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Clinical features of invasive pulmonary aspergillosis vs. colonization in COPD patients distributed by gold stage

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Summary *Objective:* To explore clinical features of invasive pulmonary aspergillosis (IPA) vs. colonization among hospitalized COPD patients.
Methods: Records of COPD patients with two respiratory cultures yielding *Aspergillus* were retrospectively reviewed. Cases categorized as proven/probable IPA or colonization was analyzed.
Results: 118 patients were identified: 70 (59.3%) colonized, 48 (40.7%) with IPA (42 probable, 6 proven). Higher percentage of IPA patients (vs. colonized) presented GOLD III + IV (77.1% vs. 57.1%, $p = 0.025$). IPA patients presented higher Charlson index (3.5 ± 2.5 vs. 2.6 ± 2.2, $p = 0.027$), higher rate of ICU admission (27.1% vs. 4.3%, $p = 0.001$) and worse prognosis

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(McCabe rapidly fatal category: 31.3% vs. 7.1%, $p = 0.001$). GOLD-I IPA patients presented risk factors other than COPD. Before hospitalization, 66.7% IPA and 28.6% colonized patients were taking steroids ($p < 0.001$). Antifungals were administered to 83.3% IPA and 21.4% colonized patients ($p < 0.001$). Mortality was higher among IPA vs. colonized patients, both in global (58.3% vs. 10.0%, $p < 0.001$), GOLD-I (75.0% vs. 10.0%, $p = 0.041$), GOLD-II (42.9% vs. 5.0%, $p = 0.042$) and GOLD-III patients (54.2% vs. 0.0%, $p < 0.001$), but not in GOLD-IV patients (69.2% vs. 31.3%, $p = 0.066$).

Conclusions: IPA should be suspected not only in GOLD-III and GOLD-IV COPD patients, with higher mortality in IPA vs. colonized patients for GOLD-II and -III COPD patients.

Introduction

Isolation of *Aspergillus* in lower respiratory tract samples is often the first suspicion of a potential aspergillosis. In non-selected patients with *Aspergillus* isolation, the probability of aspergillosis is 12%, although the probability depends on the underlying condition: 72% for patients with neutropenia, 58% for solid organ transplant recipients, 28% for critically ill patients, and almost unknown for patients with chronic obstructive pulmonary disease (COPD).[1–5] Invasive pulmonary aspergillosis (IPA) is increasingly being recognized as an emerging disease in non-neutropenic patients[5,6] with underlying conditions including connective tissue diseases requiring corticosteroid therapy, solid cancer, liver cirrhosis and COPD.[7]

Severe COPD treated with corticosteroids represents the most common underlying disease for IPA among non-neutropenic hospitalized patients. In a single centre in Spain it has been estimated an *Aspergillus* isolation rate from lower respiratory samples of 16.3 patients per 1000 COPD admissions (22.1% patients of the 163 with *Aspergillus* isolation presenting IPA), with an increase in IPA in COPD patients from 7 per 1000 admissions in 2000 to 13 per 1000 in 2007.[5] This increase is not surprising considering that COPD is a frequent disease that will become the third leading cause of death worldwide by 2020[8] and that elderly patients, a growing segment of the hospitalized population, present risk factors for aspergillosis derived from comorbidities, prolonged hospitalizations and COPD under corticosteroid treatment.[9] Since factors involved in the progression of COPD include chronic low-grade infections, recurrent acute exacerbations and pneumonia,[10] elderly patients present more frequently advanced COPD (stages III and IV of the GOLD (Global Initiative for Obstructive Lung Disease) spirometric classification[11]). These advanced stages have been correlated with a higher risk of IPA.[5,12]

The aim of this study was to analyze clinical features of probable/proven IPA (vs. colonization) in patients presenting COPD distributed by GOLD stages.

Patients and methods

A retrospective study analyzing clinical records of adult patients presenting at least two valuable cultures of respiratory samples yielding *Aspergillus* spp. in 29 Spanish hospitals (the 10 most recent valuable patients in each centre) was performed.[13] Transplant recipients and patients presenting neutropenia (<1000 neutrophils/mm^3), diagnosis of aspergilloma or allergic bronchopulmonary aspergillosis were excluded. The study protocol was approved by the Ethics Committee of Hospital Central de la Defensa Gomez Ulla, Madrid, Spain.

Only patients with COPD diagnosis and probable/proven IPA (see below) were considered and compared with those colonized. Demographic data, underlying illnesses, clinical and radiological data, laboratory data, previous treatments (corticosteroids, antibiotics, antifungals…), antifungal treatment and outcome were recorded. The age-unadjusted Charlson comorbidity index[14] (age was considered in separate) and the modified McCabe score (Sabadell score)[15] were retrospectively calculated. Criteria to retrospectively define diagnostic categories were adapted from those defined by Bulpa et al. for COPD GOLD III and IV patients,[16] and they were also applied to GOLD I and GOLD II patients in order to allow comparisons between patients with IPA and colonized patients by GOLD stage: Proven IPA (histopathological confirmation), probable IPA (presence of new respiratory signs/symptoms with suggestive chest imaging) and colonization (symptoms not attributable to *Aspergillus* without dyspnoea exacerbation, bronchospasm or new pulmonary infiltrates). The "possible" category was not applicable since all patients required at least two positive *Aspergillus* cultures as inclusion criteria.

Comparisons between proportions were performed by the χ^2 test and the Fisher's exact test, when necessary. For quantitative variables, since data did not show normality in the Kolmogorov–Smirnoff test, the Kruskal–Wallis and Mann–Whitney tests, when necessary, were used. A $p < 0.05$ was considered statistically significant.

Results

Among the 245 non-neutropenic patients with at least two valuable cultures of respiratory samples yielding *Aspergillus* spp. identified from October 2002 to July 2010 in 29 Spanish hospitals, 173 (70.6%) presented COPD in 27 centres. Of them, 70 patients were classified as colonized and 48 as patients with probable/proven IPA. Among patients with IPA, 6 presented proven aspergillosis confirmed by autopsy (2 cases) or pulmonary biopsy (4 cases). GOLD stages in these 6 proven cases were: GOLD I (1 patient), GOLD III (4 patients) and GOLD IV (1 patient).

Table 1 shows distribution of colonized and IPA patients by GOLD stage. Among IPA patients, significantly higher percentage of patients (vs. those colonized) presented GOLD III + IV (77.1% vs. 57.1%, $p = 0.025$). IPA patients presented