Clinical Features of Pseudomonas cepacia Pneumonia in an Epidemic Among Immunocompromised Patients*

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Between January 1990 and August 1991, there were 37 patients admitted to our Department of Internal Medicine with hematologic malignancies or solid tumors who showed colonization of the respiratory tract with Pseudomonas cepacia. Extensive surveillance cultures of the environmental surfaces and respiratory equipment of the hospital revealed that all nebulizing devices were contaminated with P. cepacia. To characterize this outbreak, we retrospectively reviewed the medical records of 37 patients colonized with this organism. All had used nebulizers to deliver aerosols containing polymyxin B and amphotericin B as prophylaxis against infection. Sixteen of these 37 patients developed pneumonia, which was caused in 14 by P. cepacia. The majority of the 14 patients showed lobular infiltrates on chest x-ray films. Cavity formation and pleural effusion were observed in 4 of the 14 (29 percent). All strains of P. cepacia were resistant to pipericillin, cefotiam, sulbactam/cefoxperazone, moxalactam (latamoxef), cefuzonam, amikacin, tobramycin, ofloxacin, imipenem, and carumonam. Ceftazidime was effective against 84.7 percent of the strains, while minocycline was effective against 63.5 percent of the strains. This appears to be the first report to describe the clinical features of an epidemic of nosocomial P. cepacia pneumonia in immunocompromised patients.

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Pseudomonas cepacia is an aerobic, glucose-nonfermenting Gram-negative bacillus which proliferates under conditions of minimal nutrition and can survive even in the presence of certain disinfectants.1,2 Over the past decade, this species has been increasingly recognized as a nosocomial pathogen. The incidence of pulmonary colonization with P. cepacia has also increased in patients attending certain cystic fibrosis treatment centers3-11 and has been correlated with increased rates of morbidity and mortality.4,7

Nevertheless, the clinical features of respiratory infection caused by P. cepacia have not been well documented. We recently observed a nosocomial outbreak of P. cepacia upper respiratory colonization and pneumonia in immunocompromised patients, in which nebulizers were identified as the environmental reservoir for the epidemic strains. We report the clinical features of P. cepacia pneumonia in these patients.

Materials and Methods

Background

Between January 1990 and August 1991, P. cepacia was cultured from the upper respiratory tract of 37 patients admitted to the First Department of Internal Medicine. All were immunocompromised by hematologic malignancies or solid tumors. To protect the upper respiratory tract against bacterial or fungal infections, each had received inhalations of polymyxin B and amphotericin B using nebulizers contaminated with P. cepacia.

Diagnosis of Nosocomial Pneumonia (Case Definition)

Nosocomial pneumonia was diagnosed in a patient whose chest radiographic examination showed a new or progressive infiltrate and who fulfilled at least one of these two criteria: (1) new onset of rales on physical examination; and (2) new onset of sputum production or change in character of sputum. Only those considered to have pneumonia caused by P. cepacia were included here. Criteria for a final diagnosis included isolation of the same bacterium from two or more consecutive coughed-up samples of sputum. To be considered significant, this bacterium had to be present on cultures as the only or predominant organism.4,12

Sixteen of the 37 patients (43 percent) whose upper respiratory tract was colonized with P. cepacia developed pneumonia; however, infection might be due to other organisms in two cases: (1) Streptococcus faecalis and Pseudomonas aeruginosa, isolated from the upper respiratory tract in one patient; and (2) Streptococcus faecium in the other case. Therefore, we analyzed the clinical features for those remaining 14 patients in whom P. cepacia was the only organism isolated from the upper respiratory tract.

The clinical outcome was assessed according to whether the patient was eventually cured of the P. cepacia pneumonia or died of it. Laboratory data, including the WBC count and C-reactive protein, at the onset of pneumonia were recorded when available. Chest roentgenograms were reviewed in all patients. We recorded the type of lesion (unilateral or bilateral; lobular or lobar), the lobes involved, and the presence or absence of cavity formation or pleural effusion.

Microbiologic Data

The capability of the clinical isolates of P. cepacia to release extracellular products was evaluated. The production of phospholipase (lecithinase), lipase, hemolysin, and protease was determined by plate assays; the production of phospholipase was screened according to the ability to produce phospholipase activity on egg yolk agar according to the method of Esselmann and Liu.23 Lipase activity was measured using polyoxethylene sorbitans (Tween 80).
Table 1—Characteristics of Patients Who Developed P. cepacia Pneumonia

<table>
<thead>
<tr>
<th>Case</th>
<th>Underlying Disease</th>
<th>Date of Isolation</th>
<th>Quantitative Cultures of Sputum*</th>
<th>Onset Date of Pneumonia</th>
<th>C-Reactive Protein, mg/dl†</th>
<th>WBCs/μl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute leukemia</td>
<td>1/9/90</td>
<td>1+</td>
<td>1/2/90</td>
<td>8.5</td>
<td>800</td>
</tr>
<tr>
<td>2</td>
<td>Acute leukemia</td>
<td>5/25/90</td>
<td>3+</td>
<td>5/28/90</td>
<td>22</td>
<td>200</td>
</tr>
<tr>
<td>3</td>
<td>Myelodysplastic syndrome</td>
<td>6/12/90</td>
<td>1+</td>
<td>6/13/90</td>
<td>19.5</td>
<td>3,200</td>
</tr>
<tr>
<td>4</td>
<td>Acute leukemia</td>
<td>6/18/90</td>
<td>1+</td>
<td>7/1/90</td>
<td>ND†</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Malignant lymphoma</td>
<td>7/18/90</td>
<td>1+</td>
<td>6/27/91</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Acute leukemia</td>
<td>9/10/90</td>
<td>1+</td>
<td>9/10/90</td>
<td>8.7</td>
<td>300</td>
</tr>
<tr>
<td>7</td>
<td>Acute leukemia</td>
<td>10/11/90</td>
<td>2+</td>
<td>10/17/90</td>
<td>29.5</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>Malignant lymphoma</td>
<td>10/12/90</td>
<td>1+</td>
<td>10/15/90</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>Malignant lymphoma</td>
<td>10/24/90</td>
<td>3+</td>
<td>11/3/90</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>Lung cancer</td>
<td>11/14/90</td>
<td>1+</td>
<td>11/22/90</td>
<td>23</td>
<td>300</td>
</tr>
<tr>
<td>11</td>
<td>Lung cancer</td>
<td>11/25/90</td>
<td>1+</td>
<td>1/10/91</td>
<td>32.5</td>
<td>400</td>
</tr>
<tr>
<td>12</td>
<td>Acute leukemia</td>
<td>1/28/91</td>
<td>1+</td>
<td>3/7/91</td>
<td>14.5</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>Acute leukemia</td>
<td>5/27/91</td>
<td>1+</td>
<td>12/4/91</td>
<td>28.5</td>
<td>200</td>
</tr>
<tr>
<td>14</td>
<td>Acute leukemia</td>
<td>9/30/91</td>
<td>3+</td>
<td>9/30/91</td>
<td>9.1</td>
<td>1,000</td>
</tr>
</tbody>
</table>

*1+, Less than 1 x 10⁶; 2+, 1 x 10⁶ to 1 x 10⁷; and 3+, more than 1 x 10⁷.

†Normal range, 0.1 to 0.6 mg/dl.

§ND, Not determined.

as substrates following the method of Sierra.¹⁵ Production of hemolysin was determined using plates containing 7.5 percent sheep’s blood in heart infusion agar.*¹⁵(Eiken Co. Ltd., Tokyo, Japan). Production of protease was determined using plates of dialyzed brain heart infusion (D-BHI) milk medium.¹⁵ Results were determined after incubation at 28°C for 48 h.

Isolates of P. cepacia were tested for their susceptibility to 12 antibiotics by determining the minimum inhibitory concentration (MIC 2000 Plus System; Dynatech Laboratories). Susceptibility to the following 12 antibiotics was evaluated: piperacillin; cefotaxim; sulbactam/cefoperazone; moxalactam (latamoxef); ceftazidime; ceftazidime; cefoxitin; amikacin; tobramycin; ofloxacin; imipenem; carbomycin; and minocycline.

**RESULTS**

**Profiles of Patients**

The characteristics and clinical data on the 14 patients are summarized in Table 1. Their underlying diseases included acute leukemia (8), malignant lymphoma (3), lung cancer (2), and myelodysplastic syndrome (1). Ten patients developed pneumonia within 2 weeks after *P. cepacia* was initially isolated from the upper respiratory tract. In 3 patients (cases 5, 11, and 12), although pneumonia developed more than 1 month after the initial colonization, such colonization persisted, strongly suggesting that this organism was the responsible pathogen. In 1 patient (case 1), *P. cepacia* was cultured 7 days after the onset of pneumonia. Laboratory findings showed an elevation of C-reactive protein in all patients. The median WBC count was 200/μl (range, 100/μl to 3,200/μl).

Chest roentgenographic findings are summarized in the following tabulation listing numbers of patients (numbers within parentheses are percentages):

<table>
<thead>
<tr>
<th>Location of infiltrates</th>
<th>Bilateral</th>
<th>2 (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>12 (86)</td>
<td></td>
</tr>
</tbody>
</table>

Died of pneumonia: 4 (29)

Two of the 14 patients had bilateral involvement. The presence of upper lobe involvement versus lower lobe involvement was almost evenly distributed. A lobular (bronchial) pattern was observed in ten patients; a combination of a lobular and lobar pattern was seen in three patients, and a lobar pattern occurred in one patient. No interstitial pattern was observed. Cavitation was present in 4 of the 14 patients. Four of the 14 patients had pleural effusions. Ceftazidime (4 g/d, intravenously) was administered in 12 patients, and pneumonia resolved in 9 patients. Minocycline (200 mg/d, intravenously) was administered in 10 patients, and pneumonia resolved in 7 patients. Although ceftazidime or minocycline or both were administered, four patients died of respiratory failure caused by the *P. cepacia* pneumonia, while ten survived.

Epidemiologic studies showed that all strains produced lipase and protease. Strains cultured on the east fourth floor of the internal medicine department did not produce phospholipase or hemolysin. The antibiotic susceptibility of the 137 strains of *P. cepacia* isolated in this survey were resistant to piperacillin, cefotaxim, sulbactam/cefoperazone, moxalactam, ceftazidime, cefazolin, amikacin, tobramycin, ofloxacin, imipenem, and carumonam. Ceftazidime was effective against 85 percent of the strains, while minocycline was effective against 64 percent of the strains.

**DISCUSSION**

This appears to be the first report to describe the clinical features of a hospital epidemic of *P. cepacia*.
pneumonia in immunocompromised patients. Reinarz et al. reported that the inhalation therapy equipment used in hospitals was frequently contaminated with bacteria, commonly P aeruginosa. Therefore, ill patients received massive daily inoculations of airborne organisms in the respiratory tract. Over 70 percent of the nebulizer devices at patients’ bedsides were contaminated, and 12 percent of the subjects coming to autopsy had Gram-negative necrotizing pneumonia. In our Department of Internal Medicine, patients with a WBC count lower than 1,000/µl were prophylactically administered inhalations of polymyxin B and amphotericin B, given via nebulizer devices, to protect against bacteria or fungal infections of the upper respiratory tract. Unfortunately, these devices became contaminated with P cepacia, so that aerosols containing this organism were accidentally delivered into the upper respiratory tract. This report is unusual in that it analyzes the clinical features of P cepacia pneumonia in immunocompromised patients in a relatively “pure” form.

The isolation of P cepacia from clinical specimens and the hospital environment, particularly from wet surfaces, equipment, pharmaceutical solutions, and antiseptics, has become increasingly common, and the presence of P cepacia has been shown to lead to colonization and infection. This organism has been considered to have a low virulence, and most clinical isolations have not been associated with symptoms; however, Randall warned that this species could become a potentially lethal pathogen in the compromised patient. Nevertheless, there had been only a few reports concerning respiratory tract infections caused by P cepacia, and none had described the clinical features in detail. Our findings seemed to be important to describe the clinical features of epidemic nosocomial P cepacia pneumonia in immunocompromised patients.

The role of this organism in pulmonary disease remains controversial. Unlike P aeruginosa, P cepacia is relatively nonvirulent in animals. It was not considered to be a primary human pathogen for many years because of its low degree of virulence and limited invasiveness; however, more recently, P cepacia has been implicated in a variety of respiratory tract infections, such as necrotizing and other forms of pneumonia and lung abscess. In our survey, pneumonia occurred in 16 of 37 colonized patients, in 14 of whom the pneumonia was considered to be caused solely by P cepacia.

While no roentgenographic presentation was diagnostic, certain informative patterns emerged: cavity formation and pleural effusion were each present in 4 of 14 patients. Parenchymal infections were commonly lobular. Some patients developed necrotizing pneumonia with cavity formation. Because the strains obtained from these patients produced protease, one may speculate that P cepacia can damage the pulmonary tissue directly by releasing toxins and enzymes. In our current study, because all strains produced protease, it was impossible to analyze the correlation between the presence of extracellular enzymes in the infecting strains and the type or extent of radiographic findings or clinical symptoms in patients.

The clinical course of P cepacia pneumonia was typical of a severe bacterial infection, with high fever and elevation of C-reactive protein. Cultures of blood were negative in all 14 patients. The mortality was 29 percent, which is difficult to compare with other studies, given the differences in populations; however, this relatively high mortality, coupled with the lack of an effective antibiotic, may reflect the fact that the patients with P cepacia pulmonary infection tend to have other significant illnesses (malignant disease in this study).

Treatment of P cepacia infection is made difficult by the almost universal resistance of this organism to the commonly used antipseudomonal agents. In our study, only ceftazidime and minocycline were effective against clinical isolates of P cepacia.

In summary, our results demonstrated that P cepacia is a potential pathogen which can cause nosocomial pneumonia in immunocompromised patients. Contaminated respiratory equipment was found to be an important cause of nosocomial transmission.

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