Assessment of Occult Pulmonary Involvement in Ulcerative Colitis

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Keywords

Ulcerative colitis · Pulmonary involvement · Extraintestinal manifestation · Restrictive pattern · Occult pulmonary disease

Abstract

Introduction: Nearly 50% of patients with inflammatory bowel disease (IBD) experience at least one extraintestinal manifestation. Bronchopulmonary involvement is rare in IBD. Pulmonary function test (PFT) abnormality in cases of ulcerative colitis (UC) has been reported to be 17–55%. Occult pulmonary disease may be diagnosed using variables of the PFT. Hence, we aim to evaluate the frequency and type of pulmonary dysfunction in patients with UC in remission.

Methods: Eighty-three patients of UC in remission and 48 controls underwent the PFT including forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), Tiffeneau value (FEV1/FVC), and midexpiratory flow (MEF 25–75%) rate with a spirometer. The patients were divided based on the age of onset of UC into A1 (<16 years), A2 (16–40 years), and A3 (>40 years) and based on the extent of disease into E1 (proctitis), E2 (left-sided colitis), and E3 (extensive colitis). **Results:** Patients with UC had significantly abnormal PFT compared with controls (51 [61.5%] vs. 8 [16.67%]; $p = 0.000$). Patients with UC commonly had a restrictive pattern (33 [64.47%]) of PFT followed by small airway disease (11 [21.56%]) and ob-

structive pattern (7 [13.72%]). Pulmonary involvement in cases of UC was more in E3 followed by E2 and E1. Pulmonary involvement was more in the late age of onset of disease. BMI was positively and significantly correlated with FEV1 and FVC. Hemoglobin had a positive and significant correlation with FEV1 while a negative correlation with FEV1/FVC and MEF 25–75%. All predictors except for age were found to contribute in higher risk ($OR > 1$) for PFT abnormality. **Conclusion:** Patients with UC have chronic pulmonary inflammation leading to different patterns of lung involvement in the form of restrictive, obstructive airway, and small airway disease. Patients with UC commonly have a restrictive pattern of pulmonary involvement. Impairment of the PFT is related to the disease extent and the age of onset of disease. Assessment of the PFT using a spirometer is a noninvasive, simple, cost-effective, and reliable method for early detection of occult pulmonary involvement in patients of UC.

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Introduction

Ulcerative colitis (UC) is a disease of unknown etiology, which occurs due to an abnormal immune response leading to chronic intestinal inflammation [1]. It is characterized by relapsing-remitting inflammation of the gastrointestinal tract. Nearly 50% of inflammatory bowel dis-

ease (IBD) patients will experience at least one extraintestinal manifestation [2–4]. Bronchopulmonary involvement is rare in IBD [5]. Airway disease of different types involves different parts of the bronchial tree from the glottis to small airways, leading to ventilation defects, bronchial hyperresponsiveness, and sputum or bronchoalveolar lavage lymphocytosis, as well as radiological and histological abnormalities [6–11].

Pulmonary involvement in UC was first reported in 1976 [12]. It is being increasingly reported in recent years. Pulmonary function test (PFT) abnormality in cases of UC has been reported to be 17–55% [10, 13–16], which includes decrease in the maximal midexpiratory flow rate (MEFR) [17], elevated functional residual capacity (FRC) [18], decrease in the gas transfer factor (diffusion lung capacity for carbon monoxide [DLCO]) [19, 20], or increased frequency of bronchial hyperresponsiveness [21]. Respiratory abnormalities reported in cases of UC include obstructive lung disease, interstitial lung disease [22], small and large airway disorders [12, 23], bronchitis, bronchiectasis [12, 24], bronchiolitis obliterans [25], and increase in bronchial responsiveness [21]. Most of these cases are overt or subclinical. However, most patients found to have a normal chest X-ray [24, 26].

Inflammatory bowel diseases, that is, Crohn's disease (CD) and UC, have complex pathogenesis involving interaction between genetic, environmental, immune regulatory, and microbial factors [20]. Disordered innate immunity also has a role to play [20]. The structural similarity between the intestine and the bronchus and their common origin from the primitive foregut provide a basis for the development of inflammatory changes in the bronchus in patients with IBD [20, 27]. The prevalence of pulmonary involvement in IBD has been varying in reports, and its clinical implication is not clear. However, it is important that pulmonary manifestations are diagnosed and treated early or else it will lead to irreversible damage to the airway wall or the end-stage lung disease. Occult pulmonary disease may be diagnosed using variables of the PFT. Hence, we undertook this study with the following aims: (i) to determine the type and frequency of pulmonary involvement in patients with UC, (ii) to determine the distribution of pulmonary dysfunction in patients with UC according to the disease extent and age of onset of disease.

Materials and Methods

Study Population

This case-control study was conducted at a tertiary care hospital in Central India from August 2018 to November 2019. Approv-

al from the ethics committee of the institution was obtained. The ethical committee approval number was 1322 EC/Pharmac/GMC/NGP. A total of 83 patients between 18 and 70 years of age were diagnosed as UC in remission based on clinical history; colonoscopy findings and histopathological examination of the colonic mucosa were included in the study. One control for 2 cases was enrolled, which was age and gender matched. Detailed clinical history including demographic profile, drug history, duration of the disease, and other parameters was noted in pro forma. According to the European Crohn's and Colitis Organization (ECCO), consensus remission was defined as ≤ 3 nonbloody stools per day with no abdominal pain and/or tenesmus. According to the Montreal classification, the patients were divided into 3 groups as A1 (<16 years), A2 (16–40 years), and A3 (>40 years) based on the age of onset of disease and the extent of the disease was assessed on colonoscopy as proctitis, left-sided colitis, or pancolitis. Proctitis was defined as involvement of the rectum only (E1), left-sided colitis as left colon up to splenic flexure (E2), and pancolitis as extensive disease beyond splenic flexure (E3). The duration of the disease was defined as the period between the date of diagnosis of disease and the date of PFT. Forty-eight age- and sex-matched healthy controls were also enrolled in the study.

Study Exclusion Criteria

Patients with major surgeries and skeletal deformities in the thorax, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), morbid obesity (BMI > 35 kg/m²), and/or congestive cardiac failure were excluded from the study. Pregnant females, patients aged <18 and >70 years, patients with any history of smoking in the past or active smokers, and patients with history of asthma or familial atopy were also excluded. Patients with history of occupational exposure to asbestos, silica, coal, and cotton were also excluded. Written and informed consent was obtained from all the patients and controls.

Pulmonary Function Test

All the cases and controls were subjected to the PFT. The PFT was performed utilizing Sensor Medics Corporation Spirometer (Model CA92687, SN 54065, Osaka, Japan). The predicted forced expiratory volume in the 1 s (FEV1%), the predicted forced vital capacity (FVC%), and their ratio (FEV1/FVC) as well as forced expiratory flow 25–75% (FEF 25–75%) were measured. Each measurement was repeated at least 3 times, and the highest acceptable measurement was compared with the normal predicted value. Normal physiology was defined by all measurements being >80% predicted, a restrictive defect as a reduced (<80% predicted) FVC with an FEV1/FVC ratio of >70% predicted, and an obstructive defect as a reduced FEV1 with a normal FVC and a low FEV1/FVC ratio (<70% predicted). Small airway disease was defined as a reduced FEV1 (<70% predicted), low FEV1/FVC (<70% predicted) ratio, and reduced MEF 25–75% (<60% predicted) [28].

Statistical Analysis

Data were entered in MS Excel and coded and analyzed using statistical software STATA, version 10.1, 2011. Descriptive statistics were used to summarize quantitative variables with mean and standard deviation (SD), while frequency and percentages were used to summarize categorical (qualitative) variables. Correlation between FEV1, FVC, and FEV1/FVC ratio with other

Table 1. Demographic details, clinical and laboratory parameters, and PFTs of patients and controls

Parameter	Cases (n = 83)	Controls (n = 48)	p value
Age, years	38.77±12.67	39.46±13.67	0.771
Sex (male:female)	1.18	1.28	
BMI, kg/m ²	18.90±3.6	21.23±4.67	0.001
Duration of disease, months	49.6±4.2		
Extent of disease			
E1 (proctitis), %	9 (10.84)		
E2 (left-sided colitis), %	42 (50.60)		
E3 (extensive colitis), %	32 (38.55)		
Age of onset of disease			
A1 (<16 years), %	0		
A2 (16–40 years), %	50 (60.24)		
A3 (>40 years), %	33 (39.76)		
Hemoglobin, g/L	11.27±2	12.14±2.17	0.02
Albumin, g/L	3.55±0.41	3.96±0.56	0.001
FEV1	79.21±15.53	81.21±16.73	0.491
FVC	81.07±14.86	83.27±16.86	0.4387
FEV1/FVC	97.69±15.60	98.31±17.81	0.835
MEF 25–75%	72.13±16.65	74.21±18.27	0.5075
PFTs			
Normal, %	32 (38.5%)	40 (83.33%)	0.000
Abnormal, %	51 (61.5%)	8 (16.67%)	
Pattern of abnormal PFT	(n = 51)	(n = 8)	0.000
Restrictive pattern, %	33 (64.47%)	4 (8.33%)	
Small airway disease, %	11 (21.56%)	2 (4.17%)	
Obstructive pattern, %	7 (13.72%)	2 (4.17%)	

Descriptive statistics were used to summarize quantitative variables with mean and standard deviation (SD). All continuous data are presented as mean±SD. For categorical data, figures within parenthesis indicate percentages. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mean expiratory flow; PFT, pulmonary function test.

continuous variables was assessed using Pearson's correlation coefficient (r). Inferential statistics mainly included hypothesis-testing procedures such as Pearson's χ^2 test for assessing significance of difference in categorical outcomes expressed as proportions in comparison groups. Student's t -test was also used to assess significance of difference in means in 2 independent groups and for testing hypothesis that correlation coefficient $r = 0$. A p value <0.05 was considered statistically significant for all the comparisons.

Results

Demographic Characteristics and Laboratory Parameters of Patients with UC and Controls

Out of 83 cases of UC enrolled in the study, 45 (54.21%) were male and 38 (45.78%) were female with a male-to-female ratio of 1.18. Out of 48 age- and sex-matched controls, 27 (56.25%) were male and 21 (43.75%) were female with a male-to-female ratio of 1.28. The commonest type

of presentation in UC patients was left-sided colitis (E2) ($n = 42$, 50.6%) followed by extensive colitis (E3) ($n = 32$, 38.55%), and the least common type was proctitis (E1) ($n = 9$, 10.84%). The age of onset of disease in UC patients was between 16 and 40 years (A2) in 60.24% (50) and >40 years (A3) in 39.76% (33). The mean BMI of the control group (21.23 ± 4.67) was statistically significantly higher than that in the UC group (18.90 ± 3.6 ; $p = 0.001$). The serum albumin of the control group (3.96 ± 0.56) was significantly higher than that in the UC group (3.55 ± 0.41 ; $p = 0.001$). The blood hemoglobin of the control group (12.14 ± 2.17) was significantly higher than that in the UC group (11.27 ± 2 ; $p = 0.02$) (Table 1).

Pulmonary Function Test

Patients with UC had significantly abnormal PFT compared with controls (51 [61.5%] vs. 8 [16.67%]; $p = 0.000$). Patients with UC commonly had a restrictive pattern (33 [64.47%]) of PFT followed by small airway dis-

Table 2. Distribution of PFT according to the extent of disease

Extent of disease	PFT			
	normal (%)	restrictive pattern (%)	small airway disease (%)	obstructive pattern (%)
E1 (<i>n</i> = 9)	4 (44.44)	3 (33.33)	1 (11.11)	1 (11.11)
E2 (<i>n</i> = 42)	18 (42.86)	14 (33.33)	5 (11.9)	5 (11.9)
E3 (<i>n</i> = 32)	10 (31.25)	16 (50)	5 (15.63)	1 (3.13)

$\chi^2 = 4.0697$; $p = 0.667$

Pearson's chi-square test and Fisher's exact test ($p < 0.05$ is considered as significant). E1, proctitis; E2, left-sided colitis; E3, extensive colitis; PFT, pulmonary function test.

Table 4. Spearman's correlation between pulmonary function parameters with variables

FEV1	FVC	FEV1/FVC	MEF 25–75%
Age, years			
$r = 0.0365$	$r = -0.1156$	$r = 0.1649$	$r = 0.0164$
$p = 0.7433$	$p = 0.2980$	$p = 0.1363$	$p = 0.8832$
BMI, kg/m ²			
$r = 0.2926$	$r = 0.2719$	$r = 0.0048$	$r = 0.0660$
$p = 0.0073$	$p = 0.0129$	$p = 0.9655$	$p = 0.5535$
Hemoglobin, g/dL			
$r = 0.2269$	$r = 0.1873$	$r = -0.0140$	$r = -0.0228$
$p = 0.0391$	$p = 0.0900$	$p = 0.8997$	$p = 0.8381$
Serum albumin			
$r = 0.1784$	$r = 0.2183$	$r = -0.0388$	$r = -0.0599$
$p = 1.067$	$p = 0.0474$	$p = 0.7275$	$p = 0.5904$

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, midexpiratory flow rate; FEV1/FVC, Tiffeneau value.

ease (11 [21.56%]) and obstructive pattern (7 [13.72%]). On comparison of cases and control, there was no significant difference between FEV1, FVC, FEV1/FVC, and MEF 25–75% (Table 1). Pulmonary involvement in cases of UC was more in E3 followed by E2 and E1. The restrictive pattern was common in all the 3 groups ($\chi^2 = 4.069$; $p = 0.667$). The obstructive pattern was being more commonly observed in the E2 group compared with other groups (Table 2). Pulmonary involvement in cases of UC was more common in patients with late-onset disease, that is, A3 group (>40 years) ($\chi^2 = 1.259$; $p = 0.739$). In addition, the restrictive pattern was more prevalent in this group (Table 3).

Table 3. Distribution of PFT according to the age of onset of disease

Age of onset of disease	PFT			
	normal (%)	restrictive pattern (%)	small airway disease (%)	obstructive pattern (%)
A2 (<i>n</i> = 50)	20 (40)	18 (36)	8 (16)	4 (8)
A3 (<i>n</i> = 33)	12 (36.36)	15 (45.45)	3 (9.0)	9.09)

$\chi^2 = 1.2592$; $p = 0.739$

Pearson's chi-square test and Fisher's exact test ($p < 0.05$ is considered as significant). A2, age 16–40 years; A3, age > 40 years; PFT, pulmonary function test.

Correlation between Pulmonary Function Test and Various Parameters

In Pearson correlation analysis, it was found that age was positively correlated with FEV1, FEV1/FVC, and MEF 25–75% and negatively correlated with FVC. BMI was positively and significantly correlated with FEV1 and FVC. Hemoglobin had a positive and significant correlation with FEV1 while a negative correlation with FEV1/FVC and MEF 25–75%. Serum albumin had a positive and significant correlation with FVC and a negative correlation with FEV1/FVC and MEF 25–75% (Table 4).

Binary Multiple Logistic Regression Analysis

As evident from the results of multiple logistic regression (Table 5), all other predictors except the age of onset of disease were found to contribute in higher risk (OR > 1) for PFT abnormality, but risk measures for only sex ($p = 0.04$) and BMI ($p = 0.02$) were found statistically significant. The extent of disease (OR = 1.99) and duration of disease (OR = 2) were found to contribute in higher risk for PFT abnormality, but this was not statistically significant. Females were having almost 3 times more risk of PFT abnormality compared with males when adjusted for other factors. Overweight/obese subjects carried 21% more risk of PFT abnormality than those having normal BMI when the role of other factors was accounted for in the multivariable analysis.

Discussion

UC is a chronic IBD of unknown etiology with remissions and exacerbations [26]. The actual prevalence of pulmonary disease in IBD remains unknown, though it

Table 5. Results of binary multiple logistic regression analysis for predicting outcomes (PFT abnormal/normal)

Predictor variables	OR	95% CI for OR		p value
Age of onset of disease, years	1.04	1.00	1.09	0.07
Sex (female/male)	2.93	1.06	8.13	0.04
BMI, kg/m ²	1.21	1.03	1.41	0.02
Mesalamine (duration of disease) (yes/no)	2.00	0.70	5.71	0.19
Azathioprine (yes/no)	1.50	0.34	6.65	0.59
Extent of disease (E1/E2/E3)	1.99	0.90	4.39	0.09

CI, confidence interval; OR, odds ratio; E1, proctitis; E2, left-sided colitis; E3, pancolitis colitis; PFT, pulmonary function test.

was found only in 3 of 1,400 cases in one study [29]. This suggests that this figure underestimates the true prevalence of the association. Most clinicians may not consider this association as patients with pulmonary symptoms often present years after the bowel disease change and after being discharged by a gastroenterologist [30]. Most of the pulmonary involvement is subclinical and overt; hence, it may not present to a respiratory physician [31, 32]. The pathogenesis of pulmonary involvement in autoimmune diseases is unclear. One mechanism has been proposed which shows that there is common association between the embryological derivation of the lungs and the gastrointestinal tract from the primitive foregut, along with the similar immune system of the intestinal mucosa and lungs [30]. One more theory suggests that lymphocytes sensitized from the gastrointestinal tract may induce inflammation in the mucosal surface of other organs. One study demonstrated alveolar lymphocytosis in cases of CD [6, 33]. A recently conducted study reported that induced sputum in CD patients has CD4/CD8 quotient to be abnormally high in patients with active disease relative to patients in remission [34]. The circulating cytokines such as interleukin (IL)-1, IL-2, and IL-6 and tumor necrosis factor (TNF)- α are produced by activated inflammatory cells in the bowel tissues; these cytokines along with other mediators regulate the endothelial cell adhesion molecules, increase production of damaging reactive oxygen metabolites, alter leukocyte migration, and induce damage of lung parenchyma [24, 35, 36]. In our study, we found that patients with UC had significantly abnormal PFT compared with controls. We found that 61.5% of cases of UC had abnormal PFT. Douglas et al. [37] in their study found abnormal PFT in 32% of patients with UC, while Sethy et al. [38] and Tzanakis et al. [39] found abnormal PFT in 17 and 27% of patients with UC, respectively. Labarca et al. [40] in their systemic review and meta-analysis found a relative risk (RR) of 2.02 for a

new diagnosis of IBD in the COPD patients. This may be due to negative impact on colonic mucosae resulting in increased proinflammatory cytokines and angiogenesis factor. Lee et al. [41] in their study found that there is an increased risk of IBD in cases of COPD (adjusted hazard ratio, 1.38). They also found that UC and CD were more frequently observed in severe COPD as compared with mild COPD. Our patients did not have any history of previous lung pathology or smoking. Restrictive pattern was the most common pattern in the patients included in our study. Among the patients having abnormal PFT, 64.47% had restrictive lung disease, 21.56% had small airway disease, and 13.72% had obstructive lung disease. Sethy et al. [38] reported restrictive pattern and small airway disease in 16 and 8% of UC patients with abnormal PFT. Godet et al. [10] found abnormal DLCO, obstructive pattern, and restrictive pattern in 28.8, 22.7, and 1.5% of patients with UC, respectively. Christie and Hill [42] showed that 35% reduction in body protein stores was associated with 40% physiological impairment of FEV1, FVC, and maximal voluntary ventilation in patients of CD with acute exacerbations compared with controls. BMI is an index of nutritional status, and we found that there was a significant positive correlation between BMI and PFT. Similarly, we found that age has a positive correlation with PFT. Serum albumin has a positive and significant correlation with FVC. Wang et al. [43] found correlation with FEV1/FVC ($r_s = -0.29$), FEF 75% ($r_s = -20$), and FRV ($r_s = -0.28$). They also found that in cases of ulcerative proctitis, there was a highly significant increase in FVC, FEV1, DLCO, TLC, and FRV compared with distal UC and pancolitis. However, data on association of age and serum albumin with PFT are less in the literature; hence, more studies with higher number of cases are needed to know the association. Gender, BMI, extent of disease, and drugs such as mesalamine and azathioprine contribute to high risk of pulmonary function dysfunc-

tion. Females were having almost 3 times more risk of PFT dysfunction as compared with males. Overweight/obese subjects carried 21% more risk of PFT dysfunction than those having normal BMI. A higher number of patients with disease limited to rectum (E1) and left-sided colitis (E2) had normal PFT in our study. Pulmonary involvement in cases of UC was more in E3 followed by E2 and E1. This can be explained by higher chances of lung involvement by an inflammatory process as the extent of UC increases from rectum to the whole colon. Data on the relationship between the extent of UC and PFT abnormalities are less in the literature. Hence, more studies with higher number of patients are needed to know the association between the extent of disease and pulmonary functions. A higher number of patients with an early age of onset of disease, that is, 16–40 years, had normal PFT as compared with the late age of onset of disease, that is, >40 years, in our study. This can be explained by longer duration of exposure to environmental pollutants or these patients may have some subclinical lung pathology due to longer age. Data on the relationship between the age of onset of disease of UC and PFT are less in the literature. Hence, more studies with higher number of patients are needed to know the association of age of onset of disease on pulmonary functions. Lack of HRCT scans of the thorax in patients of UC with abnormal PFT, which may have further characterized the respiratory abnormality, was the major limitation of this study. Follow-up of patients with abnormal PFT is required to know the prognosis whether they develop significant pulmonary disease or end-stage lung disease. Our study had small number of cases; hence, more studies with higher number of patients and longer follow-up are needed to throw the light on extent and significance of lung involvement in UC.

In conclusion, patients with UC have chronic pulmonary inflammation leading to different patterns of lung involvement in the form of restrictive, obstructive, and small airway disease. Patients with UC commonly have a restrictive pattern of pulmonary involvement. Impairment of PFT is related to the disease extent and the age of onset of disease. Assessment of the PFT using a spirometer is a noninvasive, simple, cost-effective, and reliable method for early detection of occult pulmonary involvement in patients with UC.

Statement of Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Institutional ethics committee approval was obtained prior to starting of the study. Informed consent was obtained from the study population.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The authors did not receive any funding.

Author Contributions

Vineet Laxmikant Gupta: enrollment of study population, collection of data, and formulation of manuscript. Sudhir Jagdish-prasad Gupta: reviewing and editing of manuscript and supervision of study. Harit Goverdhan Kothari: reviewing and editing of manuscript.

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