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ORIGINAL ARTICLE

Evaluation of Inflammatory Hematological Parameters in Cases of Glioblastoma, Primary Cerebral Lymphoma, and Metastasis Following Stereotactic Brain Biopsy

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Abstract

Introduction: Inflammation and immune reaction are influential both in the etiology and prognosis of many tumors. Inflammatory parameters that can be measured in blood, such as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio, have been found to be associated with the prognosis and course of the disease in many intra and extracranial tumors.

Methods: Between 2013-2021, lymphocyte, neutrophil, monocyte, and platelet values were measured in the preoperative blood tests of patients diagnosed histopathologically with glial tumors, metastasis, and primary cerebral lymphoma at our clinic through stereotactic biopsy. Ratios of neutrophil-lymphocyte, lymphocyte-monocyte, and platelet-lymphocyte were determined. The values identified in the three tumor groups were statistically compared.

Results: In all three tumor groups, no significant difference was observed in the values of neutrophils, monocytes, and platelets. In the metastasis group, lymphocyte values were significantly higher compared to glial tumor and lymphoma cases. No significant statistical difference was observed in the neutrophil-lymphocyte, lymphocyte-monocyte, and platelet-lymphocyte ratios among the three groups.

Discussion and Conclusion: According to the results of our study, preoperative hematological inflammation parameters do not have a diagnostic or distinguishing effect in glial tumors, metastases, and primary cerebral lymphomas.

Keywords: Glioma; Lymphocyte; Metastasis; Monocyte; Neutrophil; Platelet; Primary cerebral lymphoma.

Deep-seated, functionally important areas, or multiple intracranial lesions; or in patients with severe comorbidities, stereotactic brain biopsy emerges as a forefront method for diagnosing the lesion and starting treatment without delay[1]. Stereotactic brain biopsy is a minimally invasive method with low morbidity and mortality rates and is frequently used in neurosurgery practice due to advancements in oncological treatments[1,2]. In studies examining the pathological diagnoses of patients who underwent stereotactic brain biopsy, the rates are respectively glial malignancies 23.3-52.3%, metastases 1.7-16.2%, lymphomas 0.5-7%[2,3]. In the treatment of these diseases and in determining the prognosis, preoperative parameters specific to tumors are used, as well as general cancer-related biomarkers such as inflammation markers. The neutrophil-lymphocyte ratio (NLR) is a current indicator

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related to the inflammatory response and its elevation directly indicates a poor prognosis in cancer (colon, prostate, bladder, brain malignancies, etc.)[4]. The relationship of another inflammatory marker, the platelet-lymphocyte ratio (PLR), with malignancies has been less studied. In intracranial tumors, the relationship of NLR and PLR with prognosis and their diagnostic availability is less studied and the results are controversial[5]. Some studies have shown that high NLR and PLR values are associated with high tumor grade and poor prognosis. There are also studies showing the opposite[6]. The lymphocyte-monocyte ratio (LMR) is another hematological parameter that can be examined, and it is related to the grade of glial tumors and the course of the disease[7]. A high LMR ratio has been found to be associated with increased tumor grade and poor prognosis[8]. All these hematological parameters have been researched in both glial tumors and metastases, and increased ratios have been determined to adversely affect the course of the disease[5,8]. In primary intracerebral lymphomas, pre-treatment hemoglobin values have been indicated as a hematological parameter that may be related to prognosis[9]. However, the NLR, PLR, LMR parameters assessed in glial tumors and cerebral metastases have not been evaluated in primary cerebral lymphomas. In this study, our aim is to compare the NLR, PLR, LMR parameters in cases of glial tumor, metastasis, and primary cerebral lymphoma detected with stereotactic biopsy; to determine whether they can have a predictive value in the preliminary diagnosis.

Materials and Methods

Between 2013-2021, 97 cases who underwent stereotactic biopsy due to the detection of space-occupying lesions in the brain were included in the study. Retrospective study permission was obtained from our hospital's local ethics committee with the approval number 771.04.2020-9. All cases were determined as glial tumors, metastases, and primary cerebral lymphomas, and cases with different diagnoses (abscess, vascular lesion, degenerative disease, etc.) resulting from the biopsy were not included in the study group. The preoperative hemogram values of the cases and before any medication (such as cortisone) were initiated were examined. Neutrophil, lymphocyte, monocyte, and platelet values were recorded for each case. The neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratios were determined with the obtained values. The neutrophil, lymphocyte, monocyte, platelet, NLR, PLR, and LMR values for each case were statistically compared.

This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Initially, the mean, standard deviation, and median values of the "neutrophil, lymphocyte, monocyte, and platelet" data of the patient groups included in the study were calculated. To determine whether there was a statistically significant relationship between the groups, the Ranksum (Mann Whitney U) test was used for analysis. The p-values obtained from the test results were assessed to determine whether there was a statistically significant relationship between the groups tested, and the hypothesis that there was a significant difference between the groups with a $p<0.05$ result was accepted. Descriptive statistical parameters such as the mean, standard deviation, median, and Ranksum test results of the data belonging to the patients within the group were studied. These analyses/tests were calculated using MATLAB 2021A Statistics and Machine Learning Toolbox Version 11.2.

Results

Of the 97 patients, 63 (65%) were male (M), and 34 (35%) were female (F). The pathology of 53 (55%) (35M, 18F) patients was glial tumors, the pathological diagnosis of 29 (30%) (15M, 14F) patients was lymphoma, and the pathological diagnosis of 15 (15%) (13M, 2F) patients was metastasis. The average age of the 97 cases was 58.6±14 (Table 1). Initially, the mean, standard deviation, and median values of the neutrophil, lymphocyte, monocyte, and platelet data of the patient groups included in the

Table 1. Distribution of patients by pathological diagnosis and gender

	# of Patients	Lymphoma Group	Glial Group	Metastasis Group	Age
Total, n (%)	97	29 (30)	53 (55)	15 (15)	58.6±14
Male, n (%)	63 (65)	15 (52)	35 (66)	13 (87)	59.1±12
Female, n (%)	34 (35)	14 (48)	18 (34)	2 (13)	57.7±17

Mann Whitney U ($p<0.05$).

study were calculated; these values are presented in Table 2, and the average values for each group are shown in Figure 1. Similarly, the "NLR, PLR, and LMR" data of these three groups and the average values related to these data are shown in Table 3 and Figure 2. These values are important as the basic parameters of the data to be used to determine whether there is a significant relationship between the groups. The tumor group with the highest neutrophil values is metastases (9.4±5.7). Glial tumors are second with a value of 8.3±4.2, and the least neutrophil value is found in lymphomas (7.2±3.2). Monocyte values are also highest in metastases (0.75±0.6), followed by glial tumors (0.6±0.3), and the least monocyte value is in lymphomas (0.5±0.2). Looking at lymphocyte values, again, the highest values are in metastases (2.2±1), followed by lymphomas (1.6±0.9), and the least lymphocyte value is in glial tumors (1.56±0.7). Looking at platelet values, the

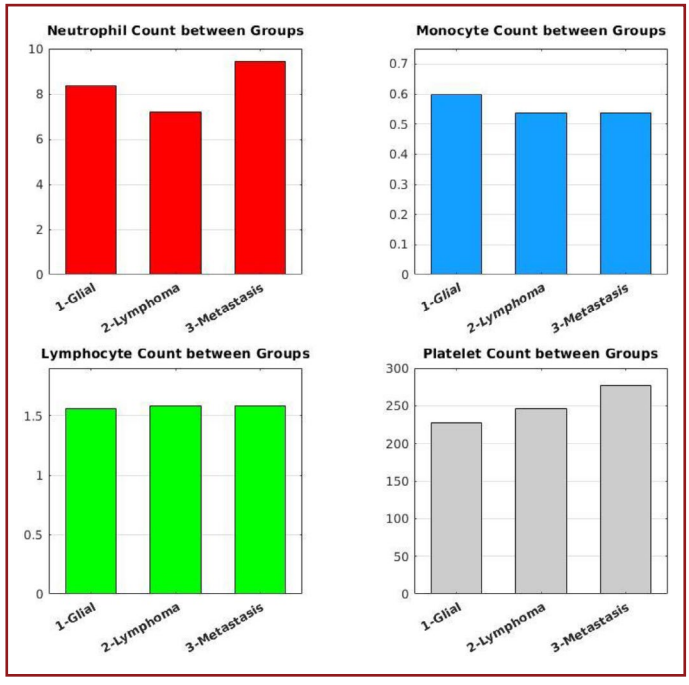

Figure 1. Distribution of neutrophil, lymphocyte, monocyte, and platelet values by groups.

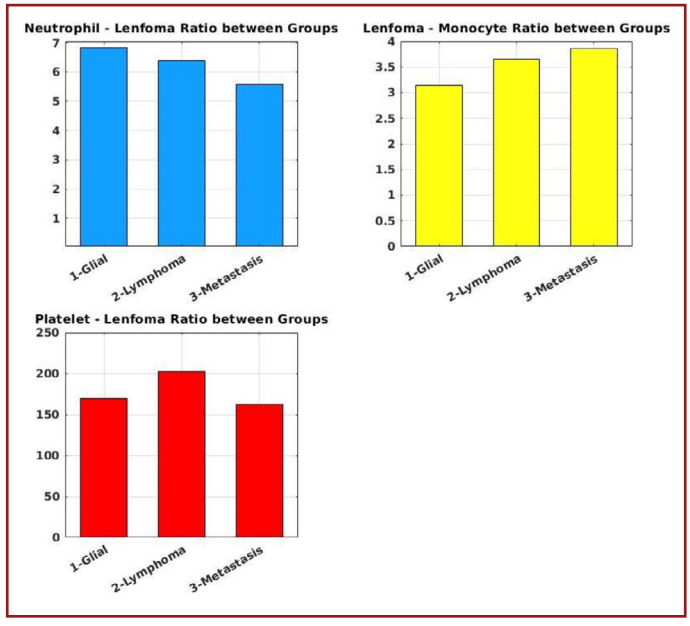

Figure 2. Comparison of NLR, PLR, and LMR values between groups.

Table 2. Distribution of neutrophil, lymphocyte, monocytes and platelet values according to groups

Group	# of Patients	Neutrophil		Monocyte		Lymphocyte		Platelet	
		Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Lymphoma	29	7.2±3.2	7.26	0.5±0.2	0.53	1.6±0.9	1.41	246±90	234
Glial	53	8.3±4.2	7.78	0.6±0.3	0.51	1.56±0.7	1.36	228±80	222
Metastasis	15	9.4±5.7	6.42	0.75±0.6	0.75	2.2±1	2.25	278±90	276

Mann Whitney U ($p<0.05$).

Table 3. Distribution of NLR, PLR and LMR values by groups

Group	# of Patients	NLR		PLR		LMR	
		Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Lymphoma	29	6.38±5.21	4.48	203±120.6	144	3.65±2.68	2.5
Glial	53	6.84±5.28	5.06	169±97.6	161	3.14±1.72	2.7
Metastasis	15	5.58±4.36	4.26	162±98.5	107	3.86±2.45	2.7

Mann Whitney U ($p<0.05$).

Table 4. Comparison of NLR, PLR and LMR values between groups

	NLR	LMR	PLR
Group Name		**p**	
Glial vs Lymphoma	0.6696	0.8235	0.5096
Glial vs Metastasis	0.3829	0.3748	0.4963
Metastasis vs Lymphoma	0.5690	0.4576	0.1979

Mann Whitney U ($p<0.05$).

highest values are again in metastases (278±90), followed by lymphomas (246±90), and the least platelet value is in glial tumors (228±80). When comparing the neutrophil, lymphocyte, monocyte, and platelet values of all three groups, no significant difference was observed ($p<0.05$) (Table 2, Fig. 1). For lymphoma cases, the NLR value was 6.38±5.21, PLR value 203±120.6, and LMR value 3.65±2.68. For glial tumor cases, the NLR value was 6.84±5.28, PLR value 169±97.6, and LMR value 3.14±1.72. For metastasis cases, the NLR value was 5.58±4.36, PLR value 162 ± 98.5, and LMR value 3.86±2.45. The p-values obtained from the comparison of NLR, LMR, and PLR data being higher than 0.05 indicated that there was no significant difference in these data between the groups (Table 4). The average survival duration for glioblastoma cases was 1,393±2.5 months, and 4% (n=2) survived. For lymphoma cases, the average survival duration was 28.23±8.04 months, and 25% (n=7) of the cases survived. For metastasis cases, the average survival duration was 11.19±2.49 months, and all the cases followed during the period had died.

Discussion

In many studies, it has been shown that chronic inflammation markers in most brain tumors are associated with the type of cancer or the degree of the tumor. Particularly, NLR and PLR are parameters that can be easily measured in the blood and can be used for early diagnosis, providing information about the tumor grade[10]. These parameters are used in colon, prostate, bladder, and lung tumors and are evaluated in monitoring the disease[10]. They are also used in assessing disease recurrence. The most studied and associated tumors in brain cancers are glial tumors, with the most significant relationship being in glioblastomas. Indeed, preoperative increased NLR and PLR ratios have been found to be associated with the grade of glial tumors[8,10]. Increased NLR ratios are associated with increased neutrophils due to inflammation and a decrease in lymphocyte-mediated anti-tumor response, secondary to decreased lymphocyte counts[11]. Neutrophil chemotactic factors and reactive oxygen products produced by the tumor can also be effective[12]. An increase in neutrophil count reduces lymphocyte activity and accelerates apoptosis, which may explain tumor-associated lymphopenia. Immunosuppressive cytokines such as IL-6, IL-8, IL-10, IL-12, TGF-β may also be associated with decreased lymphocyte counts[11,12]. However, the underlying true mechanism of increased neutrophils and decreased lymphocytes remains unclear.

It is important that neutrophil, lymphocyte, and platelet measurements are taken in blood samples collected before surgery and medical treatment; otherwise, postoperative increases in these values can be misleading. Additionally, elevations in neutrophil values can occur in conditions such as hypertension, autoimmune diseases, cardiovascular diseases, and insulin resistance[12]. The cut-off values of these ratios can also be dependent on societal and gender factors.

In studies conducted on glioblastomas, an NLR ratio of 4 or higher has been found to be associated with recurrence and poor prognosis[13]. In patients with gliomas, the NLR value was found to be higher compared to patients with epilepsy, acoustic neuromas, and meningiomas[13]. Indeed, in our cases of glial tumors, the NLR ratio was also found to be high. Similarly, in line with the literature, high NLR values were found in metastases and lymphomas. However, when comparing the cases, no significant relationship was found between the NLR values of the three tumor groups.

Increased PLR ratios, like NLR, have been studied in many tumors and higher values have been associated with poor prognosis and advanced stages, although their prognostic value is less than that of NLR[14]. In our study, the highest PLR values were found in lymphoma cases. In a study, PLR values in gliomas were found to be higher compared to non-tumoral lesions (epilepsy, acoustic neuroma, and meningioma). When comparing metastases, glial tumors, and lymphomas, no significant difference was observed in the PLR values among the three different tumor groups.

In malignant tumors, LMR ratios, unlike NLR and PLR ratios, appear to be decreased. LMR has been studied in urothelial, renal, esophageal, gastric, and colorectal tumors, and decreased LMR ratios have been found to be associated with poor prognosis and increased tumor grade[15]. LMR has been less studied in brain tumors; in a study on gliomas, decreased levels of LMR were said to be associated with poor tumor grade[7]. Decreased lymphocyte and increased monocyte values are responsible for the decreased LMR, but the underlying mechanism is not clear. In our study

group, lymphomas had the lowest LMR ratio, while there was no significant difference between other tumor groups.

Advancements in imaging methods have greatly enhanced our ability to understand lesions in the brain. However, the prospect of gaining insights into the diagnosis of brain lesions through a simple blood test before a histopathological diagnosis is made via surgery or biopsy has been an intriguing topic. In our study, NLR, PLR, and LMR values consistent with the literature were found. However, no significant difference was observed between different tumor groups that could assist in diagnosis. It should be noted that the small number of cases in our study might have influenced these results. Additionally, it should not be forgotten that these parameters could change in relation to any inflammation.

Conclusion

In our study examining NLR, LMR, and PLR ratios, similar to many malignant tumors, increased NLR and PLR ratios, and decreased LMR ratios were found. However, due to the lack of significant differences between the groups, preoperative inflammatory blood tests were not helpful in aiding differential diagnosis.

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