Evaluation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume in patients with pemphigus vulgaris

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Background: Pemphigus vulgaris (PV) is a rare autoimmune disease characterized by the development of flaccid blisters on the skin and mucous membranes. Detection of anti-desmoglein (Dsg) 1 and anti-Dsg3 antibodies are frequently used for diagnosing the disease and evaluating disease activity. Recently, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) were introduced as new biomarkers indicating inflammation in autoimmune and autoinflammatory diseases. We aimed to evaluate the possible associations of NLP, PLR, and MPV with pemphigus disease severity and anti-Dsg1/3 levels.

Methods: Thirty-three newly diagnosed cases of PV and 33 age and sex-matched controls were included in this study. A complete blood count (CBC) was obtained from the participants to evaluate NLP, PLR, and MPV. Serological anti-Dsg1/3 and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) were assessed in patients based on ELISA assay and clinical examination, respectively.

Results: The median (interquartile range) NLR and PLR values in patients were 2.50 (1.94–6.59) and 90.30 (71.60–196.80), respectively, compared with 1.69 (1.45–2.30) and 56.00 (50.00–85.00) in controls. The NLR and PLR were significantly higher in patients than in controls ($P < 0.001$ for both). However, no significant difference regarding MPV levels was detected. Neither the ABSIS nor the anti-Dsg1/3 levels correlated with the studied inflammatory markers.

Conclusion: Our study revealed that NLR and PLR are elevated in patients with PV but do not correlate with disease activity (evaluated by the ABSIS) or anti-Dsg1/3 levels. These laboratory parameters can be considered inflammatory markers of PV but cannot predict the disease activity.

Keywords: mean platelet volume, neutrophil-to-lymphocyte ratio, pemphigus vulgaris, platelet-to-lymphocyte ratio

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INTRODUCTION

Pemphigus vulgaris (PV) is a rare and potentially fatal autoimmune disease characterized by blistering and painful erosive lesions on the mucous membranes or skin [1,2]. Autoantibodies are mainly directed against desmoglein (Dsg) 1 and Dsg3 and are the key factors

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in the pathogenesis of PV, leading to acantholysis and intraepidermal blister formation [1,2]. Blister formation can be extensive and even fatal if left untreated. Thus, prompt initiation of immunosuppressive and maintenance therapies is mandatory. Corticosteroids represent the first line of treatment, though rituximab, a monoclonal antibody directed against CD20+ B cells, has also been approved for treating moderate-to-severe PV [2,3]. However, the required duration of treatment for each patient is not clear. Therefore, planning an accurate strategy with an assessment of immunologic remission in a proper clinical setting is required [4].

The level of autoantibodies appears to be an important marker of immunologic remission. Anti-Dsg1/3 antibodies can assess the inflammatory status in PV, reflect the disease activity, and even predict the prognosis [5-7]. However, these serological tests are costly and not always available. Therefore, searching for other helpful markers that indicate PV characteristics is valuable.

Recently, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) have been introduced as novel biomarkers of inflammation [8-10]. Elevated levels of these hematological markers are associated with disease severity in various autoimmune diseases such as systemic lupus erythematosus (SLE) [11], rheumatoid arthritis (RA) [12], and psoriasis [13]. As these parameters are easily obtained from a routine hematology test and can be assessed inexpensively and rapidly, we aimed to evaluate their possible associations with PV characteristics, such as disease severity and serological autoantibody levels.

METHODS

Participants

From September 2018 to October 2019, 33 newly diagnosed PV patients were included in this cross-sectional study at Shohada-e Tajrish and Loghman Hakim hospitals (Tehran, Iran), with 33 age and sex-matched healthy subjects as controls. The patients were diagnosed based on clinical examination, histopathology, direct immunofluorescence showing intraepithelial immunoglobin deposition, and detectable levels of autoantibodies against Dsg1 or Dsg3. All participants were > 18 years of age and newly diagnosed cases who had not taken prednisolone or other immunosuppressive drugs. Exclusion criteria included a history of other chronic inflammatory diseases such as cardiovascular, hematologic, chronic liver or kidney diseases, and autoimmune or neoplastic disorders.

Ethical considerations

The study protocol was approved by the Shahid Beheshti University of Medical Sciences Ethics Committee (IR.SBMU.SRC.REC.1397.011). All participants signed an informed consent form.

Clinical and laboratory assessments

Demographic, clinical, and laboratory data were collected from patients and controls. Age, sex, type of pemphigus involvement, time of diagnosis, and severity of the disease based on the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) were recorded. This score is composed of cutaneous and oral scores and ranges from 0 to 206 [14].

For each patient, a complete blood count (CBC) was obtained, which included the mean platelet volume (MPV) and counts of white blood cells (WBC), neutrophils, lymphocytes, and platelets. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and PLR was obtained by dividing the platelet count by the lymphocyte count. Anti-Dsg3 and anti-Dsg1 levels were measured using commercial enzyme-linked immunosorbent assays (ELISA) for all the patients to confirm the diagnosis.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range), and categorical variables as numbers and percentages. To check the data distribution, the Kolmogorov-Smirnov test was used. For continuous variables, the difference between groups was determined by the student t-test or Mann-Whitney U-test for variables with or without normal distributions, respectively. The categorical variables were compared using the x^2 test. Spearman's correlation test evaluated associations between laboratory findings and ABSIS. All statistical analyses were performed using SPSS version 24 (SPSS, Chicago, IL, USA), and a two-sided P-value below 0.05 was considered significant.

RESULTS

A total of 33 new cases of PV and 33 age and

sex-matched healthy controls completed this study. The general characteristics of the study participants are described in Table 1.

The median (interquartile range) NLR and PLR values in patients were 2.50 (1.94–6.59) and 90.30 (71.60–196.80), respectively, compared with 1.69 (1.45–2.30) and 56.00 (50.00–85.00) in controls. The NLR and PLR were significantly higher in patients than in controls ($P < 0.001$ for both). However, the two groups had no significant difference in MPV ($P = 0.89$) (Table 2). There was no correlation between either disease severity (ABSIS) or anti-Dsg1/3 levels and the studied hematological markers (NLR, PLR, and MPV). As expected, the anti-Dsg1 and anti-Dsg3 levels were positively correlated with disease severity (ABSIS) (r = 0.43, $P = 0.01$; and r = 0.33, $P = 0.05$, respectively).

DISCUSSION

The present study is the first prospective study evaluating the NLR and PLR in patients with pemphigus vulgaris (PV) that also focused on assessing the relationship of these factors with anti-Dsgs levels and disease severity. Our findings showed that NLR and PLR were higher in PV patients compared with the control group, though these markers did not correlate with the anti-Dsg1/3 levels or ABSIS scores.

Several studies have linked elevated NLR and PLR values with chronic inflammatory diseases and malignancies [8,15]. Also, these new inflammatory markers are useful prognostic factors and guide patients' follow-up in some diseases. In a study of patients with breast cancer, Ozyalvacli *et al.* showed that NLR was higher when compared with patients with benign proliferative breast disease as the control group [16]. Several meta-analyses have shown an association between a high NLR and worse long-term outcomes after treatment of various types of cancers [8]. In a cohort study of 437 women with breast cancer, Azab *et al.* showed that a high pretreatment NLR was a significant risk factor for increased mortality, regardless of the chemotherapy

Table 1. Baseline characteristics of patients with pemphigus vulgaris (PV) and healthy controls

Characteristic	PV patients (n = 33)	Healthy controls (n = 33)	*P*-value
Gender			
Female	17 (52%)	15 (45%)	0.62
Male	16 (48%)	18 (55%)	
Age, years			
Mean ± SD	44.88 ± 9.81	42.21 ± 9.16	0.73
Median (range)	46 (21–60)	44 (22–56)	
Type of pemphigus involvement			
Mucosal	7 (21%)		
Cutaneous	5 (15%)		
Mucocutaneous	21 (64%)		
Time to diagnosis, months Median (range); (IQR)	2.00 (0.5–5); (1–2.5)		
ABSIS	38.66 ± 26.66		
Anti-Dsg1/3 Median (range); (IQR)			
Anti-Dsg1	81.80 (70-1900); (15.55-170.70)		
Anti-Dsg3	560 (8-3740); (95.65-1275.00)		

Abbreviations: ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; IQR, interquartile range (25–75th percentiles).

Table 2. Laboratory findings of patients with pemphigus vulgaris (PV) and healthy controls

Parameters	PV patients (n = 33)	Healthy controls (n = 33)	*P*-value
	Median (range); (IQR)	Median (range); (IQR)	
NLR	2.50 (1.50-15.60); (1.94-6.59)	1.69 (0.90-4.10); (1.45-2.30)	< 0.001
PLR	90.30 (38.70-427.40); (71.60-196.80)	56.00 (38.60-139.00); (50.00-85.00)	< 0.001
MPV	8.60 (6.30-9.90); (7.98-8.95)	8.60 (6.80-10.30); (7.80-9.35)	0.89

Abbreviations: IQR, interquartile range (25-75th percentiles); MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

regimen [17]. In another study of patients with gastric cancer, Lee *et al.* showed that NLR and PLR were independent prognostic factors considering the overall survival of the patients [18].

Additional information on the diagnostic and predictive value of blood cell ratios can be derived from autoimmune disease cohorts [15]. In a meta-analysis including 1246 SLE patients and 976 healthy controls, NLR and PLR were significantly higher in the SLE patients, and higher levels of PLR and NLR were found to reflect lupus activity [19]. In another study involving 154 SLE patients and 151 healthy controls, both PLR and NLR values were again higher in the patients [11]. In the same study, patients with nephritis had higher NLR and PLR levels than those without nephritis. However, multiple regression analysis revealed that only a high NLR, not PLR, was predictive of lupus nephritis [11]. An analysis of the blood cell ratio of patients with psoriasis and psoriatic arthritis also demonstrated that NLR and PLR were significantly higher in patients with psoriasis but were unrelated to the disease's severity. Nevertheless, both NLR and PLR were strong predictors for the presence of arthritis among psoriasis patients [20,21].

To our knowledge, only one study highlights the role of NLR and PLR in PV patients. Hayta *et al.* reported that the NLR and PLR of PV patients were higher than controls but were unrelated to the disease severity. Their results are in agreement with our findings. Hayta *et al.* also showed that the MPV in patients with PV decreased in remission and increased with relapse. They concluded that the MPV index can be used as a marker of relapse in patients with PV [22]. Current literature data suggest that MPV can be used as a new marker of inflammation and provides information about the course and prognosis of some inflammatory and neoplastic conditions; however, this is still controversial [23]. Yazici *et al.* showed that the MPV is significantly higher in patients with rheumatoid arthritis (RA) and is correlated with inflammatory markers (ESR and CRP) and also disease activity (PAS-28 score in RA patients) [24]. Nevertheless, Sahin *et al.* showed that MPV inversely correlates with ESR, CRP, and DAS-28 scores in RA patients [25]. In most neoplastic diseases, such as colorectal and gastric cancers, higher levels of MPV have been reported; in some other cancers, such as non-small cell lung cancer and cervical cancer, a decreased level may be found [23]. In the current study, we did not find any difference in MPV levels between patients and controls, and there was no relationship between this parameter and anti-Dsg levels or disease severity.

The present study was limited by its relatively small population due to the rareness of PV and the inclusion of only new cases who had not received any treatment, such as steroids, cytotoxic drugs, and rituximab, which have known effects on hematological parameters [26]. We did not explore the NLR or PLR changes in the remission phase of PV because of the influence of the aforementioned drugs on hematologic parameters.

CONCLUSION

Our study revealed that NLR and PLR are elevated in patients with PV but do not correlate with disease activity (evaluated by the ABSIS) or anti-Dsg1/3 levels. These laboratory parameters can be considered inflammatory markers of PV but cannot predict the disease activity.

Authors contributions

F.G. and N.M. designed and directed the project; Z.D. collected data; N.M. analyzed data and wrote the article. All authors discussed the results and commented on the manuscript.

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