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Rare Histotypes of Canine Mammary Neoplasms

Breno Souza Salgado^{1*,2}, Lidianne Narducci Monteiro³, Geovanni Dantas Cassali³, Noeme Sousa Rocha^{2,4} and Fátima Gärtner⁵

¹Universidade José do Rosário Vellano, Unifenas, Alfenas, Brazil

²Departamento de Patologia, Faculdade de Medicina de Botucatu, Univ. Estadual Paulista– UNESP. Botucatu, Brazil³Laboratório de Patologia Comparada, Departamento de Patologia Geral, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais. Belo Horizonte, Brazil

⁴Serviço de Patologia Veterinária, Departamento de Clínica Veterinária, Faculdade de Medicina Veterinária e Zootecnia – FMVZ, Univ. Estadual Paulista – UNESP. Botucatu, Brazil

⁵Instituto de Ciências Biomédicas Abel Salazar – ICBAS, Universidade do Porto. Oporto, Portugal

***Corresponding author:** Breno Souza Salgado, Universidade José do Rosário Vellano, Unifenas, Alfenas, Brazil, Tel/Fax: +55 353299 3166; E-mail: brenosalgado@globocom

Abstract

Mammary neoplasms in dogs are heterogeneous in its presentation, classification, and clinical course. In the last years, histotypes that differ from those described in the World Health Organization classification of mammary gland tumors in dogs and cats were reported and raised a question about the importance of correctly diagnosing them. This article brings information on 4 subtypes with a very concise histopathology description and parameters helpful in the clinic. Accordingly, the aim of this paper is to provide data for mammary neoplasms caregivers which will enable a better understanding of the disease in those animals.

Keywords: Mammary carcinoma; Diagnosis; Histopathology; Dog

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Introduction

Mammary neoplasms are the most common tumors in intact female dogs with several epidemiologic studies have been conducted over the years. Such studies provide an estimate of their incidence, including those regarding histotype frequency based on the World Health Organization classification for mammary gland tumors of dogs and cats described by Misdorp et al. in 1999 [1]. The morphologic spectrum of mammary neoplasms in canine species is generally quite different from that seen in humans. However, the increase in reports regarding histologic types of mammary tumors occurring in dogs with a striking similarity with their human counterpart has been raising the interest of veterinary pathologists and clinicians about the possibility of facing distinct subtypes with particular and/or aggressive behavior, creating the need for new classification schemes [2-4]. Accordingly, the aim of this article is to comment about rare histotypes of

mammary neoplasms in dogs, consequently providing a source of information for veterinarians in order to correctly diagnose such variants.

Invasive micropapillary carcinoma

Mammary invasive micro papillary carcinoma (IMC) is a recognized type of human breast cancer that was recently described in dogs [5-7]. Such neoplasm is a morphologically distinctive variant of mammary invasive ductal carcinoma characterized by diffuse presence of neoplastic cells in morule-like clusters (micro papillae) inside cystic spaces without fibro vascular cores (Figure 1). Despite having low incidence in women, the recognition of IMC cases is extremely important because they have an aggressive behavior with high lymphotropism and lymph node metastases rate in such species [8].

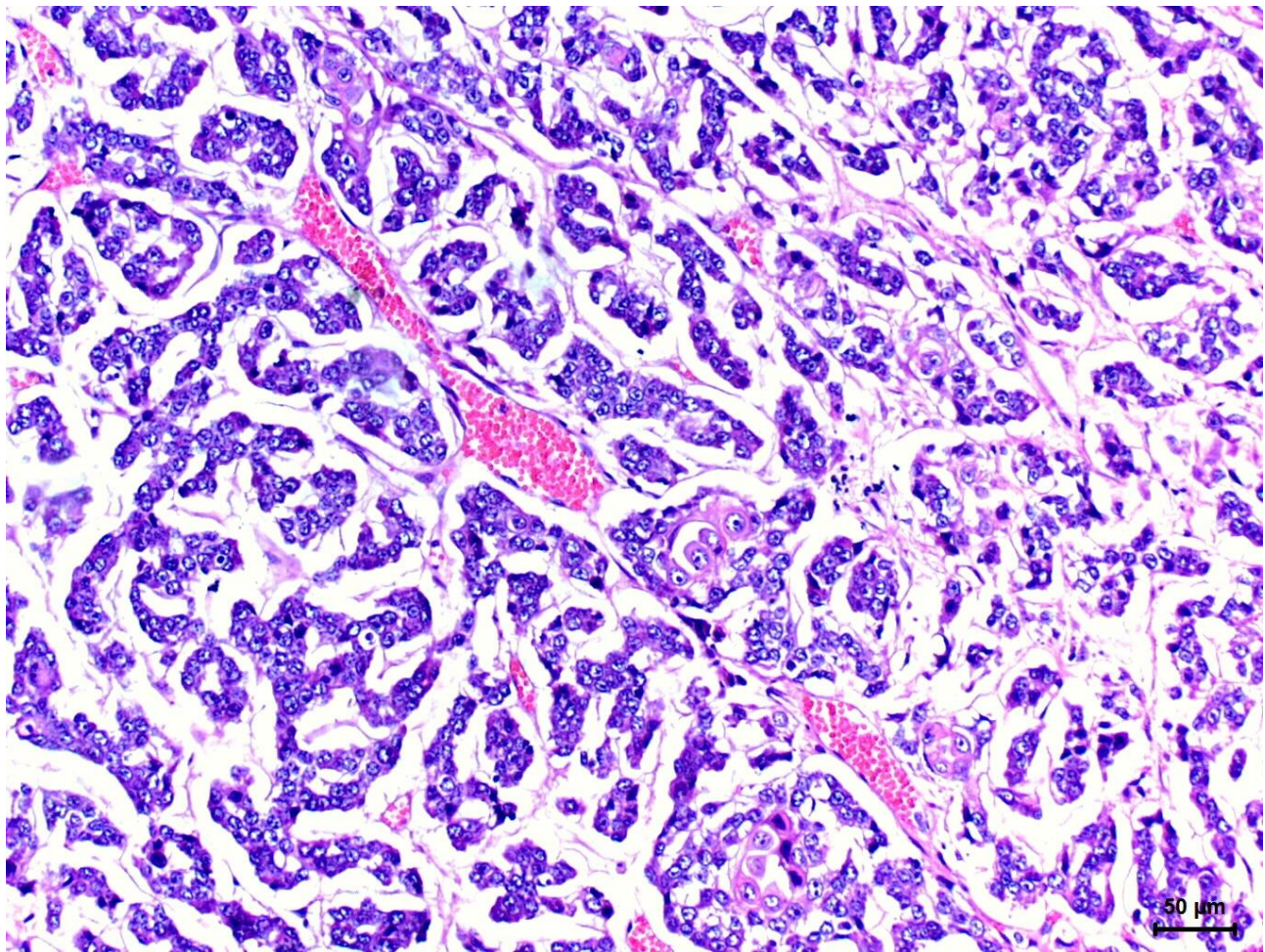


Figure 1: Invasive micropapillary carcinoma. Morulae and papillae surrounded by fusiform cells suggestive of endothelium, creating a spongiform pattern. Hematoxylin and eosin (bar = 50 μm)

IMC appears to frequently behave as inflammatory carcinoma in dogs [6,7,9] presenting a median overall [1] survival period varying from three to four months. Microscopically, a sponge-like growing pattern with many pseudocystic spaces can be observed, most of them similar but not true lymphatic vessels (Figure 1). In fact, the identification of true lymphatic tumor emboli in the vicinity of the primary tumor is difficult. Additionally, neoplastic cells reveal positive immunoreactivity for epithelial membrane antigen which stains the apical cell membrane in moruliform nests and tubules [2]. In dogs, the tumor was already characterized cytologically, [7] revealing the same morphology observed within the histologic counterpart. This tumor was further assessed immunohistochemically in dogs, showing high immunoexpression of hormonal receptors, epithelial membrane-antigen (EMA) and low immunoexpression of HER2 protein [9].

Secretory carcinoma

Secretory carcinoma of the mammary gland is an extremely rare neoplasm with limited data available both in humans and animals. Such neoplasm is also known as juvenile carcinoma in women and histologically presents itself as papillary, tubular or solid neoplasm in two distinctive patterns, with intracellular/extracellular secretion and granular eosinophilic cytoplasm of the neoplastic cells [10] (Figure 2). Additionally, the neoplastic cells are usually immunohistochemically positive for α -lactalbumin in the human species [11].

Only one case has been reported in dogs until the present moment [12]. Grossly, the neoplasm was roughly oval, white, and somewhat lobulated. In such case, the animal died fifty days after the surgery presenting lymph nodes, heart, lung, and kidney metastases, providing evidence of aggressive behavior. Immunohistochemical staining revealed positive reaction to α -lactalbumin and negative results for S100 protein in such case.

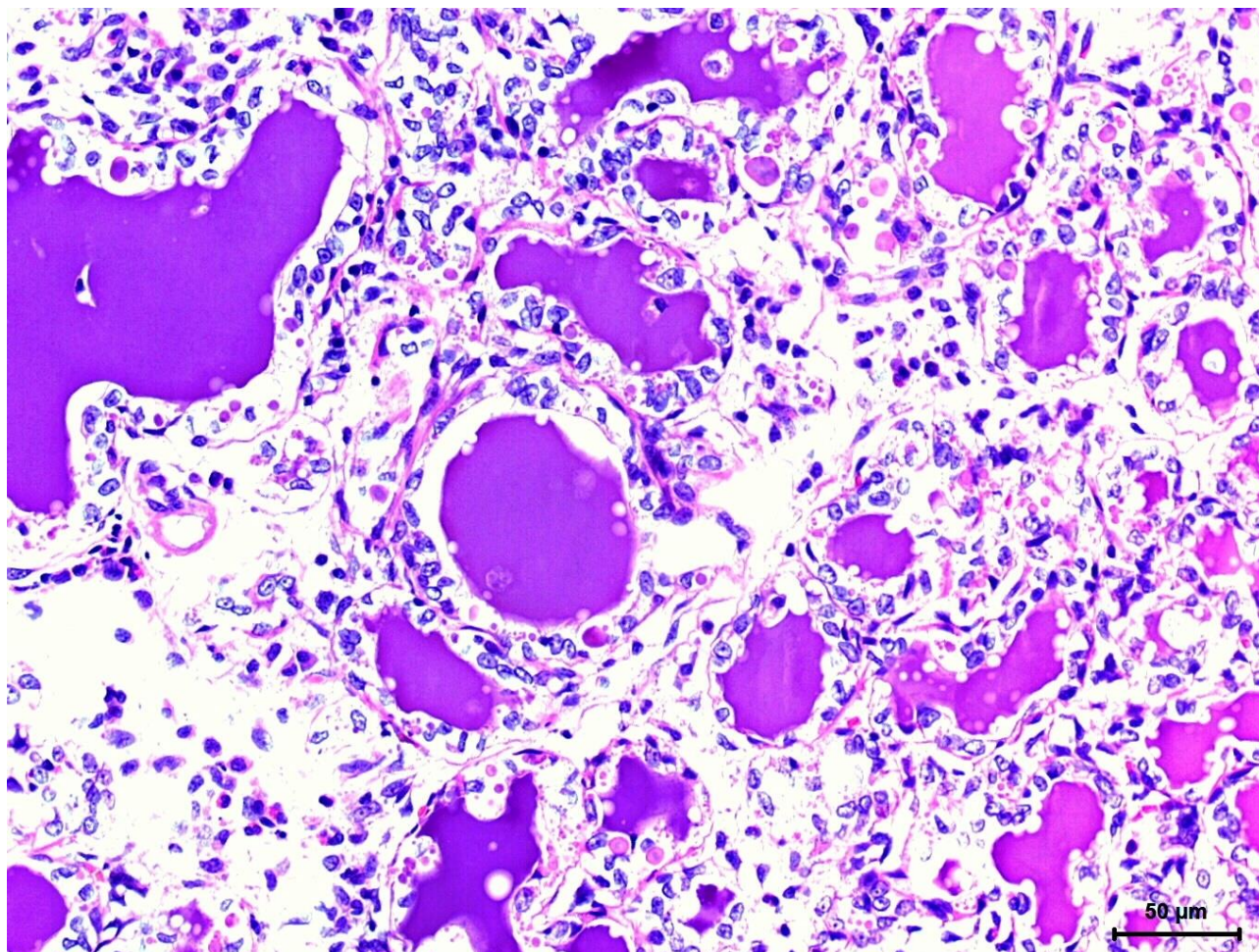


Figure 2: Secretory carcinoma. Clear cells surrounding a prominently eosinophilic amorphous material can be observed. Hematoxylin and eosin (bar = 50 µm).

Pleomorphic lobular carcinoma

Pleomorphic lobular carcinoma (PLC) of the mammary gland is recognized in humans as a subtype of invasive lobular carcinoma. This tumor has marked nuclear atypia and is characterized by a plasmacytoid, histiocytoid or apocrine morphological appearance, pleomorphic nuclei, varying degrees of contour irregularity and/or higher nuclear size [10,13] (Figure 3), consequently allowing pathologists to consider it to be different from the classical invasive lobular carcinoma. Additionally, it usually shows lack or loss of E-cadherin expression [13]. Given the possibility of showing an apocrine-like pattern, this histotype must be differentiated from those presenting apocrine differentiation in women. A significantly worse prognosis and survival rate is reported for women presenting this histological subtype [14]. In humans, its recognition is very important since it is considered to have a more aggressive behavior than the classical lobular carcinoma [13].

In dogs, the first case reported was published by Cassali et al. [15]. In such case, neoplastic cells were arranged in cords of infiltrative cells, revealed a moderately abundant eosinophilic cytoplasm, eccentric nuclei, and many cells contained PAS-positive intracytoplasmic material. Additionally, metastatic cells were observed in the left and right superficial inguinal lymph nodes. Immunohistochemistry revealed positivity for CAM 5.2, lack of E-cadherin membrane expression, similarly to what is observed in women, associated with negative immunostaining for progesterone receptor, p53, and HER-2. Subsequently, other authors [16] also observed the characteristic loss of E-cadherin (Figure 4) expression and cytologically described this tumor, revealing an important atypia within tumor cells and loss of cohesion between cell clusters.

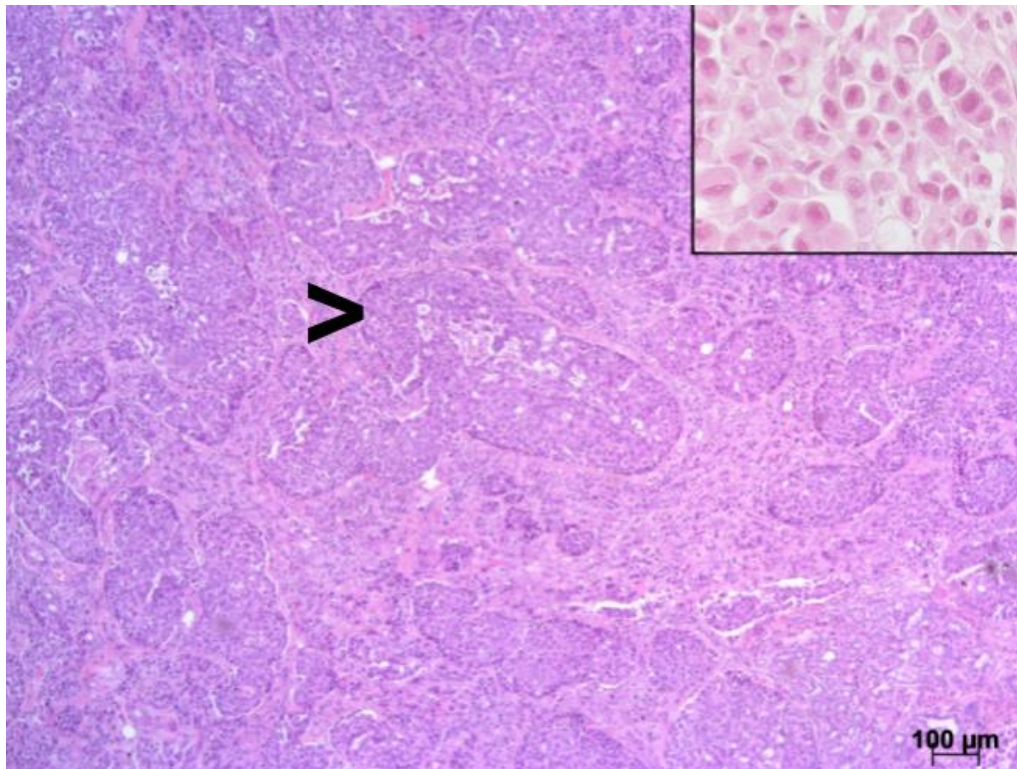


Figure 3: Pleomorphic lobular carcinoma. Neoplastic cells can be observed forming a lobular pattern (arrowhead). Invasive cells arranged in cords and presenting bizarre nuclei and plasmacytoid/histiocytoid appearance can be observed (inset). Hematoxylin and eosin (bar = 100 μm).

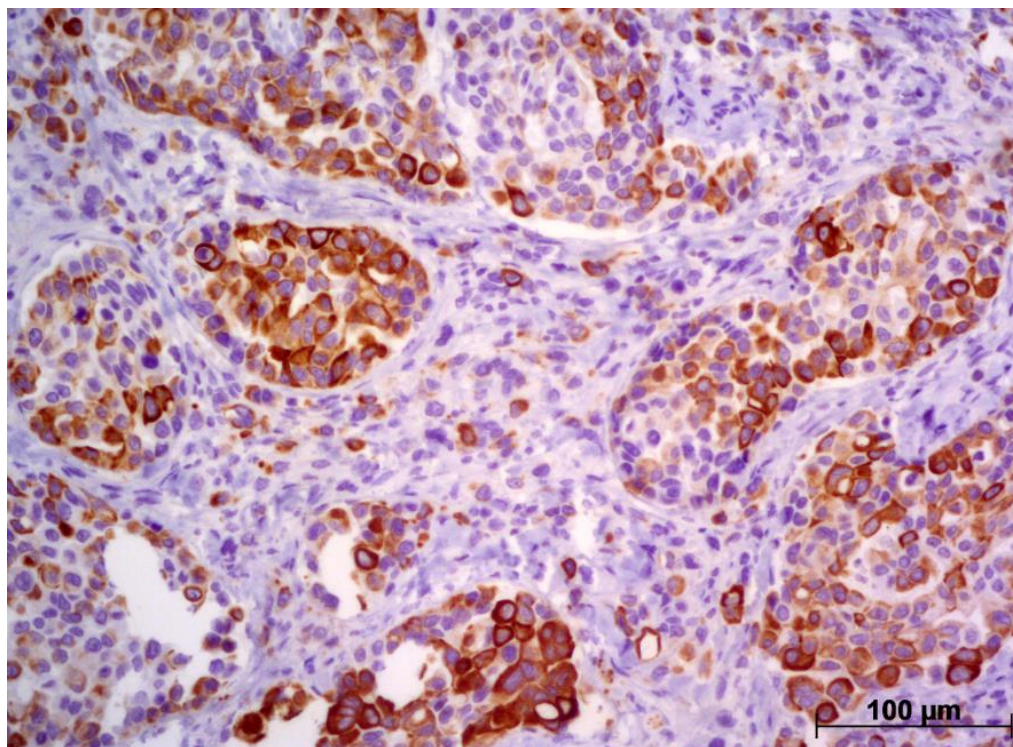


Figure 4: Pleomorphic lobular carcinoma. Areas of mammary lobules revealing loss of E-cadherin expression within the tumor. DAB immunohistochemistry, Harris hematoxylin counterstain (bar = 100 μm).

Mammary carcinoma with sebaceous metaplasia

Mammary neoplasms can present different types of metaplastic tissue both in humans and dogs, including bone, hematopoietic tissue, and squamous epithelia [4,10,17]; however, sebaceous metaplasia is rarely reported in mammary tumors in those species [18] and its importance in canines and humans is unknown. In women, this neoplasm is also known as sebaceous carcinoma of the breast and is a rare subtype of invasive breast cancer that is characterized by a lobular or nested growth pattern with adipophilin positivity by immunohistochemistry [19]. The neoplastic cells are variably admixed with those displaying sebaceous differentiation (Figure 5).

The first canine case was published by Dr. Chang and colleagues [18] in which two tumors were observed in the left inguinal mammary gland, both grossly presented as whitish to light brown multilobulated and superficially ulcerated masses. Microscopically, cells with abundant foamy cytoplasm resembling sebocytes were observed within the

intraductal papillary-like nests of mammary carcinoma, providing evidence of sebaceous metaplasia. Additionally, large areas of invasive sebaceous carcinoma were commonly seen surrounding small-sized intraductal papillary neoplastic nests. The neoplasm was negative to PAS and mucicarmine stainings; however, positive lipid droplets could be observed when using the Oil red O staining. Disseminated lymphatic spread to the lymph node was characteristic of the sebaceous carcinoma and the animal died 3 months after surgery, consequently revealing a guarded prognosis.

Subsequently, two other groups also published cases of mammary tumors with sebaceous differentiation – a mammary adenoma [20] and a non-invasive mammary carcinoma [21] – with similar morphologic features when compared with the first case published [15]. Immunohistochemical analysis revealed that tumors cells were positive for cytokeratin [14] and negative for cytokeratin [19], suggesting no luminal, but reserve cell origin in this cases.

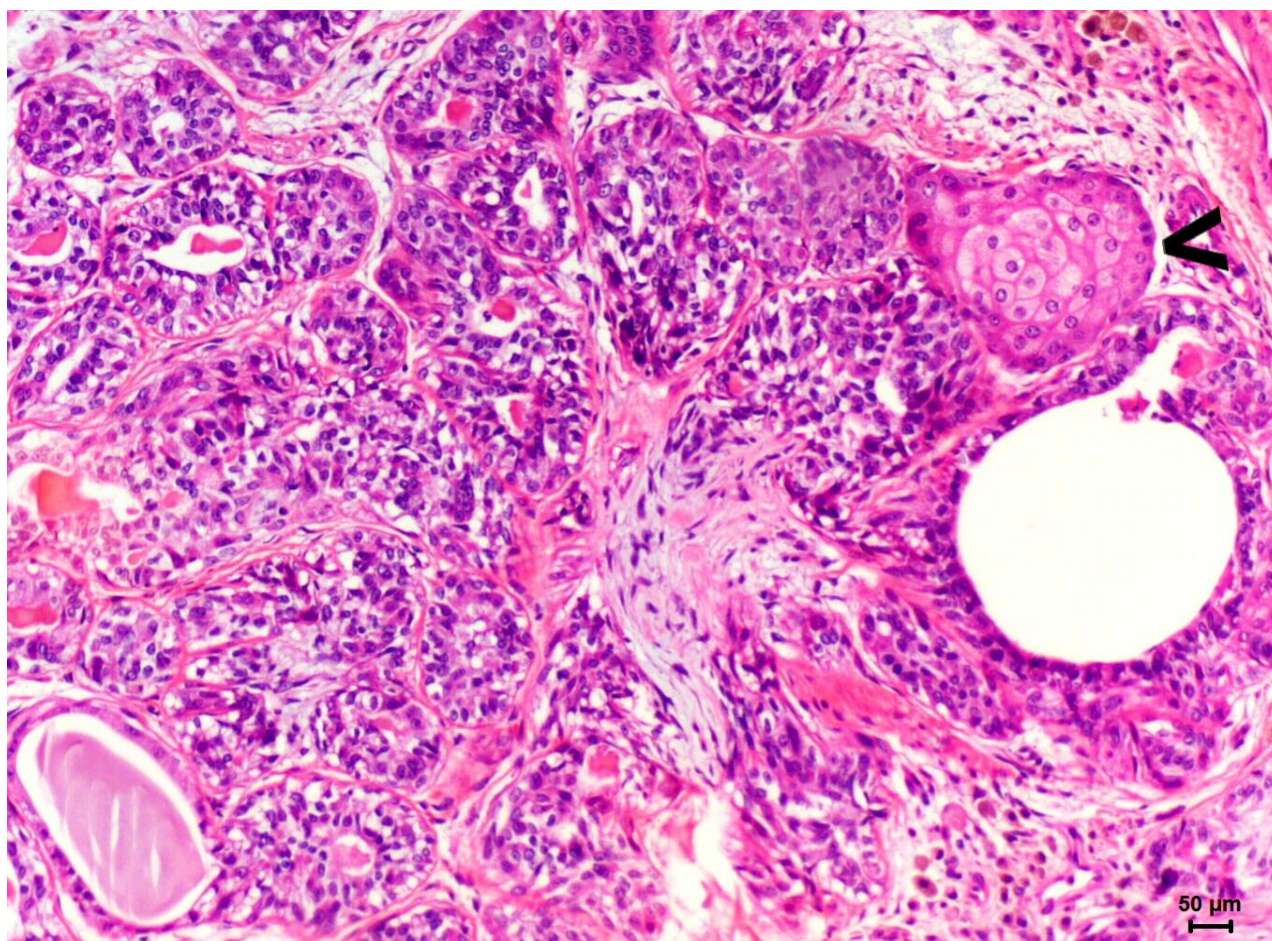


Figure 5: Mammary tumor with sebaceous differentiation. Areas with cells completely differentiated into sebocytes can be observed (arrowhead) admixed with mammary acini. Hematoxylin and eosin (bar = 50 μm).

Conclusions

Rare mammary neoplasms in dogs appear to have different behaviors and prognoses. Although histopathology has been our standard, there is now the question of whether it is time to apply better histopathological criteria associated with new technologies to further understand these rare tumors. Are they all really unique subtypes or not? We ensure that is extremely important to correctly diagnose such cases and to perform a careful follow-up in order to better evaluate differences in their clinical outcome.

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