Invasive pulmonary aspergillosis

Luís Andrade*, Luís Pedro Tavares*, Paula Ferreira**, José Luís Krug***

Abstract

Aspergillosis is caused by a fungus of the genus Aspergillus, which is present in the environment. Although human colonization is frequent, disease due to tissue invasion is uncommon and occurs primarily in the presence of immunosuppression.

In the majority of cases the prognosis is poor, given the epidemiological characteristics of the affected population and the pathogenesis of this fungus. Early diagnosis and management is therefore essential to control infection, and has repercussions on the prognosis.

Key words: aspergillus, aspergillosis, voriconazole

Introduction

Early diagnosis, although difficult, is very important, bearing in mind the poor prognosis. The authors present a clinical case of a patient admitted to an Internal Medicine Service, and give a brief overview of the theme.

Clinical case

A man aged 49 years, a stonemason, resident in Arouca, with hyperthermia, shivering, hyperhidrosis, cough associated with mucopurulent sputum and dyspnea, since 14 Sept 05.

On the 19th Sept 05 he was seen by the Oncology clinic and admitted to the Internal Medicine Service, due to worsening of the clinical condition.

The following antecedents are highlighted:

- Smoker: 18 pack units per year;
- Alcohol consumption: 100 g alcohol/day;
- Stage IV spinocellular carcinoma of the esophagus (irresectable, with pulmonary and bone metastases), diagnosed in April/05. Began chemotherapy (Cisplatin and 5-Fluorouracil) in May /05 and had the last cycle on 22th August 2005;
- Esophageal prosthesis inserted on 07th July 2005;
- Father died aged 68 (pulmonary neoplasia) and mother died aged 67 (breast neoplasia).

On physical examination, the patient was cooperative and oriented, with poor general condition, pink and hydrated mucosas, and fever (39,5ºC), normotensive (128/66 mmHg), tachycardic (118 bpm), with rhythmic, regular pulse, polypneic (32 cpm) but without chest indrawing; the vesicular murmur was decreased in the lower 1/3 of the right hemithorax, and he had disperse crepitations on the left one; the cardiac auscultation was normal; the abdomen was depressible and painless on palpitation, with no evidence of enlarged organs or palpable masses; he had no peripheral edemas and the ganglionar areas were free.

After analyses *(Table I)*, gasimetry (FiO_2 21%: pH 7,501, $paCO_2$ 36,9, paO_2 53,7, HCO_3 28,2 and Sat. O_2 90,7%) and Chest x-ray *(Fig. 1)* he was admitted with a diagnosis of Pneumonia.

He was initially medicated with piperacillin/tazobactam, with the addition of azithromycin, 2 days later. He showed a slight improvement in cough, dyspnea and expectoration, but the fever remained, therefore chest CT was performed *(Fig. 2)*. The existence of extensive parenchymatous infiltrates with pseudo-nodular appearance, and some cavitations, extending to the left lung field and part of the right lung field, suggested a fungal infection as the most probably hypothesis. Microbiological culture exams of the blood and expectoration were performed (both negative) and Aspergillus precipitin assay (positive) *(Table II)*.

Bearing in mind the presumed diagnosis of invasive pulmonary Aspergillosis, the patient was medicated with Voriconazol 400 mg bid p.o. on the first day and 200 mg bid p.o. on the subsequent days. Considerable clinical and analytical improvement was observed, and the patient was discharged on the

*Internal Medicine, **Oncology and ***Imagiology Services of the Hospital São Sebastião

Received for publication 12 February 2007
Accepted for publication 31 May 2008

9th day of hospitalization and the 3rd day after the start of antifungal treatment, only medication with Voriconazol being maintained.

The good clinical evolution was gradual and sustained, despite the slow imagiological resolution *(Fig. 3, 4 and 5)*. The treatment with Voriconazol was suspended at 13 weeks and the patient remained asymptomatic until February 2006. He was readmitted to the Internal Medicine Service with pericardiac effusion of a neoplasic nature, and died a few days later.

Discussion

Although we do not have a definitive diagnosis, we may be dealing with a case of invasive pulmonary Aspergillosis. The clinical characteristics of the patient, the imagiological alterations, and the existence of positive precipitins led us to consider this diagnosis as highly probable, and to institute therapy as quickly as possible.

The good response to therapy, and the favorable clinical evolution, reinforced our diagnostic "conviction".

Aspergillosis

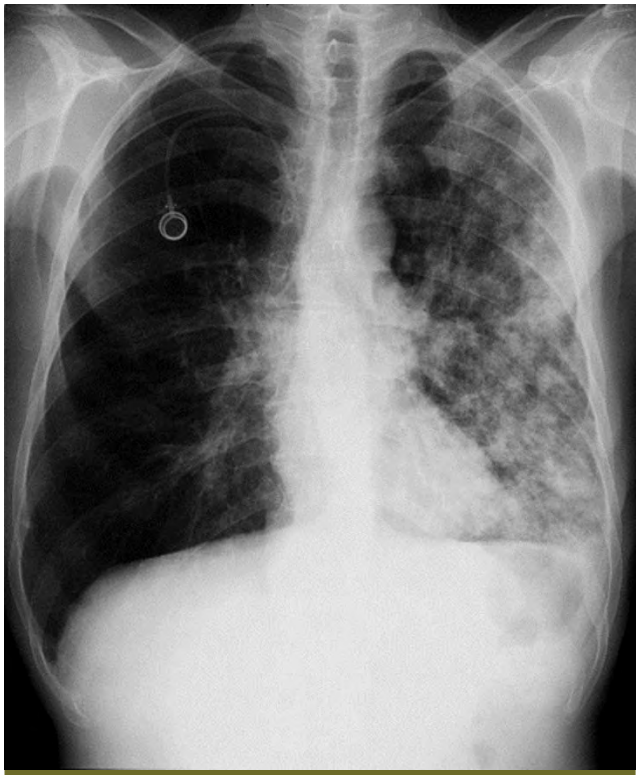
Aspergillus is a microorganism which is widespread in the environment, and exposure to its spores is common.

There are numerous manifestations of infection, varying from allergic manifestations and chronic colonization, to acute disseminated tissue invations.[1] The latter is uncommon, and basically occurs where there is suppression of the immune system. Its incidence has increased in recent years, mainly due to the increase of the population at risk.[1]

TABLE I

Analytical evolution

	19/09	21/09	26/09
Hemoglobin (g/dl)	9,2	8,4	8,9
Leucocytes (/µl)	9300	8800	8300
Neutrophiles (/µl)	7100	6400	5600
Lymphocytes(/µl)	1000	1500	2000
Platelets(/µl)	345000	353000	531000
PCR	—	252	64



Diffuse parenchymatous alveolar infiltrate in the left lung.

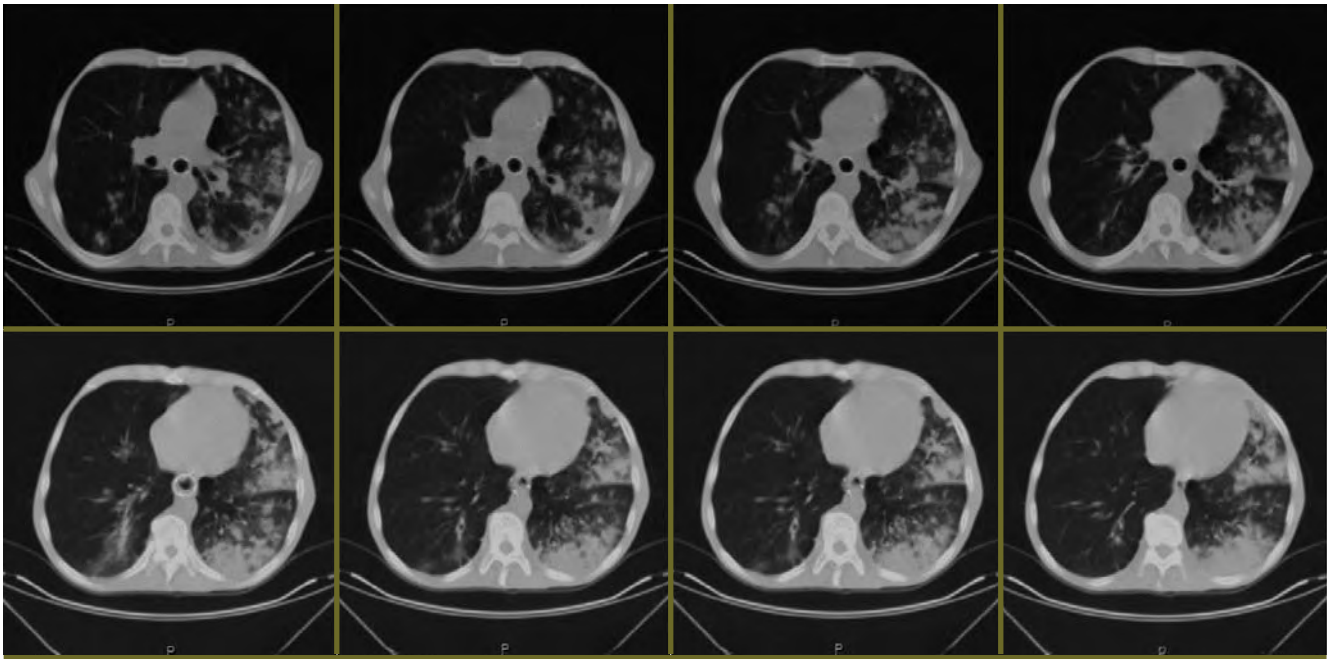
FIG. 1

It is one of the main invasive fungal pathologies in patients in the oncological field (particularly those undergoing chemotherapy), in chronic immunosuppressant therapies (as in the case of transplant patients), long-term corticoid therapy, and in the presence of HIV infection.[2,3,4,5] Less frequently, chronic invasion by Aspergillus has been described in patients with solid tumor and without apparent immunodepression.[6]

Bearing in mind the comorbidities among the population in question and the pathogeny of the fungi, mortality is very high, therefore timely diagnosis and the institution of appropriate therapeutic measures should be rapid, even if these are based *only* on clinical suspicion.

Pathogenesis

Macrophages are the first line of defense against inhaled *conidia* of *Aspergillus* which reach the alveoli. Normally, they are capable of destroying them, but in the presence of high inocula and a decrease in the



Chest CT taken on 22nd Sept 05 showing extensive parenchymatous infiltrates with pseudonodular aspects, and some cavities extending through the left lung field and part of the right lung suggesting infectious etiology, particularly fungal.

FIG. 2

number or dysfunction of immune cells (notably the macrophages), the fungus is able to survive and proliferate, leading to hyphae.[1,7]

Aspergillus produces proteases, oxidative reactive mediators, phospholipases and hemolysins, which facilitate the penetration and destruction of the pulmonary barrier, the acquisition of nutrients, and evasion of the host defenses. One of these substances is *gliotoxin,* which has high capacity to evade the immune system and the defenses, and which:[8]

- Inhibits the action of the T-cells and induces the destruction of monocytes, leading to a marked decrease in the ratio of monocytes to lymphocytes;
- Inhibits the ingestion and destruction of Aspergillus by the macrophages;
- Inhibits activation by the phagocytes of nicotinamide adenine dinucleotide phosphate oxidase (NADPH);
- Induces apoptosis of the cells of the thymus, spleen and lymph nodes;
- Inhibits the activation of the nuclear factor kappa B (NF-kB) of the B and T cells.

Gliotoxin also suppresses the immune response of the T cells following CMV infection, or with stimulation by the staphylococcal enterotoxin B. This fact demonstrates its immunomodulatory capacity, increasing the possibility of infection by another opportunist agent.[8,9]

Infection by *Aspergillus* is characterized, from the histopathological viewpoint, by vascular invasion and destruction, and subsequent infarction and tissue necrosis.

Clinical conduct

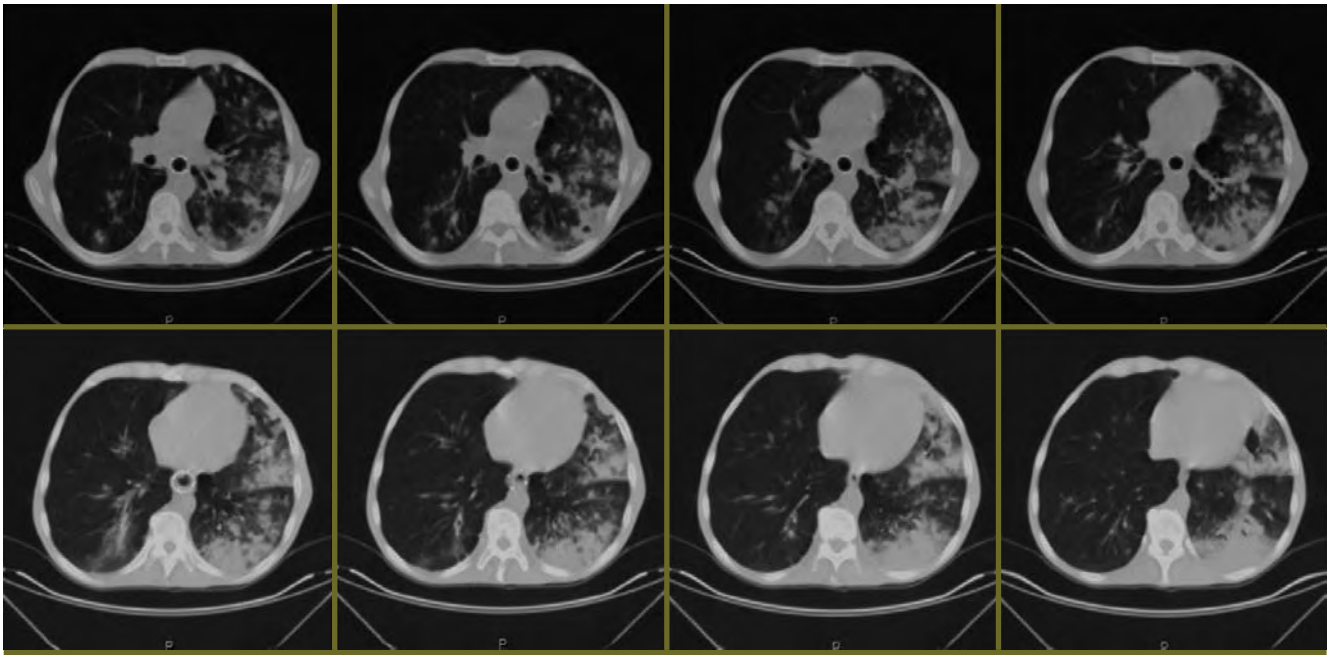
The lungs are the organs most frequently involved in invasive infection, followed by the paranasal sinuses and the central nervous system.

In the case of pulmonary infection, the clinical manifestations are variable; however, patients often present fever, chest pain, cough or hemoptyses.

TABLE II

Contributions for diagnosis

Hemoculture	Negative
Microbiological sputum	Microbe free
Aspergillus precipitins	Positive



Chest CT taken on 10/19/05 - decrease in inflammatory infiltrates of the pulmonary parenchyma.

FIG. 3

The symptoms are not sensitive or specific, and can be found in other situations (e.g. bacterial pneumonia or pulmonary thromboembolism), therefore the epidemiological situation of the patient is extremely important for a differential diagnosis.

Fever is also an important sign of infection, but neutropenic patients, or those undergoing chronic immunosuppressant or corticoid therapy, do always manage to initiate and maintain this response to aggression.

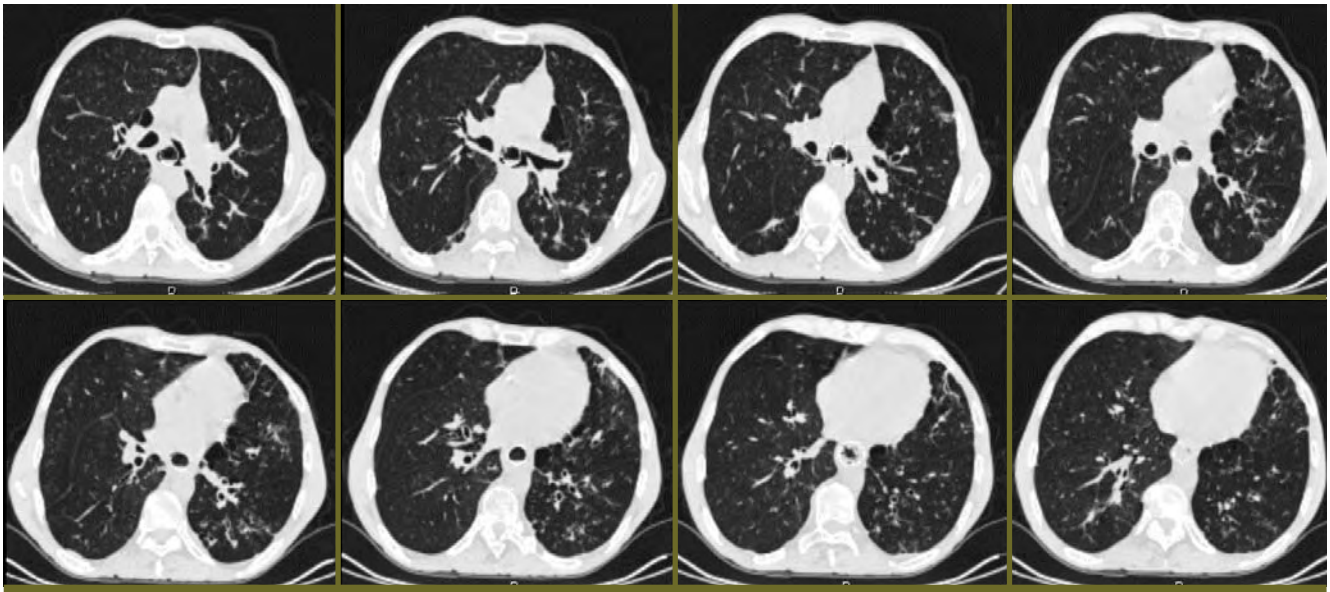
Diagnosis

The Chest radiography (x-ray) is not always suggestive, and can show nodular or cavitated lesions, and heterogenous infiltrates, or shows no relevant alterations.[10] In a series of 595 patients with invasive infection by Aspergillus, whether proven or suspected, around 10% presented no alterations in the chest x-ray.[11]

The CT is more sensitive and can reveal parenchymatous infiltrations, or cavitations caused by tissue necrosis. The progression of the infectious process is characterized by invasion of the small blood vessels, with tissue infarction and hemorrhage. These lesions may be surrounded by a low tonality halo (*halo sign*) or areas of hemorrhage and pulmonary infarction. Despite this sign, it is non-specific, and can appear in other fungal or bacterial infections.[12]

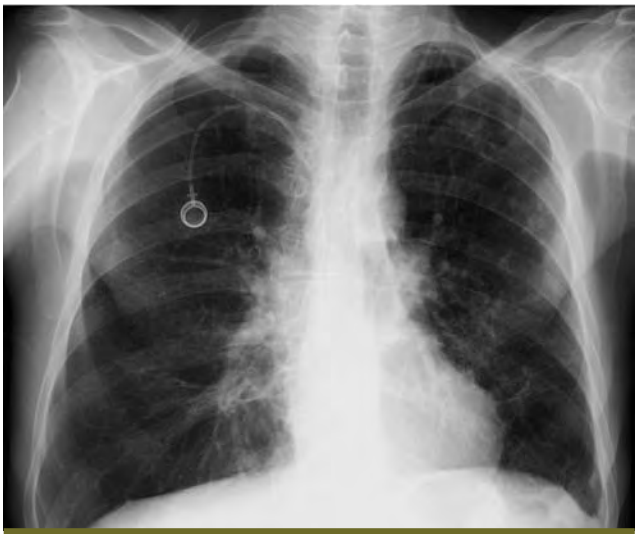
Due to its dissemination in the environment, its isolation in the airways of the patient is not indicative of invasive infection; however, it can be a strong indicator, in a patient with a corresponding epidemiological condition. The positive predictive value can be as high as 80 to 90% in patients with leukemia or who have undergone bone marrow transplant.[13,14] On the other hand, the isolation of the agent in the biopsy of the tissues involved in the infectious process enables a definitive diagnosis of this infection.

Due to the severity of the disease in question, and the debilitated condition of patients, biopsy by bronchofibroscopy or thoracotomy is not always possible, making the idea of the use of other diagnostic methods attractive, such as polimerase chain reaction (PCR) of Aspergillus, and detection of antigens (such as galactomannan) by ELISA. Galactomannan is one the main constituents of Aspergillus, and is released during the growth of the hyphae. Its detection by ELISA is early, enabling the antigen to be determined 5 to 8 days before the appearance of clinical manifestations, imagiological alterations or positivity of the



Chest TC taken on 28/12/05 – discrete images of sequelar fibrosis, resolution of parenchymatous infiltrate.

FIG. 4



Chest x-ray 01/16/2006 – resolution of the parenchymatous infiltrate, discrete images of sequelar fibrosis.

FIG. 5

culture methods. Studies have shown a sensitivity of 81 to 94% and specificity of 89 to 94%.[15] However, the use of piperacillin/tazobactam could lead to false positive results, due to the presence of galactomannan in the formula of the antibiotic.[16] On the other hand, this test also has some unresolved problems, one of which is cut-off.

The methods that use PCR enable the detection of Aspergillus fragments, presenting sensitivity values higher than those of detection of the antigen. However, they were tested in the detection of Aspergillus in body fluids in situations of suspected invasive Aspergillosis, and should be evaluated in future prospective studies.

Therapeutic

Given the poor prognosis, the timely administration of the therapy is extremely important for prognosis.

Correction of the underlying immunosuppression process

The correction of the immunological alteration should be a priority, and in the presence of febrile neutropenia, suspension of the chemotherapy or the administration of myeloid growth factors should be considered.

Medical therapeutic

Amphotericin B and voriconazol are the first line antifungals in the combat of invasive pulmonary Aspergillosis.[17]

Conventional amphotericin B has been the most commonly used drug (1 to 1.5 mg/kg/day). One of

its more dramatic side effects is nephropathy, and an increase in creatinine to 2.5 at 3.0 mg/dl is normally seen, which should be seen as a *normal* occurrence. However, if the values rise beyond these values, the amphotericin can be reduced to 0.7 at 1.0 mg/kg/day, or modified to lipid-enriched formulas, which cause less side effects (namely nephropathy) but are much more costly, and should not be used as first line therapeutic.

Voriconazol has been increasingly used as a valid alternative to amphotericin, as the first line therapeutic for the treatment of this infection. Some studies have shown that voriconazol leads to bettter responses, lower mortality and less side effects than amphotericin B. Another advantage is the oral formula, which is useful for longer term treatment in outpatients.[18,19]

Itraconazol is accepted as an alternative in situations of pulmonary aspergillosis of light to moderate intensity. The oral formula has been used as sequential therapy (400 mg/day), after the administration of endovenous amphotericin.

The precise duration of the therapy is not known, but depends on the level of recovery of immunity. Various authors recommend continuing the treatment for 6 months, or until the clinical and imagiology resolution of the pulmonary lesions.[1]

The therapeutic response is variable, depending on the level of immunosuppression and recovery of the immune system during the therapy.

Surgical therapy

Surgery can be used to remove the infected tissue, or for exeresis of a cavity in patients with isolated pulmonary lesion and recurring hemoptyses or concomitant bacterial infection. Besides the local control of the infection, surgery also provides material for microbiological evaluation, enabling a definitive diagnosis. However, these patients are generally severely debilitated and present hematological alterations (such as thrombocytopenia) which can make surgery more difficult. ■

References

1. Kieren A Marr, Thomas Patterson, David Denning. Aspergillosis pathogenesis, clinical manifestations, and therapy. Infect Dis Clin N Am 2002; 16:875-894.

2. Andriole VT. Aspergillus infections: problems in diagnosis and treatment. Infect Agents Dis 1996 ;5(1):47-54.

3. Castagnola E, Bucci B, Montinaro E, Viscoli C. Fungal infections in patients undergoing bone marrow transplantation: an approach to a rational management protocol. Bone Marrow Transplant 1996 ;18 (Suppl 2):97-106.

4. Jantunen E, Anttila VJ, Ruutu T. Aspergillus infections in allogeneic stem cell transplant recipients: have we made any progress?. Bone Marrow Transplant 2002;30(12):925-929.

5. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002 ;100(13):4358-4366.

6. Ohmagari N, Raad II, Hachem R, Kontoyiannis DP. Invasive aspergillosis in patients with solid tumors. Cancer 2004 ;101(10):2300-2302.

7. Graciete Freitas. Micoses subcutâneas e sistémicas. In: Wanda F. Canas Ferreira, João Carlos F. de Sousa. Microbiologia. Lidel. 2002; Vol 2: 329-343.

8. Segal, B. Mouldy oldy: how fungus lives among us. Blood 2005; 105:2239.

9. Stanzani M, Orciuolo E, Lewis R, Kontoyiannis DP, Martins SL, St John LS, Komanduri KV. Aspergillus fumigatus suppresses the human cellular immune response via gliotoxin-mediated apoptosis of monocytes. Blood 2005;105(6):2258-2265.

10. 8. Rau WS. Aspergillus infections of the lung: radiological signs. Mycoses 1997;40 (2):25-32.

11. Patterson TF, Kirkpatrick WR, White M, Hiemenz JW, Wingard JR, Dupont B, Rinaldi MG, Stevens DA, Graybill JR. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. Medicine (Baltimore) 2000 ;79(4):250-260.

12. Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 1985 ;157(3):611-614.

13. Yu VL, Muder RR, Poorsattar A. Significance of isolation of Aspergillus from the respiratory tract in diagnosis of invasive pulmonary aspergillosis. Results from a three-year prospective study. Am J Med 1986;81(2):249-254.

14. Horvath JA, Dummer. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am J Med 1996;100(2):171-178.

15. Wheat LJ. Rapid diagnosis of invasive aspergillosis by antigen detection. Transpl Infect Dis 2003;5(4):158-166.

16. Walsh TJ, Shoham S, Petraitiene R. Detection of galactomannan antigenemia in patients receiving piperacillin-tazobactam and correlations between in vitro, in vivo, and clinical properties of the drug-antigen interaction. J Clin Microbiol 2004;42(10):4744-4748.

17. Forrest GN, Walsh TJ. Approaches to management of invasive fungal infections in patients with hematologic malignancies. Supportive Cancer Ther 2004; 2:21.

18. Denning DW, Ribaud P, Milpied N et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002 ;34(5):563-571.

19. Herbrecht R, Denning DW, Patterson TF et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347(6):408-415.