Clinical significance of extra-pulmonary involvement of invasive aspergillosis: a retrospective autopsy-based study of 107 patients

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Summary: Disseminated aspergillus infection has a poor prognosis, but few reports have been published on extra-pulmonary involvement in aspergillosis. We reviewed 107 autopsy records of patients with invasive aspergillosis. Fifty-five patients had extra-pulmonary aspergillosis. Organs involved included heart, kidney, central nervous system, gastrointestinal tract, spleen, liver, thyroid gland and pancreas. Extra-pulmonary aspergillosis produces different manifestations according to involved organs. Risk factors associated with dissemination included cytotoxic chemotherapy within a month of death (P = 0.0087). Lack of response to empiric or preemptive treatment of amphotericin B predicted IA dissemination (P = 0.0328). To improve prognosis of IA, it is important to recognize clinical features of extra-pulmonary aspergillosis and to institute the aggressive anti-fungal treatment.

Keywords: Invasive aspergillosis; haematological malignancy; extra-pulmonary aspergillosis; retrospective study; autopsy.

Introduction

Invasive aspergillosis (IA) is a common form of fungal infection encountered in patients undergoing cytotoxic chemotherapy for haematological malignancy. The incidence of aspergillus infection has increased dramatically during the last decade with the widespread use of aggressive chemotherapy and immunosuppressive agents. Despite the improvement of its recognition, prophylaxis and treatment, it is still associated with high morbidity and high mortality. The mortality rate reaches 50–60% when IA occurs during chemotherapy-induced neutropenia and exceeds 90% in the setting of bone marrow transplantation. The survival of patients depends on early diagnosis and prompt initiation of therapeutic measures, but a critical problem is the difficulty in making an early diagnosis.

The lung is a common portal of entry for aspergillus spores, and invasive pulmonary aspergillosis (IPA) is the most common form of aspergillus infection in immunocompromised patients. Aspergillus species have angioinvasive properties and frequently disseminate from the primary...
lesions, usually the lung, to a variety of organs via haematogenous spread. These organs include the central nervous system,4,5 liver,6 spleen,7 gut,8,9 adrenal glands10 and skin.11 In some patients, aspergillus can extend directly to contiguous structures, usually the pleura, heart, stomach, liver and large vessels.10

Extra-pulmonary involvement occurs at an advanced stage of IA, and represents an ominous sign for immunocompromised patients. However, few reports have been published on extra-pulmonary involvement in cases of aspergillosis,4±11 and clinical features have not been clarified. Recent reports suggest that even aspergillosis of the central nervous system, the most severe form of IA, can respond to aggressive anti-fungal treatment if the diagnosis is established early.12 We performed a retrospective autopsy-based study to clarify the clinico-pathological features of extra-pulmonary aspergillosis.

Materials and methods

Patients and their autopsy records

The autopsy reports of 1043 patients admitted to our hospitals for the treatment of hematological malignancy between 1980 and 1998 were reviewed. One hundred and nineteen patients showed pathological evidence of IA at autopsy. Complete clinical data concerning 107 patients with IA were obtained from the autopsy request forms and the patients’ records, and the following analysis was based on these 107 cases.

Definition of IA

Diagnostic criteria of invasive aspergillosis have been reported previously.13 Patients had IA, when there was histological evidence of tissue invasion by small and uniform, dichotomously branching hyphae, septate at regular intervals, and/or culture findings positive for Aspergillus species from sputa or lung.

Cases of definite IA were divided into two groups: disseminated IA and localized IA. Infection by Aspergillus species with multiple, non-contiguous organ involvement was defined as disseminated IA. IA localized to a single organ, with or without contiguous invasion to the adjacent organs, was defined as localized IA. Sinuses were not examined routinely and information regarding the frequency of involvement of these sites was not available.

Conditions of hospitalization

The management of fungal infection was similar in all hospitals. Between 1980 and 1993, patients received non-absorbable anti-fungal agents, usually oral amphotericin B, for prophylaxis of fungal infection. When aspergillus infection was suspected or confirmed, intravenous administration of amphotericin B at a dose of 0.1 to 1.0 mg/kg was initiated.

Since 1994, absorbable anti-fungal agents, usually fluconazole were used for anti-fungal prophylaxis. The dose of fluconazole varied from 100 to 400 mg. When neutropenic fever developed, it was treated according to Pizzo et al.14 Briefly a beta lactam antibiotic and an aminoglycoside were started empirically. Intravenous administration of amphotericin B at a dose of 0.5 mg/kg was added when fever persisted for more than 5–7 days. If the diagnosis of aspergillus infection was confirmed, the dosage of amphotericin B was increased to 1.5 mg/kg. Since 1996, we have the latex agglutination test and the (1–3)-beta-D glucan assay, and chest computed tomography for early diagnosis of IA as previously reported.15

All patients undergoing haematopoietic stem-cell transplantation and some patients receiving high-dose chemotherapy were cared for in protective isolation in a room equipped with a high-efficacy particulate air (HEPA) filter throughout their period of neutropenia.

Analysis of risk factors for extra-pulmonary aspergillosis

To define the characteristics of extra-pulmonary aspergillosis, we examined the organ distribution of invasive aspergillosis, signs and symptoms of disease, and causes of death in the 107 cases of patients with IA. The direct causes of death were considered to be related to IA, unless major underlying diseases or other complications had led to an inexorable chain of events terminating in death.

To investigate risk factors for extra-pulmonary involvement of invasive aspergillosis, we examined several variables, comparing patients with limited IA and those with disseminated aspergillosis. Variables included age, sex, primary diseases and remission status, duration of neutropenia, use of laminar air flow, use of corticosteroids, use of antibiotics, treatment of haematological malignancy within a month of death, and anti-fungal prophylaxis, pre-emptive or empiric anti-fungal treatment.
Neutropenia was defined as the number of peripheral neutrophils being below $0.5 \times 10^9$ L$^{-1}$. Response to amphotericin B was defined as fever reduction with the body temperature being below $38^\circ C$ within 72 h of initiation of the drug.

**Statistical analyses**

Univariate analysis using the Chi-squared test and the Mann–Whitney test were performed for patients’ variables to evaluate the risk of extra-pulmonary aspergillosis. Multivariate analysis of the risk factors with multiple logistic regression analysis was then performed.

**Results**

**Patients’ characteristics**

We examined the cases of 107 patients with invasive aspergillosis. There were 71 men and 36 women, with a median age of 54 (range 18–86). Primary haematological malignancies included acute myeloblastic leukaemia ($N = 39$), chronic myelocytic leukaemia ($N = 27$), acute lymphoblastic leukaemia ($N = 11$), chronic lymphocytic leukaemia ($N = 1$), non-Hodgkin’s lymphoma ($N = 16$), myelodysplastic syndrome ($N = 8$) and others ($N = 5$). Disease was refractory to cytotoxic chemotherapy in 96 cases, and in remission or sensitive to the treatment in the other 11 cases. Median duration of neutropenia within a month of death was 26 days (range: 0–30 days).

Five patients received haematopoietic stem-cell transplantation, and 25 patients were cared for in protective isolation in a room equipped with a HEPA filter. Seventy-seven patients received cytotoxic chemotherapy within a month of death and 104 patients received empirical antibiotics within a week of death. A corticosteroid was administered to 69 patients.

**Administration of anti-fungal agents and response to these drugs**

Thirty-nine patients received prophylactic systemic anti-fungal agents including fluconazole ($N = 27$), miconazole ($N = 6$), itraconazole ($N = 2$), and intravenous administration of amphotericin B at a dose of 0.1 mg/kg ($N = 4$). Twenty-eight patients received oral amphotericin B.

Seventy-two patients received empirical or pre-emptive anti-fungal agents. Forty-nine patients received intravenous amphotericin B empirically for antibiotic-resistant fever or suspected fungal infection. Transient fever lysis occurred in nine of the 49 patients. Information on use of anti-fungal agents was not obtained in four cases.

**Establishment of an ante-mortem diagnosis of IA**

An ante-mortem diagnosis of IA was established in 32 of the 107 cases (29.9%). In 16 cases, the clinical symptoms associated with IA were misinterpreted as infiltration of primary haematological malignancies ($N = 3$), gastrointestinal bleeding due to thrombocytopenia ($N = 1$), steroid-induced ulcer ($N = 1$), cerebral haemorrhage due to thrombocytopenia ($N = 1$), tuberculosis pericarditis ($N = 1$), a secondary event in a patient with poor general condition ($N = 3$), drug-induced hepatitis ($N = 1$), drug-induced hypothyroidism ($N = 1$), pleuritis ($N = 1$), shingles ($N = 1$), bacterial hepatic abscess ($N = 1$), and appendicitis ($N = 1$). No clinical signs suggesting the presence of IA were observed in 34 patients (31.7%) during life. In the other 25 patients, assessments of the clinical symptoms were not recorded.

Aspergillus species were cultured from sputum during life in nine of 48 patients (18.8%). Aspergillus antigen was positive in nine of 25 patients (36%) tested using the latex agglutination test.

**Extra-pulmonary involvement in cases of aspergillus infection**

Extra-pulmonary involvement was identified in 50 patients (Table I).

**Heart**

Twenty-eight patients showed cardiac involvement of invasive aspergillosis including abscess formation ($N = 9$), pericarditis ($N = 5$), endocarditis with or without formation of vegetation ($N = 5$), mycotic embolism in the coronary arteries ($N = 8$), and localized infiltration of Aspergillus spp. hyphae in the cardiac muscles ($N = 8$).

Twenty one patients were asymptomatic during their life. The other seven patients showed some symptoms including chest pain ($N = 4$), pericardial friction rub ($N = 1$), pain in the lower extremities ($N = 1$), and dyspnoea due to pulmonary congestion ($N = 1$). Ante-mortem diagnosis of cardiac aspergillosis was made in only one case.
Four patients died of cardiac complications of invasive aspergillosis. Two patients suddenly died of acute myocardial infarction due to mycotic embolism. One died of cardiac tamponade. One died of refractory arrhythmia due to aspergillus pericarditis.

Central nervous system (CNS)
CNS aspergillosis was identified in 20 patients. The pathological findings included haemorrhage without infarction \((N = 7)\), haemorrhagic infarction \((N = 7)\), infarction without haemorrhage \((N = 2)\), abscess formation \((N = 3)\), and encephalitis \((N = 2)\).

Nine patients with CNS aspergillosis showed abrupt onset of neurological disorders. Frequent signs were seizures \((N = 3)\), coma \((N = 7)\) and focal neurological deficits \((N = 3)\). No patients showed meningeal signs. An ante-mortem diagnosis of CNS aspergillosis was not established in any case. Neurological signs were not recorded in the remaining 11 cases.

In six of the 20 patients with CNS aspergillosis, the direct cause of death was CNS aspergillosis.

Kidney
Renal involvement was identified in 17 patients. The pathological findings included renal infarction \((N = 7)\), haemorrhage \((N = 1)\), pyelonephritis \((N = 2)\), abscess formation \((N = 5)\), localized infiltration of Aspergillus spp. hyphae in the renal parenchyma \((N = 4)\).

One patient was diagnosed as having primary renal aspergillosis, in which hyphae invaded the vascular walls of the renal artery causing haemorrhagic infarction of the kidney. In the other 16 patients, disseminated to the kidney was via haematogenous spread from the lung.

The majority of cases the patients with renal aspergillosis were asymptomatic but two patients with renal infarction developed acute renal failure and microscopic haematuria was observed in five patients. Elevation of serum creatinine levels was observed in one case, however, an ante-mortem diagnosis was not established in any of these cases.

Thyroid gland
Thyroid involvement was identified in 13 patients. Pathological findings included abscess formation \((N = 11)\), haemorrhage \((N = 1)\), and mycotic infarction \((N = 1)\).

Eleven patients were asymptomatic. One patient developed hyperthyroidism with marked swelling of the thyroid gland. The enlarged thyroid compressed the trachea, and death was due to respiratory failure. The other patient developed abrupt onset of hypothyroidism. The thyroid gland was markedly enlarged. The patient died of aspergillus encephalitis. In both of these two cases, post-mortem examination revealed diffuse infiltration of hyphae in the thyroid causing extensive destruction of the thyroid gland.

Thyroid involvement with Aspergillus species was not suspected in any of these cases during life.

Gastrointestinal tract
Upper gastrointestinal tract involvement was identified in 16 patients. The pathological findings were ulcer \((N = 8)\) and abscess \((N = 8)\). Abscess was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Involved organs by Aspergillus species</th>
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<tbody>
<tr>
<td>Type of IA*</td>
<td>Involved organs</td>
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<tr>
<td>Total</td>
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<tr>
<td>Localized IA</td>
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<tr>
<td>Lung (^1)</td>
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<td>Bronchial tree</td>
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<td>Pleura</td>
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<td>Trachea</td>
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<tr>
<td>Kidney</td>
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<tr>
<td>Disseminated IA (^1)</td>
<td></td>
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<tr>
<td>Heart</td>
<td></td>
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<tr>
<td>Kidney</td>
<td></td>
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<tr>
<td>Central nervous system</td>
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<tr>
<td>Upper gastrointestinal tract</td>
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<tr>
<td>Spleen</td>
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<td>Liver</td>
<td></td>
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<td>Thyroid gland</td>
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<tr>
<td>Lower gastrointestinal tract</td>
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<td>Pancreas</td>
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<tr>
<td>Diaphragm</td>
<td></td>
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<td>Adrenal gland</td>
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<td>Tongue</td>
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<td>Peritoneum</td>
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<td>Lymph nodes</td>
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<td>Parainus</td>
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<tr>
<td>Prostate</td>
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<td>Bone marrow</td>
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<td>Skin</td>
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<td>Bone</td>
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<td>Superior vena cava</td>
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<td>Pharynx</td>
<td></td>
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<tr>
<td>Ovary</td>
<td></td>
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<tr>
<td>Abdominal wall</td>
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</table>

* IA, Invasive aspergillosis; \(^1\) All the patients had pulmonary involvement of invasive aspergillosis; \(^1\) Including pleura and bronchial tree.
observed in the oesophagus \((N = 3)\), and the stomach \((N = 3)\). The sites of abscess were not recorded in two cases. Ulcers were observed in the stomach \((N = 5)\), oesophagus \((N = 1)\), oesophagus-cardia junction \((N = 1)\), and duodenum \((N = 1)\).

Eight patients were asymptomatic. The other eight patients showed some symptoms including upper abdominal pain \((N = 5)\), and massive melaena \((N = 4)\). One patient died of massive haemorrhage from gastric ulcer. Correct ante-mortem diagnosis was not made in these cases.

Lower gastrointestinal tract involvement was identified in nine patients. The pathological findings were ulcer \((N = 7)\), abscess \((N = 1)\), and embolism \((N = 1)\). Abscesses were observed in the intestine and colon \((N = 1)\). Ulcers were observed in the large intestine \((N = 4)\), small intestine \((N = 5)\), and ileocecum \((N = 1)\). Rectal involvement was not recorded.

Four patients were asymptomatic. The other five patients showed some symptoms including bloody diarrhoea \((N = 2)\), a mass in the intestine and colon \((N = 1)\), panperitonitis \((N = 1)\), and ileus \((N = 1)\). Ante-mortem diagnosis was not made in any of these cases.

**Liver**

Hepatic involvement was identified in seven patients. The pathological findings were hepatic infarction \((N = 6)\), abscess formation \((N = 4)\), intrahepatic haemorrhage \((N = 1)\), and infiltration of hyphae in the liver parenchyma \((N = 1)\). Aspergillus lesions in the liver extended into the diaphragm in two cases.

Six patients were asymptomatic, and one patient complained of right flank pain. Serum levels of hepatic enzymes were elevated in four cases. Mass lesions were detected in two patients. An ante-mortem diagnosis of hepatic aspergillosis was established in only one patient. No patient died of a hepatic complication of invasive aspergillosis.

**Spleen**

Splenic involvement was identified in 15 patients. The pathological findings were infarction \((N = 7)\), and abscess \((N = 8)\). Severe left abdominal pain developed in four patients with splenic infarction.

**Pancreas**

Pancreatic involvement was identified in five patients. The pathological findings were infarction \((N = 2)\), and abscess \((N = 3)\). The two patients with pancreatic infarction and one patient with pancreatic abscess were diagnosed as having acute pancreatitis based upon the clinical and laboratory findings. The remaining two patients with pancreatic abscess were asymptomatic. An ante-mortem diagnosis of pancreatic aspergillosis was not established in any of these cases.

### Causes of death

Of the 107 patients, 68 patients died of causes associated with IA. Fifty-two patients died of pulmonary or bronchial complications of IA. The extrapulmonary causes consisted of acute myocardial infarction \((N = 2)\), cardiac tamponade \((N = 1)\), refractory arrhythmia due to pericarditis \((N = 1)\), cerebral vascular diseases \((N = 5)\), encephalitis \((N = 1)\), respiratory failure due to compression of the trachea by an enlarged thyroid gland \((N = 1)\), haemorrhage from a gastric ulcer \((N = 1)\) and multiple organ failure due to disseminated aspergillosis \((N = 4)\).

In the other 39 cases, IA was not the main cause of death. The causes of death in these cases included progression of the primary haematological diseases \((N = 18)\), bacterial infection \((N = 2)\), candidal infection \((N = 4)\), cytomegalovirus infection \((N = 1)\), mucor zygomycosis \((N = 1)\), pseudomembranous colitis \((N = 1)\), pulmonary alveolar proteinosis \((N = 1)\), subarachnoid haemorrhage \((N = 1)\), cerebral haemorrhage \((N = 1)\), disseminated intravascular coagulation \((N = 1)\), congestive heart failure \((N = 2)\), haemorrhagic pancreatitis \((N = 1)\), laryngeal oedema \((N = 1)\), tension pneumothorax \((N = 1)\), renal haemorrhage \((N = 1)\), peritonitis \((N = 1)\) and unknown \((N = 1)\).

### Comparison between patients with limited IA and those with disseminated IA

In some patients, aspergillus infection was localized to the lung \((N = 49)\), the tracheobronchus \((N = 2)\), or the kidney \((N = 1)\). These patients were classified as having localized IA. The other 55 patients were diagnosed as having disseminated IA. The clinical characteristics of these two groups of patients are shown in Table II.

Patients who received cytotoxic chemotherapy within a month of death tended to develop disseminated IA compared to those who had not received it, and the difference was statistically significant \((P = 0.0203)\). Cytotoxic chemotherapy
within a month of death remained a significant risk factor for IA dissemination (odds ratio, 3.4, 95% \( P = 0.0087 \)).

Compared to patients with limited IA, those with disseminated IA tended to die of IA and were more likely to be diagnosed as having IA during their life. These differences were also statistically significant (\( P = 0.0013 \) and 0.0202, respectively). Lack of response to intravenous amphotericin B was as indicator of IA dissemination (\( P = 0.0328 \)).

### Discussion

A recent increase in the incidence of IA is documented in autopsy studies with haematological malignancies,\(^1\) and IA is clinically recognized as most significant fungal infection on patients undergoing bone marrow transplantation.\(^1\) \(^7\) Groll \textit{et al.} reported the prevalence of invasive fungal infections rose mainly due to a significant increase in aspergillus infection.\(^1\) \(^3\) Autopsy studies describe the organ distribution of disseminated aspergillosis,\(^1\) \(^3\) \(^6\) \(^8\) \(^9\), but, clinicopathological findings of extra-pulmonary aspergillosis are not described, except for an old report published in 1970.\(^1\) \(^9\)

In this study, aspergillus involvement in the lung was identified in 104 of the 107 patients (97%). Two were diagnosed as having primary aspergillus tracheobronchitis and one was diagnosed as having primary renal aspergillosis. Primary renal aspergillosis is a rare manifestation of IA.\(^2\) \(^2\) \(^3\) The portal of entry of \textit{Aspergillus} species is the respiratory tract in almost all patients with invasive aspergillosis. Thus, it is reasonable that intensive examination of the lung and the bronchial trees using either computed tomography (CT) scans or BAL be undertaken for early diagnosis of IA.\(^1\) \(^5\) \(^6\) \(^7\) \(^8\) \(^9\)

Extra-pulmonary involvement was observed in 53 of the 107 patients. The organ distribution was similar to the results which were shown in another studies.\(^1\) \(^3\) \(^6\) \(^8\) \(^9\)

Interestingly, patients with extra-pulmonary aspergillosis frequently showed some subjective or objective signs unique to the organs involved. For example, approximately half the patients with CNS aspergillosis showed some neurological signs including alteration of mental status, sudden seizures, hemiparesis and diminished consciousness. In most of the patients, CNS aspergillosis was misdiagnosed as either cerebral infarction or cerebral haemorrhage. We should recognize that CNS aspergillosis can manifest as cerebral vascular disease.

The gastrointestinal tract seems to be a common target for infection. The gastrointestinal tract may be another portal of entry for \textit{Aspergillus} species. De Medeiros \textit{et al.} described the possibility of aspergillus invasion through the gastrointestinal tract after disruption of the intestinal mucosal barrier by chemotherapy and Ansorg \textit{et al.} reported that faecal galactomannan antigen may reach the circulation in patients with dysfunction of the intestinal mucosal barrier by chemotherapy and Ansorg \textit{et al.} reported that faecal galactomannan antigen may reach the circulation in patients with dysfunction of the intestinal mucosal barrier, leading to diagnostically false-positive antigenaemia.\(^2\) \(^2\) \(^4\) A high incidence of gastrointestinal aspergillosis may be related to the intensive chemotherapy causing gastrointestinal toxicity. Half the patients showed some gastrointestinal signs; abdominal pain, haematemesis, and melaena were frequent signs of gastrointestinal aspergillosis. However, a correct diagnosis of gastrointestinal aspergillosis was not established in any

### Table II Comparison between patients with limited IA and those with disseminated IA

<table>
<thead>
<tr>
<th>Factors</th>
<th>Patients with limited IA</th>
<th>Patients with disseminated IA</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>49</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Age Median (range)</td>
<td>54 (18–84)</td>
<td>52.5 (19–86)</td>
<td>0.6797</td>
</tr>
<tr>
<td>Sex Male/female</td>
<td>30/19</td>
<td>41/17</td>
<td>0.3138</td>
</tr>
<tr>
<td>Status of primary haematological malignancies</td>
<td>Sensitive/refractory</td>
<td>5/44</td>
<td>0.9809</td>
</tr>
<tr>
<td>Chemotherapy within a month of death</td>
<td>Yes/no</td>
<td>28/21</td>
<td>0.0203*</td>
</tr>
<tr>
<td>Age Yes/no</td>
<td>32/17</td>
<td>37/21</td>
<td>0.8706</td>
</tr>
<tr>
<td>Duration of neutropenia within a month of death Days, median (range)</td>
<td>28 (0–30)</td>
<td>21 (0–30)</td>
<td>0.851</td>
</tr>
<tr>
<td>Prophylactic use of absorbable anti-fungal agents Yes/no</td>
<td>31/18</td>
<td>37/21</td>
<td>0.9549</td>
</tr>
<tr>
<td>Response to empiric or pre-emptive AMPH-B Yes/no</td>
<td>21/28</td>
<td>28/30</td>
<td>0.6973</td>
</tr>
<tr>
<td>Death associated with invasive aspergilosis Yes/no</td>
<td>6/15</td>
<td>1/27</td>
<td>0.0328*</td>
</tr>
<tr>
<td>Establishment of ante-mortem diagnosis of invasive aspergilosis Yes/no</td>
<td>23/26</td>
<td>45/13</td>
<td>0.0013*</td>
</tr>
</tbody>
</table>

*Statistically significant; IA, invasive aspergillosis; AMPH-B, amphotericin B.
case. Aspergillus infection should be included in the differential diagnosis of gastrointestinal haemorrhage in patients with haematological malignancy.

In contrast to CNS and gastrointestinal aspergillosis, a majority of the patients with thyroid or cardiac aspergillosis remained asymptomatic. The findings suggest that it is difficult to make an ante-mortem diagnosis of thyroid aspergillosis. Thyroid aspergillosis may not be associated with high mortality or high morbidity, unlike cardiac aspergillosis which carries a high mortality.

It is evident that disseminated aspergillosis is an ominous sign. However, the risk factors associated with Aspergillus dissemination remain to be clarified. We therefore compared the characteristics of the patients with localized IA (N = 49) and those with disseminated IA (N = 58). The characteristics of these two groups of patients are shown in Table II. Compared with patients with localized IA, those with disseminated IA tended to die of causes associated with aspergillus infection. Patients with localized IA tended to die of causes other than IA such as leukemic progression. The difference was statistically significant (P = 0.0013) (Table II). These findings suggest that it is essential to prevent the dissemination of aspergillus infection from the primary lesions. Interestingly, this study revealed that poor response to empirical or preemptive intravenous administration of AMPH-B and a history of cytotoxic chemotherapy within a month of death were significant indicators of IA dissemination (Table II). Cytotoxic chemotherapy suppresses the immune system and may help Aspergillus species to disseminate. A poor response to AMPH-B might be indicative of resistance of Aspergillus species or the poor condition of the host. We did not analyse neutrophil recovery as a variable because the majority of patients remained neutropenic. Patients who failed to respond to anti-fungal treatment have a high risk of IA dissemination. Aggressive anti-fungal treatment including surgical resection or combination use of anti-fungal agents may be required to improve the prognosis in such cases. In the near future, intravenous infusion of itraconazole and new compounds such as voriconazole and echinocandin may become valuable alternatives to AMPH-B or be used as second-line treatment for resistant infection.

We believe that we were able to define the extra-pulmonary involvement in cases of Aspergillus infection, but our autopsy surveys have several limitations. There is a potential for selection bias in how vigorously permission for autopsy examination is pursued. Patients who survive their infection are not included in these surveys and many patients who die are not subjected to autopsy examination. Only fatal cases were investigated in this study. However, patients who appear to respond to empiric therapy are not included in clinical surveys, and there is no currently available method to determine the proportion of patients who respond to empiric therapy that are really infected with Aspergillosis. In this survey, we did not perform cultures for Aspergillus species routinely. It is difficult to distinguish Aspergillus species from other fungi such as Pseudoallescheria using autopsy samples without microbiological examination.

In conclusion, aspergillus infection frequently disseminates to a variety of organs, and extra-pulmonary aspergillosis contributes to a high morbidity and a high mortality associated with IA. To improve the prognosis in cases of IA, it is important for us fully to recognize the clinical features of extra-pulmonary aspergillosis. We have clarified some of the clinical features of extra-pulmonary aspergillosis and have succeeded in identifying risk factors associated with extra-pulmonary aspergillosis.

References


