Mucormycoses in Patients with Hematologic Malignancies: An Emerging Fungal Infection

Background and Objectives. **Mucormycoses are seen with an increasing incidence in immunocompromised patients. Most common presentations are rhinocerebral and pulmonary. We here report the experience of a single center with mucormycoses in patients with hematologic malignancies.** ***Results.*** **Mucormycoses were diagnosed in six patients, median age of 52 years (range, 26-74) treated between 2001-2004. Diagnoses included acute myeloid leukemia (AML) (n=3), acute lymphoblastic leukemia (n=1), chronic lymphocytic leukemia (n=1) and multiple myeloma (n=1). Mucormycosis was diagnosed in the neutropenic state following allogeneic hematopoietic cell transplantation (n=3) or intense chemotherapy (n=3). Sites of infections were rhinocerebral, facial and pulmonary involvement in one patient each and disseminated mucormycosis in three patients. Diagnosis was established by computed tomography followed by surgical interventions and histological diagnosis in 4 patients and post-mortem in two patients. Species identified were *Rhizopus* (n=3), *Rhizomucor* (n=2) and Absidia (n=1). Treatment responses were best if surgical resection was followed by aggressive antifungal chemotherapy. Five of 6 patients died, all of complications of mucormycosis or their underlying disease. Only one patient with facial mucormycosis is still alive.** ***Conclusion.*** **This experience demonstrates that mucormycoses have a high mortality rate and early recognition followed by aggressive surgical debridement, high dose antifungal therapy and attempts to correct the underlying immunocompromised state are crucial in the treatment of this lethal infection.**

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Mucormycosis in immunocompromised patients are seen with an increasing incidence.[1,2] Patients with hematologic malignancies especially in the neutropenic state after aggressive chemotherapy or hematopoietic cell transplantation (HCT) are particularly susceptible to fungal infections. Mucormycoses represent the third leading cause of invasive fungal infections following *Aspergillus* and *Candida species*.[1] Mucormycosis is caused by fungi of the group of zygomycetes of the order of mucorales. These pathogens have a marked capability for vascular invasion and rapidly produce thrombosis and tissue necrosis. The clinical importance of mucormycosis is underlined by its increasing incidence[2] and its high mortality rate of 70-90%.[3] We here report the experience of a single center with mucormycosis in patients with hematologic malignancies.

Results

At our institution mucormycoses were diagnosed in six patients treated for hematologic malignancies since the year 2000 (Table 1). Median age of the patients was 52 years (range, 26-74). In all patients mucormycosis was diagnosed in the neutropenic state following allogeneic hematopoietic cell transplantation (n=3) or intense chemotherapy (n=3) while receiving antifungal prophylaxis with either fluconazole (n=1), itraconazole (n=1) or voriconazole (n=3). In two patients mucormycosis was diagnosed after less than 10 days of neutropenia. Possible mucormycosis was suspected in four patients after imaging and followed by surgical interventions and histological diagnosis. Two patients diagnosis was only established post-mortem. Manifestations of mucormycosis involved skin in two patients starting with local erythema and induration progressing to local necrosis. One patient each had isolated lung involvement or involvement of sinuses and orbita. Three patients had disseminated mucormycosis involving multiple organs such as lung, heart, brain, bowel, uterus and bladder. In three patients diagnosis was established by microbiological culture of bronchio-alveolar-lavage (BAL), stool or biopsy material. In the other three patients species were identified with polymerase chain reaction (PCR) and sequencing of biopsy material. Species identified were Rhizopus in three, Rhizomucor in two and Absidia in one patient (Table 2).

Table 1.

Patient number	*Age/ Gender*	*Diagnosis*	*Preceding Therapy*	*Days ANC<500 before Diagnosis*	*Antifungal Prophylaxis*	*Site of Mucormycosis*
1	26/f	AML	Allo-HCT	11	Fluconazole	Skin left chin
2	43/f	AML	MTC	19	Itraconazole	Pansinusitis, left orbita
3	62/f	MM	Allo-HCT	1	Vori	Lung, heart, spine, brain
4	63/m	AML	MTC	9	Ampho	Lateral left calf, lung
5	74/m	CLL	Fludarabine/ MCP	29	Vori	Lung
6	34/f	ALL	Allo-HCT	16	Vori	Bowel, uterus, bladder, lung

f-female; m-male; AML-acute myeloid leukemia; MM-multiple myeloma; CLL-chronic lymphatic leukemia; ALL-acute lymphoblastic leukemia; HCT-hematopoietic cell transplantation; MTC-mitoxantrone; topotecan; ara-c; ampho-amphotericin B; posa-posaconazole; vori-voriconazole; caspo-caspofungin.

Table 2.

Patient number	*Diagnosis on*	*Year of Diagnosis*	*Species*	*Sequence of Therapy/ Diagnosis*	*Outcome*
1	Biopsy, culture	2001	Absidia	Diagnosis → Ampho → Surgery	Alive
2	Biopsy, PCR	2002	Rhizopus	Ampho →Caspo→Surgery → Ampho→Surgery→Posa	Death
3	Post PCR mortem,	2002	Rhizopus	Vori → Diagnosis	Death
4	Biopsy, PCR	2003	Rhizomucor	Diagnosis → Ampho → Posa	Death
5	BAL post mortem, culture	2004	Rhizomucor	Vori → Caspo→ Diagnosis	Death
6	Stool, histology,	2004 culture	Rhizopus	Vori→Diagnosis → Ampho → Surgery	Death

BAL-bronchio-alveolar-lavage

The fast kinetic of this infection is illustrated by the fulminant and lethal course in two of our patients succumbing to the infection within 3-5 days. In all patients in which diagnosis could be established before death, treat-

ment consisted of high dose liposomal amphothericin B (≥ 5 mg/kg) or posaconazol (on protocol P02095, Schering Plough Research Institute). Response to treatment was best if adequate antifungal treatment followed by radical surgical resection was possible. Despite adequate treatment the outcome of mucormycosis in our experience was dismal with 5 out of 6 patients dying after diagnosis, two of them with disseminated infection. Only one patient with a localized cutaneous manifestation survived, since complete surgical resection was achieved.

Discussion

Mucormycosis is an increasingly recognized infectious disease in patients treated for hematologic malignancies. At our center we observed an increasing incidence of mucormycoses since 2000 while the incidence of proven invasive aspergillosis in the same period and patient population remained virtually constant with an average of about 30 cases of probable and 15 cases of proven invasive aspergillosis per year. Reasons for the increasing incidence remain unclear but better tools of diagnosis, more patients in a state of severe and prolonged immunodefiency and the more widespread use of antifungal prophylaxis effective against other fungi are possible explanations.[4] In a retrospective study of fungal infections in HCT recipients, Marr *et al.*[2] found the following risk factors for invasive fungal infections with zygomycetes: age >40, hematologic malignancy other than chronic myeloid leukemia, mismatched or unrelated donor and GVHD.

Albeit most reports show a correlation between length of neutropenia and risk for fungal infection it is notable that mucormycosis was diagnosed after less than 10 days of neutropenia in two of our patients.

As reported previously antifungal prophylaxis with either fluconazole, itraconazole or voriconazole was ineffective against zygomycetes.[4,5] This raises the concern that due to the widespread use of antifungal prophylaxis, infections with fungi with the least sensitivity may increasingly develop in the most vulnerable patients.

Diagnosis of mucormycosis is challenging. Mucormycosis is an aerogeneous infection typically involving pulmonary and rhinocerebral disease but, like in our patients, reports about cutaneous, gastrointestinal and disseminated infections exist.[6-9] Signs and symptoms of infection in our patients included fever, painful local swelling, necrosis, paraplegia, pneumonia and ileus. In our cohort of patients possible mucormycosis was suspected after imaging and followed by surgical interventions and histological diagnosis in 4 patients and on autopsy in 2 patients. If identification of species by culture is unsuccessful, molecular diagnostic methods are helpful. In our series half of the species involved could only be identified by PCR. For successful therapy fast diagnosis und identification of the underlying organism is essential, since zygomycetes have differing sensitivity to the available antifungals.[10] Species identified were *Rhizopus* in three, *Rhizomucor* in two and *Absidia* in one patient. The fast kinetic of this infection is illustrated by the fulminant and lethal course in two of our patients succumbing to the infection within 3-5 days. The prognosis of patients developing mucormycosis is grim with an overall mortality rate of 75-80%, increasing to 95% mortality in disseminated cases.[3,11] This is confirmed by our experience with 5 out of 6 patients dying after diagnosis of mucormycosis, two of them with disseminated disease. Only one patient with a localized cutaneous manifestation survived, since radical surgical resection was possible.

For the treatment of mucormycosis early diagnosis and aggressive treatment is crucial. High dose liposomal amphotericin B (≥ 5 mg/kg) and radical surgical debridement are the mainstay of treatment. In patients with non-response to initial antifungal treatment or with high clinical suspicion for invasive mucormycosis the treatment regimen should be switched early to agents proven to be effective against zygomycetes such as liposomal amphothericin B. New antifungals like posaconazole or ravuconazole are being developed which promising activity against zygomycetes *in vitro*.[10,12-14] The clinical value of these new agents remains to be evaluated.

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