Invasive zygomycosis in India: experience in a tertiary care hospital

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ABSTRACT

Aim: To report the natural history and clinical course of zygomycosis from a single tertiary care centre in India where doctors maintain an institutional zygomycosis registry.

Methods: The clinical and laboratory data collected prospectively from patients with antemortem diagnosis for invasive zygomycosis, and retrospectively from autopsy diagnosed cases, over an 18 month period (July 2006–December 2007) were combined and analysed.

Results: During the period 75 cases (50 cases/year) of zygomycosis were reported. Antemortem diagnosis could be made in 81% of cases and 9% of patients had nosocomial zygomycosis. The spectrum of disease included rhino-orbito-cerebral (48%), pulmonary (17%), gastrointestinal (13%), cutaneous (11%), renal and disseminated zygomycosis (5% each). Uncontrolled type 2 diabetes (58%) and diabetic ketoacidosis (38%) in the rhino-orbito-cerebral type, renal failure (69%) in the pulmonary type, prematurity (70%) in the gastrointestinal type, and breach of skin (88%) in cutaneous zygomycosis, were the significant ($p<0.05$) underlying illnesses. *Rhizopus oryzae* (69%) was the most common isolate followed by *Apophysomyces elegans* (19%). Overall mortality was 45% in patients who could be treated. Outcome was significantly poor when surgical debridement could not be performed or the patients were treated only with amphotericin B deoxycholate. On multivariate analysis, patients with a Glasgow Coma Score (GCS) ≥ 9 had a better prognosis.

Conclusions: Zygomycosis is a threat in uncontrolled diabetes. New risk factors such as renal failure and chronic liver disease require attention. *A elegans* is an emerging agent in India. The need for surgical debridement in addition to medical treatment is emphasised. GCS is an independent marker of prognosis in cases of invasive zygomycosis.

Zygomycosis, a polymorphic disease, is caused by fungi of the class *Zygomycetes*, and the orders *Mucorales* and *Entomophthorales*. The *Entomophthorales* are occasionally reported to cause subcutaneous or mucocutaneous infections (entomophthoromycosis) in immunocompetent hosts in developing countries. In contrast, fungi of the order *Mucorales* are reported to cause the more severe forms of zygomycosis (earlier named mucormycosis) in immunocompromised hosts in both developing and developed countries.[1–4] During the past two decades the emergence of zygomycosis due to *Mucorales* has been observed throughout the world, in part due to the continued rise of diabetes and increased use of immunosuppressive agents,[2 3 5] but the rise in India is phenomenal.[4 6] In India, the rising trend of invasive zygomycosis is commonly associated with uncontrolled diabetes mellitus.[4 6] However, the rise of zygomycosis cases in many countries were reported in patients with haematological malignancies who are on chemotherapy and in haematological stem cell transplant recipients.[2 7 8]

Based on clinical presentation and the involvement of particular anatomical sites, the disease is categorised into: rhino-orbito-cerebral (ROC), pulmonary, gastrointestinal, cutaneous, disseminated, and miscellaneous types. These categories are believed to occur in patients with specific defects in host defence—for example, ROC type in individuals with uncontrolled diabetes and diabetic ketoacidosis, pulmonary type in patients with haematological malignancies and bone marrow transplantation, gastrointestinal type in patients with malnutrition, and cutaneous lesions following trauma or burns.[1–3]

In the management of invasive zygomycosis, early diagnosis is most important as it may help to eradicate the disease before the agents progress to involve critical structures or disseminate. Unfortunately, a large number of cases are identified at autopsy, as the disease is difficult to diagnose antemortem unless a high index of clinical suspicion is maintained.[1–4] The clinical presentations and diagnostic approach for each category are presented in box 1.

From India, we reported two large retrospective series from a single tertiary care centre: 129 cases over 10 years (1990–1999),[6] and 178 cases during the subsequent 5 years (2000–2004).[4] The observations made in those two series are presented in box 2. The two series have made our clinicians, histopathologists, and medical mycologists aware of the threat of invasive zygomycosis and they have developed an institutional zygomycosis registry. The present prospective study was carried out by analysing the data of this registry.

The present study was planned to determine: the prevalence of zygomycosis; any change in risk factors for different clinical types and fungal isolation; any improvement in antemortem diagnosis of zygomycosis; any possibility of nosocomial acquisition of zygomycosis; the clinical presentation of each clinical type; and outcome following institution of the common management protocol in patients with invasive zygomycosis.

PATIENTS AND METHODS

Place of study

The study was conducted at the Postgraduate Institute of Medical Education and Research

Box 1 Clinical presentation and diagnostic approach for clinical categories of zygomycosis

- Rhino-orbito-cerebral type (most common category): refers to the entire spectrum of the disease. The disease starts with either sinusitis or periorbital cellulitis, and when untreated it usually spreads from the ethmoid sinus to the orbit or intracranially. Depending on the site of involvement, the patient may present with: sinusitis, nasal discharge, epistaxis, nasal obstruction, crusting and necrosis of nasal mucosa (sinus involvement); swelling, pain, anaesthesia, erythema, necrosis, toothache (facial and palatal involvement); ophthalmoplegia, proptosis, loss of vision, chemosis, periorbital swelling and pain, eyelid necrosis, endophthalmitis (orbital involvement); altered consciousness, seizures, hemiplegia, cranial nerve palsies (cerebral involvement). Endoscopic biopsy from the lesion site helps in the diagnosis of the condition.
- Pulmonary type: usually no specific symptom or sign. Patient may present with dyspnoea, cough, chest pain, or fever with chills. On high resolution chest CT scan either consolidation, or nodular or cavitary lesions, are seen. The lesions may extend into the chest wall, pulmonary artery, aorta, or heart. High suspicion and open lung biopsy or CT guided needle aspiration from the lesion site help in the diagnosis.
- Gastrointestinal type: the infection is acute, rapidly fatal, and is often diagnosed postmortem. The stomach, colon, and ileum are the most commonly affected sites. Symptoms depend on the site of involvement. Non-specific abdominal pain and distension associated with nausea and vomiting are the common symptoms. The antemortem diagnosis may be made by biopsy from the suspected site during surgery or endoscopy.
- Cutaneous type: the patient may present with erythematous, ulcerative, necrotic, or bullous lesions following trauma, burn or contaminated injection. Soil contamination at the injured site and penetrating injury with plant material predispose to the disease as *Zygomycetes* are saprobes. The lesion may extend to involve tendon, muscles, and bone, and may present as necrotising fasciitis. A punch or full thickness biopsy from the lesion site is the best diagnostic method.
- Disseminated type: defined as involvement of at least two non-contiguous organs by haematogenous dissemination. It originates from any primary site of infection (most commonly from the lung) and disseminates commonly to the brain, though any other organ may be involved. Patients present with sudden onset of focal neurological deficit or coma. The diagnosis of disseminated disease is difficult unless evidence of infarction in multiple organs is noted. The closest differential diagnosis is disseminated aspergillosis.
- Renal type: isolated renal zygomycosis is rare. In India most cases have been reported in immunocompetent hosts. They present with unilateral or bilateral flank pain, and fever with haematuria or anuria. On CT scan enlarged and infarcted kidneys are observed. CT or ultrasound guided needle aspiration from the site of lesion helps in the antemortem diagnosis.

(PGIMER), Chandigarh, India (box 3) over a period of 18 months (July 2006 through December 2007) by analysing the institutional zygomycosis registry.

Box 2 Summary of main findings from two previous series of zygomycosis

- Rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus.
- Though percentage of antemortem diagnosis improved in second series, most of the patients with pulmonary, gastrointestinal and disseminated zygomycosis were diagnosed postmortem.
- Isolated renal zygomycosis is an interesting clinical entity and further studies are required to understand its pathogenesis.
- *Apophysomyces elegans* is an emerging fungus in India.
- Though combined radical surgery and amphotericin B treatment cured the majority of patients, prospective clinical trials are essential to determine the optimal therapy.

Zygomycosis case definition

The diagnosis of zygomycosis was confirmed when broad aseptate/sparsely septate, ribbon-like hyphae with right angled branching were demonstrated with inflammatory reactions in tissue specimen or aseptically aspirated material from deep tissue, with or without isolation of *Zygomycetes*. Those patients with a clinical suspicion of invasive zygomycosis but without mycology or histopathology conformation were not included in the record. Similarly, a positive culture of *Zygomycetes* unaccompanied by direct microscopic evidence of fungal hyphae in the patients' samples was disregarded for diagnosis of invasive zygomycosis due to the ubiquitous nature of the fungi.

Prospective analysis

The case histories of the patients with invasive zygomycosis were analysed prospectively regarding incidence, site of involvement, underlying disease, Glasgow Coma Score (GCS) (eye opening response, range 1–4 (none 1, spontaneous 4); verbal response, range 1–5 (none 1, oriented 5); motor response, range 1–6 (none 1, obeys command 6)),[9] findings of biochemical and haematological investigations, clinical course, mode of diagnosis, agents isolated, treatment instituted, and outcome of the disease. The clinical category of zygomycosis was defined on the basis of the anatomical site of involvement. The term ROC zygomycosis was described when the lesions originated in the nasal sinuses and might have extended contiguously to the orbit/palate/face or brain. Pulmonary, gastrointestinal, or cutaneous zygomycosis were terms assigned when the disease was restricted to respective organs. The disease was categorised as disseminated if more than one non-contiguous organ were involved. Renal zygomycosis was considered when patients presented with fever, and predominant renal findings such as flank pain, pyuria/anuria, and with evidence of an enlarged, infarcted kidney on computed tomography (CT). Nosocomial zygomycosis was considered when symptoms and signs of suspected zygomycotic infection developed in patients while staying in the hospital, and an absence of such symptoms or signs before admission. The term uncontrolled diabetes was used when the fasting blood sugar was $\geq$7.78 mmol/l ($\geq$140 mg/dl) in a patient without any dextrose infusion. The patient was further qualified for diabetic ketoacidosis when blood glucose was >11.11 mmol/l (>200 mg/dl) with low bicarbonate (<10 mmol/l), low serum pH (pH $\leq$7.2), and the presence of ketone in the urine.

Cure following the treatment for zygomycosis was defined when the patient was discharged symptom-free, or when there

Box 3 Study setting and patient population

- Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh: over 1400 bedded multi-speciality tertiary care referral hospital, funded by the government of India, located in north India, and catering for the tertiary care needs of the adjoining 4–5 states (provinces) of India.
- Around 700 medical autopsies are performed every year at this centre as a teaching–learning exercise.
- Observation of a considerable number of patients with invasive fungal infection during autopsies has made the clinicians aware of the situation.
- The mycology laboratory at the centre works as the National Mycology Reference Laboratory of this country and World Health Organization Collaborating Center for Reference and Research on Fungi of Medical Importance.
- An institutional zygomycosis registry on patients with invasive zygomycosis has been maintained since July 2006. Patients were included in this registry from the records of mycology and histopathology laboratories.

was a gross reduction in the size of the lesion on imaging or on nasal endoscopic examination. Mortality was considered as all cause mortality.

Retrospective analysis of autopsy proven cases

The cases were included from the autopsy record of the histopathology department. The diagnosis of zygomycosis was confirmed on demonstration of similar hyphae (as mentioned earlier) with inflammatory reaction on histopathology of any organ. All relevant clinical and laboratory data (as mentioned in the prospective analysis) were collected from medical records of autopsy proven cases and analysed retrospectively.

Data analysis

Information collected from the patients' records was organised in the form of a database in Microsoft Excel software. The data were analysed to study the epidemiology (including type of zygomycosis, risk factors), clinical presentation, treatment, complications, and outcome. Risk factors and outcome in the various clinical categories of zygomycosis were compared. For statistical analysis Student's t test and odds ratios were applied wherever required. Multivariate logistic regression analysis using SPSS software version 15.0 was employed for the prominent risk factors, GCS score, and mode of treatment and outcome.

RESULTS

Over the 18 month period (July 2006 through December 2007) 75 cases of invasive zygomycosis were recorded. The cases were diagnosed antemortem in 61 (81%) patients and 14 (19%) additional cases were diagnosed only at autopsy. The data collected prospectively from antemortem and retrospectively from postmortem diagnosed cases were combined and analysed together. The age of the patients ranged from 4 days to 72 years (mean (SD) 33 (21) years) and the male to female ratio was 2.6:1. The age and sex distribution of these cases are presented in table 1. Among the 75 patients, seven (9%) patients acquired infection in the hospital: three children developed cutaneous zygomycosis at the site of ECG lead (one patient), the tapes used to fix peripheral venous line (one patient), and the endobronchial tube (one patient); four adults developed either cutaneous (two patients, one acquired at the site of intramuscular injection, and the other at the site of burn wound) or pulmonary zygomycosis (two patients).

Clinical categories

Based on the site of involvement, the cases could be categorised as ROC type in 36 (48%), pulmonary type in 13 (17%), gastrointestinal type in 10 (13%), cutaneous type in eight (11%), and renal and disseminated types of zygomycosis in four (5%) patients each (table 2).

ROC zygomycosis

All patients in this group were diagnosed antemortem. Uncontrolled type 2 diabetes (58%) and diabetic ketoacidosis (38%) were the significant (odds ratio (OR) 6.4 and 24, respectively, $p<0.05$) underlying illnesses (table 3). Three of those patients were ignorant of their underlying diabetes before presenting to us with zygomycosis. Orbital presentations such as ophthalmoplegia (75%), proptosis (72%), and loss of vision (61%) were the major clinical presentations (table 4). Fever was present in only 44% of patients. The patients with ROC zygomycosis could be divided into three clinical stages based on the extent of involvement: stage I had signs and symptoms limited to sino-nasal area (six patients), stage II had sino-orbital disease (21 patients), and stage III had intracranial extension from sino-nasal disease (nine patients). Imaging techniques (CT or magnetic resonance imaging (MRI)) helped in delineation of the extension of the lesion in 73% (11 of 15) of the patients in this group. In the remaining four patients, although clinically orbital extension was observed, there was no suggestion on CT findings.

Table 1 Age and sex distribution in patients with zygomycosis

	Rhino-orbito-cerebral	Pulmonary	Gastro-intestinal	Cutaneous	Renal	Disseminated	Total (%)
Neonate	1	0	6	1	0	0	8 (11)
Infant	0	1	1	0	0	0	2 (3)
2–12 years	3	2	0	2	1	0	8 (11)
13–20 years	2	1	0	0	1	0	4 (5)
21–30 years	9	1	0	2	0	1	13 (17)
31–40 years	4	0	2	2	0	0	8 (11)
41–50 years	7	4	1	1	2	0	15 (20)
51–60 years	4	4	0	0	0	2	10 (13)
61–70 years	5	0	0	0	0	1	6 (8)
>70 years	1	0	0	0	0	0	1 (1)
Total cases	36	13	10	8	4	4	75

Table 2 Mode of diagnosis of patients with zygomycosis

Category	Number of cases (%)	Antemortem diagnosis (%)	Postmortem diagnosis (%)	Isolation of *Zygomycetes* (%)
ROC	36 (48)	36 (100)	0	23 (72)
Pulmonary	13 (17)	9 (69)	4 (31)	3 (9)
Gastrointestinal	10 (13)	1 (10)	9 (90)	0
Cutaneous	8 (11)	8 (100)	0	3 (9)
Renal	4 (5)	3 (75)	1 (25)	1 (3)
Disseminated	4 (5)	4 (100)	0	2 (6)
Total	75	61 (81)	14 (19)	32

ROC, rhino-orbito-cerebral.

Pulmonary zygomycosis

Nine (69%) of 13 patients were diagnosed antemortem (table 2). Renal failure (69%) was significantly ($p = 0.027$, $OR = 5.5$) associated with patients having pulmonary zygomycosis. Type 2 diabetes and haematological malignancies were noted in five (38%) and three (23%) patients, respectively (table 3). Imaging technique could help in the localisation of the lesions in only three (38%) of eight patients. Among nine patients who were diagnosed antemortem, open lung biopsy helped in the diagnosis of six patients (bronchoalveolar lavage was also positive in four of those six patients), while the remaining three patients were diagnosed on direct microscopy of CT guided fine needle aspiration sample. Types of lesions included consolidation in five patients, cavitation in three, nodular in two, and mixed (nodules and consolidation) in three patients. Seven patients had bilateral and six had one lung involvement; upper and lower lobes were involved in five patients each, and three patients had lesions in all three lobes. High fever with chill was the clinical presentation in 11 (85%) patients; cough with expectoration in five (38%); shortness of breath, chest pain, and pedal oedema in three patients each; and two patients had dry cough.

Gastrointestinal zygomycosis

Most (nine patients, 90%) of the gastrointestinal zygomycosis were diagnosed postmortem (table 2). Prematurity (seven patients, 70%) was the significant ($p<0.001$, $OR = 149$) underlying cause among patients with gastrointestinal zygomycosis (table 3). The patients predominantly presented with bowel gangrene and perforation (70%), and shock (90%).

Cutaneous zygomycosis

All patients in this group were diagnosed antemortem. Long term steroid or immunosuppressive therapy (88%), and metabolic acidosis (38%) besides breach of skin (88%), were significantly associated ($p<0.05$) with this group of patients (table 3).

Disseminated zygomycosis

All cases of disseminated zygomycosis died. All cases were associated with multiple risk factors, steroid and immunosuppressive therapy being the most common predisposing factor (75%).

Renal zygomycosis

Affected patients were exclusively in the young and middle age groups, with two of the four cases in apparently immunocompetent hosts. Only one of the cases with renal zygomycosis was diagnosed postmortem. All three antemortem diagnosed cases

Table 3 Analysis of underlying illness and risk factors with zygomycosis

	ROC n = 36 (%)	Pulmonary n = 13 (%)	Gastrointestinal n = 10 (%)	Cutaneous n = 8 (%)	Renal n = 4 (%)	Disseminated n = 4 (%)	Overall n = 75 (%)
Type 1 diabetes	4 (11), (p = 0.47, OR = 4.8)	1 (8), (p = 0.9, OR = 1.21)	0 (0)	0 (0)	0 (0)	0 (0)	5 (7)
Type 2 diabetes	21 (58), (p = 0.045, OR = 6.4)	5 (38), (p = 0.9, OR = 1.06)	0 (0)	0 (0)	0 (0)	2 (50), (p = 0.7, OR = 3.4)	28 (37)
Diabetic ketoacidosis	14 (39), (p = 0.035, OR = 24)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25), (p = 0.8, OR = 1.4)	15 (20)
Haematological malignancy	3 (8), (OR = 0.8)	3 (23), (p = 0.15, OR = 4.35)	1 (10), (OR = 1.1)	0 (0)	0 (0)	0 (0)	7 (9)
Steroids and ISAs	5 (14), (OR = 0.2)	6 (46), (p = 0.22, OR = 2.5)	0 (0)	7 (88), (p = 0.002,OR = 24)	1 (25), (p = 0.8, OR = 0.8)	3 (75), (p = 0.06, OR = 8.2)	22 (29)
Kidney transplant	0 (0)	2 (15), (p = 0.18, OR = 5.5)	0 (0)	0 (0)	0 (0)	2 (50), (p = 0.002, OR = 34.5)	4 (5)
Prematurity	1 (3), (OR = 0.13)	0 (0)	7 (70), (p<0.001, OR = 149)	0 (0)	0 (0)	0 (0)	8 (11)
Alcoholic chronic liver disease	6 (17), (p = 0.6, OR = 1.8)	1 (8), (OR = 0.5)	1 (10), (OR = 0.7)	1 (13), (p = 1, OR = 0.9)	1 (25), (p = 0.5, OR = 2.3)	0 (0)	10 (13)
Breach of skin	0 (0)	0 (0)	0 (0)	7 (88), (p<0.001,OR = 462)	0 (0)	1 (25), (OR = 3)	8 (11)
Bowel perforation	0 (0)	0 (0)	7 (70), (p<0.001, OR∞)	0 (0)	0 (0)	0 (0)	7 (9)
HIV infection	1 (3), (p = 0.45)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Graft versus host disease	1 (3), (p = 1, OR = 1.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25), (p = 0.037, OR = 23)	2 (3)
Renal failure	11 (31), (OR = 0.63)	9 (69), (p = 0.015,OR = 5.5)	0 (0)	1 (13), (OR = 0.23)	–	3 (75), (p = 0.08, OR = 5.9)	24 (32)
Metabolic acidosis	2 (6), (OR = 0.4)	2 (15), (p = 0.5,OR = 2.07)	0 (0)	3 (38), (p = 0.018,OR = 9.5)	0 (0)	0 (0)	7 (9)
Intensive care unit stay	1 (3), (OR = 0.25)	1 (8), (OR = 1.2)	0 (0)	2 (25), (p = 0.088, OR = 7)	0 (0)	1 (25), (p = 0.2, OR = 5.6)	5 (7)
Neutropenia	3 (8), (OR = 0.4)	3 (23), (p = 0.45, OR = 2.0)	3 (30), (p = 0.25,OR = 3)	0 (0)	0 (0)	2 (50), (p = 0.076, OR = 6.9)	11 (15)
Immunocompetent host	0 (0)	0 (0)	0 (0)	0 (0)	2 (50), (p<0.001)	0 (0)	2 (3)

ISAs, immunosuppressive agents; n, number of cases; OR, odds ratio; ROC, rhino-orbito-cerebral.

Table 4 Clinical presentations in patients with rhino-orbito-cerebral zygomycosis (36 patients)

Eye signs	Number of cases (%)	Other signs	Number of cases (%)
Ophthalmoplegia	27 (75)	Sinusitis	13 (36)
Proptosis	26 (72)	Nasal discharge	7 (19)
Loss of vision	22 (61)	Facial swelling	11 (31)
Chemosis	10 (28)	VIIth nerve palsy	2 (6)
Periorbital swelling	15 (42)	Facial anaesthesia	5 (14)
Periorbital pain	14 (39)	Palatal necrosis	9 (25)
Eyelid necrosis	1 (3)	Fever	16 (44)
Endophthalmitis	1 (3)	Toothache	3 (8)
		Altered consciousness	13 (36)
		Hemiplegia	2 (6)
		GTCS	1 (3)

GTCS, generalised tonic-clonic seizure.

survived. Patients presented with fever and chill (75%), flank pain (100%), pyuria (25%), and anuria (50%).

Fungi isolated

Zygomycetes

Zygomycetes were isolated from 32 (65%) of 49 patients' samples when cultured (table 5). The most common (69%) isolate was *Rhizopus oryzae*. *Apophysomyces elegans* was isolated from 19% of culture positive cases. *A elegans* was isolated from three cases with ROC zygomycosis and one each from cutaneous, renal, and disseminated type. *Rhizopus homothallicus* was isolated from a case of cavitary pulmonary zygomycosis.

Other fungal infections

Concomitant disseminated candidiasis was found in seven patients (five children, two adults); two of them were diagnosed at autopsy only. The five patients with antemortem diagnosis were treated with amphotericin B deoxycholate and fluconazole (three patients) or amphotericin B deoxycholate only (two patients). Only one of those five patients survived. One additional patient with pulmonary zygomycosis, who was diagnosed at autopsy, had *Candida* oesophagitis.

Concomitant aspergillosis was seen in two patients (one with disseminated zygomycosis, one with ROC zygomycosis). The patient with disseminated zygomycosis had invasive pulmonary aspergillosis (diagnosed during autopsy), and the other had cutaneous aspergillosis. The patient with cutaneous aspergillosis responded to surgical debridement and amphotericin B deoxycholate treatment.

Management and outcome in patients with zygomycosis

Treatment and outcome could be evaluated in 53 (71%) of 75 patients, as 14 patients were diagnosed only at autopsy and eight patients died before initiation or completion of adequate therapy (amphotericin B total dose <20 mg/kg of body weight) or surgical debridement. Treatment and outcome are detailed in table 6. The management protocol of these patients was similar, though they were treated by different physicians or clinical units. The management of these patients included surgical debridement of necrotic infected tissue (40 patients), treatment with amphotericin B (45 patients) (either conventional amphotericin B deoxycholate (33 patients) or liposomal amphotericin B (12 patients)), and control of underlying disease (reduction of the dose of steroid/immunosuppressive therapy, seven patients; granulocyte colony stimulating factor therapy, two patients). The minimum dose of amphotericin B was 0.7 mg/kg/day and the maximum dose was 5 mg/kg/day. The overall mortality was 45% of these 53 evaluable patients. The mortality rate was significantly high (11 (85%) of 13 patients; $p = 0.015$) in patients who were managed without surgical debridement. The debridement could not be done in those patients due to very poor general condition or severe thrombocytopenia, renal failure or severe ketoacidosis. Eight patients (four cutaneous and four ROC limited to the sino-nasal area) were managed by surgery alone; three of those patients died (two cutaneous, one ROC clinical type). Antifungal therapy could not be instituted in these three patients as they died before laboratory confirmation of zygomycosis. Two paediatric patients with cutaneous zygomycosis, where the lesions were localised at the site of the ECG lead and tapes, were treated by wide excision of the lesions only. Additionally, in three patients with localised lesions at the sino-nasal area, surgical debridement of the tissue was done and no antifungal therapy was started as the patients were symptom-free after surgery and during follow-up.

Adequate antifungal therapy (total dose of conventional amphotericin B >20 mg/kg or liposomal amphotericin B > 40 mg/kg) was instituted in 45 patients. Conventional amphotericin B deoxycholate was given in 33 patients (mean (2SD) total dose 1.99 (0.3) g) and liposomal amphotericin B in 12 patients (mean (2SD) total dose 4.46 (0.6) g); 10 patients received Fungisome (Life care Innovation, India, a recently introduced liposomal preparation of amphotericin B in India), and two patients received Ambisome (Gilead Science, marketed by Nicholas in India). Comparing different therapeutic modalities, significantly high mortality (100%, $p = 0.005$) was observed when the patients were treated with conventional amphotericin B deoxycholate only (table 7). The mean daily doses of conventional amphotericin B or liposomal amphotericin B in the first 7 days were correlated with the outcome of the 45 patients, who received amphotericin B treatment (table 8). Though no statistically significant association was found with the doses and the outcome in those patients, the cure rate was better with the increase of the mean daily dose of amphotericin B. In the small group where simultaneous control

Table 5 Species of *Zygomycetes* isolated from zygomycosis cases (culture attempted in 49 patients)

Zygomycete	ROC (%)	Pulmonary (%)	Cutaneous (%)	Renal (%)	Disseminated (%)	Total (%)	Fatal (%)
Rhizopus arrhizus	18 (56)	2 (6)	1 (3)	0	1 (3)	22 (69)	13 (59), p = 0.9
Rhizopus rhizopodiformis	1 (3)	0	0	0	0	1 (3)	1 (100), p = 0.45
Apophysomyces elegans	3 (9)	0	1 (3)	1 (3)	1 (3)	6 (19)	2 (33), p = 0.21
Absidia corymbifera	1 (3)	0	0	0	0	1 (3)	1 (100), p = 0.45
Rhizopus homothallicus	0	1 (3)	0	0	0	1 (3)	0
Syncephalastrum racemosus	0	0	1(3)	0	0	1 (3)	0

ROC, rhino-orbito-cerebral.

Table 6 Outcome in patients with zygomycosis

Category	Number of cases (%)	Death (%)	Postmortem diagnosis (%)	Died before treatment (%)
ROC	36 (48)	19 (53)	0	4 (11)
Pulmonary	13 (17)	9 (69)	4 (31)	2 (15)
Gastrointestinal	10 (13)	9 (90)	9 (90)	0
Cutaneous	8 (11)	4 (50)	0	2 (25)
Renal	4 (5)	1 (25)	1 (25)	0
Disseminated	4 (5)	4 (100)	0	0
Total	75	46 (61)	14 (19)	8 (11)

ROC, rhino-orbito-cerebral.

of the underlying illness was attempted, mortality remained high (56% of the nine patients).

Among patients who received amphotericin B deoxycholate (33 patients), transient high creatinine (>2 mg/dl) was observed in five patients, hypokalaemia in eight, hypomagnesaemia in five patients, and skin rash and diarrhoea in one patient each. Among those who received the liposomal preparation (12 patients), two patients had hypokalaemia, and transient high creatinine and hypomagnesaemia was observed in one patient each.

When outcome was compared on the basis of GCS score, significantly higher mortality (82%, $p = 0.005$) was observed in patients with GCS score $\leqslant 8$ compared to patients with GCS score $\geqslant 9$ (35% mortality). On multivariate analysis, patients with GCS score $\geqslant 9$ were found to have a significantly higher survival rate (table 9).

Outcome in patients with ROC zygomycosis

As large numbers of patients were reported with ROC zygomycosis, the outcome was also separately analysed for this group. The patients were stratified into three stages (I to III) as previously mentioned, and the outcome analysis was compared between the three stages (table 10). It was observed that patients with intracranial extension (stage III) had significantly higher (89%, $p = 0.018$) mortality compared to stages I or II of the disease.

DISCUSSION

Confirming the global increase in the number of patients with invasive zygomycosis, the rise in the number of patients at our centre continues unabated. Compared to the earlier two series of 13 cases/year[6] and 36 cases/year[4] we report here a series of 75 cases over an 18 month period (50 cases/year), the highest rate ever reported from any tertiary care centre. The rise is well correlated with the increase in population of uncontrolled diabetes mellitus in India, as ROC zygomycosis (48%) was the most common type and uncontrolled diabetes and diabetic ketoacidosis were the significant underlying illness in this clinical type. An interesting new observation was the significant association of renal failure (69%, OR = 5.5, $p = 0.027$) in patients with pulmonary zygomycosis. Observation of a further four cases of isolated renal zygomycosis in the present series highlights the need for further study of this clinical entity. Despite increased awareness about invasive fungal infection among our clinicians, a considerable number (19%) of zygomycosis cases was detected only upon postmortem examination, and the majority (64%) of them had gastrointestinal zygomycosis. The silver lining in this gloomy scenario is the gross improvement in antemortem diagnosis (69%) of patients with pulmonary zygomycosis, due to the aggressive investigation (open lung biopsy and CT guided fine needle aspiration) pursued during the present series. The emergence of *A elegans* in patients in the tropics is further confirmed, as it was the second most common isolate (19%) after *R oryzae*. During critical evaluation of the management, the combination (surgery and amphotericin B) approach was found to be most successful, as patients treated with conventional amphotericin B monotherapy without surgery had significant higher mortality. To predict the outcome in patients with invasive zygomycosis, the GCS score may play an important role, as patients with GCS score $\geqslant 9$ had a significant higher survival on multivariate analysis.

The age distribution of patients in this series suggests that invasive zygomycosis may occur in any age group, although pulmonary zygomycosis tends to occur more commonly in the elderly age group, and gastrointestinal zygomycosis in neonates and infants. The age distribution in the present series agrees with the findings of previous series,[4 6] and corroborates the largest meta-analysis of 929 cases.[2] Interestingly, the reason for the higher prevalence of invasive zygomycosis among males is still unclear.

Zygomycosis, formerly thought to be always community acquired, is also now recognised as being a nosocomial infection.[10] It has been associated with various procedures or devices used in hospitals, including antifungal prophylaxis, bandages or medication patches, intravenous catheters, and even tongue depressors.[1 3] Nine per cent of our patients had acquired nosocomial infection either at the site of the ECG leads or the adhesive tapes, or from contaminated intramuscular injections, or from air in the hospital environment.

In addition to common risk factors (uncontrolled diabetes, diabetic ketoacidosis, long term steroid therapy, haematological malignancy), renal failure and alcoholism related chronic liver disease were identified as risk factors in 32% and 13% of patients, respectively, in the present study. Both these conditions were never considered as important underlying illnesses in any series of invasive zygomycosis, though in recent years chronic liver disease has been found to be an important risk factor for the development of invasive aspergillosis in the intensive care unit.[11 12] Similar to our observation, in a report from India, chronic renal failure and hepatic disease were identified as underlying illnesses in 12% and 8% of patients, respectively, with ROC zygomycosis.[13]

Although specific underlying illnesses were implicated with a particular clinical type of zygomycosis,[1–3] a change has been observed in recent years. In addition to diabetes and ketoacidosis, recent studies have shown that patients undergoing

Table 7 Treatment and outcome in patients with zygomycosis (53 patients)

	Number of patients	Cure (%)	Death (%)
Surgery only	8	5 (63)	3 (38), ($p = 0.7$)
Surgery + conventional amphotericin B therapy	23	16 (70)	7 (30), ($p = 0.24$)
Surgery + liposomal amphotericin B therapy	9	5 (56)	4 (44), ($p > 0.95$)
Amphotericin B only			
Conventional amphotericin B deoxycholate	10	0	10 (100), ($p = 0.004$)
Liposomal amphotericin B	3	2 (67)	1 (33), ($p = 0.7$)
Amphotericin B + surgery + control of underlying disease	5	3 (60)	2 (40), ($p = 0.8$)
Amphotericin B + control of underlying disease	4	1 (25)	3 (75), ($p = 0.3$)

Table 8 Correlation of outcome with the mean daily dose of amphotericin B during the first 7 days of treatment

Mean daily dose of liposomal amphotericin B (number of patients)	Cure at the end of complete therapy (%)	Mean daily dose of conventional amphotericin B (number of patients)	Cure at the end of complete therapy (%)
1–2 mg/kg/day (n = 6)	2 (33.3)	0.7–1 mg/kg/day (n = 30)	13 (43.3)
2–4 mg/kg./day (n = 4)	3 (75)	>1 mg/kg/day (n = 3)	3 (100)
>4 mg/kg/day (n = 2)	2 (100)		

No significant association was found with any dose and outcome.

haematopoietic stem cell transplantation have the increasing problem of acquiring ROC zygomycosis.[3 14] However, the present study did not predict such a change in underlying illness in ROC zygomycosis in India, possibly due to the tremendous rise in the number of patients with diabetes. A large population of diabetic patients in India remains undiagnosed and uncontrolled due to deficiencies of the health care facilities, and they may report to the hospital only after acquiring invasive zygomycosis.[4] In the present study three patients were ignorant of their underlying uncontrolled diabetes before reporting to our hospital.

Invasive zygomycosis may occur in immunocompetent hosts as well, as was reported in 19% of patients in a large meta-analysis.[2] In our earlier two series, 12–23% of patients had no underlying disease.[4 6] However, only two (3%) patients in the present series were apparently healthy. The contrasting figure may be due to the difference in the nature of the studies (present prospective one compared to other retrospective studies). In the present series, there were serious attempts by the clinicians to identify any underlying illness by undertaking detailed investigations. This emphasised the need for thorough investigations before declaring any patient apparently healthy in any study.

The majority of ROC zygomycosis cases are diagnosed antemortem for obvious reasons of ease of sampling. Despite easier diagnosis, the mortality rate remains high unless the patients are treated with aggressive surgery and antifungal agents.[3] In the present series, though all the patients with ROC zygomycosis were diagnosed antemortem, mortality was very high (47%). Most likely it was due to delayed presentation to our hospital, as the majority (75%) of our ROC zygomycosis cases had ophthalmic presentation. This fact was further confirmed, as a significant higher death rate (89%, p = 0.018) was observed in stage III patients or patients with intracranial extension.

Pulmonary zygomycosis may have a wide variety of disease manifestations including solitary nodular lesion, lobar involvement, and cavitary or disseminated form.[1 2 15–17] Infiltrates or mass lesions without any specific lobar predilections are common findings. Pulmonary consolidation and cavitations are seen less frequently.[1 18] In the present series three of 13 patients (23%) had cavitary lesions. It was suggested that such cavities represent liquefaction of the pulmonary infarcts.[19] Large numbers (44–100%) of pulmonary zygomycosis cases are diagnosed postmortem due to a lack of specific symptoms and signs.[1 4 6 16 18] Increased awareness can improve the proportion of cases with an antemortem diagnosis.[4 6] This was evident in the present series with an antemortem diagnosis in 69% of cases. Unfortunately, though sputum or bronchoalveolar lavage (BAL) analysis is frequently employed, this process rarely leads to confirmation of diagnosis. Therefore, open lung biopsy, surgical extirpation, and transthoracic needle aspiration provide better results.[16 18] The mortality is very high (50–70%) in pulmonary zygomycosis, though there is improvement in antemortem diagnosis,[3 16 19] as was also observed (56% mortality) in the present series.

Gastrointestinal zygomycosis is the third most common (13%) type in the present series, though it is considered rare.[3] The disease presents as necrotising enterocolitis in premature neonates,[12 20 21] and rarely in neutropenic adults.[1 3 22] In the present series, 70% of patients with gastrointestinal zygomycosis were premature, and had necrotising enterocolitis, bowel perforation, and shock. Antemortem diagnosis of gastrointestinal zygomycosis is difficult and can be made by biopsy during surgery or endoscopy.[3] The lone case of antemortem diagnosis in the present series was diagnosed during histopathological analysis of resected bowel.

Cutaneous zygomycosis occurs in patients with disrupted cutaneous barrier, as a result of burn, trauma, maceration, or injection.[1 3] Isolated cutaneous zygomycosis has a favourable prognosis, but the infection may spread to distant sites by secondary vascular invasion, or spread locally and aggressively causing necrotising fasciitis, especially in immunocompromised patients, leading to mortality in up to 80% of cases.[1 3 23 24] In the present series the mortality was also considerably high (50%) in this clinical type, possibly due to immunosuppression in 88% of the patients.

Renal zygomycosis, as seen in our earlier study,[4 6] occurs in immunocompetent young adults. The exact route of entry of the pathogen is not known. Patients present with unilateral or bilateral flank pain, fever with chills, pyuria or anuria. When diagnosed antemortem, surgery accompanied with amphotericin B treatment may save the patients, as was seen in the

Table 9 Multivariate logistic regression analysis of prominent risk factors, Glasgow Coma Score, mode of treatment and outcome

	p Value	OR (95% CI)
Treatment with liposomal amphotericin B	0.859	1.1781 (0.193 to 7.173)
Diabetic ketoacidosis	0.647	0.599 (0.067 to 5.378)
Metabolic acidosis	0.746	1.508 (0.125–18.145)
Alcoholic chronic liver disease	0.999	9×10^9 (0 to ∞)
Glasgow Coma Score ⩾9	0.016	0.128 (0.024 to 0.680)
Age >50 years	0.865	0.990 (0.950 to 1.031)
Male gender	0.171	0.225 (0.027 to 1.902)

CI, confidence interval; OR, odds ratio.

Table 10 Outcome in patients with rhino-orbito-cerebral zygomycosis (36 patients)

	Number of cases	Deaths (%)
Stage I: limited sino-nasal or ophthalmic disease	6	1 (17), (p = 0.18)
Stage II: sino-nasal + orbital	21	10 (48), (p = 0.9)
Stage III: with intracranial extension	9	8 (89), (p = 0.018)

present study. However, further studies are required to understand its pathogenesis.

For diagnosis of zygomycosis, CT scan and MRI may help especially when multiple infarcts are visible. These may also help in delineating the extension of the lesion,[25] though in four of our patients with ROC zygomycosis imaging techniques failed to detect the extension of the lesion to the orbit. The imaging techniques also help to collect samples from the site of the lesion in deep tissue for diagnosis, as was done in three patients with pulmonary zygomycosis in the present series.

Among zygomycetes, members of the genera *Rhizopus, Mucor, Absidia, Rhizomucor* and *Apophysomyces* are commonly implicated in causing human infection, and overall *Rhizopus* species are the most commonly isolated agents from patients with zygomycosis.[1] *R oryzae* (= *R arrhizus*) is the most frequent cause of ROC zygomycosis, whereas *R microsporus* produces primarily cutaneous and gastrointestinal zygomycosis. *Absidia corymbifera* ranks as the second and *Mucor* species as the third most common organisms causing zygomycosis. *A elegans* is rarely isolated and is known to cause cutaneous zygomycosis.[1 2] Clearly *R oryzae* is the leading cause (69%) of invasive zygomycosis in the present series and *A elegans* the second most common agent (19%) isolated. From India we reported the emergence of *A elegans* infections and recorded infections at sites other than skin as well.[4 26] In the present series it also produced ROC, renal, and disseminated zygomycosis, besides cutaneous zygomycosis. The isolation of *S racemosum* from one patient with cutaneous zygomycosis is interesting as this agent was also isolated earlier from the cutaneous infection of a patient from south India.[27] Further study is required to determine whether this rare zygomycotic agent is as prevalent as *A elegans* in India.

Zygomycetes are ubiquitous saprophytic moulds, commonly isolated from soil and air worldwide. However, in both these environments they are outnumbered by other fungi; in air by *Aspergillus* species and *Penicillium* species; and in soil by *Aspergillus*, *Penicillium* and keratinophilic fungi. *R rhizopodiformis* is an otherwise harmless saprophyte of moss and *Crataegus* species of leaves.[28] *A elegans* was first isolated from soil samples of a mango orchard in India.[29] The genus *Absidia* is also a ubiquitous soil inhabiting fungi, and has been isolated from air.[30] *Zygomycetes* have also been isolated from diverse aerial environments such as library dust[31] and indoor air samples.[32] Many *A elegans* and *Saksenaea vasiformis* infections arise directly from traumatic inoculation of fungus in soil contaminated wounds. Though no attempt was made for environmental sampling in the present study, it would be interesting to study *Zygomycetes* in the hospital environment. In an earlier study we isolated only *Mucor* species from the environment of burn patients.[33]

The best management of zygomycosis is presumed to be aggressive surgical debridement combined with medical treatment and control of predisposing factors where possible.[1–3] Amphotericin B is the first line drug of choice in most cases. In recent years posaconazole as a substitute for amphotericin B, especially as salvage therapy, has gained popularity.[34] Surgery is considered necessary due to the massive amount of tissue necrosis occurring during zygomycosis that may prevent entry of antifungal agents in adequate concentrations. Additionally surgery is supposed to minimise the fungal load in the tissue.[1 3 34] One must exercise control in extrapolating treatment choices from the data available from the literature, which are mostly either meta-analyses or retrospective data analyses, and may be subject to a period effect. There is no prospective randomised trial available for zygomycosis to define the optimal treatment guidelines. Clinicians are forced to rely upon anecdotal case reports, limited retrospective reviews, and their own experience in determining the first line therapy for zygomycosis. In this perspective the present study is important as outcome of treatment could be evaluated prospectively in a considerable number of cases (53 patients) over a short period of time (18 months) from a single centre with a common management protocol. The overall mortality rate was 45% of these 53 patients treated, close to the rate of 46% observed in the largest meta-analysis.[2] The present study emphasises that the treatment outcome largely depends on the overall clinical condition of the patient as multivariate logistic regression analysis showed that a GCS $\geqslant 9$ had a significantly better prognosis. The process of randomisation for a prospective clinical trial in zygomycosis is complicated due to underlying illness, time of diagnosis, severity of infection, and overall clinical condition. To overcome such difficulties, the GCS type of scoring system may be taken into consideration while randomising the patient groups.

In the present series, the outcome was significantly poor (85%, $p = 0.0015$) when surgical debridement could not be performed. Though similar observations were seen in other series,[2 13 35] there is the potential for selection bias in these case series as patients who do not undergo surgery have fundamental

Main messages

- Zygomycosis is an increasingly common infection in immunocompromised patients, especially in countries with large numbers of patients with uncontrolled diabetes.
- The new underlying diseases identified include renal failure and chronic liver disease in patients with zygomycosis.
- Pulmonary zygomycosis can have a variety of presentations including consolidation, cavitations or nodule formation. Invasive procedures improve antemortem diagnosis of these patients.
- A patient with isolated renal zygomycosis is an emerging problem in India.
- Emergence of *Apophysomyces elegans* in tropical countries is recognised.
- For the management of invasive zygomycosis, a combination of early diagnosis, surgical debridement, and amphotericin B treatment, especially liposomal preparations, is emphasised.
- Glasgow Coma Score is an independent marker of prognosis in cases of invasive zygomycosis.

Box 5 Current research questions

- Improvement in early and rapid diagnosis of patients with zygomycosis, especially in gastrointestinal and disseminated type.
- Pathogenesis of isolated renal zygomycosis.
- Correlation of *Zygomycetes* isolated from the patients and their environment.
- Ecology of *Apophysomyces elegans*.
- Better management strategies especially in pulmonary, gastrointestinal or disseminated types.
- Consideration of Glasgow Coma Score in randomisation of patients in future clinical trials.

differences in severity of illness or comorbidities. In the present series, comorbid conditions such as poor general health, thrombocytopenia, and renal failure prevailed in the group in which surgery could not be done. The mortality rate was also significantly higher (100%, $p = 0.006$) when conventional amphotericin B deoxycholate was given alone compared to any other mode of treatment. In contrast, in the series of 929 cases, 61% of patients survived when treated with amphotericin B deoxycholate.[2] The contrasting result may be due to differences in the patient groups and the time of diagnosis. The higher dose of amphotericin B may produce better results, as was found in the present study. The lipid formulations of amphotericin B are significantly less toxic than conventional amphotericin B deoxycholate and can be safely administered at higher doses for a longer period of time. However, no prospective, double blind comparable dataset in patient groups has been published to enable any conclusion to be drawn. In the present study liposomal amphotericin B was used in 12 patients and the mortality was lower compared to amphotericin B deoxycholate (42% *vs* 48%), though there was no statistically significant difference in outcome.

This study has its limitation in outcome analysis, as a single physician or one team did not treat the patients, and the patients varied in age and clinical presentations. In addition, we could not substantiate the associated factors and determine the attributable mortality due to zygomycosis.

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