Transtracheal Selective Bronchial Brushing for Pulmonary Infiltrates in Patients with Cancer*

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Patients with cancer frequently develop pneumonitis for which no cause is documented ante mortem. Noninvasive diagnostic techniques, such as sputum induction, are generally inadequate, especially in myelosuppressed patients. To avoid pulmonary contamination with organisms colonizing the oronasopharynx and to obtain uncontaminated specimens, 38 patients underwent bronchial brushing utilizing a transtracheal approach after sputum induction and transtracheal aspiration failed to establish the etiology. Patients with thrombocytopenia were brushed after platelet transfusion. Eleven patients were not clinically considered to be infected; seven proved to have pulmonary metastases, of which one case was diagnosed by this technique; and four patients in whom no diagnosis was obtained by brushing subsequently proved to have interstitial fibrosis (three cases) or a collapsed lobe (one case). Twenty-seven patients were clinically presumed to be infected. Ultimately, 17 of these 27 patients were proven to have pulmonary infection, and 14 of these 17 were etiologically documented by brushing. In ten of the 27 patients presumed to be infected, no etiology could be established by any method. Seven of these ten patients were receiving broad-spectrum antibiotic therapy at the time. Significant but nonfatal complications, including hemoptysis, pneumothorax, and cervical cellulitis, occurred in seven patients; however, this procedure is a relatively safe and useful method to include in the orderly evaluation of myelosuppressed cancer patients with suspected pulmonary infections.

In the immunologically compromised and myelosuppressed patient, pulmonary infection is a common cause or a major contributing factor of death. One of the reasons for this high mortality lies in the difficulty in properly diagnosing these complications ante mortem. In a report of 50 autopsied patients with acute leukemia, Bodey et al1 found that of those patients with pneumonia, the responsible organism was isolated during life in only 23 percent. Sickles et al2 more recently found similar results among 52 episodes of pneumonia in patients with acute leukemia.

Such patients frequently fail to produce sputum,1 and noninvasive diagnostic techniques, such as sputum induction, have produced a low yield of etiologic agents.1,2 Seriously ill patients usually have a marked change in their pharyngeal flora such that the predominant organisms are usually gram-nega-

tive bacilli, *Staphylococcus aureus*, and various yeasts.5 The minimal amount of sputum which is expectorated is, therefore, contaminated with these colonizing organisms,4,5 making an etiologic diagnosis difficult, if not impossible. More invasive procedures are, therefore, usually necessary to establish a diagnosis.

Transtracheal aspiration has gained widespread acceptance as a means of obtaining uncontaminated material from the tracheobronchial tree for study4,6-8 and has been used successfully to diagnose opportunistic infections in myelosuppressed patients.9 Although complications with this technique have been noted,7,10-12 the procedure in experienced hands is associated with low morbidity and may provide information in otherwise obscure bronchopulmonary infections; however, because of the diminished inflammatory response seen in myelosuppressed patients,13,14 it may be necessary to physically scrape the causal organism from the infected site.

Bronchial brushing, originally developed to obtain material for the cytologic diagnosis of lung cancer, may increase the diagnostic yield in pulmonary infiltrates from other causes. With specially designed brushes passed through a properly positioned endobronchial catheter, it is possible to scrape off tissue for examination and culture.15,16 Washings can be obtained through the same catheter, further increasing the possibility of diagnosis. This technique has

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been associated with low morbidity in over 800 reported brushings\textsuperscript{17-23} and should be particularly well-suited to myelosuppressed patients, since it should be possible to scrape off the infectious agent.

This study was undertaken to determine the efficacy of this procedure in establishing the etiology of pulmonary infiltrates in patients with cancer. Bronchial brushing was performed by introducing the catheter through the cricothyroid membrane, bypassing the contaminating flora of the oropharynx and preventing the introduction of this potentially pathogenic flora into the lungs.

**Materials and Methods**

Patients with a new pulmonary infiltrate, regardless of antibiotic usage, were evaluated in an orderly fashion. First, sputum (rarely produced) was smeared and cultured. Transtracheal aspiration was performed after smears and cultures of expectorated and induced sputum, if produced, did not clearly reveal an etiologic agent. Bronchial brushing was considered if the results of transtracheal aspirates were non-diagnostic. When the clinical situation warranted immediate institution or addition of antibiotic therapy, brushing was performed on the basis of negative aspirate smears. In only one such case was the aspirate culture ultimately diagnostic; and this case was, therefore, excluded from the evaluation of brushing. The coagulative profile and platelet counts were checked and corrected prior to performing invasive procedures. Patients with thrombocytopenia were brushed with platelet transfusions running. Uncorrectable thrombocytopenia or coagulative profiles were considered contraindications to the procedure. Acute-phase serologic studies, blood cultures, and surveillance cultures of the nose, gingiva, axilla, and rectum\textsuperscript{24} were obtained prior to performing the brushing procedure. Informed consent was obtained in all instances.

**Apparatus and Technique**

The controllable-tip catheter and brushes\textsuperscript{5} were sterilized with gas. The controlling handle and cutaneous instruments were packaged into an autoclaved tray. A balanced electrolytic solution (Polsafl\textsuperscript{25}) was used for cytologic specimens, and 95 percent alcohol was used for frosted cytologic slides.

The patient was placed in the supine position with the neck maximally extended. After preparation of the skin, 2 ml of a 2-percent preservative-free solution of lidocaine was injected into the trachea via the cricothyroid membrane. A 12-gauge needle was then introduced into the trachea with the bevel directed caudad. A guide wire (diameter, 1.47 mm) was introduced into the trachea, and the needle was removed. The catheter (outer diameter, 2.72 mm) was introduced over the guide wire, the guide wire was removed, and the tip of the catheter was then positioned in the desired bronchial orifice using fluoroscopy. With the catheter tip maintained within the infiltrate, multiple sleeved brushes (outer diameter, 1.47 mm) were passed through the catheter into the substance of the infiltrate. The area was vigorously brushed. Brushes were then pulled back into their respective Teflon sleeves and withdrawn en bloc. Each of the seven brushes was initially stroked across a sterile slide for smears, and then the brush tips were cut off and inoculated into multiple culture media tubes. All material obtained was cultured for aerobic and anaerobic bacteria, plus fungal, viral, and Mycoplasma organisms. Smears and washings were also evaluated by cytologic techniques. The catheter was slowly withdrawn, and pressure was maintained over the puncture site for ten minutes.

**Results**

Thirty-eight patients who had been on therapy for their underlying cancer underwent transtracheal selective bronchial brushing (Table 1). Seventeen of these 38 patients were both granulocytopenic and thrombocytopenic. Overall results are shown in Table 2. Eleven patients were presumed to have noninfectious pulmonary infiltrates on the basis of their clinical course. Seven of these 11 were found to have pulmonary metastases by subsequent biopsy techniques, and only one of these seven had been identified using this brushing procedure. This patient with malignant fibrous histiocytoma was found to have malignant giant cells on smear similar to those seen on histologic sections of the tumor. Four of these 11 patients had neither tumor nor infection, as proved by follow-up studies. Three had interstitial fibrosis, and the fourth patient had a collapsed upper lobe.

Twenty-seven patients were presumed to be acutely infected on the basis of clinical course or on the basis of both fever and neutropenia;\textsuperscript{26} and 18 of them were receiving broad-spectrum antibiotic therapy prior to and during the procedure. Ultimately, 17 of these 27 patients were microbiologically documented as having an infection. The etiologic agent of infection was documented in 14 (82 percent) of these 17 patients by the brushing technique after all previous methods had failed. Ten of these 27 patients are listed as having no diagnosis. One of these patients had a clinical course suggestive of pulmonary bleomycin toxicity; however, a necropsy was denied, and confirmation is lacking. There was technical difficulty in positioning the catheter in a second patient in this group, resulting in no diagno-

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>No. with Granulocytopenia*</th>
<th>No. with Thrombocytopenia**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute nonlymphocytic leukemia</td>
<td>14</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NonHodgkin's lymphoma</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous solid tumors</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

*Granulocytopenia, granulocyte count < 1,000/μl.
**Thrombocytopenia, pretransfusion platelet count < 50,000/μl.

\textsuperscript{5}Selector Catheter System (Medi-Tech, Inc, Watertown, Mass.)

\textsuperscript{6}Cutter Laboratories, Inc, Berkeley, Calif.

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Table 2—Results of Transtracheal Bronchial Brushing in Patients with Cancer*

<table>
<thead>
<tr>
<th>Proven Etiology from Brushing</th>
<th>from Brushing</th>
<th>Microbiologically documented infections</th>
<th>Neoplastic</th>
<th>Other</th>
<th>No diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Smear, Negative Smear, Culture, and Cytologic Findings</td>
<td></td>
<td>14</td>
<td>1</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Negative Smear, Culture, and Cytologic Findings</td>
<td></td>
<td>3**</td>
<td>6</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

*Each patient had prior negative results from sputum and transtracheal aspiration cultures and smears.
**Microbiologic documentation later determined by necropsy.

therapy immediately prior to or during the brushing procedure. In these cases, either necropsy was denied (one case), or it failed to show specific pathologic findings (five cases), or the infiltrate improved with further antibiotic therapy (two cases).

For the 14 patients who had the etiology of their pneumonias diagnosed by brushing, the nature of the material obtained, the resulting therapy, and the clinical course are shown in Table 3. When obtained, necropsy confirmed the findings from brushing in all cases. The three patients in whom a bacterial etiology was established underwent brushing prior to the institution of antimicrobial therapy. In each case the organism grew in pure culture from multiple brushings and washings and responded to therapy with specific single antibiotics. Four of five patients with aspergillosis were receiving broad-spectrum antibiotic therapy when their infiltrate developed. Four

Table 3—Results of Bronchial Brushing Infectious Diagnoses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Brushing Results</th>
<th>Therapy</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Smear, gram-positive cocci Culture, Peptostreptococcus</td>
<td>Penicillin</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>2</td>
<td>Smear, gram-positive cocci Culture, ( \alpha )-hemolytic Streptococcus sp</td>
<td>Penicillin</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>3</td>
<td>Smear, negative Culture, ( \text{S. aureus} )</td>
<td>Methicillin</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>4*</td>
<td>Smear, Aspergillus Culture, ( A. fumigatus )</td>
<td>Amphotericin B</td>
<td>Died from primary disease</td>
</tr>
<tr>
<td>5*</td>
<td>Smear, negative Culture, ( A. fumigatus )</td>
<td>Amphotericin B</td>
<td>Died</td>
</tr>
<tr>
<td>6*</td>
<td>Smear, Aspergillus Culture, negative</td>
<td>Amphotericin B</td>
<td>Improved</td>
</tr>
<tr>
<td>7</td>
<td>Smear, Aspergillus Culture, negative</td>
<td>Amphotericin B</td>
<td>Improved</td>
</tr>
<tr>
<td>8</td>
<td>Smear, Aspergillus Culture, negative</td>
<td>Amphotericin B</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>9*</td>
<td>Smear, Phycomycetes Culture, negative</td>
<td>Amphotericin B</td>
<td>Died</td>
</tr>
<tr>
<td>10*</td>
<td>Smear, Phycomycetes and acid-fast bacilli Culture, ( R. oryzae ) and ( M. tuberculosis )</td>
<td>Isoniazid and ethambutol</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>Smear, acid-fast bacilli Culture, negative</td>
<td>Isoniazid and ethambutol</td>
<td>Improved</td>
</tr>
<tr>
<td>12</td>
<td>Smear, negative Culture, ( T. glabrata )</td>
<td>None</td>
<td>Spontaneous regression while off chemotherapy</td>
</tr>
<tr>
<td>13</td>
<td>Smear, negative Culture, ( T. glabrata )</td>
<td>None</td>
<td>Spontaneous regression while off chemotherapy</td>
</tr>
<tr>
<td>14</td>
<td>Smear, Pneumocystis Culture, negative</td>
<td>Pentamidine</td>
<td>Improved</td>
</tr>
</tbody>
</table>

*Necropsy confirmed results.
of these five patients had typically branching septated hyphae on smears, and therapy with amphotericin B was immediately instituted.

The previously reported patients in whom Torulopsis glabrata grew from multiple brushings and washings and was, thus, implicated as the cause of infection were clinically improving when the organism was first detected on culture, and their infiltrates resolved without antimicrobial therapy.

All three of the patients with microbiologically documented infections not diagnosed by brushing (Table 2) were receiving broad-spectrum antibiotic therapy when their infiltrate developed; at necropsy, two were shown to have aspergillosis, and one had phycomycosis.

Complications of the brushing procedure are listed in Table 4. The mild complications were clinically insignificant and required no therapeutic intervention. Mild hemoptysis was seen on four occasions, once in a patient with a normal platelet count and three times in patients who had been transfused with platelets. One patient with thrombocytopenia developed a small (2 cm × 2 cm) intrapulmonary hematoma, which was resolving at the time of death. Severe hemoptysis occurred once in a patient with thrombocytopenia and required suctioning and platelet and blood transfusions.

Pneumothorax occurred six times. One was a clinically insignificant 5-percent pneumothorax which resolved spontaneously. Three pneumothoraces required needle evacuation but did not recur, so chest tube placement was not necessary; however, chest tube placement was necessary in two cases. In each instance the brush was seen to touch the pleura; and in all but one case, the patient complained of transitory chest pain.

Subcutaneous and mediastinal emphysema occurred only in the early months of the investigation. The degree of emphysema seemed to be related to the duration and intensity of coughing during the procedure, and this complication no longer occurred when lidocaine was instilled in quantities sufficient to suppress coughing.

Cellulitis at the tracheal puncture site occurred once and was severe, life-threatening, and slow to resolve with antibiotic therapy.

**Discussion**

Several investigators have shown a low diagnostic yield from noninvasive techniques in pneumonia occurring in patients with hematologic malignancies. Clinically recognized infections are generally treated empirically with broad-spectrum antibiotic therapy, a practice not without danger of significant superinfection or toxicity. Transtracheal aspiration may lead to diagnosis in such patients; however, in the present study, brushing was performed only when the etiology was not established by either sputum induction or transtracheal aspiration. Fourteen of the 17 with proven infections (14 of 27 who were presumed to be infected) were diagnosed using this technique of transtracheal selective brushing. Identification of the infecting organism by brushing allowed for specific and less potentially toxic antimicrobial therapy in each case.

Bacterial pneumonias were identified in three patients, and *T glabrata* was identified as causal in two patients (Table 3) without confusing these organisms with those of the upper respiratory tract. The diagnosis of invasive aspergillosis in patients with cancer is usually made at necropsy, attesting to the difficulty in making this diagnosis ante mortem. This technique led to the ante-mortem diagnosis of invasive aspergillosis in five of seven patients. The early recognition of pneumonia due to *Aspergillus* sp led to prompt therapy and at least temporary improvement in clinical and roentgenographic appearance. The patient with improvement in the underlying disease then went on to resolution of the pneumonia.

This brushing technique was not particularly helpful in the group with pulmonary lymphoma or interstitial fibrosis, perhaps because of the scanty material obtained for histologic evaluation using a sleeved brush. Tranbronchial biopsy through a flexible fiberoptic bronchoscope might be more advantageous under these circumstances, especially if the patient does not have leukopenia.

Of the ten patients in whom no diagnosis was obtained, eight defined clinically as probably infected were receiving broad-spectrum antibiotic therapy at the time of the procedure. It is entirely conceivable that if the brushing had been performed

Table 4—Complications of Transtracheal Bronchial Brushing in Patients with Cancer

<table>
<thead>
<tr>
<th>Complication</th>
<th>Degree of Complication*</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td></td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td></td>
<td>1</td>
<td>3**</td>
<td>2†</td>
<td>6</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Mediastinal emphysema</td>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cellulitis at puncture site</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Mild, spontaneous resolution; moderate, requiring therapeutic intervention; and severe, life-threatening.

**Needle evacuation.

†Chest tube inserted.
prior to instituting antimicrobial therapy, a specific diagnosis might have been obtained.

Using a transphyaryngeal approach, \(^{17,18}\) bronchial brushing has been shown to be useful for diagnosis of infection with \textit{Pneumocystis carinii} in myelosuppressed patients; however, when introduced in this manner, the procedure has the theoretic possibility of introducing the potential pathogens colonizing the oronasopharynx into the pulmonary parenchyma and, thus, offers no advantage over brushing through a flexible fiberoptic bronchoscope.\(^ {58,29}\)

Serious but nonfatal complications were seen with this transtracheal bronchial brushing procedure; however, considering the patient population at risk, such complications should be anticipated when invasive diagnostic techniques are utilized. Aside from the early complications associated with insufficient instillation of lidocaine, most of these complications were associated with vigorous brushing of peripheral lesions and might have occurred equally using other techniques. To determine if brushing through a fiberoptic bronchoscope would lead to as many complications, a prospective comparison between transtracheal bronchial brushing and fiberoptic bronchoscopy using sleeved brushes would, thus, seem to be warranted.

Transtracheal selective bronchial brushing is a relatively safe and effective procedure for establishing the etiology of pulmonary infiltrates in patients with cancer and myelosuppression. It should be employed when an infectious etiology is suspected and the diagnosis cannot be made from sputum or transtracheal aspirates. Used prior to changing or adding therapy with antimicrobial agents whenever possible, this technique should increase the rate of specific diagnosis and lead to more appropriate therapy.

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