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Outbreaks of zygomycosis in hospitals

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Abstract

Zygomycosis refers to a group of uncommon and frequently fatal mycoses caused by fungi of the class Zygomycetes, the organisms of which are usually found in decaying organic matter. Disease can be transmitted by the inhalation of spores or by direct inoculation on disrupted skin or mucosa. For rare diseases such as zygomycosis, two or more cases occurring in a short time should be investigated as a probable epidemic. Twelve hospital outbreaks and two pseudoepidemics caused by Zygomycetes have been cited in the English literature. The first epidemic was recorded in 1977 and the last in 2008. Outbreaks have been reported in the USA, the UK and elsewhere in Europe. Cases have included cutaneous, disseminated, pulmonary and rhinocerebral disease. Species identified have included *Rhizopus arrhizus*, *Rhizopus rhizopodiformis*, *Rhizopus microsporus*, *Rhizopus* spp., *Absidia corymbifera* and *Rhizomucor pusillius*. Sources of infection have included Elastoplast adhesive bandage rolls, ventilation systems, wooden tongue depressors, karaya (plant-derived adhesive) ostomy bags, and water damage to a linen store and patient shower room. Patients have included cardiosurgery patients, renal transplant recipients, orthopaedic patients, adult leukaemia patients, intensive care unit neonates, immunocompromised haematology patients, and burn unit patients. Although zygomycosis outbreaks in the hospital environment are infrequent, a high index of suspicion should exist if necrotic lesions appear in proximity to a postoperative wound. Direct tissue examination and tissue culture and histopathology must be routinely performed.

Keywords: Epidemic, mucormycosis, nosocomial, outbreak, pseudoepidemic, *Rhizopus*, zygomycosis

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Introduction

Zygomycosis refers to a group of uncommon and frequently fatal mycoses caused by fungi of the class Zygomycetes, which includes two orders, Mucorales and Entomophthorales [1,2]. The organisms of the class Zygomycetes are ubiquitous in soil, are thermo-tolerant, and are usually found in decaying organic matter. Spores can be found in material related to plants or organic matter (wood, cotton). Disease can be transmitted by the inhalation of spores or by direct inoculation of disrupted skin or mucosa [1,3].

Zygomycosis is a rare disease. A study performed in Spain found an incidence of 0.43 cases per million inhabitants per year or 0.62 cases per 100 000 hospital admissions, and Zygomycetes was recovered also from specimens without concomitant active disease (92.3% of all isolations) [4]. In the USA, a population-based study estimated the incidence of mucormycosis to be 1.7 cases per million people per year (approximately 500 cases per year) [5]. In an autopsy series, the prevalence of mucormycosis has ranged from one to five cases per 10 000 autopsies, which makes it 10–50-fold less common than invasive *Candida* or *Aspergillus* infections [6,7].

Mucormycosis, formerly almost always a community-acquired infection and most often in the setting of diabetic ketoacidosis, has rapidly become a nosocomial infection in patients with malignancy, organ transplantation or haematopoietic stem cell transplantation. Nosocomial mucormycosis has been associated with iatrogenic immunosuppression or a variety of healthcare-associated procedures or devices, including antifungal prophylaxis and contaminated bandages or medication patches, intravenous catheters, medical instruments and even tongue depressors; air contamination has also been described as a source of infection [8].

This review presents all hospital outbreaks related to zygomycosis cited in the English-language literature and describes information useful in the investigation and management of similar situations.

Definition of a Hospital Outbreak

A hospital outbreak is defined as an increase in the usual incidence of an infection or side-effect [9]. The definition of an outbreak is established if the incidence of a disease or infection is known, or if an 'impression' of an increase in the incidence of an infection is present. This impression must be followed by a retrospective study recording all relevant incidents for some time in the past in order to confirm a current increase in the incidence and, thus, the presence of an epidemic. For rare diseases such as zygomycosis, in which only sporadic cases are found, with an incidence of two or three cases per year per centre [10,11], two or more cases occurring in a short period should be investigated as a probable epidemic. In this review, outbreaks related to a common source and with a common species are included. An increase in the incidence of zygomycosis has also been noted in centres where voriconazole is used as prophylaxis, but this phenomenon is not considered to represent a hospital outbreak and is not discussed further [12,13].

Zygomycosis Hospital Outbreaks 1966–2008

Twelve hospital outbreaks and two pseudoepidemics caused by Zygomycetes have been cited in the English literature. The first epidemic was recorded in 1977 in a Minnesota hospital [14]. The epidemic consisted of six cases presenting over a 2-month period. The first three cases occurred in orthopaedic patients who had undergone spinal surgery and in whom a superficial skin infection along the surgical wound was managed with debridement and topical care only, without systemic antifungal agents. The next three cases occurred in paediatric patients, including two children and a pre-term neonate. The children had acute lymphocytic leukaemia as an underlying disease and presented with buttock abscesses several weeks after bone marrow biopsy. The neonate was operated on for gastric perforation and gastrointestinal zygomycosis was diagnosed. The paediatric patients recovered fully after debridement or surgery and treatment with amphotericin B. The common source for all cases was the Elastoplast adhesive dressings used to cover the surgical wounds in the orthopaedic patients, to control superficial bleeding from the bone marrow biopsy site, and to secure a nasogastric tube and an umbilical catheter in the neonate. *Rhizopus arrhizus* was isolated in all cases and from samples of the Elastoplast adhesive bandage rolls from various sites in the hospital. As a preventive measure Elastoplast rolls were withdrawn from patient care areas.

The next cluster of cases was published in 1978 [15]. Three cases presenting over a period of 9 months were described, in all of which zygomycosis initiated as skin and subcutaneous tissue infection and was caused by *Rhizopus rhizopodiformis*. Two cases appeared as sternal wound infections in cardiosurgery patients (one infection extended to the mediastinum, with a grave outcome). The third case occurred in a renal transplant patient who had undergone a biopsy to confirm graft rejection and then developed soft tissue infection along the biopsy sinus tract with subsequent dissemination to the lungs. Again, *Rhizopus* was isolated from Elastoplast adhesive bandage rolls in the cardiosurgery intensive care unit.

In 1979, two hospital epidemics were published [16,17]. Both were recorded in orthopaedic services, the first reported by the orthopaedic physicians [16] and the second by the dermatologists who were consulted on the cases [17]. The first outbreak included two confirmed and two suspected cases over 3 months and the second outbreak consisted of three cases presenting during a 2-month period. The implicated pathogens were *R. rhizopodiformis* for the first and *Rhizopus* spp. for the second outbreak. All cases developed at the site of the surgical wound and presented as inflammatory necrotic skin ulcerations under wound dressings secured by elasticized adhesive tape. All were managed with topical treatment with favourable outcome. The initial diagnosis was contact dermatitis in most cases.

In 1992, an epidemic recorded in 1985 was published [18]. It included three cases, two with disseminated and one with rhinocerebral disease, all concerning newly diagnosed leukaemia patients. The three cases appeared over a 6-month period, before which no such cases had been described in the centre. The outbreak was attributed to the proximity of the haematology ward ventilation system to the heliport on the roof of the building. Increased use of the heliport before the outbreak caused the introduction of dust and particles into the ventilation system. The presence of Zygomycetes was confirmed in cultures of air samples and false ceiling panels from the haematology patient rooms as well as in pre-filters and bag filters in the ventilation system. High-efficiency particulate air (HEPA) filters were used and the air samples subsequently were negative for Zygomycetes.

In 1996, an epidemic of two cases occurring in adult leukaemia patients was described, related to contamination of the ventilation grating system by Mucorales [19]. Both patients presented with pulmonary and disseminated disease with a fatal outcome. The same year, an outbreak of four cases of cutaneous zygomycosis caused by *Rhizopus microsporus* within a single month in a neonatal intensive care unit was also published [20]. The source of infection was found to be the wooden tongue depressors used to construct

splints for intravenous and arterial cannulation sites. Three of the babies died.

Rhizopus microsporus appears to have a predilection for wooden material, because a year later a pseudoepidemic was reported [21]. In this pseudoepidemic, faecal samples from 17 immunocompromised haematology patients were found to be positive for *R. microsporus*; this was attributed to the wooden sticks used to suspend faeces obtained for surveillance cultures. The same Zygomycetes species was isolated from a sample of the wooden sticks which were in open boxes in the wards. A similar pseudoepidemic with 44 positive cultures from non-ill patients (42 stool, one skin, one pharynx) in a single year was reported, also with *R. microsporus* contamination of wooden tongue depressors [22]. The fungus was isolated only from spatulae derived from unmanaged forests from which harvested wood was not heated before processing, highlighting the need for the application of good manufacturing guidelines for such items.

In 2004, five cases of gastric mucormycosis (clinically related to gastric bleeding) were reported over a period of 14 weeks [23]. They occurred in the setting of an intensive care unit and were related to the wooden tongue depressors used to prepare oral medications given to patients through a nasogastric tube. *Rhizopus microsporus* var. *rhizopodiformis* was isolated from patients and from wooden tongue depressors (five of 60 samples), as well as from the air in a patient's cubicle and in the nursing staff rest room. It was hypothesized that dust containing fungal spores was released into the air when depressors were manually broken after use. The depressors were withdrawn and the unit was evacuated and disinfected. Attributable mortality was 40%.

In 2005, five cases of *Absidia corymbifera* infection in a burns unit were reported [24]. They presented over a 3-month period and were accompanied by two cases of burn wound colonization. After extensive environmental sampling, the cases were related to contaminated non-sterile Elastoplast bandages used to cover the burns. Following the epidemic, only sterile bandages were used for the outer dressing of burns.

In 2006 LeMaile-Williams and colleagues published their experience of two cases, presenting over a 3-month period, of cutaneous infection caused by *Rhizopus arrhizus* (*oryzae*) related to non-sterile karaya (plant-derived adhesive) ostomy bags in patients who had undergone recent colostomy surgery [25]. One patient died and *Rhizopus* was recovered from ten of 18 ostomy bags tested, but not from other environmental sources. An important risk factor for the development of infection was the time to the first ostomy bag change, which was longer for the cases. For the first time, a polymerase chain reaction technique was applied to prove the clonal nature of the fungal strains recovered from patients and the ostomy bags.

The last reported epidemic occurred in 2008 in a paediatric oncology department [26]. It involved two cases of rhinocerebral mucormycosis related to water damage in a linen store and patient shower room. *Rhizomucor pusillius* was isolated from one patient. Both had histopathological diagnosis of zygomycosis and fully recovered. The water damage promoted fungal growth which contaminated the surrounding air which circulated in close proximity to the infected patients' rooms. Air contamination was tested by gravity sedimentation techniques and *Rhizomucor* and *Aspergillus* were recovered. Patients were relocated until the damage was renovated and the air sample cultures became negative at 3 weeks. A summary of all outbreak characteristics is presented in Table 1.

Discussion

Zygomycosis outbreaks occurring in the hospital environment are infrequent. Only 12 are described in the English literature between 1978 and 2008. These were reported from the USA, the UK and elsewhere in Europe. Case numbers are low, ranging from two to six for each epidemic. Zygomycosis is a rare infection and the definition of an outbreak is confirmed if two or more cases are described within a short period of time (2–6 months). The outbreak is also evident from the isolation of the same fungal species in relation to a common environmental source. Genetic studies, if available, also reinforce the confirmation of the outbreak if they reveal a clonal pattern.

In the outbreaks reviewed, the species most commonly implicated were *R. arrhizus* and *R. microsporus*. In surgical patients, the cases included mostly cutaneous infection related to the direct inoculation of the fungus on the wound surface, usually from the material used for wound dressing, or to otherwise close contact. Most commonly, elastic adhesive non-sterile bandages or wooden sticks or depressors were implicated as the source. In the immunocompromised patient setting, outbreaks related most often to an airborne route of transmission and resulted in disseminated disease with a worse outcome than in surgical patients in whom topical treatment alone was adequate for healing. In the immunocompromised patient population, the environmental investigation of an epidemic must always include air sampling.

Conclusions

Although they are rare, for outbreaks of zygomycosis to be confirmed they must first be suspected. A high index of

TABLE 1. Summary of the characteristics of 12 outbreaks

References	Year of publication	Country	Setting	Number of cases	Infection site	Route	Pathogen	Source	Mortality (attributable)	Clonality
Keys *et al.* [14]	1978	USA	Orthopaedics	3	Cutaneous	Contact	*Rhizopus arrhizus*	Elastoplast adhesive bandages	None	Not done
			Haematology	2	Disseminated					
			Neonate	1	Gastrointestinal					
Gartenberg *et al.* [15]	1978	USA	Cardiosurgery	2	Cutaneous	Contact	*Rhizopus rhizopodiformis*	Elastoplast bandages	33%	Not done
			Renal transplant	1	Cutaneous/systemic					
Sheldon *et al.* [16]	1979	USA	Orthopaedics	2	Cutaneous	Contact	*Rhizopus rhizopodiformis*	Elasticized adhesive tape	None	Not done
Hammond *et al.* [17]	1979	UK	Orthopaedics	3	Cutaneous	Contact	*Rhizopus* spp.	Elastoplast adhesive bandages	None	Not done
Abzug *et al.* [18]	1992	USA	Haematology	3	Disseminated Rhinocerebral	Inhalation	Zygomycetes (no species ID)	Heliport-associated contamination of the ventilation system	No information	Not done
Levy *et al.* [19]	1996	France	Haematology	2	Disseminated	Inhalation	*Mucor*	Ventilation system	100%	Not done
Mitchell *et al.* [20]	1996	UK	Neonatal unit	4	Cutaneous	Contact	*Rhizopus microsporus*	Wooden tongue depressors	75%	Not done
Maravi-Poma *et al.* [23]	2004	Spain	Intensive care unit	5	Gastric	Contact	*Rhizopus microsporus* var. *rhizopodiformis*	Wooden tongue depressors	40%	Not done
Christiaens *et al.* [24]	2005	Belgium	Burns unit	5	Cutaneous	Contact	*Absidia corymbifera*	Elastoplast bandages	No information	Not done
LeMaille-Williams *et al.* [25]	2006	USA	Surgery	2	Cutaneous	Contact	*Rhizopus arrizus*	Karaya ostoma bags	50%	Done, present
Garner & Machin [26]	2008	UK	Paediatric oncology unit	2	Rhinocerebral	Inhalation	*Rhizomucor pusillius*	Water damage in linen store room and shower/air contamination	None	Not done

suspicion should exist if necrotic lesions appear in proximity to a postoperative wound. Direct tissue examination and tissue culture and histopathology must be routinely performed.

Transparency Declaration

The author declares no conflicts of interest.

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