Neurologia medico-chirurgica Advance Publication Date: September 1, 2021

Original Article doi: 10.2176/nmc.oa.2021-0153

Atypical Histological Features as Risk Factors for Recurrence in Newly Diagnosed WHO Grade I Meningioma

Keitaro Chiba,[1] Takashi Sugawara,[1] Daisuke Kobayashi,[2] Akihito Sato,[1] Yasuhiro Murota,[1] and Taketoshi Maehara[1]

[1]*Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan*
[2]*Department of Human Pathology, Tokyo Medical and Dental University, Tokyo, Japan*

Absract

The significance of atypical histological features (AHF) as risk factors for recurrence in benign meningioma is not well understood. This study examined risk factors of World Health Organization (WHO) Grade I meningioma (GIM) recurrence, focusing on AHF. We investigated 150 consecutive newly diagnosed GIM patients who had more than one year of follow-up after resection in our hospital between January 2007 and March 2018. The following factors were reviewed retrospectively: age, sex, tumor location, extent of resection, MIB-1 index, mitotic figures, number and distribution of AHF, and recurrence. The patients were grouped according to the presence or absence of recurrence and comparatively examined. Recurrence was observed in 10 cases (6.7%). Univariate analysis showed that patients with recurrence had a significantly higher MIB-1 index (2.0 vs. 4.3; p = 0.006) and a significantly higher proportion of male patients (21.4% vs. 70.0%; p = 0.002) and patients with sheet-like growth (6.42% vs. 30.0%; p = 0.04). In multivariate analysis, skull base location (odds ratio [OR] 31.424; 95% confidence interval [CI] 1.74–569), gross total resection (OR 0.130; 95% CI 0.0189–0.897), and MIB-1 index (OR 1.939; 95% CI 1.19–3.15) were significantly associated with recurrence. Our study revealed that skull base location, subtotal resection, and high MIB-1 index were independent risk factors for recurrence. Only the presence of sheet-like growth had a significantly higher incidence in patients with recurrence in univariate analysis of AHF. Multivariate analysis found no significant association. Sheet-like growth may be involved in malignancy and recurrence of benign meningioma.

Keywords: atypical histological features, benign meningioma, recurrence, risk factor

Introduction

Meningioma is the most common intracranial brain tumor, accounting for more than 20% of primary brain tumors.[1,2] According to the 2016 World Health Organization (WHO) classification of central nervous system tumours, meningioma is classified into three grades with 16 histological subtypes.[3] Atypical meningioma (WHO grade II) is diagnosed when at least three of the five following atypical histological features (AHF) are present: increased cellularity, increased nucleus/cytoplasm (N/C) ratio, prominent nucleoli, sheet-like growth, and necrosis.[4] In other words, AHF are important criteria in diagnosing a tumor as malignant.

WHO Grade I meningioma (GIM) accounts for approximately 22% of all tumors and has a reported 7–25% recurrence rate.[5] Although young age, male sex, subtotal resection (STR), high MIB-1 index, and both skull base and non-skull base locations have been reported as recurrence risk factors,[6–13] few studies have investigated the correlation between AHF and recurrence and there were no studies that have been considered in the presence and absence of recurrence. Thus, the significance of AHF as a risk factor for recurrence in benign meningioma is

Received May 27, 2021; Accepted August 2, 2021

not well understood. In this study, we examined risk factors for GIM recurrence in our hospital, focusing on the five AHF.

Materials and Methods

We investigated 150 consecutive newly diagnosed GIM patients who had more than one year follow-up after resection in our hospital between January 2007 and March 2018 as other articles that were investigating the recurrence of meningioma selected the follow-up period. We diagnosed GIM by the eligibility criteria, according to the 2016 World Health Organization (WHO) classification of central nervous system tumours. As brain-invasive meningiomas should be considered as grade II meningiomas in 2016 classification of WHO, brain invasion was not included in this study. The following factors were reviewed retrospectively: age, sex, tumor location (non-skull base or skull base), extent of resection (gross total resection [GTR], Simpson grade 1–2; or STR, Simpson grade 3–4), MIB-1 index, mitotic figures, number and distribution of AHF (increased cellularity, increased N/C ratio, prominent nucleoli, sheet-like growth, necrosis), and recurrence. The patients were grouped according to the presence or absence of recurrence and comparatively examined. The typical images of each are as follows (Fig. 1).

Statistical analyses were performed using SigmaPlot 10.0 software. The Fisher's exact test, chi-square test, t-test, and Mann–Whitney U test were used to investigate correlations between the clinical and pathological factors and recurrence. Multiple logistic regression was used to determine recurrence risk factors. P value less than 0.05 was considered significant. For multivariate analysis, variables whose p value was less than 0.2 in univariate analysis in our study were selected.

Results

The characteristics of the 150 GIM study patients are summarized in Table 1. The mean age of patients was 57.6 years (range, 19–86 years), and the majority were female (73.2%). The mean follow-up duration was 54.8 months (range, 12–143 months). Seventy-eight patients (52.0%) had tumors located at the skull base, and GTR was achieved in 101 patients (67.3%). The mean MIB-1 index was 2.51 (range, 0.25–8.4). Ten patients (6.7%) developed recurrence, and the mean time to recurrence was 38.3 months (range, 14–67 months). The distribution of AHF was as follows: increased cellularity (n = 25; 16.6%), increased N/C ratio (n = 16; 10.6%), prominent nucleoli (n = 20; 13.3%), sheet-like growth (n = 12; 8.0%), and necrosis (n = 6; 4.0%). The mean number of AHF was 0.51 (range, 0–2).

The results of our analysis are shown in Table 2. Univariate analysis showed that patients with recurrence had a significantly higher MIB-1 index (2.0 vs. 4.3; p = 0.006) and a significantly higher proportion of male patients (21.4% vs. 70.0%; p = 0.002) and patients with sheet-like growth (6.42% vs. 30.0%; p = 0.04). Mean age (57 years vs. 59 years;

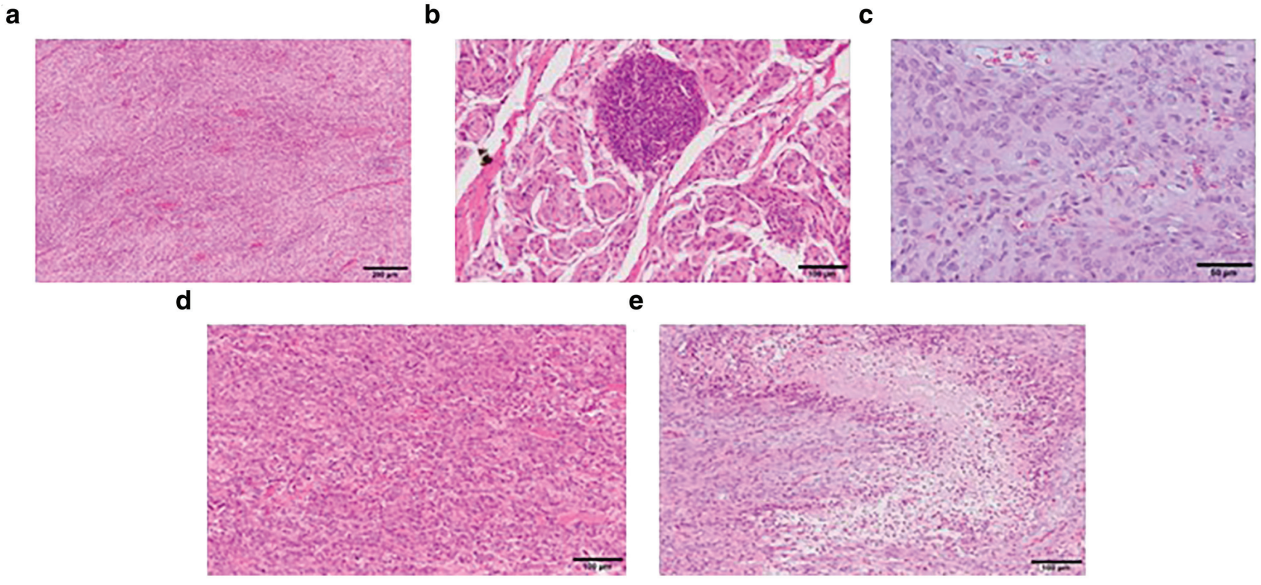

Fig. 1 Histopathology of atypical features. (a) Increased cellularity, (b) increased N/C ratio, (c) prominent nucleoli, (d) sheet-like growth, and (e) necrosis. N/C: nucleus/cytoplasm.

Table 1 Characteristics of the 150 benign meningioma patients (N = 150)

Characteristics	Value
Age, mean (years)	57.6 (19–86)
Sex	
Male, n (%)	37 (26.8)
Female, n (%)	113 (73.2)
Location	
Skull base, n (%)	78 (52.0)
Non-skull base, n (%)	72 (48.0)
Extent of resection	
GTR (Simpson grade 1 + 2), n (%)	101 (67.3)
STR (Simpson grade 3 + 4), n (%)	49 (32.6)
MIB-1 index %, mean (%)	2.51 (0–8)
Recurrence, n (%)	10 (6.67)
Time to recurrence, mean (months)	38.3 (14–67)
Number of AHF, mean	0.51 (0–2)
AHF	
Increased cellularity, n (%)	25 (16.6)
Increased N/C ratio, n (%)	16 (10.6)
Prominent nucleoli, n (%)	20 (13.3)
Sheet-like growth, n (%)	12 (8.0)
Necrosis, n (%)	6 (4.0)

AHF: atypical histological features, GTR: gross total resection, N/C: nucleus/cytoplasm, STR: subtotal resection.

p = 0.995), skull base location (50.0% vs. 80.0%; p = 0.132), GTR (69.2% vs. 40.0%; p = 0.119), mitotic figures (0.15 vs. 0.40; p = 0.307), increased cellularity (15.0% vs. 40.0%; p = 0.107), increased N/C ratio (10.0% vs. 20.0%; p = 0.646), prominent nucleoli (14.2% vs. 0%; p = 0.422), necrosis (3.57% vs. 10.0%; p = 0.867), and the number of AHF (0.48 vs. 1.00; p = 0.082) did not significantly differ between the two groups. In multivariate analysis, skull base location (odds ratio [OR] 31.424; 95% confidence interval [CI] 1.74–569), GTR (OR 0.130; 95% CI 0.0189–0.897), and MIB-1 index (OR 1.939; 95% CI 1.19–3.15) were significantly associated with recurrence. In other words, skull base location, STR, and high MIB-1 index were independent risk factors for recurrence.

Discussion

In previous studies, STR, Simpson grade 4 resection, young age, male sex, skull base and non-skull base location, presence of AHF, and high Ki-67 index have been reported as risk factors for recurrence.[6–19] In our analysis, high MIB-1 index, proportion of male patients, and presence of sheet-like growth were significantly higher in the recurrence group. Multivariate analysis showed that STR, skull base location, and high MIB-1 index were independent risk factors for recurrence.

Two previous studies have investigated the relevance of AHF in GIM recurrence. Nakasu et al. found that sheet-like growth, prominent nucleoli, and necrosis did not correlate with recurrence,[10] and Marciscano et al. reported that the presence of any AHF and the presence of necrosis and prominent nucleoli significantly increased the risk of recurrence in benign meningioma; increased cellularity and sheet-like growth were not associated with increased recurrence risk.[11] In addition, Ruiz et al. reported that only high cellularity was a significant prognostic factor for meningioma recurrence.[12] However, we found that sheet-like growth was the only AHF that had a significantly higher incidence in patients with a recurrence. In addition, results similar to our study, Barresi et al. reported that sheet-like growth was significantly associated with shorter disease-free survival in atypical meningioma.[17] Considering their finding and ours, sheet-like growth can be considered the most important factor among the five AHF to predict recurrence in GIM. We analyzed whether there was a difference in MIB-1 index between the meningiomas with and without sheet-like growth. The mean MIB-1 index was higher in the meningiomas with sheet-like growth, but no significant difference was observed. Roser et al. reported that there is no statistically significant correlation between mean Ki-67 and recurrence-free survival in patients harboring a benign meningioma.[20] The MIB-1 index is limited due to variations in results obtained in different laboratories that stain and count in different methods. Therefore, MIB-1 index may not always be a risk factor for recurrence. Furthermore, since it is relatively rare in GIM with sheet-like growth, the results may have differed. Sheet-like growth that is patternless or lacks the typical meningioma pattern[4] indicates a poorly differentiated tumor. Poor differentiation is common in higher grade malignancies.[21,22] Therefore, it is possible that sheet-like growth is involved in malignancies and recurrences. However, multivariate analysis has demonstrated that this feature was not a significant independent risk factor. Further correlative study with a larger number of patients and longer follow-up period is needed to clarify the relation between AHF and GIM recurrence.

Regarding tumor location, previous study results are contradictory. Some have reported that non-skull

Table 2 Comparison of clinical and histological factors between the benign meningioma patients with and without recurrence

Parameter	Univariate analysis			Multivariate analysis		
	Recurrence (n = 10)	No recurrence (n = 140)	p value	OR	95% CI	p value
Mean age (years)	58	57.6	0.995			
Sex			0.002			
Male	7	30		5.581	0.97–31.83	0.053
Female	3	110				
Extent of resection			0.119			
GTR (Simpson 1 + 2)	4	97		0.13	0.018–0.897	0.038
STR (Simpson 3 + 4)	6	43				
Location			0.184			
Skull base	8	70		31.424	1.74–569	0.02
Non-skull base	2	70				
MIB-1 index	4.3	2.0	0.006	1.939	1.19–3.15	0.008
Mitotic figure (/10 HPF)	0.40	0.15	0.307			
Number of AHF	1.00	0.48	0.082	0.477	0.06–3.74	0.482
AHF						
Increased cellularity	16.00%	4.80%	0.107	16.194	0.65–399.82	0.089
Increased N/C ratio	12.50%	5.97%	0.646			
Prominent nucleoli	0.00%	7.69%	0.422			
Sheet-like growth	25.00%	5.07%	0.04	11.551	0.35–380.62	0.17
Necrosis	16.70%	6.25%	0.867			

AHF: atypical histological features, GTR: gross total resection, HPF: high-power fields, N/C: nucleus/cytoplasm, STR: subtotal resection.

base meningioma has a higher recurrence than skull base meningioma; however, the proportion of skull base meningioma in these reports was as low as 32–45%.[13,18] On the other hand, another study composed of 66% skull base meningioma patients reported that skull base meningioma recurrence was higher.[19] Our study found that skull base location was an independent risk factor for recurrence in GIM; this may be related to the high proportion of tumors in this location in the study (52%).

Conclusion

This study is the first to consider AHF in the presence and absence of recurrence in GIM. As in previous reports, this study found that STR and high MIB-1 index were risk factors for recurrence in benign meningioma. In addition, skull base location was also an independent risk factor for recurrence. In univariate analysis of AHF, only the presence of sheet-like growth had a significantly higher incidence in patients with recurrence. However, multivariate analysis found no significant association between any of the AHF and recurrence. Therefore, more frequent follow-up examinations should be considered for patients with tumors that exhibit sheet-like growth as a histopathologic finding. Since the number of patients was small and the observation period was short in this study, further investigation is warranted.

Conflicts of Interest Disclosure

The authors declare that there are no conflicts of interest. All authors have registered online Self-reported COI Disclosure Statement Forms through the website for The Japan Neurosurgical Society members.

References

1) Brain Tumor Registry of Japan (2005-2008). *Neurol Med Chir (Tokyo)* 57: 9–102, 2017

2) Nakasu S, Nakasu Y: Natural history of meningiomas: review with meta-analyses. *Neurol Med Chir (Tokyo)* 60: 109–120, 2020
3) Louis DN, Perry A, Reifenberger G, et al.: The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 131: 803–820, 2016
4) Louis DN, Ohgaki H, Wiestler OD, et al.: The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 114: 97–109, 2007
5) Ostrom QT, Gittleman H, Farah P, et al.: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol* 15 Suppl 2: ii1–56, 2013
6) Oya S, Kawai K, Nakatomi H, Saito N: Significance of Simpson grading system in modern meningioma surgery: integration of the grade with MIB-1 labeling index as a key to predict the recurrence of WHO Grade I meningiomas. *J Neurosurg* 117: 121–128, 2012
7) van Alkemade H, de Leau M, Dieleman EM, et al.: Impaired survival and long-term neurological problems in benign meningioma. *Neuro Oncol* 14: 658–666, 2012
8) Matias JG, Jusue-Torres I, Martin B, et al.: Value of Ki-67 labeling index in predicting recurrence of WHO grade I cranial base meningiomas. *J Neurol Surg B Skull Base* 80: 287–294, 2019
9) Ehresman JS, Garzon-Muvdi T, Rogers D, et al.: The relevance of Simpson grade resections in modern neurosurgical treatment of World Health Organization Grade I, II, and III meningiomas. *World Neurosurg* 109: e588–e593, 2018
10) Nakasu S, Fukami T, Jito J, Nozaki K: Recurrence and regrowth of benign meningiomas. *Brain Tumor Pathol* 26: 69–72, 2009
11) Marciscano AE, Stemmer-Rachamimov AO, Niemierko A, et al.: Benign meningiomas (WHO Grade I) with atypical histological features: correlation of histopathological features with clinical outcomes. *J Neurosurg* 124: 106–114, 2016
12) Ruiz J, Martínez A, Hernández S, et al.: Clinicopathological variables, immunophenotype, chromosome 1p36 loss and tumour recurrence of 247 meningiomas grade I and II. *Histol Histopathol* 25: 341–349, 2010
13) Mansouri A, Klironomos G, Taslimi S, et al.: Surgically resected skull base meningiomas demonstrate a divergent postoperative recurrence pattern compared with non-skull base meningiomas. *J Neurosurg* 125: 431–440, 2016
14) Adegbite AB, Khan MI, Paine KW, Tan LK: The recurrence of intracranial meningiomas after surgical treatment. *J Neurosurg* 58: 51–56, 1983
15) Takahashi JA, Ueba T, Hashimoto N, Nakashima Y, Katsuki N: The combination of mitotic and Ki-67 indices as a useful method for predicting short-term recurrence of meningiomas. *Surg Neurol* 61: 149–155; discussion 155–156, 2004
16) Tyagi A, Chakrabarty A, Franks A: MIB1 proliferation index in meningiomas: does it predict recurrence? A clinicopathological study. *Br J Neurosurg* 18: 357–361, 2004
17) Barresi V, Lionti S, Caliri S, Caffo M: Histopathological features to define atypical meningioma: what does really matter for prognosis? *Brain Tumor Pathol* 35: 168–180, 2018
18) McGovern SL, Aldape KD, Munsell MF, et al.: A comparison of World Health Organization tumor grades at recurrence in patients with non-skull base and skull base meningiomas. *J Neurosurg* 112: 925–933, 2010
19) Savardekar AR, Patra DP, Bir S, et al.: Differential tumor progression patterns in skull base versus non-skull base meningiomas: a critical analysis from a long-term follow-up study and review of literature. *World Neurosurg* 112: e74–e83, 2018
20) Roser F, Samii M, Ostertag H, Bellinzona M: The Ki-67 proliferation antigen in meningiomas. Experience in 600 cases. *Acta Neurochir (Wien)* 146: 37–44, 2004
21) Hainsworth JD, Anthony Greco F: Poorly differentiated carcinoma of the mediastinum. *Gen Thorac Surg* Seventh Ed: 6413–6421, 2011
22) Adachi Y, Yasuda K, Inomata M, Sato K, Shiraishi N, Kitano S: Pathology and prognosis of gastric carcinoma: well versus poorly differentiated type. *Cancer* 89: 1418–1424, 2000

Corresponding author: Takashi Sugawara, MD, PhD
Department of Neurosurgery, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
e-mail: sugawara.nsrg@tmd.ac.jp