

OMICS PUBLISHING GROUP/Clinical

Meningioma with remarkable multiple rosette formation: A diagnostically difficult case --Manuscript Draft--

Manuscript Number:	CLINICALGROUP-18-812R1
Full Title:	Meningioma with remarkable multiple rosette formation: A diagnostically difficult case
Short Title:	Rosette forming meningioma
Article Type:	Case Report
Section/Category:	Journal of Medical & Surgical Pathology
Keywords:	meningioma; rosette formation; atypical meningioma; pseudopapillary
Corresponding Author:	Kenichi Mizutani JAPAN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
First Author:	Kenichi Mizutani, M.D.
First Author Secondary Information:	
Order of Authors:	Kenichi Mizutani, M.D. Satoko Nakada, M.D. Akira Tamase, M.D., Ph.D. Osamu Tachibana, M.D., Ph.D. Hideaki Iizuka, M.D., Ph.D. Takanori Hirose, M.D., Ph.D. Sohsuke Yamada, M.D., Ph.D.
Order of Authors Secondary Information:	
Manuscript Region of Origin:	JAPAN
Abstract:	<p>Background: Rosette formation is a rare morphological feature in meningiomas. It can be seen in angiomatous, meningothelial, transitional, secretory, papillary or rhabdoid subtype; however there are very few reports of meningiomas with rosettes, and the feature itself is not criterion for the WHO grade, so this feature sometimes makes the diagnosis difficult.</p> <p>Case presentation: A 62-year-old Japanese woman stumbled and was admitted to a hospital. Magnetic resonance imaging showed a 50 mm extra-axial tumor on the right cerebral falx. Histologically, the tumor contained multiple rosettes that had a central nuclear-free zone without a vessel core. It also showed a sheet-like or whorled growth pattern and pseudopapillary structure. Some round tumor cells had abundantly dense eosinophilic cytoplasm, displaying rhabdoid features. High cellularity, small cells with a high nuclear-to-cytoplasmic ratio and prominent nucleoli were recognized, but the mitotic activity was less than 1/10 high-power fields. The tumor was immunohistochemically positive for EMA and synaptophysin (weakly) but negative for GFAP, Progesterone, STAT6, S-100, NeuN and melan A. The Ki-67 labeling index was merely 0.5 %. Although ependymoma was considered as the first differential diagnosis, it was ruled out, as perivascular pseudorosettes and ependymal rosettes were not seen. We ultimately made a diagnosis of atypical meningioma with a rosette-like and pseudopapillary pattern, WHO grade II.</p> <p>Discussion and Conclusion: The meningiomas in this case showed remarkable rosette formation, but as this is not criterion for deciding WHO grade, grading was</p>

	<p>diagnostically difficult. Papillary meningioma was also considered as a critical differential diagnosis; however, our final diagnosis was made after considering the very low mitotic activity and Ki-67 labeling index, which were not consistent with WHO grade III. This case was very unique and diagnostically difficult. This report may be an aid for the diagnosis of pathologically unusual entity.</p>
Suggested Reviewers:	
Opposed Reviewers:	
Response to Reviewers:	<p>Response to the Editors and Reviewers</p> <p>First, we would like to express our thanks to the editors and reviewers for their comments. According to the comments of the editors and reviewers, we have revised our Case report (Meningioma with remarkable multiple rosette formation: A diagnostically difficult case).</p> <p>Our point-by-point responses to the comments are shown below.</p> <p>Response to Reviewer #1</p> <p>1. Page 4: Please change the sentence from "A study reported papillary meningioma recurred in up to 59 %" to "A study reported recurrence rate of papillary meningioma up to 59%"</p> <p>Ans: In accordance with the reviewer's comments, we made the following changes: "A study reported recurrence rate of papillary meningioma up to 59%"(page 4).</p> <p>2. Page 5, first paragraph: Please remove the word "and" in the following sentence "The tumor connected to the deeper edge of the cerebral falx and was surgically removed"</p> <p>Ans: In accordance with the reviewer's comments, we made the following changes: " The tumor connected to the deeper edge of the cerebral falx was surgically removed"(page 5).</p> <p>3. Page 5, second paragraph: Please place a "," after Histologically and correct the word "multiple" in the following sentence "Histologically the tumor contained multiple rosettes". The corrected sentence should read as "Histologically, the tumor contained multiple rosettes."</p> <p>Ans: In accordance with the reviewer's comments, we made the following changes: "Histologically, the tumor contained multiple rosettes"(page 5).</p> <p>4. Page 6 Under Discussion and Conclusion: Rewrite the following sentence "This is a very unique characteristic." The corrected sentence should read as "This is a very unique characteristic feature".</p> <p>Ans: In accordance with the reviewer's comments, we made the following changes: "This is a very unique characteristic feature"(page 6).</p> <p>5. In the list of abbreviations add the following: WHO, EMA, GFAP, STAT6.</p> <p>Ans: In accordance with the reviewer's comments, we made the following changes: "CT, computed tomography; MRI, magnetic resonance imaging; WHO, world health organization; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; STAT6, signal transducer and activator of transcription 6."(page 9).</p>

Dear Editor

According to the comments of the editors and reviewers, we have revised our Case report, entitled "Meningioma with remarkable multiple rosette formation: A diagnostically difficult case". We hope that you will consider the present manuscript for publication.

We look forward to hearing from you at your earliest convenience.

Respectfully yours,

Kenichi Mizutani, Department of Pathology and Laboratory Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Kahoku, Ishikawa 920-0293, Japan. Tel: 81-76-286-2211; Fax: 81-76-286-2339; and E-mail: mizutani@kanazawa-med.ac.jp

Response to the Editors and Reviewers

First, we would like to express our thanks to the editors and reviewers for their comments. According to the comments of the editors and reviewers, we have revised our Case report (Meningioma with remarkable multiple rosette formation: A diagnostically difficult case).

Our point-by-point responses to the comments are shown below.

Response to Reviewer #1

1. Page 4: Please change the sentence from "A study reported papillary meningioma recurred in up to 59 %" to "A study reported recurrence rate of papillary meningioma up to 59%"

Ans:

In accordance with the reviewer's comments, we made the following changes: "A study reported recurrence rate of papillary meningioma up to 59%"(page 4).

2. Page 5, first paragraph: Please remove the word "and" in the following sentence "The tumor connected to the deeper edge of the cerebral falx and was surgically removed"

Ans:

In accordance with the reviewer's comments, we made the following changes: "The tumor connected to the deeper edge of the cerebral falx was surgically removed"(page 5).

3. Page 5, second paragraph: Please place a "," after Histologically and correct the word "multiple" in the following sentence "Histologically the tumor contained multiple rosettes". The corrected sentence should read as "Histologically, the tumor contained multiple rosettes."

Ans:

In accordance with the reviewer's comments, we made the following changes: "Histologically, the tumor contained multiple rosettes"(page 5).

4. Page 6 Under Discussion and Conclusion: Rewrite the following sentence "This is a very unique characteristic." The corrected sentence should read as "This is a very unique characteristic feature".

Ans:

In accordance with the reviewer's comments, we made the following changes: "This is a very unique characteristic feature"(page 6).

5. In the list of abbreviations add the following: WHO, EMA, GFAP, STAT6.

Ans:

In accordance with the reviewer's comments, we made the following changes: "CT, computed tomography; MRI, magnetic resonance imaging; WHO, world health organization; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; STAT6, signal transducer and activator of transcription 6."(page 9).

Case report

Title

Meningioma with remarkable multiple rosette formation: A diagnostically difficult case

Author

Kenichi Mizutani^{1*}, M.D.; Satoko Nakada¹, M.D.; Akira Tamase², M.D., Ph.D.; Osamu Tachibana², M.D., Ph.D.; Hideaki Iizuka², M.D., Ph.D.; Takanori Hirose³, M.D., Ph.D.; Sohsuke Yamada¹, M.D., Ph.D.

¹Department of Pathology and Laboratory Medicine, Kanazawa Medical University, Japan;

²Department of Neurosurgery, Kanazawa Medical University, Japan;

³Department of Diagnostic Pathology, Hyogo Cancer Center, Japan.

Short running title: Rosette forming meningioma

Word count: 1162 words (Abstract 295 words); References: 5; and 1 Figure.

*Corresponding author: Kenichi Mizutani, Department of Pathology and Laboratory Medicine,

Kanazawa Medical University, 1-1 Daigaku, Uchinada, Kahoku, Ishikawa 920-0293, Japan. Tel: 81-76-286-2211; Fax: 81-76-286-2339; and E-mail: mizutani@kanazawa-med.ac.jp.

Abstract

Background: Rosette formation is a rare morphological feature in meningiomas. It can be seen in angiomatous, meningothelial, transitional, secretory, papillary or rhabdoid subtype; however there are very few reports of meningiomas with rosettes, and the feature itself is not criterion for the WHO grade, so this feature sometimes makes the diagnosis difficult.

Case presentation: A 62-year-old Japanese woman stumbled and was admitted to a hospital. Magnetic resonance imaging showed a 50 mm extra-axial tumor on the right cerebral falx. Histologically, the tumor contained multiple rosettes that had a central nuclear-free zone without a vessel core. It also showed a sheet-like or whorled growth pattern and pseudopapillary structure. Some round tumor cells had abundantly dense eosinophilic cytoplasm, displaying rhabdoid features. High cellularity, small cells with a high nuclear-to-cytoplasmic ratio and prominent nucleoli were recognized, but the mitotic activity was less than 1/10 high-power fields. The tumor was immunohistochemically positive for EMA and synaptophysin (weakly) but negative for GFAP, Progesterone, STAT6, S-100, NeuN and melan A. The Ki-67 labeling index was merely 0.5 %. Although ependymoma was considered as the first differential diagnosis, it was ruled out, as perivascular pseudorosettes and ependymal rosettes were not seen. We ultimately made a diagnosis of atypical meningioma with a rosette-like and pseudopapillary pattern, WHO grade II.

Discussion and Conclusion: The meningiomas in this case showed remarkable rosette formation, but

as this is not criterion for deciding WHO grade, grading was diagnostically difficult. Papillary meningioma was also considered as a critical differential diagnosis; however, our final diagnosis was made after considering the very low mitotic activity and Ki-67 labeling index, which were not consistent with WHO grade III. This case was very unique and diagnostically difficult. This report may be an aid for the diagnosis of pathologically unusual entity.

Key words: meningioma, rosette formation, atypical meningioma, pseudopapillary.

Background

Meningiomas are common intracranial neoplasm and categorized as WHO grade I to III. Most meningiomas correspond to WHO grade I. WHO grade II meningiomas consist of chordoid, clear cell or atypical meningioma, and those of WHO grade III contain papillary, rhabdoid or anaplastic meningioma. It has been described that recurrence rates of benign meningioma are about 7-25 %, whereas that of atypical meningioma is 29-52 %, and anaplastic meningioma recur in 50-94 % [1]. A study reported recurrence rate of papillary meningioma up to 59% [2]. Clinically, it is thus very critical to distinguish each grade meningioma only by microscopic findings.

Meningiomas show much variety of morphology and rosette formation is a rare morphological feature of the tumor. It could be seen in angiomatous, meningothelial, transitional, secretory, papillary

or rhabdoid subtype among them; however there are very few reports of the tumor with rosettes [3-5].

In addition, the feature itself is not criterion for deciding WHO grade. Therefore the feature sometimes makes diagnosis difficult.

Case presentation

A 62-year-old Japanese woman stumbled and was admitted to a hospital. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed 50 mm extra-axial tumor on the cerebral falx in the front region of right hemisphere (Figure 1A). The tumor showed calcification on CT. The mass showed iso-signal intensity on T1-weighted MRI and slight high-signal intensity on T2-weighted MRI. She was clinically diagnosed with meningioma. The tumor connected to the deeper edge of the cerebral falx was surgically removed.

Histologically, the tumor contained multiple rosettes that had a central nuclear-free zone filled with fibrillar cytoplasmic processes without vessel core (Figure 1B, C). It showed a sheet-like or whorled growth pattern and pseudopapillary structure (Figure 1D). Psammoma bodies, intranuclear pseudoinclusions, abundant hyalinized vessels and brownish-granule deposition were also seen. The tumor was consisted of spindle cells with large, oval-shaped nuclei and eosinophilic cytoplasm. Some round tumor cells had abundantly dense eosinophilic cytoplasm, displaying rhabdoid features (Figure 1E). High cellularity, small cells with a high nuclear-to-cytoplasmic ratio and prominent nucleoli were

recognized (Figure 1F), but the mitotic activity was less than 1/10 high-power fields. No obvious necrosis was seen. Immunohistochemistry revealed that the tumor was positive for EMA (Figure 1G), weakly positive for synaptophysin (Figure 1H) and negative for GFAP, Progesterone, STAT6, S-100, NeuN and melan A. Ki-67 labeling index of the tumor was merely 0.5 %. We ultimately made a diagnosis of atypical meningioma with a rosette-like and pseudopapillary pattern, WHO grade II. No recurrence has been reported for a year since the operation.

Discussion and Conclusion

The remarkable point of this case was that this tumor showed diffuse and multiple rosette formation. This is a very unique characteristic feature. Rosette formation is a morphological variant of meningioma and a rare feature. Ependymoma was considered as the initial differential diagnosis, since rosette formation is a known sign of ependymal differentiation. Perivascular pseudorosettes and ependymal rosettes are key features for the diagnosis of ependymoma. Perivascular pseudorosettes have a blood vessel core and perivascular anucleate zone. Ependymal rosettes are formed by columnar tumor cells arranged around a central lumen, and EMA immunoreactivity along the luminal surface of ependymal rosettes can be observed. Immunoreactivity for GFAP is usually observed in ependymoma. However rosettes of ependymoma were not seen in our case, and the cells were negative for GFAP. Therefore, based on these findings, ependymoma was ruled out.

Papillary glioneuronal tumor, meningeal melanocytoma and solitary fibrous tumor were also considered as differential diagnosis. Papillary glioneuronal tumor consists of glial cells forming a pseudopapillary structure with a hyalinized vessel core and neurocytes filling the interpapillary space and is usually positive for GFAP, S-100, NeuN and synaptophysin. In our case, although the tumor cells were weakly positive for synaptophysin, they were negative for GFAP, S-100 and NeuN. A pseudopapillary structure with glial cells and neurocytes was not observed. Meningeal melanocytoma and solitary fibrous tumor sometimes form a sheet-like and whorled growth pattern that resembles the morphology of meningiomas; the former is positive for melan A, while the latter is positive for STAT6. The tumor cells were also negative for these markers in the present case.

The tumor in our patient showed a whorled growth pattern and was positive for EMA. These findings were consistent with meningioma. While multiple rosette formation was undoubtedly the most remarkable feature, this is not a criterion for deciding on the WHO grade of meningioma, so grading was diagnostically difficult in this case. Papillary meningioma, which is a rare variant defined by the perivascular pseudopapillary pattern that corresponds to WHO grade III, was also considered as a critical differential diagnosis because a pseudopapillary pattern was observed; however the tumor was not consistent with WHO grade III, with its extremely low mitotic activity and Ki-67 labeling index. Considering the increased cellularity, small cells with a high nuclear-to-cytoplasmic ratio and prominent nucleoli, the final diagnosis was atypical meningioma with a rosette-like and

pseudopapillary pattern, WHO grade II.

We encountered a very rare and diagnostically difficult case of meningioma with remarkable multiple rosette formation. This unique case is worth reporting and may be an aid for the diagnosis of pathologically unusual entity.

References

1. Louis DN, Lhgaki H, Wiestler OD, Cavenee WK. WHO classification of tumours of the central nervous system, revised 4th edition. IARC, Lyon (2016).
2. Wang DJ, Zheng MZ, Gong Y, Xie Q, Wang Y, Cheng HX, Mao Y, Zhong P, Che XM, Jiang CC, Huang FP, Zheng K, Li SQ, Gu YX, Bao WM, Yang BJ, Wu JS, Xie LQ, Tang HL, Zhu HD, Chen XC, Zhou LF. Papillary meningioma: clinical and histopathological observation. *International journal of clinical and experimental pathology* 6 (2013) 878-888.
3. Liverman C, Mafra M, Chuang SS, Shivane A, Chakrabarty A, Highley R, Hilton DA, Byrne NP, Wesseling P, Perry A. A clinicopathologic study of 11 rosette-forming meningiomas: a rare and potentially confusing pattern. *Acta Neuropathol* 130 (2015) 311-313.
4. Tada T, Ishii K, Oshima S, Hara H, Kobayashi S. Secretory meningioma associated with numerous meningotheelial rosettes. *Acta Neuropathol* 84 (1992) 342-345.
5. Yamashima T. Meningotheelial Rosettes in the Canine Subarachnoid Space. *Acta Neuropathol* 66

(1985) 223-232.

List of Abbreviations Used

CT, computed tomography; MRI, magnetic resonance imaging; WHO, world health organization;
EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; STAT6, signal transducer
and activator of transcription 6.

Declarations

Funding

The authors declare that they received no funding for this report.

Conflicts of Interests

The authors declare that they have no conflicts of interests.

Acknowledgements

We would like to thank all members of our department for their expert technical assistance and general support.

Figure legends

Figure 1. An MRI scan, microscopic findings and immunohistochemical findings of specimen.

(A) T2-weighted MRI showed a 50 mm extra-axial tumor on the right cerebral falx. (B) The tumor had multiple rosettes. Bar = 500 μm (H&E staining) (original magnification: $\times 40$). (C) The rosettes had a central nuclear-free zone without a vessel core. The central area was filled with fibrillar cytoplasmic processes. Bar = 100 μm (H&E staining) (original magnification: $\times 200$). (D) The tumor also had a pseudopapillary structure. Bar = 100 μm (H&E staining) (original magnification: $\times 200$). (E) Rhabdoid features were seen. Bar = 50 μm (H&E staining) (original magnification: $\times 400$). (F) High cellularity, small cells with a high nuclear-to-cytoplasmic ratio and prominent nucleoli were seen. Bar = 50 μm (H&E staining) (original magnification: $\times 400$). (G, H) Immunohistochemistry revealed that the tumor cells were positive for EMA (G) and synaptophysin (weakly) (H). Ependymal rosettes were not observed on immunostaining for EMA (G). Bar = 50 μm (original magnification: $\times 400$).

Figure 1

