ORIGINAL ARTICLE

Clinical risk factors and bronchoscopic features of invasive aspergillosis in Intensive Care Unit patients

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Key words

Risk factors • Bronchoscopy • Invasive aspergillosis • ICU

Summary

Introduction. *Invasive aspergillosis (IA) is an important cause of morbidity and mortality in immunocompromised patients. During recent years, a rising incidence of IA in Intensive Care Unit (ICU) patients has been reported. The patterns of IA related infection may differ according to the type of underlying disease. Unfortunately little is known about the characteristics of IA in ICU patients. In the present study we assessed IA related clinical and bronchoscopy findings in ICU patients.*
Materials and methods. *This study was performed at the ICU units in Sari and Babul, Mazandaran from August 2009 through September 2010. We analysed 43 ICU patients with underlying predisposing conditions for IA. Bronchoalveolar lavage (BAL) samples were collected by bronchoscope twice a weekly. The samples were analyzed by direct microscopic examination, culture and non-culture based diagnostic methods. Patients were assigned a probable or possible diagnosis of IA according to the consensus definition of the EORTC/MSG.*
Results. *Out of 43 suspected patients to IA, 13 (36.1%) cases showed IA. According to criteria presented by EORTC/MSG, they were categorized as: 4 cases (30.8%) of possible IA and 9 (69.2%) of probable IA. The observed mortality was 69.2%. The main underlying predisposing conditions were neutropenia, hematologic malignancy, and COPD. The macroscopic finding in bronchoscopy included of Prulent secretion (46.6%), Mucosal bleeding (30.7%), Mucosal erythema (23%), Trachobronchomalasia (15.3%).*
Conclusion. *The diagnosis of IA in patients with critical illness in ICU is even more difficult. The clinical diagnostic process is often dependent on indirect circumstantial data enhancing the probability of IA. Bronchoscopy with inspection of the tracheobronchial tree, sampling of deep airway secretions and BAL can be helpful.*

Introduction

Invasive aspergillosis (IA) is a major cause of morbidity and mortality in immunocompromised patients receiving intensive chemotherapy, neutropenia, allogeneic stem cell transplantation, and solid organ transplantation [1-3]. Also intensive care unit (ICU) patients at risk for IA, which the specific defects in host defense mechanisms that increase their risk for IA [4]. During recent years, a rising incidence of IA in ICU patients (ranges from 0.3% to as much as 5.8%) has been reported and it carries an overall mortality rate exceeding 80% [5-8] This high mortality is at least partially related to difficulties in timely diagnosis, caused by insensitive and non-specific clinical signs and lack of unequivocal diagnostic criteria [7]. Thus IA must be considered as an emerging and mortal infectious disease in ICU patients even in the absence of an apparent predisposing immunodeficiency. The patterns of IA related infection may differ according to the type of underlying disease [9]. Unfortunately little is known about the characteristics of IA in ICU patients. It is often made late in the course of the infection because of clinical manifestations are usually non-specific, mycological cultures are difficult to interpret, and invasive procedures require to obtain histological specimens [10]. In Iran, there is no report on invasive fungal infections in ICU patients, in the present study we assessed IA related clinical risk factors and bronchoscopy findings IA in ICU patients.

Materials and methods

This study was performed at medical ICU units in Sari and Babul city in Mazandaran province from August 2009 through September 2010 all patients admitted to our were reviewed for inclusion in this study. We analysed ICU patients with one of the following underlying predisposing conditions who were at risk for developing IA; neutropenic patients including after chemotherapy or hematologic malignancy and non neutropenic patients including chronic obstructive pulmonary disease (COPD), solid organ transplant recipient, recipient of any other immunosuppressive treatment, and ICU stay more than 21 days. Radiological patterns of IA were classified either airway-invasive forms or angio-invasive forms, based on previ-

Tab. I. Demographic and characteristics of all patients with probable, possible and non-IA.

Characteristics	Probable IA (n = 9)	Possible IA (n = 4)	Non IA (n = 30)	All (n=43)
Age, yr., mean	47.8	62	58.4	56.5
Sex, male, (%)	6 (66.6)	2 (50)	16 (53)	24(58.8)
ICU length of stay, days	7.3	9.75	25	19.6
Mechanical ventilation, days	6.7	6.25	22	18.2
No. of deaths (%)	7 (77.8)	2 (50)	8 (26.7)	16(37)

Definition of abbreviations: IA= invasive aspergillosis; ICU= intensive care unit.

ous studies [11, 12]. Airway IA was considered when the predominant CT findings revealed a tree-in-bud pattern or peribronchial consolidation. During hospitalization, bronchoalveolar lavage (BAL) samples were collected by bronchoscope (Olympus BF20D) twice a weekly. The bronchus of the lobe in which consolidation was imaged by chest radiograph or chest CT scan was wedged, and 50 mL of 0.9% sterile saline solution at room temperature was instilled with a syringe through the working channel of the bronchoscope. The total volume of saline solution instilled into the lung was typically 150 mL, and 50 to 100 mL of BAL fluid was recovered. The presence of any tracheal or bronchial lesions was recorded by the endoscopist. The BAL samples were analyzed by culture and non-culture based diagnostic methods. BAL galactomannan (GM) antigen levels were measured by ELISA (Platelia Aspergillus GM EIA) assays. An optical density ratio of 1.0 was considered positive for GM in BAL samples [13].

Patients were assigned a probable or possible diagnosis of IA according to the consensus definition of the EORTC/MSG [14], with the modification. Probable IA was diagnosed when culture or cytology analyses of BAL fluid tested for Aspergillus species, and when one major clinical criteria (such as halo sign, air-crescent sign, or cavity within an area of consolidation on CT scan) or 2 minor clinical criteria (such as symptoms of lower respiratory tract infection, pleural rub, or a new infiltrate without an alternative diagnosis) were evident. Possible IA was defined by the presence of a host factor and either a positive culture or 1 major (or 2 minor) criteria. In this present study we were not be able to define a proven IA case (histologic evidence of tissue invasion) because there was an explicit refusal of the family to doing biopsy or autopsy.

Results

During the study period, 43 patients fulfilling the inclusion criteria were enrolled. According to the EORTC/MSG criteria, cases were classified as 9 (69.2%) of probable IA and 4 cases (30.8%) of possible IA. The median patient age was 56.5 years and 58.8% patients were male. The observed mortality in IA patients was 69.2% and 4 (30.7%) had survived. The characteristics of patients are summarized in Table I.

We found that the incidence of fever and rate of respiratory failure requiring mechanical ventilation were significantly higher in neutropenic patients than in patients with Solid organ cancer and COPD ($P < 0.001$). The macroscopic finding in bronchoscopy included of Prulent secretion (46.6%), Mucosal bleeding (30.7%), Mucosal erythema (23%), Trachobronchomalasia (15.3%). As showed in Table II, mucosal bleeding and prulent secretion were more prevalent in patient with IA. Neutropenic patients were more likely to exhibit peribronchial consolidation, mucosal bleeding, and mass-like consolidation. Hence, the airway-invasive pattern was more commonly observed in neutropenic patients (85.7%) than in other patients with IA.

Conclusions

Although a few studies have focused on the IA in ICU patients [15, 16], evaluation incidence of IA in ICU patients is important. The diagnosis of IA in patients with critical illness in ICU is even more difficult, because of Clinical manifestations are often non-specific, and diagnostic criteria have been adapted from standardized guidelines developed for ICU patients [10]. In addition, critically ill patients with prolonged stays in the ICU often develop pulmonary infiltrates, atelectasis and/or acute respiratory distress syndrome, whereas patients with prior lung disease (e.g. COPD) may present with pre-existing cavities on conventional chest radiographs [10]. In our study clinical signs are often lacking in ICU patients with IA, as reported by a previous study [8, 10, 16]. The radiological patterns of IA are usually characterized as airway-invasive or angio-invasive [17]. Therefore, our finding

Tab. II. Macroscopic finding in bronchoscopy of all patients with IA and non-invasive aspergillosis

Bronchoscopic features	IA (n = 13)	Non IA (n = 30)	p-value
Mucosal bleeding (%)	4 (30.7)	3 (10)	0.0154
Prulent secretion (%)	6 (46.6)	1 (3.3)	0.0082
Mucosal erythema (%)	3 (23)	4 (13.3)	0.0399
Tracheobronchomalasia (%)	2 (15.3)	0	0.0952

that the airway- invasive pattern was more commonly observed in neutropenic patients with IA is in agreement with previous reports [9, 17, 18]. Fiberoptic bronchoscopy with inspection of the tracheobronchial tree, sampling of deep airway secretions and BAL can be helpful [16]. This technique is a useful first procedure for the evaluation of IA patients, but a negative result does not exclude aspergillosis. Our study had several limitations. Firstly, we had a relatively small sample size which may have limited our power to detect differences between the groups. Secondly, because the critical condition of many patients did not permit an invasive diagnostic procedure and autopsy after death from patients suspected IA, has not been reported cases of proven IA.

In conclusion, the clinical and radiological features of IA differed between patients with underlying disease in ICU unit. Its occurrence in ICU usually entails a poor prognosis despite major recent improvements in the diagnosis and treatment of IA in patients with haematological diseases. Multicenter studies are warranted to explore the exact incidence and to better delineate clinical risk factors and bronchoscopy findings IA in ICU patients.

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