Rhinocerebral mycosis in immunocompromised patients. A case report and review of the literature*

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SUMMARY

Continuous awareness of systemic mycosis in immunocompromised patients is important. Early diagnosis is based on (direct) histologal examination and CT scan. Since treatment should start as early as possible, there is usually no time to await results of tissue cultures. Systemic treatment with amphotericin B and aggressive surgical débridement should be performed as soon as possible, while the place of hyperbaric oxygen and G-CSF remains to be established. In addition to routine preventive measures, prophylactic intranasal application of amphotericin B seems to be of value.

Key words: systemic mycosis, amphotericin B, itraconazol, Aspergillus, Mucor

INTRODUCTION

Systemic mycosis in patients with a compromised immune system is a potential life-threatening disease-entity (Saah et al., 1994). Systemic mycosis includes disseminated infections, as well as deep-localised infections, with fungi or yeasts. They should be distinguished from the less serious, superficial mycosis of the skin, nails or mucous membranes. Systemic mycosis in the western world is almost exclusively caused by opportunistic fungi and yeasts, occurring in patients with an impaired immune response. Apart from immunosuppression and prolonged neutropenia, the wide use of broad-spectrum antibiotics also plays a role in the development of systemic mycosis. The most common cause of systemic mycosis in the head and neck region is *Aspergillus*. Infections with *Mucor* are less frequent. Recent cases of systemic mycosis in the nose and paranasal sinuses treated at our department made us analyse our experiences and review the literature on this potentially lethal disease.

PATIENTS

The medical records of five patients with rhinocerebral mycosis seen between 1990 and 1995 were reviewed and analysed (Table 1). Of these five patients, four were male and one was female (age 8 - 70 years, mean 51 years). The predisposing immunosuppressive factor in two patients was a haematological disease, in two patients a combination of diabetes mellitus and immunosuppressive medication, while in one patient these three factors were combined.

The presenting symptoms were ophthalmologic (60%), headache (60%) or rhinologic (60%). In three patients all paranasal sinuses were involved, in one patient all but the sphenoid sinus and in one patient the ethmoidal and maxillary sinuses. The eye was involved in three patients, the lungs in one patient.

All patients received amphotericin B, which was later replaced by itraconazol in two patients. One patient received G-CSF. Four patients underwent surgery of the sinuses, one patient also of the orbit and in one patient surgical therapy could not be provided because of a therapy-resistant thrombocytopenia.

Histological examination showed fungal invasion of the mucosa of the sinuses in all the surgically treated patients.

Four of the five patients died, because the haematological disease was not cured or due to intracranial extension of the infection.

DISCUSSION

Fungal infection and predisposing patient factors

Invasive aspergillosis is caused by *A. fumigatus* or *A. flavus*. *Aspergillus* spores are found in dust on mattresses and in ventilation channels but also in soil and decaying organic material (Romett and Newman, 1982). Although colonisation in healthy persons (as in sinusitis or bronchiectasis) occurs, it probably has no clinical significance in spreading the infection since the num-

* Received for publication August 29, 1997; accepted April 7, 1998

Table 1: Clinical summary of five cases of rhinocerebral mycosis.

patient (N) age sex	predisposing factors	cause, site	presenting symptoms	medication	surgery	out-come
1) 8 M	aplastic pancytopenia (therapy resistant)	Aspergillus Fum., pansinus (R) orbita (R)	headache nosebleeds	Amphot. B, Itroconazol G-CSF	ethmoidectomy (2#) antrum lavage Claoué catheters orbital drainage	died
2) 44 M	diabetes mellitus cortico steroids	Mucor, pansinus (L) orbit (L) intracranial	headache, swelling and loss of vision left eye	Amphot. B	Denker procedure	died
3) 65 M	aplastic anemia diabetes mellitus cortico steroids, cyclosporine	Aspergillus Fum., ethmoid., max. sinus (L) orbit (L), intracranial	fever redness, swelling under left eye serosanguinolent rhinorrhoe	Amphot. B	ethmoidectomy, concha media resection	died
4) 66 M	liver transplant diabetes mellitus cyclosporine	Aspergillus Fum., S. front. S. ethmoid. S. max.	common cold headache	Amphot. B Itraconazol	s. frontalis (external approach), catheter, Denker procedure	recov-ered
5) 70 F	Waldenström pancytopenia	Aspergillus, lung pansinus	fever swelling left eye	Amphot.B	not possible because of therapy resistant thrombocytopenia	died

ber of spores that is spread is small. The fungus grows best in an anaerobic environment (De Foer et al., 1990).

Invasive mucormycosis is caused by *Mucor*. *Mucor* spores are found in dust, soil, decaying organic material as well as in the normal flora of the nose (Armstrong, 1993). An acid environment and a high glucose-concentration, as found in diabetic ketoacidosis, are favourable conditions for growth. Disorders in the iron metabolism possibly also predispose to mucormycosis (Artis et al., 1982).

Infections by *Aspergillus* or *Mucor* usually develop by inhalation of spores. Dissemination from the primary focus to other organs such as brain, liver and kidneys may occur. *Aspergillus* and *Mucor* can invade the walls of vessels, particularly arteries, resulting in thrombosis, ischemia and bleeding. The incidence of invasive aspergillosis in patients with a haematological malignancy has been reported to have risen from 6% in 1950 to 20-30% in recent surveys (Bodey et al., 1992). This rise is ascribed to the more aggressive treatment of the primary disease and the use of broad-spectrum antibiotics (De Foer et al., 1990).

Systemic mycosis in the western world almost exclusively occurs in patients with an impaired immune response such as patients with haematological malignancies, organtransplant recipients, patients receiving corticosteroid therapy for a prolonged period of time, diabetics and AIDS-patients. Interestingly, systemic mycosis is seldomly described in the latter group of patients. This could be explained by the fact that AIDS-patients mostly lack T-lymphocytes and to a lesser extent neutrophils and macrophages which are important in the development of systemic mycosis (Denning et al., 1991).

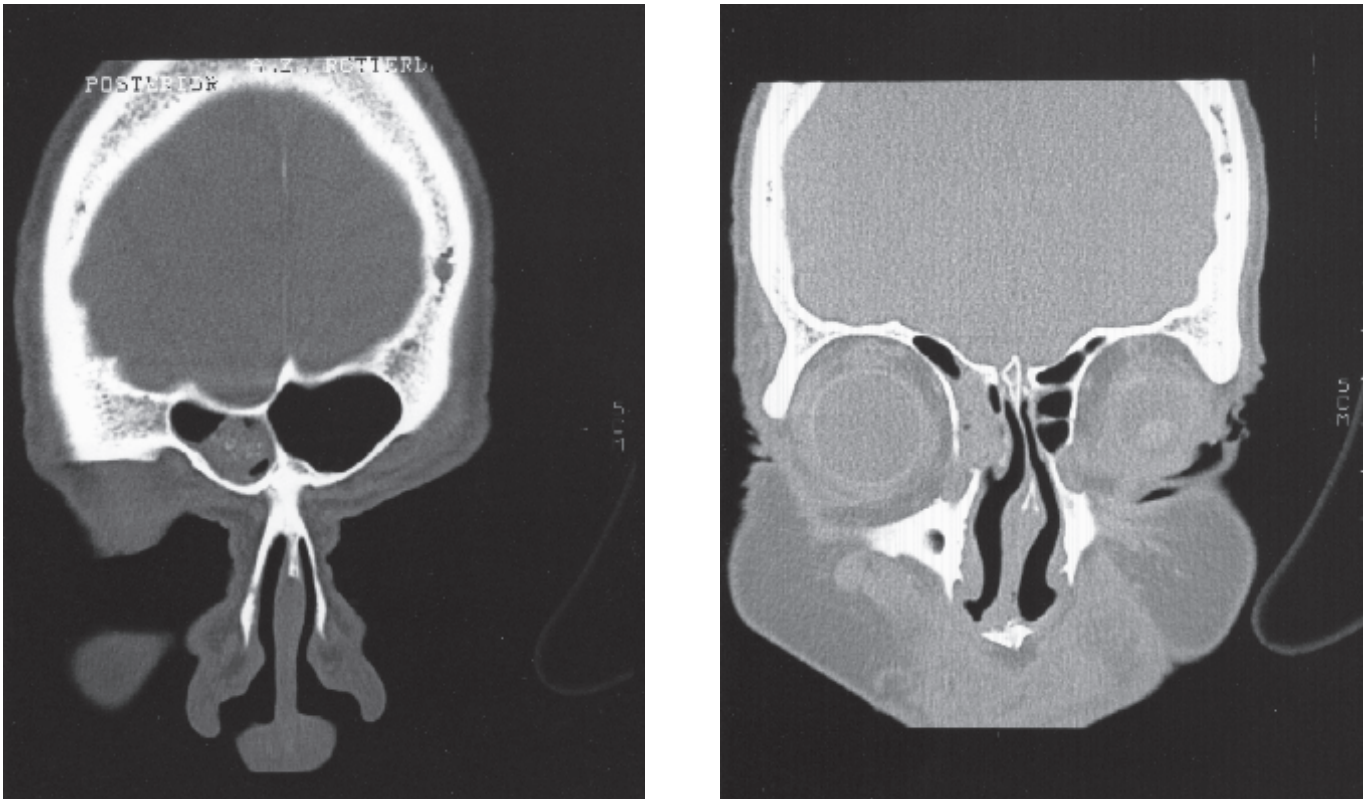
Prevention

The most effective measure to prevent invasive aspergillosis consists of the installation of ventilation systems with “high efficiency particulate airtype (HEPA)”-filters in rooms of patients who are at risk. By maintaining a high pressure in the room, entrance of unfiltered air can be reduced. The ward itself should be dust-free while sources of fungi, such as plants and flowers cannot be allowed.

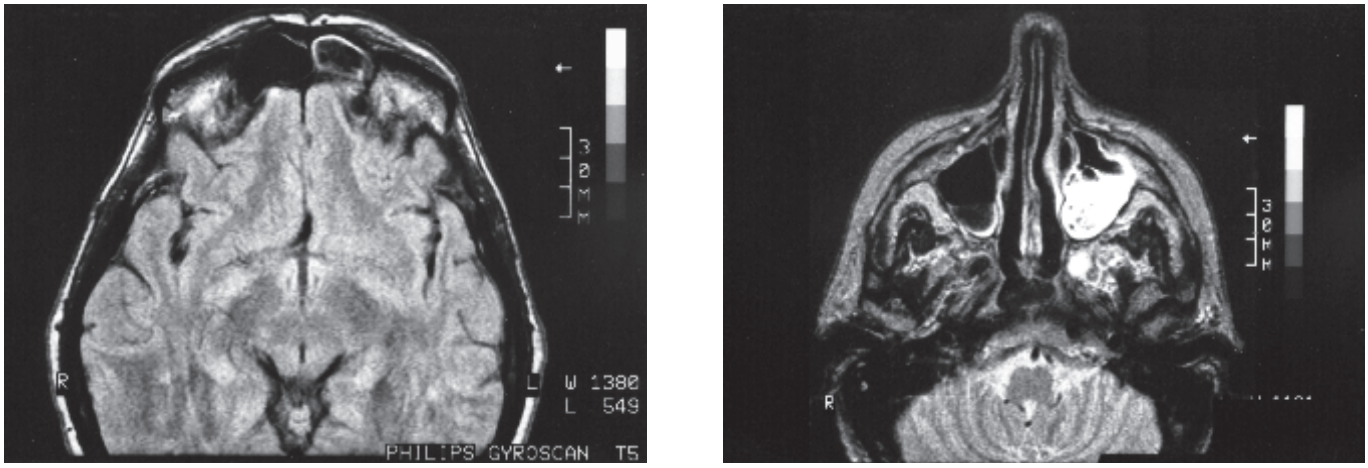
Recently, intranasal spraying with amphotericin B starting at the time of admission, has attracted attention. Jeffery et al. (1991) found that infection rates can be decreased significantly in this way.

Diagnosis

Early diagnosis and treatment of systemic mycosis in high risk patients is paramount. Diagnosing aspergillosis or mucormycosis can be difficult because the symptoms can be non-specific, especially in bone marrow transplant patients with leucopenia,



Figures 1A and 1B: Patient 4. CT demonstrates a partially opacified left frontal and ethmoidal sinus. The left frontal sinus also has a speckled pattern of high attenuation.



Figures 2A and 2B: Patient 4. T1 weighted MR shows high signal intensity in the mucosa of the left frontal sinus with areas of much lower intensity centrally. T2 weighted MR shows high signal intensity in the left maxillary sinus with small areas of low intensity. The right maxillary shows high signal intensity in the mucosa with areas of much lower intensity centrally.

fever and associated infections. When the diagnosis is suspected, it should be confirmed by histological examination and tissue cultures. Histologically, *Aspergillus* can be identified by septated hyphae and dichotomous branching; *Mucor* by broad, non-septated hyphae and right-angle branching (Meyer and Armstrong, 1973). Interpretation of positive cultures can be difficult because the fungus can also be a contaminant from the air, or a coloniser of the upper airways. In addition, the sensitivity of cultures is low. Computerised tomography can also be useful. A typical CT-image of a fungal infection shows a sinus partially opacified with a speckled pattern of high attenuation (caused by local enrichment of calcium phosphate) (Stammberger et al., 1984).

Treatment

Currently a combination of antifungal medication and radical débridement of infected tissue is considered the best treatment (Blitzer, 1980). The factors determining the survival rate are still not clear (Kennedy et al., 1997). Currently the drug of choice for systemic mycosis is amphotericin B (Fungizone). Due to poor

absorption after oral administration, intravenous administration is necessary; l mgr/kg is considered the optimal dose. The duration of treatment is variable, but usually one strives for a total cumulative dose of 2-4 gr. (Denning et al., 1991). Administration can be stopped after the granulocyte count in the peripheral blood has returned to normal. The penetration into the cerebrospinal fluid is relatively poor. Dose-related nefrotoxicity is one of the side-effects. The liposomal forms of amphotericin B may have reduced toxicity and an increased therapeutic effect over the standard form because of better cerebrospinal fluid penetration (Fisher et al., 1991).

Itraconazol (Trisporal) can also be used in case of invasive aspergillosis although clinical experience is limited. Administration can take place both orally and parenterally. The usual daily dosage in systemic mycosis is 100–400 mgr (Hay et al., 1987). Resorption after oral administration depends on the pH of the stomach and interactions both with simultaneous administration of H_2 receptor antagonists as well as with oral hypoglycaemic drugs have been described. With the exception of CSF, itraconazol reaches good tissue levels. Liver function disorders are among the side-effects. Itraconazol has not shown to be effective in the treatment of mucormycosis.

Treatment with hyperbaric oxygen has been used in cases of mucormycosis, with varying success (Ferguson et al., 1988). Hyperbaric oxygen has direct fungistatic activity. It also reduces the tissue hypoxia and acidosis caused by thrombosis.

New immunostimulating agents such as granulocyte colony stimulating factor (G-CSF) – a naturally occurring glycoprotein that stimulates the growth of granulocyte precursors and activates mature neutrophils - may also prove useful in immunocompromised patients (Clark and Kamen, 1987). In case of diabetes, serum glucose levels must be regulated.

Surgical removal of all the necrotic soft tissue material and bone with a margin of healthy tissue is necessary, because the fungus grows in the necrotic material and thrombosis of the vessels prevents the medication to reach the affected tissue. This means it may be necessary to remove the nasal conchae and the lateral wall of the nose (Denker procedure) or part of the palate or maxilla. When the frontal sinus is involved an external approach of the frontal sinus with drilling of the bony walls may be required. In one patient we left the skin covering the frontal sinus partially open, making inspection and rinsing with amphotericin B possible. Orbital exenteration may be necessary if ocular invasion exists. Some advocate routine removal of a blind eye since it is without function and can be a portal for intracranial extension (Blitzer 1980).

We conclude that a continuous awareness of systemic mycosis in immunocompromised patients is important. Early diagnosis is based on (direct) histological examination and CT-scan. Since treatment should start as early as possible, there is usually no time to await results of tissue cultures. Systemic treatment with amphotericin B and aggressive surgical débridement should be performed as soon as possible, while the place of hyperbaric oxygen and G-CSF remains to be established. In addition to routine preventive measures, prophylactic intranasal application of amphotericin B seems to be of value.

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