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The significance of preoperative hematological inflammatory markers in patients with meningiomas

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ABSTRACT

Objective: This study was designed to evaluate whether preoperative hematological inflammatory markers would be useful in predicting the pathological grade of meningiomas.
Patients and methods: A retrospective study of 944 patients with newly diagnosed meningioma was conducted. Preoperative blood results were obtained, including platelet, leukocyte, neutrophil, lymphocyte, and monocyte counts, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), albumin level, globulin level, and albumin-to-globulin ratio (AGR). Logistic regression analysis was performed to identify the independent predictive factors for high-grade meningiomas.
Results: Univariate logistic regression analysis indicated that the hematological inflammatory markers associated with tumor grade were leukocyte, neutrophil, and monocyte counts and the LMR ($P < 0.05$ for all). Multivariate logistic regression analysis showed that high leukocyte count ($P = 0.007$) and low LMR ($P = 0.041$) were independent predictive factors for high-grade meningiomas.
Conclusions: Preoperative high leukocyte count and low LMR were independent predictive factors of high-grade meningiomas, suggesting that leukocyte count and LMR could be useful in the assessment of the grade of meningiomas.

1. Introduction

Meningioma is the most common type of intracranial tumor, accounting for approximately 37% of all such tumors [1]. In accordance with the World Health Organization (WHO) classification system, meningiomas are classified as grade I, II, or III [2]. The majority of meningiomas are low-grade (grade I) benign tumors, with high-grade (grade II or III) meningiomas accounting for 6–18% of all meningiomas [3]. However, high-grade meningiomas are more likely to recur locally after initial treatment, display invasive behavior, and have increasedmorbidity and decreasedsurvival rates [4]. For grade II and III meningiomas, recurrence rates are 30–40% and 50–80% respectively [5], and the five-year overall survival rates are 78.4% and 44.0% respectively [6]. Many meningiomas are located at the base of the skull or other high-risk locations, making it difficult to remove or even biopsy the tumor [7]. Gamma knife surgery is chosen as the initial treatment strategy for patients with small meningiomas, but if they subsequently prove to be high-grade lesions, further treatmentbecomes difficult [8]. Therefore, preoperative differentiation between the high- and low-grade meningiomas may help to guide neurosurgeons in selecting an optimal treatment plan.

Inflammation has been shown to be closely correlated with tumor occurrence, progression and metastasis [9]. Preoperative hematological inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and albumin-to-globulin ratio (AGR), have been the focus of numerous studies on tumor biology and prognosis [10–13]. Moreover, it has also been demonstrated that preoperative inflammatory markers are associated with tumor pathological grade [14,15]. Therefore, the aim of this study was to investigate the correlation between the preoperative hematological inflammatory markers and the pathological grade of meningiomas.

2. Materials and methods

2.1. Patients

We retrospectively analyzed a database of patients with newly

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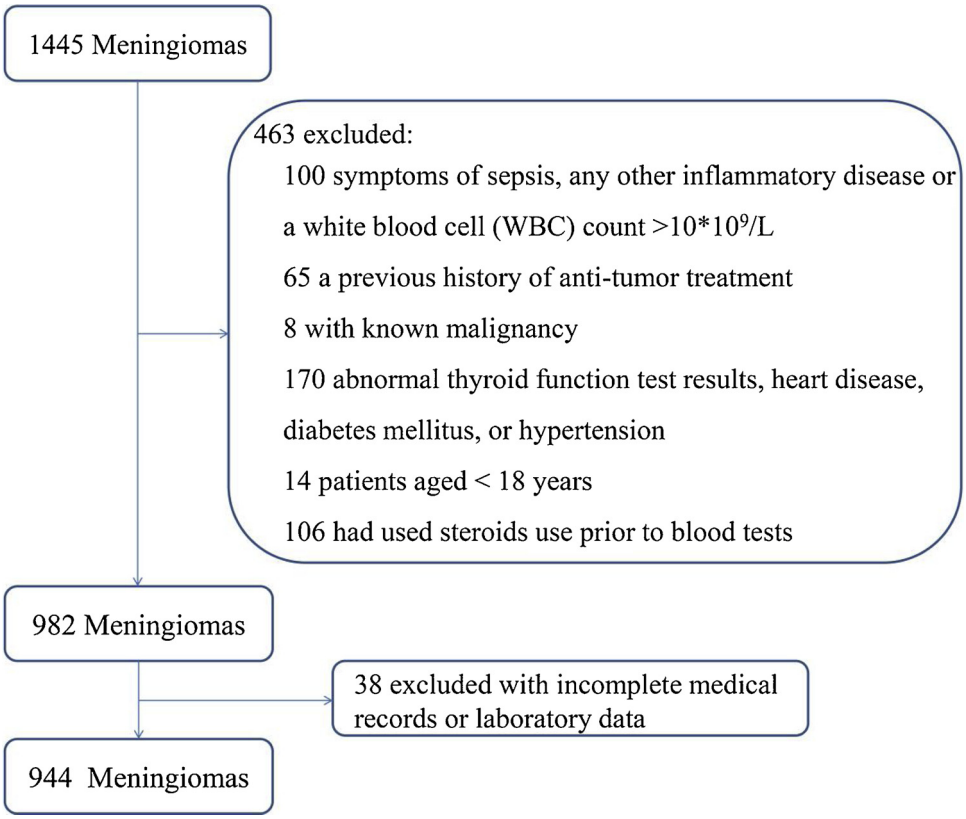

Fig. 1. Flow chart of the patients in the study.

diagnosed meningioma between January 2009 and January 2013 in West China Hospital, after the study protocol was approved by the institutional ethics committee. The database used in this study has been described previously [16]. The database contains information on the clinical presentation, demographics, pathology reports, and preoperative laboratory parameters of patients. The blood samples were routinely collected for laboratory analysis within one week before surgery. The tumors were assessed and graded according to the 2007 World Health Organization classification of tumors of the central nervous system. The exclusion criteria applied included the following: (1) patients with clinical signs or symptoms of sepsis, any other inflammatory disease or a white blood cell (WBC) count > $10*10^9$/L [17]; (2) a previous history of anti-tumor treatment; (3) those with known malignancy; (4) abnormal thyroid function test results, heart disease, diabetes mellitus, or hypertension; (5) patients aged < 18 years; (6) those with incomplete medical records or laboratory data; (7) those who had received any drug known to affect hematological inflammatory markers (such as steroids); (8) patients for whom tumor grade could not be obtained from pathology reports. In total, 944 patients with newly diagnosed meningioma were included in the analysis (Fig. 1).

2.2. Data collection

Data collected for the analysis included: age, sex, tumor grade, and preoperative blood results, including platelet, leukocyte, neutrophil, lymphocyte, and monocyte counts, NLR, PLR, LMR, albumin level, globulin level, and AGR.

2.3. Statistical analysis

Statistical analyses were performed using SPSS software (version 19.0, IBM, USA). The Chi-square test was used to compare categorical variables, while the Student's *t*-test or Mann–Whitney *U* test was used to compare continuous variables. Logistic regression analysis was performed to identify the independent predictors for high-grade meningiomas. A P–value < 0.05 was considered statistically significant.

3. Results

The characteristics and laboratory data of the patients are summarized in Table 1.

A total of 944 patients (276 males and 668 females) were included in the study. The median age was 50 years (range: 18–82 years). Specifically, our tumor distribution was: 794 patients with low-grade meningiomas (794 Grade I) and 150 patients with high-grade

Table 1
Distribution of demographic and hematological inflammatory markers in patients with meningiomas.

Variables	High-grade group	Low-grade group	P
Age(year)	53 (20-77)	50 (18-82)	0.989
Sex			< 0.001
Male	63	213	
Female	87	581	
Platelet ($\times 10^9$/L)	161 (63-383)	171 (63-601)	0.179
Leukocyte ($\times 10^9$/L)	6.09 (2.67-9.95)	5.77 (2.40-9.98)	0.002
Neutrophil ($\times 10^9$/L)	3.81 (1.46-8.23)	3.56 (0.95-8.78)	0.001
Lymphocyte ($\times 10^9$/L)	1.65 (0.65-4.13)	1.62 (0.36-5.53)	0.646
Monocyte($\times 10^9$/L)	0.32 (0.09-0.85)	0.28 (0.01-0.82)	< 0.001
NLR	2.41 (0.38-9.01)	2.16 (0.39-18.36)	0.023
PLR	99.92 (34.53-301.54)	105.85 (30.49-519.44)	0.068
LMR	5.04 (1.17-22.22)	5.79 (1.30-57.00)	0.002
Albumin(g/L)	43.10 (32.20-51.60)	43.00 (26.10-51.90)	0.916
Globulin(g/L)	27.45 (17.90-44.00)	27.10 (16.10-43.00)	0.763
AGR	1.56 (1.04-2.52)	1.58 (0.79-2.68)	0.590

NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; AGR, Albumin-to-globulin ratio.

Table 2
Univariate and multivariate analysis of variables in predicting meningiomas grade.

	Univariate analysis			Multivariate analysis		
Variables	OR	95%CI	P value	OR	95%CI	P value
Age(year)	0.999	0.984-1.013	0.872			
Sex	1.975	1.378-2.832	< 0.001	1.811	1.258-2.608	0.001
Platelet	0.998	0.995-1.001	0.157			
Leukocyte	1.208	1.075-1.358	0.002	1.179	1.046-1.328	0.007
Neutrophil	1.218	1.071-1.386	0.003			
Lymphocyte	1.069	0.782-1.461	0.677			
Monocyte	14.104	3.500-56.840	< 0.001			
NLR	1.052	0.954-1.161	0.310			
PLR	0.997	0.993-1.000	0.083			
LMR	0.910	0.846-0.979	0.011	0.929	0.865-0.997	0.041
Albumin	1.001	0.954-1.051	0.956			
Globulin	1.012	0.970-1.056	0.569			
AGR	0.998	0.522-1.905	0.984			

NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; AGR, Albumin-to-globulin ratio.

meningiomas (137 Grade II and 13 Grade III). In regard to the hematological inflammatory markers, no difference was seen between the groups with high- and low-grade meningiomas for platelet count, lymphocyte count, PLR, albumin level, globulin level and AGR ($P > 0.05$ for all). However, leukocyte, neutrophil, and monocyte counts and the NLR in the high-grade meningioma group were significantly higher than those in the low-grade meningioma group ($P < 0.05$ for all). The LMR was significantly lower in the high-grade meningioma group than in the low-grade meningioma group ($P = 0.002$).

Univariate logistic regression analysis indicated that the hematological inflammatory markers associated with tumor grade were leukocyte, neutrophil, and monocyte counts and the LMR ($P < 0.05$ for all). Multivariate logistic regression analysis showed that high leukocyte count (odds ratio [OR]: 1.179; 95% confidence interval [CI]: 1.046–1.328, $P = 0.007$) and low LMR (OR: 0.929; 95% CI: 0.865-0.997, $P = 0.041$) were independent predictors for high-grade meningiomas (Table 2). The cut-off value was found as 6.73×10^9/L ($P = 0.001$) for leukocyte count and 4.78 for LMR ($P < 0.001$) according to the Youden index.

4. Discussion

In this study, we found that preoperative high leukocyte count and low LMR were independent predictors for high-grade meningiomas. The main strength of our study was the large sample size collected from a single institution. To the best of our knowledge, this is the first study to investigate these associations, and the results suggest that the determination of the leukocyte count and LMR before surgery could help the neurosurgeons make better decision on treatment plan for patients according to the hematological inflammatory markers combined with patients' individual preferences and needs.

Inflammatory and immune cells are important constituents of the tumor microenvironment, including meningioma [18]. Inflammatory responses play an important role in the initiation, promotion, malignant conversion, invasion, and metastasis of tumors [19]. Meningiomas have been found to be infiltrated with various types of immune cells, including lymphocytes, macrophages, mast cells, monocytes, and microglias [18,20,21]. Peripheral blood tests at the time of diagnosis or before treatment may reflect inflammatory conditions within the tumor [10]. Consistent with our study, Ahlbrecht et al. found that leukocyte count was higher in patients with high-grade tumors compared with that in patients with low-grade tumors [22]. Leukocyte count was also reported to be significantly higher in patients with endometrial cancer than in those with precancerous diseases [23]. In addition, several studies showed that elevated leukocyte count was a prognostic marker for poor prognosis in epithelial ovarian cancer, non-small cell lung cancer, endometrial carcinomas, and cervical cancer [24–27]. Peripheral blood leukocyte count is used as a marker for the systemic response of the host to an inflammation or infection [28]. The mechanism underlying the association between elevated leukocyte count, and poor prognosis and unfavorable clinicopathologic features in tumors was attributed to inflammatory events elicited by the tumor cells during tumorigenesis [24].

In our study, we demonstrated that a low LMR was associated with high tumor grade. This finding is consistent with previously reported findings for other tumors, including renal cell carcinoma and colorectal cancer [29,30]. The low LMR indicated a higher monocyte or lower lymphocyte count in the peripheral blood, and it may reflect the balance between the unfavorable role of monocytes and the favorable effect of lymphocytes with respect to tumor progression. Monocytes might directly stimulate tumor cell growth by producing various proinflammatory cytokines, including tumor necrosis factor, interleukin-6 and interleukin-1 [31]. Tumor-associated macrophages can enhance solid tumor progression and metastasis, and monocyte count in the peripheral blood may reflect the formation or presence of tumor-associated macrophages [15]. Lymphocytes can migrate into the tumor microenvironment, and evolve into tumor-infiltrating lymphocytes to establish a defensive barrier against tumor cell dissemination [15,32]. Moreover, tumor cells can secrete anti-inflammatory cytokines such as transforming growth factor-β, interleukin-10 and interleukin-4, causing systemic inflammation and inhibiting lymphocyte function [33]. Therefore, a low lymphocyte count in the peripheral blood may result in weakened defenses against tumors [34].

There are some limitations in our study. First, although we found a statistically significant difference in leukocyte count between the groups with high- and low-grade meningiomas, this difference may not be relevant from a clinical point of view, particularly if someone consider the similar ranges of these values (6.09 (2.67–9.95) vs 5.77 (2.40–9.98)). Second, the grade III meningioma group consisted of 13 patients in our study; due to the small number of grade III cases in our study, we just investigated the difference of preoperative hematological inflammatory markers in low- and high-grade meningiomas. Third, the retrospective design of this study may lead to some bias. Fourth, there was missing data in the recurrence-free survival and overall survival of the included patients. Fifth, due to unavailable data, we could not investigate the relationship between the dynamic change in preoperative hematological inflammatory parameters and meningioma risk and grade.

5. Conclusion

In conclusion, we demonstrated that preoperative high leukocyte count and low LMR were independent predictors for high-grade meningiomas.

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Disclosure of conflicts of interest

None.

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