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Changing epidemiology of an emerging infection: zygomycosis

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Abstract

Aspergillosis and candidosis remain the most prevalent opportunistic fungal infections in immunocompromised patients, but diseases caused by the Zygomycetes have become of increasing importance. Exposure to antimycotic drugs with no activity against zygomycetes may be a new risk factor and an explanation for the increasing incidence of zygomycosis. The latter infection occurs only rarely in immunocompetent hosts, but in recent years *Apophysomyces elegans* has been described in many subtropical countries as an emerging pathogen causing mostly cutaneous infections after traumatic inoculation.

Keywords: *Apophysomyces elegans*, emerging pathogen, zygomycetes

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Introduction

Infections due to zygomycetes were first recognized and described by pathologists at the end of the 19th century in Germany [1]. The detailed description suggests that the first case of zygomycosis in a cancer patient was caused by *Absidia corymbifera* [2]. Furthermore, one of the oldest fungal isolates in the Centraalbureau voor Schimmelcultures in the Netherlands fungal collection is a *Rhizopus oryzae* isolate recovered from rotting fruit collected in 1892 in Indonesia.

In the second half of the 20th century, most cases of opportunistic fungal infections, including zygomycosis, can be regarded as complications of medical treatment. The increase in the incidence of cancer and the progress in intensive-care treatment, including organ transplantations, advanced myelosuppressive cancer treatments, and liberal use of corticosteroids, have resulted in more and more immunocompromised patients being vulnerable to invasive fungal infections. Aspergillosis and candidosis still remain the most prevalent opportunistic infections in such patients, but diseases caused by zygomycetes have become of increasing importance. In addition to cancer patients, those with diabetic ketoacidosis, solid organ or bone marrow transplants, or iron overload, and those receiving immunosuppressive agents, are also at high risk of developing zygomycosis. It is both interesting and worrisome that an increase in the incidence of zygomycosis in solid organ transplant recipients has been observed in recent years, in parallel with the introduction of caspofungin and voriconazole [3]. At a large centre in Austria, only three cases of zygomycosis were encountered until December 2003, but seven cases occurred in the following period, when voriconazole was used extensively [4]. This type of experience has been reported from many other centres [5,6]. Treatment or prophylaxis with voriconazole, itraconazole or caspofungin seems to be associated with the development of zygomycosis. More intensive chemotherapy and immunosuppression, combined with exposure to antimycotic drugs that are not active against zygomycetes, may be new risk factors. Patients with a dual mycotic infection, i.e. *Aspergilllus* and a zygomycete, are not uncommon. Thus, treating patients with antifungal drugs registered for aspergillosis might select the concomitant zygomycete, leading to a fatal outcome, although the *Aspergillus* infection was eradicated. In addition, there seem to be more reports of zygomycosis after traumatic inoculation due to accidents or natural disasters, where, especially on the Indian subcontinent, *Apophysomyces elegans* seems to have become an emerging pathogen [7]. This review will concentrate on the latter pathogen as an emerging infectious agent.

Epidemiology

The clinical spectrum of zygomycosis is now broader, and it can be difficult to distinguish between the well-recognized

mucormycosis and the more rarely encountered entomophthoramycosis, both of which can manifest as diseases ranging from a superficial to an angio-invasive infection with high mortality.

The overall survival rate of patients with zygomycosis is *c.* 50%, although survival rates of up to 85% have been reported more recently. Much of the variability in favourable outcome is due to the various forms of the disease. Rhinocerebral zygomycosis has a higher survival rate than does pulmonary or disseminated zygomycosis, because the rhinocerebral disease can frequently be diagnosed earlier. Both surgical intervention and treatment of the most common underlying cause of this fungal infection, diabetic ketoacidosis, account for this better survival rate. In contrast, pulmonary zygomycosis has a high mortality rate (65% at 1 year), because it is difficult to diagnose, it frequently occurs in neutropenic patients, and surgical intervention is rarely possible.

The largest and most comprehensive review to date on 929 cases of zygomycosis was published by Roden *et al.* [8]. They reported a prevalence and an overall mortality of 36% and 44%, respectively, for diabetes; of 19% and 35%, respectively, for patients with no underlying condition; and of 17% and 66%, respectively, for patients with a malignancy. The most common sites of infection were the sinuses (39%), lungs (24%), and skin (19%). Dissemination was seen in 23% of cases. Mortality varied with the site of infection: 96% of patients with disseminated disease, 85% with gastrointestinal infection, and 76% with pulmonary infection died.

The epidemiology of zygomycosis seems to be different between developed and developing countries. In developed countries, the disease is still a rare finding, and is at present mostly seen in patients with haematological malignancies those undergoing chemotherapy, in bone marrow transplant recipients, and as a breakthrough infection, as stated before, in patients receiving voriconazole therapy or prophylaxis. However, in developing countries, especially in India, the number of zygomycosis cases seems to be on the increase, occurring commonly in patients with uncontrolled diabetes [9]. The number of cases with uncontrolled diabetes is so overwhelming that other risk factors are overshadowed. Cases are also seen in patients with haematological malignancies or in transplant recipients, but the number is minuscule as compared with that in diabetics. In only one centre in India, clinicians encountered 129 cases (over 10 years) [10] in 2001, followed by 178 cases (over 5 years) in 2006, and recently already 75 cases (over 18 months) in 2009 [10a]. All cases, mostly in diabetics, were proven cases. Therefore, there seems to be a dichotomy of risk factors in zygomycosis from two parts of the world. In the developed world, diabetes has become less of a risk factor in the last 25 years. For example, in India, most diabetics are ignorant of the disease. In fact, the presence of diabetes was diagnosed in several patients during investigation for the predisposing factor for zygomycosis. In India, there are more than 30 million diabetics, and the majority are poorly compliant, putting them at risk of developing opportunistic zygomycosis [11].

However, not all members of the Mucorales are true opportunists. The genera *Apophysomyces* and *Saksenaea* can initiate invasive disease in apparently normal hosts who have sustained penetrating trauma during accidents.

Entomophthorales are endemic to regions of the world with tropical climates, where most cases of infection are seen. Entomophthoramycosis, a chronic and slowly progressive disease, includes two clinically and mycologically distinct entities called basidiobolomycosis and conidiobolomycosis, seen mostly in immunocompetent patients living in India, South America, and Africa, but also as rare emerging infections in the Western world [12–14]. As a general rule, entomophthorales, but also *Apophysomyces*, occur in immunocompetent hosts, and are locally progressive through direct extension into neighbouring tissues, but they are rarely angio-invasive and rarely become disseminated, as is seen with mucorales.

Ante-mortem diagnosis has been made infrequently in cases of pulmonary zygomycosis, because of the sudden course of the disease, and the lack of consideration of zygomycosis, despite the help from computed tomography/magnetic resonance imaging in localizing the site of the lesion for the performance of fine-needle aspiration under computed tomography guidance. Cultures of respiratory material are usually negative, but a positive culture in an appropriate host is highly suggestive of invasive disease. However, there are rarely clinical and microbiological clues available in gastrointestinal zygomycosis. Most patients with this disease are premature babies with necrotizing enterocolitis. Few ante-mortem cases of gastrointestinal zygomycosis are picked up during surgery.

Proven infection always requires histopathological demonstration of tissue invasion with the typical irregular, broad, non-septated hyphae. As culture of tissue can give variable results, histologically positive paraffin-embedded material with negative cultures should always be subjected to DNA-based identification.

Apophysomyces elegans

Before the zygomycete *A. elegans*, belonging to the family Mucoraceae, was recognized as causing severe human infections, it was first described in soil samples from a mango

orchard in India in 1979 [15]. A few years later, this pathogen was found in a clinical case with a trauma injury and was also cultured from environmental samples [16]. Infections with *Apophysomyces* are mostly acquired in tropical and subtropical areas, and cases have been described from several states in the USA (Texas [17–21], Arizona [22–25], Florida [26,27], Mississippi [28], Oklahoma [29], Georgia [30] Minnesota [31], Alabama [32], South Carolina [33]), different regions in India [34–45], Venezuela [46], Colombia [47], Mexico [20,48], Australia [16], Saudi Arabia [49], and Kuwait [50]. A case described from The Netherlands was linked to a subtropical source in the Caribbean [51]. Infection with *A. elegans* is mainly the result of the inoculation of soil or plant detritus during an accident. This was well appreciated after the tsunami disaster in 2004, when victims were found to be infected with *Apophysomyces* contracted in Sri Lanka [52] and Thailand [53]. Well-described causes of traumatic inoculation are motocycle and other road traffic accidents, but the incident can be so minor that the patient does not remember any injury, as in the case from The Netherlands [51]. Although inhalation of *A. elegans* spores can result in rhinocerebral and pulmonary infections, local wound contamination after an accident represents the single most common host risk factor. The majority of involved patients demonstrate no underlying immune system dysfunction. Only a few patients with *A. elegans* infection had risk factors for developing zygomycosis; among others, diabetes, severe burns, renal transplantation, myelofibrosis, and corticosteroid use. The most common site of disease manifestation of *A. elegans* infection is the cutaneous and subcutaneous tissue, with local invasion into muscle and fat tissue resulting in necrotizing fasciitis. Thrombosis with extensive necrosis of the involved tissues is common [16,22,29,34,46,48]. Exudates from the lesion often include necrotic debris and thick pus reminiscent of a *Staphylococcus aureus* infection [16,51].

A. elegans is a thermotolerant fungus that is capable of rapid growth at 24–43°C *in vitro* [15,51,54], and it is believed that this thermotolerance permits fungal proliferation in deep tissues. Although no specific virulence factors have yet been identified for this organism, it produces disease in much the same way as the other mucorales, with tissue and angio-invasion. *Apophysomyces* infections do not have a high death rate; this is most probably associated with its occurrence in immunocompetent patients, the relatively easy surgical treatment of cutaneous sites, and the availability of lipid preparations of amphotericin B.

The microscopic morphology seen in tissues infected with *A. elegans* is similar to that seen with other zygomycetes. Pleomorphic, thin-walled, aseptate hyphal elements invade both tissues and blood vessels. Hyphae may be twisted and collapsed, demonstrating bulbous vesicles and irregular branching. The inflammatory response seen with *A. elegans* infection is quite variable, but most histopathological descriptions show acute inflammation with necrosis and abscess formation.

A. elegans grows as a floccose aerial mycelium, demonstrating white to grey confluent growth in 2 days on standard culture medium. It is a thermophilic fungus, showing rapid growth in a temperature range from 25°C to 43°C. *A. elegans* has fastidious culture requirements for sporulation. It never sporulates on standard media, but produces only sterile hyaline hyphae. Nutrient-deficient growth medium and prolonged incubation induce sporulation, which is necessary for identification of the fungus with its distinct microscopic morphology [17,22,28,51], the very prominent flask or bell-shaped apophysis. *A. elegans* is sometimes confused with *Saksenaea vasiformis*, owing to their fastidious culture requirements and disease manifestations [54]. Like *A. elegans*, the zygomycete *S. vasiformis* generally produces sterile hyphae on routine culture media. The increasing use of molecular identification by internal transcribed spacer (ITS) sequences in clinical mycology will, in particular, facilitate a specific aetiological diagnosis of this, until recently, elusive pathogen [7].

Conclusions

The emergence of unusal agents of zygomycosis is exemplified by *Apophysomyces elegans*. Undoubtedly, other species will be described causing human infection, especially in the presence of new antifungal treatments and underlying medical condition.

Transparency Declaration

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References

1. Platauf AP. Mycosis mucorina. *Virchows Arch* 1885; 102: 543–564.
2. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev* 2000; 13: 236–301.
3. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis* 2004; 39: 743–746.

4. Stelzmueller I, Lass-Floerl C, Geltner C *et al.* Zygomycosis and other rare filamentous fungal infections in solid organ transplant recipients. *Transpl Int* 2008; 21: 534–546.
5. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med* 2004; 350: 950–952.
6. Vigouroux S, Morin O, Moreau P *et al.* Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. *Clin Infect Dis* 2005; 40: e35–e37.
7. Chakrabarti A, Ghosh A, Prasad GS *et al. Apophysomyces elegans*: an emerging zygomycete in India. *J Clin Microbiol* 2003; 41: 783–788.
8. Roden MM, Zaoutis TE, Buchanan WL *et al.* Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005; 41: 634–653.
9. Chakrabarti A, Das A, Mandal J *et al.* The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. *Med Mycol* 2006; 44: 335–342.
10. Chakrabarti A, Das A, Sharma A *et al.* Ten years' experience in zygomycosis at a tertiary care centre in India. *J Infect* 2001; 42: 261–266.
11. Diabetes India. 2003. Available at: http://www.diabetesindia.com (last accessed 29 July 2009).
12. Lyon GM, Smilack JD, Komatsu KK *et al.* Gastrointestinal basidiobolomycosis in Arizona: clinical and epidemiological characteristics and review of the literature. *Clin Infect Dis* 2001; 32: 1448–1455.
13. van den Berk GE, Noorduyn LA, van Ketel RJ, van Leeuwen J, Bemelman WA, Prins JM. A fatal pseudo-tumour: disseminated basidiobolomycosis. *BMC Infect Dis* 2006; 6: 140. doi: 10.1186/1471-2334-6-140.
14. Fischer N, Ruef C, Ebnöther C, Bächli EB. Rhinofacial *Conidiobolus coronatus* infection presenting with nasal enlargement. *Infection* 2008; 36: 594–596.
15. Misra PC, Srivastava KJ, Lata K. *Apophysomyces*, a new genus of the Mucorales. *Mycotaxon* 1979; 8: 377–382.
16. Cooter RD, Lim IS, Ellis DH, Leitch IO. Burn wound zygomycosis caused by *Apophysomyces elegans*. *J Clin Microbiol* 1990; 28: 2151–2153.
17. Huffnagle KE, Southern PM, Byrd CT, Gander RM. *Apophysomyces elegans* as an agent of zygomycosis in a patient following trauma. *J Med Vet Mycol* 1992; 30: 83–86.
18. Lawrence RM, Snodgrass WT, Reichel G, Padhye AA, Ajello L, Chandler FW. Systemic zygomycosis caused by *Apophysomyces elegans*. *J Med Vet Mycol* 1986; 24: 57–65.
19. Okhuysen PC, Rex JH, Kapusta M, Fife C. Successful treatment of extensive posttraumatic soft-tissue and renal infections due to *Apophysomyces elegans*. *Clin Infect Dis* 1994; 19: 329–331.
20. Kimura M, Smith MB, McGinnis MR. Zygomycosis due to *Apophysomyces elegans*: report of 2 cases and review of the literature. *Arch Pathol Lab Med* 1999; 123: 386–390.
21. Wang J, Harvey CM, Calhoun JH, Yin LY, Mader JT. Systemic *Apophysomyces elegans* after trauma: case report and literature review. *Surg Infect* 2002; 3: 283–289.
22. Weiden MA, Steinbronn KK, Padhye AA, Ajello L, Chandler FW. Zygomycosis caused by *Apophysomyces elegans*. *J Clin Microbiol* 1985; 22: 522–526.
23. Lesueur BW, Warschaw K, Fredrikson L. Necrotizing cellulitis caused by *Apophysomyces elegans* at a patch test site. *Am J Contact Dermat* 2002; 13: 140–142.
24. Brown SR, Shah IA, Grinstead M. Rhinocerebral mucormycosis caused by *Apophysomyces elegans*. *Am J Rhinol* 1998; 12: 289–292.
25. Burrell SR, Ostlie DJ, Saubolle M, Dimler M, Barbour SD. *Apophysomyces elegans* infection associated with cactus spine injury in an immunocompetent pediatric patient. *Pediatr Infect Dis J* 1998; 17: 663–664.
26. Eaton ME, Padhye AA, Schwartz DA, Steinberg JP. Osteomyelitis of the sternum caused by *Apophysomyces elegans*. *J Clin Microbiol* 1994; 32: 2827–2828.
27. Weinberg WG, Wade BH, Cierny G, Stacy D, Rinaldi MG. Invasive infection due to *Apophysomyces elegans* in immunocompetent hosts. *Clin Infect Dis* 1993; 17: 881–884.
28. Padhye AA, Ajello L. Simple method of inducing sporulation by *Apophysomyces elegans* and *Saksenaea vasiformis*. *J Clin Microbiol* 1988; 26: 1862–1863.
29. Naguib MT, Huycke MM, Pederson JA, Pennington LR, Burton ME, Greenfield RA. *Apophysomyces elegans* infection in a renal transplant recipient. *Am J Kidney Dis* 1995; 26: 381–384.
30. Ferguson TD, Schniederjan SD, Dionne-Odom J *et al.* Posaconazole treatment for *Apophysomyces elegans* rhino-orbital zygomycosis following trauma for a male with well-controlled diabetes. *J Clin Microbiol* 2007; 45: 1648–1651.
31. Liang KP, Tleyjeh IM, Wilson WR, Roberts GD, Temesgen Z. Rhino-orbitocerebral mucormycosis caused by *Apophysomyces elegans*. *J Clin Microbiol* 2006; 44: 892–898.
32. Carter JE, Ulusarac O. Widespread cutaneous involvement by invasive *Apophysomyces elegans* in a gravid patient following trauma. *Cutis* 2003; 72: 221–224.
33. Garcia-Covarrubias L, Bartlett R, Barratt DM, Wassermann RJ. Rhino-orbitocerebral mucormycosis attributable to *Apophysomyces elegans* in an immunocompetent individual: case report and review of the literature. *J Trauma* 2001; 50: 353–357.
34. Lakshmi V, Suda Rani T, Sharma S *et al.* Zygomycotic necrotizing fascitis caused by *Apophysomyces elegans*. *J Clin Microbiol* 1993; 31: 1368–1369.
35. Mathews MS, Raman A, Nair A. Nosocomial zygomycotic post-surgical necrotizing fasciitis in a healthy adult caused by *Apophysomyces elegans* in South India. *J Med Vet Mycol* 1997; 35: 61–63.
36. Chakrabarti A, Panda N, Varma SC *et al.* Craniofacial zygomycosis caused by *Apophysomyces elegans*. *Mycoses* 1997; 40: 419–421.
37. Chakrabarti A, Kumar P, Padhye AA *et al.* Primary cutaneous zygomycosis due to *Saksenaea vasiformis* and *Apophysomyces elegans*. *Clin Infect Dis* 1997; 24: 580–583.
38. Chugh KS, Padhye AA, Chakrabarti A, Sakhuja V, Gupta KL, Kathuria P. Renal zygomycosis in otherwise healthy hosts. *J Mycol Med* 1996; 6: 22–25.
39. Reddy IS, Rao NR, Shankar Reddy VM, Rao R. Primary cutaneous mucormycosis (zygomycosis) caused by *Apophysomyces elegans*. *Indian J Dermatol Venereol Leprol* 2008; 74: 367–370.
40. Thomas AJ, Shah S, Mathews MS, Chacko N. *Apophysomyces elegans*—renal mucormycosis in a healthy host: a case report from south India. *Indian J Med Microbiol* 2008; 26: 269–271.
41. Devi SC, Kanungo R, Barreto E *et al.* Favorable outcome of amphotericin B treatment of zygomycotic necrotizing fascitis caused by *Apophysomyces elegans*. *Int J Dermatol* 2008; 47: 407–409.
42. Kindo AJ, Shams NR, Kumar K *et al.* Fatal cellulitis caused by *Apophysomyces elegans*. *Indian J Med Microbiol* 2007; 25: 285–287.
43. Goyal A, Tyagi I, Syal R, Marak RS, Singh J. *Apophysomyces elegans* causing acute otogenic cervicofacial zygomycosis involving salivary glands. *Med Mycol* 2007; 45: 457–461.
44. Suryanarayan Rao S, Panda NK, Pragache G, Chakrabarti A, Saravanan K. Sinoorbital mucormycosis due to *Apophysomyces elegans* in immunocompetent individuals—an increasing trend. *Am J Otolaryngol* 2006; 27: 366–369.
45. Jain D, Kumar Y, Vasishta RK, Rajesh L, Pattari SK, Chakrabarti A. Zygomycotic necrotizing fasciitis in immunocompetent patients: a series of 18 cases. *Mod Pathol* 2006; 19: 1221–1226.
46. Caceres AM, Sardina C, Marcano C *et al. Apophysomyces elegans* limb infection with a favorable outcome: case report and review. *Clin Infect Dis* 1997; 25: 331–332.

47. Ruiz CE, Arango M, Correa AL, López LS, Restrepo A. Necrotizing fasciitis in an immunocompetent patient caused by *Apophysomyces elegans*. *Biomedica.* 2004; 24: 239–251.
48. Radner AB, Witt MD, Edwards JE. Acute invasive rhinocerebral zygomycosis in an otherwise healthy patient: case report and review. *Clin Infect Dis* 1995; 20: 163–166.
49. Kordy FN, Al-Mohsen IZ, Hashem F, Almodovar E, Al Hajjar S, Walsh TJ. Successful treatment of a child with posttraumatic necrotizing fasciitis caused by *Apophysomyces elegans*: case report and review of literature. *Pediatr Infect Dis J* 2004; 23: 877–879.
50. Schütz P, Behbehani JH, Khan ZU *et al.* Fatal rhino-orbito-cerebral zygomycosis caused by *Apophysomyces elegans* in a healthy patient. *J Oral Maxillofac Surg* 2006; 64: 1795–1802.
51. Meis JF, Kullberg BJ, Pruszczynski M, Veth RPH. Severe osteomyelitis due to the zygomycete *Apophysomyces elegans*. *J Clin Microbiol* 1994; 32: 3078–3081.
52. Andresen D, Donaldson A, Choo L *et al.* Multifocal cutaneous mucormycosis complicating polymicrobial wound infections in a tsunami survivor from Sri Lanka. *Lancet* 2005; 365: 876–878.
53. Snell BJ, Tavakoli K. Necrotizing fasciitis caused by *Apophysomyces elegans* complicating soft-tissue and pelvic injuries in a tsunami survivor from Thailand. *Plast Reconstr Surg* 2007; 119: 448–449.
54. Holland J. Emerging zygomycoses of humans: *Saksenaea vasiformis* and *Apophysomyces elegans*. *Curr Top Med Mycol* 1997; 8: 27–34.