

Invasive pulmonary aspergillosis: retrospective case record review

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Summary Invasive pulmonary aspergillosis is a severe infection, with a sharp increase during the last decades. Our study aimed at identification of the epidemiological characteristics of invasive pulmonary aspergillosis during a period of four years. All clinical records with pulmonary isolation of *Aspergillus* species were reviewed, as a part of surveillance program at Reina Sofia University Hospital, from January 1995 to December 1998. Diagnosis of invasive pulmonary aspergillosis was based on criteria of Centers for Disease Control and Prevention. Of the 50 patients identified 78% were males and 44% were current or ex-smokers. Chronic respiratory diseases were identified in 64% of them, and 60% were receiving immunosuppressives. Twenty percent of our patients had been subjected to lung transplantation and 28% to organ transplantation in general. Only 78% had received specific antifungal treatment and 56% had fatal prognosis. Our findings match with previous studies, apart from the high frequency of lung transplantation in our series. We recommend further studies on large prospective cohorts.

Key words Invasive pulmonary aspergillosis, Surveillance program, Risk factors

Aspergilosis pulmonar invasora: revision retrospectiva de historias clínicas

Resumen La aspergilosis pulmonar invasora es una infección severa que ha experimentado un brusco incremento en las últimas décadas. El objetivo del presente estudio ha sido establecer las características epidemiológicas de esta enfermedad en un periodo de cuatro años. Se revisaron todos los datos clínicos obtenidos de los casos con aislamiento de *Aspergillus*, parte de un programa de vigilancia del hospital universitario Reina Sofia, de enero de 1995 a diciembre de 1998. El diagnóstico de aspergilosis pulmonar invasora se basó en los criterios establecidos por los *Centers for Disease Control and Prevention*. De los 50 pacientes incluidos en el estudio, el 78% eran hombres y un 44% eran fumadores o ex-fumadores. Un 64% presentaba alguna enfermedad respiratoria crónica, y un 60% recibió tratamiento inmunosupresor. Un 28% de los pacientes fueron sometidos a trasplante de órgano, siendo un 20% del total trasplantados pulmonares. Solo el 78% de los pacientes recibieron tratamiento antifúngico, teniendo un 56% un pronóstico fatal. Nuestros hallazgos coinciden con lo descrito en estudios previos, al margen del alto porcentaje de trasplantados pulmonares de nuestro estudio. Son necesarios estudios prospectivos con grupos mayores de pacientes.

Palabras clave Aspergilosis pulmonar invasora, Programa de vigilancia, Factores de riesgo

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Invasive pulmonary aspergillosis is a severe infection, which occurs mainly in immunosuppressed patients [1]. Diagnosis of the infection is often difficult and lately made, and usually bears a dismal prognosis [6]. During the last decades there has been a sharp increase in the occurrence of invasive pulmonary aspergillosis with a high mortality, reaching 85% in immunosuppressed patients [10]. The use of powerful new chemotherapy protocols for malignancies and certain immunological disorders, and the increase use of organ transplantation may have contributed to this sharp increase [1,6,7]. In Spain, the commission of infection control of La Paz Hospital, Madrid has recommended aspergillosis surveillance system based on retrospective revision of medical records every 3 months [4]. Since January 1995, an active epidemiological surveillance program for isolation of *Aspergillus* was implemented in our university hospital. Constructions of new buildings and remodelling of the hospital prompted active registration of new cases with aspergillosis.

The main objective of this study is describing the epidemiological characteristics of invasive pulmonary aspergillosis patients who were identified during a period of four years.

Material and Methods

Medical records of all patients with positive isolation of *Aspergillus* species in Reina Sofia University Hospital from January 1995 to December 1998 were retrospectively studied. This hospital is a tertiary referral centre with 1500 beds, fully equipped to receive trauma patients. In addition, hospital activities extend to include organ and bone marrow transplantations. Owing to its location in the centre of Andalusia, it serves over one million persons.

In our study, all patients were diagnosed by the Microbiology Laboratory as positive by pulmonary isolation of *Aspergillus* (sputum, bronchoalveolar lavage, and histopathological examination and tissue culture of lung biopsy).

Patients were considered to have definite diagnosis of invasive pulmonary aspergillosis if *Aspergillus* was identified on histopathological examination and tissue culture of lung biopsy.

Probable diagnoses of invasive pulmonary aspergillosis included patients whom *Aspergillus* was recovered either from a lower respiratory tract specimen obtained by bronchoalveolar lavage or from two or more sputum specimen. Confirmatory evidence for these patients consisted of characteristic findings suggestive of aspergillosis on chest radiograph and computerised tomography scan, and no evidence of a concurrent pathogen [4,7]. Granulocytopenia was not an exclusive criterion for diagnosis.

Variables described in the medical literature as being intrinsic risk factors for invasive pulmonary aspergillosis were collected: age, gender and in terms of their presence or absence in a particular patient; chronic respiratory disease, chronic relevant diseases as diabetes or cancer, lung transplantation, organ transplantation in general, granulocytopenia in the last 6 months and granulocytopenia in the last hospital admission. Granulocytopenia was defined as granulocytic count less than 1,000 / μ l.

Extrinsic risk factors for invasive pulmonary aspergillosis were also studied: smoking, residence area, past history (PH) of immunosuppression, immunosuppression in the last hospital admission, number of hospital admissions, number of hospital admissions in the last year (a rough indicator for the general health condition during the last year), PH of surgical intervention, surgical inter-

vention in the last year. Immunosuppression was defined as receiving daily dosage of corticosteroids or/and chemotherapy for more than three weeks.

Risk factors were considered as such only when they occurred prior to the onset of the symptoms of invasive pulmonary aspergillosis. We also investigated the administration of specific antifungal treatment and the outcome.

Finally, incidence rates of invasive pulmonary aspergillosis according to the number of hospital admissions were calculated.

Clinical and epidemiological data, including risk factors for invasive pulmonary aspergillosis, were collected and analyzed using the statistical package Statistix.

Results

A total of 160 subjects were reported by the Microbiology Laboratory as positive isolation of *Aspergillus*, of which 132 (82.5%) were studied because of positive pulmonary isolation. The clinical evidence of invasive pulmonary aspergillosis was identified in 50 (37.9%) of them. The other 82 patients had a-symptomatic pulmonary isolation of *Aspergillus*.

Of the identified 50 patients invasive pulmonary aspergillosis was definite in 33, and probable in 17. Thirty-three symptomatic patients were diagnosed by histopathological examination and tissue culture of lung biopsy, meanwhile 16 had positive culture of bronchoalveolar lavage, characteristic findings suggestive of aspergillosis on chest radiograph and computerised tomography scan, and no evidence of a concurrent pathogen. Only one patient had repeated positive sputum culture with characteristic findings of invasive pulmonary aspergillosis on chest radiograph and computerised tomography scan.

Of the 50 patients with invasive pulmonary aspergillosis, 78% were males, 44% were current or ex-smokers and 42% were living in a rural area. The mean age of the identified patients was 47.6 ± 21.14 years. Only 78% had received specific treatment for invasive pulmonary aspergillosis, and 56% had fatal prognosis. All patients who did not receive antifungal treatment were diagnosed post mortem, and of those who received specific antifungal treatment 43.6% had fatal prognosis. Antifungals used were amphotericin B, fluconazole, ketoconazole and itraconazole.

The table shows the principal epidemiological characteristics of diagnosed patients with invasive pulmonary aspergillosis. The incidence rates of invasive pulmonary aspergillosis according to the hospital admissions were 0.34, 0.26, 0.17, and 0.40 in years 1995, 1996, 1997, and 1998 respectively.

Discussion

Hospital surveillance programs, based on retrospective revision of medical records, are very important in invasive pulmonary aspergillosis, because this is a potentially preventable disease in many patients, and associated with high morbidity and mortality [4]. Revision of medical records has shown to be the most easy and rapid method to collect a sufficient sample for such rare events [9], and several researchers have employed such methods to study the occurrence of invasive aspergillosis [8,11,13-15].

Reviewing the medical literature, a variety of factors that increase the risk of invasive pulmonary aspergillosis have been described as; chronic respiratory diseases,

Table. Descriptive analysis of 50 cases with invasive pulmonary aspergillosis.

Variables	Cases with invasive pulmonary aspergillosis
Age in years	47.6 ± 21.14
Gender (male)	39 (78)
Chronic respiratory disease	32 (64)
Chronic disease of relevance	29 (58)
Past history of immunosuppression	29 (58)
Immunosuppression in the last hospital admission	30 (60)
Granulocytopenia in the last 6 months	13 (26)
Granulocytopenia in de last hospital admission	12 (24)
Surgical intervention	24 (48)
Organ transplantation	14 (28)
Lung transplantation	10 (20)
Number of hospital admission in the last year	2.58 ± 1.81

* Quantitative data are expressed as mean ± SD; Number in parentheses adjacent to the actual number indicates percentage of cases.

chronic diseases of relevance such as cancer and diabetes, immunosuppressive drugs and neutropenia [2,3,5,7]. Our study supports this and shows that there may be many possible risk factors for invasive pulmonary aspergillosis; chronic respiratory disease was identified in 64% of our patients and 58% of them had chronic diseases as cancer or diabetes, risk factors previously reported by the U.S. Centers for Disease Control and Prevention (CDC) [3].

In addition, 60% of our patients were receiving immunosuppressive drugs and 24% had granulocytopenia in the last hospital admission. This agrees with the Morbidity and Mortality Weekly Report (1997), which emphasized that the primary risk factor for invasive pulmonary aspergillosis is severe and prolonged granulocytopenia, both disease and therapy induced [7]. The CDC has identified immunosuppressive therapy and prolonged granulocytopenia as the most important risk factors for invasive pulmonary aspergillosis [3]. Twenty percent of our patients were subjected to lung transplantation and 28% to organ transplantation in general; this explains the high percentage of patients who were receiving immunosuppressive drugs and with granulocytopenia.

Of note, our study defined granulocytopenia as granulocytic count less than 1,000 / μ l, while the CDC considered only moderate granulocytopenia less than 500 / μ l or severe granulocytopenia less than 100 / μ l as risk factor. Patients at risk for invasive pulmonary aspergillosis may therefore include patients with mild granulocytopenia. Furthermore, one fourth of our invasive pulmonary aspergillosis patients had normal granulocytic counts, denoting that invasive pulmonary aspergillosis can occur in immunocompetent patients more frequently than normally considered.

The CDC did not identify gender difference in invasive pulmonary aspergillosis, in contrast to our results where 78% of our patients were males. Forty four percent of our patients were current or ex-smokers, known risk factor for invasive pulmonary aspergillosis [1,3,6,7]. The higher prevalence of smoking among males in Spain could be the explanation for gender difference in our study.

Only 78% of our patients had received specific treatment for invasive pulmonary aspergillosis, which could be attributed to delay and difficulty in diagnosis. This problem has been previously reported [1,6,8,12,15], and could be responsible for part of the high fatal prognosis (56%) in our patients, although nearly similar figures (47.6%) was observed among patients who received specific antifungal treatment. This suggests a need for prospective cohort studies to evaluate the effectiveness of different antifungal treatment in invasive pulmonary aspergillosis.

The four years surveillance period was quite useful to our institution in establishing a baseline "endemic" rate of invasive pulmonary aspergillosis and determining groups of patients who were at risk. In addition, we have learned that the general health condition of the patient, roughly indicated by the number of hospital admissions in the past year, correlates with disease activity.

Our results suggest the need for prompt preventive measures and special attention for patients with these risk factors. These measures include, respectively, the use of granulocyte-colony-stimulating factors and intranasal application of amphotericin B or oral or systemic antifungal drug prophylaxis, this is together with reducing the exposure of patient under immunosuppressive therapy by using high-efficiency particulate air (HEPA) filters in the hospital environment [3,7,12]. Moreover, more attention by the physicians to *Aspergillus* as a causative agent of pulmonary infection among patients with previously reported risk factors, to be treated pre-emptively and aggressively.

Of course, these results pertain solely to our hospital and should not be considered to apply generally. However, the retrospective surveillance methodology can be applied in different hospitals. Inspection of our findings with their consistency and coherency strongly suggests the external validity of the study.

Our results call for further investigation of invasive pulmonary aspergillosis risk factors; future study preferably should be performed on large prospective cohorts, to increase their internal validity.

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