Pathology

Immunohistochemical study of autophagy associated molecules and cell adhesion molecules in canine intracranial granular cell tumors

Ryo SAITO1), James K CHAMBERS1)*, Kazuyuki UCHIDA1)

1)Laboratory of Veterinary Pathology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan

ABSTRACT. Granular cell tumors (GCTs) are characterized by abundant eosinophilic cytoplasmic granules. Based on the hypothesis that canine intracranial GCT is a subtype of meningioma and its cytoplasmic granules are formed through autophagy processes, histopathological and immunohistochemical examination were performed on biopsy samples from 7 cases of canine intracranial GCTs and 15 cases of conventional meningiomas. Histopathologically, 7/7 cases of GCTs involved the meninges; foci of meningothelial-like cells were observed in 3/7 cases; brain invasion was observed in 2/7 cases. Immunohistochemically, neoplastic cells of GCTs were positive for E-cadherin and negative for S100, cytokeratin, CD204, and β-catenin in 7/7 cases. Neoplastic cells of 15/15 cases of meningiomas were positive for E-cadherin, and negative for S100 and CD204. Immunoreactivity of meningiomas for cytokeratin and β-catenin was observed in 6/15 cases and 8/15 cases, respectively. Cytoplasmic granules of GCTs were positive for ubiquitin (5/7), p62 (5/7), and LC3 (7/7). Compared to GCTs, the ratios of ubiquitin (6/15) and p62 (3/15) positive cases were lower in meningiomas, and 15/15 cases were negative for LC3. These findings indicate that the biological natures of GCTs including anatomical location, histopathological features and immunoreactivity for E-cadherin are almost in conformity with those of meningiomas. The immunoreactivity for autophagy associated molecules may suggest the possible involvement of autophagy in cytoplasmic granule formation of canine intracranial GCTs.

KEYWORDS: autophagy, brain, dog, granular cell tumor, immunohistochemistry

Granular cell tumors (GCTs) are characterized by polygonal neoplastic cells with abundant cytoplasmic eosinophilic granules that are periodic acid–Schiff (PAS) positive and diastase resistant [8, 14]. In animals, GCTs have been reported in dogs, cats, horses, a bird, and rats [8, 10]. Although canine GCTs mostly occur in the oral tissue, intracranial GCT cases have been reported [2, 5, 10, 11, 17]. The derivation of GCT remains controversial; skeletal muscles, neurons, fibroblasts, histiocytes, and myoepithelial origin have been suggested [12, 13]. Based on immunohistochemical and electron microscopic studies, however, most GCTs in humans and dogs are considered to be derived from Schwann cells [6, 9, 11, 13, 16].

The autophagosome is the double-membrane structure without the proteolytic enzymes, and it becomes autolysosome when it is fused with a lysosome. If the LC3-attached phagosome or the phagosome sequestered by autophagosome is fused with a lysosome, the product is called the autophagolysosome [4]. The cytoplasmic granules of GCTs have been shown to be lysosomes, autophagosomes, or autophagolysosomes based on immunohistochemistry and electron microscopy findings [6, 9, 16]. Autophagy associated molecules, such as LC3, p62, and ubiquitin, have been detected in canine lingual GCTs, which suggest that the cytoplasmic granules of lingual GCTs are autophagosomes and autophagolysosomes [17].

Meningioma originates from arachnoid cap cells and meningothelial cells that derives from the neural crest tissue during development. As for canine lingual GCT, all cases were immunopositive for vimentin and negative for Iba-1 and α-SMA, which is consistent with immunohistochemical feature of meningioma [17]. Moreover, GCT shares some features with rhabdoid meningioma, i.e. their round and discohesive tumor cells [7, 15]. Another report on canine intracranial GCTs described invasive growth in the brain parenchyma on magnetic resonance (MR) and histopathological examinations [1].

Based on the hypothesis that canine intracranial GCT is a histological subtype of meningioma and its cytoplasmic granules are...
formed through autophagy, histopathological and immunohistochemical examinations were performed on 7 cases of canine intracranial GCT and 15 cases of canine intracranial meningioma.

MATERIALS AND METHODS

Cases

The histopathological database maintained in the Laboratory of Veterinary Pathology, Graduate School of Agricultural and Life Sciences, The University of Tokyo was searched for biopsy samples of canine intracranial GCT with PAS-positive cytoplasmic granules between 2016 and 2021 (Table 1). MR images of GCTs showed T1- and T2-weighted masses in the meninges. Additionally, 15 biopsy cases of canine intracranial meningioma with various histological subtypes and grades determined according to the classification described in Tumors in Domestic Animals 5th edition were selected as control cases: [8] including 4 meningotheelial (grade 1), 2 transitional (grade 1), 1 fibrous (grade 1), 3 atypical (grade 2), 1 papillary (grade 3), and 4 rhabdoid (grade 3) types (Table 2). Hematoxylin and eosin (HE) stained sections were reviewed and diagnosed according to the consensus of 3 pathologists (R.S., J.K.C., and K.U.).

Immunohistochemistry

Tissue samples were fixed in 10% phosphate-buffered formalin solution and embedded in paraffin. The immunohistochemistry procedure was as follows, using the following primary antibodies (Table 3): rabbit anti-S100 (polyclonal; Dako, Glostrup, Denmark), mouse anti-cytokeratin (AE1/AE3; DAKO), mouse anti-CD204 (SRA-E5; Trans Genic, Fukuoka, Japan), and mouse anti-E-cadherin (36/E-cadherin; BD Biosciences, Franklin Lakes, NJ, USA), mouse anti-b-catenin (14/Beta-Catenin; BD Biosciences), rabbit anti-LC3 (polyclonal; MBL), rabbit anti-p62 (polyclonal; MBL, Tokyo, Japan), rabbit anti-ubiquitin (polyclonal; CST, Danvers, MA, USA), and mouse anti-Ki-67 (MIB-1; Dako). Deparaffinized 4-µm-thick tissue sections were treated with 3% hydrogen peroxide (H2O2) in methanol at room temperature for 4 min. The sections were then incubated in 8% skim milk-Tris-buffered saline at 37°C for 40 min to prevent nonspecific reactions and subsequently at 4°C overnight with each primary antibody. Anti-mouse or anti-rabbit Envision

| Table 1. Profiles of granular cell tumor cases examined in the present study |
| --- |
| Case | Age (years) | Sex | Breed | Tumor location | Brain invasion | Dural invasion |
| 1 | 13 | F/S | Maltese | ND | + | - |
| 2 | 10 | M | Chihuahua | Frontal lobe | NA | - |
| 3 | 11 | F | Toy Poodle | Temporal lobe | + | - |
| 4 | 13 | F | Pekingese | Temporal lobe | NA | + |
| 5 | 13 | M/C | Toy Poodle | ND | NA | + |
| 6 | 7 | F/S | Mix | Frontal lobe | NA | + |
| 7 | 13 | F/S | Chihuahua | Olfactory bulb | NA | + |

M=male, M/C=male castrated, F=female, F/S=female sterilized, ND=no data, NA=brain parenchyma was not included in biopsy sample.

| Table 2. Profiles of meningioma cases examined in the present study |
| --- |
| Case | Subtype | Age (years) | Sex | Breed | Tumor location |
| 1 | Meningothelial | 10 | M/C | Toy Poodle | ND |
| 2 | Meningothelial | 10 | M | Shiba Inu | Frontal lobe |
| 3 | Meningothelial | 11 | F/S | Toy Poodle | Brain stem |
| 4 | Transitional | 13 | F/S | Toy Poodle | Frontal lobe |
| 5 | Atypical | 9 | F | Chihuahua | Base of the brain |
| 6 | Atypical | 11 | M | Pomeranian | Frontal lobe |
| 7 | Atypical | 10 | M | French Bulldog | Frontal lobe |
| 8 | Atypical | 5 | M | Toy Poodle | Temporal lobe |
| 9 | Atypical | 9 | F/S | Mix | Occipital lobe |
| 10 | Atypical | 12 | M/C | Chihuahua | Frontal lobe |
| 11 | Papillary | 11 | M | Mix | Base of the brain |
| 12 | Rhabdoid | 11 | M | Toy Poodle | Frontal lobe |
| 13 | Rhabdoid | 11 | M/C | Toy Poodle | Pariental lobe |
| 14 | Rhabdoid | 13 | F | Golden Retriever | Frontal lobe |
| 15 | Rhabdoid | 14 | F/S | Toy Poodle | Frontal lobe |

M=male, M/C=male castrated, F=female, F/S=female sterilized, ND=no data.
horseradish peroxidase-labelled polymer (DAKO) was then applied at 37°C for 40 min. Finally, the reactions were visualized with 0.05% 3,3′-diaminobenzidine and 0.03% hydrogen peroxide in Tris-hydrochloric acid buffer, followed by a counterstain with Mayer’s hematoxylin.

To calculate the Ki-67 index, the numbers of positive and negative tumor cells were counted in 5 high power fields (HPF, 400X), and the percentage of positive tumor cells among all counted cells was used. The percentage of immunopositive cells was scored: -, negative; +, 1–25% positive cells; ++, 26–50% positive cells; ++++, >50% positive cells.

RESULTS

Histopathologically, all GCT cases in the present study involved the meninges, and all but one case (case 7) mostly consisted of large round to polygonal cells with abundant eosinophilic cytoplasmic granules (Fig. 1) which were PAS positive and diastase resistant. As for case 7, both granular and meningothelial-like cells were observed equally, and PAS-positive and diastase-resistant granules were also observed. In 2 cases (cases 1, 2), foci of meningothelial-like cells were observed (Fig. 2). Brain parenchyma was included in the biopsy tissue of 2 cases (cases 1 and 3), and brain invasion of the tumor cells was observed in these cases. Dural invasion was observed in 4 cases (cases 4–7). As for meningiomas, brain invasion was observed in all cases of grade 2 and 3.

The immunohistochemistry results are summarized in Table 4. Immunohistochemical analysis for S100 and CD204 produced negative results in all cases of GCT and meningioma (Fig. 3). Neoplastic cells of all GCT cases were negative for cytokeratin, while those of 6/15 cases of meningioma were positive for cytokeratin. In meningiomas, the percentage of immunopositive cells for cytokeratin was 1–25% in 1 case, 26–50% in 2 cases, and >50% in 3 cases. The cytoplasm and membrane of neoplastic cells was weakly positive for E-cadherin in 7/7 GCT cases: cell positivity was >50% in 7 cases (Fig. 4). Similarly, the cytoplasm and cell membrane of neoplastic cells of all meningiomas cases examined (15/15 cases) were positive for E-cadherin (Fig. 5): the cell positivity was 1–25% in 1 case, 26–50% in 3 cases, and >50% in 11 cases. Neoplastic cells of GCTs were negative for β-catenin except for case 7, and >50% of meningothelial-like cells and granular cells were positive for β-catenin in case 7. In contrast, neoplastic cells of meningiomas were positive for β-catenin in 8/15 cases: the cell positivity was 1–25% in 2 cases, 26–50% in 3 cases, and >50% in 10 cases. As for proliferation activity, the mean Ki-67 index of GCT cases was 1.1%, which was lower than that of meningioma cases (3.6%).

Immunopositivity for autophagy molecules including LC3, p62, and ubiquitin, was observed in cytoplasmic granules of GCTs. Neoplastic cells of 7/7 GCT cases were positive for LC3 (Fig. 6): the cell positivity was 26–50% in 1 case, and >50% in 6 cases. In 5/7 cases of GCTs, the cytoplasmic granules were positive for p62 (Fig. 7): the cell positivity was 26–50% in 1 case, and >50% in 4 cases. In 5/7 GCT cases, cytoplasmic granules were positive for ubiquitin (Fig. 8): the cell positivity was 26–50% in 1 case, and >50% in 4 cases. In meningiomas, neoplastic cells of 15/15 cases were negative for LC3 (Fig. 9). Neoplastic cells of meningiomas were immunopositive for p62 in 3/15 cases (cases 1, 6, and 15; Fig. 10): the cell positivity was 26–50% in 1 case, and >50% in 2 cases. Furthermore, the neoplastic cells of meningioma were immunopositive for ubiquitin in 6/15 cases (cases 1, 5, 6, 11, 14, and 15; Fig. 11): the cell positivity was >50% in 6 cases.

DISCUSSION

In 3 cases of GCTs, foci of meningothelial-like cells, which were thought to be tumor cells, were observed. Moreover, the tumor tissue in all cases of GCT involved the meninges, which is consistent with a previous study of intracranial GCT in rats [19].

The most recent guidelines for assessing autophagy activity shows that LC3 positive puncta is the best evidence of autophagy involvement [4]. In the present study, cytoplasmic granules were positive for autophagy markers and immunohistochemistry showed LC3 puncta reactivity (Fig. 8), which is consistent with previous studies of human or canine lingual GCTs [16, 17]. Furthermore, meningiomas showed lower or no expression of autophagy markers compared to GCTs. These results suggest that cytoplasmic granules of GCTs are thought to be autophagosomes or autophagolysosomes and that autophagy may be involved in the development of GCTs based on the expression of LC3 and/or p62. Expression of p62, not LC3 is observed in 3/15 cases of meningiomas, but the
Fig. 1. Granular cell tumor (GCT), case 5. Polygonal cells with abundant eosinophilic cytoplasmic granules contiguous to the dura matter (upper layer). Hematoxylin and eosin (HE).

Fig. 2. Case No. 2. Foci of meningotheial-like tumor cells in tumor tissue (asterisk). HE.

Fig. 3. Granular cell tumor (GCT), case 3. GCT is negative for S100 (upper right, asterisk). Neuropil and astrocytes of brain parenchyma are immunolabeled (lower left). IHC for S100.

Fig. 4. Granular cell tumor (GCT), case 3. Cytoplasm and membrane of GCT is immunolabeled for E-cadherin (>50% positive cells). Immunohistochemistry (IHC) for E-cadherin.

Fig. 5. Meningioma, case 12. Cytoplasm and membrane of meningioma are immunolabeled for E-cadherin (>50% positive cells). IHC for E-cadherin.

Fig. 6. Granular cell tumor (GCT), case 5. The cytoplasmic granules of GCT are immunolabeled for LC3 (>50% positive cells). Immunohistochemistry (IHC) for LC3.

Fig. 7. Granular cell tumor (GCT), case 5. The cytoplasmic granules of GCT are immunolabeled for p62 (>50% positive cells). IHC for p62.

Fig. 8. Granular cell tumor (GCT), case 5. The cytoplasmic granules of GCT are immunolabeled for ubiquitin (>50% positive cells). IHC for ubiquitin.

Fig. 9. Meningioma, case 2. The cytoplasm of meningioma is negative for LC3. IHC for LC3.

Fig. 10. Meningioma, case 1. The cytoplasm of meningioma is immunolabeled for p62 (>50% positive cells). IHC for p62.

Fig. 11. Meningioma, case 1. The cytoplasm of meningioma is immunolabeled for ubiquitin (>50% positive cells). IHC for ubiquitin.
significance of its expression is unknown.

A previous study has shown that normal arachnoid cells are positive for E-cadherin [3]. In the present study, neoplastic cells of all meningiomas examined were immunopositive for E-cadherin. Neoplastic cells of all GCT cases were also immunopositive for E-cadherin, while the cytoplasm and membrane of neoplastic cells showed weak immunoreactivity. Among 15 cases of meningiomas, 6 were immunopositive for cytokeratin. Canine meningiomas are typically negative for cytokeratin, however rhabdoid meningioma has been reported to be cytokeratin-positive [7, 8, 15]. In the present study, rhabdoid type meningiomas were immunopositive for cytokeratin in all 4 cases. On the other hand, most other meningiomas examined (11 cases) were negative for cytokeratin, which is almost consistent with the immunohistochemical features of GCT.

In addition, the negative immunoreactivity for CD204 and S100 of GCTs may support that GCT is not derived from macrophages or neural tissue. However, the negative immunoreactivity for S100 was inconsistent with previous studies of GCT although S100 positivity was variable in these studies [2, 5, 10, 11, 13, 16, 17]. This discordance may be caused by instability of S100 antibody in immunohistochemistry, that is immunoreactivity for S100 varies depending on antigen retrieval. In this study, brain tissue was used as positive control. This result also indicates that intracranial GCT is not derived from nerve sheath cells, which were thought to be the origin of extracranial GCT [13, 16].

In addition, the negative immunoreactivity for CD204 and S100 of GCTs may support that GCT is not derived from macrophages or neural tissue. However, the negative immunoreactivity for S100 was inconsistent with previous studies of GCT although S100 positivity was variable in these studies [2, 5, 10, 11, 13, 16, 17]. This discordance may be caused by instability of S100 antibody in immunohistochemistry, that is immunoreactivity for S100 varies depending on antigen retrieval. In this study, brain tissue was used as positive control. This result also indicates that intracranial GCT is not derived from nerve sheath cells, which were thought to be the origin of extracranial GCT [13, 16].

In conclusion, the biological natures of GCTs including anatomical location, histopathological features and immunoreactivity for E-cadherin are almost in conformity with those of meningiomas, suggesting both of these tumors originate from meninges. Moreover, immunoreactivity for autophagy associated molecules in GCTs suggests the possible involvement of autophagy in cytoplasmic granule formation. However, this study has some limitations. One is the lack of specific antibody for meningioma, and the other is observation of tumor cell structure by transmission electron microscopy. The relationship between autophagy activity and the characteristics of GCTs, such as low expression of E-cadherin and high proliferation activity, may be disputable.

CONFLICT OF INTEREST. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

| Subtype      | Case | S100 | Cytokeratin | CD204 | E-cadherin | β-catenin | LC3 | p62 | Ubiquitin | Ki-67* LI | Mean Ki-67* LI |
|--------------|------|------|--------------|-------|------------|-----------|-----|-----|------------|-----------|---------------|
| GCT          | 1    | -    | -            | +++   | -          | +++       | +++ | +++ | -          | 0.5%      |                |
|              | 2    | -    | -            | +++   | -          | +++       | +++ | +++ | -          | 0.7%      |                |
|              | 3    | -    | -            | +++   | -          | ++        | -   | -   | -          | 0.9%      |                |
|              | 4    | -    | -            | +++   | -          | +++       | +++ | +++ | -          | 1.6%      | 1.1%          |
|              | 5    | -    | -            | +++   | -          | +++       | +++ | +++ | -          | 1.3%      |                |
|              | 6    | -    | -            | +++   | -          | ++        | -   | -   | -          | 1.6%      |                |
|              | 7    | -    | -            | +++   | -          | +++       | +++ | ++  | -          | 1.1%      |                |
| Meningioma   | 1    | -    | -            | +++   | ++         | -          | +++ | +++ | -          | 0.8%      |                |
| Meningothelial | 2  | -    | -            | +++   | ++         | -          | +++ | +++ | -          | 2.4%      |                |
|              | 3    | -    | -            | ++    | -          | +++       | -   | -   | -          | 3.5%      |                |
| Transitional | 4    | -    | -            | -     | -          | -         | -   | -   | -          | 2.1%      |                |
| Atypical     | 5    | -    | -            | ++    | -          | -         | -   | -   | -          | 4.3%      |                |
|              | 6    | -    | -            | +++   | -          | +++       | -   | -   | -          | 4.3%      |                |
|              | 7    | -    | -            | +++   | -          | ++        | -   | -   | -          | 7.2%      |                |
|              | 8    | -    | -            | ++    | -          | -         | -   | -   | -          | 2.1%      | 3.6%          |
|              | 9    | -    | -            | +++   | -          | -         | -   | -   | -          | 8.3%      |                |
|              | 10   | -    | -            | +++   | -          | -         | -   | -   | -          | 2.1%      |                |
| Papillary    | 11   | -    | -            | +++   | -          | +++       | -   | -   | -          | 4.1%      |                |
| Rhabdoid     | 12   | -    | -            | +++   | -          | -         | -   | -   | -          | 2.4%      |                |
|              | 13   | -    | -            | +++   | -          | -         | -   | -   | -          | 6.2%      |                |
|              | 14   | -    | -            | +++   | -          | -         | -   | -   | -          | 4.7%      |                |
|              | 15   | -    | -            | +++   | -          | -         | -   | -   | -          | 0%        |                |

-, negative; +, 1–25% positive cells; ++, 26–50% positive cells; +++ >50% positive cells. *The Ki-67 labeling index (LI) represents the percentage of positive tumor cells among the total tumor cells.
REFERENCES

1. Anwer CC, Vernau KM, Higgins RJ, Dickinson PJ, Sturges BK, LeCouteur RA, Bentley RT, Wisner ER. 2013. Magnetic resonance imaging features of intracranial granular cell tumors in six dogs. *Vet Radiol Ultrasound* **54**: 271–277. [Medline] [CrossRef]

2. Higgins RJ, LeCouteur RA, Vernau KM, Sturges BK, Obradovich JE, Bollen AW. 2001. Granular cell tumor of the canine central nervous system: two cases. *Vet Pathol* **38**: 620–627. [Medline] [CrossRef]

3. Ide T, Uchida K, Suzuki K, Kagawa Y, Nakayama H. 2011. Expression of cell adhesion molecules and doublecortin in canine anaplastic meningiomas. *Vet Pathol* **48**: 292–301. [Medline] [CrossRef]

4. Klionsky DJ, Abdel-Aziz AK, Abdelfatah S, et al. 2021. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). *Autophagy* **17**: 1–382.

5. Liu CH, Liu CI, Liang SL, Cheng CH, Huang SC, Lee CC, Hsu WC, Lin YC. 2004. Intracranial granular cell tumor in a dog. *J Vet Med Sci* **66**: 77–79. [Medline] [CrossRef]

6. Lu JE, Dubielzig R. 2012. Canine eyelid granular cell tumor: a report of eight cases. *Vet Ophthalmol* **15**: 406–410. [Medline] [CrossRef]

7. Mattyja E, Grajowska W, Nauman P, Bonicki W, Bojarski P, Marchel A. 2010. Necrotic rhabdoid meningiomas with aggressive clinical behavior. *Clin Neuropathol* **29**: 307–316. [Medline] [CrossRef]

8. Meuten DJ. 2017. Tumors of the nervous system. pp. 834–891. In: Tumors in Domestic Animals, 5th ed. (Higgins RJ eds.), Wiley-Blackwell, Hoboken.

9. Miwa K, Hattori T, Hosokawa Y, Nakamura Y, Isobe Y, Fujisawa K, Nakagawara G. 1986. Granular cell tumor of the esophagus. *Gastroenterol Jpn* **21**: 508–512. [Medline] [CrossRef]

10. Patnaik AK. 1993. Histologic and immunohistochemical studies of granular cell tumors in seven dogs, three cats, one horse, and one bird. *Vet Pathol* **30**: 176–185. [Medline] [CrossRef]

11. Rallis TS, Tontis DK, Soubasis NH, Patsiaura KK, Papazoglou LG, Adamama-Moraitou KK. 2001. Immunohistochemical study of a granular cell tumor on the tongue of a dog. *Vet Clin Pathol* **30**: 62–66. [Medline] [CrossRef]

12. Rao D, Rylander H, Drees R, Schwarz T, Steinberg H. 2010. Granular cell tumor in a lumbar spinal nerve of a dog. *J Vet Diagn Invest* **22**: 638–642. [Medline] [CrossRef]

13. Rejas RA, Campos MS, Cortes AR, Pinto DD, de Sousa SC. 2011. The neural histogenetic origin of the oral granular cell tumor: an immunohistochemical evidence. *Med Oral Patol Oral Cir Bucal* **16**: e6–e10. [Medline] [CrossRef]

14. Rickert CH, Kuchelmeister K, Gullotta F. 1997. Morphological and immunohistochemical characterization of granular cells in non-hypophyseal tumours of the central nervous system. *Histopathology* **30**: 464–471. [Medline] [CrossRef]

15. Saito A, Nakazato Y, Yoshi Y, Hyodo A, Harakuni T, Toita T, Ogawa K, Horikawa K, Terada Y, Kinjo S, Minei S. 2001. Anaplastic meningioma with papillary, rhabdoid, and epithelial features: a case report. *Brain Tumor Pathol* **18**: 155–159. [Medline] [CrossRef]

16. Shintaku M. 2011. Immunohistochemical localization of autophagosomal membrane-associated protein LC3 in granular cell tumor and schwannoma. *Virchows Arch* **459**: 315–319. [Medline] [CrossRef]

17. Suzuki S, Uchida K, Harada T, Nibe K, Yamashita M, Ono K, Nakayama H. 2015. The origin and role of autophagy in the formation of cytoplasmic granules in canine lingual granular cell tumors. *Vet Pathol* **52**: 456–464. [Medline] [CrossRef]

18. Utsumi S, Oka H, Sato Y, Kawano N, Tsuchiya B, Kobayashi I, Fujii K. 2005. Invasive meningioma is associated with a low expression of E-cadherin and beta-catenin. *Clin Neuropathol* **24**: 8–12. [Medline]

19. Yoshida T, Mitsumori K, Harada T, Maia K. 1997. Morphological and ultrastructural study of the histogenesis of meningial granular cell tumors in rats. *Toxical Pathol* **25**: 211–216. [Medline] [CrossRef]