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High-resolution computed tomographic findings of *Aspergillus* infection in lung transplant patients

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ABSTRACT

Objective: The aim of this study was to assess high-resolution computed tomographic (HRCT) findings at presentation in lung transplant patients diagnosed with pulmonary *Aspergillus* infection.
Materials and methods: We retrospectively reviewed HRCT findings from 23 patients diagnosed with pulmonary aspergillosis. Imaging studies were performed 2–5 days after the onset of symptoms. The patient sample comprised 12 men and 11 women aged 22–59 years (mean age, 43.6 years). All patients had dyspnea, tachypnea, and cough. Diagnoses were established with Platelia *Aspergillus* enzyme immunoassays for galactomannan antigen detection in bronchoalveolar lavage and recovery of symptoms, and HRCT findings after voriconazole treatment. The HRCT scans were reviewed independently by two observers who reached a consensus decision.
Results: The main HRCT pattern, found in 65% ($n = 15$) of patients, was centrilobular tree-in-bud nodules associated with bronchial thickening. This pattern was described in association with areas of consolidation and ground-glass opacities in 13% ($n = 3$) of patients. Consolidation and ground-glass opacities were the main pattern in 22% ($n = 5$) of patients. The pattern of large nodules with and without the halo sign was observed in 13% ($n = 3$) of patients, and were associated with consolidation and ground-glass opacities in one case.
Conclusion: The predominant HRCT findings in lung transplant patients with pulmonary aspergillosis were bilateral bronchial wall thickening and centrilobular opacities with the tree-in-bud pattern. Ground-glass opacities and/or bilateral areas of consolidation were also common findings. Pulmonary nodules with the halo sign were found in only 13% of patients.

1. Introduction

Lung transplantation is an important treatment modality for many end-stage lung diseases [1–3]. However, the long-term survival of patients undergoing lung transplantation remains relatively limited compared with survival rates in those receiving other solid organ transplants (SOTs) [1–3]. Infection is a significant problem and major cause of mortality after lung transplantation. *Aspergillus* infection, documented in 6–8% of all lung transplant recipients, is among the most significant opportunistic infections after lung transplantation [1–5].

In severely immunocompromised individuals with pulmonary aspergillosis, computed tomography (CT) commonly reveals a combination of poorly defined nodules, cavitary opacities, wedge-shaped pleural-based consolidation, ground-grass opacities, and nodules surrounded by a halo of ground-glass attenuation ("halo sign") [6]. In the later stages of infection, an air crescent is frequently observed. The evaluation of CT findings in association with the results of serum galactomannan (GM) assays has been reported to help predict the outcome of empirical antifungal therapy in patients undergoing allogeneic hematopoietic stem-cell transplantation [6,7].

However, few reports have described the CT findings of aspergillosis in patients after lung transplantation [8,9]. The aim of this study was to assess high-resolution computed tomography

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(HRCT) findings at presentation in lung transplant patients diagnosed with pulmonary *Aspergillus* infection.

2. Materials and methods

The study was approved by our institutional review board. This retrospective study reviewed data from all lung transplant recipients with pulmonary aspergillosis treated in two hospitals. The inclusion criteria for patients were: dyspnea, tachypnea, and cough; acute respiratory disease; recovery of symptoms and HRCT findings after exclusive treatment with antifungal therapy (oral voriconazole, 400 mg/day); and an index exceeding the cutoff value of 1.5 on a Platelia *Aspergillus* enzyme immunoassay (EIA) for GM antigen detection in bronchoalveolar lavage (BAL). The latter criterion has shown 90.4% specificity for the detection of *Aspergillus* infection [10]. Patients diagnosed with concomitant viral infections potentially affecting the lung, including cytomegalovirus, based on a review of clinical and laboratory data were excluded from this study.

The study sample comprised 23 patients (12 men, 11 women) with a mean age of 43.6 (range, 22–59) years who were diagnosed with *Aspergillus* infection and met the inclusion criteria. All patients were considered to have proven or probable invasive aspergillosis according to the criteria proposed by the European Organization for Research and Treatment of Cancer/Mycoses Study Group, and as previously reported in lung transplant recipients [11]. Isolated *Aspergillus* cultures from BAL and/or sputum were obtained from 12/23 patients. No patient showed eosinophilia in blood or BAL.

HRCT examinations were performed using a 64-multidetector scanner (LightSpeed VCT; GE Healthcare, Waukesha, WI, USA) with the following parameters: 120 kVp; 250 mA; time, 0.8 s; and pitch, 1.375. The technical parameters included inspiratory volumetric acquisition with 1 mm collimation at 1 mm increments using a high-spatial-frequency reconstruction algorithm. Images were obtained with mediastinal (width, 350–450 HU; level, 20–40 HU) and parenchymal (width, 1200–1600 HU; level, −500 to −700 HU) window settings, and reconstructions were performed in the axial and coronal planes.

The HRCT scans were assessed according to criteria defined in the Fleischner Society's *Glossary of Terms* [12]. The presence and distribution of nodules, centrilobular opacities with the tree-in-bud pattern, ground-glass opacities, and consolidations were evaluated. A nodule was defined as a rounded or irregular opacity that was well or poorly defined and ≤3 cm in diameter. Nodules were classified as small (diameter < 10 mm) or large (diameter > 10 mm). The halo sign was defined as a CT finding of ground-glass opacity surrounding a nodule or mass. The tree-in-bud pattern refers to centrilobular branching structures that resemble a budding tree. Ground-glass opacities were defined as hazy areas of increased opacity or attenuation, with no obscuration of the underlying vessels. Consolidation was defined as homogeneous opacification of the parenchyma with obscuration of the underlying vessels. The distribution of abnormalities was categorized as focal (unilobar) or diffuse (more than one pulmonary lobe) and stratified using the categories of upper, middle, and lower lung lobes.

Two chest radiologists with more than 10 years of experience who were blinded to the patients' clinical information, except *Aspergillus* infection, independently assessed CT scans in random order. After the two radiologists had conducted independent analyses, the images were reviewed together with a third chest radiologist (with > 40 years of experience) to reach a final consensus decision. For each patient, reviewers identified one or two predominant CT patterns: tree-in-bud nodules/bronchial wall thickening; airspace consolidation/ground-glass opacity; and/or large nodules with and without the halo sign. We also evaluated white blood cell counts and correlated them with imaging findings.

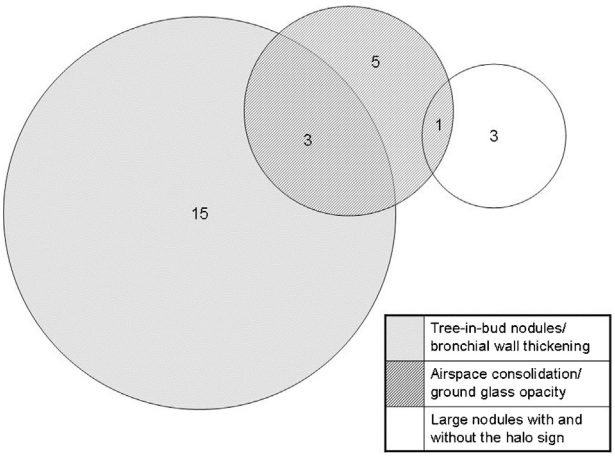

Fig. 1. High-Resolution computed tomography patterns. Footnote: [1]Algorisms represent the number of patients in each group.

3. Results

3.1. Patients

Among the sample of 23 patients, 13 patients had undergone bilateral and 10 had undergone unilateral lung transplantation. The mean interval between lung transplantation and infection diagnosis was 7.4 (standard deviation, 1.7) months. The underlying lung diseases were emphysema ($n = 5$, 21%), idiopathic pulmonary fibrosis ($n = 7$, 30%), cystic fibrosis ($n = 1$, 4%), pneumoconiosis ($n = 2$, 8%), non–cystic fibrosis bronchiectasis ($n = 4$,17%), retransplantation ($n = 1$,4%), and lymphangioleiomyomatosis ($n = 3$,12%).

3.2. HRCT patterns

The main HRCT pattern (Fig. 1), found in 65% ($n = 15$) of patients, was centrilobular tree-in-bud nodules associated with bronchial wall thickening (Fig. 2).

Consolidation and ground-glass opacities were observed in 22% ($n = 5$) of patients (Fig. 3). Centrilobular tree-in-bud nodules/bronchial wall thickening was associated with areas of consolidation/ground-glass opacities in 13% ($n = 3$) of patients.

The pattern of large nodules with and without the halo sign was observed in 13% ($n = 3$) of patients (Fig. 4) and was associated with consolidation and ground-glass opacities in one case.

The mean white blood cell count was 6547 ± 1546 (cells/μL), and no correlation was observed between imaging findings and white blood cell counts. However, only one patient had neutropenia (498 cells/μL) and HRCT showed large nodules with the halo sign.

3.3. Distribution of abnormalities

Abnormalities were bilateral in 20 (87%) patients, among whom the lower lobes were affected in 17 patients and exclusively affected in 13 patients. All three patients with unilateral abnormalities had undergone unilateral transplantation, and abnormalities were described in the transplanted lung in two of these patients.

The results are summarized in Table 1.

4. Discussion

Infection is the most common cause of perioperative mortality and the second most common cause of late (>90 days) mortality