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Pneumococcal Bacteremia in Patients with Neoplastic Diseases

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Abstract—*To evaluate the morbidity and mortality of pneumococcal bacteremia in patients with cancer, we reviewed the* 36 *case records of patients with one or more blood cultures positive for pneumococci, observed over a* 6*-year period at the Institut Jules Bordet. The most frequent underlying neoplasms were lung cancer* (25%), *chronic lymphocytic leukemia and multiple myeloma* (25%). *In* 80% *of the patients, the respiratory tract was the source of the infection. A bacteriological clue for pneumococcal infection was available in* 21 *patients at the onset of bacteremia; pneumococci were seen on Gram-stained smears in* 52% *and grown in culture in* 76% *of all the patients. Most patients* (33/36) *received adequate empirical treatment as soon as the infection was clinically suspected. Nevertheless, the overall mortality during the week following the infection was* 42%; 10 *of these deaths could be directly attributed to the pneumococcal infection and occurred during the first* 3 *days after its onset. Among these* 10 *patients,* 8 *had been appropriately treated.*

INTRODUCTION

INFECTION remains an important cause of morbidity and mortality in cancer patients [1]. Gram-negative rods are the most frequent pathogens in patients with neoplastic diseases; the causes, nature and treatment of Gram-negative bacteremia complicating cancer have deserved particular attention in the last few years [2, 3].

Pneumococci are important pathogens in the general population [4], but their role in cancer patients has been less often appreciated. Sixty cases of pneumococcal bacteremia in patients with neoplastic diseases, observed at the Memorial Hospital, NY, between 1955 and 1971, were reported by Folland *et al.* [5]; in their series, patients with leukemia and lymphoma were found to be particularly susceptible and, despite appropriate treatment, 53% of the patients died. Kilton *et al.* [6] recently reported 57 bacteremias due to Gram-positive cocci in patients with a wide variety of neoplastic diseases; among these patients, 14 were infected with a pneumococcal bacteremia and 5 out of the 14 pneumococcal bacteremia resulted in death.

To study further the mortality and morbidity of pneumococcal bacteremia in patients with cancer, we reviewed the records of 36 patients with at least one blood culture positive for pneumococci, observed at the Institut Jules Bordet, the Cancer Center of Brussels University, over a six-year period.

MATERIALS AND METHODS

Patients selection

The study population was identified by reviewing the records of positive blood cultures, obtained at the microbiology laboratory at the Institut Jules Bordet over a 6-year period, commencing February 1973 and ending June 1979. Criteria for patients inclusion required proved neoplastic disease and at least one pre-

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mortem blood culture that grew pneumococci. During that period of time, 36 patients with a neoplastic underlying disease and pneumococcal bacteremia could be identified.

Microbiological studies

The identification of bacteria was performed using standard microbiological methods. Antimicrobial susceptibilities were determined by the Kirby and Bauer method and/or by a tube dilution technique. Patient's blood was inoculated, for aerobic cultures, in flasks containing brain heart infusion broth with sodium polyanethol sulfonate (SPS); for anaerobic cultures, the blood was inoculated in flasks containing Schaedler's broth with vitamin K and SPS (Biomerieux). After incubation, subsequent cultures of turbid flasks were made and smears of the culture medium were stained by the Gram technique.

Blood agar (Biomerieux) was used to plate blood cultures and other clinical isolates. Bacterial colonies suspected to be pneumococci were identified by the optochin test (Biomerieux).

Definitions

Anti-microbial therapy was defined as adequate, as based on the anti-microbial susceptibility of pneumococci and the administration by the parenteral route of a dose of antibiotics generally accepted to be adequate for the treatment of serious pneumococcal infections.

Anti-microbial treatment was considered to be effective if, after 48 hr, the temperature had diminished by at least 1°C, and the bronchopulmonary infection, if present, had clinically improved.

Death was considered to be related to the pneumococcal bacteremia if it occurred as the consequence of a septic shock, or if the response to anti-microbial therapy was inadequate and was associated with death within the first week following the diagnosis.

Nosocomial infection was defined as the onset of the infection-related symptoms less than 1 week after hospital admission.

RESULTS

There are approximately 1000 admissions per year at this institution; 36 cases of pneumococcal bacteremia could be documented over a period of 6 years. As a basis for comparison, over a 3-year period (1976–1978) Gram-negative bacteremias were six times more frequent (79 cases vs 13 cases of pneumococcal bacteremias). Although an exact incidence of pneumococcal bacteremia cannot be calculated, it clearly appears that pneumococcal bacteremia constitutes a relatively uncommon problem in our cancer patients.

Patient's characteristics

Among the 36 patients of this series, 27 were males and 9 females. The median age was 62 years (range: 33–86). Thirteen patients each had a hematologic malignancy: 7 chronic lymphocytic leukemia, 2 multiple myeloma, 2 Hodgkin's disease, one primitive myelofibrosis and one acute myeloblastic leukemia. The other 23 patients were each infected with a solid tumor: 9 with bronchogenic carcinoma, 3 with breast cancer, 3 with gastro-intestinal cancer, 4 with brain tumors, 2 with urinary tract neoplasia and 2 with upper respiratory tract tumors. The incidence of the different kinds of cancer among our patients with pneumococcal bacteremia was compared with the general incidence of these tumors in the patients admitted to the Institut Jules Bordet during the same period of time. It can be seen in Table 1 that, although chronic lymphocytic leukemia and multiple myeloma represented only 1% of the admissions, 25% of our patients with pneumococcal bacteremia had such a neoplasm. Similarly, although bronchogenic carcinoma was present in only 12% of the patients admitted to our hospital, it was the

Table 1. Underlying diseases in cancer patients with pneumococcal bacteremia at the Memorial Hospital (NY) and at the Institut Jules Bordet (Brussels)

	Memorial Hospital 1955–1971	Institut Jules Bordet 1973–1979
	60 patients	36 patients
Underlying disease		
CLL and multiple myeloma	6 (10%)	9 (25%)
Lymphoma	14 (23%)	2 (5%)
Other hematologic malignancies	9 (15%)	2 (5%)
Lung cancer	4 (7%)	9 (25%)
Miscellaneous solid tumor	26 (43%)	14 (40%)

underlying disease in 25% of the patients with pneumococcal bacteremia.

At the time of bacteremia, 21 (58%) patients had a disseminated cancer and 15 (42%) had a pulmonary neoplastic disease, either primary or metastatic. The incidence and the type of the anti-neoplastic treatment administered during the 3 months preceeding the pneumococcal bacteremia has been analyzed; 18 (50%) patients received anti-neoplastic chemotherapy, and corticosteroids and radiation therapy were administered to 13 (36%) and 12 (33%) of the patients, respectively. Three patients had been splenectomized 2 days, 1 week and 2 months before the onset of the pneumococcal sepsis; none of these 3 patients had a lymphoma as the neoplastic underlying disease.

Nine patients (25%) had a history of chronic bronchitis and/or clinical signs of obstructive lung disease.

Granulocytopenia (neutrophil count $< 1000/mm^3$) was present in 5 (14%) patients.

As far as the blood levels of immunoglobulins are concerned, 16 (44%) patients had a level of immunoglobulins lower than 1 g/100 ml and 2 (5%) had a monoclonal gammopathy.

The median duration of hospitalization before the onset of pneumococcal bacteremia was 5 days (range 0–63). For 10 (28%) patients, the admission was precipitated by symptoms related to the infection. The pneumococcal infection appeared to be nosocomial in 17 (47%) patients.

Clinical features and bacteriologic results

Most patients appeared acutely ill at the onset of bacteremia. The initial median temperature was 38.8°C (range: 36.5–40.0°C); temperature was above 38.0°C in 32 cases, but in 4 patients it was below 37.5°C. In 10 (28%) patients, pneumococcal bacteremia appeared initially as a septic shock syndrome.

Twenty-one (58%) patients showed obvious clinical and/or radiological symptoms of pneumonia; in 8 of these patients, pneumococci could be isolated from sputum. In 7 patients (19%), broncho-pulmonary infection was doubtful, but the respiratory source of pneumococcal bacteremia was documented by positive sputum cultures. In one additional patient, the most likely source was a pneumococcal sinusitis. Therefore, the respiratory tract was the source of the bacteremia in 29 (80%) of our patients. As a basis for comparison, the respiratory tract represented the likely portal of entry in only 13% of the 79 cases of Gram-negative septicemias documented between 1976 and 1978. In 7 (20%) patients of this series, the source for the pneumococcal sepsis could not be identified.

As far as microbiological studies are concerned, appropriate specimens were obtained for Gram strain and/or culture in 21 patients at the onset of the bacteremia. Gram strains of these specimens showed characteristic Gram-positive diplococci in 11/21 (52%) patients, and pneumococci could be cultured as predominant organisms in 16/21 (76%) patients (14 sputa or tracheal aspirates, 1 sinusal pus, 1 pleural fluid).

By *in vitro* sensitivity tests, all the pneumococci were sensitive to penicillin and erythromycin, but 5 were resistant to tetracycline when tested with the Kirby–Bauer method, using 15 micrograms discs.

Treatment and outcome

In this series, 33 patients received empirical antibiotic treatment as soon as the infection was clinically suspected. The nature of this treatment is indicated in Table 2. It can be seen that 17 patients received initial therapy with a single antibiotic; penicillin was given parenterally in 12 patients. Among the patients who received this type of empirical therapy, 13/17 responded favourably to the initial treatment. On the other hand, 16 patients received initial treatment with 2 drugs, a beta-lactam antibiotic and an aminoglycoside in 15 patients, with a favourable response in 8. Three patients did not receive early treatment.

Usually, initial treatment was replaced by penicillin as soon as the isolation of pneumococcus from the blood culture was known; overall, 19 patients received penicillin alone, either empirically (8 patients) or after the blood culture results (11 patients). Usually, benzylpenicillin was used intravenously, at a dose of 6 millions units daily, or procaine penicillin was used intramuscularly, at a dose of 2 millions units daily.

The overall mortality during the week following the onset of pneumococcal bacteremia was 42% (15/36 patients). Ten of these deaths could be directly attributed to the pneumococcal infection and occurred during the first three days after its onset. Among these 10 patients who died during the first 3 days, 8 had been appropriately treated (2 with penicillin alone and 6 with a penicillin-containing combination) but 2 did not receive any initial empirical treatment.

DISCUSSION

Pneumococcal pneumonia remains a serious problem in the general population [4] and has

Table 2. Empirical antimicrobial treatments (administered before the blood culture results were available): evaluation of clinical effectiveness after 24 hr of therapy

	No. of patients	No. of favourable responses
Patients who received 1 antibiotic		
—penicillin iv or im	12	9
—amoxycillin orally	1	1
—cefalexine orally	1	1
—cotrimoxazole iv	1	1
—doxycycline iv	1	1
—chloramphenicol iv	1	0
Patients who received 2 or 3 drugs		
—β-lactam + aminoglycoside	15	8
—clindamycine + aminoglycoside	1	0
Patients who received no empiric treatment	3	0

a mortality approximately two times higher when it is associated with bacteremia [7]. Bacterial infections are a major cause of morbidity and mortality in cancer patients, with Gram-negative bacteremias having the highest incidence. In a recent series published by Kilton *et al.* [6], Gram-positive bacteremia represented 40% of the bacteremic episodes experienced by patients with a wide variety of malignant diseases; this incidence was no different from that observed in the general population seen in the hospital during the same period of time. Among the 57 bacteremias analyzed in that study, there were 14 pneumococcal bacteremias, 17 bacteremias due to other streptococci and 26 due to *Staphylococcus aureus*; the mortality rate was greatest in pneumococcal bacteremias.

Humoral immunosuppression related to therapy [8] and/or to the underlying disease [9], splenectomy, particularly in patients with lymphoma, and splenic dysfunction [10, 11], has been related to an increase in susceptibility to pneumococcal bacteremia. Chronic lymphatic leukemia and multiple myeloma represented 25% of our patients with pneumococcal bacteremia; a high incidence of pneumococcal infection in this type of patient has already been previously reported [12, 13] and was correlated to impairment of the antibody responsiveness which is common in these disorders [14]. Both granulocytopenia and a low level of immunoglobulins may predispose to pneumococcal infections, but these conditions were present in too few patients in the present series to allow meaningful conclusions. Splenectomy was present in 3 patients in this study and, although one of them died from pneumococcal bacteremia, none of them presented the fulminant form of pneumococcal bacteremia with coagulopathy described in splenectomized patients. None of these 3 patients had lymphoma.

Reviewing pneumococcal bacteremia in cancer patients at the Memorial Hospital, NY, Folland *et al.* [5] found that patients with lymphoma, even if not splenectomized, or leukemia were particularly susceptible to pneumococci; in contrast to that study, we did not find that these diseases predisposed pneumococcal bacteremia. The incidence of pneumococcal infections also appears to be low in other studies analyzing infectious episodes in patients with lymphoma or leukemia [15, 16].

Patients with lung cancer represented, in our series, 25% of the patients with pneumococcal bacteremia. An increased frequence of pneumococcal sepsis among patients with lung cancer was also found by Kilton *et al.* [6]: in their series, bronchogenic carcinoma represented 32% of the underlying neoplasms, and 57% of the pneumococcal bacteremias occurred in these patients.

In summary, in our series, the patients who appeared to have a high risk of pneumococcal infection were those with chronic lymphatic leukemia, or multiple myeloma, and those with lung cancer.

In most patients, the lower respiratory tract was the apparent portal of entry of the pneumococcus: the high incidence of lung cancer in this series suggests that alterations of the respiratory mucosal barrier may have predisposed pneumococcal infection.

Fifty-three percent of our patients developed pneumococcal bacteremia during the first week of hospitalization; as a matter of fact, 28% of the patients were hospitalized because of the

infection. Therefore, pneumococcal bacteremia often appears as a community-acquired infection, in contrast to Gram-negative bacteremia, which is often nosocomial.

Clinical diagnosis of pneumococcal infection in cancer patients may be difficult; indeed, in accordance with the observations of Folland *et al.* [5], the clinical features of pneumococcal infection were atypical in most of our patients. Twenty-eight percent exhibited a septic shock syndrome. Although the respiratory tract could be documented as the likely portal of entry of the pneumococcus in 80% of our patients with pneumococcal bacteremia, typical lobar pneumonia was never seen and the radiologic picture of associated lung infection was often not specific. In addition, in 20% of our patients pneumococcal bacteremia appeared only as fever without an obvious source: this presentation has been well described in cancer patients [5] and is not unlike that described in children [17].

As far as microbiological diagnosis is concerned, appropriate specimens showing typical Gram-positive diplococci on Gram-stained preparations led to an early suspicion of pneumococcal infection in 52% of our patients; 76% of the sputa gave rise to pneumococci. The diagnostic value of a growth of pneumococcus from the sputum has been discussed earlier in the literature; these studies, in accordance to ours, have indicated that sputum cultures positive for pneumococci can be a sensitive index for presumed diagnosis of bacteremic pneumococcal pneumonia [18, 19].

Mortality of bacteremic pneumococcal pneumonia remains high, even in the general population [4, 20], in spite of the use of adequate anti-microbial thereapy with penicillin. In cancer patients, a fatality rate of 53% has been reported by Folland *et al.* [5]; in our series it was 42%, and 10/15 deaths (66%) occurred during the first 3 days after the onset of the bacteremia. It must be also emphasized that 8/10 of these early deaths occurred in patients who were receiving appropriate empiric treatment. Two out of three patients who did not receive early empiric treatment died, one of them before any treatment could be started.

Early mortality in patients with pneumococcal sepsis is probably related to both the serverity of the infection and the delay in treatment. Animal experiments have shown that penicillin cannot prevent death in the presence of massive bacteremia [21] and that there is no reduction in mortality from pneumococcal bacteremia in rabbits when penicillin is administered several hours after the onset of the infection (22). Therefore, although it does not cure all the patients, it would appear reasonable to treat early cancer patients suspected to have a pneumococcal bacteremia with adequate doses of penicillin [23, 24]. Gram-negative bacteremia is more frequent than pneumococcal bacteremia in cancer patients; when bacteremia is suspected in a cancer patient, the use of an empirical anti-microbial combination, including a beta-lactam antibiotic, would be appropriate. Penicillin can be substituted as soon as the blood cultures are known to be positive for pneumococci. If one suspects pneumococcal sepsis, on the basis of clinical and microbiological data, penicillin alone might be given as initial therapy, except in granulocytopenic patients.

The persisting high mortality of pneumococcal bacteremia in patients with cancer, in spite of treatment with penicillin, suggests the need for prophylaxis in cancer patients at high risk for pneumococcal infection. It might therefore be useful to investigate the antibody response to pneumococcal vaccine and its protective effect in cancer patients who are predisposed to pneumococcal infections [25]. For patients with lung cancer, who generally have a normal immune function prior to antineoplastic treatment, the most rational prophylaxis should be immunization before antineoplastic treatment is begun.

Another prophylatic approach should be chemoprophylaxis with penicillin [26], or possibly with other regimens [8]; chemoprophylaxis could be indicated in patients with impaired response to pneumococcal vaccine [27]. However, the cost and risk benefit of chemoprophylaxis has been questioned [28] and firm recommendations regarding their use in cancer patients with a high risk of pneumococcal infection requires further prospective studies.

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