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Clinical significance of lower respiratory tract *Aspergillus* culture in elderly hospitalized patients

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Abstract In order to evaluate the clinical significance of *Aspergillus*-positive culture results from the lower respiratory tract specimens of elderly hospitalized patients, and to identify the clinical variables that differentiate between colonization and infection with *Aspergillus* spp. in this patient population, a retrospective study was conducted. The records of 66 elderly patients whose lower respiratory tract specimens yielded *Aspergillus* spp. between January 1995 and July 2000 were examined. The majority of the patients ($n=61$) were determined to be colonized with *Aspergillus* spp., and serious lung infection due to *Aspergillus* spp. was rare. Clinical, radiological, and microbiological data did not help differentiate between infection and colonization.

Introduction

Aspergillus is a ubiquitous fungus that causes a variety of clinical manifestations in humans. These manifestations range from colonization of the respiratory tract with no clinical consequences, to aspergilloma that is mainly seen in patients with chronic cavitary lung disease. Chronic necrotizing aspergillosis is a rare infection that is seen in those who are mildly immunocompromised or who have chronic lung disease. Allergic bronchopulmonary aspergillosis, on the other hand, is a hypersensitivity reaction to *Aspergillus* antigens that mainly affects patients with asthma. The most serious lung infection due to *Aspergillus* spp. is invasive pulmonary aspergillosis (IPA), which is seen in patients who are severely immunocompromised [1].

The diagnosis of lung infection due to *Aspergillus* spp. is difficult, and serological tests to detect *Aspergillus* antigens are not commercially available. The value of isolating *Aspergillus* spp. from lower respiratory tract (LRT) specimens is debatable. Several reports have shown that this finding is associated with colonization in 36–91% of cases, depending on the patient population studied [2–6]. In the case of IPA, the reported sensitivity of isolating *Aspergillus* spp. from LRT specimens ranges from 5 to 75% [1, 3, 7, 8]. As a result of this low sensitivity, invasive procedures are commonly necessary to diagnose this serious lung infection.

Elderly individuals comprise a growing segment of hospitalized patients. They commonly have a variety of medical problems including chronic lung diseases and underlying malignancies that may predispose them to serious lung infections with *Aspergillus* spp. When LRT cultures of elderly patients with pulmonary problems are positive for *Aspergillus* spp. concerns of IPA are generally raised and extensive work up is triggered. The study presented here was conducted to evaluate the clinical significance of *Aspergillus*-positive culture results of LRT specimens in elderly hospitalized patients, and to identify the clinical variables that differentiate between LRT colonization and infection with *Aspergillus* spp. in this patient population.

Materials and methods

The records of the Pathology Department of Detroit Medical Center from January 1995 to July 2000 were searched to identify all patients who had *Aspergillus* spp. isolated by culture from LRT specimens, including sputa, endotracheal aspirates, and bronchoalveolar lavage (BAL). Upper respiratory tract samples such as nasal or throat swabs were not included. Patients who had *Aspergillus* spp. isolated on more than one occasion were counted once. At the same time, the records were searched for all patients who had histologically proven IPA. From this pool of patients, the medical records of those patients aged 65 years or older were thoroughly reviewed for demographic data, underlying illnesses, reasons for hospitalization, clinical and radiological picture, leukocyte count, other respiratory isolates, final diagnosis, treatment, and hospitalization outcome.

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Neutropenia was defined as a neutrophil count lower than 1,000 cells/mm³. Corticosteroid therapy was recorded if the patient had received any dose of systemic corticosteroids for at least 48 h within the month prior to the first positive LRT culture result.

Patients were diagnosed as having airway colonization when *Aspergillus* spp. were isolated from LRT specimens (expectorated sputum, endotracheal aspirates, or BAL), without clinical or histological evidence of invasive disease. These patients were not treated with antifungal agents, and they remained free of *Aspergillus*-related disease during their hospitalization period. Patients were diagnosed as having IPA when they had a compatible clinical and radiological picture, characteristic histological evidence of lung tissue invasion by the fungus, and a culture result positive for *Aspergillus* spp. Aspergilloma was diagnosed when a characteristic fungal ball was detected within a lung cavity by chest radiograph or computed tomography (CT), and when *Aspergillus* spp. was isolated from culture of LRT specimens.

Results and discussion

During the study period, *Aspergillus* spp. were isolated from the cultures of non-biopsy LRT samples of 66 elderly patients. Of these patients 61 were colonized with *Aspergillus* spp., 3 had IPA, and 2 had aspergilloma. None of the patients was diagnosed with chronic necrotizing aspergillosis or allergic bronchopulmonary aspergillosis. The most commonly isolated species was *A. fumigatus* (60%). Other *Aspergillus* spp. isolated included *A. niger* (20%), *A. flavus* (12%), *A. terreus* (2%), and unidentifiable *Aspergillus* spp. (6%). None of the culture specimens grew more than one *Aspergillus* spp. From the 66 LRT specimens examined, an *Aspergillus* sp. was isolated from sputum in 57 cases, BAL in 4, and both sputum and BAL in 5.

The clinical characteristics of the 61 patients who had LRT colonization by *Aspergillus* spp. are described in Table 1. The clinical symptoms were non-specific: 44 patients had cough, 29 had fever, 16 complained of chest pain, and none had hemoptysis. Radiological evaluation was based on chest radiograph, since CT of the chest was performed for only five of the 61 patients, and the findings were as follows: 27 patients had focal infiltrates, 12 had diffuse infiltrates, 3 had cavitory lesions, 1 had a mass, and for 18 patients the chest radiograph was normal. The final diagnoses for the patients with abnormal radiological findings were bacterial or aspiration pneumonia in 31 patients, pulmonary edema in 5, tuberculosis in 3, lung cancer in 3, and pulmonary fibrosis in 1. *Aspergillus* spp. were isolated from sputum in 57 patients, from BAL in 2 patients, and from both in 2 patients. Ten of the 61 patients had more than one positive sputum sample. Again, *A. fumigatus* was the most commonly isolated species ($n=35$ patients), followed by *A. niger* ($n=13$), *A. flavus* ($n=8$), *A. terreus* ($n=1$), and an unidentified *Aspergillus* spp. ($n=4$). Concomitant microorganisms were isolated from the LRT samples of 39 patients, i.e., bacteria in 23 patients, *Candida* spp. in 22, and mycobacteria in 3 patients (more than one microorganism was isolated from many of the patients).

Sixteen patients died during hospitalization because of conditions not related to *Aspergillus* infection. None of the

Table 1 Clinical characteristics of 61 elderly patients with lower respiratory tract colonization by *Aspergillus* spp.

Characteristic	No. of patients (%)
Age in years (mean \pm SD)	75.25 \pm 6.94
Sex (male/female)	30/31
Smoking history	33 (54)
Alcohol use	13 (21)
ICU stay	31 (51)
Mechanical ventilation	28 (46)
Underlying risk factors ^a	
Chronic lung disease	33 (54)
COPD	25 (41)
Asthma	6 (10)
Tuberculosis	2 (3)
History of lung surgery	4 (7)
Solid tumor	12 (20)
Hematological malignancy	4 (7)
Corticosteroid therapy	13 (21)
Chemotherapy	1 (2)
Neutropenia	2 (3)
In-hospital mortality	16 (26)

^aMany of the patients had more than one risk factor.

patients with LRT colonization by *Aspergillus* spp. received antifungal treatment, and the treating physicians did not consider any of them to have *Aspergillus* lung infection. Follow-up medical records were available for 26 of the 45 patients who were discharged alive from the hospital. These patients were followed up for 1–97 months (mean \pm SD, 31.2 \pm 24.4 months; median, 29 months); none had evidence of *Aspergillus* lung infection, and their chest radiograph findings were reported as either stable or improved.

Two patients were diagnosed with aspergilloma. Both had underlying chronic obstructive pulmonary disease and lung cancer. Chest radiograph showed a cavity with fungal ball in both cases. *Aspergillus fumigatus* was isolated from sputum and BAL in both cases. One of these two patients died in the hospital due to massive pulmonary hemorrhage, probably secondary to aspergilloma.

Of the 66 elderly hospitalized patients with an LRT culture positive for *Aspergillus* spp., three were diagnosed with IPA, based on histological confirmation of invasive disease. One patient had lung cancer, one had a hematological malignancy and was undergoing chemotherapy, and the third had HIV infection. None of these patients was neutropenic (mean leukocyte count, 6,210 cells/mm³). An *Aspergillus* sp. was cultured from BAL in two of these patients and from sputum and BAL in one patient. The diagnosis of IPA was confirmed by open lung biopsy in two, and pleural biopsy in one. All three patients had fever, two complained of chest pain, and one had hemoptysis. The radiological evaluation was based on CT of the chest that showed cavitory lesions in two patients and pleural effusion in one; none of the patients had a

normal radiological result. The *Aspergillus* sp. isolated from all patients was *A. fumigatus*. Two patients had other organisms isolated from LRT secretions (1 *Pneumocystis carinii*, 1 *Candida* sp.). All three patients were treated with antifungal agents (1 with amphotericin B preparation alone, and 2 with amphotericin B and itraconazole). The total dose and duration of therapy could not be determined from this retrospective analysis. All three patients died in the hospital, probably as a direct result of IPA.

Patients who had lung infection due to *Aspergillus* spp. (aspergilloma or IPA) had higher in-hospital mortality compared to those who had LRT colonization (80 vs 26%, respectively; $P=0.03$, Fisher's exact test). The number of patients with *Aspergillus* lung infection was too small to make a meaningful comparison between the clinical characteristics of the two groups.

The value of recovering *Aspergillus* spp. from culture of LRT secretions depends on the patient population. In non-immunocompromised patients, most studies have shown that this finding represents colonization or contamination. However, in immunocompromised patients, the value of LRT culture results positive for *Aspergillus* spp. varies significantly. Strimlan et al. [2] reported that 90% of 169 non-biopsy respiratory tract cultures positive for *Aspergillus* spp. were due to colonization, and most of these patients had chronic lung disease due to chronic obstructive pulmonary disease, asthma, or bronchiectasis. The remaining 10% had *Aspergillus* lung disease, including only 3.6% with IPA. Similar findings were reported by Treger et al. [4]. On the other hand, Nalesnik et al. [3] showed that only 36% of patients with positive LRT cultures had colonization, but 80% of the patients they studied had known risk factors for *Aspergillus* infection. Horvath et al. [6] also found that 49 of 78 cases with positive LRT cultures were associated with definite or probable IPA, even though the vast majority of the patients studied were at high risk for IPA. In a large prospective study of 108 consecutive patients, Yu et al. [5] found that none of the 57 non-immunocompromised patients (or patients with solid tumors or lymphoma) whose culture results were positive for *Aspergillus* spp. had IPA, while 21 of 54 immunocompromised patients (i.e., patients with corticosteroid therapy, transplantation, neutropenia, or leukemia) had IPA. To our knowledge, our study is the first to examine the significance of LRT cultures positive for *Aspergillus* spp. in elderly hospitalized patients. The results show that colonization is the most common etiology (92.5%) in this patient population. Additionally, we found that lung infection with *Aspergillus* spp. is rare (4.5% IPA and 3% aspergilloma).

The characteristics of patients who have LRT colonization by *Aspergillus* spp. are not clear from the existing literature. Yu et al. [5] reported that patients with chronic lung disease and a history of smoking were more likely to have colonization than serious *Aspergillus* infection. In the report by Strimlan et al. [2], 78% of patients with LRT *Aspergillus* colonization had chronic lung disease. Nalesnik et al. [3] observed that the frequency of cancer and other serious medical problems among patients with

Aspergillus LRT colonization was significantly higher than in a non-selected population of hospitalized patients, and they attributed this to prolonged hospitalization and increased frequency of antibiotic usage. Elderly patients exhibit many of the factors that may increase their susceptibility to LRT colonization by *Aspergillus* spp. For example, they are more likely to have chronic lung disease, multiple medical problems, and prolonged hospitalization. In addition, the isolation of *Aspergillus* spp. from LRT samples may indicate that these patients are mildly immunocompromised, or it may be a marker of underlying critical illness. Indeed, more than half of our patients with LRT colonization had chronic lung disease, 26% had underlying malignancies, and almost half of them were in the intensive care unit and on mechanical ventilation when the *Aspergillus* spp. were isolated. Furthermore, the mortality rate in our patients with LRT colonization by *Aspergillus* spp. was 26%, which is much higher than the reported mortality in non-selected elderly hospitalized patients [9].

Specific radiological signs did not differentiate between LRT colonization and lung infection with *Aspergillus* spp. in our patient population. All patients with *Aspergillus* lung infection had an abnormal radiological result, while 70% of those with *Aspergillus* colonization of the LRT had an abnormal result; the difference between the two groups was not statistically significant. Radiological signs that are characteristic of IPA, such as the halo sign and air-crescent sign, could not be assessed in this retrospective study because in the majority of cases the radiological evaluation was based on a chest radiograph, which is insensitive and cannot detect such signs [10]. Several studies have shown that high resolution CT of the chest is the best radiological method to evaluate patients suspected of having IPA [11, 12]. Caillot et al. [12] showed that routine use of this method in the evaluation of febrile neutropenic patients suspected of having IPA, leads to earlier diagnosis and improved survival. In addition, a CT of the chest is better than chest radiograph for revealing the characteristic fungal ball present in patients with aspergilloma [13]. Therefore, it is recommended that a high resolution CT scan of the chest be performed as early as possible if there is clinical suspicion of *Aspergillus* lung infection.

The limitations of this study include the retrospective nature of the analysis, the fact that the majority of patients did not have a CT scan of the chest in the evaluation of their pulmonary disease, and only a small number of patients underwent histological examination of the lung. Furthermore, the study did not identify variables that could differentiate between patients with LRT colonization by *Aspergillus* spp. and those with more serious lung infection. A prospective study that systematically evaluates elderly patients with LRT culture results positive for *Aspergillus* spp., and that includes routine high resolution CT of the chest and further diagnostic studies for those with a suspicious clinical and radiological picture for IPA seems warranted.

In conclusion, the results of our study show that isolation of *Aspergillus* spp. by culture of LRT specimens

in elderly patients is usually due to colonization. These patients commonly have underlying chronic lung disease, tend to be acutely ill, and have relatively high in-hospital mortality. Serious lung infection due to *Aspergillus* spp. is rare, and clinical, radiological, and microbiological data could not differentiate between infection and colonization. High clinical suspicion of IPA and further diagnostic studies are warranted in elderly hospitalized patients with an underlying immunocompromising condition who present with fever, abnormal chest radiograph, and an LRT sample yielding *A. fumigatus*.

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