

ASSESSMENT OF ANTINUCLEAR ANTIBODY AND INFLAMMATORY MARKERS IN ROSACEA PATIENTS

Rosacea Hastalarında Antinükleer Antikor ve İnflamatuar Belirteçlerin Değerlendirilmesi

Didem KAZAN¹, Burcu Bahar İNCİ²

¹Acıbadem Kartal Hastanesi,
Dermatoloji Kliniği,
İstanbul,
Türkiye.
²İzmir Sevgiyolu Hastanesi,
Dermatoloji Kliniği,
Balıkesir,
Türkiye.

Didem KAZAN, Dr.
(<https://orcid.org/0000-0001-5398-0215>)
✉ didem.senses_343@hotmail.com
Burcu Bahar İNCİ, Dr.
(<https://orcid.org/0000-0002-6414-9643>)
✉ burcubaharinci@gmail.com

İletişim:

Dr. Didem KAZAN
Acıbadem Kartal Hastanesi, Dermatoloji
Kliniği, İstanbul, Türkiye.

Geliş tarihi/Received: 09.09.2025

Kabul tarihi/Accepted: 15.12.2025

DOI: 10.16919/bozoktip.1780348

Bozok Tıp Derg 2026;16(1):32-36

Bozok Med J 2026;16(1):32-36

ABSTRACT

Objective: Rosacea is a chronic inflammatory skin disorder with a potential association with systemic inflammatory and autoimmune conditions. This study aimed to investigate inflammatory markers, including antinuclear antibody (ANA) and complement levels, in patients with rosacea.

Material and Methods: In this retrospective case-control study, 178 patients aged 18 years and older who were diagnosed with rosacea between March 2022 and March 2023 were evaluated. Forty-nine age- and sex-matched healthy individuals were included as controls. Demographic data and laboratory parameters-including leukocyte and platelet counts, hemoglobin, hematocrit, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement C3 and C4 levels, and ANA titers-were recorded and analyzed.

Results: Among the rosacea patients, ANA positivity was detected in 7.9% (14/178). No statistically significant differences were found between the patient and control groups in terms of leukocyte count ($p=0.482$), platelet count ($p=0.567$), hemoglobin ($p=0.828$), hematocrit ($p=0.877$), ANA titer ($p=0.946$), C3 ($p=0.665$), ESR ($p=0.083$) or CRP levels ($p=0.690$). However, serum C4 levels were significantly lower in rosacea patients compared to the control group ($p=0.029$).

Conclusion: Patients with rosacea may present with decreased serum C4 levels, suggesting a potential link with systemic inflammatory or autoimmune processes. Further prospective studies are warranted to clarify the clinical significance of these findings.

Keywords: Rosacea; Inflammation; Autoimmune Disease

ÖZET

Amaç: Rosacea, sistemik inflammatuar ve otoimmün hastalıklarla ilişkili olabileceği düşünülen kronik inflammatuar bir cilt hastalığıdır. Bu çalışmada, rosacea hastalarında antinükleer antikor (ANA) ve kompleman düzeyleri de dâhil olmak üzere inflammatuar belirteçlerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif olgu-kontrol çalışmasında, Mart 2022 ile Mart 2023 tarihleri arasında rosacea tanısı alan, 18 yaş ve üzerindeki 178 hasta değerlendirilmiştir. Yaş ve cinsiyet açısından eşleştirilmiş 49 sağlıklı birey kontrol grubunu oluşturmuştur. Katılımcıların demografik özellikleri ile lökosit ve trombosit sayısı, hemoglobin, hematokrit, eritrosit sedimentasyon hızı (ESH), C-reaktif protein (CRP), kompleman C3 ve C4 düzeyleri ile ANA titresi gibi laboratuvar parametreleri retrospektif olarak analiz edilmiştir.

Bulgular: Rosacea hastalarının %7,9'unda (14/178) ANA pozitifliği saptanmıştır. Lökosit ($p=0,482$), trombosit ($p=0,567$), hemoglobin ($p=0,828$), hematokrit ($p=0,877$), ANA titresi ($p=0,946$), C3 ($p=0,665$) ve CRP ($p=0,690$) düzeyleri açısından hasta ve kontrol grupları arasında istatistiksel olarak anlamlı fark bulunmamıştır. Ancak, rosacea hastalarında serum C4 düzeyleri kontrol grubuna kıyasla anlamlı derecede daha düşük bulunmuştur ($p=0,029$).

Sonuç: Rosacea hastalarında ANA pozitifliği, ESH yüksekliği ve serum C4 düzeylerinde azalma gözlemlenebilir. Bu durum, rosacea ile sistemik inflammatuar ya da otoimmün süreçler arasında olası bir ilişkiye işaret edebilir. Bulguların klinik öneminin netleştirilebilmesi için ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Rozase; İnflamasyon; Otoimmün Hastalık

INTRODUCTION

Rosacea is a chronic inflammatory skin disease. It usually affects fair-skinned women over 30 but can manifest in individuals of any age or sex (1). While its etiology remains partially elusive, it is thought to be influenced by genetic, neurovascular, immune, and psychological factors (2). Traditionally, diagnosis relied on clinical observation and history; however, the National Rosacea Society Expert Committee's novel classification system has significantly enhanced diagnostic precision, mitigating the risk of misdiagnosis with other facial skin conditions, such as malar rash due to systemic lupus erythematosus (SLE) (3,4).

Recent studies have unveiled a complex interplay between rosacea and autoimmune diseases (5,6). Genetic studies (genome wide association study) have identified genetic risk loci associated with autoimmune diseases for rosacea (7). In addition to autoimmunity, systemic inflammation has also been demonstrated in individuals with rosacea, further contributing to the disease's complex pathophysiology. Because of that various systemic comorbidities are known to accompany rosacea. These comorbid conditions can significantly reduce patients' quality of life, emphasizing the need for comprehensive evaluation and long-term follow-up in this population(8). These factors can challenge clinicians to make an accurate diagnosis.

Our study addressed these diagnostic challenges by comprehensively comparing various inflammatory laboratory indicators in rosacea patients and healthy individuals. We examined the counts of leukocyte and platelet, levels of hemoglobin (HB) and hematocrit (HTC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement-3 (C3), complement-4 (C4), and anti-nuclear antibody (ANA) titers. This analysis allowed us to identify key similarities and differences between rosacea, autoimmune and inflammatory diseases.

MATERIAL AND METHOD

This is a descriptive, retrospective, and case-control study. The ethic committee of the institution has approved the study according to the Helsinki Declaration. (Approval date: 11/05/2023, approval number: 2023/06-16).

The study included patients over 18 years old diagnosed with rosacea and age and gender-matched healthy controls admitted to our outpatient clinic between March 2022 and March 2023. We excluded patients with systemic diseases, autoimmune disorders, and those using systemic drugs from the study. All patients who participated in the study provided informed consent.

The hospital registry system was used to retrieve and record patients' age, gender, Fitzpatrick skin type, disease duration, additional systemic disease, systemic drug use, and laboratory results. The complete blood count (including leukocyte and platelet count, HB, and HTC), ESR, CRP, C3, C4, and ANA levels were among the laboratory results accessed.

A flow cytometry device (Mindray BC 6800) was used to measure total blood count. A photometric autoanalyzer (Beckman Coulter AU 5800) and its standard kits were used to measure serum levels of CRP.

The patients' serum ESR levels were counted using an automatic sedimentation analyzer (Vision). The patients' ANA levels were determined using enzyme-linked immunosorbent assay (ELISA) tests. The test was considered positive if the ANA titer was equal to or greater than 1/80. The serum C3 and C4 levels were calculated using a nephelometric analyzer (Turbox). The serum C3 levels normal range 0.9-1.8 g/L, whereas the serum C4 levels normal range 0.16-0.48 g/L.

Statistical Analysis

Researchers used IBM SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Continuous variables were given as mean \pm standard deviation or median with interquartile range. Categorical data were presented as frequency (percentage) and evaluated by chi-square test.

Researchers calculated the uniform distribution of the data with the Kolmogorov-Smirnov test, and used student's t-test to compare mean values of quantitative variables. Authors performed logistic regression test for univariate and multivariate analysis. Statistical significance was considered for p-values less than 0.05.

RESULTS

A total of 227 patients, 178 patients with rosacea, and 49 healthy controls participated in the study. The study

group was conducted with 154 (86,5%) females and 24 (13,5%) males. The median disease duration was 3,1+2,9 years. The most common type was erythema-telangiectatic rosacea in 99 (55,6%). Table 1 shows that the demographic features of the study group were homogenous and matched the control group. ANA positivity was 7,9% (14/178) in rosacea patients. We found no statistically significant difference between the two groups in terms of mean total leucocyte and platelet count, HB, HTC, ESR, ANA, C3, and CRP levels (p=0.482, p=0.567, p=0.828, p=0.877, p=0.083, p=0.946, p=0.665, and p=0.690; respectively) (Table 2). Serum C4 levels were statistically lower in the study group (p=0.029) (Table 2). Additionally, according to univariate and multivariate tests, serum C4 level was

the only independent predictive test for the rosacea patients compared to healthy controls (Table 3).

DISCUSSION

Our study involved 227 patients, 178 with rosacea and 49 healthy controls. Serum C4 levels were significantly lower in patients with rosacea compared to control group. Serum C4 level was the only independent predictive marker for the rosacea patients., These findings underscore the potential link between chronic inflammation, autoimmune diseases and rosacea. Our results align with previous studies (9,10). For instance, Lazaridou et al. reported that 21.1% (19/90) of patients with rosacea had ANA positivity, 6,7% with

Table 1. Demografic features of the patients

Demografic features of the patients	Study group (n= 178)	Control group (n=49)	p value
Gender			
Male	24 (13.5%)	9 (18.4%)	0.390 ^a
Female	154 (86.5%)	40 (81.6%)	
Mean of age+SD (year)	41.6+12.7	39.9+9.9	0.159 ^b
Fitzpatrick skin type			
2	156 (87.6%)	45 (91.8%)	0.414 ^a
3	22 (12.4%)	4 (8.2%)	
Mean duration of the disease+SD (year)	3.1+2.9	-	-
Type of the disease			
Erythema-telangiectatic papulopustular	99 (55.6%)		
Phimatous	71 (39.9%)	-	-
	8 (4.5%)		

Abbreviations: a: Chi square tes, b: Students t-test, SD: Standard deviation

Table 2. Evaluation of the systemic inflammation and systemic lupus erythematosus markers of the patients

Laboratory finding of the patients	Study group (n=178)	Control group (n=49)	P value
Leucocyte count (mean + standard deviation)	7212+1993	6919+1835	0.482 ^a
Platelet count (mean + standard deviation)	271707+56920	266413+58527	0.567 ^a
Heamoglobin (mean + standard deviation)	13.74+1.40	13.79+1.59	0.828 ^a
Hematocrit (mean + standard deviation)	40.73+3.52	40.82+4.14	0.877 ^a
C- reactive protein (mean + standard deviation)	3.67+4.68	3.95+2.81	0.690 ^a
Erythrocyte sedimentation rate (mean + standard deviation)	9.95+7.17	8.04+6.73	0.083 ^a
Complement - 3 (mean + standard deviation)	1.22+0.18	1.23+0.20	0.665 ^a
Complement - 4 (mean + standard deviation)	0.26+0.06	0.29+0.10	0.029 ^{a*}
Antinuclear antibody			
Positive	14 (7.9%)	4 (8.2%)	0.946 ^b
Negative	164 (92.1%)	45 (91.8%)	

a: Students t-test, b: Chi-square test, SD: Standard deviation

positive indirect immunofluorescence assay, and 6.4% with direct immunofluorescence assay (9). They declared that none of the rosacea patients with ANA positivity had developed SLE. Therefore, they attributed this positivity to sun exposure, as had been suggested by other authors (9-11). However, they did not investigate serum inflammation markers, serum C3 and serum C4 levels, in their patients. On the other hand, Anderson found ANA positivity in 9% of normal subjects between 41 and 60 years of age (12). They associated this positivity with repeated viral infections and genetic predisposition. Our study observed ANA positivity at 7.9% in patients with rosacea, which was not significantly different from healthy controls. These results suggest that ANA detection in rosacea patients may be due to various environmental and genetic factors. The test should not be considered a diagnostic or differential laboratory test. Other lupus diagnostic criterias such as hematological, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal involvement, antiphospholipid and SLE-specific antibodies should be checked in the patients with suspected SLE (13). According to our current knowledge, rosacea is not a disease limited to the skin. Many previous reviews and meta-analyses demonstrate the relationship between rosacea and other systemic comorbidities, such as hypertension, dyslipidemia, cardiovascular diseases, inflammatory bowel diseases, diabetes mellitus, anxiety, and depression, mainly due to systemic chronic inflammation (14,15). From our country, Caf N. et al. reported that systolic and diastolic blood pressures and plasma neutrophil/lymphocyte ratio were higher than healthy controls in the rosacea patients (16). Similarly, the groups had no significant difference in platelet/lymphocyte ratio, CRP, and ESR. They did not investigate serum C3 and C4 levels in both groups. On the other hand, Karaosmanoğlu N. et al. reported monocyte and platelet count, SII index, ESR and CRP were significantly higher in patients with rosacea (17). The difference in the patients' characteristics and the methods of studies could vary these results. However, these findings emphasize the relationship between inflammation and rosacea. Further investigation could explain the exact mechanism behind this relationship. A multicenter study from our country, reported no

additional autoimmune disease in the rosacea patients (18). However, a case-control multi-institutional survey from Korea declared that a statically significant association between Sjögren syndrome, systemic sclerosis, rheumatoid arthritis, ankylosing spondylitis, autoimmune thyroiditis, alopecia areata, vitiligo, and rosacea (19). Our patients had no additional systemic diseases; however, we found lower serum C4 levels in rosacea patients compared to healthy controls. Therefore, these findings may underscore the relationship between rosacea and complement-dependent autoimmune diseases. Further investigation and long-term follow-up should be done on these patients.

The main limitation of our study is the lack of extractable nuclear antigen (ENA) panel testing in patients with positive ANA results. In our center, ANA positivity was reported only qualitatively as positive or negative, without further specification of antibody subsets such as anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP, anti-Scl-70, or anti-centromere antibodies. Therefore, we were unable to determine whether ANA-positive rosacea patients had specific autoantibody patterns that could suggest an underlying connective tissue disease. This constitutes an important limitation, as ENA profiling is crucial for interpreting ANA positivity in clinical context. The retrospective design can also be thought of as a limitation. The strengths of this study include the relatively large sample size, the case-control structure, and the use of standardized laboratory procedures for all participants. All serum inflammation markers were evaluated systematically in the study population.

In addition, although serum C4 levels were significantly lower in rosacea patients in our study, the use of serum C4 as a screening tool for autoimmunity in routine clinical practice requires careful consideration. Serum C4 may be evaluated in rosacea patients with suspected autoimmune comorbidities; however, given that C4 is not disease-specific and may not be cost-effective as a broad screening test, its use should be individualized based on the patient's clinical findings and risk profile.

CONCLUSION

Rosacea could be associated with other systemic disorders. Systemic comorbidities, such as chronic

inflammation and genetic background, could be related to rosacea. Autoimmune disease could be detected in rosacea patients; however, study results are still controversial. Further studies could enlighten our knowledge about this issue.

Acknowledgment

The authors declared that this study has received no financial support and no conflict of interest between the authors.

REFERENCES

1. van Zuuren EJ, Fedorowicz Z, Tan J, van der Linden MMD, Arents BWM, Carter B. et al. Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments. *Br J Dermatol* 2019;181(1):65-79.
2. Wollina U. Recent advances in the understanding and management of rosacea. *Prime Rep* 2014;6:50.
3. Thiboutot D, Anderson R, Cook-Bolden F, Draelos Z, Gallo RL, Granstein RD. et al. Standard management options for rosacea: The 2019 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol* 2020;82(6):1501-10.
4. Sitohang IBS, Parrol F, Fitri EM, Nora RD. Papulopustular and Ocular Rosacea with an Alleged Coincidence of Cutaneous Lupus Erythematosus: A Case Report. *Case Rep Dermatol.* 2021;13(1):62-8.
5. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Clustering of autoimmune diseases in patients with rosacea. *J Am Acad Dermatol* 2016;74(4):667-72.e1.
6. Rainer BM, Fischer AH, Luz Felipe da Silva D, Kang S, Chien AL. Rosacea is associated with chronic systemic diseases in a skin severity-dependent manner: results of a case-control study. *J Am Acad Dermatol* 2015; 73: 604-8.
7. Chang ALS, Raber I, Xu J, Li R, Spitale R, Chen J. et al. Assessment of the genetic basis of rosacea by genome-wide association study. *J Invest Dermatol* 2015;135(6):1548-55.
8. Sinikumpu SP, Huilaja L, Auvinen J, Jokelainen J, Puukka K, Ruokonen A. The Association Between Low Grade Systemic Inflammation and Skin Diseases: A Cross-sectional Survey in the Northern Finland Birth Cohort 1966. *Acta Derm Venereol.* 2018;98(1):65-9.
9. Lazaridou E, Apalla Z, Sotiraki S, Ziakas NG, Fotiadou C, Ioannides D. Clinical and laboratory study of rosacea in northern Greece. *J Eur Acad Dermatol Venereol* 2010;24(4):410-4.
10. Woźniacka A, Salamon M, McCauliffe D, Sysa-Jędrzejowska A. Antinuclear antibodies in rosacea patients. *Postepy Dermatol Alergol* 2013;30(1):1-5.
11. Nunzi E, Rebora A, Hamerlinck F, Cormane RH. Immunopathological studies on rosacea. *Br J Dermatol* 1980;103(5):543-51.
12. Andersen P. Correlation of smooth-muscle and nuclear antibodies in normal subjects. *Clin Exp Immunol* 1977;27(1):74-7.
13. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN. et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(6):736-45.
14. Haber R, El Gemayel M. Comorbidities in rosacea: A systematic review and update. *J Am Acad Dermatol* 2018;78(4):786-92.e8.
15. Chen Q, Shi X, Tang Y, Wang B, Xie HF, Shi W. et al. Association between rosacea and cardiometabolic disease: A systematic review and meta-analysis. *J Am Acad Dermatol* 2020;83(5):1331-40.
16. Caf N, Özkök Akbulut T, Can MM, Sarı M, Atsü AN, Türkoğlu Z. Evaluation of subclinical atherosclerosis in rosacea patients by flow-mediated dilatation method. *J Cosmet Dermatol* 2023;22(3):1001-10.
17. Karaosmanoglu N, Ozdemir Cetinkaya P, Orenay OM. Evaluation of inflammatory status in blood in patients with rosacea. *Sci Rep.* 2023;13(1):9068.
18. Aksoy B, Ekiz Ö, Unal E, Ozaydin Yavuz G, Gonul M, Kulcu Cakmak S. et al. Systemic comorbidities associated with rosacea: a multicentric retrospective observational study. *Int J Dermatol* 2019;58(6):722-8.
19. Woo YR, Kim HS, Lee SH, Ju HJ, Bae JM, Cho SH., et al. Systemic Comorbidities in Korean Patients with Rosacea: Results from a Multi-Institutional Case-Control Study. *J Clin Med* 2020;9(10):3336.