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Recurrent Micropapillary Carcinoma with Lymph Node Metastasis in bitch: Unilateral Mastectomy and OncoMap-Guided Therapeutic Approach – Case Report

Carcinoma Micropapilar Recidivante com Metástase Linfática em Cadela: Mastectomia Unilateral e Abordagem Terapêutica Guiada por Oncomapa – Relato de Caso

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Abstract
Mammary neoplasms are among the most common oncological disorders in small animals, with most cases being malignant and strongly influenced by hormonal factors, particularly estrogen and progesterone. Mastectomy remains the treatment of choice, with the surgical approach determined by the affected gland(s) and tumor size. Before surgery, the presence of metastases should be evaluated using imaging modalities such as abdominal ultrasonography, thoracic radiography, and/or computed tomography. Adjuvant therapies, including chemotherapy or targeted treatments, are indicated according to the histological type, tumor grade, clinical stage, and immunohistochemical profile. This report describes a case of micropapillary carcinoma with lymphatic metastasis in a female dog that developed tumor recurrence despite appropriate surgical management and adjuvant chemotherapy. Following recurrence, mastectomy of the remaining mammary chain was performed, and genomic analysis using OncoMap guided a change in therapeutic strategy, revealing the ineffectiveness of the previous protocol and resulting in a survival outcome that differed from reports in the literature.

Keywords: Hormones. Mammary Neoplasm. Metastasis. Surgery.

Resumo
As neoplasias mamárias estão entre as principais afecções oncológicas em pequenos animais, sendo, em sua maioria, de caráter maligno e fortemente associadas à influência hormonal, especialmente dos hormônios estrogênio e progesterona. A mastectomia é o tratamento de escolha, cuja técnica deve ser definida com base na glândula acometida e no tamanho do tumor. Previamente à intervenção cirúrgica,

é fundamental a avaliação da presença de possíveis metástases por meio de exames como ultrassonografia abdominal, radiografia torácica e/ou tomografia computadorizada. O tratamento adjuvante, com quimioterapia ou terapia alvo, é indicado conforme o tipo histológico, grau tumoral, estadiamento e perfil imuno-histoquímico. Este trabalho teve como objetivo relatar um caso de carcinoma micropapilar com metástase linfática em uma cadela que apresentou recidiva tumoral, apesar da abordagem cirúrgica adequada e do uso de quimioterapia adjuvante. Após a recidiva, realizou-se mastectomia na cadeia mamária remanescente, seguida de análise genômica por OncoMapa, a qual permitiu reorientar a conduta terapêutica, evidenciando a ineficácia do protocolo anterior e uma sobrevida divergente daquela descrita na literatura.

Palavras-chave: Hormônios. Neoplasia Mamária. Metástase. Cirurgia.

1 Introduction

Mammary neoplasms are the most prevalent oncological disorders in female dogs, accounting for approximately 50% of all tumors diagnosed in this population (Souza *et al*., 2018). In most cases, these lesions display malignant behavior, with occurrence influenced by hormonal, genetic, and environmental factors. Consequently, they represent a significant concern in veterinary public health due to their impact on morbidity and mortality (Andrade *et al*., 2017; Souza *et al*., 2018).

These tumors are divided into benign and malignant forms. Malignant neoplasms are typically characterized by vascular invasion, necrosis, a high mitotic index, and marked cellular pleomorphism, whereas benign lesions are generally encapsulated and non-invasive (Nosalova *et al*., 2024). Notably, malignant tumors predominate in roughly half of all cases, with adenocarcinomas, carcinosarcomas, solid carcinomas, papillary carcinomas, and complex carcinomas being the most frequent. In contrast, benign variants include ductal papillomas, fibroadenomas, simple adenomas, and benign mixed tumors (Nosalova *et al*., 2024).

Clinical staging follows the TNM system, which considers tumor dimensions (T), regional lymph node status (N), and the presence of distant metastases (M). T1 lesions measure <3 cm; T2, 3–5 cm; and T3, >5 cm. Lymph node status is classified as N0 (no metastasis) or N1 (metastasis present). For distant spread, M0 indicates the absence and M1 the presence of metastases. Based on these criteria, stages are defined as: I (T1/N0/M0), II (T2/N0/M0), III (T3/N0/M0), IV (any T/N1/M0), and V (any T/any N/M1) (Cassali *et al*., 2024; Schmidt *et al*., 2010).

Age and reproductive status play a central role. Middle-aged and older females, particularly those who have not undergone ovariectomy or ovariohysterectomy, are at greater risk. This increased susceptibility results from prolonged exposure to estrogen and progesterone, which stimulate mammary epithelium and promote proliferative and neoplastic changes. Additionally, the use of hormonal contraceptives has been identified as another predisposing factor, potentially contributing to higher disease incidence (Jesus *et al*., 2022).

Regarding therapeutic approaches, available options include surgery, radiotherapy, hormone therapy, chemotherapy, targeted therapy, and virotherapy (Nosalova *et al*., 2024). Among these, surgical removal remains the primary treatment, as it offers effective local control and enables histopathological assessment, which can improve survival rates (Nosalova *et al*., 2024; Sleeckx *et al*., 2011). Surgical techniques range from partial to total, unilateral, or bilateral mastectomy, and the choice of method depends on tumor size, anatomical location, involvement of regional lymph nodes, tissue adherence, and the number of affected glands (Cassali *et al*., 2024; Papazoglou *et al.,* 2012). Following surgery, the decision to implement adjuvant therapy is influenced by clinical stage, histopathological type and grade, tumor biology, and immunohistochemical profile. Chemotherapy and targeted therapy are the most frequently recommended modalities (Cassali *et al.,* 2024).

It is important to note that mammary cancer is a heterogeneous disease, and therapeutic responses can vary significantly among patients. In this context, precision oncology has emerged as a promising strategy, enabling individualized treatment plans based on the tumor's molecular characteristics. OncoMap is a genomic platform designed to detect specific genetic changes in histological samples. The primary genes evaluated in mammary tumors include RRM1, MDM2, NRAS, and TP53. Such molecular profiling has demonstrated potential for refining prognostic assessment, predicting systemic therapy outcomes, and facilitating personalized disease monitoring, ultimately improving clinical results (Sarhangi *et al*., 2022).

Therefore, this report aims to describe a female dog with recurrent micropapillary mammary carcinoma and lymphatic metastasis, in which therapeutic decision-making was guided by the tumor's genomic profile obtained through OncoMap.

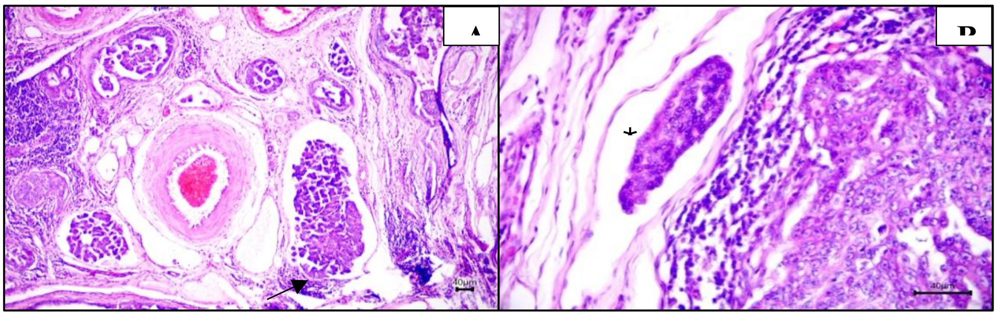
2 Material and Methods

An eight-year-old intact female Pinscher dog, weighing 3.2 kg, with a 4 - 5 body condition score (BCS) (scale 1 to 9) (Laflamme *et al*., 1997), stage B1 heart disease, and stage I chronic kidney disease, was presented for an oncology consultation. During anamnesis, the owner reported that a mammary nodule had developed approximately one year earlier, and showed slow growth, absence of ulceration or pain, and presence of secretion. The patient was nulliparous, had a history of recurrent pseudopregnancy, had never received hormonal contraceptives, and had undergone multiple estrous cycles. Based on the clinical findings, a total unilateral mastectomy of the right mammary chain was performed, along with axillary and inguinal lymphadenectomy and complementary dental treatment.

Subsequently, an adjuvant chemotherapy protocol with doxorubicin (1 mg/kg) was administered intravenously at 21-day intervals, totaling six sessions. To ensure treatment safety, hematological and biochemical tests were performed before each session, including complete blood count and serum measurements of alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, creatinine, total protein, albumin, and globulins. The main adverse effects observed during the protocol were mild nausea and hyporexia. The clinical response was considered satisfactory, with no evidence of local recurrence or detectable distant metastases.

Histopathological examination of the primary tumor revealed a nodular mass located between the right M4 and M5 mammary glands, measuring 3 x 2 x 1.5 cm, diagnosed as invasive micropapillary mammary carcinoma, grade II. Microscopically, the nodule showed malignant neoplastic proliferation of epithelial cells with moderate to marked anisocytosis and anisokaryosis. These cells formed micropapillary arrangements, occasionally with morule formation within cystic spaces and in areas lined by epithelium and basement membrane (Figure 1A), with six mitotic figures in 2.37 mm² (FN 22 = 10 high-power fields, Obj. 40x), lymphovascular invasion (Figure 1B), and no evidence of neoplastic infiltration at the surgical margins. The right inguinal lymph node presented macrometastasis with extranodal infiltration. In addition, a cutaneous melanocytoma was identified in M4. These findings allowed the neoplasm to be staged as stage IV (T2/N1/M0), according to the criteria described by Cassali *et al*. (2020).

Figure 1 - Micropapillary carcinoma in a female dog. (**A**) Neoplastic proliferation of epithelial cells in a micropapillary arrangement, forming morulae within cystic spaces (*) and in spaces delineated by epithelium and basal membrane (arrow). H&E, Obj. 10x (**B**) Embolus of neoplastic cells within a lymphatic vessel (*). H&E, Obj. 40x



Source: the authors.

Considering the need for greater prognostic and therapeutic definition, immunohistochemistry was performed using estrogen receptor, progesterone receptor, cyclooxygenase-2 (Cox-2), and Ki-67 markers.

Additional imaging examinations included abdominal ultrasonography, thoracic radiography, echocardiography, and electrocardiography.

Immunohistochemistry was carried out on a paraffin-embedded tumor block. The results showed negative estrogen receptor expression, positive progesterone receptor expression, negative Cox-2 expression, and Ki-67 expression in approximately 60% of neoplastic cells. Echocardiography revealed mild mitral valve alteration with a fractional shortening of 43%. Abdominal ultrasonography showed biliary sludge and renal morphological changes.

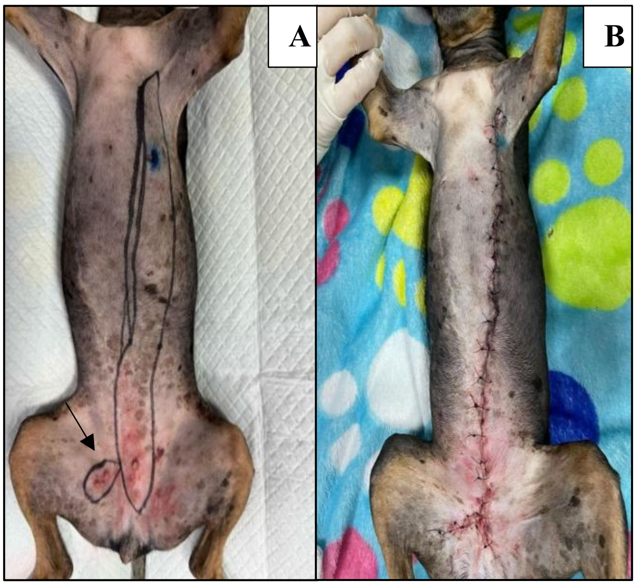
Thoracic radiography demonstrated grade II tracheal collapse and a broncho-interstitial pattern consistent with senescence. Electrocardiography indicated a normal sinus rhythm. Laboratory tests (complete blood count, ALT, ALP, urea, creatinine, total protein, albumin, and globulin) showed no relevant abnormalities.

Due to the positive progesterone receptor status, an ovariectomy was indicated. The anesthetic protocol included acepromazine (0.02 mg/kg) and fentanyl (1 mg/kg) as pre-anesthetic medication, administered intravenously in the same syringe. Induction was achieved with propofol (4 mg/kg, IV), and anesthesia was maintained with isoflurane (1%) in an open system.

Postoperative management included oral supplementation with omega-3 fatty acids (150 mg/kg), coenzyme Q10 (10 mg/kg), beta-glucans (10 mg/kg), vitamin B complex (5 mg/kg), and zinc (1 mg/kg) to promote immunomodulation and anti-inflammatory effects.

Three months after the ovariectomy, the patient returned for oncological reassessment. Small cutaneous eruptions were observed near the contralateral mammary chain. Swelling was also noted at the mastectomy scar and in the left M5 mammary gland region (Figure 2).

Figure 2 - (**A**) Surgical planning, cutaneous eruptions, and swelling at the surgical scar of the left M5 mammary gland (arrow). (**B**) Immediate postoperative view following left unilateral mastectomy and intraoperative electrochemotherapy



Source: the authors.

Fine-needle aspiration cytology revealed the presence of neoplastic epithelial cells, suggestive of carcinoma. Based on this finding, a total unilateral left mastectomy was indicated, along with axillary and inguinal lymphadenectomy and electrochemotherapy applied to the surgical bed.

The anesthetic protocol for the surgical procedure included pre-anesthetic medication (PAM) composed of ketamine (3 mg/kg), methadone (0.2 mg/kg), and lidocaine (2 mg/kg), administered intravenously in combination in the same syringe. Anesthesia was induced with propofol (4 mg/kg, IV), followed by endotracheal intubation and maintenance with isoflurane (1%) in an open circuit system, combined with continuous intravenous infusion of remifentanil (0.3 μg/kg/h).

Histopathological examination of the new specimen revealed a nodular mass located in the left M5 mammary gland, measuring 1.2 x 0.9 x 0.3 cm. The diagnosis was invasive micropapillary mammary carcinoma, grade III. Microscopically, the nodule exhibited a malignant epithelial proliferation with marked anisocytosis and anisokaryosis, arranged in micropapillary patterns, occasionally forming morules within cystic spaces and epithelial and basement membrane-lined spaces. Five mitotic figures were observed in 2.37 mm² (FN 22 = 10 high-power fields, Obj. 40x), with lymphovascular invasion and no evidence of neoplastic infiltration at the surgical margins. In the left M4 gland, multiple emboli of neoplastic epithelial cells were present within lymphatic vessels, and the left inguinal lymph node showed macrometastasis of mammary carcinoma.

Given this new clinical scenario, a chemotherapy protocol with carboplatin (250 mg/m², IV) was instituted. It was administered in three sessions at 21-day intervals. Hematological and biochemical analyses were performed before each session, with no relevant abnormalities detected. The patient tolerated the treatment well, without adverse effects, and clinical evaluation showed no evidence of additional metastases.

Concurrently, a molecular OncoMap test was requested. It was performed using tumor material from the second surgical procedure, analyzed by quantitative RT-PCR. The results showed a 3.4-fold reduction in RRM1 gene expression, indicating sensitivity to gemcitabine. Overexpression of MDM2 (7.3-fold) and NRAS (3.6-fold) was also detected, suggesting potential benefit from rapamycin and trametinib, respectively. Additionally, a 7.3-fold reduction in TP53 expression was observed, indicating resistance to doxorubicin.

Based on these molecular findings, the carboplatin protocol was discontinued, and targeted therapy with rapamycin (0.1 mg/kg, PO, SID) was initiated. Subcutaneous administration of *Viscum album* D2 was added on alternate days as an adjuvant immunomodulator. Since the primary diagnosis, the patient has remained under continuous oncological treatment, free of metastases, with clinical evaluations and diagnostic monitoring every three months.

3 Results and Discussion

This case report describes an intact female Pinscher diagnosed with invasive micropapillary mammary carcinoma, a histological variant of invasive ductal carcinoma considered rare and aggressive in both dogs and humans (Rodrigues *et al*., 2021). Owing to the aggressive nature of this subtype, complete clinical staging was performed, comprising abdominal ultrasonography and thoracic radiography. According to Reese *et al.* (2011), thoracic radiography can detect only metastatic nodules larger than 7 mm in diameter, which may underestimate the presence of micrometastases. Computed tomography offers greater sensitivity for pulmonary evaluation; however, it was not employed in this case due to the high cost of the examination. Periodic imaging re-evaluation using abdominal ultrasonography, thoracic radiography, or computed tomography is recommended to monitor for recurrence or the emergence of new lesions, with intervals tailored to the patient's stage and clinical progression.

The surgical technique employed was total unilateral mastectomy with axillary and inguinal lymphadenectomy, as described by Cassali *et al*. (2024), who recommend this approach for mammary tumors exceeding 3 cm in diameter. When tumors are smaller, and depending on their location, less invasive techniques such as partial mastectomy may be considered to reduce surgical trauma and the release of procarcinogenic factors (Rodigheri *et al.,* 2023).

Lymph node macrometastasis and extranodal metastasis were confirmed in both histopathological reports. According to Gonçalves *et al*. (2021), extracapsular extension of tumor cells within lymph nodes is associated with greater metastatic potential and poorer prognosis, underscoring the severity of the clinical condition described.

Mitotic index assessment revealed six mitotic figures in the first histopathological report and, in the second, eleven figures in cutaneous lesions and five in the tumor area. Cassali *et al.* (2024) classify a mitotic index of up to eight figures as score 1 and between nine and sixteen figures as score 2. Based on this criterion, the patient presented scores 1 and 2. However, lymph node metastasis was already present despite the lower mitotic index, suggesting that this parameter alone is insufficient to determine the tumor's biological behavior. Similarly, Amine *et al*. (2016) reported that Ki-67 is a more accurate indicator of cell proliferation than the mitotic index, consistent with the findings in the present case.

The decision to initiate adjuvant chemotherapy was based on the guidelines described by Cassali *et al*. (2024), which recommend this approach for grade III neoplasms and staging IV or V. The patient was staged as IV (T2N1M0), with lymph node metastasis and a highly aggressive histological subtype (micropapillary carcinoma), justifying the chosen treatment. The initial protocol included doxorubicin; following tumor recurrence, carboplatin was selected. This choice aligned with the recommendations of Cassali *et al.* (2024), who also cite gemcitabine, cyclophosphamide, and 5-fluorouracil as alternatives. Minckwitz *et al.* (2014) reported a positive response to carboplatin in human mammary carcinomas, while Nicoletto and Ofner (2022) observed doxorubicin efficacy despite its cardiotoxicity risk. In the present case, the patient maintained normal cardiac function after doxorubicin administration, as confirmed by echocardiography, allowing a safe transition to carboplatin.

Dental treatment was performed before chemotherapy to reduce oral bacterial load and, consequently, minimize the risk of bacteremia during immunosuppression. This measure is supported by Brennan *et al*. (2008), who identified the oral cavity as a potential source of infectious complications in oncology patients undergoing chemotherapy.

Micropapillary mammary carcinomas in dogs are considered highly malignant, with clinical and histopathological features indicating tumor aggressiveness. Gamba *et al.* (2017) reported lymph node metastasis in 100% of evaluated cases, with positivity for estrogen and progesterone receptors, absence of distant metastases, histological grade II, a Ki-67 proliferative index of 14%, and a mean survival of 120 days. In the present report, the diagnosis was compatible with micropapillary carcinoma and included lymph node metastasis and histological grade II. However, notable differences were observed: the tumor was estrogen receptor-negative, progesterone receptor-positive, and had a Ki-67 index of 60%, indicating higher proliferative activity. Despite the elevated Ki-67, the patient's survival exceeded that described by Gamba *et al*. (2017), possibly due to the use of adjuvant therapies.

COX-2 expression was negative in the patient, which is associated with a better prognosis. Queiroga *et al.* (2011) and Lavalle *et al*. (2009) reported a correlation between positive COX-2 expression, greater tumor aggressiveness, and reduced survival. Therefore, COX-2 inhibitors were not indicated in this case. Immunohistochemical analysis of Ki-67, estrogen receptor, and p53 has been previously studied by Brunetti *et al*. (2021), who reported that patients with positive estrogen receptor expression generally exhibit longer survival and lower Ki-67 levels (mean 33%). Although the correlation with p53 remains unclear, the findings in the present case partially support this association. The patient had negative estrogen receptor expression, and a high Ki-67 index, consistent with a less favorable prognosis. Gene p53 expression was not investigated.

Ovariectomy was performed after mastectomy, based on the immunohistochemical results (estrogen receptor-negative and progesterone receptor-positive). Although Rodigheri *et al.* (2023) noted that combining ovariectomy with mastectomy may increase surgical trauma, Sorenmo *et al.* (2019) demonstrated that the recurrence rate was significantly lower in spayed bitches (31.5%) compared to intact animals (58.6%), highlighting the role of ovarian hormones in tumor progression. Corriveau *et al*. (2017) reported that ovariectomy alone offers benefits comparable to ovariohysterectomy, with shorter surgical time and lower contamination risk, while preserving the positive effects of hormonal suppression and preventing future pyometra. In this case, ovariectomy was chosen to minimize surgical trauma and reduce anesthesia time, considering the patient's age and comorbidities.

The patient also underwent intraoperative electrochemotherapy at the surgical site during excision of the recurrent tumor. This approach is supported by Wichtowski *et al*. (2017), who demonstrated that electrochemotherapy effectively reduces local tumor regrowth in mammary neoplasms with narrow surgical margins, providing improved locoregional control. The presence of cutaneous metastasis justified the use of this technique, contributing to better control of tumor dissemination.

Adjuvant therapy with Viscum album was prescribed for its immunomodulatory effects. Studies by Park *et al.* (2023) and Thronicke *et al.* (2022) have demonstrated the antiproliferative, pro-apoptotic, and immunoregulatory properties of *Viscum album*, as well as its synergistic action with doxorubicin, supporting its use as adjuvant therapy in the management of mammary neoplasms.

Genomic analysis using OncoMap was critical for guiding therapeutic decisions. Sarhangi *et al.* (2022) emphasize that genomic profiling enables a more personalized and effective approach, increasing survival chances. In the present case, OncoMap identified resistance to doxorubicin. Had this information been available earlier, the initial choice of this chemotherapeutic agent could have been avoided, potentially preventing tumor regrowth and subsequent metastasis.

4 Conclusion

In conclusion, micropapillary mammary carcinoma in dogs represents a neoplasm with aggressive behavior and a high potential for lymphatic metastasis. These findings underscore the importance of performing lymphadenectomy in conjunction with mastectomy, following consensus guidelines on mammary tumors, which recommend selecting the surgical technique based on tumor size and the affected mammary gland. Hormonal control through ovariectomy is particularly relevant, given the high prevalence of hormone-dependent tumors, and is preferred due to its lower surgical trauma compared with ovariohysterectomy. The use of adjuvant therapies, including chemotherapy and targeted treatments guided by genomic profiling (OncoMap), constitutes an effective precision medicine strategy, allowing individualized treatment and contributing to improved cure rates and survival in oncology patients.

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