Investigation and management of an outbreak of mucormycosis in a paediatric oncology unit

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Received 5 March 2008; accepted 15 May 2008
Available online 14 July 2008

KEYWORDS
Mucormycosis; Outbreak; Environment; Posaconazole; Paediatrics; Oncology

Summary  Mucormycosis is an aggressive and often fatal infection, despite conventional methods of treatment, which predominantly affects immunocompromised patients. This report describes an outbreak of rhinocerebral mucormycosis in a university hospital paediatric oncology department secondary to water damage in a linen store and parents’ shower room. The source of the outbreak was successfully determined using simple environmental sampling techniques. Sampling allowed timely and successful implementation of infection control measures to contain the source and protect patients. Two cases were treated with posaconazole and made a complete recovery, with no discernible impact on the management of their cancer. Fifteen other children identified as having a high risk of developing infection were given posaconazole prophylaxis. None of the children, including one that was only five years old, experienced any adverse events from taking posaconazole.

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Introduction

Mucormycosis is an uncommon, rapidly progressive fungal infection with a reputation for diagnostic difficulties, unsatisfactory treatment and a high mortality. Conventional management of this condition, including extensive surgical debridement and lipid formulations of amphotericin B, is expensive and potentially disfiguring. The mortality of mucormycosis associated with haematological malignancy despite treatment is >60%.¹ This mortality increases to 100% in paediatric haematology patients with rhinocerebral mucormycosis.² There are concerns that more powerful immunosuppressant protocols for the management of haematological malignancies will result in an increase in the incidence of this unusual condition.
In 2006 our university hospital experienced an outbreak of mucormycosis among paediatric oncology patients. Due to the high mortality of this condition, and the difficulties with its management, we implemented an aggressive plan to manage the cases and contacts involved in the outbreak and discover the source of infection. Environmental sampling techniques were used to find the source of infection allowing infection control measures to be implemented to protect other children. The second-generationazole antifungal, posaconazole, was used to treat cases and prophylax children identified as at high risk of developing infection. This report describes the steps taken to treat the patients and investigate and control this outbreak.

Methods

Setting

The paediatric oncology unit is a tertiary referral centre in addition to serving the local population of children; it receives up to 80 new referrals a year. The majority of these children have haematological malignancies and brain tumours, for which the unit has a special research interest.

The unit consists of a single ward with attached day case unit. The ward is divided into two four-bedded open bays, with eight side rooms and cubicles.

Outbreak description

Case 1 was a five-year-old boy undergoing chemotherapy for acute lymphoblastic leukaemia (ALL). The child was admitted with febrile neutropenia and five days later developed seizures. On magnetic resonance imaging (MRI) lesions were found in the right temporal, parietal lobes and the left paracentral lobules. The child underwent excision biopsy; the histology confirmed an invasive fungal infection, although the microbiological cultures were negative. Treatment was commenced with a liposomal formulation of amphotericin B (AmBisome at 5 mg/kg). Repeat MRI, taken two weeks later, to assess response to therapy showed the lesions to have increased in size. Further examination of the histology by the Health Protection Agency Mycology Reference Laboratory, Bristol, led to a presumptive identification of acute mucormycosis rather than the more common aspergillosis on the basis of non-septate hyphae with $>45^\circ$ branching. Oral posaconazole 400 mg twice daily was added to the child’s therapy as it has been reported to have better in vitro activity against mucormycosis.3,4

Case 2 was a 15-year-old boy with newly diagnosed ALL admitted two weeks after Case 1 was diagnosed with mucormycosis. The child developed a necrotic lesion at the site of an intravenous cannula, which was found to be unresponsive to antibiotics. The child became acutely short of breath and the chest X-ray suggested a cavitating pneumonia. The child was started on a liposomal formulation of amphotericin B (AmBisome at 5 mg/kg) but subsequently developed cerebellar ataxia and dysarthria. MRI showed multiple cerebellar lesions and lesions in the occipital cortex. The histology of a biopsy specimen from the cannula site showed a mould and cultures yielded Rhizomucor pusillus. The child subsequently went on to have samples taken from his sinuses that grew mixtures of Rhizomucor spp. and Aspergillus spp. Oral posaconazole 400 mg twice daily was added into the child’s therapy.

An outbreak meeting was called on the day that tissue from the infected cannula site of Case 2 suggested mucormycosis, to discuss the two cases of rare fungal infection occurring within a short period of time in the hospital on the same ward.

Outbreak investigation

In the outbreak meeting a member of the oncology ward staff commented on the presence of a leaking shower on the ward. Capillary motion of moisture had caused severe damage to the walls surrounding the parents’ shower room, including the adjacent walls of a linen store, the wall forming the outside corridor and the shower cubicle itself (Figure 1).

Review of the clinical cases revealed that both children had been located on the ward with the water damage and in the two hospital beds closest to the affected linen store where the most damage had occurred (Figure 1). It was proposed that the water-damaged plaster could be the source of the mould causing the outbreak. Environmental sampling was used to investigate this hypothesis.

Environmental sampling method

Samples from the ward environment were collected onto Sabouraud agar plus chloramphenicol (Oxoid, Basingstoke, UK) using a number of methods. These included 1 m$^3$ air samples collected using an air IDEAL sampler (bioMérieux,
Basingstoke, UK), settle plates exposed to the environment for 4 h to allow inoculation by gravity sedimentation and samples from damaged surfaces directly inoculated into the agar. The agar plates were incubated for 72 h at 30 °C, and colonies of mould identified using conventional laboratory techniques. The Health Protection Agency Mycology Reference Laboratory, in Bristol, confirmed the identification of the moulds.

Results

Protection of patients and containment measures

The doors to the linen store and shower cubicle were closed and sealed internally with plastic sheeting. The areas of affected plaster on the adjacent walls of the linen store and the wall forming the outside corridor were covered with ply board and sealed with silicone sealant. It was then painted with a fungicidal paint to improve its appearance. The estates department reviewed the ward ventilation and found that there was no extraction of air from either the linen store or parents’ shower room. Both rooms remained closed until the damaged walls could be repaired. In order for this to occur a previously vacant ward was recommissioned allowing the paediatric oncology patients to relocate permitting the building work to commence.

As soon as an outbreak situation became apparent, all patients considered to be at high risk of acquiring mucormycosis were transferred to a general paediatric ward within the hospital. This was judged to be of less risk than leaving these high-risk patients exposed to the potential risk of mucormycosis. The identification of those at risk was based upon the immunosuppressive qualities of underlying disease and chemotherapy protocols. Due to the variable attendance on the ward prior to the children developing mucormycosis, it was difficult to assess the incubation period from the date of exposure. Therefore, patients, who had been inpatients on the ward four weeks prior to the diagnosis of mucormycosis in Case 1, were also considered high risk. Despite not knowing the incubation period for mucormycosis, the outbreak team concluded that four weeks was an acceptable timescale as, if there had been significant exposure earlier, cases would probably have presented sooner.

The 15 patients identified as having had significant exposure were offered oral posaconazole as prophylaxis for four weeks. No cases developed in the prophylaxis group. The decision was taken not to actively case-find due to the lack of investigative methods for diagnosing early mucormycosis. Following transfer of the high-risk patients from the ward, all linen and curtains were removed and the domestic staff and ward nurses undertook an extensive deep clean using hypochlorite. Freshly laundered linen and curtains from supplies outside of the ward were then used to replenish the ward supplies.

Results of environmental sampling

Initial sampling of the environment on the paediatric oncology ward showed high levels of
fungal contamination inside the linen store and the ward area immediately outside of the linen store. This included the two bed areas occupied by both cases. All other areas of the ward were negative (Figure 2). The moulds isolated were identified as *Rhizopus* and *Rhizomucor* spp., as well as *Aspergillus* spp. Seventy-two hours after containment measures were put in place, the ward contamination had dropped to low levels. This corresponded to the time expected to allow any spores suspended in the air within the ward to settle out under gravity. Only two colonies of mucoraceous mould were found on the settle plates and air sampling in the immediate vicinity of the linen store. This was thought to be consistent with background levels of environmental colonisation. The environment was sampled again at one week and three weeks to ensure that levels of fungal contamination remained low and did not pose a further threat to patients. One week after the control measures were put in place the contamination had gone entirely. There was still no evidence of contamination at three weeks at which time measures were undertaken to repair the water damage. It was not possible to sample within the parents’ shower or linen room at 72 h, one week and three weeks, as these were sealed in order to prevent further spread of fungal spores.

**Patient outcomes**

Case 1 made steady progress, with the clinical signs of mucormycosis resolving completely. At six months his radiological signs showed marked reduction in size of the mucormycosis lesions and loss of signal enhancement. It is planned that the child will continue on posaconazole for the duration of his cancer therapy in order to prevent relapse during periods of profound neutropenia.

Within two weeks of starting posaconazole Case 2 had no residual clinical neurological signs. It is planned that the child will continue on posaconazole for the duration of his cancer therapy.

Neither Case 1 nor Case 2 experienced any adverse effects from taking posaconazole. None of the 15 patients identified as being at high risk of developing mucormycosis, who were given posaconazole as prophylaxis, experienced any adverse affects from taking posaconazole. None of the posaconazole prophylaxis group developed clinical signs of mucormycosis. The outbreak of mucormycosis had no discernable impact on the long-term cancer management of the patients involved.

**Discussion**

Cases and outbreaks of mucormycosis have been reported but no definitive documentation of the source of such infections has been published, although airborne spread has been proposed as the source in some. Building and renovation work has also previously been proposed as a source of contamination. Previous studies into environmental fungal contamination have only looked at levels of *Aspergillus* spp. not zygomycetes, using air sampling techniques, finding counts of 10–20 cfu/m³ of air sampled for patient care areas and 120 cfu/m³ in outdoor air. It has been claimed that as little as 1 cfu/m³ can be enough to cause disease in a susceptible patient. One study showed a large increase in levels of *Aspergillus* spp. due to damage from a leaking water pipe in a ceiling.

The circumstances of this outbreak are unusual because the mucormycosis was not linked to building and renovation work but was associated with water damage to a linen store and parents’ shower room on a paediatric oncology unit. Although this investigation adds to the body of knowledge about potential sources of invasive fungal infections, it also demonstrates that building and renovation work may not always be the source.

A combination of environmental sampling techniques was used to investigate the source of the outbreak, including air sampling, settle plates and direct sampling and inoculation of material onto agar plates. This investigation found both air sampling and settle plates to be equally consistent in terms of documenting the source. The main advantage of using settle plates was that a large area could be screened rapidly, allowing staff to perform other tasks while samples were being collected. This was critical in demonstrating the high concentration of airborne spores close to the water-damaged area, which dropped to nothing at either ends of the ward (Figure 2). Air sampling would have required a member of staff to operate the single air sampler, 29 times in various locations. This would have taken ~5 h of continuous staff time. The other advantage of using settle plates was that there was no specific training required for the collection of samples. The authors conclude that gravity sedimentation methods such as settle plates are cheap, reliable, readily available and therefore a useful technique for investigating outbreaks of invasive mould infections in the hospital environment.

The environmental investigation gave the evidence that damaged plaster was responsible
Figure 2 Results of environmental sampling on paediatric oncology ward showing positive and negative samples by type. Settle plates: ●, +ve; ○, −ve. Swabs/scrapes: ▲, +ve; △, −ve. Air samples: ■, +ve; □, −ve.
for the outbreak of mucormycosis in two paediatric oncology children. This evidential link allowed definitive action to be taken, to protect further children from the source; to be confident that the source had been contained and posed no further risk to patients, and to ensure that the causal damage was repaired in a timely manner.

Previous investigators have suggested a need for genetic comparison of fungal isolates in an outbreak situation. Our investigation showed a significant mixture of organisms in both the patients and the environment including Rhizomucor spp. and Aspergillus spp. Within an environmental source e.g. damaged plaster, one would not necessarily expect to find a single dominant organism. The genetic diversity of the fungi in this outbreak would mean looking for genetic relatedness in the patient and environmental isolates would be of academic interest only, as a negative comparison would not necessarily exclude a single common source. The authors therefore feel that this kind of comparison is not always necessary to inform clinical infection control decisions.

In this outbreak posaconazole was used for the prophylaxis of 15 children identified as at high risk of developing mucormycosis and the treatment of the two confirmed cases of disease. The dosage regimen for posaconazole in children was unknown; it was not clear if the adult dose of posaconazole would be enough as often doses of antifungal drugs in children have to be higher than those given to adults due to differences in metabolism and elimination. Discussion with the manufacturer revealed that posaconazole’s licence for the treatment of invasive fungal infection in adults was imminent, and that it had been used at the adult dose of 400 mg bd with no ill effects in children as young as eight years old. On the basis of these data the adult dose was used in Case 1 and Case 2, despite Case 1 only being five years old.

Posaconazole was found to be effective in the treatment of both of the cases despite the absence of an option for surgical intervention in Case 2 due to the location of the intracerebral lesions in the optical cortex and cerebellum. This supports the finding of other investigators who used posaconazole as salvage therapy for the treatment of mucormycosis that was unresponsive to liposomal amphotericin B.

Posaconazole was well-tolerated in all of the 17 children and no child experienced any adverse events necessitating discontinuation of the drug. This is consistent with the findings of other investigators who found posaconazole to be well-tolerated in adult patients with invasive fungal infections.

In conclusion, this outbreak of mucormycosis was investigated using predominantly gravity sedimentation techniques, such as settle plates. It has demonstrated the risk of water damage to plaster as a cause of environmental fungal contamination. The use of settle plates allowed timely and successful implementation of infection control measures to contain the source and protect patients. The use of posaconazole off licence to treat the cases and provide prophylaxis resulted in a successful outcome and was well-tolerated in children as young as five years old. Both cases survived their illness and no further high-risk children developed signs or symptoms. It is the authors’ opinion that this investigation and management of a mucormycosis outbreak should give others the confidence and enthusiasm to tackle these types of situations in a proactive, timely and effective manner.

Acknowledgements

The authors wish to thank the extensive outbreak management team that successfully controlled this incident so efficiently and in particular the local infection control team who worked so hard to pull it all together.

Conflict of interest statement

None declared.

Funding sources

None.

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