Original article

Cerebral zygomycosis

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Summary

Fifty-six patients with cerebral zygomycosis (mucormycosis) were seen during the period 1971–2001 in two tertiary care hospitals located in south India with tropical climate and catering to neurological diseases. Forty-four patients had rhinocerebral and twelve patients had isolated central nervous system (CNS) zygomycosis. Of these, ten were culture proven (*Rhizopus oryzae* in eight and *Mucor* in two); 30 were diagnosed as probable and 16 were diagnosed possible; mixed infections were seen in three patients. Diabetes mellitus was the predisposing condition in a majority (31/44) of patients with the rhinocerebral form of zygomycosis. The tissue obtained at biopsy/autopsy in either form showed necrotic/infarcted tissue with neutrophilic infiltration with broad non-septate hyphae showing irregular branching. The outcome was poor despite surgical excision and antifungal therapy. The high concentration of spores in a mouldy environment, the bird population and improper disposal of hospital waste may facilitate healthy hosts presenting with primary CNS disease.

Key words: zygomycosis, mucormycosis, rhinocerebral, central nervous system, south India.

Introduction

In 1800s, Platauf [1] described zygomycetes as pathogenic organisms causing disseminated disease in cancer. Zygomycosis includes the fungi of the family *Mucoraceae* that include *Mucor*, *Rhizopus*, *Rhizomucor* and *Absidia*.[2] The earlier communications refer to the identification of these organisms on tissue morphology rather than cultural characteristics. The term zygomycosis is preferred to mucormycosis when the diagnosis is made on tissue sections without culture confirmation. The frequency of zygomycosis and other fungal infections are increasing because of the increasing life span of patients with neoplasms and widespread use of immunosuppressive therapy.[2, 3] Zygomycosis is an opportunistic infection that may be localized to the site of entry like nasal sinus, lungs, gut and skin or can be disseminated.[4, 5] Zygomycosis usually occurs in patients with an underlying disorder, most commonly diabetes mellitus with keto acidosis but can also occur in apparently healthy subjects.[2] Other predisposing conditions include immunosuppressive therapy, leukaemia, lymphoma, burns, glomerulonephritis, gastroenteritis, haemodialysis and desferroxamine therapy.[2, 6–10]

Zygomycosis involving central nervous system (CNS) is rapidly fatal and the syndrome of rhino-orbital zygomycosis with intra cerebral extension is well described in literature. The isolated form of zygomycosis essentially involving CNS without apparent peripheral involvement is less well characterized. In this communication, we describe our experience of pathology of CNS zygomycosis from two tertiary care hospitals located in South India with tropical climate and catering to neurological diseases. Both centres are

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located in tropical zone with hot and humid weather and heavy tropical vegetation around with tropical birds. Eucalyptus is grown in large areas for industrial purposes. Majority of the population belong to low income group, living in heavily populated house holds. These factors favour fungal growth and spread to cause pathology in susceptible individual.

Material and methods

The patients of CNS zygomycosis diagnosed at autopsy/biopsy during the period 1971–2001 from two tertiary care hospitals of neurological and neurosurgical services located in south India were included in the study. The age, gender, predisposing illness, clinical syndrome, pathology, organism isolated and treatment outcome were reviewed in all the patients (Table 1). The cases were diagnosed primarily by tissue morphology, utilising periodic acid Schiff (PAS) and Gomori's methenamine silver (GMS) stain on tissue sections in all the patients and aided by fungal culture whenever possible. 'Broad non-septate hyaline ribbon like hyphae with irregular branching' was the basis for identification as zygomycetes on histology. Culture positive cases were diagnosed as proven, clinical syndrome with predisposing condition and histology as probable and clinical syndrome with histology as possible cases.

Results

There were thirty patients (six of them reported earlier)[11] from Nizam's Institute of Medical Sciences, Hyderabad (period 1991–2001) and 26 patients from National Institute of Mental Health and Neurosciences, Bangalore (period 1971–2001). Twelve patients were diagnosed at autopsy and 44 by biopsy. Cultural characterization was carried out in 13 patients. The 56 patients in the study (36 males and 20 females) were in the age range of 12–72 years (mean age of 41.67 years). For purposes of description, patients were divided into two groups: rhino-cerebral and isolated CNS zygomycosis (Table 1).

Rhinocerebral zygomycosis

Forty-four patients had rhinocerebral zygomycosis. (Table 1). Diabetes mellitus was the underlying disorder in 31 patients, acute myeloid leukaemia under chemotherapy in one and renal transplantation with immunosuppression in two patients (one patient had diabetes mellitus and underwent renal transplantation) (Table 1). There was no identifiable risk factor in the remaining 10 cases, and hence the fungal infection was considered clinically only as a differential diagnosis. The most frequent symptoms were headache, fever, oedema on one side of face, visual disturbances and loss of vision. Black coloured discharge from eye or palate was also observed.

Pathology

The tissue examined at autopsy/biopsy obtained from rhino-facial and cerebral areas consisted of necrotic/infarcted tissue. There were broad nonseptate hyaline pale acidophilic hyphae in haematoxylin and eosin stained sections in the necrotic tissue (Fig. 1). The morphology was better delineated with PAS and GMS stains that demonstrated the irregular branching and angio-invasion. Vasculitis, thrombosis and infarction with neutrophilic infiltration were frequent. There was meningitis in two patients, and granulomatous response in three patients, involving the brain (Table 1).

Culture

Culture from tissue was available in 12 of 44 patients. It was sterile in two, grew *R. oryzae* in seven, *Mucor* in two and, *R. oryzae* with *Candida* in one patient (Table 1).

Treatment outcome

Debridement and excision of necrotic tissue from rhinofacial zone was performed and patients were treated with amphotericin B. Six patients survived and the rest succumbed to the illness (Table 1).

Isolated zygomycosis

There were 12 patients in this group and the diagnosis was established only at autopsy in six patients. There was no evidence of pulmonary, gastro intestinal, cutaneous or sino/orbital involvement in any of the cases by routine radiological and laboratory tests. The predisposing factors included diabetes mellitus in only two patients, immunosuppression following renal transplantation in one, renal failure with disseminated candidiasis in two, gastroenteritis in one, hypoplastic anaemia on steroid therapy in one. One of the patients with diabetes mellitus has undergone surgery for meningioma (Table 1). In five patients no predisposing risk factor for a fungal infection was found. Six patients presented with 'cerebral stroke like syndrome', two with meningitis and four with features of space occupying lesion in the brain (Table 1).

Table 1 Age, sex, predisposing condition, clinical form, site of lesion, pathology, culture and outcome of central nervous system zygomycosis.

S. no.	Biopsy /autopsy hospital	Sex/age in years	Predisposing condition	Clinical form	Site of lesion	Pathology	Fungal morphology	Culture	Diagnosis	Outcome
Rhinocerebral form										
1	Biopsy NIMS 1994[11]	M 57	Diabetes mellitus	Rhino-orbital	Ethmoid sinus	Neutrophilic infiltrate vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
2	Biopsy NIMS 1996[11]	M 62	Diabetes mellitus	Rhino-orbito cerebral	Left maxillary ethmoid sphenoid sinus orbit	Neutrophilic infiltrate vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	*Mucor* sp.	Proven	Died
3	Biopsy NIMS 1998[11]	F 58	Diabetes mellitus	Rhino-orbital	Ethmoid sinus	Haemorrhagical necrosis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
4	Biopsy NIMS 1996[11]	M 58	Diabetes mellitus	Rhino-orbito cerebral	Maxillary sinus, cheek, forehead	Haemorrhagical necrosis neutrophilic Infiltrate	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	Negative	Probable	Died
5	Biopsy NIMS 1997	M 35	Diabetes mellitus, postrenal transplant	Cavernous orbitocerebral	Orbit, maxillary sinus	Haemorrhagical infarct vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	*Rhizopus oryzae*	Proven	Died
6	Biopsy NIMS 1998	F 15	Acute myeloid leukaemia	Rhinocerebral	Palate, facial edema	Infarction	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
7	Biopsy NIMS 1998	M 40	None	Rhinocerebral	Sphenoid sinus, clivus destruction	Neutrophilic infiltrate granulation tissue	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
8	Biopsy NIMS 1998	M 18	Juvenile diabetes mellitus	Rhinocerebral	Palate, ethmoid, maxillary, sphenoid	Haemorrhagical infarction vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	*Mucor* sp.	Proven	Died

9	Biopsy NIMS 1998	M 50	Diabetes mellitus	Rhino-orbital	Orbit	Vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
10	Biopsy NIMS 1998	M 62	Diabetes mellitus	Rhino-orbital	Orbit	Necrosis, neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
11	Biopsy NIMS 1998	M 18	Juvenile Diabetes mellitus	Rhino-orbital	Sphenoid sinus nasopharynx	Vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
12	Biopsy NIMS 1999	M 70	Diabetes mellitus	Rhino-orbital	Sphenoid sinus	Granuloma with giant cell reaction	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
13	Biopsy NIMS 1999	F 68	Diabetes mellitus	Supraorbital fissure syndrome	Right maxillary sinus	Infarction vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
14	Biopsy NIMS 1999	M 55	Renal transplant	Rhino-orbital	Ethmoid sinus retrobulbar	Infarction vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	*Rhizopus oryzae*	Proven	Survived
15	Biopsy NIMS 1999	F 72	Diabetes mellitus	Rhino-orbital	Orbit	Infarction, neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
16	Biopsy NIMS 1999	F 50	Diabetes mellitus	Rhino-orbito cerebral	Ethmoid sinus	Necrosis	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
17	Biopsy NIMS 1999	F 50	None	Rhino-orbito cerebral	Orbit	Necrosis	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
18	Biopsy NIMS 2000	M 56	Diabetes mellitus	Rhinocerebral	Right maxillary ethmoid sinus	Necrosis	Broad, irregular branching, aseptate hyphae in tissue	*Rhizopus oryzae*	Proven	Died

Table 1 *Continued*

S. no.	Biopsy /autopsy hospital	Sex/age in years	Predisposing condition	Clinical form	Site of lesion	Pathology	Fungal morphology	Culture	Diagnosis	Outcome
19	Biopsy NIMS 2000	M 60	Diabetes mellitus	Rhino-orbito cerebral	Orbit	Necrosis	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
20	Biopsy NIMS 2000	M 30	None	Rhino-orbital	Maxillary ethmoid sinus	Necrosis, neutrophilic infiltrate vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Possible	Survived
21	Biopsy NIMS 2000	M 12	Juvenile diabetes mellitus	Rhino-orbital	Palate, cheek, face, eyeball	Necrosis, neutrophilic infiltrate vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	Negative	Probable	Survived
22	Biopsy NIMS 2000	M 72	Diabetes mellitus	Rhinocerebral	Orbit	Necrosis, neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue	*Rhizopus oryzae*	Proven	Died
23	Biopsy NIMS 2000	M 50	None	Rhinocerebral	Maxillary antrum	Haemorrhagical infarction: neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Posssible	Died
24	Biopsy NIMS 2001	M 65	None	Rhino-orbital	Maxillary sinus orbit	Necrosis, neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
25	Biopsy NIMS 2001	F 45	Diabetes mellitus	Rhino-orbito cerebral	Orbit	Necrosis, neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Survived
26	Biopsy NIMS 2001	F 45	Diabetes mellitus	Rhino-orbito cerebral	Pansinusitis orbital cellulitis	Necrosis neutrophilic infiltrates	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Survived
27	Biopsy NIMS 2001	M 18	Juvenile diabetes mellitus	Rhino-orbito cerebral	Left Eye, ethmoid sinus, retinal artery occlusion	Necrosis, neutrophilic infiltrates	Broad, irregular branching, aseptate hyphae in tissue	*Rhizopus oryzae*	Proven	Survived

28	Autopsy NIMHANS 1987	F 46	Diabetes mellitus	Rhino-orbito cerebral	Left eye and nostrils meninges orbitofacial with basal meningitis	Infarcts with thrombosis of vessel	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
29	Autopsy NIMHANS 1987	M 50	Diabetes mellitus	Rhino-orbito cerebral	Meninges	Meningitis with infarction left basal ganglia	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	*Rhizopus oryzae*	Proven	Died
30	Biopsy and autopsy NIMHANS 1988	M 55	Diabetes mellitus	Rhino-orbito cerebral	Left ethmoid mass, left temporal	Left temporal abscess with basal meningitis	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
31	Autopsy NIMHANS 1993	F 48	Diabetes mellitus	Rhino-orbito cerebral	Orbitofrontal + frontal	Neutrophilic infiltration	Broad, irregular branching, aseptate hyphae in tissue	*Rhizopus oryzae* + *Candida*	Proven	Died
32	Autopsy NIMHANS 1996	M 19	None	Rhino-orbito cerebral	Orbitofrontal lobes, basal ganglia, thalamus (both sides), left internal capsule	Neutrophilic infiltrate with infarction	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	*Rhizopus oryzae*	Proven	Died
33	Biopsy NIMHANS 1996	M 58	Diabetes mellitus	Rhino-orbito cerebral	Temporal poles and unci	Meningitis	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
34	Biopsy NIMHANS 1983	F 40	Diabetes mellitus	Rhino-orbital	Orbit + cavernous sinus	Neutrophilic infiltrate with infarction	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
35	Biopsy NIMHANS 1983	F 50	Diabetes mellitus	Rhino-orbito cerebral	Orbit/eyelid	Infarction	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
36	Biopsy NIMHANS 1988	F 50	Diabetes mellitus	Rhino-orbito cerebral	Right eye/orbit	Infarction	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
37	Biopsy NIMHANS 1988	M 40	Diabetes mellitus	Rhino-orbital	Maxillectomy specimen	Abscess	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died

Table 1 *Continued*

S. no.	Biopsy /autopsy hospital	Sex/age in years	Predisposing condition	Clinical form	Site of lesion	Pathology	Fungal morphology	Culture	Diagnosis	Outcome
38	Biopsy NIMHANS 1986	F 64	Diabetes mellitus	Cavernous thrombosis	Nose	Abscess	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
39	Biopsy NIMHANS 1987	M 49	Diabetes mellitus	Rhino-orbital	Necrotic lesions ethmoid, maxillary antrum	Abscess	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
40	Biopsy NIMHANS 1988	M 60	None	Rhino-orbital	Maxillary antrum	Infarction	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
41	Biopsy NIMHANS 1995	M 65	None	Rhino-orbital	Periorbital sinuses	Infarction	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
42	Biopsy NIMHANS 1996	M 35	None	Rhinocerebral	Left maxillary antrum	Granuloma	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
43	Biopsy NIMHANS 1997	F 60	None	Rhino-orbital	Left maxillary nasal cavity (nasal mucosal and submucosal)	Necrosis and neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
44	Biopsy NIMHANS 1988	M 48	None	Rhino-orbital	Orbital	Necrosis and neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
Isolated form										
45	Biopsy and autopsy NIMS 1991[11]	M 60	Hypoplastic anaemia	Stroke like syndrome	Right deep fronto parietal	Haemorrhagical infarction vasculitis	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died

46	Autopsy NIMS 1994[11]	F 19	Renal failure	Stroke like syndrome	Left fronto temporal	Haemorrhagical infarction zygomycetes *Vasculitis* + *Candida*	Broad, irregular branching, aseptate hyphae in tissue and vessel wall + pseudohyphae and budding yeast forms of *Candida*	ND	Probable	Died
47	Autopsy NIMS 2000	F 30	Renal failure	Multiple abscess	Frontoparietal	Abscess with zygomycetes + *Aspergillus* + *Candida*	Broad, irregular branching, aseptate hyphae in tissue with thin septate acute angle branching *Aspergillus* and pseudohyphae and budding yeast forms of *Candida*	*Candida tropicalis*	Probable	Died
48	Autopsy NIMHANS 1978	M 12	None	Isolated cerebral	Left temporal region	Multiple areas of infarct	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
49	Autopsy NIMHANS 1992	M 20	None	Isolated cerebral	Postfrontal deep seated lesion	Haemorrhagical necrosis	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
50	Autopsy NIMHANS 1993	M 45	None	Isolated cerebral	Sub arachnoid haemorrhage	Mycotic aneurysm	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Possible	Died
51	Biopsy NIMHANS 1987	M 33	None	Isolated cerebral	Middle cranial fossa mass	Necrosis neutrophilic infiltrate	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
52	Biopsy NIMHANS 1992	M 20	None	Isolated cerebral	Right parietal region	Granuloma	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died
53	Biopsy NIMHANS 1995	F 35	None	Isolated cerebral	Meninges	Necrosis	Broad, irregular branching, aseptate hyphae in tissue	ND	Possible	Died

Table 1 *Continued*

S. no.	Biopsy /autopsy hospital	Sex/age in years	Predisposing condition	Clinical form	Site of lesion	Pathology	Fungal morphology	Culture	Diagnosis	Outcome
54	Biopsy NIMHANS 1997	M 47	Postrenal transplant	Isolated cerebral	Left frontal	Vasculitis, thrombosis and infarction	Broad, irregular branching, aseptate hyphae in tissue and vessel wall	ND	Probable	Died
55	Biopsy NIMHANS 1999	F 46	Diabetes mellitus postoperative meningioma	Isolated cerebral	Left frontal	Chronic abscess	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died
56	Biopsy NIMHANS 2001	F 45	Diabetes mellitus	Isolated cerebral	Right frontal	Infarction haemorrhage	Broad, irregular branching, aseptate hyphae in tissue	ND	Probable	Died

NIMS, Nizam's Institute of Medical Sciences; NIMHANS, National Institute of Mental Health and Neurosciences; ND, not performed.

Figure 1 Photomicrograph showing broad aseptate irregularly branching hyphae. Silver methenamine × 40. Biopsy from sphenoid sinus in 18-year-old male patient with juvenile diabetes mellitus, (Serial number 11, Table 1) diagnosed as probable zygomycosis based on clinical presentation as rhino-orbital syndrome with a predisposing factor of diabetes mellitus and the fungal hyphal morphology.

Pathology

Haemorrhagical infarction with vasculitis was observed in five patients and mycotic aneurysm with rupture in one patient. There was suppurative inflammation in four, granulomatous response in one and meningitis in two patients. The morphology of fungus was same in all cases and culture was available in one case. One patient had fungi morphologically belonging to zygomycetes sp., *Aspergillus* sp. and *Candida* in the abscess on tissue sections while the blood culture grew only *Candida tropicalis*. One patient had multiple cerebral tuberculomata, with basal arachnoiditis and obstructive hydrocephalus. She underwent ventriculoperitoneal shunt, followed by resection of tuberculomata. Later she had subdural haematoma as a complication of surgical procedure, which was drained. She was on assisted ventilation. During the prolonged hospital stay, she developed renal failure, paralytic ileus and succumbed. At postmortem examination, she was found to have multiple cerebral tuberculomata, disseminated candidiasis involving kidneys, lungs and brain. In the brain a solitary, necrotic acute area of cerebritis, which yielded zygomycosis was observed, sparing other systemic organs. Another patient with diabetes mellitus was operated for meningioma and developed a chronic abscess of zygomycetes postsurgically, as a nosocomial infection. One patient with hypoplastic anaemia on parenteral steroid therapy developed heamorrhagical infarction in brain secondary to zygomycosis.

Culture

Culture from tissue was available in one case which grew *Candida tropicalis* only in a mixed infection.

Treatment and outcome

In six patients with isolated zygomycosis, diagnosis was established only at autopsy. The other six patients, in whom the diagnosis was established antemortem by biopsy, received appropriate antifungal therapy, but succumbed to the disease (Table 1).

Discussion

Although literature regarding CNS mycosis from India is scant, aspergillosis is the most common etiological agent in histologically verified series.[12–15] However, cryptococcosis was the most frequently reported culture proven cause of fungal meningitis from India especially with the advent of acquired immuno deficiency syndrome (AIDS).[12, 16, 17] Zygomycosis is infrequently reported from India.[11, 18, 19] Zygomycetes are ubiquitous saprophytic organisms found on bread, soil, air and hospital ward rooms especially in tropical countries with vegetation.[20] The disease is transmitted by inhalation of spores from the atmosphere. Although exposure to spores is frequent, disease is infrequent because of avirulence of the organism.[21] The infection manifests most often in a person with underlying state of diabetic ketoacidosis. It is also being reported more frequently in immunosuppressed individuals because of hematological disorders, organ transplantation, renal failure with acidosis, gastroenteritits, haemodialysis and rarely following therapeutic/investigative injections, as iatrogenic infection and application of surgical adhesive tape contaminated with fungal spores.[2, 7–10, 22] In the present study, culture positive cases were diagnosed as proven, clinical syndrome with predisposing condition and histology as probable and clinical syndrome with histology as possible cases. In the cases where culture or predisposing factor was not present, histological identification of fungus, based on hyphal morphology provided important clue to diagnosis.

Animal experiments suggest that the failure to suppress the germination of spores and failure to kill proliferating hyphal element are the factors for increased risk of developing zygomycosis in individuals with diabetic ketoacidosis.[23] In a diabetic individual, the monocytes in the blood are dysfunctional, the ketaoacidotic state inhibits neutrophilic chemotaxis, phagocytosis and oxidative burst, and diabetic ketotic serum permits exuberant growth of spores.[24, 25] Lack of dialyzable inhibitory factors in sera of diabetics and the glucose rich milieu facilitates fungal growth.[26] Neutropenia, altered bacterial flora in nasopharynx and availability of iron ferritin complex in tissues are some of the factors facilitating the colonisation and proliferation of the contaminating fungi.[6, 27]

Diabetes mellitus was the predisposing underlying disorder in 58.9% of cases (33/56 patients) in the present series. It is reported that rhinocerebral zygomycosis occurs in a setting of diabetic ketoacidosis in 70% of cases. After inhalation of spores, the infection settles in the paranasal sinuses or palate and spreads to the ipsilateral orbit and thence to the retro-orbital and intracranial compartments.[7]

Brain involvement in the absence of sinus involvement has also been demonstrated as in the present series. In literature it is mainly documented in intravenous drug abusers.[28] There is no history of drug abuse in our sample although inoculation of the fungus during therapeutic parenteral administration or invasive investigative procedures is strongly suspected. With instances of recycling of used syringes and catheters for intravenous administration especially in underdeveloped and developing countries, hematogenous inoculation of fungal spores can lead to primary CNS lesions, without overt predisposing factors.

Isolated CNS zygomycosis may also originate from any of the primary sites of infection and spread by hematogenous route following angioinvasion without manifesting at the primary site.[22]

The clinical manifestations of rhinocerebral form starts as sinusitis, rapidly progressing to involve neighboring tissues like orbit, eye and optic nerve and extend to the brain. Facial oedema, pain, necrosis, loss of vision, black discharge, along the nasal cavity and angle of the eye and proptosis are the usual features. As angioinvasion is very frequent, occlusion of sphenopalatine artery, and central retinal artery can occur mostly effecting blindness as is seen in our study.

In isolated brain involvement, without sinus or orbital infection, the clinical presentation was stroke – like syndrome/meningitis/or intracranial space occupying mass lesion. One patient had a ruptured, mycotic aneurysm following zygomycotic infection. The diagnosis was established only at autopsy in 6 of 12 patients in this group, due to lack of specific clinical findings and failure to culture the organism from blood, cerebrospinal fluid or other fluids.[20] The pathology comprised cerebral infarction with neutrophilic infiltration of the lesional area and angio-invasion in majority of cases of rhinocerebral form. It is well

known that zygomycetes have a predilection for angioinvasion. Brain is involved by extension of infection along the subarachnoid space around optic/olfactory nerves or leptomeningeal vessels causing a number of clinical syndromes like sinusitis, cellulitis of orbit, orbital apex syndrome, cavernous sinus syndrome or hemiparesis because of thrombosis of internal carotid artery.[21] Disseminated candidiasis with renal failure associated with isolated CNS zygomycosis was noted in the present series as a coinfection during the hospital stay with assisted ventilation highlighting the potential sources and spread of infection. Meningitis and granuloma were infrequently reported. Bichili *et al.* [29] reported meningitis and granulomatous response following zygomycotic infection in healthy subjects.

Rhizopus oryzae was the commonest species isolated in the present study. This fungal infection can be rapidly progressive and fatal if left untreated and mortality rates of 90% have been reported. With the development of diagnostic methods and sophisticated laboratory tools, more patients are being diagnosed early. Awareness, early diagnosis, management based on radical surgical excision of the infected and necrotic tissue, appropriate antifungal therapy and treatment of underlying predisposing systemic, metabolic disorders improved the prognosis.[4, 21, 30]

Patients suffering from the rhinocerebral form of zygomycosis in our series succumbed although recent availability of antifungal therapy in India has improved the survival rate. As the diagnosis could not be established early in cases of primary cerebral involvement, the clinical outcome remained poor, all succumbing to the illness. Availability of serological tests and panfungal PCR (polymerase chain reaction) testing, for early diagnosis may change the scenario.

The pathogenesis of CNS zygomycosis in healthy subjects is not known and may as well be similar to sinocranial aspergillosis that occurs in tropical countries in immunocompetent individuals.[14, 15] The high concentration of spores in a mouldy humid environment and spore carrying and spreading bird population were proposed as factors facilitating clinical infection by aspergillosis.[12, 14, 15] Similar mechanism could be operational in maintaining the spore density of zygomycosis in the environment close to human habitat and invasion of susceptible individuals. The improper disposal of hospital waste and inadequate sterilisation facilities in hospitals and clinics in developing countries could be facilitating the invasion of unsuspecting, non-immunocompromised healthy host, by zygomycosis, at times presenting as primary CNS disease with protean manifestations and thus delaying the diagnosis.

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