Inflammatory biomarkers in rosacea patients

Nese Gocer Gurok

Fethi Sekin City Hospital, Department of Dermatology, Elazig, Türkiye

Abstract

Aim: Rosacea is an inflammatory disease characterized by telangiectasia, papules and pustules associated with immune response. Several factors, especially inflammatory factors, have been investigated in its etiopathogenesis. The Systemic Immune Inflammation Index (SII) is a new inflammation marker. It has recently been used to evaluate the inflammatory and immune status of the patients. Also, several studies investigated other inflammation markers like neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR). The present study aims to investigate the correlation between rosacea, an inflammatory disease, and inflammatory markers such as platelet (PLT), lymphocyte (LYM), neutrophil (NEU), NLR, PLR, and especially SII.

Materials and Methods: The study was conducted with 100 papulopustular rosacea patients and 100 healthy controls. The patient and control groups were similar in age and gender. Participant data and laboratory results were obtained retrospectively from the patient files.

Results: Seventy-eight of the rosacea patients were female and 22 were male. The mean participant age was 47.97. There was no significant difference between rosacea patients and the control group based on age and gender. The PLT and LYM markers were significantly lower in the patient group when compared to the control group, and NLR, PLR and SII markers were significantly higher in the patient group ($p<0.05$).

Conclusion: The significant difference between the investigated inflammatory parameters suggested that rosacea could be a systemic inflammatory disease rather than a simple skin inflammation. More comprehensive studies are required to clarify this premise and the correlation between rosacea and systemic inflammation.

Introduction

Rosacea is a common chronic inflammatory dermatosis. Rosacea characterized by erythema, telangiectasia, papules/pustules, especially on the cheeks, nose, forehead, and chin [1]. It could be observed at any age; however, it usually onsets between 30 and 50. It is more common in females; however, the number of male patients has increased in recent years [1]. Rosacea is a skin disease that affects an average of 5.46% of the adult population globally [2]. Rosacea is generally categorized into four subtypes based on morphological properties: erythema telangiectatic, papulopustular, phymatous, and ocular rosacea [3].

Although the etiology of the disease is characterized by the induction of innate immune response and abnormal neurovascular signal by various environmental stimuli and endogenous factors, the diversity in clinical forms has pre-vented the clear understanding of the pathophysiology of rosacea [4,5].

The Systemic Immune Inflammation Index (SII) is a new inflammation marker that employs platelet, neutrophil and lymphocyte counts (platelet count × neutrophil/lymphocyte ratio). It has recently been used to evaluate the inflammatory and immune status of patients. Systemic inflammation has been considered an indicator of prognosis, disease severity and survival in several inflammatory and malignant diseases [6-8]. In dermatology, the correlation between SII and hidradenitis suppurativa, psoriasis, psoriatic arthritis, Behçet's disease, recurrent apthous stomatitis has been investigated [6,7,9,10]. Furthermore, several studies investigated inflammation markers like neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) [11].

The present study aimed to investigate the correlation between rosacea, an inflammatory disease, and inflammatory markers such as platelet (PLT), lymphocyte (LYM), neutrophil (NEU), NLR, PLR, and especially SII.

Corresponding author:
Email address: dr.n_g@hotmail.com (Nese Gocer Gurok)

Materials and Methods

The research was approved by the Fırat University Non-invasive Research Ethics Committee (Number: 2023/12-11). One hundred patients who were presented to Health Sciences University, (XXX) ??? Urban Dermatology Clinic between January 2022 and April 2023 and were diagnosed with papulopustular rosacea based on clinical examination were included in the study. Papulopustular rosacea patients without any concomitant dermatological, systemic, or local inflammatory diseases who were 18-65 years old, were not pregnant, did not abuse alcohol or substances, no history of anti-inflammatory medicine intake in the previous 3 months in the system were included in the study group. Patients who met the study criteria at the specified time were included. The control group included 100 healthy individuals who presented to the hospital for screening. The healthy control group included individuals without a dermatological, systemic, or local inflammatory disease who were between 18 and 65 years old, were not pregnant, and without a history of anti-inflammatory drug use in the previous 3 months in the system. The patient and control group members has similar age and gender distribution. The correlations between PLT, LYM, NEU, NLR, PLR, and SII parameters were investigated in the patient and control groups. Participant data and laboratory findings were obtained retrospectively from patient files.

Statistical analysis

The study data were analyzed with the Statistical Package for Social Science for Windows (SPSS) 24.0 software. Kolmogorov Smirnov test was applied to test whether the data were normally distributed and all parameters were found to be normally distributed ($p > 0.05$). Therefore, parametric tests were used in data analysis. Independent samples t-test was used to investigate the differences between PLT, LYM, NEU, NLR, PLR and SII of the patient and control groups. Furthermore, the statistical difference between the gender distribution of the groups was determined with the chi-square test. Roc Analysis was conducted on the SII figures of the patient group and the cut off, sensitivity and specificity values are presented. The findings were considered significant at 95% ($p < 0.05$) confidence levels.

Results

Seventy-eight percent of the rosacea patients were female and 22% were male. The mean participant age was 47.97. There was no significant difference between rosacea patients and the control group based on age and gender. The differences between the analyzed parameters in the groups are presented in Table 1.

There were significant differences between rosacea and control group PLT (t:-3.056; $p < 0.05$), LYM (t:-3.320; $p < 0.05$), NLR (t:3.168; $p < 0.05$), PLO (t:1.924; $p < 0.05$) and SII (t:2.316; $p < 0.05$) findings. Thus, the patient PLT and LYM findings were lower when compared to the controls, the patient NLR, PLR and SII findings were higher.

The Roc curve analysis revealed that the SII cut-off was 586.95 with 84.6% sensitivity and 82.3% specificity (Area under the curve: 0.892; 95% (CI) confidence interval: 0.806 - 0.977; p:0.000<0.05).

Table 1. The differences between PLT, LYM, NEU, NLR, PLR and SII in rosacea patients and the control group.

Parameter (mean ± sd)	Rosacea (n:100)	Control (n:100)	P
PLT	273.53±60.28	296.47±76.47	**.005***
LYM	2.10±0.61	2.36±0.82	**.003***
NEU	4.26±1.42	4.17±1.41	.586
NLR	2.28±1.46	1.89±0.79	**.002***
PLR	140.25±49.12	135.28±47.91	**.042***
SII	602.34±60.82	562.66±77.19	**.021***

Independent Samples t-Test, *p<0.05. (PLT: Platelet, LYM: Lymphocyte, NEU: Neutrophil, NLR: Neutrophil Lymphocyte Ratio, PLR: Platelet Lymphocyte Ratio, SII: Systemic Immune Inflammation Index).
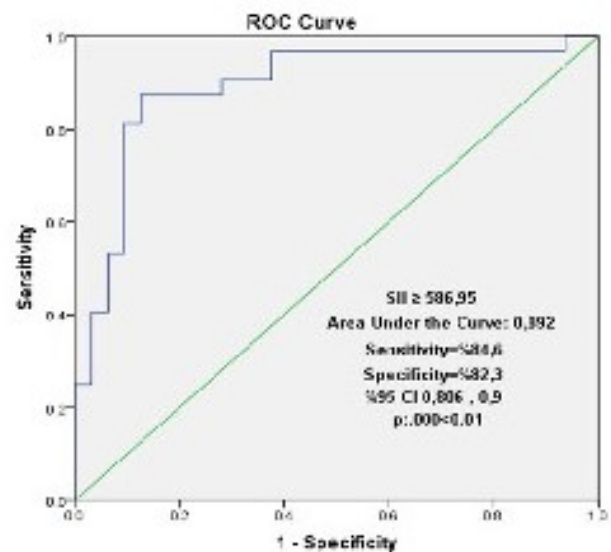
Figure 1. ROC Analysis.

Discussion

Rosacea is a chronic inflammatory skin disease characterized by erythema, papules and pustules associated with immune response [12]. Several studies reported that inflammatory pathways play a key role in the pathogenesis of rosacea [13-15]. In the present study, we investigated the role of systemic inflammation in rosacea pathogenesis based on various parameters. Belli et al. [16] compared the NLR, monocyte/high-density lipoprotein (HDL), cholesterol (MHR), and PLR ratios of rosacea patients and controls. NLR, mean low-density lipoprotein (LDL) and total cholesterol, triglyceride, C-reactive protein (CRP), systolic and diastolic blood pressures, and insulin resistance (IR) were significantly higher in rosacea patients when compared to controls. MHR was significantly higher in rosacea patients with IR and metabolic syndrome. Caf et al. [17] compared rosacea patients and the control group for endothelial dysfunction, systolic and diastolic blood pressures, hemogram, CRP, erythrocyte sedimentation rate (ESR), total cholesterol, triglyceride, LDL, HDL, NLR, PLR, mean platelet volume and fasting blood sugar. Metabolic syndrome, blood pressure, and NLR were higher in the patient group. These findings suggested that rosacea

could lead to an atherogenic effect and exhibit systemic involvement.

Karaosmanoglu et al. [13] retrospectively analyzed CBC, CRP, ESR, triglyceride, HDL and LDL findings in rosacea patients. NLR, monocyte/lymphocyte ratio and PLR, MHR and SII were compared between patient and control groups. Monocyte and platelet counts, SII, ESR and CRP were significantly higher in rosacea patients, and no statistically significant difference was determined between other parameters. Ertekin et al. [18] compared various inflammatory parameters (high-sensitivity C-reactive protein, interleukin-1 beta, interleukin-6, tumor necrosis factor alpha) between rosacea and healthy controls. And they found the levels of these parameters to be significantly higher in the patient group.

Limitations

This is a retrospective study. Thus, although a meticulous screening was conducted, the details of medical patient data were limited by the data available in hospital system. In the study, only certain inflammatory parameters were analyzed, and inflammatory markers such as CRP, ESR, interleukins and tumor necrosis factors were not analyzed. Prospective studies that would be conducted with larger samples and more inflammatory markers would provide further knowledge that could clarify the issues associated with rosacea.

Conclusion

Blood inflammatory parameters are inexpensive and easily determined inflammation markers. Significant findings in rosacea patients could be employed as inflammatory biomarkers. Similar to the above-mentioned studies, we determined significant differences between inflammatory parameters in rosacea patients and healthy controls. PLT and LYM were significantly lower in rosacea patients when compared to the control group, NLR, PLR and SII were significantly higher in the patient group. The significant difference between the analyzed blood inflammatory parameters, especially the SII, suggested that rosacea could be a systemic inflammatory disease rather than just a skin inflammation. The association between rosacea and systemic inflammation and metabolic conditions has been reported in various studies [19-21]. However, it is not clear whether rosacea could lead to systemic and metabolic conditions or whether these conditions induce rosacea. Further comprehensive studies are required to clarify this ambiguity and the correlation between rosacea and systemic inflammation.

Ethical approval

This research was approved by the Fırat University Non-invasive Research Ethics Committee (Number: 2023/12-11).

References

1. Esther J. van Zuuren, Bernd W. M. Arents, Mireille M. D. van der Linden, et al. Rosacea: New Concepts in Classification and Treatment. American Journal of Clinical Dermatology. 2021;22:457–65.
2. Gether, L, Overgaard, L.K, Egeberg, A, et al. Incidence and prevalence of rosacea: A systematic review and meta-analysis. Br. J. Dermatol. 2018;179:282–9.
3. Thiboutot D, Anderson R, Cook-Bolden F, 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. Anna D Holmes, Martin Steinhoff. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. Exp Dermatol. 2017;26(8):659-67.
5. Aimee M Two, Wiggin Wu, Richard L Gallo, et al. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. J Am Acad Dermatol. 2015; 72(5): 749-58.
6. Hayran Y, Şen O, Aktaş A. Systemic Immune-Inflammation Index (SII) Correlates with Disease Severity in Hidradenitis Suppurativa Patients.Indian J Dermatol. 2023;68(2):208-9.
7. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20:6212–22.
8. Yorulmaz A, Hayran Y, Akpinar U, et al. Systemic Immune-Inflammation Index (SII) Predicts Increased Severity in Psoriasis and Psoriatic Arthritis. Curr Health Sci J. 2020;46:352–7.
9. Tanacan E, Dincer Rota D, Erdogan FG, et al. A cutoff value for the Systemic Immune- Inflammation Index in determining activity of Behçet disease. Clin Exp Dermatol. 2021;46(2):286-91.
10. Tanacan E, Dinçer Rota D, Oktem R, et al. The correlation of systemic immuneinflammation index, neutrophil-to-lymphocyte ratio, derived neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio with disease severity in recurrent aphthous stomatitis. J Cosmet Dermatol.2022;21(10):4858-63.
11. Wang WM, Wu C, Gao YM. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and other hematological parameters in psoriasis patients.BMC Immunol. 2021;22(1):64.
12. Yoon SH, Hwang I, Lee E. Antimicrobial Peptide LL-37 Drives Rosacea-Like Skin Inflammation in an NLRP3-Dependent Manner. J Invest Dermatol. 2021;141(12):2885-94.
13. Karaosmanoglu N, Ozdemir Cetinkaya P, Orenay ÖM. Evaluation of inflammatory status in blood in patients with rosacea. Sci Rep. 2023(5);13(1):9068.
14. Deng Z, Chen M, Liu Y et al. A positive feedback loop between mTORC1 and cathelicidin promotes skin inflammation in rosacea. EMBO Mol Med. 2021(7);13(5):e13560.
15. Xi-Min Hu, Zhi-Xin Li 3, Dan-Yi Zhang. Current research and clinical trends in rosacea pathogenesis. Heliyon. 2022 (13);8(10):e10874.
16. Belli AA, Kara A, Gok SO. Can Hematologic Parameters be an Indicator of Metabolic Disorders Accompanying Rosacea? Acta Dermatovenerol Croat.2017;25(2):145-50.
17. Caf N, Akbulut TÖ, Can MM, et al. Evaluation of subclinical atherosclerosis in rosacea patients by flow-mediated dilatation method. J Cosmet Dermatol. 2023;22(3):1001-10.
18. Ertekin SS, Koku Aksu AE, Koçyiğit A, et al. Carotid intima-media thickness and serum proinflammatory cytokine levels in rosacea patients without cardiovascular risk factors. Dermatol Ther. 2021;34(1):e14733.
19. Wollina U. Is rosacea a systemic disease? Clin Dermatol.2019;37(6):629-35.
20. Vera N, Patel NU, Seminario-Vidal L. Rosacea Comorbidities. Dermatol Clin.2018;36(2):115-22.
21. Yi JZ, Chen SX, Lukac D, McGee JS. Systemic comorbidities of rosacea: practice gaps among dermatologists. Arch Dermatol Res. 2022;314(10):995-97.