Review article

Zygomycosis – a case report and overview of the disease in India

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Summary

A case of zygomycosis caused by *Rhizopus oryzae* in a diabetic patient previously misdiagnosed as invasive pulmonary aspergillosis and an overview of the disease in India are presented. The case was diagnosed by direct microscopy, histopathologic examination and culture. Following surgical resection of pulmonary cavity under cover of amphotericin B administration, the patient recovered completely. Of 461 cases reported to-date, approximately 70% had been diagnosed at the Postgraduate Institute of Medical Education and Research, Chandigarh, in north India. This may be attributed to better awareness, expertise and infrastructural facilities for mycological diagnosis than to any particular regional preponderance of the disease. Rhino-orbito-cerebral manifestations were the most common feature of zygomycosis (269 cases), followed by cutaneous disease (66 cases), which is in conformity with the pattern prevalent worldwide. The etiologic agents encountered were *Rhizopus oryzae*, *Apophysomyces elegans*, *Saksenaea vasiformis*, *Cunninghamella bertholletiae*, *Absidia corymbifera*, *Basidiobolus ranarum* and *Conidiobolus coronatus*. In contrast to cases from the developed world where transplant recipients and patients with haematological malignancies seem to be most vulnerable to zygomycosis, the most common risk factor in India was uncontrolled diabetes mellitus. Amphotericin B was the mainstay of various treatment modalities employed. The relevance of a strong clinical suspicion and early diagnosis of zygomycosis for favourable prognosis can hardly be over-emphasised.

Key words: zygomycosis, pulmonary, overview, India, diabetes, amphotericin B, surgery.

Introduction

Zygomycosis refers to a group of uncommon but frequently fatal mycoses caused by fungi of the class Zygomycetes, which is subdivided into the Mucorales and the Entomophthorales both containing human pathogens. Zygomycetes are found ubiquitously in soil and grow rapidly on carbohydrate substrates with luxuriant sporulation.[1] The disease is usually an opportunistic infection in patients with diabetes, immunosuppression, trauma, burn wounds and other chronic debilitating diseases.[2,3] Besides, there are numerous reports showing involvement of immunocompetent hosts. Zygomycosis of the respiratory tract may manifest as rhino-cerebral and sinus infection, which in fact is its most common clinical form.[2] In addition, the lung is the single most common site of involvement in disseminated zygomycosis.[4–6] Extensive necrosis leading to vascular invasion and infarction with dissemination to other sites is often seen if therapy is not initiated promptly.[2] Although numerous cases of zygomycosis have been reported from India, the number of pulmonary cases is only a handful. Clinical awareness and thorough mycological investigations are required for an early

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diagnosis and successful treatment. We herein report a case of pulmonary zygomycosis in a diabetic patient who had been misdiagnosed as invasive pulmonary aspergillosis before its reference to our laboratory.

Case report

A 61-year-old, male farmer, an ex-smoker was referred to the Clinical Research Centre of V. P. Chest Institute on 3 August, 2004, with a history of 5–6 days of fever, productive cough, anorexia and generalised weakness for the past 1 month and pain in right infra-scapular region since 2 days. The patient had been diagnosed with diabetes mellitus 15 days ago and was put on treatment for it. At the time of admission, his general physical examination revealed clubbing but the respiratory and other systems were unremarkable. His total leukocyte count was 14 450 cells/ml with 58% lymphocytes and serum glucose level (fasting) on admission was 252 mg/dl. The patient did not give any history of symptoms suggesting metabolic disturbances such as diabetic ketoacidosis, nor was there any laboratory-based evidence to suggest the same. Kidney and liver function tests were normal. Chest X-ray film (postero-anterior view) showed a thick-walled cavity in the hilar region (Fig. 1). Sputum examination yielded negative results for acid fast bacilli, pyogenic organisms and malignant cells. Mantoux test was negative. CECT

Figure 1 Chest X-ray showing a cavitory lung lesion in the right hemithorax.

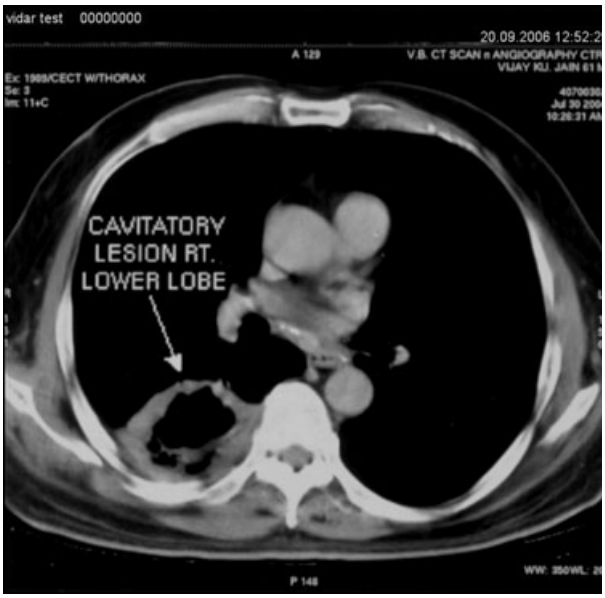

Figure 2 CT scan of the lesion showing a thick-walled cavity in the right lower lobe.

chest revealed a cavitating lesion, measuring $6.5 \times 5 \times 6$ cm in the apical segment of the right lower lobe abutting the posterior chest wall (Fig. 2). A CT-guided fine needle aspiration biopsy (FNAB) had already been performed in a private laboratory in Delhi and histologically diagnosed as invasive aspergillosis. A review of H&E stained biopsy sections in the Department of Medical Mycology, V. P. Chest Institute, led to its diagnosis as zygomycosis based on the presence of broad, aseptate, branching hyphae with focal bulbous dilatations (Fig. 3). This was confirmed by repeated isolation of *Rhizopus oryzae* in culture from six consecutively collected sputum samples. His bronchoscopy showed healthy endobronchial mucosa and no obvious deformities. Culture of his bronchial aspirate and BAL also yielded *Rhizopus oryzae*. The patient's serum proved negative for precipitins against our laboratory's in-house prepared culture filtrate antigens of *Aspergillus fumigatus*, *A. flavus* and *A. niger*.[7] CT of the head and para-nasal sinuses did not show any abnormality. ELISA for HIV was negative. He was put on amphotericin B i.v. 10 mg/day and the dose was gradually increased to 70 mg/day till a cumulative dose of 1.2 g had been administered. Patient was kept under tight glycemic control with human insulin. Although his fever subsided, serial chest X-rays did not show any significant clearing and the back pain persisted. After 25 days of antifungal treatment, *en bloc* surgical removal of the lesion was performed. Gross examination

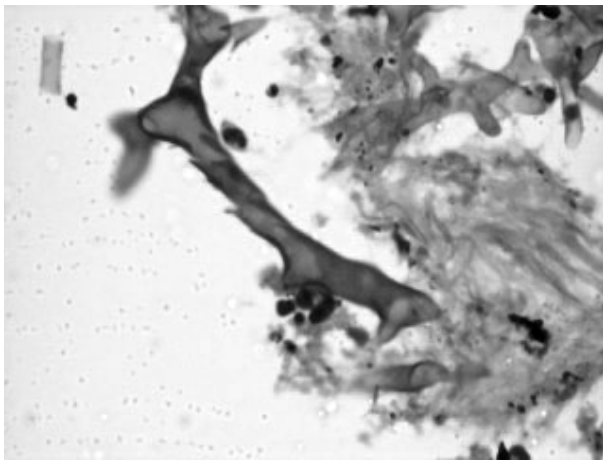

Figure 3 H&E stain showing broad, aseptate hyphae with bulbous dilatations in fine needle aspiration biopsy specimen (400×).

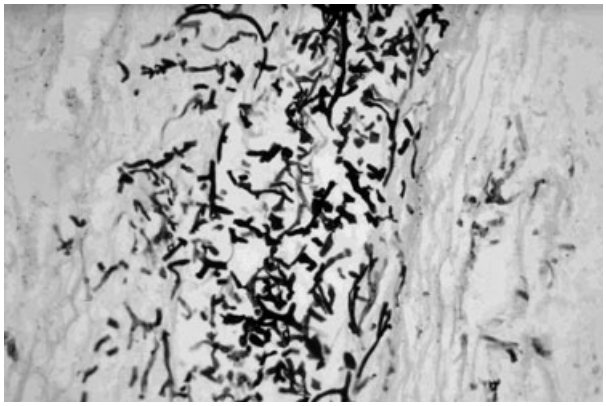

Figure 4 Gomori methenamine silver stain showing lumen of a large vessel filled with aggregates of broad aseptate hyphae forming a mycotic thrombus in the resected lung specimen (200×).

of the resected lung showed multiple infarctions, a cavity and scattered grey spots in the lobules. Histopathologic examination of the resected lung specimen revealed extensive necrosis and focal polymorpho-nuclear infiltration. Interspersed in the tissue were characteristic broad aseptate hyphae with focal bulbous dilatations and non-dichotomous irregular branching. The hyphae at places appeared folded and twisted. They were readily demonstrable with haemotoxylin and eosin (H&E) and silver methenamine (SM) stains. The fungus was seen infiltrating lung tissue as well as vessel walls. Necrosis of vessel walls and mycotic thrombi were observed (Figs 4 and 5). Mycological culture of the resected lung specimen was found to be negative. Amphotericin B was continued for 5 weeks after surgery till a cumulative dose of 3 g was administered.

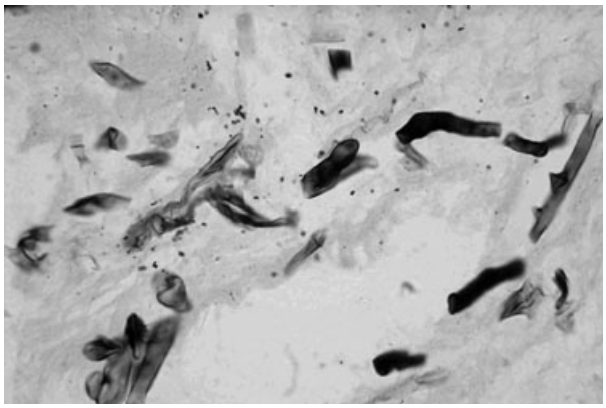

Figure 5 Gomori methenamine silver stain showing broad, aseptate hyphae with irregular branching invading the vessel wall of resected lung specimens (400×).

The kidney function tests were elevated (serum urea – 63 mg/dl, creatinine – 1.75 mg/dl) during drug therapy but returned to baseline after amphotericin B administration was stopped. The patient developed hypokalaemia after 2 weeks of therapy, which was corrected with oral potassium supplements. He became asymptomatic and has remained so till date.

Discussion

Fungi of the class Zygomycetes have been implicated in human disease since 1885. The evidence was primarily histopathologic and rarely by culture.[3] The disease was then known as 'Mucormycosis' and diagnosed by the demonstration of coenocytic and angioinvasive hyphae.[3] With confirmation of the diagnosis by culture in the following decades it became evident that *Rhizopus* spp. and not *Mucor* spp. were the predominant etiologic agents.[8] Over the years, the number of species causing the disease expanded. In addition to *Rhizopus*, *Mucor* and *Absidia* spp., several other genera emerged as the etiologic agents, which represented the Orders Mucorales as well as Entomophthorales.

Cases of systemic zygomycosis are mostly caused by species belonging to the Mucorales and they are characterised by a rapidly evolving clinical course, tissue destruction and invasion of blood vessels. In contrast, subcutaneous zygomycosis is caused by species of *Conidiobolus* and *Basidiobolus*, which belong to the Entomophthorales, and it involves immunocompetent hosts.[1] However, many cases of subcutaneous zygomycosis involving other body sites such as the gastrointestinal tract, lymph nodes and muscles have also been reported in immunocompromised hosts. Zygomycosis

has been associated with various risk factors notably, cancer,[9] antibiotic and steroid use[10] diabetes,[11,12] deferoxamine/desferrioxamine therapy,[13] transplantation and its associated immunosuppressive therapies.[14]

The principle route of infection in zygomycosis is believed to be respiratory and the infection is acquired by inhalation of the fungal spores from environmental sources. Percutaneous routes of exposure are important in causing cutaneous/subcutaneous tissue infection.[3] The ingestion of fermented milk, bread products and other carbohydrate substrates contaminated by fungi may have a role in inciting gastro-intestinal zygomycosis.[9] Following diagnosis of zygomycosis, prompt institution of medical therapy and extensive surgical debridement of all devitalised tissues are considered to be the best therapeutic approach.[2] Besides, treatment of any underlying predisposing condition is a vital component of therapeutic approach and amphotericin B has been the drug of choice.

Although the first description of zygomycosis in humans was made by Platauf [15] in his paper entitled Mycosis Mucorina, the first reference to the disease in India was in 1963 by Balasubrahmanyan *et al.* [16] who reported a case of pulmonary mucormycosis. This was followed by the first report of *antemortem* clinical diagnosis and *postmortem* identification of the fungal culture by Grover *et al.* [17]. The next reference to this disease was made by Hazarika *et al.* [18] who described a case of rhinocerebral infection. Since then, the number of case reports has been steadily increasing. Altogether, 461 cases of zygomycosis have been compiled in our literature review. Information on the regional distribution, species spectrum of etiologic agents, diagnostic criteria, underlying disease and organ distribution of lesions, therapy and its outcome are summarised in Tables 1 and 2 and depicted in Fig. 6. It is noteworthy that approximately 70% of the reported cases had been diagnosed at a single medical center, namely, the Postgraduate Institute of Medical Education and Research, Chandigarh, in north India.[21,25] This may be attributed to better awareness, expertise and infrastructural facilities for mycological diagnosis in this institute rather than to a particular regional preponderance of the disease. Here, it may also be borne in mind that our current knowledge of the geographic or regional distribution of mycoses does not depict their true prevalence. In a scholarly review about 4 decades ago, Ainsworth [50] had aptly observed that the available literature reflected the distribution of medical/veterinary mycologists and their special interests at a given time more accurately than it did their actual distribution and relative importance in various parts of the world. His observations hold equally good for the distribution pattern of zygomycosis as we see today in India.

The cases reviewed further reveal that rhino-orbito-cerebral manifestations were the most common feature of zygomycosis (269 cases), followed by cutaneous/subcutaneous disease (66 cases), which is consistent with the pattern of the disease prevailing world-wide. Renal and gastrointestinal zygomycosis was seen in 34, disseminated in 32 and pulmonary in 28 cases. There were a few cases with involvement of donor kidneys [51,28] and a solitary case involving prosthetic heart-valve involvement.[52] The etiologic agents encountered in the reported cases are *Rhizopus oryzae*, *Apophysomyces elegans*, *Saksenaea vasiformis*, *Cunninghamella bertholletiae*, *Absidia corymbifera*, *Basidiobolus ranarum*, *Conidiobolus coronatus*. The main risk factors identified were diabetes mellitus, cancer and post-transplant immunosuppresion. The number of individuals apparently without a predisposing factor was also significant. Furthermore, of the 194 patients whose follow-up and outcome were recorded 62 (32 %) died. Amphotericin B was the mainstay in the various treatment modalities employed.

Among the 28 cases showing pulmonary infection, 25 were out of the landmark series of 315 cases reported by Chakrabarti *et al.* [21,25] from a single tertiary-care hospital in Chandigarh indicating that actual prevalence of the disease in India would be much higher than is indicated by the published reports. In all of the pulmonary zygomycosis cases, the disease was confined only to the lungs. Pulmonary zygomycosis usually presented with fever and lung infiltrates not responding to broad-spectrum antibacterial antibiotics. Also, dyspnoea, cough and life-threatening heamoptysis have been described. In such cases CT is a valuable diagnostic tool that enables the early detection of lesions suggestive of infection by filamentous fungi. Furthermore, CT-guided FNAB is simple, easy to perform and provides reliable material for a definitive diagnosis and identification of the etiologic agent.[53] In the present case, diagnosis of zygomycosis was established by histopathologic examination of CT guided FNAB and culture. With growing clinical awareness and augmentation of mycological investigative facilities, one can look forward to enhanced ante-mortem diagnosis, and hence improved survival of patients because of timely institution of specific antifungal therapy combined with surgical intervention if warranted. In contrast to cases from the developed world where transplant recipients and patients with haematological malignancies seem to be most vulnerable to zygomycosis, the most common

Table 1 Statewise distribution, predisposing factors, diagnostic criteria and etiologic agents in 461 reported cases of zygomycoses from India

No. cases	Place/state	Predisposing factors	Diagnostic criteria	Etiologic agents	Ref. no.
1	Chandigarh, UT*	Idiopathic myelofibrosis	Direct microscopy, culture	*Apophysomyces elegans*	19
1	Chandigarh, UT	Systemic lupus erythematosus	Histopathology	Not given	20
129	Chandigarh, UT	Miscellaneous risk factors (74)** None (22)	Histopathology of tissue/aspirate and/or culture	*R. arrhizus* (11)** *A. elegans* (8)	21
6	Chandigarh, UT	Renal transplant (6)	Not specified	Not given	22
8	Chandigarh, UT	Diabetes mellitus (1) Chronic alcoholism (1)	Direct microscopy/histopathology/culture	*Apophysomyces elegans*	23
6	Chandigarh, UT	Diabetes mellitus (type I)	Direct microscopy/histopathology/culture	*Rhizopus arrizus* (2) Mucorales	24
178	Chandigarh, UT	Uncontrolled diabetes (131)	Direct microscopy/histopathology/culture	*Rhizopus oryzae* (41) *A. elegans* (17)	25
1	Ludhiana, Punjab	Diabetes mellitus with multisystem failure	Histopathology	Not given	26
1	Varanasi, Uttar Pradesh	None	Histopathology	Not given	27
1	Lucknow, Uttar Pradesh	Renal transplant	Biopsy, culture	*Mucor*	28
8	Delhi, UT	Not given	Resection/biopsy	Not given	29
1	Delhi, UT	None	Direct microscopy, culture	*Rhizopus* sp.	30
1	Delhi, UT	Acute lymphocytic leukemia, on chemotherapy	Histopathology, culture	*Rhizopus* sp.	31
9	West Bengal	None	Direct microscopy, biopsy and culture	*Conidiobolus coronatus*	32
15	Kolkata, West Bengal	None	Biopsy and culture	*Conidiobolous coronatus* (8) *Basidiobolus ranarum* (7)	33
4	Pune, Maharashtra	Lepromatous Leprosy (1)	Biopsy	*Entomophthorales*	34
1	Pune, Maharashtra	Diabetes mellitus	Direct microscopy, histopathology, culture	Mucorales	35
2	Nagpur, Maharashtra	Not given	Fine needle aspiration cytology	Not given	36
1	Nagpur, Maharashtra	Diabetes with ketoacidosis	Direct microscopy, culture	*Rhizopus oryzae*	17
56	Hyderabad, Andhra Pradesh	Diabetes mellitus (31)	Autopsy (12), Biopsy (44), Culture (13)	*Rhizopus oryzae* (8), Mucor (2)	37
1	Visakhapatnam, Andhra Pradesh	None	Direct microscopy, culture	*Saksenaea vasiformis*	38
2	Vellore, Tamil Nadu	Not given	Histopathology	Not given	39
1	Vellore, Tamil Nadu	None	Biopsy, culture	*Saksenaea vasiformis*	40
1	Vellore, Tamil Nadu	None	Culture	*Conidiobolus*	41
19	Vellore, Tamil Nadu	Not mentioned	Culture	Mucorales (14) Entomophthorales (5)	42
1	Vellore, Tamil Nadu	None (Lower Segment Caesarean Section)	Direct microscopy, culture	*Apophysomyces elegans*	43
1	Vellore, Tamil Nadu	Bone marrow transplant	Culture	*Cunninghamella bertholletiae*	44
1	Chennai (formerly Madras), Tamil Nadu	Acute lymphoblastic leukemia (on chemotherapy)	Direct microscopy, culture	*Rhizopus*	45
1	Madras, Tamil Nadu	Not given	Histopathology	Not given	46
1	Banglore, Karnataka	Acute promyelocytic leukemia (on chemotherapy)	Direct microscopy, culture	*Absidia corymbifera*	47
1	Pondicherry, UT	None	Direct microscopy, culture	*Basidiobolus ranarum*	48
1	South India	None	Colon biopsy, urine culture, serology	*Basidiobolus ranarum*	49

*UT, union territory; **Figures in parentheses denote number of cases.

Table 2 Organ-wise distribution, therapy and clinical outcome in 461 reported cases of zygomycosis from India

	Organs involved								
No. cases	ROC*	Cutaneous/ subcutaneous	Pulmonary	GI**	Renal	Disseminated	Treatment	Outcome	Ref. no.
1	1	–	–	–	–	–	–	Fatal	19
1	–	–	1	–	–	–	Not known	Fatal	20
129	57	20	13	6	18	15	Amphotericin B + debridement	Cured (20)*** Fatal (13)	21
6	6 (CNS)	–	–	–	–	–	Not known	High mortality rate	22
8	1	3	–	–	3	1	Surgery and/or medical therapy	Cured (6) Fatal (2)	23
6	6	–	–	–	–	–	Amphotericin B + surgery	Cured (4) Fatal (2)	24
178	97	26	12	15	12	16	Amphotericin B and/or surgery	Cured (90) Fatal (35)	25
1	–	–	–	1 (gastric)	–	–	Surgery + Amphotericin B	Cured	26
1	–	–	1	–	–	–	Surgery + Amphotericin B	Not known	27
1	–	–	–	–	1	–	Graft nephrectomy	Fatal	28
8	–	–	–	8	–	–	Antifungal therapy	Cured (1)	29
1	–	1	–	–	–	–	Debridement + Amphotericin B + Skin graft	Cured	30
1	–	–	–	1	–	–	Surgical Resection	Fatal	31
9	9	–	–	–	–	–	Oral KI and/or Keto/Fluconazole	Cured	32
8	8	–	–	–	–	–	Not known	Not known	33
7	–	7	–	–	–				
4	–	4	–	–	–	–	Not known	Not known	34
1	1	–	–	–	–	–	Debridement, antifugal drugs, glycemic control	Cured	35
2	2	–	–	–	–	–	Antifungal therapy + debridement	–	36
1	1	–	–	–	–	–	No antifungal given	Fatal	17
56	56	–	–	–	–	–	Amphotericin B + debridement	Cured (6) Fatal (50)	37
1	–	1	–	–	–	–	Amphotericin B	Fatal	38
2	–	–	–	1(intestine) 1(gastric)	–	–	Not specified	Fatal	39
1	–	1	–	–	–	–	Amputation + Skin Graft + KI****	Cured	40
1	1	–	–	–	–	–	KI + Cotrimoxazole + Prednisolone	Cured	41
19	19	–	–	–	–	–	Surgery + Amphotericin B	Cured	42
1	–	1	–	–	–	–	Debridement + Amphotericin B	Cured	43
1	–	–	1	–	–	–	Amphotericin B	Fatal	44
1	–	1	–	–	–	–	Amphotericin B	Cured	45
1	1	–	–	–	–	–	Itraconazole	Cured	46
1	1	–	–	–	–	–	Amphotericin B	Fatal	47
1	–	1	–	–	–	–	Oral KI	Cured	48
1	–	–	–	1	–	–	Amphotericin B	Fatal	49

*ROC, rhino-orbito-cerebral; **GI, gastrointestinal tract; ***Figures in parentheses denote number of cases; ****KI, potassium iodide.

risk factor in India is uncontrolled diabetes mellitus. Chakrabarti *et al.* [25] have emphasised that the rising trend in the number of patients with invasive zygomycosis in their study was significantly associated with increasing number of patients with uncontrolled diabetes. Amongst sporadic case studies, Jindal *et al.* [20] have reported a solitary case of pulmonary mucormycosis in their autopsy studies of 25 fatal complications of systemic lupus erythematosus (SLE). Lahiri *et al.* [27] reported a case of zygomycetous fungal ball in a post-tubercular cavity. In the present case, it seems pertinent to point out that this patient had been misdiagnosed as a case of invasive aspergillosis before he was referred to our institute. The point that needs to be emphasised in this context is that histopathologic diagnosis of zygomycosis should not be confused with aspergillosis or

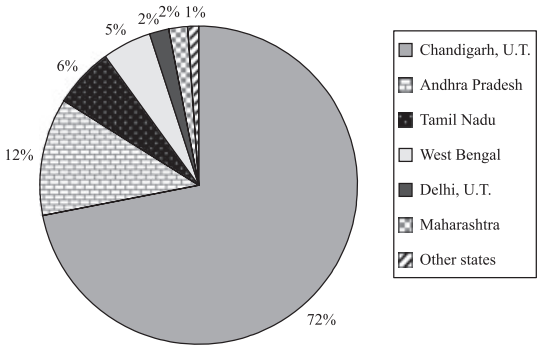

Figure 6 Statewise percent distribution of 461 reported cases of zygomycosis in India.

infections due to other hyalohyphomycetes such as species of *Scedosporium* and *Fusarium* characterised by hyaline septate mycelium. The consequences of such a mistaken diagnosis could prove fatal as zygomycosis responds only to aggressive management with amphotericin B therapy combined with surgery if necessary and not with flucytosine and azoles.[54,55]

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