

Mucormycosis of the paranasal sinuses in a patient with acute myeloid leukemia

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SUMMARY

Introduction Invasive fungal infection is among the leading causes of morbidity, mortality, and economic burden for patients with acute leukemia after induction of chemotherapy. In the past few decades, the incidence of invasive fungal infection has increased dramatically. Its management has been further complicated by the increasing frequency of infection by non-*Aspergillus* molds (e.g. Mucorales). Neutropenic patients are at a high risk of developing an invasive mucormycosis with fulminant course and high mortality rate (35–100%).

Case Outline We are presenting the case of a 72-year-old male with an acute monoblastic leukemia. The patient was treated during five days with hydroxycarbamide 2×500 mg/day, followed by cytarabine 2×20 mg/sc over the next 10 days. He developed febrile neutropenia, headache, and edema of the right orbital region of the face. Computed tomography of the sinuses revealed shadow in sinuses with thickening of mucosa of the right paranasal sinuses. Lavage and aspirate from the sinuses revealed *Rhizopus oryzae*. Mucormycosis was successfully treated with amphotericin B (5 mg/kg/day) followed by ketoconazole (400 mg/day). Two months later the patient died from primary disease.

Conclusion In patients with acute leukemia who developed aplasia, febrile neutropenia, and pain in paranasal sinuses, fungal infection should be taken into consideration. New and non-invasive methods for taking samples from sinuses should be standardized in order to establish an early and accurate diagnosis of mucormycosis with the source in paranasal sinuses, and to start early treatment by a proper antifungal drug. Clear communication between physician and mycologist is critical to ensure proper and timely sampling of lavage and aspirate from sinuses and correct specimen processing when mucormycosis is suspected clinically.

Keywords: acute leukemia; neutropenia; mucormycosis; paranasal sinuses; invasive fungal infection

INTRODUCTION

Patients with acute leukemia (AL) are considered a population at high risk for developing an invasive fungal infection (IFI) [1]. In the United States, in the past few decades, the incidence of IFI increased dramatically by approximately 200% between 1979 and 2000 [2]. In a recent study, the cumulative probability of developing IFI after a diagnosis of AL was 11.1% at 100 days [3]. Patients undergoing treatment for hematologic malignancies have estimated cause-specific mortality due to IFI of 35% [4]. The most common causes of IFI are *Candida* and *Aspergillus*, but most recent reports show an increasing frequency of infection by non-*Aspergillus* molds, especially Mucorales order.

Mucormycosis is an aggressive opportunistic fungal infection with fulminant course caused by various members of the Mucorales order. The disease-causing genera in humans include *Absidia*, *Rhizopus*, and *Mucor*, which are widespread in nature. They produce airborne spores that enter the body mostly through inhalation or ingestion; occasionally, infection may be through hematological dissemination from a different site, but sinuses and lungs are usually the entry points [5]. Fungi in sinuses cause fun-

gal rhinosinusitis (FRS), which has a spectrum from noninvasive disease to acute fulminant FRS [6]. Predisposing factors for the development of acute fulminant FRS are numerous, but neutropenia is the leading one, especially when neutrophils are below $0.5 \times 10^9/L$. Invasive forms of FRS have very rapid course in neutropenic patients and because of that require early diagnosis, early induction of antifungal therapy, and sometimes surgery [7, 8].

We present a case of a patient with acute monoblastic leukemia (AML) and invasive mucormycosis of paranasal sinuses.

CASE REPORT

A 72-year-old male patient with diagnosed AML and body mass index of 27.7 kg/m^2 , Eastern Cooperative Oncology Group (ECOG) performance status of 1 and Sorrow score of 2, was admitted to the Clinic for Hematology of the Clinical Centre of Serbia. At presentation, laboratory data were as follows: hemoglobin 95 g/l, white blood cell count $76.5 \times 10^9/L$, and platelets $45 \times 10^9/L$. In hypercellular bone marrow 92% of blasts predominantly myeloperoxidase positive were found. Morphologic finding

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was in accordance with AML M5a. Immunophenotyping with flow cytometry revealed a population of mononuclear cells with immunophenotype HLA-DR, cMPO, cLizozim, CD13, CD33, CD15, CD11b, CD11c, CD64, CD14, CD163, CD36 and CD56+, indicating the diagnosis of AML CD56+ with monocytic differentiation. Karyotype was normal 46XY, and molecular analyses for FLT3 and NPM were negative. The patient was ranged in intermediate group I according to European Leukemia Net classification. Hemostasis tests showed the following: fibrinogen 6.59 g/L, prothrombin time 70%, partial thromboplastin time 30.7 sec., and D dimer 2.1 µg/L. Biochemical analyses of blood showed elevation of lactate dehydrogenase 1,497 U/L, blood urea nitrogen 15.9 mmol/L, creatinin 388 µmol/L, and acidum uricum 917 µmol/L. Liver function tests were within normal limits. Echocardiography showed ejection fraction of 67%, while chest radiography was normal. Abdominal ultrasound showed normal size of the liver and splenomegaly of 195 mm. The patient was treated for five days with hydroxycarbamide 2 × 500 mg/day including rehydration and xanthine oxidase inhibitors in order to decrease the number of white blood cells. The therapy was continued with cytarabine 2 × 20 mg/sc during the next ten days. More aggressive treatment was not recommended because of the previous renal failure. After chemotherapy, the patient became neutropenic and febrile. He was treated with broad spectrum antibiotics without effects. Twenty days after the last dose of chemotherapy, the patient felt pain in the right maxillary and zygomatic region, as well as nasal congestion and headache. On the following day, the patient's right palpebrae started swelling and the pain was spread all over the right half of the face. The radiography of paranasal sinuses revealed opacification of the right maxillary sinus with central illumination. Fungal hyphae was detected in an inducted lavage and aspirate of the right maxillary sinus, while culture isolation showed growth of *Rhizopus oryzae* (Figure 1). X-ray of paranasal sinuses showed filled lumen of cavities with oedematous epithelium. Computed tomography (CT) revealed mucosal thickening, hypoattenuation, opacification of sinuses as soft tissue attenuation of the right maxillary, sphenoidal, and both ethmoidal sinuses, as well as partly of the right frontal sinus, but without signs of invasion of endocranium. In the right nasal cavity the thick mucin like material was also present (Figure 2). After positive CT finding and mycological identification of *Rhizopus oryzae*

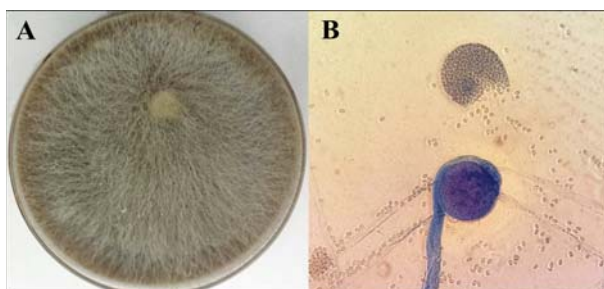


Figure 1. *Rhizopus oryzae*: A) culture on Sabouraud dextrose agar; B) microscopy (lactophenol cotton blue, 40× magnification)

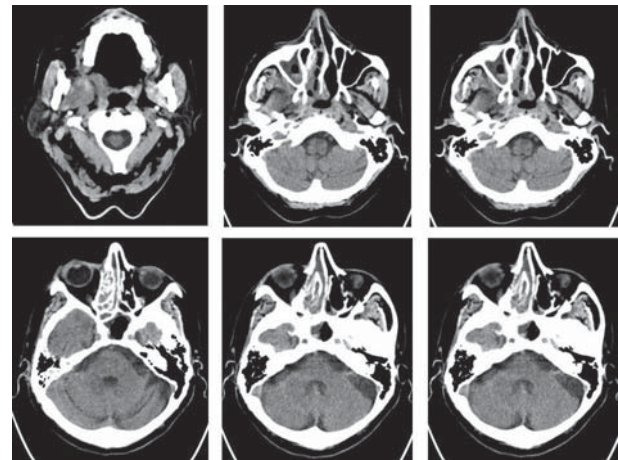


Figure 2. CT showing the presence of fluid-like content in the right maxillary, sphenoidal and both ethmoidal sinuses, predominantly in the right, as well as partly in the right frontal one, but without invasion of endocranium; in the right nasal cavity, the thick mucin-like material was also noted

in sinonasal lavage and aspirate, the diagnosis of mucormycosis of the nose and paranasal cavities was established. Invasive mucormycosis was successfully treated with amphotericin B (5 mg/kg/day), followed by ketoconazole 400 mg/day, according to the results of antimycogram. Symptoms, pain, and changes over the paranasal region were resolved after treatment with antifungal therapy. Control aspirate and lavage of sinuses after two weeks of the last dose of antimycotic drugs were negative. Unfortunately, control bone marrow aspirate again showed the presence of 87% of monoblasts. Two months later the patient died due to the primary disease.

DISCUSSION

IFI is a major cause of morbidity and mortality in patients with AL. Despite increased number of diagnosed cases of IFI, due to development of prompt and accurate diagnostic approaches and continual education about fungal diseases, the death rate due to IFI has dropped nearly 50% in the past two decades, from 44% during the 1995–2000 period to 28% during the 2001–2004 period [4]. The most frequent causing agents are *Aspergillus*, *Dematiaceous* molds such as *Bipolaris*, *Curvularia*, and *Alternaria* species and the Mucormycetes *Rhizopus*, *Mucor*, and *Lichthemia* [6]. *Mucoraceae* are ubiquitous fungi that are commonly found in soil and particularly in decaying matter [5]. In a study of patients with hematologic malignancies, the most frequent sites of mucormycosis were the lungs (64%) and the orbito-sinus-facial structures (24%), while cerebral involvement and disseminated infection were observed in only 19% and 8% of the cases, respectively [9, 10]. Predisposing factors for these infections are neutropenia, especially when neutrophils are lower than $0.5 \times 10^9/L$, long-lasting glucocorticosteroid therapy, radiotherapy, malnutrition, diabetes, and other accompanied diseases that have impact on a patient's immune system [7, 8, 9, 11, 12]. Mucormycosis is an aggressive infection that can cause a significant disease in immunocompromised patients. Although many

patients with rhinocerebral mucormycosis undergo similar treatment, pathogen speciation should not be underappreciated; it may be imperative to guide antifungal drug selection, as some mucoraceous fungi may exhibit variable resistance to conventional therapy [13].

Mucormycosis due to inhalation of fungal spores begins in the nose and paranasal sinuses with spreading to orbital or intracranial structures either by direct invasion or through blood vessels. The mortality rate is high, ranges 50–85%, while in disseminated and untreated forms it could be 100% [3, 4, 14]. An immediate CT scanning of the paranasal sinuses and an endoscopic examination of nasal passages with biopsies of any suggestive lesions should be performed. Samples from sinuses should be obtained by non-invasive methods, due to condition of patients with neutropenia. Proper samples include induced sinonasal lavage and aspirate, and should be taken at the onset of the disease before deterioration of symptoms. Clinical samples should be cultured and examined by histology and direct microscopy. Delays in diagnosis and treatment lead to increased mortality [11, 12].

We suppose that our patient had previous fungal colonization of paranasal sinuses, without symptoms, before diagnosis of AL was established. After worsening of AL, developing aplasia of bone marrow and febrile neutropenia IFI had rapidly progressed due to immunocompromised state. Positive CT finding, absence of response to broad spectrum antibiotics, and deterioration of symptoms were indications that FRS should be considered. CT scan revealed spread of the disease over paranasal sinuses and

aspirate and lavage of the sinuses were taken. *Rhizopus oryzae* was identified and according to antimycogram two antimycotic drugs, amphotericin B and ketoconazole, were successfully applied. Although the mucormycosis was successfully solved, AL was resistant to chemotherapy and the patient died as a more aggressive therapy could not have been applied because of the previous chronic renal failure.

In hematologic patients with prolonged febrile neutropenia, headache, painful paranasal sinuses, fungal infection should be seriously taken into consideration. An early diagnosis of fungal infections of paranasal sinuses could be relatively easily established nowadays based on the radiography, CT scan visualization, and endoscopy with the invasive sampling as biopsy and histology of suspected lesion. New and non-invasive methods for taking samples from sinuses should be developed in order to make early and accurate diagnosis of mucormycosis with the source in the paranasal sinuses and to start early treatment by proper antifungal drug in patients with neutropenia. Clear communication between physician and laboratory is critical to ensure correct specimen processing when mucormycosis is suspected clinically.

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Инвазивна мукормикоза код пацијента са акутном мијелоидном леукемијом

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КРАТАК САДРЖАЈ

Увод Инвазивне гљивичне инфекције (*IFI*) водећи су узрок морбидитета, морталитета и финансијског оптерећења за пацијенте са акутном леукемијом после примене индукционе хемотерапије. Неколико последњих деценија инциденца *IFI* се драматично повећала. Лечење *IFI* је додатно отежано и због повећане учесталости инфекција изазваних не-*Aspergillus* плеснима (нпр. *Mucorales*). Пацијенти са неутропенијом су под високим ризиком за развој инвазивне мукормикозе која има фулминантни ток и високу стопу морталитета (35–100%).

Приказ болесника Приказан је случај пацијента старог 72 године, мушкарца, са акутном монобластном леукемијом, који је лечен током пет дана хидроксикарбамидом у дози од 2×500 mg/дан, праћено цитарабином у дози од 2×20 mg/sc током наредних 10 дана. Пацијенту се појављују симптоми главобоље, неутропенија и едем десне половине лица. Компјутеризована томографија (*СТ*) параназалних синуса је открила засенчење синуса, са задебљањем мукозе десних параназалних синуса и са деструкцијом кости. У лавату и

аспирату синуса је показано присуство гљивице *Rhizopus oryzae*. Инвазивна мукормикоза је успешно излечена амфотерицином Б (5 mg/kg/дан) праћено кетоконазолом (400 mg/дан). Два месеца касније пацијент је егзитирао због примарне болести.

Закључак Код хематолошких пацијената са акутном леукемијом код којих постоји присуство аплазије, пролонгиране фебрилне неутропеније и бола у параназалним синусима, потребно је размотрити могућност присуства гљивичне инфекције. Требало би стандардизовати нове неинвазивне методе за узорковање клиничког материјала из синуса, са циљем да се правовремено и тачно успостави дијагноза мукормикозе, чији извор се налази у параназалним синусима и да се започне рана терапија са одговарајућим антигљивичним леком. Добра комуникација између клиничара и миколога је неопходна како би се осигурало правилно и правовремено узорковање лавата и аспириата синуса код сумње на мукормикозу.

Кључне речи: акутна леукемија; неутропенија; мукормикоза; параназални синуси; коинвазивна гљивична инфекција

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