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# Pathological and immunohistochemical features of 45 cases of feline meningioma

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**ABSTRACT.** Meningioma is the most common primary brain tumor in cats, although there are few reports about their pathological features. To investigate the histopathological subtypes and immunohistochemical features including expression of cytokeratin and cell adhesion molecules, 45 cases of feline meningioma were examined. The mean age was 12.5 years (range 6–21 years). No statistically significant sex predilection was observed. Regarding the anatomical location of meningioma, tumors mostly developed in the cerebrum, followed by spinal cord and cerebellum, and multiple meningioma was observed in one cat. Microscopically, linear or focal mineralization was observed in 40 cases and cholesterol cleft was observed in 14 cases. Based on histopathological subtypes, there were 15 fibrous, 22 transitional, 2 meningothelial, 5 atypical, and 1 anaplastic meningiomas. These subtypes are classified into grade 1 (39 cases), grade 2 (5 cases), and grade 3 (1 case). There was no significant difference in the Ki-67 index among histological subtypes or grades. Immunohistochemically, the tumor cells were positive for cytokeratin in 5 cases (12.8%), vimentin in 17 cases (43.6%), E-cadherin in 36 cases (92.3%), β-catenin in 21 cases (53.8%), and N-cadherin in 1 case (2.6%), demonstrating the utility of E-cadherin-immunohistochemistry for the diagnosis of feline meningiomas.

**KEY WORDS:** cat, E-cadherin, immunohistochemistry, meningioma, proliferation index

Meningioma is the most common primary brain tumor in cats, comprising 59.0% of intracranial neoplasms [28]. Meningioma is considered to originate from the cap cells covering the arachnoid granulations (arachnoid villi) [11, 17, 21]. Although meningioma is commonly regarded as a benign tumor because of its slow growth and low recurrence rate, it often causes neurological deficits [23, 27]. Furthermore, it is considered that surgical excision is a beneficial method of treatment of feline meningioma because of its low recurrence rate [5, 9]. Histopathologically, most feline meningiomas are transitional and fibrous subtypes, in contrast to canine or human meningioma which exhibits variable morphological patterns [15]. Moreover, feline meningioma often demonstrates cholesterol cleft formation and linear or focal calcification unlike psammoma bodies [15].

The mitotic index is used in grading meningiomas, and the Ki-67 antigen is widely used to investigate the proliferative activity of tumor cells in humans [1, 14, 19, 20, 25]. However, there is few reports about the relationship between the proliferation index and histopathological subtypes or other factors, such as gender and tumor location in cats [12, 13, 16]. Tumor invasion of the brain parenchyma is also associated with aggressive progression in human meningioma, and cell adhesion molecules, such as E-cadherin and N-cadherin, play a role in tumor cell invasion [6, 7, 10, 26]. That is, decrease of E-cadherin expression and increase of N-cadherin expression causes mesenchymal transition and invasive growth of the tumor [7, 10]. However, there are no studies on the expression of cell adhesion molecules in feline meningioma. In addition to cell adhesion molecules, cytokeratin, vimentin, and claudin-1 are also used for the diagnosis of human and canine meningiomas [3, 15, 22]. However, there are few reports about the expression of these molecules in feline meningioma [24].

It is important to collect data regarding feline meningioma in order to improve our understanding of its epidemiology and histopathology because there are few retrospective studies especially from histopathological point of view [18]. Furthermore, there is no published classification for feline meningioma. Therefore, a classification of human meningioma adapted to canine meningioma was used in the present study to investigate whether this classification is suitable for feline meningioma [15]. According to this classification, histological subtypes of meningioma are grouped into grades 1, 2 and 3. However, pathological significance of this grading system has not been examined in animal species. The purpose of the present study was to investigate histopathological and immunohistochemical features and assess the correlation between proliferative activity and histopathological classification when grading feline meningioma.

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## MATERIALS AND METHODS

The histopathological database maintained in the Laboratory of Veterinary Pathology, Graduate School of Agricultural and Life Sciences, the University of Tokyo was searched for cats diagnosed with meningioma between 2010 and 2020. As a referral diagnostic center of neuropathology, intracranial tumor cases were submitted to our institution from veterinary clinics across Japan, covering a wide geographic region. Biopsy and necropsy cases with a diagnosis of meningioma occurring in the brain and spinal cord were both examined. Feline breed, age at the time of diagnosis, sex, anatomical location of the tumor, pathological features, and proliferation activity were examined in each case. Histology slides were reviewed and diagnosed by consensus of 3 diagnosticians (R.S., J.K.C., and K.U.), and all cases were then classified into histological subtypes of meningiomas according to the published classification [15].

Immunohistochemistry (IHC) was performed in 39 cases, of which paraffin embedded tissues were available. Deparaffinized tissue sections were treated with 10% hydrogen peroxide ($H_2O_2$) in methanol at room temperature for 4 min. Antigen retrieval was performed by autoclave for 10 min at 120°C. The sections were 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 the following primary antibodies: mouse anti-cytokeratin (AE1/AE3; DAKO, Tokyo, Japan), mouse anti-vimentin (V9; DAKO), rabbit anti-claudin-1 (polyclonal; abcam, Cambridge, UK), mouse anti-E-cadherin (36/E-Cadherin; BDbiosciences, Franklin Lakes, NJ, USA), mouse anti-β-catenin (14/Beta-Catenin; BDbiosciences), mouse anti-N-cadherin (D-4; Santa Cruz Biotechnology, Santa Cruz, CA, USA), and mouse anti-Ki-67 (MIB-1; DAKO). Anti-mouse or Anti-rabbit Envision 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 nuclei were counted in 5 high power fields (HPF, 400×), and the percentage of positive tumor cells among all counted cells was used. The degrees of immunoreactivity of tumor cells for cytokeratin, E-cadherin, β-catenin, and N-cadherin were graded as follows: the percentage of immunopositive cells was scored: 0, negative; 1, 1–25% positive cells; 2, 26–50% positive cells; 3, >50% positive cells. The intensity of the immunopositive cells was scored: 1, weak; 2, moderate; 3, strong. These two scores were combined and defined as the immunostaining score.

Statistical analysis was performed using Statcel 4 software (OMS Publishing Inc., Saitama, Japan). Gender predilection, and significant differences in gonadectomy, breed, histological subtype, and immunoreactivity for cytokeratin, E-cadherin, N-cadherin, and β-catenin were examined using Pearson's chi-squared test. The Kruskal-Wallis test was performed to assess the differences between the mean Ki-67 index and histological subtypes. The Student's *t* test was used to confirm the significant differences between the mean Ki-67 index by sex or castration. Pearson correlation coefficient analysis was conducted to examine the correlation between the mean Ki-67 index and the immunostaining scores of E-cadherin and β-catenin. Differences were considered significant at a *P*-value <0.05.

## RESULTS

During the 11 years that the study covered, 2,330 feline cases were histopathologically examined and included 1,189 males (987 neutered and 202 intact), 1,102 females (231 neutered and 871 intact), and 39 unknown. In this case series, 1,275 cases were diagnosed with neoplastic disease. A total of 45 cases were diagnosed with meningioma, which accounted for 1.9% and 3.5% of all cases and tumor cases, respectively. The mean age of those cases was 12.5 years (range 6–21 years). There were 29 males (24 neutered and 5 intact), 15 females (10 neutered and 5 intact), and 1 unknown (Table 1). There was no significant sex predilection (*P*=0.065). No significant correlation was found between the occurrence of meningiomas and castration (*P*=0.971) or sterilization (*P*=0.244). The breeds of affected cats consisted of American Shorthair (n=9; 20.0%), Scottish Fold (n=3; 6.7%), Chinchilla (n=2; 4.4%), Norwegian Forest Cat (n=2; 4.4%), Turkish Van (n=1; 2.2%), and mixed breed (n=28; 62.2%) (Table 1). American Shorthair (*P*=0.002) and Norwegian Forest Cat (*P*=0.046) had a significantly higher risk of developing meningiomas. The anatomical location of meningiomas were recorded in 41 cats. The cerebrum was most commonly affected (n=37; 90.2%), followed by spinal cord (n=2; 4.9%) and cerebellum (n=2; 4.9%). Regarding cerebral meningiomas, 5 (12.1%) were located in the frontal lobe, 8 (19.5%) in the parietal lobe, 17 (41.5%) in the temporal lobe, 2 (4.9%) in the occipital lobe, 2 (4.9%) in the convexity, and 2 (4.9%) in the third ventricle. In 1 case (2.4%), tumors were recognized in the frontal lobe and temporal lobe (Table 1). Spinal meningiomas were located in thoracic and lumber spinal cord. Mitotic count per 10 HPF was less than 1 in all cases.

As for histopathological subtypes, 39 cases (86.7%) were classified into grade 1, 5 cases (11.1%) were grade 2, and 1 case (2.2%) was grade 3. Among grade 1 meningiomas, transitional meningioma was the most common subtype (n=22; 48.9%, Fig. 1), followed by fibrous (n=15; 33.3%, Fig. 2), and meningothelial (n=2; 4.4%, Fig. 3). All grade 2 meningiomas were atypical meningioma characterized by an irregular growth pattern, necrosis, increased cellularity, nuclear atypia, a high N/C ratio, and 4 or more mitotic figures per 10 HPF (Fig. 4). Grade 3 was anaplastic meningioma defined by cellular anaplasia and high mitotic activity of over 20 mitoses per 10 HPF. Regardless of histological subtypes, cholesterol clefts and mineralization were observed in 14 cases (31.1%, Fig. 5) and in 40 cases (88.9%, Fig. 6), respectively.

Immunohistochemical results are summarized in Table 2. The tumor cells of meningiomas examined were positive for cytokeratin in 5 cases (12.8%, Fig. 7) and vimentin in 17 cases (43.6%), and all cases were negative for claudin-1 (data not shown). The tumor cells were positive for E-cadherin and β-catenin in 36 (92.3%, Fig. 8) and 21 (53.8%) cases, respectively. Nuclear immunoreactivity of tumor cells for β-catenin was not observed. The tumor cells were positive for N-cadherin only in 1 case (2.6%). There was no significant correlation between histological subtype and immunoreactivity of these molecules (cytokeratin, *P*=0.476; E-cadherin, *P*=0.075; β-catenin, *P*=0.294; N-cadherin, *P*=0.914). Furthermore, there was no significant correlation between the immunostaining scores of E-cadherin and β-catenin

**Table 1.** Profiles of cats with meningioma in the present study

| Case | Age (years) | Sex | Breed | Necropsy/ Biopsy | Tumor location | Subtype | Mineralization | Cholesterol cleft | Ki-67 index |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 10 | F/S | Mix | Biopsy | Parietal lobe | Transitional | + | + | 1.4 |
| 2 | 13 | F/S | American Shorthair | Biopsy | Frontal lobe | Transitional | + | + | 3.2 |
| 3 | 12 | F/S | Turkish Van | Biopsy | Temporal lobe | Transitional | + | + | 0.7 |
| 4 | 11 | M/C | Mix | Biopsy | Temporal lobe | Transitional | + | + | 1.4 |
| 5 | 11 | M/C | Mix | Biopsy | Convexity | Transitional | + | + | 1.0 |
| 6 | 16 | M/C | Chinchilla | Necropsy | Third ventricle | Fibrous | + | - | 0.3 |
| 7 | 16 | M | American Shorthair | Necropsy | Parietal lobe | Fibrous | + | - | 5.2 |
| 8 | 14 | M/C | Norwegian Forest Cat | Biopsy | Parietal lobe | Transitional | + | - | 2.4 |
| 9 | 13 | F/S | Mix | Necropsy | ND | Fibrous | + | - | NI |
| 10 | 13 | M | Mix | Biopsy | Temporal lobe | Transitional | + | + | 2.2 |
| 11 | 13 | F | American Shorthair | Biopsy | Temporal lobe | Meningothelial | + | - | 10.8 |
| 12 | 14 | M/C | Mix | Biopsy | Cerebellum | Meningothelial | + | - | 10.2 |
| 13 | 14 | F | American Shorthair | Biopsy | Parietal lobe | Transitional | + | + | 3.5 |
| 14 | 13 | M/C | American Shorthair | Biopsy | Lumber spinal cord | Transitional | + | - | 7.3 |
| 15 | 14 | F | Mix | Biopsy | Temporal lobe | Transitional | + | + | 3.7 |
| 16 | 12 | M | Chinchilla | Biopsy | Frontal lobe | Transitional | + | - | NI |
| 17 | 8 | M/C | American Shorthair | Biopsy | Frontal lobe | Fibrous | - | - | 3.1 |
| 18 | 11 | M/C | American Shorthair | Biopsy | ND | Transitional | + | - | 1.0 |
| 19 | 13 | F/S | Scottish Fold | Necropsy | Temporal lobe | Fibrous | + | - | 0 |
| 20 | 11 | M/C | Mix | Biopsy | Parietal lobe | Atypical | + | - | 2.5 |
| 21 | 13 | M/C | Mix | Necropsy | Occipital lobe | Atypical | + | - | NI |
| 22 | 12 | M/C | Mix | Biopsy | Multiple lobe | Anaplastic | + | - | 8.8 |
| 23 | 10 | M/C | Mix | Biopsy | Temporal lobe | Transitional | + | + | 6.5 |
| 24 | 14 | F/S | Mix | Biopsy | Temporal lobe | Fibrous | - | - | 12.6 |
| 25 | 9 | ND | Mix | Biopsy | Temporal lobe | Fibrous | + | - | 2.4 |
| 26 | 21 | F/S | Mix | Necropsy | Temporal lobe | Fibrous | + | - | 7.8 |
| 27 | 11 | M/C | American Shorthair | Biopsy | Frontal lobe | Fibrous | + | - | NI |
| 28 | 7 | F | Mix | Biopsy | Parietal lobe | Fibrous | + | - | 8.1 |
| 29 | 13 | M/C | Mix | Biopsy | Frontal lobe | Transitional | - | - | NI |
| 30 | 14 | F/S | Mix | Biopsy | Temporal lobe | Fibrous | + | - | 2.7 |
| 31 | 14 | M/C | Mix | Necropsy | ND | Fibrous | + | - | NI |
| 32 | 12 | F/S | Scottish Fold | Biopsy | Temporal lobe | Transitional | + | - | 6.5 |
| 33 | 13 | M/C | Mix | Necropsy | Parietal lobe | Transitional | + | + | NI |
| 34 | 10 | M/C | Mix | Biopsy | Occipital lobe | Transitional | + | - | 3.7 |
| 35 | 13 | F/S | Scottish Fold | Biopsy | Temporal lobe | Atypical | + | - | 8.2 |
| 36 | 6 | M/C | Mix | Biopsy | Thoracic spinal cord | Atypical | + | - | 2.6 |
| 37 | 9 | M/C | Mix | Biopsy | Convexity | Atypical | + | + | 10.1 |
| 38 | 11 | M/C | Mix | Biopsy | Temporal lobe | Fibrous | + | - | 14.6 |
| 39 | 8 | M/C | Norwegian Forest Cat | Biopsy | Frontal lobe | Transitional | - | + | 0.7 |
| 40 | 12 | M/C | Mix | Biopsy | Third ventricle | Fibrous | + | + | 3.5 |
| 41 | 7 | M/C | American Shorthair | Biopsy | Temporal lobe | Transitional | + | + | 0 |
| 42 | 15 | F | Mix | Biopsy | Cerebellum | Transitional | - | - | 7.3 |
| 43 | ND | M | Mix | Biopsy | Temporal lobe | Transitional | - | + | 1.8 |
| 44 | 11 | M/C | Mix | Biopsy | Temporal lobe | Transitional | + | + | 9.3 |
| 45 | ND | M/C | Mix | Biopsy | ND | Fibrous | - | - | 3.7 |

M=male, M/C=male castrated, F=female, F/S=female spayed, ND=no data, NI=not investigated, Ki-67 index represents the percentage of positive tumor cells.

($P$=0.098). There was no significant association between the mean Ki-67 index and histological subtype, immunostaining score of E-cadherin ($P$=0.542) and β-catenin ($P$=0.268), sex ($P$=0.801), or gonadectomy (male, $P$=0.832; female, $P$=0.179).

## DISCUSSION

Meningioma has a female predilection associated with the expression of female hormone receptors in human, and previous studies revealed that feline meningiomas also express female hormone receptors, such as progesterone receptors [2, 4, 12]. In the present and also in previous studies, male cases outnumbered female cases in the occurrence of meningioma [18, 27, 28]. However, there was no statistically significant sex predilection in the present study. In this study, the most commonly affected breed was American Shorthair, followed by Scottish Fold, Chinchilla, Norwegian Forest Cat, and Turkish Van, although most cats were of mixed breed. Statistically,

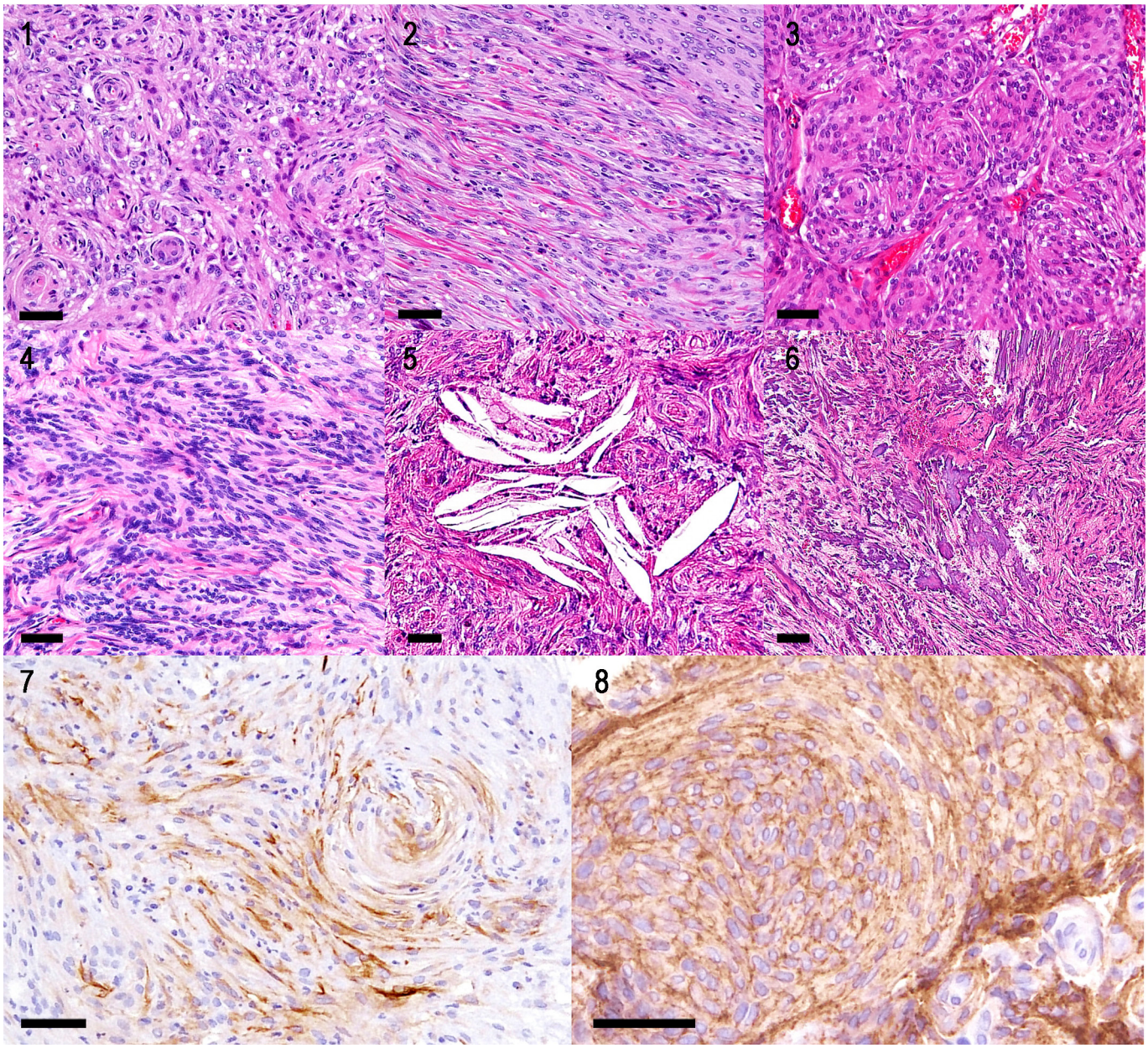


**Fig. 1.** Intracranial; meningioma, cat. Transitional meningioma; case 32. Tumor comprises meningothelial meningioma and fibrous meningioma components. Hematoxylin and eosin (HE). Bar=50 µm.

**Fig. 2.** Intracranial; meningioma, cat. Fibrous meningioma; case 38. Spindle tumor cells arranged in bundles or streams. HE. Bar=50 µm.

**Fig. 3.** Intracranial; meningioma, cat. Meningothelial meningioma; case 11. Polygonal tumor cells form whorls, separated by fibrovascular stromal tissue. HE. Bar=50 µm.

**Fig. 4.** Intracranial; meningioma, cat. Atypical meningioma; case 20. Pleomorphic tumor cells show increased cellularity. HE. Bar=50 µm.

**Fig. 5.** Intracranial; meningioma, cat. Transitional meningioma; case 1. Cholesterol clefts in the tumor tissue. HE. Bar=50 µm.

**Fig. 6.** Intracranial; meningioma, cat. Transitional meningioma; case 39. Linear and focal mineralization in the tumor tissue. HE. Bar=50 µm.

**Fig. 7.** Intracranial; meningioma, cat. Atypical meningioma; case 35. The cytoplasm of spindle-shaped tumor cells is moderately positive for cytokeratin. Percentage of positive cells: 1+. Intensity of positive cells: 2+. Immunohistochemistry (IHC) for cytokeratin. Bar=50 µm.

**Fig. 8.** Intracranial; meningioma, cat. Transitional meningioma; case 44. The cytoplasm and membrane of tumor cells are moderately positive for E-cadherin. Percentage of positive cells: 2+. Intensity of positive cells: 2+. IHC for E-cadherin. Bar=50 µm.

**Table 2.** Results of immunohistochemistry in the present study

| Subtype | The number and percent of positive cases* | | | | | Mean Ki-67 index*** |
|---|---|---|---|---|---|---|
| | Cytokeratin | Vimentin | E-cadeherin | β-catenin** | N-cadherin | |
| Transitional (n=20) | 2 (10%) | 12 (60%) | 20 (100%) | 13 (65%) | 1 (5%) | 3.3 |
| Fibrous (n=12) | 1 (8.3%) | 4 (33.3%) | 11 (91.7%) | 5 (41.7%) | 0 (0%) | 5.3 |
| Meningothelial (n=2) | 1 (50%) | 0 (0%) | 1 (50%) | 0 (0%) | 0 (0%) | 10.5 |
| Atypical (n=4) | 1 (25%) | 1 (25%) | 3 (75%) | 2 (50%) | 0 (0%) | 5.9 |
| Anaplastic (n=1) | 0 (0%) | 0 (0%) | 1 (100%) | 1 (100%) | 0 (0%) | 8.8 |

*The number includes all positive cases regardless of intensity or percentage score. **The cytoplasm of tumor cells was positive for β-catenin. ***The mean Ki-67 index represents the percentage of positive tumor cells among all tumor cells.

American Shorthair and Norwegian Forest Cat had a significantly higher risk of developing meningioma. However, in previous studies that were conducted in Europe and the United States, mixed breed cats were predisposed to developing meningioma [27, 28]. This difference may be associated with genetic factors or different breed populations in Japan and in other geographic regions.

Previous studies showed that the locations of feline meningioma are commonly the third ventricle, the supratentorial meninges and, rarely, the cerebellar meninges [17, 28]. Besides, multiple meningiomas are recognized in 14–17% of feline meningioma cases [8, 18, 28]. In the present study, however, the temporal lobe was the most common site of meningioma, and only one case developed meningioma in the third ventricle. Moreover, multiple meningioma was only recognized in one case, representing 2.4% of all cases. These differences seemed to be caused by two reasons. One is the distinction of breed populations between Japan and other countries. The other is the way to collect samples. Previous studies were totally or more than half comprised of necropsy samples [18, 28]. In contrast, our study contained only 8 cases (17.8%) confirmed by post-mortem examination. In the present study, 2 cases of meningioma in the third ventricle had low Ki-67 index, suggesting a benign biological behavior and absence of significant clinical signs. Anatomical location is also attributed to make surgical removal of meningiomas developed in the third ventricle difficult. Therefore, meningiomas of the third ventricle would be rarely provided for biopsy.

Compared to canine meningiomas, feline meningiomas exhibit less morphological variations, and the biological behavior of feline meningioma is generally considered benign, except for the anaplastic type [17]. In the present study, transitional (48.9%) and fibrous (33.3%) meningiomas were the two major histological subtypes in the cat, which is different from human and canine meningiomas that exhibit various histological subtypes [15]. Furthermore, cholesterol clefts and mineralization were widely observed, which is consistent with previous study on feline meningioma [15].

In previous studies, the immunoreactivity of cytokeratin in human and canine meningiomas was up to 100% and 86%, respectively [3, 22]. The only other comprehensive study investigating feline meningiomas demonstrated that tumors exhibited no cytokeratin staining in all examined cases [24]. In our study, the expression of cytokeratin was only observed in 5 cases (12.8%). Such reduction of cytokeratin compared to human and canine meningiomas expression may be associated with the specific histopathological characteristics of fibrous and transitional type meningiomas being dominant in cats, unlike in humans and dogs. To the best of our knowledge, there is no retrospective study on expression of vimentin in feline meningioma, and 17 cases (43.6%) were positive for vimentin in our study. Moreover, all cases were negative for claudin-1, which is inconsistent with a previous study that used a different antibody for claudin-1 [24]. Furthermore, most feline meningiomas (92.3%) were positive for E-cadherin and there was no significant difference between each histological type and the expression of the molecule. Therefore, immunohistochemistry for E-cadherin may be a stable tool for the diagnosis of feline meningiomas. In canine meningiomas, nuclear localization of β-catenin was more frequently detected in anaplastic meningiomas than in its benign counterparts [11]. Although cytoplasmic and/or cell membrane expression of β-catenin was detected in more than half of the feline meningiomas, nuclear translocation of the molecule was not observed even in atypical or anaplastic types. Previous studies reported that N-cadherin is often expressed in high grade meningiomas in humans and dogs [7, 10]. However, most feline meningiomas examined in the present study were negative for N-cadherin. In addition, the correlation between the immunostaining score of E-cadherin and β-catenin was not significant, which is also inconsistent with the previous study of canine meningiomas [10]. This suggests a different mechanism of tumorigenesis or malignant transformation of meningiomas between dogs and cats.

The Ki-67 antigen is considered to be a reliable biochemical marker reflecting the growth and recurrence of meningiomas in humans [1, 14, 19, 20, 25]. However, no statistically significant correlation between the mean Ki-67 index and histological subtypes or grade of feline meningioma was found in our study. There was no significant difference in Ki-67 index between gender and gonadectomy. We also noted no significant correlation between the Ki-67 index and the immunostaining scores of E-cadherin and β-catenin. This may have been caused by the small study population, especially that of atypical and anaplastic meningiomas, which hampered an efficient comparison between benign and malignant meningiomas.

In conclusion, the present cohort study describes the histopathological subtypes and grades in a case series of feline meningiomas, which has not been reported to date. However, no statistically significant correlation between Ki-67 index and histological subtypes or grades were found. In any case, further study is necessary to give a conclusion, since the number of cases with higher grade tumors (i.e. grade 2 and 3) were small, and also information on clinical outcomes were not available in the present study. The present study shows that immunohistochemistry for E-cadherin and β-catenin may be useful for the diagnosis of feline meningiomas, regardless of histological subtype and grade.

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

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