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CAN IT MAY BE A MIXED NEOPLASIA WITH THE COMPONENT OF BOTH CARCINOMATOUS MASTITIS AND T-CELL LYMPHOMA WITH SKINL LOCATION - COMPARATIVE STUDY

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Abstract

Carcinomatous mastitis or the inflammatory mammary carcinoma is a malignant entity described in human, dog and cat clinical oncology; it is characterized by a sudden onset, edema, erythema, peau d'orange, hardening and increased local temperature of the mammary gland, with or without the presence of mammary nodules. Blockage of superficial lymphatics with neoplastic cells is the cause of severe edema in the region. This type of cancer is characterized by an extremely fast rate of growth, development and invasiveness. Tumor cells break the basement membrane and invade regional lymphatic vessels and satellites lymph nodes. Cutaneous T-cell lymphoma in the dog is a rare neoplastic condition with unknown etiology. The reaction at dermis level is characterized by infiltration of neoplastic T lymphocytes with a specific tropism for the epidermis and the ancillary structures. The abnormal division of lymphocytes present plaques or other lesions within the skin. It often involves enlarged satellite lymphnodes, edema, erythema and hardening of the malignant nodules. The link between the immune role of the T-cells and the fulminant inflammatory reaction of the carcinomatous mastitis, frameable in the category of autoimmune diseases, is just one of the puzzles researchers are trying to solve in order to prove the connections between the two neoplasias. One of the pieces is the role of cytokines, having value both in canine inflammatory mammary cancer and T-cell lymphoma. Their purpose of these small proteins that act as cell-to-cell messengers and play an important role within the immune system by stimulating or inhibiting cells in response to a range of stresses has been evaluated due to it's valuable contribution as diagnostic biomarker, biologic predictive marker and the therapeutic significance. The purpose of this study was to characterize the two malignant pathologies clinically, histopathologically and regarding response to treatment in order to identify common ground. Following the information obtained from the studies considered for this article, supplemented with personal case studies, the presence of a mixed neoplasm in the form of an undifferentiated carcinoma interspersed with T lymphoblasts is suspected.

Key words: *inflammatory carcinoma, carcinomatous mastitis, cutaneous T-cell lymphoma.*

INTRODUCTION

Developed on a biological substrate and with a similar endocrine metabolism, the diseases of the mammary gland in humans, dogs and cats have many similarities in clinical evolution and in therapy.

Carcinomatous mastitis is a neoplasm composed of undifferentiated mammary neoplastic cells possibly epithelial and mesenchymal stem. It is characterized clinically by evolutionary bursts (EB).

These EBs are the expression of acute development between the degree of neoplastic aggression and metabolic and immunological antitumor resistance of the affected body. Stage EB1 represents the initial moment, the equivalent of T1, EB2 is in the case of localized forms (T2) and EB3 in the case of diffuse, extended (T3-T4), it has a local pseudoinflammatory appearance manifested by edema with erythema of the entire breast, local hyperthermic, with the characteristic appearance of peau d'orange. It usually represents the clinical stage T4, being characterized by the lymphatic dissemination, in the intradermal structure of the epithelium of the gland, of the highly anaplasic undifferentiated malignant cells from an invasive ductal carcinoma. Clinically in inflammatory mammary carcinoma or the acute EB undifferentiated form, the affected mammary gland is severely edematous, with infiltrated skin, intense congestive blush

coloration, with characteristic appearance of "flush" caused by stenosis of dermal lymph capillaries, hypodermic and glandular parenchymal structure with microscopic tumor thrombi but with embolizing effect. (Crînganu, 2009)

Following selected studies, we present essential information that demonstrates the presence of similarities that indicate the possibility of a mixed form of cancer.

This data is essential for updating diagnostic and treatment protocols, thus leading to their efficiency. This comparative essay is essential for the development of ideas related to the similarity of neoplastic pathologies at this level, which cannot be differentiated from a clinical point of view.

Given the aggressiveness of this type of cancer, the poor response to treatment and the prognosis, it is necessary to continue the studies we have so far.

A COMPARATIVE REVIEW OF THE EXISTING SPECIALTY LITERATURE

There are few reports concerning histological aspects of IMC[1]. Infiltrating ductal carcinomas, other carcinomas and unspecified malignant tumors have been described as involved with IMC. Mammary involvement be can be localized to one or both glands with or without regional lymph node involvement known as PBL[2]. It can be a part of disseminated disease considered as secondary involvement of the breast. Lymphoepithelial lesions in ducts, lobules and vascular involvement have been seen in breast lymphomas. In both primary and secondary breast lymphomas, diffuse large B cell lymphoma (DLBCL) is the most common type. Diagnosis is not often delayed due to the similarity of signs with inflammatory mammary carcinoma.

According to Vianello most cases of LBL[3] have T-cell phenotype, the majority of breast NHLs[4] are B-cell phenotype. Cases with this atypical presentation of lymphoma mimicking an inflammatory mammary carcinoma are rare, but raise questions about clinical diagnosys of malignant formations.

This is because, extensive observation of clinical cases have identified that the most common signs and symptoms of breast lymphoma include a painless enlarged palpable mass. Local inflammatory signs such as skin retraction, erythema, and peau d'orange are usually associated with high-grade lymphoma or diffuse parenchymal involvement. Which means, a clinical differentiation between mammary lymphoma and inflammatory mammary carcinom is impossible (Pena, 2003).

Cytokines released in the tumor microenvironment play a major role in cancer pathogenesis. In human cancers and corresponding animal models, cytokine expression contributes to tumor growth and progression, as well as regulation of the host anti-tumor response. The elucidation of the function and importance of cytokines in canine cancers is still in an early stage, although relevant data have been obtained in classical examples of comparative models of human cancers, such as osteosarcoma, melanoma, mammary tumor and lymphoma.

Cytokines are another piece of the puzzle that links the inflammatory mammary carcinoma and mammary/skin lymphoma together.

Cytokines are small proteins that act as cell-to-cell messengers and play an important role within the immune system by stimulating or inhibiting cells in response to a range of stresses. They also control the differentiation, activation and growth of different cell types. The effects of individual cytokines on immunity depend on the local cytokine concentration, the expression of specific receptors and the activation of multiple signalling pathways (Irac, 2019).

Canine lymphoma represents the most well-studied cancer in terms of cytokine or blood biomarker involvement. T cell lymphoma associated with increased levels of IL-6, whilst IL-10 and De Andres et al. (2013) have demonstrated increased serum levels and tissue expression of IL-6 and IL-10 in dogs with inflammatory mammary carcinoma compared with the non-inflammatory malignant mammary tumors.

Thus similar effects of the cytokines are found in both types of cancers.

[1] inflammatory mammary carcinoma
[2] Primary Breast Lymphoma
[3] Lymphoblastic leukemia/lymphoma
[4] Non-Hodgkin Lymphomas

Cancer often originates from a site of persistent inflammation, and the mechanisms turning chronic inflammation into a driving force of carcinogenesis are intensely investigated. Cyclooxygenase-2 (COX-2) is an inducible key modulator of inflammation that carries out the rate-limiting step in prostaglandin synthesis. Aberrant COX-2 expression and prostaglandin E2 (PGE2) production have been implicated in tumor genesis.

Malignant T cells isolated from skin specimens of patients with MF[5] showed COX-2 expression, whereas non-malignant T cells did not. Moreover, lymphocytes with a malignant phenotype also showed COX-2 expression in situ, indicating that malignant T cells express COX-2 in vivo in a large fraction of patients with advanced MF.

Furthermore expression of COX-2 has been uncovered in inflammatory mammary carcinoma biopsy specimens which mirrors the results obtained from the MF patients.

Anaplastic lymphoma kinase (ALK) gene has been found to be altered in several solid and hematologic tumors. Immunohistochemical analysis showed ALK is overexpressed in a substantial proportion of inflammatory mammary carcinoma and possibly plays a significant role in the aggressive behavior of this cancer. In order to confirm the common ground for these markers in inflammatory mammary carcinoma and/or mammary/skin lymphoma we have selected a canine patient, Mops, 9-year-old female, previously treated for a histopathological diagnosis of undifferentiated carcinoma (Figure 1).

The formation is recurrent after radical mastectomy, with an unfavorable evolution due to the incomplete therapuetic protocol.

Clinically, the dog presents massive thoraco-abdominal edema extended to the hind limbs.

Complete blood-work, thermography (Figure 2) and histopathology have lead to the diagnosis.

The treatment consisted of a complex approach to the patient. Chemotherapy: multi-agent second-line cytostatic drug consisting of the combination of Ifosfamide at a dose of 200 mg/m^2 i.v., every 14 days alternating with Epirubicin, (anthracyclinic pivot) at a dose of 20 mg/m^2 iv, every 21 days.

Recommended approach for this case is a complete mastectomy with axillary and inguinal lymph node excision after first the preoperative protocol described above.

Postoperatively, we recommend cytostatic chemotherapy to prevent lung and bone metastases (Gemcitabine 200 mg/m^2 iv at 14 days and Carboplatin 30 mg/m^2 at 21 days). In this case postoperative cytostatic therapy for IMC was supplemented with Leukeran 2 mg/m^2, every 14 days, per os, as a specific alkylating agent for lymphoma and Massivet 10mg./m^2 per os, daily, for 30 days as a tyrosine-kinase inhibitor to prevent the onset of cytostatic resistance by suppressing MDR genes[6]. Additional therapy with Cefort 25 mg /kg iv, Furosemide 0.2 ml sc, Meloxicam 0.35 ml sc. Adjuvant therapy included liver protection (Samilyn, Hepatiale, Ornitil), cardiac protection (Cardiostrength), renal protection (Renalvet), immunotherapy (Impromune, Corpet) and paraneoplastic syndrome therapy (antiemetics, transfusion, painkillers).

RESULTS AND DISCUSSIONS

The values of the presented markers fall both in the category of mammary carcinoma and in the category of a skin lymphoma.

Their prognostic value is confirmed by the patient's response to treatment.

Results of the patiens evaluation have been consistent with the specific characteristics determined by these markers.

Biochemical:

Elevated ALP: 520 (0-212) U/L

Hematologic:

Increased neutrophils: 13.71 billion/liter (3-12 billion/liter)

Low percentage lymphocytes: 6.8% (12-30%)

Monocytes percentage increase: 7.6% (2-4%)

Low percentage eosinophils: 0.7% (1-8%)

MCV (average volume of citrate) increased: 78% (60-77)

MCHC (mean hemoglobin concentration) low: 29.4 - g/dL (31-34 g/dL)

[5] Mycosis fungoides - cutaneous T-cell lymphoma

[6] Multidrug resistance gene

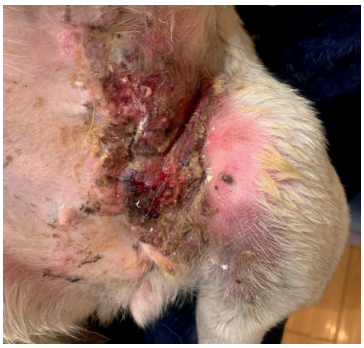

Figure 1. Mops, 9-year-old female, diagnosis of undifferentiated carcinoma (original)

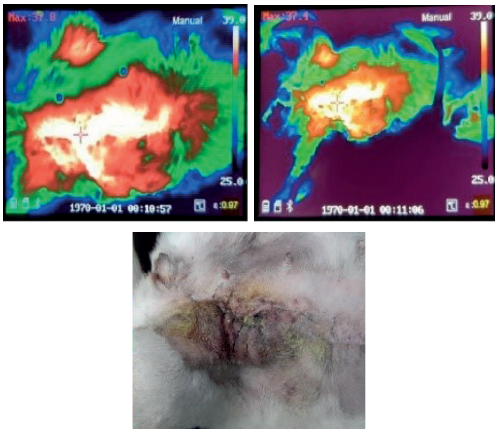

Figure 2. Thermography revealed important changes in the physiological perimeters that demonstrate the presence of inflammation (original)

Two hypotheses exist regarding the origin of PBL. The more accepted concept suggests lymphoma arises from existing intramammary masses. The less accepted notion theorizes that PBL has a connective tissue origin from the intralobular periacinar regions of lymphocytes, plasmocytes, and other cell types from undifferentiated mesenchymal cells. Our theory of a potential mixed tumor is based on the first concept.

Differential diagnosys is mostly done through cytodiagnosis of the primary breast lymphoma and the inflammatory mammary carcinoma. PBL presents lymphoepithelial lesion characterized by infiltration of lymphoma cells into the sparsely present duct epithelium of the breast . The major problem is obtaining adequate material due to thick skin, edematous stroma, and lack of a discrete mass so diagnosis of PBL by fine-needle aspiration cytology (FNAC) is reported infrequently. The same issue rises in inflammatory mammary carcinom (Militaru 2010).

Histopathologically, there is a weakly differentiated ductal carcinoma with lympho-plasma cell infiltrates that includes the wall of galactophore ducts, invasion of vascular spaces, lymphatic embolization and dermal infiltration, the tumor comprising both the skin and the subcutaneous and glandular connective tissue and with possible T lymphocyte entanglement that virtually determines an associated skin lymphoma with mammary involvement although they are different histo-structurally and ontogenetically .

The mark of histological confirmation is the invasion of dermal lymphatic vessels by undifferentiated malignant neoplastic cell embolisms associated with possible T cell lymphocyte infiltrate which must be confirmed by Parr test for lymphocyte phenotyping.

The aberrant COX-2 expression involved in the regulation of proliferation of malignant MF T-cells is mirrored in inflammatory mammary carcinoma although inflammatory cell infiltrates are no a common histologic finding and do not differentiate IMC from other forms of locally aggressive breast cancer, despite the clinical signs of inflammation. The presence of inflammatory cytokines is negligible (de Souza, 2009; Kopp, 2010).

Anaplastic lymphoma kinase (ALK), a tyrosine kinase receptor residing on chromosome 2p23 was first described in a subset of anaplastic large cell lymphoma (ALCL) patients. ALK alterations such as increased ALK copy number, gene amplification and translocation have been shown to be present in 80 % of inflammatory breast cancer and 25 % of triple-negative breast cancers (TNBC), which are considered to be the most aggressive subtypes of breast cancers. ALK positive anaplastic large cell lymphoma (ALCL) of the breast masquerades as a inflammatory mammary carcinoma with an increased incidence following a repetitive and/or frequent trauma (in humans the use of breast implants is incriminated) (Sathyanarayanan, 2010).

Based on the importance of these common factors, we evaluated a case of undifferentiated inflammatory breast carcinoma.

CONCLUSIONS

Clinical cases confirm that these common markers predict response to treatment and have prognostic value. Therapy result are inconsistent and palliative.

Histological study of the skin in our selected studies demonstrated embolization of lymphatic dermal vessels.

The exam showed various histological patterns of neoplastic dermal invasion: one of a tubular/papillary pattern with well-differentiated structures, one very anaplastic with independent highly malignant cells resembling a sar-coma (sarcomatous-like type). Adding serum levels of selected cytokines to diagnostic options in canine cancer patients would allow a better prognostic evaluation and would assist therapeutic decisions. Moreover, cytokines may give reliable information on the efficacy of therapy and very early response for cases that involve IMC, PBL, NHL or even mixed cancers.

COX-2 is expressed in MF, and a dependent growth factor for malignant T cells and has a strong presents in IMC thus being able to improve novel therapeutic targets in MF, IMC or mixed tumors with cyclooxygenase-2 expression. The recommended therapy took into account the markers presented in this paper, predictors of response to treatment and prognosis, and cases treated with a complete protocol had a favorable respons. The case presented emphasizes the importance of following all the steps.

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