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Unusual forms of subacute invasive pulmonary aspergillosis in patients with solid tumors

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Summary *Objectives: Aspergillus* spp. can cause acute invasive disease in severely immunocompromised patients. Nonetheless, there are few reports of solid tumors complicated with subacute invasive pulmonary aspergillosis (subacute IPA).
Methods: Retrospective observational cohort study, performed in patients with primary lung cancer or secondary lung metastasis complicated with subacute IPA in three referral hospitals.
Results: From 2008 to 2011, 14 episodes of subacute IPA were diagnosed, including 11 (78.6%) probable and 3 proven (21.4%). Nine patients (64.3%) had primary lung cancer. Thirteen patients (92.9%) had more than one local or systemic predisposing factor for subacute IPA. No patient had previous fungal colonization. *Aspergillus* spp. was isolated in 6 specimens of bronchoalveolar lavage, 6 sputum, 2 biopsies, and 1 percutaneous lung puncture. At the time *Aspergillus* spp. was isolated, the most common radiologic findings on chest computed tomography (CT) were cavitary masses, and development or expansion of cavitation in existing masses or nodules (10/14, 71.4%). On CT follow-up, most patients (8/12, 66.7%) had new cavity

Abbreviations: BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CPA, chronic pulmonary aspergillosis; CNPA, chronic pulmonary aspergillosis; CT, computed tomography; HIV, human immunodeficiency virus; IPA, invasive pulmonary aspergillosis.

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formation or expansion of one or more existing cavities. All patients were treated with azoles and two underwent surgery. Ten (71.4%) patients died after *Aspergillus* spp. was detected (median time 73 days, IQR 33—243): 2 (20%) deaths were subacute IPA-attributable and 6 (60%) were related.

Conclusions: Primary lung cancer and secondary lung metastasis seem to be triggering factors for *Aspergillus* spp. implantation, and predispose to subacute IPA. Once localized in the damaged lung, the mold can grow and cause or expand cavities. In lung cancer patients, *Aspergillus* spp. detection is associated with a very poor prognosis.

Introduction

Invasive pulmonary aspergillosis (IPA) encompasses a spectrum of disease related to underlying conditions that compromise the pulmonary and systemic immune response to inhaled *Aspergillus* spp.[1] Classically, IPA has been described as a serious acute disease in severely immunocompromised hosts, such as those with prolonged neutropenia[2] and recipients of high doses of glucocorticoids.[3] Nowadays, the profile of patients considered at risk of invasive aspergillosis is expanding, as IPA is seen to occur in hosts that are less immunosuppressed, such as patients with chronic obstructive lung disease (COPD)[4] or chronic liver disease[5] and those hospitalized in the intensive care unit.[6] Furthermore, in less severely immunosuppressed patients, IPA can manifest with unusual clinical and pathologic features, such as those of subacute invasive pulmonary aspergillosis (subacute IPA) or chronic necrotizing pulmonary aspergillosis (CNPA), a locally invasive form of this infection.[7,8]

Growing evidence suggests that patients with solid malignancies are an emerging group among the new hosts at risk.[9] However, the current knowledge of solid lung tumors complicated with IPA has come from single case reports or single-center series.[9—14] There are no reports specifically focused on subacute IPA in patients with primary lung cancer and secondary lung metastasis. The diagnosis is difficult in this population, because the clinical and radiologic signs are nonspecific and could be attributed to cancer, and the sensitivity of fungal culture is low. Hence, this entity may be underdiagnosed.

The aim of this study is to describe the predisposing factors, clinical presentation, and outcome of patients with primary lung cancer or secondary lung metastasis complicated with subacute IPA.

Patients and methods

Study setting and patient population

A retrospective, observational, cohort study of all consecutive cases of invasive aspergillosis from January 2008 to December 2011 was performed in three tertiary care university hospitals in Barcelona, Spain. We identified all cases of proven or probable subacute IPA in patients with primary lung cancer or secondary lung metastasis. Cases were detected through the General Hospital, Microbiology, and Histopathology databases, using a standardized protocol. All case report forms and available radiologic results were carefully reviewed by a single investigator.

Definitions

The criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG)[15] were used to define cases of proven or probable IPA.

Chronic pulmonary aspergillosis (CPA) includes aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), and CNPA or subacute IPA. Classification of subacute IPA was made following Denning's et al. definitions,[1,7,8] as described in Table 1 and patients with subacute IPA were included.

Neutropenia was established on an absolute neutrophil count of $<500/mm^3$ at the onset of infection.

Corticosteroid therapy was defined as an amount of corticosteroid (the equivalent of 10 mg daily doses of prednisone during the last month) given as therapy or pulses.

Galactomannan was detected in bronchoalveolar lavage (BAL) using the Platelia™ *Aspergillus* commercial enzyme immunoassay kit (Bio-Rad), according to the manufacturer's instructions. A value >0.5 was considered positive.

Response to antifungal treatment was defined as resolution, improvement, or stability of clinical, microbiological, and radiologic manifestations of subacute IPA. Failure of antifungal treatment was established on progression of the clinical symptoms and/or positive culture for the same *Aspergillus* species and/or worsening of radiologic manifestations of subacute IPA, despite therapy.

Mortality was classified as follows: *subacute IPA-attributable* if subacute IPA was the cause of death or played a major role in the patient's death; *subacute IPA-related* if subacute IPA played a minor role in the patient's death; and *subacute IPA-unrelated* if subacute IPA had no role in the cause of death.

Statistical analysis

A descriptive analysis was performed. Continuous variables were expressed as the median and range. All proportions were calculated as percentages of patients with available data. Data analysis was performed with SPSS Statistics 16 (IBM SPSS, Chicago, IL).

Results

Epidemiology of invasive aspergillosis and solid cancer

During the four-year study period, we identified 180 patients with invasive aspergillosis, and 90% of them had lung involvement (IPA). Overall, a solid tumor was a host factor for IPA in 18 patients (10%). Fourteen cases (77.7%) were ultimately classified as subacute IPA.