Invasive fungal rhinosinusitis in patients with diabetes

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Abstract
Introduction: We report the clinical and radiological features as well as outcomes of invasive fungal rhinosinusitis in patients with diabetes from a tertiary care center in North India.

Methodology: All patients admitted with a diagnosis of invasive fungal rhinosinusitis with pre-existing or newly diagnosed diabetes from 1st January 2008 to 31st December 2015 were included. Hospital records were used to identify clinical features, biochemical investigations and treatment modalities used. The imaging findings were reported at baseline, 30, 60, 90 and 120 days of admission and progression of disease was reported as static, worse or improved. The outcomes were sight loss and survival at end of hospital stay.

Results: 22 patients of invasive fungal sinusitis and diabetes were identified. At presentation, 5 had ketoacidosis, all of whom died at the end of hospital stay. Loss of vision in one eye was seen in 70% cases. The survival at end of hospital stay was 72.7% and at six months after end of study period was 57.8%. No patients had radiological improvement at day 30 imaging (including those who subsequently improved).

Conclusion: Radiological improvement is not apparent before two months of therapy. Ketoacidosis is a predictor of mortality in invasive fungal sinusitis with diabetes.

Key words: invasive fungal rhinosinusitis; diabetes; liposomal amphotericin B; mucormycosis.


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Introduction
Fungal rhinosinusitis refers to the infection of nasal cavity and paranasal sinuses by pathogenic fungi. Fungal rhinosinusitis is classified into invasive fungal sinusitis (characterized by histological evidence of tissue invasion) and non-invasive (saprophytic fungal infestation, fungal ball and fungus-related eosinophilic sinusitis). Invasive fungal rhinosinusitis is a rare but life-threatening infection typically affecting immunocompromised hosts. Despite the sharp rise in the incidence of invasive fungal rhinosinusitis in patients on immunosuppressive therapies, the most common risk factor for this infection continues to be diabetes. The literature on diabetes and invasive fungal rhinosinusitis is scarce and most of data is regarding patients with hematological malignancies and solid organ transplant. However, poorly controlled diabetes in developing countries continues to predispose patients to invasive fungal rhinosinusitis. In view of the paucity of literature, there is difficulty in planning and monitoring treatment of these patients. We report presentation, management and outcome of 22 cases of invasive fungal rhinosinusitis from a tertiary care center in North India with an emphasis on the radiological changes seen in response to treatment.

Methodology
This study was carried out in the Endocrinology Department of tertiary care hospital in North India. The inclusion criteria were diabetes mellitus (type 1 as well as type 2 diabetes) with clinical features suggestive of invasive fungal rhinosinusitis with either histological evidence, positive fungal staining (KOH mount) or fungal culture. The patients with history of glucocorticoid therapy within 6 months of onset of symptoms, immunosuppression due to either chemotherapeutic agents or HIV infections, active malignancy, solid organ or bone marrow transplantation and deferoxamine therapy were excluded from the study. The hospital records were retrieved and searched to identify cases of invasive rhinosinusitis with diabetes admitted in Endocrinology Department.
and Metabolism ward from 2008 to 1\(^{st}\) January 2015. Patients admitted between January 2015 and December 2015 were prospectively studied after obtaining informed consent. Study protocol was approved by the institute ethics committee. Thus, this is an ambispective study and patients were recruited both retrospectively and prospectively.

Medical records were used to identify clinical characteristics including type of diabetes, duration of diabetes, status of glycemic control, presence of ketoacidosis at time of presentation, presenting symptoms, duration between onset of symptoms and starting therapy. Diabetic ketoacidosis was defined as the presence of blood glucose more than 250 mg/dl with serum pH < 7.35 or serum bicarbonate < 18 meq/L in the presence of positive moderate to large urine ketones (by dipstick test). Radiological findings from computed tomography and/or magnetic resonance imaging of paranasal sinuses and head were recorded. The imaging findings were reported at baseline, 30, 60, 90 and 120 days. The day 30 represents imaging findings of any radiological study done between 2-6 weeks of admission. Day 60 represents study done between 6-9 weeks, day 90 represents study done at 9-12 weeks and day 120 represents after 12 weeks. Disease was staged at these intervals as sinonasal, orbital or intracranial. Sinonasal disease was defined as radiological evidence of involvement of sinuses and nasal cavity without any orbital or intracranial extension. Orbital disease was defined as radiological evidence of orbital invasion without any intracranial extension. Intracranial disease was defined as radiological evidence of intracranial extension of sinonasal or orbital disease.

The progression of disease was also studied at day 30, 60 and 90 and reported as static, worse or improved.

Table 1. Baseline characteristics of the patients (n = 22).

<table>
<thead>
<tr>
<th>Age (yrs) (^a)</th>
<th>44.1 ± 13.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (^b)</td>
<td>12 (54.5%)</td>
</tr>
<tr>
<td>Female (^b)</td>
<td>10 (45.5%)</td>
</tr>
<tr>
<td>Type 2 DM (^b)</td>
<td>19 (86.4%)</td>
</tr>
<tr>
<td>Type 1 DM (^b)</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>Duration of diabetes (yrs) (^a)</td>
<td>4.40 ± 5.06</td>
</tr>
<tr>
<td>Diabetic retinopathy (^b)</td>
<td>4 (18.1%)</td>
</tr>
<tr>
<td>Diabetic nephropathy (^b)</td>
<td>4 (18.1%)</td>
</tr>
<tr>
<td>Diabetic neuropathy (^b)</td>
<td>2 (9.0%)</td>
</tr>
<tr>
<td>BMI (kg/m(^2)) (^a)</td>
<td>25.86 ± 3.40</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (^b)</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Diabetic ketosis (^b)</td>
<td>4 (18.1%)</td>
</tr>
<tr>
<td>HBAlc (% (^b))</td>
<td>10.9 ± 1.7</td>
</tr>
<tr>
<td>Hemoglobin (gm/dL) (^b)</td>
<td>10.8 ± 1.5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL) (^b)</td>
<td>1.2 ± 1.2</td>
</tr>
<tr>
<td>Serum albumin (gm/dL) (^b)</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

\(^a\) mean ± SD, \(^b\) n (%).

‘Static’ was defined as disease which is similar to the previous imaging (for example, baseline imaging for the day 30 imaging report). ‘Worse’ was defined as evidence of increase in the disease with respect to the previous imaging. ‘Improved’ was defined as reduction of disease as compared to the previous imaging. The criteria used to assess progression were extent of disease, involvement of new areas, abscess formation and contrast enhancement.

Reports of histopathological examinations, fungal staining and fungal culture, details of therapy including type and dose of antifungal agents along with surgical procedures for control of infection were also recorded.

The outcomes of the study were assessed as visual loss, death at end of hospital stay or death till the last follow up of the patient. The time of last follow up was 6 months after the end of recruitment period. The patients were followed up by OPD visits or phone calls after discharge.

The patient characteristics were reported as mean with standard deviation or median and range wherever appropriate. After obtaining the data, factors associated with mortality or poor response to treatment was studied using appropriate statistical tests. For the purposes of determining impact on survival/death, the association of various risk factors with death were studied using Fisher’s exact test for proportions. The continuous variables were compared between the survivors and expired patients using Mann Whitney’s U test. A p value < 0.05 was considered significant.

**Results**

A total of 22 patients of invasive fungal sinusitis and diabetes were identified. Out of the 22 patients, ten (45.5%) were females and 12 (54.5%) were males. The mean age of the subjects was 44.1 ± 13.9 years while median age was 45 years (range 16-73 years). Three patients (13.6%) had type 1 diabetes while 19 (86.4%) had type 2 diabetes mellitus. Invasive fungal sinusitis was the diabetes defining illness in five patients (23%). The duration of diabetes ranged of 0-16 years with a median duration of 2.0 years. Pre-existing microvascular complications were present in the form of retinopathy in four cases (moderate non proliferative retinopathy in two cases, mild non proliferative diabetic retinopathy in one and proliferative diabetic retinopathy in one case), diabetic nephropathy in four patients (chronic kidney disease stage 3 in three and chronic kidney disease stage 5 in one case) and diabetic peripheral sensory neuropathy in two patients. None of the cases had history of macrovascular complications including coronary artery disease, cerebrovascular
disease or peripheral arterial disease. The mean BMI was $25.86 \pm 3.4$ kg/m$^2$. Five patients (22.7%) had diabetic ketoacidosis at presentation while diabetic ketosis was present in another four cases (18.1%). (Table 1)

Facial pain and swelling was the most common presentation (71.4%), followed by loss of vision (68.2%), periorbital swelling and proptosis (63.6%). The time lag between onset of symptoms and start of antifungal therapy varied from three days to 94 days with a mean of 25.0 ± 24.1 days.

Computed tomography of the paranasal sinuses was the initial investigation in 19 patients. MRI of the paranasal sinuses was performed as the initial investigation in three patients. At presentation, the most commonly involved sinuses were maxillary (86.4%) and ethmoid (77.3%). The frontal sinus was involved in five (22.7%) and sphenoid sinus in three (13.6%) patients. The radiological extent of disease is shown in Figure 1. Eleven patients (50.0%) had orbital disease at baseline while four (18.2%) patients had evidence of intracranial disease at baseline. Of the 7 patients who had only sinonasal disease at baseline, two progressed to orbital disease (one case at day 30 imaging and one case at day 60 imaging). Of the 11 cases with orbital extension at baseline, six developed intracranial disease during follow up. Intracranial abscess and palatal necrosis developed in four cases each during the hospital stay. The radiological progression of disease is shown in Figure 2. The disease progression was evaluable in 17 cases at day 30 (four patients had expired before day 30 imaging and no imaging was done in this period in one case). The disease was static in 11 cases while it worsened in 6 cases. None of the cases had improvement at day 30. At day 60, the progression was evaluable in 16 cases (no imaging available in one case). Three cases had worsening, disease was static in nine cases and four cases had improved. At day 90, the progression was evaluable in 11 cases (no imaging available in five cases). Ten cases had improved and one case worsened. Figure 3 shows serial imaging with progressive worsening of the disease in one of the patients while Figure 4 depicts the progressive improvement in another case.

Mucormycosis was diagnosed by positive histology and KOH mount in 11 cases, histology alone in three cases and KOH alone in eight cases. Rhizopus was grown on culture in four cases with Rhizopus microsporus being the species in three cases. Aspergillus flavus was grown in one case.

The duration of hospital stay ranged from 3 days to 153 days with a median of 70 days. Thirteen patients received conventional amphotericin deoxycholate alone while nine patients received liposomal amphotericin B (six received liposomal amphotericin B alone while three received liposomal amphotericin B along with intermittent use of conventional amphotericin B whenever the supply of liposomal amphotericin B was interrupted). The daily doses of liposomal amphotericin B ranged from 2-5 mg/kg body weight while that of conventional amphotericin B was 0.5 to 1.0 mg/kg bodyweight. Cumulative doses of liposomal amphotericin B ranged from 0.1 gm to 16.6 gm while cumulative doses of conventional amphotericin B ranged from 0.1 to 3.0 gm. Posaconazole was used as a stepdown therapy in a daily dose of 800 mg in 3 cases for duration of 8-12 weeks. Voriconazole was used as step down therapy in a dose

Figure 1. Radiological disease extent.

![Figure 1](image1)

Figure 2. Radiological disease progression.

![Figure 2](image2)
of 400mg daily for 6 weeks in one case that grew *Aspergillus flavus*.

Surgical debridement was done in 19 cases. Endoscopic debridement of sinuses was done in 19 cases. Orbital exenteration was performed in 9 cases while neurosurgical intervention for intracranial disease (burr hole drainage of abscess) was done in 2 cases. Multiple debridements were needed in 5 cases. The first surgical procedure was done after a gap of 1 to 60 days after admission with a median gap of 8.5 days.

Six patients died during their hospitalization while two succumbed after discharge (one 9 months after discharge and one 12 months after discharge). Follow up information was not available for three patients. At the end of hospital stay, 72.7% had survived and loss of vision in one eye was seen in 70% cases. At last follow up (six months after study period), the survival was 57.8%. The time lag between the onset of symptoms in the four patients who died at the end of hospital stay was 4, 7, 8, 14 and 24 days. Loss of vision in the affected eye after completion of treatment was present in 14 patients (70%). All these also had loss of vision at presentation. This was due to extensive orbital disease requiring exenteration in 10 cases, orbital apex syndrome in 3 cases and conservatively treated endophthalmitis in 1 case. No other focal neurological deficit was present in any patients at discharge or last follow up. Duration of follow up ranged from 9 months to 7 years with a median duration of 2 years in 11 patients who were alive till last follow up.

Possible factors associated with mortality were studied using Fisher’s exact test or Mann Whitney’s U
Diabetic ketoacidosis was significantly associated with death at end of hospital stay \((p = 0.001)\). All the five patients who had diabetic ketoacidosis at baseline expired. Baseline intracranial disease and lower hemoglobin at baseline were associated with death at end of hospital stay \((p = 0.01\) for each). Time lag was associated with death with a median time lag of 22.5 days in the patients who survived at end of hospital stay and 8.5 days in those who died at end of hospital stay with \(p\) value approaching statistical significance \((p = 0.051)\). Presence of retinopathy, nephropathy, neuropathy, proptosis and loss of vision were not associated with death. Baseline orbital involvement and serum albumin were not significantly associated with death \((p = 0.26\) and \(p = 0.50\) respectively). The survival in patients treated with conventional amphotericin B was 69.2\% while among those treated with liposomal amphotericin B, the survival was 71.4\% \((p = 1.00)\).

**Discussion**

Invasive fungal rhinosinusitis is an uncommon infection typically caused by Zygomycetes (Mucor, Rhizopus, Rhizomucor) and Aspergillus species. These infections have been reported more commonly in patients with immunosuppression in relation to solid organ transplantation or haematological malignancies. However, patients with diabetes are also susceptible to this infection. The available literature on invasive fungal sinusitis is mainly in the form of small case series and case reports. In reviews on invasive fungal sinusitis, it was found that 47.8-60\% patients were having diabetes [1,2]. The largest case series of diabetes with rhino-orbito-cerebral mucormycosis is from another tertiary care center in India [3].

The presence of diabetic ketoacidosis is a known risk factor for invasive fungal sinusitis. The reduced affinity of transferrin for iron and conversion of ferric iron to ferrous form by the enzyme ketone reductase in presence of metabolic acidosis increases availability of free iron promoting growth of fungi. Angioinvasion, a hallmark of mucormycosis, is mediated by glucose regulated protein 78 (GRP78), which is expressed on vascular endothelial cells and serves as a receptor that promotes the ability of Mucorales to invade endothelial cells lining blood vessels. Elevated concentrations of glucose and iron, consistent with those seen during diabetic ketoacidosis, enhance GRP78 expression and resulting invasion and damage of endothelial cells in a receptor-dependent manner [4]. The percentage of patients with ketoacidosis at presentation varies from 14.2\% to 23.1\% [1,3]. Therefore, factors other than ketoacidosis are also involved in the pathogenesis [2]. Despite its role in the infection, ketoacidosis has not been shown to be a negative prognostic factor in most studies [1-3]. However, in a case series, three out of eleven cases died. All the three deaths were associated with diabetic ketoacidosis and death occurred within one month of admission [5]. This pattern is similar to what we observed in our study.

The presenting symptoms commonly seen are facial swelling, proptosis, ophthalmoplegia, loss of vision, and facial pain. The percentage of loss of vision in other studies is reported to be ranging from 49.8-80\% [1-3]. Our study had loss of vision in 68\% cases. Maxillary and ethmoid sinuses are reported to be the most commonly involved sinuses at presentation which is similar to the pattern in our study [3,5]. In our study, 50\% patients had baseline orbital extension while this varied from 52 to 80\% in other studies [3,6]. We found a higher percentage of patients with intracranial extension both at baseline (18.2\%) as well as overall (45.2\%) compared to other series where it varied from 8 to 20\% [2,3]. It is possible that the repeated imaging done in our study enabled us to identify more patients with intracranial spread of the disease even in patients showing clinical improvement. Mortality rate in our study was not markedly different from these studies suggesting that the intracranial extension occurred early in the course of disease but responded to therapy and radiological evidence appeared later on in the serial imaging.

Another interesting finding came from the assessment of the progression of the disease radiologically. None of the patients had any evidence of radiological improvement in imaging done at day 30 (between 3-6 weeks of admission) while only 25\% showed radiological improvement at day 60 (6-9 weeks of admission). At day 90 (9-12 weeks), 90\% of the cases had improvement. It can be argued that this improvement is because of a survival bias as only those who improved, survived till day 90 imaging. However, four of the six deaths that occurred during the hospital stay, had happened prior to the day 30 imaging. Therefore, it seems that radiological improvement is apparent only after 2-3 months of therapy and hence is not a useful marker of response to treatment. However, asymptomatic intracranial extension in the day 30 imaging was noted in two cases, one out of which required neurosurgical intervention. Thus, it is unlikely to see radiological improvement in initial 2 months of therapy but repeated imaging can detect asymptomatic intracranial extension at that time. Advanced age and intracranial extension are significant negative prognostic factors after multivariate analysis [1,3].
In our study, intracranial extension was approaching statistical significance while presence of orbital disease at baseline and day 30 had no association with death.

There is limited data comparing response to liposomal and conventional amphotericin B in invasive fungal rhinosinusitis. A review of 929 cases of zygomycosis did not find a significantly better survival with liposomal amphotericin B (69% vs 61%,) although all the patients were not having rhinosinusitis [7]. Similarly, a survival of greater than 60% with liposomal formulations of amphotericin B compared to less than 50% for amphotericin B deoxycholate was noticed in another review but this difference was not significant in the multivariate model [1]. However, better survival with liposomal amphotericin B as compared to conventional amphotericin B has been reported in patients with mucormycosis and haematological malignancies (67% vs 39%, p = 0.02) [8]. In our study, survival was not significantly better in patients treated with liposomal amphotericin B (71.4%) compared to conventional amphotericin B (69.2%) (p = 1.0). The cumulative dose of liposomal amphotericin B is variable and depends upon the time taken to achieve radiological and clinical response [9]. However, as high as 32 grams of liposomal amphotericin B has been used in one case [10]. The overall mortality varies from 32% to 49.7% [1,3].

The delay in start of treatment has been associated with mortality. Patients with lag time of seven to 12 days had a survival of 63% while those with a lag time of 13 to 30 days had a survival of 44% [2]. Similarly, another study reported that three to nine days lag led to a survival of 85% while those with lag time of 10 to 45 days had survival of 55% only [3]. Paradoxically, we found a shorter delay to be associated with death at end of hospital stay (median delay of 8.5 days in those who died versus a delay of 22.5 days in those who survived; p = 0.05). The survival was 50% in those with time lag of one to nine days while it was 83% in those with a lag of more than 10 days. This paradox in our study probably represents a heterogeneity in the presentation of the disease. Patients with a more aggressive disease had a rapid evolution of symptoms and and therefore sought medical attention earlier. These cases, therefore, had a shorter time lag than other patients who had a more indolent disease course. The more aggressive disease in such patients lead to a higher mortality. Two of the patients who died had presented with aggressive disease, probably due to accompanying ketoacidosis and both succumbed before surgical debridement could be performed or antifungal therapy could take effect. The presence of diabetic ketoacidosis in all the in-hospital deaths might have transformed the disease into a more aggressive form. This reflects that the disease behaves variably in different patients, either because of variation in the virulence of the causative organism or the presence of associated factors such as diabetic ketoacidosis and hence these with risk factors should be treated aggressively. However, the mortality rates in invasive fungal sinusitis with diabetes is lower than that seen with other immunosuppressed states like hematological malignancies and solid organ transplant. This is probably due to the fact that poor glycemic control is a potentially reversible risk factor [11]. The unique points raised by our study include the delay in radiological improvement upto 2 months after start of therapy and the association of diabetic ketoacidosis with death.

Conclusion
Invasive fungal sinusitis continues to be a disease with a high mortality despite the use of liposomal amphotericin B as well as surgical treatment. The presence of ketoacidosis at presentation is associated with mortality. Repeated imaging can aid in detecting intracranial extension early. However radiological improvement is delayed even in those patients who eventually survive. The emphasis should be on clinical response in initial two months, subsequently radiological imaging can guide therapy. Until more effective treatment modalities emerge, a better understanding of this rare disease may enable physicians to reduce the mortality.

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