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Bronchial bacterial colonization in patients with lung cancer

Abstract

Introduction: Infections are a part of the natural course of lung cancer but few studies have looked at the clinical and microbiological documentation of infections in these patients.
The aim of this study is to analyze the profile of potentially pathogenic bacteria that colonize the bronchial tree in patients with primary lung cancer.
Material and methods: The study was conducted from January 2006 to August 2007. It included 44 consecutive patients (34 males and 10 females) with primary lung cancer aged from 38 to 77 (mean age of 57.9 years). In all patients, bronchoalveolar lavage (BAL) was performed during bronchofiberoscopy. Obtained BAL fluid was subjected to microbiological examination. The number of bacteria present in 1 ml of fluid was estimated by quantitative culture. A diagnostic level was set on $\geq 10^4$ cfu/ml.
Results: In 26 (59.1%) of 44 patients physiologic bacterial flora was found in the bronchial tree. In three cases (6.8%), potentially pathological bacteria were cultured but their number was $< 10^4$ cfu/ml. In 15 (34.1%) cases, the colonization of potentially pathogenic bacteria was $\geq 10^4$ cfu/ml. Both Gram-positive and Gram-negative bacteria were isolated. The most frequently isolated bacterium in the first group was *Streptococcus pneumoniae* (n = 7), and in the second group *Haemophilus influenzae* (n = 3). Multibacterial colonization was found in five patients (11.4%). In four cases (9.1%), the bronchial tree was colonized simultaneously by two and in one case [2.3%] by three types of micro-organism. Multi-drug-resistant strains were not found in the examined materials but among *Streptococcus pneumoniae* the constitutive MLS_B phenotype was observed.
Conclusions:
1. Approximately 30% of patients with lung cancer had a respiratory tract colonized by micro-organisms whose number was higher than the assumed diagnostic level.
2. Among micro-organisms colonizing the lower respiratory tract, Gram-positive cocci such as *Streptococcus pneumoniae* and *Staphylococcus aureus* were dominant.
3. The analysis of antibiotic-resistance did not detect multi-drug-resistant micro-organisms but some strains of *Streptococcus pneumoniae* exhibited resistance to macrolide, lincosamide and streptogramin B.

Key words: lung cancer, bacterial colonization of the lower respiratory tract, antibiotic-resistance

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Introduction

Infections are a natural part of the course of lung cancer. Only a few studies have presented clinical and microbiological documentation of them in patients with the malignancy. However, some conditions exist in this group that make it prone to infections. They are: immunodepression, neutropeny along with changes in endogenic bacterial flora and local inflammatory reaction caused

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by co-existing bronchiectases, and chronic obturatory pulmonary disease (COPD) [1]. Multi-directional treatment of patients with lung cancer can lead to the development of opportunistic infections [2]. The clinical course of lung cancer is often complicated by lung infections proved in 9.5% to 84% of cases [3, 4]. Their diagnosis is very difficult due to non-typical clinical presentation. The interpretation of x-ray images showing lobar inflammatory infiltration, atelectasis or pleural fluid is ambiguous.

It is estimated that the incidence of lung infections in patients who underwent pulmonary resection ranges from 2% to 20% [5–8]. Previous colonization of the respiratory tract by potentially pathogenic micro-organisms may increase the risk of post-operative infection and be a reason for lung infections in the natural course of lung cancer [9]. Identification of bacteria colonizing the lower respiratory tract in patients with lung cancer may influence the choice of perioperative antibiotic prophylaxis and administration of a more efficient empiric antibiotic therapy for lung infections.

The objective of this study is to analyze the profile of potentially pathogenic bacterial strains colonizing the respiratory tract in patients with lung cancer.

Material and methods

The analyzed group consisted of 44 patients with a primary malignant lung tumour aged from 38 to 77 (mean age of 57.9): 34 males aged 38–77 (mean age of 58.5), and 10 females aged 46–77 (mean age of 56.0). In 36 (82.8%) cases non-small cell lung cancer (NSCLC) was diagnosed (squamous carcinoma in 17 patients [39.6%]), anaplastic small cell carcinoma in six cases (13.6%) and carcinoid in two cases (4.5%). Twenty three tumours (52.3%) were in the right lung and 21 (47.7%) in the left one. In six patients (13.6%) with small cell lung carcinoma (SCLC), localized disease was diagnosed in four cases (9.1%) and extended disease in two cases (4.5%).

In patients with NSCLC and carcinoid, stage IA was found in 13 cases (26.5%), stage IB in 22 cases (44.9%), stage IIB in four cases (8.2%), stage IIIA in five cases (10.2%), stage IIIB in one case (2.1%) and stage IV in two cases (4.1%). Fourteen patients (28.6%) were classified as T1 tumour, 32 patients as T2 (65.3%), two patients as T3 (4.1%) and one as T4 (2.1%). Thirteen patients (29.6%) out of the analyzed group underwent radical anatomical lung resection.

Two patients in the analyzed group were treated with inhalation drugs due to COPD. No other comorbidities in the patients could influence the development of pathological bacteria within the bronchial tree.

Bronchofibroscopy was performed in each patient with a bronchofibroscope sterilized in ethylene oxide. The bronchoscope was fixed during the procedure in the lobar bronchus where a tumour was localized and 150 ml of normal saline in fractionated doses was administered and then bronchoalveolar lavage (BAL) was removed from the bronchus by suction and collected in a sterile suction device. 10 ml out of the collected BAL (120––130 ml) was separated for cytology. The rest was for microbiological examination. When BAL was collected, bronchial biopsy was performed if any pathology was found. 100 ml of the fluid was mixed in a vortex for approximately one minute and then a quantitative culture on growth media was made with calibrated loops and a culture for Gram (–) bacilli. The following media were used: Columbia Agar +5%, ram blood, chocolate Agar for Haemophilus and MacConkey's Agar (bioMérieux, France). The obtained material was also centrifuged and a microscopic specimen stained with Gram method was made of sediment. Cultures were incubated in conformity with regulations established for microbiological departments. The identification of bacteria and their antibiotic resistance was done by manual or automatic methods. Results were presented in cfu/ml (cfu = colony forming units). To interpret quantitative cultures, a diagnostic level was set at $\geq 10^4$ cfu/ml [10]. The analysis comprised only potentially pathogenic micro-organisms responsible for infections of the lower respiratory tract and present at the level of $\geq 10^4$ cfu/ml.

Results

In 26 (59.1%) of 44 analyzed patients physiological bacterial flora was found in BAL. In three cases (6.8%), potentially pathogenic bacterial strains at the level of $< 10^4$ cfu/ml were detected, and in 15 cases (34.1%), at least one potentially pathogenic bacterial strain was present at the level of $\geq 10^4$ cfu/ml. Among bacteria isolated at the significant level were Gram-positive ones such as *Streptococcus pneumoniae* (*S. pneumoniae*) (n = 7), *Streptococcus agalactiae* (*S. agalactiae*) (n = 1) and *Staphylococcus aureus* (*S. aureus*) (n = 4) and Gram-negative ones such as *Haemophilus influenzae* (*H. influenzae*) (n = 3), *Moraxella catarrhalis* (*M. catarrhalis*) (n = 1), *Klebsiella oxytoca* (*K. oxytoca*) (n = 1), *Escherichia coli* (*E. coli*) (n = 1), *Pseudomonas aeruginosa* (*P. aeruginosa*) (n = 2) and *Alcaligenes* spp. (n = 1). The frequency of identi-

Table 1. Microorganisms cultured from bronchoalveolar lavage in count ≥ 10^4 cfu/ml in 44 patients with lung cancer

Microorganism	Number of isolates	Frequency (%)
S. pneumoniae	7	33.3
S. agalactiae	1	4.8
S. aureus	4	19.0
H. influenzae	3	14.2
M. catarrhalis	1	4.8
K. oxytoca	1	4.8
E. coli	1	4.8
P. aeruginosa	2	9.5
Alcaligenes spp.	1	4.8
Total	21	100

Table 2. Microorganisms isolated from 15 patients who had positive bronchoalveolar lavage culture with at least one pathogen in count ≥ 10^4 cfu/ml

Lp.	Results [cfu/ml]	Number of patients
1.	*S. pneumoniae* $>10^4$ *E. coli* 10^2	1
2.	*S. pneumoniae* 10^4 *H. influenzae* 10^2	1
3.	*S. pneumoniae* $>10^4$ *E. coli* 10^4	1
4.	*S. pneumoniae* 10^4	2
5.	*S. pneumoniae* $>10^4$ *H. influenzae* $>10^4$	1
6.	*S. pneumoniae* 10^4 *H. influenzae* $>10^4$ *P. fluorescens* 10^3	1
7.	*S. aureus* $>10^4$ *S. agalactiae* $>10^4$	1
8.	*M. catarrhalis* $>10^4$ *S. aureus* 10^1	1
9.	*S. aureus* 10^4 *H. influenzae* 10^3	1
10.	*K. oxytoca* $>10^4$ *S. aureus* 10^3 *P. aeruginosa* $>10^4$ *Alcaligenes spp.* $>10^4$	1
11.	*P. aeruginosa* $>10^4$ *K. oxytoca* 10^3	1
12.	*H. influenzae* $>10^4$	1
13.	*S. aureus* $>10^4$	2

fied bacteria is presented in Table 1. Polymicrobial flora was found in five patients. In four cases (9.1%) two, and in one case (2.3%) three, bacterial species were isolated at the level of ≥ 10^4 cfu/ml. Micro-organisms isolated from patients with positive cultures are presented in Table 2. Three out of seven strains of *S. pneumoniae* were resistant to erythromycin and clindamycin and resistant or intermediately susceptible to tetracycline. One of the strains exhibited lowered susceptibility to penicillin (MIC 0.38 μg/ml) but was susceptible to III-generation cephalosporines (cephotaxime MIC 0.125 μg/ml). Two strains exhibited resistance and intermediate susceptibility to trimethoprim/sulfamethoxazole respectively. All isolated strains of *S. aureus* were metycillin-susceptible. They were also susceptible to erythromycin, clindamycin and trimethoprim/sulfamethoxazole. None of isolated strains of *H. influenzae* produced β-lactamase. However, one strain exhibited resistance to trimethoprim/ /sulfamethoxazole. *M. catarrhalis* produced no β-lactamase. Isolated strains of *K. oxytoca* and *E. coli* exhibited no ability to produce extended-spectrum β-lactamases (ESBLs). Similarly, among *P. aeruginosa* no multi-drug-resistant or metallo-β-lactamases (MBL) producing strains were found.

Thirteen patients out of the 44 underwent radical anatomical lung resection. In this group, perioperative antibiotic prophylaxis was administered: four 2 g doses intravenously every six hours (II-generation caphalosporine-Tarcefandol). The first dose was administered 30 minutes before the induction of general anaesthesia. Before surgery, potentially pathogenic bacteria were isolated from BAL at the level of ≥ 10^4 cfu/ml in six patients and at the level of < 10^4 cfu/ml in two patients and physiological bronchial bacterial flora was detected in five cases. No post-operative infections of surgical wounds or the respiratory tract developed in the patients. No infections of the lower respiratory tract were diagnosed in patients not undergoing surgery. In two patients with COPD, no positive cultures were present.

Discussion

Infections in patients with lung cancer, especially pulmonary ones, can thwart the effect of oncological treatment and affect the survival of patients [11]. Mortality due to post-operative pneumonia in this group of patients is high and ranges from 22% to 67% [5, 12, 13]. Berghmans et al. [14], analyzing the localisation and frequency of infections in 275 patients with lung cancer, found that the most frequent were infections of the bronchial tree (56%) caused by *S. pneumoniae*, *S. aureus*, *H. influenzae*, *E. coli*, *P. aeruginosa* and *M. catarrhalis*. Other authors [4, 11, 15] pay attention both to Gram-negative bacilli such as *H. influenzae*, *K. pneu-*

moniae, *E. cloacae* and *P. aeruginosa* isolated in 68% of patients and the Gram-positive coccus *S. aureus*.

The development of the lower respiratory tract infection is preceded by bacterial colonization. A relation was found between bacterial colonization of the bronchial tree and pneumonia in patients in intensive care units [16]. A similar relation was found in cases of inflammatory complications in patients after pulmonary resections due to lung cancer [12].

Schussler et al. [13] proved that post-operative pneumonia not only is diagnosed more frequently in patients with preceding bacterial colonization but also has earlier clinical manifestation during the post-operative period. Other authors [17–19] found a statistically significant relation between the presence of *H. influenzae* in a pre-operative culture of sputum, pharyngeal swab and its tracheal colonization during intubation and pulmonary infections. According to Sok et al., strains of pathogenic bacteria detected in BAL obtained from a resected lung in intraoperative aspirates from the bronchial tree, were a significant cause of inflammatory complications within the chest [20].

Ioanas et al. [21] estimated that bacterial colonization of the bronchial tree in patients with resectable lung cancer is as high as 41%. They were of the opinion that the risk factor of such colonization is central localization of a tumour and high body mass index (BMI). The authors, however, demonstrated no correlation between the colonization and post-operative pulmonary infections. In our study, potentially pathogenic micro-organisms responsible for the lower respiratory tract infections were found in 30% of patients. The most frequently isolated bacteria were Gram-positive cocci such as *S. pneumoniae* and *S. aureus*. However, *S. pneumoniae* was a dominant pathogen. The bacterium is the most frequent factor responsible for pulmonary infections including lobar pneumonia [3]. In patients who underwent surgery and were earlier colonized, *S. pneumoniae* causes early post-operative pneumonia. In the analyzed group of patients, we found no strains resistant to penicillin, but three out of seven examined isolates exhibited resistance to macrolide, lincosamide and streptogramin B (MLS_B phenotype) that excludes the antibiotics from therapy. The analysis of antibiotic resistance shows no multi-drug-resistant strains. The isolated micro-organisms were susceptible to antibiotics commonly used for the treatment of respiratory tract infections.

Our results are similar to those reported by Ionas et al. [21] who also found no multi-drug-resistant bacterial strains in their clinical material. On the other hand, Radu et al. [22] highlighted the need for verification of recommendations on perioperative antibiotic prophylaxis in thoracic surgery due to its low effectiveness. First generation cephalosporine used as a prophylaxis was inefficient in 84% of microbiologically documented post-operative pneumonias.

In our study, no pneumonias were observed, despite the fact that in some cases bacterial growth exceeded the level assumed as clinically significant. It should be emphasized, however, that only a small group of our patients with positive cultures underwent surgery. Due to the fact that post-operative infections in patients with lung cancer are a serious clinical problem, they require close co-operation between doctor and microbiologist. It seems appropriate to supervise bacterial colonization and infections in this group of patients. Supervision over bacterial flora colonizing the respiratory tract and its antibiotic resistance in relation to the stage of lung cancer and risk factors for infections, along with the analysis of post-operative infections in the patients, enables efficient perioperative antibiotic prophylaxis and should be the object of analysis on a bigger group of patients.

Conclusions

1. Approximately 30% of patients with lung cancer had a respiratory tract colonized by micro-organisms whose number was higher than the assumed diagnostic level.
2. Among micro-organisms colonizing the lower respiratory tract, Gram-positive cocci such as *Streptococcus pneumoniae* and *Staphylococcus aureus* were dominant.
3. The analysis of antibiotic-resistance did not detect multi-drug-resistant micro-organisms but some strains of *Streptococcus pneumoniae* exhibited resistance to macrolide, lincosamide and streptogramin B.

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