

Outbreak of invasive pulmonary aspergillosis among patients hospitalized in a bone marrow transplant ward: tomographic findings*

Surto de aspergilose pulmonar invasiva em enfermaria de transplante de medula óssea: achados tomográficos

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Abstract

Objective: To evaluate the main aspects on CT scans of six patients hospitalized in a bone marrow transplant ward, diagnosed with invasive pulmonary aspergillosis (IPA), during an in-hospital outbreak of the disease. **Methods:** We reviewed 10 chest CT scans of six neutropenic or immunocompromised patients hospitalized in the hematology and bone marrow transplant ward of the *Hospital São Paulo*, in the city of São Paulo, Brazil, who were diagnosed with IPA between April of 2007 and October of 2007. The diagnosis of IPA was confirmed by anatomopathological findings (in 2 cases), culture (in 3 cases) or appropriate treatment response (in 1 case). **Results:** We evaluated the CT scans of three male and three female patients, ranging from 22 to 58 years of age. The most common tomographic findings were nodules (5/6 cases) and areas of consolidation (2/6 cases). The nodules were more often multiple (3/5 cases), with irregular contours (4/5 cases) and accompanied by the halo sign (3/5 cases). One case presented multiple, centrally distributed areas of consolidation, and another presented an isolated, peripheral area of consolidation. Areas of ground-glass attenuation and septal thickening were found in three and two patients, respectively. Bilateral pleural effusion occurred in three cases. **Conclusions:** Consolidation, nodules, septal thickening, pleural effusion and ground-glass opacities were the principal tomographic findings in the six patients hospitalized in the abovementioned ward during the IPA outbreak. The nodules were often (in 67% of the cases) accompanied by the halo sign, a classically described finding in patients with IPA.

Keywords: Aspergillosis; Lung diseases, fungal; Neutropenia; Bone marrow transplantation; Tomography, X-Ray computed.

Resumo

Objetivo: Avaliar os principais aspectos encontrados na TC de seis pacientes internados em uma enfermaria de transplante de medula óssea, diagnosticados com aspergilose pulmonar invasiva (API) durante um surto intra-hospitalar da doença. **Métodos:** Foram revisadas 10 TC de tórax de seis pacientes internados na enfermaria de hematologia e transplante de medula óssea do Hospital São Paulo em São Paulo (SP) entre abril de 2007 e outubro de 2007, neutropênicos ou imunossuprimidos, que evoluíram com API. O diagnóstico de API foi comprovado por exames anatomopatológicos (2 casos), cultura (3 casos) ou por resposta terapêutica adequada (1 caso). **Resultados:** Foram avaliadas imagens tomográficas de três homens e três mulheres com idades variando de 22 a 58 anos. Nódulos (5/6 casos) e áreas de consolidação (2/6 casos) foram os achados tomográficos mais comuns. Os nódulos eram mais frequentemente múltiplos (3/5 casos), de contornos irregulares (3/5 casos) e com sinal do halo (3/5 casos). Foram encontradas consolidações múltiplas e de distribuição central em um caso e consolidação isolada e periférica em outro. Áreas de atenuação em vidro fosco e espessamento septal foram achados, respectivamente, em três e dois pacientes. Derrame pleural bilateral ocorreu em três casos. **Conclusões:** Consolidação, nódulos, opacidades em vidro fosco, derrame pleural e espessamentos septais foram os principais achados tomográficos dos seis pacientes internados na enfermaria acima citada durante o surto de API. O sinal do halo, classicamente descrito na literatura para esta condição, foi um achado frequente quando associado a nódulos (67%).

Descritores: Aspergilose; Pneumopatias fúngicas; Neutropenia; Transplante de medula óssea; Tomografia computadorizada por raios X.

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Financial support: None.

Submitted: 26 January 2009. Accepted, after review: 6 March 2009.

Introduction

Invasive pulmonary aspergillosis (IPA) is a severe infection, generally associated with tissue destruction, that affects immunocompromised patients.⁽¹⁾ The principal risk factors for IPA are prolonged neutropenia (granulocyte count lower than 500 cells/ μ L for more than 10 days) and myeloablative chemotherapy or bone marrow transplantation (BMT) due to hematologic malignancies.^(1,2)

The frequency of IPA ranges between 5% and 15% in patients submitted to BMT, and it is approximately 70% after 34 days of neutropenia in individuals with any kind of hematologic malignancy.⁽²⁻⁵⁾ In addition to being commonly found in such patients, IPA presents mortality rates as high as 94% according to certain studies.^(2,4,6,7) This is probably due, at least in part, to the difficulty in diagnosing the disease in an early phase and, consequently, to the delay in initiating antifungal therapy.⁽⁸⁾

The gold standard for the diagnosis of IPA is the histopathological finding of tissue invasion by the microorganism.^(8,9) However, histopathological studies require an invasive procedure that is difficult to execute in these patients, who are immunocompromised or have pancytopenia. The efficacy of bronchial lavage is variable (0-93%), being approximately 50% in most studies.^(6,10) In addition, noninvasive molecular techniques for detecting *Aspergillus* sp. antigens (galactomannan) in the blood or in the bronchial lavage fluid have not been clearly defined and present limited practical application.^(6,8,9) One group of authors⁽¹¹⁾ demonstrated that IPA lesions on chest CT scans precede the detection of the galactomannan antigen in serum through molecular

biology. Therefore, chest CT has been recommended as the principal method for establishing an early diagnosis of IPA.^(8,9)

Since it is essential to recognize tomographic alterations in order to diagnose and determine the prognosis of patients with IPA, the purpose of the present study was to evaluate the principal aspects on chest CT scans of six patients hospitalized in a hematology/bone marrow transplant ward and evolving to IPA.

Methods

We reviewed 10 chest CT scans of six neutropenic or immunocompromised patients hospitalized in the hematology and bone marrow transplant ward of the São Paulo Hospital/Paulista School of Medicine, São Paulo, Brazil, who were diagnosed with IPA between April of 2007 and October of 2007. The cases occurred during the remodeling of the physical structure of the institution and, based on previous years, exceeded the number of cases expected for the period in question. The present study was approved by the Research Ethics Committee of the Federal University of São Paulo/Paulista School of Medicine.

The patients were three males and three females, ranging from 22 to 58 years of age (mean age: 41.5 years). Five patients were neutropenic at the time of diagnosis, and one of them was immunocompromised due to BMT (corticosteroid therapy for more than 60 days). The interval between the onset of neutropenia and the diagnosis of IPA was 16 days on average, ranging from 10 to 25 days. The underlying disease was acute leukemia in four patients, chronic leukemia in one patient and

Table 1 – Clinical and radiological characteristics of the patients under study.

Patient/Gender/ Age (years)	Underlying malignancy	Neutrophil count (cells/ μ L)	Principal tomographic findings
1/M/40	BL	14	Central areas of consolidation and irregular nodules with the halo sign, septal thickening and bilateral pleural effusion
2/M/22	ALL	50	Solitary nodule of regular contours and the halo sign
3/F/25	ALL	24	Solitary nodule of regular contours
4/F/52	CML	27	Nodule accompanied by the halo sign
5/M/58	AML	3	Peripheral consolidation and bilateral pleural effusion
6/F/52	AML and BMT	Normal ^a	Multiple nodules of irregular contours, septal thickening and bilateral pleural effusion

BL: biphenotypic leukemia; ALL: acute lymphoid leukemia; CML: chronic myeloid leukemia; AML: acute myeloid leukemia; and BMT: bone marrow transplantation. ^aImmunosuppression.

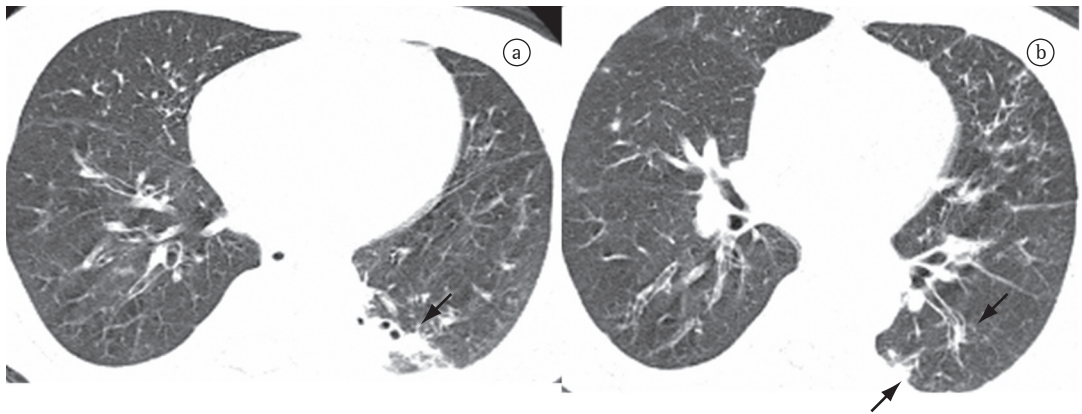


Figure 1 – Chest CT scan showing multiple nodules of irregular contours (black arrows).

biphenotypic leukemia in one patient. All patients presented clinical and host criteria for invasive aspergillosis (IA) at the time of diagnosis, according to the criteria established by the committee composed of members of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC).⁽⁹⁾ The diagnosis of IA was confirmed through histopathological examination (2/6 cases), bronchial lavage fluid culture (1/6 cases), sputum culture (2/6 cases) or appropriate treatment response (1/6 cases). Therefore, according to the EORTC criteria,⁽⁹⁾ three patients were classified as confirmed cases of IA, two were classified as probable cases of IA, and one was classified as a possible case of IA.

Among the CT scans of the patients under study, we selected for analysis those that dated closer to the time of anatomopathological or bacteriological diagnosis of IPA. The CT scans

were taken using HRCT (1-mm thick slices and 10-mm intervals) and spiral CT (7-mm thick slices and 10-mm intervals). For image analysis, lung parenchyma windows ranging from 1,200 to 1,600 HU, with the center ranging from -450 to -650, and mediastinal windows ranging from 250 to 500 HU, with the center ranging from 30 to 50 HU, were used.

The scans were independently reviewed by two radiologists. In discrepant cases, a consensus was reached. The terminology used was that recommended by the Terminology Consensus of the Brazilian College of Radiology.⁽¹²⁾

Results

The most common tomographic findings were as follows: nodules (5/6 cases); areas of ground-glass attenuation (3/6 cases); bilateral pleural effusion (3/6 cases); areas of consolidation (2/6 cases); and septal thickening (2/6 cases).

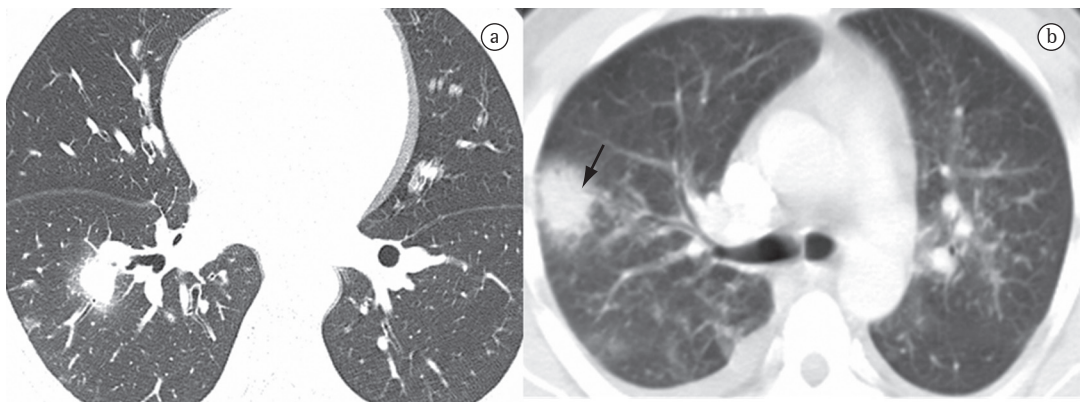


Figure 2 – Chest CT scan showing lung nodules with the halo sign (black arrows). The nodule has regular contours in a) and irregular contours in b).

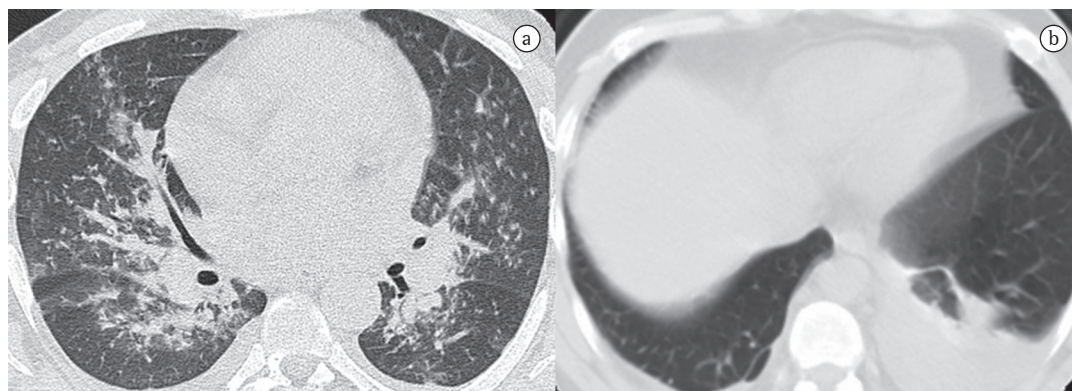


Figure 3 – Chest CT scan showing multiple, centrally distributed, areas of consolidation in a) and an isolated, peripheral area of consolidation in b). Note also bilateral pleural effusion.

The clinical and radiological characteristics of the patients under study are summarized in Table 1.

The nodules were more often multiple (3/5 cases), with irregular contours (3/5 cases; Figure 1). The halo sign was observed in three of the five cases of nodules (67%; Figure 2).

One case presented multiple, centrally distributed areas of consolidation, and another presented an isolated, peripheral area of consolidation (Figure 3). One case presented areas of consolidation and nodules.

As associated findings, areas of ground-glass attenuation and septal thickening were found in three and two patients, respectively. Bilateral pleural effusion, generally in small quantities, occurred in three cases.

Discussion

The present study described the tomographic findings in six patients with leukemia after chemotherapy or BMT, diagnosed with IPA.

In neutropenic patients, the presence of *Aspergillus* sp. deep in the basal membrane is considered diagnostic of IA.⁽¹³⁾ In such cases, *Aspergillus* sp. invades blood vessels, resulting in thrombosis and subsequent hemorrhagic pulmonary infarction.^(1,14,15) When the anatomopathological findings are correlated with the tomographic findings, foci/areas of infarction can present as nodules or as consolidation in the shape of a wedge, with a pleural base.^(2,16) Either finding can be accompanied by the halo sign,

Table 2 – Frequency (in %) of the tomographic findings in patients with invasive pulmonary aspergillosis reported in the literature.

Study	n	Nodule	Consolidation	Halo	PE	GG	ST	Crescent
Freitas	6	83	33	63	50	50	33	0
Althoff ⁽¹⁶⁾	32	84	84	NA	NA	44	NA	16
Brodoefel ⁽²⁾	40	72.5	15	87.5	NA	NA	NA	45
Bruno ⁽⁶⁾	68	76.5	24	25	NA	NA	NA	9
Caillot ⁽¹⁷⁾	25	96	NA	100	NA	NA	NA	8
Hachem ⁽⁸⁾	47	32	13	NA	NA	NA	NA	NA
Haugard ⁽³⁾	21	95	57	100	NA	NA	NA	10
Horger ⁽¹⁹⁾	46	64	26	82	NA	NA	25	63
Kuhlman ⁽¹⁵⁾	9	100	11	22	NA	NA	NA	66
Leão ⁽¹⁸⁾	19	31.6	63.2	83.3	36.8	15.8	10.5	NA
Logan ⁽¹³⁾	9	55	44	NA	NA	11	NA	NA
Won ⁽¹⁴⁾	5	40	80	100	NA	NA	NA	NA

Halo: nodule accompanied by the halo sign; PE: pleural effusion; GG: areas of ground-glass attenuation; ST: septal thickening; Crescent: the air crescent sign; and NA: not available.

which would correspond to alveolar hemorrhage accompanied by inflammation.^(2,3)

Nodules and areas of consolidation are the principal findings in patients with IPA.^(2,3,8,13-19) According to one group of authors,⁽¹⁵⁾ nodules are the initial findings, and a halo sign is indicative of progression to consolidation and, subsequently, cavitation. Therefore, the variation in the time elapsed between the onset of the pathophysiology of IA and the time of diagnosis might explain why certain studies report nodules as being the most common finding and others report areas of consolidation as being the most common finding.

Pleural effusion, septal thickening and areas of ground-glass attenuation (as were found in the present case series) accompanied by nodules and areas of consolidation have also been described in the literature, at varying frequencies of occurrence.^(2,3,8,13-19) Table 2 summarizes the frequency of our findings in relation to that of other studies.

The halo sign was first described in 1985 by Kuhlman et al. and is considered highly suggestive of IPA.⁽¹⁵⁾ One group of authors reported that the frequency of the halo sign decreases with time in the course of IPA, suggesting that the halo sign is useful for the early diagnosis of IPA and therefore correlates with a better prognosis.⁽¹⁹⁾ According to the EORTC criteria, the finding of the halo sign in a specific population warrants antifungal therapy initiation.⁽⁹⁾ In the present study, the nodules were often (in 67% of the cases) accompanied by the halo sign, which is in accordance with the literature regarding the frequency of such finding (ranging from 20% to 100%) in patients with IPA.^(2,3,6,8,15-17,19) Other authors have suggested that the halo sign can also be used as a marker of fungal activity and therefore as a marker of treatment response.⁽²⁾

Although the halo sign is the most suggestive tomographic finding for the diagnosis of IPA, its sensitivity and specificity are controversial issues in the literature. The halo sign has also been reported in association with other fungal infections (mucormycosis and actinomycosis), bacterial infections (*Pseudomonas* sp. and *Legionella* sp.) and viral infections (herpes simplex and cytomegalovirus), as well as with certain noninfectious processes such as Wegener's granulomatosis, Kaposi's sarcoma, bronchioloalveolar carcinoma and metastasis.^(2,8,19,20) Particularly in immuno-

compromised patients, the halo sign has been linked to IPA, Kaposi's sarcoma and lymphoproliferative disorders.⁽²⁰⁾ However, most of the studies of IPA that address the tomographic finding of the halo sign are retrospective and include individuals in different phases of the disease, which results in great variation in the evaluation of the sensitivity and specificity of such sign.

Some studies have demonstrated that, principally after antifungal therapy initiation and on average 16 days after diagnosis,⁽²⁾ fragments of lung infarction can detach themselves from the adjacent parenchyma, resulting in air-filled cavitation in the shape of a crescent (the air crescent sign).^(14,15) Such sign was not, however, found in the present study, which is probably due to methodological issues, since our sample was small and we selected CT scans that were obtained as close as possible to the time of diagnostic confirmation, before treatment initiation.

In conclusion, nodules, consolidation, septal thickening, pleural effusion and ground-glass opacities were the principal tomographic findings in the six patients hospitalized in the hematology and bone marrow transplant ward during the IPA outbreak. The nodules were often (in 67% of the cases) accompanied by the halo sign, a classically described finding in patients with IPA. Therefore, chest CT scans of patients with leukemia after chemotherapy or BMT who are diagnosed with IPA can play an important role in early diagnosis, in early antifungal therapy initiation and, consequently, in improving the chance of survival in such cases.

Acknowledgments

The authors are especially grateful to Dr. Matheus Gonçalves and Dr. Carlos Alberto Pereira for their aid in collecting the clinical data related to the patients included in the present study.

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