Inflammatory mammary carcinoma in dogs: 33 cases (1995–1999)

Mª Dolores Pérez Alenza, DVM, PhD; Enrique Tabanera, DVM, PhD; Laura Peña, DVM, PhD

Objective—To determine epidemiologic, clinical, and pathologic characteristics of inflammatory mammary carcinoma (IC) in dogs.

Design—Retrospective study.

Animals—33 dogs with IC and 153 dogs with malignant mammary tumors other than IC.

Procedures—Medical records were reviewed, and signalment, history, physical examination findings, and results of thoracic radiography and necropsy were obtained.

Results—33 of 436 (7.6%) dogs examined at a veterinary teaching hospital because of dysplasia or tumors of the mammary glands and 33 of 186 (17.7%) dogs with at least 1 malignant tumor had IC. Thirty-two of the 33 dogs were sexually intact. Dogs with IC were significantly older than were dogs with other malignant mammary tumors, and in dogs with IC, the tumor was initially noticed a mean of 52 days after the beginning of the last observed estrus, whereas in dogs with other mammary tumors, the tumor was initially noticed a mean of 137 days after the beginning of the last observed estrus. Dogs with IC were more likely to be anorectic and to have generalized weakness, weight loss, and thoracic metastases. Dogs with IC survived a mean of 25 days with palliative treatment. Histologically, involvement of dermal lymphatic vessels was identified in 14 of 19 (74%) dogs with IC. Two clinical forms of IC (primary and secondary) were identified. Dogs with primary IC had a worse clinical condition.

Conclusions and Clinical Relevance—Results suggest that IC is an uncommon but distinct entity in dogs. A histologic finding of dermal lymphatic involvement should be considered a hallmark for the pathologic diagnosis of IC in dogs. (*J Am Vet Med Assoc* 2001;219:1110–1114)

The term **inflammatory carcinoma (IC)** refers to a specific type of locally advanced mammary cancer. This condition appears to be uncommon in dogs, but clinical signs are similar to those associated with mastitis or dermatitis, and the condition may sometimes be misdiagnosed, making the true incidence unknown. To our knowledge, only 1 report[1] of IC in dogs has been published. In that study, clinical and pathologic abnormalities in 10 female dogs with IC were described. Clinical signs of IC included edema, erythema, firmness, and warmth of the mammary glands. However, little else is known about this condition in dogs.

From the Department of Animal Pathology II, Veterinary Teaching Hospital, School of Veterinary Medicine, Complutense University, Madrid 28040, Spain.

The authors thank Dr. Pedro Cuesta for assistance with statistical analyses.

The apparent low incidence of this type of mammary tumor in dogs could explain the lack of specific studies. On the other hand, the high incidence of mammary tumors in dogs in some European countries such as Spain, where ovariectomy is not routinely performed on bitches that are < 2 years of age, facilitates the development of studies on these tumors, including those with low incidence. Our hypothesis was that dogs with IC have distinct characteristics, compared with dogs with other types of malignant mammary tumors. The purpose of the study reported here was to identify epidemiologic, clinical, and pathologic characteristics of IC in dogs.

Criteria for Selection of Cases

Medical records of the Veterinary Teaching Hospital of Madrid were reviewed to identify female dogs examined between 1995 and 1999 that were found to have dysplasia or tumors of the mammary glands. Records of dogs with histologic evidence of at least 1 malignant tumor, with or without concurrent mammary gland dysplasia or benign mammary tumors, were selected for further review, and dogs were classified as having or not having IC. The diagnostic criteria for IC that were used were based on clinical features described for dogs[1] and women.[2] In brief, IC was suspected in dogs with rapidly growing disease of the mammary glands and overlying skin characterized by diffuse involvement of multiple glands (with or without formation of nodules), firmness, warmth, edema, erythema, thickening, and signs of pain. Cytologic examination of fine-needle aspirates was done to differentiate neoplastic versus inflammatory processes. Dogs not euthanatized at the time of diagnosis were given palliative treatment (administration of antibiotics and glucocorticoids) and followed-up until they died, and an absolute lack of response was observed in all dogs. These diagnostic criteria were adopted so that other diseases such as mastitis, dermatitis, and ulcerated mammary gland tumors other than IC would be ruled out.

Procedures

For dogs with at least 1 malignant mammary tumor, information on signalment, history (including reproductive history), physical examination findings, and results of thoracic radiography (2 lateral projections) was obtained from the medical records. For dogs with IC, information on the presence of pain, edema, erythema, firmness, and warmth in the skin of the mammary region and extremities and on results of pathologic evaluations was also obtained. Necropsy reports were reviewed when available, along with results of histologic evaluation of previous mammary

nodules. Histologic sections of tumors from the dogs with IC were reviewed to determine whether there was any evidence of invasion of dermal lymphatic vessels by neoplastic cells.

Statistical analyses—The following variables were compared between dogs with IC and dogs with other malignant tumors that did not have any evidence of IC: age; breed; spay status; whether hormonal treatments had been used to prevent estrus; frequency and regularity of estrus periods and duration and date of the most recent estrus; whether the dog had a history of pseudopregnancy or pseudolactation; how long the tumor had been present (number of days between the time the tumor was first noticed and the time the dog was examined at the veterinary teaching hospital); activity level; appetite; and whether the dog had any signs of polydipsia, polyuria, pain, coughing, vomiting, or diarrhea. Routine physical examination variables were also compared between groups, along with specific mammary gland examination variables, including whether there was any evidence of regional lymph node involvement (axillary or inguinal) or any radiographic evidence of pulmonary metastases.

Statistical analyses were performed with computer software.[3] Pearson and Yates χ^2 tests were used to analyze categorical variables; Pearson correlation coefficients were used to analyze continuous variables. To study differences in mean values for continuous variables between groups, Levene *F*-tests were used to analyze the homogeneity of variances. If variances were equal, then *F*-tests or pooled *t*-tests were chosen to evaluate the variables. If variances were not equal, then Welch tests or separate variance *t*-tests were selected. A Mann-Whitney test was done to confirm differences between categorical and continuous variables. For all analyses, values of $P < 0.05$ were considered significant.

Results

Prevalence of IC—Four hundred thirty-six female dogs were examined during the study period because of dysplasia or tumors of the mammary glands. Of these, 186 had at least 1 malignant tumor. Thirty-three of the 186 dogs with malignant tumors had clinical evidence of IC. This represented 7.6% (33/436) of the dogs examined because of dysplasia or tumors of the mammary glands and 17.7% (33/186) of the dogs with at least 1 malignant tumor.

Only 15 of the 33 dogs with IC had cytologic evidence of a neoplastic process (ie, cohesive or noncohesive epithelial cells with evident features of malignancy). In the remaining dogs, fine-needle aspiration yielded samples with scant cellularity.

Characteristic of dogs with IC and dogs with other malignant mammary tumors—Dogs with IC were significantly ($P < 0.001$) older (mean ± SEM, 11.4 ± 0.3 years; range, 7 to 15 years) at the time of diagnosis than were dogs with malignant mammary tumors other than IC (9.9 ± 0.1 years; range, 4 to 16 years). The dogs with IC consisted of 15 mixed-breed dogs, 4 German Shepherd Dogs, 3 Poodles, 3 Doberman Pinschers, 2 Yorkshire Terriers, 2 Cocker Spaniels, 1 Bobtail, 1 Boxer, 1 Fox Terrier, and 1 Spaniel Breton. Breed distribution of dogs with IC was not significantly different from that of dogs with other malignant mammary tumors. Thirty-two (97%) of the dogs with IC and 128 (92%) of the dogs with other malignant mammary tumors were sexually intact ($P = 0.32$).

Development of IC was significantly associated with phase of the ovarian cycle. In dogs with IC, the tumor was initially noticed between 7 and 240 days after the beginning of the last observed estrus (mean ± SEM, 51.6 ± 9.4 days). However, in dogs with other mammary tumors, the tumor was initially noticed between 0 and 730 days after the beginning of the last observed estrus (136.6 ± 15.6 days; $P < 0.001$). Previous exogenous administration of progestins was not significantly related to development of IC. Thirty of 118 (25%) dogs with other mammary tumors had been treated with progestins, compared with 4 of 25 (17%) dogs with IC.

Most dogs with IC were in poor clinical condition when examined at the teaching hospital. Thirty-one of the 33 (94%) dogs with IC had generalized weakness (lack of energy and decreased activity), compared with 28 of the 156 (18%) dogs with other mammary tumors ($P < 0.005$). Seventeen of 32 (53%) dogs with IC had anorexia, compared with only 11 of 139 (8%) dogs with other mammary tumors ($P < 0.005$). Eleven of 32 (34%) dogs with IC had polydipsia and polyuria at the time of diagnosis, in contrast with 27 of 138 (20%) dogs with other mammary tumors, but this difference was not significant ($P = 0.07$). The most important clinical signs in dogs with IC were signs of pain involving the mammary region, axillae, groin, and inner aspect of the proximal part of the limbs, along with edema and signs of inflammatory changes. Owners of all 33 dogs with IC reported that their dogs appeared to be in pain, and palpation of the affected areas elicited signs of pain in all dogs; severity of the pain was subjectively categorized as ranging from moderate to severe. In contrast, only 23 of 140 (16%) dogs with other mammary tumors had signs of local pain, and in all of these dogs, signs of pain were attributed to ulcerated mammary lesions.

Body condition of dogs with IC at the time of diagnosis was significantly ($P < 0.001$) different from that of dogs with other mammary tumors. Twelve of 28 (43%) dogs with IC were thin, 10 (36%) were normal, and 6 (21%) were obese. In contrast, 5 of 88 (6%) dogs with other mammary tumors were thin, 48 (55%) were normal, and 35 (40%) were obese. Results of routine physical examination were not otherwise significantly different between dogs with IC and dogs with other mammary tumors.

Axillary or inguinal lymph nodes were macroscopically enlarged in 23 of 24 (96%) dogs with IC, compared with 63 of 124 (51%) dogs with other mammary tumors ($P = 0.001$). Seven of 22 (32%) dogs with IC in which thoracic radiography was performed had evidence of thoracic metastases, compared with 18 of 145 (12%) dogs with other mammary tumors ($P = 0.03$).

Clinical and pathologic features of IC—In all dogs with IC, multiple mammary glands were affected; in 18 (55%), both mammary chains were affected. Eight (24%) dogs had a palpable mammary gland mass, and 20 (61%) had edema of the proximal portion of the limb, which was associated with lameness. In 2 dogs, plaques affected the skin of the limb. Severity of signs of pain during physical examination was characterized as moderate in 18 (55%) dogs and severe in 15 (45%).

A CBC was performed in 12 dogs with IC. Packed cell volume ranged from 38.9 to 47.6% (reference range, 38 to 55%); mean ± SEM PCV was 43.4 ± 1.6%. Five dogs had low platelet counts; mean ± SEM platelet count (n = 12) was 290.1 ± 65.0 × 10^3/µl (range, 142 to 562 × 10^3/µl; reference range, 180 to 500 × 10^3/µl). White blood cell count ranged from 8.3 to 29.1 × 10^3/µl (mean ± SEM, 18.0 ± 3.4 × 10^3/µl; reference range, 6 to 17 × 10^3/µl).

Thirteen dogs with IC were euthanatized without treatment because of their poor clinical condition. In the other 20 dogs, palliative treatment with antibiotics and glucocorticoids (prednisone at dosages ranging from 0.5 to 1.5 mg/kg of body weight/d [0.23 to 0.68 mg/lb/d]) was administered. Survival times for these dogs ranged from 4 to 55 days (mean ± SEM, 25.5 ± 1.7 days).

Owners of 21 dogs with IC consented to a necropsy. The most important gross findings were skin abnormalities (21 dogs; 100%), regional lymph node metastases (21; 100%), severe tumor infiltration of adipose and muscular tissues (19; 90%), and substantial subcutaneous edema (18; 86%). Metastases were found in the lungs (13; 62%), heart (2; 10%), uterus (2; 10%), and urinary bladder (1; 5%).

Histologically, the tumors corresponded with tubular and solid mammary carcinomas (n = 20) or with malignant mixed tumors (1). All tumors had a high degree of malignancy. Involvement of the skin was histologically reevaluated in 19 dogs; massive embolization of tumor cells in dermal lymphatic vessels was found in 14 of the 19.

Types of IC—Two clinical forms of IC were identified: primary IC, in which IC developed suddenly without any history of mammary nodules, and secondary IC, in which IC developed in a dog with previous mammary tumors. Fourteen (42%) dogs had primary IC; mean ± SEM time between initial development of the lesion and its definitive diagnosis was 19.1 ± 3.1 days (range, 8 to 45 days). The remaining 19 (58%) dogs had secondary IC.

Eight of the dogs with secondary IC had a history of a mammary nodule that had not been treated surgically. These nodules had a slow rate of growth and were suspected to be benign, although histologic evaluation was not performed. In all 8 dogs, these nodules suddenly developed clinical features of IC. Mean ± SEM time from the appearance of the primary mammary tumor until development of IC was 498 ± 104 days (range, 162 to 738 days). Mean time between the owner's perception of clinical features of IC and our diagnosis was 55 ± 18 days (range, 12 to 152 days).

In the remaining 11 dogs with secondary IC, IC developed as a local recurrence of a previous mammary tumor that had been removed surgically. Mean ± SEM time from surgical resection to the development of IC was 48 ± 12 days (range, 16 to 152 days). In 3 of these dogs, the resection had been performed at the veterinary teaching hospital; therefore, histologic slides were retrieved and H&E-stained sections were re-examined for evidence of dermal lymphatic invasion. Two of these 3 dogs had histologic evidence of dermal lymphatic embolization.

Nine of 14 dogs with primary IC were euthanatized at the time of diagnosis. Signs of local pain were significantly (P = 0.01) more severe in dogs with primary IC than in dogs with secondary IC; 11 dogs with primary IC had signs of severe pain, and 3 had signs of moderate pain, whereas 4 dogs with secondary IC had signs of severe pain, and 15 had signs of moderate pain. The proportion of dogs with evidence of metastasis to the lungs and other organs at the time of diagnosis was not significantly different between dogs with primary and secondary IC. However, at necropsy, the proportion was significantly (P = 0.03) higher for dogs with secondary IC (9/13) than for dogs with primary IC (4/13).

Discussion

In the present study, 33 of 436 (7.6%) dogs examined at the Veterinary Teaching Hospital of Madrid between 1995 and 1999 because of dysplasia or tumors of the mammary glands and 33 of 186 (17.7%) dogs with at least 1 malignant tumor had IC. In the only previous published report[1] of IC in dogs, 10 of 225 (4.4%) dogs examined at a referral center in Colorado during a 5-year period because of mammary tumors had IC. The authors of that report did not consider these dogs to be representative of the general canine population because of the small number of cases (not all dogs with IC were included in the study) and the selectivity of cases seen at referral hospitals. Similarly, the prevalence of IC in dogs in the present study is higher than expected for the general population, because many dogs with IC were referred to us with an incorrect diagnosis (mostly dermatitis) or to confirm the presence of IC. On the other hand, considering that the incidence of IC in women during the 1990s was double that in the 1970s,[4] a possible increase in the incidence of this type of mammary tumor in dogs may also have taken place in the years since the report by Susaneck et al.[1]

Dogs with IC were significantly older than were dogs with other malignant mammary tumors in the present study. This coincides with results of older studies[5,6] in women but contrasts with findings of a more recent study,[4] in which IC was more common in young women. On the other hand, aging may have a different role in humans with breast cancer than in dogs with mammary tumors, as several studies[7-9] have shown that age has been independently related to a worse prognosis in dogs with mammary tumors.

The high prevalence of IC in the present study could be related to the high number of sexually intact female dogs in Spain, even though the proportion (97%) of sexually intact dogs was similar for dogs with

IC and dogs with other malignant mammary tumors (92%). Development of IC was associated with the diestrus phase of the ovarian cycle, and in this phase, progesterone concentrations are maximal. Thus, this hormone may play a direct or indirect role (by induction of growth hormone) in the development of IC in dogs. In this sense, there is no information about whether ovariohysterectomy of adult dogs has a preventive effect on the development of inflammatory carcinoma, and ovariohysterectomy at the time of surgical resection of malignant mammary tumors does not influence the prognosis.[10,11] However, it has been recently found that timing of ovariectomy in adult life is associated with survival time for dogs with mammary carcinoma.[12]

The history and results of physical examination suggested that dogs with IC had an advanced stage of the disease at the time of diagnosis, and in many of these dogs, the condition had initially been diagnosed as mastitis or dermatitis. Most (94%) of the dogs with IC had generalized weakness, 53% were anorectic, and all had signs of pain according to the owners. In all dogs, palpation during physical examination resulted in signs of local pain, attributable mainly to edema. The cause of the polydipsia and polyuria in 34% of the dogs with IC could not be further investigated; a possible explanation is that most of the animals were in diestrus, so these signs could have been a result of progesterone influence inducing growth hormone release and insulin resistance.

A clinical diagnosis of IC is made on the basis of established clinical features.[1] In many instances, however, the diagnosis is difficult to make, especially in the early stages of the disease. Detection of systemic alterations, reflected by findings such as weight loss, signs of pain during physical examination, and lameness, helps to establish the diagnosis, since these signs are not common in dogs with other malignant mammary tumors. In the present study, 23 of 24 (96%) dogs had metastasis to the regional lymph nodes, and 7 of 15 (32%) had evidence of thoracic metastases at the time of diagnosis, which is similar to findings in a previous study.[1] On the other hand, all 21 dogs that underwent necropsy had evidence of regional lymph node metastasis, and 13 (62%) had evidence of lung metastases.

Because of the poor prognosis for dogs with IC, some owners did not give permission for further studies, and a CBC was performed in only 12 dogs. Thrombocytopenia was observed in 5 dogs. Whether any of these dogs had hemostatic abnormalities could not be determined, because coagulation tests were not done; however, hemostatic alterations have been observed in dogs with advanced mammary carcinoma.[13]

In 15 dogs in this study, cytologic examination of fine-needle aspirates revealed malignant cells, which contributed to the diagnosis of IC by helping to rule out similar-appearing conditions such as mastitis and dermatitis. However, fine-needle aspiration cannot by itself be used to confirm the diagnosis of IC, because fine-needle aspiration will not reveal the dermal lymphatic involvement that is the histologic hallmark of IC.

In dogs, IC is the most aggressive type of mammary tumor and is associated with a poor prognosis. Mean survival time for dogs in the present study was only 25 days.

In our experience, IC in dogs is frequently misdiagnosed not only by clinicians but also by pathologists. The pathologic diagnosis of IC in humans requires the histologic finding of dermal lymphatic involvement,[2] and results of the present and a previous study suggest that dermal lymphatic involvement should also be considered in the histologic diagnosis of mammary tumors in dogs. In the previous study,[1] 9 of 10 dogs had dermal lymphatic involvement, whereas in the present study, 14 of 19 did. This is similar to the percentage (50 to 68%) of women with IC who have evidence of dermal lymphatic involvement.[14,15]

In reviewing the medical records of dogs included in the present study, we found 2 clinical forms of IC (primary and secondary). In humans, primary and secondary IC have been described.[16-19] Secondary IC refers to the development of inflammatory signs after surgical excision of a mammary lesion,[16,17,19] as well as to palpable masses with inflammatory signs beneath a lesion that has been present for at least 4 months.[18] Secondary IC occurs in women after surgical excision of so-called "occult" IC, in which there is histologic evidence of IC (neoplastic emboli in lymphatic vessels of the dermis) but no clinical signs of IC.[20] In the present study, 2 of 3 dogs with secondary IC had previously had mammary tumors removed that were determined to be carcinomas with dermal lymphatic embolization.

Statistical analyses confirmed that the 2 clinical forms of IC, primary and secondary, had different clinical features. Primary IC (14 dogs) was more aggressive, had a faster growth rate, and was associated with a poorer clinical condition, which led to euthanasia at the time of diagnosis in most (9/14) dogs. Secondary IC was more common (19 dogs) in the present study and is also believed to be more common in women, representing 70% of IC cases.[21]

Early detection of IC appears to be important, and IC should be included in the differential diagnosis when examining any sexually intact female adult dog with a sudden onset of erythema, firmness, and warmth of the ventral aspect of the abdomen. Histologic evidence of dermal lymphatic involvement appears to be the hallmark for pathologic diagnosis of IC and can warn clinicians about the possible development of secondary IC. Further studies on the treatment of IC in dogs will reveal whether the clinical form of IC has an effect on outcome.

References

1. Susaneck SJ, Allen TA, Hoopes J, et al. Inflammatory mammary carcinoma in the dog. *J Am Anim Hosp Assoc* 1983; 9:971–976.

2. Tavassoli FA. Infiltrating carcinoma: special types. Inflammatory carcinoma. In: Tavassoli FA, ed. *Pathology of the breast*. 2nd ed. Hong Kong: McGraw-Hill Book Co, 1999; 538–541.

3. Dixon W. *BMDP Statistical software, release 7.0*. Los Angeles: University of California Press, 1993.

4. Chang S, Parker SL, Pham T, et al. Inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program of the National Cancer Institute, 1975–1992. *Cancer* 1998;82:2366–2372.

5. Robbins GH, Shah J, Rosen P, et al. Inflammatory carcinoma of the breast. *Surg Clin North Am* 1974;54:801–810.

6. Stocks LH, Patternson FM. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1976;143:885–889.

7. Peña L, Nieto A, Pérez Alenza MD, et al. Ki-67 and PCNA in canine mammary tumors. Relationship with clinical and pathological variables. Prognostic value. *J Vet Diagn Lab Invest* 1998;10:237–246.

8. Hellmen E, Bergström R, Holmberg L, et al. Prognostic factors in canine mammary tumors: a multivariate study of 202 consecutive cases. *Vet Pathol* 1993;30:20–27.

9. Nieto A, Peña L, Pérez Alenza MD, et al. Immunohistologic detection of estrogen receptor alpha in canine mammary tumors: clinical and pathologic associations and prognostic significance. *Vet Pathol* 2000;37:239–247.

10. Yamagami T, Kobayashi T, Takahasi K, et al. Prognosis for canine malignant mammary tumors based on TNM and histologic classification. *J Vet Med Sci* 1996;58:1079–1083.

11. Morris JS, Dobson JM, Bostock DE, et al. Effect of ovariohysterectomy in bitches with mammary neoplasms. *Vet Rec* 1998;142:656–658.

12. Sorenmo KU, Shofer FS, Goldschmidt MH. Effect of spaying and timing of spaying on survival of dogs with mammary carcinoma. *J Vet Intern Med* 2000;14:266–270.

13. Stockhaus C, Kohn B, Rudolph R, et al. Correlation of haemostatic abnormalities with tumour stage and characteristics in dogs with mammary carcinoma. *J Small Anim Pract* 1999; 40:326–331.

14. Charpin C, Bonnier P, Kkouzami A, et al. Inflammatory breast carcinoma: an immunohistochemical study using monoclonal anti-pHER-2/neu, pS2, cathepsin, ER and PR. *Anticancer Res* 1992;12:591–597.

15. Brooks HL, Mandava N, Pizzi WF, et al Inflammatory breast carcinoma: a community hospital experience. *J Am Coll Surg* 1998; 186:622–629.

16. Taylor GW, Meltzer A. 'Inflammatory carcinoma' of the breast. *Am J Cancer* 1938;33:33–49.

17. Richards GJ, Lewison EF. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1961;113:729–733.

18. Attia-Sobol I, Ferriere IP, Curb H, et al. Treatment results. Survival and prognostic factors in 109 inflammatory breast cancers: univariate and multivariate analysis. *Eur J Cancer* 1993; 29:1081–1088.

19. Nishimura R, Koyama H, Kasumi F, et al. A case control study on risk factors involved in inflammatory breast recurrence after breast-conserving surgery. *Oncology* 1998;55:391–399.

20. Saltzstein SL. Clinically occult inflammatory carcinoma of the breast. *Cancer* 1974;34:382–388.

21. Dershaw DD, Moore MP, Liberman L, et al. Inflammatory breast carcinoma: mammographic findings. *Radiology* 1994; 190:831–834.