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ORIGINAL ARTICLE

Canine Inflammatory Mammary Carcinoma as a Promising Model for Cancer Pathology and Anticancer Drug Development: Lessons from a Case Series

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OBJECTIVE

The prognosis of Inflammatory Breast Carcinoma (IBC) in women is weaker than other types of breast cancer. Inflammatory Mammary Carcinoma (IMC) is a spontaneous breast malignancy in dog which, according to some scientific evidence, can be a good model for women's IBC studies. This study aimed to describe the clinical, pathological, immunohistochemistry characteristics and clinical findings of relapse in IMC compared with IBC.

METHODS

This study was a case series, and 10 dogs confirmed for IMC diagnosis were included. Their clinical and pathological parameters and recurrence findings and Disease-Free Survival Rate (DFS) were calculated, and paraffinic blocks were stained by ER, PR, HER2, Ki67, TP53 and COX2 markers and their relationships with DFS was obtained.

RESULTS

In 40% of cases the lymph nodes were involved. All tumors were high-grade and had 70% of vascular invasion and dirty margins. Evaluation with IHC showed only 10% of them were hormone receptor positive and 70% were HER2 positive. Ki67 was high in all patients and HER2 and triple negatives molecular subtypes accounted for 70% and 30% of cases, respectively. 80% of cases were p53, and the COX2 enzyme was positive in all cancers. Statistical analysis showed that DFS was associated with Ki67 expression and the risk of recurrence increased with the elevation of its expression.

CONCLUSION

In dogs, IMC mimics many of the clinical, pathological, and molecular characteristics of human IBC, and is likely to be a suitable model for comparative oncology studies.

Keywords: COX2 enzyme; disease-free survival; inflammatory breast carcinoma; inflammatory mammary carcinoma; molecular subtype.

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Introduction

In 1814, Charles Bell first described inflammatory breast carcinoma (*IBC*) as a terrible disease.[1] On the one hand, its clinical appearance was different from other common breast cancers, and, on the other, it was a deadly cancer.[2] IBC is said to be a clinicopathologic term and pathology alone cannot distinguish it from other breast carcinomas. Therefore, IBC should be diagnosed following clinical and pathologic findings.[3]

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In IBC, histopathologic findings are not specific, but one of the most important diagnostic hallmarks is dermal lymphatic invasion (*DLI*). However, DLI is also not specific and may be seen in other types of breast cancer.[4] Pathological and molecular studies showed that 90% of IBCs are invasive ductal carcinoma (*IDC*), and most are high grade.[5,6] Moreover, triple-negative and ERBB2 in IBC constitutes the most common molecular subtype.[7,8]

Surgical treatments are not very successful, and the risk of local recurrence and metastasis is high.[3,9] Current chemotherapy also does not significantly improve patients' living standards. Targeted therapies in this type of breast cancer are still underdeveloped,[2,9] although scientific evidence suggests a high expression of cyclooxygenase 2 (COX2) in the IBC. COX2 is one of the most important inflammatory mediators and plays a role in promoting neoplasm development. COX2 is also a prognostic factor in breast cancer and patients with overexpression of this enzyme in cancer tissue have a lower survival rate.[10]

Despite the complexity of the diagnosis and treatment of IBC, research in this area also presents challenges. Mouse models can never exhibit the clinicopathologic features of IBC. Although the IBC xenograft tumor models (cell lines isolated from pleural effusion of IBC) are biologically capable of mimicking the characteristics of human disease, they lack some of the pathological features such as dermal lymphatic invasion.[11-13]

In recent years, canine mammary cancer (*CMC*) has been the focal point of cancer research, because CMC has many biological, pathological and behavioral parallels with human breast cancer (*HBC*).[14] Inflammatory mammary carcinoma (*IMC*) is as rare as IBC and statistics show that it accounts for 1-3% of all CMCs.[15] Some researchers believe that IMC also limits patients' lives and that surgical treatments are unsuccessful.[16]

One of the weaknesses of pet oncology studies is the challenge in assessing overall survival rate (*OS*) and disease-free survival (*DFS*) for the reason that follow-upped patients have many problems after diagnosis until relapse or death. In this case series study, we attempted to record patients accurately, and to obtain DFS, by precisely recording the information regarding clinical, surgical, and IMC pathology of the dogs. We then determined the molecular subtype of IMC and evaluated the diagnostic biomarkers of tumor proliferation status, p53 status, and COX2 enzyme expression in the cancerous tissue in order to compare the similarities and differences with IBC.

Materials and Methods

This study was a "case-series study" and the samples were selected from pet-animal pathology reports at the laboratory of Cancer Biology Research Center (*CBRC*) of the Cancer Institute of Iran. Pathology reports from canine tumors were reviewed from 2014 to 2018. Basis of pathology reports was relied on the registry of "International Classification of Diseases for Oncology Registry 3rd revision (*ICD-O-3*). Although this code is used in the human cancer registry system, its modified form can also be used in the pet animal cancer registry system.[17] Searches include C50.9 (coding for the canine mammary gland anatomical region) and histo-morphological codes M: 8010/3 (for epithelial tumor, malignant type) and M: 8530/3 (inflammatory mammary carcinoma) were selected. All pathologic reports were reviewed, and 14 IMCs that were definitive in their pathology report were selected and clinical and pathological records were reviewed. Some files had information deficiencies that were resolved by contacting the animals' owners and the veterinarians concerned. However, the records of 4 patients were excluded due to a lack of clinical information. Therefore, a total of 10 patients were included in this study. Patient information was recorded in the following three sections:

a. Patients' clinical records: The following parameters were determined: Patient records, the age, breast number involved, tumor laterality, tumor size (present in patient's clinical record or report), the status of axillary or inguinal lymph nodes (according to cytological or histopathologic information), postoperative complications, symptoms of clinical recurrence of cancer, DFS (Time from surgery to cancer recurrence), and the fate of the patient after recurrence was determined.
b. Pathology report: In the pathology reports of the patients, the following were stated: tumor histology (based on Goldschmidt classification),[15] tumor grade (based on Nottingham grading system),[15] dermo-lymphoid invasion status, vascular invasion status, necrosis & microcalcifications status, and the status of surgical margins.
c. Study by Immunohistochemistry (IHC): Patients' slides were reviewed and an appropriate paraffin block was selected from each patient's tumor, and six 3-micron slides were prepared for IHC. After deparaffinization of the slides and tissue rehydration, the retrieval antigen stage was performed with a microwave. Neutral peroxidases were neu-

Turk J Oncol 2021;36(1):52–60
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tralized with oxygenated water, and after washing in buffered solutions, the primary antibodies (according to Table 1) were incubated with tissue sections for 60 min at room temperature. The slides were washed in PBS and the secondary antibody and Polymer HRP were added to the tissues using Bio-care medical kits. Finally, amplification was performed using DAB staining. Tissue staining was done with the hematoxylin-Harris method. Finally, tissue dehydration was performed using ascending alcohols and the slides were mounted after three changes of xylene container. Slides were studied under light microscopy. After the determination of estrogen receptor (ER), progesterone receptor (PR) and HER2 status, the molecular subtype status of the mammary tumor was determined. The proliferation index was determined by Ki67 marker, and p53 status was also determined. Furthermore, according to the modified Allred scoring system, expression of COX2 enzyme was evaluated and reported as negative, weakly positive, moderately positive, and strongly positive (Fig. 1).

d. Statistical analysis: Significance level was set at 0.05. To assess the correlation between Ki-67 expression and DFS, we used linear regression analysis. DFS curves between different groups were assessed by log-rank (Mantel-Cox) test. All analyses were performed by Graphpad Prism 6.0.

Table 1 Characteristics of the IHC antibodies used in this study

No	Antibody	Company	Catalog Number	Dilution
1	ER	Biorbyt	Orb14796	1:100
2	PR	Biorbyt	orb106338	1:100
3	HER2	Biorbyt	orb315778	1:200
4	Ki67	Biocare Medical	APF3156AA.H	Ready to use
5	TP53	Biorbyt	orb389251	1:100
6	COX2	Biocare Medical	SKU: 306	1:200

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; TP 53: Tumor protein 53; COX2: Cyclooxygenase 2

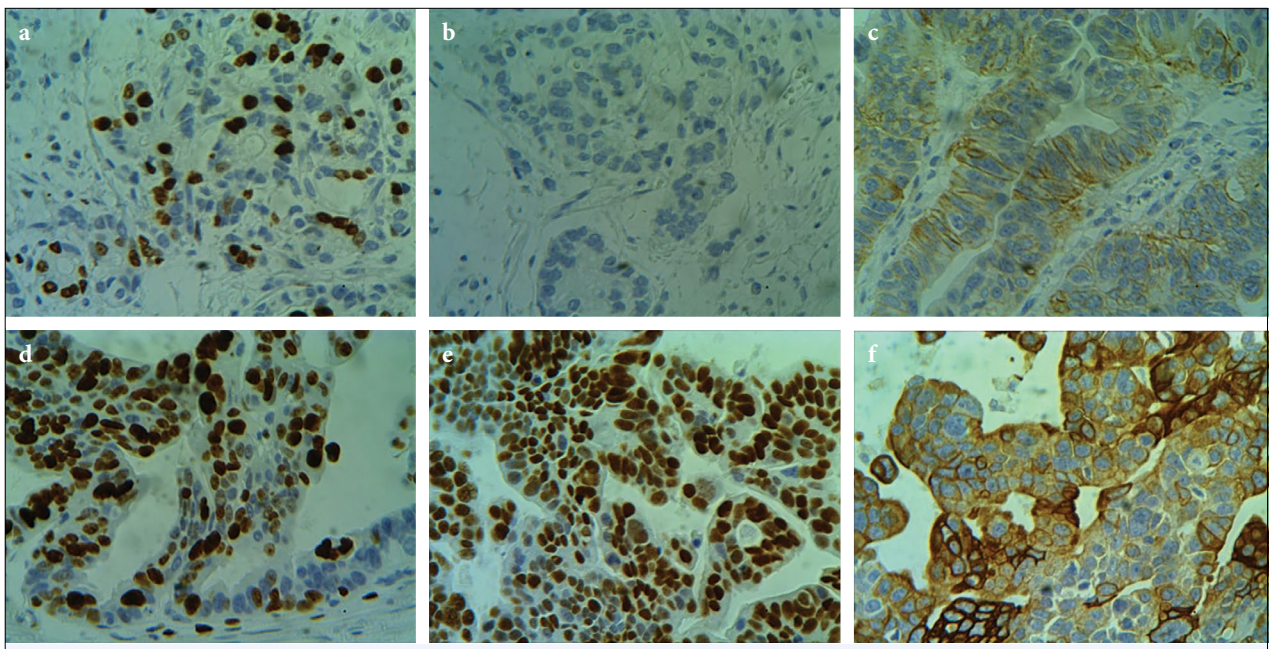

Fig. 1. Microscopic images of Inflammatory Mammary Carcinoma (IMC) on x400 magnification are shown as above. (a) This image was stained with ER marker and only in one of the studied IMCs were there immune-reactive nuclei in malignant cells. (b) As can be seen in the picture, PR was not reported positive in any of the studied IMCs. (c) This shows HER2 staining. In our study, 70% of the membranes of malignant immune-reactive cells were marked with HER2 marker as moderate to strong. (d) All malignant nuclei in Ki67 showed high proliferation, and it is likely that the aggressive characteristics of IMC can be shown with this marker. (e) Evaluation of TP53 function in our study by IHC showed that in 80% of the studied tumors, the function of this tumor suppressor gene was impaired and probably one of the mechanisms of invasion and metastasis in IMC was somatic disorder of this gene. (f) The COX2 enzyme was expressed throughout the cytoplasm of malignant cells in this study and could possibly provide an opportunity for IMC treatment.

Results

In this study, 10 female dogs with inflammatory mammary cancer were evaluated clinically, pathologically, immunohistochemically, and were followed up. The results of the study are described separately below.

1. Description of Clinical Condition: Dogs were ranging from 4 to 12 years old with a mean of 8.1±2.4 years. For finding clinicopathologic relationships, they were divided into two groups of <8 years (younger cases) and >8 years (older cases). 50% of cases were 4-8, and the other 50% were 8-12 years (Table 2). From the laterality point of view, 60% of tumors happened in the left mammary gland (*MG*) and the rest (40%) were located in the right MGs. MG #4 had the highest involvement on both sides (Table 2). The mean size of the tumors was 4.2±1.0 cm and based on TNM staining for inflammatory mammary cancer (*IMC*), all tumors were considered as T4,[18] irrespective of the size. From the surgical point of view, 60% of cases were operated for unilateral mastectomy and the rest were operated for simple mastectomy (Table 2). Presurgical cytologic evaluation and/or histopathologic evaluation of the surgical specimens revealed that lymph nodes were involved in 4 cases. In 4 cases they were not involved and there was no information accessible for the rest (20%) (Table 2).

Table 2 Clinical Aspects of Inflammatory mammary carcinoma (IMC)

Parameter	Category	Percentage (%)
Age (4-12 Y/O)	4-8	3 (30)
	8-12	7 (70)
Tumor location	Left	6 (60)
	Right	4 (40)
Number of mammary gland	MG#1	1 (10)
	MG#22	(20)
	MG#3	0 (Null)
	MG#4	6 (60)
	MG#5	1 (10)
Tumor size	Up to 3 cm	0 (Null)
	3-5 cm	6 (60)
	Over than 5 cm	4 (40)
Type of surgery	Unilateral mastectomy	6 (60)
	Simple mastectomy	4 (40)
Regional lymph-node status	Free	4 (40)
	Involve	4 (40)
	Unclear	2 (20)

IMC: Inflammatory mammary carcinoma; MG: Mammary gland

2. Description of histopathologic condition: Results of the study demonstrated that the tumor histology of tubulopapillary carcinoma had the highest frequency; tubular carcinoma and comedo type carcinoma were placed in the next categories. From the grading system point of view, 60% of tumors were in grade III and the rest of them were in grade II. No tumor was classified as grade I (Table 3). Dermo-lymphoid invasion was found as a microscopic finding in 100% of

Table 3 Histopatologic and IHC Aspects of Inflammatory mammary carcinoma (IMC)

Parameter	Category	Percentage (%)
Tumor histology	Tublo-papillary carcinoma	5 (50)
	Tubular carcinoma	4 (40)
	Comedo type carcinoma	1 (10)
Tumor grade	Grade I	0 (null)
	Grade II	4 (40)
	Grade III	6 (60)
Dermo-lymphoid invasion	Present	10 (100)
	Absent	0 (Null)
Lymphovascular invasion	Present	6 (70)
	Absent	3 (30)
	Equivocally	1 (10)
Necrosis	Present	7 (70)
	Absent	3 (30)
Microcalcification	Present	3 (30)
	Absent	7 (70)
Surgical margin status	Free	7 (70)
	Involve	3 (30)
ER	Positive	1 (10)
	Negative	9 (90)
PR	Positive	0 (Null)
	Negative	10 (100)
HER2	Positive	7 (70)
	Negative	3 (30)
Ki67	Negative (up to 4%)	0 (Null)
	Moderate (5-14%)	0 (Null)
	High (over than 15%)	10 (100)
Molecular subtype	Luminal A	0 (Null)
	Luminal B	1 (10)
	HER2	6 (60)
	Triple negative	3 (30)
TP53	Positive	8 (80%)
	Negative	0 (Null)
COX2	Negative (0)	0 (Null)
	Weak (1+)	0 (Null)
	Intermediate (2+)	2 (20)
	Strong (3+)	8 (80)

IMC: Inflammatory mammary carcinoma; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; TP53: Tumor protein 53; COX2: Cyclooxygenase 2

Turk J Oncol 2021;36(1):52–60
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IMC tumors and this hallmark was seen in all samples (Table 3). Based on the pathology reports of the patients, 70% of tumors were vascular invasion positive and in 20%, it was negative while it was equivocal in 1 case. On the other hand, in 70% of the patients, tumor necrosis was observed, but micro-calcification happened only in 30% of cases (Table 3). Evaluation of tumor margins showed that 70% of patients possessing surgical margins were involved in 1 or more directions, while only 3 patients were detected as surgical margin-free (Table 3).

a. Description of the situation of IHC: Evaluation and reporting of ER & PR: The interpretation method was accomplished using All-Red Scoring System. Immunoreactivity above 1% of malignant foci was taken as positive cases. Our study showed that progesterone receptors were absent in all 10 tumors, and tumor growth was estrogen-receptor dependent only in 1 patient (Table 3).
b. Evaluation of HER2: In this research work, 70% of patients showed an over-expression of HER2 protein and the microscopic pattern +3, whereas 30% of them demonstrated negative and equivocal scores (Table 3).
c. Evaluation of Ki67: Based on the findings of the present study, the proliferation coefficient ranged between 15-35%, and, according to the St. Gallen Guideline (2011), all mammary gland tumors were in the situation of a highly proliferation index (Table 3).
d. Evaluation of molecular subtype: In this study, 60% of patients were categorized in the HER2 group and 30% in the triple-negative subgroup. Only one patient was in luminal B molecular group while no one was in Lumina A (Table 3).
e. Evaluation of TP53 gene: In this study, 80% of patients were recognized as IHC positive and 2 patients were reported as negative (Table 3).
f. Evaluation of COX2 enzyme: The results of this study showed that the expression of COX2 enzyme was strong in 80% of IMCs and intermediately positive in the remaining 20%. Neither negative nor weakly positive case was found among the patients (Table 3).

4-Description of post-operative complications, recurrence of clinical findings & metastasis, DFS rate and patient outcome: The results of post-operative follow-up showed that surgical complications were observed in 50% of cases (n=5), so that the main problems after surgery were related to the opening of sutures and inflammation of the urethra. In one case, infectious and secretory lesions in the surgical area were reported (Table 4). Symptoms of recurrence in all cases were local recurrence, with 100% of animal owners appealing to the clinician for recurrence of skin lesions in the breast area. In one case (10%), there was

Table 4 Postoperative complications, relapse, disease free survival rate and patient outcome

Case	Postoperative complications	Clinical findings after recurrence and metastasis	Disease free survival (days)	Patient outcome after relapse
1	Open sutures and swelling were created in the area	Local recurrence, edema and redness in skin	63	Euthanasia
2	No	Recurrence of multiple lesions on the skin	32	Euthanasia
3	No	Recurrence and cough and canonball in the right lung	76	Euthanasia
4	Problem with surgical wound healing	Nodular lesions on the skin with redness of the skin	88	Chemotrapy+COX2 inhibitor
5	Open sutures and swelling were created in the area	Numerous lesions on the skin	75	Euthanasia
6	No	Local recurrence, edema and redness in skin	34	Unclear
7	No	Recurrence of multiple lesions of tumors in the skin	70	Unclear
8	Open sutures and swelling were created in the area	Local recurrence, edema and redness in skin	27	Euthanasia
9	No	Wounds and edema in the skin of the surgical area	40	Euthanasia
10	Open sutures and swelling were created in the area	Recurrence of multiple lesions of tumors in the skin	18	Unclear

COX2: Cyclooxygenase 2

a cough in addition to skin lesions; in this patient, Cannonball metastases were reported in the chest X-rays (Table 4). The term "DFS" in this paper relates to the number of days the dogs under lived free of a breast tumor, and this time interval was calculated from the day of surgery to the day the tumor was clinically proven to recur. In this study, the earliest and latest diagnosis of cancer recurrence was reported on 18 and 88 days after the surgery, respectively. The average DFS in this study was 52.3±24.7 days (Table 4). The follow-up of patients showed that most dogs were euthanized after diagnosis of IMC recurrence (70%), and only in one case chemotherapy-based treatment was performed together with a COX2 inhibitor; this single patient had died soon later due to septicemia. The final fate of 30% (*n=3*) of patients was unknown (Table 4).

5- Data Presentation and Statistical Analysis: Regression analysis showed that there was an inverse relationship between Ki67 and DFS values, which was statistically significant (p=0.0129; R2=0.5591 (In other words, with the increase of tumor proliferation coefficient, the time of tumor recurrence had decreased (Fig. 2). Statistical analysis of Log-rank (Mantel-Cox) showed that there was no relationship between the expression of grade 2 and grade 3 COX2 enzyme and DFS (p=0.0512; Median DFS in 2+=88 days; Median DFS in 3+=35 days). Statistical analysis of Log-rank (Mantel-Cox) showed that there was no relationship between the expression of grade 2 and grade 3 COX2 enzyme and DFS (p=0.0512; Median DFS in 2+=88 days; Median DFS in 3+=35 days) (Fig. 3). Regarding the relationship between p53 and DFS, patients were first divided into two groups, p53+ and p53-, and the data were calculated based on mean and SEM, and then the means of two groups were compared using unpaired t test. No significant statistical relationship was found between the two groups (p=0.1954; Median DFS in positive group =42 days; Median DFS in negative =71 days).

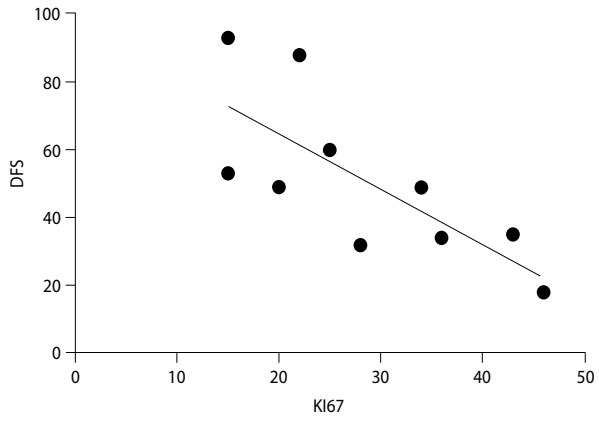

Fig. 2. Regression analysis between Ki67 (x axis) and DFS (y axis) values in canine with inflammatory mammary carcinomas. There was an inverse relationship between Ki67 and DFS values (P < 0.05). Regression coefficient (r) = -0.7478; Y = (-1.633*X) + 97.48.
DFS: Disease-free survival.

Discussion

In recent years, life expectancy in *IBC* patients has somewhat increased. A 20-year long study of a population of over 7,000 women with stage III IBC found that survival rates had increased in recent years and that one of the main reasons was the introduction of new pharmacotherapeutic agents.[19] The biology of cancer is very complex, and new laboratory facilities have created the conditions for researchers to be able to move cancer therapies to targeted therapy and individualized-therapy. However, the rate of death in IBC is higher than in comparison to other breast malignancies.[9]

Veterinarians reported a disease in dogs similar to that of IBC in women, and epidemiological and molecular evidence suggests that *IMC* may be similar with human IBC.[20] In this study, we investigated IMC from the clinical, pathological, immunohistochemical, and *DFS* aspects, the results of which are discussed. In our study, the average age of breast cancer was 8 years. In a similar study, Souza and colleagues reported that the average age of female dogs participated in the study was 10 years.[21] Medical studies show that the average

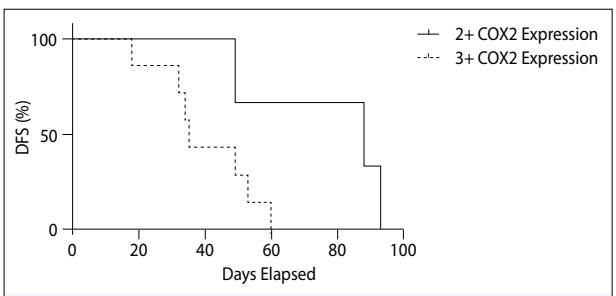

Fig. 3. Relationship between COX2 expression (graded as 2+ and 3+) and DFS (as days) in dogs with inflammatory mammary carcinoma. Although there was no significant relationship between the expression of grade 2 and grade 3 COX2 enzyme with DFS, there was a tendency between the two.
COX2: Cyclooxygenase 2, DFS: Disease-free survival.

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age of women with IBC is 57 years.[22] Some articles indicate that ages 8-10 in dogs are equivalent to ages 48-60 in humans.[23]

In terms of laterality, the tumors on the left side were slightly larger than on the right. This is also mentioned in breast cancer in women, but its biological causes have not yet been elucidated.[24] In our study, the mean tumor size was 4.2±1.0 cm, and most studies have shown that the IMC and IBC sizes are larger because of the biological nature of this type of cancer cell, it is found to be poorly cohesive and in some cases does not form a solid mass.[25] 40% of the dogs in this study showed an attack on the lymph nodes. Scientific evidence suggests that the risk of lymph node involvement in IBC is high.[26,27] Pathological evaluation of lymph nodes is still one of the important challenges of TNM staging in pet oncology and, unlike human oncology, surgical protocols and pathological evaluation of lymph nodes has not yet been developed.[28]

Microscopic studies showed that more than 90% of IMC tumors were tubular and tubulo-papillary carcinomas and were in grade II-III. Our findings were consistent with many studies on dogs and women, i.e., in most cases the tumor grade is high at the time of diagnosis.[3,5] Dermal lymphatic invasion (DLI), which is one of the hallmarks of IMC pathology and IBC was reported to be 100% positive for DLI in our samples. 70% of the margins in this study were free, probably due to the type of surgery. 60% of the dogs had unilateral mastectomy. However, despite the cleanliness of surgical margins, local recurrence often occurred. The biological nature of breast cancer seems to be different from other types of cancers. The poor nature of cohesiveness causes the misidentification of the malignant cells of single margins in H&E staining,[29] so it is also recommended to use IHC staining to evaluate surgical margins in IMC patients.

An IHC study showed that 90% of the tumors studied lacked hormonal receptors (90% had a negative ER and 100% had a negative PR). On the other hand, HER2 was reported to be 70% positive. Scientific evidence suggests that the lack of hormonal receptors and positive HER2 increase the invasive potency of breast cancer.[30]

A study with Ki67 showed that 100% of the tumors were highly proliferated, and this alone indicates that the IMC was aggressive. Ning and colleagues studied 257 women with stage III IBC and concluded that the average Ki67 was higher than 48% and had a significant relationship with the reduction of overall survival.[31] Our study on dogs with IMC was in line with human studies so that Ki67 was inversely related to disease-free survival. Also, in our study, there was no relationship between tumor size and Ki67, which was probably related to IMC biology, so that the lack of solid mass formation caused an error in measuring tumor size.

From a molecular subtype point of view, more than 90% of tumors were in the HER2 and triple-negative categories. Most studies in women show that most inflammatory breast cancers fall into these two categories.[15] However, research results at the National Oncology Institute (NIO) in 2018 differed from previous IBC findings.[32] It seems that determining the molecular subtype profile of this type of breast cancer requires further study.

p53, also known as the TP53 gene, was positive in 80% of the cases in this study. This biomarker is one of the most important control genes in the cell cycle; its wrong over-expression causes the loss of function of the control factor in the cell cycle. As a result, the prognosis of the patient becomes weaker.[33] In our study, there was no relationship between p53 and DFS, which is probably due to the low sample size.

COX2 enzyme, which is an inducible enzyme in cases of inflammation and tissue irritation, acts as a cancer-promoting agent in tumors. Most of the effects of this enzyme are attributed to prostaglandin E2 (PGE2).[34] PGE2 plays a key role in stimulating tumor angiogenesis and increases the mitosis coefficient35. The role of this enzyme and its overexpression in IBC and IMC is well described. Some believe that the therapeutic intervention of this enzyme may reduce the invasive power of the tumor in inflammatory cancers.[35] In our study, 100% of patients showed moderate to high expression of this enzyme.

The statistical results of this study showed that there was no significant correlation between the expression of $COX2^{++}$ and $COX2^{+++}$ with DFS, although according to Figure 3, there is a tendency between COX2 and DFS enzyme expression. It is possible that if the sample size of the study was large, there would be a significant correlation. Lack of expression of COX2 enzyme in our studied tumors indicates the possible role of COX2 selective inhibitors in disease control or survival improvement. In this regard, it is suggested that further studies should be conducted about this subject in the field of comparative oncology.

The limitations of this study were the low sample size and lack of access to patients' overall survival rates. In pet oncology, measuring the overall survival rate cannot be accurate as the animals are euthanized at the end-stage due to moral considerations. The DFS is said

to be a possible surrogate for the overall survival rate in estimating survival rates.[36]

Over time, the value of comparative oncology increases and the influence of the science pet oncology over human oncology becomes more prominent every day. Previous studies have shown the similarities between IBC in women and IMC in female dogs. In this study, we studied the clinical, pathological, and immunohistochemical aspects of IMC dogs and followed them and obtained their DFS. Our results showed that canine IMC is similar to women's IBC in many biological and clinical aspects. However, molecular studies are not yet sufficient in the field of dogs' IMC.

It is suggested that, by initiating clinical trials, the therapeutic value of COX_2 enzyme inhibition and other genes involved in the molecular pathway, the production of this inflammatory mediator in IMC should be studied. This would be an important step taken toward comparative oncology goals. Multidisciplinary team studies between various animal oncology specialists and intra-disciplinary medical oncology teams will improve the treatment of pet animal cancers and the results may be extended to human cancer.

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Authorship contributions: Concept – P.M., S.R.; Design – S.M., S.R.; Supervision – P.M.; Funding – S.R.; Materials – S.R.; Data collection and/or processing – S.R.; Data analysis and/or interpretation – S.M.; Literature search – S.R.; Writing – S.R.; Critical review – P.M.

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