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Invasive disease due to *Mucorales*: a case report and review of the literature

毛黴菌入侵病：病例報告及文獻總覽

Objective. To review the mycology, pathogenesis, clinical characteristics, investigations, and treatment modalities of mucormycosis.
Data sources. A local case of mucormycosis; MEDLINE and non-MEDLINE search of the literature.
Study selection. Key words for the literature search were 'mucormycosis' and '*Mucorales*'; all available years of study were reviewed.
Data extraction. Original articles, review papers, meta-analyses, and relevant book chapters were reviewed.
Data synthesis. Mucormycosis is a fungal infection that is rare but increasingly recognised in the growing population of immunocompromised patients. It is caused by saprophytic non-septate hyphae of the order *Mucorales*. The pulmonary and disseminated forms commonly occur in patients with haematological malignancy, especially acute leukaemia and lymphoma, and those receiving treatment with immunosuppressive effects. The rhinocerebral form is more prevalent in patients with diabetes mellitus, particularly those with the complication of diabetic ketoacidosis. The use of amphotericin B combined with surgery remains the mainstay of treatment. The prognosis largely depends on prompt correction of the underlying risk factors. New strategies to combat this life-threatening infection will result from better understanding of its pathogenesis.
Conclusion. A high index of suspicion is needed, in appropriate clinical settings, to diagnose and aggressively treat this infection in view of the high mortality rate for susceptible patients.

目的：總覽毛黴菌病的真菌學、發病機制、臨床特徵、研究調查和治療模式。
資料來源：一宗本地毛黴菌病的病例；MEDLINE 和非 MEDLINE 的文獻檢索。
研究選取：文獻搜索的關鍵詞是「毛黴菌病」；包括所有現有的文獻。
資料選取：論著、錄述、後分析及有關書籍。
資料綜合：毛黴菌病屬於一種真菌傳染病，由毛黴菌目中腐生物的非隔膜菌絲引起。這種傳染病雖然罕見，但因越來越多缺乏免疫力的病人受感染，所以日漸被人認識。有些毛黴菌病型會散佈在患者肺部，這類型通常出現在有血液惡性瘤(尤其是急性白血病及淋巴瘤)的患者中，又或者經常接受免疫抑製劑治療的病人中。毛黴菌的鼻腦型普遍在糖尿病患者，特別是患有糖尿病酮酸併發症的患者中出現。使用兩性黴素B結合外科手術仍然是主要的診治方法，而預後很大程度取決於及時消除潛在的危險因素。只有增加了解這種危及生命的傳染病，才可以研究出對付這種病的新的策略。
結論：由於容易感染此病的患者死亡率相當高，在有適當臨床設備的環境下，要用高度懷疑的指標去診斷和積極地治療這種傳染病。

Key words:
Amphotericin B;
Diabetes mellitus;
Immunosuppression;
Leukemia;
Mucormycosis

關鍵詞：
兩性黴素 B；
糖尿病；
免疫抑制；
白血病；
毛黴菌病

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Introduction

Mucormycosis is an opportunistic fungal infection caused by a filamentous fungus.[1,2] The infection is relatively uncommon but cases are being recognised early and treated effectively with a combination of antifungal agents and surgery, leading to improved survival.[1,3] The increasing prevalence of mucormycosis is due to wider use of cytotoxic chemotherapy and immunosuppressive agents, resulting in a more severe and prolonged immunocompromised state.[4] Risk factors for mucormycosis include haematological malignancy, namely leukaemia and lymphoma, diabetes mellitus, especially in poorly controlled patients and those with complications of diabetic ketoacidosis.[2] The use of steroids and immunosuppressive agents in bone marrow and solid organ transplantation,[5] broad-spectrum antibiotics and cytotoxic chemotherapy, and dialysis for uraemic patients, particularly with desferrioxamine therapy, are known predisposing causes.[1,5-7] Malnutrition in children in developing countries also carries a risk of mucormycosis with gastrointestinal involvement, and cerebral mucormycosis has been reported in intravenous drug user via the haematogenous route.[7] Thus, the infection is often an indication of a serious predisposing condition. This review focuses on the epidemiology, presenting signs and symptoms, diagnosis, treatment, and new directions in the approach to management of mucormycosis.

Case report

A 57-year-old HIV-negative Filipino presented with fever and prostration. He had a known history of poorly controlled non–insulin-dependent diabetes mellitus, managed with self-administered oral hypoglycaemic agents for 18 months. On admission, his fasting blood glucose and glycosylated haemoglobin (HbA_{1c}) were 10.3 mmol/L (normal range, 3.9-6.1 mmol/L) and 11.4% of total haemoglobin (normal range, 4-7% of total haemoglobin), respectively. On admission, he had a fever (temperature, 39.2°C), chills, and rigor. Examination showed a grossly overweight patient with fever, sternal tenderness, and borderline hypotension. Chest radiography was unremarkable. Peripheral blood smear revealed blasts and a leucoerythroblastic picture (white blood cell count, 4.9 x 10^9/L [normal range, 3.2-9.8 x 10^9/L]; neutrophil count, 0.83 x 10^9/L [normal range, 1.8-7.8 x 10^9/L]; lymphocyte count, 2.16 x 10^9/L [normal range, 1.0-4.8 x 10^9/L]; blast count, 1.67 x 10^9/L [normal range, 0 x 10^9/L]; haemoglobin level, 115 g/L [normal range, 140-175 g/L]; and a platelet count of 61 x 10^9/L [normal range, 150-450 x10^9/L]. Bone marrow examination confirmed acute monoblastic leukaemia-M5. Blood culture grew *Salmonella enteritides* (group D).

The patient was given intravenous cefoperazone-sulbactam 1 g twice daily for 14 days and ciprofloxacin 200 mg twice daily for 5 days. Induction chemotherapy including cytarabine 190 mg daily for 7 days and daunorubicin 95 mg daily for 3 days was started on day 9 of admission to hospital. Six days after chemotherapy, he developed a neutropenic fever, with a temperature of 38.8°C, which did not respond to broad-spectrum antimicrobial therapy. Examination for sepsis, including blood culture, sputum, and urine analysis was negative. Two days later, he was noted to have blood-tinged sputum, associated with increasing shortness of breath. Repeated chest X-rays showed enlarging multiple round lesions in both lung fields. Antimicrobial therapy was reviewed and imipenem, amikacin, and amphotericin 0.7 mg/kg/d were commenced on the same day.

The patient further deteriorated with acute respiratory distress, arterial hypoxaemia, and systemic hypotension requiring mechanical ventilation and intensive care. Bronchoscopy was performed, which showed diffuse inflammation of the bronchial mucosa. Apart from scanty enterococci recovered from bronchoalveolar lavage (BAL), the concentrated BAL smear showed numerous broad, non-septated hyphae with wide-angled branching, suggestive of mucormycosis, and fungal culture of the specimen later yielded *Cunninghamella bertholletiae*. The diagnosis was pneumonia due to *Cunninghamella* spp. Despite increasing the dose of liposomal amphotericin to 3 mg/kg/d, he developed multiorgan failure and finally died 24 hours later. Tissue invasion by fungal hyphae and the presence of disseminated infection could not be confirmed by histology, as his relatives did not consent to autopsy.

Discussion

Mycology

Mucormycosis is an infection caused by ubiquitous fungal agents of the order *Mucorales*.[2] The fungi occur in air, soil, and food and are filamentous consisting of broad irregular hyphae of 15 to 20 mm in diameter, mostly non-septated with right-angled branching (Fig). The infection is commonly due to *Rhizopus, Rhizomucor, Absidia,* and *Mucor* from the family of Mucoraceae and, rarely, *C bertholletiae* caused by Cunninghamellaceae (Table 1). Differentiation among these genera is based on the morphology

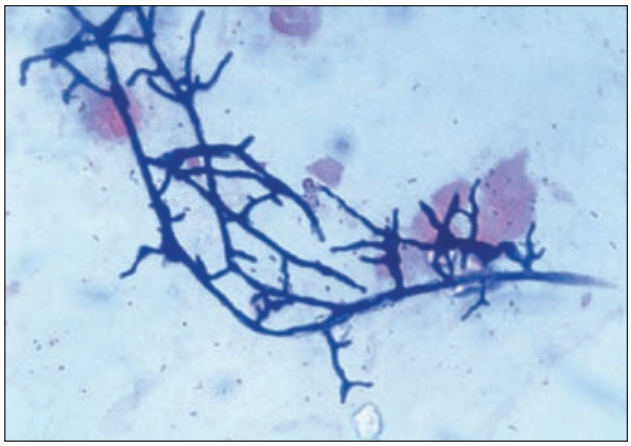

Fig. Microscopic view of fungal hyphae

of the asexual cycle, physiologic characteristics, and zygospore production.[2] The fungi are aerobic organisms that grow in most culture media after 2 to 5 days of incubation at temperatures of 25°C to 55°C, producing fluffy white, grey, or brownish colonies.[2] Positive growth is highly suggestive of infection in relevant clinical settings, although it is not diagnostic owing to occasional colonisation.[8] Histological examination showing tissue invasion by this fungus is diagnostic.

Pathogenesis

Rhinocerebral and pulmonary mucormycosis is an airborne infection acquired by inhalation of spores (3 mm to 6 mm in diameter) into the paranasal sinuses, lower airways, and alveoli.[1,9] As the fungi are aerobic, they have a special predilection for the nasal sinuses and lungs. Similar to *Aspergillus*, *Mucorales* characteristically spreads in the tissues by vascular invasion, since blood vessels are the best source of oxygen.[1] The invasion of blood vessels by hyphae leads to arterial thrombosis, tissue infarction, and necrosis, whereas venous invasion causes haemorrhage, exemplified by haemoptysis in pulmonary mucormycosis. There is no unifying theory of the predisposing underlying immunological defect. Immunity against mucormycosis is likely to occur at multiple levels, from the inhibition of spore germination by alveolar macrophages, to the damage of hyphae by serum factors, alveolar macrophages, and neutrophils. A study has shown that the combined effects of diabetes, ketosis, and low pH negated the inhibitory property of serum towards spore germination.[10] Investigators have demonstrated that the fungistatic activity of serum is caused by the presence of transferrin in the serum, which reduces the free iron available to the fungus for growth.[10] Acidosis temporarily disrupts the capacity of transferrin to bind iron in the serum, thereby reducing the host inhibition of fungal growth. The presence of a ketoreductase in the fungi may allow them to utilise ketone bodies in their metabolism, accounting for the increased susceptibility in diabetic ketoacidosis. Waldorf,[11] however, could not detect any significant differences in germination of *Rhizopus oryzae* between normal and diabetic sera with the addition of iron that saturated the total iron-binding capacity, nor with the addition of sufficient transferrin to bind all free serum iron. Reduced neutrophil chemotaxis and adhesion to hyphae in diabetes mellitus have been demonstrated.[12] Alveolar macrophages in diabetes are also defective in inhibition of spore germination and hyphae damage.[11,13] Desferrioxamine therapy for patients undergoing dialysis is associated with mucormycosis.[7] The fungus can accumulate iron to stimulate growth by utilising desferrioxamine as a siderophore.[7,14] These combined effects of acidosis and desferrioxamine accumulation in uraemic patients may account for the prevalence of mucormycosis in this group of patients. Mucormycosis is rare in patients with AIDS,[5,7] possibly reflecting the relative importance of innate immunity against this infection.

Table 1. Families and genera of *Mucorales* of medical importance

Family	Genera
Mucoraceae	*Absidia, Apophysomyces, Mucor, Rhizomucor, Rhizophus*
Cunninghamellaceae	*Cunninghamella*
Mortierellaceae	*Mortierella*
Saksenaeaceae	*Saksenaea*
Syncephalastraceae	*Syncephalastrum*
Thamnidiaceae	*Cokeromyces*

Clinical manifestations

Mucormycosis can manifest as different clinical forms, namely rhinocerebral, pulmonary, disseminated, gastrointestinal, cutaneous, and other rare forms.[1,2] The rhinocerebral form mainly occurs in patients with diabetes, particularly those with the complication of diabetic ketoacidosis, and presents with facial pain, headache, fever, and mental obtundation.[1,2,15] Orbital involvement results in orbital cellulitis, ophthalmoplegia, proptosis, and chemosis, and may extend upwards to form a frontal lobe abscess. A black necrotic scar may be seen in oral extension. Radiological investigations, including computed tomography scanning and magnetic resonance imaging, are useful in defining the anatomical extent of the rhinocerebral mucormycosis when planning surgery. The scans may show opacification of the sinuses, bony destruction, and arterial or venous occlusion.[1] Cerebral involvement may be seen as lucency on a computed tomography scan. Imaging is helpful for planning intervention rather than establishing the diagnosis.

Pulmonary mucormycosis commonly involves the upper lobes with better aeration. The endobronchial form is mainly found in patients with diabetes,[4,16] presenting with bronchial obstruction and haemoptysis.[9,17] Signs and symptoms are non-specific. Cough, dyspnoea, chest pain, and haemoptysis are common symptoms, and fever is the most consistent sign. The typical clinical picture is a profoundly ill neutropenic patient with unremitting fever despite broad-spectrum antibiotics, progressive infiltration as shown on chest X-ray, and rapidly deteriorating respiratory failure. Findings on chest X-ray include patchy consolidation, single or multiple areas of rounded pneumonia of increasing size and number, and a cavitating lesion. The actual extent of pulmonary involvement can be much greater than that shown in chest X-rays, since the vasoinvasion causes tissue necrosis which may not be apparent on X-ray.[1] Eighty-seven patients with pulmonary mucormycosis have been reviewed by Lee et al[4] since 1970—49 (56%) patients had diabetes mellitus, of whom 10 (20%) patients had the complication of ketoacidosis. The second largest group comprised 28 (32%) patients with haematological malignancy. Neutropenia occurred in 13 (46%) patients in this group.The last group comprised 11 (13%) patients with renal insufficiency, of whom 10 (11%) were organ transplant recipients, and all 11 (13%) patients had no apparent underlying predisposing illness.

A high index of suspicion is needed to avoid delay in diagnosis and treatment. Only 33% of mucormycosis cases in haematological patients were diagnosed by biopsy and bronchoalveolar lavage in the antemortem period in Pagano et al's study.[18] The overall survival rate of pulmonary mucormycosis is 44%, depending on underlying predisposing conditions and extent of the lesion. The cutaneous form is usually related to trauma and an outbreak was associated with Elastoplast bandages contaminated by spores.[2,19] In addition, cutaneous disease may be part of the picture in its disseminated form, which mainly occurs in patients with leukaemia. The gastrointestinal form may present with gastrointestinal bleeding and features of intra-abdominal sepsis, and is found in children with protein-calorie malnutrition.[1]

Clinical syndromes caused by individual genera of *Mucorales* were reviewed in a MEDLINE literature search. Only those reports containing detailed descriptions of the characteristics and species of *Mucorales* were selected for analysis and have been summarised in Table 2.[20-51] The underlying diseases included haemic malignancy (30), diabetes mellitus (10), solid organ transplant recipients (6), and chronic renal failure (2). Ten patients, who were immunocompetent, were mainly infected with a cutaneous manifestation of *Apophysomyces*, which has the highest survival rate among the

Table 2. Case reports of Mucoraceae and Cunninghamellaceae in the literature

Report	Sex/age (years)	Organism	Underlying risk factor/disease	System involvement	Treatment and outcome
Amin et al, 1998[20]	NM*	*Absidia*	Premature infant	Disseminated	Death
Amin et al, 1998[20]	NM	*Absidia*	Congenital heart disease	Pulmonary	Death
Lake et al, 1988[21]	M/45	*Absidia*	Immunocompetent	Pulmonary	Pneumonectomy/ amphotericin B Survived
El-Ani and Dhar, 1982[22]	F/50	*Absidia*	Metastatic anaplastic carcinoma—receiving chemotherapy	Pulmonary	Death
Brown et al, 1998[23]	M/54	*Apophysomyces*	Severe sinusitis—receiving oral steroids	Rhinocerebral	Surgery/amphotericin B Survived
Chakrabarti et al, 1997[24]	M/52	*Apophysomyces*	Idiopathic myelofibrosis	Craniofacial	Death
Mathews et al, 1997[25]	F/ -	*Apophysomyces*	Immunocompetent	Necrotising fasciitis of abdominal wound following lower segment caesarean section	Surgery/amphotericin B Survived
Naguib et al, 1995[26]	M/50	*Apophysomyces*	Renal transplant recipient	Post-traumatic cutaneous infection	Surgery/amphotericin B Survived
Radner et al, 1995[27]	M/19	*Apophysomyces*	Immunocompetent	Rhinocerebral	Surgery/amphotericin B Survived
Meis et al, 1994[28]	M/69	*Apophysomyces*	Immunocompetent	Osteomyelitis of humerus	Intertroracoscapular amputation/ amphotericin B Survived

Continued on page 184

Continued from page 183

Report	Sex/age (years)	Organism	Underlying risk factor/disease	System involvement	Treatment and outcome
Eaton et al, 1994[29]	M/ -	*Apophysomyces*	Immunocompetent	Post-traumatic chest wall/sternal infection	Surgery/amphotericin B Survived
Okhuysen et al, 1994[30]	M/ -	*Apophysomyces*	Immunocompetent	Cutaneous infection with secondary renal invasion	Surgery/amphotericin B/ gamma-interferon Survived
Weinberg et al, 1993[31]	M/59	*Apophysomyces*	Immunocompetent	Invasive cellulitis/ osteomyelitis	Surgery/amphotericin B Survived
Lakshmi et al, 1993[32]	M/ -	*Apophysomyces*	Immunocompetent	Necrotising fasciitis of abdominal wall following inguinal herniorrhaphy	Surgery/amphotericin B Survived
Huffnagle et al, 1992[33]	NM	*Apophysomyces*	Multiple trauma	Musculoskeletal	Amputation/amphotericin B Survived
Cooter et al, 1990[34]	NM	*Apophysomyces*	25% full thickness burn	Burn wound infection	Amputation/amphotericin B Survived
Lawrence et al, 1986[35]	M/56	*Apophysomyces*	Immunocompetent	Left kidney/urinary bladder	Surgery/amphotericin B Survived
Wieden et al, 1985[36]	F/ -	*Apophysomyces*	Diabetes mellitus	Musculocutaneous	Surgery/amphotericin B Survived
Webb et al, 1998[37]	M/32	*Mucor*	Liver transplant recipient	Rhinocerebral	Death
Szelenyi et al, 1996[38]	NM	*Mucor*	Lymphoma—receiving 2-chlorodeoxyadenosine	Pulmonary	Death
Fingeroth et al, 1994[39]	F/23	*Mucor*	Acute leukaemia—receiving chemotherapy	Cutaneous	Amphotericin B Survived
Santo et al, 1986[40]	M/37	*Mucor*	Behçet's disease/ diabetic ketoacidosis	Pulmonary	Pneumonectomy/ amphotericin B Survived
Barnert et al, 1985[41]	M/51	*Mucor*	Diabetic ketoacidosis	Rhinocerebral	Surgery/ketoconazole Survived
St-Germain et al, 1993[42]	M/40 F/48 M/18	*Rhizomucor*	Acute leukaemia—receiving chemotherapy	Pulmonary	Death
St-Germain et al, 1993[42]	F/53 M/18	*Rhizomucor*	Acute leukaemia	Disseminated	Death
St-Germain et al, 1993[42]	F/48 F/40	*Rhizomucor*	Acute leukaemia	Pulmonary	Death
St-Germain et al, 1993[42]	F/41	*Rhizomucor*	Diabetes mellitus	Cutaneous	Amphotericin B Survived
St-Germain et al, 1993[42]	M/38	*Rhizomucor*	Acute leukaemia	Disseminated	Death
St-Germain et al, 1993[42]	M/72 F/42	*Rhizomucor*	Acute leukaemia	Rhinofacial	Death
St-Germain et al, 1993[42]	M/11	*Rhizomucor*	Acute leukaemia	Rhinofacial	Unknown
St-Germain et al, 1993[42]	F/20 M/58	*Rhizomucor*	Acute leukaemia	Disseminated	Death
St-Germain et al, 1993[42]	M/76	*Rhizomucor*	Myeloid metaplasia	Disseminated	Death
St-Germain et al, 1993[42]	M/86	*Rhizomucor*	Uncertain	Pulmonary	Death
Kameh et al, 1997[43]	M/13 months	*Rhizopus*	Diabetic ketoacidosis	Rhinocerebral	Death
Winkler et al, 1996[44]	NM	*Rhizopus*	Renal transplant recipient	Gastric perforation	Amphotericin B Survived
Branton et al, 1991[45]	M/61	*Rhizopus*	Chronic renal failure/ diabetic ketoacidosis	Continuous ambulatory peritoneal dialysis peritonitis	Death
Nakamura et al, 1989[46]	NM	*Rhizopus*	Chronic renal failure—receiving desferrioxamine therapy	Disseminated	Death
Dennis et al, 1980[47]	NM (2 cases)	*Rhizopus*	Acute leukaemia—receiving chemotherapy	Gangrenous cellulitis of buttock	Surgery/amphotericin B Survived

Continued on page 185

Continued from page 184

Report	Sex/age (years)	Organism	Underlying risk factor/disease	System involvement	Treatment and outcome
Dennis et al, 1980[47]	NM	*Rhizopus*	Premature infant	Gastric perforation	Surgery/amphotericin B Survived
Hammer et al, 1975[48]	M/53	*Rhizopus*	Renal transplant recipient	Rhinocerebral	Death
Cohen-abbo et al, 1993[49]	M/8	*Cunninghamella*	Lymphosarcoma—receiving steroids, chemotherapy, and radiotherapy	Disseminated	Death
Cohen-abbo et al, 1993[49]	M/13	*Cunninghamella*	Post-necrotic cirrhosis	Disseminated	Death
Cohen-abbo et al, 1993[49]	M/3	*Cunninghamella*	Acute leukaemia—receiving chemotherapy	Pulmonary	Amphotericin B Survived
Cohen-abbo et al, 1993[49]	M/7	*Cunninghamella*	Acute leukaemia—receiving chemotherapy	Pulmonary	Death
Cohen-abbo et al, 1993[49]	M/54	*Cunninghamella*	Chronic leukaemia with splenectomy	Pulmonary	Death
Cohen-abbo et al, 1993[49]	M/53	*Cunninghamella*	Chronic leukaemia—receiving steroids and chemotherapy	Pulmonary	Death
Cohen-abbo et al, 1993[49]	M/69	*Cunninghamella*	Diabetes mellitus, asthma—receiving steriods	Cutaneous	Amphotericin B and amputation Survived
Cohen-abbo et al, 1993[49]	M/59	*Cunninghamella*	Thalassaemia, liver cirrhosis	Pulmonary and hepatic	Death
Cohen-abbo et al, 1993[49]	M/70	*Cunninghamella*	Thalassaemia minor with haemochromatosis, diabetes mellitus	Rhinocerebral	Death
Cohen-abbo et al, 1993[49]	M/40	*Cunninghamella*	Renal transplant recipient	Disseminated	Death
Cohen-abbo et al, 1993[49]	M/42	*Cunninghamella*	Thalassaemia major—receiving desferrioxamine therapy	Cutaneous and lymph node	Amphotericin B Survived
Cohen-abbo et al, 1993[49]	M/66	*Cunninghamella*	Chronic leukaemia—receiving steroids and chemotherapy	Disseminated	Death
Cohen-abbo et al, 1993[49]	F/48	*Cunninghamella*	Myelodysplasia—receiving desferrioxamine therapy	Pulmonary	Death
Cohen-abbo et al, 1993[49]	F/19	*Cunninghamella*	Liver transplant recipient for Wilson's disease	Disseminated	Death
Cohen-abbo et al, 1993[49]	M/27	*Cunninghamella*	AIDS, intravenous drug abuse	Skin and knee joint	Death
Cohen-abbo et al, 1993[49]	M/55	*Cunninghamella*	Chronic leukaemia, diabetes mellitus	Pulmonary	Death
Cohen-abbo et al, 1993[49]	M/61	*Cunninghamella*	Immunocompetent	Pulmonary	Death
Ng et al, 1994[50]	M/70	*Cunninghamella*	Myelodysplasia, diabetes mellitus	Sinuses	Amphotericin B Survived
Kontoyianis et al, 1994[51]	M/66	*Cunninghamella*	Chronic leukaemia	Disseminated	Death
Kontoyianis et al, 1994[51]	M/51	*Cunninghamella*	Acute leukaemia	Pulmonary/sinuses	Death
Kontoyianis et al, 1994[51]	M/51	*Cunninghamella*	Acute leukaemia	Pulmonary	Death

* NM not mentioned

Mucoraceae family. *Rhizomucor* was the most commonly encountered organism in patients with leukaemia, with a mortality rate approaching 100%. Infections due to *Cunninghamella* from Cunninghamellaceae also carried a high mortality rate of 81%.[49] *Cunninghamella* mainly causes pulmonary and disseminated infection. There is intrinsic resistance by in vitro sensitivity testing to amphotericin, which may account for the higher mortality rate compared with infections by other *Mucorales.*

Investigation

Serology currently has no place in diagnosis.[2,4] The yield in sputum is low if the specimen is homogenised before culture inoculation. This dicing procedure

destroys the aseptate fungus and decreases the sensitivity of sputum culture. Demonstration of tissue invasion by hyphae in a biopsy specimen is the gold standard.[2,19] Differential diagnosis of vascular involvement in tissue invasion includes *Aspergillus* spp. and *Pseudomonas* spp. infection that can only be differentiated with certainty by culture.[1] Detection of hyphae in bronchial washings obtained by fibreoptic bronchoscopy after dissolving in 10% potassium hydroxide is also highly suggestive of infection, although the histology from open lung biopsy or transthoracic fine needle aspiration is more diagnostic.[2,8] It is important to screen for coexisting sites of mucormycosis. For instance, sinus involvement needs to be excluded in pulmonary mucormycosis.

Treatment

The present increased overall survival of patients with mucormycosis is related to improved diagnosis, and use of surgical intervention combined with effective antifungal agents.[1,3] Since survival is associated with early diagnosis, a high index of suspicion and prompt diagnosis by aggressive investigation such as tissue biopsy, significantly affects the treatment outcome. The importance of correcting or controlling the underlying predisposing condition cannot be overemphasised. Better glycaemic control in diabetes and adjustment of immunosuppressing drugs are important factors in determining the treatment outcome. There are reports that show that correction of diabetic ketoacidosis alone may cure mucormycosis.[52] Higher mortality rates in haematological and neutropenic patients (up to 76% in a study by Pagano et al[18]) is due to an inability to rapidly correct the host defence abnormalities accompanying the underlying haemic conditions, which become the determining factor in prognosis.[18] Early and repeated surgical debridement of all grossly involved tissue is important for local control of the condition, especially in rhinocerebral, pulmonary, and cutaneous mucormycosis,[2] and early resection of the pulmonary lesion is often necessary to prevent severe haemoptysis. Amphotericin B is the most reliable antifungal agent that is effective against mucormycosis. Although the in vitro sensitivity is variable from isolate to isolate, amphotericin B is clinically effective. The recommended dose is 1 mg/kg/d, but a dosage of up to 1.5 mg/kg/d may be needed for serious infection. The duration of treatment is between 3 to 6 weeks with a total dose of 2.0 to 4.0 g administered, depending on the clinical response, underlying disease, and toxicity.[1] Liposomal amphotericin B is advocated because of its reduced nephrotoxic effect and improved cell penetration.[5] The synergistic effect of amphotericin B and rifampicin or fluorocytosine is not well proven.[1,2] Azoles have no consistent activity against mucormycosis. Paradoxically, hyperbaric oxygen therapy to inhibit mucor growth has been used as auxiliary treatment in cutaneous and rhinocerebral mucormycosis.[53] The mechanism may be related to generation of free radicals damaging the membranes, inactivating the enzymes, and enhancing the bactericidal action of neutrophils. Hyperbaric oxygen may reverse vascular insufficiency by vascular invasion and occlusion, reducing the acidosis that would otherwise enhance fungal growth. Oral antifungal prophylaxis is ineffective. The use of a high efficiency particulate air filter ventilation system to reduce the exposure of neutropenic patients to the environment may be considered for prophylaxis.[54] There are preliminary reports using an intranasal or aerosol form of amphotericin B to prevent mucormycosis.[9]

New directions for treatment of mucormycosis depend on a better understanding of the mycology and mechanisms of host resistance. Improved survival in mucormycosis relies on the efficacy of new antifungal agents and methods to reverse host defence abnormalities. Due to the angioinvasive nature of the fungus, selective angioembolisation may be considered to deprive the fungus of oxygen and nutrients and achieve local control of the fungal growth. Manipulation of the microenvironment of the fungus to inhibit its growth may be considered. Reversing an acidic environment by systemic alkalisation, as in diabetic ketoacidosis, is a logical way to inhibit fungal growth. The role of unsaturated transferrin to diminish iron availability thereby inhibiting mucor growth warrants further exploration. Immunomodulators may be used to augment host defence. The use of growth factors such as granulocyte-macrophage colony-stimulating factor may shorten the period of neutropenia and stimulate the phagocytic activity of neutrophils and the proliferation of macrophages.[55] The efficacy of granulocyte transfusion for patients with prolonged neutropenia requires further investigation.

Conclusion

Mucormycosis has growing importance because of the increasing population of immunocompromised patients. Due to the high mortality and morbidity rates of the fungal infection in this group of patients, a high index of suspicion is warranted in the relevant clinical situation. Early diagnosis by an aggressive investigative approach to obtain tissue biopsy and early surgical intervention, combined with systemic antifungal therapy will optimise the treatment outcome. Correction of the underlying risk factors is essential to achieve

a cure. Advances in treatment rely on better understanding of the interaction of the host and fungus.

References

1. Sugar AM. Mucormycosis. Clin Infect Dis 1992;14 (Suppl 1): 126S-9S.
2. Lehrer RI, Howard DH, Sypherd PS, Edwards JE, Segal GP, Winston DJ. Mucormycosis. Ann Intern Med 1980;93:93-108.
3. Parfrey NA. Improved diagnosis and prognosis of mucormycosis: a clinicopathological study of 33 cases. Medicine (Baltimore) 1986;65:113-23.
4. Lee FY, Mossad SB, Adal KA. Pulmonary mucormycosis. Arch Intern Med 1999;159:1301-9.
5. Boelaert JR. Mucormycosis (zycomycosis): is there news for the clinician? J Infect 1994;28 (Suppl 1):1S-6S.
6. McNab AA, Mckelvie P. Iron overload is a risk factor for zygomycosis. Arch Ophthalmol 1997;115:919-21.
7. Abe F, Inaba H, Katoh T, Hotchi M. Effects of iron and desferrioxamine on *Rhizopus* infection. Mycopathologia 1990; 110:87-91.
8. Bigby TD, Serota ML, Tierney LM Jr, Matthay MA. Clinical spectrum of pulmonary mucormycosis. Chest 1986;89:435-9.
9. Skahan KJ, Wong B, Armstrong D. Clinical manifestations and management of mucormycosis in the compromised patient. In: Warnock DW, Richardson MD, editors. Fungal infection in the compromised patient. 2nd ed. Chichester: Wiley; 1991: 153-90.
10. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. Diabetes 1982;31: 1109-14.
11. Waldorf AR. Pulmonary defense mechanisms against opportunistic fungal pathogens. Immunol Ser 1989;47:243-71.
12. Chinn RY, Diamond RD. Generation of chemotactic factors by *Rhizopus oryzae* in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. Infect Immun 1982;38:1123-9.
13. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against *Rhizopus*. J Clin Invest 1984;74: 150-60.
14. Boelaert JR, de Locht M, Van Cutsem J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. J Clin Invest 1993;91:1979-86.
15. Maniglia AJ, Mintz DH, Novak S. Cephalic phycomycosis: a report of eight cases. Laryngoscope 1982;92:755-60.
16. Donohue JF. Endobronchial mucormycosis. Chest 1983;83: 585.
17. Hansen LA, Prakash UB, Colby TV. Pulmonary complications in diabetes mellitus. Mayo Clin Proc 1989;64:791-9.
18. Pagano L, Ricci P, Tonso A, et al. Mucormycosis in patients with haematological malignancies: a retrospective clinical study of 37 cases. Br J Haematol 1997;99:331-6.
19. Gartenberg G, Bottone EJ, Keusch GT, Weitzman I. Hospital-acquired mucormycosis (*Rhizopus rhizopodiformis*) of skin and subcutaneous tissue: epidemiology, mycology and treatment. N Engl J Med 1978;299:1115-8.
20. Amin SB, Ryan RM, Metlay LA, Watson WJ. *Absidia corymbifera* infections in neonates. Clin Infect Dis 1998;26:990-2.
21. Lake FR, McAleer R, Tribe AE. Pulmonary mucormycosis without underlying systemic disease. Med J Aust 1988;149: 323-6.
22. EI-Ani AS, Dhar V. Disseminated mucormycosis in a case of metastatic carcinoma. Am J Clin Pathol 1982;77:110-4.
23. Brown SR, Shah IA, Grinstead M. Rhinocerebral mucormycosis caused by Apophysomyces elegans. Am J Rhinol 1998; 12:289-92.
24. Chakrabarti A, Panda N, Varma SC, et al. Craniofacial zygomycosis caused by Apophysomyces elegans. Mycoses 1997;40:419-21.
25. 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; 35:61-3.
26. 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: 381-4.
27. Radner AB, Witt MD, Edwards JE Jr. Acute invasive rhinocerebral zygomycosis in an otherwise healthy patient: case report and review. Clin Infect Dis 1995;20:163-6.
28. Meis JF, Kullberg BJ, Pruszczynski M, Veth RP. Severe osteomyelitis due to zygomycete Apophysomyces elegans. J Clin Microbiol 1994;32:3078-81.
29. Eaton ME, Padhye AA, Schwartz DA, Steinberg JP. Osteomyelitis of the sternum caused by Apophysomyces elegans. J Clin Microbiol 1994;32:2827-8.
30. 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; 19:329-31.
31. Weinberg WG, Wade BH, Cierny G 3rd, Stacy D, Rinaldi MG. Invasive infection due to Apophysomyces elegans in immunocompetent hosts. Clin Infect Dis 1993;17:881-4.
32. Lakshmi V, Rani TS, Sharma S, et al. Zygomycotic necrotizing fasciitis caused by Apophysomyces elegans. J Clin Microbiol 1993;31:1368-9.
33. Huffnagle KE, Southern PM Jr, Byrd LT, Gander RM. Apophysomyces elegans as an agent of zygomycosis in a patient following trauma. J Med Vet Mycol 1992;30:83-6.
34. Cooter RD, Lim IS, Ellis DH, Letich IO. Burn wound zygomycosis caused by Apophysomyces elegans. J Clin Microbiol 1990;28:2151-3.
35. Lawrence RM, Snodgrass WT, Reichel GW, Padhye AA, Ajello L, Chandler FW. Systemic zygomycosis caused by Apophysomyces elegans. J Med Vet Mycol 1986;24:57-65.
36. Wieden MA, Steinbronn KK, Padhye AA, Ajello L, Chandler FW. Zygomycosis caused by Apophysomyces elegans. J Clin Microbiol 1985;22:522-6.
37. Webb M, Dowdy L, Bundschu C, Nery J, Schiff E, Tzakis AG. Cerebral mucormycosis after liver transplantation: a case report. Clin Transplant 1998;12:596-9.
38. Szelenyi H, Foss HD, Kreuser ED, Knauf W, Thiel E. Fatal Mucor pneumonia after treatment with 2-chlorodeoxyadenosine for non-Hodgkin's-lymphoma. Ann Hematol 1996;73:145-7.
39. Fingeroth JD, Roth RS, Talcott JA, Rinaldi MG. Zygomycosis due to Mucor circinelloides in a neutropenic patient receiving chemotherapy for acute myelogenous leukemia. Clin Infect Dis 1994;19:135-7.
40. Santo M, Levy A, Levy MJ, et al. Pneumonectomy in pulmonary mucormycosis complicating Behçet's disease. Postgrad Med J 1986;62:485-6.
41. Barnert J, Behr W, Reich H. An amphotericin B-resistant case of rhinocerebral mucormycosis. Infection 1985;13:134-6.

42. St-Germain G, Robert A, Ishak M, Tremblay C, Claveau S. Infection due to Rhizomucor pusillus: report of four cases in patients with leukemia and review. Clin Infect Dis 1993;16: 640-5.
43. Kameh DS, Gonzalez OR, Pearl GS, Walsh AF, Gambon T, Kropp TM. Fatal rhino-orbital-cerebral zygomycosis. South Med J 1997;90:1133-5.
44. Winkler S, Susani S, Willinger B et al. Gastric mucormycosis due to Rhizopus oryzae in a renal transplant recipient. J Clin Microbiol 1996;34:2585-7.
45. Branton MH, Johnson SC, Brooke JD, Hasbargen JA. Peritonitis due to Rhizopus in a patient undergoing continuous ambulatory peritoneal dialysis. Rev Infect Dis 1991;13:19-21.
46. Nakamura M, Weil WB Jr, Kaufman DB. Fatal fungal peritonitis in an adolescent on continuous ambulatory peritoneal dialysis: association with deferoxamine. Pediatr Nephrol 1989; 3:80-2.
47. Dennis JE, Rhodes KH, Cooney DR, Roberts GD. Nosocomial Rhizopus infection (zygomycosis) in children. J Pediatr 1980;96:824-8.
48. Hammer GS, Bottone EJ, Hirschman SZ. Mucormycosis in a transplant recipient. Am J Clin Pathol 1975;64:389-98.
49. Cohen-abbo A, Bozeman PM, Patrick CC. Cunninghamella infections: review and report of two cases of Cunninghamella pneumonia in immunocompromised children. Clin Infect Dis 1993;17:173-7.
50. Ng TT, Campbell CK, Rothera M, Houghton JB, Hughes D, Denning DW. Successful treatment of sinusitis caused by Cunninghamella bertholletiae. Clin Infect Dis 1994;19:313-6.
51. Kontoyianis DP, Vartvarian S, Anaissie EJ, Samonis G, Bodey GP, Rinaldi M. Infections due to Cunninghamella bertholletiae in patients with cancer: report of three cases and review. Clin Infect Dis 1994;18:925-8.
52. Mendoza-Ayala R, Tapia R, Salathe M. Spontaneously resolving pulmonary mucormycosis. Clin Infect Dis 1999;29: 1335-6.
53. Bentur Y, Shupak A, Ramon Y, et al. Hyperbaric oxygen therapy for cutaneous/soft-tissue zygomycosis complicating diabetes mellitus. Plast Reconstr Surg 1998;102:822-4.
54. Lueg EA, Ballagh RH, Forte V. Analysis of the recent cluster of invasive fungal sinusitis at the Toronto Hospital for Sick Children. J Otolaryngol 1996;25:366-70.
55. Leleu X, Sendid B, Fruit J, et al. Combined anti-fungal therapy and surgical resection as treatment of pulmonary zygomycosis in allogeneic bone marrow transplantation. Bone Marrow Transplant 1999;24:417-20.