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Original Article

Invasive pulmonary aspergillosis: high incidence of disseminated intravascular coagulation in fatal cases

Chih-Cheng Lai[1], Shwu-Jen Liaw[2], Li-Na Lee[3,4], Cheng-Hsiang Hsiao[5], Chong-Jen Yu[3], Po-Ren Hsueh[3,4]

[1]Division of Critical Care Medicine, Department of Emergency and Critical Care Medicine, Lotung Poh-Ai Hospital, Yi-Lan; [2]School of Medical Technology, National Taiwan University College of Medicine, Taipei; and Departments of [3]Internal Medicine, [4]Laboratory Medicine, and [5]Pathology, National Taiwan University Hospital, Taipei, Taiwan

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Background and Purpose: Disseminated intravascular coagulation (DIC) is a rarely described finding in invasive pulmonary aspergillosis (IPA) with unclear impact on mortality.

Methods: This study included patients with positive cultures of *Aspergillus* spp. from respiratory specimens, serological evidence of aspergillosis, or lung biopsy findings supporting aspergillosis treated at National Taiwan University Hospital from January 1999 to June 2005. IPA was defined based on the consensus of the European Organization for Research and Treatment of Cancer, and the Mycosis Study Group of the National Institute of Allergy and Infectious Diseases. Univariate logistic regression analysis was used to evaluate the factors associated with mortality.

Results: Proven or probable IPA was diagnosed in 26 patients. Hematological malignancy was found in 11 patients (42%) and immunosuppressive agents had been administered to 17 patients (65%). Among 20 culture-proven infections (77%), the most frequently encountered fungi were *Aspergillus fumigatus* (46%) and *Aspergillus flavus* (23%). The overall mortality rate was 62%. Univariate and multivariate analyses revealed that DIC was the only factor that was significantly associated with death attributable to IPA ($p<0.01$).

Conclusions: IPA is associated with a high mortality rate, particularly for patients with DIC.

Key words: Aspergillosis; *Aspergillus fumigatus*; Blood coagulation; Mortality

Introduction

Invasive aspergillosis (IA) has emerged as a worldwide health care problem for several reasons, including the advent of human immunodeficiency virus infection; the development of new intensive chemotherapy regimens for solid tumors, or hematological malignancy; increase in the number of organ transplant recipients; and increased use of immunosuppressive regimens for autoimmune diseases [1-5]. With improvements in supportive care and successful treatment of most bacterial infections, the importance of IA has increased so that it is now one of the major direct or contributory causes of death, especially in patients receiving chemotherapy for leukemia and immunosuppressive agents for bone marrow transplant or solid organ transplantation.

Following environmental exposure to *Aspergillus* conidia, primary infection usually involves the respiratory tract, but may involve other organs in severely immunocompromised patients [6,7]. *Aspergillus fumigatus* and *Aspergillus flavus* are the most common causative species of invasive mold infections [8-10]. Differences in incidence are related to environmental factors that support the growth of a particular species [11]. Other species of *Aspergillus*, such as *Aspergillus niger* and *Aspergillus terreus*, have also been identified as rare causes of invasive infections [5,6,8,9]. Although the diagnosis of IA would ideally be based on histological documentation of typical hyphae and a positive culture for *Aspergillus*, in clinical practice, such a diagnosis is infrequently achieved. Therefore, blood, fluid, and aspirates from infected lesions tested by

Corresponding author: Dr Po-Ren Hsueh, Departments of Internal Medicine and Laboratory Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: hsporen@ha.mc.ntu.edu.tw

specific enzyme-linked immunosorbent assay (ELISA) and/or by molecular diagnostic methods may play an important role in the diagnosis of *Aspergillus* infection.

Despite the improvements in medical and surgical treatments for invasive pulmonary aspergillosis (IPA), during the last decades there has been a sharp increase in the occurrence of IPA, with a high mortality, reaching 85% in immunocompromised patients [12]. The prognosis of focal disease (and, in particular, nodular disease) is much more favorable than that of diffuse and bilateral disease, as focal disease tends to progress more slowly [13]. Severely ill patients, such as those needing mechanical ventilation or transfusion therapy and patients with central nervous system involvement were at higher risk for death [14]. Although several studies have investigated the association between coagulopathy and IPA [15-17], no study has evaluated the relationship between disseminated intravascular coagulation (DIC) and outcomes of patients with IPA.

This study investigated the clinical features of patients with IPA, including the microbiological spectra, outcome, and prognostic factors.

Methods

Setting and study population

National Taiwan University Hospital (NTUH) is a tertiary referral center with 1800 beds. Most of the patients in this series, especially those needing critical care, chemotherapy or transplant, were referred from local hospitals. There were 175 beds in the intensive care unit (ICU) and 150 beds in the hemo-oncology ward of this hospital during the study period. Medical records of all patients with positive cultures of *Aspergillus* spp. from respiratory specimens (including sputum, bronchioalveolar lavage, needle aspiration, or biopsy specimens), serological evidence of aspergillosis, and pathological findings supporting aspergillosis from biopsied lung specimens at NTUH from January 1999 to June 2005 were retrospectively analyzed. Standardized criteria from the European Organization for Research and Treatment of Cancer, and the Mycosis Study Group of the National Institute of Allergy and Infectious Diseases were applied for the diagnosis of definite and probable IPA [18]. The following data were collected for each patient: age and gender; predisposing factors, including underlying diseases, and associated medical conditions; peripheral white blood cell count and differential cell counts; coagulation profiles; chest radiography findings; strains of pathogens isolated or found in biopsy specimens; antifungal therapy regimens and durations; invasive or surgical procedures; hospitalization duration; and outcome.

Microbiological and pathological evaluation

For isolation of fungi, specimens were inoculated on Sabouraud's dextrose agar plates (BBL Microbiology Systems, Cockeysville, MD, USA). Identification of *Aspergillus* was based on gross colony morphologies and microscopic images. Cornmeal agar (BBL Microbiology Systems) slide cultures were used to identify molds. The detection of galactomannan in serum by the Platelia *Aspergillus* test (Bio-Rad, Marnes-la-Coquette, France) was carried out according to the manufacturer's instructions. All the positive samples were retested with a new sample obtained from the patient because of the possibility of false-positive results due to sample contamination or lack of reproducibility. Two consecutive positive patient samples were required for the classification of suspected IA. Immunohistochemical staining of biopsied lung tissue was performed using monoclonal antibody of anti-*Aspergillus*, which reacts with a 106-kDa band of cell wall fraction (Mab-WF-AF-1). Positive results were found in *A. fumigatus*, *A. niger*, and *A. flavus*.

Definition

IPA developing more than 48 h after hospital admission and before the clinical diagnosis of fungal infection was regarded as nosocomial; otherwise, the fungal infection was considered to be community acquired. Previous use of antibiotics was defined as receiving antibiotic therapy before hospital admission or >48 h after hospital admission before a clinical diagnosis of fungal pneumonia was made. Antecedent chemotherapy was defined as receiving anticancer chemotherapy <1 month before the clinical diagnosis of fungal infection. Fever was defined as a body temperature of >37.5°C. Prolonged neutropenia was defined as an absolute neutrophil count <500/μL in peripheral blood for more than 10 days. Respiratory failure was defined as oxygen pressure <60 mm Hg and/or partial pressure of carbon dioxide ≥50 mm Hg while breathing room air. The diagnosis of DIC was made following the criteria established by the International Society of Thrombosis and Haemostasis [19].

Statistical analysis

Differences in mortalities among subgroups were analyzed by chi-squared test or Fisher's exact test, as appropriate. A forward stepwise logistic regression

model was run, with significance level for entry or retention in the model both set at $p<0.05$; only variables that were significantly associated with survival in the univariate analysis were included in the multivariate model. Overall survival was analyzed by the Kaplan-Meier method and differences in survival were assessed for significance by the log rank test. Time 0 was the date of listing and censoring was performed at the time of IPA diagnosis. Analysis was performed using Statistical Package for the Social Sciences (SPSS) software (Version 11.5; SPSS, Chicago, IL, USA).

Results

Clinical characteristics

The clinical evidence of IPA was identified in 26 patients. Of the identified cases, IPA was definite in 13 and probable in 13. The medical and microbiological records of all 26 patients with IPA infection treated from January 1999 to May 2004 were reviewed. A variety of invasive diagnostic methods were employed including thoracostomy, thoracoscopy, and percutaneous ultrasound-guided biopsy. The yearly distribution of these 26 cases included less than 5 cases from 1999 to 2003, increasing to 7 cases in 2004 and 4 cases in the first half of 2005, with the latter increases mainly comprising hospital-acquired infections (Fig. 1).

The demographic characteristics, clinical course, treatment, and outcome of the 26 patients are summarized in Table 1. Eight patients (31%) were >60 years old. IPA was nosocomially acquired in 14 cases (54%), but none of these infections were acquired in the ICU.

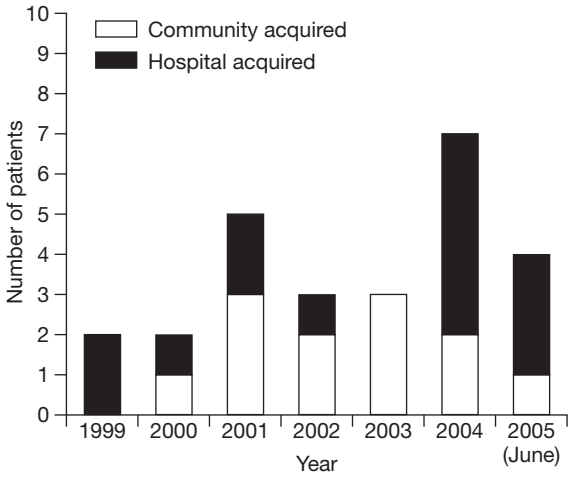

Fig. 1. Annual number of cases of invasive pulmonary aspergillosis at National Taiwan University Hospital from January 1999 to June 2005.

All patients had underlying disease or associated medical conditions. Immunocompromised condition was most commonly due to immunosuppressive therapy, followed by malignancy, long-term steroid use, diabetes mellitus, organ transplantation, and autoimmune diseases. Among the 13 patients (50%) with malignancy, hematological malignancies were the most common and 5 of these patients were bone marrow transplant recipients.

The most common manifestations were productive cough (88%), fever (85%), dyspnea (73%), and hemoptysis (23%). Shock was an initial presentation in 12 patients (46%). Leukocytosis was noted in 8 patients

Table 1. Clinical characteristics, clinical course, treatment, and outcome of patients with invasive pulmonary aspergillosis

Variable	Total (n = 26) No. (%)
Age (years; mean ± SD)	47.5 ± 33
Gender (male/female)	13/13
Hospital acquired	14 (54)
Underlying conditions	
Malignancy	13 (50)
Hematologic[a]	11 (42)
Solid[b]	2 (7)
Diabetes mellitus	6 (23)
Immunosuppressive therapy	17 (65)
Long-term steroid use	8 (31)
Organ transplantation[c]	5 (19)
Uremia	1 (4)
Chronic obstructive pulmonary disease	3 (12)
Previous tuberculosis	1 (4)
Autoimmune diseases[d]	3 (12)
Absolute neutrophil count <500/μL	7 (27)
Hospital stay (days; mean ± SD)	53 ± 33
Antifungal therapy[e]	
Amphotericin B	20 (77)
Fluconazole	3 (12)
Itraconazole	2 (8)
Voriconazole	1 (4)
Caspofungin	6 (23)
Surgical intervention	7 (27)
Intensive care unit admission	17 (65)
Death	16 (82)

Abbreviation: SD = standard deviation

[a]Includes 5 with acute lymphoblastic leukemia, 3 with acute myelogenous leukemia, 2 with multiple myeloma and 1 with chronic myelogenous leukemia.

[b]Includes one each with breast carcinoma and primary neuroectodermal tumor.

[c]All had received bone marrow transplant.

[d]Includes 2 with systemic lupus erythematosus and one with dermatomyositis.

[e]Seven patients received combination or sequential antifungal therapy.

(31%), but seven (27%) had infection during the granulocytopenia stage after chemotherapy. DIC was present at the time of diagnosis of IPA infection in 15 patients (58%).

Chest radiographic findings included pleural-based cavitary lesions in 15 patients, multiple consolidations in 11 patients, nodular lesions (with or without cavitation) in 8 patients, and pleural effusion in 5 patients. Only 2 patients presented with halo and air crescent sign in computed tomography (CT) scans.

Microbiological and pathological findings

Fungi were cultured from 20 patients. *A. fumigatus* comprised the majority of fungal species encountered (60%), and 58% of these infections were hospital acquired. The second most common species was *A. flavus* (30%), followed by *A. terreus* (10%), and only half of these infections were nosocomially acquired. Five patients had additional infectious pathogens isolated concurrently with IPA, including *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Acinetobacter baumannii*, enterococcus, and cytomegalovirus. Pathological examinations of biopsy specimens revealed the presence of IPA infection in 13 patients. Thoracostomy had been performed in 7 patients, thoracoscopy in 3, and percutaneous ultrasound-guided biopsy in 3. The biopsied lung tissues of 5 patients without culture proof were further managed with monoclonal anti-*Aspergillus* antibody and all had positive results. A positive fungal culture result from a sample obtained by sterile procedure from a normally sterile site showing clinical or radiological abnormality consistent with infection was found in 10 patients. Isolates were obtained from thoracostomy or thoracoscopy in 4 patients, from percutaneous ultrasound-guided biopsy in 3, from pleural effusion in 2, and from blood in 1. Platelia *Aspergillus* test was performed in only 6 patients and all of them had positive results (optical density index >1.5; range, 1.821-30).

Treatment and outcomes

The mean hospital stay was 53 days. Systemic antifungal therapy was given in 24 patients. Surgical resection of a pulmonary lesion was performed in 7 patients. Respiratory failure leading to ICU admission occurred in 17 patients. Sixteen patients (62%) died. *A. flavus* infection had the highest mortality (5/6), followed by *A. fumigatus* (8/12) and *A. terreus* (1/2).

Analysis of the clinical characteristics and outcome of patients with IPA revealed that patients with DIC had a higher risk of mortality (Table 2). The Kaplan-Meier survival curves for patients with or without DIC are shown in Fig. 2.

Discussion

DIC was present in 15 (58%) of the patients with IPA in this series, of which 14 (93%) died. Although severe infection is generally associated with DIC, the incidence of DIC in patients with IPA has not been previously reported. Previous reports of IPA with coagulopathy have been exclusively in liver and renal transplant recipients [15,16]. Unlike previous studies, our series had no solid organ transplant recipients. The association of coagulopathy with IPA has been described by Minna et al [17]. They proposed that since *Aspergillus* had a predilection for vascular structure, followed by fibrin in the microvasculature, heavy infiltration with fungal hyphae may help trigger consumption coagulopathy. The possibility that coagulopathy may be due to proteolytic enzyme elaborated by *Aspergillus* has also been suggested [16]. Mortality was significantly associated with mortality and was markedly lower in patients without DIC (19% versus 93%, $p<0.001$). Although sex, age, neutropenia, site of infection, shock, previous usage of antibiotics, and radiographic presentation (focal or diffuse) were included in the analysis, DIC was the only risk factor for mortality identified in this study.

The incidence of IA is significantly increased in neutropenic patients, transplant recipients, and patients who receive aggressive immunosuppressive regimens that impair macrophage functions (steroids, chemotherapy, etc.) [20,21]. Most of our patients had underlying immunocompromised conditions such as malignancy, organ transplant, chronic steroid use, or other immunosuppressive therapies. The rising incidence of IPA at our hospital in recent years could represent an actual increase or previous underestimation of case numbers. In fact, as we used strict criteria to define IPA and excluded patients who had only typical clinical and radiographic manifestations but did not have microbiological evidence, the frequency of IPA may have been underestimated. In this study, more than half the cases were hospital acquired. The decrease in hospital-acquired cases in 2003 was attributable to fewer hospital visits due to severe acute respiratory syndrome outbreak; otherwise, the annual incidence of nosocomial acquired IPA resumed its increasing trend. Nosocomial IPA now represents a very important cause of morbidity and mortality.

Table 2. Prognostic factors of invasive pulmonary aspergillosis (IPA) in 26 patients: univariate and multivariate analyses of relative risk of death

Variable	No. of patients		Univariate analysis Odds ratio (95% CI)	Multivariate analysis *p*
	No. in each category	No. died (%)		
Age (years)				
<20 or >65	10	7 (70)	1.0	
20-65	16	9 (56)	1.815 (0.34-9.687)	NS
Gender				
Female	13	9 (69)	1.0	
Male	13	7 (54)	0.519 (0.104-2.581)	NS
Underlying condition				
Non-malignant	14	5 (35)	1.0	
Malignant	12	7 (58)	0.778 (0.159-3.795)	NS
Previous antibiotics				
No	3	1 (33)	1.0	
Yes	23	15 (65)	3.75 (0.293-47.989)	NS
Shock at diagnosis				
No	12	8 (75)	1.0	
Yes	14	8 (57)	1.5 (0.303-7.432)	NS
Absolute neutrophil count				
≥500/μL	19	12 (63)	1.0	
<500/μL	7	4 (57)	0.778 (0.133-4.536)	NS
Nosocomial infection				
No	12	8 (75)	1.0	
Yes	14	8 (57)	1.5 (0.3.3-7.432)	NS
Chest radiography				
Focal	15	8 (53)	1.0	
Diffuse	11	8 (78)	0.429 (0.081-2.277)	NS
DIC during episode of IPA				
No	11	2 (18)	1.0	
Yes	15	14 (93)	63 (4.957-800.677)[a]	<0.01

Abbreviations: CI = confidence interval; DIC = disseminated intravascular coagulation; NS = not significant
[a]$p<0.01$.

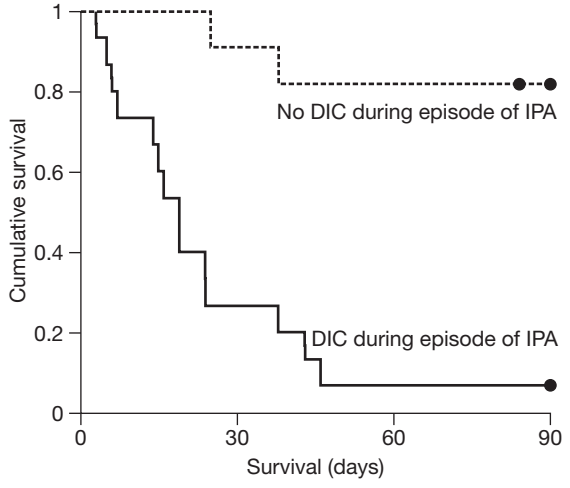

Fig. 2. Kaplan-Meier survival curves for invasive pulmonary aspergillosis (IPA) patients with or without disseminated intravascular coagulation (DIC). Black dots represent patients who were still alive at 90 days after the diagnosis of IPA.

Previous studies showed neutropenia to be a major risk factor for the development of IA [2,6,22]. In this series, only 7 patients (27%) with neutropenia developed IPA. Among culture-proven cases, 2 of 6 patients with neutropenia developed *A. flavus* infection during hospitalization. In comparison, *A. fumigatus* was isolated from 2 of 12 neutropenic patients who developed IPA and neither of the 2 patients with *A. terreus* infection developed neutropenia during the course of infection. The result is in contrast to the findings of a previous study, which suggested that *A. terreus* might require a higher degree of immunosuppression before infection can occur [23]. Although this series included a small number of IPA cases, the results suggest the need for inclusion of IPA in the differential diagnosis of patients with prolonged fever and lower respiratory tract infection or typical radiographic findings even in the absence of neutropenia.

IPA has a heterogeneous appearance on plain chest radiographs and CT [24-27]. In this series, radiographic findings included cavitary lesions, consolidations, and nodular lesions. In contrast to a previous report that found no pleural effusions in patients with IPA [13], 5 patients (19%) exhibited pleural effusions in the present series. Although both halo and air crescent sign in CT are highly distinctive imaging findings for IPA, only 2 of our patients had these findings. This illustrates that radiographs may be of limited value in the diagnosis of IPA, and that use of additional diagnostic modalities is essential.

Timely isolation and identification of the causative agent of aspergillosis are important for definitive diagnosis and early antifungal therapy; however, the time-consuming nature of the required procedures and frequent difficulty in obtaining an adequate deep tissue specimen for examination necessitate the use of alternative diagnostic modalities. Among these, the rapid detection of *Aspergillus galactomannan* using a commercial ELISA method (Platelia *Aspergillus* test) may be helpful in early diagnosis [28]. Our finding of 100% sensitivity of the Platelia *Aspergillus* test is in contrast to a previous report, which found a sensitivity of only 50% for patients with proven or probable IA [29]. These differences may be attributable to the limited number of cases, however, and further studies are needed to determine the diagnostic value of *A. galactomannan* detection.

Hypoxemia resulting in acute respiratory failure developed in 17 patients in this series. All of them were admitted to the ICU and 16 (94%) of them died during hospitalization. The complication of respiratory failure might reflect the severity of pulmonary fungal infection or deterioration of underlying pulmonary function due to other causes.

Extrapulmonary spread of *Aspergillus* was noted in 2 of our patients; in 1 case, *A. flavus* infection had disseminated to the skin and the other had positive blood culture for *Aspergillus* spp. (unidentified). These manifestations are in contrast to previous reports that showed heart or brain as the most common site of dissemination [3,7], but do support previous observations that disseminated infection is associated with a dismal prognosis [23]. The mortality rate associated with the various species of *Aspergillus* in patients was highest when caused by *A. flavus* (83%), followed by *A. fumigatus* (75%) and *A. terreus* (50%), with a combined survival of 62%. The result is in contrast to a previous study [23], which showed highest mortality due to *A. flavus* (92.7%), followed by *A. terreus* (90.9%) and *A. fumigatus* (86%). The previously reported [2,30] ineffectiveness of amphotericin B in the treatment of aspergillosis is supported by this study, which showed that 12 of 20 patients who received amphotericin B died. In contrast, aggressive surgical intervention was utilized in 7 patients and all had favorable outcomes. This finding suggests the need for greater consideration of the potential benefits of pulmonary resection for immunocompromised patients with IPA.

In conclusion, the recent increase in incidence of IPA at our hospital was largely attributable to hospital-acquired infection. IPA was associated with a high mortality, particularly in patients with DIC. Application of rapid diagnostic modalities, such as *Aspergillus* antigen test, is needed to facilitate early diagnosis and prompt appropriate antifungal therapy. Our findings suggest the need for further emphasis on the role of aggressive surgical intervention in the management of patients with IPA. Surveillance of environmental contamination of *Aspergillus* spp. and reinforcement of measures for preventing environmental contamination and nosocomial transmission are crucial due to the presence of similar strains in 3 patients with IPA in the hospital.

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