DOI: 10.2478/romneu-2018-0079

Diagnostic value of preoperative systemic inflammatory markers in patients with intracranial meningiomas

Rahsan Kemerdere[1], Mehmet Yigit Akgun[1], Sureyya Toklu[1], Orkhan Alizada[1], Oguz Baran[2], Taner Tanriverdi[1]

[1]Department of Neurosurgery, Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, TURKEY
[2]Neurosurgery Clinic, Istanbul Research and Training Hospital, Istanbul, TURKEY

Abstract: *Introduction:* The role of inflammation in cancer has been defined, and now, inflammation is accepted as one of the hallmarks of cancer development. The aim of this study was to evaluate the difference regarding preoperative neutrophil to lymphocyte (NLR) and platelet to lymphocyte ratios (PLR) in patients with meningioma between patients and healthy controls and between grade-I and grade-II meningiomas. *Methods:* Retrospective analysis of preoperative neutrophil, lymphocyte, monocyte, and platelet counts and NLR, and PLR were evaluated in 61 patients underwent meningioma surgery. *Results:* Neutrophil count was significantly increased while lymphocyte count significantly decreased patients compared to controls. Similar findings were obtained in grade-II meningiomas compared with grade-I meningiomas. NLR were significantly higher in both grade-I and grade-II meningiomas than controls. *Conclusion:* We for the first time provided that higher NLR may be associated with grading of meningioma and be a predictive factor for progression of meningiomas. The use of medication against neutrophil-related inflammation may be helpful for patients with higher grade of meningioma decreasing peritumoral edema before and after surgery.

Key words: Inflammation; Meningioma; Neutrophil-lymphocyte ratio; Platelet-lymphocyte ratio

Introduction

Meningiomas are the most commonly seen intracranial extra-axial tumors, accounting for 25% of all intracranial space-occupying lesions. Females are affected more predominantly than males due to estrogen functions (1). Although meningiomas are accepted as generally benign in nature, the recurrence rate in some cases is extremely high, even after the total surgical removal of the lesion. Thus, in 2007, the World Health Organization classified meningiomas into three grades. Grade I is more commonly encountered when compared to grades II and III, and the recurrence rate for grade I tumors

is very low. However, in grade II or III tumors, a high recurrent rate is common, and radiotherapy is required after surgery (2). Meningiomas originate in the arachnoid cap cells, but the exact nature of the development of these common tumors remains unknown.

The role of inflammation in cancer has been defined, and now, inflammation is accepted as one of the hallmarks of cancer development (3). With regard to inflammation in brain tumors, meningiomas have been focused on less when compared to gliomas. However, recent evidence has suggested that inflammation plays a pivotal role in the development and progression of brain tumors, including gliomas (4, 5). Finding a useful biomarker to predict the progression of brain tumors would be exciting for a neurosurgeons because there has been no such marker used in brain tumors, as opposed to certain other solid tumors such as breast cancer (6). Recent studies have shown that the preoperative blood inflammatory markers, such as the neutrophil to lymphocyte ratio (NLR) or platelet to lymphocyte ratio (PLR), can be used as indices of glioma progression. For example, it has been reported that a high NLR (increase in the neutrophil count and decrease in the lymphocyte count) has a diagnostic value, and it correlates with the glioma grade (4, 5, 7-10). Those studies emphasized the fact that local inflammation around the tumor microenvironment can be reflected systemically, and that the inflammation severity can be tested by using peripheral blood tests that are cheap, reproducible, and effective.

Surprisingly, there have been no reports focusing on the preoperative blood markers in intracranial meningiomas. Therefore, in this retrospective analysis, we wanted to show how the preoperative NLR and PLR levels change when compared to the controls. We hypothesized that the NLR and PLR would be higher in meningiomas cases (compared to controls), and that the levels would correlate with the meningioma grade, given that the same inflammatory processes take place in both glioma and meningioma cases.

Materials and Methods

Patients

The patient group included here underwent surgeries for intracranial-supratentorial meningiomas by a single surgeon between 2010 and 2017. A total of 100 cases were retrieved from the medical records, but only 61 patients were included, according to the following criteria: 1) the meningioma grade was verified by a histopathological study, 2) no chemotherapy, radiotherapy, and steroids were taken before the surgery, 3) no co-morbidities or extracranial tumors were seen, 4) there was no previous surgery due to any intracranial pathology; 5) there was a complete blood count (CBC) before surgery; and 6) an informed consent form was completed.

Data collection

The demographic, clinical, radiological and histopathological data were retrieved from each patient's medical records. After hospitalization, blood samples were taken for a CBC and other tests, including hepatic function, serology and the electrolyte level, as a standard preoperative work-up. The neutrophil (103/mm3), lymphocyte

(103/mm3), and platelet (103/mm3) counts were recorded. Additionally, the preoperative NLR (quotient of the absolute number of the neutrophil count to the lymphocyte count) and PLR (quotient of the absolute number of the platelet count to the lymphocyte count) were calculated.

All of the patients underwent cranial magnetic resonance imaging (MRI) with contrast enhancement. The anterior-posterior diameter (cm) was measured by using T1-weighted contrast-enhanced axial images, and the presence of peritumoral edema was noted by using T2-weighted and fluid-attenuated inversion recovery (FLAIR) images.

Controls

The control group in this study was composed of 35 subjects who were admitted to our clinic and underwent CBC testing for some other reason, such as a headache. None of the subjects exhibited any abnormalities in their cranial MRI scans and no other organ system illnesses were detected. The blood samples were obtained during their admission to our outpatient clinic.

Statistical Analysis

The statistical analysis was performed by using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). The results were reported here as the mean ± standard deviation. An independent samples t-test and chi-squared test were used in the appropriate comparisons and the correlation analysis was judged using Pearson's correlation coefficient. The area under the curve (AUC) for the NLR and PLR with a receiver operating characteristics (ROC) curve analysis was used for the diagnostic performance. A probability value (p value) < 0.05 was considered to be statistically significant.

Results

Demographic characteristics

The patient group included 26 males (42.6 %) and 35 females (57. 4 %) with a mean age of 51.91 ± 13.01 years old (range = 23 to 76 years). The control group had 19 males (54.3 %) and 16 females (45.7 %) with a mean age of 32.08 ± 10.09 years old (range = 10 to 51 years). Based on the cranial MRI scans, there were 26 (42.6 %) and 35 (57.4 %) right and left-sided meningiomas, respectively. Peritumoral edema was noted in 37 patients (60.7 %). The histopathological diagnoses revealed grade I meningiomas in 48 patients (78.7 %) and grade II in 13 patients (21.3 %). All of the patients with grade II meningiomas had peritumoral edema. The mean of the anterior-posterior diameters of the tumors was 36.73 ± 13.6 cm.

Inflammatory markers: patients versus controls

Table I shows a summary of the comparisons between the patients and the controls with regard to the preoperative inflammatory markers studied here. The mean of the neutrophil count levels was significantly higher in the patients when compared to controls (p = 0.001). The lymphocyte and platelet counts were lower in the patients; however, the differences were not significant. As expected, the NLR was significantly higher in the patient group (p = 0.001). Moreover, the mean PLR level was higher in the patients than the controls, but the difference was not significant. However, there was a trend toward

significance in the PLR levels of the patients (p = 0.05).

Inflammatory markers: meningioma grade and edema versus controls

Given that inflammation has been shown to play an important role in upgrading of tumors and the presence of peritumoral edema, we compared how the preoperative inflammatory marker levels change. Table II shows that the neutrophil count increases, whereas the lymphocyte and platelet counts decrease in grade II when compared to grade-I meningiomas.

TABLE I

Preoperative inflammatory markers in patients and controls

Marker	Patients (n = 61)	Controls (n = 35)	P value
Neutrophils	5.42 ± 2.63	4.20 ± 0.81	0.001*
Lymphocytes	2.11 ± 1.09	2.39 ± 0.54	0.15
Platelets	252.54 ± 76.18	271.57 ± 57.66	0.20
NLR	3.42 ± 3.62	1.83 ± 0.49	0.001*
PLR	136.46 ± 57.27	118.51 ± 34.24	0.05

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.
*Denotes statistically significant difference.

TABLE II

Preoperative inflammatory markers according to meningioma grade and controls

Marker	Neutrophils	Lymphocytes	Platelets	NLR	PLR
Grade-I	5.14 ± 2.54	2.21 ± 1.13	255.46 ± 61.29	2.75 ± 2.17	128.78 ± 48
Grade-II	6.45 ± 2.81	1.71 ± 0.82	241.73 ± 118.9	5.90 ± 6.28	164.83 ± 79.15
Controls	4.20 ± 0.81	2.39 ± 0.54	271.57 ± 67.66	1.83 ± 0.49	118.51 ± 34.24
Edema+	5.84 ± 2.96	2.03 ± 0.87	252.82 ± 85.73	4.0 ± 4.47	141.18 ± 66.95
Edema-	4.77 ± 1.91	2.22 ± 1.37	252.10 ± 60.28	2.52 ± 1.39	129.19 ± 30.07
		Grade-I *versus* Grade-II			
P value	0.11	0.14	0.69	0.09	0.13
		Grade-I *versus* Controls			
P value	0.02*	0.4	0.22	0.006*	0.28
		Grade-II *versus* Controls			
P value	0.01*	0.002*	0.4	0.03*	0.06

			Edema present *versus* absent		
P value	0.12	0.49	0.96	0.06	0.37

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.
*Denotes statistically significant difference.
Edema+: Presence of peritumoral edema.
Edema-: Absence of peritumoral edema.

As expected, the NLR and PLR were increased in the grade II meningiomas but no significant differences were found between these two grades. However, there was a trend toward significance with regard to the NLR.

When the grade I meningiomas and the controls were compared, we found that the neutrophil count and NLR increased, while the lymphocyte count, platelet count, and PLR decreased in the grade I cases. However, the difference reached significance only regarding the neutrophil count and NLR. Findings supporting the role of inflammation in the upgrading of a meningioma were found when a comparison between the grade II meningiomas and the controls was performed. The neutrophil count, platelet count, NLR, and PLR were higher and the lymphocyte count and platelet count were lower in the grade II cases than in the controls. The differences were significant regarding the neutrophil count and lymphocyte count, and NLR levels. The presence and/or absence of peritumoral edema caused differences in the inflammatory marker levels, but none reached a significant level. Here, we must emphasize the fact that the neutrophil and lymphocyte counts increased and decreased, respectively, suggesting that inflammation may play a role in the development of peritumoral edema. Although we did not find significant differences between the presence and absence of peritumoral edema with respect to the NLR and PLR, both showed elevations in the presence of peritumoral edema.

Correlations

The strong positive correlations were as follows: neutrophil count and NLR (r = 0.65, p = 0.00001), neutrophil count and PLR (r = 0.28, p = 0.005), lymphocyte count and platelet count (r = 0.32, p = 0.001), platelet count and PLR (r = 0.21, p = 0.03), and NLR and PLR (r = 0.61, p = 0.00001). Contrarily, the strong negative correlations were as follows: lymphocyte count and NLR (r = - 0.47, p = 0.00001), lymphocyte count and PLR (r = - 0.63, p = 0.00001), and platelet count and NLR (r = - 0.26, p = 0.008).

Diagnostic efficacy

When the patients with meningiomas were tested against the controls (Figure 1), the AUCs were 0.70 [95 % confidence interval (CI) 0.59-0.80, p = 0.001] for the NLR and 0.57 (95 % CI = 0.45-0.69, p = 0.22) for the PLR.

However, when grade I meningiomas were tested against the grade II meningiomas (Figure 2), the AUCs were 0.70 (95 % CI = 0.53-0.86) for the NLR and 0.64 (95 % CI = 0.45-0.83, p = 0.1) for the PLR. The findings showed that the NLR exhibited the best

accuracy for a meningioma diagnosis and predicting the meningioma grade.

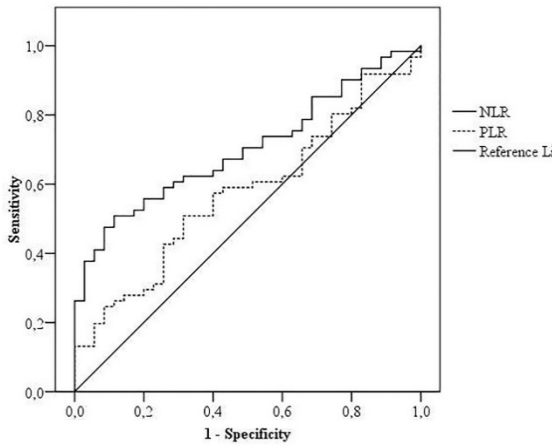

Figure 1 - ROC curve analysis showing diagnostic efficacy when patients with meningioma were tested against healthy subjects

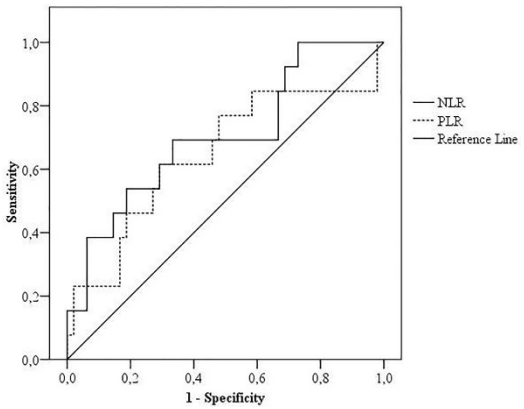

Figure 2 - ROC curve analysis showing diagnostic efficacy when patients with meningioma were tested against those with grades I and II

Discussion

The role of chronic inflammation in both the development and progression of cancer has been identified, and it has been strongly suggested that inflammation-related neutrophils and lymphocytes, as well as platelets, participate in angiogenesis and the proliferation of tumor cells (11, 12). Meningiomas, especially grade I lesions are slow-growing tumors, and obviously, chronic inflammation may take place in their development and progression. However, the exact mechanism(s) behind the neutrophilia and lymphopenia that are commonly found in cancer is poorly understood. Some researchers have suggested that the cytokines and chemokines secreted by tumor cells can cause neutrophil infiltration, thus causing an elevation in their counts in both the tumor microenvironment and the peripheral blood (13, 14). The increased neutrophil levels subsequently inhibit the white blood cells, including lymphocyte activity, and this leads to lymphocyte apoptosis.

The studies reported during the last decade showed that higher neutrophil and lower lymphocyte counts are associated with poor prognoses in various cancers, including glial tumors of the brain (4, 5, 7-10, 15, 16). Unfortunately, there have been a limited number of studies focusing on brain tumors with regard to the preoperative inflammatory markers, when compared to the other organ system tumors, and there have been no reports focusing on meningiomas. A few studies have reported the preoperative inflammatory markers, such as the NLR, PLR, and lymphocyte to monocyte ratio (LMR), in some extra-axial tumors, such as vestibular schwannomas and craniopharyngiomas (15, 16). For example, Kontorinis, et al. (15) demonstrated that a very high NLR is a reliable marker for vestibular schwannoma growth

and that it can predict grooving schwannomas. Chen, et al. (16) found that the levels of white blood cells, neutrophils, NLR, and PLR were higher in craniopharyngiomas when compared to other sellar tumors, and they emphasized the fact that these markers can be used to differentiate craniopharyngiomas. Moreover, Zheng et al. (5) provided the first evidence that patients with gliomas have higher NLR levels than patients with non-lesional epilepsy, vestibular schwannomas, meningiomas, and healthy controls.

Because there have been no previous reports studying preoperative inflammatory markers in meningioma cases, we could not compare our results with those from the current literature. However, we did discuss our results with regard to previous reports including gliomas. First, we would like to emphasize the fact that our results were strongly in line with those of other studies including patients with gliomas (4, 5, 7-10). A significantly higher neutrophil count and NLR were found in our patient group when compared to the healthy controls. Although we did not find a statistically significant difference regarding the PLR, there was a trend toward significance. The lymphocyte count was also lower in the meningioma patients, but the difference was not significant. These results mentioned above support the previous glioma studies in which a higher neutrophil count, lower lymphocyte count, higher NLR, and, in some studies, a higher PLR were found to be strongly associated with the prognosis (5, 8). More importantly, the glioma grade was associated with a higher NLR, and it was stated that the NLR can be used as an index for glioma progression, with an NLR ≥ 4 showing a poor prognosis (5, 8).

It is clear that as tumor grade increases, the inflammatory reaction increases and the levels of the inflammatory markers, such as the neutrophil count, NLR, and PLR, increase. For the first time, we demonstrated preoperative inflammatory marker levels in different meningioma grades (grade I and II). We obtained very supportive findings that malignancy increases, the inflammation-related markers increase. The grade II patients showed higher and lower levels of neutrophils and lymphocytes, respectively, when compared to the grade I patients, but more importantly, the NLR and PLR were higher in the grade II patients although the differences were not significant. This may be due to the fact that the number of grade II patients (n = 13) was smaller than that of the grade I patients (n = 48). We believe that if we were able to include an equal number of patients in each grade, the differences would be significant. The neutrophil counts and NLR were also clearly higher in each grade when compared to the healthy subjects but the biggest differences were found when comparing the grade II and the healthy subjects, suggesting that inflammation may play a role in tumor progression, as in the current literature on glioma patients (4, 5, 7-10).

From a clinical standpoint, we know that as the tumor malignancy increases, the peritumoral edema, which can sometimes cause life-threatening conditions, increases. Recent studies have shown that inflammatory cells play roles in the formation of peritumoral edema, and they have been found in

edematous tissues (17). We hypothesized that because peritumoral edema is associated with inflammation, the levels of the inflammatory markers studied here, would increase in those patients who exhibited peritumoral edema on their cranial MRI scans. We note the fact that peritumoral edema was observed in all 13 of the patients who were diagnosed with grade II meningiomas. The neutrophil count and lymphocyte count were increased and decreased, respectively, in the patients with peritumoral edema when compared to those who had no peritumoral edema, and there were higher NLR and PLR levels in those patients with peritumoral edema. These finding supported our hypothesis that inflammation may play an important role in the development of peritumoral edema, and an anti-edematous treatment including a medication inhibiting neutrophil action in addition to steroids would be beneficial.

As in the few studies including extra-axial tumors, such as vestibular schwannomas and craniopharyngiomas (15, 16), and the studies including gliomas (4, 5, 7-10), the NLR compared to the PLR exhibited the highest diagnostic value in predicting meningiomas. This can differentiate grade I meningiomas from grade II meningiomas, and it could be used as an index for possible tumor progression after surgery.

Limitations

The authors contributed to this study are aware that there are a few limitations. First, this is a retrospective study that may cause selection bias although we had strict selection criteria. Second, our patient sample consisted of a relatively small number of patients with meningioma, in particular, limited number of grade I meningiomas thus the literature needs prospective studies with larger cohort of meningioma patients. Third, higher levels of neutrophil count, NLR, and PLR can be a reflection of non-specific inflammatory response due to meningioma thus we have a risk of having false-positive results. We underline that until we have enough number of studies including larger cohort of patients, the results obtained from the current literature and from the present study should be evaluated carefully.

Conclusion

Apart from the limitations mentioned above, we for the first time provided that higher NLR may be associated with grading of meningioma and a predictive factor for progression of meningiomas. The use of medication against neutrophil-related inflammation may be helpful for patients with higher grade of meningioma for decreasing peritumoral edema before and after surgery. We were not able to compare our results with the current literature due to absence of studies included same type of tumor. Thus, further studies are needed.

Correspondence
Oguz Baran, M.D.
Istanbul Research and Training Hospital,
Neurosurgery Clinic, Istanbul; Turkey.
E-mail: oguzbaran@gmail.com
Telephone Number: +905325990034 Fax : +90 (212) 459 62 30
Mailing Address: Istanbul Egitim ve Arastirma Hastanesi, Beyin ve Sinir Cerrahisi Klinigi. Kasap

Ilyas Mah. Org. Nafiz Gurman Cad. 34098 Samatya/Istanbul

References

1. Carroll RS, Zhang J, Black PM. Expression of estrogen receptors alpha and beta in human meningiomas. J Neurooncol 1999;42:109–16.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109.
3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
4. Zadora P, Dabrowski W, Czarko K, Smolen A, Kotlinska-Hasiec E, Wiorkowski K, et al. Preoperative neutrophil-lymphocyte count ratio helps predict the grade of glial tumor- A pilot study. Neurol Neurochir Pol 2015;49:41-4.
5. Zheng SH, Huang JL, Chen M, Wang BL, Ou QS, Huang SY. Diagnostic value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study. J Neurosurg 2017;3:1-10.
6. Banin Hirata BK, Oda JM, Lost GR, Ariza CB, de Oliveira CE, Watanave WA. Molecular markers for breast cancer: prediction on tumor behavior. Dis Markers 2014;2014:513158.
7. Bambury RM, Teo MY, Power DG, Yusuf A, Murray S, Battley JE, et al. The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme. J Neurooncol 2013;114:149-54.
8. Han S, Yang L, Qingchang L, Zhonghua L, Haipei H, Anhua W. Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma. BMJ Cancer 2015;15:617-26.
9. Wang PF, Song HW, Cai HQ, Kong LW, Yao K, Jiang T, et al. Preoperative inflammation markers and IDH mutation status predict glioblastoma patient survival. Oncotarget 2017;8:50117-23.
10. Auezova R, Ryskeldiev N, Doskaliyev A, Kuanyshev Y, Zhetpisbaev B, Aldiyarova N, et al. Association of preoperative levels of selected blood inflammatory markers with prognosis in gliomas. Onco Targets Ther 2016;9:6111-7.
11. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation and cancer. Cell 2010;140:883-99.
12. Malietzis G, Giacometti M, Kennedy RH, Athanasiou T, Aziz O, Jenkins JT. The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. Ann Surg Oncol 2014;21(12):3938-46.
13. Del Prete A, Allavena P, Santoro G, Fumarulo R, Corsi MM, Mantovani A. Molecular pathways in cancer-related inflammation. Biochem Med 2011;21:264-75.
14. Gregory AD, Houghton AM. Tumor-associated neutrophils: new target for cancer theraphy. Cancer Res 2011;71:2411-26.
15. Kontorinis G, Crowther JA, Iliodromiti S, Taylor WAS, Locke R. Neutrophil to lymphocyte ratio as a predictive marker of vestibular schwannoma growth. Otol Neurotol 2016;37:580-5.
16. Chen M, Zheng SH, Yang M, Chen ZH, Li ST. The diagnostic value of preoperative inflammatory markers in craniopharyngioma: a multicenter cohort study. J Neurooncol 2018;138:113-22.
17. Polyzoidis S, Koletsa T, Panagiotidou S, Ashkan K, Theoharides TC. Mast cells in meningiomas and brain inflammation. J Neuroinflammation 2015;12:170.