JIVS JOURNAL OF ISTANBUL VETERINARY SCIENCES

Canine transmissible venereal tumor: etiology, diagnosis and treatment

Çağla Nur Küçükbekir[1], Zeynep Günay Uçmak[2], Çağatay Tek[2*]

1. Istanbul University-Cerrahpaşa, Institute of Graduate Studies, Istanbul, Turkey. 2. Istanbul University-Cerrahpaşa, Faculty of Veterinary Medicine, Department of Obstetrics and Gyneacology, Istanbul, Turkey. Küçükbekir, Ç. N. ORCID: 0000-0002-9687-1702, Günay Uçmak Z. ORCID: 0000-0003-2530-1291, Tek Ç. ORCID: 0000-0002-6429-658X.

Review Article

Volume: 5, Issue: 1
April 2021
Pages: 57-65

ABSTRACT

Transmissible venereal tumor (TVT) is a round cell type neoplasia that is transmitted by mating and physical transfer of tumor cells. It is one of the most common benign tumors in dogs that can be seen in both gender. The external genital area is the main location of the tumor. However, internal organ metastasis has been reported. The most common clinical signs are lobular masses which are seen in the caudal part of the penis, in the posterior region of the vagina and at the vestibulovaginal junction. Nodular lesions with rapid bleeding are the most pronounced clinical finding. Initially, the small tumor forms into a large ulcerated mass in the next periods. Simultaneously, the volume of the tumor increases and the lesions are seen multilobular, cauliflower-like, brittle, hyperemic, and hemorrhagic. The most practical diagnostic method of the tumor is vaginal cytology. Cytology findings are characterized by the round or oval cells which have, pale blue or colorless cytoplasm with cytoplasmic vacuoles and a prominent nucleus. Chemotheraphy is the most effective treatment method. The weekly intravenous administration of vincristine suplhate given for 3 weeks on average reveals that the treatment success rate is beyond 90%. In this review, etiology, clinical findings, diagnosis and treatment of TVT are presented .

Article History

Received: 18.02.2021
Accepted: 28.04.2021
Available online: 29.04.2021

Keywords: dog, neoplasia, vagina, venereal, vincristine

DOI: https://doi.org/10.30704/http-www-jivs-net.882280

To cite this article: Küçükbekir, Ç. N., Günay Uçmak, Z., Çağatay Tek, Ç. (2021). Canine transmissible venereal tumor: etiology, diagnosis and treatment. ***Journal of Istanbul Veterinary Sciences, 5*(1),** 57-65. **Abbreviated Title*: J. İstanbul vet. sci.***

Introduction

Transmissible venereal tumor (TVT) is one of the most uncontrolled tumors in dogs which spread through mating (Uçar, 2016). It can also be named as sticker tumor or sarcoma, venereal granuloma, infectious granuloma, canine condyloma, and infectious lymphosarcoma (Murhia et al., 2006; Regmi et al., 2020). This tumor is usually transmitted during mating (Tella et al., 2004) and mostly occur in young, sexually active animals (Rogers, 1997). It has been described as a benign reticuloendothelial tumor that mainly affects the external genitalia and less frequently the internal genitalia (Tella et al., 2004; Abedin, 2020). Although the metastasis of TVT is rarely seen, the metastasis is more frequently observed in immunocompromised animals (Rivera et al., 2005).Unlike the canine breeds have 78 chromosomes in nature, TVT cells have abnormal number of chromosomes ranging from 57 to 64, 59 on average. Transmissible venereal tumor is the only proven example of a naturally occurring tumor that is transmitted as an allograft by cell transplantation, and the tumor becomes autonomous apart from the original host (Abedin, 2020).

*Corresponding Author: Çağatay Tek
E-mail: catek@istanbul.edu.tr

Journal home page: www.jivs.net
http://dergipark.gov.tr/http-www-jivs-net

Ethiopathology

Transmissible venereal tumor was described as a contagious neoplasm by Novinsky (Novinsky, 1876). Although the exact source of TVT cells has been unclear, which is morphologically a round cell tumor, studies have revealed its histiocytic and mesenchymal origins. Since it has been thought to originate from lymphocytes, histiocytes and reticulum cells, its etiology is not fully defined yet. The presence of inclusion bodies in the cytoplasm of the tumor cell has lead to the suspicion of a viral agent (Do Amaral et al., 2007). Predisposing factors consist of the rapid increase in the number of stray dogs, aging, and the circumstances of the immune suppression. Because rapid tumor growth and metastasis can be seen in dogs whose immune system is suppressed (Chikweto et al., 2013). It is primarily found in dogs with a weakened immune system in the southern regions, especially in the Mediterranean (Hithem et al., 2020). Compromised immune system plays a major role in acquiring and spreading of TVT (Das et al., 2020). The cases can be listed as localized necrosis in some parts of the tumor or secondary bacterial infection (Vermooten, 1987; Das and Das, 2000; Kabuusu et al., 2010; Macotpet et al., 2019).

In many countries, TVT occurs between the ages of 2 and 8 in both genders (Smith and Washbourn, 1998; Boscos and Ververidis, 2004; Strakova and Murchison, 2014; Günay Uçmak et al., 2019). However, the bitches are more likely affected than male dogs. Incidence is high in urban areas where mating of young and sexually active stray dogs is not controlled (Hayes et al., 1983; Rogers, 1997; Das and Das, 2000; Gurel et al., 2002). Stray dogs are at risk factor for contracting and transmitting this disease (Hithem et al., 2020). It occurs mostly in tropical and subtropical climates (Hayes et al., 1983; Rogers, 1997; Uçar, 2016). Besides, the researchers reported that TVT is formed in the presence of ovarian remnant syndrome and stump pyometra cases in bitches (Sontaş et al., 2010; Turna Yılmaz et al., 2013). Ayala-Diaz et al. (2017) have been detected that the red, hemorrhagic and irregularly-edged TVT mass protrudes into the vaginal mucosa during pregnancy. After the diagnosis of a TVT, chemotherapy is suitable for the expectant mother to eliminate the tumor. However, it represents risks to the developing fetus. Salpingo-oophorectomy and hysterectomy might be preferred when the bitch is in the early period of pregnancy. A recovery period of 21 days and then chemotherapeutic treatment with Vincristine has been advised subsequent with the surgery. A 50% reduction after the second treatment, no obvious tumor mass on vaginal examination and tumor cells on cytological smears have been reported (Ayala-Diaz et al., 2017).

The disease is mainly observed on the mucosal surface of the external genitalia of male dogs and bitches (Kabuusu et al., 2010; Ostrander et al., 2016; Hiblu et al., 2019). The tumor is transmitted by living tumor cells from one dog to another by mating, licking, or sniffing. This explains cases occurring in the oral mucosa and nose (Purohit, 2009; Stockmann et al., 2011; Behera et al., 2012; Lopes et al., 2015). Neoplastic cells contaminated by physical contact are thought to be transferred to the genital system, nasal and oral mucosa, rectum or skin (Albanese et al., 2002; Do Amaral et al., 2007; Rezaei et al., 2016). Therefore, in primal TVT cases, it is possible to see lesions in the skin, face, nose or oral cavity, eyes and subcutaneous tissues along with the external genital area (Rogers, 1997; Das and Das, 2000; Brandao et al., 2002; Uçar, 2016; Kumar et al., 2018). Although tumors are located in the genital tract, extragenital cases have been observed including the conjunctival mucosa (Ferreira et al., 2000; Rodrigues et al., 2001) and central nervous system (Ferreira et al., 2000; Faccini et al., 2019). The presence of tumors involving the ocular area is less common than others, and TVT metastases occur by contact in these sides (Ginel et al., 1995; Souza et al., 2020). More aggressive and metastatic cases are observed in young dogs with poor body resistance and immunosuppression (Çeşme et al., 2015). It has been reported that TVT metastasis was also detected in the caudal mammary lobes of a 4 year old bitch (Günay Uçmak et al., 2019). In addition, TVT is seen in 5% of the extragenital organs other than genital localization. This placement is either together with the genital form or only extragenitally (Çeşme et al., 2015).

Clinical findings

Transmissible venereal tumor in male dogs usually occurs in the caudal part of the penis, from the corpus to the bulbous or glans penis (Das and Das, 2000). Clinical findings appear less striking in males. In affected males, bloody discharge, redness, deformation and ulceration can be seen in the preputial opening (Das and Das, 2000; Ferreira et al., 2000). Phimosis and paraphimosis can develop (Das and Das, 2000; Birhan and Chanie, 2015). In bitches, the development of TVT is mostly seen in the posterior wall of the vagina, and the vaginal vestibule (Stockmann et al., 2011). The affected bitches may have difficulty in urination or dystocia due to mechanical obstruction. Macroscopically, solitary or multiple tumor masses with cauliflower-like ulceration, hemorrhagic, friable and irregular appearance can be seen. Lesions are fragile and mostly hemorrhagic as a result of low cohesion between neoplastic cells. Therefore, the first clinical sign is tend to be bleeding (Ferreira et al., 2000; Faccini et al., 2019). Tumor size ranges from millimeters (mm) to several centimeters (cm) with a dark red to grayish pink color (Das and Das, 2000; Purohit, 2009; Lopes et al., 2015). Lesions are small (1 - 3 mm in diameter), superficial and colored pink to red at the onset of tumor formation (Purohit, 2009). Afterwards, the shape of the tumor takes on a cauliflower-like appearance. It has a fragile, red, hemorrhagic and hard structure. The mass can reach 5 - 7 cm in diameter. If the multilobular subcutaneous lesions invade to the deeper mucosal layers, the diameter of the mass may be reached to 10 - 15 cm. The mass is observed as petiolate, nodular, papillary and multilobule structures. The tumor can cover the orificium urethra externa and may protrude through the vulva labia (Purohit, 2009). The tumor surface is often inflamed and can be infected (Brown et al., 1980). Tumors can have petechial or simple bleeding as well as infection or ulceration (Das and Das, 2000; Ferreira et al., 2000; Purohit, 2009). Weakness, loss of appetite, constipation, refusal of mating and weight loss are less common symptoms (Ganguly et al., 2016). Laboratory result of a research (Boyd, 1983; Kerr, 2002) has been showed the increasing concentrations of leukocytosis, hemoconcentration, microcytic hypochromic regenerative anemia, hypernatremia, and Aspartate transaminase (AST), Alanine Transaminase (ALT), Alkaline phosphatase (ALP), and Creatine Kinase (CK). Microcytic hypochromic regenerative anemia is associated with hemorrhagic anemia due to severe bleeding on tumor, while hemoconcentration and hypernatremia are associated with dehydration. Leukocytosis is related to infection in and around the tumor tissue. Increased serum AST, ALT and ALP activities have been reported to be associated with liver damage, and increased AST and CK concentrations are related to muscle tissue damage (Boyd, 1983; Kerr, 2002).

Serosanguineous secretion, vulvar and preputial deformities may occur due to tissue damage, intense odor, ulceration and itching, aggression, and in severe cases, urinary retention in the affected area (Costa, 1999; Martins et al., 2005; Kolawole et al., 2020). Due to the risk of bacteriuria development in TVT affected animals, urinary retention can occur (Batamuzi and Kristensen, 1996). Prolonged serosanguineous vaginal discharge is seen in infected dogs (Purohit, 2009). The general health of the dogs is not compromised unless the lesions become infected and necrotic or the mass covers the urethral opening (Ganguly et al., 2016; Uçar, 2016).

Diagnosis

Diagnosis is mostly based on anamnesis, clinical findings, cytology and histopathology. As compared with other round cell tumors, TVT has a microscopic appearance to diagnose. Immunohistochemistry can be used to differentiate this neoplasm from other round cell tumors (Ferreira et al., 2000; Faccini et al., 2019). Prooestrus bleeding, cystitis, urethritis and prostatitis should be considered in the differential diagnosis (Das and Das, 2000).

Macroscopic Findings: Clinical symptoms vary according to the location of the tumors. On physical examination, small pink to red nodules are observed at 1 mm to 3 mm in diameter which can be visible 2 or 3 weeks after the TVT cell contamination. Initial lesions are superficial or pedunculated. Later, multiple nodules combine to form larger, red, bleeding, cauliflower-like masses (Aprea et al., 1994; Martins et al., 2005). There is

hemorrhagic discharge with genital localization of TVT in bitches. Lesions in males are usually cranially on the glans penis, preputial mucosa or bulbus glandis (Higgins, 1966; Mc Evoy, 1987; Martins et al., 2005). Regional lymph node involvement is common with large tumors in males. In bitches, tumors may be localized in the vestibule and / or caudal vagina, protruding from the vulva and often causing a deformation in the perineal region. Persistent hemorrhagic discharge may cause anemia. Rarely, TVT may be localized in the uterus (Aprea et al., 1994; Martins et al., 2005). Clinical diagnosis is usually more difficult in cases of TVT with extra genital localization because TVT cause various symptoms such as sneezing, nosebleeds, epiphora, shortness of breath and tooth loss, exophthalmos, skin lumps, regional lymph node enlargement and facial or oral deformation depending on the anatomical location of the tumor (Rogers, 1997; Martins et al., 2005). Definitive diagnosis is based on tumors, fine needle aspiration or physical examination and cytological findings (Moulton, 1978; Richardson, 1981; Daleck et al., 1987; Martins et al., 2005).

Cytological diagnosis: A definite diagnosis is made according to physical examination and cytological findings (Kroger et al., 1991). Since the cytology is non-invasive and painless method, it is the best choice for diagnosis. In addition to being simple and cheap, it causes much less deterioration in cell morphology than formalin-fixed biopsy samples (Das et al., 2020; Do Amaral et al., 2007). Cytological examination is a complementary test in a simple, fast, non-invasive and cost-effective method, which is guiding the appropriate type of treatment for the animal (Lopes et al., 2015). Wet fixation smears can be stained with Harris Hematoxylin and Eosin (Bancroft and Stevens, 1996). However, for air-drying preparations, Wright-Giemsa (WG), Wright's (W), MayGrünwald-Giemsa (MGG) and Leishman-Giemsa (LG) methods are used. Fixation of smears is performed by wet fixation with absolute isopropanol or 95% ethanol (Allen et al., 1986) for 20 minutes or immediately dried in air (Das et al., 2020). Also, TVT has a typical cytological appearance. The shape of cells in cytology ranges from round to oval structures. Cells mostly have a pale blue or colorless cytoplasm with a single distinctive nucleus. They also contain small, light, clear intracytoplasmic vacuoles, and numerous mitotic figures (Rogers, 1997; Hayes et al., 1983; Purohit, 2009).

Histological diagnosis: The definitive diagnosis is made by histopathological examination of the biopsy specimen. Large cells, round or oval vague contours are observed on histological examination. Another feature of this neoplasm is that it has inflamed cells and mitotic figures. The TVT can be confused with mastocytoma, histiocytoma and lymphoma. Therefore the importance of differential diagnosis should be emphasized (Do Amaral et al., 2007; Lopes et al., 2015). In histopathology, abundant round, oval or variable-shaped tumor cells are usually found around the blood or lymphatic vessels (Purohit, 2009; Birhan and Chanie, 2015). The size of the cell nucleus is larger than the size of the cytoplasm. Cytoplasmic vacuoles are often visible. The nuclei are oval or round and centrally-located, with delicate chromatin and large nucleoli; the cytoplasm is slightly acidophilic and contains finely granular, delicate vacuoles, and cells do not display anisokaryosis, anisocytosis, hyperchromasia or nuclear macrokaryosis. The cTVT is histopathologically classified based on the predominant cell type as lymphoid, plasmacytoid or mixed. The lymphoid type of tumor predominantly includes cells with a rounded morphology, scant and finely granular cytoplasm, the presence of vacuoles, and round nuclei with coarse chromatin and the presence of one or two evident nucleoli. In plasmacytoid tumors, most cells have an ovoid morphology, a smaller relative nucleus: cytoplasm ratio and eccentrically-located nucle. Cytoplasm is slightly basophilic and usually small and slightly multiple vacuoles accompanying the cell board (Stockmann et al., 2011). Lymphocytes, plasma cells, and macrophages are frequently observed (Birhan and Chanie, 2015). Tumor growth leads to tightly integrated, irregular cell formation, with fibroblasts forming between them (Purohit, 2009). Immunohistochemistry can be used in the diagnosis of metastatic tumors following a combination of clinical findings (Birhan and Chanie, 2015; Uçar, 2016).

Molecular Diagnosis: Transmissible venereal tumor has a molecular property based on

rearrangement of a c-myc gene that is not found in normal somatic cells, gametes and other tumor cells (Katzir et al., 1985). Transmissible venereal tumor cells allow a diagnostic polymerase chain reaction (PCR) based on the diagnosis of nuclear elements (LINE) added to the stream of a myc gene. Therefore, the presence of this LINE element near c-myc (LINE-c-myc) has been used for the definitive diagnosis of TVT cases using in situ polymerase chain reaction (PCR) and conventional PCR in controversial cases (Liao et al., 2003; Park et al., 2006). Generally, the PCR test has increased the accuracy of the diagnosis. It may also facilitate the decision to terminate chemotherapy by performing the diagnosis between tumor cells and fibrotic tissue (Setthawongsin et al., 2016).

Auxiliary diagnosis: Doopler ultrasonography can be used to evaluate the blood flow in the tissue / organ, where metastasis occurs in TVT cases and it may also be useful to examine vascular perfusion in the affected tissues (Günay Uçmak et al., 2019).

Treatment

Radiotherapy, chemotherapy, immunotherapy, biotherapy and excisional surgery can be applied for the treatment of TVT (Purohit, 2009; Günay Uçmak et al., 2019). Self-healing may occur following the animal's immune system fight the tumor cells (Andrade et al., 2009; Lapa et al., 2012).

The preferred treatment for TVT is chemotherapy. Recently, many agents and chemotherapy protocols such as cyclophosphamide, vincristine sulfate, vinblastine, doxorubicin and methotrexate are widely used. These drugs are used as a single agent or in combination with each other. The most effective, safe and appropriate treatment in clinical practice is the use of vincristine sulfate as a single agent. Immunotherapy should be performed by using substances effective on the immune system in immunocompromised animals (Das and Das, 2000). However, the widespread use of vincristine in TVT treatment and the presence of malignant neoplasm features have increased the number of applications of the drug. The resistance against vincristine has been associated with overexpression of a protein molecule called P-glycoprotein of the plasma membrane (Pouliot et al., 1997). This molecule found in various tissues such as kidney, liver, colon, brain, lung, peripheral blood, and normal bone marrow. Tumors derived from tissues expressing high amounts of P-glycoprotein exhibit intrinsic resistance to chemotherapy (Gaspar et al., 2010). Because this molecular membrane acts as both a carrier and a flow pump dependent on the energy produced by ATP hydrolysis (Korystov et al., 2004; Gaspar et al., 2010). The studies (Andrade et al., 2009) have shown that vincristine sulfate in combination with ivermectin is beneficial. Because this antiparasitic drug is used as P-glycoprotein substrate, that reduces the amount of molecules in the tissue. Thus it strengthens the antitumor therapy and slows the treatment resistance (Andrade et al., 2009; Lopes et al., 2015).

Favorable results were obtained from the intravenous (iv) use of vincristine sulfate, a chemotherapeutic agent, at doses of 0.5 - 0.7 mg / m2 body surface area or 0.025 mg / kg once a week for approximately three weeks (Amber et al., 1990; De Lorimier and Fan, 2007). Before the starting chemotherapy with vincristine sulfate, the animal's general health should be evaluated. It is important to analyze the total blood count weekly during treatment (Ganguly et al., 2016). The vincristine sulfate should be diluted with a isotonic solution and this combination should be administered as a very slow iv infusion. The drug should be avoided from direct sunlight. Treatment should be continued until the symptoms disappear and the duration of administration is approximately 2 - 6 weeks. The overall success rate varies between 90 - 95% (De Lorimier and Fan, 2007). Male dogs treated with vincristine sulfate may experience a temporary deterioration in semen quality, which rapidly returns to normal within 15 days following the last administration (Saratsis et al., 2000; Gobello and Corrada, 2002). Following chemotherapy, a marked regression of neoplastic formation usually begins two weeks after the first treatment. Although no significant decrease was detected in AST and ALP enzymes, a significant decrease in total serum protein, hemoglobin, total erythrocyte and total leukocyte count can be observed. Possible side effects of the

chemotherapeutic agent include loss of appetite, vomiting, diarrhea, myelosuppression, and alopecia. When the desired result is not obtained from vincristine sulfate, doxorubicin can be used as iv at a dose of 1 mg / kg for a maximum of 3 weeks (Amber et al., 1990). One of the treatment approaches for the TVT is also the combination of vincristine sulfate (0.0125 mg / kg / week, iv), methotrexate (0.3 – 0.5 mg / kg / week, iv) and cyclophosphamide (1 mg / kg / day). It should also be used until visible symptoms disappear. The application takes about 4 - 6 weeks (Purohit, 2009). Although adriamycin (30 mg / m^2, every three weeks, iv) is also effective, it should only be used when vincristine sulfate is not effective due to the side effects of adriamycin (De Lorimier and Fan, 2007). Good prognosis can be expected in most TVT cases after the treatment with chemotherapy (Vermooten, 1987; Rogers, 1997; Uçar, 2016).

Surgery can also be performed in the treatment of TVT. Although surgery can be effective for small and localized tumors, postoperative recurrence rate can be up to 30 - 75% in metastatic cases (De Lorimier and Fan, 2007). During surgery, the surgical site may be contaminated with TVT cells and this increase the risk of recurrence (De Lorimier and Fan, 2007; Purohit, 2009). Therefore, surgery is not usually preferred treatment method for TVT. However, cauterization, electrosurgery, or cryosurgery can be utilized to prevent recurrence of TVT after surgery (Idowu, 1985; Rao et al., 1993; Hoque, 1995; Das et al., 2020).

As an alternative to chemotherapy treatment for TVT, radiotherapy can be used in treatment-resistant lesions or lesions in the brain, testicle, or eyes. However, the main disadvantages of this method are the difficulties in implementation, the lack of sufficient equipment, the economical burden of the equipment, and the need for longer application time compared to chemotherapy (Rivera et al., 2005).

Biotherapy for TVT treatment has limited effect. Three weeks of intratumoral Bacillus Calmette-Guérin (BCG) application has low success (Johnston, 1991). High recurrence rates have been reported following treatment (Richardson, 1981; Vermooten, 1987).

Conclusion

In conclusion, etiology, clinical findings, diagnotic and treatment options of TVT were reviewed. The TVT is more common in sexually active and stray male and female dogs. Preventive approaches and appropriate treatment methods are very important in terms of restrain the spread of the disease. The recovery rate is high when TVT is accurately treated. When a long treatment period is considered, the protective approaches for TVT become important.

Acknowledgement

This review did not receive any specific grant from funding agencies in the public, commercial or not for profit sectors.

References

Abedin, S. N. (2020). Canine transmissible venereal tumor: A review. *Journal of Entomology and Zoology Studies, 8*(2), 596-599.

Albanese., F, Poli, A., Millanta, F. & Abramo, F. (2002). Primary cutaneous extragenital canine transmissible venereal tumour with Leishmania laden neoplastic cells: a further suggestion of histiocytic origin. *Veterinary Dermatology, 13,* 243-246.

Allen, S. W., Prasse, K. W. & Mahaffey, E. A. (1986). Cytologic differentiation of benign from malignant canine mammary tumours. *Veterinary Pathology, 23,* 649-655.

Amber, E. I., Henderson, R. A., Adeyanju, J. B. & Gyang, E.O. (1990). Single-drug chemotherapy of canine transmissible venereal tumor with cyclophosphamide, methotrexate, or vincristine. *Journal of Veterinary Internal Medicine, 4,* 144-147.

Andrade, S. F., Sanches, O. C., Gervazoni, E. R., Lapa, F. A. S. & Kaneko, V. M. (2009). Comparação entre dois protocolos de tratamento do tumor venéreo transmissível em cães. *Clínica Veterinária, 14*(82), 56 -62.

Aprea, A. N., Allende, M. G. & Idiard, R. (1994). Tumor venéreo transmisible ıntrauterino: descripción de un caso. *Veterinaria Argentina XI, 103*, 192-194.

Ayala-Diaz, S., Medina, D. A. V., Lizano, M. & Manzo-Merino, J. (2017). Transmissible cancer: a canine transmissible venereal tumor during pregnancy, case report. *Journal of Cancer Research, 1*(1), 1-4.

Bancroft, J. D. & Stevens, A. (1996). *Theory and Practice of Histological Techniques. 3rd ed.*

Batamuzi, E. K. & Kristensen, F. (1996). Urinary tract infection: the role of canine transmissible venereal tumour. *Journal of Small Animal Practice, 37,* 276-279.

Behera, S. K., Kurade, N. P., Monsang, S. W., Das, D.P. & Mishra, K.K. (2012). Clinico-pathological findings in a case of canine cutaneous metastatic transmissible venereal tumor. *Veterinarski Arhiv, 82* (4) 401 – 410.

Birhan, G. & Chanie, M. (2015). A review on canine transmissible venereal tumor: from morphologic to biochemical and molecular diagnosis. *Academic Journal of Animal Diseases, 4*(3), 185-195.

Boscos, C. M. & Ververidis, H. N. (2004, October 6-9). TVT-Clinical findings, diagnosis and treatment. In: Proceedings of the 29th *World Congress of the World Small Animal Veterinary Association. Rhodes, Greece*.

Boyd, J. (1983). The mechanisms relating to increases in plasma enzymes and isoenzymes in diseases of animals. *Veterinary Clinical Pathology, 12*, 9-24.

Brandão, C. V. S., Borges, A. G., Ranzani, J. J. T., Rahal, S.C., Teixeira, C.R. & Rocha, N.S. (2002). Tumor venéreo transmissível: estudo retrospectivo de 127 casos (1998-2000). *Revista de Educação Continuada, 5*(1), 25-31.

Brown, N. O., Calvert, C. & Mac Ewen, E. G. (1980). Chemotherapeutic management of transmissible venereal tumour in 30 dogs. *Journal of the American Veterinary Medical Association*, 176, 983-986.

Chikweto, A., Kumtheka, S., Larkin, H., Deallie, C., Tiwari, K. P., Sharma, R. N. & Bhaiyat, M. I. (2013). Genital and extragenital canine transmissible venereal tumor in dogs in Granada, West Indies. *Open Journal of Veterinary Medicine, 3 (2),* 111-114.

Costa, M. T. (1999). O tumor venéreo transmissível canino. *Revista de Educação Continuadaem Medicina Veterináriae Zootecnia do CRMV-SP, 2*(3), 46 – 52.

Çeşme, H., İpek, V., Akkoç, A. & Salcı, H. (2015). Bir köpekte primer intranazal transmissible venereal tümör (tvt). *Uludag University Journal of the Faculty of Veterinary Medicine, 1*(2), 85-88.

Daleck, C. L. M., Ferreira, H. I., Daleck, C. R. & Santana, A.E. (1987). Novos estudos sobre o tratamento do tumor venéreo transmissível canino. *Ars Veterinaria, 3*(2),203-209.

Das, D., Kumthekar, S., Manikantha, K. G. V. & Achary, K.H. (2020). Sticker tumour (Transmissible venereal tumour) in dog. *The Pharma Innovation Journal, SP-9(*9), 126-130.

Das, U. & Das, A. K. (2000). Review of canine transmissible venereal sarcoma. *Veterinary Research Communications, 24*(8), 545-556.

De Lorimier, L. P. & Fan, T. M. (2007). Canine transmissible venereal tumour. In: Withrow SJ, Vail DM (Ed). Withrow & MacEwen's *Small animal clinical oncology 4th ed.* (pp. 799-804). Elsevier, USA: Saunders.

Do Amaral, A. S., Bassani-Silva, S., Ferreira, I., Da Fonseca, L. S., De Andrade, F. H., Gaspar, L. F. J. & Rocha, N. S. (2007). Cytomorphological characterization of transmissible canine venereal tumor. *Revista Portuguesa de ciências veterinárias, 102*:253-260.

Faccini, L. S., Legramanti, W. M., Castro, L. T., Coelho, A. C. B., Teixeira, M. C., Shild, A. L. & Pereira, C. M. (2019). multiple metastases of a transmissible venereal tumor in a dog. *Acta Scientiae Veterinariae, 47*(Suppl 1), 444.

Ferreira, A. J. A., Jaggy, A., Varejão, A. P., Ferreira, M. L. P., Correia, J. M. J., Mullas, J. M., Almeida, O., Oliveira, P. & Prada, J. (2000). Brain and ocular metastases from a transmissible venereal tumour in a dog. Journal of Small Animal Practice, 41(4): 165-168.

Ganguly, B., Das, U. & Das, A.K. (2016). Canine transmissible venereal tumour: A review. *Veterinary and Comparative Oncology, 14*(1), 1-12.

Gaspar, L. F. J., Ferreira, I., Colodel, M. M., Brandao, C. V. S. & Rocha, N. S. (2010). Spontaneous canine transmissible venereal tumour: cell morphology and influence on P-glycoprotein expression. *Turkish Journal of Veterinary and Animal Sciences, 34,* 447-454.

Ginel, P. J., Molleda, J. M., Novales, M., Martin, E., Margarito, J. M. & Lopez, R. (1995). Primary transmissible venereal tumor in the nasal cavity of a dog. *Veterinary Record, 136*, 222-223.

Gobello, C. & Corrada, Y. (2002). Effects of vincristine treatment on semen quality in a dog with a transmissible venereal tumour. *Journal of Small Animal Practice, 3*, 416-417.

Gurel, A., Kuscu, B., Gulanber, E.G. & Arun, S.S. (2002). Transmissible veneral tumors detected in the extragenital organs of dogs. *Israel Journal of Veterinary Medicine, 57*(2), 23-26.

Günay Uçmak, Z., Kırşan, I., Uçmak, M., Erdoğan Bamaç, Ö. & Gürel, A. (2019). Clinical approaches for genital and extragenital metastasis of transmissible venereal tumor in a bitch with ovarian remnant syndrome. *Ankara Üniversitesi Veteriner Fakültesi Dergisi,* 417-421.

Hayes, H. M., Biggar, R. J., Pickle, L. W., Hoover, R. & Toft, J. D. (1983). Canine transmissible venereal tumor: a model for Kaposi's sarcoma. *American Journal of Epidemiology, 117*, 108-109.

Hiblu, M. A., Khabuli, N. M. & Gaja, A. O. (2019). Canine transmissible venereal tumor: First report of three clinical cases from Tripoli, Libya. *Open Veterinary Journal, 2*, 103-105.

Higgins, D. A. (1966). Observations on the canine transmissible venereal tumor as seen in the Bahamas. *Veterinary Record, 79*(3), 6771.

Hithem, B., Said, B., Abdelaziz, A., Khouloud, B. & Adel, A. (2020). Surgical treatment of transmissible venereal tumor (sticker sarcoma). *Bangladesh Journal of Veterinary Medicine, 18*(1), 25-29.

Hoque, M. (1995). Different modes of therapy for canine transmissible venereal tumor. *Veterinarian, 19,* 1-2.

Idowu, A. L. (1985). Cryosurgery of canine transmissible venereal tumor. *Tropical Veterinarian, 3,* 74-78.

Johnston, S. D. (1991). Performing a complete canine semen evaluation in a small animal hospital. *Veterinary Clinics of North America Small Animal Practice, 21*(3), 545-551.

Kabuusu, R. M., Stroup, D. F. & Fernandez, C. (2010). Risk factors and characteristics of canine transmissible venereal tumours in Grenada, West Indies. *Veterinary and Comparative Oncology, 8*(1), 50-55.

Katzir, N., Rechavi, G., Cohen, J. B., Unger, T., Simoni, F., Segal, S., Cohen, D. & Givol, D. (1985). "Retroposon" insertion into the cellular oncogene c-myc in canine transmissible venereal tumor. *Proceedings of the National Academy of Sciences, 82*, 1054-1058.

Kerr, M. G. (2002). Clinical biochemistry and haematology. In: Veterinary Laboratory Medicine 2nd ed. (pp. 135-147). USA: Blackwell Science Ltd.

Kolawole, B. J., Samuel, U. F., Erin, J. P. & Ifenkwe, D. C. (2020). Canine transmissible venereal tumour in four year old bull mastiff dog: a case report. *Animal Research International, 17*(2), 3723-3728.

Korystov, Y. N., Ermakova, N. V., Kublik, L. N., Levitman, M. K. H., Shaposhnikova, V. V., Mosin, V. A., Drinyaev, V. A., Kruglyak, E. B., Novik, T. S. & Sterlina, T. S. (2004). Avermectins inhibit multidrug resistance of tumor cells. *European Journal of Pharmacology, 493*, 57-64.

Kroger, D., Grey, R. M. & Boyd, J. W. (1991). An unusual presentation of canine transmissible venereal tumor. *Canine Practice, 16*(6), 17-21.

Kumar, D., Kumar, A., Kumar, P., Lal Yadava, C. & Yadav, S. P. (2018). Ovarian remnant syndrome: A review. *Journal of Entomology and Zoology Studies, 6*(6), 1139-1142

Lapa, F. A. S., Andrade, S. F., Gervazoni, E. R., Kaneko, V. M., Sanches, O. C. & Lrag, F. (2012). Histopathological and cytological analysis of transmissible venereal tumor in dogs after two treatment protocols. *Colloquium Agrariae, 8*, 36-45.

Liao, K. W., Lin, Z. Y., Pao, H. N., Kam, S. Y., Wang, F. I. & Chu, R. M. (2003). Identification of canine transmissible venereal tumor cells using in situ polymerase chain reaction and the stable sequence of the long interspersed nuclear element. *Journal of Veterinary Diagnostic Investigation, 15,* 399-406.

Lopes, P. D., Santos, A. C. A. A. & Silva, J. E. S. (2015). Canine transmissible venereal tumor in the genital area with subcutaneous metastases in the head - case report. *Revista Portuguesa de Ciências Veterinárias, 110(*593-594), 120-123.

Macotpet, A., Pattarapanwichien, E. & Suksawat, F. (2019). Single-agent L-asparagenase for the treatment of vincristine and doxorubicin-resistant canine transmissible venereal tumour. Veterinary Practitioner, 20(1).

Martins, M.I.M., Souza, F.F. & Gobello, C. (2005). The

canine transmissible venereal tumor: etiology, pathology, diagnosis and treatment. Recent Advances in Small Animal Reproduction, A1233.0405.

Mc Evoy, G. K. (1987). American hospital formulary service drug information. In: Bethesda, md. *American society of hospital and pharmacists.*

Moulton, J. E. (1978). Tumor of genital systems. In: Moulton JE (Ed). *Tumors in domestic animals 2 ed*. (pp. 326-330).California: University of California.

Murgia, C., Pritchard, J. K., Kim, S. Y., Fassati, A. & Weiss, R. A. (2006). Clonal origin and evolution of a transmissible cancer. Cell, 126(3), 477-487.

Novinsky, M. A. (1876). Zur frage über die ımpfung der krebsigen geschwülste. *Zentrum für Medizinische Wissensch, 14*, 790-791.

Ostrander, E. A., Davis, B. W. & Ostrander, G. K. (2016). Transmissible tumors: breaking the cancer paradigm. *Trends Genet, 32*, 1-15.

Park, M. S., Kim, Y., Kang, M. S., Oh, S. Y., Cho, D. Y., Shin, N. S. & Kim, D. Y. (2006). Disseminated transmissible venereal tumor in a dog. *Journal of Veterinary Diagnostic Investigation, 18*, 130-133.

Pouliot, J. F., L'Heureux, F., Liu, Z., Prichard, R. K. & Georges, E. (1997). Reversal of glycoprotein- P associated multidrug resistance by ivermectin. *Biochemical Pharmacology, 53*, 17-25.

Purohit, G. (2009). Canine transmissible venereal tumor: A review. *The Internet Journal of Veterinary Medicine, 6*(1), 1-7.

Rao, T. M., Kumar, V. G., Raghvender, K. B. P., Joshi, M. R. & Rao, R. L. N. (1993). Cryosurgical treatment of transmissible venereal tumors. *Journal of Veterinary Medicine and Animal Sciences, 24*, 149-152.

Regmi, S., Mahato, P., Devkota, I., Neupane, R. P., Khulal, A. & Tiwary, A. K. (2020). A Case report on canine transmissible venereal tumor. *Journal of Zoological Research, 2*(2), 12-14.

Rezaei, M. S., Azizi, S., Shahheidaripour, S. & Rostami, S. (2016). Primary oral and nasal transmissible venereal tumor in a mix-breed dog. *Asian Pacific Journal of Tropical Biomedicine, 6*(5), 443-445.

Richardson, R. C. (1981). Canine transmissible veneral tumor. *Compendium on Continuing Education for the Practising Veterinarian, 3*, 951-956.

Rivera, B., Ahrar, K., Kangasniemi, M. M., Hazle, J. D. & Price, R. E. (2005). Canine transmissible venereal tumor: A large-animal transplantable tumor model. *Comparative Medicine, 55*(4), 335-343.

Rogers, K. S. (1997). Transmissible venereal tumor. *Compendium on Continuing Education for the Practising Veterinarian, 19*(9),1036-1045.

Saratsis, P. H., Ypsilantis, P. & Tselkas, K. (2000). Semen quality during vincristine treatment in dogs with transmissible venereal tumor. *Theriogenology, 53* (5), 1185-1192.

Schneider, R. (1978). General Considerations. In: Moulton JE (Ed). *Tumors of domestic Animals 2nd ed.* (pp. 1-15). Berkeley, USA: University of California Press.

Setthawongsin, C., Techangamsuwan, S., Tangkawattana, S. & Rungsipipat, A. (2016). Cell-based polymerase chain reaction for canine transmissible venereal tumor (ctvt) diagnosis. *The Journal of Veterinary Medical Science, 78(*7),1167-1173.

Smith, G. B. (1998). Infective sarcomata in dogs. *British Medical Journal, 2*, 1346-1347.

Sontaş, H., Altun, D., Turna Yılmaz, Ö., Arun, S., Şenünver, A. & Ekici, H. (2010). bir köpekte eş zamanlı seyreden ovaryan remnant sendromu, bulaşıcı veneral tümör ve stump pyometra olgusu. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi,* 16 (4): 675-680.

Souza, V. J. T., Rorig, M. C. L., Possamai, L. M. & Ferreira, C. H. (2020). Tumor venéreo transmissível na córnea de um cão: relato de caso. *Pubvet, 14*(6), 1-10.

Stockmann, D., Ferrari, H. F., Andrade, A. L., Lopes, R. A., Cardoso, T. C. & Luvizotto, M. C. R. (2011). Canine transmissible venereal tumors: aspects related to programmed cell death. *Brazilian Journal of Veterinary Pathology, 4*(1), 67-75.

Strakova, A. & Murchison, E. P. (2014). The changing global distribution and prevalence of canine transmissible venereal tumor. *BMC Veterinary Research, 10*(168),1-10.

Tella, M. A., Ajala, O. O. & Taiwo, V. O. (2004). Complete regression of transmissible venereal tumor (TVT) in Nigerian mongrel dogs with vincristine sulphate chemotherapy. *African Journal of Biomedical Research, 7*(3), 133-138.

Thomson, R. G. (1984). *General Veterinary Pathology*. London, Philadelphia, US: W.B.Saunders Company.

Turna Yılmaz, Ö., Uçmak, M., Günay, Z. & Kırşan, I. (2013). Vaginal fold prolapse and transmissible venereal tumour related to ovarian remnant syndrome in a bitch: a case report. *Veterinary Medicine, 58*(12), 628-632.

Uçar, M. (2016). Transmissible venereal tumor: A Review. *Kocatepe Veterinary Journal, 9*(3):230-235.

Vermooten, M. I. (1987). Canine transmissible venereal tumour (TVT): a review. *Journal of the South African Veterinary Association, 58*, 147-150.