

Dyspnea, Fatigue, and Generalized Weakness in a 67-Year-Old Man: Approach to the Patient Between Guidelines and Clinical Judgment

Antonio Giovanni Solimando^{1,2*}, Antonella Argentiero³, Peter Kraus², Anna Ruckdeschel², Claudia Covelli⁴, Angelo Vacca¹ and Hermann Einsele²

¹Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine "G. Baccelli", University of Bari Medical School, Bari, Italy

²Department of Internal Medicine, Hematology and Medical Oncology, University Medical Center Würzburg, Germany

³Department of Biomedical Sciences and Human Oncology, Section of Medical Oncology, University of Bari Medical School, Bari, Italy

⁴Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

Abstract

Mucormycosis are an emerging group of life-threatening fungal infections caused by filamentous fungi of the Mucorales family. Mucormycosis are most common in stem-cell transplant recipients and patients with underlying hematologic malignancies, poorly controlled diabetes mellitus, trauma, neutropenia, corticosteroid and deferoxamine therapy due to deficiency of phagocytic function, elevated serum levels of available iron and host-pathogen interaction. The fungi penetrate blood vessels causing endothelial damage and extensive angioinvasion with infarction, necrosis, and thrombosis of different tissues. Mucormycosis carries a very high mortality in cases of pulmonary disease, with even higher rates when there is difficulty establishing the diagnosis. We present a case of 67-year-old man with pulmonary form of mucormycosis presenting as opportunistic infection post induction chemotherapy for acute myeloid leukemia FAB M2. We treated the patient with intravenous amphotericin B for 4 weeks and endobronchial resection, after which he clinically and radiographically improved. Overall, early consideration of mucormycosis can lead to an earlier diagnosis, medical and surgical therapy, and an increased survival rate. Furthermore, we provide a real example of multiple thinking strategies, needed for a patient oriented clinical practice. Overall, this case is a challenging example between clinical judgment and available validated guidelines.

Keywords: Pulmonary mucormycosis; Acute myeloid leukemia; Opportunistic infection; Hematologic malignancies; Chemotherapy related immunosuppression; Empiric antimicrobial therapy

Case Presentation

A 67-year-old man presents with 2 weeks of easy bruising, nasal bleeding, dyspnea, fatigue, and generalized weakness. He had no significant past medical history and he denied any recent travel, tobacco use, or use of illicit drugs. His examination was substantial for multiple bruises without lymphadenopathy. We admitted him to the hospital for evaluation of his dyspnea, weakness, and bleeding signs.

After the lab results and the peripheral smear were acquired, (Figure 1) we performed bone marrow aspirates, showing blast cells consistent with the diagnosis of AML (Acute myeloid leukemia) FAB M2. The patient underwent a subsequent bone marrow biopsy and clinical and biological factors staging. As shown in Figure 1 the diagnosis was

confirmed and the presence of a complex karyotypes (complex: 1p-, -17, 17q+, 20q+, -22); ECOG 0 performance status; normal laboratory tests and organ function; no comorbidities were recognized.

He received induction chemotherapy with cytarabine and daunorubicin (100 mg/m² IV Days 1-7 and 90 mg/m² IV Days 1-3, respectively), developing pancytopenia with a 21-day bone marrow biopsy showing chemotherapeutic effect. Febrile neutropenia and vancomycin-sensitive *S. aureus* bacteremia then complicated the patient's hospital course. He was treated with linezolid antibiotic therapy (1200 mg/24 h IV/PO in 2 equally divided doses). Nevertheless, he developed a generalized blotchy rash and he still suffers persistent fevers.

On day 30 post-induction, the respiratory involvement worsened, with shortness of breath and a progressive, nonproductive cough. His vital signs were a blood pressure of 126/60 mm Hg, heart rate of 95 beats/min, temperature of 38.6°C, respiratory rate of 32 breaths/min, and pulse oximetry reading of 92% on a non-rebreather face mask. Laboratory investigations revealed $27.0 \times 10^3/\mu\text{L}$ ($27.0 \times 10^9/\text{L}$) platelets and an absolute neutrophil count of 800 cells/mm³.

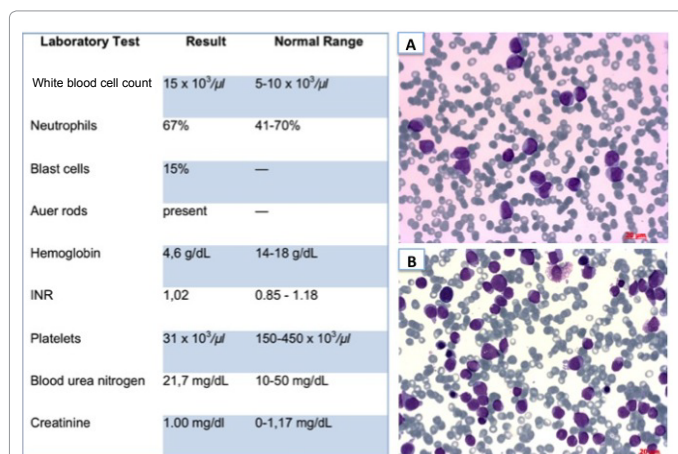


Figure 1: Laboratory results, peripheral smear (A) and bone marrow aspirates (B) showing findings consistent with the diagnosis of AML FAB M2.

***Corresponding author:** Solimando AG, Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine "G. Baccelli", University of Bari Medical School, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy, Tel: +393395626475; Fax: +390805478895; E-mail: antonio.solimando@uniba.it

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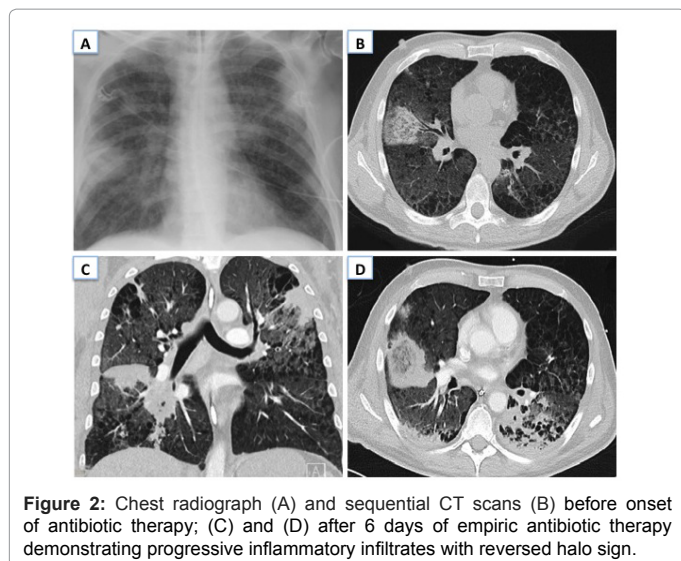


Figure 2: Chest radiograph (A) and sequential CT scans (B) before onset of antibiotic therapy; (C) and (D) after 6 days of empiric antibiotic therapy demonstrating progressive inflammatory infiltrates with reversed halo sign.

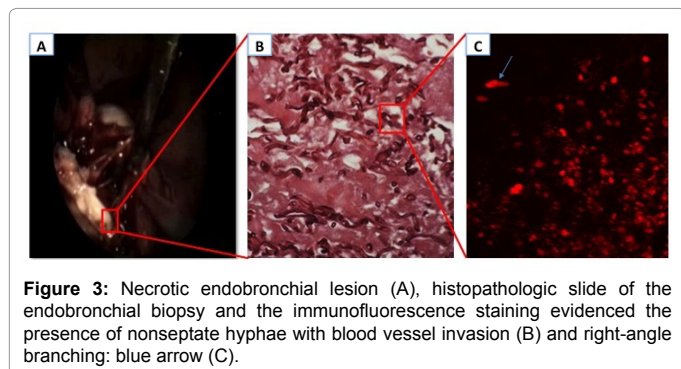


Figure 3: Necrotic endobronchial lesion (A), histopathologic slide of the endobronchial biopsy and the immunofluorescence staining evidenced the presence of nonseptate hyphae with blood vessel invasion (B) and right-angle branching: blue arrow (C).

We acquired a chest radiograph, that clearly defined bilateral infiltrates with the right of midfield and in the left upper field, pleura involved (Figure 2). The CT scan of the chest showed progressive atypical infiltrates, especially in the middle lobe, mediastinal lymphadenopathy, and a possible pulmonary fluid retention (Figure 2).

The patient received therapy with meropenem 2g q8h i.v. Phosphomycin 1 q8h and linezolid 600 mg q8h. Since we did not observe improvement, and given the compromised general status, further imaging analysis were performed. The CT found a graphically severe fungi-like pneumonia within a clearly progressive inflammatory infiltrate with reversed halo sign in the right upper lobe with a diameter of about 6 cm, in the lower right lobe with a diameter of approximately 5 cm and in left apical lobe with a diameter of 7 cm.

Remarkably, the infiltrate along the upper lobe fissure revealed a slight deviation of the trachea towards is indicative of lobar collapse (Figure 2).

We than performed a flexible bronchoscopy, demonstrating a necrotic endobronchial lesion fully obstructing the anterior segment of the right upper lobe (Figure 3). We approached the endobronchial lesion with rigid bronchoscopy and subsequent electrocautery, gaining a near-complete restitution of the right upper lobe anterior segment lumen, without complications.

The histopathologic analysis performed after microbiologic cultures on Sabouraud Dextrose agar medium and the immunofluorescence

obtained from the pathologic tissue of the endobronchial biopsy (Figure 3), led to the diagnosis of endobronchial mucormycosis. The patient in this case was treated with intravenous amphotericin B (AmB deoxycholate, with a starting dosage of 1 mg/kg per day for) for 4 weeks and endobronchial resection, after which he clinically and radiographically improved.

Discussion

Zygomycosis, also known as Mucormycosis, are an emerging group of life-threatening fungal infections caused by the orders of Mucorales and Entomophthorales. While the Entomophthorales are related to rare cutaneous and subcutaneous infections in immunocompetent hosts, the Mucorales are the third most common cause of invasive and lethal fungal infections in immunocompromised patients [1,2].

Rare until the advent of antimicrobial, immune-suppressant, and antineoplastic treatments, the Mucormycosis are most common in stem-cell transplant recipients and patients with underlying hematologic malignancies [3]. The European confederation of medical mycology (ECMM) has prospectively collected 230 cases of zygomycosis in 13 European countries occurring between 2005 and 2007, showing that the hematological malignancies accounts for 44% of mucormycosis cases, followed by trauma (15%), hematopoietic stem cell transplantation and diabetes mellitus (9%), and corticosteroid therapy (7%) [4].

Concerning the underlying mechanism related to the development of mucormycosis, the authors described a deficiency of phagocytic function, elevated serum levels of available iron and the host-pathogen interaction [2,5,6].

Mucor species are molds found in the environment that develop hyphal forms in the body tissues and invade blood vessels to produce tissue infarction, necrosis, and thrombosis [7].

Mucormycosis carries a very high mortality rate of 50% to 85% in cases of pulmonary and gastrointestinal disease, with even higher rates when there is difficulty establishing the diagnosis. Rhinocerebral disease causes significant morbidity in patients who survive because treatment usually requires extensive and disfiguring facial surgery [8].

The common presentation of the pulmonary mucormycosis is a rapidly progressive diffuse lung involvement. Patients usually complain pleuritic chest pain with severe cough and fever, in association with marked gas-exchange abnormalities and acute respiratory failure despite antibiotic therapy. Radiographic chest abnormalities include nodular, lobar, or wedge-shaped infiltrates, which may be seen in 58% of cases [1,2]. CT findings can be similarly broad, ranging from widespread nodules with areas of consolidation to a halo sign representing pulmonary infarct, hemorrhage, and edema [9] (Table 1).

Histologic examination of sputum or biopsy results are the best tools available in order to get the diagnosis certain. Because the history, physical examination, and laboratory examinations are generally unspecific and given the broad spectrum of radiographic findings, it is unlikely to diagnose or rule out pulmonary mucormycosis on a radiographic basis. Histologic identification of characteristic broad (5 μ m to 50 μ m), non-septate hyphae with right-angle branching and blood vessel invasion are mandatory for this purpose [10,11].

The gold standard to perform a biopsy is still uncertain. Although percutaneous needle biopsy, open lung biopsy, and pleural fluid culture have been successfully employed, bronchoscopic examination is often chosen as a relatively safe and less invasive technique [12].

Mucor Clinical manifestations	Risk factors for developing Mucor Infection
Most common manifestation	
Rhinocerebral	Stem cell transplant recipient
Pulmonary (50% and 75% in patients with hematologic malignancies [1])	Hematologic malignancies
	Neutropenia
Less common manifestation	
Cutaneous	Neutrophil dysfunction
Gastrointestinal	Diabetes mellitus patients
Central Nervous System	Chronic steroid use
Disseminated	AIDS

Table 1: Angioinvasion mucormycosis: Disease and host interaction. Mucor clinical manifestations and risk factors are summarized.

Treatment includes control of immunosuppressive factors, pharmacologic treatment, and resection for localized disease. Early and aggressive surgery appears to offer the best chance of recovery, especially in diabetic persons with hemoptysis [8-10].

Even if mucormycosis can be straightforward (such as the periorbital infection), endobronchial disease is seldom identified. Given the vascular invasion and infarction, amphotericin would be ineffective without previous surgical resection [12]. Overall, early consideration of mucormycosis can lead to an earlier diagnosis, medical and surgical therapy, and an increased survival rate [8].

Moreover, older patients with AML have shorter median overall survival (OS) Median OS is poor regardless of treatment option in population-based, real-life studies best supportive care (BSC) + hypomethylating agents + allogeneic stem cell transplant (allo-SCT) showed 3 months.

On the other hand, in clinical trials, intensive chemotherapy and hypomethylating agents showed 11-13 and 7.7-12.6 months, respectively [13]. Historical approach to treatment focused on chronological age, nevertheless the age cut-offs for using aggressive treatment is likely biased by lesser intent to induce remission and local variability [14]. Current approach considers patient-specific clinical and biological factors. The case presented is about a fit patient with poor-risk Cytogenetics [15]. Definitive evidence for optimal treatment approach is lacking. The given options are allo-SCT if donor is available, intensive chemotherapy only if no donor or patient is unwilling to undergo transplant and hypomethylating agents. However, given poor outcomes from all treatments is mandatory to consider trial available and clinical judgment, as exposed in this clinical case. Indeed, decisions on treatment selection are individualized to the patient performance status and cytogenetics. Standard-risk patients low-dose cytarabine (Ara-C) should be considered. In high-risk hypomethylating agent seem to offer a valid option. Also patient preference matters, indeed azacitidine and SCT are available only in patients settings. Finally, comorbidity index/risk scores are useful when considering allo-SCT [16]. Nevertheless it is plausible to speculate that in this particular case, in light of the clinical setting, the medical judgment offered an

unpredictable chance despite the given guidelines. Indeed is possible to hypothesize that a more prolonged iatrogenic immunosuppression would have compromised the prognostic outcome.

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