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Evaluating Complete Blood Count Parameters in Early-Stage Mycosis Fungoides Patients

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Abstract

Mycosis Fungoides (MF) is the most common form of primary Cutaneous T cell lymphoma. The disease courses with a slow progression, it progresses into plaque and tumor stage following patch stage. Complete blood cell count is the most frequently used blood test providing basic hematological counts. It is known that the rise in blood cells and the elevation of their rates are related to inflammation and increase in thrombotic risk. We aimed to evaluate the condition of inflammatory and thrombotic markers in early-stage MF patients by comparing complete blood counts and CRP measurements of early-stage MF patients to a healthy control group.

The research is a retrospective study. Between 2007 and 2017, 45 patients diagnosed with early stage MF in our clinic and 45 healthy individuals as a control group were included in the study. Complete blood count parameters and CRP values of the patient and control groups were recorded. In addition, NLR, LMR, PLR, ELR and ENR ratios were calculated. Statistically, $p < 0.05$ was considered significant.

Neutrophil ($p=0.001$), neutrophil-lymphocyte ratio (NLR) ($p=0.040$), platelet ($p=0.021$), platecrit ($p=0.026$), platelet distribution width (PDW) ($p=0.009$) and CRP ($p=0.026$) values were detected as significantly high in MF patients compared to the control group. No statistically significant difference was found between both groups in other parameters.

Neutrophil, NLR, and CRP markers may be guide the assessment of systemic inflammation in early-stage MF patients. Furthermore, platelet, platecrit and PDW values may be used for determining inflammation and thrombotic risk in MF patients. As a result, the complete blood count parameters may be used as simple, useful, and cost-effective biomarkers for determining the inflammation and thrombotic risk in cancer.

Keywords: Mycosis Fungoides, complete blood count parameters, biomarker.

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Introduction

T cell lymphomas of the skin is a rare group of Non-Hodgkin lymphomas. The most widespread type of T cell lymphomas of the skin is Mycosis Fungoides (MF). MF is an idiopathic skin lymphoma with a good prognosis. Its incidence is ~5.6/million annually. The disease begins at the skin. In the beginning, malign T lymphocytes (MF cells) with the hyperchromatic, irregular, cerebriform nucleus are localized within the skin. At the advanced stage, MF cells spread to lymph nodes and viscera or the disease may transform into a high-grade lymphoma type (erythrodermic MF, Sezary syndrome). Skin lesions develop primarily in areas not subject to sun and begin with erythematous, scaly, atrophic patch lesions. The disease courses with a slow progression, it progresses into plaque and tumor stage following patch stage. The diagnosis is based on the combination of histopathological and immunological data. TNMB system is used to stage the disease. Early-stage MF patients [stage IA (T1, N0,M0,B0/1), stage IB (T2,N0,M0,B0/1), stage IIA (T1/2,N1/2,M0,B0/1)] can be treated effectively using agents for skin (topical corticosteroid/ nitrogen/ mustard/ bexarotene, local radiotherapy and PUVA/ narrowband UVB). In case the skin treatments are ineffective or an advanced stage disease progresses, interferon-alpha, systemic bexarotene, photophoresis, total skin electron beam, cytotoxic chemotherapy, allogenic hematopoietic stem cell transplantation treatments may be used. Prognosis of MF depends on the stage of the disease, size and type of lesions, and the presence of extracutaneous disease (1-3).

Complete blood count (CBC) is the most frequently used blood test providing basic hematological counts. Many studies are showing that quantitative measurement and high rate of blood cells are related to inflammation and increase in thrombotic risk (4,5).

In this study, we aimed to evaluate the condition of inflammatory and thrombotic markers in early-stage MF patients by comparing CBC values and CRP measurements of early-stage MF patients to a healthy control group.

Materials and Methods

The study is a monocentric, retrospective study. The local ethics committee approved the study protocol considering the guidelines determined by the Helsinki Declaration. 45 patients of early-stage MF (27 males, 18 females) who was clinically and histopathologically diagnosed and whose treatment was not started in Hatay Mustafa Kemal University

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Faculty of Medicine Dermatological and Venereal Disease Clinic between 2007-2017 and 45 (27 males, 18 females) healthy individuals matched in terms of age and sex as a control group was involved in the study.

Patients under 18 years old, immunosuppressive patients, patients with an additional chronic disease and additional dermatological disease were not involved in the study.

Complete blood parameters of patient and control group; neutrophil, lymphocyte, monocyte, eosinophil, basophil, platelet counts, red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), platecrit (PCT) were recorded as an absolute value. Neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), eosinophil-lymphocyte ratio (ELR) and eosinophil-neutrophil ratio (ENR) were calculated. Furthermore, CRP values were recorded. CBC measurements were done using a complete blood count device (Mindray BC 6800-China). All recorded data were statistically compared. IBM SPSS Statistics 21.0 software was used in the statistical analysis of data. Pearson chi-square test was used to compare the relationship between categorical varieties, and the Student t-test was used to compare averages between groups. Statistically, $p<0.05$ was considered significant.

Results

Our study included 90 individuals, 45 (27 men, 18 women) with early stage MF and 45 (27 men, 18 women) healthy. The mean age of the control group and the patient group at the time of diagnosis was 44 ± 13 years. Patient and control groups were matched in terms of age and gender ($p = 1.000$).

When values of early stage MF patients and control group were compared; it was determined that neutrophil ($p=0.001$), platelet ($p=0.021$), PCT ($p=0.026$), NLR ($p=0.040$) and CRP ($p=0.026$) values of the patient group were significantly high compared to the control group. PDW value was low in the patient group compared to the control group, and there was a statistically significant difference ($p=0.009$). There was not a statistically significant difference between the groups ($p>0.05$) based on the comparison of lymphocyte, monocyte, eosinophil, basophil, RDW, MPV values, and LMR, PLR, ELR and ENR values (table 1).

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Table 1. Comparison of the complete blood count parameters of early-stage Mycosis Fungoides patients and the healthy individuals.

Parameters	Normal Range	MF patients group mean ± SD	Control group mean ± SD	p
Neutrophil (10^3/µl)	2.00-7.00	4.76 ± 1.24	3.90 ± 1.00	**0.001**
Lymphocyte (10^3/µl)	0.80-4.00	2.32 ± 0.57	2.27 ± 0.53	0.709
Monocyte (10^3/µl)	0.12-1.20	0.56 ± 0.18	0.51 ± 0.13	0.144
Eosinophil (10^3/µl)	0.02-0.50	0.23 ± 0.16	0.21 ± 0.15	0.508
Basophil (10^3/µl)	0.00-0.10	0.04 ± 0.04	0.05 ± 0.03	0.172
Platelet (10^3/µl)	100.00-300.00	270.93 ± 66.10	242.28 ± 47.96	**0.021**
RDW (%)	11.00-16.00	14.22 ± 1.72	14.24 ± 1.27	0.961
MPV (fl)	6.50-12.00	9.20 ± 1.46	9.06 ± 1.62	0.682
PCT (%)	0.11-0.28	0.24 ± 0.06	0.21 ± 0.05	**0.026**
PDW (%)	15.00-17.00	15.35 ± 2.61	16.66 ± 1.98	**0.009**
NLR		2.15 ± 0.71	1.83 ± 0.74	**0.040**
ELR		0.099 ± 0.062	0.093 ± 0.064	0.683
ENR		0.051 ± 0.038	0.056 ± 0.043	0.578
LMR		4.48 ± 1.50	4.70 ± 1.56	0.492
PLR		121.24 ± 36.98	113.10 ± 38.52	0.310
CRP		4.87 ± 4.47	3.15 ± 0.10	**0.026**

Abbreviations: MF, Mycosis Fungoides; RDW, red cell distribution width; MPV, mean platelet volume; PCT, Platecrit; PDW, platelet distribution width; NLR, neutrophil-lymphocyte ratio; ELR, eosinophil-lymphocyte ratio; ENR, eosinophil-neutrophil ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio.
Student -t Test were performed. $p < 0.05$ is defined statistically significant.
Note: P-values that are considered statistically significant are shown in boldface.

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Discussion

The complete blood count is the most frequently used routine blood test providing numerical measurements of the formed elements of blood. Variations in the numerical values and ratios of blood cells can be evaluated as biomarkers reflecting inflammation and an increase in thrombotic risk (4,5).

Studies are predicting that CBC parameters can be used both in determining the increase in inflammation and thrombotic risk and follow-up of the progression of diseases. Neutrophils, one of the formed elements of blood, are cells known to have an active role in inflammation. Lymphocytes, monocytes, eosinophils, and basophils are also among inflammation markers (5). Platelets are the cells involved in many pathophysiological processes such as blood coagulation, haemostasis, thrombosis, atherosclerosis, autoimmune and inflammatory diseases (6,7). Platelets be exposed to morphological and biochemical changes when they encounter physical and chemical stimuli. This condition is called as platelet activation. Platelets are transformed from disk shape to spherical shape when they are activated, and pseudopodium is formed. MPV and PDW are known as inflammation and platelet activation indices (6). PDW indicates the homogeneity of platelet sizes. Increased PDW shows anisocytosis, and this is related to the formation of pseudopodium (8). MPV indicates that platelets are active and platelet production. Increased MPV has been reported in vascular diseases such as pulmonary thromboembolism (7). One of the inflammation markers is RDW. An increase in RDW, which is a sign of chronic inflammation, shows erythrocyte membrane deformability, and that there are changes within erythropoiesis (9). CRP and the ratios of the absolute value of cells of blood are also inflammation markers. It has been reported that the increase in PLR and NLR is associated with venous thrombosis and coronary artery disease (10,11).

There are studies showing that NLR, LMR, PLR has prognostic value in hematological malignancies such as multiple myeloma, diffuse large B cell lymphoma, Hodgkin lymphoma and solid tumors (12-15). Mei et al. conducted a meta-analysis of 66 cohort studies with more than 14 cancer types, including 24536 individuals. They determined that pretreatment high NLR is related to poor prognosis in advanced cancer. They emphasized that large-scale prospective studies should be conducted for specific types of cancer (16).

In recent years, studies with conflicting results have been published on the prognostic value of NLR in early stage MF. There is no other study in the literature evaluating all CBC parameters and all ratios in MF, except for parameters such as NLR, PLR, MPV.

Beltran et al., reported that NLR can help determine survival prognosis in patients with T-cell lymphoma, and that NLR is an independent prognostic factor. They suggested that NLR≥ 4 had an independent association with worse overall survival ($p < 0.001$) (17).

Kaito et al., retrospectively analyzed the duration from the first step

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chemotherapy to the failure of treatment in 59 patients with peripheral T cell lymphoma. It was reported that high lactate dehydrogenase level, hypoalbuminemia, and high NLR (>4) were important prognostic factors in the multivariable analysis conducted for the duration which passed until the failure of treatment (18).

Cengiz et al., investigated the importance of NLR in MF patients. They retrospectively identified the stages of 119 patients and evaluated all data. They determined the NLR value as 2.07 ± 1.17 in the patient group and 1.76 ± 0.53 in the control group. They reported that the NLR value of 2.85 corresponds to the maximum combined sensitivity and specificity in the ROC curve. They grouped the patients accordingly. They reported that the NLR ratio of 2.85 or higher at the time of diagnosis was positively correlated with a high Beta-2 microglobulin level, advanced stage of the disease and accordingly disease progression. They revealed that the high NLR represents a poor prognostic factor for identifying high-risk MF patients for diagnosis of MF (19).

Eren et al. researched the relation between NLR and type of treatment (systemic PUVA and/or chemotherapy), duration of treatment, a progression of the stage, and duration of progression of the stage. They retrospectively examined the data of 117 patients who were followed up with a diagnosis of MF. They determined the cutoff score as 2 according to the median NLR level of 1.96. They reported that there was not a significant relationship between NLR and type of treatment, the time that passed until treatment, progression in the stage, and the time of progression in the stage in stage I and stage II early MF patients with NLR ≥ 2 and NLR <2 values (20).

Ozbagcivan retrospectively examined 67 patients diagnosed with early-stage MF and with at least 5 years follow-up and determined in her research that the disease migrated to advanced stages in 15 (22.4%) of patients. She reported that pre-treatment NLR and PLR has a significant relationship with the increase of disease progression in early-stage MF. She detected that involvement of ≥10% on the surface area, the existence of lymphopenia, and increased NLR (>2.60) and PLR (>138.3) was connected to poor prognosis, and NLR was an independent prognostic marker. She reported that MPV was not a prognostic marker for the progression of the disease. She reported that NLR and PLR would be an easy and cheap way to be used in order to determine high-risk patients in early stages in MF (21).

Uysal et al. retrospectively examined 112 patients diagnosed with early-stage MF. They recorded the stage of the disease, the initial laboratory tests, and response to the treatment. They evaluated the number of eosinophils, NLR, lactate dehydrogenase (LDH) and beta-2 microglobulin level, flow cytometry, and initial modified severity-weighted evaluation scale (mSWAT) score. They reported that beta-2 microglobulin was significantly high within all parameters in stage IA, IB, and IIA. Furthermore, they suggested that mSWAT score, beta-2 microglobulin, and LDH levels were high, and plaque-type lesions existed in patients

who were non-responsive to treatment. They reported that comprehensive screening tests would not be very significant, and mSWAT score, beta-2-microglobulin and LDH tests would be useful measurements for predicting the response to the treatment. They reported that the median NLR value was 1.98 (range 1,53-2,53), and NLR> 2 was observed in 55 patients (49%). They did not find any difference between staging groups in terms of NLR (p> 0.05). They reported that there was not any correlation between clinical response and NLR results. Furthermore, they reported that there was not any significant difference between levels of eosinophil and presence of eosinophil in terms of staging and clinical response (22).

Lindhal et al. performed a nationwide population-based cohort study to examine the risk of venous thromboembolism in 525 MF patients. They determined the 10-year VTE risk in patients with MF to be 3.4%. They reported that this risk was highest in the first 5 years after diagnosis (23).

The condition of inflammation markers and thrombocyte activation indices present in CBC parameters in early-stage MF patients in our study were evaluated. Similar to the studies within the literature, it was determined in our study that NLR value in early-stage MF patients was statistically significantly higher than the control group. It was considered that increased NLR levels in MF patients compared to healthy individuals may be related to inflammation due to cancer and may provide insight for progression. Furthermore, it was determined that neutrophil, which is the inflammation marker, CRP levels were significantly high in the patient group.

Besides, no significant difference was detected between patient and control group in terms of the ratio of eosinophil levels and eosinophil absolute value to the absolute values of other shaped elements of the blood (ELR, ENR). Conflicting results were obtained in our study in terms of MPV, PDW values, which are inflammation and thrombocyte activation markers, and which are referred to as thrombocyte activation indices. No significant difference was detected upon the comparison of the patient and control group in terms of MPV values. The number of platelets and PCT increased, but the PDW value was significantly reduced in the patient group. It was considered that the reason for obtaining conflicting results would be due to the lack of the number of individuals involved in our study. The limitations of our study are that the detailed stages, skin involvement percentages and disease progression records of early-stage MF patients (stage IA, IB and IIA) could not be reached and these data were not evaluated due to the retrospective study.

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Conclusion

Neutrophil, NLR, and CRP markers may be used in assessment of systemic inflammation in early-stage MF patients. Furthermore, platelet, PCT and PDW markers can be used for MF patients to predict the prothrombotic condition and to evaluate inflammation. However, comprehensive prospective research is required to evaluate such markers.

References

1. Larocca C, Kupper T. Mycosis Fungoides and Sézary Syndrome An Update. Hematol Oncol Clin North Am. 2019;33(1):103-120.
2. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/ Sézary syndrome - Update 2017. Eur J Cancer. 2017;77:57-74.
3. Engin B, Uzun A, Kutlubay Z, Tüzün Y. Mikozis Fungoides Güncel. Dermatoz. 2016;7(1):1-9.
4. Rögnvaldsson S, Lund SH, Hultcrantz M, et al. Markers for Increased Thrombotic Risk within the Complete Blood Count. Blood. 2016;128(22):1429.
5. Germolec DR, Shipkowski KA, Frawley RP, Evans E. Markers of Inflammation. Methods Mol Biol. 2018;1803:57-79.
6. Xu XR, Zhang D, Oswald BE, et al. Platelets are versatile cells: New discoveries in hemostasis, thrombosis, immune responses, tumor metastasis and beyond. Crit Rev Clin Lab Sci. 2016;53(6):409-430.
7. Ghaffari S, Parvizian N, Pourafkari L, et al. Prognostic value of platelet indices in patients with acute pulmonary thromboembolism. J Cardiovasc Thorac Res. 2020;12(1):56-62.
8. Vagdatli, E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia. 2010;14(1):28.
9. Lippi G, Targher G, Montagnana M, Salvagro GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133:628-632.
10. Kounis NG, Soufras GD, Tsigkas G, Hahalis G. White Blood Cell Counts, Leukocyte Ratios, and Eosinophils as Inflammatory Markers in Patients With Coronary Artery Disease. Clin Appl Thromb Hemost. 2015;21(2):139-143.
11. Artoni A, Abbattista M, Bucciarelli P, et al. Platelet to lymphocyte ratio and neutrophil to lymphocyte ratio as risk factors for venous thrombosis. Clin Appl Thromb Hemost. 2018;24:808-814.
12. Zeng Q, Liu Z, Li Q, Liu T. Prognostic value of neutrophil to lymphocyte ratio and clinicopathological characteristics for multiple myeloma: A meta-analysis. Medicine (Baltimore). 2018;97:e12678.

IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies (IJBCS)
2020; 9(1): 56-64 Celik E.

13. Stefaniuk P, Szymczyk A, Podhorecka M. The Neutrophil to Lymphocyte and Lymphocyte to Monocyte Ratios as New Prognostic Factors in Hematological Malignancies – A Narrative Review. Cancer Manag Res. 2020;12:2961-2977.
14. Marcheselli R, Bari A, Tadmor T, Marcheselli L, Cox MC, Pozzi S. Neutrophil-lymphocyte ratio at diagnosis is an independent prognostic factor in patients with nodular sclerosis Hodgkin lymphoma: results of a large multicenter study involving 990 patients. Hematol Oncol. 2017;35(4):561-566.
15. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23:1204-1212.
16. Mei Z, Shi L, Wang B, Du P, Wang Q, Yang W. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors:A systematic review and meta-analysis of 66 cohort studies. Cancer Treatment Reviews. 2017;58:1-13.
17. Beltran BE, Aguilar C, Quiñones P, et al. The neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with peripheral T-cell lymphoma, unspecified. Leuk Lymphoma. 2016;57:58-62.
18. Kaito S, Kanemasa Y, Sasaki Y, et al. A new prognostic score comprising lactate dehydrogenase, albumin and neutrophil to lymphocyte ratio to predict sensitivity to first-line chemotherapy in patients with peripheral T-cell lymphomas. Int J Hematol. 2018;107:451-459.
19. Cengiz FP, Emiroglu N, Ozkaya DB, Bahali AG, Su O, Onsun N. Prognostic Evaluation of Neutrophil/Lymphocyte Ratio in Patients with Mycosis Fungoides. Ann Clin Lab Sci. 2017;47:25-28.
20. Eren R, Nizam N, Doğu MH, Mercan S, Erdemir AV, Suyanı E. Evaluation of neutrophil-lymphocyte ratio in patients with early-stage mycosis fungoides. Ann Hematol. 2016;95:1853-1857.
21. Ozbagcivan O. Prognostic significance of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and mean platelet volume in the early stage mycosis fungoides. DEU Tıp Fakültesi Dergisi. 2019;33(2):149-157.
22. Uysal PI, Akdogan N, Falay M, Sahin B, Ozet G, Yalcın B. The Importance of Baseline Screening Investigations and Modified Severity Weighted Assessment Tool in Patients with Early Stage Mycosis Fungoides: A Four-year Retrospective Study. Turk J Dermatol. 2019;13:1-7.
23. Lindahl LM, Schmidt M, Farkas DK, Sørensen HT, Iversen L. Risk of venous thromboembolism in patients with mycosis fungoides and parapsoriasis: A Danish nationwide population-based cohort study. J Am Acad Dermatol. 2018;78(6):1077-1083.e4.