Primary Cutaneous Zygomycosis in India

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Abstract Cutaneous zygomycosis remains underdiagnosed despite being frequently encountered. Delay in the diagnosis contributes to delay in treatment, and a resultant high morbidity and mortality. A retrospective analysis of the reported cases of cutaneous zygomycosis from India was made using various search engines and cross-referencing from available manuscripts. A total of 42 publications from India on the topic were identified, since the first reported case of primary cutaneous zygomycosis by Veliath et al. (1976). There are 130 described cases of cutaneous zygomycosis with an overall mortality of 35 %. The commonest zygomycete identified was *Apophysomyces elegans*, and the commonest predisposing factor was breach of the skin. Surprisingly, diabetes was reported only in 36 cases (27.69 %). It is important to be aware of this unusual but fatal infection in order to manage it properly and have a good outcome.

Keywords Necrotizing fasciitis · Mucormycosis · Antifungal drugs · Sepsis · Renal failure · Diabetes · Immunocompetent · Amphotericin B

Introduction

Zygomycosis is an infrequently encountered fungal infection caused by fungi of the phylum Zygomycota. This phylum has two main classes—Trichomycetes (which does

not contain any human pathogens) and Zygomycetes, which contains the orders Mucorales and Entomophthorales, both of which can cause infection in humans.

The order Mucorales contains genera such as *Mucor*, *Rhizopus*, *Rhizomucor*, *Absidia*, *Apophysomyces*, *Cunninghamella*, *Saksenaea*, *Syncephalastrum*, and *Cokeromyces*, whereas Entomophthorales contains the genera *Basidiobolus* and *Conidiobolus*. Mucorales usually causes human infections in six main clinical forms—rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous—whereas Entomophthorales is less common in causing human infection as compared to Mucorales. The term “zygomycosis” (or phycomycosis) encompasses infections by both of these orders (Mucorales and Entomophthorales). These ubiquitous fungi are present in soil and vegetation, with a worldwide distribution (with the exception of *Cokeromyces* which is exclusively seen in North America), but they are unable to cause infections under normal conditions [1–3].

Rhinocerebral infection is the commonest form of zygomycosis in humans, followed by pulmonary infection. Cutaneous involvement is less common than these, and mainly occurs in two forms—a “benign” well-localized subcutaneous form, which usually occurs due to infection by the Entomophthorales, and a more fulminant cutaneous infection with necrotizing fasciitis, systemic sepsis, and a fatal outcome if the diagnosis and consequently the appropriate treatment is delayed [1–3].

This study reviews the existing Indian literature on the fulminant cutaneous variety of zygomycosis.

Materials and Methods

At the outset, the aim of the study was established to identify all cases of primary cutaneous mucormycosis from India, as opposed to the more benign and localized form of

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subcutaneous disease that usually presents as nodular masses in the subcutaneous tissues. Primary cutaneous disease was defined as cutaneous disease in the absence of demonstrable disease elsewhere in the body. The distinction from the subcutaneous disease was made on the basis of skin involvement (ulceration, sinuses, fistulae, necrotizing fasciitis) with or without systemic sepsis, since these are the cases that are associated with a high mortality if they remain undiagnosed.

Having defined the disease parameters, a search was made of available English language literature on the topic of cutaneous zygomycosis in humans through Pubmed (and Google) using various combinations of keywords such as “cutaneous,” “zygomycosis,” “mucormycosis,” “necrotizing fasciitis,” and “India”. The search pattern was further refined by using “India” along with the individual genera such as *Mucor*, *Rhizopus*, *Rhizomucor*, *Absidia*, *Apophysomyces*, *Cunninghamella*, *Saksena*, *Syncephalastrum*, and *Cokeromyces* and searching for cutaneous involvement of each.

The full text of all relevant obtained articles was analyzed for their relevance to the topic and to our country, and the bibliography of each was scanned to pick up any other relevant papers on the topic.

Results

The first reported case of primary cutaneous zygomycosis from India was by Veliath et al. in 1976 [4], in a patient with chronic pyelonephritis and uremia, who eventually succumbed to massive pulmonary infarction as a result of dissemination of the disease from its primary site—an ulcer on the right calf (diagnosis was made postmortem). Following this, another 41 publications dealing with the topic of primary cutaneous mucormycosis in India are documented in available English language literature from 1976 till date (August 2011). Of these, 34 publications are case reports documenting 39 cases of necrotizing fasciitis due to zygomycetes and are tabulated as Table 1 [4–37]. The other 8 publications are institutional series documenting the occurrence of 96 cases of cutaneous zygomycosis among the overall spectrum of zygomycotic infections and are tabulated as Table 2 [38–45]. Another series by Mohapatra [46] did not clearly mention the number of cases of cutaneous infection, and is therefore not included in the final analysis. Thus, a total of 135 cases of cutaneous zygomycosis have been documented from India till date. Although such infections have been reported from all over India, the majority of cases have been reported from a single institution, the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh.

However, there seems to be some overlapping of the data, since, after reporting a few cases of cutaneous infection,

some institutions have later documented their experience with the overall spectrum of zygomycosis or zygomycotic necrotizing fasciitis, thus giving a slightly higher figure for the total number of cases reported from India in this review than is actual. These include the reports of three cases by Chakrabarti et al. in 1997 [10], which were later included in their review of zygomycosis over a 10-year period [38], one by Thami et al. [12], which was later included in the series by Chander et al. [43], and the one by Saraiya [19], which was later reanalyzed in 2011 [45]. These cases were deducted from the total of 135 reported cases (as above) to yield 130 reported cases of zygomycotic cutaneous infection from India. Similarly, the series by Jain [41] on zygomycotic necrotizing fasciitis is bound to have included some previous cases from the same institution, but this could not be ascertained clearly. Therefore, this series was included in the overall total cases.

Overall, 128 risk factors for the development of zygomycotic necrotizing fasciitis were documented. The commonest factor was breach of the skin barrier, by surgery, trauma, burns, injections, etc., that was seen in 77 cases. Next common factor was diabetes mellitus (36 cases); surprisingly, HIV infection was documented in only 1 case (Table 3).

Species identification was available in only 65 reported cases (Table 4). The commonest zygomycete identified was *Apophysomyces elegans* (35 cases), followed by *Rhizopus* (11 cases), and *Saksena* (7 cases). A new species of *Apophysomyces* (*A. variabilis*) was documented in a case reported from Chandigarh in 2011 [35], and on review, four previously documented infections as *Apophysomyces elegans* from the same institution were found to be due to this new species, thus bringing the number of cases due to *Apophysomyces elegans* down to 31.

Of the outcomes available (80 cases), there were 25 deaths, and three patients left against medical advice, possibly not having survived the infections, giving a mortality rate of 35 %.

Discussion

Being a retrospective analysis, this review has all the limitations of such a study, as one can only analyze what already exists in literature. The main limitation that immediately comes to mind is there is a lack of clarity in clearly identifying the two different varieties of cutaneous zygomycosis—the fulminant cutaneous infections and the more “benign” subcutaneous variety. This is true especially in the major series that have dealt with this topic, and this distinction has not been made clearly, even though both patterns of disease have a markedly different clinical presentation, geographical incidence, and fungal profile. As mentioned previously, the disease can present with cutaneous involvement in the form

Table 1 Previously reported cases of primary cutaneous zygomycosis from India

Author (Year) [Ref]	Age/Sex	Site	Previous intervention/trauma	Underlying illness	Isolate	Treatment	Outcome
1. Valiath (1976) [4]	25/M	Right calf	Nil	Uraemia	Mucormycosis	Nil	Died
2. Kamalam (1980) [5]	50/M	Left thumb	Nil	DM	Synecephalastrum	NA	Survived
3. Padhye (1988) [6]	29/M	Left foot	Crush injury	Nil	Saksenaeva vasiformis	Amputation + KI	Survived
4. Lakshmi (1993) [7]	27/M	Left inguinal region	Post hernioplasty	Nil	Apophysomyces elegans	D + AMB	Died
5. Verma (1995) [8]	45/M	Anterior abdominal wall	Fall from height	Nil	Non septate fungal hyphae with right angle branching	D + AMB	Died
6. Mathews (1997) [9]	32/F	Lower abdomen	Post LSCS	Nil	Apophysomyces elegans	D + AMB	Survived
7. Chakraborty (1997) [10]	30/F	Left deltoid	Intramuscular injection at site	Nil	Apophysomyces elegans	D	Survived
8. Chakraborty (1997) [10]	70/M	Abdominal wall, right elbow, left thigh	Hit by bull	Nil	Saksenaeva vasiformis	D	Survived
9. Chakraborty (1997) [10]	70/M	Site of surgery on abdominal wall	Transvesical prostatectomy	DM	Saksenaeva vasiformis	D	Survived
10. Kumar (2003) [11]	50/M	Right upper anterior abdominal wall	Nil	Nil	Rhizopus	D + AMB Later LAMB	Survived
11. Thami (2003) [12]	28/M	Appendectomy incision	Post appendectomy	Nil	Absidia corybifera	D + AMB + KI	Survived
12. Trivedi (2004) [13]	59/M	Site of transplant	Post renal transplant	DM, ESRD	Aseptate branching hyphae	D + LAMB	Survived
13. Sundararajan (2004) [14]	07/F	Right thigh	Nil	ALL	Rhizopus	Hyperbaric O2 D + AMB	Survived
14. Srivani (2005) [15]	47/F	Both legs	Nil	DM	Mucor	Oral antifungals	Survived
15. Kumar (2005) [16]	10 days/M	Back	Nil	Premature	Zygomycosis	D + AMB	Survived
16. Rajakannu (2006) [17]	40/M	Left chest	Nil	DM	Zygomycosis	D + AMB	Died
17. Rajakannu (2006) [17]	55/M	Left hand amputation stump	Dry gangrene	DM	Zygomycosis	D + AMB	Survived
18. Padmaja (2006) [18]	35/M	Appendectomy incision	Post appendectomy	Nil	Saksenaeva	D + AMB	Died
19. Saraiya (2006) [19]	71/M	Pectoralis major myocutaneous flap donor site	Post resection Nil right side buccal carcinoma	Nil	Mucor	D + AMB	Died
20. Shah (2006) [20]	8 mths/M	Right leg	Site of IV cannula	Nil	Mucor	D + AMB	Survived
21. Shah (2006) [20]	Newborn/M	Left perineum	Nil	Premature	Mucor	D + AMB	Survived
22. Thapar (2006) [21]	70/F	Left breast	Nil	DM, Steroids	Aseptate branching hyphae	Mastectomy + AMB	Survived
23. Chawla (2007) [22]	48/M	Sterotomy incision	Post coronary artery bypass	DM	Rhizopus arrhizus	D + LAMB	Died
24. Kindo (2007) [23]	49/M	Left side of face	Laceration at site in a road side accident	DM	Apophysomyces elegans	D + AMB	Died
25. Kindo (2007) [24]	60/M	Left leg	Nil	DM	Absidia corymbifera	D + AMB	Survived
26. Ram (2007) [25]	52/M	Lower abdomen	Exit site of CAPD cannula	DM, CRF	Detailed mycological identification not done	D + AMB	LAMA/Death ?

Table 1 (continued)

Author (Year) [Ref]	Age/Sex	Site	Previous intervention/trauma	Underlying illness	Isolate	Treatment	Outcome
27. Tehmeena (2007) [26]	26/F	Left gluteal region	Injection at site 2 years ago	Nil	Mucor	D + AMB	Survived
28. Reddy (2008) [27]	53/M	Right thigh	RSA	DM	Apophysomyces elegans	D + AMB + Itr Later POS	Survived
29. Garg (2009) [28]	23/F	Right gluteal region	Injection at site	Nil	Zygomycosis	D	LAMA/Death ?
30. Garg (2009) [29]	26/F	Nose	Nil	DM	Rhizopus arrhizus	D + AMB	Survived
31. Sankar (2009) [30]	03/M	Back	Site of lumbar puncture	B cell ALL	Aseptate branching hyphae	D + AMB + RIF	Survived
32. Tilak (2009) [31]	26/F	Lower abdomen	Surgery for twisted ovarian cyst	Nil	Rhizopus arrhizus	D + AMB	Died
33. Tilak (2009) [31]	24/F	Lower abdomen	LSCS	Nil	Rhizopus arrhizus	D + AMB	Survived
34. Patel (2010) [32]	75/M	Laparotomy incision	Laparotomy for mesenteric vascular insufficiency	DM	Aseptate branching hyphae	D + AMB	Died
35. Madhke (2010) [33]	29/F	Fungating ulcerated mass on left upper arm	Nil	Nil	Non septate hyphae	KI + Itr	Survived
36. Sahu (2010) [34]	45/F	Anterior abdominal wall	Spider bite	Nil	Mucormycosis	D + LAMB	Survived
37. Guarro (2011) [35]	45/F	Right breast	Nil	Nil	Apophysomyces variabilis	D	Died
38. Gupta (2011) [36]	56/M	Abdominal wall	Insulin injection site	DM, Renal Transplant	Mucormycosis	D + AMB	Survived
39. Shivananda (2011) [37]	25/M	Right knee	Road traffic accident	Nil	Rhizomucor	D + AMB, Later LAMB	Survived

NA Details not available

DM Diabetes mellitis

D Debridement

IV Intravenous

ALL Acute lymphoblastic leukaemia

ESRD End stage renal disease

CRF Chronic renal failure

LAMA Left against medical advice

LSCS Lower segment cesarian section

RIF Rifampicin

AMB Amphotericin B

LAMB Liposomal AMB

Itr Itraconazole

KI Potassium iodide

POS Posaconazole

CAPD Continuous ambulatory peritoneal dialysis

Table 2 Series from India dealing with primary cutaneous zygomycosis

Author (Year) [Ref]	Institution	Period	n	Risk factors	Isolates	Outcome
Chakraborty (2001) [38]	PGIMER Chandigarh	1990–1999	20	DM (3) Malignancy (3) Post op/Trauma/Burns (6)	A elegans (4) Saksenaea (2) Rhizopus (1) Mucor (1)	NA
Chakraborty (2003) [39]	PGIMER Chandigarh	1999–2001	04	DM (1) Breach of skin (2)	Apophysomyces (4)	LAMA (1) Survival (3)
Chakraborty (2006) [40]	PGIMER Chandigarh	2000–2004	26	DM (12) Breach of skin (12) HIV (1) Chronic alcoholism (1)	A elegans (12) R oryzae (1) R microsporus (1)	Death (3) Survival (14)
Jain (2006) [41]	PGIMER Chandigarh	1998–2004	18	DM (1) Malignancy (2) Breach of skin (16)	A elegans (5)	NA
Chakraborty (2009) [42]	PGIMER Chandigarh	2006–2007	08	Breach of skin (07)	R arryzzhus (1) A elegans (1) S racemosus (1)	Death (4) Survival (4)
Chander (2010) [43]	GMCH Chandigarh	2001–2007	09	DM (1) Breach of skin (06)	A elegans (04) A coymbifera (1) S vasiformis (1)	Death (5) Survival (4)
Kindo (2010) [44]	SRMCRI Chennai	2005–2007	03	DM (3)	A elegans (1) Rhizopus (1) A corymbifera (1)	NA
Saraiya (2011) [45]	Saraiya Hospital Ahmedabad	NA	08	Breach of Skin (07) DM (1)	NA	Death (3) Survival (5)

PGIMER Postgraduate Institute of Medical Education and Research, Chandigarh

GMCH Government Medical College and Hospital, Chandigarh

SRMCRI Sri Ramachandra Medical College, Chennai

DM Diabetes mellitus

NA Information not available

LAMA Left against medical advice

of sinuses, ulcers, or necrotizing fasciitis with local and systemic sepsis, or as subcutaneous masses with no inflammatory component or sepsis. It is important that this distinction should be made very clearly in future reports since the

true “cutaneous” form is usually caused by Mucorales, and the subcutaneous form by Entomophthorales, which is more common in the southern parts of the country. Since the sepsis component is not present in the subcutaneous variety,

Table 3 Risk factors in primary cutaneous zygomycosis reported in Indian literature

Risk factor	Number of cases
Breach of skin barrier (post operative state /Trauma/Burns/injections)	77
Diabetes mellitus	36
Malignancy	06
Renal Failure	04
Acute Leukaemia	02
Prematurity	02
Chronic alcoholism	01
HIV	01
Steroids	01

Table 4 Species of *Zygomycetes* identified in primary cutaneous zygomycosis in Indian literature

Zygomycete	Number of cases
Apophysomyces elegans ^a	31
Rhizopus	11
Saksenaea	07
Mucor	06
Apophysomyces variabilis ^a	05
Absidia corymbifera	03
Syncephalastrum	02

^a New sub-species of Apophysomyces (Apophysomyces variabilis) identified in 2010. 04 of previously reported cases as Apophysomyces elegans were later identified to be Apophysomyces variabilis [35]

it has a much better outcome and prognosis. Even in a major review of the spectrum of zygomycosis in India in 2007 [47], the authors did not make any distinction between these two forms, and they were clubbed together as the cutaneous variety. Therefore, again it is stressed that we should clearly document whether the disease is cutaneous or subcutaneous, especially in major reviews, where the two may be clubbed together.

Having noted this, the number of 130 cases of cutaneous zygomycosis since the first report in 1976 is probably much lower than the actual incidence of the disease in India. This may be due to many reasons, main among them a lack of awareness of this disease among our various health care providers—the mortality in these patients with cutaneous zygomycosis who remain undiagnosed and therefore improperly treated contribute to the low reported incidence (since the patient may die prior to the correct diagnosis having been made). It is therefore important to spread awareness of this disease so that the diagnosis can be made early, timely treatment can be started, and hopefully, a good outcome assured to the patient.

As a rule, cutaneous infection by these fungi does not occur in healthy individuals, or across an intact skin barrier. The major risk factors documented for the development of zygomycosis can be broadly classified as immunosuppressive states (hematological or other malignancies, neutropenia, steroids, anticancer therapy, malnutrition, posttransplant states and immunosuppression), breach of the skin barrier (surgery, trauma, burns, injections, IV lines, insect bites, and even from contaminated dressings), desferrioxamine therapy, and diabetes [1–3, 47, 48]. For cutaneous infection, a breach in the skin barrier is probably the most important risk factor, and has been reported in 77 of these 130 cases from India (59.23 %), slightly lower to that reported in literature. In a major review, Roden et al. calculated penetrating trauma to be present in 72.7 % of cases with cutaneous involvement [48]. Of the 53 (40.76 %) underlying diseases reported in these 130 patients, diabetes was an important underlying condition/risk factor, seen in 36 patients (27.69 %)—again, very similar to what has been reported previously in literature [48]. However, it is also important to realize that nearly 73 % of these patients did not have diabetes, thus making the disease more common in nondiabetic patients. Equally important to note is that in nearly 60 % of the patients, there was no underlying disease condition at presentation. It is well known that cutaneous involvement is the form of zygomycosis that is least likely to be associated with any underlying illness, and our literature seems to support this [1, 3].

The presentation of cutaneous zygomycosis is wide and varied, and it can present as necrotizing infections (cellulitis

or ulcerations), sinuses, blisters, or fungating masses with an aggressive local disease progression, along with severe systemic sepsis. The infection should be classified as *localized* (infection remains confined to the skin and subcutaneous tissue), *deep* (spread into the deeper tissues such as muscles, tendons, or bones), or *disseminated* (involvement of another noncontiguous site). It is rare for cutaneous zygomycosis to develop secondarily from infection at other sites, and it remains mainly a primary disease, where the portal of entry is through the skin [3]. Documenting the patients clearly with the level of infection will help in further prognostication of outcomes in the future.

The diagnosis of zygomycotic cutaneous infection is made by showing the fungus within the cells along with angioinvasion, and not merely on the basis of staining or wound cultures, since this can simply represent contamination. In suspicious cases (e.g., a patient with history of intervention, local necrotizing infection, and systemic sepsis), it is advisable to get a frozen section of the tissue specimen to help in early diagnosis and treatment planning, rather than to wait for the biopsy to come in routine (by which time it may already be too late for the patient). The cultures and other morphological features help in the species identification, which was available in 65 reported cases (Table 4); the commonest zygomycete identified was *Aphophysomyces elegans* (in 31 cases), which usually causes the cutaneous variety of infection, more so in patients who are not immunocompromised [3].

The treatment for cutaneous zygomycosis is aggressive surgical debridement along with antifungal therapy. Amphotericin B is the drug of choice since these fungi are resistant to the majority of the antifungal drugs available. Posaconazole is also effective, but itraconazole and voriconazole have shown no efficacy in these infections. The main side effect of amphotericin B is renal failure, and starting it in incremental doses (not to exceed a dose of 0.5–0.75 mg/kg/day) may help to reduce its side effects. Liposomal amphotericin B is less nephrotoxic than amphotericin B deoxycholate, but the costs of the drug may preclude usage in poor patients, contributing to the mortality (34.28 %) seen from India. Recently, Saraiya from Ahmedabad has reported better survival in patients who undergo debridement at least 10 days after starting amphotericin, based on the reported experiences in the management of orbital mucormycosis [45]. Maybe this gives time for the drug to reach desirable concentration in the blood, and also helps to tackle the fungi that may have invaded the bloodstream and be responsible for the failures after early debridement. This is an important concept that needs to be evaluated further, but the main drawback of this is that necrotizing fasciitis is usually debrided at the earliest—this protocol can only be followed once the diagnosis is made—and for that, a high index of suspicion is required on the part of the treating surgeon.

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