
©1996-2015 All Rights Reserved. Online Journal of Veterinary Research . You may not store these pages in any form except for your own personal use. All other usage or distribution is illegal under international copyright treaties. Permission to use any of these pages in any other way besides the before mentioned must be gained in writing from the publisher. This article is exclusively copyrighted in its entirety to OJVR. This article may be copied once but may not be, reproduced or re-transmitted without the express permission of the editors. This journal satisfies the refereeing requirements (DEST) for the Higher Education Research Data Collection. Linking: To link to this page or any pages linking to this page you must link directly to this page only here rather than put up your own page.

OJVR™

Online Journal of Veterinary Research®

Volume 19(3): 155-161, 2015

Malignant adenomyo-epithelioma in a feline mammary gland

De Campos CB^{1,2} DVM Ms, [Gamba CO](#)² DVM Ms, [Damasceno KA](#)² DVM Ms, Lavalle GE³ PhD, Cassali GD² DVM Ms PhD

¹Department of Veterinary Clinic and Surgery, School of Agricultural and Veterinary Sciences of the Sao Paulo State University (FCAV/UNESP) Jaboticabal Campus, ²Laboratory of Comparative Pathology, Department of General Pathology, Biological Science Institute (ICB), Federal University of Minas Gerais (UFMG), Belo Horizonte, ³ Veterinary Hospital, Veterinary School, Department of Veterinary Clinic and Surgery, Federal University of Minas Gerais (UFMG), Belo Horizonte, Research was conducted at the Laboratory of Comparative Pathology, Department of General Pathology, Biological Science Institute (ICB), Department of General Pathology, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil.

ABSTRACT

De Campos CB, Gamba CO, Damasceno KA, Lavalle GE, Cassali GD., Malignant adenomyo-epithelioma in a feline mammary gland, Onl J Vet Res., 19(3): 155-161, 2015. Mammary neoplasms are the third most frequent tumor in felines. We describe clinical, histopathological, and immuno-histochemical findings from a malignant adenomyo-epithelioma (MA) from a domestic queen. The cat presented with mammary masses and underwent radical unilateral mastectomy followed by chemotherapy. The tumor recurred and the animal survived 125 days but then died. Microscopy revealed a highly cellular malignant myoepithelial solid cell proliferation pattern with moderate pleomorphism and malignant epithelial proliferation in a tubular and papillary arrangement. The myoepithelial nature of the neoplastic cells was confirmed by p63 target antigen clone test. Based on histopathological and immunohistochemical findings and histological similarity between women and feline tumors, a diagnosis of MA was made.

Key-Words: feline, mammary gland, neoplasm, malignant adenomyoepithelioma

INTRODUCTION

Mammary neoplasms are the third most frequent tumor that affects domestic felines ([MacEwen et al. 1984](#); [Misdorp 2002](#); [Overley et al. 2005](#); [Lana et al. 2007](#)). The average age for diagnosis is 10-11 years ([Misdorp 2002](#)), and regional and distant

metastasis are common (Lana et al. 2007). Frequent histological types include tubular, papillary, solid, cribriform, and *in situ* carcinomas (Misdorp et al. 1999; Misdorp 2002; Lana et al. 2007). Surgery remains treatment of choice (Misdorp 2002) and may be used alone or in combination with chemotherapy or other therapies (Lana et al. 2007).

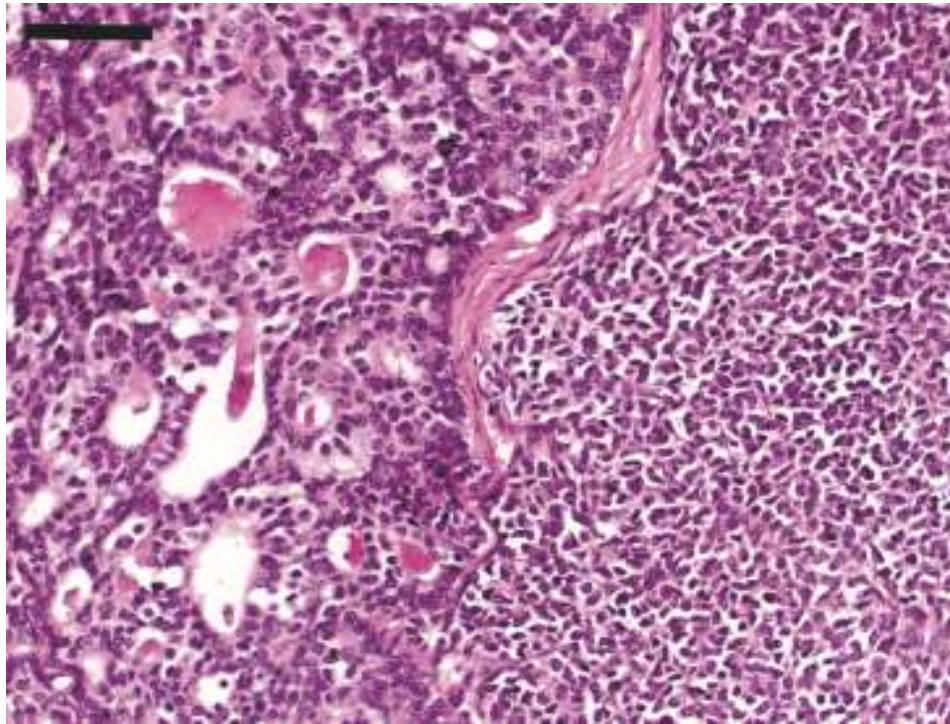
Adenomyo-epithelioma of the human breast is a rare histological type characterized by proliferation of luminal glandular components as well as myoepithelial cells. Most tumors are benign, but malignant transformation of one or both cellular components may occur (Ahmed and Heller 2000; Howlett et al. 2003; Jones et al. 2003; Rosen 2009; Lakhani et al. 2012). Neoplasms derived from myoepithelial cells have been reported in the skin, salivary glands, breast, and lungs (Gatti et al. 2004). Malignant adenomyoepitheliomas (MA) in feline mammary gland has not to our knowledge been described in the literature. We report clinical, histopathological, and immunohistochemical findings from feline malignant adenomyo-epithelioma.

CASE REPORT

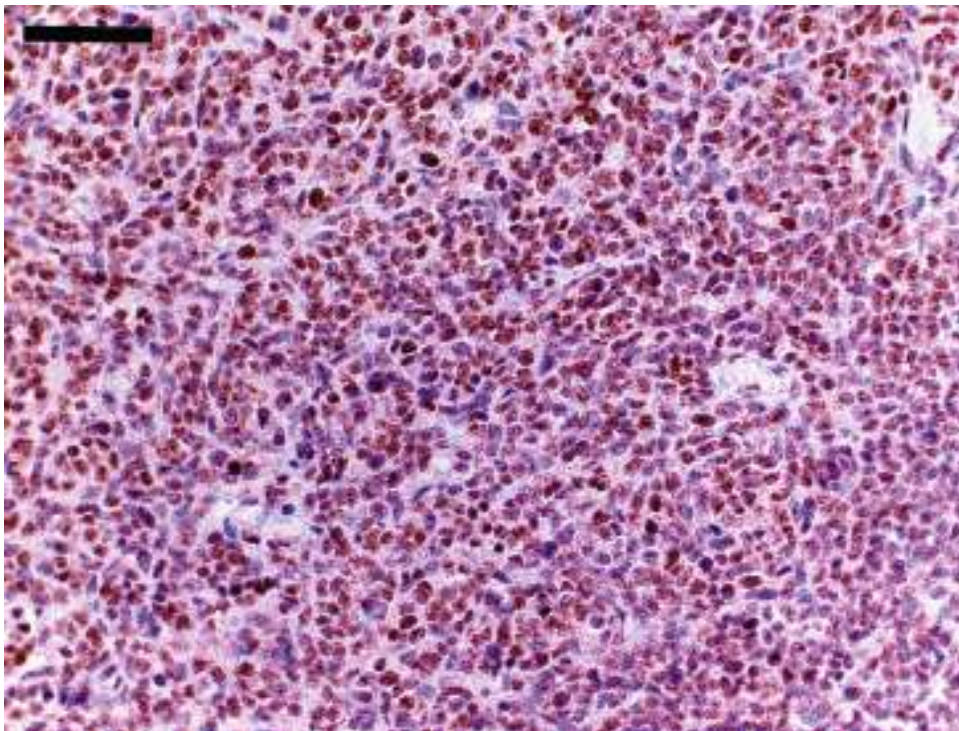
A fifteen-year-old neutered domestic shorthair queen was presented with ~6 month old mammary tumor. Radical unilateral mastectomy with inguinal and axillary lymph node removal was performed. Chemotherapy was commenced twenty days later with intravenous carboplatin 200mg/m² at 21d intervals. After 2 treatments, the tumor recurred and the animal died 125 days after surgery.

Macroscopic evaluation of the resected samples demonstrated a 3.0 x 1.8 x 1.5 cm lobulated subcutaneous nodular formation between the caudal thoracic and cranial abdominal mammary glands. The cut surface presented a firm mass presenting coalescent nodules of approximately 1.0 cm with whitish color and cystic areas of approximately 0.2 cm diameter containing a brownish vitreous material. The inguinal lymph node measured 2.0 x 1.5 x 1.0 cm, and the cut surface revealed loss of delimitation between the cortical and medullar regions, and a cystic central area of 0.6 cm. Samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections were stained with H&E.

Microscopic evaluation of the primary neoplasm showed highly cellular malignant myoepithelial cell proliferation arranged in a solid pattern, with moderate pleomorphism, loose chromatin, and prominent nucleoli associated with malignant epithelial proliferation in tubular and papillary arrangements, presenting multiple *in situ* carcinomatous and stromal invasion areas (Figure 1A and B below). Epithelial neoplastic cells were characterized by a moderate cytoplasm, moderate nuclear pleomorphism, and multiple and prominent nucleoli. Both components presented low mitotic index, evidence of lymphatic invasion and compromised surgical margins. Histological analysis was done due to a predominance of myoepithelial components and insufficient invasive epithelial areas (Figure1B)



A



B

Figure 1. Photomicrographs illustrating the features of a malignant myoepithelioma in a feline mammary gland. **A.** Malignant neoplastic epithelial and myoepithelial cells. HE, stain, 40x. Bar=50 μ m. **B.** Neoplastic epithelial cells presenting nuclear positivity for p63 antigen (Polymeric detection system anti-p63, counterstained with Harris's haematoxylin), 40x. Bar=50 μ m.

The cortex and medulla of the inguinal lymph node presented macro-metastasis of epithelial and myoepithelial cells similar to malignant adenomyo-epithelioma described. Epithelial cells were characterized by moderate nuclear pleomorphism, and multiple and prominent nucleoli. Myoepithelial cells were characterized by a solid pattern, with moderate pleomorphism, loose chromatin, and prominent nucleoli.

Immuno-histochemical methods are described in Table 1 below. The tests of the primary tumor and lymph node confirmed the myoepithelial nature of the neoplastic cells using the p63 antigen test (positive 3+). Other immuno-histochemical results are shown in Table 2, below.

Table 1. Immuno-histochemical staining for Ki-67, Estrogen Receptor (ER), Progesterone Receptor (PR), Cyclooxygenase-2 (Cox-2), Vascular Endothelial Growth Factor (VEGF), Human Epidermal Growth Factor Receptor type 2 (HER-2), and p63.

Target Antigen (Clone)	Dilution	Antigen Retrieval Method	Incubation Time (h)/Temp	Analysis
Ki-67 (MIB-1)	1:25	Pressurised Heat (125°C/2min) with citrate buffer pH 6.0	1h Room Temp	Dutra et al., 2004
ER (1D5)	1:20	Pressurised Heat (125°C/2min) with EDTA buffer pH 9.0	1h Room Temp	Hammond et al., 2010
PR (HPRA2)	1:20	Pressurised Heat (125°C/2min) with EDTA buffer pH 9.0	1h Room Temp	Hammond et al., 2010
HER-2 (Polyclonal)	1:200	Water bath (98°C/20min) with citrate buffer pH 6.0	16h/ 4°C	Wolff et al., 2007
Cox-2 (SP21)	1:80	Water bath (98°C/20min) with citrate buffer pH 6.0	1h Room Temp	Lavalle et al., 2012
VEGF (Ab-1)	1:200	No antigen retrieval	1h Room Temp	Tsai et al., 2012
p63 (4A 4)	1:80	Water bath (98°C/20min) with citrate buffer pH 6.0	1h Room Temp	Bertagnolli et al., 2009

Table 2. Immunohistochemical results for Ki-67, Estrogen Receptor (ER), Progesterone Receptor (PR), Cyclooxygenase-2 (Cox-2), Vascular Endothelial Growth Factor (VEGF), and Human Epidermal Growth Factor Receptor type 2 (HER-2) analysis in a malignant adenomyoepithelioma (MA).

Neoplasm		Ki-67 (%)	ER (+/-)	PR (+/-)	Cox-2 (score)	VEGF (score)	HER-2 (score)
MA	Primary Tumor	3	+	+	2	1	1+
	Regional Lymph Node	22	+	+	4	1	1+

Note: ^a + = Nuclear staining present in 1% or more of the tumor cells, considered as positive for ER and PR, evaluation defined by the American Society of Clinical Oncology, College of American Pathologists (ASCO/CAP). ^b 1+ = Weak or incomplete membrane staining of any proportion of the tumor cells for HER-2, evaluation defined by the American Society of Clinical Oncology, College of American Pathologists (ASCO/CAP).

The patient also presented 5 other primary mammary neoplasms and regional metastasis to the axillary lymph node that were removed during the surgical procedure. Two cribriform carcinomas with tubular areas and lymphatic invasion in the cranial and caudal thoracic mammary glands, one carcinoma in mixed tumor with lymphatic invasion located between the cranial and caudal thoracic mammary glands, one cribriform carcinoma with mucinous areas in the caudal abdominal mammary gland, and one tubulopapillary carcinoma located between the cranial and caudal

abdominal mammary gland were diagnosed. The axillary lymph node presented metastasis containing only epithelial cells, with a pattern resembling a cribriform carcinoma. The histopathological and immune-histochemical findings of the primary tumor suggested a diagnosis of MA.

DISCUSSION

In humans, MA with a biphasic growth patterns at the primary site and in metastasis has been reported (Rosen 2009), as found in the present report. The epithelial component may form solid nests or groups, ducts, cystic, trabecular, pseudo-papillary, and papillary structures. The myoepithelial component is arranged around the epithelial component and can form solid strands, trabeculae or even larger sheets, and is usually polygonal or spindle shaped (Jones et al. 2003). In the present report, the epithelial component formed tubular and papillary patterns, while the myoepithelial component had a solid arrangement, similar to the description of larger sheets.

A clear diagnosis of this tumor type was enabled through immune-histochemical markers for myoepithelial cells such as the p63 antigen test described by Rosen (2009); and Lakhani et al. (2012). The results to ER and PR positive, lack of HER-2 and VEGF overexpression, a low Ki-67 index, and low Cox-2 score in the primary tumor, all characteristic of a better prognosis in feline mammary gland neoplasms (Millanta et al. 2002ab, 2005ab, 2006; Dias Pereira et al. 2004; Rasotto et al. 2011; Seixas et al. 2011). The lymph node metastasis presented higher proliferation indexes and Cox-2 scores, indicating a selection of more aggressive neoplastic cells. Metastasis of adenomyoepitheliomas with one or two malignant components generally occurs in 40% of humans, mostly to the lungs, but may also involve liver, bone, brain, and other sites. Regional lymph node metastasis, as was reported the queen, is unusual (Lakhani et al. 2012). Diagnosis of the MA was possible due to histological similarities in women and in queens. The understanding of special types of tumors in veterinary medicine are important, especially when larger number of cases are studied and the prognostic of specific lesions are established, leading to appropriate treatment of patients.

Acknowledgements

This study was supported in part by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Fundação de Amparo a Pesquisa de Minas Gerais (FAPEMIG), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

REFERENCES

- Ahmed AA, Heller DS. Malignant adenomyoepithelioma of the breast with malignant proliferation of epithelial and myoepithelial elements: a case report and review of the literature. Archives of Pathology & Laboratory Medicine 124(4):632-636, 2000.
- Bertagnolli AC, Cassali GD, Genelhu MCLS, Costa FA, Oliveira JFC, Gonçalves PBD. Immunohistochemical expression of p63 and p63 in mixed tumors of canine mammary glands and its relation with p53 expression. Veterinary Pathology 46(3):407-415, 2009.

- [Dias Pereira P, Carvalheira J, Gartner F. Cell proliferation in feline normal, hyperplastic and neoplastic mammary tissue – an immunohistochemical study. *Veterinary Journal* 168\(2\):180–185, 2004.](#)
- [Dutra AP, Granja NVM, Schmitt FC, Cassali GD. C-erbB-2 expression and nuclear pleomorphism in canine mammary tumors. *Brazilian Journal of Medical and Biological Research* 37\(11\):1673-1681, 2004.](#)
- [Gatti G, Viale G, Simsek S, Zurrada S, Intra M, Caldarella P, Luini A. Adenomyoepithelioma of the breast, presenting as a cancer. *Tumori* 90:337-339, 2004.](#)
- Hammond MEH, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Archives of Pathology & Laboratory Medicine* 134(7):48-72, 2010.
- [Howlett DC, Mason CH, Biswas S, Sangle PD, Rubin G, Allan SM. Adenomyoepithelioma of the breast: spectrum of disease with associated imaging and pathology. *American Journal of Roentgenology* 180\(3\):799–803, 2003.](#)
- [Jones C, Tooze R, Lakhani SR. Malignant adenomyoepithelioma of the breast metastasizing to the liver. *Virchows Archives* 442\(5\):504–506, 2003.](#)
- Lakhani SR, Hayes M, Eusebi V. Adenomyoepithelioma and adenomyoepithelioma with carcinoma. In: Lakhani SR, Ellis IO, Schnitt SJ, et al (4th ed). WHO Classification of tumours of the breast. International Agency for Research on Cancer, Lyon, France, 2012:122-123.
- Lana SE, Rutteman GR, Withrow SJ. Tumors of the mammary gland. In: Withrow SJ, Vail DM (4th ed). Withrow & MacEwen's Small Animal Clinical Oncology. W. B. Saunders Company, Philadelphia, USA, 2007:619-636.
- [Lavalle GE, Campos CB, Bertagnolli AC, Cassali GD. Canine malignant mammary gland neoplasms with advanced clinical staging treated with carboplatin and cyclooxygenase inhibitors. *In Vivo* 26\(3\):375-379, 2012.](#)
- [MacEwen EG, Hayes AA, Harvey HJ, Patnaik AK, Mooney S, Passe S. Prognostic factors for feline mammary tumours. *Journal of the American Veterinary Medical Association* 185\(2\):201–204, 1984.](#)
- [Millanta F, Lazzeri G, Mazzei M, Vannozi I, Poli A. MIB-1 labeling index in feline dysplastic and neoplastic mammary lesions and its relationship with postsurgical prognosis. *Veterinary Pathology* 39\(1\):120-126, 2002a.](#)
- [Millanta F, Lazzeri G, Vannozi I, Viacava P, Poli A. Correlation of vascular endothelial growth factor expression to overall survival in feline invasive mammary carcinomas. *Veterinary Pathology* 39\(6\):690-696, 2002b.](#)
- [Millanta F, Calandrella M, Bari G, Niccolini M, Vannozi I, Poli A. Comparison of steroid receptor expression in normal, dysplastic, and neoplastic canine and feline mammary tissues. *Research in Veterinary Science* 79\(3\):225-232, 2005a.](#)
- [Millanta F, Calandrella M, Citi S, Della Santa D, Poli A. Overexpression of HER-2 in feline invasive mammary carcinomas: an immunohistochemical survey and evaluation of its prognostic potential. *Veterinary Pathology* 42\(1\):30–34, 2005b.](#)
- [Millanta F, Citi S, Della Santa D, Porciani M, Poli A. Cox-2 expression in canine and feline invasive mammary carcinomas: correlation with clinicopathological features and prognostic molecular markers. *Breast Cancer Reserch Treatment* 98\(1\):115-120, 2006.](#)
- Misdorp W, Else RW, Hellmén E, Lipscomb TP. Histological classification of mammary tumors of the dog and the cat. 2nd Series. v. VII. American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology. Armed Forces Institute of Pathology, Washington DC, USA, 1999:1-59.
- Misdorp W. Tumors of the mammary gland. In: Meuten DJ (4th ed). Tumors in Domestic Animals. Iowa State press, Ames, USA, 2002:575-606.

- Overley B, Shofer FS, Goldschmidt MH, Sherer D, Sorenmo KU. Association between ovariohysterectomy and feline mammary carcinoma. *Journal of Veterinary Internal Medicine* 19:560-563, 2005.
- [Rasotto R, Caliarì D, Castagnaro M, Zanetti R, Zappulli V. An immunohistochemical study of HER-2 expression in feline mammary tumours. *Journal of Comparative Pathology* 144\(2-3\):170-179, 2011.](#)
- Rosen PP. Myoepithelial neoplasms. In: Rosen PP (3rd ed) *Rosen's Breast Pathology*. Lippincott Williams & Wilkins, Philadelphia, USA, 2009:612-615.
- [Seixas F, Palmeira C, Pires MA, Bento MJ, Lopes C. Grade is an independent prognostic factor for feline mammary carcinomas: A clinicopathological and survival analysis. *Veterinary Journal* 187\(1\):65–71, 2011.](#)
- [Tsai HL, Yang IP, Lin CH, Chai CY, Huang YH, Chen CF, Hou MF, Kuo CH, Juo SH, Wang JY. Predictive value of vascular endothelial growth factor overexpression in early relapse of colorectal cancer patients after curative resection. *International Journal of Colorectal Disease* 28:415-424, 2012.](#)
- [Wolff AC, Hammond MEH, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, Mcshane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, Vijver M, Wheeler TM, Hayes DF. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Journal of Clinical Oncology* 131\(1\):18-43, 2007.](#)