

A Comparative approach to phyllodes tumors in women and phyllodes-like tumors in female dogs

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ABSTRACT

Mammary gland tumors, a significant concern for both humans and dogs, often carry a malignant prognosis. The diagnosis of these tumors is primarily based on their histopathological appearance in both species. This study delves into the pathological features of Phyllodes tumors in female dogs, a type not typically included in the histopathological classification of canine mammary tumors but well-documented in women. By comparing the recently described Phyllodes tumor cases in dogs with those in women, we aim to shed light on the shared vulnerability of women and female dogs to these tumors. The increasing number of studies exploring the common features between breast cancer in women and mammary tumors in female dogs makes the comparative evaluation of this rare tumor type in both species not only interesting but also crucial.

Keywords: breast cancer, phyllodes tumor, canine mammary tumor, comparative medicine

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Introduction

Mammary glands play a vital role in providing essential nutrition and passive immunity to newborns. Structurally, they are ductal, lobular, and alveolar organs embedded in fibrovascular connective and fatty tissue (Sorenmo et al., 2011). Similar to the human mammary gland, in dogs, the ductal system begins with the papillary ducts of the nipple and culminates with the development of secretory alveoli. This process is vital for the health and well-being of the animal (Silver, 1966). What is more, studies conducted in recent years have revealed that there are shared clinicopathological, morphological, and biochemical features between human and canine mammary gland cancers (Kumaraguruparan et al., 2006; Liu et al., 2014; Reis et al., 2020; Seung et al., 2020). This shared knowledge and collaboration between human and veterinary medicine fields are crucial in advancing our understanding and treatment of mammary tumors in

both species. In recent years, breast cancer has been the most frequently diagnosed type of cancer, with an estimated number of 2.3 million new cases worldwide, according to GLOBOCAN 2020 data, and ranks 5th (fifth) in the list of cancer-related deaths (Sung et al., 2021). Among domestic animals, dogs have the highest incidence of mammary tumors, with a rate of 25-42%. As in humans, mammary tumors are among the most common tumors in dogs (Klopfleisch et al., 2011). Mammary tumors are common in females but rare in male dogs (Goldschmidt et al., 2016). The frequency of mammary gland tumors in dogs varies by geographical region and is directly linked to the age at which ovariectomy is performed. Extensive studies have consistently shown that early ovariectomy significantly reduces the risk of later mammary gland neoplasia. Reports indicate a staggering 99.5% reduction in the risk of developing mammary tumors when

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ovariectomy is performed before the first estrus cycle. Furthermore, the risk is reduced by 92% and 74% when ovariectomy is performed before the second and third cycles, respectively. Even after the fourth cycle, ovariectomy still provides some level of protection against developing mammary neoplasms (Beaudu-Lange et al., 2021; Schneider et al., 1969). The average age for the occurrence of mammary tumors in dogs is typically between 10 and 11 years. Benign neoplasms tend to appear in dogs between 7 and 9 years of age, while malignant neoplasms are more common in older dogs, typically between 9 and 11 years of age. The development of tumors varies based on the specific breed and size of the dog. Mammary gland neoplasms tend to occur at a younger age in large breeds compared to small breeds (Goldschmidt et al., 2016; Murphy, 2008). The use of exogenous hormones, both progestins and estrogen, may cause mammary gland neoplasms to appear at an earlier age. Please remember the following important information: Low doses of progestin can encourage the growth of non-cancerous neoplasms, while combinations of progestin and estrogen may influence the development of cancerous neoplasms. When many cats and dogs are brought to the clinic due to masses, these masses are typically found in more than one gland. Tumors are usually detected in the caudal mammary glands. Smaller neoplasms (less than 1 cm in diameter) are more likely to be non-cancerous (benign), while larger neoplasms (greater than 3-5 cm in diameter) are more often cancerous (malign). It is essential to have all mammary nodules evaluated histologically to distinguish malignancy, regardless of their size (Murphy, 2008).

The features listed so far, such as its higher incidence compared to other cancers, its prevalence in middle and upper middle age, the risk of tumor development in the mammary gland after exogenous hormone use, and the relationship between mass size and malignancy, have many commonalities in both species. Phyllodes tumors of the breast are a captivating and rare category of fibroepithelial neoplasms. They bear a striking resemblance to intracanalicular fibroadenomas at the benign end of the spectrum, but they display enhanced stromal cellularity and a distinctive leaf-like architecture. Within this fascinating tumor, the stromal part is considered neoplastic and plays a pivotal role in determining whether the tumor is benign, borderline, or malignant based on the intricate pathophysiology of epithelial-stromal interactions (Tan et al., 2020). This rare tumor accounts for less than 1% of all breast tumors in women and 2-3% of all fibroepithelial

tumors (Cook et al., 2024).

Although mammary tumors in women and dogs have many histologic and clinical features in common, the fact that this unusual tumor, which is also rare in women, has never been included in the classification of canine mammary tumors caught the authors' attention. This article aims to delve into the intriguing topic of phyllodes tumors of the breast and explore existing literature for evidence of its presence in female dogs.

Classification of mammary gland tumors

In women, breast cancer presents as a complex disease with numerous subtypes, each displaying distinct biological properties that significantly impact treatment responses and clinical results. The heterogeneity of breast cancer affects diagnosis, treatment, and, therefore, prognosis (Eliyatkin et al., 2015). Identifying whether a mammary gland tumor is benign or malignant in dogs can be complex and risky. Although rapid growth, tumor size, and skin ulceration may indicate malignancy, distinguishing between benign and malignant tumors using cytological diagnostic methods is challenging. Studies have shown a diagnostic accuracy rate as low as approximately 20% due to factors such as cellular differentiation and mixed tumor structure. (Goldschmidt et al., 2016). Histopathology stands as the gold standard for establishing an accurate diagnosis, including tumor type, malignancy, grade, and prognosis. Through histopathological evaluation, we gain insight into the tissue architecture of the tumor and its intricate connections with the surrounding tissue. Benign tumors are identifiable by their well-defined boundaries, soft margins, and dense fibrous connective tissue. In contrast, malignant tumors exhibit irregular margins, immature fibrous connective tissue, and multifocal necrosis fueled by rapid neoplastic cell proliferation. These characteristics underscore the critical importance of histopathology in guiding treatment decisions and predicting patient outcomes (Goldschmidt et al., 2016; Murphy, 2008). Histopathological classification of mammary gland tumors

The traditional classification of breast cancer is performed using a microscopic method, known as histological or morphological classification. This method is based on the cancer cells' size, shape, and arrangement. It also takes into account the region in which breast cancer develops in women. Two critical questions are addressed in this classification: First, is the tumor confined to the area where it originated within the breast epithelial component, or if it has

spread to surrounding tissues? Second, it determines whether the tumor originated in the milk duct or the mammary gland (do Nascimento & Otoni, 2020). If the cancer develops in the milk ducts, it is classified as ductal; if it develops in the mammary gland alveoli, it is termed lobular. It is worth noting that, although rare, breast cancer can develop in the connective tissue outside the mammary glands and ducts (do Nascimento & Otoni, 2020).

The spread of breast cancer also influences its type. In this regard, breast cancer is classified into two types: in situ and invasive. In situ, breast cancer is limited to the area where it originated and did not spread to the rest of the mammary gland tissue. Invasive breast cancer, on the other hand, refers to the type that spreads into the surrounding breast tissue. Among the types of breast cancer, the most predominant type, accounting for 70% of cases, is invasive ductal carcinoma NOS (no specific type). Invasive lobular carcinoma, a specific histological subtype, ranks second, accounting for approximately 10% of cases. Subtypes such as tubular, mucinous, cribriform, and papillary carcinoma are generally associated with favorable prognoses. Medullary and mucinous carcinoma incidence is approximately 5%, while tubular carcinoma varies between 1-5%. Other microscopic types are rare (DeSantis et al., 2019; do Nascimento & Otoni, 2020).

Canine mammary tumors have been classified histologically for many years, starting with studies conducted by the World Health Organization (Misdorp et al., 1999). This initial classification focused on histological and descriptive morphological features of breast tumors and histological and prognostic features related to increased malignancy. Goldschmidt et al. (2011) developed a more detailed alternative classification that emphasizes the morphology of neoplastic cells and the involvement of myoepithelial cells in the neoplastic process. In the 2018 consensus on "Classification and grading of canine mammary tumors" organized by the Oncology-Pathology working group of the Veterinary Cancer Society (VCS) and the American Academy of Veterinary Pathology (ACVP), it was suggested to use Goldschmidt et al. (2011) classification. According to this classification, mammary tumors in dogs are classified under eight main headings, including Hyperplasia/Dysplasia, Benign tumors, Malignant epithelial tumors, Malignant epithelial tumors-special types, Malignant mesenchymal tumors-sarcoma, Malignant mixed mesenchymal tumors-Carcinosarcoma, Nipple tumors, and Hyperplasia/dysplasia of the nipple (Goldschmidt et al., 2011).

Beyond classifying by histomorphological features, the histological grading system is a crucial prognostic indicator for canine mammary tumors. This system uses a numerical method to evaluate three morphological features: tubule formation, nuclear pleomorphism, and mitotic number. It allows for evaluating the heterogeneity of mammary tumors in dogs, as well as how to assess complex and mixed tumors, and the variability in the size of nuclei and nucleoli. This simplifies histological interpretation and enables the prediction of the biological behavior of mammary gland carcinomas based on determining the tumor grade along with its histological subtype (Goldschmidt et al., 2016).

Phyllodes tumors in women

The Phyllodes tumor is a rare fibroepithelial neoplasm, accounting for less than 1% of all primary breast tumors (Tan et al., 2020). It was initially described by Chelios in 1828 as a hydatid cyst-like structure in the breast and later named Cystosarcoma Phyllodes by Johannes Müller in 1838 (Nabi et al., 2013). Histologically, it is a biphasic tumor consisting of benign epithelial elements and a cellular stroma formed by spindle cells (Tavassoli, 1999).

Although similar to fibroadenomas, Phyllodes tumors require careful examination due to their stromal cellularity, local recurrence, and malignant potential. These tumors occur in women aged 4-5 decades, but can also be seen in adolescents, though less frequently (WHO, 1983). Studies have shown different origins of stromal cells in Phyllodes tumors, with fibroblasts and myofibroblasts being the most common (Aranda et al., 1994).

Phyllodes tumors present as a palpable mass in the breast, and other symptoms include dilated skin veins, skin discoloration, nipple retraction, fixation to the skin or muscle, skin ulcers, skin necrosis, or palpable lymph nodes (Chen et al., 2005).

Prognosis is influenced by tumor size, development pattern, stromal atypia, and mitotic activity, although there is no clear correlation between histological parameters and clinical course. The local recurrence rate in benign and malignant cases is reported to be 15-25%, and metastasis in high-grade tumors has been reported at 20% (Norris & Taylor, 1967). Progesterone and estrogen-binding proteins have been detected in Phyllodes tumors (Lewko et al., 1990).

Phyllodes tumors may grow rapidly during adolescence but typically have a low malignancy potential. The effects of hormonal stimulation during adolescence and exposure during the intrauterine and

prepubertal periods on breast morphology and malignancy are controversial. A genetic predisposition may be present if there is a history of ovarian cancer in the patient's mother or grandmother (Tan & Köprülü, 2013). Long-term follow-up is important, as local recurrence and distant metastasis may occur, and in some cases, the disease may result in death (Barth, 1999).

The connection between clinical behavior and histological type in phyllodes tumors is debatable (Contarini et al., 1982). Even though numerous biological markers have been scrutinized in phyllodes tumors, along with their correlation to tumor grade, their application in defining grade and predicting clinical behavior in individual cases remains constrained (Tan et al., 2016). While metastases are more common in those with malignant histological structures, they have also been observed in benign and borderline types (Norris & Taylor, 1967). No distinct clinical features can differentiate phyllodes tumors from other breast tumors. Phyllodes tumors are unequivocally considered de-novo lesions originating from the periductal and specialized lobular stroma. The initiation of tumorigenesis is contingent upon epithelial–stromal interactions. However, the histological similarity between fibroadenoma and phyllodes tumors undeniably raises the question of pathogenetic closeness (Tan et al., 2016). However, histological examination sets it apart from fibroadenoma by the presence of a broad leaf-like stroma rich in stromal cells (Sarsu et al., 2015). On the other end of the spectrum, the malignant phyllodes tumor could easily be mistaken for primary breast sarcoma or spindle cell metaplastic carcinoma. These compelling similarities highlight the importance of accurate diagnosis and further research (Tan et al., 2016). In certain aggressive phyllodes tumors, the stromal overgrowth is particularly conspicuous, making it challenging to distinguish the epithelial component. The stroma of these tumors may exhibit diverse sarcomatous differentiation, including prevalent liposarcoma and less common myosarcoma, angiosarcoma, chondrosarcoma, and osteosarcoma. A spindle cell metaplastic breast carcinoma presents with varying proportions of a malignant epithelial component such as squamous, glandular, or adenosquamous cells. These unique carcinomas can also lack typical epithelial elements or exhibit diverse mesenchymal differentiation. The presence of ductal carcinoma in situ alongside a malignant mammary spindle cell tumor strongly signals a diagnosis of metaplastic carcinoma. Additionally, primary breast sarcomas are exceedingly rare, and sarcomas

metastatic to the breast are exceptionally uncommon. They do not exhibit unique histological features that differentiate them from phyllodes tumors or metaplastic breast carcinomas. It's important to consider a patient's history of previous or metastatic sarcoma, and thorough imaging and clinical correlation can be extremely beneficial. Besides, demonstrating diffuse cytokeratin or p63 immunoreactivity in the malignant spindle cells supports a confident diagnosis of metaplastic carcinoma. Harnessing the power of immunohistochemical characterization of tumors is a crucial tool for accurately distinguishing phyllode tumors from other malignant breast tumors.

Mammography and ultrasound, which are employed in diagnosing breast masses, are not very reliable for grading phyllodes tumors and differentiating them from fibroadenomas. Although fine needle aspiration biopsy is not the preferred preoperative histopathological diagnostic method for phyllodes tumors due to its high false negativity rate, core biopsy results are more reliable for diagnosis. The most effective treatment is wide surgical excision. Lymph node involvement is rare, so lymph node dissection is not recommended. Even though age, surgical approach, tumor diameter, and mitotic activity are important for developing local recurrence, tumor cell positivity at the surgical margin is the most crucial factor. To prevent local recurrence, wide excision with negative surgical margins (at least 1-2 cm) is recommended, irrespective of the histopathological type in the surgical approach (Foxcroft et al., 2007).

The effectiveness of chemotherapy and radiotherapy is uncertain. Radiotherapy may enhance local control but may not improve overall survival in borderline and malignant phyllodes tumors. The 5-year overall survival rates for patients with phyllodes tumors were 91% and 82% for benign and malignant cases, respectively, in the MD Anderson series; in the analysis of SEER data, it was 91% for malignant cases. The primary factors affecting overall survival and systemic metastasis are findings of stromal overgrowth, positive surgical margins, and cytonuclear atypia. Malignant phyllodes tumors mainly spread to the lungs through hematogenous spread and may rarely spread by the lymphatic route (Macdonald et al., 2006).

Histopathology of phyllodes tumor

Phyllodes tumors can be macroscopically benign, round, encapsulated, and with limited masses. Malignant and borderline Phyllodes tumors have a cross-sectional surface that is curved, circumscribed, and protruding to the outer surface in an infiltrative,

leaf-like pattern. Skin ulcers, bleeding, and cystic changes may occur in large lesions (Yoneyama et al., 2020). Phyllodes tumors generally exhibit benign cytomorphology. They have a lower epithelial/stromal ratio than fibroadenomas and fibromyxoid stromal clusters. Higher-grade phyllodes tumors may show higher nuclear atypia and cellularity. Multinucleated tumor cells and significant stromal anaplasia have been reported in malignant phyllodes tumors (El Hag et al., 2010).

Phyllodes tumors are categorized as benign, borderline, or malignant based on specific criteria. Benign tumors have 0-4 mitosis/10x magnification, minimal or moderate stromal cellularity, minimal or moderate stromal overgrowth, and intact surgical margins. Borderline tumors exhibit 5-9 mitoses/10x magnification, moderate stromal cellularity, atypia, overdevelopment, and intact or invaded surgical margins. Malignant tumors feature over 10 mitoses/10x magnification, moderate or advanced stromal cellularity, atypia, overgrowth, and invaded surgical margins.

The following markers are used in immunohistochemistry to diagnose Phyllodes tumors. Epithelial cells: Cytokeratin, Estrogen receptor (ER), Progesterone receptor (PR), Gross cystic disease fluid protein 15 (GCDFP-15). Stromal cells: Vimentin, CD34, Bcl-2, Estrogen receptor beta, c-KIT, p53, Ki-67 (High c-KIT, p53, and Ki-67 expressions mean high-grade phyllodes tumor.) Negatively labeled in immunohistochemistry: Stromal cells: Cytokeratin, p40, p63 (except malignant phyllodes tumor) (Cimino-Mathews et al., 2014; Chia et al., 2012). Since malignant proliferation is generally in the stromal component (Cook et al., 2024), the immunohistochemical reaction of markers such as Bcl-2, c-KIT, p53, and Ki-67 are preferred to evaluate in the stromal cells. Detection of diffuse cytokeratin or p63 immunoreactivity in the malignant spindle cells strongly supports a diagnosis of metaplastic carcinoma (Tan et al., 2016). However, pathologists should be cautious when interpreting focal keratin or p63 expression, as these features have been observed in stromal cells of phyllodes tumors. The use of p40 in a similar diagnostic context is currently under investigation, showing higher specificity but lower sensitivity than p63. Nevertheless, it is important to note that p63 and p40 may occasionally exhibit staining in stromal cells of phyllodes tumors. CD34 reactivity, well established in the stromal cells of phyllodes tumors, has been found to have an inverse relationship with adverse histological features. This holds significance if CD34 is to be employed for

diagnostic purposes in distinguishing high-grade spindle cell lesions of the breast, given the lower likelihood of CD34 expression in malignant phyllodes tumors. Further markers, such as Bcl-2 (frequently expressed in phyllodes tumors), CD117 (demonstrating increased expression in higher-grade phyllodes tumors), and sarcoma-specific molecular cytogenetic alterations, can serve as valuable diagnostic adjuncts (Cimino-Mathews et al., 2014; Chia et al., 2012; Noronha et al., 2011).

Phyllodes tumor cases identified in dogs

Mixed tumors containing epithelial and mesenchymal components are included in the histological classification of canine mammary tumors and are frequently encountered. However, neoplasms in which epithelial and mesenchymal (fibroepithelial) components are organized similarly to phyllodes tumors have rarely been described in dogs. According to our research, Shahzamani et al. (2013) were the first to describe a benign phyllodes tumor in a female dog. This study reported that this case was the first description of a phyllodes tumor in the canine species. In another study published by De Araújo et al. (2014), the anatomopathological features and immune phenotype of five phyllodes tumors diagnosed in female dogs were reported for the first time. All phyllodes tumors diagnosed in this study were detected as solitary. In canine mammary tumors, the expression of hormone receptors is associated with a good prognosis. According to the literature, both benign and malignant phyllodes tumors have a well-differentiated epithelial component with estrogen and progesterone receptors. In the study, immunohistochemistry results were consistent for ER and PR. The stroma of high-grade malignant phyllodes tumors in women may have different biological behavior than in dogs. Studies involving the expression of the c-KIT proto-oncogene and the development of phyllodes tumors in dogs may elucidate this conundrum. However, while c-KIT, which marks the stromal component of tumors, was positive in phyllodes cases in women, De Araújo et al. (2014) did not label any of the cases presented, and this result is consistent with Tse et al. (2004), who found an increase in c-KIT expression. Some morphological features of phyllodes tumors in dogs are defined as follows (De Araújo et al., 2014). High-grade malignant phyllodes tumors are characterized by marked stromal cellularity, high mitotic index, and marked stromal cellular pleomorphism. Pseudoangiomatous stromal hyperplasia may also be seen in high-grade malignant phyllodes tumors. Occasionally, the stroma contains

angiosarcoma, liposarcoma, chondrosarcoma, myosarcoma, or osteosarcoma. Mixed canine mammary tumors, characterized by a stromal component with myoepithelial and mesenchymal cell proliferation giving rise to a myxoid, chondroid, or bone matrix with epithelial cell proliferation, are among the most common tumor types (De Araújo et al., 2014).

Conclusion

The striking parallels in the epidemiological and clinicopathological features of spontaneous tumors in companion animals and their human counterparts, along with the shared exposure to similar risk factors, have elevated companion animals as crucial models in human cancer research. Cats and dogs, as companion animals, experience expedited cancer development due to their shorter lifespans. This unique attribute presents valuable opportunities for comparative oncology studies (Cannon, 2015).

Veterinary pathologists must be cautious in recognizing this tumor because phyllodes tumors have epithelial, mesenchymal, and even associated myoepithelial components like mixed tumors. Definitive diagnosis of phyllodes tumors can be achieved by identifying excessive intratumoral stroma and accompanying leaf-like structures in the epithelial component, rarely seen in mixed tumors. According to the data presented in this article, the observed morphological and immunophenotypic features indicate similarities between phyllodes tumors diagnosed in female dogs and women. The presence of this neoplasm in dogs may serve as a model for women, and revealing such similarities for future studies on common features in pathogenesis is of great importance for the discipline of pathology.

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