

Pulmonary Mycosis: An Under-Rated Aetiology of Acute on Chronic COPD Exacerbations

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Abstract

COPD is leading cause of morbidity and mortality worldwide. The step decline course of lung functions is the hallmark of COPD with exacerbation being marked events that increases inflammation overall and further accelerates process of decline. Events that cause exacerbation are both variable and subjective. Viral and bacterial are thought to be main cause of exacerbation. This is confounded by the factor that in past, as the technique to detect pulmonary mycosis was flawed. Direct microscopy and fungal culture were both non specific due to ubiquitous nature of fungi.

50 patients each were recruited among stable COPD and COPD patients in acute exacerbation. Respiratory samples were obtained in a sterile manner and KOH microscopy and SDA culture was done. 36 patients out of 50 in the COPD exacerbation group were found to have a microbiological isolate of one or more form of fungi, when compared to 19 patients out of 50 in the stable COPD group. This study attracts further interest in bio-immunology of COPD patients where either the exacerbations are secondary to fungal infestation, or it may be possible the fungal infestation of respiratory system leads to an atmosphere where other pathogen flourish and immunity is unable to neutralize the threat.

Keywords: *Pulmonary Mycosis; Chronic COPD Exacerbations*

Abbreviations

COPD: Chronic Obstructive Pulmonary Disease; SDA: Sabouraud Dextrose Agar; PCR: Polymerase Chain Reaction

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a common preventable and treatable disease characterized by persistent and progressive airflow limitation that is caused due to enhanced chronic inflammatory response of the airways and lungs to noxious particles and gases [1]. COPD is a spectrum of disease which involves airway, parenchyma, and vasculature. COPD is a major cause of morbidity and mortality which varies across countries. Globally estimates vary around 210 million patients who suffer with COPD. Out of which, approximately 30 million people suffer with COPD in India. In the United States of America alone, approximately 24 million people suffer with COPD and has emerged as the third leading cause of death [2,3]. Exacerbation marks a significant event for a COPD patient.

As each exacerbation cause a further acceleration to the already declining lung function. Exacerbation result in reduced physical activity, poorer quality of life, and an increased risk for mortality [4]. In severe exacerbations the patient may end up in respiratory failure, needing intensive care admission. In-Hospital mortality of patients admitted for a hypercarbic COPD exacerbation is approximately 10%, but the long-term outcome remains poor. As it is known prevention is best therapy, the cause of these exacerbation needs to be studied in detail and focussed attempts need to be made by pulmonologist to prevent any exacerbation, if possible.

Research done in Pulmonary Mycosis are always viewed with a sense of doubt, differentiating between colonizer and disease-causing agent is always a debate. Bacterial infections are the most common known causes of acute exacerbation of COPD, rest 50% may be sterile or viral [5]. We hypothesised that the presence of any kind of mycosis in the airways of patients with COPD is associated with disease increased number of exacerbations.

Aim of the Study

1. To evaluate the spectrum of pulmonary fungal infection in COPD patients.
2. To compare the spectrum of fungal infection among respiratory samples in stable COPD patients and with patients of COPD with acute exacerbation.

Methods

The study was conducted in the Department of Tuberculosis and Respiratory Medicine with support of Department of Microbiology at an Apex Level institute of Haryana, India.

Patients were initially divided in to two groups:

- 1) COPD patients with acute exacerbation
- 2) Stable COPD patients.

Fifty patients of each group (total 100 patients) were included in the study. COPD was diagnosed according to GOLD Guidelines. Exacerbations were defined as a sustained worsening of the patients' condition from the stable state and beyond day-to-day variation that is acute in onset and necessitates change in regular medications.

Inclusion criteria:

1. COPD, as per GOLD guidelines.

Exclusion criteria:

1. Any co-existing respiratory disease.
2. Patients who were not give written consent.
3. Patient with chronic disease other than COPD (diabetes, hypertension, chronic kidney disease, chronic liver disease etc).

Sample collection

Sputum and induced sputum samples were collected in sterile vials and transported to microbiology department within 2 hours of collection.

Processing

Sputum sample was subjected to direct microscopy by using KOH wet mount, then specimen was divided into two parts:

1. Part-1: This part of sample was first inoculated on Sabouraud dextrose agar slant at 25 degree Celsius for culture.
2. Part-2: Sample of second part put at 37 degree C in biological oxygen demand (BOD) for 3 weeks. Culture was observed daily for any fungal growth till 21 days. If any fungal growth was found then it was identified as per standard protocol.

Statistical analysis

The data was collected and subjected to statistical analysis by using Chi-square test, descriptive statistics i.e. means and standard deviations by using IBM Statistical Package for Social Sciences (SPSS) version 24.0.

Results

Patients who were recruited in the COPD with acute exacerbation group were found to have a significant increase (p =.001) in fungal isolation from their respiratory samples as displayed by table 1.

Diagnosis Fungus found in respiratory sample(KOH mount or culture positive)	Frequency (%)		Significance
	COPD with acute exacerbation (n = 36)	Stable COPD(n = 19)	
Present	36 (72.0)	19 (38.0)	p = 0.001
Absent	14 (28.0)	31 (62.0)	

Table 1: Distribution of subjects as per fungal isolation in stable COPD and COPD with acute exacerbation group.

When patients were stratified as per GOLD spirometric grades (Table 2), it was consistently observed that, COPD with acute exacerbation subset had a higher rate of fungal isolation except GOLD grade 1.

GOLD Spirometric Grade	Frequency (%)	
	COPD with acute exacerbation with fungal isolation (n = 36)	Stable COPD with fungal isolation (n = 19)
GOLD 1	Nil	3 (16)
GOLD 2	7 (20)	5 (26)
GOLD 3	11 (30)	8 (42)
GOLD 4	18 (50)	3 (16)

Table 2: Stratification of subjects as per fungal isolation in stable COPD and COPD with acute exacerbation group as per COPD severity defined by GOLD.

When the 2 subset of population being studied, i.e. Stable COPD and COPD with acute exacerbations were studied for species level association of fungus which was isolated found no significance (Table 3).

Diagnosis Fungus found in respiratory sample(KOH mount or culture positive)	Frequency (%)		Significance
	COPD with acute exacerbation (n = 36)	Stable COPD(n = 19)	
<i>Aspergillus flavus</i>	5 (13.9)	2 (10.56)	p = 0.722
<i>Alternaria</i> spp.	0	1 (5.3)	p = 0.165
<i>Aspergillus fumigatus</i>	8 (22.2)	3 (15.8)	p = 0.571
<i>Aspergillus niger</i>	3 (8.3)	2 (10.5)	p = 0.788
<i>Candida albicans</i>	13 (36.1)	8 (42.1)	p = 0.663
<i>Fusarium</i> spp.	1 (2.8)	0	p = 0.463
Non-mornifiipenicillium	4 (11.1)	2 (10.5)	p = 0.947
<i>Trichophyton</i>	2 (5.6)	1 (5.3)	p = 0.964

Table 3: Distribution of study group as per fungal isolation on a species level.

Discussion

In the present study we find that patients who present to our hospital with COPD exacerbation have significant difference in terms of fungal isolation from respiratory samples when compared to stable COPD patients (Table 1), (p = 0.001). This seems to be consistent with similar studies done in past. In 2019, 80 COPD patients with COPD were studied by Mahmoud EM., et al. [6], 19 patients had possible PFI, and 61 patients had probable pulmonary fungal infection, out of them only 12 patients had positive Beta D Glucan Assay. 49 patients had negative Beta D Glucan Assay. Usage of either steroids and/or antibiotics in the past 3 months was associated with higher probable fungal infection than those with possible pulmonary fungal infection (P = 0.003).

Barberán J published a study in 2014, which described incidence of aspergillosis, which is increased in the patients suffering from COPD due to Mucociliary activity impairment, immunosuppression due to the inhibition of alveolar macrophages and neutrophils by steroids, and receiving broad-spectrum antibiotics [7].

Bafadhel M., et al. from UK, in 2014 investigated the frequency of filamentous fungal culture and the relationship to clinical outcomes in COPD subjects [8]. Non-smoking and non obstructed smoking controls were invited to attend a single study visit, with lung function testing, sputum induction and demographic data collection. Filamentous fungi were cultured at baseline in 49% (63 out of 128) of COPD subjects, of which 75% (47 out of 63) were *Aspergillus fumigatus*. Fungus was cultured in 3 out of 22 controls, out of which two were *A. fumigatus*.

Conclusion

Respiratory tract is always at a risk to develop fungal infection due to the humid atmosphere associated with it. Fungal organisms are ubiquitous.

Chances of fungal colonization and subsequent infection increase in COPD patients due to

1. Structural changes causing increased adherence of fungus to airway

2. Impaired ciliary function causing lack of clearance
3. Altered lung biome resulting in uncontrolled growth
4. Repeated broad spectrum antibiotic use for exacerbations
5. Malnutrition
6. Chronic steroid use (Inhaled or systemic)
7. Coexisting diabetes
8. High environmental exposure (in patients working in areas having high fungal load, like hay farm).

There is a firm belief amongst pulmonologist that fungal organism don't cause exacerbation, rather bacteria and virus are considered to be the top causative aetiologies for an exacerbation in COPD patients. This belief is backed by excellent technology to detect bacterial and viral organism. But fungal organism has always been difficult to capture as culture reports arrive after a delayed duration due to slow growing nature of fungus. This however does not mean that fungal organism do not cause exacerbation. In our study, we find a consistent increase in fungal isolation amongst patients having COPD exacerbations. We infer that either fungal organism cause exacerbation or create an easy environment for bacteria or virus. The need of identifying these fungal organisms and their protocol-based treatment still stands unmet. Colonization may be considered normal but the rate of colonization in COPD patients is higher than normal counterparts. Fungal organism may also play a role in biofilm formation and may harbour drug resistant organism under it, making them not amenable to conventional treatment. We strongly recommend that fungal infection in COPD needs to be thoroughly assessed and a common consensus needs to be developed in form of a guideline to screen and treat these subgroups of patients. As fungal culture takes very long duration, by the time culture report arrives, it is seldom of help because the illness has either progressed or has been tided over.

Moreover, as anticholinergic drugs like glycopyrronium, ipratropium gain popularity their use in fungal infection remains unprobed. It is our belief that as reducing airway secretion, this class of drugs do seem to have odds on tackling fungal infection.

New technologies like Pan-fungal Polymerase Chain Reaction (PCR) needs to be assessed and a correct threshold needs to be decided which would translate into an effective treatment.

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