The Clinical Characteristics, Therapeutic Outcome and Prognostic Factors for Invasive Pulmonary Aspergillosis: A Single-Center Experience and Review of the Literature

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= Abstract =

Background: Despite advances in microbiological diagnosis and effective antifungal treatment, invasive pulmonary aspergillosis (IPA) is a still major cause of mortality in immunocompromised patients.

Objective: The aim of this study is to analyze clinical characteristics, treatment outcome and prognostic factors for IPA.

Methods: Between May 2003 and March 2011, we retrospectively studied all patients with IPA in our facility.

Results: A total 37 cases were identified. Hematologic malignancies were the leading underlying disease for 27 (27/37, 73.0%) patients. Neutropenic period between the onset of neutropenia and the diagnosis of IPA was 15.0 days. The most common symptom was fever (35/37, 94.6%). The principal findings of chest computed tomography (CT) were segmental or air space consolidation (17/37, 45.9%) followed by halo sign (13/37, 35.1%), and ground-glass attenuation (11/37, 29.7%). Amphotericin B was the initial treatment for 36 (36/37, 97.3%) patients. Voriconazole was subsequently substituted for Amphotericin B in 25 (35/36, 97.2%) patients. The 30-day mortality rate was 24.3% (9/37). The 30-day mortality rate was associated with a failure to recover from neutropenia (p=0.048) or persistent fever during treatment (p=0.003). Two patients were lost to follow-up. Overall mortality was 62.9% (22/35).

Conclusion: IPA remains a serious condition with failure to recover from neutropenia or persistent fever during treatment associated with a high 30-day mortality rate.

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Key Words: Invasive pulmonary aspergillosis

INTRODUCTION

Invasive pulmonary aspergillosis (IPA) is a well known potentially life-threatening infection among immunocompromised patients[1]. Despite aggressive efforts to minimize its occurrence by means of antifungal prophylaxis, the incidence of IPA has increased during the past two decades due to widespread use of chemotherapy and immunosuppressive agents[2].

Because the clinical features of IPA share many

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similarities with those of other more benign respiratory infections, early diagnosis of IPA in immunocompromised patients is challenging. A high index of suspicion is necessary in patients with risk factors for IPA. It is well known that an early diagnosis and prompt initiation of antifungal therapy can lead to successful outcomes in patients with IPA[3].

Serial screening for galactomannan (GM) associated with imaging studies have been validated to have high diagnostic accuracy for IPA in patients with hematologic malignancies and in stem cell transplant patients[4,5]. Such a preemptive diagnostic approach for proper treatment of IPA is known to reduce the use of systemic antifungal agents[6]. In our institution, the aspergillus antigen test was performed twice weekly among hematologic patients with neutropenia who were febrile for more than 5 days since April 2006. Chest computed tomography (CT) scan was requested if the patient exhibited a new infiltrate on chest x-ray. However, in 2010 the mortality rate did not improve (5/9, 50%) compared to preceding years (2003-2009) (4/28, 20~100%).

Therefore, to further improve the outcomes of patients of IPA, we decided to investigate for potential risk factors that might influence therapeutic outcomes in IPA patients.

MATERIALS AND METHODS

1. Patients

Medical records of patients in our institution were retrospectively analyzed from May 2003 through March 2011. Cases were identified using our computerized database using the Korean version of the International Statistical Classification of Disease (ICD)-10 codes; B44.0 (invasive pulmonary aspergillosis), B44.0P (s/p invasive pulmonary aspergillosis), B44.0A (invasive pulmonary aspergillosis), B44.0B (Aspergilloma, invasive, pulmonary), B44.0R (r/o Invasive pulmonary aspergillosis), B44.1 (other pulmonary aspergillosis), B44.1R (r/o pulmonary aspergillosis, other), B44.8 (other forms of aspergillosis). A total of 134 patients were enrolled. Among the 134 patients, 38 patients were diagnosed with invasive aspergillosis, based on the definitions of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer /Mycoses Study Group (EORTC-IFIG/MSG)[7]. A total of 37 patients with IPA excluding 1 patient diagnosed with an oral cavitary invasive aspergillosis were finally enrolled into our study (Fig. 1).

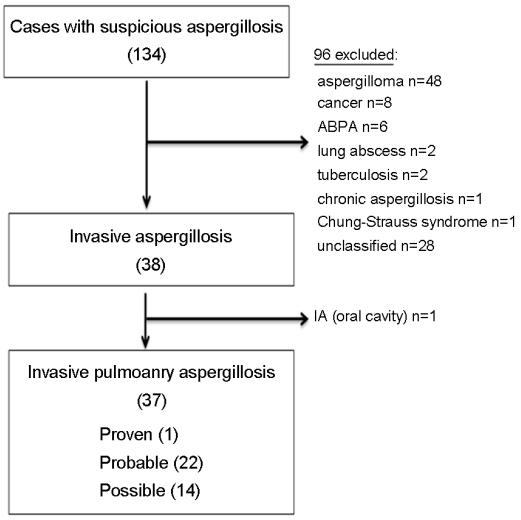

Fig. 1. Algorithm of the study.
ABPA: allergic bronchopulmonary aspergillosis, IA: invasive aspergillosis

2. Definitions

We followed the 2008 EORTC criteria for diagnosing invasive pulmonary aspergillosis: Proven - requires histopathological documentation of infection and culture from a normally sterile site; Probable - requires fulfillment of criteria in 3 categories: host factors (eg, immune status), clinical manifestation (signs, symptoms, radiological features) and mycological evidences (including nonculture-based surrogates [eg, serum aspergillus

galactomannan antigen]); Possible - at least one criterion from the host factors category but does not have clinical features or mycological evidences[8].

Neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 2 days. Failure to recovery from neutopenia is defined as a neutropenic status during treatment after IPA diagnosis. Fever is defined as a single oral temperature of ≥38.3℃ or a temperature of ≥38.0℃ for ≥1 hour. Persistent fever during treatment is defined as having an ongoing fever during treatment after IPA diagnosis. Use of steroids is defined as a daily dose equivalent to 20 mg prednisone for at least 2 weeks or 30 mg for at least 1 week before identification of IPA.

3. Data collection

The following data were recorded: demographic data (age, sex), clinical signs at diagnosis (fever, cough, dyspnea, hemoptysis), serum aspergillus galactomannan antigen (≥0.5 considered positive), the date of onset and recovery of neutropenia, the duration of neutropenia, the date of onset of fever and defervescence, the time between diagnosis and antifungal therapy, whether the central venous catheter was performed at diagnosis of IPA, whether prophylactic antifungal therapy was performed at diagnosis of IPA, treatment regimen of IPA and cause of modifying antifungal agents.

4. Statistical analysis

We performed statistical analysis using SPSS soft ware, version 18.0 (Apache Software Foundation, Chicago, Illinois, USA). A p-value <0.05 was accepted as statically significant.

RESULTS

1. Clinical characteristics of IPA

There were 37 patients with IPA. Most patients developed pneumonia and a prolonged fever that did not respond to broad-spectrum antibacterial therapy. IPA was diagnosed on average at 16.1 days (0 to 76) after the onset of fever. Prior to the onset of IPA, 13 (13/37, 35.1%) patients received prophylactic itraconazole, 2 (2/37, 5.4%) patients received prophylactic fluconazole and 2 (2/37, 5.4%) patients received both itraconazole and fluconazole. Broad spectrum antibacterial agents and corticosteroids were administered to 36 (36/37, 97.3%) and 8 (8/37, 21.6%) patients, respectively. The most common symptom was fever (35/37, 94.6%). Other symptoms included cough (10/37, 27.0%), dyspnea (4/37, 10.8%) and hemoptysis (4/37, 10.8%).

Hematologic malignancies were the leading underlying disease for 27 (27/37, 73.0%) patients follows: acute myeloid leukemia for 14 (14/27, 51.9%), acute lymphoid leukemia for 5 (5/27, 18.5%), aplastic anemia for 3 (3/27, 11.1%), myelodyplastic syndrome for 2 (2/27, 7.4%), lymphoma for 1 (1/27, 3.7%), chronic lymphoid leukemia for 1 (1/27, 3.7%) and bone marrow transplantation was performed for 8 (8/37, 21.6%) patients (allogenic stem cell transplantation, 6 and autologous stem cell transplantation, 2). Solid organ cancer accounted for 18.9% (7/37). Chronic obstructive pulmonary disease was present in 1 patient (Table 1).

2. Diagnostic methods

1) Mycological examination

Aspergillus fumigates was confirmed by histological examination in only one patient. *Aspergillus* galactomannan antigen test was performed on 35 (35/37, 94.6%) patients. Twenty seven (27/35, 77.1%) patients were positive; as many as 13 (13/27, 48.1%) patients had normal chest CT at the moment of testing.

2) Imaging

Chest CT was performed for all 37 patients

Table 1. Baseline characteristics of 37 IPA patients at first diagnosis

	No. (%)
Male/Total	23/37 (62.2)
Underlying disease	
Acute myeloid leukemia	14/37 (37.8)
Acute lymphoid leukemia	5/37 (13.5)
Aplastic anemia	3/37 (8.1)
Myelodysplastic syndrome	2/37 (5.4)
Multiple myeloma	2/37 (5.4)
Chronic lymphoid leukemia	1/37 (2.7)
Lymphoma	1/37 (2.7)
Solid organ cancer*	7/37 (18.9)
Miscellaneous†	3/37 (8.1)
IPA Case classification	
Proven	1/37 (2.7)
Probable	22/37 (59.5)
Possible	14/37 (37.8)
Presenting symptoms at IPA diagnosis	
Fever, Chill	35/37 (94.6)
Cough, Sputum	10/37 (27.0)
Hemoptysis	4/37 (10.8)
Dyspnea	4/37 (10.8)
Thoracic CT sign	
Segmental areas of consolidation	16/37 (43.2)
Halo sign	14/37 (37.8)
Ground-grass attenuation	13/37 (35.1)
Nodule	6/37 (16.2)
Pleural effusion	1/37 (2.7)

*Rectal cancer 2, nasopharyngeal cancer 2, Hypopharyngeal cancer 1, pancreatic cancer 1, advanced gastric cancer 1
†Drug induced neutropenia, pancytopenia, and pneumothorax.
Presenting symptoms at IPA diagnosis and thoracic CT signs were can be overlap.

with a median 4.3 (1 to 21) days after abnormal chest radiographs were obtained. The dominant findings were segmental or air space consolidation (17/37, 45.9%) followed by halo sign (13/37, 35.1%), ground-glass attenuation (11/37, 29.7%), nodular consolidation (5/37, 13.5%), cavitary lesion (1/37, 2.7%) and pleural effusion (1/37, 2.7%).

3. Relationship between neutropenia and IPA

Among the 37 patients, 21 patients were analyzed underwent further to assess for any relationships between neutropenia and IPA. The remaining 16 patient were excluded due to various reasons (6 patients did not recover from neutropenia, 4 patients exhibited neutropenia since admission, 2 patients had IPA before neutropenia, 2 patients were transferred out, 2 patients had no neutropenia). During neutropenia, IPA was diagnosed in 15 (15/21, 71.4%) patients. IPA was diagnosed at an average of 15.0 days (2 to 60) after the onset of neutropenia. IPA was diagnosed in 6 (6/21, 28.6%) patients after recovering from neutropenia.

4. Treatment

Amphotericin B was the initial treatment for 36 (36/37, 97.3%) patients. The median treatment duration for amphotericin B was 13.4 (2~76) days. Nineteen (19/37, 51.4%) patients received at least two kinds of antibacterial treatment. Vancomycin was used in 19 (19/37, 51.4%) patients and carbapenem was used in 22 (22/37, 59.5%) patients at the time of IPA diagnosis. The median dosage for amphotericin B was 885.6 mg (125 to 5092). Amphotericin B was changed to voriconazole in 25 (25/36, 69.4%) patients, to ambisome in 4 (4/36, 11.1%) patients, to caspofungin in 1 (1/36, 2.8%) patients and to micafungin in 1 (1/36, 2.8%) patients. Amphotericin B was maintained in only 1 patient. The most common reason for changing to a second drug was infusion related toxicity (15/35, 42.9%) followed by treatment failure (9/35, 25.7%), renal toxicity (8/35, 22.9%) and formulation changes to an oral antifungal agents (3/35, 8.6%) to accommodate for hospital discharge.

Table 2. Prognostic factors of higher mortality with IPA

	N (%)	95% CI	*p*
Male/Total	23/37 (62.2)	1.375 (0.322~5.877)	0.724
Total parenteral nutrition	5/37 (13.5)	1.286 (0.183~9.021)	1.000
Persistent fever during treatment	8/37 (21.6)	2.556 (1.535~4.255)	0.003
Central venous catheterization	25/37 (67.6)	1.273 (0.214~7.581)	1.000
Prophylactic antifungal agent	14/37 (37.8)	1.185 (0.286~4.992)	1.000
Failure to recover from neutropenia	5/37 (13.5)	2.167 (1.430~3.282)	0.048
Hematologic disease	22/37 (59.5)	2.000 (0.396~10.090)	0.456
Bone marrow transplantation	6/37 (16.2)	0.786 (0.132~4.680)	1.000
Steroid use	8/37 (21.6)	3.273 (0.542~19.746)	0.240
Glycopeptide use	19/37 (51.4)	1.071 (0.233~4.919)	1.000
Carbapenem use	22/37 (59.5)	3.500 (0.609~20.130)	0.244

5. Outcome and prognostic factors

Two patients were lost to follow-up. Overall mortality was 62.9% (22/35). 30-day mortality was 24.3% (9/37). Failure to recover from neutropenia (p=0.048) or persistent fever during treatment (p=0.003) were significantly associated with an increased 30-day mortality (Table 2).

DISCUSSION

Hematologic malignancies still accounted for 73% of patients with IPA in our institution, with the most common underlying condition being acute myeloid leukemia. Similar to many previous studies[9~11], our study showed that failure to recover from neutropenia (p=0.048) or persistent fever during treatment (p=0.003) were factors associated with an increased 30-day mortality. Gender, steroid use and hematologic diseases were not related with mortality which was concordant with a retrospective case review[10]. A comparative study on transplant recipients and neutropenic patients showed that persistently positive *Aspergillus* antigen levels and the need for renal replacement therapy were associated with mortality[12]. Also, according to one retrospective study, patients not receiving allogenic stem cell transplantation had prolonged survival compared to allogenic stem cell transplant recipients (relative harzard ratio of death of 3.4)[13]. Another retrospective study showed that receipt of non-myeloablative conditioning and peripheral blood stem cells was associated a decreased risk of all-cause in mortality[11]. In our study, allogenic stem cell transplantation per se was not associated with higher mortality (odds ratio 0.786, 0.132~4.680) (p=1.000).

An early diagnosis of IPA is generally considered to contribute to a better survival rate[14]. However, even supported by available definition of IPA[7], accurate diagnosis to improve patient's survival is always a challenging task due to the nonspecific nature of the clinical, radiologic findings and the feasibility issue of invasive diagnosis in critical situations. In this study, as much as 18 patients (18/37, 48.6%) with IPA had no respiratory symptoms such as cough, sputum, or hemoptysis. The mean duration between appearance of an abnormal chest radiograph and performance of a chest CT scan was 4.3 (±5.2) days, which shows

that there can be a delay in diagnosing IPA radiographically. However, since as many as 48.1% of IPA patients diagnosed with a positive galactomannan antigen test had normal initial chest CT, galactomannan assay potentially facilitate earlier diagnosis of IPA.

Six patients (28.5%) were diagnosed with IPA after recovery from their neutropenia. Although the immunosuppresion resulting from chemotherapy induced neutropenia can persist even after the recovery, it is important to maintain a high clinical suspicion even after the recovery from the neutropenia.

The halo sign and segmental consolidations were the most common finding on CT. Traditionally there are two radiological patterns for IPA: the airway-invasive pattern and the angio-invasive pattern[12]. Pathologic findings of neutropenic patients and hematopoietic stem cell transplantation recipients have a similar pattern of predominantly angioinvasion and infarction, whereas that of non-neutropenic host have a predominant pattern of inflammatory necrosis with minimum angio-invasion[15]. Given that most IPA patients had neutropenia, angio-invasive pattern was indeed a dominant findings on their chest CT.

Patients with acute myeloid leukemia undergoing intensive chemotherapy have a 7~11% risk of developing proven or probable IPA[16], while under conditions of high burden of airborne *Aspergillus* spores such as reconstruction activities, this incidence can dramatically increase to up to 40%[17]. Therefore, the preventive measures, which is aimed to eliminate *Aspergillus* from the environment, such as particulate air (HEPA) filtration systems, with or without laminar air-flow (LAF), have been shown to reduce the incidence of hospital-acquired aspergillosis[18]. Our hospital, exchange of HEPA filtration has been routinely performed twice a year, but records were insufficient to analyze a potential temporal relationships linked to specific hospital reconstructions.

There was limitation to this study. We were not able to report any open lung biopsies, autopsies or culture confirmed cases which could establish a definite diagnosis of IPA in our study. As a result, most of our cases were classified as probable or possible IPA. The reason we had only one definite case might be explained by the fact that most patients were critically ill making an invasive surgical diagnosis or lengthy fungus culture not generally feasible. It is therefore not possible to exclude the involvement of other emerging mould pathogens such as *Fusarium*, *Zygomycetes*, and dematiaceous fungi[19].

IPA is a severe and fatal disease in immunocompromised patients. There are many risk factors for IPA currently known such as profound neutropenia and immunosuppressive therapy. However, there are only a few studies focusing on prognostic factors for IPA. We reviewed our single center experience of 37 IPA patients over a 9 year period. IPA remains a serious infection in immunocompromised patients despite current advances in treatment. In conclusion, a higher mortality rate is significantly associated with the failure to recover from neutropenia or persistent fever during treatment.

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