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Exploring Colonization and Bronchiectasis in Individuals with Advanced Chronic Obstructive Pulmonary Disease: An In-depth Analysis of Prevalence, Clinical Implications, and Associated Risk Factors

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Abstract

Background: Pathogenic organisms detected in the sputum of patients with Chronic Obstructive Pulmonary Disease (COPD) are known to be associated with an elevated risk of exacerbations and a higher prevalence of bronchiectasis. This study aims to assess the colonization rate in patients with advanced COPD and its correlation with the severity of bronchiectasis.

Methods: A retrospective evaluation was conducted at a single center, involving 378 patients with advanced COPD attending the pretransplant outpatient clinic between October 2008 and June 2011. The analysis included lung function assessments, exacerbation rates over the previous 12 months, and microbiological examination of lung and sputum samples. Computed tomography (CT) scans were evaluated by blinded radiologists for the presence and severity of bronchiectasis.

Results: Sputum expectoration was reported by 196 patients (52%), with potential pathogens identified in 77 cases (20%). Dominant bacterial strains included Pseudomonas aeruginosa (20%) and Staphylococcus aureus (21%). Patients with positive sputum cultures were more likely to be hospitalized due to exacerbations (p=0.01) and exhibited more severe bronchiectasis in standardized CT examinations (p=0.002). Ninety-four patients (25%) underwent lung transplantation during the observation period, with evidence of potential pathogens found in 21 patients (22%) upon examination of explanted lungs.

Conclusion: In this cohort of advanced COPD patients, nearly 1 in 5 exhibited positive respiratory cultures, indicating bacterial colonization. Pathogenic bacterial colonization was correlated with more severe bronchiectasis and a significant increase in hospitalizations due to exacerbations.

Keywords: Colonization; COPD; Lung transplantation; Bronchiectasis.

Abbreviations

BAL: Broncho Alveolar Lavage; COPD: Chronic Obstructive Pulmonary Disease; CT: Computed Tomography (high resolution); ERS: European Respiratory Society; FEV1: Forced Expiratory Capacity in one second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IQR: Interquartile Ranges; PP: Potential Pathogen; QOL: Quality Of Life.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent, nonreversible airway obstruction and chronic cough, often presenting as distinct emphysematous and obstructive subtypes. The use of high-resolution CT (HRCT) scanning has revealed a growing prevalence of bronchiectasis in COPD patients, ranging from 4% to 57%. The development of bronchiectasis

appears linked to declining pulmonary function and airway colonization by potential pathogens (PP), notably Pseudomonas species, creating a self-perpetuating proinflammatory state. Bacterial colonization, aside from contributing to bronchiectasis, is associated with increased exacerbation rates and hospitalization in COPD patients [1].

Existing data, derived from heterogeneous cohorts and no standardized CT protocols, underscores the need for comprehensive microbiological characterization in COPD patients with bronchiectasis. This understanding is crucial for developing targeted therapies like inhaled antibiotics or long-term macrolide prophylaxis. Moreover, bacterial colonization may have implications for subsequent management, particularly in the context of lung transplantation, where prior colonization is a known risk factor for increased infection rates and chronic allograft dysfunction.

Aim of the Study

The study aims to assess bacterial colonization, along with the presence and extent of bronchiectasis in patients with end-stage COPD [2]. The sub-group of patients who underwent lung transplantation will be examined to review bacterial status from explanted lungs. The primary goals include evaluating the bacterial status in advanced COPD patients, analyzing CT morphologic changes in patients with proven bacterial colonization versus those without, and assessing the outcomes associated with these variables.

Methods

Study Design and Study Population

This retrospective single-center study included 378 patients with advanced COPD (GOLD III and IV) attending the lung transplantation evaluation clinic at Hannover Medical School from October 2008 to June 2011. COPD was defined based on GOLD criteria, and all patients were aged 18 or older. The study received approval from the local Ethic Board (No 1120-2011) [3,4].

Pulmonary Function Tests

Patients underwent pulmonary function testing, including spirometric or body plethysmography function testing and capillary blood gas analysis following ERS guidelines. A six-minute walk test was performed for all patients.

Assessment of Clinical Parameters and Outcome

At each visit, patients underwent physical examination, and relevant parameters such as height, weight, heart and respiratory rate, oxygen requirements, and current treatment were recorded. A questionnaire assessed the exacerbation rate, antibiotic treatment, and sputum color. Patient quality of life was measured using a visual analog scale.

Microbiological Status

Microbiology reports for individual patients, including sputum and bronchoalveolar lavage (BAL) results, were reviewed to determine colonization status. Patients were considered "colonized" if bacterial evidence was obtained. Antibiotic resistance testing was performed for cases with positive bacterial growth.

Analysis of Computed Tomography Scans

Multi-detector CT scans from 22 patients with bacterial colonization and 22 randomly selected CT scans from patients without colonization were analyzed by two blinded radiologists. Morphological descriptions of bronchiectasis and emphysematous changes followed criteria described by Hansell et al. Additionally, a score quantifying the degree of bronchiectasis was used.

Statistical Analysis

Numeric data were reported as median and interquartile ranges. Group comparisons used the student's t-test. P values less than 0.05 were considered statistically significant. Categorical variables were analyzed using chi-square tests. Correlation analysis was performed using univariate one-way ANOVA comparing bronchiectasis score against various parameters.

Results

Patient characteristics are summarized in Table 2.

A total of 378 patients were included in the analysis. Regarding symptom profile, 51.7% exhibited chronic cough with >5 ml/day sputum production. Patients without chronic cough and expectoration were considered not colonized [5-7].

Seventy-seven patients demonstrated bacterial colonization (20%). Comparing colonized and non-colonized cohorts, no differences were identified in age, tobacco consumption, life quality, and functional status. Men were more often colonized, and colonized patients were more often lung transplanted. The median exacerbation rate in the preceding 12 months for the entire cohort was 2 (IQR 1-3) with increased exacerbations in colonized patients (p=0.01). Hospitalization rates were significantly higher (p=0.02).

Microbiological material was available in 151 patients, with the remaining 227 patients unable to provide specimens, the majority of whom denied significant expectoration. Sputum analysis was reviewed in 107 patients, and tissue examination from explanted lungs was available in 94 patients (Figure 1).

In 22% of histological lung examinations, pathogenic organisms were identified. Sputum analysis identified potential pathogens (PP) in 62% of patients. Considering the entire cohort collectively, sputum analysis revealed a colonization rate of 17%.

In 50 patients, both lower respiratory secretions and explanted lung tissue were available for comparison. Of the 94 transplant

recipients, 63 previously denied significant expectoration and finally demonstrated no PP in the explanted lung. Another 10/94 patients reporting sputum tested negative for PP in sputum but demonstrated PP in the explanted lung. Only one expectorating patient had both sterile sputum and, in the explant, [8-14].

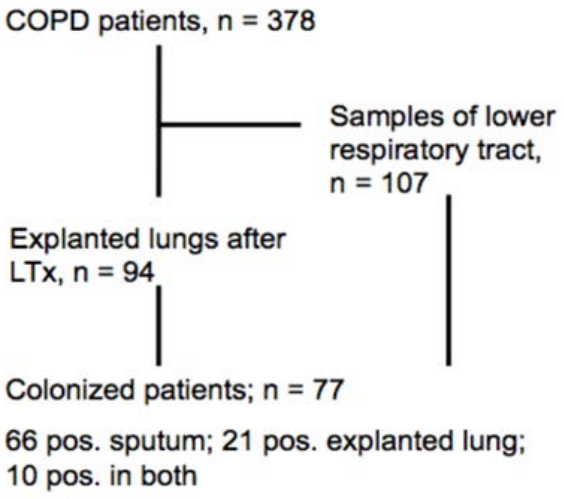

Figure 1: Flow chart of analysis.

The calculated sensitivity and specificity of sputum in comparison to lung tissue were 0.77 and 0.64, respectively, returning a positive predictive value of 0.416. In patients with corroborating positive findings, 5 of 10 organisms were identical.

The most common pathogenic organisms identified were Pseudomonas aeruginosa and Staphylococcus aureus (Table 1). Eight patients cultured Aspergillus. Colonization with multiple organisms in lower respiratory samples was observed in 22 patients (Table 1).

Comparison between colonized patients exhibiting multiple vs. single PP revealed a tendency (p=0.058) towards lower quality of life (QOL) in patients with multiple PPs, with other baseline characteristics revealing no significant differences. We furthermore analyzed the histograms of the isolated bacteria (Table 2).

CT assessment for bronchiectasis was performed in 44 patients, with significantly more severe bronchiectasis in patients with airway colonization (p=0.002), see Table 1.

Additional correlation analysis comparing bronchiectasis scoring and patient baseline characteristics did not demonstrate any significant findings, although a trend was found suggesting a

Table 1: Patient characteristics.

	all patients (n=378)	Colonized patients (n = 77)	Non-colonized patients (n = 301)	Significance
Age at first presentation, years (IQR)	54 (49; 58)	54 (47; 59)	54 (49; 58)	0.2
Lungtransplantation, n (%)	94 (25)	34 (36)	60 (64)	0.0001
Age at transplantation, years (IQR)	55 (51; 59)	55 (50; 60)	55 (51; 59)	0.46
Gender: Male / Female	191/187	51/26	140/161	0.03
Body mass index (IQR)	23 (20; 26)	23 (22; 27)	23 (21; 26)	0.2
Packyears (IQR)	30 (20; 44)	30 (15; 40)	30 (20; 45)	0.3
Oxygen, n (%)	275 (73)	54 (70)	221 (73)	0.36
6 MWT, m (IQR)	264 (165; 374)	235 (110; 375)	271 (174; 374)	0.4
Respiratory infections per year, n (IQR)	2 (1; 3)	3 (1; 5)	2 (1; 3)	0.01
Respiratory infections with hospitalization per year, n (IQR)	1 (0; 1)	1 (0; 2)	1 (0; 1)	0.02
QoL – VAS (IQR)	4 (2.5; 5)	4 (3; 5)	4 (2; 5)	0.7
FEV1 % predicted (IQR)	19 (15; 25)	20 (16; 25)	19 (15; 25)	0.4
FVC % predicted (IQR)	62 (51; 76)	61 (48; 74)	63 (53; 78)	0.4
pO_2, mmHg (IQR)	69 (62; 77)	69 (59; 77)	69 (62; 77)	0.6
pCO_2, mmHg (IQR)	43 (38; 49)	43 (38; 50)	43 (39; 49)	0.7

Table 2:CT findings.

	all patients (n=44)	Colonized patients (n = 22)	Non-colonized patients (n = 22)	Significance
Bronchiectasis, n	35	18	17	1
- mild	23	7	16	0.01
- severe	12	11	1	0.002
Score bronchiectasis, median (IQR)	6 (2; 12)	11 (2; 17)	5 (0.75; 6.25)	0.006
Bronchial wall thickening, n	37	19	18	0.5
Infiltrates, n	4	2	2	1
Pleural effusion, n	1	0	1	0.3
Mucus plugging, n	18	10	8	0.3
Tree in bud phenomenon, n	4	3	1	0.3
Homogenous emphysema, n	19	10	9	0.8

shorter time from first presentation until lung transplantation (p=0.09).

Treatment plans were available in 311 patients and corresponded with current GOLD treatment guidelines (www.goldcopd.org, December 2012), consisting of a combination of inhaled steroids, long-acting β-sympathomimetics, and anticholinergic drugs.

In the remaining patients, no medication plan was available. Oral steroids or steroid-equivalent drugs were recorded in 100 patients. Among patients receiving inhaled steroids, no significant increase in colonization or specifically Aspergillus rates was observed.

Discussion

In evaluating the rates of bacterial colonization and bronchiectasis in patients with advanced COPD, the main findings of our study may be summarized as follows:

Low Rate of Airway Colonization: Only 77 (20%) out of 378 patients awaiting lung transplantation for COPD exhibited airway colonization with potential pathogens. Even with the use of the gold-standard microbiological assessment (tissue analysis from explanted lungs in 94 patients), potential pathogens were identified in only 22% of patients [9-14].

Sputum Culture Sensitivity and Specificity: The sensitivity and specificity of sputum culture were 77% and 64%, respectively. A negative sputum result does not reliably exclude chronic colonization.

Association with Severe Bronchiectasis: Evidence of pulmonary bacterial colonization was associated with a higher incidence of severe bronchiectasis (50% vs. 4.5%) and correlated with a significant increase in exacerbations requiring hospitalization (p=0.02) and lung transplantation (p=0.0001).

While previous studies have hinted at different phenotypes within COPD patients, our study specifically focuses on the phenotypes of colonized and bronchiectatic patients. Colonized patients exhibited higher rates of sputum production and were more likely to be hospitalized due to infectious exacerbations.

Previous studies examining the relationship between colonization, bronchiectasis, and COPD have been limited by small and heterogeneous study cohorts. Our data focused specifically on patients with end-stage disease. Over half of our cohort (52%) demonstrated significant expectoration. These findings align with data from Patel et al., who observed daily cough and sputum production in 50% of patients with moderate or severe COPD. Within our cohort, almost one-third of expectorating patients demonstrated airway colonization. Colonization rates in our study were comparable with other recent observations. Soler et al. reported bronchoalveolar lavage colonization rates of 33% in COPD patients. Similar rates were observed by Monso et al. (25%), in 41 samples of patients with chronic bronchitis. Previous studies have demonstrated decreasing FEV1 and continued smoking as independent risk factors for lower respiratory bacterial colonization in advanced COPD [15].

In our study, 94 patients (25%) underwent lung transplantation. Microbiological examination of the explanted lung was performed in all cases, with 22% of the specimens identifying pathogenic

organisms. However, comparing the 22% colonization rate revealed by intraoperative smear versus 62% by sputum (significant expectoration) is challenging. Despite these findings, the calculated sensitivity of 77% and positive predictive value of 42% suggest that sputum analysis remains a relevant screening tool in patients with chronic expectoration. Positive sputum results appeared relevant when compared with results obtained from explanted lungs.

Discordance in cultures between different sampling modalities can be attributed to various reasons, including sputum contamination in the upper respiratory tract, changes in treatment, lung harvesting under sterile conditions but with possible contamination, and variations in colonization throughout the year. While lower respiratory samples offer better sensitivity than sputum, bronchoscopy cannot be considered a routine procedure in end-stage COPD due to high complication rates in patients with profoundly reduced FEV1. In contrast, sputum sampling is relatively straightforward in such patients, especially given the reported corroboration in our colonization rates for sputum and explanted lungs.

Our findings revealed that airway colonization was associated with higher rates of lung transplantation and hospitalization. These results broadly concur with Patel et al., who reported a positive correlation between lower airway bacterial colonization and exacerbation frequency. In contrast to previous reports associating tobacco exposure with rates of bacterial colonization, we observed no difference. Given the requirement for tobacco abstinence before lung transplantation evaluation, rates of active smoking in our cohort were extremely low.

Regarding sputum analysis, the most common pathogenic organisms were Pseudomonas aeruginosa and Staphylococcus aureus, contradicting previous studies reporting Hemophilus influenzae as the most frequent pathogen. The discordance most likely reflects the end-stage nature of the COPD patients in our study, exemplified by the fact that 22 patients exhibited multiple bacterial colonization and 7 patients demonstrated Mult resistant organisms. Similarly, the detection of Aspergillus in eight patients (4%) is in line with advanced disease. Little was known about Aspergillus colonization rates in advanced COPD until now, with previous studies not referring to fungal colonization. An association between Aspergillus colonization and the use of inhaled steroids could not be established in the current cohort.

In assessing the relationship between lower airway bacterial colonization and the development of bronchiectasis on CT in COPD patients, limited previous data exists. Previous studies have examined the association between changes in CT and functional parameters in COPD, specifically about α1-antitrypsin disease but did not quantify the severity of bronchiectasis. Regarding bronchiectasis in moderate to severe COPD, Martinez-Garcia et al. reported a prevalence of 57.6%, with a frequency distribution like that of Patel et al. (50%) despite using heterogeneous and non-standardized radiological assessment. In contrast, we employed a standardized bronchiectasis CT protocol and focused on end-stage patients. The prevalence of bronchiectasis in our study was 79%. This higher rate may merely reflect the advanced COPD stage in our cohort, as suggested by Martinez-Garcia et al., who observed a greater prevalence of bronchiectasis (70%) in patients with severe functional impairment (FEV1 <50%). Interestingly, differentiation between mild and severe bronchiectasis revealed important differences between non-colonized and colonized patients, with significantly higher bronchiectasis scores being recorded in colonized patients (11 vs. 5; p=0.006). These findings suggest that colonization is a risk factor for severe bronchiectasis in patients with advanced COPD.

This retrospective study has several strengths and limitations. It currently represents the first study comparing lung tissue and lower respiratory samples in many patients with advanced COPD. Nevertheless, CT scans were analyzed in 44 patients but under blind conditions. The small number of CT examinations results from either insufficient quality or the date of CT scan (a long period between CT scan and the last presentation to the ambulance). A limitation is that in lower respiratory samples, quantification of colonization forming units was not possible, and no repetitive cultures were obtained by the patients.

Conclusion

Our data provides another perspective on the truly heterogeneous nature of COPD and the growing acceptance of the need for individual tailored therapy.

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