# Coinfection by Mucoraceae and Aspergillus species in a patient with acute leukemia: a clinical case report

Atousa Hakamifard[1], Mohammadsaleh Peikar[1], and Seyed Amirhossein Dormiani Tabatabaei[1]

[1]Isfahan University of Medical Sciences

September 01, 2024

**Introduction**

Hematological malignancies (HMs) are a group of malignant clonal disorders that mainly affect the blood and hematopoietic tissues. They are broadly categorized into myeloid and lymphoid lineages \RL (1)\RL. Acute lymphoblastic leukemia (ALL) is classified as acute \RL lymphoid lineage disorder. All hematological malignancies engage the immune system and raise the chances of opportunistic infections mainly invasive fungal infections \RL)IFIs\RL( (2).

*Aspergillus* and *Mucorales* species are emerged as increasingly relevant and most common agents responsible for highly lethal IFIs (3). The implementation of prophylaxis targeting*Candida* species in individuals with HMs has resulted in a higher occurrence of Aspergillosis compared to Candida infections (4).

*Aspergillus* spp., the airborne microorganisms, can manifest in three principal forms: invasive, saprophytic, and allergic (5). Although*Aspergillus fumigatus* (*A. fumigatus* ) is the predominant species associated with disease, other species can also result in invasive infections in profound immunocompromised patients (6). Statistics indicate that invasive aspergillosis occurs in 4-15% of cases and has a mortality rate between 60% and 85% (7). Mucormycosis, a less frequent occurrence compared to aspergillosis, is a devastatingly angioinvasive fungal infection caused by ubiquitous filamentous fungi belonging to the Mucorales order (8). The main damage is rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, and disseminated, with a high mortality rate, estimated between 32% and 70% (9). Although lung is the most prevalent site of infection in patients with hematologic malignancies, rhino-orbito-cerebral mucormycosis (ROCM) is the most common form classically described in diabetic patients (10).

Severe neutropenia (absolute neutrophil count below 500 cells/mm3) due to toxic antineoplastic chemotherapies and myelosuppressive agents or allogeneic hematopoietic stem cell transplantation (allo-HSCT) placing HMs at a higher risk of evolving life-threatening infections with few symptoms (11).

Herein we report a case of concomitant acute invasive fungal rhinosinusitis (AIFR) and invasive pulmonary fungal infection with*Aspergillus* and *Mucoraceae* species in a patient with pre B cell ALL. This research was approved by the Ethics committee of Isfahan University of medical sciences (IR.ARI.MUI.REC.1403.094), and written informed consent was obtained from the patient.

**Case History/ Examination**

In late November 2023, a 21-year-old man with the diagnosis of Pre-B-cell ALL admitted to the hematology department of Omid hospital affiliated to Isfahan \RL University of Medical Sciences (Isfahan, Iran) for receiving induction chemotherapy. The chemotherapy regimen was CALGB 10403. The prophylactic regimen during chemotherapy were levofloxacin, co-trimuxazole, acyclovir and fluconazole. 5 days after the end of the course of induction chemotherapy the patient became febrile (T: 38.5).

He presented fatigue, \RL occasional dry cough, and left pleuritic chest pain with normal vital signs and physical examination. Oxygen saturation was 96% while the patient was breathing ambient air.

**Methods**

Laboratory testing were as follows: white blood cell (WBC) of 1100/mm$^3$, polymorphonuclear neutrophils (PMN) of 400/mm$^3$, hemoglobin of 7 g/dl, platelets (PLT) of 91000/mm $^3$ and C-reactive protein (CRP) of 15 mg/dL.**Figure 1** revealed the neutrophil trend during the chemotherapy.

Considering patient's febrile neutropenia and dry cough, chest High-resolution computed tomography (HRCT) and paranasal sinuses CT scan (CT PNS) were performed which revealed multiple peripheral and central nodular opacities and sinusitis respectively [**Figure 2, 3**] . According to nodular pneumonia and sinusitis with febrile neutropenia, prophylactic antibiotics were discontinued and treatment with meropenem 1gr IV every 8 hours, ciprofloxacin 400 mg every IV every 8 hours, vancomycin 1 gr IV every 12 hours, and liposomal amphotericin B (5mg/kg) 350 mg IV daily were initiated.

Nucleic acid amplification test for influenza A and B and Real-time reverse-transcriptase–polymerase-chain-reaction (rRT-PCR) for SARS-CoV-2 were negative. Blood cultures and serum galactomannan antigen test with Platelia Aspergillus ELISA kit (Bio-Rad) were reported negative (0.3).

According to sinusitis and pneumonia with nodular pattern the patient underwent bronchoscopy with bronchoalveolar lavage (BAL). The sample was sent for bacterial and fungal smear and culture, and also galactomannan. The culture of BAL revealed colonies consistent with *Mucoraceae* species [**Figure 4**] . The BAL galactomannan antigen test with Platelia *Aspergillus* ELISA kit (Bio-Rad) was reported 3.8 index which was high. Cytopathology testing for malignancy was negative.

In addition according to sinuses endoscopy which showed scattered areas of pale, necrotic tissue concerning for invasive fungal sinusitis, the patient underwent functional endoscopic sinus surgery (FESS) and the sample sent for smear, culture and histopathological evaluation. The culture revealed colonies consistent with *Aspergillus flavus* [**Figure 5**] . The histopathologic evaluation showed extensive necrosis with invasive broad aseptated hyphae compatible of invasive mucormycosis [**Figure 6**] .

**Conclusion and Results**

Based on these results the diagnosis of concomitant probable invasive*Aspergillus* rhinosinusitis and confirmed invasive *Mucor* rhinosinusitis with concomitant probable invasive pulmonary aspergillosis (IPA) and probable pulmonary mucormycosis was made. After 7 days of therapy the patient underwent sinuses endoscopy for second look and no evidence of necrosis was reported. Meropenem, ciprofloxacin, and vancomycin were stopped and treatment based on liposomal amphotericin B was continued\RL. He was afebrile on day 5 of treatment.

Repeated lung HRCT showed a slight reduction in the size and number of the nodular lesions after 22 days of antifungal therapy. According to the patient's need to start consolidation chemotherapy, high dose methotrexate with leucovorin and ara-C regimen was started after 22 days from the start of liposomal amphotericin B.

The patient underwent 4 ENT consults and no evidence of necrosis was reported in endoscopies. The lung HRCT revealed significant improvement and after 37 days the liposomal amphotericin B was overlapped with posaconazole suspension 200 mg every 6 hr for 5 days and then liposomal amphotericin B was discontinued. The posaconazole suspension was continued with this therapeutic dose for 30 days. At the time of writing this paper, 5 months follow-up demonstrated no evidence of infection recurrence and the courses of chemotherapies are continued under posaconazole secondary prophylaxis. The timeline of the patient treatment was showed in [**Figure 7**] .

This case report highlights the implication of considering the sinopulmonary *Aspergilosis* and *mucor* mycosis coinfection in a patient with acute leukemia as there are not so many cases described in the literature.

The keys to optimize the management of these coinfectional situations include a high index of suspicion for the disease with early detection of the signs and symptoms by a multidisciplinary approach, rational antifungal therapy and if necessary, aggressive surgical resection.

As there is no evident consensus concerning the therapy in mixed fungal-infections, more potent and focused line of treatment as compared to infection with a single fungal agent will be required.

**Discussion**

Simultaneous dual invasive mold infections is exemplified by a rare condition, even in profoundly immunocompromised hosts, evolving to disseminating progression and poor outcome (12).

Here we report the case of the concurrent sino-pulmonary aspergillosis and mucormycosis infection complicating a leukemic 21-year-old man clinical course with severe prolonged neutropenia induced by the initial induction chemotherapy regimen as a significant risk factor .

Multidisciplinary correlation of radiological, histological, microbiological, and serological findings is critical for making a definite diagnosis and improving outcome in high risk patients.

Recent data associating to the diagnosis of fungal pneumonia in adults indicates that a high-resolution CT scan (HRCT) is the preferred radiological method regarding to it's sensitivity and availablity. Among neutropenic patients with invasive pulmonary aspergillosis, nodules or oapcities with a "halo sign" remain practical indicators (13). Likewise, CT scans confirm sinus involvement and lesion severity, signifying the presence of fungal sinus infection (14).

A tissue diagnosis can be achieved through an appropriate biopsy, which identifies the characteristic invasive hyphae, positive culture, or both. Initially, the culture of the affected tissue may yield negative results, making histopathologic examination necessary for early detection (15).

PCR methods sufficiently provide a prompt diagnostic test for IFIs that is performable on whole blood, serum, plasma, and BAL fluid (16). Furthermore, PCR is directly capable of specifying mutations linked to drug resistance and monitoring treatment progress an is linked to improved survival rates when treatment initiation results in negativity (17).

Distinct assays considering different thresholds were adopted for *Aspergillus* galactomannan (GM) antigen (18).

The European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria for invasive aspergillosis and mucormycosis are appropriate for hematologic malignancy patients, and our patient was considered to have probable IPA based on an abnormal CT scan of the lungs and BAL GM results, probable AIFR due to aspergillosis based on positive culture, confirmed AIFR due to mucormycosis based on pathology and probable pulmonary mucormycosis based on positive BAL culture (19). The European Confederation of Medical Mycology (ECMM) and the European Conference on Infections in Leukemia (ECIL) guidelines recommend first-line mold active antifungal therapy combined with surgery and control of underlying conditions. While voriconazole are the agent of choice for the management of IPA, They both firmly support liposomal amphotericin B (L-AmB) as a mucormycosis first-line treatment in adults (20,21).

Also, some previous reports noted that invasive pulmonary Aspergillus and Mucor coinfections were countered sufficiently using high doses of liposomal AmB alone (22).

The administration of liposomal amphotericin B, in comparison to other amphotericin B formulations, has been found to have significantly lower occurrence rates of probable side effects, including nephrotoxicity and, infusion-related reactions (fever and rigors), as well as hypokalaemia (23).

It is recommended initial empirical therapy for possible invasive mold infection regarding to its broad spectrum of activity considering local epidemiological prevalence of pathogens. Patients who received the highest dose regimens tended to have a greatest rate of cure, despite more frequent renal adverse effects (24). To date

combination treatment of antifungals is not recommended as a first-line therapy due to their no significant reduction trend in mortality rate and is conserved for patients who are refractory to standard regimen or unable to tolerate high dose of L-AmB adverse effects (25).

Even though the treatment options for patients with HMs remain relatively restricted, this patient survived because of an early diagnosis and prompt treatment.

**Figure legends:**

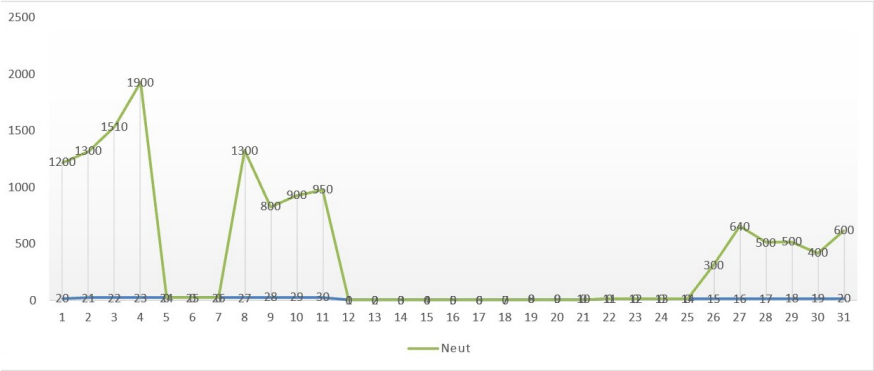


**Figure 1.** Graphical trend of absolute neutrophil count (ANC) during the patient's induction chemotherapy.

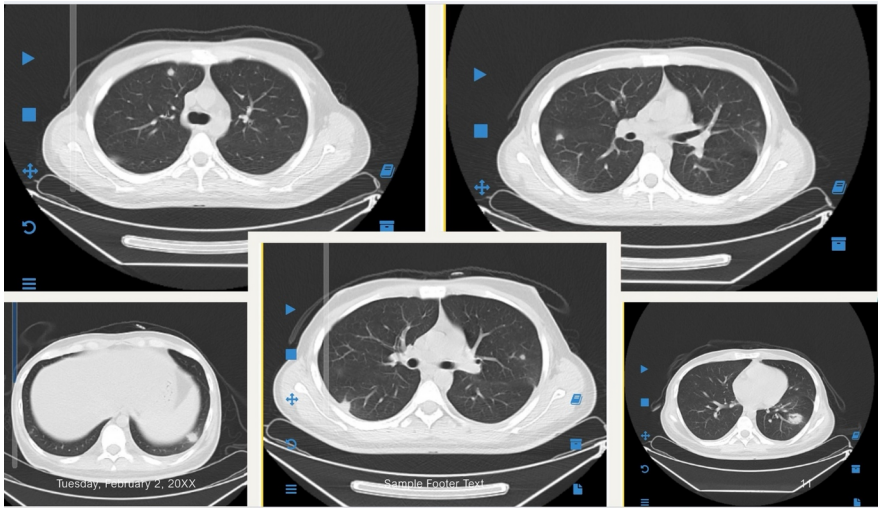


**Figure 2.** Chest CT scan revealed multiple nodular opacities with central and peripheral distribution.

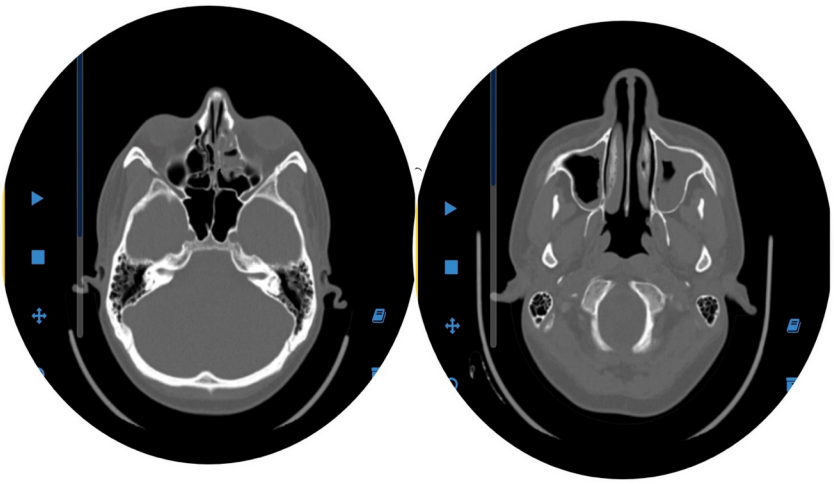

**Figure 3.** CT scan of sinuses (axial and coronal) revealed opacity in the left maxillary and ethmoidal sinuses.

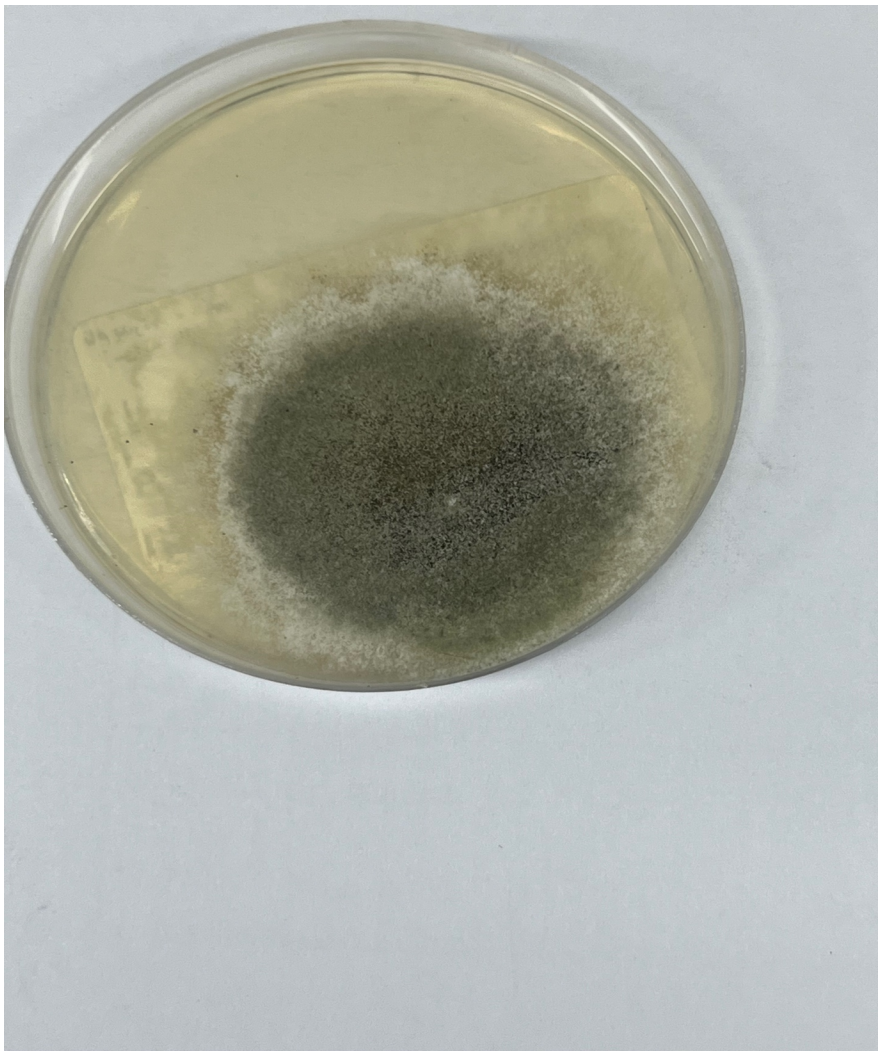

**Figure 4.** BAL culture phenotypically identified as*Mucoraceae* species.

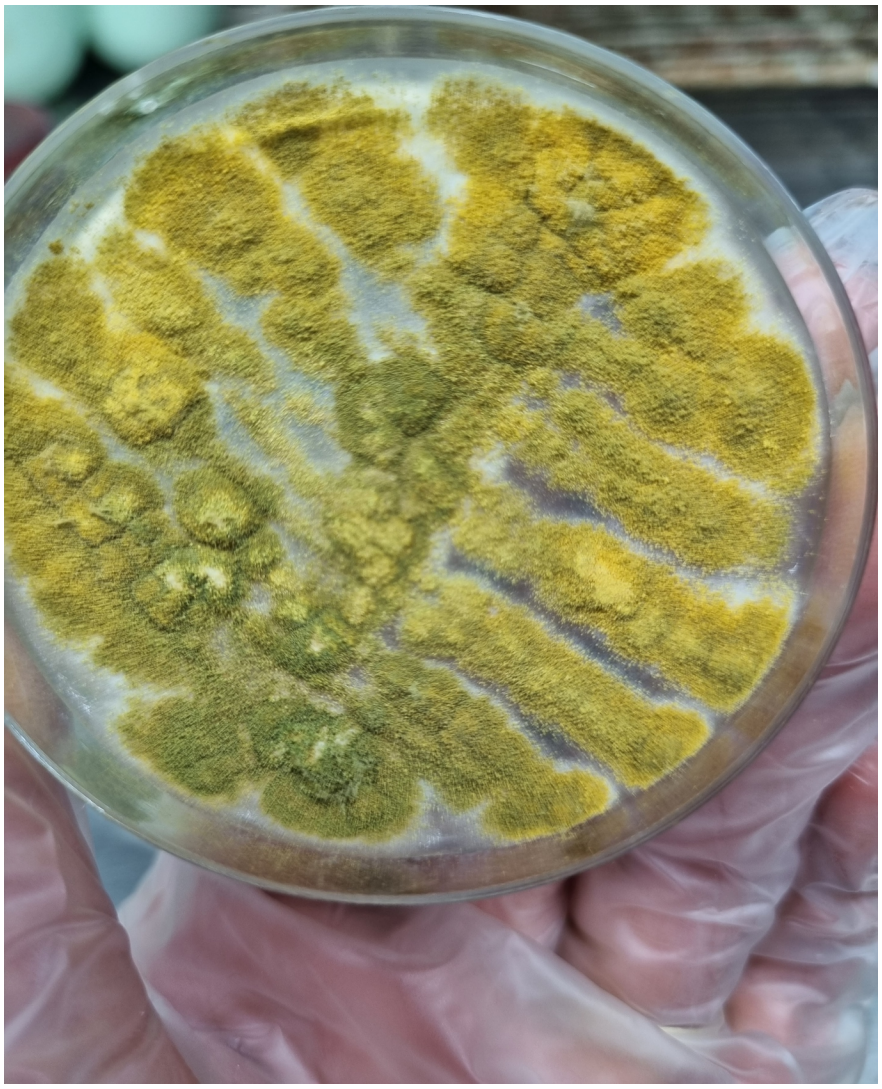

**Figure 5.** Sinus culture revealed colonies phenotypically identified as *Aspergillus flavus* .

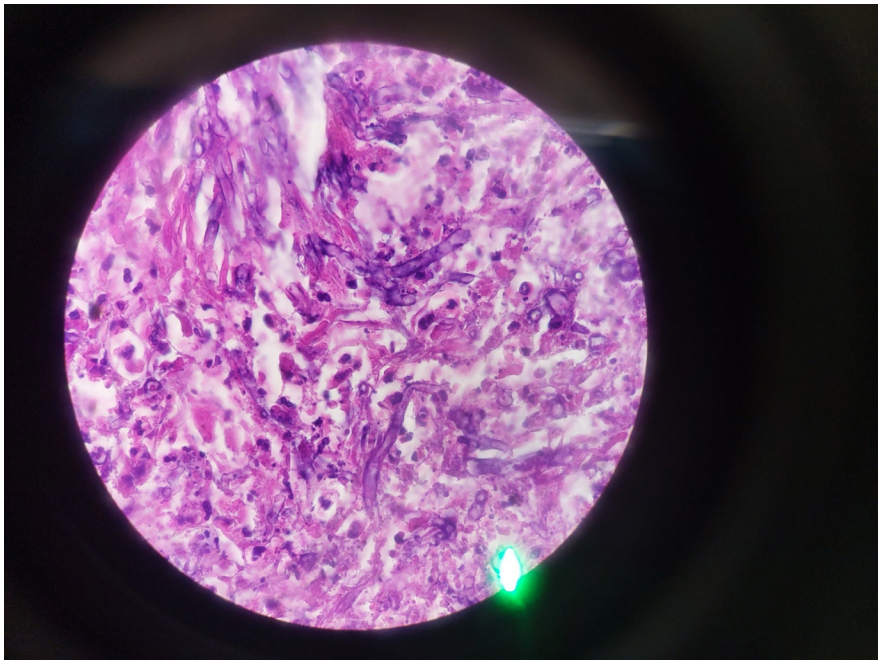

**Figure 6.** Sections show sinonasal tissue composed of mucosal gland covered by respiratory epithelium. Extensive necrosis with invasive broad aseptated hyphae (mucormycosis) are noted.

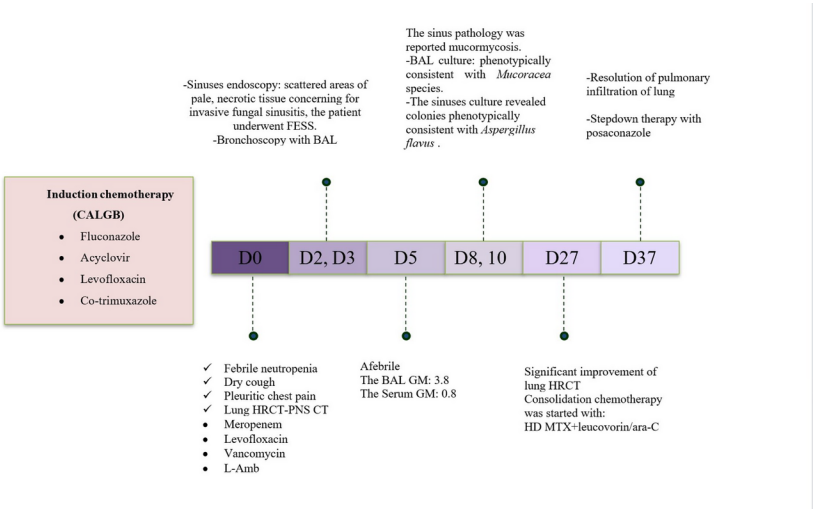


**Figure 7.** The figure containing history and interventions provided the course of the presented case.