



## Mucormycosis in hematologic malignancies: an emerging fungal infection

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### ABSTRACT

**Background and Objectives.** In recent years pulmonary mucormycosis has been reported in patients with leukemia and lymphoma and bone marrow transplant recipients. It carries an extremely poor prognosis. We report our experience of clinical findings, diagnostic procedures, treatment and outcome of mucormycosis diagnosed in neutropenic patients affected by hematologic neoplasms admitted to our Department.

**Design and Methods.** From November 1987 to July 1999 we observed 13 patients with mucormycosis. Their median age was 61 years (range 20-75), and they were predominantly in the aplastic post-chemotherapy period (12/13), affected by acute myeloid leukemia (11 cases) or non-Hodgkin's lymphoma (2 cases). Six patients (all with leukemia) were receiving induction-consolidation therapy, 7 had progressive hematologic disease. At the onset of infection all patients were neutropenic ( $N < 0.5 \times 10^9/L$ ). No patients had diabetes mellitus. Two patients had been receiving steroid therapy for 5 and 7 days.

**Results.** The lung was involved in all cases (13/13); disseminated disease was present in 8/13 patients. All cultures (blood, sputum, nasal swabs and bronchoalveolar lavage) were negative. In 3 patients a histologic diagnosis was made *in vivo*: in 1 patient by percutaneous pulmonary biopsy, in 1 patient by pulmonary lobectomy, and in the last patient by percutaneous pulmonary biopsy confirmed by excision of a cerebellar abscess. In the remaining 10 cases diagnosis was made *post-mortem*. Five patients were not treated, 2 because of poor clinical condition and 3 because fungal infection was not suspected. Amphotericin B (1 mg/kg/day) was given empirically to 6 patients and 2 responded to treatment. The remaining 2 patients with neurologic symptoms at the onset of infection were treated with liposomal amphotericin, Ambisome®, one with 3 and one with 5 mg/kg/day; of these two patients the first died in 4 days; the second, with both pulmonary and cerebellar localizations, was treated successfully with 5 mg/kg/day for 4 weeks and then with 3 mg/kg/day, and excision of a brain abscess at neutrophil recovery (total dose of Ambisome®: 12,000 mg). The 3 surviving leukemic patients were able to complete

subsequent consolidation therapy using amphotericin B or liposomal amphotericin as secondary prophylaxis during aplasia.

**Interpretation and Conclusions.** Mucormycosis in neutropenic hematologic patients is rarely suspected. In our patients infection was often characterized by disseminated disease and a rapidly fatal course; only early aggressive amphotericin B (or Ambisome®) treatment together with neutrophil recovery appeared to improve the outcome. Diagnosis is very important for programming antifungal therapy and secondary prophylaxis with amphotericin B, because *Mucor* is usually resistant to itraconazole.

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Mucormycosis is the preferred name for disease caused by fungi of the order of *Mucorales* in compromised hosts. There are 14 families in this order, of which 4 have been associated with human disease. Members of *Mucoraceae* are widespread in nature. These fungi are common in the soil and can also be found on decomposing plant and animal matter. Large numbers of small sporangiospores are released into the air; because they are ubiquitous, the likelihood of infection following inhalation, ingestion or inoculation depends on the host's resistance mechanisms rather than on the number of infectious particles. The increasing incidence of mucormycosis has been attributed to several predisposing conditions including diabetes, malnutrition, acidosis, steroid therapy and severe neutropenia. In recent years pulmonary mucormycosis has been reported in patients with leukemia, and lymphoma and in bone marrow transplant recipients,<sup>1-3</sup> with an extremely poor prognosis in all of them.

Clinical presentation includes rhinocerebral involvement, pulmonary disease, gastrointestinal and cutaneous localizations, and disseminated infection.

We report our experience of mucormycosis diagnosed in our Department between 1987 and 1999 in neutropenic patients affected by hematologic neoplasms.

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## Design and Methods

In our Department 75 cases of invasive filamentous fungal infections were diagnosed between 1987 and 1999; of these we identified 13 hematologic patients with mucormycosis, 10 males, 3 females, median age 61 years (range 20-75), predominantly in the aplastic post-chemotherapy period, (12/13), affected by acute myeloid leukemia (11 cases) or non-Hodgkin's lymphoma (2 cases). Six patients were receiving induction-consolidation therapy, 7 patients had progressive hematologic disease. At the onset of infection all patients were neutropenic (neutrophils  $< 0.5 \times 10^9/L$ ). Median days of previous neutropenia were 10, range 5-18. Median days of previous antibiotic therapy (ceftazidime, amikacin, vancomycin) were 5, range 4-15. No patients had diabetes mellitus. Two patients had been receiving steroid therapy (prednisone 25 mg/day) for 5 and 7 days.

## Results

### Incidence

Among 653 new cases of acute leukemia observed in the same period, the approximate incidence of *Mucor* in acute leukemia was 1.6%.

### Clinical characteristics

Fever was the first sign of infection; cough and acute pleural pain were very frequent. All patients had pneumonia with a radiologic picture similar to that of aspergillosis. Disseminated disease, defined as infection in 2 or more non-contiguous organs, was found in 8/13 cases (nose, liver, kidneys, heart, esophagus: *post-mortem* findings) and 4 of them had cerebral invasion. Mild hemoptysis occurred in only 1 patient; none had rhinocerebral infection.

At the onset of pulmonary infection chest computed tomography (CT) scan performed early in 7 patients was able to demonstrate infiltrates with the halo sign in 5 patients, including 2 patients with a negative standard chest X-ray.

### Diagnosis

A definitive diagnosis of *Mucor* was made *in vivo* and at autopsy when biopsy specimens showed irregularly shaped, broad, non-septate hyphae with branches occurring at right-angles. The hyphae were visualized in tissue sections stained with periodic acid-Schiff reaction and Grocott-Gomori methanamine-silver nitrate. In only 3 patients was it possible to obtain the diagnosis *in vivo* and it was always histologic: in the first case diagnosis was obtained by percutaneous pulmonary biopsy, in the second by pulmonary lobectomy and in the third by percutaneous pulmonary biopsy confirmed by the excision of a cerebellar abscess. Cultures were always negative. Bronchoalveolar lavage was performed in 4

cases and was negative.

In 3 patients with progression of hematologic malignancy, the diagnosis of infection was not suspected, but disseminated fungal disease was found at *post-mortem* examination.

### Antifungal therapy and clinical outcome

Five patients were not treated, 2 because of poor clinical condition and 3 because fungal infection was not suspected; they died rapidly. Antifungal therapy was given to 8 patients; 6 cases were treated with amphotericin B (1 mg/kg/day), and 2 cases with Ambisome®. Of the first 6 patients, 2 patients with only pneumonia responded to treatment and continued antimycotic treatment with amphotericin B up to total doses of 2,170 and 2,560 mg; 2 patients with disseminated disease and cerebral invasion had rapidly fatal outcomes in 2-4 days despite prompt antifungal therapy administration; 2 patients with disseminated disease progressively worsened and died in 1-2 weeks during amphotericin B therapy. One patient who responded underwent pulmonary lobectomy for hemoptysis; surgery permitted the histologic diagnosis. Two patients with both pneumonia and neurologic symptoms at the onset of infection were treated with liposomal amphotericin, Ambisome®, one with 3 mg and one with 5 mg/kg/day; the first patient died in 4 days; the second, a 26-year old, treated with 5 mg/kg/day for 4 weeks, survived and when neutrophils and platelets recovered he successfully underwent drainage of a cerebellar abscess for hypertensive encephalopathy. He then completed antifungal therapy with Ambisome® 3 mg/kg/day up to a total dose of 12,000 mg. The 3 surviving leukemic patients were able to complete the subsequent consolidation chemotherapy using amphotericin B (0.8-1 mg/kg/day) or Ambisome® (2-3 mg/kg/day) during aplasia. The patient with the cerebellar abscess underwent autologous bone marrow transplantation 5 months later with Ambisome® 3 mg/kg as secondary prophylaxis, without relapse of mycosis.

At follow-up 1 patient with pneumonia presented mucormycosis at leukemia relapse after 1 year, during prolonged aplasia subsequent to salvage chemotherapy, in progression of hematologic disease; the other 2 remaining patients have not had fungal relapses after 128 and 15 months of follow-up.

Year of diagnosis, main clinical characteristics, therapy and outcome are summarized in Table 1.

## Discussion

Filamentous fungal infections are increasing in immunocompromised hosts, particularly in those with hematologic diseases. In our hematologic population 153 *post-mortem* examina-

tions performed in the period 1989-1995 showed mycotic infections in 31% of autopsies;<sup>4</sup> *Aspergillus* was by far the commonest species encountered (73%), *Candida spp.* accounted for 14% and *Mucor* for 13%. This rate is similar to that reported by Tonso *et al.*<sup>5</sup> in a study performed by 18 Italian hematologic departments, in which the incidence of mucormycosis among filamentous mycoses observed during the same period was 12%.

In a review of 1,186 consecutive patients who underwent bone marrow transplantation between 1974 and 1989 at the University of Minnesota Hospital, mucormycosis accounted for 2% of non-*Candida* fungal infections.<sup>6</sup> Recently, Penalver *et al.*<sup>7</sup> reported 4 cases of mucormycosis (0.9%) diagnosed between 1984 and 1997 among 345 patients undergoing bone marrow transplantation. The incidence of mucormycosis can be underestimated because diagnosis of this specific fungus is difficult and the clinical picture is similar to that produced by *Aspergillus*.

There are 2 main clinical manifestations of *Mucor*: rhinocerebral infection starting in the nasal sinuses and spreading to the face, palate, orbits and brain, and pulmonary infection with possible multivisceral embolic dissemination, with a high mortality.<sup>8</sup> In our hematologic neutropenic patients the course of *Mucor* disease was very aggressive and disseminated disease was present in 8/13 patients with the main localization being the lung, but also with involvement of the kidneys, liver, heart, brain, and esophagus. Patients with pulmonary mucormycosis had a clinical and radiologic picture similar to that of invasive pulmonary aspergillosis and in 7 patients prompt chest CT scan appeared helpful

in diagnosing filamentous fungal infection; only 1 patient had hemoptysis and was treated by surgery, which also defined the correct histologic diagnosis. In our experience cerebral localizations were always a consequence of embolic dissemination in patients with pulmonary disease, as previously described.<sup>9</sup>

Establishing the diagnosis is the central issue in the management of mucormycosis. In neutropenic patients *ante-mortem* diagnosis is unusual because blood cultures are invariably negative; in pulmonary disease sputum cultures are seldom helpful and bronchial washings have yielded hyphal forms only on rare occasions. Berns *et al.*<sup>9</sup> noted that a mucoraceous fungus was recovered from only 1 of 1,440 consecutive bronchial brushing specimens, but that 1 instance was an autopsy-proven case of mucormycosis. We obtained diagnosis *in vivo* only by invasive methods (biopsy or surgery) (Table 1).

In hematologic patients the most important good prognostic factor is the outcome of the hematologic disease.<sup>3</sup> The importance of reversing underlying factors is evident in the experience with mucormycosis in transplant recipients.<sup>10</sup> In the University of Minnesota Hospital study none of 3 allotransplanted patients with *Mucor* was a long-term survivor,<sup>6</sup> probably because of immunosuppression. Neutrophil recovery is particularly significant because neutrophils play an important role in the host defence against *Mucorales*.<sup>11</sup> Of our 8 treated patients, 5 had progression of hematologic malignancy and none of these responded to therapy; the 3 surviving patients, on the other hand, were in complete remission from leukemia.

**Table 1. Year of diagnosis, clinical characteristics, localizations, diagnostic procedures, therapy and outcome of patients with mucormycosis.**

Patient	Diagn. (year)	Age/sex	Underlying disease	Steroids	Hematologic therapy	Localizations	Diagnostic procedures	Antifungal therapy	Outcome
1	1987	73/M	AML (resistant)	No	No	Lungs, esophagus	Autopsy	No	died
2	1988	60/M	AML	No	Chemotherapy	Lungs	Autopsy	No	died
3	1989	63/M	AML (resistant)	No	Chemotherapy	Lungs, brain, kidney, heart	Autopsy	Ampho B 1 mg/kg	died
4	1994	75/M	AML	No	No	Lung	Autopsy	No	died
5	1994	64/F	AML (resistant)	yes	HD ARA-C	Lung, heart	Autopsy	Ampho B 1 mg/kg	died
6	1995	75/M	AML	No	No	Lung	Autopsy	No	died
7	1995	49/M	NHL (resistant)	yes	Chemotherapy	Lung, liver, kidney	Autopsy	No	died
8	1996	20/M	NHL	No	HD ARA-C	Lung, heart, liver, brain, kidney	Autopsy	Ambisome 3 mg/kg	died
9	1997	63/M	AML	No	Chemotherapy	Lung	Lobectomy	Ampho B 1 mg/kg	survived
10	1997	61/M	AML	No	Chemotherapy	Lung, liver, brain	Autopsy	Ampho B 1 mg/Kg	died
11	1998	37/F	AML (resistant)	No	HD ARA-C	Lung, liver, heart, kidney	Autopsy	Ampho B 1 mg/kg	died
12	1999	26/M	AML	No	HD ARA-C	Lungs, brain	Biopsy	Ambisome 5 mg/kg	survived
13	1999	57/F	AML	No	HD ARA-C	Lungs	Biopsy	Ampho B 1 mg/Kg	survived

Despite the risk of renal toxicity, amphotericin B at a high dose (1-1.5 mg/kg/day) remains the gold standard antifungal agent against mucormycosis and early aggressive pre-emptive therapy to prevent cerebral involvement provides the best chance of a favorable outcome. Mucormycosis was almost invariably fatal if untreated.

Recently, the use of lipid formulations of amphotericin B have been reported to be effective in the treatment of mucormycosis.<sup>7,12-14</sup> In our patient with cerebellar localization, Ambisome® (5 mg/kg daily) was able to limit cerebral expansion of infection until neutrophils and platelets recovered and it was possible to drain the cerebellar abscess; it may be possible that the lipid vehicle of amphotericin permits a higher concentration of drug in the cerebral tissue.

Surgery is curative in some cases of filamentous mycoses and is an important component of treatment in others;<sup>3</sup> it is the treatment of choice in patients with localized disease of sinuses or the lung.<sup>8</sup> In our experience surgery was an emergency procedure in 2 patients, because of the appearance of hemoptysis in one and of cerebral hypertension in the other.

In conclusion, a high index of suspicion and careful clinical and radiologic examinations are the key to early identification of probably infected patients. In most severely ill neutropenic patients, only aggressive antifungal therapy together with immune reconstitution appears to improve the outcome of patients with mucormycosis. Moreover culture results and/or histologic diagnosis are indispensable for programming secondary prophylaxis with amphotericin B or liposomal amphotericin, because *Mucor* is not responsive to azoles.<sup>15</sup> The outcome, however, remains critical: in hematologic neutropenic patients mucormycosis is frequently characterized by disseminated disease and a rapidly fatal course.

#### Contributions and Acknowledgments

AN designed the study with the contribution of PO and wrote the paper. PO was also responsible for the post-mortems and histology. GC was responsible for imaging and critical revision of the article. AN, MM, MD, GM and AM were responsible for clinical management and acquisition of clinical data. MM, GM and EM were involved in critically revising the intellectual content of the manuscript, EM also gave the final approval for its submission.

#### Disclosures

Conflict of interest: none.  
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#### Manuscript processing

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#### Potential implications for clinical practice

- ◆ *Mucor* infections can complicate hematologic infections. They may be misdiagnosed as *Aspergillus* infections. Invasive diagnosis, early aggressive treatment with amphotericin B and treatment of the underlying hematologic disease seem to be particularly important for a favorable outcome of this frequently fatal infection.