Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2014;23:65-67
doi: 10.15570/actaapa.2014.16

Neutrophil to lymphocyte ratio in Behçet's disease as a marker of disease activity

Emine Nur Rifaioglu[1] ✉, Bilge Bülbül Şen[1], Özlem Ekiz[1], Asena Cigdem Dogramaci[1]

Abstract

Introduction: Behçet's disease (BD) is a rare autoimmune disease. The neutrophil to lymphocyte ratio (NLR) is used as a marker of inflammation in several diseases nowadays. This study investigated the NLR as an inflammation marker in BD.
Methods: Sixty-five patients diagnosed with BD and 100 healthy subjects were enrolled in this study retrospectively. The white blood cell (WBC), neutrophil, and lymphocyte counts were recorded, and the NLR was calculated from these parameters.
Results: The NLR and the CRP and WBC levels were higher in patients with BD than controls ($p < 0.001$, $p < 0.001$, and $p = 0.026$, respectively). In addition, the NLR was higher in patients with active BD than in those with inactive BD ($p = 0.033$).
Discussion: The results demonstrate that the NLR is higher in patients with active BD compared to controls and those with inactive BD.

Keywords: Behçet's disease, C-reactive protein, inflammation, neutrophil to lymphocyte ratio

Received: 13 August 2014 | **Returned for modification:** 28 September 2014 | **Accepted:** 2 October 2014

Introduction

Behçet's disease (BD) is a systemic autoimmune disease. Recurrent oral and genital mucosal ulcers, uveitis, and skin lesions are characteristic findings for BD (1). Histopathological features of BD lesions include perivascular lymphocytes, monocyte and neutrophil infiltration, and surrounding tissue necrosis (2). However the diagnosis of BD is made with clinical findings. The diagnostic criteria of the International Study Group for Behçet's Disease include the presence of oral ulceration plus any two of the following: genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test (3).

Recently, the neutrophil to lymphocyte ratio (NLR) has been widely used to determine the severity of inflammation in cardiovascular disease, malignancies, diabetes mellitus, hypertension, and autoinflammatory diseases (5–9). It is well known that neutrophil chemotaxis problems have been shown in BD (10). The NLR has not been previously studied in patients with BD. Therefore, the current study investigated the relation between the NLR and BD.

Methods

Patients

Sixty-five patients with BD and 100 healthy subjects that visited the outpatient dermatology clinic between May 2010 and June 2013 were enrolled in the study retrospectively. BD was diagnosed according to the criteria reported by the International Study Group for Behçet's Disease (3). The patients' ages, duration of the disease, family history, presence of oral ulcers, genital ulcers, erythema nodosum, acneiform eruptions, epididymitis, arthralgia and arthritis, and vascular, pulmonary, gastrointestinal, neurological, and ophthalmic involvement were recorded. The patients included in the active group had two of the following clinical findings: oral ulcers, genital ulceration, pathergy test positivity, active uveitis, papulopustular or pseudofollicular cutaneous lesions, neurological involvement, and arthritis (10).

Laboratory analyses

A complete blood count and CRP were obtained from the patients with BD and the controls. The complete blood count was measured with a laser-based flow cytometric impedance device (Mindray BC-6800, Nanshan, Shenzhen, China 2012), and the CRP was measured with a Beckman Coulter Immage nephelometry device. The white blood cell (WBC), neutrophil, and lymphocyte counts were also recorded, and the NLR was calculated from these parameters (4). The reference values for the CRP, WBCs, neutrophils, and lymphocytes in the hematology laboratory were 0–0.8 mg/dl, 4.6–10.2 × 103/μl, 2–6.9 × 103/μl, and 0.6–3.4 × 103/μl, respectively.

Statistical analysis

All statistical analyses were performed with SPSS version 19 software (IBM SPSS Statistics 19). Data were expressed as mean ± standard deviation. The Kolmogorov–Smirnov test was used to assess the normality of the groups. Comparisons between the groups with the nonparametric test were done using the Mann–Whitney U-test because the groups were not distributed normally. A chi square test was used for the categorical variable. A p value of 0.05 was considered significant.

Results

Thirty-eight (58.5%) men and 27 (41.5%) women (n = 65) with BD and 56 (56%) men and 44 (44%) women without BD (n = 100) were included in the study ($p > 0.05$). The mean age of the patients with BD and the controls was 37.7 ± 12.3 and 38.8 ± 11.3 years, respectively ($p = 0.57$). Thirty-eight (58.5%) patients were active and 27 (41.5%) patients were inactive with regard to clinical finding of BD at the time of admission. The mean duration of BD was 7.4 ± 1 years. The clinical features of the patients are given in Table 1. Nine patients had a family history of BD. The NLR of the patients with BD and controls were 2.5 ± 1.5 and 1.7 ± 0.8, respectively ($p < 0.001$). Moreover, the CRP and WBC levels were higher in the BD group than

[1]Department of Dermatology, Mustafa Kemal University School of Medicine, Hatay, Turkey. ✉ Corresponding author: eminenurrifai@gmail.com

controls (p < 0.001 and p = 0.026, respectively; Table 2) The NLR was higher in the active BD group than the inactive BD group (p = 0.033, Table 3). The NLR was also correlated with the levels of CRP and WBCs, both of which are major inflammation markers (p < 0.001 and p = 0.043, respectively).

Table 1 | **Clinical findings of BD.**

Clinical findings of BD*	Patients (n = 65)	(%)
Oral ulcer	65	100
Genital ulcer	58	89
Pathergy	14	22
Erythema nodosum	22	34
Acneiform lesion	22	34
Arthritis	9	14
Deep vein thrombosis	5	7.7
Thrombophlebitis	4	6.2
Ophthalmic involvement	11	17
Gastrointestinal involvement	4	0.6
Pulmonary involvement	1	0.2
Neurologic involvement	7	10.8
Epididymitis	1	0.2

* BD = Behçet's disease

Table 2 | **Demographic features of patients and controls and comparison of inflammation markers between control and BD groups (mean ± SD).**

Variables	BD* (n = 65)	Control (n = 100)	p
Age	37.7 ± 12.3	38.8 ± 11.3	0.57
Gender (M/F)	38/27	56/44	› 0.05
WBC† (10^3/µl)	8.68 ± 2.50	8.09 ± 6.34	0.026
CRP‡ (mg/dl)	1.25 ± 2.46	0.12 ± 0.84	‹ 0.001
NLRδ	2.55 ± 1.57	1.79 ± 0.89	‹ 0.001

* BD = Behçet's disease
† WBC = white blood cells
‡ CRP = C-reactive protein
δ NLR = neutrophil to lymphocyte ratio

Table 3 | **Demographic features of patients and controls and comparison of inflammation markers between control and BD groups (mean ± SD).**

Variables	Active BD (n = 38)	Inactive BD* (n = 27)	p
WBC† (103/µl)	9.43 ± 2.78	7.62 ± 1.54	0.006
CRP‡ (mg/dl)	1.89 ± 3.07	0.36 ± 0.21	‹ 0.001
NLRδ	2.92 ± 1.83	2.02 ± 0.90	0.033

* BD = Behçet's disease
† WBC = white blood cells
‡ CRP = C-reactive protein
δ NLR = neutrophil to lymphocyte ratio

Discussion

The main finding of our study relates to identification of the NLR as a novel non-invasive marker of disease activity in patients with BD. Our results demonstrate that the NLR is higher in patients with active BD compared to controls and BD patients in remission. High NLR levels in the sera of active BD patients, compared to inactive BD and controls, support the view that neutrophils play a role in the inflammatory cascade of BD and disease pathophysiology.

BD is an inflammatory disease, characterized by the activation of innate and adaptive immunity (interaction of T lymphocytes and activated neutrophils) on the basis of genetic (HLA B 51) and infectious factors (*Streptococcus sanguinis*). This inflammation results in tissue damage in the organs affected (11). Innate immune system dysfunction such as neutrophil hyperactivity is the major pathogenetic factor in BD (12). The role of neutrophils in the pathogenesis of BD has been investigated in many studies (3, 13). Neutrophils are directly involved in specific lesions of BD. BD lesions show venous and arterial infiltrates of neutrophils in histopathological analysis (14). Due to these characteristics, BD is considered a neutrophilic inflammatory disease.

BD could lead to varying degrees of dysfunction, depending on the severity of the disease and the affected organ (1). Although many cytokines and biomarkers have been studied as indicators of activation in BD, there is no method available to predict the severity and activity of BD (15, 16). In a study by Aygündüz et al., serum amyloid A protein and serum beta 2 microglobulin levels were associated with disease activity (15). Sari et al. reported that E-selectin levels were higher in an active BD group compared to controls and inactive BD (16). In another study, the serum endocan levels were higher in patients with active BD (17). Although these biomarkers are effective indicators for disease activity, the biomarkers were not routinely measured due to cost-effectiveness. The use of the NLR in autoimmune diseases was recently reported in some studies. Ahsen et al. reported that NLR levels were higher in patients with familial Mediterranean fever than in controls (7). Celikbilek et al. found a higher NLR in patients with ulcerative colitis compared to controls (8). In addition, in another study, the NLR was found to be higher in patients with psoriasis than controls (18). In this study, we found a higher NLR in patients with BD compared to controls. To our knowledge, this is the first study indicating a higher NLR in BD.

On the other hand, in several chronic inflammatory diseases the NLR has been associated with disease activity. In a study by Torun et al., the NLR indicated the disease activity of ulcerative colitis. It was found that the NLR predicted disease activity in patients with ulcerative colitis with 81.8% sensitivity and 80.5% specificity (19). Celikbilek et al. showed that the NLR was significantly higher in active ulcerative colitis patients compared to inactive patient and controls (8). In this study, NLR elevation was found in active patients with BD compared to inactive patients and controls. We suggest that the NLR may be used as a routine test for BD activity because the NLR is an inexpensive and readily available test.

C-reactive protein (CRP), a major component of inflammatory reaction, is a plasma protein secreted by the liver. CRP can rapidly increase in inflammation, infection, and tissue injury as an acute-phase marker (20). CRP has been shown to increase during the active period of neutrophilic autoimmune diseases such as pyoderma gangrenosum and ulcerative colitis (21, 22). It was previously well demonstrated that CRP was higher during active disease in BD (23). In this study, elevated CRP levels were found in the active BD group compared to the inactive group and controls. In many studies, the NLR–which is an easily calculated and inexpensive routine laboratory test–shows inflammation and active disease to be correlated with CRP (7, 8). In particular, it has been shown that NLR levels are higher in the active BD group than inactive BD group and control in correlation with CRP.

In summary, our study demonstrates that the NLR is statistically higher in active BD. Unlike many other noninvasive markers of BD, the NLR is inexpensive and readily available.

References

1. Pineton de Chambrun M, Wechsler B, Geri G, Cacoub P, Saadoun D. New insights into the pathogenesis of Behcet's disease. Autoimmun Rev. 2012;11:687-98.
2. Macey M, Hagi-Pavli E, Stewart J, Wallace GR, Stanford M, Shirlaw P, et al. Age, gender and disease-related platelet and neutrophil activation ex vivo in whole blood samples from patients with Behcet's disease. Rheumatology (Oxford). 2011;50:1849-59.
3. International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. Lancet. 1990;335:1078-80.
4. Neves FS, Carrasco S, Goldenstein-Schainberg C, Goncalves CR, de Mello SB. Neutrophil hyperchemotaxis in Behcet's disease: a possible role for monocytes orchestrating bacterial-induced innate immune responses. Clin Rheumatol. 2009;28:1403-10.
5. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11:55-9.
6. Ozturk ZA, Kuyumcu ME, Yesil Y, Savas E, Yıldız H, Kepekçi Y, et al. Is there a link between neutrophil-lymphocyte ratio and microvascular complications in geriatric diabetic patients? J Endocrinol Invest. 2013;36:593-9.
7. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88:218-30.
8. Ahsen A, Ulu MS, Yuksel S, Demir K, Uysal M, Erdogan M, et al. As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. Inflammation. 2013;36:1357-62.
9. Celikbilek M, Dogan S, Ozbakır O, Zararsız G, Kücük H, Gürsoy S, et al. Neutrophil-lymphocyte ratio as a predictor of disease severity in ulcerative colitis. J Clin Lab Anal. 2013;27:72-6.
10. Sarican T, Ayabakan H, Turkmen S, Kalaslioglu V, Baran F, Yenice N. Homocysteine: an activity marker in Behçet's disease? J Dermatol Sci. 2007;45:121-6.
11. Emmi G, Silvestri E, Squatrito D, D'Elios MM, Ciucciarelli L, Prisco D, et al. Behçet's syndrome pathophysiology and potential therapeutic targets. Intern Emerg Med. 2014;9:257-65.
12. Cho S, Kim J, Cho SB, Zheng Z, Choi MJ, Kim DY, et. al. Immunopathogenic characterization of cutaneous inflammation in Behçet's disease. J Eur Acad Dermatol Venereol. 2014;28:51-7.
13. Tuzun B, Tuzun Y, Yurdakul S, Hamuryudan V, Yazici H, Ozyazgan Y. Neutrophil chemotaxis in Behcet's syndrome. Ann Rheum Dis. 1999;58:658.
14. Kapsimali VD, Kanakis MA, Vaiopoulos GA, Kaklamanis PG. Etiopathogenesis of Behcet's disease with emphasis on the role of immunological aberrations. Clin Rheumatol. 2010;29:1211-16.
15. Aygunduz M, Bavbek N, Ozturk M, Kaftan O, Kosar A, Kirazli S. Serum beta 2-microglobulin reflects disease activity in Behcet's disease. Rheumatol Int. 2002;22:5-8.
16. Sari RA, Kiziltunc A, Taysi S, Akdemir S, Gundogdu M. Levels of soluble E-selectin in patients with active Behcet's disease. Clin Rheumatol. 2005;24:55-59.
17. Balta I, Balta S, Koryurek OM, Demirkol S, Mikhailidis DP, Celik T, et al. Serum endocan levels as a marker of disease activity in patients with Behçet disease. J Am Acad Dermatol. 2014;70:291-6.
18. Sen BB, Rifaioglu EN, Ekiz O, Inan MU, Sen T, Sen N. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. Cutan Ocul Toxicol. 2014;33:223-7.
19. Torun S, Tunc BD, Suvak B, Yildiz H, Tas A, Sayilir A, et al. Assessment of neutrophil-lymphocyte ratio in ulcerative colitis: a promising marker in predicting disease severity. Clin Res Hepatol Gastroenterol. 2012;36:491-7.
20. Ansar W, Ghosh S. C-reactive protein and the biology of disease. Immunol Res. 2013;56:131-42.
21. Rowe IF, Deans AC. Serum C-reactive protein measurement in pyoderma gangrenosum. Dermatologica. 1986;173:216-9.
22. Turner D, Mack DR, Hyams J, LeLeiko N, Otley A, Markowitz J, et al. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. J Crohns Colitis. 2011;5:423-9.
23. Coskun B, Saral Y, Gödekmerdan A, Erden I, Coskun N. Activation markers in Behçet's disease. Skinmed. 2005;4:282-6.