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Matrix Metalloproteinase 9 as Biomarker for Malignant Mammary Tumors in Dogs

Islam S Alani*, Huda S Al Biaty

Department of Microbiology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq

***Correspondence**:
islam.saadin@uofallujah.edu.iq
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A B S T R A C T

Canine mammary tumors (CMTs) are frequently occurring types of tumor in female dogs. Matrix metallopeptidase 9 (MMP-9) plays a role in dismantling the extracellular matrix during normal bodily functions and diseases, including cancer. The goal of this research was to evaluate the serum levels of MMP-9 as a potential diagnostic indicator for CMTs using the ELISA method. We collected tissue samples from mammary glands and blood specimens from 50 dogs suspected of having CMTs and 30 healthy control dogs. Histological examination was used to diagnose the mammary tumors, with findings indicating that 88% of the cases were malignant CMT and 12% were benign. According to ELISA results, there was a statistically considerable elevation in the mean serum level of MMP-9 in malignant cases (199.09 ng/ml) compared to benign cases (56.721 ng/ml) and controls (36.055 ng/ml). MMP-9 serum levels were significantly correlated with dogs aged 10–15 years, as well as with female dogs. In terms of stage and grade of the disease, the mean levels of MMP-9 increased as the disease progressed (Stage IV: 343.235 ng/ml). However, there was no correlation with the grade of the disease, and in regard to MMP-9 serum levels, it was not feasible to distinguish between newly diagnosed cases and recurring cases. In conclusion, measuring serum MMP-9 levels may aid in assessing the presence of malignancies in dogs with mammary tumors.

Keywords: Canine mammary tumors, Matrix metallopeptidase 9, ELISA, serum, Histopathology, biopsies

INTRODUCTION

Canine mammary tumors (CMT) are common types of cancer in dogs, with approximately 50% of cases being malignant (1). The morbidity rate for canine mammary tumors is three times higher than that of women (2-4). Mammary tumors are often categorized histologically as either benign or malignant tumors (5). Canine mammary cancers are more prevalent in dogs that are in the middle and older age groups, showing a higher incidence in the age range of 8 to 11 years (6,7). The clinical stage of the disease is determined based on the size of the tumor, involvement of regional lymph nodes, and the presence of metastases (8). The majority of mammary tumors found in female dogs are of epithelial origin. Additionally, some cancers originate from myoepithelial cells, stromal cells, and a combination of different histological tissues (5). The tumor stroma is consists of inflammatory cells, blood and lymphatic vessels, and specific cells known as cancer-associated fibroblasts (CAFs) that are linked to neoplasms. CAFs play a role in epithelial-mesenchymal transition (EMT), a critical process in tumor growth and spread, and also help alter extracellular matrix (ECM) proteins (9-12). Additionally, cancer-associated fibroblasts (CAFs) release metalloproteinases (MMPs) (9). Matrix metalloproteinase (MMP) is a zinc-dependent endopeptide and are responsible for regulating the breakdown and restructuring of the extracellular matrix (ECM) (13). There are different types of MMPs, such as gelatinases, collagenases, stromelysins, matrilysins, and membrane-type MMPs (14). Extracellular matrix degradation is facilitated by MMP activity, making MMP activity essential in assessing the metastatic potential of a cancer cell(15,16). MMP-9 has a crucial function in cell proliferation,

differentiation, migration, angiogenesis, host defense mechanisms, and apoptosis (17, 18). Epithelial cancer cells and CAFs produce MMP-9, which plays a significant role in the development of malignant tumors in the mammary glands of dogs (19). A study by Fathipour et al. (20) demonstrated that dogs with cutaneous neoplasia have higher levels of MMP-9 serum activity compared to healthy dogs. Similarly, Nowak et al. (21) observed a reduced survival time in dogs with elevated MMP-9 expression in mammary tumors. Therefore, MMP-9 is considered an important prognostic biomarker for malignant mammary tumors in dogs (8, 22). This study aimed to evaluate the serum levels of MMP-9 as a possible tumor biomarker in canine mammary tumors.

MATERIALS AND METHODS

Ethical Statement

The research received approval from the Local Animal Care and Use Committee at the College of Veterinary Medicine, University of Baghdad, under Approval Number 553 P.G., on March 10, 2024. Furthermore, permission to carry out the study was granted by the Aden Square Veterinary Hospital and Veterinary Clinics after confirming adherence to ethical guidelines. Before collecting each sample, permission was sought from the respective owner.

Serum samples

Before performing mastectomy, blood samples were taken from 50 dogs suspected to have mammary gland tumors, as well as from 30 control dogs.

Assessment of MMP-9 by ELISA

The blood samples underwent centrifugation at 3000 rpm for 10 minutes at a temperature of 4°C. The serum that resulted from this process was then preserved at a temperature of −80°C in a deep freeze until examination. Prior to analysis, the samples were gradually thawed and subjected to centrifugation once more at 3000 rpm for 5 minutes. The levels of MMP-9 in the blood serum were quantitatively assessed using a solid phase sandwich Enzyme Link Immune Sorbent Assay from Abcam, UK.

Histopathological Examination

Fifty biopsies were taken from dogs suspected to have mammary carcinoma, along with 10 normal biopsies from control dogs, were placed in containers with 50 ml of 10% formalin to preserve the specimens for histopathological procedures. The biopsies underwent a process that involved fixation in neutral buffered formalin (10%), dehydration in ethanol, and clearing in xylenes. Subsequently, the biopsies were embedded in paraffin and stained with hematoxylin, and eosin for examination to classify mammary tumors in female dogs, following Goldschmidt et al. (5). The histological grading was determined using the Nottingham grading system (23) and staging was based on pathological staging (24).

Statistical Analysis

The Statistical Analysis System (SAS (2018) program was used to detect the effect of different factors on study parameters. The least significant difference (LSD) test (Analysis of Variation, ANOVA) was used to significantly compare the means in this study.

RESULTS

Clinical Manifestation of Examined Dogs.

An unusual tumor was found in the abdominal region during the clinical examination. Some cases also presented with edema and inflammation, causing pain in certain dogs. Some animals show systemic symptoms like loss of appetite, weight loss, muscle weakness, and a slight increase in body temperature. The gross pathology analysis of the tumors revealed that the majority had a single gland. Upon palpation, the majority of the masses felt solid and varied in shape, either being normal (oval or spherical) or irregularly shaped.

Histopathological Examination

The animals examined in this research were divided into two categories based on the histological analysis of mammary tumors: benign and malignant. Out of the 50 tumors examined, 12% (n = 6) were identified, while 88% (n = 44) were classified as malignant, including 38 newly diagnosed cases and six recurrent cases (Table 1).

Table 1. The percentages of total animals and their distribution according to gender and groups

	Gender		
Group	**Male No (%)**	**Female No. (%)**	**Total No. (%)**
Newly diagnosed	4 (28.5)	34 (51.5)	38 (47.5)
Recurrent	0 (0.00)	6 (9.10)	6 (7.50)
Benign	0 (0.00)	6 (9.10)	6 (7.50)
control	10 (71.5)	20 (30.3)	30 (37.5)
Total No. (%)	14 (17.5)	66 (82.5)	80 (100)

Table 2. The percentages of total animals and their distribution according to age

Age (year)	**Newly diagnosed No. (%)**	**Recurrent No. (%)**	**Benign No. (%)**	**Control No. (%)**	**Total No. (%)**
≥ 5	8 (21.1)	0 (0.00)	2 (33.3)	16 (53.3)	26 (32.5)
5-10	20 (52.6)	2 (33.3)	4 (66.7)	10 (33.3)	36 (45.0)
10-15	10 (26.3)	4 (66.7)	0 (0.00)	4 (13.4)	18 (22.5)
Total No. (%)	38 (74.5)	6 (7.5)	6 (7.5)	30 (37.5)	80 (100)

The different types of cancer found were invasive mammary carcinoma (Figure 1 A), ductal carcinoma (Figure 1 B), papillary carcinoma (Figure 1 C), intra-ductal papillary carcinoma (Figure 1D), lobular carcinoma (Figure 1 E), and benign (Figure 1 F). The distribution of the age groups of the dogs included in the study is presented in Table 2.

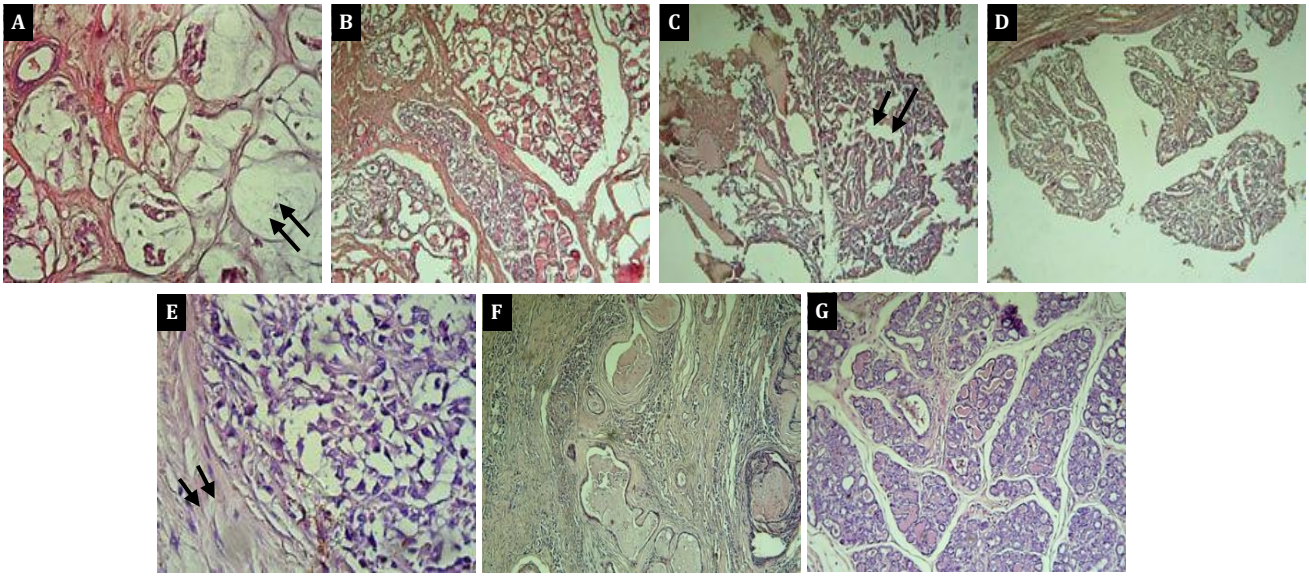

Figure 1. Histopathological section of mammary gland tissue of dog showing: **(A)** Invasive mammary glands carcinoma (grade 2) mucinous variant (special type) with extensive necrosis (mucinous) (black arrows). **(B)** Invasive ductal mammary carcinoma (grade 1) tubular carcinoma (special type). **(C)** Invasive papillary carcinoma (special type) (grade 2) with in situ papillary carcinoma (black arrows). **(D)** Intra-ductal papillary carcinoma (grade 1). **(E)** Invasive lobular carcinoma (grade 3), with extensive fibrosis (black arrows). **(F)** Benign tumor contain fibrocystic changes with diluted cystic ducts. **(G)** Normal mammary glands tissues including lobules and ducts composed of cuboidal epithelial cell, myoepithelial cell and intact basement membrane surrounded by stromal tissue. A, E: 40×; B, C, D, F: 10×; G: 4×

Table 3. Serum MMP-9 levels in canine mammary cases: comparison across control, tumor types, diagnosis status, gender, age groups, tumor grades, and stages

Parameter	Group	Animals No.	Mean MMP-9 Level (ng/mL)	*P*-value
	Control	30	36.06±2.38 ^{c}	
Tumor Types	Benign	6	56.72±1.82 ^{b}	0.0001
	Malignant	44	199.1±12.4 ^{a}	
	Control	30	36.06±2.27 ^{b}	
Diagnosis Status	Newly diagnosed	38	196.5±7.94 ^{a}	0.00001
	Recurrence	6	195.8±6.02 ^{a}	
Gender	Male	4	157.4±9.27 ^{b}	0.049
	Female	40	203.3±16.7 ^{a}	
	≤ 5 years	8	125.4±33.7 ^{c}	
Age Groups	5 - 10 years	22	182.2±51.7 ^{b}	0.0001
	10 - 15 years	14	267.8±66.0 ^{a}	
	Grade I		171.1±12.1 ^{b}	
Tumor Grades	Grade II		220.4±22.7 ^{a}	0.0397
	Grade III		192.2±13.6 ^{b}	
	Stage 0		78.45±5.45 ^{d}	
	Stage I		136.7±9.05 ^{a}	
Tumor Stages	Stage II		141.8±7.96 ^{c}	0.0001
	Stage III		214.2±13.6 ^{b}	
	Stage IV		343.2±24.6 ^{a}	

Means with different superscript letters within the same parameter are statistically different ($P \leq 0.05$)

Serum MMP-9 Levels in Canine Mammary Cases

Serum MMP-9 levels in dogs with mammary carcinoma, benign tumors, and normal controls were assessed using a sandwich ELISA test. The results of this analysis, including comparisons across tumor types, diagnosis status, gender, age groups, tumor grades, and stages, are presented in Table 3. The analysis revealed significantly higher MMP-9 levels in dogs with malignant mammary tumors compared to benign cases and controls (P=0.001). Regarding diagnosis status, MMP-9 levels were elevated in both newly diagnosed and recurrent cases of mammary tumors compared to control animals, with a significant difference (P=0.00001). Gender-specific analysis showed higher

serum MMP-9 levels in females than males (*P*=0.049). Additionally, MMP-9 levels significantly increased with age, reaching the highest values in the 10–15 years age group (*P*=0.001). When comparing tumor grades, MMP-9 levels were notably higher in Grade II tumors compared to Grades I and III (*P*=0.0397). Tumor stage analysis indicated a significant rise in MMP-9 levels in stage IV malignancies, with a mean value of 343.2 ng/ml (*P*=0.0001).

DISCUSSION

Cancer progresses more quickly in dogs due to their shorter lifespan (25). Mammary gland tumors are among the most frequent tumors in female dogs. In general, 40% of tumors found in female dogs were mammary tumors (26), and around 30-50% of these tumors were cancerous (27). The majority of tumors presented in the current study were malignant, with a percentage of 88%, and only 12% were benign, that agrees with the findings of Ariyarathna et al.(28). Among the malignant tumors of the presented cases, several of the malignant tumors recurred after initial mastectomy, this is consistent with the finding of Pastor et al. (29) who stated that dogs with an initial malignant tumor were more prone to developing a new tumor compared to dogs whose original tumor was benign. Malignant tumors have higher levels of neo-vascularization in comparison to benign tumors. Higher micro vessel density is linked to increase risk of local recurrence, the presence of lymph node metastasis, and histologic differentiation (30).

Numerous studies have explored the various functions of MMP9 in the progression and development of cancer, as well as its effects on patient survival and prognosis. In recent years, researchers have been investigating the potential use of MMP-9 as a prognostic marker for breast cancer (31, 32). MMP-9, a part of the MMPs group, is often known as gelatinase. It has the ability to break down type IV collagen, gelatin, and type V collagen within the ECM, ultimately disrupting the ECM structure, initiating epithelial-mesenchymal transition (EMT), and facilitating invasion and metastasis of tumor cells (33). Labrèche et al. (34) demonstrated that cancer-associated fibroblast and EMT are crucial factors in the advancement and dissemination of cancerous cell. EMT is intricately linked to the remodeling of the extracellular matrix. Additionally, MMP-9 helps in the activation of growth factors and the release of angiogenic factors during the host's immune response, as well as in preventing the apoptosis of tumor cells (35, 36). Our results showed a significant rise in serum MMP-9 levels (P≤0.01) in cancerous animals compared to the control group, which is consistent with previous findings of (37), who found that patients with benign breast diseases and the healthy control group had lower levels of MMP-9 in plasma compared to those with breast malignancies. The serum MMP-9 concentration in the cancer group of this study was substantially higher than that in the benign group. These findings suggest that MMP-9 plays a vital role in the intricate processes taking place at the interface between the tumor and the host and can differentiate between the benign and malignant condition. Research in 2014 measured the MMP-9 blood levels in 77 breast cancer patients using ELISA and found that MMP-9 levels were significantly higher in the breast cancer group compared to those with benign tumors (38). According to the findings of the current study, the mean of serum MMP-9 in recurrent cases and the newly diagnosed were 195.81±6.02 and 196.5±7.94, respectively. However, there was a significant decrease in MMP-9 levels in the benign and control groups. Sung et al. (39) mention that patients with elevated levels of MMP-9 were at a much higher risk of experiencing recurrence or death compared to patients with low levels of this protein.

The current study reported a significant increase in MMP-9 serum levels in female animals compared to male animals. Blanco-Pritet et al. observed significant differences in MMP-9 serum levels based on gender, with higher levels in males (40). However, Zhang, et al. (41) did not find any association between gender and MMP-9 serum levels. The results presented in the study indicate high serum levels of MMP-9 with advancing age, reaching 267.8±66 ng/mL in individuals aged 10-15 years. Cai, et al. (42) did not find any statistically significant variation in MMP-9 serum levels among individuals of different age groups.

MMP-9 was linked to the clinical stages and grade of breast malignancies (43). Regardless of the specific type of tumor in the mammary gland in presented study, there was a strong association between high levels of MMP-9 and advanced stages of mammary gland cancer. This correlation was also seen with histological grade (G II), as reported by Cai et al. (42). MMP-9 is involved in restructuring the cancer micro-environment and tumor-related macrophages release MMP-9, making its levels indicative of the severity and prognosis of the tumor (44, 45).

MMP-9 serum levels correlate with malignancy, advanced clinical stages (Stage IV), and high histological grades (grade II) of mammary carcinoma. The majority of malignant tumors were found in female dogs, which aligns with existing research. The results revealed that serum MMP-9 levels were significantly higher in female dogs, advanced age (10–15 years) with malignant tumors compared to those with benign tumors or healthy controls, indicating its potential role as a diagnostic biomarker. Furthermore, MMP-9 not only an independent diagnostic biomarker for CMT but also provide valuable insights into the aggressiveness of the tumor. Monitoring MMP-9 levels could assist in early detection, treatment planning, and enhancing the prognosis for dogs with mammary gland tumors.

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N/A

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ماتريكس ميتالوبروتينيز ٩ في المصل وأورام الثدي في الكلاب

اسلام سعدي ناجح العاني ، هدى سعدون جاسم البياتي

فرع الأحياء المجهرية ، كلية الطب البيطري، جامعة بغداد، بغداد، العراق

الخلاصة

تعد أورام الثدي في الكلاب (CMTs) واحدة من أكثر الأورام شيوعًا الموجودة في إناث الكلاب. ويشارك ماتريكس ميتالوبيتيداز ٩ (MMP-9) في تحطيم المصفوفة خارج الخلية في كل من العمليات الفسيولوجية الطبيعية والعمليات المرضية، مثل السرطان. كان الهدف من هذه الدراسة هو تقييم مستوى MMP-9 في مصل الدم كمؤشر حيوي في الكلاب المصابة بأورام الثدي باستخدام تقنية ELISA.تم الحصول على خزعات من الغدد الثديية وعينات الدم من ٥٠ كلبًا يشتبه في إصابتهم بـ بأورام الثدي و ٣٠ كلبًا ضمن مجموعة السيطرة. تم تشخيص أورام الثدي من خلال الفحص النسيجي، وأظهرت النتائج أن ٨٨٪ من الحالات كانت مصابة بسرطان الثدي الخبيث، في حين أظهرت ١٢٪ من النتائج نمواً حميداً. أظهرت نتائج اختبار الأليزا زيادة ذات دلالة إحصائية في متوسط مستوى MMP-9 في مصل الدم (نانوغرام/مل) في الحالات المصابة بالسرطان (١٩٩,٠٩ نانوغرام/مل) مقارنة بالحالات الحميدة (٥٦,٧٢١ نانوغرام/مل) ومجموعة السيطرة (٣٦,٠٥٥ نانوغرام/مل). كان هناك ارتفاع كبير في مستويات MMP-9 بين الكلاب التي تتراوح أعمارهم بين ١٠-١٥ سنة وبين إناث الكلاب. فيما يتعلق بمرحلة المرض ودرجته، ارتفع متوسط مستويات MMP9 مع تقدم مرحلة الورم (المرحلة الرابعة: ٣٤٣,٢٣٥ نانوغرام/مل). ومع ذلك، لم يكن هناك ارتباط مع درجة الورم، ولم يكن من الممكن التمييز بين الحالات المشخصة حديثًا والحالات التي تكرر بها الورم بواسطة مستويات ال MMP-9 في الكلاب المصابة باورام الثدي. في النهاية، تحديد مستويات MMP- 9 في مصل الدم يمكن أن يساعد في تقييم وجود الأورام الخبيثة في الكلاب المصابة بأورام الثدي.

الكلمات المفاحية:أورام الثدي في الكلاب، ماتريكس ميتالوبيتيدايز ٩، الإليزا، المصل، التشريح المرضي، الخزعات