



Case Report

# Polymicrobial Infection in a Patient with Acute Myeloid Leukemia: The Importance of an Early Diagnosis and Treatment

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## Abstract

Acute myeloid leukemia (AML) is a hematological neoplasm with high infectious risk, due to the disease and its treatment, which causes prolonged and profound neutropenia. The prognosis is variable, depending, among other factors, on the cytogenetic and molecular alterations of the disease and on the age and status of the patient. In fit patients, the usual management consists of intensive chemotherapy and, occasionally, hematopoietic stem cell transplantation. We report the case of a 73-year-old woman with AML secondary to myelodysplastic syndrome who presented simultaneous infectious complications caused by fungi and bacteria during induction treatment with liposomal daunorubicin and cytarabine, including an infrequent case of pneumonia due to vancomycin-resistant *Enterococcus faecium*. An early diagnosis and treatment are important in both types of infection. If there is suspicion of pulmonary invasive fungal infection and a compatible imaging test, empirical treatment should be started, and bronchoalveolar lavage should be performed without delay.

**Keywords:** Acute myeloid leukemia; Febrile neutropenia; Fungal invasive infection

## Introduction

Acute myeloid leukemia (AML) is a blood cancer that arise from clonal expansion of malignant hematopoietic precursor cells (blasts) producing a decrease in production of normal blood cells: red blood cells, non-pathological white cells and platelets (causing anemia, neutropenia and thrombocytopenia respectively, with an increased risk of infection and bleeding) [1,2]. However, it is a heterogeneous group in which the cytogenetic and molecular characteristics of each disease must be analyzed, which can change the prognosis and even the treatment. Some acute myeloid leukemias are the final evolution of other hematological neoplasms,

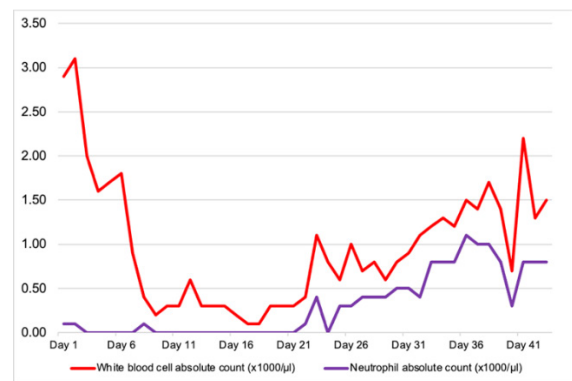
such as myelodysplastic syndromes or myeloproliferative syndromes, generally having a worse prognosis compared to normal leukemias [3]. It is a disease with a poor prognosis, more frequent in elderly people (with a median age at diagnosis of 68 years in the USA). In fact, age is an important prognostic factor: more than 50% of patients under 40 years of age achieve 5-year survival, but less than 2% of patients under 80 years of age do [4]. In fit patients, the goal is healing, with intensive chemotherapy and in many cases allogeneic transplantation. In unfit patients, the goal is usually to try to control the disease to prolong survival, but it is rare to achieve a cure. The profound neutropenia produced by both the disease and the treatments, generating prolonged aplasia, represent a significant increase in the risk of infection by bacteria and fungi [5].

## Case report

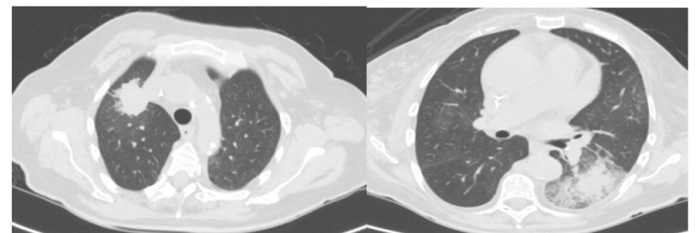
A 73-year-old woman with heterozygous beta thalassemia and chronic liver disease due to hepatitis B virus (in treatment with tenofovir) was diagnosed with myelodysplastic syndrome with excess blasts 1 in 2018 without cytogenetic alterations. The patient began treatment with azacitidine, receiving 28 cycles. In May 2021, the patient had leukocytosis, with 53% blasts in peripheral blood and 30% blasts in bone marrow, so the disease was classified as acute myeloid leukemia (AML with myelodysplasia-related changes). The patient was simultaneously diagnosed with infiltrating breast carcinoma, but the treatment of hematological neoplasia was prioritized. Figure 1 shows chest X-ray on admission. On the second day of treatment, the patient had a fever and systemic antibiotic therapy with meropenem and colistin was started, in compliance with the protocol of our unit. The chest X-ray was normal and a blood culture from the peripherally inserted central catheter (PICC) isolated *Leptotrichia trevisanii*; the possible infection origin was gingivitis. As usual, primary prophylaxis for filamentous fungus with posaconazole was established. 15 days after starting treatment, the patient had a constant dry cough and fever, and a computed tomography scan of the chest was pending. The patient was profoundly neutropenic (Figure 2). A chest CT was performed, in which 3 consolidations were observed, being compatible with invasive fungal infection (Figure 3). Treatment was started with isavuconazole and liposomal amphotericin B (dose of 5 mg/kg/day), withdrawing primary prophylaxis with posaconazole, in addition to restarting meropenem and colistin. Besides, vancomycin-resistant *Enterococcus faecium* was isolated in the blood and urine cultures, so antibiotic therapy was adjusted: meropenem, ceftaroline and daptomycin, plus daptomycin catheter lock. The patient required low-flow oxygen therapy with nasal cannulas, and *Enterococcus faecium* was isolated in the bronchoalveolar lavage, so tigecycline was added to the treatment. Transthoracic echocardiography showed no vegetations. She was discharged home after 40 days of admission. In the bone marrow reevaluation, the patient had a complete response with a possible minimal residual disease of 0.15%. The patient refused to continue with AML treatment after these complications.



**Figure 1:** Chest X-ray on admission.



**Figure 2:** White blood cell and neutrophil absolute count during hospitalization.



**Figure 3:** CT on day 15, in which 3 consolidations were observed, being compatible with invasive fungal infection.

## Discussion

Intensive treatment of AML, especially during induction, produces profound and prolonged neutropenia that increases the risk of infection, especially due to Gram-negative rods and fungi. Novel use of liposomal anthracyclines and cytarabine in induction therapy has shown similar infection rates [6]. Therefore, it is important to start broad-spectrum antibiotic treatment early in patients with AML undergoing induction treatment with fever. In addition, patients should be monitored for fungal infection; in these patients, prophylaxis that includes coverage for filamentous fungi is recommended [7]. In the majority of febrile neutropenia episodes, there is no obvious clinical focus of infection. Guidelines used in our country recommend to use a beta-lactam antibiotic with antipseudomonal activity as monotherapy, or in combination with another antibiotic, depending on the risk of infection due to multidrug-resistant microorganisms and clinical presentation [8]. Invasive fungal infection (IFI) is an important cause of morbidity and mortality in hematologic patients, especially in AML and allogeneic transplant patients. Regarding antifungal prophylaxis, azoles are the most widely used drugs. Fluconazole is a cheap drug with little toxicity, useful against most species of *Candida* but not against molds. Posaconazole is the most widely used agent in antifungal prophylaxis in the induction of AML, but it can interact with some new drugs, such as midostaurin (a drug for FLT3-TKD/ITD mutated AML) because this anti-leukemic agent is metabolized via P450 3A4 (CYP3A4) and posaconazole is a strong CYP3A4 inhibitor [9,7,10,11]. In these cases there are some options, such as closer monitoring of possible adverse effects or the use of other drugs such as isavuconazole, which has fewer interactions and shortens the QT interval (although it is not approved as primary antifungal prophylaxis) [12,13]. Voriconazole is a first-line agent for treatment of invasive aspergillosis but has not been approved for use as primary prophylaxis. IFI must be suspected when a neutropenic patient has a persistent fever despite broad-spectrum antibiotic therapy, absence of microbiological isolates, and good control of the focus, if any. A chest CT is recommended. In addition, the request for fungal markers, such as galactomannan and beta D-glucan, may be useful. The microbiologic diagnostic of IFI is difficult, because obtaining appropriate specimens can be difficult due to coagulopathy or hemodynamic instability of the patient, but early bronchoscopy with bronchoalveolar lavage (BAL) is essential to obtain adequate microbiological samples; if this test is delayed, the diagnostic performance is lower, because antifungal therapy should be started with suspicion by imaging test; if the CT is positive, treatment should be started, changing the antifungal if the patient was with prophylaxis, trying to administer a targeted treatment, although in

many cases there are no microbiological isolates [14,10]. In our patient, vancomycin-resistant *Enterococcus faecium* was isolated in blood cultures and BAL. It's a ubiquitous Gram-positive bacteria present in the commensal flora of the digestive tract and vagina and can contaminate the surface of inanimate objects in the hospital, where it survives for a long time. Also, it can be transmitted through the hands of health personnel. This bacterium usually produces primary bacteremia or bacteremia secondary to endocarditis, vascular catheter, urinary catheter, infected wound or ulcer, or an intra-abdominal focus [15]. Pneumonia is rare, and in this case probably secondary to bacteremia. In this case, the patient was being treated with daptomycin, but this drug has poor lung penetrance and tigecycline was added to the treatment. In conclusion, this case is an example of the high risk of infection in AML patients by bacteria and fungi, although the risk of viral infection should not be underestimated, especially in times of COVID-19. In these patients, infections by different microorganisms can coexist simultaneously, and care must be taken to administer an appropriate therapy, bearing in mind the high risk of toxicity with the use of a large number of drugs. In a patient undergoing induction of AML, with a high suspicion of IFI, with a positive CT, empiric antifungal treatment should be started and BAL should be performed as soon as possible.

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