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Can Neutrophil/Lymphocyte Ratio Be Used As a Marker in the Diagnosis of Bullous Pemphigoid?

Nötrofil/lenfosit Oranı Büllöz Pemfigoid Tanısında Bir Belirteç Olarak Kullanılabilir mi?

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Öz

Amaç: Büllöz pemfigoid (BP) dermo-epidermal bileşkede yer alan antijenlere karşı oluşan antikorların neden olduğu, sıklıkla ileri yaş döneminde izlenen büllöz bir dermatozdur. Otoantikorların tetiklediği inflamasyon sonucunda hasta serumlarında ve büllerde inflamatuar mediatörlerin artmış olduğu ve artan bu mediatörlerin hastalık şiddeti ile ilişkili olabileceği bildirilmiştir. Nötrofil lenfosit oranı (NLO); nötrofil sayısının lenfosit sayısına bölünmesi ile elde edilen; daha önce ürtiker, psoriazis, pemfigus vulgaris ve kutanöz vaskülit gibi inflamatuar hastalıklarda incelenmiş ve hastalıkla ilişkili bulunmuş bir parametredir. Bu çalışmada; sistemik inflamasyonun bir belirteci olan NLR'nin BP'li hastalarda kullanılabilecek bir belirteç olup olmadığı araştırılmada çalışılmıştır.
Hastalar ve Yöntem: Ocak 2013 – Aralık 2017 tarihleri arasında BP tanısı konulmuş hastaların medikal kayıtları incelendi. Dosyalarındaki laboratuar sonuçları değerlendirilerek; ortalama trombosit hacmi (MPV), nötrofil sayısı, lenfosit sayısı ve nötrofil sayısının lenfosit sayısına bölünerek hesaplandığı nötrofil lenfosit oranı kayıt edildi.
Bulgular: Çalışmaya, 26 BP'li hasta ve 25 kontrol grubu hasta dahil edildi. BP'li hastalarda nötrofil sayısının (P = 0,005) ve NLO'nın (P = 0,04) kontrol grubundan yüksek olduğu görüldü. Lenfosit sayısının BP'li hastalarda kontrol grubundan farklı olmadığı saptandı.
Sonuç: Çalışmamız; etyopatogenezinde inflamasyonun yer aldığı BP'li hastalarda bildiğimiz kadarı ile NLO'yi araştıran ilk çalışmadır. Sistemik inflamasyon için tam kan sayımı ile kolayca hesaplanabilecek bir parametre olan NLO'nın BP tanısında kullanılabilecek bir belirteç olabileceğini düşünmekteyiz.

Anahtar kelimeler: Büllöz pemfigoid, İnflamasyon, Nötrofil lenfosit oranı, Ortalama trombosit hacmi.

Abstract

Aim: Bullous pemphigoid (BP) is a bullous dermatosis frequently seen in advanced age that is caused by antibodies reacting to antigens in the dermoepidermal junction. It has been reported that as a result of autoantibody-induced inflammation, inflammatory mediators are increased in patient sera and bullae, and that these increased mediators might be related to disease severity. Neutrophil lymphocyte ratio (NLR) is determined by dividing the number of neutrophils by the number of lymphocytes; it is a parameter that has been previously studied in inflammatory diseases such as urticaria, psoriasis, pemphigus vulgaris and cutaneous vasculitis and has been associated with the disease. The present study investigated the utility of NLR, the marker of systemic inflammation, as a marker in patients with BP.
Patients and Methods: Medical records of patients diagnosed with BP between January 2013 and December 2017 were reviewed. By evaluating the laboratory results in their files, the mean platelet volume (MPV), neutrophil count, lymphocyte count, and neutrophil lymphocyte ratio calculated by dividing the number of neutrophils by the number of lymphocytes were recorded.
Results: The study included 26 patients with BP and 25 control patients. Neutrophil count (P = 0.005) and NLR (P = 0.04) were found to be higher in patients with BP compared with the control group. No difference was found in lymphocyte count and MPV between the groups.
Conclusion: To our knowledge, this is the first study to investigate NLR in patients with BP in the etiopathogenesis of which inflammation takes a part. We believe that NLR, a parameter that can be easily calculated by a whole blood count for systemic inflammation, can be a marker that can be used in the diagnosis of BP.

Keywords: Bullous pemphigoid, Inflammation, Neutrophil lymphocyte ratio, Mean platelet volume.

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune dermatosis characterized by subepidermal bullae, often seen with advanced age (1). This bullous disease is characterized by dermoepidermal dissociation caused by autoantibodies reacting to BP180 and BP230 antigens that are one of the hemidesmosomal proteins in the basal membrane (2). Dermatological examination reveals often transparent, stretched vesicles and bullae developing on normal-looking skin or itchy urticarial plaques (Fig 1) (3). Approximately 20% of cases present with non-specific skin findings

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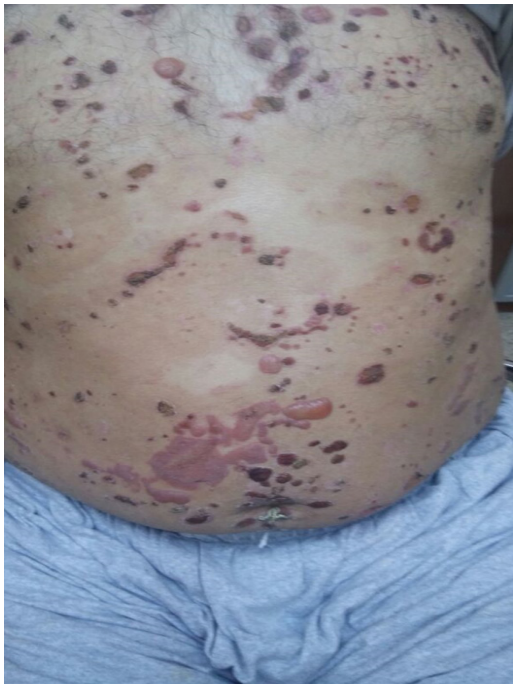

Figure 1. Stretched vesicles and bullae in trunk.

also called non-bullous BP that are not accompanied by vesicles and bullae (4). Involvement of oral mucosa and anogenital mucosa and ocular involvement are rare, and patients usually complain of itching (5). The resulting bullae are eroded with itching and trauma and heal without leaving a scar (5).

This autoimmune bullous dermatitis can occur together with cardiovascular disease, diabetes, pernicious anemia, neurological diseases, drug use, internal malignancies and other dermatoses (6, 7). The risk of mortality and morbidity of the disease depends on the age of the patient, disease severity and immunosuppressive therapies administered (5).

In the pathogenesis, mast cells, eosinophils, neutrophils and basophils accumulate in the dermoepidermal junction due to the inflammatory response initiated by autoantibodies (8). These inflammatory cells cause tissue damage by releasing histamine, cytokines, chemokines, and proteinases, and result in the migration of more inflammatory cells to the skin lesions (9). Inflammatory mediators were reported to be elevated in both serum and bullae of patients with BP, and this increase was reported to be associated with disease activity (8-10).

Neutrophil lymphocyte ratio (NLR) is a whole blood count test that is obtained by dividing the total number of neutrophils by the total lymphocyte count, and it has been reported that it can be an easily calculated parameter in indicating systemic inflammation (11, 12). It is known that NLR is increased in many diseases such as malignancies, diabetes and myocardial infarction (13-15). Although BP is a disease in which inflammation takes part in its etiology, to our knowledge, there is no previous study in the literature investigating the relationship of NLR with this disease.

There are studies showing that coagulation activation and thrombotic risk are high in patients with BP (16, 17). The mean platelet volume (MPV) is a widely used measure of platelet size, and it was also found to be directly related to the metabolic activities of platelets (18). MPV has previously been found to be elevated in many inflammatory skin diseases such as pemphigus vulgaris, urticaria and psoriasis (19, 20). It has been reported that MPV may increase due to bone marrow stimulation caused by inflammation and may be used as an inflammatory marker (20). Previously, MPV was found to be higher in patients with BP than in the control group, and it was not related to disease severity and not altered by treatment (21). In this study, NLR and MPV levels were evaluated together in patients with BP to investigate whether they are useful markers that can be used in the diagnosis of the disease.

PATIENTS AND METHODS

The study was conducted by recording the complete blood count parameters of patients diagnosed with BP in Necmettin Erbakan University Meram Medical Faculty Hospital Skin and Venereal Diseases Outpatient Clinic between January 2013 and December 2017, and age- and gender-matched control patients who were diagnosed with non-inflammatory dermatosis in dermatology outpatient clinic. Patients diagnosed with BP, who had a complete blood test in the pre-treatment period, and did not have systemic infection or malignancy were included in the study. Among complete blood count results in patient files (patients in the control group and patients diagnosed with BP), mean platelet volume, neutrophil count, lymphocyte count, and neutrophil lymphocyte ratio calculated by dividing the number of neutrophils by the number of lymphocytes were recorded. The study was approved by the Necmettin Erbakan University, Meram Faculty of Medicine local ethics committee (2018/1243).

Statistical analyzes were performed using the SPSS 15.0 program. In the comparison of blood

parameters of patients and controls, the independent samples t-test was used for normally distributed data and the Mann-Whitney U test was used for non-normally distributed data. Sensitivity and specificity values of these limits were calculated in the presence of significant limit values, and $P < 0.05$ was considered significant.

RESULTS

Twenty-six patients with BP and 25 control patients were included in the study. The mean age of 12 female patients with BP was 74 ± 12.78 years, while the mean age of 14 male patients was 69 ± 13.25 years. The mean age of 13 female patients in the control group was 73 ± 13 years, while the mean age of 12 male patients was 66 ± 13.5 years. There was no difference between the groups in terms of age and gender distribution.

Neutrophil counts were significantly higher in BP patients (7.47 ± 3.13) than the control group (5.36 ± 1.84) ($p = 0.005$). Lymphocyte counts were not different between the two groups. The mean NLR of patients with BP (4.81 ± 4.18) was significantly higher than that of the control group (2.88 ± 1.86) ($p = 0.04$). There was no difference in MPV between the groups (Table 1).

DISCUSSION

BP is a bullous dermatosis characterized by subepidermal dissociation developed by inflammatory response triggered by autoantibodies against BP180 and BP230 antigens in the dermoepidermal junction (22). Histopathological examination of these bullous lesions reveals inflammatory cell infiltration in the dermis and IgG and C3 deposition in the basal membrane (23).

Treatment options include anti-inflammatory agents, immunosuppressants, immunomodulators, and agents aimed at removing pathogenic autoantibodies and inflammatory mediators from the circulation, such as systemic and topical corticosteroids, tetracycline and nicotinamide, dapsone, azathiopurine, methotrexate, cyclophosphamide, plasmapheresis, intravenous immunoglobulin, rituximab and omalizumab (24).

In the etiopathogenesis of the disease, the immune system is activated after autoantibody formation, and especially neutrophils, macrophages, eosinophils and mast cells play an important role in the development of skin lesions (5, 25, 26). In BP, proinflammatory molecules (cytokines, chemokines, adhesion molecules, prostaglandins and proteases) such as IL-1, IL-6 IL-8, IL-18 and Tumor necrosis factor-α are found to be increased in the sera and bullous fluid of patients (10, 27, 28). It has been reported that the nucleoside-binding domain leucine-rich family proteins 3 (NLRP3) inflammasome that is known to be one of the key triggers of inflammation and myeloperoxidase activity that is an indicator of neutrophil activation are elevated in BP (29, 30).

There is a need for an easy to use, cheap, and easily accessible marker that can be used in BP, where elevated inflammation markers are observed. NLR, which is used as a marker of systemic inflammatory condition, is an easily detectable parameter reported to be elevated in psoriasis, atopic dermatitis, pemphigus vulgaris, Behçet's disease and cutaneous vasculitis (31-33).

In a previous study on patients with pemphigus vulgaris, it was found that NLR, neutrophil count, C-reactive protein and erythrocyte sedimentation rate were found to be higher than in the control group, and it was reported that NLR could be used as a disease marker in pemphigus patients (33). In our study, NLR was found to be higher in BP patients than in age- and gender-matched control patients, suggesting that NLR might be an easy-to-use marker in the diagnosis of BP.

Previous studies on patients with bullous pemphigoid revealed that the procoagulant pathways are more active and there is an increased risk of thrombotic events in patients with BP than in the control group (34). The MPV is a marker of platelet activation

Table 1. Age, gender, neutrophil, lymphocyte, NLR and MPV values of bullous pemphigoid patients and control group. (MPV: mean platelet volume, NLR: neutrophil lymphocyte ratio)

	Bullous Pemphigoid	Control	P value
Age	71±13	70±13.9	0,6
Gender	Female:12/Male:14	Female:13/Male:12	0,6
Neutrophil count /Ul	7.47±3.13	5.36±1.84	0.005*
Lymphocyte count /Ul	2.01±1.15	2.15±0.77	0.6
MPV /fL	9.33±1.68	8.67±1.69	0.16
NLR	4.81±4.18	2.88±1.86	0.04*

and it has been identified as a parameter that can be used in diseases such as myocardial infarction and pulmonary embolism (35, 36). It is indicated that it may be increased due to inflammation and may be used as a convenient marker of inflammation (37). MPV is a parameter that has been investigated in the practice of dermatology in psoriasis, urticaria, Behçet's disease, pemphigus vulgaris, and diseases including BP, and it yields conflicting results in some diseases (19, 21, 38-42). Although there are studies showing that MPV is increased in patients with psoriasis (19, 38), Işık et al. stated in their study that there was no difference in MPV levels between psoriasis patients and the control group (39).

In Behçet's disease, which is an inflammatory disease, there are different results on MPV. Alan et al. reported that there was no difference in MPV levels between patients with Behçet's disease and the control group (40), whereas Ekiz et al. found that MPV was higher in patients with Behçet's disease (41).

MPV was found to be low in patients with pemphigus vulgaris, one of the autoimmune bullous diseases (42), and high in patients with BP, but it was reported that there is no association with disease severity and the levels did not change with treatment (21). In our study, the reason for the non-significant MPV levels in BP may be due to the fact that comorbid diseases where procoagulant pathways are activated, such as anticoagulant drug use, atherosclerotic heart disease, diabetes, asthma, chronic pulmonary disease, peripheral or cerebral vascular diseases, which can often be accompanied by BP and which can also influence MPV, were not excluded from the study in both patient group and the control group (5).

In conclusion, NLR, rather than MPV which is an indicator of platelet activity, may be an auxiliary parameter that can be used in the diagnosis of BP. In our study, which was the first study in the literature to evaluate NLR in patients with BP, we think that NLR, one of the markers of inflammation, can also be used for disease follow-up and there is a need for large-scale studies on this subject with larger patient groups.

CRP, sedimentation rate and autoimmune bullous skin disorder intensity score were not evaluated in the study, and these absences is the limitations of the article.

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