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Clinical profile and management of acute invasive fungal rhinosinusitis - our experience with 21 patients

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Abstract : Objective- Acute invasive fungal rhinosinusitis (AIFR) is a rapidly progressive disease, which usually develops in patients with uncontrolled diabetes mellitus (DM) and immunocompromised patients. The purpose of this study was to look retrospectively at the clinical profile, management and outcome of these patients. Study design- Retrospective chart review Settings- Tertiary care hospital Materials and methods- A retrospective chart review was done of patients diagnosed with AIFR between the years 2006 to 2011. RESULTS- Among the 21 patients, 17 (80.9) had uncontrolled diabetes mellitus. Nasal obstruction was the predominant symptom (16 patients, 76.2 percent). Mucosal changes were most commonly observed in the middle meatus (18 patients, 85.7 percent) and rhino-orbital disease was the most common presentation (11 patients, 52.4 percent). The most common causative fungal agent was Rhizopus (16 patients, 76.2 percent). Multiple surgeries were required in all except those patients who underwent endoscopic debridement with orbital exenteration. The mortality rate was 14.3 percent (3 patients). Conclusions- Early and aggressive surgical debridement, intravenous amphotericin B and prompt treatment of the underlying disease are the mainstay of AIFR treatment. Orbital involvement leads to higher mortality. Early orbital exenteration in patients, when indicated, has a better outcome because of reduced intracranial spread. Long term follow up and multiple surgical debridements when required, particularly in those who have not had orbital exenteration, are essential for a good outcome.

Keyword : Invasive fungal sinusitis, Aspergillus, Mucor, Amphotericin B

Introduction Acute invasive fungal rhinosinusitis (AIFR) is a rapidly progressive disease, which usually develops in patients with uncontrolled diabetes mellitus (DM) and immunocompromised patients. It is rarely seen in individuals with a normal immune system and is described as a clinical entity characterized by infiltration of the mucosa, submucosa, blood vessels or bone by mycotic organisms and may extend to the orbit and intracranial structures.[1] This entity needs early diagnosis and management otherwise mortality rates could range from 50 to 80%.[2]

The term fulminant fungal rhinosinusitis is also used in literature instead of AIFR because of the rapidly destructive and fatal nature of the disease.[3] The disease is defined by a time course of less than four weeks and with predominant vascular invasion.[4]

Multiple fungal species have been identified in patients with AIFR. Aspergillus and Mucoraceae are the most common pathogens.[3,4] Successful treatment is based on early diagnosis, treatment of underlying diseases, surgical debridement either by endoscopic or external approach, and systemic administration of amphotericin In this article we present the data on 21 cases with histologically proven AIFR and review the current literature on invasive fungal rhinosinusitis.

Materials and methods

A retrospective chart review was done of patients diagnosed with AIFR attending the ENT outpatient clinic or Emergency department in a tertiary care hospital and referral centre from 2006 to 2011. Demographic data, evaluation for diabetes mellitus or underlying disease resulting in the immunocompromised state, ENT examination, CT scan of paranasal sinuses and brain (if done), identified fungal organisms, management and outcome of the patients were reviewed.

Results

Of the 21 patients with AIFR, 15 were male and six were female. The age of the patients ranged between 7 and 78 years with a mean of 49 years. All the patients had an underlying disease process that made them susceptible to fungal infection. Among the patients, 17 (80.9%) had uncontrolled diabetes mellitus, two had aplastic anemia, one patient had acute disseminated encephalomyelitis and one patient had acute lymphoblastic leukemia. Nasal obstruction was the predominant symptom (76.2%), followed by nasal discharge (61.9%), headache (42.9%), fever (38.09%), and facial swelling (4.77%). The most common eye sign was proptosis, which was noted in 10 (47.6%) patients (Table 1)

Table 1- Eye signs:

Eye signs	Patients
Proptosis	10(47.6%)
Perception of light- negative	9
Frozen eye	9
Pale disc	7
Perception of light- Negative & frozen eye	7
Restricted extraocular movements	5

Nasal endoscopic examination revealed discoloration of the mucosa and crusting, in 20 (95.2%) patients. Mucosal changes were most commonly observed in the middle meatus (18 patients, 85.7%). AIFR involved the middle turbinate in 16 (76.2%) patients. Involvement of the inferior turbinate (6 patients, 28.6%), inferior meatus (3 patients, 14.3%), septum (3 patients, 14.3%), sphenoethmoidal recess (2 patients, 9.5 %) and roof (1 patient, 4.8%) were also observed.

Figure 1:

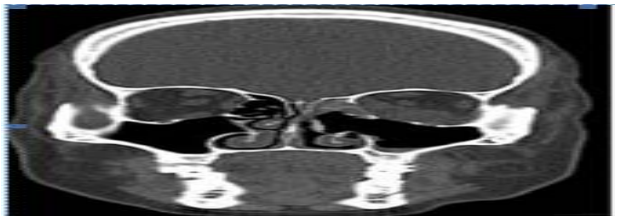


Figure 1: CT-PNS depicts rhino-orbital disease. Soft tissue density is seen in left ethmoidal sinus and floor of left orbit involving the inferior and medial rectus. CT PNS showed involvement of posterior ethmoid sinuses (20 patients, 95.2%), maxillary sinus (19 patients, 90.5%), anterior ethmoid sinuses (19 patients, 90.5%), sphenoid sinus (14 patients, 66.7%) and frontal sinus in 10 patients (47.6%). Bone erosion was noted in lamina papyracea (9 patients, 42.8%), floor of orbit (3 patients, 14.3%), roof of orbit (2 patients, 9.5%) and ethmoidal roof (1 patients, 4.8%). Intraorbital extension was noted in 11 (52.4%) patients and intracranial extension was noted in 1(4.8%) patients (table 2)

Table 2-Extension of disease in AIFR:

Disease extension	Patients
Sino-nasal disease	9(42.9%)
Rhino-orbital disease	11(52.4%)
Rhino-orbito-cerebral disease	1(4.8%)

Rhizopus species were found to be the causative agent in 16 (76.2%) patients as seen in table 3.

Table 3-Mycology in AIFR:

Mycology	Patients
Rhizopus arrhizus	16(76.2%)
Rhizopus arrhizius+ Aspergillus flavus	3
Mucor	2
Aspergillus flavipus	1
Aspergillus flavus	1

Antifungal therapy was initiated after a diagnosis of AIFR was made. The various agents were used as shown in Figure 2 and various surgeries were done as shown in Figure 3.

Figure 2-Medical management:

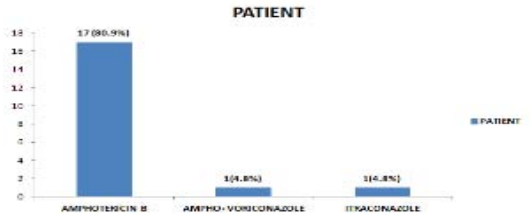
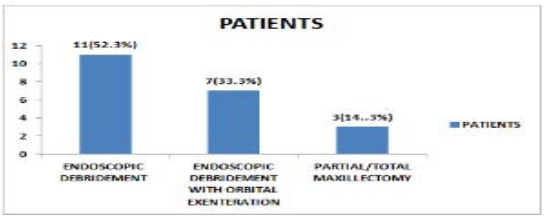


Figure 3 –surgical management:



Amphotericin B was administered in all except 3 patients who were not willing for Amphotericin B (Figure 2). Multi ple surgeries were not required in endoscopic debridement with orbital exenteration group as seen in figure 3. Figure 4 shows a patient with rhino-orbital disease and the outcome following management of AIFR

Figure 4: A-Patient with rhino-orbital disease, **B**- Post op endoscopic debridement with orbital exenteration, **C**- With ocular prosthesis (six months after orbital exenteration)

The overall mortality rate was 14.3 % (3 patients). The mortality rate of patients with orbital invasion was66.7 percent (2 of 3). Two patients underwent multiple surgeries between 0-3 months of follow up, 1 patient between 3-6 months of follow up and one patient underwent multiple debridements between 6-12 months of follow up (Figure 5).

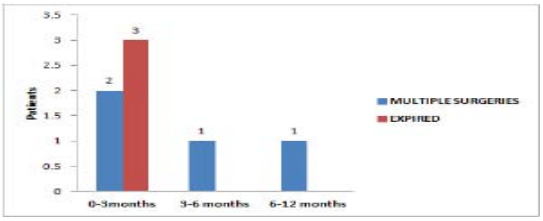


Figure 5- Follow up:

Discussion

DeShazo et al described three forms of invasive fungal rhinosinusitis: granulomatous, chronic, and acute fulminant. The term AIFR or fulminant fungal sinusitis is used to describe fungal sinusitis in an immuno compromised patient when vascular invasion is prominent in histopathological examination and disease duration is less than four weeks. Aspergillus and Mucoraceae are the most common pathogens in AIFR.[3,4] In chronic invasive fungal rhinosinusitis (CIFR),

vascular invasion is absent or minimal and disease duration is more than four weeks. Most patients with CIFR are immunocompetent.[3]
These fungal organisms are normally found in dust, soil and sometimes in nasal mucosa. Aspergillus and Mucor can invade the vessel walls, resulting in thrombosis and ischemia. The ketone reductase system of fungi impairs the phagocytic function of polymorphonuclear leukocytes and helps fungi to adapt to the environment. These organisms may proliferate in paranasal sinuses and cause ischemic
necrosis of the tissues and then spread to invade the eye and the brain rapidly.[3,6] Agents of mucormycosis primarily invade the nose, lungs, and gastrointestinal system, whereas Aspergillus species primarily invade the lungs and later spread to other organs.[7] Early diagnosis of AIFR is vital in immunocompromised patients, but unnecessary mucosal trauma due to recurrent nasal examinations and superficial biopsies from normal mucosa should be avoided as it has been reported that Aspergillus can invade through these mucosal lesions. An acidic environment and high glucose concentration, such as in diabetic ketoacidosis, are ideal conditions for Mucoraceae.[8] Disorders of iron metabolism or excessive iron storage predispose to mucormycosis. Mucor spreads by angio-invasion as this organism has predilection for the internal elastic lamina of arteries. [9]In our study Rhizopus species was found to be the most common causative agent (16 patients, 76.2%). Aspergillus species were isolated in 2(9.5%) patients, Mucor in 2 (9.5%) patients and Rhizopus with Aspergillus species in 3(14.3%) patients.(table 3) Mucormycosis was the most common infection in our patients and was in accordance with the study done by Peterson et al.[8]

Identifying patients at-risk for AIFR is critical in order to make an early diagnosis. Poorly controlled type 1 diabetes mellitus, malnutrition, excessive storage of iron in haematological diseases and diseases resulting in immunosuppresed state like hematologic malignancies, aplastic anemia, long term steroid use and acquired immunodeficiency syndrome are predisposing factors for the development of AIFR.[3,10] There is an increased risk of developing AIFR in bone marrow and solid organ transplantation patients, due to use of chemotherapeutic agents and immunosuppressive drugs.[3] Neutropenic patients are more likely to have invasive Aspergillosis than Mucor.[11] The most common predisposing factor in our study was poorly controlled diabetes mellitus. Patients with diabetes may succumb rapidly to the disease because of late diagnosis.[11]
The initial symptoms of AIFR are often non-specific. Localizing symptoms like facial pain, nasal obstruction, rhinorrhea, and headache are variably present in 20–60% of patients.[12,13] As the disease progresses, symptoms like facial swelling, ophthalmoplegia, loss of visual acuity, proptosis, and change in mental status may occur.[10,14] The most common symptom in bone marrow transplant patients is fever which does not respond to broad-spectrum antibiotics.[12] In our patients, nasal obstruction was the most common symptom at the time of presentation, followed by nasal discharge, headache, fever, and facial swelling. These observations were in consistent with the study done by Süslü et al.[10] A combination of 2 or more of the above mentioned symptoms were the most common presentation of patients in our series. The most common eye sign was proptosis which was noted in 10 (47.6%) patients (table 1). Symptoms related to orbital involvement or cavernous sinus disease, ulcerated necrotic tissues in the hard palate or gingiva, suspicious mucosal lesions in the nasal cavity, or abnormal features in CT scan should raise suspicion of AIFR.[13,15] Therefore diabetic and immunocompromised patients with history of nasal symptoms and eye symptoms should be evaluated immediately to rule out AIFR.

Disease limited to the nasal cavity occurs during the earlier stages of AIFR, therefore rigid nasal endoscopic examination should be performed in immunocompromised patients with fever (not responding to antibiotics) or with localizing symptoms. Alteration in appearance of nasal mucosa is the most consistent sign. Granulation, ulceration, whitish discoloration (ischaemia) and blackish discoloration (necrosis) of nasal mucosa can be seen on nasal examination.[13] Gillespie et al.[13]

reported that mucosal abnormalities were most commonly seen on the middle turbinate (67%), followed by the septum (24%), hard palate (19%), and inferior turbinate (10%). Süslü et al[10] reported septum as the most common site of involvement . Decreased sensation of nasal mucosa and decreased bleeding are important signs suggestive of fungal invasion. In the present study, characteristic mucosal lesions were observed in 20 (95.2%) patients and were most commonly observed in the middle meatus followed by middle turbinate. Although immunocompromised state and haematological disorders limit the endoscopic examination, rigid nasal endoscopic examination is mandatory in suspected patients as anterior rhinoscopy alone may be normal in early cases.[10]
Computed tomography (CT) of nose and paranasal sinuses should be considered in the evaluation of patients with suspected AIFR, however, in early stages of the disease CT findings may be non-specific and CT without nasal endoscopic examination may delay the diagnosis. Süslü et al[10] demonstrated that they had patients with normal CT findings while characteristic mucosal lesions were noted on endoscopic examination. Del Gaudio et al[16] reported unilateral nasal mucosal thickening(91% of cases in their study) as an early CT finding which was not typical in bacterial or viral rhinosinusitis. However in our series unilateral sinonasal involvement was seen in 38.1 %. A review of the literature reveals that CT findings such as oedema of nasal cavity soft tissue, sinus mucoperiosteal thickening, bone erosion, orbital invasion, facial soft tissue swelling, and periantral soft tissue infiltration are all findings suggestive of AIFR.[3,16,17,18] Osseous erosion and bony destruction are obvious signs of the disease
and are noted in late stages of AIFR.[16,17] However bony erosion and destruction may not be present in the late stage of the disease as these fungi tend to extend along the vessels without bony destruction. CT scanning with contrast is preferred to assess bone changes while magnetic resonance imaging (MRI) is preferred to assess intracranial and intraorbital extension of the disease.[19] CT should be performed in both axial and coronal planes at <3 mm intervals to assess disease involvement and its extension.[16] Unfortunately, there are no standard diagnostic imaging criteria of AIFR.[19] Howells and Ramadan proposed early evaluation by MRI in patients at risk due to rapid progression of the disease and nonspecific findings obtained with CT.[20] In this study, the most common sinus involved was posterior ethmoid followed by maxillary sinus and the most common bone erosion was noted in lamina papyracea followed by the floor of orbit. Intraorbital extension was noted in 12 (57.1%) patients and intracranial extension was noted in 1 (4.8%) patient.
Histopathological examination of biopsy tissue is required to confirm the diagnosis of AIFR. Hyphal forms within the submucosa, with or without angiocentric invasion, and tissue necrosis with minimal host inflammatory cell infiltration are the criteria for histopathological diagnosis of AIFR.[21] Identified mucosal abnormalities and suspicious lesions should be biopsied at the time of nasal endoscopy.

Since the middle turbinate is the most common site of invasion, Gillespie et al[22] recommended superficial mucosal biopsies in case of mucosal changes. However Süslü et al suggested deep diagnostic biopsies of suspected lesions in operating room with presence of electro-cautery.[10]

Frozen sections are highly specific and sensitive in the early diagnosis of AIFR, especially in case of mucormycosis.[23] Frozen section examination helps in early diagnosis and management. [13,24] In our study fungal culture and biopsy of suspicious lesions were done simultaneously during nasal endoscopic examination.

Diagnostic criteria for AIFR are presence of clinical and radiological findings of rapidly progressing sinusitis in at risk patients and typical endoscopic findings such as discoloration, granulation, ulceration of nasal mucosa and purple- black crusting. Definitive diagnosis is established by histopathologic observation of hyphal forms in mucosa, submucosa, blood vessels, or bones of the sinuses and cultures of biopsy materials.[3,13] Necrosis and neutrophilic recruitment can be observed in the infected tissues.[6]

The mainstay of treatment should include antifungal agents, aggressive surgical debridement and prompt treatment of the underlying systemic disease.[10,16,25,26] In mucormycosis, primary antifungal therapy is amphotericin-B (amp-B). The optimal dosage is not known, but the commonly administered doses are 1 mg/kg/day for amp-B, 5 to 7.5 mg/kg/day for amp-L (liposomal form), and amp-B lipid complex. The duration of treatment is tailored to each individual according to resolution of the clinical signs of infection and radiological findings and as well as according to the status of underlying disease. This period is usually six to eight weeks.[27] The safe cumulative dose of Amphotericin B is 2-3 gram.[28] The Lipid formulation of amphotericin B is preferred because it is less nephrotoxic and can be safely administered at higher doses for a longer period of time than conventional amphotericin B. Posaconazole may be an option of antifungal prophylaxis if amphotericin B cannot be used for prolonged periods in patients who are on immunosuppressive medications.[27] In our patients, amphotericin-B was administered in doses of 0.5-1.5 mg/kg/day and Liposomal amphotericin was administered in doses of 3.0-5.0 mg/ kg/day. The cumulative dose of 2.0-
3.0 gm of amphotericin B was given in our study. Süslü et al[10] advised administration of amphotericin B before the exact histopathological report. In our study we too started Amphotericin B on the basis of clinical features and positive fungal smear report before histopathological diagnosis. Eliashar et al also[29] advocated local antifungal therapy, but according to Kasapoglu F et al, local therapy has no effect.[25]

Early aggressive sinonasal debridement should be performed in all patients with biopsy-proven AIFR. Debridement of necrotic tissue should be done until bleeding bone and soft tissue surfaces are reached. In case of abundant necrosis radical excisions should be preferred to limited endoscopic debridement.[21] Successful outcomes have been reported with endoscopic surgery by various studies. [15,25,30] Early limited endoscopic debridement can also be done on the basis of clinical, radiological findings and positive fungal smear report, as we did in our study. Jiang and Hsu[30] performed only endoscopic surgery in nine patients and reported that one patient died due to carotid artery occlusion while eight patients survived (88%). Park et al[15] reported that seven of nine patients treated by endoscopy alone survived. In our study endoscopic debridement was done in 18(85.7%) patients.

Monitoring patients with nasal endoscopy is essential for diagnosing recurrent or residual disease. In our study, two patients underwent multiple surgeries between 0-3 months of follow up, one patient between 3-6 months of follow up and one patient underwent multiple debridements between 6-12 months of follow up (figure 5). This shows that there is a need of long term follow up in these patients.

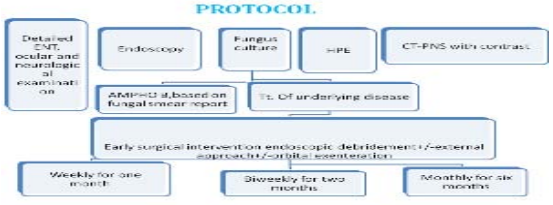
Both in the early and late stages of AIFR, surgical debridement should be combined with medical treatment. Medical management is directed towards the prompt management of immunocompromised status and antifungal therapy. This may include correction of acidosis and hyperglycemia, or reversal of immunosuppresion when possible. In neutropenic patients, granulocyte colony -stimulating factor (GCSF) has been shown to be effective in promoting bone marrow recovery and AIFR patients also showed good prognosis with GCSF as reported by Gillespie et al.[13] High efficiency particulate filters and prophylactic use of amphotericin nasal spray in neutropenic patients may play a role in preventing AIFR. [31,32]

Kasapoglu et al[25]preferred open surgery in the presence of intraorbital extension, palatal and/or intracerebral involvement in their study. In this present study open approach (partial or total maxillectomy) was performed in case of palatal involvement. Alobid et al suggested that if the underlying cause of immunodeficiency is reversible then orbital exenteration was not mandatory in patients with evidence of orbital disease.[5] Nityanandam et al [33] classified their patients into sino-nasal, rhino-orbital and rhino-orbito-cerebral disease and suggested that orbital exenteration should be prescribed in advanced involvement of orbit and conservative management can be considered in patients with isolated extraocular muscle involvement, preserved vision and in absence of progression. In our study orbital exenteration was done in seven (33.3%) cases and in this group, two patients died due to non fungal related causes. Multiple surgeries were not required in patients who underwent endoscopic debridement with orbital exenteration. In all probability, therefore, early orbital exenteration when indicated, leads to a good outcome.

In our study, the mortality rate was 14.3 % (3 patients) which was also the case in a study done by Parikh et al.[11] Roden et al reviewed 929 reported zygomycosis cases. They found the survival rate to be 61 % in cases treated with amp-B, 57 % in those treated only with surgery, 69 % in those treated with lipid amp-B, and 70 % in those treated with surgery and amp-B.[34] Intracranial and intraorbital extension increase surgical morbidity and decrease the survival rate.[29] In our patient group, intraorbital invasion was associated with a higher mortality rate of 66.7 % (2 of 3) which was similar in a study done by Kasapogulu et al .[25]We believe that successful outcomes in our patients depended on early commencement of systemic antifungal treatment (on the basis of clinical and radiological findings and fungal smear report), aggressive surgical debridement and with prompt treatment of underlying disease.

Early diagnosis and management of AIFR, requires a multidisciplinary team approach which includes the otorhinolaryngologist , infectious disease specialist, a pathologist, a radiologist, and a microbiologist.[10]

Based on our experience of managing patients with AIFR we suggest the following management protocol in patients suspected to have AIFR.



Conclusions:

Diabetic and immunocompromised patients with history of nasal symptoms and eye symptoms should be evaluated for the possibility of AIFR at the earliest. As initial symptoms and radiological features are nonspecific, rigid nasal endoscopic examination and biopsies with fungal culture of mucosal and submucosal tissues from suspected sites should be performed as early as possible. Based on positive fungal smear report and suspected clinical features, Amphotericin B should be administered. Early endoscopic debridement is essential if disease is limited to sinonasal region to limit further progression of the disease. Maxillectomy and orbital exenteration may be required in cases of extensive necrosis (intraorbital extension, palatal involvement). Orbital involvement leads to higher mortality. Orbital exenteration, when indicated, leads to a good outcome. Early and aggressive surgical debridement, intravenous amphotericin B and prompt treatment of underlying disease are the mainstay of AIFR treatment. Long term follow up and multiple surgical debridements when required, particularly in those who have not had orbital exenteration, are essential for a good outcome.

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