ORIGINAL ARTICLE
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Asthma

Effect of Cromoglycate in Preventing of Nebulized Distilled Water Induced Bronchospasm

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Abstract

Background: Ultrasonically nebulized distilled water (UNDW) is thought to cause bronchospasm via changing the preciliary fluid osmolarity and thus, yielding to mediator release from mast cells or through the activation of cholinergic reflex. Sodium chromoglycate (SCG) known to inhibit mediator release from mast cells and neurogenic activation of bronchial submucousa is considered capable of preventing water induced bronchospasm. **Methods:** Thirteen atopic asthmatic patients observed to be hyperreactive to UNDW are included in this study to test this hypothesis. SCG was inhaled by the patients and FEV1 was evaluated 30, 60 and 90 minutes post-inhalation. One week later the same procedure was repeated on the same patients by inhalation of placebo normal saline. Then 2-8 ml of distilled water was inhaled by the patients and FEV1 was measured again. **Results:** Before UNDW inhalation, FEV1 was similar between the study and placebo groups whereas it was significantly higher in the study group after UNDW inhalation than that in placebo group ($p<0.01$). **Conclusions:** SCG was considered to be effective in early and late response to UNDW in asthmatic patients. In this circumtance, SCG may have protective effect against bronchial hyperreactivity againts mist of water and air humidity in the ligths of our study.

Keywords: Asthma, children, sodium-cromoglycate, ultrasonically nebulized distilled water.

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INTRODUCTION

Several bronchoconstrictor agents are used for challenge tests to show airway hyperreactivity in children with bronchial asthma (BA). Since hypotonic solutions cause cough and bronchoconstriction in asthmatics, those have been utilised in these tests as non-specific bronchospasm for more than ten years [1]. Current evidences suggested that hypotonic solutions are thought to cause release of endogenous mediators by altering periciliary fluid osmolarity or by stimulating neural mechanisms with subsequent bronchospasm [2,3]. Therefore, inhalation of ultrasonically nebulized distilled water (UNDW) alters the osmolarity of periciliary fluid linig [4]. It resulted in bronchoconstruction by a number of possible mechanisms, such as vagal reflex activation due to alteration of epithelial permeability, release of mast cell mediators, stimulation of C-fiber endings included non-cholinergic and non-adrenergic excitatory system [5,6,7]. In the lights of these explanations, increased air humidity of climate may cause bronchial hyperrractivity in asthmatic children [8].

Sodium cromoglycate (SCG) is an antiallergenic mast cell stabiliser agent; it also has nonsteroidally anti-inflammatory effects. It is claimed to inhibit bronchospasm due to both early and late allergic reactions [9,10,11]. It exerts its effect not only by inhibiting mediator release from mast cells but also by blocking the activation of C-fiber endings with subsequent non-cholinergic and non-adrenergic neural activity [2]. Neurogenic inflammation established by bronchial non-cholinergic and non-adrenergic system is an important portion of the pathogenesis of BA [12]. Sodium cromoglycate is thought to suppress the bronchospasm due to hypotonic solution inhalation and air humidity by these two mechanisms [13,14,15].

We planned a study in patients who were previously diagnosed as BA and shown to be hyperreactive to UNDW to investigate the effect of SCG in these patients. We aimed to determine whether inhaled SCG was prophilactially effective when administered before UNDW challenge tests.

MATERIALS AND METHODS

Subjects

Thirteen patients (7 male, 6 female) aged 8-15 years (12.2 ± 2.4) with diagnosed allergic asthma were included in the study. Inclusion criteria and demographic and clinical characteristics of the patient group were depicted on Table 1 and 2 respectively. All of the patients were followed up at Department of Pediatric Allergy. They were symptoms free during experiments and their baseline FEV1 values were higher than 80% of predicted value. No patient used any inhaled or systemic anti-inflammatory or antiallergenic therapy for at least a month before study.

Study Protocol

Patients who were administered inhaled 20mg of SCG (Intal nebules ampul, 2ml, Fsion Co, UK) on entry to the

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Table 1. Inclusion criteria of the patients

1. To have proven atopic asthma.
2. To be symptom free during study interval.
3. To develop bronchospasm in response to UNDW [a].
4. Pretest basal FEV1[b] >75%.
5. To have stopped bronchodilators 24 hours prior to investigation.
6. To have stopped all antiinflammatory and antihistaminic drugs one month prior to investigation.

a. UNDW: ultrasonic mist of distilled water.
b. FEV1: forced expiratory volume in one second.

Table 2. Demographic and clinical characteristics of the patients.

Characteristics	Results
Age (year)	12.2±2.4
Gender (F/M)	6/7
Baseline FEV1 (% pred)	
Before placebo	84.5±6.7
Before SCG	86.8±5.6
Sensitized allergen	
HDM	7
Grass	6

FEV1, forced expiratory volume in one second. % pred, percentage, of predicted value. HDM, house dust mite.

study and offered provocation test by UNDW. The same procedure was repeated on a second visit to the same patients except by administering placebo (2ml normal saline) instead of SCG. Forced expiratory volume in one second (FEV1) was determined 0, 30, 60, 90 minutes after both challenge tests.

Provocation test by UNDW

UNDW was generated by an ultrasonic nebuliser (Hico-Neb Ultrasonic Nebuliser, 906 HC, Köln, Germany) and a spacer to increase patient adaptation to the instrument was used during the test. The test was started 90 minutes after inhalation of SCG or placebo. The nebulizer was calibrated to deliver 2 ml/min and its water container was weighed before and after each challenge. Distilled water was inhaled for 4 times at 5 minute intervals by increasing the amount 2, 4 and 8ml each time (cumulative inhaled volumes of 2, 4, 8, 16ml at consecutive administration). FEV1 was determined after each inhalation. Patients were monitored for 6 hours after the completion of the test.

Anaphylaxis due to Type I hypersensitivity and bronchospasm, which are the rather unusual side effects of SCG, were taken into the consideration and preventive measurements were taken.

Statistics

Statistical analysis was done by variance analysis (Repeated Measures ANOVA) and student's t test for paired data as post hoc test. Statistically significance was accepted as a p value of less than 0.05.

RESULTS

Basal average of FEV1 values before the inhalation of SCG and placebo were 84.5±6.7ml/sec and 86.8±5.6ml/sec respectively. The difference was not statistically significant (p>0.05). FEV1 values after inhalation of placebo and SCG were measured at 0, 30, 60, 90 minutes and shown on Figure 1. After SCG inhalation, 6 patients had increased FEV1 at 60 and 90 minutes but there was still no statistically significant difference between the groups compared to prechallenge FEV1 measurements (p>0.05).

FEV1 measurement after inhalation of 2ml distilled water was 85.2±7.2 and 80.6±6.9ml/sec in the SCG and placebo groups respectively, which were both similar to the basal measurements in both groups (p>0.05). However as the amount of inhaled water increased (cumulative 2, 4, 8, 16ml), significantly higher FEV1 measurements were found in the SCG group (p<0.05) (Figure 2). This result was shown to be independent of the effects of factors such as age, gender, body length and weight as well as pre-test basal FEV1 (p>0.05).

After the provocation test with UNDW, two cases (placebo group) in the study group suffered from bronchospasm and improving was observed by β2 agonist inhalation in a short time. However, no case from in the study group experienced post-test bronchospasm (p>0.05).

DISCUSSION

SCG is a safe agent administered to mild and moderate asthmatic patients either alone or with a bronchodilator [9]. It was shown to suppress the early and late onset asthmatic reaction in response to bronchoprovocation by allergens. It is also non-specifically effective in bronchial hyperreactivity [16,17,18]. Simultaneously, our results in this study show that the SCG inhibits bronchoconstruction caused by inhalation of UNDW in children with atopic asthma.

In spite of the fact that SCG attenuated UNDW induced bronchospasm in a greater number of adult subjects, the anti-inflammatory mechanisms of effect of SCG at cellular level is not clear. However, it is claimed to inhibit primarily the mediator release from inflammatory cells, especially from mast cell [10,19]. It also blocks the activation of C-fiber endings and antagonizes platelet-activating factor in addition to inhibiting protein kinase C activity and

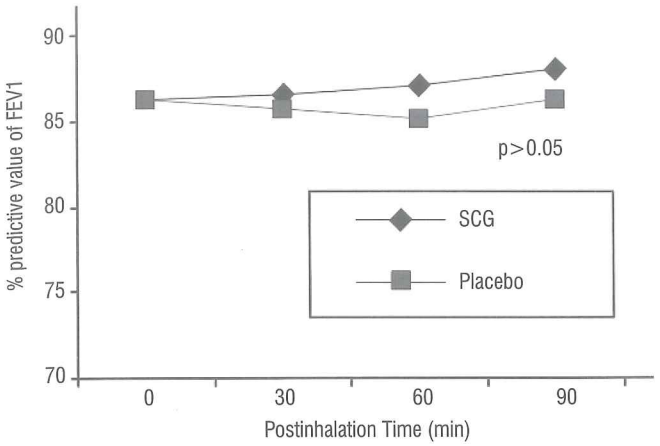

Figure 1. Percentage change in baseline FEV1 (mean±SEM) in 13 asthmatic patients, after inhaling placebo and SCG.

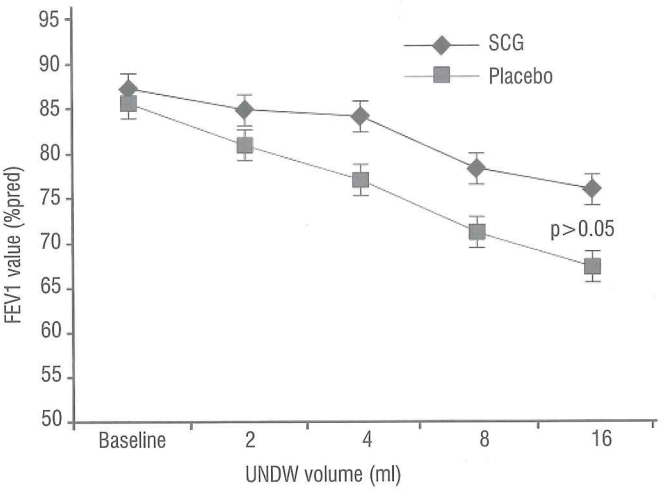

Figure 2. Effects of increasing doses of distilled water on FEV1 with placebo and SCG after treatments.

thus prevents bronchospasm and neurogenic inflammation in asthma pathogenesis [2,20,21). In an experimental study in rats, it was shown to inhibit vascular leakage in the airways due to hypertonic saline inhalation which was claimed to be due to tachykinin antagonism [22]. In the present study, we observed that SCG significantly protected UNDW induced bronchospasm in children with atopic asthma. Subsequently it is hypothesised that SCG may be effective in preventing bronchospasm due to inhalation of hypotonic solutions and air humidity.

Tranfa et al. reported that SCG plus ipratropium bromide combination was more effective in decreasing bronchospasm due to UNDW in adults compared to placebo [2]. They also showed that single agents were less effective compared to combination therapy. This result attributed to the additional effect of ipratropium bromide leads to the idea that cholinergic mechanism might also have a role in the pathogenesis of bronchospasm due to UNDW. However it is not proven yet, since bronchodilator and preventive effects of ipratropium bromide are interfering with each other. SCG as a single agent in preventing bronchospasm was shown to be more effective than ipratropium bromide alone, but the difference was insignificant.

SCG, which has been used safely for a while, was administered alone in this study. FEV1 values measured at 30, 60 and 90 minutes after administration of SCG were not significantly different from those of the placebo, although expected bronchodilatation did not occur in the SCG before the test, as the amount of distilled water was increased the protective effect due to SCG increased during the test as well. There was no difference between the FEV1 measurements of the SCG and placebo at the beginning. However, as cumulative 4, 8 and 16ml distilled water inhalation was performed, significantly higher FEV1 measurements in the SCG inhalation period were obtained.

After the provocation test with UNDW, two cases of placebo inhalation in the study suffered bronchospasm and improved with β2 agonist inhalation in a short time. No side effects due to SCG was observed. Anaphylaxis, type-I hypersensitivity and bronchospasm due to SCG were not observed in any patient in the literature [9, 23]. We also did not observed those in any patient in this study.

In conclusion, in this study, we have shown that SCG prevented the decrease in FEV1 due to UNDW provocation in the early onset bronchospasm of asthmatic children. This result may support that SCG may use the protection of airway hyperreactivity secondary to fog inhalation or symptoms during increased air humidity in the climate. However further studies are needed with greater study and control groups to confirm the clinical importance of our results.

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Clinical Problems

Lung Involvement in Inflammatory Bowel Diseases

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Abstract

Aim: This study is aimed to evaluate the pulmonary involvement in inflammatory bowel disease. **Material and methods:** 17 cases (15 ulcerative colitis, 2 Crohn's disease) were included. Respiratory symptoms, physical findings, pulmonary function tests, bronchial hyperreactivity, high resolution computed tomography (HRCT) of thorax, skin tests, serum IgE and eosinophil levels were evaluated. Bronchoscopy, bronchoalveolar lavage (BAL) and mucosal biopsy were performed in 15 cases. **Results:** Mean age of 10 female (58.8%) 7 male (41.2%) cases was 41,0±12,5 year and the mean duration of disease was 5,6±5,9 year. 11 cases were in remission and 6 had active disease. Mean age in active group was lower than the remission group (36,10/43,72), while there was no difference in duration (5,2/6,3). 4 cases (23%) had symptoms like cough, dyspnea, wheezing. Pulmonary functions of the study group were in normal ranges except one. 15 cases (88,2%) had abnormal HRCT findings (air trapping, emphysema, peribronchial thickening, bronchiectasis, fibrosis, groung glass opacity, bullae). 7 cases (46,6%) had alveolitis in BAL. Biopsy specimens of 2 cases (11,8%) revealed submucosal inflammatory cell infiltration. These 2 cases had positive bronchial hyperreactivity (BHR) and skin tests also. No relation between disease activity with HRCT findings, BAL values and BHR was found. **Conclusion:** Pulmonary involvement is frequently seen in IBD and may have various presentations. We did not find any correlation between the radiological and histological findings of the cases. A possible relationship may be masked as a result of the treatment and the small number of the study group. However, we suggest that pulmonary involvement should be evaluated in inflammatory bowel disease even in the absence of respiratory symptoms.

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, lung involvement

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INTRODUCTION

Extraintestinal involvement rates in inflammatory bowel diseases (IBD) were reported between 21-41% [1]. It was indicated that as the duration of the disease increased the incidence also increased and the incidence of Crohn's disease was higher compared to ulcerative collitis [1]. Organs reported to be involved were joints (peripheral or axial arthropathy), skin (pyoderma gangrenosum, erythema nodosum, dermatitis), eye (episcleritis, anterior uveitis, conjunctivitis), liver (pericholangitis, fatty liver, hepatitis, primary biliary cirrhosis) and others [1-4].

Pulmonary involvement related with IBD was first reported in 1946 by Kraft et al. [5]. The pathogenesis is explained by the development of gastrointestinal system and respiratory system from the same embriological origin (primitive gout) and the antigen theory [1]. Pulmonary involvement has been described as tracheobronchitis, tracheal stenosis, bronchitis, bronchiectasis, cryptogenic organising pneumonia, interstitial lung disease, necrobiotic nodule, serositis and pulmonary vasculitis [2-4, 6, 7].

It is aimed to evaluate pulmonary involvement in 17 cases with IBD in this study

MATERIALS AND METHODS

17 patients diagnosed as IBD in Gastroenterology Clinic between April 2004 and January 2005 were included in the study. Approval of a Localy Ethic Comitee was obtained. A signed informed consent form was received from all patients. History of all patients was recorded and their physical examinations were carried out.

Activity of IBD was evaluated by clinical, endoscopical, and histopathological findings. In clinical evaluation, general status, inflammatory symptoms (rectal bleeding, diarrhea) were questioned; fever, blood count and sedimentation rate were examined. Oedema, hyperemia, ulceration, fragility, spontaneous bleeding, blood in lumen, presence of mucus were evaluated in the endescopical analysis. Patients with Crohn's disease were evaluated by Crohn Disease Activity Index (CDAI) [8]. This index questioned the general status, stomach ache, number of defecations, abdominal mass, and complications, also included measurement of haematocrit and sedimentation rate. The cases were sepa-

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Table 1. Demographic features of IBD cases according to disease activity

	Active (n=6)	Remission (n=11)	p values
Gender (F/M)	5/1	5/6	p>0.05
Age	36.10 ± 18.44	43.72 ± 7.69	p<0.05
Duration of disease (year)	5.2 ± 5.2	6.3 ± 7.6	p>0.05

rated into two groups as active and remission according to their disease activity.

Patients with an accompanying lung disease (asthma, chronic obstructive lung disease, diffuse interstitial fibrosis, tuberculosis) were dropped out of the study.

For the evaluation of pulmonary involvement, shortness of breath, cough, sputum production, wheezing, and chest pain were questioned. Existance of at least one of these was regarded as symptoms presence.

Pulmonary function test (PFT) was carried out using Jaeger Master Screen Pneumo device by the same person. Forced expiratory volume in first second (FEV1), forced vital capacity (FVC), FEV1/FVC, and peak expiratory flow rate (PEF) values were measured. FEV1/FVC values under 89%, 88% of the expected values in women and men respectively were regarded as an indicator of airway obstruction [9].

Patients with normal PFT values were examined for bronchial hyperreactivity (BHR) with methacholine using tidal expiratory method for two minutes. The dose which caused 20% or more decrease in FEV1 compared to the initial value was accepted as provocative dose (PD20). The test was regarded to be positive in case the PD20 was under 8-11mg/ml.

Chest radiogram and high resolution computed tomography (HRCT) were also performed. HRTC was obtained using Siemens Emotion Spiral BT device. Images were obtained in supine position in inspirium and expirium by 1,5mm colimation, by 10mm inspirum and 30mm expirium intervals. Results were blind evaluated by two independent radiologists.

Fiberoptic bronchoscopy was performed to the 15 of 17 patients. Bronchoalveolar lavage (BAL) was done through right middle lobe, medial segment. Using BAL technique, 20cc fractions of serum physiologic with a total dose of 100cc was given and aspirated. Centrifuged preparations of BAL liquids were evaluated by cytospine device. Giemsa and Papanicolau staining techniques were applied to cytospine preparations. Cell counts of BAL specimens were performed and their ratios were evaluated. After BAL process mucosa biopsies were taken using biopsy forceps from middle lobe through lower lobe carina on the right, and upper lobe through lingula carina on the left. Biopsy samples were analysed by Hematoxyline & Eosin staining.

Table 2. Findings of thorax HRCT and BAL in all IBD cases

Case no	Thorax HRCT	BAL (%)
1†	Fibrosis	M: 94, N: 4, L: 2, E: 0
2*†	Empysema	M: 76, N: 1, L: 23, E: 0
3**†	Ground glass	Inappropriate BAL
4**	Air-trapping	M: 80, N: 2, L: 18, E: 0
5*	Emphysema, air-trapping	M: 64, N: 1, L: 35, E: 0
6*†	Fibrosis, peribronchial thickening, air-trapping	M: 70, N:3, L: 27, E: 0
7*	Ground glass	M: 80, N: 14, L: 6, E: 0
8	Normal	M: 98, N:1, L:1, E: 0
9	Ground glass, peribronchial thickening, bul	M: 91, N:4, L: 5, E: 0
10*	Peribronchial thickening, air-trapping, bronchiectasy	M: 68, N:1, L: 31, E: 0
11	Normal	M:93, N.3, L: 4, E: 0
12	Peribronchial thickening, air-trapping, emphysema	M: 99, N:0, L:0, E: 0
13†	Air-trapping	M: 89, N:4, L:7, E: 0
14*	Air-trapping	M: 53, N: 2, L: 45, E: 0
15	Fibrozis, air-trapping	-
16	Ground glass, air-trapping	M: 90, N: 2, L: 8, E: 0
17†	Normal	-

HRCT: High resolution computed tomography, BAL: Bronchoalveolar lavage, M: Macrophage, L: Lymphocyte, N: Neutrophil, E: Eosinophil
*Cases with alveolitis
**Cases with inflammatory cell infiltration in mucosa biopsy
†Active IBD cases

Allergen skin tests were performed to all patients. Serum IgE levels were analysed by Dadebehring device in the serology laboratuary by the nefelometric method using an n-latex-IgE monoreagent kit. By peripheric diffusion, blood eosinophil ratio was also evaluated.

SPSS software (SPSS, 10,0 Inc. Chicago, IL, USA) was used for the analysis of the data. Arithmetic mean±standard deviation was calculated for all variables. Fisher exact test was used for comparison of disease activity with other parameters and p<0,05 was regarded as statistically significant.

RESULTS

A total of 17 patients, 15 of whom had ulcerative colitis and 2 with Crohn's disease were involved in the study. 10 patients were female (58,8%) and 7 (41,2%) were male. Mean age and mean duration of disease was 41,0±12,5 years and 5,6±5,9 years, respectively. Only one case had extraintestinal involvement (ankylosing spondylitis + uveitis). Symptoms like cough, shortness of breath, and wheezing were observed in 4 (23%) cases. Physical examination results were normal for all cases.

Table 3. Clinical features of IBD cases according to disease activity

	Active n (%)	Remission n (%)	p values
Respiratory symptoms	2 (33.3%)	2 (18.8%)	p> 0.05
Abnormal thorax HRCT	5 (83.3%)	10 (90.9%)	p> 0.05
Alveolitis in BAL	2 (50%)	5 (45%)	p> 0.05

6 of the cases were regarded to have active disease while the remaining 11 were regarded as in remission. Demographic datas of these two groups can be seen in Table 1.

Pathology (air-trapping, emphysema, peribronchial thickening, bronchiectasis, fibrosis, ground glass opacity, bullae) was found in thorax HRCT analyses of 15 cases (88,2%) (Table 2). BAL and forceps biopsy were performed to 15 of 17 patients who accepted bronchoscopy. BAL cell counts of 7 cases (46,6%) revealed alveolitis, whereas in mucosa biopsy of 2 cases (11,8%) submucosal inflammatory cell infiltration was observed. Thorax HRCT and BAL analysis of the patients are summarized in Table 2.

PFT parameters were normal in all patients except one who had restrictive pattern. Bronchial hyperreactivity was found to be positive in 5 cases irrespective of respiratory symptoms.

No relationship was found between disease activity and thorax HRCT findings, PFT parameters and BAL values (p=0,5) (Table 3).

There were symptoms of atopy in 7 (41%) of the cases. IgE levels were found to be high in 3 cases (17,6%). Eosinophil counts of all the patients was normal. Allergen prick tests were found to be positive in 6 cases (35,3%). There was no correlation between disease activity and atopy, BHR, or IgE levels (p=0,5). However, allergen prick tests were significantly more positivitive in the remission group (p=0,037).

15 of the cases were under treatment and using mesalamine. Patients with active disease were receiving adjuvant steroid treatment.

DISCUSSION

Despite the great number of researches that have been carried out on extraintestinal findings in IBD, the pathogenesis still needs clarification. In these diseases, since there is an impairment in the mucosal immune regulation of the gastrointestinal system antigens and digestive enzymes, bacteria in the luminal content do activate the immune regulatory cells by systemic circulation [10]. It is also thought that existence of humoral and cellular immunity impairment, activation of the complement system, and presence of defective leucocyte functions have led to formation of extraintestinal findings. Respiratory system pathologies secondary to the IBD were first defined in 1976 by Kraft et al. [5]. Respiratory system pathologies can be classified as: airway disease (upper airway obstruction, acute bronchitis, chronic bronchitis, chronic bronchial suppuration, bronchiectasis, bronchiolitis), parenchymal disease (cryptogenic organising pneumonia, pulmonary infiltrates and peripheral eosinophilia, interstitial lung disease, necrotic nodule), and serositis (pleural effusion, pleuropericarditis) [2]. Respiratory pathologies generally arise after diagnosis of IBD. However, they may onset simultaneously or previously [11]. Cough and shortness of breath are defined as the most frequent symptoms of respiratory system pathologies [3, 7].

Abnormalities of pulmonary function tests are not so common. The most frequent disorders are decrease in FEV1/FVC ratio and total lung capacity, increase in the residual volume and functional residual capacity, and increase in frequency of bronchial hyperreactivity [2, 4, 12]. These findings become significant especially in the activation period of the disease. In our study only one (5%) of our patients had a restrictive pattern. However, the majority (64%) of our patients were in remission period. Douglas et al. detected disorders in the pulmonary function tests of 32%, and a decrease in carbon monoxide diffusion capacity (DLCO) of 16% of patients with diagnosis of IBD [13]. Kuzela et al. showed that there was a decrease in DLCO of 56% of cases with ulcerative colitis who had no radiological findings and 57% of Crohn's disease, stating that it suggested interstitial lung disease [14]. DLCO decrease was observed in 17,6% of patients in the study performed by Tzanakis et al. [15]. Marvisi et al. showed that there was a statistical correlation between serological and biochemical disease activity markers and DLCO abnormality [16]. DLCO was ignored in our study.

Ceyhan et al. demonstrated BHR in 17% of 30 cases with the diagnosis of IBD [17]. Louis et al. showed a significant BHR in 45% of 38 IBD cases compared to the control group [18]. Allergen prick test was found to be positive in 42% of the cases in this study group. BHR was also detected in 29% of our cases. Allergen prick tests were positive in 35% our cases and it was significantly higher in the remission group compared to the active group (p= 0,03). BHR and positivity of the skin tests were consistent with previous findings.

Abnormalities may be observed in HRCT even in the absence of respiratory symptoms in IBD. Mahadeva et al. detected bronchiectasis in HRCT analysis of 13 (76%) cases out of 17 [12]. Changes like air-trapping and tree-in-bud apperance were observed in 9 patients and in 5 patients respectively. Camus et al. identified bronchiectasis

in 3 cases days and even weeks after colectomy and found that respiratory symptoms continued 7,4±1,9 years after diagnosis of IBD [11].

Songur et al. found pathology in 53% of 36 patients in HRCT analysis. Air-trapping and fibrosis was observed in 33% and 19,4% of all cases, respectively [7]. No relationship was found between HRCT pathologies and PFT. Our study did not yield any correlation between HRCT pathologies and PFT, either.

Karadag et al. found pathology in 4 (26%) out of 15 cases with diagnosis of ulcerative colitis in HRCT analysis [4]. 3 of these 4 cases showed ground glass opasity, and 1 showed bilateral pneumocyst and hyperlucency. They indicated that there is a relationship between HRCT findings and disease activity. In our study, on the other hand, no relationship was found between HRCT findings and disease activity.

Karadag et al. detected mixed type alveolitis in BAL in half of these 10 patients [4]. However, they noted that this situation might also be related with smoking or drugs related lung injury. Lymphocytic alveolitis was demonstrated in BAL of Crohn's cases [19, 20]. Lymhocytic alveolitis can be seen as a characteristic of all granulomatosis diseases such as sarcoidosis, hypersensitivity pneumonia, and beryllliosis.

Furthermore, recently attention is being drawn to coalescence of Sarcoidosis and Crohn's disease [21-24]. These two diseases have many common characteristics: their etiologies are obscure; they proceed with noncaseating granulomas; they show accumulation of eritema nodosum, scleritis, uveitis, and CD4 lymphocyte and respond well to steroids. Sarcoidosis effects mediastinal lymph nodes while Crohn's disease effects gastrointestinal lymph nodes.

Camus et al. have shown the dominance of neutrophils in BAL of patients with bronchial supuration and bronchiectasis [11]. In addition, they reported that eosinophilia can be seen in BAL as a complication of sulphasalazine therapy or in eosinophilic syndromes together with pulmonary infiltrates.

In our study, alveolitis was found in 7 (46,6%) out of 15 patients in BAL. There existed lymphocytic alveolitis in 6 (40%) of 7 patients, and neutrophilic alveolitis in 1 (6,6%) patient. Ground glass opasity was monitored in HRCT analysis of the case with neutrophilic alveolitis, and besides, a restriction was observed in his PFT.

Camus et al. investigated bronchial biopsies in 11 patients and lobectomy material in one patient. Bronchial biopsies showed that there was an intense infiltration of lymphocyte and plasma cells in submucosa. In lobectomy material they found follicular bronchiectasis [11].

Karadag et al. have identified mononuclear cell (lymhocyte) infiltration in alveolar septas of 5 patients out of 10 [4]. They also noticed that 4 of the patients had an accompanying interstitial fibrosis and thickening in alveolar septas. They reported that small airways and blood vessels were surrounded by lymphocytes and connective tissue in 2 patients which indicated bronchiolitis and vasculitis.

West et al. defined tracheobronchial involvement in tracheal mucosa biopsy of 6 cases with Crohn's disease [6]. Granulomatous inflammation and chronic inflammation composed of lymphocyte and plasma cells were demonstrated in 3 and 6 cases, respectively. Tracheobronchitis is an extraintestinal manifestation of Crohn's disease and it responds very well to inhaled budesonide therapy. Chronic inflammatory changes were identified in submucosa in 2 of our cases.

Many medications are used in the treatment of IBD and they may cause lung injury also. Sulfasalazine may cause pneumonitis, pulmonary infiltrates and eosinophilic syndromes, interstitial lung disease, cryptogenic organising pneumonia, granulomatous lung diseases, and Wegener's granulomatosis [11, 25, 26]. Eosinophilic pneumonia is the most common disease caused by sulfasalazine and mesalamine. Reactions depending on these two drugs are most frequently seen 2-6 months after the onset of the treatment. More than half of the cases show eosinophilia in peripheric blood, majority show a decrease in diffusion capacity and bilateral infiltrates are seen in their chest X-rays. By stopping medication resolution can be obtained but steroids are needed to accelerate the recovery in general. 5-ASA may cause eosinophilia and bronchiolitis obliterans [11, 26]. It was reported that in IBD, oral or inhaled steroids, azathiopurine and 6-Mercaptopurine does not cause lung disease [2]. However, long term use of oral steroids may increase the risk of tuberculosis. There are published case reports of small series stating that methotrexate in low doses may cause acute interstitial pneumonia or hypersensitivity pneumonia. Imokawa et al. have identified interstitial pneumonia dependent on methotrexate in 9 patients [27].

Recently, TNF-α antagonists are currently used as the novel and the most advanced therapy options for immune system disorders and Crohn's disease. Infliximab, which is one of these agents, have been shown to increase the risk of tuberculosis reactivation [28].

15 of our cases were using mesalamine. 6 of them were in activation period and receiving simultaneous steroid treatment. It is not possible to differ mesalamine dependent lung injury from lung involvement of IBD. The most frequent radiological findings depending on mesalamine

are interstitial infiltrates, consolidation, and pleural effusion [29]. HRCT findings of our cases were not consistent with drug injury.

CONCLUSIONS

In conclusion, there was not any relationship between the radiological and hystopathological findings of respiratory system in IBD patients. In our study, this may be due to the small number of the study group. However, even in the absence of respiratory symptoms, cases with IBD should be evaluated for pulmonary involvement because extraintestinal involvement is frequently observed in IBD.

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