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Original Article

Do Levels of Inflammatory Markers Differ in Rheumatoid Arthritis and Collagen Vascular Disease Associated with Pulmonary Symptoms?

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ABSTRACT

Objective: The symptoms of rheumatoid arthritis (RA) and other collagen vascular diseases (CVD) range from cough to acute respiratory failure. This study is an evaluation of serum inflammatory biomarkers in patients with RA and other CVD with pulmonary symptoms to investigate potential differences.

Methods: A retrospective, observational, cross-sectional study was conducted in the chest disease department of a training and research hospital. The data of RA and other CVD patients admitted to hospital between January 2016 and December 2017 were retrieved from the hospital information management system and the investigated data were patient characteristics, symptoms, comorbid diseases, hemogram values, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, platelet/mean platelet volume ratio, C-reactive protein level, erythrocyte sedimentation rate, and biochemical values.

Results: A total of 130 patients (male: 23%) with a median age of 54 years (43–63 years) were included. The gender distribution was similar in both groups. The RA patients were older than the other CVD patients (57 vs 49 years: p<0.002) and the RA patients were determined to have more respiratory symptoms than the other CVD patients (16.7% vs 34.2%; p <0.026). The hemogram values were similar, with the exception of eosinophilia. Eosinophils were detected in 2.0% of the RA patients, while they were observed in 1.4% of the other CVD patients (p<0.026).

Conclusion: The results indicated that inflammatory biomarkers may not differ in RA and other CVD patients, but the analysis indicated that RA patients may be older and have more respiratory symptoms.

INTRODUCTION

Rheumatoid arthritis (RA) and other collagen vascular disease (CVD) are autoimmune diseases with systemic involvement. When they involve the respiratory system, there may be a wide spectrum of symptoms, ranging from coughing and hemoptysis to respiratory failure. Therefore, when the respiratory system is involved, these patients are followed up not just in clinics of rheumatology, but also in clinics of chest diseases.[1–3]

RA-associated pulmonary involvement is often observed as a rheumatoid nodule, interstitial lung disease, or pleurisy. Less frequently, pulmonary hypertension, obliterative bronchiolitis, or cryptogenic organizing pneumonia have been observed.[1–5] Wegener granulomatosis (WG), Behçet's disease (BD), and systemic lupus erythematosus (SLE) are among the examples of other CVD that may manifest symptoms ranging from hemoptysis to respiratory failure, as well as radiological evidence of a cavity, nodule, or mass.[5–8]

Findings of respiratory system involvement in cases of RA and other CVD can be confused with other chest diseases clinically and radiologically. The treatment approach and prognosis of these patients are similar, but there are also differences. The best known and the most frequently used inflammatory biomarker is C-reactive protein (CRP), which is also a marker of infection.[9] In clinical practice, the measurement of hemogram parameters has also been adopted as an easily applied and inexpensive test. The neutrophil/lymphocyte ratio (NLR), platelet count/mean platelet volume (PLT/MPV) ratio, and the platelet count/lymphocyte ratio (PLR), which may be estimated from

hemogram results, have been examined for their role in the diagnosis, treatment response, and severity of respiratory system diseases. NLR, PLR, and PLT/MPV values have been examined in chronic obstructive pulmonary disease (COPD) by investigators at this center,[11–14] as well as in sarcoidosis[15,16] and interstitial lung diseases.[17]

Chronic inflammatory diseases with respiratory system involvement, such as RA and other CVD, are known to have similar symptoms and signs. Among the most common means of evaluating and following up on symptom severity and the treatment of anti-inflammatory conditions are the CRP value and erythrocyte sedimentation rate. NLR, PLR, and PLT/MPV have been investigated in RA and other CVD;[18–20] however, the data are limited.

In this study, the CRP, NLR, PLR, and PLT/MPV values of patients with RA and other CVD with respiratory system symptoms were compared to assess potential differences.

MATERIAL AND METHODS

This was a retrospective, observational, cross-sectional study conducted at a university training and research hospital department of chest diseases and thoracic surgery. The study was approved by the scientific committee of Istanbul Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital (14.05.2018/033), and ethics approval was obtained in accordance with the Helsinki Declaration. All of the study data were collected retrospectively from the hospital electronic information management system. The retrospective nature of the study did not require informed consent to be obtained from the patients for the use of medical data for publication. The information of all of the study patients was strictly protected.

Patients

Adult patients who presented at the outpatient clinic between January 1, 2016 and December 31, 2017 whose diagnoses were entered into the hospital registry system using the International Classification of Diseases (ICD-10-TRM Disease and Health İnterventions Classification System, 10th revision) for RA (M05-06), BD (M35.2), WG (M31.3), or SLE (L93), and for whom hemogram results were available, were included in the study. The demographic details of the patients, findings (cough, dyspnea, hemoptysis, pleurisy, pneumothorax), and additional diseases (diabetes, hypertension, COPD, asthma, anemia) were recorded. NLR, PLR, PLT/MPV, CRP, erythrocyte sedimentation rate, and biochemical values were also recorded for comparison.

Calculations

Neutrophil/lymphocyte ratio: NLR, as a marker of systemic inflammation, was defined as the absolute number of neutrophils divided by the absolute lymphocyte count.[10]

Platelet count/lymphocyte ratio: PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.[10]

Platelet count/mean platelet volume: The PLT/PMV was the ratio between platelet count and mean platelet volume.[10]

C-reactive protein: The recorded value of CRP, an acute phase reactant protein.[9]

Recorded data

The details of the admission and discharge hemograms and their subparameters were recorded from information in the hospital information management system, as well as demographic characteristics, additional diseases, and values for CRP, NLR, PLT/MPV, PLR were calculated and recorded.

Statistical analysis

Statistical analyses were performed using the portable version of the IBM SPSS Statistics for Windows, Version 20.0 (SPSS Inc., Armonk, NY, USA) package program. Patient demographic characteristics were summarized using descriptive analysis of clinical data. Student's t-test was used for continuous variables, such as age, hemogram values, biochemical values, NLR, PLR, PLT/MPV, and CRP.

Values obtained from the Student's t-test analysis were expressed as median±SD. The non-parametric Mann-Whitney U-test was used for non-normal numerical distributions, and the values were expressed as median and interquartile range (SCA 25% and 75%). Binary values of sex and the presence of additional disease were analyzed using a chi-square test. A p value <0.05 was considered significant.

RESULTS

A total of 130 patients (23% male) between January 1, 2016 and December 31, 2017 with a diagnosis of RA or other CVD according to the hospital data system were included in the study. The median age was 54 years (43–63 years). There were 76 RA patients and 54 other CVD patients. The other CVD group consisted of 32 cases of SLE, 14 cases of BD, and 8 cases of WG. Gender distribution was similar in all groups. The RA group was older than the other groups (57 vs 49 years; p<0.002). The other CVD group consisted of significantly younger patients and had fewer cases with airway stenosis (COPD, asthma) (Table 1). Respiratory symptoms were more frequently found in RA patients (34.7 vs 16.7%; p<0.026).

Demographic characteristics, findings, hemogram and biochemistry values, the presence of anemia (hemoglobin <12 mg/L), and NLR, PLR, PLT/PMV, and CRP values of the RA and other CVD groups were compared. The hemogram values of the groups were similar, with the exception of

Table 1. Demographic characteristics, pulmonary symptoms, and findings of patients with rheumatoid arthritis or collagen vascular disease upon presentation at the chest disease outpatient clinic

	Rheumatoid arthritis (n=76)	Collagen vascular disease (n=54)	p
Female, n (%)	58 (76.3)	46 (85.2)	0.85
Median age (interquartile range) years	57 (48–64)	49 (39–56)	0.002
≥40 years, n (%)	65 (85.5)	39 (72.2)	0.06
Pulmonary symptoms, n (%)			
Dyspnea	1 (1.3)	1 (1.9)	0.81
Coughing	2 (2.6)	1 (1.9)	0.77
Pulmonary findings, n (%)			
Hemoptysis	–	1 (1.9)	0.23
Pleurisy	2 (2.6)	1 (1.9)	0.77
Pneumonia	6 (7.9)	7 (13)	0.34
Pulmonary embolism	1 (1.3)	1 (1.9)	0.81
Disease with chronic airway narrowing (asthma, COPD)	26 (34.2)	9 (16.7)	0.026
Anemia n (%)	23 (30.2)	20 (37.0)	0.42

COPD: Chronic obstructive pulmonary disease.

eosinophilia (Table 2). Eosinophils were detected in 2.0% of the RA patients and in 1.4% of the other CVD cases ($p<0.026$) (Table 3).

DISCUSSION

In this study, NLR, PLR, PLT/MPV, and CRP values were similar in patients with RA and other CVD. Age and the number of clinical respiratory complaints were significantly greater in RA patients.

Inflammation in RA and other CVD affects the number, configuration, and size of cells in the bone marrow and peripheral blood. However, according to some literature reports, the effects of the inflammatory process on hematological markers are debatable.[21] Intense systemic inflammation in RA disease may be demonstrated in biochemical markers (neutropenia, thrombocytopenia, and anemia, etc.).[21] The erythrocyte sedimentation rate and CRP are frequently used parameters. An elevated CRP value has been shown to suggest a more severe and a destructive course.[22] The sedimentation and CRP values measured in this study were normal.

In RA disease, neutrophilia often occurs due to systemic inflammation. Neutrophilia has been reported in 15% of cases with lymphopenia and the NLR ratio has been indicated to be a marker of activity in RA disease in the literature, although some studies do not fully support this finding.[18,23,24] An increase in the MPV has been said to be a biomarker in RA and many inflammatory diseases.[20] In our study, the NLR in the RA patients was within normal limits.

Elevated platelet activation is an indication of activation in RA disease. Platelet volume (MPV) in RA activation has been reported to be a positive marker.[25,26] In our study, the PLT and MPV values were normal in patients with RA. Hogan et al.[19] have suggested that an increased CRP and neutrophil level in patients with granulomatous vasculitis could be used to predict relapse.[19] In a large systematic review of Behçet's disease, Hatemi et al.[27] reported that sedimentation rate and CRP were not associated with activity. In other studies investigating the importance of biomarkers for the diagnosis and treatment of Behçet's disease as well as predicting relapses, the rate of sedimentation was significantly higher in CRP, MPV and NLR patients than in healthy adults.[20,28]

It has been reported that a high NLR was associated with poor prognosis and renal involvement in WG, which may include an elevated sedimentation rate, anemia, leukocytosis, thrombocytosis, and rarely, thrombopenia.[29] Systemic infections have been reported to lead to a raised NLR in WG with lymphopenia.[30] Yolbas et al.[21] compared RA, BD, scleroderma, and SLE patients (total n=434) with a healthy control group and reported that MPV, PLR, and NLR could be used as disease activity indicators in 51 SLE patients.[21] In the same study the authors reported that MPV and SLE were higher than RA, and that MPV and NLR values were indicative of activity in SLE and BD.[21]

In our study, the biomarkers of NLR, PLT, PLR, CRP, MPV, and PLT/MPV observed in patients with RA, WG, BD, and SLE were compared and the results were similar. The eosinophil ratio was found to be higher in RA patients.

Very few studies have investigated increased eosinophil levels in RA. Some researchers have indicated that high levels may be related to the development of arthritis, but other studies have reported that eosinophilia may be related to other causes (parasites, allergy, etc.) or drugs used in RA treatment (leflunomide, etc.). Some studies have also investigated potential markers of disease activity; however, CRP and sedimentation rate revealed no such association.[29,31–33]

Table 2. Hemogram and biochemical values of patients with rheumatoid arthritis or collagen vascular disease at presentation to the chest disease outpatient clinic

	Rheumatoid arthritis		Collagen vascular disease		p
	n	Median (IQR)	n	Median (IQR)	
Hemogram parameters					
Leukocyte 10^9/L	76	7.13 (6.00–8.89)	54	7.15 (5.80–9.20)	0.62
Neutrophil 10^9/L	76	4.46 (3.50–5.40)	54	4.25 (3.0–6.5)	0.93
Monocyte 10^9/L	76	0.56 (0.42–0.70)	54	0.50 (0.40–0.60)	0.030
Lymphocyte 10^9/L	76	2.00 (1.53–2.50)	54	1.95 (1.54–2.42)	0.73
Neutrophil %	76	61.89 (55.30–66.45)	54	63.59 (56.44–71.10)	0.33
Monocyte %	76	7.75 (5.90–9.10)	54	7.05 (5.71–8.45)	0.10
Lymphocyte %	76	26.80 (22.30–32.50)	54	26.20 (21.30–32.80)	0.84
Eosinophil %	76	2.00 (1.16–2.70)	54	1.40 (0.80–2.10)	0.026
Basophil %	76	0.50 (0.40–0.80)	54	0.52 (0.40–0.75)	0.91
Erythrocyte 12/9L	76	4.47 (4.19–4.89)	54	4.44 (4.14–4.77)	0.79
Hemoglobin g/dL	76	12.95 (11.30–14.10)	54	12.60 (11.20–13.60)	0.34
Hematocrit %	76	38.90 (35.97– 42.20)	54	38.30 (34.90–41.00)	0.45
MCV fL	76	87.35 (83.70–90.80)	54	86.48 (81.20–88.80)	0.13
Platelet 10^9/L	76	271.50 (238.00–306.00)	54	255.50 (218.00–309.40)	0.34
MPV fL	76	8.35 (7.60–8.96)	54	8.40 (7.70–9.40)	0.35
RDW-CV fL	76	14.95 (13.90–16.60)	54	15.70 (14.00–16.80)	0.48
Biochemical values					
Fasting blood sugar mg/dL	35	97 (89–120)	19	92 (90–103)	0.58
BUN mg/dL	37	29 (24–39)	27	30 (24–41)	0.85
Creatinine mg/L	42	0.68 (0.58–0.77)	26	0.72 (0.63–0.84)	0.26
Protein g/dL	16	7.0 (7.0–8.0)	8	7.0 (6.7–7.6)	0.19
Albumin g/dL	22	4.0 (4.0–4.0)	10	4.3 83.9–4.6)	0.29
Sodium mmol/L	25	139 (137–140)	13	139 (135–140)	0.86
Potassium mmol/L	25	4.0 (4.0–5.0)	13	4.3 (4.1–4.6)	0.22
Calcium mg/dL	27	9.0 (9.0–10.0)	8	9.6 (9.6–9.7)	0.83
LDH U/L	16	195 (175–251)	12	204 (196–223)	0.54
SGOT U/L	37	23 (18–26)	19	21 (16–31)	0.76
SGPT U/L	39	20 (15–37)	20	23 (12–36)	0.95

BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; IQR: Interquartile range; MCV: Mean corpuscular volume; MPV: Mean platelet volume; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase.

Table 3. Comparison of biomarkers of patients with rheumatoid arthritis and collagen vascular disease at presentation to the chest disease outpatient clinic

	Rheumatoid arthritis		Collagen vascular disease		p
	n	Median (IQR)	n	Median (IQR)	
NLR	74	2.32 (1.74–2.99)	54	2.51 (1.71–3.48)	0.52
PLR	74	138.33 (105.52–176.01)	54	126.75 (104.12–195.45)	0.69
PLT/MPV	74	34.33 (26.6–40.69)	54	30.74 (23.85–36.12)	0.14
Sedimentation rate mm/h	38	35 (24–49)	20	27 (12–54)	0.40
CRP mg/dL	48	6 (3–16)	22	6 (3–14)	0.82

CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; PLT/MPV: Platelet/mean platelet volume.

The increasing age of the onset of RA (≥60 years) within the last 50 years has led researchers to consider that RA has become a disease of advanced age. The patients in our study had a median age of 54 years.[34]

Limitations

The study was a single-center retrospective study. Patients who were included in the study were identified using the hospital information management system. Every effort

was made to eliminate patients with conditions that might affect the outcome of the study, but that may not have been entirely avoided.

Since the study included only a small number patients, the data may be statistically different with a larger group. In our study, analysis of hemogram was performed using blood counts. The addition of peripheral smears for eosinophil counts might have led to different results.

Peripheral blood NLR, PLR, PLT/MPV, and CRP values may not provide a clinical benefit in the differentiation between RA and other CVD. However, the finding of a high percentage of eosinophils in the peripheral blood of RA patients may be useful to a subsequent investigation to determine potential utility in a differential diagnosis with other CVD.

As a result of respiratory system involvement, RA and other CVD are frequently encountered in chest disease departments and outpatient clinics. Practical, accessible parameters that will enable an accurate diagnosis of RA and other CVD will contribute to earlier diagnosis and proper treatment.

Ethics Committee Approval

Approved by the local ethics committee.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: A.F.A.; Design: A.F.A.; Data collection &/or processing: A.F.A.; Analysis and/or interpretation: A.F.A.; Literature search: A.F.A.; Writing: A.F.A.; Critical review: A.F.A.

Conflict of Interest

None declared.

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Romatoid Artrit ve Kollagen Vasküler Hastalıklarda Solunum Sistemi Semptomu Varlığında Enflamatuvar Belirteçler Farklı Mıdır?

Amaç: Romatoid artrit (RA) ve kollagen vasküler hastalıkların akciğer tutulumunda öksürükten, akut solunum yetersizliğine uzanan geniş yelpazede semptomlar görülebilir. Bu çalışmada solunum şikayeti olan romatoid artrit ve kollagen vasküler hastalığı olanların serumdaki enflamatuvar belirteçlerinde farklılık olup olmadığını araştırıldı.

Gereç ve Yöntem: Geriye dönük, gözlemsel kesitsel çalışma Sağlık Bilimleri Üniversitesi Göğüs Hastalıkları Eğitim Hastanesi'nde Ocak 2016–Aralık 2017 tarihleri arasında yapıldı. RA ve kollagen vasküler hastalık (KVH) (sistemik lupus, Wegener ve Behçet) tanılı hastalar hastane elektronik sisteminden kayıt edildi. Demografik özellikleri, göğüs hastalıkları semptomları, ek hastalıklar kayıt edildi. Nötrofil lenfosit oranı, platelet lenfosit oranı, platelet ortalama platelet hacmi oranı, C-reaktif protein ve eritrosit sedimentasyon hızı, rutin biyokimya incelemeleri kayıt edildi. Hastalık grupları karşılaştırıldı.

Bulgular: Çalışmaya ortanca yaşları 54 (43–63) olan 130 (n=30, %23 erkek) hasta alındı. Gruplar cinsiyet dağılımı benzer idi. RA grubu KVH'a göre daha yaşlı idi (57 yaş vs 49 yaş, p<0.002). RA'da daha fazla solunum kaynaklı semptom bulundu (%34.2 iken 16.7, p<0.026). Grupların hemogram değerleri eozinofil fazlalığı hariç benzer idi. RA'da eozinofil %2.0 iken KVH'ta %1.4 idi (p<0.026).

Sonuç: Romatoid artrit ve KVH'da solunum semptomları olduğunda serum enflamatuvar belirteçleri farklılık göstermeyebilir, ancak hastaların RA'da, KVH göre daha yaşlı ve solunum sistemi semptomları daha fazla olabilir.

Anahtar Sözcükler: Biomarkırlar; kollagen vasküler hastalıklar; romatoid artrit.