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RESEARCH ARTICLE

Evaluation of Erythrocytes Indices Platelet Indices and Complete Blood Count in Feline Mammary Carcinomas

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ABSTRACT

The aim of this study was to evaluate the differences in the platelet (PLT) indices, erythrocytes indices and complete blood count (CBC) parameters between the cats with mammary tumor and healthy queens. Also, the differences in above mentioned parameters are going to be investigated in cats with mammary tumors with regard to clinicopathological characteristics of the primary tumor. A total of 44 queens were included in the study. The study groups consisted of cats with mammary tumors (Group MT, n=22) and healthy cats presented for neutering (Group H, n=22). The ages of the cats were ranged between 5-15 years. The mean ages of the cats in Group MT was 10.77±0.80 and in Group H was 6.75±1.21 years. All data on CBC, thoracic radiography, clinical examination findings and histopathology were obtained from the the patient archive in the animal hospital automation system. While the highest red blood cell (RBC) and hemoglobulin (HGB) levels were observed in Group H, Group MT had the highest white blood cell (WBC), mean platelet volume (MPV) and plateletcrit (PCT) levels. The mean corpuscular volume (MCV) level in T1 was significantly lower than in T2-T3. The MCV level in G1-G2 tended to be higher compared to G3.In Group MT, CBC parameters were not significantly different related to the presence of metastasis, presence of ulceration and inflammation on the tumor. It was concluded that evaluation of CBC and PLT indices in cats with mammary tumors would be useful in understanding the hematological effects of the disease and tumor characteristics (tumor size and histological grade).
Keywords: Erythrocytes indices, Female cat, Mammary carcinoma, Platelet indices

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Kedi Meme Karsinomlarında Eritrosit İndeksleri, Trombosit İndeksleri ve Tam Kan Sayımının Değerlendirilmesi

ÖZ

Bu çalışmanın amacı, meme tümörlü kediler ile sağlıklı dişi kediler arasındaki trombosit (PLT) indeksleri, eritrosit indeksleri ve tam kan sayımı (CBC) parametrelerindeki farklılıkları değerlendirmektir. Ayrıca meme tümörlü kedilerde yukarıda belirtilen parametrelerdeki farklılıklar, primer tümörün klinikopatolojik özellikleri açısından araştırılacaktır. Çalışmaya toplam 44 dişi kedi dahil edildi. Çalışma grupları, meme tümörlü kediler (Grup MT, n=22) ve kısırlaştırma için getirilen sağlıklı kedilerden (Grup H, n=22) oluşturuldu. Kedilerin yaşları 5-15 arasında değişiyordu. Grup MT'deki kedilerin yaş ortalaması 10,77±0,80, Grup H'deki kedilerin yaş ortalaması ise 6,75±1,21 yıldı. Tam kan sayımı, toraks radyografisi, klinik muayene bulguları ve histopatolojik incelemeye ilişkin tüm veriler, hayvan hastanesi otomasyon sistemindeki hasta arşivinden elde edildi. En yüksek kırmızı kan hücresi (RBC) ve hemoglobin (HGB) düzeyleri Grup H'de görülürken, Grup MT en yüksek beyaz kan hücresi (WBC), ortalama trombosit hacmi (MPV) ve platelekrit (PCT) düzeylerine sahipti. T1'deki ortalama korpüsküler hacim (MCV) seviyesi T2-T3'e göre anlamlı derecede düşüktü. G1-G2'deki MCV seviyesi G3'e kıyasla daha yüksek olma eğilimindeydi. Grup MT'de CBC parametreleri tümörde metastaz varlığı, ülserasyon ve inflamasyon varlığına bağlı olarak anlamlı farklılık göstermedi. Meme tümörlü kedilerde CBC ve PLT indekslerinin değerlendirilmesinin hastalığın ve tümör özelliklerinin (tümör boyutu ve histolojik derecesi) hematolojik etkilerinin anlaşılmasında faydalı olacağı sonucuna varıldı.
Anahtar kelimeler: Dişi kedi, Eritrosit indeksleri, Meme karsinomu, Trombosit indeksleri

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INTRODUCTION

Mammary tumors are the third frequent cancer type in queens (Thomas 2015). Feline mammary tumors are mostly malignant (80%-90%) and tend to metastasize (Lana et al. 2007; Goldschmidt et al. 2017). Histopathological examination is very important to evaluate the course of the disease (Klopfleisch 2017). Histological classification of malignant mammary tumors in cats have 3 origins as epithelial (carcinomas), mesenchimal (sarcomas) and, carcinosarcomas (Zappulli et al. 2008). Feline mammary carcinomas are biologically aggressive and usually associated with poor outcome (Ito et al. 1996; Dagher et al. 2019). Middle-aged, intact and fed with high-fat diet cats have high incidence of the mammary tumor development. Persian and Siamese cats are breeds that are predisposed to mammary tumors (Günay Uçmak and Kırşan 2021).

Mammary tumors in humans and cats exhibit similar pathophysiological structures, epidemiological and clinicopathological patterns (Nascimento and Ferreira 2021; Uçmak et al. 2023). Malignant mammary tumors can cause hematological disorders such as anemia, erythrocytosis, thrombocytosis, hyperproteinemia, and leucopenia both in humans (Mantas et al. 2016) and dogs (Günay Uçmak and Güvenç 2019; Uçmak et al. 2021). Da Silva Soares et al. (2023) reported that monocytes, platelets, mean corpuscular hemoglobin concentration and creatinine may be important noninvasive presurgical prognostic markers for the median overall survival in feline mammary carcinomas. Hristov and Binev (2018) reported that dogs which were over 8 years old and with mammary carcinomas had mean corpuscular volume (MCV, fL), mean corpuscular haemoglobin (MCH, pg) and mean corpuscular haemoglobin concentration (MCHC, g/L) within narrow limits. Platelets (PLT) are cytoplasmatic fragments of bone marrow megakaryocytes, which have an important role in the blood coagulation mechanism (Üstündağ Budak et al. 2016). PLT indices which are used to measure the total amount of PLT, PLT morphology and proliferation kinetics, are Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and Plateletcrit (PCT) (Koenhemsi et al. 2020). It has been reported that neutrophils and platelets contribute to cancer development and progression by directly affecting tumor growth, angiogenesis and metastasis (Nash et al. 2001; Coffelt et al. 2016; Contursi et al. 2018). The presence of high amounts of platelets increases the risk of metastasis, the prognosis becomes poor, and the incidence of multiple tumor types increases in humans (Buergy et al. 2012; Ji et al. 2015). The evaluation of leukocyte and platelet amounts in cancer patients may be useful in determining the potential for thrombosis formation (Naess et al. 2007). It has been reported that in tumor hypoxia or necrosis, an imbalance between neutrophils and lymphocytes may occur and this may be associated with antiapoptotic effects (Avcı et al. 2017). The absolute leukocyte count and the neutrophil/lymphocyte ratio (NLR) provide prognostic information in cats with mammary carcinoma (Petrucci et al. 2021).

Complete blood count parameters are routinely evaluated in clinical examination. However, limited information are presented about the alterations in hematological parameters in cats with mammary tumors. The aim of this study is to evaluate the differences in the PLT indices, erythrocytes indices and complete blood count parameters between the cats with mammary tumor and healthy queens. Also, the differences in above mentioned parameters are going to be investigated in cats with mammary tumors with regard to clinicopathological characteristics of the primary tumor.

MATERIALS and METHODS

Animals and Experimental Design

A total of 44 queens were included in the study. The study groups consisted of cats with mammary tumors (Group MT, n=22) and healthy cats presented for neutering (Group H, n=22). The ages of the cats were ranged between 5-15 years. The ages of the cats in Group MT were between 8 and 15 years, while the ages of the cats in Group H were between 5 and 9 years. The races of the cats were mostly mixed breed (n=32) and the rest of 12 cats were Iranian (n=6), Sphenx (n=2) and Siamese (n=4). Complete blood count (Procyte Dx Hematology Analyzer, Idexx, USA) and three-view thoracic radiographs (Orex PcCR 1417 and Viztekdiagnostic imaging program, USA) were performed to avoid anesthesia risk and to detect the possible metastasis. Red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), mean platelet volume (MPV), plateletcrit (PCT) results were incorporated into the study. In clinical examination, mass size, localisation of the mass/masses, presence of metastasis, presence of ulceration and inflammation on the tumor were noted. As a treatment, total mastectomy was performed for the cats in Group MT. Histopathology was performed as the researchers' reported (Günay Uçmak et al. 2023). In histopathological examination, tumor type and histological grades of the tumor were determined in cats belong to Group MT and the histological tumor type of the primary mass was taken into account in this study. All operative interventions (both ovariohysterectomy and total mastectomy) were performed under general anesthesia. Initially, the cats were premedicated with atropine sulfate (Atropin®, Teknovet, Turkiye) (0.03 mg/kg, sc). For the induction of anesthesia, propofol (Pofol ampoule, Dongkook Pharm, Korea) was given at a dose of 4 mg/kg/iv, and

then the anesthesia was continued by applying inhalation anesthesia with 3% isofluorane (Foran liquid, Abbott Laboratories, England) and 1% oxygen (Küçükbekir et al. 2020). All data on complete blood count, thoracic radiography, clinical examination findings and histopathology were obtained from the the patient archive in the animal hospital automation system.

Statistical Analysis

All statistical analysis were perfomed by SPSS 23.0 program (SPSS 23.0, IBM, USA). Normal distribution of the data was checked with Saphiro Wilk test. The differences of the data belong to the complete blood count parameters between the study groups was evaluated by t-test and Mann Whitney U test. In Group MT, differences in complete blood count parameters with regard to the clinicopathological parameters were checked with t-test and Mann Whitney U test. Statistical significance was accepted as $p<0.05$.

RESULTS

The mean ages of the cats in Group MT was 10.77±0.80 and in Group H was 6.75±1.21 years ($p<0.05$). The mean of the complete blood count result belong to the groups and their significancies were presented in Table 1. In Group MT, the mean HCT level tended to be lower than in Group H ($p=0.069$) while the mean MCV level in Group MT tended to be higher than in Group H ($p=0.070$) but they both could not reach the significance.

Table 1. The mean of the complete blood count result belong to the groups and their significancies.

	Group MT	Group H	Significance (p)
RBC (M/μL)	8.89±0.40[a]	10.10±0.27[b]	**0.017**
HGB (g/dL)	12.61±0.47[a]	13.8±0.29[b]	**0.011**
HCT (%)	37.63±1.43	41.02±1.10	0.069
MCV (fL)	42.31±0.72	40.77±0.67	0.070
MCH (pg)	14.31±0.29	13.74±0.31	0.198
MCHC (g/dL)	33.56±0.39	33.83±0.44	0.661
WBC (10^9/L)	15.16±2.02[a]	8.30±0.53[b]	**0.003**
PLT (10^9/L)	298.27±43.86	272±18	0.742
MPV (fL)	15.61±0.46[a]	10.6±0.32[b]	**0.000**
PCT (%)	0.55±0.05[a]	0.2±0.00[b]	**0.000**

[a,b] Different letters in the same line indicate the significance.

In Group MT, all cats have multiple tumoral masses which were all belong to malignant epithelial tumor type. Clinicopathological characteristics of the primary tumor belong to the cats in Group MT were presented in Table 2. Differences in complete blood count parameters were also evaluated related to the clinicopathological characteristics of the primary tumor. Due to the lack of statistically sufficient numbers in tumor sizes of T2 and T3, they were evaluated as a single group (T2-T3). The mean MCV level in T1 was significantly lower than in T2-T3 (41.19±0.99 vs 44.04±0.89, $p<0.046$). The mean WBC level in T1 was tended to be lower compared to T2-T3 (11.03±1.43 vs 19.29±3.42, $p=0.056$). Also the mean PCT level in T1 was tended to be lower than in T2-T3 (0.47±0.06 vs 0.63±0.08, $p=0.076$). However, the rest of the evaluated blood parameters did not exhibit a significance in terms of the tumor sizes ($p>0.05$). Due to the lack of statistically sufficient numbers in histological gades of G1 and G2, they were also evaluated as a single group (G1-G2). The mean MCV level in G1-G2 tended to be higher compared to G3 (43.86±0.85 vs 41.37±1.08, $p=0.085$). However, the rest of the evaluated blood parameters did not exhibit a significance in terms of the histological grades ($p>0.05$). In Group MT, complete blood count parameters were not significantly different related to the presence of metastasis, presence of ulceration and inflammation on the tumor ($p>0.05$).

Table 2. Clinicopathological characteristics of the primary tumor belong to the cats in Group MT.

Clinicopathological Parameters		Affected Numbers
Localization of the primary tumor	Axillar lobes	5
	Abdominal lobes	8
	Inguinal lobes	9
Tumor size (T)	T1 (0-3 cm)	11
	T2 (3-5 cm)	5
	T3 (>5 cm)	6
Histological grades	Grade 1	5
	Grade 2	6
	Grade 3	11
Presence of distant metastasis	(+)	10
	(-)	12
Presence of ulceration on tumor	(+)	11
	(-)	11
Presence of inflammation on tumor	(+)	12
	(-)	10

DISCUSSION

Complete blood count is a routinely available test which is usually performed as part of standard clinical care (Petrucci et al. 2021). Mammary carcinomas in cats have aggressive biological behavior (Hassan et al. 2017). Tumor progression and prognosis depend on tumor microenvironment, inflammation, and immune response (Fridman et al. 2017). Leukocytes which include lymphocytes, monocytes and neutrophils play important roles on proliferation, inflammation and immunity in various cancer types both in humans and animals (Nascimento and Ferreira 2021; Petrucci et al. 2021; Alan et al. 2022; Köse et al. 2023). Petrucci et al. (2021) investigated the association between the prognosis and neutrophil-to-lymphocyte ratio, neutrophil and WBC amounts in feline mammary carcinoma cases. Da Silva Soares et al. (2023) searched the changes in the blood count and serum biochemical profiles prior to mastectomy and their relation with the median overall survival and the disease-free survival in cats with mammary carcinoma. In our study, the differences in complete blood count parameters, which have been determined to have prognostic importance in previous studies (Petrucci et al. 2021; da Silva Soares et al. 2023), between feline mammary carcinoma cases and healthy queens, and the changes of these parameters according to clinical and pathological features in cats with mammary tumors were investigated.

Paraneoplastic syndromes (PNS) usually occur as a result of indirect effects of neoplasia in the body (Elliott 2014). Anemia which is the most common PNS in veterinary oncology, is strongly associated with tumor hypoxia (Elliott 2014; Gaspar et al. 2015). The most common in cancer patients with disseminated or metastatic tumors is anemia of chronic disease. As the disease progresses, iron metabolism and storage are disrupted. Anemia occurs due to the shortening of the lifespan of red blood cells and the decrease in the bone marrow's response to it. As a result of miscellaneous chronic infections, systemic diseases and oncology cases, normocytic normochromic anemia is usually observed (Elliott 2014; Tvedten 2022). Decrease in HGB levels are usually associated with both tumor hypoxia and poor prognosis in cancer patients (Varlotto and Stevenson 2005). Lallo et al. (2016) observed anemia and erythrocytosis in bitches with malignant mammary tumors. Uçmak et al. (2021) reported that HCT, HGB and MCHC levels in bitches with epitelial mammary tumors regardless of the tumor subtypes were lower than healthy ones. Even though the animal species that constituted our study were different, RBC, HGB and HCT levels were lower in feline mammary carcinoma cases compared to healthy ones, similar with the researchers (Lallo et al. 2016; Uçmak et al. 2021). As Gaspar et al. (2015) stated, it is thought that the decrease in RBC, HGB and HCT levels may lead to tumor hypoxia in cases of feline mammary carcinoma.

Erythrocytes indices which are MCV, MCH and MCHC elucidate the prognostic value of feline mammary carcinomas (da Silva Soares et al. 2023). In dogs with mammary tumors, Hristov and Binev (2018) observed the mean values of red blood cell indices within the reference ranges while MCV and MCHC levels were significantly higher than in healthy controls. Similarly, MCV levels in feline mammary carcinoma cases were tended to be higher compared to healthy queens in this study. Viste et al. (2002) indicated that tumor size in feline mammary adenocarcinomas is a prognostic indicator and tumors greater than 3 cm have poor prognosis. In this study, the highest MCV levels were determined in the increased tumor sizes (T2 and T3) which may reflect the worsening prognosis as the researchers' reported (Viste et al. 2002; da Silva Soares et al. 2023).

The most common hematological abnormalities described in animal oncology are anemia, leukocytosis, thrombocytopenia, and coagulopathies (Bailey 2020). However, Lallo et al. (2016) reported that leukocytosis and thrombocytopenia were less hematologic changes in dogs bearing mammary tumors. It has been reported that in tumor hypoxia or necrosis, an imbalance between neutrophils and lymphocytes may occur and this may be associated with antiapoptotic effects (Avcı et al. 2017). Also, pathologies in genital system such as vagina (Köse et al. 2023), ovary (Uçmak et al. 2018) and uterus (Hirota et al. 2014) causes leukocytosis in dogs and cats. In line with the previous reports, elevated levels of WBC in feline mammary carcinoma cases were detected compared to healthy queens in this study. Leukocytosis with neutrophilia could occur as a consequence of inflammation that results from the presence of the tumor as Lallo et al (2016) reported. Olivera et al. (2022) investigated hematological and biochemical alterations in female dogs with mammary cancer according to clinical staging and they determined the lowest WBC levels in dogs with early clinical stage ($T_{1,2,3}N_0M_0$). Similary, WBC levels in cats with T_1 sized tumor were tended to be lower compared to T_2 and T_3 in this study.

Platelet indices such as MPV, PDW, PCT are recognized as surrogate markers of platelet activation. Mean platelet volume (MPV) is the average platelet size. The variability in the size of the platelet is defined by PDW and the percentage of the blood volume that consists of platelets is expressed by PCT (Saran et al. 2022). In humans, increased levels of MPV have been a predictive and prognostic factor for invasive breast cancer (Gu et al. 2016). Alan et al. (2022) determined increased MPV levels in cats diagnosed with lymphoma compared to healthy queens. However, Uçmak et al. (2021) did not determine the significant changes between the dogs with epithelial mammary tumor and healthy ones. Contradictory with previous report, MPV levels in cats with mammary carcinoma were significantly higher than in control group in this study. The contradictory results can be obtained due to the differences in species (dogs vs cats) of the study material. Similar with Gu et al. (2016) reported, it is thought that increased MPV levels may be a predictive factor for feline mammary carcinoma cases. In humans, elevated PCT levels in ovarian and endometrial cancers were detected (Ma et al. 2014; Karateke et al. 2015). It has been reported that PCT levels in dogs with transmissible vaginal tumors tend to increase compared to healthy controls (Köse et al. 2023). Similar with the previous reports (Ma et al. 2014; Karateke et al. 2015; Köse et al. 2023), PCT levels in feline mammary carcinoma group were significantly higher than in control group in this study. Zhao et al. (2024) investigated the potential predictive value of PCT for early-stage breast cancer and they stated that PCT can't be neglected in humans. In this study, PCT levels in cats with mammary tumor less than 3 cm were tended to decrease compared to the cats with mammary carcinoma more than 3 cm. As Zhao et al. (2024) reported in breast cancer patients, it is thought that PCT levels may also be predictor for early stage feline mammary carcinomas. It further studies, it should be investigated with large number of patients.

CONCLUSION

It was concluded that the concentrations of RBC, HGB, MCV, WBC, MPV and PCT could exhibit the significant difference in the presence of tumor and in regard to the characteristic of the primary tumor such as tumor size and histological grades. It will be useful to evaluate the CBC and PLT indices in cats with mammary tumor to understand the hematological effect of this pathology.

Conflict of interest: The authors have no conflicts of interest to report.

Authors' Contributions: İbrahim Kurban and Zeynep Günay Uçmak contributed to the project idea, design and execution of the study. İbrahim Kurban and Zeynep Günay Uçmak contributed to the acquisition of and analysed the data, drafted, wrote and reviewed the manuscript critically. All authors have read and approved the finalized manuscript.

Ethical approval: All animal-related procedures were approved by the local ethic committee (approval İU-C HADYEK 2024/28).

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