http://dx.doi.org/10.4322/rbcv.2016.020

Hematologic abnormalities in dogs bearing mammary tumors*

Alterações hematológicas em cadelas portadoras de tumores de mama

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Abstract

In this study we describe the occurrence of hematological disorders in bitches with mammary neoplasm and analyze the possibility that alterations present can be used as a diagnostic parameter and prognosis. Two hundred and forty-six dogs with mammary neoplasms (123 with malignant and 123 with benign mammary tumor) and the same number of female dogs without mammary tumors were investigated for observation of hematologic abnormalities. The full blood test and measurement of proteins was carried out before any treatment for breast tumor. The diagnosis of mammary neoplasm was done by histopathology. Few animals with benign tumors had hematological disorders, but in malignant neoplasm the prevalence was 55%, and thrombocytosis, hyperproteinemia (hypergammaglobulinemia) and leucopenia (neutropenia) were the most prevalent abnormalities. Anemia and erythrocytosis had equilibrated occurrence (22 and 21%, respectively). Leukocytosis and thrombocytopenia were less hematologic changes observed. We concluded that because of the high prevalence of thrombocytosis, leukopenia and hyperproteinemia (hypergammaglobulinemia) in bitches bearing mammary tumors, the hematological abnormalities may be signaling of malignant neoplasm.

*Keywords***:** dogs, hematology, mammary neoplasm.

Resumo

Neste estudo descrevemos a ocorrência de distúrbios hematológicos em cadelas com neoplasia mamária e sua possível relação com o diagnóstico e o prognóstico. Duzentos e quarenta e seis cadelas com neoplasias mamárias (123 com maligno e 123 com tumor mamário benigno) e o mesmo número de cadelas sem tumores mamários foram investigadas para a observação de anormalidades hematológicas. O exame de sangue completo e mensuração de proteínas foram realizados antes de qualquer tratamento para o tumor de mama. O diagnóstico de neoplasia mamária foi feito por exame histopatológico. Poucos animais com tumores benignos tinham distúrbios hematológicos, mas em neoplasia maligna a prevalência foi de 55%, sendo trombocitose, hiperproteinemia (hipergamaglobulinemia) e leucopenia (neutropenia) as anormalidades mais prevalentes. Anemia e eritrocitose tiveram ocorrência equitativa (22 e 21%, respectivamente). Leucocitose e trombocitopenia foram alterações hematológicas menos observadas. Concluiu-se que, devido à alta prevalência de trombocitose, leucopenia e hiperproteinemia (hipergamaglonulinemia) em cadelas com tumores mamários malignos, tais alterações hematológicas podem ser sinalização para o diagnóstico das malignidades e seu prognóstico.

Palavras-chave: cães, hematologia, neoplasias de mama.

Introduction

Hematological abnormalities are frequently encountered in small animal cancer patients, and can result from the direct effects of tumor growth or from paraneoplastic syndromes; however a few epidemiological studies show the occurrence of these hematological abnormalities in dogs with specific tumors. Cancer-related hematologic disorders can be decreases or increases in the absolute numbers of circulating formed elements of the blood, alterations of hemostasis, or plasma protein dyscrasias (Childress, 2012). The veterinarians could be able to recognize there hematological alterations that characterize neoplastic diseases for several reasons: 1- hematologic changes may be clinical markers of specific types of cancer and facilitate their identification decrease the time of diagnosis; 2- hematological alterations may help as markers of therapeutic response and tumor remission; 3- hematological changes may require specific treatment, in addition to cancer treatment; 4- hematological alterations may influence the prognosis of certain tumors (Couto, 1984; Childress, 2012).

Anemia is one the most common hematologic abnormalities found in human cancer patients about 30 to 50% of patients with solid tumors are anemic at the time of initiating cancer treatment (Spivak et al., 2009) but the prevalence of anemia in veterinary patients with cancer is unknown. Thrombocytopenia is frequently noted in veterinary cancer patients, more than 36% of untreated canine cancer patients presented with thrombocytopenia (Madewell et al., 1980). As in humans with mammary carcinoma, these hemostatic abnormalities might be used as prognostic indicators, but their clinical importance remains unknown. Hence,

*Recebido em 31 de janeiro de 2015 e aceito em 17 de junho de 2016.

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the objectives of this study were to (1) describe the occurrence of hematological disorders in bitches with mammary neoplasm; (2) and analyze the possibility that alterations present can be used as a diagnostic parameter and prognosis.

Material and methods

Two hundred and forty-six dogs with mammary neoplasm and the same number of dogs without mammary neoplasm presented to our institution between 2011 and 2013 were evaluated. These animals were divided in three groups - G1 (n = 123) dogs with malignant mammary tumor, G2 (n = 123) dogs with benign mammary tumor and G3 (n = 246) dogs without mammary neoplasm (control group). The animal use protocol for this study was approved by the University Research Ethics Board for Health Sciences Research (146/2010) and dogs were enrolled in the study after signed owner's consent.

The animals of groups 1 and 2 were selected randomly according to the following exclusion criteria: presence of metastases, tumor ulceration, secondary infection and necrosis; history of infectious disease or blood disease; presence of heat; use of medications (i.e., anti-inflammatory and chemotherapy), and comorbidities responsible for hematological disorders. Group 3 consisted of healthy dogs that randomly selected according to the following exclusion criteria: history of infectious disease or blood disease; presence of heat; use of medications (i.e., anti-inflammatory and chemotherapy), and comorbidities responsible- for hematological disorders.

The diagnosis of mammary neoplasm was done by histopathology (Misdorp et al., 1999) (excisional biopsy after surgical treatment). Staging of the disease included regional lymph node aspiration cytology or histopathology, abdominal ultrasonography, and thoracic radiography (three views).

Two mL of blood were taken and transferred to a silicone coated vacutainer tube containing anticoagulant (0.1 mL of 10% EDT A – ethylene-diamine-tetra-acetic acid). Three mL of blood were placed in a tube without anticoagulant for serum extraction and were centrifuged at 2,500 rpm for 5 min. The serum was then extracted with a micropipette and transferred to conical-bottom polypropylene tubes, which were stored at -20 °C until the moment of the exam. Hematology tests were performed on automated analyser (Diatron®, Abacus). The following data were taken into analysis: erythrocyte parameters - red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HT), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and red blood cell distribution width (RDW); leukocyte parameters - white blood cell (WBC), granulocyte, monocyte, and lymphocyte counts; platelet parameters - platelet count (PLT) and mean platelet volume (MPV). Serum biochemical assays were done by spectrophotometric methods and included the determination serum proteins (total protein, albumin, globulin, and albumin/globulin ratio – A/G).

For evaluation of the effects of mammary tumors on hematologic parameters one-way ANOVA was used. Mann-Whitney for data with non Gaussian distribution or Student's t test for normally distributed data was used. Statistical analyses were performed using Chi-squared test or the Fisher's exact test for categorical variables using commercial software. Pearson's and Spearman's rank correlation coefficients were used for correlation analysis. Statistical significance was set at $P < 0.05$. A commercial statistical software package (Prism version 4.0, GraphPad Software) was used to analyze the data.

Results

In this study, we have demonstrated that the prevalence of general hematologic abnormalities in dogs with breast cancer was 29% (73/246) against prevalence of 2% (5/246) observed in the control group, showing a significant difference ($P < 0.012$) between the groups due to presence of mammary tumors (Table 1).

In the group of dogs with benign mammary tumors, the prevalence of hematological abnormalities was low, being only observed anemia in 4% (5/123) of the survey animals. Adenomas and fibroadenomas were the most prevalent benign mammary tumors (110/123, 89%). However, the group of dogs with malignant mammary tumors showed high prevalence of hematologic abnormality that reached 55% (68/123) of the animals, which showed high statistical association between hematologic alterations and cancer ($P < 0.01$). Histological analysis demonstrated that 115 dogs had carcinoma, including tubular carcinoma (66/123, 53%), papillary carcinoma (9/123, 7%), solid carcinoma (25/123, 20%) and complex carcinoma (15/123, 12%). Only eight dogs had tumors characterized as osteosarcoma (8/123, 6%) and all this dogs showed hematological alterations.

The main hematological abnormalities were thrombocytosis (47/123, 38%), hyperproteinemia (42/123, 34%) and leucopenia with a predominance of neutropenia (42/123, 34%); and these abnormalities were significantly more prevalent in dogs with malignant tumors compared to benign and healthy group without breast tumor. There was a balance between the increase (26/123, 21%) and decreased (28/123, 22%) of hematocrit among the cases studied. Leukocytosis with a predominance of neutrophilia (18/123, 14%) and thrombocytopenia (17/123, 13%) were less hematologic changes observed in this study (Table 2). To further clarify the possible relationship of hyperproteinemia with mammary cancer in female dogs, the protein fractions (albumin, globulin and A/G ratio) were evaluated. All animals had hypergammaglobulinemia and the A/G was low (mean 0.24±0.12).

In this study, mean age of the bitches with mammary tumor was 10 years (SD 3.0), and of the 246 dogs with mammary tumors examined, 118 (48%) were mixed breed, 72 (29%) in poodle, 16 (6%) in Rottweiler and the rest were of various other breeds.

Table 1: Hematological abnormalities observed in dogs with mammary tumors and healthy control.

Results	Age (years) mean (SD) [samples]	↑ HT (%) mean ± SD (range) [positive cases]	↓ HT (%) mean ± SD (range) [positive cases]	↑ Platelet count mean (U x 10^9/L) ± SD (range) [positive cases]	↓ Platelet count mean (U x 10^9/L) ± SD (range) [positive cases]	Total proteins (g/dL) ± SD (range) [positive cases]	↑ Leukocyte (x 10^3/**µL**) ± SD (range) [positive cases]	↓ Leukocyte (x 10^3/**µL**) ± SD (range) [positive cases]
Mammary tumor groups	10.5 (3.7) [246]	58 **± 1.1** [26]	30 **± 2,6** [28]	750 **± 350** [47]	125 **± 30** [17]	8.4 **± 0.53** [42]	21.3 **± 14.4** [18]	5.1 **± 0.7** [42]
Healthy control	9.5 (5.6) [246]	-	33 **± 1.4** [2]	-	110 **± 30** [3]	-	-	-
P	0.95	<0.01	<0.02	<0.012	<0.023	<0.01	<0.011	<0.014

SD – standard deviation, HT – Hematocrit, Fisher's test, Mann-Whitney and Student's t test were used to generate P values.

Table 2: Hematological abnormalities observed in dogs with different types of mammary cancer

Mammary cancer (positive cases)	↑ HT (%) mean ± SD (range) [positive cases]	↓ HT % mean ± SD (range) [positive cases]	↑ Platelet count mean (U x 10^9/L) ± SD (range) [positive cases]	↓ Platelet count mean (U x 10^9/L) **± SD** (range) [positive cases]	Total proteins (g/dL) ± SD (range) [positive cases]	↑ Leukocyte (x 10^3/**µL**) **±** SD (range) [positive cases]	↓ Leukocyte (x 10^3/**µL**) **±** SD (range) [positive cases]
Tubular carcinoma (n=66)	58 ± 0.91 (57 –60) [23]	31 **±** 2.23 (16 –35) [15]	778 **±** 230 (623 – 1,000) [30]	113 **±** 34 (41 – 140) [13]	8.2 **±** 0.46 (8-9.4) [23]	21.4 **±** 16.5 (17.7 – 74.2) [12]	5.0 **±** 0.8 (4.5 – 5.7) [29]
Papillary carcinoma (n=9)	-	32 ± 1.73 (30 –35) [3]	-	-	-	-	-
Solid carcinoma (n=25)	-	30 ± 4.84 (21 –37) [5]	665 **±** 276 (615 – 1,110) [14]	132 **±** 51 (117 – 140) [3]	8.2 ± 0.81 (8-10.8) [11]	21.0 **±** 3.1 (17 – 23.13) [3]	4.7 **±** 0.7 (5.3 – 5.6) [10]
Complex carcinoma (n=15)	57 ± 0.86 [2]	-	-	-	8.5 **±** 0.14 (8.4-8.6) [2]	-	5.7 **±** 1.1 (5.0 – 6.0) [3]
Osteosarcoma (n=8)	64 [1]	29 **±** 1.78 (27 –33) [5]	769 **±** 90 (540 – 910) [3]	140 [1]	8.8 **±** 0.72 (8.0-9.6) [6]	21.2 **±** 10.2 (18.1 – 37.2) [3]	-
Total (%)	26 (21.14)	28 (22.76)	47 (38.21)	17 (13.82)	42 (34.14)	18 (14.63)	42 (34.14)
Reference range	37-55	37-55	165 - 460	165 – 460	6 - 7.5	6.0 – 17.0	6.0 - 17.0

SD- standard deviation, HT – Hematocrit

Discussion

Although cancer-related hematologic abnormalities are frequently described in the veterinary literature, the incidence, prevalence, and clinical significance of these abnormalities are less defined (Childress, 2012). We have demonstrated that the prevalence of hematologic abnormalities in dogs with mammary tumors reached 29% of all dogs affected with this type of tumor and reached 55% prevalence in the analysis of malignant mammary tumors, showing a strong association between breast cancer in dogs and hematological abnormalities.

Recently, hematological abnormalities had been described in dogs with breast tumor, such as anemia and leukocytosis, which were associated with the advanced state of neoplasms and chronicity of these cases (Da Silva et al., 2014). However, we demonstrated the presence of blood abnormalities in dogs with mammary tumors without apparent metastases and tumor ulceration, showing that these changes should be associated with the pathogenesis of mammary tumors. Mammary extramedullary hematopoiesis is a rare condition and it is generally associated with non-neoplastic hematopoietic masses in both woman and bitches, however, the presence of hematopoietic activity can also be seen as an incidental finding associated with mammary neoplasm (Cufer and Bracko, 2001) and was described in a female dog with benign mixed mammary tumor (Grandi et al., 2010).

Reports of the occurrence of malignant forms vary from 26 to 73% and in this study carcinoma being the most common malignant type (Lana et al., 2007) and was strongly associated with hematologic abnormalities. It has been shown that the thromboelastographic carcinoma with dogs have hypercoagulability and hyperfibrinogenemia (Saavedra et al., 2011), which reinforces our findings.

We observed that 3 hematologic abnormalities were more prevalent, with statistical significance compared to control animals (healthy) and other abnormalities within the group of animals with tumors (G1 and G2) they were thrombocytosis, hyperproteinemia and leukopenia. Although thrombocytosis occurs in up to 60% of human cancer patients, it is infrequently documented in association with cancer in the veterinary literature (Hogan et al., 1999; Rizzo et al., 2007; Saavedra et al., 2011), but it is possible that these data are underestimated, because we observed that thrombocytosis was one of the most prevalent hematologic changes in bitches with breast cancer.

Thrombocytosis is also a relatively common laboratory abnormality in lung-cancer human patients, with a prevalence of 16–46% (Gislason e Nou, 1985; Engan and Hannisdal, 1990) and was noted in 46% of dogs with hepatocellular carcinoma (Liptak et al., 2004). The etiology of thrombocytosis in dogs may be classified as physiologic, reactive or neoplastic. Reactive thrombocytosis has been suggested to be part of the systemic inflammatory reaction for which interleukin-1 beta and interleukin-6 or hematopoietic growth factors (Alexandrakis et al., 2002) and is likely to be the etiology of these cases as described thrombocytosis physiological origin is transient and the marrow neoplasm was not considered in these animals. Thrombocytosis is an independent predictor of poor prognosis in lung-cancer patients (Gislason and Nou, 1985; Engan and Hannisdal, 1990) perhaps it is also a prognostic marker in canine mammary cancer, but this association should be evaluated in the future.

In this study, hyperproteinemia was a hematologic change very much seen in dogs with breast cancer and was due to increased globulins. The perturbations in plasma protein concentrations are common in small animal cancer patients as seen in this study and the most diagnostically relevant of these is hypergammaglobulinemia as a result of acute or chronic inflammatory (Childress, 2012). It has been increasingly recognized that systemic inflammation is associated with poor prognosis in human patients with cancer (Roxburgh and Mcmillan, 2010). Recent study has demonstrated that an increased systemic inflammatory response before surgery is an independent prognostic factor of survival following resection of human esophageal cancer (Dutta et al., 2011) and albumin/globulin ratio can be used as a prognostic indicator, being observed increased survival of patients with esophageal cancer in individuals with lower A/G (Zhang, 2016). In this study we just observe that there is a decrease in A / G ratio in dogs with malignant breast tumor, but the association of this index with prognosis should be better evaluated in future studies.

In cancer patient, leukopenia is most often characterized by neutropenia and is often associated with therapy against cancer that has myelosuppressive effect. True cancer-associated neutropenia is less common, and usually is due to myelophthisis caused by hematopoietic malignancies (Childress, 2012). In female dogs examined in this study, leucopenia due the neutropenia was very prevalent and was not linked to the myelosuppressive treatment and apparently also not the result of mielophthisis. Neutropenia of unknown origin has been described in dogs and cats with untreated solid tumors, without the disclosure of mielophthisis or concomitant immunosuppressive diseases (Couto, 1985) and the remission of the primary tumor resulted in resolution of the neutropenia in all animals. It was suggested an immune-mediated origin, which can really make a lot of sense considering that the immune response is a limiting factor in tumor development. The leukopenia finding becomes very important for dogs that potentially will be subject to anti-tumor therapy because usually this involves myelosuppressive drugs.

Anemia has also been reported in association with cancer and is one of the most common hematologic abnormalities encountered in human and animal cancer patients, despite this was rarely observed in this study. Anemia and coagulopathies are major causes of morbidity and mortality in human cancer patients, and may have a tremendous impact on disease progression and tumor response to antineoplastic therapy (Spivak et al., 2009). The pathogenic mechanisms common to all anemias, including blood loss, increased red blood cell destruction (hemolysis), and decreased red blood cell production, may each play a role in cancer-related anemia (Childress, 2012). Hemolytic anemias in cancer patients may be immune-mediated or non-immune-mediated caused by microangiopathy, oxidative damage to erythrocytes or tumor cell erythrophagocytosis (Madewell et al., 1980). As blood loss was not identified, it is likely that the most present etiologies are increased red blood cell destruction (hemolysis) and decreased red blood cell production.

As we observed in this study, erythrocytosis is uncommon in veterinary cancer patients, but when present, cancer related erythrocytosis may be due to a primary myeloproliferative disease or may be a paraneoplastic syndrome (Couto et al., 2014). Erythrocytosis has also been reported in other types of cancer in dogs such as transmissible venereal tumor (Cohen, 1985), nasal

fibrosarcoma (Couto et al., 2014) and cecal leiomyosarcoma (Sato et al., 2002) or associated with renal tumors.

Thrombocytopenia and leukocytosis with neutrofilia were the least changes found in this study. The mechanisms underlying cancer-associated thrombocytopenia include decreased platelet production, increased platelet sequestration, increased platelet destruction, and increased platelet consumption or utilization. Thrombocytopenia in human and veterinary cancer patients is typically secondary to chemotherapy administration, but in this case as the animals in this study had not undergone this type of treatment to low prevalence is justified (Bergman, 2007).

In most cases, leukocytosis in canine and feline cancer patients can be attributed to acute or chronic inflammation (Childress, 2012). A high leukocyte count, especially with a predominance of granulocytes, is often presumed to be secondary to a bacterial infection. However, as explained above, we have not included in this study animals with mammary ulcers to prevent secondary bacterial infections could be to confounding factor. Thus, we believe that leukocytosis with neutrophilia is a consequence of inflammation that results from the presence of the tumor.

We concluded that thrombocytosis, hyperproteinemia (hypergammaglobulinemia) and leucopenia (neutropenia) were the most hematological abnormalities found in dogs with malignant mammary tumors, followed by anemia and erythrocytosis. The importance of these findings should be further explored with the monitoring of the evolution of these cases, once the thrombocytosis is clearly associated with poor prognosis of renal cell carcinomas in man.

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