Journal of Clinical Case Reports
ISSN: 2165-7920

Parahym et al., J Clin Case Rep 2014, 4:6
DOI: 10.4172/2165-7920.1000368

Case Report Open Access

Fatal Invasive Aspergillosis in Acute Lymphoblastic Leukemia Patient

Parahym AMRDC[1]*, Neto PJR[1], Silva CMD[1], Gonçalves SS[2], Motta CMDS[1], Filho GADTMH[3], Correia TTDS[1] and Neves RP[1]

[1]Federal University of Pernambuco, Recife, PE, Brazil
[2]Special Mycology Laboratory, São Paulo, SP, Brazil
[3]Hematology and Hemotherapy Foundation of Pernambuco-HEMOPE, Recife, PE, Brazil

Abstract

Invasive aspergillosis (IA) is one of the most common fungal infections in immunocompromised patients. 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 immuno compromised 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/mm^3, 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 6.5×4.7×4.2 cm and 7.0×6.0×5.5 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

***Corresponding author:** Ana Maria Rabelo de Carvalho Parahym, Avenida Nelson Chaves, s/n, Cidade Universitária, Recife-PE, 50670-420, Brazil, Tel: (+5581) 21268570; Fax: (+5581) 21268482; E-mail: aana_mrc@hotmail.com

Received May 08, 2014; **Accepted** May 20, 2014; **Published** May 22, 2014

Citation: Parahym AMRDC, Neto PJR, Silva CMD, Gonçalves SS, Motta CMDS, et al. (2014) Fatal Invasive Aspergillosis in Acute Lymphoblastic Leukemia Patient. J Clin Case Rep 4: 368. doi:10.4172/2165-7920.1000368

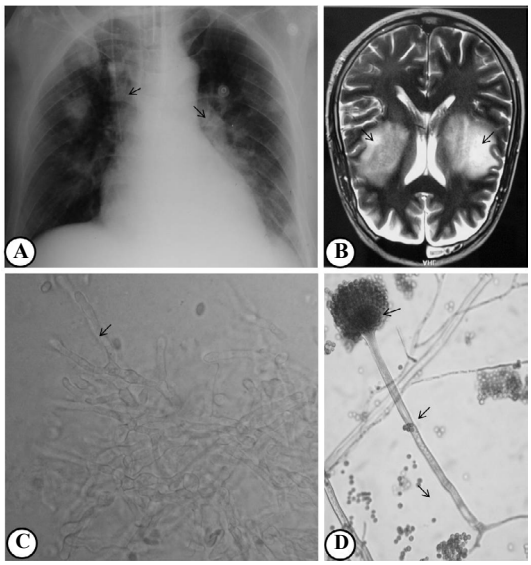

Figure 1: a. Chest X-ray showing pulmonary infiltration suggestive for fungal infection. **b.** Brain magnetic resonance imaging showing abscesses in both cerebral hemispheres. **c.** Septate hyphae in acute angle dichotomous evidenced on direct examination (without addition of dye or clarifier, X400). **D.** Microscopic characteristics of *Aspergillusflavus* showing vesicules slightly spherical and stipes smooth and conidia globose (Amann's lacto-phenol, X 400).

[11]. The antifungal drugs amphotericin B (AMB) and fluconazole (FLZ) were tested. Quality control was performed by testing CLSI recommended strain *Candida parapsilosis* ATCC 22019 and *C. krusei* (ATCC 6528).

Blood cultures were negatives, but in three samples of tracheal secretions were found on direct examination numerous septate hyaline hyphae in acute angle from dichotomous branching (Figure 1c). In cultures was isolated *A. flavus* identified by traditional and molecular taxonomy.

The colonies presented velutinous texture, color olive, with white mycelium and reverse uncolored. The microscopic examination for the culture showed conidiophores variable in length, vesicles spherical and conidia globose (Figure 1d).

A BLAST search produced a 100% match between all the *A. flavus* ITS rDNA sequences in the GenBank database. The DNA sequence was submitted to GenBank with the accession number (HQ693703).

The isolation of *A. flavus* in tracheal secretions associated with the pulmonary infiltration detected in the Chest X-ray, confirmed the case of invasive pulmonary aspergillosis (IPA) by this fungus. However because the thrombocytopenia the CNS aspergillosis was diagnosed only to brain MRI associated with lowering of consciousness. Susceptibility testing showed that the isolate was susceptible to all tested antifungal with minimum inhibitory concentrations of 1 µg/mL and 0.03 µg/mL for AMB and FLZ respectively.

Physicians prescribed intravenous AMB (0.5 mg/kg/day) for 17 days and after voriconazole (400 mg/day). However, the patient died 13 days after the voriconazole treatment started. The autopsy was not permitted by the family. These results suggest the occurrence of IA with pulmonary and cerebral involvement. The respiratory tract was the possible source of infection. The strain has been maintained under mineral oil (number 5915) at the internationally recognized URM 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 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 pathogenetic 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 dificult 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 withpre-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.

Acknowledgements

We are particularly grateful to Dr. David Bousfield for critical reading of the manuscript and to Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco for financing the research.

References

1. Bergeron A, Porcher R, Menotti J, Poirot JL, Chagnon K, et al. (2012) Prospective evaluation of clinical and biological markers to predict the outcome of invasive pulmonary aspergillosis in hematological patients. J Clin Microbiol 50: 823-830.
2. Pagano L, Ricci P, Montillo M, Cenacchi A, Nosari A, et al. (1996) Localization of aspergillosis to the central nervous system among patients with acute leukemia: report of 14 cases. Clin Infect Dis 23: 628–630.
3. Ali R, Ozcelik T (2006) Invasive pulmonary aspergillosis in acute leukemia: current issues for pathogenesis, diagnosis and treatment. Curr Respir Med Rev 2: 3-13.
4. Marr KA (2008) Fungal infections in hematopoietic stem cell transplant recipients. Med Mycol 46: 293-302.
5. Yeghen T, Kibbler CC, Prentice HG, Berger LA, Wallesby RK, et al. (2000) Management of invasive pulmonary aspergillosis in hematology patients: a review of 87 consecutive cases at a single institution. Clin Infect Dis 31: 859-868.
6. Holding KJ, Dworkin MS, Wan PC, Hanson DL, Klevens RM, et al. (2000) Aspergillosis among people infected with human immunodeficiency virus: incidence and survival. Adult and Adolescent Spectrum of HIV Disease Project. Clin Infect Dis 31: 1253-1257.
7. Vandewoude KH, Dirk Vogelaers D, Blot SI (2006)Aspergillosis in the ICU-The new 21st century problem? Med Mycol 44:71–76.
8. De Carvalho Parahym AM, De Melo LR, De Morais VL, Neves RP (2009) Candidiasis in pediatric patients with cancer interned in a university hospital. Braz J Microbiol 40: 321-324.
9. Raper KB, Fennell DI (1965) The genus Aspergillus. Baltimore: The Williams and Wilkins Company: 686.
10. Gonçalves SS, Stchigel AM, Cano JF, Godoy-Martinez PC, Colombo AL, et al. (2012) Aspergillusnovoparasiticus: a new clinical species of the section Flavi. Med Mycol 50: 152-160.
11. Clinical and Laboratory Standards Institute (2008) Reference method for broth dilution antifungal susceptibility testing of filamentous fungi. Approved Standard-Second Edition. CLSI document M38-A2. Wayne, PA: Clinical and Laboratory Standards Institute.
12. Chamilos G1, Luna M, Lewis RE, Bodey GP, Chemaly R, et al. (2006) Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003). Haematologica 91: 986-989.
13. Denning DW (1998) Invasive aspergillosis. Clin Infect Dis 26: 781-803.
14. Hadrich I, Makni F, Neji S, Cheikhrouhou F, Sellami H, et al. (2011) A review molecular typing methods for Aspergillusflavus isolates. Mycopathologia 172: 83-93.
15. Pagano L, Fianchi L, Caira M (2008) Pulmonaryaspergillosis in hematologic malignancies: lights and shadows. Haematologica 93: 1611-1616.
16. JorienD'Haese J, Theunissen K, Vermeulen E, Schoemans H, VliegerGc, et al. (2012) Detection of Galactomannan in Bronchoalveolar Lavage Fluid Samples of Patients at Risk for Invasive Pulmonary Aspergillosis: Analytical and Clinical Validity. J ClinMicrobiol 5: 1258-1263.
17. Horger M, Einsele H, Schumacher U, Wehrmann M, Hebart H, et al. (2005) Invasive pulmonary aspergillosis: frequency and meaning of the "hypodense sign" on unenhanced CT. Br J Radiol 78: 697-703.
18. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, et al. (1984) Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 100: 345-351.
19. Lin SJ, Schranz J, Teutsch SM (2001) Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 32: 358-366.
20. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, et al. (2008) Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 46: 327-360.
21. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, et al. (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347: 408-415.
22. Seyedmousavi S, Mouton JW, Verweij PE, Brüggemann RJ (2013) Therapeutic drug monitoring of voriconazole and posaconazole for invasive aspergillosis. Expert Rev Anti Infect Ther 11: 931-941.
23. Arendrup MC, BilleJ, Dannaoui E, Ruhnke M, Heusse CP, et al. (2012) ECIL-3 classical diagnostic procedures for the diagnosis of invasive fungal diseases in patients with leukaemia. Bone Marrow Transplant 47: 1030-1045.