COMPUTED TOMOGRAPHY IN THE ASSESSMENT OF ANGIOINVASIVE PULMONARY ASPERGILLOSIS IN PATIENTS WITH ACUTE LEUKEMIA*

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Abstract **OBJECTIVE: The aim of this study was to evaluate the main findings of computed tomography in patients presenting acute leukemia complicated by angioinvasive aspergillosis. MATERIALS AND METHODS: Computed tomography images of 19 patients were retrospectively studied for the presence of consolidations, nodules and masses, with or without presentation of halo sign, cavitation and air crescent sign. RESULTS: Consolidation was the most frequent finding, occurring in 12 of the 19 cases, most of them presenting the halo sign; cavitation was found in 5 of 12 cases, one of them with air crescent sign. Nodules and masses occurred respectively in six and four cases, most of them with halo sign. Cavitation was found in only one case of mass. Other findings observed were: crazy-paving pattern (two cases), patchy areas of ground-glass attenuation opacity (three cases) and pleural involvement (seven cases) under the form of effusion or thickening. CONCLUSION: Areas of consolidation, mass or nodule, even a solitary one, presenting halo sign on CT images evaluated in an appropriate clinical context are highly suggestive of angioinvasive aspergillosis.**
Keywords: Angioinvasive pulmonary aspergillosis; Acute leukemia; Computed tomography.

Resumo *Tomografia computadorizada na avaliação da aspergilose pulmonar angioinvasiva em pacientes com leucemia aguda.*

OBJETIVO: O objetivo deste trabalho foi avaliar os principais achados na tomografia computadorizada de pacientes portadores de leucemia aguda complicada com aspergilose pulmonar angioinvasiva. MATERIAIS E MÉTODOS: Foram estudadas, retrospectivamente, tomografias computadorizadas de 19 pacientes, avaliando-se a presença de consolidações, nódulos e massas, com ou sem sinal do halo, escavação e sinal do crescente aéreo. RESULTADOS: Áreas de consolidação foram o achado mais comum, ocorrendo em 12 dos 19 casos. A maioria delas apresentou o sinal do halo, enquanto escavação foi encontrada em 5 dos 12 casos com consolidações, sendo um deles com sinal do crescente aéreo. Nódulos e massas ocorreram em, respectivamente, seis e quatro casos, a maioria com sinal do halo. Escavação foi encontrada em apenas um caso de massa. Outros achados observados foram pavimentação em mosaico (dois casos), áreas de vidro fosco esparsas (três casos) e envolvimento pleural (sete casos), sob a forma de derrame ou espessamento. CONCLUSÃO: Áreas de consolidação, massas ou nódulo, mesmo solitário, com sinal do halo, quando vistos na tomografia computadorizada em um contexto clínico apropriado, são altamente sugestivos de aspergilose angioinvasiva.
Unitermos: Aspergilose pulmonar angioinvasiva; Leucemia aguda; Tomografia computadorizada.

INTRODUCTION

Pulmonary aspergillosis is a mycotic infection caused by species of *Aspergillus*, usually *A. fumigatus*, whose main presentations are allergic bronchopulmonary aspergillosis and sensitivity pneumonitis, which are the most frequent forms of hypersensitivity reaction against the *Aspergillus*, aspergilloma, semi-invasive aspergillosis and invasive aspergillosis. The disease is characterized by a spectrum of clinical and radiological findings directly related to the immunologic condition of the host or to the presence of structural pulmonary disease[1–3].

The invasive form of pulmonary aspergillosis occurs primarily in deeply immunocompromised individuals, especially in patients presenting malignant hematological disease, most commonly acute leukemia. Invasive pulmonary aspergillosis may be bronchoinvasive or angioinvasive, clinically very similar, but presenting different radiological and histological aspects. The angioinvasive form is the most frequent one[4–6].

Computed tomography (CT), especially high resolution computed tomography (HRCT), has been systematically utilized to support the early diagnosis of angioinvasive aspergillosis, allowing an effective antifungal treatment and consequential improvement of the disease prognosis[7–9].

The most significant radiological finding is the halo sign, characterized by a halo of ground-glass attenuation surrounding the nodule, mass or consolidation, highly indicative of angioinvasive aspergillosis,

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detectable only early in the course of the disease, i.e. during the neutropenic period. Cavitation frequently develops later in the course of immunological recovery[4,10–13].

The present study objective was to evaluate the main findings on chest CT images of 19 patients with acute leukemia associated with angioinvasive pulmonary aspergillosis.

MATERIALS AND METHODS

The retrospective analysis covered 19 chest CT of patients presenting acute leukemia with angioinvasive pulmonary aspergillosis diagnosis confirmed by anatomopathological studies, clinical radiological correlation or an appropriate therapeutic response. These cases were randomly gathered from files of several institutions in Rio de Janeiro, São Paulo and Salvador – Brazil.

In this study, an adequate standardization of protocols was unfeasible because CT imaging was performed in different institutions. The greatest part of the CT examinations applied the high-resolution technique, consisting of very narrow X-ray beam collimation (1-2 mm thick slices) at 10 mm intervals, from the pulmonary apex to the diaphragmatic cupula, and a so called "high spatial reconstruction algorithm, in a supine patient. Images were recorded on radiological films with windows ranging between 1,200 and 1,600 UH and center between –450 and –650 UH for evaluating pulmonary parenchyma, and windows ranging between 250 and 500 UH, and center between 30 and 50 UH for evaluating mediastinum, depending on the equipment utilized in each institution.

The images were independently analyzed by two radiologists and decisions were made by consensus.

The criteria for definition of tomographic patterns are in compliance with the Fleischner Society Definitions[14]. The terminology applied was that of the consensus elaborated by Colégio Brasileiro de Radiologia (Brazilian College of Radiology)[15].

RESULTS

The study covered 19 cases of angioinvasive pulmonary aspergillosis in patients with acute leukemia, 12 female and seven male, age range between two and 72 years, mean age 36 years.

Consolidation occurred in 12 of the 19 cases (63.2%) (Figure 1), three of them (25%) associated with nodules. In eight cases (66%), consolidations were multiple and in four (33.3%), solitary. As for localization, consolidations were peripheral in ten of 12 cases (83.3%) and central in five (41.6%) and, in three of these 12 cases, both (peripheral and central) were associated (25%). Air bronchogram was observed in six patients (50%). Halo sign was found in nine of the 12 cases of consolidation (75%), while cavitation occurred in six of

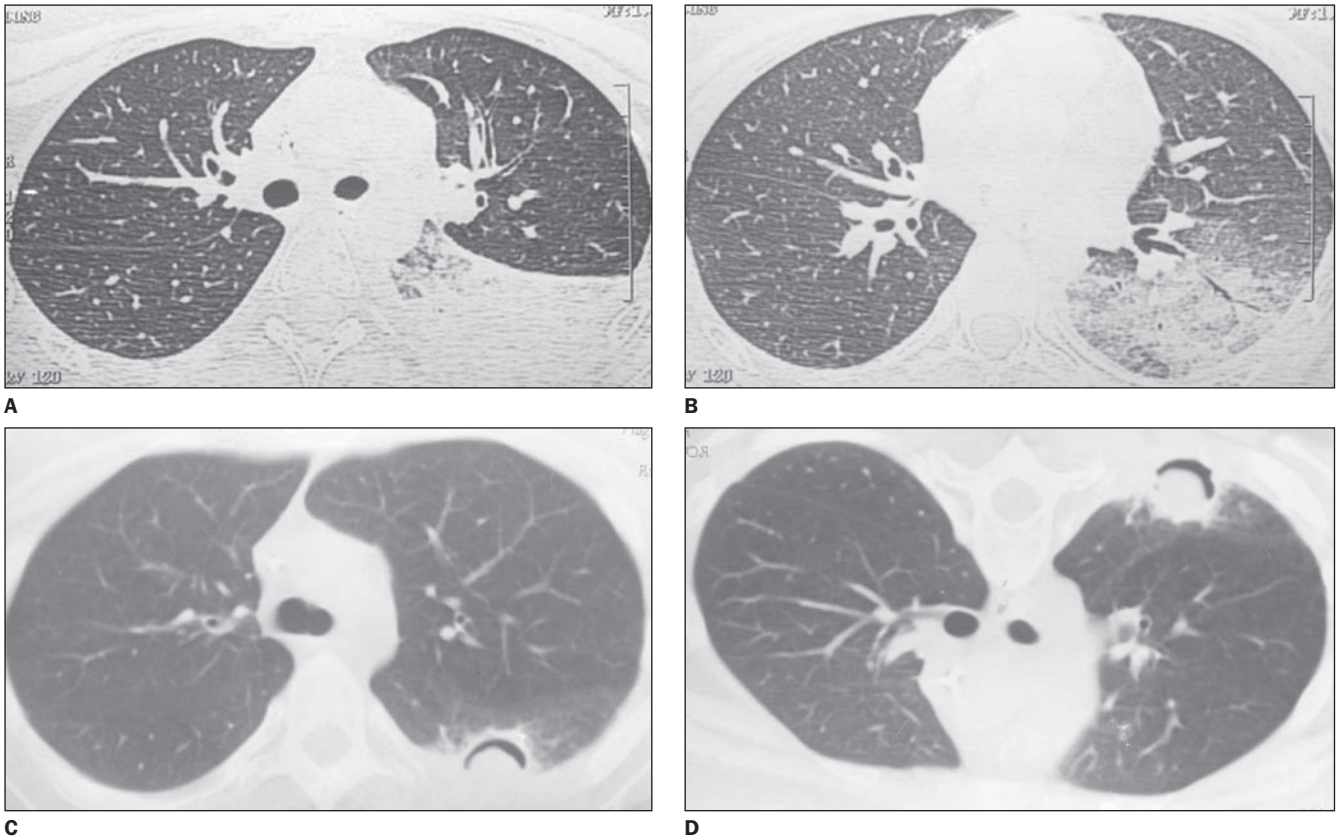


Figure 1. On **A** and **B**, HRCT images demonstrating consolidation in the lower left lobe, with air bronchograms associated with areas of ground-glass attenuation. On **C**, CT scan performed 13 days after, demonstrated that the consolidation had been partially reabsorbed and suffered cavitation and now a cavity is observed containing mobile material with density in the soft parts with change in decubitus (**D**), and air surrounding the cavity wall, forming the air crescent sign.

these cases (50%), two with air crescent sign (16.7%).

Nodules were found in six of the 19 cases (31.6%) (Figure 2A), multiple in five (83.3%) and solitary in only one case (16.7%). In four (66.7%) of the six cases, nodules presented well-defined borders. Small nodules occurred in all of the six cases (100%), and in one of them small and large nodules were associated. Halo sign was observed in five of the six cases (83.3%), while in none of them cavitation was found.

Masses with irregular contour were found in four of the 19 cases (21.1%) (Figures 2B and 2C), three of them being solitary. Halo sign surrounding these masses was observed in three (75%) of the four cases, while cavitation occurred in only one of these cases (25%).

Areas of ground-glass attenuation non-associated with nodules and consolidations were found in three of the 19 cases (15.8%).

Superimposition of ground-glass opacities and thickened interlobular septa (crazing paving) was found in two of the 19 cases (10.5%), one of them associated with masses and another with consolidation (Figure 3).

Pleural involvement occurred in seven cases (36.8%), in three of them under the form of a very small effusion (42.9%) and in the other four, as pleural thickening (57.1%). The finding was unilateral in four (57.1%) and bilateral in three cases (42.9%).

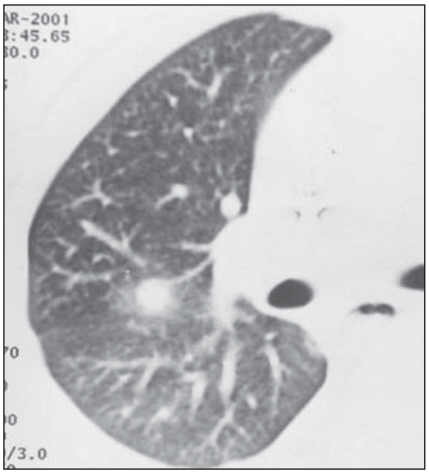
DISCUSSION

All of the 19 patients with angioinvasive pulmonary aspergillosis were immunocompromised as a result of chemotherapy for treatment of acute leukemia which is in compliance with the literature since it describes extended granulocytopenia in patients undergoing treatment with chemotherapy as the most usual context where the angioinvasive pulmonary aspergillosis develops[4,7,10,16,17]. There are studies demonstrating that about 50% of neutropenic patients undergoing treatment with chemotherapy, or submitted to bone marrow transplantation, present severe fungal infection at some phase of their evolution[16,18].

Clinical and radiographic presentations of angioinvasive pulmonary aspergillosis are similar to those of other infectious pneumonias. Additionally, by the time when the antifungal therapy could change the patient's survival, the sputum culture results positive in less than 10% of patients, and invasive procedures like biopsy usually are contraindicated because of severe thrombocytopenia and respiratory compromising, besides presenting a very low diagnostic sensitivity and high rates of false-negative results[4,10–12,16].

Computed tomography has produced a high impact on the conduct in relation to patients with angioinvasive pulmonary aspergillosis, since it is an important resource for the early diagnosis of this disease, especially when invasive procedures offer high risks. Compared to CT, HRCT provides a more clear definition of lesions, particularly ground-glass opacities present in the early phases of the disease[1,4,8,10–12,16–18].

Recent studies have reported the relevance of HRCT for the early diagnosis of angioinvasive pulmonary aspergillosis, through the detection of the typical halo sign. This sign is highly suggestive for the diagnosis of angioinvasive pulmonary aspergillosis in an early phase when radiographic findings are non-specific and the sputum culture presents negative results[4,9–11,16]. Although non-pathognomonic and possibly associated with a range of infectious and non-infectious processes, the halo sign is highly suggestive of angioinvasive pulmonary aspergillosis when detected in neutropenic patients, and some authors consider it sufficiently characteristic to jus-



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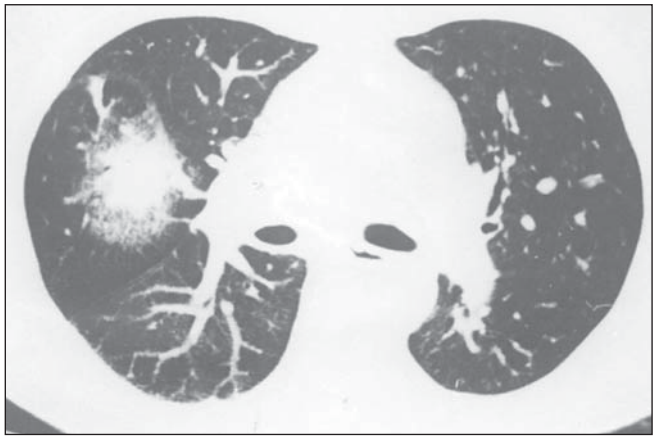

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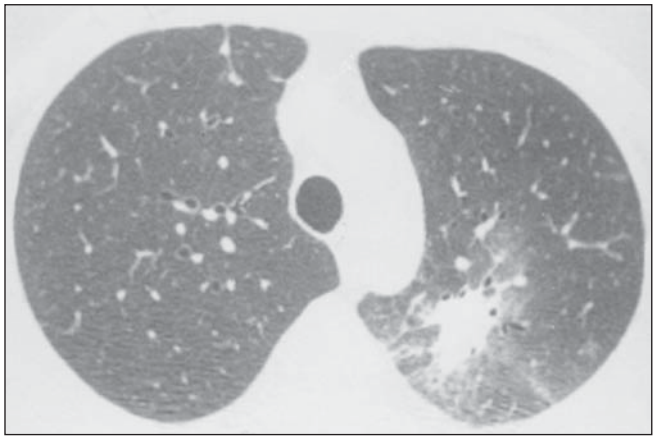

C

Figure 2. HRCT images of three different patients, presenting halo sign. On **A**, nodule with halo sign in the middle lobe. On **B** and **C**, masses with halo sign, one of them in the middle lobe, and another in the upper left lobe.

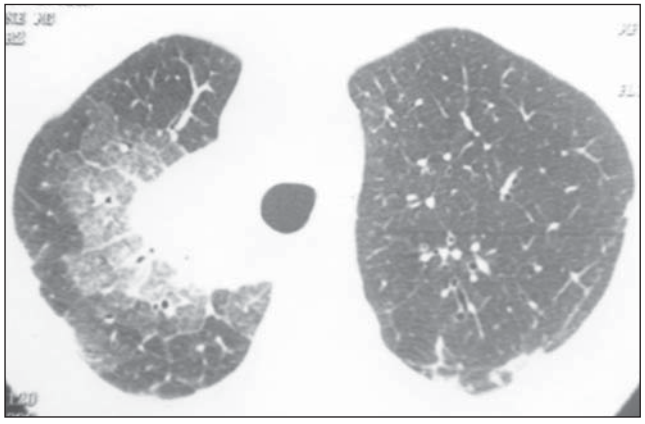

Figure 3. HRCT image showing parenchymal consolidation surrounded by area with ground-glass attenuation localized in the right upper lobe; associated with thickened septa, characterizing mosaic pattern of attenuation (crazy paving). Discreet opacities in the region of the left upper lobe.

tify the commencement of the antifungal therapy[4,8,10,18,19].

Another finding considered as suggestive of angioinvasive pulmonary aspergillosis is the air crescent sign when associated with an appropriate clinical presentation. However, contrarily to the halo sign, the air crescent sign appears later in the course of the disease and is seen in the phase of the infection resolution, coinciding with the improvement of neutropenia. This fact makes the clinical value of this finding limited in the early diagnosis of the disease, but is reported as an indication of good prognosis[4,8,10,11,16,18,19].

Won *et al*.[19] have found consolidation in 80% of leukemic patients with angioinvasive pulmonary aspergillosis, such consolidations being associated with nodules in 20% of the cases, a data that is similar to those found in this study, where consolidations occurred in 12 of 19 cases (63%), and associated with nodules in 25% of cases. Consolidations were predominantly peripheral in 83.3% in this casuistic, while in the great majority of studies in the literature these percentages have reached approximately 100%. In our study, consolidations were multiple in 66.6% of cases which is in agreement with authors like Kuhlman *et al*.[11] and Won *et al*.[19].

The halo sign in consolidations was found in nine of our 12 cases (75%), which coincides with the findings of Won *et al*.[19], where this percentage was 81%. Cavitation was observed in just six of our 12 cases (50%), with air crescent sign in only two of them. Franco *et al*.[16] have found consolidation in two of their seven cases (28.5%), both cavitary, one of them with air crescent sign. Kuhlman *et al*.[4] have found cavitary consolidations in five of the seven cases (71.4%).

In our study, nodules occurred in 31.6% of cases, 83.4% being multiple and 16.7% solitary, which is different from the study of Kuhlman *et al*.[9], whose percentages were respectively 55% and 45%.Well defined nodules were found in 66.7% of our cases, differently from studies like that of Franco *et al*.[16], where all the nodules presented regular contours.

A ground-glass halo was found in 83.4% of cases presenting nodules, which is in agreement with the studies of Kuhlman *et al*.[11] and Franco *et al*.[16], where the halo sign in nodules was found respectively in 88.8% and 80% of cases. On the other hand, Mori *et al*.[18] and Won *et al*.[19] have found this sign respectively in only 19% and 40% of cases. No cavitation was found in any case, differently from the findings of Kuhlman *et al*.[11], where cavitation was observed in five of seven cases (71.4%). In the histopathological study areas of necrosis were found with radially-disposed hyphae in the central region of the lesions, involved by inflammatory cells and blood-filled alveoli. This finding is compatible with those of the studies of Logan *et al*.[9] and Santos *et al*.[20].

Masses were found in 21% of our cases, the halo sign being present in 75% of them. This finding is different from those of Kuhlman *et al*.[11], whose percentages were respectively 55% and 22%. Cavitation was found in only one of our cases of mass (25%), while Kuhlman *et al*.[4] observed percentages of up to 71%.

Pleural involvement was observed in seven of our patients (35%), similarly to the majority of the referred authors[7,20,21]. In five cases, the pleural involvement occurred in the form of an effusion, while in the other two cases only pleural thickening was observed, probably with no relationship with the fungal lesion.

The mosaic pattern of attenuation (crazy paving) (thickened interlobular septa associated with ground-glass opacity) occurred in two cases (10.5%), which is in agreement with the findings of Franco *et al*.[16], who have found this aspect in only one of the eight cases studied (12.5%). Data in the literature about this finding in patients with angioinvasive pulmonary aspergillosis are scarce, difficulting its analysis.

The clinical diagnosis of angioinvasive pulmonary aspergillosis is difficult and, generally, the prognosis is poor, with very high mortality rates. The role of computed tomography, especially HRCT, has become significant in the whole course of the disease, from its early detection, indicating the commencement of the antifungal therapy, to the monitoring of possible recurrences during the chemotherapy treatment[10,12,16]. So, in patients with neutropenia under the risk of angioinvasive pulmonary aspergillosis, the systematic use of HRCT is justified since this is the best way to establish an early and probably specific diagnosis, once the halo sign is detected. Because of the short period during the course of the disease in which the halo sign is detectable by HRCT, the scan should be performed as soon as the clinical suspicion is raised, allowing an early diagnosis with a consequential effect on the morbidity and mortality rates. Additionally, HRCT is a rapid and non-invasive method, while invasive procedures like biopsy usually are contraindicated because of the poor condition of the patients and because sputum culture usually presents positive results in less than 10% of cases[4,8,11,12,18].

Serial CT studies also have played a significant role in the follow-up of such patients, since findings like cavitation usually represent a phase of immunological recovering with reabsorption of devitalized tissue[8,10].

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