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Review Article

An Overview Diagnosis and Treatment Methods in Cases of Transmissible Venereal Tumor in Female Dogs

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ABSTRACT

The aim of this review is to examine an overview diagnostic and treatment methods applied in cases of transmissible venereal tumors (TVT) in female dogs. TVT is a highly transmissible neoplasm affecting dogs of all ages, breeds, and genders, primarily involving the genital areas and organs such as the eyes, nose, and mouth. Various clinical manifestations are observed depending on its localization. In cases involving the genital system, cauliflower-like neoplastic masses, bloody vulvar discharge, and consequent anemia may occur. All these clinical findings, along with histopathological or cytological examinations of tissue samples obtained through methods such as excisional biopsy or fine needle aspiration biopsy, can lead to a definitive diagnosis. Once a definitive diagnosis is made, various treatment options are available, including surgical excision of tumor tissue, chemotherapy using agents such as vincristine, doxorubicin, cyclophosphamide, methotrexate, and lomustine, radiotherapy with specific dose ranges, and immunotherapy using agents like *Bacillus Calmette-Guérin* and *staphylococcal* protein A. In conclusion, with the correct diagnosis, every patient can be individually evaluated and provided with the most appropriate treatment option to ensure recovery.

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Dişi Köpeklerde Transmissible Venereal Tümör Vakalarında Tanı ve Tedavi Yöntemlerine Genel Bakış

ÖZET

Bu derlemenin amacı dişi köpeklerde görülen transmissible veneral tümör olgularında uygulanan güncel tanı ve tedavi yöntemlerini incelemektir. Transmissible veneral tümör dişi köpekler başta olmak üzere köpeklerin tüm yaş, ırk ve cinsiyet gruplarında; özellikle iç-dış genital bölge ve göz, burun, ağız gibi organları etkileyen çok bulaşıcı bir neoplazidir. Lokalizasyonuna göre çok farklı klinik bulgulara rastlanmaktadır. Genital sistemi tutan olgularda karnabahar benzeri neoplazik kitle, kanlı bir vulvar akıntı ve buna bağlı olarak anemi tablosu görülmektedir. Tüm bu klinik bulgular, eksizyonel biyopsi, ince iğne aspirasyon biyopsisi gibi yöntemlerle alınan doku örneklerinin histoplatolojik veya sitolojik muayeneleri ile değerlendirilerek kesin teşhise gidilebilmektedir. Kesin teşhisi yapılan olgularda tümöral dokunun alındığı cerrahi; vinkristin, doksorubisin, siklofosfamid, metotreksat ve lomustin gibi ajanların uygulandığı kemoterapi; belirli doz aralığında radyasyon uygulanan radyoterapi ve *Bacillus Calmette-Guérin*, staflilokok protein A etkenlerinin kullanıldığı immünoterapi gibi birçok farklı tedavi seçeneği bulunmaktadır. Sonuç olarak doğru teşhisi koyulan her hastanın, bireysel olarak değerlendirilerek seçilen en uygun tedavi seçeneği ile iyileşmesi sağlanabilmektedir.

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INTRODUCTION and TRANSMISSIBLE VENERAL TUMOR

Vaginal and vulvar tumors constitute approximately 2.5-3% of all tumors in dogs. Among these, Transmissible Venereal Tumor (TVT) is the most frequently observed type, accounting for 11-63% of cases in the vagina and vulva (Nak and Kaşıkçı, 2019). This percentage may vary due to the disease being spread by free-roaming stray dogs. Additionally, TVT is not limited to the vulva and vagina; it can also occur in areas such as the skin, nose, mouth, and eyes. It can be observed in dogs of all ages and is found in both males and females (Abedin, 2020; Abeka, 2019; Martins, Gobello, and Souza, 2005).

The aim of this review is to examine current approaches for accurately diagnosing common cases of TVT in female dogs and determining the most appropriate treatment options.

TVT is a highly transmissible neoplasm of reticuloendothelial origin that can affect both external and internal genital organs, especially in the genital area. It can also be referred to as *infectious sarcoma*, *venereal granuloma*, or *contagious lymphosarcoma*. Although it primarily affects young animals, it can be seen in all age groups. There is a higher incidence of TVT in females compared to male dogs, but male dogs are the main transporters of TVT transmission. No breed predisposition has been identified (Abeka, 2019). In the early stages of the disease, it was thought to be viral in origin. However, research has shown that the agent cannot be a virus. Transmission primarily occurs through the transfer of neoplastic cells during mating. Additionally, neoplasms can be found on body parts such as the nose, eyes, and oral mucosa during behaviors such as licking and sniffing. Any damage to the relevant mucosa makes transmission easier (Abedin, 2020; Murgia et al., 2006). Metastasis to surrounding tissues is rarely reported; however, metastases are commonly found in regional lymph nodes surrounding the neoplastic tissue. In the case of oral TVT, it is reported to spread to the lips and tonsils (Abedin, 2020).

DIAGNOSTIC APPROACHES

Although some physical examination findings such as history and hyperemia around the vulva, cauliflower-like neoplastic mass, serous discharge may suggest the presence of TVT, neoplastic structure cytology and/or histopathologically should be evaluated for a definite diagnosis. For these evaluations, vaginal smear test, fine needle aspiration biopsy or excisional biopsy may be preferred (Abeka, 2019).

Clinical Findings

Depending on the localization of neoplastic tissue, different clinical symptoms can be encountered. However, these symptoms may not always be sufficient for a differential diagnosis. For instance, symptoms such as sneezing, tooth loss, bad breath, exophthalmos can be observed, which may be confused with various other diseases (Abeka, 2019).
In severe cases of TVT involving the genital system, cauliflower-like neoplastic tissue is observed protruding from the vulvar lips. Additionally, there is intense hemorrhagic vulvar discharge, leading to anemia. This vulvar discharge can attract male dogs to bitches, and therefore, pet owners may interpret the discharge as spontaneous proestrus bleeding (Abedin, 2020; Abeka, 2019).

Histopathological Findings

After excisional biopsy samples are obtained from the neoplastic tissue under local anesthesia, they can be stained with hematoxylin-eosin and examined according to pathological principles. In examinations, high mitotic activity, polychromasia, and abundant cytoplasmic pleomorphic neoplastic cells are observed (Abeka, 2019; Mukaratirwa and Gruys, 2003; Park et al., 2006).

Cytological Findings

It is highly preferred due to being minimally invasive, cheap, simple, and less painful. Additionally, the detection methods required for histopathological examination cause significant distortion in cell morphology. In contrast, morphological distortion is much less in cytological examination. It particularly yields a very high rate of accurate positive results in cases of TVT affecting the external genital system (Abedin, 2020; Abeka, 2019).

In cases where the external genital organs are affected, samples should be obtained using a gynecological sample brush, while in cases affecting the internal genital organs, samples should be obtained using fine needle aspiration biopsy. These samples should then be stained using one of the Giemsa or Romanowsky staining methods for examination. Based on the predominant cell type of the tumor, the examinations can be categorized into three groups (Abeka, 2019; Nepomuceno de Oliveira et al., 2022).

The cells observed in the first group, which is the lymphoid-type tumor, generally have round morphologies. They contain round nuclei with scant cytoplasm and thick chromatin (Nepomuceno de Oliveira et al., 2022). The cells observed in plasmacytic-type tumors typically have ovoid morphologies. The nucleus size and cytoplasmic volume are smaller compared to the lymphoid type. These cells are considered malignant (Abeka, 2019).

In cases where both lymphoid-type and plasmacytic-type cells are observed together, it is termed as a mixed-type tumor (Nepomuceno de Oliveira et al., 2022).

TREATMENT APPROACHES

There are various treatment protocols available for TVT cases, including surgical, chemotherapy, immunotherapy, and radiotherapy, either individually or in combination. Each patient should be evaluated individually, considering factors such as the patient's overall condition, localization, and severity of the disease, and a treatment protocol should be selected accordingly.

Surgery

In cases where the tumor has not metastasized, surgical removal of the tissue is highly successful. If the tumor is small, easily accessible, and in clinical stage 1, surgical methods can be used. However, contamination of the surgical site with TVT cells can lead to recurrence in patients. Therefore, the combined use of surgical and chemotherapeutic methods is recommended (Abeka, 2019). In cases of larger tumors, surgical methods have been reported to result in recurrence rates of 50-68% (Ferreira et al., 2017; Martins et al., 2005). Electrocautery and cryosurgery are preferred surgical methods (Vicky Bahr Arias et al., 2016). However, due to recent success in chemotherapy applications in TVT cases, surgery is not recommended.

Chemotherapy

In modern times, many chemotherapy treatments are available that eliminate the risk of anesthesia associated with surgical operations. There are numerous protocols available for individual or combined use of drugs such as Vincristine, Cyclophosphamide, Doxorubicin, Methotrexate, Lomustine, and Vinblastine, with Vincristine being the most preferred (Table 1) (Abeka, 2019; Martins et al., 2005; Sewoyo and Made Kardena, 2022).

Vincristine is the most preferred and most reliable chemotheropeutic agent that can used even cases with metastase outside the genital organs. In cases lasting less than one year, there is a success rate of nearly 100% (Abeka, 2019).

Vincristine is an agent that inhibits the cell division during the metaphase stage. For this reason, it should be administered slowly and ensure that it does not inflitrate to subcutaneous tissue during the intravenous administrations (Küçükbekir et al., 2021).

Doxorubicin is a chemotherapeutic agent commonly used in carcinoma-type tumors such as hemangiosarcoma, osteosarcoma and lymphoma. Some researchers have indicated successful result when used in patients developing resistance of Vincristine. However doxorubicin has cardiotoxicity, which can lead to a decrase in systolic functions and arrhytmias. Therefore, it should be used with great care, especially in patients with cardiovascular disorders (Çizmeci et al., 2012; Sewoyo and Made Kardena, 2022).

Lomustine is a chemotherapeutic agent that can cross the brain-blood barrier. It is used in dogs with the brain tumors under normal circumstances. In 2021, for the first time, Lomustine was tried in patients who had developed resistance to Vincristine sulfate and could not use Doxorubicin due to heart disease, which causes cardiotoxicity. In studies conducted, TVT was successfully treated without any side effects observed. When

the blood parameters of animals treated with Lomustine were examined, no abnormalities were found (Barboza et al., 2021).

Table 1. *Chemotherapy protocols used in TVT treatment*

Agent	Dosage	Effect	Side Effect	*Referances*
Vincristine	0.025 – 0.035mg/kg IV Once per week, 2-6 week	A serious positive effect have been reported in treatment.	Mild side effects have been reported.	Küçükbekir et al., 2021
Cyclophosphamide	5mg/kg PO	A mild positive effect have been reported in treatment.	Gastrointestinal toxicity have been reported.	Martins et al., 2005
Doxorubicin	1.5mg/kg IV	A serious positive effect have been reported in treatment.	Cardiotoxicty have been reported.	Çizmeci et al., 2012; Sewoyo and Made Kardena, 2022
Methotrexate	0.125mg/kg PO	It has been reported that it did not provide a positive response when used alone in treatment.	Serious side effect have not been reported.	Sewoyo and Made Kardena, 2022
Lomustine	3mg/kg PO Once per week, 3 week	A serious positive effect have been reported in treatment.	Serious side effect have not been reported.	Barboza et al., 2021

IV: intravenous, PO: per os

Radiotherapy

Wong and K'Ang (1932) are researchers who first reported that TVT is highly sensitive to radiation. Radiation can completely eliminate all TVT cells. A dose between 1500 to 3000 rad is sufficient for effective treatment. It has been reported that if radiotherapy is administered in divided doses of 400-500 rad over a period of 1-2 weeks, it can be 100% successful without leaving any scars. However, due to the need for advanced technical equipment and specially trained personnel, it is not widely preferred today (Abeka, 2019; Sewoyo and Made Kardena, 2022).

Immunotherapy

Currently, there are a limited number of experimental immunotherapy methods available for the treatment of TVT. Studies have reported partial positive responses to the intratumoral application of *Bacillus Calmette-Guérin* (BCG) for three weeks. Another agent used for this purpose is *Staphylococcal* protein A. However, serious recurrence rates have also been reported in immunotherapy protocols using both agents (Nak and Kaşıkçı, 2019; Ramos-Zayas et al., 2019; Uçar, 2016).

CONCLUSION

In conclusion, TVT is a highly transmissible malignant tumor that affects various parts of the body, particularly the external genital organs, but also internal genital organs, nose, eyes, and oral cavity. It can affect dogs of all genders and ages. Physical examination findings may include vulvar hyperemia, cauliflower-like neoplastic mass protruding from the vulvar lips, and bloody discharge. Diagnosis of the disease can be confirmed through biopsy sampling, followed by histopathological examination and cytological examination of samples stained with dyes like Giemsa or Romanowsky. Once TVT is definitively diagnosed, various treatment protocols such as surgery, chemotherapy, radiotherapy, and immunotherapy can be employed to achieve patient recovery.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

All authors contributed equally.

ETHICAL APPROVAL

During the writing process of the study titled "**An Overview Diagnosis and Treatment Methods in Cases of Transmissible Venereal Tumor in Female Dogs**", scientific rules, ethical and citation rules were followed; No falsification has been made on the collected data and this study has not been sent to any other academic media for evaluation. Ethics committee approval is not required.

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