Fatal Invasive Aspergillosis in Acute Lymphoblastic Leukemia Patient

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Abstract

Invasive aspergillosis (IA) is one of the most common fungal infections in immunocompromised patients. It is an air-borne disease and the majority of patients develop pneumonia or sinusitis. However central nervous system (CNS) aspergillosis may also occur. Infections by Aspergillus fumigatus are most prevalent although in recent years, non-fumigatus Aspergillus species such as A. flavus has become common as causal agents this mycosis. The major risk factors associated include neutropenia, hematological malignancy, and transplantation of hematopoietic stem cells and solid organs. Therefore, here we report a fatal case of pulmonary aspergillosis and CNS due Aspergillus flavus in neutropenic patient with acute lymphoblastic leukemia. The diagnosis of pulmonary infection was based in the isolation of A. flavus in tracheal secretions associated with the pulmonary infiltration detected in the Chest X-ray. Because of the thrombocytopenia the CNS aspergillosis was diagnosed only by brain magnetic resonance imaging. This case underscores the importance of IA as a serious disease and late diagnosis leading to a poor prognosis with fatal course due to worsening clinical.

Keywords: Invasive aspergillosis; Cerebral aspergillosis; Invasive pulmonary aspergillosis; Acute lymphoblastic; Leukemia; Aspergillus flavus

Introduction

Invasive Aspergillosis (IA) is an important cause of mortality and morbidity in patients with hematological malignancies [1]. This is a severe infection in patients with acute leukemia, representing 14%-23% of all infectious complications and is lethal in 13% to 87% of affected patients [2].

The etiologic agents of this mycosis are Aspergillus species ubiquitous fungi that infect humans through inhalation of spores and may cause fatal infections especially in immunocompromised patients [3]. IA due to A. fumigatus is more common. Although infections by others species such as A. flavus and A. terreus have become frequent and are associated with high mortality rates [4].

The major risk factors associated with this mycosis include neutropenia, hematological malignancy, and transplantation of hematopoietic stem cells and solid organs. The duration and degree of neutropenia are related to the occurrence of infection and the majority of cases are diagnosed in patients that received potent cytotoxic regimens for hematologic malignancies [5]. The clinical manifestations are varied. However, the most common are pneumonia or sinusitis, although central nervous system-CNS aspergillosis may also occur in 14% to 42% of the cases [2].

The prognosis of IA is related with the organ involvement. Localized pulmonary disease has the lowest reported mortality, whereas to CNS aspergillosis and disseminated, the mortality rate can reach over 90% [6]. Early diagnosis of aspergillosis in highly immunocompromised patients remains difficult, and definitive diagnosis often require invasive procedures. Although the isolation of Aspergillus species from sputum or bronchoalveolar lavage is highly predictive of invasive disease in neutropenic patients [7]. Here we report a fatal case of invasive aspergillosis with pulmonary and cerebral involvement due to A. flavus in acute lymphoblastic leukemia (ALL) patient.

Case Report

A 46 year-old male with acute lymphoblastic leukemia (ALL) was admitted to Foundation of Hematology and Hemotherapy of Pernambuco-HEMOPE for chemotherapy treatment. After the initiation of chemotherapy the patient presented febrile neutropenia with absolute neutrophil count <100 cells/mm³, thrombocytopenia, respiratory insufficient, hemoptysis and lowering of consciousness and was transferred to the intensive care unit (ICU) for mechanical ventilation.

The Chest X-ray was realized in ICU and showed pulmonary infiltration (Figure 1a). Intravenous broad spectrum antibiotics were started. Because of the lost consciousness, a brain magnetic resonance imaging (MRI) was taken, showing an abscesses in both cerebral hemispheres with 6.5 x 4.7 x 4.2 cm and 7.0 x 6.0 x 5.5 cm in left and right hemispheres respectively (Figure 1b). According to the clinical aspects a probable invasive fungal infection was suspected and clinical samples were collected for mycological diagnosis.

Samples of tracheal secretion and blood cultures were collected on three consecutive days. Venous blood samples were collected aseptically from the central and peripheral veins by venipuncture and tracheal secretion samples were obtained via endotracheal aspiration. Because of severe thrombocytopenia, it was not possible to perform more invasive collections. All samples were processed immediately after collection by standard methods of mycological diagnosis (direct examination and isolation in culture) at the Medical Mycology Laboratory, Federal University of Pernambuco, Recife, Brazil [8].

Microbiological identification was achieved using traditional taxonomy through morphological characteristics [9], and by sequencing fragments of the internal transcribed spacer region of the rDNA using primers ITS-1 and ITS-4 [10]. Antifungal susceptibility testing was performed in accordance with protocols defined by the Clinical and Laboratory Standards Institute (CLSI) M38-A2 method.

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Mineral oil (number 5915) at the internationally recognized URM the possible source of infection. The strain has been maintained under pulmonary and cerebral involvement. The respiratory tract was permitted by the family. These results suggest the occurrence of IA 13 days after the voriconazole treatment started. The autopsy was not submitted to GenBank with the accession number (HQ693703).

A BLAST search produced a 100% match between all the A. flavus ITS rDNA sequences in the GenBank database. The DNA sequence was obtained from the Culture Collection of Department of Mycology, Federal University of Pernambuco, Brazil.

**Discussion**

The incidence of IA has increased during the past two decades due to widespread use of chemotherapy and immunosuppressive agents, and is a frequently lethal complication of acute leukemia patients that occurs following chemotherapy [12]. In accordance with previous studies it has been established that patients with acute leukemia or myelodysplastic syndrome have a high risk of *Aspergillus* infection [13].

*Aspergillus* are ubiquitous in the environment and more than 180 species have been identified; however only few are considered as pathogenic in human beings, notably *A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus* and *A. nidulans* [3]. *A. flavus* is the second most common of *Aspergillus* species in human infections [14].

The lung continues to represent the most frequently involved site. Pulmonary infection can be understood as a phenotypical representation of interaction between lowered defense mechanisms in the host and the virulence of the fungus [15].

IPA is a significant cause of morbidity and mortality in immunocompromised patients [16], especially in those with haematological malignancies and bone marrow aplasia [17]. The risk of IPA in neutropenic patients is estimated to be 1% per day for the first 3 weeks, after which time it increased to 4% per day [18]. Here in our case report, the patient remained neutropenic for 45 days and was also undergoing chemotherapy which may have favored the development of IA.

The IA diagnostic is difficult. *Aspergillus* spp. cultures isolated from non-sterile body sites did not represent disease. However, for high-risk patients, such as allogeneic bone marrow transplant recipients (60%), persons with hematologic cancer (50%), and those with signs of neutropenia (60%) or malnutrition (30%), positive culture is associated with invasive disease [7].

Tissue sampling remains the golden diagnostic standard; however, tissue sampling in critically ill patients are often difficult because of high-grade ventilatory and inotropic support, and coagulation deficiencies [7]. Direct microscopic examination is important in the appreciation of a culture positive sample; the demonstration of septate hyphae increases the probability of disease [7].

High mortality occurs among patients with IA, despite therapy and clinical conditions. Only about one-third of patients infected and treated with conventional AmB survive [19], being voriconazole the drug of choice [20] associated with better survival [21].

Here despite the use of appropriate antifungal therapy our patient died due to disease severity. However even for isolates susceptible to voriconazole in less accessible areas as the brain the drug dosage should be increased to the satisfactory response [22]. We might have gotten a better prognosis with more aggressive therapeutic regimen. The poorest prognosis occurs in extrapulmonary forms, with successful therapeutic in 34% of patients with CNS aspergillosis [6]. The diagnosis and antifungal therapy later causes a poor prognosis leading to death [21]. Screening of the CNS not make recommended in aspergillosis pulmonary cases [23]. However in our opinion neutropenic and leukemia patients with sings of neurological deficits our experience suggest that a cerebral involvement should be investigated and according with recent study MRI a good choice of the diagnosis [23].

This report underscores the Importance of IA as a severe disease
usually fatal when associated with pre-existing conditions such as haematologic malignancies, with a poor prognosis and death. The manuscript is in accordance with the ethical standards of the responsible committee on human experimentation of the Hematology and Hemotherapy Foundation of Pernambuco.

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