Case report

Aspergillus niger infection in patients with haematological diseases: a report of eight cases

Fallbericht. *Aspergillus niger*-Infektionen bei Patienten mit hämatologischen Erkrankungen

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Summary

In this paper we analysed clinical, laboratory characteristics and outcome of patients with haematological diseases who developed an *Aspergillus niger* infection, in a multicentre study involving 14 Italian Haematological Divisions during a 10-year period. The study recorded 194 consecutive microbiologically documented aspergilloses, eight of which (4%) were due to *A. niger*, and were observed only in five of the participating centres. The primary localization of infection was lung in seven cases and paranasal sinus in one case. Seven patients died at the end of follow-up. The death was mainly attributable to *A. niger* progression in six of them. Our study that collected the largest number of cases of *A. niger* infection in haematological malignancies confirms that this infrequent complication is characterized by a high mortality rate.

Zusammenfassung

In dieser Multizenterstudie von 14 italienischen Abteilungen für Hämatologie über zehn Jahre hinweg wurden 194 dokumentierte Aspergillosen erfasst, von denen acht (4%) durch *Aspergillus niger* bedingt waren; diese Fälle traten nur in fünf der beteiligten Einrichtungen auf. Primärlokalisation waren in sieben Fällen die Lunge und in einem die Nebenhöhlen. Sieben Patienten verstarben am Ende der Beobachtungsperiode. Bei sechs von diesen war überwiegend die *A. niger*-Progression für den Tod verantwortlich. Unsere Studie umfasst die größte Zahl von *A. niger*-Infektionen bei hämatologischen Grunderkrankungen und bestätigt, dass diese seltene Komplikation mit einer hohen Mortalität verknüpft ist.

Key words: *Aspergillus niger*, aspergillosis, pneumonia, lung, paranasal sinus, leukaemia.

Schlüsselwörter: *Aspergillus niger*, Aspergillose, Pneumonie, Lunge, Nasennebenhöhle, Leukämie.

Introduction

Invasive mould infections are a major cause of morbidity and mortality in patients with haematological malignancies.[1] The number of patients affected by malignancies who develop deep fungal infections has dramatically increased during the recent decades together with the use of more aggressive chemotherapy regimes, which lead to a longer duration of postchemotherapy neutropenia.[2] This increase is probably due to multiple factors: host defence impairments due to intensive cytotoxic chemotherapies, use of steroids or other immunosuppressive agents (cyclosporin, azathioprin), increase of environmental exposure, the use of parenteral nutrition, the destruction of the mucous barriers due to

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chemotherapy or other invasive procedures, the use of broad-spectrum antibiotics.[3] The majority of invasive mould infections occurs in patients with haematological malignancy and particularly in acute myeloid leukaemia patients.[2]

Among invasive fungal infection, *Candida* spp. have been the most frequent cause in neutropenic patients, but, while its incidence is substantially unchanged in the years, an increase of invasive mould infections has been observed in recent years due to an increase of *Aspergillus* spp. infection.[4] Among aspergillosis, *Aspergillus niger* represents a rare cause of infections in patients with haematological diseases. In the immunocompetent host this filamentous fungus constitutes the most frequent aetiological agent isolated in cases of otomycosis.[5,6]

In this retrospective analysis we reviewed the records of eight patients affected by haematological malignancies who developed an *A. niger* infection in order to evaluate the underlying disorder, the clinical presentation of the disease and the factors that influenced the outcome in these patients.

Patients and methods

Between January 1988 and December 1997, 194 microbiologically documented infections due to *Aspergillus* were observed in 14 Haematological Divisions who participated in the study: 108 episodes were caused by *A. fumigatus* (56%), 58 episodes by *A. flavus* (30%), 15 episodes by *A. terreus* (8%), four episodes by *A. versicolor* (2%) and one episode by *A. nidulans* (0.5%). An infection due to *A. niger* was documented only in the remaining eight patients (4%).

The diagnosis of proven, probable or possible aspergillosis was made following the criteria of the EORTC/MSG group.[7]

The charts of all patients with *A. niger* isolation were examined and the following main parameters were considered: demographic characteristics of patients, type and stage of the malignancy, clinical symptoms and signs of infection, radiological findings, site of infection, laboratory findings (i.e. neutrophil count, microbiological isolates, etc.), treatment administered, outcome, autopsy findings.

Results

The characteristics of the eight patients with *A. niger* infection are reported in Table 1.

They were seven males and one female with a median age of 65 years (range 22–71). In six patients

Table 1 Clinical characteristics of eight patients with haematological malignancies and *Aspergillus niger* infection.

Case	Age	Sex	HD	Treatment of HD	Site of infection	Signs and symptoms	Proof of diagnosis[1]	Serological results	Positive microbiological finding	Positive histological specimen
1	59	M	AML	Induction	Lung	Fever; cough	Proven	Not performed	Sputum	Autopsy
2	67	M	AML	Induction	Lung	Fever; cough	Proven	Not performed	Sputum	Autopsy
3	58	M	NHL	Induction	Lung	Fever	Proven	Not performed	Culture of autoptic lung sample	Autopsy
4	65	M	AML	Induction	Lung	Fever; cough	Probable	Positive	Bronchoalveolar lavage fluid	Not performed
5	71	F	AML	Salvage	Lung	Fever; dyspnoea	Probable	Positive	Sputum	Not performed
6	22	M	ALL	Salvage	Paranasal sinus	Fever; facial pain; nasal obstruction; facial oedema	Probable	Not performed	Nasal plugging	Not performed
7	65	M	AML	Induction	Lung	Fever; chest pain	Probable	Not performed	Sputum	Not performed
8	65	M	Aplasia anaemia	None	Lung	Fever; dyspnoea respiratory failure	Proven	Positive	Bronchoalveolar lavage fluid	Trans-bronchial biopsy

HD, haematological disease; AML, acute myeloid leukaemia; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia.
[1]According to the EORTC/MSG group criteria.[7]

the underlying haematological disease was represented by acute leukaemia, myeloid in four patients and lymphoid in the other two. The last two patients were affected by lymphoma and aplastic anaemia, respectively.

Seven patients underwent chemotherapy within 30 days before aspergillosis was diagnosed: five patients received induction chemotherapy and two patients salvage chemotherapy for haematological disease progression. Only the patient with aplastic anaemia did not receive chemotherapy. This patient developed *A. niger* pneumonia before the diagnosis of haematological disease and the fungal complication represented the first sign of his underlying condition. None of these patients underwent bone marrow transplantation procedures. Three patients received steroids before *A. niger* infection, with a methyl-prednisolone dosage of 60, 600 and 1600 mg respectively, for a median duration of 15 days (range 3–20). Seven patients were deeply neutropenic (ANC $<500\ \mu l^{-1}$), for a median of 14 days (range 6–30). Six patients received oral antifungal prophylaxis: in three cases with fluconazole, in two with topic amphotericin B and in one case with topic nystatin.

All signs and symptoms presented by patients are reported in Table 1. All patients presented fever with a median temperature of 38.5 °C. In particular one patient presented fever only, without other signs or symptoms suggestive for fungal infection, and diagnosis of aspergillosis was made at autopsy.

According to the EORTC/MSG criteria[7] proven aspergillosis was diagnosed in four cases, probable in four cases.

The primary site of infection was the lung in the majority of cases, seven patients, while the last patient had paranasal sinus infection with a concomitant orbital involvement. Interestingly none of these eight patients had an otomycosis.

Thorax X-ray exam was positive in four of the seven patients with primary pulmonary aspergillosis. Thorax CT-scan was performed only in those four patients with positive thorax X-ray and it was suggestive for aspergillosis in all cases. In the other three patients with negative thorax X-ray diagnosis was made only with lung examination at autopsy.

In the patient with paranasal sinus infection, cranial CT-scan showed a pattern compatible with aspergillosis.

Microbiological detection of *A. niger* was made from: sputum in four patients, bronchoalveolar lavage fluid in two patients, nasal plugging in one patient, and from the culture of autoptic lung sample in one case. Histopathological examination showing hyphae from trans-bronchial biopsy specimen was performed in one patient.

Autopsy was carried out in three patients only, and it confirmed the diagnosis of aspergillosis in all cases.

Treatment and outcome of the eight patients with *A. niger* infection are reported in Table 2.

Antifungal treatment was empirically administered in seven of these patients after a median of 90 h of unresponsive fever to broad-spectrum antibiotics (generally aminoglycoside plus cephalosporins and/or glycopeptide in those patients with central venous catheter). One patient died of fungal infection progression on day 4 after onset of the symptoms without receiving antifungal treatment. Deoxycholate amphotericin B (AmB) was employed in six cases at a median dose of 1 mg kg^{-1} day^{-1} (range 0.5–1.2). The total median dose of AmB administered was 26.5 mg kg^{-1} (range 10.7–40) for a median duration of 29 days (range 11–54). One patient was treated with liposomal AmB (l-AmB) for renal impairment (median daily dose 4 mg kg^{-1}).

Of the seven cases treated, two were responsive with disappearance of fever and improvement of clinical status, but one patient died after 55 days for leukaemia progression. In the remaining five cases aspergillosis progressed and patients died within 30 days from diagnosis. At 6 months from aspergillosis diagnosis only one patient was alive. Overall the death was mainly attributable to *A. niger* in six cases (75%).

Discussion

Despite the advances in antimicrobial therapy and supportive care, invasive fungal infections (IFI) have remained over the past decades a significant problem in patients with haematological malignancies. IFI are increasing in frequency in this population, and are also occurring earlier during the course of chemotherapy. Moreover, new fungi are increasingly recognized as potentially lethal pathogens.[8–15] Historically, *Candida* spp. has represented the main cause of invasive fungal infection. However, in recent years, autoptic studies confirm that the incidence of invasive mould infections is on the rise.[4,16–18] Among the invasive mould infections, aspergillosis is becoming the most relevant cause of death in patients with haematological malignancies, despite the availability of new antifungal agents and new formulations of old agents.[1,19–27] Of the more than 200 *Aspergillus* species known, *A. fumigatus* and *A. flavus* are frequently noted to cause infections in neutropenic patients. Conversely *A. niger*

Table 2 Treatment and outcome of the eight patients with *Aspergillus niger* infection.

Case	Antifungal prophylaxis	Antifungal therapy		Outcome
		Drug employed	Daily dosage (total days)	
1	Topic AmB	AmB	1 mg kg^{-1} day^{-1} (5)	Dead for infection
2	Fluconazole	AmB	1 mg kg^{-1} day^{-1} (2)	Dead for infection
3	Topic AmB	None		Dead for infection
4	Fluconazole	AmB	1 mg kg^{-1} day^{-1} (12)	Dead for infection
5	Topic nystatin	L-AmB	3 mg kg^{-1} day^{-1} (10)	Dead for leukaemia
6	Fluconazole	AmB	1 mg kg^{-1} day^{-1} (5)	Dead for infection
7	None	AmB	1 mg kg^{-1} day^{-1} (25)	Recovery from infection
8	None	AmB	1 mg kg^{-1} day^{-1} (10)	Dead for infection

AmB, amphotericin B; L-Amb, liposomal-amphotericin B.

is rarely demonstrated in immunocompromised hosts.[28,29]

There are several reports on its detection in patients suffering from otomycosis.[5,6]

Particularly *A. niger* is reported to be a frequent agent of external otitis in categories of immunocompetent subjects with mechanical removing devices or in subjects working in gardens. Few case reports on the onset of *A. niger* in haematological malignancies patients have been published.[28,29]

In this study we identified among a large number of haematological disease patients, eight cases of *A. niger* infection and this observation allows some interesting consideration.

In this subgroup of patients, pulmonary aspergillosis is the most frequent complication and none of our patients presented an otomycosis. These data suggest that the behaviour of *A. niger* in immunocompromised haematological patients appears to be similar than the other more frequently observed *Aspergillus* species.[30] We confirm that patients with acute leukaemia, in particular myeloid subtypes, represent the highest risk category.

Diagnostic procedures, both invasive and non-invasive, are necessary to reduce the risk that the infection is misdiagnosed or not identified. Frequently it is impossible to achieve a diagnosis with invasive procedures because of the bad general clinical conditions of the patient or because of thrombocytopenia. However, radiological procedures alone give information that does not always indicate whether an aspergillosis is present or what the infectious organism is.

The outcome of this infection is heavily influenced by the degree and duration of neutropenia. The impairment of the immune response by underlying haematological malignancies or immunosuppressive therapy may play a role in the onset and diffusion of aspergillosis, during the early phases of the treatment, in colonized patients. In our small series, the majority of patients developed *A. niger* complication during the first induction treatment.

In the great majority of patients, amphotericin B was the first line treatment. The treatment, most frequently empirically started, was effective in 25% of patients, while about 75% of patients died from fungal infection within 30 days from diagnosis. The mortality rate is higher than that observed in other larger series on cases of invasive mould infections.[30,31] Of course, the small number of cases reported here does not allow any statistical conclusion.

Although amphotericin B is the main antifungal drug, other agents, i.e. itraconazole or voriconazole, could be effective in the prevention and treatment of invasive mould infections. Future studies should be focused on preventive strategies aimed at reducing both environmental and host risk factors.

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