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Does cryptogenic organizing pneumonia change seasonal?

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SUMMARY

BACKGROUND AND AIM: Meteorological factors affect the respiratory system, and the most important factor is the change in ambient temperature and humidity. We aimed to investigate the seasonal characteristics of patients diagnosed with cryptogenic organizing pneumonia.

METHODS: The study included 84 cryptogenic organizing pneumonia, 55 chronic obstructive pulmonary disease, and 42 asthma patients. To determine the characteristics of the disease according to the seasons, the number of attacks and admissions was grouped according to the seasonal characteristics and analyzed for three groups.

RESULTS: Among cryptogenic organizing pneumonia and chronic obstructive pulmonary disease patients, males significantly predominated ($p<0.001$). The hospitalization rate was highest in chronic obstructive pulmonary disease patients but similar to cryptogenic organizing pneumonia and asthma patients ($p<0.001$). The highest admission rate in cryptogenic organizing pneumonia patients was observed in spring (39.3% in spring, 26.2% in fall, 22.6% in winter, and 11.9% in summer). In winter, cryptogenic organizing pneumonia patients were admitted less frequently than chronic obstructive pulmonary disease and asthma patients. The neutrophil-to-lymphocyte ratio was higher in cryptogenic organizing pneumonia patients than in asthma patients and similar to chronic obstructive pulmonary disease patients.

CONCLUSION: As a result of our study, the high rate of diagnosis and admission in the spring in cryptogenic organizing pneumonia suggested that the effect of allergens on the formation of cryptogenic organizing pneumonia should be investigated. In contrast, it should be kept in mind that cryptogenic organizing pneumonia may develop as a prolonged finding of involvement that may occur in the lung parenchyma due to lung infections and/or cold weather triggering during the winter months. In this regard, further studies can be conducted in which allergens and/or the history of infection in patients and meteorological variables are also evaluated.

KEYWORDS: Organizing pneumonia. COPD. Asthma. Infection. Weather.

INTRODUCTION

Cryptogenic organizing pneumonia (COP) is a rare but very characteristic clinicopathological picture among pulmonary diseases. When no underlying cause is found, it is referred to as "idiopathic/cryptogenic" organizing pneumonia. In contrast, if it occurs as a result of another disease or drug use, it is called secondary organizing pneumonia. The incidence of COP in men and women is similar. Although the age range is from 20 to 80 years, it occurs most frequently between the ages of 50 and 60 years[1,2]. It is more common in nonsmokers and former smokers[3]. The diagnosis of COP is made histopathologically by the presence of granulation tissue composed of fibroblasts, collagen, and fibrinous exudate in the alveolar structure and by demonstrating a specific finding, the Masonic bodies[1]. The basic radiological appearance is peripherally located multifocal airspace consolidation. The consolidations are rarely unilateral, may be recurrent and migratory, and range from a ground-glass appearance to consolidation with air bronchograms[4]. The clinical presentation of patients may resemble upper respiratory tract infection or pneumonia[5].

Chronic obstructive pulmonary disease (COPD) is an increasing cause of morbidity and mortality worldwide. Acute exacerbations negatively impact health status, hospitalization rates, disease progression, and mortality in COPD[6]. In COPD, an acute worsening of respiratory symptoms requiring additional treatment is defined as an exacerbation. Triggering factors for an acute exacerbation are infections and noninfectious conditions. However, the etiology is unknown in more than 30% of exacerbations[7].

Asthma is a disease resulting from the interaction of environmental and genetic factors. While genetic factors play an important role in the development of asthma, environmental factors are important in both the onset and exacerbation of the disease[8,9].

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Meteorological factors affect the respiratory system, and the most important factor is the change in ambient temperature and humidity[10-12]. It has been reported that the increase in outdoor temperature, in which atmospheric pressure increases, leads to decreased peak expiratory flow rate and morning dyspnea in COPD patients[13]. Asthma attacks such as COPD increase during the winter months[14].

Our study aimed to investigate the seasonal characteristics of our patients diagnosed with COP.

METHODS

Between January 1, 2012, and December 31, 2020, 84 patients diagnosed clinically, radiologically, and pathologically with COP in our hospital, and 55 COPD and 42 asthma patients diagnosed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma (GINA) guidelines were included in our study[6,9]. The demographic and clinical characteristics of our patients, who were divided into three groups, and the laboratory data (white blood cell, neutrophils, lymphocytes, eosinophils, thrombocytes, hemoglobin, C-reactive protein, erythrocyte sedimentation rate, and albümin values) at the time of initial diagnosis were retrospectively collected. To determine the characteristics of the disease according to the seasons, the number of attacks and admissions in our study was grouped according to the seasonal characteristics and analyzed for three groups. Patients with comorbid malignant disease, collagen tissue disease, and secondary organizing pneumonia were excluded from the study.

The study was approved by the Ethics Committee of the University of Health Sciences, Atatürk Sanatorium Training and Research Hospital (2012-KAEK-15/2535). The study was conducted according to the Declaration of Helsinki.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 21.0 was used for statistical analysis. Categorical variables are presented as frequency and percentage. Continuous variables were evaluated using the Kolmogorov-Smirnov test and histograms to determine whether their distribution was normal. Normally distributed numeric parameters were compared in groups using Student's t-test or one-way analysis of variance (ANOVA), whereas those without normal distribution were analyzed using the Mann-Whitney U test or the Kruskal-Wallis test. As appropriate, categorical variables were compared with the chi-square test or Fisher's exact test.

RESULTS

Our study evaluated 122 COP patients diagnosed in our hospital between January 1, 2012, and December 31, 2020. Of the patients with COP, 27 were excluded due to concomitant malignancy and 11 were excluded due to infection. Our study group consisted of 84 COP, 55 COPD, and 42 asthma patients. The mean age of patients with COP was 59.4±11.7 years, and 55% were male. Age was similar in patients with COP and asthma and younger than in patients with COPD ($p<0.001$). Among patients diagnosed with COP and COPD, males significantly predominated ($p<0.001$). In the COP group, 30 (35.7%) individuals had never smoked, 36 (42.9%) were former smokers, and 18 (21.4%) were active smokers. Regarding pulmonary function test results, FEV1 was higher in patients with COP than in patients with COPD and asthma ($p<0.001$ and $p<0.001$, respectively). The hospitalization rate was highest in patients with COPD but similar in patients with COP and asthma ($p<0.001$). The highest admission rate in COP patients was observed in spring (39.3% in spring, 26.2% in fall, 22.6% in winter, and 11.9% in summer). In winter, COP patients were admitted less frequently than COPD and asthma patients. The main characteristics of the study participants are shown in Table 1.

While 78 (92.9%) COP patients had a pathological diagnosis, 6 of them were diagnosed by clinical-radiological examination. The most common pattern on thorax computed tomography (CT) in patients diagnosed with COP was a nodule (31%). This finding was observed as focal infiltration in 28.6%, ground-glass consolidation in 25%, air bronchograms in 13.1%, and cavity in 2.4%. The clinicopathological characteristics of patients with COP are summarized in Table 2.

As can be seen in Table 3, albumin and hemoglobin levels were lower and erythrocyte sedimentation rate was higher in patients with COP than in the other two groups ($p=0.001$, $p=0.003$, and $p=0.001$, respectively). The neutrophil-to-lymphocyte rate was higher in COP patients than in asthma patients and similar to COPD patients.

DISCUSSION

The aim of this study was to see if there is a seasonal variation in COP patients. It was found that the highest admission rate in COP patients was observed in spring. In winter, COP patients were admitted less frequently than COPD and asthma patients.

It is well known that changes in meteorological parameters increase mortality and morbidity in adults with respiratory diseases (COPD, asthma, bronchiectasis, etc.) and have a triggering function for hospital admissions. While an increase in temperature and humidity leads to clinical worsening in asthmatics, exposure

to cold air and cold increases the risk of infection, especially in COP[15]. Seasonal variations in COP were also noted in our study.

Cryptogenic organizing pneumonia typically occurs in the fifth to sixth decades of life, and both sexes are equally affected[16]. History of smoking is not considered a risk factor for COP, and most patients do not smoke[17]. In our study, the mean age of patients with COP was similar to that reported in the literature, but the male sex was more represented in contrast to the literature. In agreement with the literature, the proportion of patients who were active smokers was also lower in COP.

Open lung biopsy is the gold standard in the diagnosis of COP. However, the chance of obtaining a diagnostic sample is high with high-resolution CT-guided transbronchial lung biopsy[18]. In our study, 78 (92.9%) patients had a pathological diagnosis, while 6 were diagnosed by clinical-radiological evaluation.

Radiological findings in COP usually consist of patchy, diffuse consolidations involving bilateral subzones. Other described findings include migratory, irregular, linear, or nodular opacities[19]. In our study, nodular opacities and focal infiltrations were common and usually unilateral. The reason for this difference may be due to early detection of pulmonary infiltrates.

The results of laboratory tests in patients with COP are not specific. However, inflammatory markers such as erythrocyte sedimentation rate, CRP level, and leukocyte count are often elevated[17,20]. In our study, the erythrocyte sedimentation rate was higher in our patients with COP than in the other two groups, and the white blood cell count was higher than in asthma patients.

Table 2. Main diagnostic characteristics of patients with cryptogenic organizing pneumonia.

	Cryptogenic organizing pneumonia (n=84)
Pathological diagnosis (biopsy-proved)	
Yes, n (%)	78 (92.9)
Type of diagnosis	
Transbronchial	37 (44)
Tru-cut	32 (38.1)
Wedge	9 (10.7)
Clinical/radiological	6 (7.1)
CT findings	
Distribution	
Unilateral, n (%)	50 (59.5)
Bilateral, n (%)	34 (40.5)
Pattern	
Cavity, n (%)	2 (2.4)
Focal infiltration, n (%)	24 (28.6)
Ground-glass opacification, n (%)	21 (25)
Nodule, n (%)	26 (31)
Air bronchograms, n (%)	11 (13.1)
Exacerbation season	
Spring, n (%)	33 (39.3)
Summer, n (%)	10 (11.9)
Autumn, n (%)	22 (26.2)
Winter, n (%)	19 (22.6)

Table 1. Characteristics of study group.

	Cryptogenic organizing pneumonia (n=84)	Chronic obstructive pulmonary disease (n=55)	Asthma (n=42)	p
Age	59.4±11.7*	66.7±8.1*#	56.6±12.9#	**<0.001**
Female, n (%)	29 (34.5)*	5 (9.1)*#	22 (52.4)#	**<0.001**
Tobacco smoking				
Never smoker, n (%)	30 (35.7)*	0 (0)*#	14 (33.3)#	**<0.001**
Past smoker, n (%)	36 (42.9)*	50 (90.9)*#	12 (28.6)#	
Current smoker, n (%)	18 (21.4)	5 (9.1)*	16 (38.1)*	
Pulmonary function test findings				
FEV1, lt, median (min–max)	2.47 (0.65–4.42)*	1.05 (0.45–3.07)*	1.98 (0.85–3.93)*	**<0.001**
FEV1, %, median (min–max)	78.5 (21–123)*	38 (16–94)*	68.5 (33–90)*	**<0.001**
Exacerbation season				
Spring, n (%)	33 (39.3)*	15 (27.3)	6 (14.3)*	**0.009**
Summer, n (%)	10 (11.9)	2 (3.6)	3 (7.1)	
Autumn, n (%)	22 (26.2)	14 (25.5)	11 (26.2)	
Winter, n (%)	19 (22.6)*#	24 (43.6)#	22 (52.4)*	
Admission number, median (min–max)	1 (1–6)*	2 (1–10)*#	1.5 (1–7)#	**<0.001**

*#p-values are significantly different between groups.

Table 3. Laboratory results of the patients.

	Cryptogenic organizing pneumonia (n=84)	Chronic obstructive pulmonary disease (n=55)	Asthma (n=42)	p
White blood cell, median (min–max)	8,910 (1,230–24,000)*	9,120 (4,370–23,000)#	7,605 (3,900–13,310)*#	0.011
Neutrophils, median (min–max)	5,735 (1,100–16,900)*	6,200 (1,480–17,000)#	4,280 (1,000–10,550)*#	0.002
Lymphocytes, median (min–max)	1,945 (300–8,200)	1,860 (396–6,620)	2,265 (1,190–4,550)	0.332
Neutrophils/lymphocytes ratio, median (min–max)	2.97 (0.21–17.83)*	3.48 (0.22–19.45)#	1.95 (0.56–6.17)*#	0.001
Eosinophils, median (min–max)	177 (0–3,700)	150 (0–610)	215 (10–890)	0.237
Hemoglobin±SD	13.1±1.8*#	13.9±1.9*	14.1±1.7#	0.003
Thrombocytes, median (min–max)	288,500 (119,000–1,314,000)*#	247,000 (24,900–497,000)*	254,000 (23,000–409,000)#	0.001
C-reactive protein, median (min–max)	4.90 (0.01–175)	3.70 (0.01–85)	3 (0.3–25.40)	0.607
Erythrocyte sedimentation rate, median (min–max)	45 (7–120)*#	20 (2–120)*	17 (4–29)#	<0.001
Albumin±SD	36.7±5.5*	38.3±5.6#	41±3.1*#	<0.001

*#p-values are significantly different between groups.

The CRP level was higher than the other two groups, but not statistically significant. This may be due to the fact that CRP values in the other groups were measured during the exacerbation phase.

Seasonal factors are known to influence the frequency of COPD and asthma attacks. The number of hospital admissions due to exacerbation of COPD increases when temperatures decrease and/or triggering factors such as viral infections become more common during the winter months[15]. Meteorological factors weaken the body's immunity and favor the spread of pathogens that cause infections[21,22]. The incidence of viral respiratory infections has been shown to increase in cold weather[10].

In general, morbidity and mortality are known to increase in patients with chronic diseases, advanced age, and male gender; however, the number of studies examining the effects of environmental factors is limited. The literature has also found that seasonal factors such as air temperature and humidity increase the incidence of pneumonia[23]. No study was found in the literature investigating COP's seasonal association. In our study, the rate of admissions and diagnoses in COP patients was highest in the spring. In winter, COP patients were admitted less frequently than COPD and asthma patients.

The clinical presentation in COP is quite characteristic. The patient presents with a viral, infection-like clinical picture that has persisted for several weeks. Diagnosing patients with these causes takes several weeks[1,2]. The fact that the diagnosis of COP in our study was made in the spring suggests that patients' symptoms begin in the winter months and the diagnosis may not be made until the spring. In contrast, pollen is known to cause an increase in asthma attacks in spring[24]. This may be related to the high diagnosis and admission rate in the spring in COP.

This study has some limitations. First, it was performed in a single center as a retrospective study. Second, the study included a relatively small number of COP patients. Due to the small number of cases because of missing data, some cases that may have an impact on the results may have been excluded from the study. Another limitation of our study is that we could not access the allergy history of the patients and allergy tests, if any, from the hospital information registry system.

CONCLUSION

As a result of our study, the high rate of diagnosis and admission in the spring in COP suggested that the effect of allergens on the formation of COP should be investigated. In contrast, it should be kept in mind that COP may develop as a prolonged finding of involvement that may occur in the lung parenchyma due to lung infections and/or cold weather triggering during the winter months. In this regard, further studies can be conducted in which allergens and/or the history of infection in patients and meteorological variables are also evaluated.

ETHICS COMMITTEE APPROVAL

This study was approved by the Ethics Committee of the University of Health Sciences, Atatürk Sanatorium Training and Research Hospital (2012-KAEK-15/2535).

INFORMED CONSENT

Written informed consent was obtained from all participants who participated in this study.

AUTHORS' CONTRIBUTIONS

TSO: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **SB:** Data curation, Investigation, Methodology, Writing – original draft. **ESA:** Formal Analysis, Methodology, Writing – review & editing. **ZEO:** Data curation, Formal Analysis. **MHE:** Data curation, Formal Analysis. **FD:** Data curation, Formal Analysis. **BAO:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing.

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