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CASE REPORT
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# Secretory Mammary Carcinoma *In Situ* in a Cat

**Marina Possa dos Reys[1], Fernanda Rezende Souza[1], Érica Almeida Viscone[2], Karen Yumi Ribeiro Nakagaki[1,2] & Geovanni Dantas Cassali[1]**

## ABSTRACT

***Background*:** Secretory carcinoma is a rare mammary neoplasm observed in humans and animals. It was 1st called juvenile carcinoma. Secretory carcinoma is characterized by eosinophilic secretory material, both intra- and extracellularly, and neoplastic cells with a signet ring appearance. It is usually invasive, with a few rare reports of its non-invasive form, secretory carcinoma *in situ*, in humans. In veterinary medicine, only 2 cases of secretory carcinoma have been reported, both in dogs. This case is the 1st report of secretory carcinoma in a cat and the 1st instance of secretory carcinoma *in situ* in veterinary medicine, highlighting its histopathological, histochemical and immunohistochemical features.

***Case*:** A 15-year-old female mixed-breed cat was presented with multiple small nodules located in the right mammary chain. The cat underwent a mastectomy to remove the affected tissue. Upon histological examination of the cranial abdominal mammary gland (A1), a well-delimited neoplasm was identified. The tumor exhibited tubular and cluster formations of cells, with no evidence of invasion beyond the basal membrane. There was a significant deposition of both inter- and extracellular eosinophilic material, and the neoplastic cells showed prominent vacuolation, giving them a signet ring appearance. To further support the suspected diagnosis of secretory carcinoma, histochemical and immunohistochemical tests were conducted. Histochemical staining using Periodic Acid-Schiff (PAS), both with and without diastase digestion, revealed positive results for the neoplastic cells, indicating the presence of secretory material. Additionally, the cells tested positive for the alpha-lactalbumin antibody, further supporting the diagnosis of secretory carcinoma. The Ki67 proliferation index was measured at 30%, which is considered relatively high, indicating a notable degree of cell proliferation. Furthermore, immunohistochemical analysis confirmed the presence of myoepithelial cells surrounding the tubules and cell clusters, as demonstrated by the positivity for alpha-smooth muscle actin and p63. This confirmed the *in situ* nature of the neoplasm, as the absence of invasion was confirmed, leading to the definitive diagnosis of secretory carcinoma *in situ*. Unfortunately, no follow-up information was available regarding the cat's post-surgical condition.

***Discussion*:** The diagnosis of secretory mammary carcinoma in animals can be made based on the characteristic morphology, which includes the presence of both intra- and extracellular eosinophilic secretion and the vacuolated, signet ring appearance of the neoplastic cells. Histochemical and immunohistochemical techniques are essential to confirm the diagnosis. PAS staining, with and without the diastase reaction, is useful in identifying the secretory material within the cells. Furthermore, the positivity for alpha-lactalbumin in both the cytoplasm of the neoplastic cells and the extracellular secretion helps corroborate the diagnosis. It is important to differentiate secretory carcinoma *in situ* from other tumor types with a similar morphology, given the potential for aggressive behavior associated with this neoplasm. However, in the present case, the prognosis is likely more favorable due to the absence of invasion and metastasis, as evidenced by the *in situ* nature of the tumor. More cases of secretory carcinoma and secretory carcinoma *in situ* need to be diagnosed and described in veterinary medicine to gain a better understanding of their biological behavior and prognosis.

**Keywords:** feline, alpha-lactalbumin, mammary neoplasm, PAS, secretion.

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[1]Departamento de Patologia Geral, Instituto de Ciências Biológicas (ICB), Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil. [2]Celulavet - Centro de Diagnóstico Veterinário, Belo Horizonte. Correspondence: G.D. Cassali [geovanni.cassali@gmail.com]. ICB - Universidade Federal de Minas Gerais (UFMG). Av. Pres. Antônio Carlos n. 6627. Bairro Pampulha. CEP 31270-901 Belo Horizonte, MG, Brazil.

## INTRODUCTION

Secretory carcinoma is a rare breast neoplasm, comprising less than 1% of cases, 1st described by McDivitt & Stewart [21] in women [2]. Initially termed juvenile carcinoma due to its occurrence in children and young adults [1,21,30], secretory carcinoma exhibits various histological patterns, primarily characterized by eosinophilic secretory material and neoplastic cells with vacuoles and a signet ring appearance [7,10,20,26].

Breast carcinomas *in situ* are malignant epithelial proliferations confined to mammary ducts, without invasion beyond the basal membrane [4]. Secretory carcinoma is typically invasive, with only rare reports of secretory carcinoma *in situ* [16,17,24,27].

In veterinary medicine, 2 cases of secretory carcinoma have been reported: 1 in a German Shepherd [5] and another in a mixed-breed dog [26]. No feline cases or secretory carcinoma *in situ* in animals have been recorded.

Secretory carcinoma is diagnosed through immunohistochemistry, identifying intracellular and extracellular positivity for alpha-lactalbumin [7,12,13,26]. In turn, the diagnosis of the *in situ* component requires immunohistochemical confirmation of myoepithelial cells surrounding neoplastic formations, proving the absence of invasion [3,16,24].

While secretory carcinoma shows a favorable prognosis in humans, it is aggressive in animals, however more epidemiological data is needed [1,7]. Regarding secretory carcinomas *in situ*, there is also a lack of data about prognosis and behavior [24]. This study aims to report a rare case of secretory carcinoma *in situ* in a cat, highlighting its histopathological, histochemical and immunohistochemical characteristics.

## CASE

A 15-year-old female mixed-breed cat presented nodules in the right mammary chain, located in the cranial abdominal mammary gland (A1), measuring approximately 0.8 x 0.5 cm, and in the caudal abdominal mammary gland (A2), measuring approximately 3.5 x 1.2 x 0.6 cm. The patient underwent total mastectomy, and the removed tissues were sent to Celulavet - Centro de Diagnóstico Veterinário laboratory, where they were routinely processed for histopathological examination.

In the A1 fragment, histopathological analysis revealed a well delimited proliferation of neoplastic epithelial cells, arranged in tubules, without invasion of basal membranes (*in situ*). The cells exhibited moderate cytoplasm, with poorly delimitation, vacuolated, sometimes with peripheral nuclei (signet ring appearance), round nuclei, small and evident nucleoli, with moderate nucleus: cytoplasm ratio, mild anisocytosis, and anisocariosis; a large amount of eosinophilic amorphous intraluminal and occasionally intracytoplasmic material was present; 9 mitotic figures were observed in 10 high power fields (40x/2.37 $mm^2$) [Figure 1A]. The initial conclusion was of an *in situ* carcinoma [6]. However, due to the presence of vacuolated cells and eosinophilic amorphous intracellular and extracellular material, the hypothesis of secretory carcinoma was raised. The nodule in A2 was diagnosed as tubular carcinoma with cribriform areas.

For confirmation of the secretory carcinoma diagnosis, immunohistochemical examination was performed by the Laboratório de Patologia Comparada, ICB - UFMG. The sample was sectioned in 4 µm sections and put on gelatin slides. The antibodies used were: alpha-lactalbumin[1] (polyclonal, 1:500) [Figure 1D], alpha-smooth muscle actin[2] (αSMA) (myoepithelial cell marker, clone 1A4, 1:200) [Figure 1E], p63[2] (myoepithelial cell marker, clone DAK-P63, 1:100) [Figure 1F], Ki67[2] (cell proliferation marker, clone MIB-1, ready to use) [Figure 2A], estrogen receptor[2] (ER) (clone ID5, ready to use) [Figure 2B], progesterone receptor[1] (PR) (clone HPRA-2, 1:50) [Figure 2C], and HER-2[2] (ready to use) [Figure 2D]. Antigen retrieval was performed in wet heat at 125°C (and 95°C for p63 and α-actin), and sections were incubated with primary antibodies for 16 h at 4°C. The streptavidin-biotin-peroxidase complex method was used as the detection method, according to the manufacturer's instructions. Reactions were visualized by incubating the slides with chromogen 3,3´-diaminobenzidine tetrachloride[2] and counterstained with hematoxylin. The antibody specifications and results are detailed in Table 1.

Histochemical technique for Periodic Acid-Schiff (PAS) with and without diastase digestion was also performed, with positive labeling of both intra- and extracellular secretion, in both techniques (Figure 1B-C). By associating the findings of histopathology, histochemistry, and immunohistochemistry, the diagnosis of secretory carcinoma *in situ* was confirmed.

**Table 1.** Antibody specifications and immunohistochemical results of a secretory mammary carcinoma *in situ* in a cat.

| Antibodies | Clone | Dilution | Results |
|---|---|---|---|
| α-lactoalbumin[1] | Polyclonal | 1:500 | Positive (intracytoplasmic staining in neoplastic cells and secretion) |
| p63[2] | DAK-P63 | 1:100 | Positive (nuclear staining in myoepithelial cells around tubules) |
| α-smooth muscle actin (αSMA)[2] | 1A4 | 1:200 | Positive (intracytoplasmic staining in myoepithelial cells around tubules) |
| Ki67[2] | MIB-1 | Ready to use | Positivity in 30% of neoplastic cells (assessed in 500 cells) |
| ER[2] | ID5 | Ready to use | +++ (positivity in 51 to 75% of neoplastic cells) |
| PR[1] | HPRA-2 | 1:50 | ++++ (positivity in more than 75% of neoplastic cells) |
| HER-2[2] | - | Ready to use | 1+ (incomplete/weak membranous positivity in 10% or more of neoplastic cells) |

The assessments of the markers were performed qualitatively for α-lactalbumin, p63, and αSMA, quantitatively for Ki67, and semi-quantitatively for ER, PR, and HER-2.

## DISCUSSION

Confirmation of the diagnosis of secretory carcinoma in this case was achieved through morphological analysis by HE, as well as histochemical and immunohistochemical techniques. The neoplasm exhibited vacuolated cells, often under a signet ring appearance, along with the accumulation of eosinophilic secretion both inside and outside the cells, as previously described in the literature for this tumor type [7,18,23]. Secretory carcinoma presents various

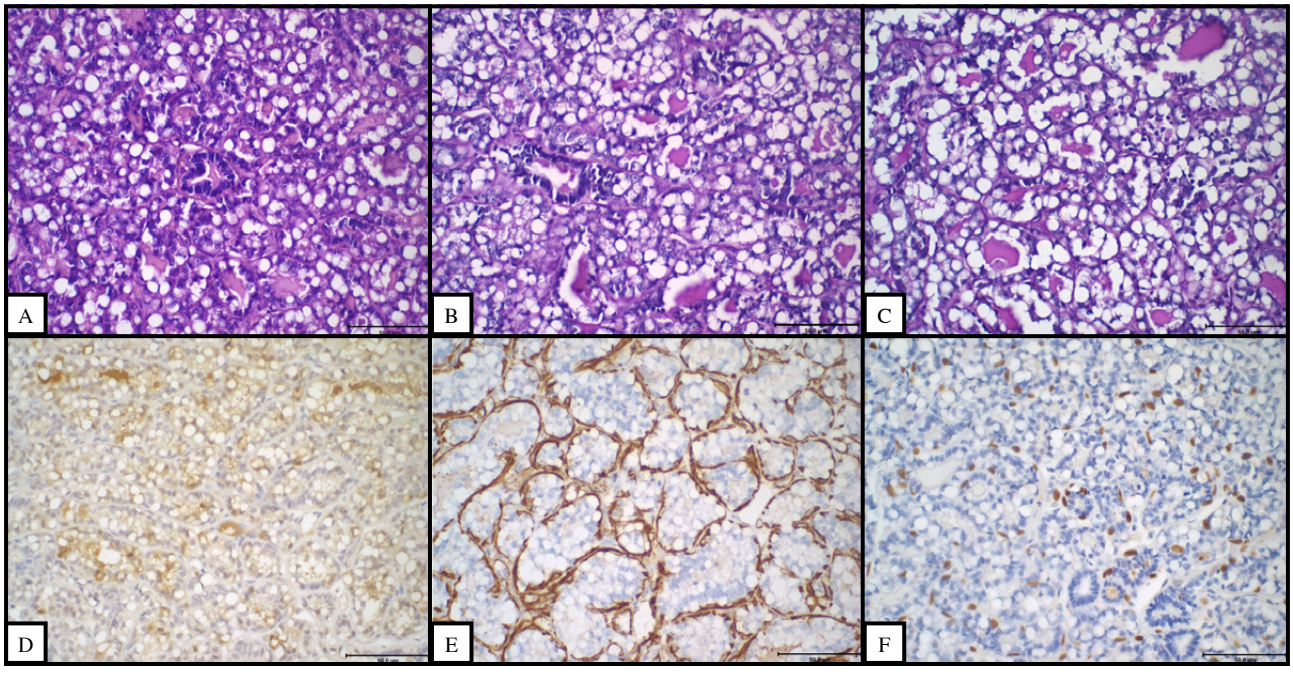


**Figure 1.** Secretory mammary carcinoma *in situ*. A- Proliferation of well-delimited tubules, delineated by epithelial vacuolized cells, with intra and extracellular eosinophilic material. [HE; 40x]. B- The secretory material is PAS positive. [PAS; 40x]. C- The secretory material is PAS positive after diastase digestion. [PAS after diastase digestion; 40x]. D- Alpha-lactalbumin: Positive intracytoplasmic staining in neoplastic cells and secretion [40x]. E- αSMA: Positive intracytoplasmic staining in myoepithelial cells [40x]. F- p63: Positive nuclear staining in myoepithelial cells [40x].

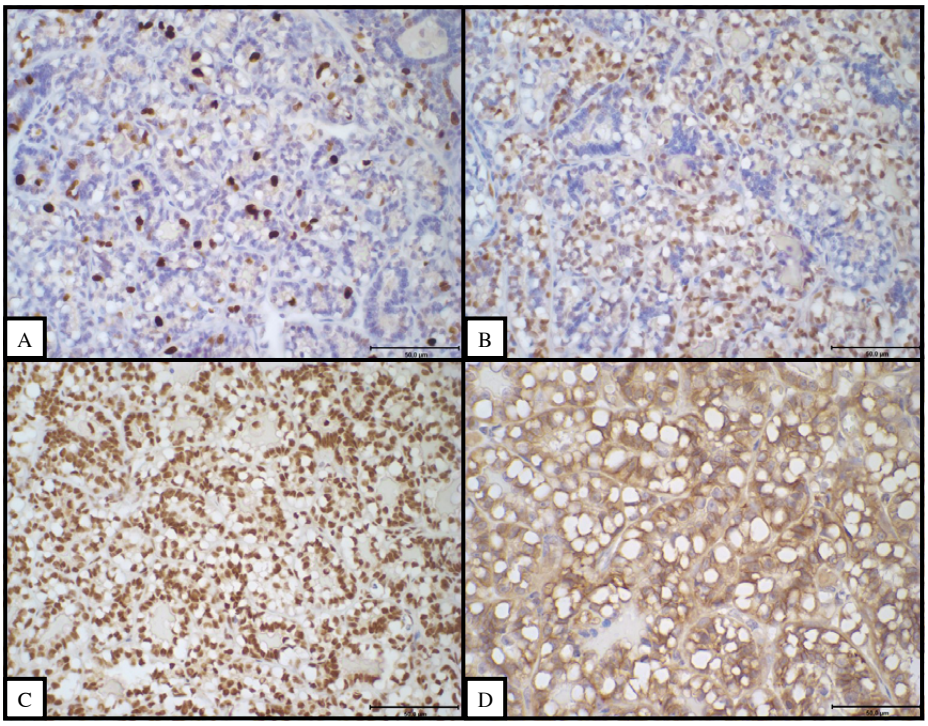


**Figure 2.** Secretory mammary carcinoma *in situ.* A- Ki67: Positivity in 30% of neoplastic cells (assessed in 500 cells). B- ER: Positivity in 51 to 75% of neoplastic cells. C- PR: Positivity in more than 75% of neoplastic cells. D- HER-2: Incomplete / weak membranous positivity in 10% or more of neoplastic cells.

histological patterns in humans, such as solid, microcystic, and ductal, and may present a combination of them [10,18,20,23]. In veterinary medicine, the pattern found by Cassali *et al.* [5] was solid and tubular, and Silva *et al.* [26] found a solid pattern. In the present case, we observed a predominantly tubular/ductal pattern.

Regarding histochemistry, we observed positivity for PAS of both intra- and extracellular content, before and after diastase digestion, corroborating the presence of diastase-resistant material, characteristic of secretory carcinoma [18,32]. Immunohistochemistry showed positive immunolabeling for alpha-lactalbumin both in the cytoplasm of neoplastic cells and in extra- and intracellular secretion. Alpha-lactalbumin is a diastase-resistant protein, and its cytoplasmic evidence is frequently expressed in secretory carcinomas, which can help in the diagnosis [5,6,12,13,18,32]. The essential diagnostic criteria for secretory carcinoma is their characteristic morphological and immunophenotypic features as described, especially the extracellular and intracytoplasmic secretions [18]. In the most recent version of the World Health Organization (WHO) Classification of Breast Tumors, secretory carcinoma is classified under the rare and salivar gland-type tumours, which carry a similar morphology and immunoprofile of neoplastic lesions of their salivary glands' counterparts [18].

Secretory carcinoma exhibits a characteristic morphology; however, its identification requires distinction from other lesions with a similar pattern. In humans, it is important to differentiate it from: lactating adenoma, hypersecretory cystic hyperplasia, apocrine carcinoma, hypersecretory cystic carcinoma, juvenile papillomatosis, among others [24]. Similarly, in animals, secretory carcinoma must be distinguished from lipid and glycogen-rich carcinomas and mucinous carcinomas [7], which can be done by confirming alpha-lactoalbumin immunoreactivity and/or by histochemical techniques. The intracellular and extracellular content of secretory carcinoma is PAS-positive after diastase digestion. Mucinous carcinoma presents slightly basophilic amorphous PAS-positive material (mucin), which is not found in secretory carcinoma; glycogen-rich carcinoma is PAS-positive but negative after diastase digestion; and lipid-rich carcinoma is negative for PAS [7,32].

Secretory carcinoma is usually invasive, and only rare cases of secretory carcinoma *in situ*, or secretory carcinoma with intraductal components, have been reported in the human literature [16,17,24,27]. In the veterinary literature, both cases described

were invasive and affected dogs [5,26]. However, in the present case, the neoplasm was organized within tubular formations and apparently did not invade beyond the basal membrane. This was confirmed by positive immunostaining for p63 and αSMA around the ductal components, thus indicating the presence of myoepithelial cells, and consequently demonstrating an *in situ* growth pattern. The same pattern was observed in cases of secretory carcinoma *in situ* in human literature, with immunostaining of myoepithelial cells around the intraductal neoplastic component [16,24]. Studies show that *in situ* and invasive components of secretory carcinoma present the same immunological and molecular profile, demonstrating their genetic similarities [24], but this still needs to be studied in animals.

The occurrence of secretory carcinoma is more prevalent in young women, although it can also affect older women, being generally more aggressive in these cases [23]. On the other hand, cases of secretory carcinoma *in situ* show a higher average age (48.5 years) [24], indicating a disparity regarding the invasive form of the disease. In the canine reports, the animals were 3 and 10 years old in the 1st and 2nd reported cases, respectively [5,26], while in this feline report, the animal was 15 years old. This variability of age in animals may indicate that secretory carcinoma does not follow the pattern of affecting younger individuals, as in humans; however, more reports are needed to corroborate this statement, especially in felines.

Unlike the human counterpart, wherein the triple-negative phenotype prevails (negative for estrogen, progesterone, and HER-2 receptors) in secretory carcinoma cases, in this report, a luminal B HER-2 negative phenotype was identified, similar to that found by Silva *et al*. [18,26]. This demonstrates a difference in the phenotypic profile of these tumors in animals. Despite the triple-negative phenotype and expression of a basal profile, secretory carcinoma generally presents an indolent behavior in women, rarely leading to metastasis [1,7,19,20,21,23,31,32]. In contrast, both the cases reported in dogs exhibited aggressive behavior. In the case reported by Cassali *et al.* [5], the animal had tumor recurrence and disseminated metastasis, with a survival of 50 days. In the case reported by Silva *et al.* [26], metastases were observed in the humerus and lymph nodes of the animal, which survived for 133 days after surgery.

In the present case, no metastases were observed; however, clinical follow-up of the animal after surgery was not possible. Nevertheless, it is not expected for a carcinoma *in situ* to cause metastases, corroborating the findings of the literature on this neoplasm in humans [24]. There is still not enough information about the biological behavior and long-term prognosis of secretory carcinoma *in situ*, although it is believed they present a good prognosis due to their non-invasive nature [24]. It is important to emphasize that although it is likely that the animal in this case does not have an unfavorable prognosis due to the presence of an *in situ* carcinoma, other lesions in the mammary gland were identified, including a diagnosis of tubular carcinoma with cribriform areas in the adjacent mammary gland, whose prognosis is known to be unfavorable in this species [7]. Furthermore, it is also not known if a secretory carcinoma *in situ* can evolve into an invasive form.

The treatment of secretory carcinoma in women is surgical, both in the invasive and *in situ* forms, and may require adjuvant therapy with chemotherapy in invasive cases and cases with lymph node metastasis [24,32]. In the 3 cases from the veterinary literature, including the present one, surgical treatment was performed, involving partial or total mastectomy, with no history of adjuvant chemotherapy [5,26]. Given the non-invasive nature of the neoplasm in this case, surgery is considered an effective treatment [5]. However, due to the concomitant diagnosis of an aggressive mammary neoplasm, it cannot be stated that surgical treatment alone would be sufficient. Unfortunately, the lack of clinical data after the animal's surgery precludes obtaining more information about the prognosis.

In conclusion, the diagnosis of secretory mammary carcinoma in animals is possible through the analysis of its characteristic morphology and with the aid of histochemical and immunohistochemical techniques, thus allowing the differentiation from other tumor types with similar morphology. Although rare, the diagnosis of secretory carcinoma and its distinction from other types of carcinomas are crucial in the diagnostic routine due to the potential aggressive behavior of this neoplasm. However, this case of secretory carcinoma *in situ*, which is unprecedented in veterinary literature and rare in the human literature, is probably associated with a better prognosis due to the absence of invasion and occurrence of metastases. However,

more cases of both secretory carcinoma and secretory carcinoma *in situ* need to be reported and studied in animals, along with their epidemiological, clinical, and phenotypic characteristics, in order to better elucidate their prognosis, both in dogs and cats.

MANUFACTURERS

[1]Agilent Dako. Santa Clara, CA, USA.

[2]Invitrogen - Thermo Fisher Scientific. Waltham, MA, USA.

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