CASE 3-2011: INVASIVE MUCORMYCOSIS (ZYGOMYCOSIS)
AFTER BONE MARROW TRANSPLANTATION IN A 26-YEAR-OLD MAN
WITH RELAPSING ACUTE MYELOID LEUKAEMIA

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Key words: Mucormycosis; Zygomycosis; Invasive fungal disease

Clinical data

Patient J.S., 26-year-old man, was first seen by his general practitioner because of chest pain, dyspnoea, weakness, vomiting, headache, dizziness and recent fever on January 29th 2010. Blood samples were taken and revealed leukocytosis $149 \times 10^9$/L. His previous medical history was unremarkable. He was immediately referred to our University Hospital with suspicion of acute leukaemia.

On admission in the evening of the same day, his leukocyte blood count was already $248 \times 10^9$/L and mild anaemia and thrombocytopenia was present. The diagnosis of acute myeloid leukaemia (myelomonocytic according to WHO classification) was made. There also was a severe syndrome of leukostasis on admission, and the patient developed acute myocardial infarction and respiratory insufficiency. Immediate leukoreduction with leukapheresis and hydroxyurea was started. When leukocyte count was reduced below $50 \times 10^9$/L chemotherapy with intermediate dose cytarabine (total dose 24 g) and idarubicin (total dose 70 mg) was started. Despite drastic leukoreduction our patient developed systemic inflammatory response syndrome (SIRS) with multiorgan failure reflecting tumor lysis syndrome following chemotherapy. He received artificial ventilation for respiratory failure caused by diffuse alveolar haemorrhage, and continuous renal replacement therapy for renal failure was started. The course of his disease was further complicated by shock, disseminated intravascular coagulation and liver failure. With full supportive care and corticosteroids patient was stabilised and eventually, after 5 days, he was successfully extubated and his renal and liver function recovered. Unfortunately, the induction chemotherapy did not lead to remission of the leukaemia. Patient received reinduction chemotherapy with FLAG IDA regimen (fludarabine, cytarabine, idarubicin, G-CSF) on March 6th. The remission was not achieved once again and another reinduction with HAM chemotherapy (cytarabine, mitoxantrone) was instituted on April 18th. Finally, there was a complete remission on bone marrow examination on May 27th. Patient obtained consolidation treatment (again HAM chemotherapy) and was scheduled for allogeneic stem cell transplantation.

On August 18th he was admitted for allogeneic peripheral blood stem cell transplantation. His donor was unrelated woman with 3 mismatches (7/10). Unfortunately, before transplantation his bone marrow examination revealed a relapse of acute leukaemia, and we decided to proceed to fully ablative approach enforced with cytarabine and mitoxantrone. The remission with 96% donor chimerism was achieved on September 29th. After transplantation he developed grade 3 skin acute graft versus host disease and BK virus hemorrhagic cystitis. Graft versus host disease resolved with corticosteroids treatment and hemorrhagic cystitis with reduced immunosuppression.

On November 11th, second relapse of the disease was diagnosed. The patient received chemotherapy and again developed multiorgan failure with respiratory failure and was artificially ventilated. He recovered and still cytopenic he refused further hospital stay and was discharged. Voriconazol was used as a prophylaxis during neutropenia. He was admitted shortly afterwards with the clinical signs of sepsis. Physical examination and X-ray revealed left side pneumonia and pericarditis. On pulmonary high resolution CT scan (HRCT), there was bilateral pneumonia with atypical pattern (Fig. 1). He also complained of vision disturbance, and an ischemic lesion in the occipital area on brain CT scan was found (Fig. 2). Lumbar puncture did not reveal any pathogen. Immediate treatment with antibiotics (meropenem and amikacin) and amphotericin B in combination was started. The patient died within 2 days (November...

**Pathological findings**

Grossly, the signs of generalized fungal infection and septic shock dominated. Invasive fungal infection with thromboses of the vessels (both arteries and veins) was found in the brain, lung, spleen and heart, leading to massive tissue oedema and necrosis. The brain was particularly affected, with two voluminous malacic lesions, almost com-

**Fig. 1:** Non-contrast-enhanced CT scan of the thorax. The left lower lobe with homogenous consolidation with air bronchogram and the left upper lobe also with consolidation surrounded by ground glass opacities. Free fluid in the left pleural cavity. All changes in connection with mycotic infection

**Fig. 2:** Non-contrast-enhanced CT scan of the brain. In the left occipital cerebral lobe there is a hypodense lesion (50 × 30 mm), not surrounded by oedema, with no hemorrhage or calcification. The normal brain structure is destroyed in this lesion. This is a typical pattern of brain mycotic infection

**Fig. 3:** Mucormycosis involving the lung. Thrombotic occlusion of a pulmonary vein branch with destruction of the vessel wall and massive infiltration with filamentous fungal elements. In detail – Rhizomucor with typical wide fungal septa-lacking hyphae with rectangular branching. (Grocott staining)

**Fig. 4:** Brain tissue with thrombotic occlusion of vessels and fungal infiltration. In detail – Rhizomucor. (HE staining)
Invasive fungal diseases (IFD) are important causes of morbidity and mortality in immunocompromised patients. *Aspergillus* species and *Candida* species account for most cases of IFD but various fungi, including Zygomycetes (Mucorales), may be involved. The diagnosis of zygomycosis (mucormycosis) is rather difficult despite the availability of modern laboratory methods and the course of this illness is rapid and devastating.

IFD are quite often diagnosed in patients with acute leukemia and myelodysplastic syndrome, and they may severely complicate the clinical course following allogeneic stem cell transplantation. There is a trend towards pulmonary involvement as the main clinical form in haematologic patients (1). Especially the patients with ongoing or previous treatment with corticosteroids for graft versus host disease, as in our case, are very often affected. In this case, there were other high risk factors for IFD: relapsing leukemia, and neutropenia after high dose chemotherapy (2). It was suggested that prophylactic use of voriconazol may play a role in the increased occurrence of zygomycosis (3, 4), and our patient had voriconazol prophylaxis.

Diagnosis of IFD is rather difficult. The cultivations are not reliable and may only be positive rather late in the disease course. In our institution we perform prospective measurement of serum *Aspergillus* galactomannan level (in all transplanted patients), and early HRCT of chest and paranasal sinuses whenever there is a clinical suspicion of IFD (i.e. sustained fever or new fever on broad spectrum antibiotics). Pulmonary infiltration or sinusitis is an indication for bronchoalveolar lavage or sinus puncture, respectively, with broad range of pathogen testing (including PCR test for zygomycosis). If this examination does not lead to pathogen detection and mycotic infection is suspected from the HRCT pattern or if the infiltration is progressively worsening, then biopsy is indicated. PCR technique is an emerging method aiding the diagnosis of zygomycosis, although it also has several limitations regarding sensitivity and specificity (5, 6).

In this case, the course of disease was so quickly devastating that we were not able to perform the full diagnostic panel. However, we had a strong suspicion of IFD, due to the clinical presentation (pneumonia, pericarditis, ischemic brain lesion) and a high risk in this patient. Since serum galactomannan was negative we began empirical treatment with conventional amphotericin B. Despite this treatment, his clinical status deteriorated and patient died very quickly after disease manifestation. Such a rapid progression is typically seen in neutropenic patients, in whom invasive mucormycosis often leads to prompt death in spite of any treatment.

**Message from the Editor (Prof. Šteiner)**

The case is presented of a 26-year-old man with acute myeloid leukemia who died after a 10-month-course of the disease from generalized mucormycosis.

Mucormycosis is an uncommon opportunistic infection limited to immunocompromised hosts, particularly those with severe diabetes or leukemia-associated neutrophil defects and those receiving high-dose glucocorticoid treatment. The disease is caused by Phlycomycetes fungi including *Mucor*, *Absidia*, *Rhizopus*, and *Cunninghamella*. These fungi, while widely distributed in nature and causing no harm to immunocompetent individuals, may infect immunosuppressed patients though somewhat less frequently than *Candida* or *Aspergillus* do.

The fungus assumes mycelial forms in lesions. The hyphae are nonseptate, irregularly wide (6 to 50 µm) with frequent right-angle branching. The organisms are preferentially localized in the nose (from where they may rapidly spread to the sinuses and brain), lungs, and gastrointestinal tract. The agent causes a nondistinctive, supplicative, sometimes granulomatous reaction with a predilection for invading blood vessel walls, causing vascular thrombi and distal infarctions.

Mucormycosis is often hospital-acquired. Leukemic patients contract the disease from mucoraceous fungi in the hospital. It is usually fatal.

Clinical diagnosis of mucor infection is difficult. The organism mostly fails to grow on cultivation media. Recently, PCR has been introduced into diagnostics, with promising results (5, 6). The diagnosis may be established by means of histology; however, poor condition of the patient usually precludes a biopsy. Radical treatment, both antimycotic and surgical, is recommended.

**Acknowledgement**

This study was supported by research project MZO 00179906 from the Ministry of Health, Czech Republic

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