Role of Fiberoptic Bronchoscopy in the Diagnosis of Invasive Pulmonary Aspergillosis in Patients with Acute Leukemia

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The utility and safety of fiberoptic bronchoscopy in the diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia have not been examined. The results of 21 bronchoscopic procedures in 19 patients with invasive pulmonary aspergillosis and acute leukemia were reviewed. Analysis was confined to the 16 patients who had histopathologically documented infection on biopsy or at autopsy. Fiberoptic bronchoscopy established or suggested the diagnosis of invasive pulmonary aspergillosis in eight of 16 (50 percent) patients. Transbronchial or bronchial biopsy added only one diagnosis to those obtained by bronchial washing and brushing. Although fiberoptic bronchoscopy was a safe and well-tolerated procedure in our patients with invasive pulmonary aspergillosis and acute leukemia, its success rate was only 50 percent overall, and it appeared to be even less successful when performed early in the course of the disease. Fiberoptic bronchoscopy is a useful first procedure for the evaluation of patients with acute leukemia and possible invasive pulmonary aspergillosis, but a negative result does not exclude aspergillosis. Further diagnostic procedures, including repeated bronchoscopy, or institution of empiric antifungal therapy may be warranted if the clinical suspicion of invasive pulmonary aspergillosis is high.

Invasive fungal disease is a major cause of morbidity and mortality in immunocompromised hosts [1,2]. Invasive pulmonary aspergillosis, which occurs in as many as 15 to 20 percent of patients with acute leukemia [3–5], is one of the most common of these fungal infections. Although invasive pulmonary aspergillosis was once a uniformly fatal disease [6,7], recent reports have demonstrated that early diagnosis and treatment with amphotericin B can be curative [7–12], especially for those leukemic patients in whom chemotherapy-induced granulocytopenia resolves [4,8–12].

Unfortunately, antemortem diagnosis of invasive pulmonary aspergillosis is difficult [4,6–11,13]. Microscopic and culture analysis of expectorated sputum, although simple and noninvasive, has been reported to lack both sensitivity and specificity [3,5–7,10,11,13]. Nasal swab surveillance cultures provide supportive evidence if they reveal Aspergillus fumigatus or A. flavus [4,14]; however, false-positive and false-negative results occur, and a histologic diagnosis of pulmonary infection is not obtained. Serologic detection of Aspergillus antigen in blood [15,16] and bronchoalveolar lavage fluid [17] is a promising technique, but this assay is not yet widely available.

More invasive techniques are required to confirm the diagnosis of invasive pulmonary aspergillosis. The most invasive procedure, open

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lung biopsy, has risk in pancytopenic leukemic patients [18–21]. "Closed" techniques that have been employed include transtracheal aspiration [22], percutaneous needle biopsy [10,23,24], fluoroscopically guided bronchial brushing [25–27], and fiberoptic bronchoscopy [10,28–36]. The success rate of these techniques—in particular of fiberoptic bronchoscopy—in invasive pulmonary aspergillosis has not been defined. This study was undertaken in the Oncology Study Unit of the Hospital of the University of Pennsylvania to determine the role of fiberoptic bronchoscopy in establishing the diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia.

PATIENTS AND METHODS

Study Design. Cases of invasive pulmonary aspergillosis among patients hospitalized on the Oncology Study Unit between July 1, 1978, and December 31, 1982, were identified by retrospective review of all patients admitted prior to November 1980 and by prospective evaluation of all subsequently admitted patients. Data were collected by review of patient charts, pathology records, the bronchoscopy suite logbook, and the mycology laboratory logbook.

Invasive pulmonary aspergillosis was diagnosed in 27 of the 130 adult patients with acute leukemia (including chronic myelogenous leukemia in blast crisis) admitted during the study period. Nineteen of these 27 patients from the study population underwent fiberoptic bronchoscopy. Bronchoscopy was not performed in eight patients at the discretion of their physicians, because of the apparent stability of their pulmonary process, response to empiric treatment with amphotericin B, thrombocytopenia unresponsive to platelet transfusions, or a rapidly deteriorating clinical course.

Patients were placed into one of two groups. Those with pathologically documented invasive pulmonary aspergillosis (Group I) had antemortem or postmortem histopathologic demonstration of pulmonary parenchymal invasion by septate hyphae morphologically consistent with Aspergillus species, with or without culture confirmation. Those with clinically documented invasive pulmonary aspergillosis (Group II) were patients for whom histologic evidence of Aspergillus infection was lacking, but who fulfilled the following criteria: (1) progressive pulmonary infiltrate(s) unresponsive to broad-spectrum antibiotic therapy with no other microbiologic or histopathologic diagnosis; (2) granulocytopenia and persistent fever; (3) either expectorated sputum culture evidence of Aspergillus species, nasal swab culture evidence of A. flavus or A. fumigatus, or nasal biopsy evidence of septate hyphae.

Results of bronchoscopy were considered "positive" when washings, brushings, or biopsy specimens either revealed typical septate, acutely branching hyphae by histochemical staining or grew Aspergillus species in culture, or both. Pathologic specimens labeled "transbronchial" but without alveolar tissue were described as bronchial specimens.

Radiographically defined pulmonary infiltrates were characterized as having one of the following patterns: 1) nodule(s); (2) cavitary alveolar infiltrate(s) (cavities); (3) wedge-shaped, pleural-based defect(s) (infarct pattern); (4) nonspecific alveolar infiltrate(s). Day 0 was used to designate the first day on which the infiltrate ultimately diagnosed as invasive pulmonary aspergillosis was recognized. Review and interpretation of chest radiographic findings was performed by one of the investigators (W.T.M.) without knowledge of the clinical course of the patients.

Techniques. The decision to proceed with bronchoscopy was made by the attending hematologist/oncologist, in conjunction with the pulmonary and infectious diseases consultation services. In all cases, bronchoscopy was performed by first-year pulmonary fellows under the supervision of a staff pulmonologist. If, at the time of bronchoscopy, the prothrombin time was more than two seconds above control, the partial thromboplastin time five seconds above control, or the platelet count less than 50,000/mm^3 despite platelet transfusions, bronchial or transbronchial biopsy was not attempted.

Patients were premedicated with atropine and meperidine and given supplemental oxygen by single nasal prong or by mask. The fiberoptic bronchoscope (Olympus model BF type B2 or B3) was introduced nasally after local anesthesia was induced with topical lidocaine. The tracheobronchial tree was inspected. The area of abnormality noted on chest radiography was identified by fluoroscopy. A standard cytology brush was introduced into this area, and specimens were obtained for cytologic and microbiologic staining. Washings were performed by instilling and then aspirating 20 to 40 ml of sterile saline into the appropriate segmental or subsegmental bronchus. If no bleeding had occurred, any endobronchial lesions were biopsied, and two to six transbronchial biopsy specimens of the abnormal area(s) were obtained with Olympus cup-type forceps under fluoroscopic guidance, using the technique described in detail by Zavala [33]. Bronchoscopic findings were recorded on a standardized bronchoscopy data sheet, which was included in each patient's permanent record.

Bronchial brushing, washing, and biopsy specimens were stained for fungus with Grocott stain, in addition to the standard histochemical stains. Washing, biopsy, and expectorated sputum specimens were cultured for fungus using conventional techniques [37].

Data Analysis. Data were analyzed for statistical significance by the two-tailed Fisher's exact test or the Wilcoxon rank-sum test.

RESULTS

Twenty-one bronchoscopies were performed in 19 patients. **Table I** summarizes the relevant findings in the 16 patients with pathologically documented invasive pulmonary aspergillosis (Group I) and the three patients with clinically documented invasive pulmonary aspergillosis (Group II). The Group II patients are included for comparison, but analysis of outcome is based only on the Group I patients.

The diagnosis of invasive pulmonary aspergillosis was established or suggested by eight of 18 bronchoscopies (44 percent) in eight of the 16 Group I patients (50 percent), as summarized in **Table II.** The

TABLE I Bronchoscopy and Other Diagnostic Tests in Invasive Pulmonary Aspergillosis

Patient Number	Type of Leukemia*	Day† of Bronchoscopy	Findings on Washings‡§	Findings on Brushings‡§	Findings on Biopsy‡§	Type of Biopsy	Sputum Cultures**	Day† Aspergillus flavus Identified from Sputum Culture	Confirmatory Tests for Invasive Pulmonary Aspergillosis§
Group I: Pathologically Confirmed Invasive Pulmonary Aspergillosis, "Positive" Bronchoscopic Result									
1	AML	2	−	+ (H)	ND	ND	2/2	9	Autopsy (H)
2	AML	3	+ (H,C)	+ (H)	−	Bronchial††	2/3	7	Autopsy (H)
3	AML	5	+ (C)	−	−	Bronchial††	0/1	−	Needle biopsy of lung (H)
4	ALL	1	+ (H,C)	+ (H)	+ (H)	Trans-bronchial	1/1	6	Nasal swab (C), pleural fluid (H)
5B‡‡	ALL	19	+ (H)	−	+ (H)	Trans-bronchial	1/1	18	Nasal swab (C)
6B‡‡	AML	8	+ (H)	ND	−	Trans-bronchial	0/7	−	Autopsy (H,C)
7	AML	2	+ (H,C)	+ (H)	ND	ND	1/2	8	Sinus biopsy (H), autopsy (H)
8	AML	6	−	−	+ (H,C) −	Bronchial Trans-bronchial	1/3	26	
Group I: Pathologically Confirmed Invasive Pulmonary Aspergillosis, Negative Bronchoscopic Result									
5A‡‡	ALL	3	−	−	ND	ND	1/1	18	Second bronchoscopy
6A‡‡	AML	2	−	−	−	Trans-bronchial	0/7	−	Autopsy (H,C)
9	ALL	2	−	−	ND	ND	3/5	19	Nasal swab (C), sinus (C§§), autopsy (H)

* ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CML-BC = chronic myelogenous leukemia in blast crisis.
† Number of days after the infiltrate ultimately identified as invasive pulmonary aspergillosis appeared on chest radiography; Day 0 = first day infiltrate noted.
‡ + = organisms consistent with Aspergillus species visualized or cultured; − = no organisms consistent with Aspergillus species visualized or cultured.
§ H = 45-degree septate branching hyphae consistent with Aspergillus species visualized; C = Aspergillus flavus cultured.
** Number growing Aspergillus flavus/number of fungal sputum cultures.
†† Transbronchial biopsy attempted but no alveolar tissue was visualized.
‡‡ Bronchoscopy was carried out twice; A designates first, B second bronchoscopy.
§§ Aspergillus niger cultured.

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TABLE I (cont'd) Bronchoscopy and Other Diagnostic Tests in Invasive Pulmonary Aspergillosis

Patient Number	Type of Leukemia*	Day† of Bronchoscopy	Findings on Washings‡§	Findings on Brushings‡§	Findings on Biopsy‡§	Type of Biopsy	Sputum Cultures**	Day† Aspergillus flavus Identified from Sputum Culture	Confirmatory Tests for Invasive Pulmonary Aspergillosis§
10	AML	1	–	–	–	Trans-bronchial	0/0	–	Open lung biopsy (H)
11	AML	1	–	–	–	Bronchial††	0/0	–	Open lung biopsy (H)
12	CML-BC	5	–	–	–	Trans-bronchial	0/0	–	Autopsy (H,C)
13	AML	0	–	–	ND	ND	0/0	–	Nasal biopsy (H,C), open lung biopsy (H)
14	AML	1	–	–	–	Trans-bronchial	0/0	–	Nasal swab (C), autopsy (H,C)
15	AML	2	–	–	–	Trans-bronchial	0/0	–	Nasal swab (C), autopsy (H,C)
16	AML	11	–	–	–	ND	0/4	–	Autopsy (H,C§§)
Group II: Clinically Documented Invasive Pulmonary Aspergillosis									
17	ALL	8	+ (H)	+ (H)	–	Trans-bronchial	0/2	–	Nasal swab (C), nasal biopsy (H,C)
18	AML	5	–	–	–	Trans-bronchial	2/2	17	
19	AML	5	–	–	–	Bronchial††	2/2	25	

* ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CML-BC = chronic myelogenous leukemia in blast crisis.
† Number of days after the infiltrate ultimately identified as invasive pulmonary aspergillosis appeared on chest radiography; Day 0 = first day infiltrate noted.
‡ + = organisms consistent with Aspergillus species visualized or cultured; – = no organisms consistent with Aspergillus species visualized or cultured.
§ H = 45-degree septate branching hyphae consistent with Aspergillus species visualized; C = Aspergillus flavus cultured.
** Number growing Aspergillus flavus/number of fungal sputum cultures.
†† Transbronchial biopsy attempted but no alveolar tissue was visualized.
‡‡ Bronchoscopy was carried out twice; A designates first, B second bronchoscopy.
§§ Aspergillus niger cultured.

success rate in finding Aspergillus organisms in bronchial washing specimens was six of 18 (33 percent), in bronchial brushing specimens four of 17 (24 percent), in bronchial biopsy specimens one of four (25 percent), and in transbronchial biopsy specimens two of nine (22 percent). Only one of seven biopsy specimens from patients with negative washing and brushing results revealed Aspergillus organisms.

At least one expectorated sputum sample was obtained from all eight patients with "positive" bronchoscopic results but from only two patients with nondiagnostic results ($p = 0.006$, two-tailed Fisher's exact test). A. flavus was recovered from 16 of 43 (37 percent) of the sputum samples collected. Six of eight patients with "positive" bronchoscopic results and one of eight patients with nondiagnostic results had culture-positive sputum. The median interval between Day 0 and the identification of A. flavus from expectorated sputum cultures was nine days (range, six to 26 days). In contrast, the median interval between Day 0 and the day that the eight "positive" bronchoscopic results were obtained was four days (range, one to 19 days). In only one patient (Patient 5) was the positive result of sputum culture available before the "positive" bronchoscopic result was obtained.

No complications occurred during or following bronchoscopy. There were no deaths or episodes of uncorrected hypoxia, pneumothorax, or hypotension. Significant hemorrhage (greater than 30 ml) after bronchoscopy was not observed, perhaps because biopsy was not attempted in patients with abnormal coagulation parameters or uncorrected thrombocytopenia.

TABLE II Yield of Diagnostic Procedures for Invasive Pulmonary Aspergillosis*

Procedure	Positive Results/ Number Performed		Percent
Fiberoptic bronchoscopy (total)	8/18		44
Washings or brushings	7/18		39
Washings		6/18	33
Brushings		4/17	24
All biopsies	3/13		23
Bronchial		1/4	25
Transbronchial		2/9	22
Sputum collection	16/43		37

* Group I patients only.

To determine whether any features were predictive of "positive" bronchoscopic results, a comparison of the following variables was performed between the eight instances in which a diagnosis of invasive pulmonary aspergillosis was suggested or established by bronchoscopy and the 10 instances in which bronchoscopy gave false-negative results: radiographic appearance, appearance of the tracheobronchial tree, the effects of prior treatment with amphotericin B, and the timing of bronchoscopy (**Table III**).

TABLE III Factors Associated with "Positive" Bronchoscopic Results*

Factor	Total Studies (n = 18)	Studies with "Positive" Bronchoscopic Results (n = 8) Number	Percent
Chest radiographic finding			
Cavity	1	1	100
Nonspecific alveolar infiltrate	12	6	50
Nodules	3	1	33
"Wedge-shaped infarct" pattern	2	0	0
Findings on visualization of the tracheobronchial tree			
Bronchial ulceration	1	1	100
Mucosal edema and erythema	8	5	62.5
Hemorrhage	3	1	33
Purulent secretions	3	0	0
Normal	3	1	33
Prior treatment with amphotericin B			
Studies performed in patients treated less than five days before study	15	7	46
Studies performed in patients treated more than five days before study	3	1	33
Timing of bronchoscopy			
Studies performed more than five days after the appearance of lesion on chest radiography	5	4	80
Studies performed within five days after the appearance of lesion on chest radiography	13	4	31

* Group I patients only.

The small number of patients in each of the radiographic groups makes conclusions difficult. There was no definite correlation between a positive bronchoscopic result and any particular radiographic pattern. In 15 of 18 bronchoscopic studies, abnormalities were noted on visualization of the tracheobronchial tree. However, patients with abnormalities did not invariably have "positive" bronchoscopic findings. Specifically, the presence of blood or purulent secretions did not appear to increase the success rate. Conversely, one of three patients with a normal tracheobronchial tree on inspection had a "positive" bronchoscopic result. Prior amphotericin B therapy, likewise, did not seem to affect the bronchoscopic success rate; however, there were only three patients who had been treated for more than five days before bronchoscopy was performed.

In contrast, the timing of bronchoscopy may have had an effect on the success rate. The median interval between Day 0 and the time that bronchoscopy was performed was four days (range one to 19 days) in the group with "positive" results and two days (range zero to 11 days) in the group with nondiagnostic results. Four of five (80 percent) studies performed more than five days after Day 0 gave "positive" results as opposed to only four of 13 (31 percent) of the studies performed within five days of Day 0. It appeared that the "positive" bronchoscopic results were obtained later after Day 0 than the nondiagnostic results. This difference approached, but did not achieve, statistical significance ($p = 0.12$, Wilcoxon rank-sum test).

COMMENTS

The utility of fiberoptic bronchoscopy for the evaluation of new pulmonary infiltrates in immunocompromised patients has been extensively studied [13,20,28–36]. Definitive diagnosis has been reported in 5 percent [19] to 85 percent [29] of cases. This wide variation in success seems to depend on a number of variables: the experience of the bronchoscopist and laboratory [34]; radiographic appearance of the infiltrate (localized versus diffuse) [30,32]; underlying disease entity (e.g., renal failure versus lymphoma versus leukemia); diagnostic procedures performed (washing, brushing, or biopsy); local endemic pulmonary disease (e.g., coccidioidomycosis) [30]; and the study definition of "definitive diagnosis" (some studies include "cytotoxic lung," "toxic reactions," or "fibrosis" as distinct disease entities) [30,32,38].

This study provides data about the ability of bronchoscopy to establish the diagnosis of a specific infectious process. Information of this sort exists only for a few diseases, such as Pneumocystis carinii pneumonia, in which fiberoptic bronchoscopy has a 60 to 90 percent true-positive rate [10,28,31,39]. We found that fiberoptic bronchoscopy established or suggested the correct diagnosis in 50 percent of cases of pathologically confirmed invasive pulmonary aspergillosis in our population of patients with acute leukemia. In contrast to the experience in tuberculosis and P. carinii pneumonia, in which transbronchial biopsy significantly increases the diagnostic yield of fiberoptic bronchoscopy [31,40], the relative contribution of transbronchial or bronchial biopsy in demonstrating the presence of Aspergillus species was minimal. Bronchial washing, the most useful study, gave "positive" results in six of eight patients (75 percent) in whom the diagnosis was established by bronchoscopy. Biopsy added only one additional "positive" diagnosis to those suggested by bronchial washing or brushing.

We were unable to identify any feature that was unequivocally predictive of a "positive" bronchoscopic result. There was no correlation between "positive" results and the findings on gross inspection of the tracheobronchial tree, the radiographic abnormalities visualized, or prior treatment with amphotericin B. Bronchoscopy performed later in the course of the infection appeared to have a higher success rate, but this trend was not significant at the $p < 0.05$ level.

The diagnostic significance of tracheobronchial specimens obtained by bronchoscopy or sputum collection remains controversial [11,13]. To establish unequivocally a diagnosis of invasive pulmonary aspergillosis, evidence of both parenchymal invasion of lung tissue and a growth of fungus should be demonstrated [11,41]. Many authors, however, consider the visualization of the characteristic septate hyphae in bronchial washing or brushing specimens, combined with a compatible clinical and radiographic picture, sufficient evidence to establish the diagnosis of invasive pulmonary aspergillosis [4,5,8,9,42]. Our data support this assumption. False-positive results appear to be unusual, since patients without chronic lung diseases rarely show colonization of the lower tracheobronchial tree with Aspergillus species [4,5,43,44].

In our group of 130 patients with acute leukemia, expectorated sputum samples also appeared to be helpful. There was a high correlation between the ability to obtain expectorated sputum samples and "positive" bronchoscopic results. Furthermore, all but one of the patients with "positive" bronchoscopic results and one patient with a nondiagnostic bronchoscopic result had one or more sputum samples that grew A. flavus. There were no Aspergillus-positive sputum samples in patients without convincing clinical or histopathologic evidence of invasive pulmonary aspergillosis. This association may be strongest for A. flavus and A. fumigatus, as opposed to other Aspergillus species, which may be found as contaminants.

The diagnostic information gained from sputum collection has one major limitation: there is an un-

avoidable and sometimes considerable delay before results are available. In our patients, at least six days elapsed between Day 0 and the day that a definite identification of A. flavus could be made from expectorated sputum. Immediate examination of potassium-hydroxide-processed sputum might eliminate this delay.

There are a number of potential sources of bias in this study that deserve mention. First, it is possible that some patients with undiagnosed invasive pulmonary aspergillosis underwent bronchoscopy with negative results. Second, eight of 27 patients were not subjected to bronchoscopy for reasons previously described. Finally, it should be noted that, by design, the population studied was a specific one. All patients had acute leukemia, and all were treated in a single oncology study unit. The prevalence of invasive pulmonary aspergillosis during the study was relatively high, and almost all the infections were due to A. flavus. The use of bronchoscopy in different clinical and epidemiologic situations may yield different results.

In conclusion, fiberoptic bronchoscopy established or suggested the diagnosis of invasive pulmonary aspergillosis in eight of 16 patients with acute leukemia. Transbronchial or bronchial biopsy added only one additional "positive" diagnosis to those suggested by bronchial brushing and washing. No complications occurred, and no significant bleeding was encountered when biopsy was not attempted if coagulation parameters were abnormal or platelet counts were below 50,000/mm^3. Bronchoscopy seemed to be more useful when performed later in the course of the infection.

Sputum collection was also valuable in helping to establish the diagnosis of invasive pulmonary aspergillosis, although positive results of sputum cultures were most often received late in the course of the infection. Fiberoptic bronchoscopy is a useful first procedure for the evaluation of patients with acute leukemia and possible invasive pulmonary aspergillosis, but a negative result does not exclude the diagnosis. Further diagnostic procedures, including repeated bronchoscopy, or institution of empiric antifungal therapy may be warranted if the clinical suspicion of invasive pulmonary aspergillosis is high.

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