Original Research Article

A prospective analytic study of invasive fungal rhinosinsitis

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ABSTRACT

Background: Fungal sinusitis is more commonly found in immunocompromised patients with systemic illnesses, e.g., uncontrolled diabetes mellitus, chronic renal failure, patient on prolonged systemic steroid therapy, hematological malignancies, HIV/AIDS, etc. Invasive fungal sinusitis is subdivided into acute and chronic. Less than 4 weeks duration separates the acute stage from the chronic stage of the disease. Management of invasive fungal sinusitis consists of sinonasal debridement with or without Caldwell-Luc surgery followed by antifungal therapy.
Methods: Total 30 cases of both types of invasive fungal sinusitis were included in this study. The demographic profile, clinical presentation, underlying immunocompromised status, complication, mortality and management of all these 30 patients were analyzed.
Results: Invasive fungal sinusitis was most commonly observed in 3rd and 4th decade of life with male predominance. Prolonged uncontrolled diabetic mellitus was the most common underlying immunocompromised status. Mucor was the most common isolated fungal species. Preseptal cellulitis was the most common complication.
Conclusions: For early detection of mucosal changes one has to do endoscopic examination in all immunocompromised patients with symptoms like headache, facial or periorbital pain and swelling, purulent nasal discharge, etc. All clinician should think vigilantly in immunocompromised patients with above symptoms or in pyrexia of unknown origin not responding to antibiotics. To reduce mortality, one has to go for immediate sinonasal debridement even in local anaesthesia also if patient is not fit for general anaesthesia.

Keywords: Fungal rhino-sinusitis, Diabetic mellitus, HIV

INTRODUCTION

Fungal rhinosinusitis can occur in any age group, but symptoms are different based on the immunity status of the individual. Fungal rhinosinusitis is more likely suspected when patients present with symptoms similar to chronic sinus infection resistant to conventional antibiotic therapy. The spectrum of disease varies from allergic fungal sinusitis to acute fulminant invasive fungal sinusitis. Fungal infections more commonly occur in immunocompromised patients with systemic illnesses, e.g., uncontrolled diabetes mellitus, chronic renal failure, haematological malignancies, HIV, etc. Invasive fungal sinusitis is subdivided into acute and chronic invasive fungal sinusitis. Some authors further subdivided chronic invasive sinusitis to granulomatous & non-granulomatous invasive sinusitis.[1,2] Many severe complications like nasal deformity, visual loss, cavernous sinus thrombosis, cranial invasion, death, etc. can be found in invasive fungal sinusitis. The incidence of morbidity and mortality of invasive fungal rhinosinusitis ranged from 20 to 80%.[3]

Acute fulminant invasive fungal rhinosinusitis

The diagnosis of this disease is difficult, especially in the early stages. Less than 4 weeks duration separates the

acute stage from the chronic stage of the disease.[4] It is a life-threatening disease present usually in immunocompromised patients with impaired neutrophilic response. These patients include those with uncontrolled diabetes mellitus, AIDS, organ transplantation and haematological malignancies, renal impairment, patients on long-term systemic or local corticosteroids. Common reported clinical symptoms include fever, cough, black eschar, crusting of the nasal mucosa, purulent nasal discharge particularly in middle meatus, nasal obstruction, swelling over nose and face, epistaxis, headache, vision loss and diplopia. A high index of suspicion of this disease entity should be present in any immunosuppressed patients with localizing sinonasal symptoms and unilateral sinonasal involvement. Often fever of unknown origin that has failed to respond to 48 hours of broad-spectrum intravenous antibiotics may be the initial presenting symptom. *Mucor*, *Aspergillus* and *Rhizopus* species are most common isolated fungal pathogen.[5,6]

In the early stages, nasal endoscopic findings, particularly mucosal colour changes and the purulent discharge may be as subtle as the presenting symptoms. Alteration in mucosal appearance in nasal endoscopy, such as a discoloration, granulation and ulceration are the most consistent physical findings. Compared to allergic fungal sinusitis, invasive tends to have more focal bony erosions, lacks expansion of the sinuses, has more limited sinus disease and has more disease outside of the sinuses than within, when there is intraorbital or intracranial extension. MRI brain and orbit has more sensitivity to diagnose intracranial and intraorbital extensions.

Chronic invasive fungal rhinosinusitis

The clinical picture of chronic invasive FRS is similar to that of acute invasive FRS. The ethmoid and sphenoid sinuses are most commonly involved. On histology, chronic invasive FRS demonstrates invasion of fungi into the sinonasal mucosa with a dense accumulation of fungal hyphae, occasional vascular invasion and chronic or sparse inflammatory reaction. There is no difference in the prognosis or the management of both chronic invasive and granulomatous invasive FRS.

Management of invasive fungal sinusitis

Management of invasive fungal sinusitis consists of sinonasal debridement with or without Caldwell luc surgery followed by antifungal therapy. Acute invasive fungal sinusitis requires more aggressive sinonasal debridement (both external and endoscopic) because of high recurrence, mortality and morbidity rate. Amphotericin-B 1 to 1.5 mg/kg/day for a total dose of 2 grams or more is the gold standard antifungal therapy. Long-term itraconazole or voriconazole treatment recommended after intravenous amphotericin-B therapy, for invasive fungal sinusitis.[7]

The aim of this study was to analyze various clinical presentation, underlying immunocompromised condition, complication of invasive fungal sinusitis.

METHODS

Study design

This prospective analytic study was designed.

Data collection

Total 30 patients of both types of invasive fungal sinusitis that underwent treatment as inpatient basis from January 2016 to October 2019, at Department of Otorhinolaryngology Government medical college and Sir T hospital, Bhavnagar were included in this study. Patients giving consent are included in this study. A detailed history was obtained from all the patients, with emphasis on a history of immunocompromised status. An immunocompromised host is an individual who does not have the ability to respond normally to an infection due to an impaired immune system. Immunocompromised status includes uncontrolled diabetes mellitus, renal impairment, human immunodeficiency virus infection, malnutrition, cancers, long-term systemic steroid therapy and solid organ transplantation. Apart from anterior rhinoscopy and routine clinical examinations, detailed nasal endoscopic examinations were performed in every patient to collect fungal specimen from middle meatus and nasal cavity. Nasal swabs from the middle meatus were subjected to potassium hydroxide mount and if fungal elements were identified, then fungal culture was done. Post-operatively, tissue removed from the sinuses was sent for histopathological examinations.

The data collected from the patients include age, sex, associated co-morbidities and immunocompromised status, and clinical symptoms and signs, including details of any complications the patients had at the time of presentation. The patients included in the study presented with nasal discharge, nasal obstruction, headache, or facial pain; with radiologic evidence of sinus involvement; and without any response to conventional antibiotic therapy. Statistical significance was assessed to establish if the presence of certain symptoms could be an alarming sign for the likelihood of fungal rhinosinusitis. Most of above-mentioned symptoms were part of the inclusion criteria, although other symptoms of chronic rhinosinusitis were also taken into account. Radiographic and computed tomography imaging of nose and paranasal sinuses were done in all the cases of fungal rhinosinusitis to assess the patency of the osteomeatal complex, involvement of sinuses and erosion of bony margins or expansion of the sinus cavity or intracranial extension. Patients were categorized based on the co-morbid systemic diseases and underlying immunocompromised status.

Urgent sinonasal debridement (external and endoscopic) with or without Caldwell-Luc approach was used in all cases. Antifungal therapy included use of intravenous amphotericin-B. Parenteral amphotericin-B was the drug of choice for invasive fungal rhinosinusitis; the dose was titrated based on periodic monitoring of renal function parameters and electrolytes. The patients were discharged on oral antifungal. All the patients were instructed to perform routine alkaline nasal douching during the postoperative period. The patients were asked to follow up on 1st week, 3rd week, 6th week, 3rd month and 6th month, after surgery for suction clearance of the sinonasal cavity. The patients were evaluated clinically for improvement in symptoms, clinical examination and periodic diagnostic nasal endoscopy to assess for any relapse or recurrence of fungal infection.

Inclusion criteria

Patient of any age, sex; with immunocompromised status like uncontrolled diabetes mellitus, chronic renal failure, patient on prolonged systemic steroid therapy, hematological malignancies, HIV, etc. and having clinical features like fever of unknown origin, cough, black eschar, crusting of the nasal mucosa, purulent nasal discharge particularly in middle meatus, nasal obstruction, swelling over nose and face, epistaxis, headaches, vision loss and diplopia were included.

Exclusion criteria

Patients giving negative consent to participate in study and pregnant women were excluded.

Statistical analysis

Simple proportions were calculated.

RESULTS

In this study of 30 cases of invasive fungal rhinosinusitis, 30% of the patients had a proven fungal aetiology, with a highest prevalence in the third and fourth decades of life 66.6% (n=30), with a male preponderance 66.6% (n=30).

Table 1: Demographic data of invasive fungal sinusitis (n=30).

Total	Acute invasive fungal sinusitis (n=17)	Chronic invasive fungal sinusitis (n=13)
Sex (male:female)	11:6	9:4
Age (mean)	47 (16-78)	51.5 (32-71)

In this study, patients having Diabetes Mellitus (50% for acute and 33.3% for chronic) more susceptible to both acute and chronic variant of invasive fungal sinusitis. In Some patients multiple underlying immunocompromised conditions were observed.

Table 2: Underlying immunocompromised status in invasive fungal sinusitis.

Underlying diseases	Acute invasive fungal sinusitis (n=17)	Chronic invasive fungal sinusitis (n=13)
	N (%)	N (%)
DM	15 (88.24)	10 (76.92)
Renal disease	05 (29.41)	02 (15.38)
Long term steroids	01 (5.88)	02 (15.38)
Malnutrition	00	01 (7.9)

Table 3: Symptoms of acute and chronic invasive fungal sinusitis.

Symptom	Acute invasive fungal sinusitis (n=17)	Chronic invasive fungal sinusitis (n=13)
	N (%)	N (%)
Headache	9 (52.94)	8 (61.53)
Facial swelling	8 (47.05)	5 (38.46)
Facial pain	4 (23.52)	3 (23.076)
Purulent Rhinorrhea	8 (47.05)	6 (46.15)
Nasal obstruction	12 (70.58)	7 (53.84)
Epistaxis	10 (58.82)	6 (46.15)
Fever	6 (35.29)	4 (30.76)
Decreased vision	2 (11.76)	1 (7.69)
Diplopia	1 (5.88)	0

The patients presented with symptoms of nasal obstruction (n=19) 63.33%, purulent rhinorrhea (n=14) 46.66%, headache (n=17) 56.66%, facial pain (n=12) 40%, and facial swelling (n=13) 43.3%, epistaxis (n=16) 53.33%, fever (n=10) 33.33%, decreased vision (n=2) 6.6%, diplopia (n=1) 5.88%.

Table 4: Rhinology signs of acute versus chronic invasive fungal sinusitis.

	Acute invasive fungal sinusitis (n=17)	Chronic invasive fungal sinusitis (n=13)
	N (%)	N (%)
Mucosal necrosis	10 (58.82)	6 (46.15)
Black crust or debris	4 (57.14)	3 (23.07)
Pus in middle meatus	2 (11.76)	3 (23.07)
Septum involvement	1 (5.88)	1 (7.69)

The rhinology findings likes mucosal necrosis, black crust or debris, and pus in middle meatus and septum

involvement are shown Table 4. Patients with mucosal necrosis have a significantly higher risk for acute IFS.

Table 5: Complications of acute invasive fungal sinusitis versus chronic invasive sinusitis.

Complications	Acute invasive fungal sinusitis (n=17)	Chronic invasive fungal sinusitis (n=13)
	N (%)	N (%)
Preseptal cellulitis	4 (23.53)	1 (7.69)
Orbital cellulitis	2 (11.76)	1(7.69)
Orbital abscess	1 (5.88)	1 (7.69)
Cavernous sinus thrombosis	1 (5.88)	0
Intracranial involvement	3 (17.65)	0
Death	2 (11.76)	0

Orbital cellulitis was the most common complication of invasive fungal rhino sinusitis. 3 patients had intracranial extension. Out of 30 patients 2 patients expired due to complication of fungal invasive fungal rhino sinusitis.

DISCUSSION

More numbers of invasive fungal sinusitis are detected nowadays because of advanced medical treatment and increase in the lifespan of immunocompromised patients like DM, chronic renal failure, haematological malignancy, AIDS, etc. Another reason for increasing invasive fungal sinusitis is prolonged use of systemic or local steroids without any interruption along with anibiotics leading to superinfection. A review of literature revealed 17 cases of primary paranasal sinus aspergilloma from Sudan reported by Milosev et al.[8] Stammberger reported having treated 140 patients with massive fungal sinusitis during 1976 to 1985.[9] Hazarika et al. reported three cases of rhino cerebral mucormycosis, all of whom were elderly and with diabetes.[10] Chakrabarti et al isolated fungi in 50 of the 119 patients with clinically suspected cases in North India over a 2-year period.[11] According to a literature review, the highest incidence of allergic fungal rhinosinusitis was noted in Mumbai, India, as reported in the study by Ferguson.[1] Total 30 cases of invasive fungal sinusitis were reported in this study, out of which 17 cases are acute and 13 cases are chronic. Patorn et al reported 76.3% cases of acute and 23.7% of chronic invasive fungal sinusitis in their study.[12] In both studies, cases of acute invasive fungal sinusitis are more in number.

In this study, 20 patients (66.7%) were male and 10 patients (33.3%) were female. In the study of Patorn Patorn et al, 44.1% patients were male and 55.9% patients were female.[12] According to Patorn et al. the

mean age of acute group (52.27±15.2) was slightly higher than chronic group (49.86±15.2).[12] In this study, mean age was 44 (16-78) in acute group and 30 (32-71) was in chronic group.

The symptoms and signs of paranasal sinusitis (such as nasal discharge, stuffiness, epistaxis, periorbital swelling, and maxillary tenderness) are nonspecific for invasive fungal sinusitis.[13] Most common presenting symptoms were headache, facial/periorbital swelling, facial pain and purulent rhinorrhea. In this study, symptoms were slightly different from the study of Patorn et al like headache, visual loss, facial pain and fever (59.3, 47.5, 35.6 and 33.9 percent respectively). Symptoms and signs such as nose ulceration, eschar of the nasal mucosa, black necrotic lesions, and perforation of the hard palate are more specific, but these findings are present only at an advanced stage.[13]

Prolonged uncontrolled state of diabetic mellitus was the most common associated immunocompromised status in this study (acute group 50% and chronic group 33.3%). Chronic renal failure was second most common associated immunocompromised status in this study. According to Moghadami et al, diabetic mellitus was the most predisposing factor followed by haematological malignancy.[14] In the study of Parikh et al hematologic malignancy was the most common immunocompromised status associated with invasive fungal sinusitis and diabetes mellitus was the second most common associated immunocompromised status.[3] But in this study in any case, haematological malignancy was not been reported as underlying immunocompromised status.

Most common complication reported in this study was preseptal cellulitis. Out of 17 patients of acute group, in 4 patients preseptal and in 2 patients' orbital cellulitis were observed. Out of 13 patients of chronic group, in 1 patient peseptal cellulitis and in another 1 patient orbital cellulitis, in 1 patient orbital abscess and 1 patient cavernous sinus thrombosis were observed. In 3 patients of acute FRS group intracranial extension was found. No such intracranial complications were detected in chronic group in this study. While in Patorn et al, 76.2% have orbital complications and the most common orbital complication was cavernous sinus thrombosis.[12]

Chen et al founded that Aspergillus flavus was the most common isolate, but in this study, most common fungal isolate was mucor mycosis.[6] All patients underwent extensive endoscopic sinonasal debridedment. Eight patients from both the group require Caldwell Luc approach for complete removal of disease from maxilla. Out of these 30 patients, 6 patients were not fit for general anaesthesia (because of altered renal function, cardiac problems, electrolytes imbalance, etc. reasons) undergone surgery under only local anaesthesia while rest of patients were undergone surgery under general anaesthesia. Two patients in acute group died (mortality 6.6%) while no mortality was seen in chronic group.

Patorn et al show 31.1% mortality in acute group and no mortality in chronic group.[12] Low mortality in this study might because of sensitized approach of endoscopic examination in all immunocompromised patients, those who either present or refer to ENT department and in patients having unusual presentation of sinusitis and pyrexia of unknown origin not responding to antibiotics.

Being a single analytic study at only one tertiary care center, this study cannot reflect all demographic, etiological and clinical aspects of invasive fungal sinusitis. One has to do multicentric comprehensive study regarding invasive fungal sinusitis to evaluate various underlying factors, etiology, early clinical features and prognosis.

CONCLUSION

Due to a high mortality rate, the diagnosis and management of invasive fungal sinusitis continues to present as challenge to the otorhinolaryngologist. Acute invasive fungal sinusitis is most common in immunocompromised patients, with the highest incidence in patients with uncontrolled diabetes mellitus. The most consistent finding of invasive fungal sinusitis was mucosal necrosis and black crust/debris. For early detection of mucosal changes one has to do endoscopic examination in all immunocompromised patients with symptoms like headache, facial or periorbital pain & swelling, purulent nasal discharge, etc. All clinician should think vigilantly in immunocompromised patients with above symptoms or in pyrexia of unknown origin not responding to antibiotics. CT scan finding of sinus wall erosion may help in diagnosis of chronic invasive fungal sinusitis. To reduce mortality, one has to go for immediate sinonasal debridement even in local anaesthesia also.

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