Article

Inflammatory mammary carcinoma in 12 dogs: Clinical features, cyclooxygenase-2 expression, and response to piroxicam treatment

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Abstract — Canine inflammatory mammary carcinoma (IMC) is a rare, locally aggressive, highly metastatic tumor that is poorly responsive to treatment. The purposes of this study were to retrospectively evaluate the history, signalment, and clinical signs of dogs with IMC; compare the outcome of affected dogs treated with traditional chemotherapy with those treated with piroxicam; evaluate Cox-2 expression of IMC cells; and correlate Cox-2 expression with outcome based on treatment. Strong cyclooxygenase-2 expression was present in all tumors. Improvement in clinical condition and disease stability was achieved in all dogs treated with piroxicam, with mean and median progression-free survival of 171 and 183 days, respectively. Median survival time of 3 dogs treated with doxorubicin-based protocols was 7 days, which was significantly less than that of dogs treated with piroxicam (median, 185 days). In conclusion, piroxicam should be considered as a single agent for the treatment of dogs with inflammatory mammary carcinoma.

Résumé — Carcinome mammaire inflammatoire chez 12 chiens : caractéristiques cliniques, expression de la cyclo-oxygénase-2 et réponse au traitement au piroxicam. Le carcinome mammaire inflammatoire (CMI) canin est une tumeur rare, localement agressive et fortement métastatique qui répond mal au traitement. Les buts de cette étude étaient d'évaluer rétrospectivement l'anamnèse, le signalement et les signes cliniques des chiens atteint d'un CMI; de comparer les résultats des chiens affectés traités par la chimiothérapie traditionnelle avec ceux des chiens traités au piroxicam; d'évaluer l'expression de la Cox-2 des cellules du CMI; et d'établir un lien entre l'expression de la Cox-2 avec le résultat basé sur le traitement. Une forte expression de la cyclo-oxygénase-2 était présente dans toutes les tumeurs. L'amélioration de la condition clinique et de la stabilité de la maladie a été réalisée chez tous les chiens traités au piroxicam, avec une survie moyenne et médiane sans progression de 171 et de 183 jours, respectivement. La durée de survie médiane des 3 chiens traités avec des protocoles basés à la doxorubicine était de 7 jours, ce qui était une durée considérablement inférieure à celle des chiens traités au piroxicam (médiane de 185 jours). En conclusion, le piroxicam devrait être considéré comme un agent individuel pour le traitement des chiens atteints du carcinome mammaire inflammatoire.

(Traduit par Isabelle Vallières)

Introduction

Inflammatory mammary carcinoma (IMC) is a rare, fast growing, highly malignant form of mammary tumor that affects humans and dogs (1–3). Approximately 7.6% of mammary tumors in dogs are classified as IMC, based on clinical and histologic findings (2). In European countries where routine ovariectomy is not performed, the overall prevalence of mammary tumors is higher than it is in the United States. Occurrence of IMC seems to be greater in Europe than in North America, although the true prevalence of IMC is unknown (2). Affected dogs usually have generalized edema, erythema, and pain in the neoplastic glands; clinical signs may be present in 1 or both mammary chains. Associated clinical signs of inflammation may mimic mastitis and severe dermatitis (Figure 1) (2,3). Histological features include a high grade carcinoma (correspondent with tubular and solid carcinomas) with dermal lymphatic invasion (2–4). The local inflammatory reaction (lymphocytes, plasma cells, and macrophages) has been described in a recent study as irrelevant (4). Two clinical forms of IMC have been described: primary IMC, which occurs in animals without a history of previous mammary nodules, and secondary IMC, which develops in dogs with a history of previous mammary tumors (2).

Canine patients with inflammatory mammary carcinoma have the poorest survival rates among mammary tumor patients. Mean survival rate for 20 dogs receiving palliative treatment

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(antibiotics and prednisone) for IMC was 25 d (range 4 to 55 d), in contrast with a mean survival time of 14.2 mo with surgical treatment alone for dogs with non-IMC malignant mammary tumors (2,5). Because of the extremely invasive nature and, consequently, poor prognosis with IMC, surgery is not usually recommended for treatment (3).

Previous research has supported the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for decreasing the occurrence of colon cancer in humans and for treatment of transitional cell carcinoma of the bladder in dogs; however, the specific mechanism of action of NSAIDs for prevention and treatment of cancer has not been fully elucidated (6–9). Nonsteroidal anti-inflammatory drugs inhibit the activity of cyclooxygenases 1 and 2 (Cox-1 and Cox-2). Cyclooxygenase-1 is constitutively expressed in a wide variety of tissues and is primarily responsible for maintenance of homeostasis, such as gastric mucous production and cell proliferation and renal blood flow, while Cox-2, in the majority of tissues, is induced in inflammatory states and cancer (7). In humans and dogs, carcinomas such as colonic, pancreatic, and mammary have been shown to overexpress Cox-2 (7,8,10). In humans, Cox-2 is virtually undetectable in normal breast tissues but is overexpressed in approximately 40% of breast carcinomas (11).

Cyclooxygenase-2 overexpression in canine mammary carcinomas and other tumors is associated with a high tumor histologic grade, greater tumor metastatic and recurrence rates, and shortened patient survival time (12–14). Among canine mammary tumors, IMC had the highest levels of Cox-2 expression (15).

The NSAID piroxicam (Feldene; Pfizer, New York, New York, USA) has shown activity against transitional cell carcinoma, squamous cell carcinoma, and mammary carcinoma in dogs; however, its activity against IMC in dogs has not been reported (9,16,17). The purpose of the present study was to retrospectively evaluate the history, signalment, clinical signs, and results of treatment in 12 female dogs diagnosed with IMC, to prospectively evaluate Cox 2 expression on biopsy samples, and to correlate this expression with outcome based on treatment.

Materials and methods
Patient inclusion criteria
The medical records of 12 dogs with IMC that had been presented to the Instituto Nacional de Proteção Animal (INPA) Veterinary Hospital in Rio de Janeiro, Brazil from 1996 to 2001 were reviewed. Dogs were included in the study if they had had clinical signs of IMC; if histologic criteria (high grade carcinoma with dermal lymphatic invasion) had been noted on incisional biopsies obtained at the INPA prior to medical treatment; and if follow-up information had been available. Signalment, history, physical examination findings, results of thoracic radiographs taken at the time of presentation, treatment regimen, response to therapy, and survival data were recorded for analysis. Abdominal ultrasonography was not available at the time of the study.

Histopathology
Slides of all cases were reviewed by the same pathologist (ETP) according to the WHO classification scheme. For dogs that had
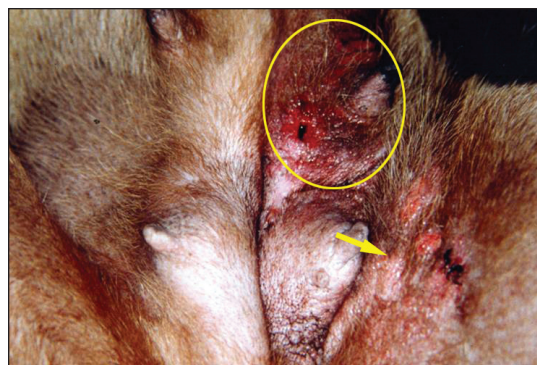

Figure 1. Inflammatory mammary carcinoma affecting the 4th and 5th left mammary glands. Note the erythematous discoloration, and ulceration (circle). The tumor invades the medial aspect of the left thigh (arrow).

presented with IMC after a previous mammary mass removal, slides from the initial mass were also reviewed.

Immunohistochemistry
Unstained slides were prepared for prospective evaluation of Cox-2 expression by means of the streptavidin-biotin peroxidase method, as previously described (10). Antibodies against Cox-2 (PG-27b polyclonal) were purchased from Oxford Biochemical Research, Oxford, Michigan, USA. Slides were evaluated by the same pathologist (RLA), who was blinded to the method of treatment and clinical outcome. As previously described (12), the percentage of tumor cells positive for Cox-2 was classified semi quantitatively as grade 0 (no cells); grade 1 (1% to 10% of positive cells); grade 2 (11% to 50%); grade 3 (51% to 80%); or grade 4 (> 80%). The staining intensity of the neoplastic cells was subjectively scored as 0 (no reaction); 1 (weak reaction); 2 (moderate reaction); and 3 (strong reaction).

Follow-up examinations
Physical examination and weight monitoring had been performed monthly or more frequently, as needed, on all surviving animals to obtain treatment response and survival data. Blood analyses and thoracic radiographs had been declined by all owners because of cost.

Statistical analysis
Endpoints evaluated included response to therapy, progression-free survival, and survival times in dogs that had been treated with either doxorubicin or piroxicam. Progression-free survival times were defined as time from initiation of therapy until first noticeable clinical sign of disease progression. Survival times were defined as time from diagnosis until death or euthanasia because of disease progression. The percentage of positive tumor cells for Cox-2 was evaluated and compared between treatment groups. An unpaired t-test was used to compare treatment groups; statistical significance was set at $P < 0.05$.

Results
All bitches had been intact at the time of diagnosis. Mean age was 10.2 y (median, 10.5; range 6 to 14 y). Breeds included
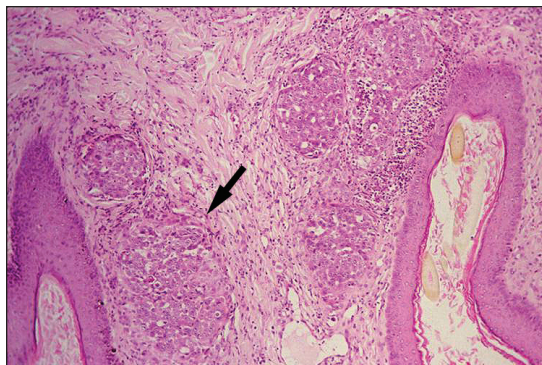
Figure 2. Hematoxylin and eosin (20×). Anaplastic carcinoma displaying dermal lymphatic invasion (arrow).

Table 1. The treatment, percentage of cells positive for Cox-2 on histochemical staining, and survival time for 12 dogs diagnosed with inflammatory mammary carcinoma

Animals	Treatment	Cox-2 %	Survival (days)
1	D,C[a]	33.3	6
2	Euthanasia	66.1	0
3	Piroxicam	28.7	191
4	Piroxicam	69.7	185
5	Piroxicam	69.2	199
6	Piroxicam	74.6	238
7	D,C[a]	82.6	7
8	Piroxicam	54.0	128
9	Piroxicam	77.9	153
10	Piroxicam	91.0	129
11	Euthanasia	60.2	0
12	D,C,F,P[b]	41.3	30

[a] Doxorubicin, cyclophosphamide.
[b] Doxorubicin, cyclophosphamide, 5-fluorourcil, prednisone.

cocker spaniel (2), Doberman pinscher (1), German shepherd (1), Chihuahua (1), Fila Brasileiro (1), and mixed breed (6). Acute onset of clinical signs was noted in all 12 dogs. Mean and median times from detection of 1st clinical signs to presentation were 4.5 and 6 d, respectively. Four dogs had been diagnosed with primary IMC; onset of clinical signs had occurred 2–7 d before presentation and there was no evidence previous history of a mammary mass or surgery. Eight dogs had been diagnosed with secondary IMC. Onset of clinical signs had occurred 1 to 10 d after surgical removal of a mammary carcinoma. Review of slides from the initial mass in the 8 dogs with secondary IMC confirmed that the tumor was a mammary carcinoma without histologic features of IMC.

Clinical findings at presentation had included erythematous discoloration of the affected skin (11 dogs; 91.7%); presence of multiple cutaneous nodules or plaques (10 dogs; 83.5%); increased skin warmth (9 dogs; 75%); firmness of the affected mammary glands and involvement of the medial aspect of the thigh (8 dogs; 66.7%); pain on palpation (7 dogs; 58.3%); bilateral involvement (7 dogs; 58.3%); edema of the affected skin (7 dogs; 58.3%); hind limb edema (3 dogs; 25%); and enlargement of the ipsilateral inguinal lymph node (1 dog; 8.5%). Mean number of glands affected at presentation was 2 (median 3; range, 1 to 10), with the 4th and 5th glands being most commonly affected (84%). Clinical differences in the history or severity of the clinical signs or survival times between primary and secondary IMC were not detected.

Metastatic disease had not been detected on lateral and ventrodorsal thoracic radiographs taken at presentation. Pleural effusion, characterized as hemorrhagic effusion at necropsy, had been detected on thoracic radiographs in 1 dog. Metastasis to an inguinal lymph node had been confirmed after fine-needle aspirates and cytologic examination in 1 dog at the time of initial presentation.

Presence of anaplastic carcinoma with dermal lymphatic invasion had been confirmed in all 12 dogs on histologic evaluation of incisional biopsies obtained prior to treatment. Inflammatory cell infiltrate had not been a prominent feature in any of the dogs (Figure 2).

Two dogs had been euthanized at the time of diagnosis because of severe pain and poor clinical condition (1 dog) or generalized hemorrhage suggestive of disseminated intravascular coagulation (1 dog).

Two dogs had received 1 dose of doxorubicin (generic), 30 mg/m², IV, on day 1 (day of presentation), and cyclophosphamide (generic), 200 mg/m², PO, on day 4. Both had been presented for re-evaluation on an emergency basis, one at 6 d and the other at 7 d after initiation of the chemotherapy; the clinical signs included severe lethargy ($n = 2$); pale mucous membranes ($n = 2$); melena ($n = 2$); and hematemesis ($n = 1$), abdominal hemorrhagic effusion ($n = 1$), and inguinal hematomas ($n = 1$). Additional diagnostic tests were not allowed by the owners and both dogs died on the day of presentation. A 3rd dog had been treated with a combination of doxorubicin (generic), 30 mg/m², IV, at day 1, cyclophosphamide (generic), 200 mg/m², PO at day 4, 5-fluorouracil (generic), 150 mg/m², IV, on day 11, and prednisone (generic), 20 mg/m², PO, daily. This dog was found dead by the owner 30 d later; a necropsy was not performed. A complete blood cell count had been performed only on day 11, prior to the administration of the 5-fluorouracil, and had not revealed any significant abnormalities. Mean and median survival for the chemotherapy group ($n = 3$) was 14 and 7 d, respectively (Table 1). None of the 3 dogs had shown clinical improvement during treatment.

Seven dogs had been treated with piroxicam alone, 0.3 mg/kg BW, PO, q24h. Owners of all 7 dogs had reported a positive clinical response, including decreased erythema, edema, and pain, and improved quality of life (increased activity level and appetite). Progression-free survival (PFS) was defined as the time, after the initiation of piroxicam therapy, from the detection of clinical improvement until clinical confirmation of disease progression, as judged by the owners and by one of the study investigators (CHMS) at monthly physical examinations. Clinical improvement had been observed in all 7 dogs and PFS ranged from 120 to 210 d (mean 171 d; median 183 d). Upon return of clinical signs, dramatic deterioration of the clinical status had occurred and euthanasia performed within a 30-day period from the 1st sign of progression in all 7 dogs. Mean and median survival times for the piroxicam group were 174 and 185 d, respectively (Table 1). Mean survival time for dogs treated with piroxicam was significantly longer than that for dogs treated with doxorubicin ($P < 0.01$). The decision to
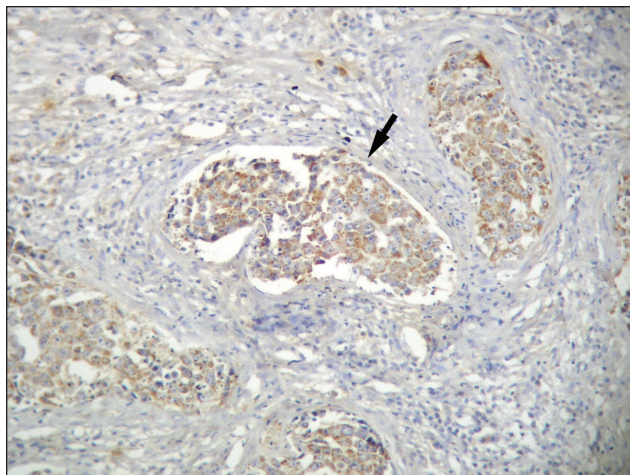
Figure 3. Numerous neoplastic cells are present inside dermal lymphatics (arrow). Steptavidin-biotin peroxidase stained positively for COX-2 (40×).

treat with chemotherapy or piroxicam had been made by the owners and a difference in clinical signs had not been observed between groups.

Cyclooxygenase-2 expression was detected in all incisional biopsies (Figure 3). Strong staining immunohistochemical reaction (intensity score 3) was present in all specimens. In each specimen, 28.7% to 91% of cells expressed Cox-2 (median, 67.7%; mean, 62.6%). Median semi-quantitative scoring for percentage of positive tumor cells was 3; 3 dogs had a score of 2, 7 dogs had a score of 3, and 2 dogs had a score of 4. Mean Cox-2 positive scores for the group receiving chemotherapy and for the group receiving piroxicam were 53.4% and 65.72%, respectively (Table 1). Differences in percentage and intensity of Cox-2 expression in the piroxicam and chemotherapy groups were not statistically significant ($P > 0.3$).

Discussion

In the dogs reported here, history, clinical signs, and frequency of primary and secondary IMC were similar to those in previous reports (2,4). The metastatic rate at presentation was low (8%). In 2 previous studies, metastatic disease was diagnosed by lymph node palpation and thoracic radiographs in 39% and 100% of dogs, respectively (2,3). Abdominal ultrasonography was not performed in those studies. Differences in metastatic rates between these studies and ours may be a result of poor sensitivity of thoracic radiographs or physical examination in our dogs. Additionally, dogs in our study may have been presented before abnormalities on lymph node palpation or thoracic radiographs were detectable. The mean time from 1st detection of clinical signs to presentation was 4.5 d in our study (range, 1–10 d), compared with 4 wk (range, 7 d to 4 mo) in the study by Susaneck et al (3). Perez-Alenza (2) reported that many animals had been referred with an incorrect diagnosis (mostly dermatitis), which most likely led to the late stage of the disease at diagnosis. Metastatic rate might have been higher if abdominal ultrasonography had been performed.

In agreement with a previous report (4), histopathologic evaluation of the tumors in our study did not reveal signs of inflammation. In women with IMC, inflammatory cell infiltrates are not a common histologic finding and do not differentiate IMC from other forms of locally aggressive breast cancer, despite the clinical signs of inflammation (18,19); White blood cells, when present, are primarily lymphocytes. The presence of inflammatory cytokines is negligible (20).

In our study, clinical response had not been seen in 3/3 dogs treated with doxorubicin and cyclophosphamide protocols and all 3 dogs had died within 1 mo of presentation. Aggressive chemotherapy with bone marrow ablation followed by bone marrow autotransplantation improves survival time in women with IMC (18,19). The use of chemotherapy in dogs with IMC has not been described, but, in a recent study, the use of either doxorubicin or docetaxel after surgery in dogs with invasive malignant mammary gland tumors was evaluated and no significant difference was seen in dogs that received adjuvant chemotherapy versus surgery alone, although there was a tendency toward higher long-term local control and survival rates in the dogs receiving chemotherapy; however, it is possible that the low patient numbers affected statistical significance in that study (21). In women with locally advanced breast cancer, which mimics many of the features of IMC, the combination of the prodrug capecitabine and taxanes provided improved survival times when compared with times in studies that had used doxorubicin-based protocols (22). Although combinations of doxorubicin, cyclophosphamide, and 5-fluorouracil have been reported to be effective against inflammatory breast cancer in women, the same may not be true in dogs. Evaluation of different drug combinations are warranted (23).

In our study, expression of Cox-2 was noted in all pretreatment IMC biopsy specimens. Percentage of positive cells and intensity scores were similar to those previously reported for anaplastic and IMCs in dogs, which have been shown to express the highest levels of Cox-2 expression (12–15,24). Since Cox-2 expression and staining intensity correlate with clinical and histologic features of mammary tumor malignancy, it has been hypothesized that Cox-2 inhibitors may be useful in the treatment of mammary tumors in dogs (9,14,15). In a recent study that evaluated the expression of Cox-2 in mammary tumor cell lines, 1 out of 5 (20%) cell lines expressed Cox-2. Inhibition of prostaglandin E-2 (PGE2) production and decrease in cell proliferation was achieved with the use of a specific Cox-2 inhibitor NS-398, which strengthened the above hypothesis (25). In our study, clinical response was seen in 7/7 dogs with IMC treated with piroxicam. Despite the fact that the percentage of Cox-2 positive cells varied among tumors (range 28.71% to 91%; mean 65.72%), a clinical difference in response to piroxicam was not observed. Tumor levels of PGE-2 were not measured and although immunohistochemical differences were observed, PGE-2 levels would have been a true function of enzymatic activity. Response rates and survival times of dogs with transitional cell carcinoma treated with piroxicam are comparable with those of dogs treated with traditional chemotherapeutic drugs (9,16). Response of transitional cell carcinoma to Cox-2 inhibitor therapy, however, is also independent of Cox-2 expression and PGE-2 concentrations (26).

Mechanisms of action of NSAIDs on carcinomas are not well understood. Cycloxygenase-2 and PGE-2 increase cell proliferation, angiogenesis, and cell motility, and decrease apoptosis and local immune response by decreasing T-cell activation, among other effects (6,8,11). In rodent models of mammary cancer, Cox-2 inhibitors suppress mammary tumor formation. Knockout of the Cox-2 gene reduces mammary tumorigenesis and angiogenesis; conversely, transgenic Cox-2 overexpression induces mammary tumor formation (11). Piroxicam does not appear to have apoptotic effects on tumor cells. Its antineoplastic actions may be associated with Cox-2 inhibition (decrease in cell proliferation and inhibition of angiogenesis) or with increase in the local immune response to the tumor (6,8,9,16,20,26,27).

Weaknesses of this study include its retrospective nature, small number of cases, and lack of treatment randomization. Because IMC is rare in dogs, multi-institutional studies may be required to evaluate response to treatment prospectively.

In conclusion, Cox-2 was expressed in all IMC dogs. Despite variations in the percentage of cells expressing Cox-2, dogs treated with piroxicam as a sole agent had an improved quality of life and significantly increased survival rates compared with dogs treated with traditional chemotherapy protocols.

Authors' contributions

Dr. de M. Souza selected the cases, collected the data, conducted the surgical biopsies and medical treatments, and wrote the manuscript. Dr. Toledo-Piza evaluated the slides prepared for histopathologic examination. Dr. Amorin evaluated the immunohistochemically stained slides. Dr. Barboza prepared the slides for immunohistochemical evaluation. Dr. Tobias was involved with the design of the study and critical review of the manuscript. All authors read and approved the manuscript. CVJ

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