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Evaluation of the Effects of systemic Therapy on Inflammatory Markers and Disease Severity in Patients with Pemphigus

Mehmet Enes Güner[1], Perihan Öztürk[1], Mine Müjde Kuş[1]

1 Sutcu Imam University Hospital of Health, Practice and Research, Kahramanmaras Sutcu Imam University, Department Of Dermatology, Kahramanmaras, Turkey

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Corresponding Author: Mehmet Enes Güner, MD, Department of Dermatology, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey. E-mail: mehmetenesguner171@hotmail.com

ABSTRACT

Introduction: In recent years, various inflammatory markers that can change in inflammatory states have been investigated. On the basis of these, we thought that inflammatory markers could also be used in the follow-up of pemphigus disease and monitoring its activity.

Objectives: In this study, our objective was to investigate changes in the inflammatory markers neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), lymphocyte to monocyte ratio (LMR), C-reactive protein (CRP) erythrocyte sedimentation rate (ESR), which are inflammatory markers, before treatment and during follow-up, and the correlation of disease severity with these markers in patients with pemphigus receiving intravenous immunoglobulin (IVIG) and/or systemic immunosuppressant agents.

Methods: Seventy-six pemphigus patients (69 had pemphigus vulgaris, 5 had pemphigus foliaceus, 2 had paraneoplastic pemphigus) who received IVIG and/or systemic immunosuppressant agents such as corticosteroids and azathioprine and used these treatments for at least 6 months were included. Changes in NLR, PLR, LMR, MPV, CRP and sedimentation values were examined in patients who received systemic treatment for at least 6 months, before the start of treatment and 3 and 6 months after the start of treatment.

Results: Significant changes in inflammatory markers and correlation values were found in all patients.

Conclusions: We think that neutrophil, platelet, NLR and PLR values can be used to monitor the response to treatment in pemphigus, since they show a significant decrease with treatment and are significantly positively correlated with Pemphigus Disease Area Index, which indicates the severity of the disease. LMR values were indicators of a poor prognosis. We found that the duration of remission was longer in the group receiving IVIG. Although there was no difference between the treatments in terms of disease recovery, only IVIG prolonged the duration of remission.

Introduction

Pemphigus is a group of chronic autoimmune diseases characterized by bullae. The pemphigus group can be divided into four main subtypes: pemphigus vulgaris, pemphigus foliaceous, paraneoplastic pemphigus and IgA pemphigus. Pemphigus herpetiformis and drug-induced pemphigus are rarer forms that show some clinical, histological and immunopathological features that differ from the classical types [1,2]. The inflammatory response, also known as inflammation, is a process in which the immune system responds to tissue damage, infection, or other types of stress, and is a dynamic process involving a variety of different cell types, signaling pathways, and mediators. Its primary purpose is to remove any harmful stimuli, such as pathogens or damaged tissue and to promote healing and repair of the affected area [3]. In recent years, various inflammatory markers that can change in inflammatory states have been investigated.

Neutrophils constitute 50%-70% of circulating leukocytes and are the most abundant innate immune cell type in circulation. Its amount can be measured with simple blood count examinations. During the inflammatory reaction, neutrophils are stimulated and activated by inflammatory cytokines to increase their phagocytic and bactericidal effects. They also play an important role in the resolution and healing of inflammation [4]. Since neutrophils have long been focused only on their lethal function by researchers, their importance in diseases has not been adequately understood. Studies conducted in recent years shed light on the role of neutrophils in inflammatory diseases and malignancies. Statistically significant elevation of neutrophils has been detected in patients with breast cancer and lung cancer [4-6]. Recently, it has been understood that platelets play an important role in immunological and inflammatory processes [7-8]. Since platelets increase in number in systemic inflammation, their role has been investigated in various malignancies and inflammatory diseases such as Crohn disease and vasculitis, and platelet elevation has been found to be associated with disease severity and poor prognosis [9-13]. Platelets have also been studied in various dermatological diseases. The condition shown to be most clearly related to its pathogenesis is atopic dermatitis [7]. Many studies have been conducted on inflammatory diseases and lymphocyte-related malignancies, which are important components of the immune system. It has been suggested that the number of lymphocytes in peripheral blood decreases with bexarotene treatment in mycosis fungoides and may be a prognostic factor in the follow-up of mycosis fungoides [14].

The role of platelets in various inflammatory disorders is understood, and the activation and function of platelets can be seen with the mean platelet volume (MPV), one of the parameters included in the whole blood analysis. Neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), C reactive protein (CRP) and erythrocyte sedimentation values (ESR), which can be measured by simple blood tests, increase in cases of systemic inflammation and can be easily detected. Their place in the diagnosis and prognosis of malignancies and inflammatory diseases has been investigated. These markers have been investigated in response to psoriasis treatment and in correlation with disease severity, and significant results have been found. On the basis of these, we thought that inflammatory markers could also be used in the follow-up of pemphigus disease and monitoring its activity.

Objectives

In this study, our objective was to investigate the changes in the values of the inflammatory markers NLR, PLR, MPV, LMR, CRP and ESR values, which are inflammatory markers, before treatment and during follow-up, and the correlation of disease severity with these markers in pemphigus patients who received IVIG and/or systemic immunosuppressant agents such as corticosteroids, azathioprine and/or mycophenolate mofetil (Figure 1).

Methods

The approval for the study was received from Clinical Research Ethics Committee of Kahramanmaras Sutcu Imam University. (Date: 11.01.2022 Session: 2022/02 Decision no: 03).

It was planned to compare the efficacy of these drugs with changes in inflammatory markers and Pemphigus Disease Area Index (PDAI) in different groups. Additionally,

Figure 1. Flowchart of materials and methods. Abbreviations. CRP: C-reactive protein; LMR: lymphocyte-to-monocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PDAI: pemphigus disease area index; PLR: platelet-to-lymphocyte ratio; PLT: platelet.

the duration of patients staying in remission from the time they entered their first remission was recorded according to the remission criteria determined by the International Pemphigus Committee [15]. We diagnosed all of our patients based on the results of the direct immunofluorescence method applied by the pathology department on the biopsies we took from our patients, in addition to the clinical findings. We use the guideline by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV) for the management and treatment of pemphigus patients in our clinic [16].

The analyzes were evaluated in IBM BM SPSS (Statistical Package for Social Sciences; SPSS Inc.) Statistics 22, statistic software. In the study, descriptive data are shown with n and % values when using categorical data, while they are shown with mean ± standard deviation (Mean±SD) values when using continuous data. The suitability of continuous variables for normal distribution was evaluated with the Kolmogorov-Smirnov test. The Mann Whitney U test was applied to compare paired groups. Friedman analysis was applied to compare the measurement parameters over time. In the analyses the level of statistical significance was accepted as P less than 0.05.

Results

Seventy-six patients with pemphigus with an average age of 49.59±16.03 (min=18-max=99) were included in the study. 34 (44.7%) of the patients are male and 42 (55.3%) are female.

It was observed that 45 (59.2%) of the patients received intravenous immunoglobulin (IVIG), systemic steroid and azathioprine treatment, and 31 (40.8%) received azathioprine and systemic steroid treatment without IVIG. In all patients, the value of neutrophil count at 6 months was found to be significantly decreased (P = 0.039) compared to the baseline value. Additionally, neutrophil counts showed a significant positive correlation (baseline P = 0.037; 6th month P = 0.030) with simultaneously measured PDAI scores at the beginning of treatment and at 6 months of treatment. There was a significant decrease (P = 0.049) in platelet values at 6 months from baseline in all patients, but there was no significant correlation between platelet values and PDAI at any time. In all patients, both NLR and PLR values were found to decrease significantly in the third month of treatment (P = 0.019 for NLR; P = 0.014 for PLR) compared to the baseline value, and also showed a significant positive correlation with PDAI at 3 and 6 months. LMR values in all patients showed a negative and significant correlation with PDAI scores at 3 months and 6 months (3 months r = -0.318 P = 0.005; 6 months r = -0.353 P = 0.002). MPV and CRP values in all patients showed a significant positive correlation with PDAI (P = 0.027; P = 0.005, respectively). There was no significant change in sedimentation at any time of treatment and no correlation with PDAI was found. The change in PDAI did not differ significantly in the group of patients who received IVIG compared to the group of patients who did not receive IVIG. Furthermore, when the 6-month change in inflammatory markers was examined in the treatment groups, no significant differences were found between the two groups in the change of any parameter other than LMR (P > 0.05). LMR change was found to be significantly higher in the group that received IVIG than in the group that did not. While the mean 6-month LMR change in the IVIG group was 0.54 in the positive direction, the mean LMR change in the group that did not receive IVIG was 0.51 in the negative direction, and these findings were statistically significant (P = 0.002). Taking into account the duration of the first remission after treatment, the duration of the first remission in the group receiving IVIG was found to be significantly higher in the IVIG group (30.95±20.17 months) than in the group that did not receive IVIG (11.87±10.53 months) (P < 0.001). LMR values measured at all times in IVIG patients were found to be significantly positively correlated with the duration of the first remission of the disease (baseline P = 0.007; 3rd month p=0.005; 6th month pP 0.02).

A significant decrease in neutrophil (p=0.039) and PLT (p=0.049) values was observed between the baseline and the 6th month. In all patients, there was a significant decrease in the lymphocyte values in the sixth month compared to the values of the third month (P = 0.029). There was a significant decrease in NLR (P = 0.019) and PLR (P = 0.014) in all patients at the third month. There was a significant decrease in the PDAI value between all times (Table 1).

When the initial parameters were examined, a significant positive correlation was observed between PDAI and neutrophils. When the 3rd month parameters are examined, there is a positive relationship between 3rd month PDAI and NLR and PLR; a significant negative correlation was observed between PDAI and lymphocyte and LMR. When

Table 1. Evaluation of parameters according to time.

	Beginning Mean±SD	3rd month Mean±SD	6th month Mean±SD	P
Neutrophil	6.81±3.08[a]	5.92±2.58[a.b]	5.84±2.66[b]	0.039
Lymphocyte	2.03±1.00[a.b]	2.22±1.01[a]	1.97±.89[b]	0.029
PLT	306.42±111.05[a]	296.79±108.11[a.b]	275.96±106.26[b]	0.049
MPV	9.71±1.65	9.90±1.21	10.06±1.49	0.204
CRP	11.78±23.91	9.14±14.51	6.02±4.72	0.083
NLR	4.51±4.53[a]	3.30±2.62[b]	3.54±2.31[a.b]	0.019
LMR	3.66±1.70	3.99±1.79	3.77±1.51	0.196
PLR	184.03±121.34[a]	161.94±103.86[b]	162.06±83.28[a.b]	0.014
PDAI	13.01±11.91[a]	7.74±8.33[b]	7.07±9.37[b]	<0.001
Sedimantation	20.26±16.38	22.29±17.98	19.83±16.61	0.370

Friedman analysis was applied. [a.b.c]. The groups from which the statistical significance found in the analysis originates. Abbreviations. CRP: C-reactive protein; LMR: lymphocyte-to-monocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PDAI: pemphigus disease area index; PLR: platelet-to-lymphocyte ratio; PLT: platelet; SD: standart deviation.

Table 2. Correlation of PDAI values with other parameters over time.

	PDAI at the beginning		PDAI at 3 months		PDAI at 6 months	
	r	P	r	P	r	P
Neutrophil	.237	.039	.142	.222	.249	.030
Lymphocyte	-.110	.346	-.238	.039	-.226	.049
Monocyte	-.016	.891	.023	.841	.152	.189
PLT	-.026	.822	.072	.538	-.004	.975
MPV	.002	.989	.148	.203	.254	.027
CRP	-.082	.482	.195	.091	.322	.005
Sedimantation	.001	.990	.109	.350	.089	.445
NLR	.213	.065	.282	.014	.386	.001
LMR	-.064	.582	-.318	.005	-.353	.002
PLR	.073	.531	.240	.037	.236	.041

Abbreviations. CRP: C-reactive protein; LMR: lymphocyte-to-monocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PDAI: pemphigus disease area index; PLR: platelet-to-lymphocyte ratio; PLT: platelet.

Table 3. Comparison of changes in parameters according to treatment status.

	Receiving IVIG Mean±SD	Not receiving IVIG Mean±SD	P
Duration of remission	30.95±20.17	11.87±10.53	<0.001
Change of MPV value	.50±1.97	.15±1.30	0.330
Change of CRP value	5.02±18.59	6.84±28.61	0.232
Change of sedimantation	-.60±16.69	1.94±19.32	0.582
Change of NLR	1.50±5.55	.22±3.74	0.234
Change of LMR	.54±1.38	-.51±1.49	0.002
Change of PLR	31.76±109.30	7.75±102.87	0.456
Change of PDAI	6.62±7.13	4.97±6.03	0.186

*Mann Whitney U analysis was applied. Abbreviations. CRP: C-reactive protein; IVIG: Intravenous immunoglobulin; LMR: lymphocyte-to-monocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PDAI: pemphigus disease area index; PLR: platelet-to-lymphocyte ratio; PLT: platelet; SD: standart deviation.

the parameters of the 6th month were examined, there was a positive correlation between the PDAI of the 6th month and neutrophils, MPV, CRP, NLR and PLR; A significant negative correlation was observed between PDAI and lymphocytes and LMR (Table 2).

The mean follow-up period of the patients was found to be 57 months (min = 18, max 123). The duration of remission in the IVIG-treated group was significantly longer than the duration of the group not receiving IVIG ($P < 0.001$). The change in LMR in the group that received IVIG was significantly higher than the change in the group that did not receive IVIG ($P = 0.002$). There was no significant difference between those who received IVIG and those who did not ($P > 0.05$) in terms of changes in other parameters (Table 3).

A significant positive correlation was observed between the duration of remission and the LMR value at baseline. 3rd and 6th months in patients receiving IVIG (Table 4).

Table 4. Correlation of the duration of remission and the LMR value in patients receiving IVIG.

	Duration of remission	
	r	P
LMR at the beginning	0.398	0.007
LMR at 3 months	0.414	0.005
LMR at 6 months	0.350	0.020
Change of LMR	-0.077	0.617

Abbreviations. LMR: lymphocyte-to-monocyte ratio

Conclusions

Currently, there is no biomarker that shows the efficacy of pemphigus treatment and the duration of disease remission. We think that neutrophil, platelet, NLR and PLR values can be used to monitor the response to treatment in pemphigus,

since they show a significant decrease with treatment and are significantly positively correlated with PDAI, which indicates the severity of the disease. LMR values were indicators of a poor prognosis. We found that the duration of remission was longer in the group receiving IVIG, and although there was no difference between the treatments in terms of disease recovery, it should be noted that IVIG treatment prolonged the duration of remission.

Neutrophils have also been studied in dermatological diseases. Park et al reported that neutrophil counts were positively correlated with disease severity in bullous pemphigoid patients [17]. Ameglio et al reported that there was a significant correlation between antibody titers and the number of lesions in patients with PV and the number of neutrophils in peripheral blood [18]. In our study, similar to the studies above, neutrophil count and disease severity were positively correlated, and although all patients received systemic steroid treatment, which is known to increase the number of neutrophils, there was a significant decrease in the number of neutrophils in the sixth month. We thought that the change in neutrophil values in PV patients could be used in disease treatment and follow-up.

There are no studies in the literature on the role of platelet counts in pemphigus disease. From this perspective, our work has gained importance. In our study, platelet counts decreased significantly at 6 months compared to baseline. However, it did not correlate significantly with PDAI at any time point. Consequently, we think platelet count may be a parameter that can be measured at the beginning and sixth month of treatment to evaluate the response to treatment in pemphigus, but more studies are needed to investigate the role of platelets in the follow-up of the severity and treatment of pemphigus disease.

The role of lymphocytes in pemphigus has been investigated in various studies. When lesional biopsies in pemphigus were examined, a large number of lymphocytes were detected in the infiltrates of the lesions, and it was suggested that they played an important role in the pathogenesis of pemphigus [19]. El-Naby et al found that the number of T lymphocytes in the lesional infiltrate was correlated with the severity of the disease in 40 PV patients [20]. In a study conducted by Kowalska-Kępczyńska et al, it was determined that the lymphocyte count of 32 patients with pemphigus was correlated with the PDAI score [21]. However, no studies were found in the literature on the use of the absolute lymphocyte value in peripheral blood, which we evaluated in our study, in pemphigus disease. In our study, the absolute lymphocyte value measured in peripheral blood decreased in the sixth month. Furthermore, a significant negative correlation was found between the absolute lymphocyte value measured in peripheral blood at 3 and 6 months and the PDAI values measured at the same time. In this regard, we think that the number of lymphocytes measured in peripheral blood can be used in pemphigus diseases after the beginning of treatment, both in estimating the severity of the disease and in the follow-up of the treatment.

NLR levels, obtained by dividing the number of neutrophils measured in peripheral blood by the number of lymphocytes, have been investigated for use in the follow-up of many different diseases such as malignant, inflammatory and psychiatric diseases [22-28]. NLR was also investigated in dermatological diseases such as bullous pemphigoid [29], psoriasis [30] and lichen planus, and significantly higher values were found in the patient group compared to healthy controls [31]. In the study by Ucmak et al, it was determined that the value of NLR was higher in patients with PV than in healthy controls, but was not correlated with the severity of the disease [32]. In the study by Lyakhovitsky et al, a significant positive correlation was observed between disease activity and the value of NLR in pemphigus. NLR was found to be high at diagnosis, showed a significant decrease in remission, and increased again in relapse [33]. In our study, consistent with the study by Lyakhovitsky et al, it was found that the NLR value showed a significant difference ($P = 0.019$) and decreased significantly in the third month of treatment compared to the beginning of treatment, and there was also a significant positive correlation with PDAI, which indicates disease activity, at 3 and 6 months (3 months $P = 0.014$; 6^{th} month $P = 0.001$). These findings demonstrate the potential utility of NLR to monitor treatment response early and predict disease severity at follow-up.

PLR, obtained by dividing the number of platelets measured in peripheral blood by the number of lymphocytes, is a marker that reveals changes in platelet and lymphocyte numbers due to acute inflammatory and prothrombotic conditions [34]. In the study by Hayta et al, the PLR value was found in pemphigus patients to be higher than in healthy controls, but no relationship was found between the PLR value and the course of the disease [35]. On the contrary, in the study conducted by Lyakhovitsky et al, it was revealed that there was a significant decrease in PLR in remission compared to baseline [33]. In our study, a significant decrease in PLR values was observed in the third month, consistent with the study by Lyakhovitsky et al Additionally, a significant positive correlation was detected between the PDAI score and the PLR value at 3 and 6 months. In these respects, it can be said that PLR and NLR show similar features in our study, consistent with the study by Lyakhovitsky et al. Therefore, both the PLR and NLR values may play a role in monitoring the response to treatment in pemphigus disease in the early stages and predicting the severity of the disease during follow-up.

LMR is a marker obtained by dividing the number of lymphocytes in peripheral blood by the number of monocytes. Low LMR values have been thought to be an indicator

of a poor prognosis in several types of tumor [36-38]. In the study by Sirin et al with patients with psoriasis vulgaris, it was found that LMR levels did not differ significantly between healthy controls and the group of patients, but LMR was negatively correlated with the psoriasis area severity index (PASI), which expresses the severity of the disease in psoriasis [39]. In the literature, no study investigating the relationship between pemphigus disease and LMR was found. In our study, LMR values showed a significant negative correlation with PDAI scores at 3 and 6 months. In this case, it can be thought that LMR values may be an indicator of a poor prognosis for the disease. Again, we think that LMR values can be used to predict the severity of the disease in the third and sixth months of treatment in Pemphigus. Another issue that draws attention in our study is a significant difference in LMR was observed between the treatment groups. The LMR change in the group receiving IVIG was significantly higher than the LMR change in the group not receiving IVIG. To investigate whether the significant difference in LMR change in those receiving IVIG compared to those not receiving IVIG was related to the difference in the duration of remission between treatment groups, the duration of remission in the group receiving IVIG was found to be significantly higher than the duration in the group not receiving IVIG. In patients receiving IVIG, a significant positive correlation was observed between the duration of remission and the LMR values measured at baseline, 3 months and 6 months. We propose that LMR levels can be used to predict the length of time the disease remains in remission.

In our study, no significant differences were found in changes in inflammatory markers and disease severity in the group receiving IVIG, except for the LMR value. In our study, the mean follow-up period of the patients was determined to be 57 months (min = 18, max 123). According to the consensus determined by the International Pemphigus Committee, the criteria for complete remission under minimal treatment or without treatment were taken into account, and when the duration of the first remission after treatment was considered, the duration of remission in the group receiving IVIG was found to be significantly longer. In the study by Svecova et al, 10 PV patients receiving IVIG were followed for 12 months, and long remission periods were observed and a significant decrease in PDAI was observed [40]. More studies are needed to investigate the duration of remission of treatments in pemphigus.

Pemphigus is a serious disease that can lead to mortality. A treatment modality that provides complete remission is not yet available. The existence of markers that can be used in daily practice, which can evaluate the effectiveness of existing treatments and provide guidance for remission periods, will facilitate the follow-up and treatment of the disease for the physician.

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