Disseminated Mucormycosis in a Patient with Acute Myeloblastic Leukemia Misdiagnosed as Infection by *Enterococcus faecium*

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Mucormycosis is a rare complication in cancer patients. This report presents the case of a acute myeloblastic leukemia patient who developed an ascending paralysis due to disseminated mucormycosis. The presentation was unusual because the early symptoms were fever and pain, and the disease was misdiagnosed because of a concomitant infection by *Enterococcus faecium*.

CASE REPORT

A 70-year-old female was admitted to our hospital for acute myeloblastic leukemia (French-American-British type M1). On day 4 after induction chemotherapy, during the treatment-related aplasia, the patient became febrile, and *Staphylococcus epidermidis* and *Staphylococcus mitis* were detected in blood cultures. She was given antibiotics (ceftazidime and amikacin), and the fever rapidly resolved. On day 11, the patient presented a right flank pain that, in the following days, spread into the lumbar region bilaterally, with a band irradiation in the upper abdomen. At this time there was no evidence, either clinically or in the chest X ray or in the echo tomography of the kidney and liver, of any localized infection. On day 16, the patient presented again high fever and abruptly developed an acute paraplegia, which rapidly became an ascending paralysis. The lumbar pain was still present, and it extended to each thigh's anterior surface, with hyperesthesia and numbness in the legs. Nuclear magnetic resonance imaging of the spinal marrow showed altered T1-T2 signal intensity between D12 and L1, suggestive of an edematous ischemic lesion. Blood and spinal fluid cultures at that time were positive for *Enterococcus faecium*, and a specific antibiotic therapy was started (meropenem). However, the patient rapidly developed a comatose status and died on day 18. The postmortem examination showed mucormycosis invasion of blood vessels associated with tissue necrosis in the central nervous system, liver, lung, and heart (Fig. 1). The morphological pattern (large ribbon-like nonseptate hyphae with irregular diameters and branches arising from almost all main hyphal trunks) was so typical for mucormycosis that a postmortem fungal culture was felt not to be needed for diagnosis.

The *Mucoraceae* are ubiquitous fungi and are common inhabitants of decomposing plant and animal matter. There are 14 families in this order, 4 of which have been associated with

human diseases. Large numbers of small sporangiospores are released into the air, and therefore inhalation of conidia must be a daily experience (14). However the potential virulence in the human host is very low, as witnessed by the low incidence of such infection in the general population; infection is mainly observed in patients with severe immunodeficiency, diabetes mellitus, or trauma (14). In addition invasive fungal infections, including mucormycosis, are common complications in cancer patients (6, 8), particularly in those with hematological malignancies (1, 4, 5), as a consequence of myeloablative chemotherapies and compromised immune system. The infection rate is strongly correlated with the type of cytotoxic regimens administered and with the duration of bone marrow aplasia (2). In recent years, pulmonary mucormycosis has been reported in patients with leukemia and lymphoma as well as in bone marrow transplant recipients, with an extremely poor prognosis in all of them (3, 10, 12).

The most common symptom of mucormycosis infection is fever, occurring in 51% of patients (12). Moreover, on the basis of clinical presentation, this infectious disease can be arbitrarily divided into separate entities: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system related, and miscellaneous, in addition to a disseminated disease resulting from progression of localized infection. Confirmation of the clinically suspected diagnosis of systemic mycosis and exact identification of the fungal pathogen are often difficult. The hallmarks of disease caused by the *Mucorales* are vascular invasion and tissue necrosis, due to their special affinity for blood vessels. Diagnosis depends on demonstrating the organism in the tissue of a biopsy specimen. Typically, the fungi appear as broad (10 to 20 μ m in diameter), nonseptate hyphae with ramifications. At the present, serodiagnosis of mucormycosis remains investigational and cannot yet be recommended for routine clinical use (7, 9, 16).

Establishing the diagnosis is the central issue in the management of mucormycosis. Nevertheless antemortem diagnosis is uncommon because blood cultures are invariably negative; in addition, pulmonary disease sputum cultures are seldom helpful and bronchial washings have yielded hyphal forms only on rare occasions. Thus a correct diagnosis in vivo is reached only by invasive methods (biopsy) (11).

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FIG. 1. Photomicrograph of liver (a; hematoxylin and eosin), heart (b; hematoxylin and eosin), lung (c; Grocott), and brain (d; hematoxylin and eosin), demonstrating the broad, irregularly shaped hyphae with right-angle branching typical of *Mucorales*. The arrows indicate the most evident fungal hyphae.

In oncohematological patients the most important favorable prognostic factor is the outcome of the underlying disease (12). Timing of neutrophil recovery is particularly important because neutrophils play an important role in the host defense against *Mucorales* (13).

In our patient, clinical signs and symptoms caused by the fungal infection developed during severe neutropenia (neutrophil count $< 0.5 \times 10^9/\text{liter}$). The initial physical findings were fever and pain, which were suggestive of a pulmonary infection with pleural involvement as well as of a subfrenic abscess despite a normal chest X ray and kidney and liver echo tomography. It is clear, now, that the pain was a consequence of spinal localization of the infective disease with metamer distribution (T_{10} - S_2). Additional factors which contributed to the misdiagnosis were the documentation in the blood and spinal fluid of *E. faecium* sepsis and the clinical evolution as ascending paralysis, previously described in only one case of disseminated mucormycosis (15). According to our interpretation, the presence of *E. faecium* in the spinal fluid could be attributed to abnormal vascular permeability due to the fungal invasion of blood vessels.

In conclusion, a suspicious infection and careful clinical and

radiological examinations are the keys for the early identification of infected patients. In the most severely ill neutropenic patients, only aggressive antifungal therapy together with immune reconstitution appears to improve the prognosis. The outcome remains critical because, in these patients, mucormycosis is frequently characterized by disseminated disease leading to a rapid and fatal outcome.

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