



## Changes in Hematological Parameters Associated with Vaginal Hyperplasia and Vaginal Tumors in Bitches

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### Abstract

The aim of the study is to evaluate the changes in clinical, hematological and histopathological parameters of the bitches with vaginal hyperplasia (VH), vaginal tumors (VT) and healthy reproductive tract (H), respectively. The study groups formed as; group VH (n=9), group VT (n=10) and group H (n=13). All bitches were examined clinically (vaginal cytology, vaginoscopy), hematologically and histopathologically. The bitches in group H were in anestrus and the bitches in group VH and group VT were in oestrus. Reduced levels of RBC, HGB, HCT and increase in WBC were detected in group VT. The averages of HGB level in group VH was tended to be lower than group H (P=0.05) while the averages of HCT level in group VH was significantly lower than to group H. The averages of RBC, HGB, HCT and WBC were not significantly associated with the degree of vaginal fold prolapse (VFP) (P>0.05) while the averages of PLT and PCT in bitches with type 2 VH were tended to be higher than type 3 VH (P=0.07). The histopathological examination of the vaginal masses in group VH revealed thickening of squamous epithelium and significantly loose and edematous connective tissue in the lamina propria. Histological diagnosis of the tumors in group VT were fibroma (n=4), leiomyoma (n=3), peripheral nerve sheath tumor (n=1), transmissible venereal tumor (TVT) (n=1) and leiomyosarcoma (n=1). In conclusion, hematological changes in bitches with vaginal mass were evaluated and mild anemia and leukocytosis were determined in bitches with VH and VT. To our knowledge, this is the first study that demonstrates the detection of mild anemia in bitches with VH and the differences in PLT and PCT related to the degree of VFP.

**Anahtar Kelimeler:** Bitches, hematology, vaginal mass

### Dişi Köpeklerde Vajinal Hiperplazi ve Vajinal Tümörler ile İlişkili Hematolojik Parametrelerde Değişiklikler

#### Öz

Çalışmanın amacı, vajinal hiperplazili (VH), vajinal tümürlü (VT) ve sağlıklı genital kanala sahip (H) köpeklerde klinik, hematolojik ve histopatolojik değişimlerin incelenmesidir. Çalışma grupları; grup VH (n=9), grup VT (n=10), grup H'dan (n=13) oluştu. Tüm dişi köpekler klinik (vajinal sitoloji, vajinoskopi), hematolojik ve histopatolojik olarak değerlendirildi. Grup H'deki dişiler anöstrustaydı, grup VH ve grup VT'deki dişiler ise östrustaydı. Grup VT'de azalmış RBC, HGB, HCT seviyeleri ve WBC'de artış tespit edildi. Grup VH'deki HGB düzeyi ortalamaları grup H'den daha düşük olma eğilimindeyken (P=0,05), grup VH'deki HCT düzeyi ortalamaları grup H'ye göre önemli ölçüde azdı. Ortalama RBC, HGB, HCT ve WBC değerleri, vajinal kıvrım sarkması derecesi ile önemli ölçüde ilişkili değilken (P>0,05), tip 2 VH'li dişi köpeklerde PLT ve PCT ortalamaları, tip 3 VH'den daha yüksek olma eğilimindeydi (P=0,07). Grup VH'deki dişilerde histopatolojik incelemede skuamöz epitelde kalınlaşma ve lamina propriada belirgin ödem saptandı. Grup VT'de yer alan tümörlerin histolojik teşhisi; fibrom (n=4), leiomyom (n=3), periferik sinir kılıfı tümörü (n=1), bulaşıcı venereal tümör (n=1) ve leiomyosarkomdu (n=1). Sonuç olarak, vajinal kitlesi olan dişilerde hematolojik değişiklikler değerlendirildi ve VH ve VT'li köpeklerde hafif anemi ve lökositöz belirlendi. Bildiğimiz kadarıyla bu, VH'li dişi köpeklerde hafif anemiyi ve vajinal kıvrım sarkmasının derecesi ile ilgili PLT ve PCT değerlerindeki farklılıkları saptayan ilk çalışmadır.

**Key Words:** Hematoloji, köpek, vajinal kitle

### INTRODUCTION

Vaginal masses protruding from the vulva can arise due to vaginal fold prolapse (VFP), true vaginal prolapse (TVP), vaginal neoplasms, uterine prolapse, urethral neoplasia, clitoral hypertrophy, vaginal polyps, vaginal abscessation, or hematomas (1,2). Regardless of age and breed, all females that are intact or spayed, are susceptible to the formation of vaginal and vestibular masses (1, 3). Canine vaginal hyperplasia

occurs during pro-oestrus and oestrus due to estrogenic response of the vaginal mucosa (hyperaemia and edema) (4), and spontaneously regress during dioestrus (5). The highest incidence of VFP is indicated in nulliparous (60.71%) and in intact bitches (100%) (6). Besides, VFP cases in last trimester of pregnancy and following the parturition are reported in the literature (7-9). The degree of vaginal protrusion has been clinically classified into three types (2, 10). Type 1 is

defined as slight to moderate protrusion of the vaginal floor cranial to the external urethral orifice. The protruded tissue can be diagnosed in vaginal or vaginoscopic examinations but not through the vulva (10). In type 2, vaginal tissue which originates from the floor of the cranial vagina, prolapses through the vulva and becomes visible from the vulvar cleft. It usually arises as a tongue-shaped mass with a narrow base or a dome-shaped mass (11). Type 3 is described as a complete prolapse of the entire circumference of the vaginal wall (12). It visualizes as a doughnut-shaped or ring-shaped mass (13). The urethral opening can easily be determined on the ventral side of the prolapsed mass (2).

Vulvar and vaginal neoplasms are relatively uncommon, accounting for 2.4-3% of all tumors in bitches (14). They usually occur in bitches with older ages (15). The presence of a mass protruding from the vulva and vaginal discharge are the frequent symptoms which are seen in vaginal neoplasms (16). Benign smooth muscle tumors (leiomyoma, fibroleiomyoma, fibroma and polyps) account for 83% of vaginal neoplasms in bitches (14). Vaginal cytology, vaginoscopy and histopathology have to be performed to differentiate the vaginal masses (17). The treatment of benign vaginal neoplasm is possible with surgical intervention (18, 19). While complete blood count and chemistry profiles of the affected bitches are usually within normal ranges (1, 2, 19), leukocytosis has been reported in a bitch which had both vaginal hyperplasia and vaginal neoplasm (18).

The aim of the present study is to evaluate the changes of clinical, hematological and histopathological parameters of the bitches with vaginal masses (hyperplasia and tumor) and healthy reproductive tract, respectively.

## MATERIAL AND METHODS

### Animals and Study Design

A total number of 32 intact bitches were enrolled in the study. All bitches were clinically and gynaecologically examined. On clinical examination, trans-abdominal ultrasonography and three-view thoracic radiography were also performed. The groups were designed according to the vaginal examination (vaginoscopy, exfoliative vaginal cytology) and histopathological diagnosis (only for study groups). Control group was consisted of healthy intact bitches (group H; n=13) which were presented to the clinic for ovariohysterectomy. The age of the bitches in group H ranged between 4-9 years and body mass ranged between 5-25 kg. Study groups consisted of 19 bitches which were presented to the clinic with a complaint of mass protruding through the vagina. The age of the bitches with VH (group VH; n=9) ranged from 1 to 11 years and body mass ranged from 5 to 35 kg. The VFP was staged as described previously (10). The bitches with a VT (group VT; n=10) aged 5 to 17 years and weighted 6 to 35 kg.

### Ethical Approval

Ethics approval for the study was obtained from the unit Ethics Committee at Istanbul University-Cerrahpaşa, Faculty of Veterinary Medicine (Approval number: 2020/33).

### Hematological Examination

Two milliliter blood samples were obtained with the puncture of the vena cephalica antebrachii by using sterile 18 gauge cannula into the ethylenediaminetetra-acetic acid (EDTA) containing vacutainer tube for each bitch. Hematological analysis was performed by using hematology analyzer (ProCyte Dx, IDEXX Laboratories, USA). Red blood cell (RBC, M/ $\mu$ L), Hemoglobin (HGB, g/dL), Hematocrit (HCT, %), White blood cell (WBC, K/ $\mu$ L), Platelet (PLT, K/ $\mu$ L), Plateletcrit (PCT, %) measurements were incorporated into the study for all bitches.

### Vaginal Cytology

The samples were collected with a cotton swab from all the bitches. The smears were stained with Diff Quick method according to manufacturers' instructions (Hemacolor® stain; Merck, Darmstadt, Germany). The slides were examined by using a light microscope (BAB-LAM, BAB, Turkey) at X400 magnification.

### Histopathology

Vaginal tissue samples collected from the bitches of group VH and group VT were fixed in 10 % neutral buffered formalin, paraffin embedded, sectioned at 4  $\mu$ m, and stained with hematoxylin and eosin (HE) for histopathological examination by light microscopy.

### Statistical Analysis

The SPSS 13.0 packet program was used for the statistical analyses (SPSS Inc. Chicago, Illinois, USA). The normal distribution of the data was checked by using Shapiro-Wilk test. The comparison of the groups in terms of the hematological parameters was performed by Kruskal-Wallis test and Mann Whitney-U test. The significance level was accepted as  $P < 0.05$ .

## RESULTS

### Clinical Examination Results

All bitches had three-view thoracic radiography and abdominal ultrasonography during the clinical examination and any disorders or pathologies were not observed. The mean age and weight of the bitches in group H were  $6.23 \pm 0.63$  years and  $13.07 \pm 2.49$  kg. The bitches in group VH aged  $5.44 \pm 1.90$  years and weighted  $19.22 \pm 5.49$  kg. The mean age and weight of the bitches in group VT were  $11.30 \pm 1.36$  years and  $17.85 \pm 3.94$  kg. The mean age and standard error of mean (SEM) in group VT was significantly higher than group VH ( $P < 0.05$ ) and group H ( $P < 0.05$ ). The races in group VH were Terrier (n=4), German Shepherd (n=2), Kangal (n=2), Pug (n=1). The existed races in group VT were Terrier (n=3), Golden Retriever (n=3), Pekingese (n=1), Cocker Spaniel (n=1), Irish Setter (n=1) and mix breed (n=1). The bitches in group H had pro-oestrous bleeding at five months ago. Parabasal and intermediate cells were observed in cytology smears of group H. However, the smears that belong to bitches in study groups had superficial cells and predominance of enucleated superficial epithelial cells indicating the

oestrus phase of the cycle. Additionally, cytologic examination of one case in group VT which was histologically diagnosed as TVT, revealed round to oval cells with pale blue cytoplasm and cytoplasmic vacuoles resembling TVT cells. Also, erythrocytes and neutrophil leucocytes were observed in smears of a terrier bitch which was histologically diagnosed as TVT. The bitch diagnosed with TVT had multi-lobular, diffuse, cauliflower-like, brittle and hemorrhagic mass that protrude from the vagina. Also, intermittent urination was observed due to the mechanic partial obstruction of the TVT mass on the orificium urethra externa. Except the TVT case, all masses in group VT were solid, unilobular, pedunculated masses located in a position that did not prevent urination. According to the protrusion degree of the vagina in group VH, type 2 (n=6) and type 3 (n=3) VFP were diagnosed. The mean age and weight of the bitches with Type 2 VFP were  $7.33 \pm 2.53$  years and  $13.33 \pm 4.98$  kg, whereas the mean age and weight of the bitches with Type 3 VFP were  $1.67 \pm 0.66$  years and  $31 \pm 11.59$  kg; respectively. Although the mean age of the bitches with type 2 VFP was tended to be higher than the bitches with type 3 VFP, it failed to reach a statistical significance ( $P=0.08$ ). The mean body weight of the bitches with type 3 VFP was tended to increase but it did not achieve the significance ( $P=0.06$ ).

### Hematological Examination Results

The mean values of hematological parameters and their significances related to the groups are presented in Table 1. In group VT, the mean RBC value was significantly lower than the group VH and group H ( $P<0.05$ ). Also, the mean HGB level in group H was significantly higher than group VT ( $P<0.05$ ). However, the mean HGB level in group VH was tended to be lower than group H but failed to reach a statistical significance ( $P=0.05$ ). The mean HCT level in group H was significantly higher than group VH and group VT ( $P<0.05$ ,  $P<0.01$ ; respectively). Besides, the mean HCT level in group VH was tended to be higher than group VT but the differences could not achieve a statistical significance ( $P=0.06$ ). The mean WBC level in group H was significantly lower than group VH and group VT ( $P<0.05$ ). However, the mean WBC level in group VT was higher than group VH ( $P<0.05$ ). Hematological parameters were evaluated with regard to the protrusion degree of the vagina in group VH. The mean values and SEM of RBC, HGB, HCT and WBC were not significantly associated with the degree of VFP ( $P>0.05$ ). However, the mean values and SEM of PLT and PCT in bitches with type 2 VFP were tended to be higher than type 3 VFP but failed to reach a statistical significance ( $P=0.071$  and  $P=0.070$ ; respectively).

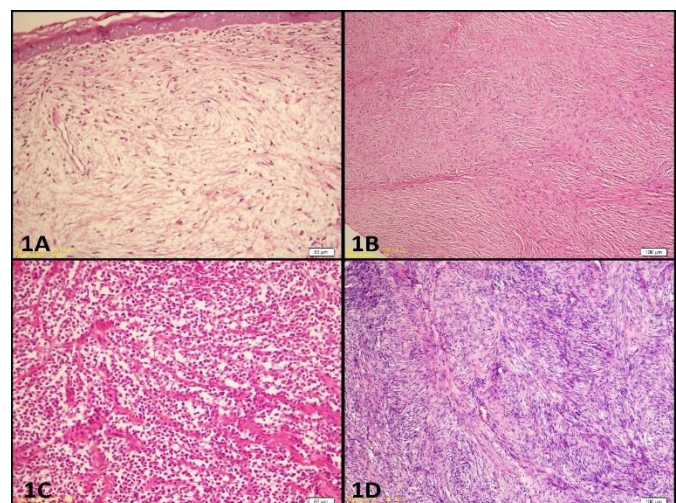
**Table 1.** The mean values of hematological parameters and their significances related to the groups.

	Group H	Group VH	Group VT
RBC (M/ $\mu$ L)	$7.28 \pm 0.19^a$	$6.70 \pm 0.27^a$	$5.78 \pm 0.51^b$
HGB (g/dL)	$16.57 \pm 0.50^a$	$15.06 \pm 0.47^{ab}$	$14.09 \pm 2.16^b$
HCT (%)	$48.19 \pm 1.83^a$	$42.15 \pm 1.42^b$	$32.73 \pm 3.99^b$
WBC (K/ $\mu$ L)	$14.30 \pm 3.97^a$	$18.60 \pm 2.99^b$	$22.24 \pm 5.60^c$
PLT (K/ $\mu$ L)	$362.85 \pm 22.58^a$	$410.22 \pm 58.95^a$	$364.20 \pm 57.30^a$
PCT (%)	$0.35 \pm 0.02^a$	$0.45 \pm 0.06^a$	$0.40 \pm 0.05^a$

<sup>a,b,c</sup> Different letters in the same line indicate significant differences ( $P<0.05$ ). Red blood cell (RBC, M/ $\mu$ L), Hemoglobin (HGB, g/dL), Hematocrit (HCT, %), White blood cell (WBC, K/ $\mu$ L), Platelet (PLT, K/ $\mu$ L), Plateletcrit (PCT, %)

### Histopathological Examination Results

Vaginal tissue samples belong to nine of the bitches in group VH revealed thickening of squamous epithelium and significantly, loose and edematous connective tissue in the lamina propria. (Figure 1A). Histological diagnosis of the tumors in group VT were leiomyoma (n=3), fibroma (n=4), peripheral nerve sheath tumor (n=1) (Figure 1B), transmissible venereal tumor (TVT) (n=1) (Figure 1C) and leiomyosarcoma (n=1) (Figure 1D).



**Figure 1.** Histological features of vaginal hyperplasia and tumors

**1A.** Hyperplasia of the vagina. Mononuclear cell infiltrates and loose and edematous connective tissue in the lamina propria (HE staining, bar: 50  $\mu$ m)

**1B.** Benign peripheral nerve sheath tumor. Bundles of fusiform cells with areas of different cellular densities (HE staining, bar: 100  $\mu$ m)

**1C.** Transmissible Venereal Tumor (TVT). Sheets of round cells with vesicular nuclei and scanty stroma (HE staining, bar: 50  $\mu$ m)

**1D.** Leiomyosarcoma. Highly cellular, poorly organized irregular bundles and streams of spindle-shaped cells (HE staining, bar: 100  $\mu$ m)

## DISCUSSION AND CONCLUSION

In the present study, clinical, hematological and histopathological changes in the bitches with the vaginal masses (hyperplasia and tumor) and the bitches with healthy reproductive tract were evaluated. Johnston (20) reported that the mean age of the bitches with VH was to be between 1.5 to 2.7 years whereas Greenberg et al. (21) indicated the occurrence of VH in older bitches. In contrast with Johnston (20), the mean age of the affected bitches with VH was  $5.44 \pm 1.90$  years in this study. However, the mean age of the bitches with VT was reported as being more than 10 years (15, 16). In accordance with the previous reports (15, 16), the mean age of the affected bitches with VT was  $11.30 \pm 1.36$  years in the present study. The occurrence of VH was usually seen in intact bitches (5, 6, 20), except Nak et al. (3) reported the occurrence of VH in a bitch four months after spaying. In the present study, all of the bitches with VH were intact in accordance with previous studies (5, 6, 20). As Type 1 VFPs are usually overlooked by the owners, Type 2 and type 3 VFPs are more frequently seen in clinical presentation (5, 13). In the present study, absence of Type 1 VFP in group VH could be interpreted with the same occasion. The occurrence of VT was usually reported in intact bitches (22). However, there are two reports on the occurrence of VT in a spayed bitch (23) and in a hysterectomized Poodle bitch (24). Similar to findings of Klein (22), all of the bitches with VT were intact in the present study. Leiomyoma, fibroleiomyoma, fibroma and polyps are benign mesenchymal tumors that constitute 83% of vaginal tumors in bitches (14). In the study, fibroma and leiomyoma were the most frequent tumor types in group VT, as described by McEntee (14).

Total blood count and biochemical parameters were indicated within normal limits in bitches with VH (2, 25). In line with the previous reports, RBC values were not significantly different between group H and group VH ( $P > 0.05$ ). However, the HGB value in group VH was tended to reduce compared to group H ( $P = 0.05$ ) while HCT values in group VH was significantly lower than group H. It is related to the effect of oestrogen in the formation of VH. It has been reported that VH occurred as a result of strong response of vaginal mucosa to the oestrogens during pro-oestrous and early oestrus (2, 4, 18). Hyperestrogenism cause hypoplasia in bone marrow and in consequence of anemia (26). To our knowledge, this is the first report that demonstrates decreased levels of HGB and HCT in the presence of VH.

In this study, the lowest RBC, HGB and HCT values were observed in group VT. Besides, the mean HCT level in group VT was tended to be lower than group VH ( $P < 0.05$ ). These results could be explained by the paraneoplastic anemia occurrence as an initial symptom of malignancy in the presence of neoplasms (26, 27).

In veterinary oncology, the increase in circulating neutrophils in dogs may sometimes be related to different tumor types such as lymphoma, renal tubular carcinoma, primary lung tumor, rectal adenomatous polyp and metastatic fibrosarcoma (28). The highest WBC levels that observed at group VT is consistent with the studies indicating neutrophilic leukocytosis is one of the hematological signs of

neoplasms (26, 27). In addition to group VT, the mean WBC level in group VH was significantly higher than group H in this study. The protruding mass could be ulcerated or necrotic in prolonged cases and consequently the vaginal mucosa might be infected (2, 4). Similar with the previous reports, elevated WBC levels in group VH could be the result of vaginitis due to the necrosis or ulceration in protruding mass.

The PLTs participate in cancer progression, metastasis and prognosis (29-31). Thrombocytosis is associated with poor prognosis in humans with gynaecological (ovarian, endometrial, cervical) neoplasms (32). Elevated PLT levels were determined in bitches with malignant mammary tumors by the researchers (33). In this study, PLT and PCT levels were not statistically different related to the groups. The opposite results of this study were thought to be due to the absence of metastatic potential of VH and VT cases in bitches. However, PLT and PCT levels in type 2 VFP were tended to be higher than type 3 VFP. Carlin et al. (34) reported that women with severe pelvic organ prolapse had strong immunoreactivity to transforming growth factor  $\beta 1$  specific antibody. Besides, Anitua et al. (35) indicated that PLTs are a reservoir of many growth factors (GFs) that play a crucial role in hard and soft tissue repair mechanisms. Elevated levels of PLT and PCT in type 2 VFP might be associated with the growth factors crucial role in the prolapsed vaginal mucosa as Anitua et al. (35) reported. To our knowledge, this is the first report to give an insight into the differences on PLT indices related to the degree of VFP.

Gonadotropin releasing hormone (GnRH), human chorionic gonadotropine (hCG) (36) or progestagen (37) administration can be used for medical treatment of VH. In contrast with the previous reports (36, 37), surgical amputation of the prolapsed mass was performed for all types of VFP in this study (2, 12). Genital tract tumors are usually treated with surgery (22). However, Rollon et al. (38) reported a vaginal fibroma initially treated with a progesterone receptor antagonist before the surgical removal. In the present study, surgical amputation of neoplastic masses was performed with exception of the TVT case.

In conclusion, hematological changes in bitches with vaginal mass were evaluated and mild anemia and leukocytosis were determined in bitches with VH and VT. To our knowledge, this is the first report that demonstrates the detection of mild anemia in bitches with VH and the differences in PLT and PCT related to the degree of VFP.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest with respect to the publication of this manuscript.

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