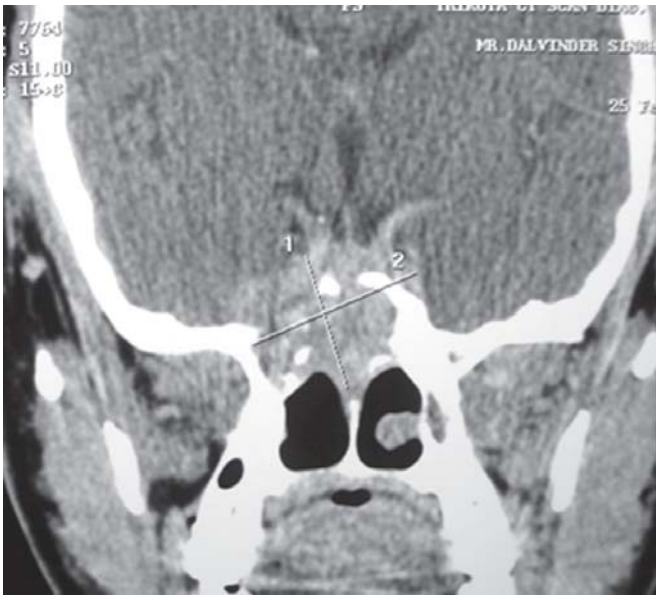



**Figure 2:** Preoperative CT scan showing involvement of sphenoid sinus with parasellar extension secondary to erosion of lateral wall of sphenoid sinus

in the form of diplopia and muscle palsies improved gradually. All the cases having diminished vision had significant improvement in vision following therapy. Maxillary sinus involvement was treated with Voriconazole alone and both the cases showed improvement by gradually decreasing cheek swelling and gradual improvement in facial numbness (Figs 3 and 4). The lone case with isolated orbital involvement refused for Amphotericin B and showed improvement of proptosis after four months of therapy with voriconazole that was continued for 6 months (Figs 5 and 6).

All these cases had four fold decrease in serum values of fungal serology during the course of treatment. Our protocol was successful in 11 (84.61%) cases excluding one, which was lost to follow-up. They are now free of disease for a period ranging from 12 to 96 months and are on regular follow-up. For the cases on Amphotericin B, renal profile was maintained during the therapy by adequate hydration and dyselectronemia was prevented by regular monitoring and timely correction of electrolytes. During the course of treatment with itraconazole the hepatic profile in some patients was found to be temporarily deranged but not to an extent where we had to discontinue the therapy. Patients on Voriconazole tolerated the therapy well without any major side effects.

## DISCUSSION

Aspergillosis of the paranasal sinus can either be noninvasive or invasive. Invasive disease has been further categorized as localized or fulminant.[7] Localized disease spreads to adjacent structures by focal bony erosions.[6,7] Fulminant aspergillosis of the paranasal sinuses represents an important cause of morbidity and mortality in patients in who defense system has been altered by primary disease or immunosuppressive therapy. But the pattern of involvement by this fungus is changing. There are reports of invasive paranasal sinus aspergillosis in an immunocompetent host.[6,8,9]

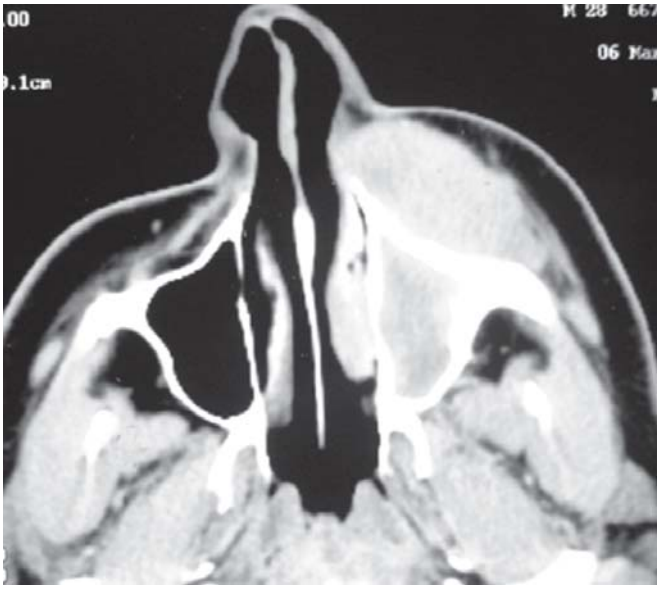


**Figure 3:** Preoperative CT scan showing involvement of maxillary sinus with subcutaneous involvement secondary to erosion of anterior wall of maxilla

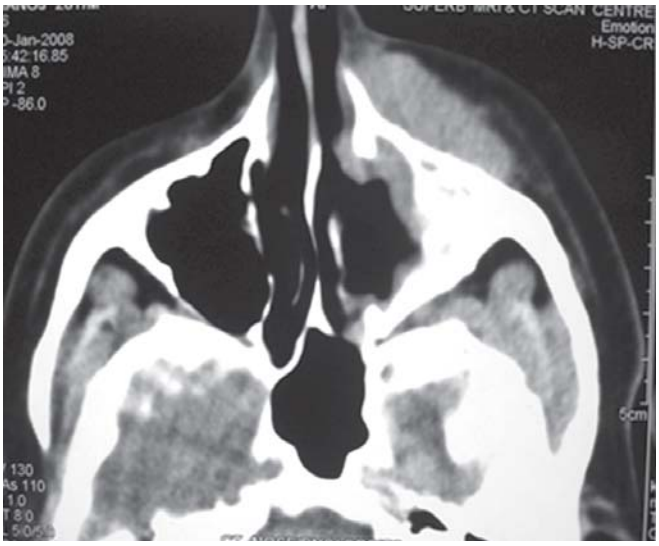
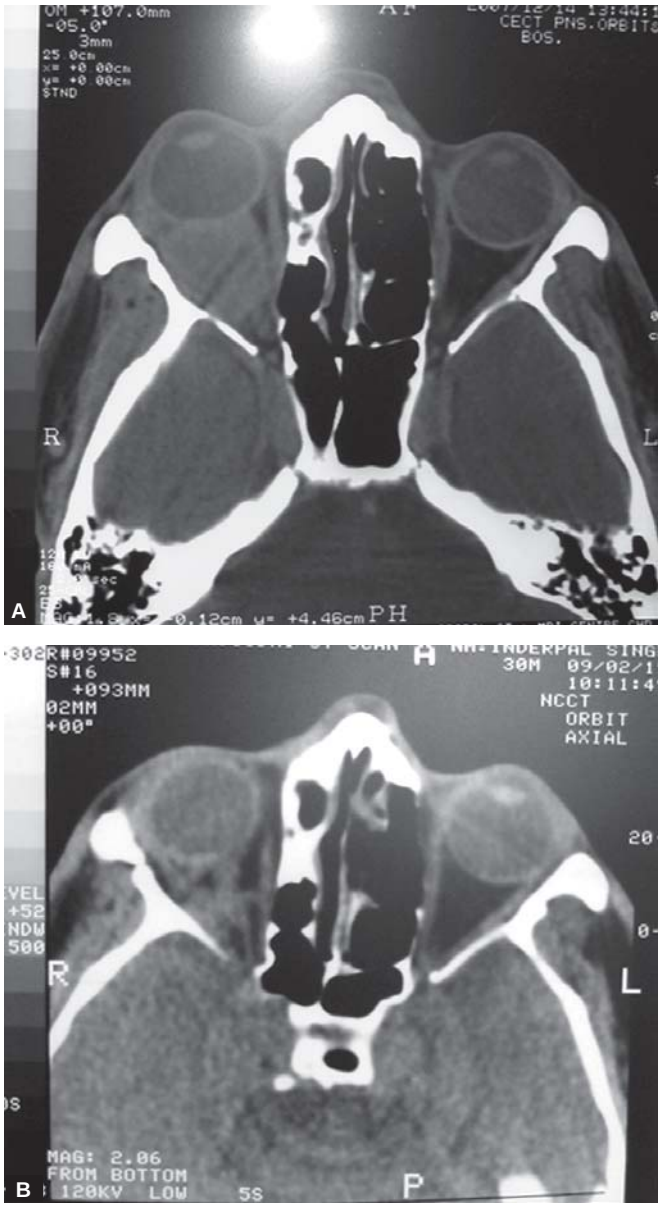


**Figure 4:** Postoperative CT scan at 1 month showing clear maxillary sinus with persistent subcutaneous disease

Although in these patients, invasive aspergillosis has an indolent course but delay in the diagnosis can be fatal especially in cases of sphenoid sinus involvement due to early intraparenchymal spread.[7] In our series, one case succumbed to the disease process due to extensive intracranial extension.

Isolated involvement of the sinuses is rare and when the patient does not present with any sinonasal symptoms it becomes a diagnostic dilemma for the clinician. Almost 80% of the cases in our series had sphenoid sinus involvement. There have been cases of isolated sphenoid sinus involvement in the literature.[10,11] The predilection for the sphenoid sinus is poorly understood but it has been proposed that infection occurs when the drainage of the sinus is impaired leading to a low oxygen tension environment or it could be due to a difference in the local metabolic environment of the sphenoid sinus.[12] Two of our cases presented only with a cheek swelling and were diagnosed as invasive aspergillosis only after endoscopic clearance and histopathological examination of the tissue.

This presence of isolated involvement of the maxillary sinus in two of our cases and the orbit in one case probably refutes the latter theory. Isolated involvement of the maxillary sinus by this entity has not been reported.




**Figures 5 A and B:** Pre- and post-treatment scans of intraorbital intraconal invasive aspergillosis

The presentation in our patients was atypical as they were immunocompetent and had no nasal symptoms suggestive of sino-aspergillosis. They had headache, diplopia, inability to move the eyeball, diminution of vision and two presented with only swelling in the cheek while one presented with orbital swelling alone which in absence of nasal symptoms was quite unlikely for aspergillosis.

The optimal treatment for invasive aspergillosis is yet to be defined. With the advent of newer diagnostic techniques, improvement in imaging modalities and development of new antifungals the options for the diagnosis and management of these patients have evolved over the years. Surgical debridement and medication with systemic Amphotericin B in combination with azoles has been accepted as the standard therapy.[13,14]

Effective surgical treatment requires adequate debridement of the devitalized tissues to ensure adequate aeration of the sinuses and create an aerobic environment which is not conducive for the growth of aspergillosis. Removal of the disease also helps in better penetration of the bloodstream by the antifungal agents.[9] In our series of cases, it was done endoscopically in all the cases except in one cases of isolated orbital aspergillosis in which lateral orbitotomy was done to take the tissue for histopathological diagnosis.

Combination antifungal therapy has been of interest because of the poor outcomes associated with treatment with either azole antifungals or Amphotericin B formulations alone. Itraconazole has good *in vitro* and *in vivo* activity against aspergillosis species and some clinical trials compare its efficacy to Amphotericin B. Combinations of Itraconazole and Amphotericin B concomitantly have been used though there is evidence of *in vitro* antagonism in some of the studies.[15-17]

Kieren et al showed that the combination of Voriconazole and caspofungin was associated with better outcomes, compared with Voriconazole administered alone, for patients receiving salvage therapy to treat aspergillosis.[18] However in our study all the five patients receiving Voriconazole had excellent results. Studies show Voriconazole to be the most effective drug currently available for the treatment of invasive aspergillosis and that should be used in place of Amphotericin B if there are no contraindications to its use.[19] Voriconazole (UK-109,496) 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.[20] The drug is fungicidal *in vitro* for a majority of isolates. The drug can also be given orally and intravenously, making switch therapy easier. Treatment with voriconazole does carry some risk of toxicity.[21] In most patients, this is trivial or nonexistent. Temporary visual disturbances, skin rash, and abnormal liver function are most frequent but were usually of little consequence. Some patients receiving intravenous Voriconazole may develop adverse effects (e.g. hypoglycemia, electrolyte disturbance and possibly, confusion and pneumonitis) without any remarkable abnormal alterations in liver-function test values. These events have been associated with higher concentrations of the drug. Hence, caution is required in the use of larger doses, because plasma concentrations increase disproportionately, relative to dose increases.

In cases of orbital involvement, the extent of debridement becomes controversial. Although some authors recommend orbital exenteration to achieve surgical margins,[22] others note that vision-sparing orbital debridement is adequate[23,24] for cure, especially when supplemented with antifungal agents. In our cases we treated the orbital involvement conservatively and did not resort to orbital exenteration in view of normal vision and no features of extraocular muscle involvement.

## CONCLUSION

The study highlights few points:

- The clinician should have a high clinical index of suspicion to suspect and diagnose such entity especially in immunocompetent individuals that too with atypical presentation.
- The need of aggressive management of the cases that have disease in close proximity to the intracranial structures to achieve best results.
- Voriconazole alone can treat cases of invasive aspergillosis even for cases that showed poor response to amphotericin.

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