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Fatal haemoptysis in pulmonary filamentous mycosis: an underevaluated cause of death in patients with acute leukaemia in haematological complete remission. A retrospective study and review of the literature

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Summary. A retrospective study on a consecutive series of 116 patients affected by acute leukaemia with documented pulmonary filamentous mycosis (FM) admitted between 1987 and 1992 to 14 tertiary-care hospitals in Italy was made in order to evaluate the characteristics of those patients who developed fatal massive haemoptysis.

In 59/116 cases of pulmonary FM the infection was the principal cause of death and in 12 of these patients a massive haemoptysis was responsible for death. The diagnosis of FM infection was made ante-mortem in only four out of these 12 patients. The autopsy was performed in 11/12 patients and documented a FM infection. The mycetes isolated were: *Hyphomycetes* spp. (three patients), *Mucorales* spp. (two patients), *Aspergillus* spp. (seven patients).

At the time of the massive haemoptysis the mean neutrophil count was $7{\cdot}2\times10^9$/l, and no patient had relevant thrombocytopenia (mean 184×10^9/l, range 28–350) or coagulative abnormalities. The mean time which elapsed between resolution of chemotherapy-induced neutropenia (WBC $<10^9$/l) and occurrence of haemoptysis was 7 d. No signs or symptoms predictive of this fatal complication were identified.

Massive haemoptysis can be the cause of death in patients with acute leukaemia and pulmonary FM which in the majority of patients was not diagnosed *in vivo*. This complication occurs most frequently shortly after the recovery from chemotherapy-induced aplasia. The mechanism of lesion is unknown, but it may involve the vascular tropism of FM and the release of leucocyte enzymes. Better preventive and therapeutic antifungal treatments are needed to avoid this serious, albeit rare, complication.

Keywords: filamentous mycosis, acute leukaemia, haemoptysis.

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Infectious complications continue to represent an important cause of morbidity and mortality in neutropenic patients with haematological malignancies. Among pathogens liable to cause these infections, fungi are responsible with increased frequency in patients with acute leukaemia as a result of prolonged neutropenia which follows the aggressive chemotherapy. Fungal infections in these patients have a high mortality rate and those caused by filamentous fungi (*Aspergillus* spp. and *Mucorales* spp.) are the most severe. The incidence of filamentous mycotic (FM) infections in patients with acute leukaemia ranges from 14% to 23% (Denning & Stevens, 1990; Burch *et al*, 1987) and infection-related mortality has been reported to occur in 13–100% of patients within 2 months from diagnosis (Denning & Stevens, 1990;

Ruutu *et al*, 1987). The main clinical features are necrotizing bronchopneumonia or mycetoma. Pulmonary cavitation complicated by fatal haemoptysis has rarely been reported.

This promoted us to review the clinical features of a series of 12 patients who died of haemoptysis, identified by a retrospective analysis of 116 patients with acute leukaemia affected by *Aspergillus* or *Mucorales* pulmonary infection.

PATIENTS AND METHODS

Fourteen Haematology Departments took part in this study. Between January 1987 and December 1992, 1989 new cases of acute leukaemia (1496 AML and 493 ALL) were observed. The charts of 116 patients who had a diagnosis of microbiologically documented FM pneumonia were examined.

Microbiologically documented FM pneumonia was defined as: (a) histologic demonstration at autopsy of lung invasion by branched septate hyphae; or (b) multiple expectorated sputum cultures positive for FM during an episode of clinically and radiologically documented pneumonia; or (c) histology and/or culture of bronchoscopically obtained pulmonary bronchoalveolar lavage fluid positive for FM infection.

Haemoptysis was defined as >300 ml of blood loss in 24 h (Karas *et al*, 1976).

The following main parameters were taken into consideration: type of haematological malignancy; demographic characteristics of patients; clinical symptoms and signs of infection; radiological findings; WBC and platelet count, microbiological isolates from lung and blood; cause of death; autopsy findings; treatment received.

RESULTS

Eighty-six acute myeloid leukaemia (AML) and 30 acute lymphoid leukaemia (ALL) were found to have microbiologically documented FM pneumonia (*Aspergillus* spp. = 90, *Mucorales* spp. = 13, unidentified FM = 13). 59 of these (51%) died of the infection and 12 of them (20%) died of haemoptysis that caused acute asphyxia due to pulmonary flooding. None of the other patients presented any history or sign of even minor haemoptysis.

The clinical characteristics of the 12 patients who died of haemoptysis are summarized in Table I. 11 patients developed the infection after the first course of induction therapy, one patient after induction treatment for first relapse. All patients were hospitalized between chemotherapy and death.

Eleven patients, when haemoptysis occurred, had recovered from neutropenia due to chemotherapy treatment.

At the time of death, nine patients were in CR (seven AML and two ALL), two patients were resistant (one ALL, one AML) and one patient had an aplastic bone marrow. None of the patients had a history of previous mycotic infection. The mean duration of neutropenia (neutrophils $<0{\cdot}5 \times 10^9$/l) was 21 d (range 14–28). During neutropenia, all patients had received oral antifungal prophylaxis (four with amphotericin B, six with fluconazole, two with nystatin) for an average of 18 d (range 6–49). While neutropenic, 11 patients became febrile and received empirical treatment with broad-spectrum antibiotics (beta-lactam plus aminoglycoside with or without a glycopeptide), which was administered for an average of 8 d (1–17). In three patients a pneumonia was both clinically and radiologically evidence, bacteraemia was diagnosed in two cases (*Staphylococcus aureus* 1, *Streptococcus viridans* 1), and fever of unknown origin occurred in the other six patients. 10 patients received methylprednisone (mean total dose 1180 mg, range 120–2820; the mean daily dose being 60 mg (25–100), for a mean time of 17 d (range 4–34)). In four cases glucocorticoids were administered for the haematological disease (ALL); in three cases for the symptoms related to pneumonia (bronchospasm, dyspnoea) and in other three cases for transfusion reactions.

A correct *in vivo* diagnosis of FM was made in only four patients (see Table I). In two cases the presence of hyphomycetes in bronchial fluid was documented by cultural and cytologic study of the BAL; in one case *Aspergillus fumigatus* was cultured in the sputum; in the fourth case an elevated titre of serum antibodies against *Aspergillus* and clinical and radiographic findings confirmed the correct diagnosis. An elevated titre of serum antibodies was found in the other three patients.

The serology in our patients resulted diagnostic in four out of the seven cases in which it was performed.

An antifungal treatment was administered in seven patients. In six patients amphotericin B, mean total dose 650 mg (120–1080) was given i.v. and the mean time between the start of treatment and haemoptysis was 16 d. In another patient, who was unable to tolerate the amphotericin B, myconazole (total dose 11 g) was administered. None of the patients received granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF).

At the time of occurrence of the haemoptysis, 9/12 patients were in CR and 11/12 patients were no longer neutropenic. They had a mean neutrophil count of $7{\cdot}2 \times 10^9$/l (range 1·1–18) and a mean platelet count of 184×10^9/l (range 28–350). None of the patients presented coagulative abnormalities. In 11 patients the time between the end of neutropenia (increase of neutrophil count over 1×10^9/l) and the occurrence of haemoptysis was 7 d (range 1–31).

None of the patients presented premonitory symptoms or signs of haemoptysis, but all patients showed abnormal radiographic findings. Pulmonary cavitation was observed in four cases. The chest X-ray showed multiple infiltrates in four patients, and a single lesion in seven patients.

In five cases the pulmonary infection was characterized by a very mild symptomatology; one patient was completely asymptomatic and died suddenly without having had a chest X-ray performed. In six other cases the infection showed a dramatically progressive course, characterized by rapid worsening of the clinical status and of the radiological picture (Figs 1a–c show the typical evolution of the radiological picture of one of these patients). It is remarkable that the treatment with amphotericin B, performed in these six cases, was not able to prevent the haemoptysis.

Table I. Patient characteristics and radiographic, clinical and microbiological findings.

Case	Age/sex	Disease status*	Radiographic findings	Lung CT scan	Symptoms	Diagnosis	Mycotic agent
1	34/f	ANLL CR	Multiple nodular infiltrates in left upper and right lower fields	Not done	Pain, cough	BAL, autopsy, sierology	*Mucorales* spp.
2	67/m	ANLL CR	Singular nodular infiltrate in left middle field	Not done	Cough, fever, bronchospasm	Autopsy	*Hyphomycetes* spp.
3	30/f	ANLL CR	Multiple nodular infiltrates in right upper and left middle fields	Not done	Pain, cough, bronchospasm, dyspnoea, fever	Autopsy	*Aspergillus fumigatus*
4	48/m	ANLL CR	Singular nodular infiltrate in left lower field	Nodular mass with air crescent sign and halo phenomena	Pain, dyspnoea, cough, fever	Autopsy, sierology	*Aspergillus flavus*
5	25/m	ALL CR	Singular infiltrate in right middle field	Not done	Pain, fever	Autopsy	*Hyphomycetes* spp.
6	69/m	ANLL CR	Singular infiltrate in right middle field	Not done	Pain, cough, fever	Autopsy	*Aspergillus* spp.
7	54/m	ANLL PR	Not done	Not done	Completely asymptomatic	Autopsy	*Mucorales* spp.
8	39/m	ANLL CR	Multiple infiltrates in left and right middle fields	Not done	Cough, fever	BAL, autopsy, sierology	*Aspergillus* spp.
9	57/f	ALL aplasia	Singular infiltrate in left upper field	Fungus ball (0·3 cm) with pleural based infiltrate	Pain, cough, fever	Autopsy	*Aspergillus* spp.
10	66/f	ANLL resistant	Multiple infiltrates in left and right middle fields	Multiple nodular infiltrates without air crescent sign	Cough, fever	Autopsy	*Hyphomycetes* spp.
11	36/f	ALL CR	Singular nodular infiltrate in right middle field	Not done	Pain, cough, fever	Autopsy	*Aspergillus* spp.
12	42/m	ANLL CR	Singular nodular infiltrate in left middle field	Not done	Pain, dyspnoea, cough, fever	Sierology, sputum	*Aspergillus fumigatus*

* At the time of fatal event.

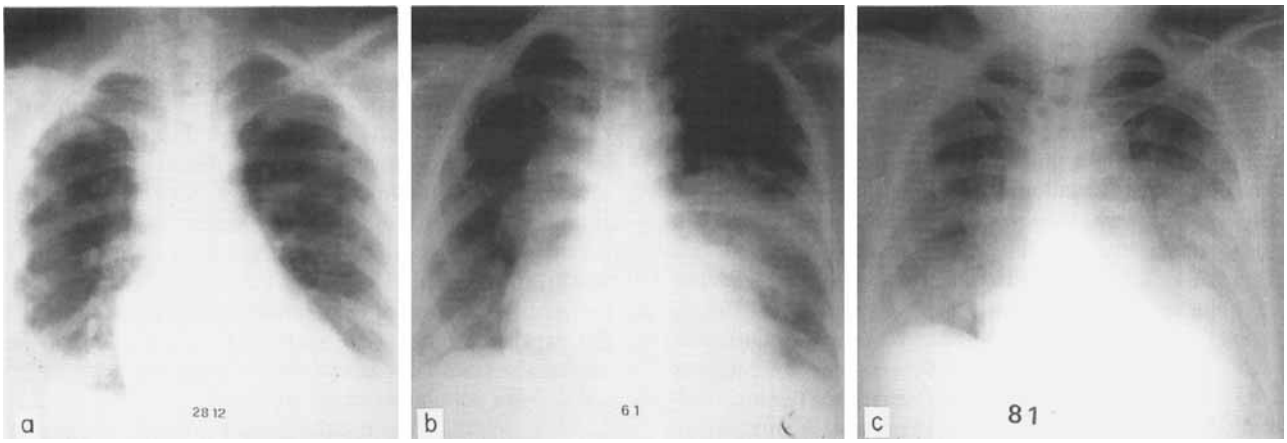

Fig 1. Case 3. (a) At the onset of the infection, the patient presented a right basal and a left parailar infiltrates. The patient was febrile and the neutrophil count was $<0{\cdot}5 \times 10^9$/l. (b) At day 10 the clinical status with cough, pain and bronchospasm and the radiologic picture worsened. The neutrophils were $1{\cdot}7 \times 10^9$/l. (c) At day 12 a further worsening of the X-ray was documented. The patient developed intense dyspnoea as well. Neutrophils were $15{\cdot}5 \times 10^9$/l. The patient died the following day of haemoptysis.

Autopsy was performed in 11 cases and in all patients their lungs were infiltrated by FM; in one patient a cerebral mycetoma was also present. The mycotic agents identified were: *Hyphomycetes* spp. 3, *Mucorales* spp. 2, *Aspergillus* spp. 4, *Aspergillus fumigatus* 2, *Aspergillus flavus* 1.

DISCUSSION

Pulmonary FM infections occur frequently in patients with acute leukaemia undergoing intensive chemotherapy as a result of deep and prolonged neutropenia that allows the fungus to become invasive. Almost all patients with an FM pneumonia, usually a pulmonary aspergillosis, die if the neutrophils do not return to normal. When patients recover from neutropenia the mortality rate falls significantly (Burch *et al*, 1987; Ruutu *et al*, 1987). However, fatal haemoptysis represents a significant risk of death related to the fungal infection in patients who recover from neutropenia. Table II summarizes the features of the 16 single case reports traced in the literature between 1977 and 1993, describing the death from haemoptysis due to pulmonary aspergillosis in patients with acute leukaemia.

A review of the characteristics of these case reports shows that they are very similar to those found in our patients. The haemoptysis developed when the neutrophil count was $>0{\cdot}5 \times 10^9$/l, and none of the patients was severely thrombocytopenic ($<26 \times 10^9$/l) or had coagulation abnormalities (Kibbler *et al*, 1988). The mean time between diagnosis of FM pneumonia and haemoptysis was 7 d and in nine cases CR was documented. The use of glucocorticoids

Table II. Case reports of fatal haemoptysis in leukaemic patients reported in the literature between 1977 and 1993.

Reference	Case	Underlying leukaemia	Status of disease	Fungal agent identified
Aisner *et al* (1977)	1	ANLL	CR	*Aspergillus* spp.
Luce *et al* (1979)	2	ANLL	Recovery after BMT	*Aspergillus niger*
Borkin *et al* (1980)	3	ALL	Not remission	*Aspergillus flavus*
Stein *et al* (1982)	4	ANLL	CR	*Aspergillus* spp.
	5	ANLL	nr	*Aspergillus* spp.
Albenda *et al* (1985)	6	AL	BM recovery	*Aspergillus* spp.
Capnist *et al* (1986)	7	ANLL	CR	*Aspergillus* spp.
Kibbler *et al* (1988)	8	ANLL	nr	nr
	9	ANLL	nr	*Aspergillus* spp.
Martino *et al* (1990)	10	ANLL	CR	*Aspergillus fumigatus*
	11	ANLL	nr	nr
Shpilberg *et al* (1991)	12	AL	CR	nr
Groll *et al* (1992)	13	ALL	CR	*Aspergillus* spp.
Young *et al* (1992)	14	AL	nr	nr
	15	AL	nr	nr
Turner *et al* (1993)	16	ALL	CR	*Aspergillus* spp.

nr = not reported; CR = complete remission.

(in 10/12 in our series of patients) and previous occurrence of bacterial pneumonia were considered contributing factors to the massive haemoptysis (Borkin *et al*, 1980).

Various hypotheses about the aetiology of haemoptysis have been suggested. During the aplastic phase following chemotherapy the hyphae colonize bronchi and bronchioles and, due to their vasculotropism, penetrate into the adjacent arteries. This might cause mycotic thrombosis of the vessels and local infarction, resulting in the formation of a mycetoma (Przyjemsky & Mattii, 1980). Glucocorticoids might facilitate the diffusion of the infection (Bodey & Vartivarian, 1989). Later on, when the bone marrow recovers and the neutrophil count rapidly increases, proteolytic enzymes are released from leucocytes, causing the destruction of lung tissue (Janoff *et al*, 1972; Weiss, 1989). As a consequence, the mycetoma liquefy and the infiltrated arteries are eroded causing a massive pulmonary bleeding (Fig 2). It has been suggested that this phenomenon may be caused by virulent strains of *Aspergillus*, which by producing elastase might contribute to the destruction of tissue (Kothary *et al*, 1984; Staib, 1985). *Mucorales* spp. have, to date, not been reported to be able to produce these effects, but we found this pathogen at autopsy in the lungs of two of our patients who died of haemoptysis.

All our patients received antifungal prophylaxis which was not able to prevent the occurrence of fungal pneumonia, and seven patients also received antifungal treatment (three empirically) without success. Alternative approaches to the prevention of these severe complications of FM pneumonia are of doubtful effectiveness.

In some cases the embolization of the damaged vessel (Kamesaki *et al*, 1989) or the surgical resection of the mycetoma (Young *et al*, 1992) have been suggested. The surgical procedure, in our experience, is not feasible in most cases due to the condition of the patient (low platelet count, low performance status), and to the frequent presence of multiple mycotic infiltrates in the lungs. A surgical approach is indicated only in those cases where a single lesion, proximal to the pulmonary arteries, is documented by a CT scan (Durand *et al*, 1993). On the other hand, with our patients, the absence of premonitory symptoms or signs and the rapidity of the event prevented embolization of the damaged vessels. The patients rapidly died of asphyxia due to the massive pulmonary blood flooding.

Other approaches to the treatment of pulmonary cavitations such as percutaneous intracavitary therapy with amphotericin B or the instillation of endobronchial antifungal agents used for the treatment of relapse of haemoptysis in sarcoidosis or tuberculosis (Shapiro *et al*, 1988; Fernandez, 1984; Hamamoto *et al*, 1983; Lee *et al*, 1993) do not seem feasible due to the high risk of bleeding in patients with acute leukaemia.

There is some anedoctal evidence that once the pulmonary cavitation has been diagnosed it might be useful to associate with amphotericin B a treatment with an anti-proteolytic agent such as aprotinin. This drug seems to reduce the release of elastase by neutrophils, preventing destruction of lung tissue (Thomson *et al*, 1978). These data require confirmation.

Noteworthy is the fact that pulmonary cavitation has

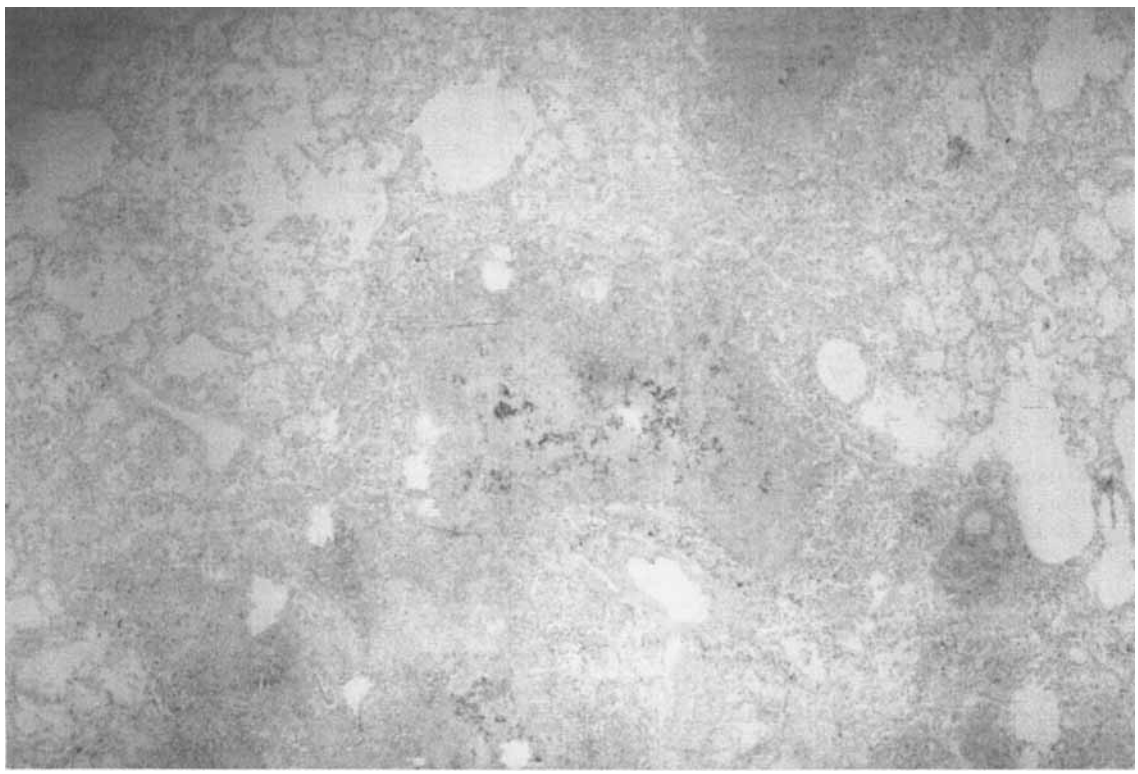

Fig 2. Case 5. Diffuse haemorrhagic infiltrate with presence of hyfae in a destroyed lung tissue documented by histological sections obtained during autopsy. (e.e. ×2·5).

been shown in only 4/12 patients. Although that could be an underestimate of the incidence of pulmonary cavitation due to the fact that only three patients underwent CT lung scan examination, the small percentage of patients in which such a condition is diagnosed limits even further the possibility of preventive treatments.

In conclusion, haemoptysis complicating FM pneumonia is a rare event but always fatal. The importance of this complication is increased by the fact that the group at risk for this complication includes patients in CR who could otherwise have a chance of cure. Fungal infections require more careful attention from haematologists, and more efficacious prevention of and treatment for FM pneumonia are needed.

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