Acute Invasive Fungal Rhinosinusitis: Survival Outcomes Related to Predefined Parameters as Variables

ABSTRACT
The aim of this study was to determine outcomes and identify factors that may affect survival in patients with acute invasive fungal rhinosinusitis (AIFRS). Thirty patients of AIFRS were identified. The underlying reasons for immunosuppression were diabetes mellitus (19 patients), chronic renal failure (5 patients), leukemia (3 patients), acquired immunodeficiency syndrome (2 patients) and post organ transplant (1 patient).

We have found the overall survival rate directly related to AIFRS to be 56.7%. The survival rate is higher for young patients (below 50 years age group), diabetic patients than aspergillosis and those treated with liposomal Amphotericin B as compared to conventional form in addition to surgical debridements. Intracranial and orbital involvement and failure to recover are the factors that led to poor prognosis in this series.

KEYWORDS acute invasive fungal rhinosinusitis, absolute neutrophil count, mucormycosis, aspergillosis

INTRODUCTION
Inhalation is the mode of entry of various funguses present in the environment. Most healthy people do not react to the presence of fungus due to a functioning immune system. Plaignaud first reported on fungal sinusitis in 1791. Fungal sinusitis has included noninvasive and invasive fungal sinusitis. Invasive fungal sinusitis can be divided further by de Shazo as acute, granulomatous and chronic. Acute invasive fungal rhinosinusitis (AIFRS) is also called fulminant or rapidly invasive fungal rhinosinusitis. It is a serious disease with a high mortality and morbidity rate. AIFS is characterised by a mycotic infiltration of the mucous membrane of the nasal cavity and/or paranasal sinuses. It occurs in immunocompromised patients like type I diabetes mellitus, chronic renal failure and immunosuppressive states secondary to chemotherapy, hematologic disorders, transplantation and acquired immunodeficiency syndrome (AIDS) as a result of functional leukopenia, most importantly neutropenia, there are rare documented cases in the literature of AIFRS in otherwise healthy individuals also.

The initial symptoms are often subtle, even in at risk patients. Fever of unknown origin or rhinorrhoea are the most common first symptoms. More extensive disease may present with visual complaints – proptosis, ophthalmoplegia and focal neurological deficits.

AIFRS presents a complicated diagnostic and therapeutic challenge. In immunocompromised patients with unilateral symptoms, nasal endoscopy is essential, and pale or ischemic mucosae are characteristic of this entity. Meticulous nasal endoscopy is the crux of the diagnosis to identify discoloration (often a black necrotic turbinate), granulation, ulceration or crusts in the nose.

For assessing the extent of disease, radiographic evaluation has to be done with CT and MRI. CT better defines soft tissue invasion, necrosis and early bone erosion. MRI best evaluates early changes in major vessels, including carotid artery thrombosis, cavernous sinus thrombosis and intracranial extension.

The current management strategy of AIFRS requires reversal of the underlying predisposing condition, appropriate systemic antifungal therapy and surgical debridement.

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The present study shows the survival outcomes of 30
cases with AIFRS in relation to different variables including
age, sex, underlying cause of immunosuppression, causative organism, extent of spread and modality of treatment used etc.

MATERIALS AND METHODS
This study was carried out at the Department of ENT at a
tertiary care academic hospital for 3 years from 2008 to 2010. The study was done on diagnosed immunocompromised patients with AIFRS including all age groups and both sexes. All immunocompromised patients pre-
senting in the OPD with complaints of fever of unknown origin and unilateral nasal problem were suspected for AIFRS. In all these suspected cases a diagnostic nasal endoscopy was performed and simultaneously biopsy from the nasal mass or mucosa done and sent imme-
diately for histopathological evaluation. The confirmed
cases of AIFRS were included in the study. The following inclusion criteria were used while selecting the cases:

1. A histopathological diagnosis of invasive fungal sinusitis from surgical specimen or biopsy.
2. Evidence of nasal mucosal ischemia or necrosis by endoscopy or sinus destruction by radiographic studies along with a positive nasal or sinus fungal culture.
3. The underlying diagnosed medical comorbid state like diabetes mellitus, chronic renal failure, leukemia, AIDS and post organ transplantation cases on immunosuppressant medications.

The mycological diagnosis was established and the
assessment of immunological status based on absolute neutrophil count (ANC) was done. These cases were
further monitored and evaluated for the assessment of extension, response to treatment and probable outcome with repeated nasal endoscopies, CT scan and MRI of paranasal sinus. All patients underwent combination of aggressive surgical debridement and systemic antifungal therapy in addition to the correction of underlying compromised immunological status. In our set up defined protocol for management of AIFS has been followed. The patients with bilateral extensive polyposis invariably show thick mucus lodged in the sinus cavities. These tests are positive for fungus in the mucus but negative in mucosal biopsy and are hence termed ‘noninvasive’. The aggressive surgical clearance of this mucus at the time of surgery, along with postoperative systemic ste-
roids and topical steroid sprays reduces the rate of recur-
rence. All the diseased mucosa needs to be addressed
and the endpoint of endoscopic clearance of disease

should demonstrate the maxillary, sphenoidal and fron-
tal ostia to be widely exposed to the empty ethmoid cavity, with the middle turbinate medially, skull base posteriorly and the lamina papyracea laterally. If required one
should not hesitate to correct a septal deviation to enable
good visibility and easy access to all areas. The same surgi-
cal protocol is to be followed for fungal ball/mycetoma. Surgery for invasive fungal sinusitis (mucormycosis)
is radical, and the end stage of disease is until bleeding
occurs from the dissected area indicating normal tissue has been reached. However, repeated debridements are done as and when required depending on the patient’s
clinical improvement, in combination with Amphotericin B. To improve the outcome of the therapy in inva-
sive fungal rhinosinusitis, we follow a comprehensive approach involving the ENT surgeon, ophthalmologist, endocrinologist, neurophysician, intensive care unit and oculoplastic surgeon with a neurosurgeon; all treating the same patient in the different stages of the disease.

All patients were kept on follow up with peri-
odic endoscopic examination. The clinical parameters
included for study were demographic information, pre-
senting signs and symptoms, extent of disease, under-
lying medical illness, causative organism, medical and surgical treatment and was subsequently analysed for survival outcome.

OBSERVATIONS AND RESULTS
The study included 30 patients of AIFS; only 17 patients
survived depicting overall survival rate of 56.7%. The percentage survival rate of each predefined parameter under study is recorded in Table 1.

The age of the patients ranged from 25 years to 75
years. Mean age was 45.5 years. Out of total 30 patients, 20 were less than 50 years of age and 10 were more
than 50 years. Survival rate was 70% for patients below 50 years of age as compared to 30% of age above 50
years (chi-square value = 0.822, P < 0.05). Among 30 patients 19 were male and 11 were female i.e. M: F ratio was 1.73. There was no significant difference in the sur-
vival outcome in case of AIFS among the two sexes.

All selected 30 patients of AIFS were suffering from
some underlying comorbid illness. Out of 30 patients, 19 were diabetic, 5 had chronic renal failure, hematolu-
logical malignancies like leukemia in 3 patients, 2 had AIDS and 1 patient was on immunosuppressant therapy following organ transplantation. The survival percentage
was 57.9 in diabetics, 40 in CRF, 33.34 in leukaemias, 50 in AIDS patients and only the patient with post organ transplant died during follow up.

Out of 30 AIFS patients, the disease was limited to
nose and paranasal sinuses in 14 patients (46%), hard
palatal involvement in 8 patients (26.67%), orbital involvement in 7 patients (23.33) and intracranial exten-
sion in 1 patient (3.33%). The rate of survival falls with extension from 71.42% in limited disease to nil with intracranial extension.
The outpatient biopsies in all cases confirmed the fungal invasion to the nasal mucosa. The fungi isolated were of Aspergillus family in 11 patients (36.66%) and Mucoraceae in 19 patients (63.33%). The rate of survival was 36.36% in cases of aspergillosis as compared to 68.42% in mucormycosis (chi-square value = 0.092).

All patients underwent surgical debridement and systemic antifungal therapy. In 6 patients conventional amphotericin B was used whereas liposomal amphotericin B was used in 18 patients in addition to endoscopic surgical debridement; 6 patients underwent orbital exenteration in addition to the surgical debridement including endoscopic debridement of all sites involved, maxillary antrostomy and anterior ethmoidectomy. The percentage survival rate was highest in patients on liposomal amphotericin B in addition to endoscopic surgical debridement as compared to others.

**DISCUSSION**

AIFRS is though an uncommon opportunistic infection it is commonly seen affecting severely immunocompromised individuals. The spores of these fungi are ubiquitous and gain entrance to the human body through inhalation. Immunocompetent individuals mount a macrophage response, which will phagocytose these spores; thus they do not develop the disease. Immunocompromised patients are unable to mount such a response, allowing germination of spores to form hyphae, which eventually result in vascular invasion. It spreads to adjacent structures with destruction of bony boundaries and behaves alike malignancy as described by Hora. Blitzer and Lawson enlisted the common clinical signs of AIFRS as proptosis, facial swelling, palatal ulcer, cranial nerve deficit, stupor and coma in the order of severity. The immediate sequelae of vascular invasion are rapid spread through vascular invasion to central nervous system presenting with toxic, severely ill patient with changes in mental status. Intracranial extension needs urgent hospitalization, immediate surgical intervention and systemic antifungal drugs along with aggressive control of basic cause like diabetes, renal function etc. Mortality has been reported to be as high as 80%.

**Table 1** The data of study sample of 30 (n = 30) cases analysed for the statistical significance of predefined parameters in terms of survival rate.

<table>
<thead>
<tr>
<th>Predefined parameters</th>
<th>Survived (n = 17)</th>
<th>Died (n = 13)</th>
<th>% age survival</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 50 years</td>
<td>14</td>
<td>6</td>
<td>70.00</td>
<td>0.045</td>
</tr>
<tr>
<td>Above 50 years</td>
<td>3</td>
<td>7</td>
<td>30.00</td>
<td>0.209</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>9</td>
<td>52.63</td>
<td>0.421</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>4</td>
<td>63.63</td>
<td>0.421</td>
</tr>
<tr>
<td>Co-morbid illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13</td>
<td>6</td>
<td>57.90</td>
<td>0.092</td>
</tr>
<tr>
<td>Chronic renal failure (CRF)</td>
<td>2</td>
<td>3</td>
<td>40.00</td>
<td>0.36</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>1</td>
<td>2</td>
<td>33.34</td>
<td>0.39</td>
</tr>
<tr>
<td>AIDS</td>
<td>1</td>
<td>1</td>
<td>50.00</td>
<td>0.68</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>0</td>
<td>1</td>
<td>00</td>
<td>NA</td>
</tr>
<tr>
<td>Extension of disease; as detected radiological on CT/MRI &amp; with nasal endoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited to Nose and PNS</td>
<td>10</td>
<td>4</td>
<td>71.42</td>
<td>0.133</td>
</tr>
<tr>
<td>Hard Palate</td>
<td>4</td>
<td>4</td>
<td>50.00</td>
<td>0.48</td>
</tr>
<tr>
<td>Orbit</td>
<td>3</td>
<td>4</td>
<td>42.86</td>
<td>0.33</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0</td>
<td>1</td>
<td>00</td>
<td>NA</td>
</tr>
<tr>
<td>Organism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucor</td>
<td>13</td>
<td>6</td>
<td>68.42</td>
<td>0.092</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>4</td>
<td>7</td>
<td>36.36</td>
<td>0.092</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + Amphotericin B (conventional)</td>
<td>2</td>
<td>4</td>
<td>33.33</td>
<td>0.20</td>
</tr>
<tr>
<td>Surgery + Amphotericin B (liposomal)</td>
<td>14</td>
<td>6</td>
<td>70.00</td>
<td>0.045</td>
</tr>
<tr>
<td>Surgery + Amphotericin B (liposomal) + Orbital Exenteration</td>
<td>1</td>
<td>3</td>
<td>25.00</td>
<td>0.20</td>
</tr>
</tbody>
</table>

The statistical tests used were mean and chi-square test at a 5% level of significance. The ‘p’ value was calculated which denotes the probability that the difference between two samples occurred by chance. The ‘p’ value less than 0.05 is considered to be statistically significant. This indicate that the difference occurred by chance has a probability of 5% or in other words, the examiner can be 95% sure that the difference is not by chance. A ‘p’ value less than 0.01 is termed as highly significant.
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pharmacotherapy received and degree of surgical resection. Their study concluded that only intracranial and/or orbital involvement is predictive of poor outcome and that a significant portion of patients is also significantly higher in patients with mucor. Although the difference in mortality among diabetic patients affected with mucor versus aspergillosis, it was not statistically significant. Blitzer and Lawson found that diabetic patients are more predisposed to fungi from the family Mucoraceae because these organisms thrive in an environment rich in glucose and ketoacids. Invasive Mucormycosis is more likely to be found in patients with diabetes than Aspergillosis, which has a much poorer prognosis and greater morbidity in survivors. More rapid invasion and greater degrees of tissue necrosis require greater surgical debridement. It is in these patients that aggressive resection and attempts to remove all involved tissue are necessary for optimal outcome.

The present study differs from the previous ones in this; outpatient biopsies in all cases confirmed the fungal invasion to the nasal mucosa. The fungi isolated were of Aspergillus family in 11 patients (36.66%) and Mucor in 19 patients (63.33%). The rate of survival was 36.36% in cases of aspergillosis as compared to 68.42% in mucormycosis. (chi-square value = 0.092). Even on being more aggressive and virulent, the higher survival rate of cases of AIFS due to mucormycosis as compared to aspergillosis reflects the role of other factors to be more predicting for mortality and survival rates. These other factors were related to patient’s demographical status like age, socioeconomic status, general physical conditions and status of immunity, severity of underlying condition of immunodeficiency and early diagnosis and treatment resulting in decreased morbidity and mortality due to less spread of the disease to involve intracranial or orbital involvement. Aggressive treatment including surgical debridement, antifungal pharmacotherapy and correction of underlying cause of immune compromise are thought to be essential for a favourable outcome. Out of 30 AIFS patients in the present study, the disease limited to nose and paranasal sinuses in 14 patients (60%), hard palatal involvement in 8 patients (26.67%), was limited to nose and paranasal sinuses in 14 patients (60%), hard palatal involvement in 8 patients (26.67%), orbital involvement in 7 patients (23.33%) and intracranial extension in 1 patient (3.33%). The rate of survival falls with extension from limited disease to extensive orbital and intracranial involvement.

Sivak Callcott et al. also reported that factors associated with poor prognosis were delayed diagnosis, intracranial extension of infection, and histopathology demonstrating hyphal invasion in blood vessels or adjacent tissue. Gillespieand O’Malley in their review concluded that complete surgical resection with negative margins and the reversal of neutropaenia appear to be critical factors for survival in the patients of AIFS. Talmi et al., in their retrospective study of 19 patients, found an overall mortality rate of 53%, with aggressive antifungal pharmacotherapy and surgical debridement the most important factors for survival with AIFS. Blitzer and Och inclusion separately that AIFS needs surgery and systemic antifungal agents. With radical debridement, the survival rate was 76%...
while the rate dropped to 57.5% with medical treatment alone. They could achieve 81% survival rate by combining surgery and Amphotericin B therapy. The underlying cause of the immunocompromised status was taken care of adequately in all cases. Debridement of infected and devitalised tissue is necessary because the fungus thrives in necrotic tissue. Management often combines surgical debridement along with systemic antifungal drug therapy. Antifungals are used, such as polyenes (Amphotericin) and azoles (Itraconazole and Voriconazole), among them, Amphotericin B is a conventional drug for treatment of invasive fungal rhinosinusitis. However treatment is often prolonged and can be complicated by adverse effects. The most serious complication is renal dysfunction. Never formulations, including lipid complex and liposomal forms, have been developed to decrease the toxicity of Amphotericin B and indeed seem to be less toxic.

In our series, all the patients got surgical resections including orbital exenteration in four patients with orbital/intracranial extensions, antifungal medication ‘Amphotericin B’ either in conventional or liposomal form in addition to the adequate management of underlying cause of the compromised immune state. In the present series, the patients got surgical resections (range, 1–4 resections) averaged 1.5. Although surgical debridement is beneficial in reducing fungal load, negative fungal margins do not appear to be a critical factor for survival. Almost all patients were admitted and received antifungal medication ‘Amphotericin B’ either in conventional form (6 of 30 patients) or in liposomal form (24 of 30 patients) in addition to surgical resections. Our data indicate that the survival in patients receiving liposomal form of ‘Amphotericin B’ was significantly better than the patients receiving conventional form (chi-square value = 0.822).

CONCLUSION

Diagnosing and treating AIFRS is a clinical challenge as high mortality rates of the disease is related to compromised immune status out of comorbidity and extensive capabilities of causative agent to spread in critical areas like orbital, intracranial etc. The series reported here has an overall lower mortality rate when compared with previous studies. Early diagnosis with aggressive medical and surgical intervention is the key for survival. The age of the patients and the extension of disease i.e. intracranial spread is the highest predictive indicator for mortality. AIFRS and the underlying cause of poor immunity should not be considered a single disease altogether but as two different entities that need to be approached and treated aggressively. Patients with uncontrolled diabetes even though have a predisposition for the more virulent species of fungus i.e. mucormycetes for having AIFRS, but when coupled with high index of suspicion, early diagnosis and adequate treatment; reduces morbidity and mortality to a very high extent. Aggressive surgical debridement is the mainstay of treatment, along with correcting the underlying metabolic abnormality. The survival in patients receiving ‘liposomal form’ of amphotericin B was significantly better than the patients receiving ‘conventional form’. Therefore a comprehensive outlook towards the surgical and medical management has further scope for improvement in the survival rate in cases of invasive fungal disease of sinonasal tract.

REFERENCES

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