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Papillary meningioma in the dog: A clinicopathological case series study

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ABSTRACT

Papillary meningioma (PM) is one of the most aggressive variants of meningioma in humans and classified as grade III by WHO system. To date, the biological behavior of PM is still not clear in dogs. This study investigated the correlation between histopathological findings of 16 canine PMs and follow up data. Moreover, the expression of doublecortin, E-cadherin, and N-cadherin was investigated by immunohistochemistry. The supratentorial compartment resulted the most common involved. Despite the low grade of histological malignancy, 87.5% of dogs that underwent surgery experienced tumor recurrence. Intratumoral necrosis was observed in a strict correlation with malignancy histological parameter and tumor recurrence. The post-surgery mean survival time was much lower than thus observed in the most common histological subtypes. This data were also confirmed in dogs that received a conservative treatment alone. Tumors with a severe clinical behavior showed a high N-cadherin expression versus a low or absent E-cadherin expression.

1. Introduction

Meningiomas are common tumors arising from the arachnoidal cap cells of the meninges (Wu et al., 2011). They represent approximately 30–46% of all intracranial central nervous system (CNS) tumors in dogs (Keyerleber et al., 2013; Snyder et al., 2006). Because of striking similarities between canine and human meningiomas (Dickinson et al., 2006; Kraft et al., 1997; Platt et al., 1986), in the recent years the human WHO classification system has been applied to canine meningiomas (Mandara et al., 2010; Sturges et al., 2008). The major component of this classification is the grouping of tumors into 3 histological grades, conforming to clinical behavior prediction and outcome in people (Perry et al., 2007; Sturges et al., 2008). This classification recognizes 15 different histological variants most of which are considered as grade I. Except for anaplastic form of meningiomas, included into grade III, four meningioma variants are considered innately more aggressive, due to their high rate of recurrence and mortality (Perry et al., 2007; Wu et al., 2011). Human papillary meningioma (PM) is characterized by perivascular pseudopapillary pattern either entirely or more commonly in combination with other histological pattern of meningioma (Perry et al., 2007). Despite its histological pattern, it is classified as grade III (Perry et al., 2007) for its high prevalence to brain invasion, local recurrence and distant metastases it expresses (Ludwin et al., 1975; Perry et al., 2007). In human beings PM is a rare subtype accounting for 1%–2.5% of all meningiomas (Avninder et al., 2007; Perry et al., 2004; Russel and Rubinstein, 1989).

To improve the knowledge on the biological behavior of meningioma, in the last years the expression of a series of molecules associated with cell adhesion and invasion have been investigated in human and canine meningiomas (Akat et al., 2008; Daou et al., 2005; Ide et al., 2011; Panagopolous et al., 2008; Shimada et al., 2005). Doublecortin (DCX), which plays a crucial role in neuroblast migration during the development of the cerebral cortex, is highly expressed in invasive brain tumors (Daou et al., 2005). Epithelial cadherin (E-cadherin) is expressed in normal arachnoidal tissue as well as in epithelial tissues (Shimada et al., 2005). It represents the main cadherin protein expressed in human neoplastic meningeal cells (Akat et al., 2008; Shimada et al., 2005). Loss of E-cadherin is considered a triggering event in neoplastic cell detachment from the primary tumor as well as in invasion of the surrounding tissues (Hazan et al., 2004; Perl et al., 1998; Vleminckx et al., 1991). In contrast to E-cadherin, N-cadherin expression in neoplastic cells produces a promigratory effect, promoting tumor

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infiltration in the connective tissue, possibly by favoring association of cancer cells with endothelial and other stromal cells (Agiostratidou et al., 2007; Nieman et al., 1999; Péglion and Etienne-Manneville, 2012). Although changes in cadherin expression during carcinomatous progression are today well documented in man and domestic animals (Buendia et al., 2013; Gheldof and Berx, 2013; Gunasinghe et al., 2012; Osisami and Keller, 2013), the possibility that such changes occur in meningiomas has only recently begun to be explored in humans (Celebre et al., 2013; Figarella-Branger et al., 1994) and dogs (Ide et al., 2011).

The aim of this study is to investigate the clinicopathologic correlations of sixteen canine PMs in order to define if PM would be considered of high grade in dogs as in humans. To provide more information regarding the biological behavior of this meningioma subtype in dogs, we investigated DCX, E-cadherin, and N-cadherin by immunohistochemistry. Finally follow up data were compared with those observed in the most common histological subtypes of canine meningiomas.

2. Materials and methods

2.1. Dogs

Sixteen tumors previously recorded as PMs in the archive of our Neuropathology Laboratory were selected for this study. They consisted in 8 biopsy samples collected during surgical excision and 8 necropsy samples. None of the necropsy samples were examined paired to a previous biopsy sample. For each tumor, clinical data, including breed, age, sex, tumor localization, tumor size, treatment, and clinical follow up were obtained from medical records (Table 1). Post-surgery survival time was compared to that referred to the most common histotypes of canine meningioma (transitional, meningothelial, fibrous) coming from the same archive (personal unpublished data). During clinical management, in fourteen cases brain magnetic resonance imaging (MRI) had been advised and performed under general anesthesia [0.22T MR scanner (MrV, Paramed, Genoa, Italy) and 0.2T MR scanner (Vet-MR, ESAOTE, Genoa, Italy)] providing details about size of tumors and perilesional edema. Additional radiation therapy was performed in none of the cases.

2.2. Histopathology and grading

Surgical and necropsy specimens were promptly fixed in neutral buffered formalin and processed by routine paraffin embedding. Sections were cut at 5 μm and stained with hematoxylin and eosin (H&E). Histological classification and grading were performed accordingly to the criteria of the latest human WHO international histological classification of tumors of the nervous system (Mandara et al., 2010; Perry et al., 2007). The benign histological subtypes (grade I) were those lacking criteria of atypical and anaplastic grades. An elevated proliferation index, defined as ≥4 mitoses/10 high-power fields (HPF) was considered diagnostic criterion for atypical meningiomas (grade II). In the absence of increased mitotic activity, atypical meningiomas were diagnosed by the presence of either nervous tissue invasion or at least three of the five following parameters: increased cellularity, high nuclear/cytoplasmatic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of spontaneous necrosis (Perry et al., 2007). Anaplastic meningiomas (grade III) included tumors showing an excessive mitotic rate (≥20 mitoses/10 HPF), and/or frank anaplasia (Perry et al., 2007).

2.3. Immunohistochemistry

In ten cases additional 4 μm sections were used for immunohistochemistry (IHC) investigations that were performed with avidin–biotin–peroxidase complex method (ABC, Dako, Milan, Italy). The primary antibodies and the positive control tissues used in this study are listed in Table 2. After deparaffinization and rehydration, antigen retrieval was obtained in microwave at low power cycle for 20 min (Table 2). Endogenous peroxidase was neutralized by peroxidase block (3% H2O2 for 5 minutes). Sections were then incubated at 4 °C overnight with the primary antibodies. Immunoreactivity was revealed by the avidin–biotin method using 3-aminoetile-9-carbazole (AEC). Carazzi's hematoxylin was used as a counterstain. Negative controls were carried out in the same manner with omission of the primary antibody. For each tumor, area of labeling was assessed in five grades (– = absent; + = <25%of tumor; ++ = 25–50% of tumor; +++ = 50–75% of tumor; ++++ = >75% of tumor), and the staining intensity in three grades (W = weak; M = moderate; S = strong).

3. Results

3.1. Incidence and signalment

In the last 9 years, 121 cases of canine meningiomas have been diagnosed in our laboratory. Nineteen (15.7%) of them were archived as PMs. The tumors came from twelve male and seven female dogs, with a male/female ratio of 1.7. The most common affected breed were Boxer (n = 7) and mixed breed dogs (n = 5), followed by German Shepherd (n = 2) and single cases of Springer Spaniel, Poodle,

Table 1
Clinical data and outcome addressed to the examined dogs.

Case Number	Breed	Gender	Age (years)	Localization	Tumor size	PTE	Surgical resection	Surgery-–recurrence interval	Survival time
1	Siberian husky	F	12	Left retrobulbar	n.a.	n.a.	Y	NR	43 months
2	Boxer	M	11	Spinal (C1–C2)	n.a.	n.a.	Y	n.a.	n.a.
3	Poodle	M	14	Left olfactory and frontal	28 × 27 × 17 mm	Y	N	–	2 days
4	Mixed breed	M	8	Right parietal	n.a.	Y	Y	8 months	12 months
5	Mixed breed	M	12	Right olfactory and frontal	37 × 16 × 18 mm	N	N	–	2.5 months
6	German Shepherd	M	9	Olfactory bulb	10 × 5 × 5 mm	n.a.	Y	4 months	16 months
7	Boxer	F	7	Left temporal	19 × 21 × 24 mm	Y	Y	2 months	4 months
8	Mixed breed	M	11	Left temporal and olfactory	13 × 26 × 27 mm	Y	Y	17 months	24 months
9	Boxer	F	11	Right frontal	22 × 16 × 16 mm	Y	N	–	1 day
10	Shih-tzu	F	18	Right cerebellar pontine angle	n.a.	n.a.	N	–	2 days
11	German Shepherd	M	9	Spinal (C2)	10 × 16 × 14 mm	N	Y	4 months	5 months
12	Mixed breed	M	12	Olfactory-frontal region	27 × 18 mm	Y	Y	4 months	4 months
13	Boxer	F	11	Right midbrain and diencephalon	n.a.	N	N	–	4 days
14	American Pit Bull Terrier	M	10	Bilateral frontal and parietal	15 × 32 × 25 mm	Y	N	–	10 days
15	Boxer	M	10	Middle frontal	20 × 12 × 20 mm	Y	N	–	11 days
16	Springer Spaniel	F	10	Right frontal	13 × 18 mm	n.a.	N	–	3 months

M = male; F = female; Y = yes; N = no; NR = no recurrence; n.a. = not available; PTE = peritumoral edema.