Ann Hematol (1995) 70:135–141

ORIGINAL ARTICLE

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Pulmonary fungal infections in patients with hematological malignancies – diagnostic approaches

Received: 9 September 1994 / Accepted: 28 November 1994

Abstract In a retrospective study of 56 patients with hematological malignancies and fungal pneumonia we have analyzed the value of different diagnostic procedures. In all patients (*Candida* $n = 29$, *Aspergillus* $n = 23$, mixed fungal infection $n = 4$) bronchoscopy and/or high-resolution computed tomography of the lungs was performed. Cultural detection of fungi in bronchoalveolar lavage was successful in 23/32 *Candida* and 11/23 *Aspergillus* pneumonias. Other relevant pathogens were identified by bronchoscopy in 21 cases. Thorax CT scans showed diagnostic evidence of fungal pneumonia in 10/13 *Candida* and in 16/18 *Aspergillus* infections. Blood cultures were positive in 9/33 *Candida* pneumonias and in none of aspergillosis cases. Serological testing and surveillance cultures had only limited value for the early diagnosis of pulmonary mycosis. Our data suggest that bronchoscopy and high resolution CT scans are mutually complementary diagnostic tools with high sensitivity in patients with hematological malignancies and new pulmonary infiltrates. These procedures facilitate the early and reliable recognition of invasive fungal disease which may have a bearing on the initiation, length, and differential therapy of antimycotic drugs.

Key words *Candida* pneumonia · Aspergillosis · Bronchoscopy · High resolution CT scan

Introduction

Fungal infections, *Candida* and *Aspergillus* spp. being the prevalent pathogens, constitute a major increasing problem during the treatment of patients with malignant diseases [8, 10, 12, 19, 21, 22, 29]. The use of more potent cytotoxic agents with consecutive prolonged neutropenia, the wide use of glucocorticoids and broad spectrum antibiotics, and the employment of other supportive measures sustaining life during intense cytotoxic therapy propagate the occurrence of opportunistic mycoses.

Antemortem diagnosis of invasive fungal infections is difficult [1, 19, 30). The initial clinical and radiographic presentation is indistinguishable from those of other infectious pneumonias [5, 7, 16]. Clinical and radiographic findings in the lung are often absent especially in patients with severe neutropenia, when the patients first present [15, 18, 20]. Biopsy is often contraindicated because thrombocytopenia or blood coagulation disorders are frequent in this population. Bronchoalveolar lavage (BAL) is a safe and available technique with a high diagnostic yield in differentiating pulmonary infiltrates in immunocompromised patients [14, 18, 28]. High-resolution CT has been advocated in the early diagnosis of opportunistic fungal pneumonias [13, 16, 17].

Between January 1987 and December 1992, 56 patients at the University Hospital with hematological malignancies developed fungal pneumonia. In all these patients either bronchoscopy or computed tomography of the lungs or both was performed for the differential diagnosis of new pulmonary infiltrates. We here present our experience with this population, review the clinical features, and discuss the diagnostic and therapeutic approach.

Patients and methods

The patients' records and the respective autopsy results were evaluated. The following parameters were analyzed in addition to the clinical courses:
- Histological examination of tissue collected in vivo and/or post mortem,
- Conventional chest radiographs and CT scans of the thorax

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- Microbiological findings in bronchoscopic specimens, blood, and surveillance cultures
- *Candida*–IgM-antibody titers (*Candida* HA-test, Roche), *Candida*–antigens (Candtec-kit, Ramco), and *Aspergillus*–IgM-antibody titers (*Aspergillus*–HA-test, Roche)

CT scan

CT scans were performed with a Philips-Tomoscan 350-Scanner. In all cases scans were obtained at 0.9-cm intervals using 0.9-cm collimation. The lungs were viewed and photographed at a level of 600–700 Hounsfield units (H) and at a window width of 1000–1200 H. For the mediastinum, a window level between 40 and 60 H and a window width between 300 and 500 H was used.

Bronchoscopic studies

For BAL the bronchoscope was advanced and wedged into a segmental bronchus supplying an area of radiographic abnormality. Alveolar lavage was performed by the sequential installation and suctioning of 50-ml volumes of sterile physiological saline. The procedure was repeated four times, and the fluid returns were pooled. Aliquots of BAL fluid were used to culture aerobic bacteria, *Legionella*, mycobacteria, fungi and viruses. Cell smears were routinely stained with Grocott for detection of Pneumocystis carinii and fungal organisms, with Gram's stain for bacteria, and with auramine-rhodamine for mycobacteria. They were examined by direct immunofluorescence assay for Legionella and cytomegalovirus. Papanicolaou stains were examined for malignant cells, intracytoplasmic or intranuclear viral inclusion bodies, and hemosiderin-loaded macrophages. Bronchial secretions were aspirated via the working channel of the bronchoscope and examined for bacteria, fungi, mycobacteria, and legionellae.

Diagnostic criteria

A diagnosis of *fungal pneumonia* was established in patients presenting with new pulmonary infiltrates and fever resistant to antibiotic treatment for more than 5 days, using the following criteria: histological demonstration of pulmonary invasive disease, or positive cultures in bronchoscopic specimens of *Aspergillus* spp. or *Candida* spp. plus positive blood cultures and/or positive serological results increasing *Candida*-specific IgM antibodies $\geq$ 3 titer steps and/or elevated *Candida* antigen-titers $\geq$ 1:8. Positive cultures from sputum were also considered to be diagnostic for *Aspergillus* spp. If both *Candida* and *Aspergillus* spp. were isolated from the bronchoscopic specimens and patients fulfilled the criteria mentioned above, we regarded these cases as mixed fungal infections. These were included in the evaluation for the respective single pathogens with careful mention of their contribution.

Diagnosis of *Pneumocystis carinii* pneumonia required the detection of typical cysts in lavage fluid or in lung tissue. Cytomegalovirus pneumonia was assumed if the characteristic inclusion bodies were seen, or if the organism was grown from lung tissue or bronchoscopic specimens together with a significant rise of specific antibodies. Bacterial pneumonia was diagnosed by isolation of the organism in sputum, bronchoscopic specimens, pleural fluid or lung tissue. *Enterococcus* species, *Streptococcus viridans*, coagulase-negative *Staphylococci* and *Neisseria* species were regarded as etiologic agents of pneumonia only if the same species was concurrently isolated from blood, pleural fluid, or lung tissue and no other pathogen was identified.

The CT criteria for an invasive pulmonary *aspergillosis (IPA)* were angiotropic nodular parenchymal lesions ($>$ 0.5 cm) with or without an accompanying so-called halo-sign and/or wedge-shaped, pleural-based infiltrates [13, 16, 17]. Disseminated miliary lesions ($\leq$ 0.5 cm) were the typical CT presentation of *pulmonary candidiasis (PC)* [24–26]. The CT findings described above for IPA and PC were valid only with regard to patients with antibiotic-resistant fever.

Sensitivity was defined as the number of cases in which bronchoscopy and/or CT scans correctly established the final diagnosis of fungal pneumonia divided by the total number of cases in which a final diagnosis was established retrospectively by regarding all clinical, radiological, microbiological, serological, and histological information.

Statistical analysis

For statistical analysis the chi-Square and Student's *t*–Test were used.

Results

Fifty-six patients had fungal pneumonia. Of these, 29 patients had candidiasis and 23 patients had aspergillosis, and in four additional patients fungal infection was mixed.

Candidiasis was established histologically in eight cases (three ante mortem, five post mortem). The other 25 cases were clinically diagnosed on the basis of fever and pulmonary infiltrates unresponsive to antibacterial drugs, bronchoscopic specimens positive for *Candida*, and positive serological results. Additionally, either positive blood cultures (n = 9) or clinical and radiological response to antifungal treatment (n = 16) were demonstrated. *Aspergillosis* was diagnosed in 11 cases histologically (five ante mortem, six post mortem). In the other 16 cases *Aspergillus* spp. were cultured in BAL, bronchial secretions, and/or sputum, with characteristic CT changes (n = 10), significant *Aspergillus* antibodies in serum (n = 2), and clinical and/or radiological response to antifungal treatment (n = 11).

Clinical features

The patients' characteristics concerning sex, age, underlying diseases, and clinical features are given in Tables 1 and 2. Their clinical features did not distinguish patients with *Candida* pneumonia from those with aspergillosis. Fifty-two patients had received intensive cytostatic treatment, including 19 with relapsed leukemia, and 40 of them had consecutively developed severe neutropenia ($<$ 100 neutrophils/mm^3). Twenty-one patients were pretreated with steroids ($>$ 20 mg prednisone daily $\geq$ 5 days).

All patients had had fever refractory to broad-spectrum antibiotic therapy. On the average, temperatures above 38.4° C were documented for 16 days (range 4–62). Eighteen patients had two or more episodes of fever during hospitalization; the first bout of fever, usually responsive to antibiotic therapy, was followed by a second, persistent febrile episode. Cough and shortness of breath were common respiratory symptoms. Sputum was produced by less than half of the patients. Characteristic physical signs of pneumonia were often missing. Nine patients reported a history of preexisting lung disease (chronic obstructive lung disease n = 3, tuberculosis n = 4, fungal pneumonia n = 2).

Table 1 Patients' characteristics and clinical features [average (range; median)]

	Candida pneumonia $n=33$	Aspergillosis $n=27$
Male/female	23/10	12/15
Age: range, years	17–70	18–73
median	58	56
No. of patients with intensive cytostatic treatment	30	25
Days of neutropenia		
($<1000/mm^3$)	45 (7–95; 42)	48 (15–83; 46)
($<100/mm^3$)	20 (1–58; 16)	23 (6–54; 24)
Onset of pneumonia (days after neutropenia $<1000/mm^3$)	16 (1–46; 12)	17 (1–50; 15)
Duration of pneumonia (days)	32 (3–117; 27)	32 (16–65; 28)
No. of patients with mechanical ventilation	11	8
(days)	9 (1–21; 8)	10 (1–23; 7)
Start of antimycotic treatment (days after onset of pneumonia)	9 (1–33; 6)	9 (1–41; 6)
Treatment days	24 (1–82; 22)	24 (2–57; 21)
Total dosage	$n=29$	$n=26$
– Amphotericin B (g)	0.75 (0.04–1.40; 0.90)	0.98 (0.1–2.75; 0.88)
– 5-Fluorocytosine (g)	133 (10–380; 97)	157 (20–480; 130)
Outcome: Survivors (n)	15	13

Table 2 Underlying diseases

	Candida pneumonia $n=33$	*Aspergillus* $n=27$
Acute leukemia		
Acute myelogenous leukemia	22	14
Acute lymphoblastic leukemia	2	3
Blastic transformation of chronic myelogenous leukemia	1	2
Other hematological malignancies		
Hodgkin's disease	2	—
Non-Hodgkin's lymphoma	—	4
Chronic lymphocytic leukemia	2	3
Myelodysplastic syndrome	4	1

Table 3 Microbiological findings in bronchoalveolar lavage fluid (*BAL*) and bronchial secretions (*BS*)

Microorganisms	*Candida* pneumonia $n=32$		Aspergillosis $n=24$	
	BAL	BS	BAL	BS
Fungi				
Candida spp.	23	27	4	8
Aspergillus spp.	2	4	11	16
Pneumocystis carinii	—	—	1	—
Viruses				
Cytomegalovirus	3	—	1	—
Gram-negative bacteria				
Escherichia coli	2	1	—	—
Proteus mirabilis	1	—	—	1
Pseudomonas aeruginosa	1	—	1	2
Legionella pneumophila	1	3	3	1
Gram-positive bacteria				
Staphylococcus aureus	—	—	2	1
Staphylococcus epidermidis	14	11	7	8
Streptococcus pneumoniae	—	1	—	—
Streptococcus viridans	1	1	2	4
Enterococcus species	5	3	2	1

Time sequence of investigations

CT scans were performed prior to bronchoscopy in 21 patients. The median time to CT investigation counted from the onset of fever was 7 (range 2–48) days, to bronchoscopy 9 (range 0–53) days. The median interval between the emergence of radiographic infiltrates and CT scans was 2 (2–4) days and to bronchoscopy 3 (0–25) days.

Bronchoscopic findings

The bronchoscopic microbiology is listed in Table 3; the pathogens finally regarded as the major cause of pneumonia are listed in Table 4. Single cultures of *Candida* or *Aspergillus* spp. were grown in 27 episodes. In 19 episodes, candidiasis was mixed with *Aspergillus* ($n = 4$), bacteria ($n = 15$), or cytomegalovirus ($n = 2$). In 14 episodes, aspergillosis was mixed with *Candida* ($n = 4$), bacteria ($n = 11$), or cytomegalovirus ($n = 2$).

The sensitivity of BAL and bronchial secretions for diagnosing *Candida* pneumonia was 72 and 84%, re-

Table 4 Pathogens finally regarded as the major cause of pneumonia*

Microorganisms	*Candida* pneumonia $n=33$	Aspergillosis $n=27$
Fungi		
Candida spp.	33	4
Aspergillus spp.	4	27
Pneumocystis carinii	—	1
Viruses		
Cytomegalovirus	2	2
Gram-negative bacteria		
Escherichia coli	2	—
Klebsiella oxytoca	—	1
Proteus mirabilis	3	1
Pseudomonas aeruginosa	3	3
Pseudomonas maltophilia	—	1
Legionella pneumophila	5	4
Gram-positive bacteria		
Streptococcus pneumoniae	1	1
Staphylococcus aureus	1	3
Staphylococcus epidermidis	—	1

* Determined retrospectively using all clinical information with extended follow-up and results of microbiological, serological, and histological specimens

Table 5 Positive diagnostic results of bronchoscopy, CT scans, serology, blood and sputum cultures in patients with Candida pneumonia and aspergillosis* (*Hist.* histologically proven invasive disease)

	Candida pneumonia		Aspergillosis	
	$n=33$	Hist. $n=8$	$n=27$	Hist. $n=11$
Bronchoscopy	29/32	4/7	17/24	3/8
BAL	23/32	2/7	11/23	2/8
BS	27/32	3/7	16/24	3/8
Thorax CT	10/13	3/3	17/18	7/8
Serology	29/33	3/7	3/21	1/9
Blood culture	9/33	3/8	0/27	0/11
Sputum	14/19	2/4	4/19	2/9

* The denominator represents the total number of patients in whom the described procedure was applied

spectively. In aspergillosis the sensitivity of lavage fluid and bronchial secretions was 48 and 66%, respectively. Among patients with histologically proven invasive fungal diseases, three of eight aspergilloses and four of seven *Candida* pneumonias were diagnosed by bronchoscopy (Table 5). *Candida* spp. were also cultured in bronchial secretions of patients with aspergillosis, where they were retrospectively regarded as colonizers and not as etiologic agents. In comparison to BAL, the sensitivity of bronchial secretions in detecting *Aspergillus* and *Candida* pneumonia was higher; however, the specificity in diagnosing *Candida* pneumonia was lower. The specificity for detection of aspergillosis was 100% for BAL and bronchial secretions. Complications of bronchoscopy were noted in one patient studied: epistaxis requiring Bellocq's tamponade.

Positive *serological findings* were documented in 81% of patients with *Candida* and in 14% of patients with *Aspergillus* pneumonia. Among patients with histologically proven fungal pneumonia, a significant rise of IgM antibodies and/or positive antigen tests was found in three of seven with *Candida* pneumonia and in only one of nine with aspergillosis (Table 5). Early appropriate antibody response was lacking in the majority of patients, only ten of 33 *Candida* pneumonias and only one patient with aspergillosis showed positive serological findings during the first week of fungal pneumonia. None of the patients with aspergillosis, but 9/33 patients with *Candida* pneumonia had positive blood cultures.

We analyzed 481 surveillance cultures. In patients with *Candida* pneumonia the frequencies for at least one positive culture were as follows: oropharynx 66%, sputum 74%, urine 39%, anal smears 63%, and feces 82%. However, the specificity of these positive *Candida* surveillance cultures was low. In patients with aspergillosis, surveillance cultures for *Candida* spp. were positive in 19% as well. Surveillance cultures for *Aspergillus* spp. were negative, with the exception of three patients who showed positive sputum cultures.

Radiographic features

All patients showed new pulmonary infiltrates on their X-rays. On average, infiltrates were documented 8 (range 1–25, median 8) days after the onset of fever. Patients with neutropenia developed radiographic abnormalities significantly later compared with patients without neutropenia [9 (1–25) vs 3 (1–8) days, $p < 0.001$].

In *Candida* pneumonias conventional chest radiographs showed bilateral infiltrates in 22, localized lobar or bilobar infiltrates in 11 patients. Pleural effusions were documented in 14 patients. In patients with aspergillosis radiographic abnormalities included rounded pneumonias ($n = 17$). Cavitation was identified in three patients. Diffuse bilateral pulmonary infiltration was documented in 12 patients; in five episodes a reticular pattern occurred. Fourteen patients had pleural effusions.

CT scans were obtained for 31 patients and were helpful in the diagnosis of fungal disease in 26 episodes. Altogether, thoracic CT had a sensitivity of 84%; in diagnosing histopathologically proven fungal pneumonia CT even had a sensitivity of 91% (Table 5). CT findings of *Candida* pneumonia with multiple small nodules (miliary nodular pattern) were found in ten episodes (Fig. 1 a,b). A localized or diffuse nonspecific bronchopneumonia was observed in five patients with a *Candida* infection.

Typical CT signs of invasive pulmonary aspergillosis were found in 16 of 18 episodes. The CT' 'halo sign', a zone of lower attenuation surrounding a pulmonary mass, was present in seven patients who had early CT

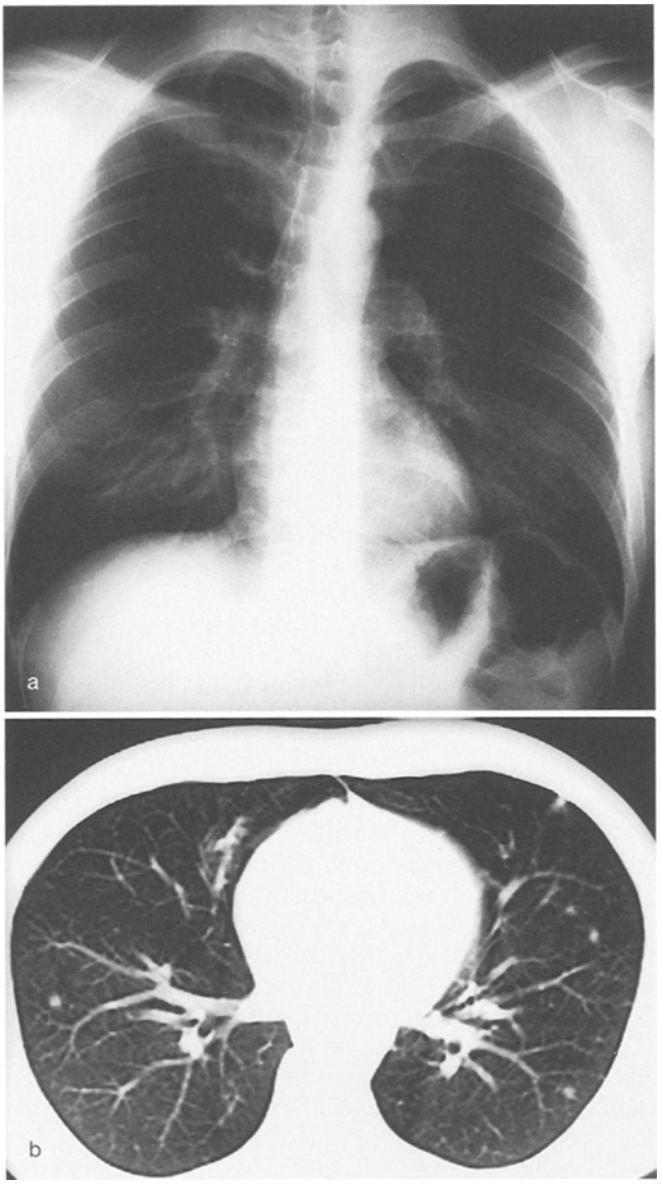

Fig. 1a,b Early pulmonary candidiasis in a patient with AML in aplasia. **a** No evidence of pulmonary infiltrates (standing chest X-ray). **b** Small angiotropic nodular lesions in both lungs (CT scans at the infracarinal level)

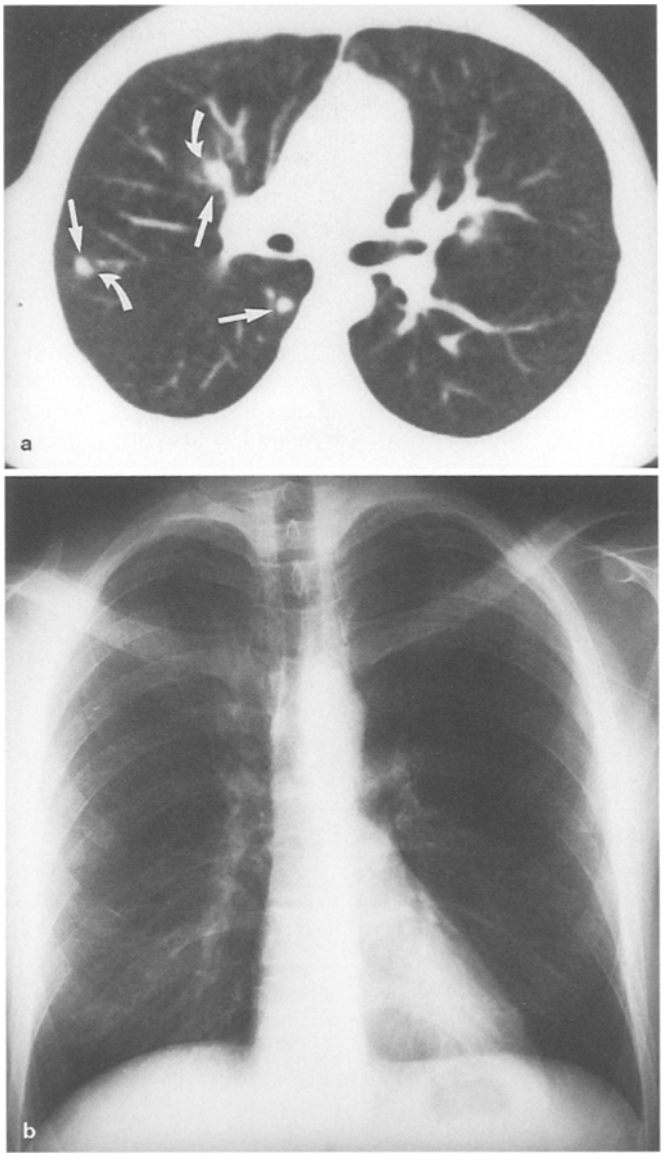

Fig. 2a,b Early invasive pulmonary aspergillosis (IPA). **a** No evidence of pulmonary infiltrates (standing chest X-ray). **b** Small angiotropic nodular lesions in the right lung (*arrows*) The nodules in the upper lobe show a typical halo sign (*curved arrows*) (CT scan at the infracarinal level)

scans obtained during bone marrow aplasia (Fig. 2b). An "air-crescent" formation during bone marrow recovery was documented in four of these patients. In addition, CT scans showed pulmonary cavitation ($n = 3$), angiotropic lesions ($n = 7$), pulmonary infarction ($n = 5$), and atelectasis ($n = 3$). The rounded pneumonias were equally distributed among all lobes and were 1–2 cm in diameter in 11 patients and greater than 2 cm in another nine patients. Twelve had bilateral lobar disease. CT established the presence of pulmonary infection before plain films were able to detect infiltrates in three patients (Fig. 1, 2).

Antimicrobial treatment

All patients had had empirical antibiotic treatment, starting with a double combination, usually comprising a third-generation cephalosporin and an aminoglycoside. For nonresponse antibiotics were changed between day 4 and 6, usually to imipenem plus cilastine and vancomycin. Empirical antibacterial treatment was adapted to different sources, mainly to microbiological results from either bronchoscopy or blood cultures. However, patients in the study did not show defeverescence or clearing of pulmonary infiltrates. Two patients did not receive any antifungal treatment, because fungal infection was not clinically evident. In the other pa-

tients i.v. antimycotics were started 9 (4–33) days after the onset of pneumonia with documented pulmonary infiltrates and/or body temperature elevated above 38.4° C. Antifungal treatment was given for 24 (1–82) days on the average.

Twenty-nine patients died during hospitalization. Mortalities of aspergillosis and *candida* pneumonia were similar (Table 1). Antifungal treatment and its timing influenced the mortality as follows: The two fungal infections without any i.v. antifungal treatment were fatal. Of 34 (38%) patients who were treated with i.v. antifungal drugs in the first 10 days after onset of pneumonia, 13 died. Yet, when i.v. antifungal therapy was started later, mortality increased to 70% (14/20, $p < 0.05$). The prognosis of our patients with fungal pneumonias has improved during the past few years. *Candida* and *Aspergillus* pneumonia treated between 1986 and 1989 had a mortality of 63% (15/24) and 67% (8/12), respectively. Between 1990 and 1992 the mortality decreased to 33% (3/9) and 40% (6/15) (n.s.). In these time periods the interval between onset of pneumonia and start of i.v. antifungal treatment was shortened from 11 (3–29) to 7 (2–27) days ($p < 0.05$). The duration of pneumonia of surviving patients was shortened from 33 (14–65) to 29 (19–45) ($p < 0.05$) days.

Discussion

Antemortem diagnosis of invasive fungal infections is difficult and yet must be made as early as possible to start specific treatment [1, 3, 9, 16, 21].

Serodiagnosis was rarely helpful in the early diagnosis of fungal infections, because an early antibody response was often lacking. In particular, there was no reliable serodiagnostic test for aspergillosis. The problems of antibody testing in these severely ill patients are well known [4, 6, 7, 11]. However, positive blood cultures and elevated antigen titers for *Candida* were helpful in the early diagnosis of this disease in about one third of the patients with candidiasis. Surveillance cultures were of rather limited value. For aspergillosis we found only negligible sensitivity. *Candida* spp. were detected with high sensitivity, yet the specificity was low.

There is little information to date on the role of fiberoptic bronchoscopy in the diagnosis of fungal pneumonia. No lethal complications were observed in published studies [2, 14, 18, 23, 27, 28]. In this study one minor complication occurred. *Candida* spp. were cultured with a high sensitivity, particularly in the bronchial secretions, but they were often regarded as colonizers and not as etiologic agents of pneumonia. A low specificity of *Candida* cultures in bronchoscopic specimens was also reported by others [18, 23, 27]. *Aspergillus* was diagnosed in BAL in 48%, in BS 66%, and there were no false-positive cultures of *Aspergillus* in our bronchoscopic specimens. In the investigation of Albelda et al. [2], bronchial washings and brushings established or suggested the diagnosis of invasive pulmonary aspergillosis in 8/16 patients. In another series, BAL detected none of the nine *Aspergillus* pneumonias in 22 adults with acute leukemia [27]. The significance of isolation of *Aspergillus* from the respiratory tract in patients with neutropenia was also affirmed by others [31].

Due to the retrospective nature of this investigation and our diagnostic criteria for fungal pneumonia, sensitivities of bronchoscopic specimens can be calculated only in relation to the highly selected patient population studied. Thus, sensitivities reported here appeared to be relatively high compared with other published data.

Although all patients had pulmonary infiltrates on X-ray, the radiographic findings were usually nonspecific and indistinguishable from those of other infectious pneumonias, particularly in patients with neutropenia. In contrast, CT lung scans were often helpful in the early diagnosis of fungal infection. Seven patients with presumptive aspergillosis showed the halo sign – a distinctive zone of lower attenuation surrounding a pulmonary mass – during the period of profound marrow aplasia. These lesions enlarged and progressed to cavitation on marrow recovery from chemotherapy. In pulmonary *Candida* infection, multiple small nodules were shown on CT scans, even in profound aplasia: The contribution of CT to the early diagnosis and management of invasive pulmonary aspergillosis and candidiasis was also described by several authors [13, 16, 17, 24]. In our retrospective analysis, CT diagnosis had the highest sensitivity in the early diagnosis of invasive fungal disease. Although we did find a median of 7 days (range 2–48) between the performance of fever and CT scans, this time changed considerably during the study period. For the last 2 years CT scans were routinely performed significantly earlier to exploit the higher sensitivity of this method in the detection of pulmonary infiltrates, thereby guiding the BAL towards the segments most likely involved in the infection. In the appropriate clinical setting, the presence of a CT halo sign or multiple small nodules strongly supported the diagnosis of invasive fungal disease. Yet the specificity of the CT halo sign and/or air-crescent sign has to be determined in future studies. In accordance with the experience of Kuhlman et al. [17], to date we have not found a documented infection, except of *Aspergillus*, in neutropenic patients demonstrating these signs.

In the period between 1990 and 1992, the survival of our patients with invasive pulmonary disease improved compared with the period between 1986 and 1989. This improval can be explained mainly by the significantly earlier start of i.v. empirical antifungal treatment in the later years. The structure of our antibacterial treatment was rather stable during the later period. CT diagnosis had a decisive influence on initiating, prolonging, and, in some cases, changing the antimycotic drugs. Bronchoscopy was of additional value, in order to prove the diagnosis and to identify organisms not covered by em-

pirical antimicrobial treatment such as *Pneumocystis carinii*, herpesviruses, or *Legionella*. From the data reported here, we derive the following recommendations: Because of the high frequency of mixed fungal and bacterial infection, empirical treatment with antibiotics and antimycotics should be started as soon as infiltrates are detected on X-ray in patients with severe neutropenia. Performance of a high-resolution CT scan as early as possible is warranted in this patient population. In case of negative chest X-rays, CT scans raise the sensitivity in the detection of minimal pulmonary infiltrates; in case of positive chest X-rays the specificity of the infiltrate patterns is improved. Additional bronchoscopy with BAL would help to establish the diagnosis of atypical pneumonias. Bronchoscopy can be established as a routine procedure with a reasonable amount of effort. As an in-house procedure it is well tolerated even by compromised patients.

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