HAFİF VE ORTA DERECE KOAH ALEVLENMELERİNDE EOZİNOFİLİNİN ROLÜ

THE ROLE OF EOSINOPHILS AT MILD AND MODERATE COPD EXACERBATIONS

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ÖZ

Amaç: *Hafif ve orta derece KOAH alevlenmesi olan hastalarda serum eozinofil değerlerinin alevlenme şiddeti ile ilişkisini belirlemek.*

Yöntem ve Gereç: *01 Ocak-31 Aralık 2017 tarihleri arasında Göğüs hastalıkları polikliniğine müracaat eden KOAH tanılı 254 hastanın dosya verileri retrospektif olarak tarandı. Klinik ve laboratuvar bulgularına göre ayaktan tedavi ile takip edilen hastalar "hafif derecede alevlenme, grup 1" ve hospitalize edilerek takip edilen hastalar ise "orta derecede alevlenme, grup 2" olarak iki gruba ayrıldı. İki grup arasında hastaların demografik özellikleri ve başta eozinofil olmak üzere biyokimyasal değerleri karşılaştırıldı.*

Bulgular: *Hafif derecede alevlenme tanılı hastalarda serum eozinofil (2.4±1.7'e karşılık 1.1±1.3, p<0.001) ve lenfosit (23.7±9.2'e karşılık 14.7±8.5, p<0.001) oranları anlamlı derecede daha yüksek bulundu. Bunun aksine nötrofil oranları ise orta derecede alevlenme tanılı hastalarda daha yüksek (%75.5±10.6'e karşılık %64.5±10.2, p<0.001) idi. Benzer şekilde hS-CRP (62.1±56.9'e karşılık 18.7±11.6, p<0.001) ve nötrofil/lenfosit oranı (9.1±12.8'e karşılık 3.5±2.6, p<0.001) orta derecede alevlenme tanılı hastalarda anlamlı derecede daha yüksek idi. Çalışmamızda serum eozinofili için üst limiti olarak %2 değeri alındığında, orta derecede alevlenme tanılı hastalarda, %2 nin altında olan hasta oranının anlamlı derecede daha yüksek (%78.8'e karşılık %46.3, p<0.001) olduğu sonucuna varıldı.*

ABSTRACT

Aim: *To determine the relationship between serum eosinophil values with exacerbation severity in patients with mild and moderate Chronic Obstructive Pulmonary Disease Exacerbation.*

Material and Methods: *Data of 254 patients diagnosed as COPD who applied to the Chest Diseases Polyclinic between January 1st with December 31th of 2017 were retrospectively reviewed. Patients were divided into two groups according to their clinical and laboratory findings; patients treated and followed up with outpatient treatment named as "mildly exacerbated-group 1", and patients treated and followed up as hospitalized named as " moderately exacerbated-group 2". The demographic characteristics of the patients and their biochemical values, especially eosinophil value, were compared between the two groups.*

Results: *Serum eosinophils (2.4±1.7 vs 1.1±1.3, p <0.001) and lymphocytes (23.7±39.2 versus 14.7±8.5, p <0.001) were significantly higher in patients with mild exacerbation. In contrast, neutrophil rates were higher in patients diagnosed with moderate exacerbation (75.5±10.6% versus 64.5±10.2%, p <0.001). Similarly, hS-CRP (62.1±56.9 versus 18.7±11.6, p <0.001) and neutrophil / lymphocyte ratio (9.1±12.8 versus 3.5±2.6, p <0.001) were significantly higher in patients with moderate exacerbation. In our study, when the upper limit for serum eosinophilia was 2%, it was found that the rate of patients with less*

Sonuç: *KOAH alevlenmelerinde, serum eozinofil sayısının değişken olabileceği, bu hastalarda verilecek optimal tedavi şeklinin belirlenmesinde klinik ve laboratuvar bulgularının birlikte değerlendirilmesi gerekir.*

than 2% in patients with moderate exacerbation was significantly higher (78.8 % versus 46.3 %, p <0.001).

Conclusion: *In COPD exacerbations, serum eosinophil value may be variable, clinical and laboratory findings should be evaluated together to determine the optimal treatment modality in these patients.*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) remains a major public health problem, particularly in developing and underdeveloped countries. It is estimated that COPD has a 11.7% of worldwide prevalence. COPD will be expected to affect 384 million people and become as the fourth most important cause of death by 2030 (1,2). COPD disease is a heterogeneous clinical condition involving patients with different clinical and pathophysiological characteristics. It is thought that identification of phenotypes with different characteristics will enable the development of treatment strategies targeting specific biological pathways (3). Most of the deaths due to COPD occur in periods when the symptoms of the patients are defined as exacerbation and worsening their symptoms and requiring additional treatment (4).

Although the prevalence of eosinophilic inflammation in patients with COPD is not known, it is known that patients with COPD exacerbations have increased eosinophil levels (3) in airways, alveoli and blood, as well as neutrophils and other inflammatory cells (5,6).

In this study, we aimed to determine the relationship between serum eosinophil levels and exacerbation severity in chronic obstructive pulmonary disease exacerbation.

MATERIALS AND METHODS

After the approval of the local ethics committee, the data of the patients who were followed-up with the diagnosis of COPD in the chest diseases policlinic between January 1st and December 31st of 2017 were retrospectively reviewed. Patients who had been using regular bronchodilator medication for at least one year with the diagnosis of COPD were selected.At the time of admission, patients with at least one of the complaints of dyspnea, cough and sputum production and/or increased sputum purulence were identified. Patients were evaluated according to their treatment management as outpatient with treatment changing or inpatient treatment at hospital. Radiological findings (chest radiography and / or computerized tomography) of all patients were evaluated. Patients without any radiological examination were excluded from the study. The demographic data such as age and gender and biochemical values of the patients were recorded. The diagnosis of COPD exacerbation was accepted as increase in respiratory symptoms (especially in shortness of breath, sputum quantity and purulence) in the last month.

The patients whose current bronchodilator treatments were revised and followed-up at home were called as " mild exacerbation, group1", the patients that were treated as hospitalized called as "moderate exacerbation, group 2" and the patients having the life-threatening condition requiring intensive care unit were called as "severe exacerbation, group 3. The patients required to the ICU were not included to the study. The patients having the diagnoses of pneumonia, pneumothorax and pulmonary embolism that resemble clinically to the exacerbation were excluded.

STATISTICALLY ANALYSES

SPSS for Mac Version of 20.00(SPSS Inc. Chicago, IL, USA) package program was used at the statistical analyses of the study. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as number and percentage (%). Chi-square test was used for categorical variables. The normal distribution was assessed by Kolmogorov-Smirnov test. Mann Whitney U test and / or Student-t tests were used to determine the difference between the groups. Statistical significance was taken as $p < 0.05$.

RESULTS

Data of 254 patients were used for the study. 101 patients who did not comply with the study criteria were excluded from the study. These were the patients having no biochemical analysis (n = 25) and no regular use of bronchodilator drug (n = 27), patients having radiological findings consistent with pneumonia (n = 13), patients diagnosed concomitantly pulmonary embolism (n = 4) with COPD and spontaneous secondary pneumothorax (n = 2) and the patients whose data could not be reached (n = 30). The mean age of the study population was 67.8 years (41-95) and 193 (76%) were male. The mean age of men and women was 67.4 years (41-90) and 69.2 years (42-95), respectively (p = 0.202).

Of the study population, 108 were treated at their home with the diagnosis of mild COPD exacerbation and 146 were treated in the hospital with moderate COPD exacerbation. Demographic data such as age and gender and biochemical results like whole blood parameters and hS-CRP (high sensitivity C-reactive protein) values compared between group 1 and group2 were presented at table-1. Gender distribution from demographic data was similar in both groups, whereas patients with moderate exacerbation were older (68.9 ±8.4 versus 66.4± 11, p = 0.044). Considering whole blood parameters like wbc, hemoglobin, hematocrit and platelet values, their ratio were similar in both two groups. When eosinophil ratios, which are the main aim of our study, were compared between group1 and group 2, it was concluded that serum eosinophil levels were significantly higher in group 1 patients (2.4±1.7 versus 1.1 ±1.3, p <0.001) (Figure 1). Similarly, serum

Table 1.Distribution of demographicandlaboratoryfindingsamonggroups.

Variables	**Group 1 * (n=108)**	**Group 2 ** (n=146)**	**p**
Age, year	66.4±11 (41-95)	68.9±8.4 (51-91)	**0.044**
Men/Women	85/23	108/38	0.383
WBC (x $10^3/\mu L$)	9813.4±9189	11353±6453	0.118
Hemoglobin (g/dL)	14.2±1.8	13.7±2.7	0.108
Hematocrit (%)	43.5±5.3	43.5±8.6	0.944
Platelet (x $10^3/\mu L$)	263.6±81.4	243.4±86.1	0.060
RDW (%)	45.7±5.7	50.5±8.6	**<0.001**
PDW (%)	12.4±2.4	12.5±3.6	0.663
#Neut (%)	64.5±10.2	75.5±10.6	**<0.001**
#Lyph (%)	23.7±9.2	14.7±8.5	**<0.001**
#Eos (%)	2.4±1.7	1.1±1.3	**<0.001**
hS-CRP (mg/L)	18.7±11.6	62.1±56.9	**<0.001**
NLR	3.5±2.6	9.1±12.8	**<0.001**

Abbreviations: **WBC**:white blood cell, **RDW:**red cell distribution width, **PDW**: platelet distribution width, **hS-CRP**: high sensitivity c reactive protein, **NLR**: neutrophil lymphocyte ratio

*Patients group with mild exacerbations

**Patients group with moderate exacerbations

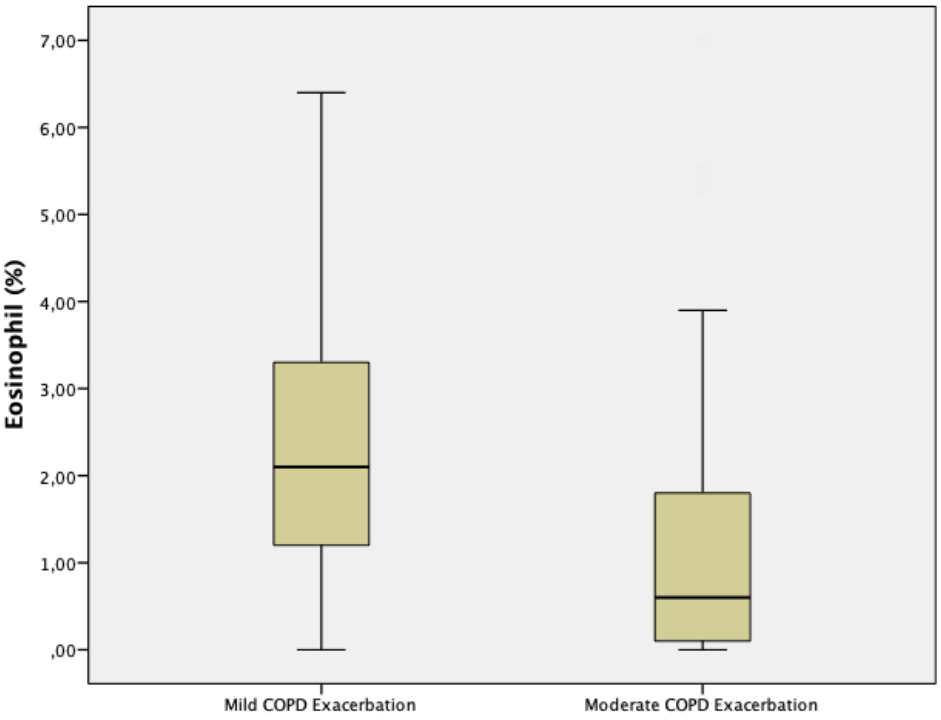

Figure 1: Serum eosinophil rates between groups.

lymphocyte levels were higher in group 1 patients (23.7±9.2 versus 14.7 ±8.5, p <0.001). In group 2 patients, neutrophil levels (75.5±10.6% versus 64.5 ±10.2%, p <0.001) and hS-CRP were significantly higher (62.1± 56.9 versus 18.7±11.6, p <0.001). NLR (neutrophil / lymphocyte ratio) values were also significantly higher in the hospitalized group 2 patients (9.1±12.8 versus 3.5 ±2.6, p <0.001). On the other hand, when the cut-off value for blood eosinophilia was determined as 2%, the rate of patients with less than 2% in group 2 patients (78.8% vs. 46.3%, p <0.001) was significantly higher.

DISCUSSION

We retrospectively evaluated the data of COPD patients with mild and moderate exacerbation. We found serum eosinophil and lymphocyte levels significantly high in patients with mild exacerbations.

In addition, we concluded that patients with serum eosinophil values below 2% had a higher rate in patients with moderate COPD exacerbations. Eosinophilic airway inflammation has been reported in 10-40% of patients with COPD, both stable and exacerbation states (3,7-9). In the Copenhagen study of Vedel-Krogh et al., COPD patients were followed for 3 years, and blood eosinophil levels were reported to be 0.34 x109 in these patients. This elevated blood eosinophil level was found to be consistent with a 1.76-fold increased risk of exacerbation (10). Also, it was shown that exacerbations can be reduced with the use of inhaled steroids due to increased blood eosinophil level in COPD. In the same study, it was reported that serum eosinophil levels may be a potential prognostic biomarker due to elevated blood eosinophil values associated with increased exacerbation frequency (11,12).

In post hoc analysis of the study of Pascoe et al., it was stated that inhaled corticosteroid

treatment decreased the exacerbation rate in patients with blood eosinophil levels of 2% and up to 29% (11). In addition, it was suggested that systemic steroid treatment could be used in exacerbations which were determined as increased blood eosinophil value by the authors of the study (13). In the Copenhagen study of Vedel-Krogh et al., increased blood eosinophil levels in patients with COPD were found to be related to the prevalence of frequent infections and wheezing, viral infections in cold weather. It has been emphasized that increased blood eosinophil reflects the history of frequent exacerbations with respiratory viruses, but that there is a need for more studies describing the relationship between high eosinophil and predisposition to viral infections, degree of difference of exacerbation, and flare recovery (10). In the ECLIPSE study of Singh D et al., 49% of patients with COPD had a variable eosinophil levels, that was lower and higher than 2 % at 3-year follow-up (3). For this reason, the increase in the level of eosinophilor its normal course and how the exacerbation triggered is still the subject of the research.

In our study, neutrophile, hS-CRP and NLR values were significantly higher in patients with moderate exacerbations. When we look at the literature on this subject (5,6) most of the exacerbations of COPD have shown the presence of neutrophilic inflammation in the airways as a result of viral and bacterial infections. It has been announced that the exacerbations caused by viral infections are more severe and prolonged, but this is only indicated by clinical findings and cannot be defined by any airway inflammatory profile (14,15). Also in the ECLIPSE study of Hurst et al., it was declared that the serum neutrophile levels were found to be significantly higher in COPD phenotypes with frequent exacerbation (16). It has also been reported that frequent exacerbated COPD phenotypes may have also increased airway inflammation during stable periods (17). Inflammation observed in COPD exacerbations had been mostly neutrophilic and in patients it was mostly associated with increased sputum eosinophilia (18,19). Colak et. all emphisazed that procalcitonin and CRP levels were significantly higher in patients with community-acquired pneumonia than in patients with COPD exacerbations (20). On the otherhand, at Aksoyet.al's study, the COPD patients hospitalized with acute exacerbations were divided into two groups according to the level of peripheral blood eosinophilia. The level of CRP was similar in both groups (21).

In most COPD exacerbations, neutrophilic inflammation due to viral and bacterial infections has been reported (5,6). Another remarkable aspect of our study was that patients with serum eosinophil values below 2% were significantly higher in patients with moderate exacerbations. Blood eosinophillevels of 1483 COPD patients who were followed in the ECLIPSE study of Vestbo J et al. were checked for all 3-year visits. In all of these visits, it was reported that blood eosinophil level was found higher than 2% in 554 patients (37.4%), less than 2% in 201 (13.6%) patients, and variable (> 2% and <% 2) in 728 (49%) patients.

Interestingly, similar rates were found in healthy subjects, who were the control group of the same study; 73 (36%) of the 203 healthy controls had a blood eosinophil level of more than 2% in all 3-year follow-up visits. In addition, COPD patients with blood eosinophil levels above 2% were found to be older, female gender, and the rate of active smokers was lower (22).

All these data suggest that the disease severity of patients with COPD exacerbation with persistent elevated blood eosinophil (> 2%) are milder, but this result should be supported by more cohort studies. Similarly, in our study, statistically significant elevated blood eosinophil values were found at the patients having mild symptoms and mild exacerbation. In some studies, blood eosinophil levels were reported to be reproducible (11,13,19). In another study, high eosinophil levels in patients with severe exacerbations were found

to be more prominent in non-smokers (23). These results show that high levels of eosinophils can be detected in both COPD patients and intact individuals during long-term follow-up.

In our study, patients with moderate exacerbations were older. This condition was found to be more severe in patients with moderate exacerbation and as a result of this, the treatment and follow-up was performedinaccordance with hospitalization. Finally, we concluded that serum eosinophil values could not be lonely associated with exacerbation severity in mild and moderate COPD exacerbations. We propose that, at the evaluation and treatment planning of COPD exacerbated patients, the assessment of only serum eosinophil, neutrophil and hs-CRP values and neutrophil / lymphocyte ratios could not be sufficient, and these values should be taken into consideration with many factors of the patients such as symptom level, disease stage and age in order to generate more effective follow-up and treatment results.

***Limitations of the study*:** We are aware of the presence of many limitations of our study. Inadequate patients number and the retrospective design of the study are the preliminary of that limitations. In addition, the fact that respiratory function test parameters and smoking status are not known constitute other important limitations.

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