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Canine transmissible venereal tumor: A review

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Abstract
Canine Transmissible Venereal tumor (TVT) is one of the most commonly occurring benign reticulo-endothelial tumor of dogs affecting both the sexes. It is mostly transmitted by coitus with incidence rates ranging from 2 to 43% of all tumors prevalent in temperate climate and both young and sexually mature age groups are affected. Such tumor presents abnormal numbers of chromosomes ranging from 57 to 64 and averaging 59 (58 ± 5), in contrast to the normal 78 chromosome found in the species and is the only proven example of tumor that is transplanted as an allograft during cell transplantation. Metastases cases are uncommon but puppies and immune-compromised dogs are at greater risk. The etiology appears to be tumoral cell transplantation from affected host to healthy animals. Prevalence of this tumour was reported to be 23.5% to 28.6% in Punjab 28.6% in Andhra Pradesh and 42.8% in the state of Assam. Clinical cases are usually presented with tumor localized in the shaft of penis in males and along the vestibule of vagina in females. Small nodular lesions that bleed easily are the most consistent clinical finding. Cytological studies of smears made from such tumor reveals round cells with clear cytoplasmic vacuoles, mitotic figures with chromatin clumping and presence of one or two prominent nucleoli. The tumor is self-limiting and vincristine sulfate is currently the most effective therapy. Immune modulation therapy is yet to be validated for treatment purposes. The present review throws a light and narrates some of the critical aspects such as incidence, prevalence, transmission pattern, gross and microscopic findings and the treatment regime of dogs affected with TVT.

Keywords: Transmissible veneral tumor, canine, etiopathology

1. Introduction
Transmissible venereal tumor (TVT) also known as venereal granuloma, infectious sarcoma, transmissible lymphosarcoma or sticker tumor has been described as a benign reticulo-endothelial tumor of the dog affecting mainly the external genitalia and occasionally the internal genitalia of dogs. Such tumors were usually transmitted during coitus (Tella *et al*., 2004) [29] and mostly transmission favoured in young, sexually mature animals (Rogers, 1997) [25]. The tumor usually spreads through coitus since there is extensive abrasion, bleeding of the penile mucosa and vagina, making easy transplantations of the tumor. Innumerable cases have demonstrated the transplantation of the tumor through coitus with the presence of intact viable cells across major histocompatibility complex (MHC) barriers within the same species (Mukaratirwa, 2003) [20] and sometimes to wild canidae family members such as foxes, coyotes and jackals (Higgins, 1966) [11]. Abnormal numbers of chromosomes ranging from 57 to 64 and averaging 59 were present in such cells, in contrast to the normal 78 chromosome found in the species. TVT is the only proven example of a naturally occurring tumor that is transmitted as an allograft by cell transplantation and the tumor becomes autonomous from the original host. Metastasis of this tumor is uncommon, susceptible group for tumor metastasis includes puppies and immuno-compromised dogs. Cohen, (1973)[7] reported that immunologically compromised animals presented higher severity for developing the tumor and the capacity of immunologic response of the host animal plays a major role in the expansion of the tumor.

2. Incidence and distribution of the disease
Frequency of occurrence of such tumor was capped equally in both males and females (Smith, 1998) [27] common at 2-5 years of age (Higgins, 1966 and Pandey *et al*., 1985) [11, 23]. Temperate climate favors the occurrence of this disease (Withrow and McEwen, 1996; Rogers, 1997 and Ndirty *et al*., 1977) [33, 25, 21]. The tumor was found to be mostly associated with dogs that are in close contact with one another, or in stray and wild dogs that exhibit unrestrained sexual activity.

In India, TVT is the commonest of all the tumors in dogs owing to uncontrolled breeding practices. The prevalence of such tumour was reported to be 23.5% to 28.6% of the total number of tumours in canine patients in Punjab. A similar prevelance pattern of 28.6% was found in the state of Andhra Pradesh, while in the state of Assam its prevelance was the highest which was capped at 42.8%. Clinical cases were also reported in the deserts of Rajasthan, arid zones of Haryana, Madhya Pradesh, the Ganges basin of Uttar Pradesh and in the Himalayan cities of Nainital. Such distribution pattern is suggestive of a homogenous distribution of the neoplasm irrespective of diversified altitudes and climates.

3. Transmission

TVT is mostly transmitted during coitus by transfer of cells from the affected to the healthy dog. The tumor may also be transmitted to nongenital areas such as the nose, the eyes, and the oral cavity by social behaviors such as licking and sniffing. The tumor appears to be more easily transmitted if there are abrasions or breaks in the integrity of the mucosal surface.

4. Unique features of TVT

Such tumor is unique in dog in its natural form. It has been demonstrated that this is the only tumor transplantable to adult, allogenic and immune-competent dogs. Chromosomal compliment of this tumor is constant worldwide with 58 ± 5 chromosomes found in the tumor (Normal canine chromosomal compliment is 78). And above all**,** these tumors are transmitted by direct transmission of cells from carrier to recipient.

5. Is metastasis seen in such tumor??

Metastasis is rare although has been reported in some cases. Commonest site of metastasis include the regional lymph nodes. Direct extension of the tumor may be seen in the oral cavity, tonsils and lips. Social behaviors of the animals such as sniffing and licking may result in its transmission to nongenital areas such as the nose, the eyes, and the oral cavity.

6. Etiopathology

The tumor could be transplanted from one susceptible host to another by inoculating it with tumoral cells (Richardson, 1981) [24]. Some authors attributed that the cytoplasmatic inclusions found in the tumoral cells causing neoplasia were due to the presence of virus (Cockrill and Beasly, 1975) [6]. Present school of thought believes that TVT arises from allogenic cellular transplants and the abnormal cells of the neoplasm are the vectors of its transmission (Richardson, 1981) [24] and the abnormal cells presented by the neoplasm are the vectors of its transmission. Physical contact potentiates the transplantation of these neoplastic cells onto genital mucosa during mating and also onto nasal or oral mucosa while licking of the affected genitalia (Cohen, 1985 and Johnston, 1991) [8, 15]. Implantation was also facilitated by the presence of mucosal lesion or any breach in the mucosal integrity (Vermooten, 1987) [31]. Tumor growth was apparent 15 to 60 days after implantation, such growth can be slow and unpredictable for years or invasive, eventually become malignant and metastasize (Lombard and Cabanie, 1968 and Moulton, 1978) [18, 19]. TVTs were described as immunogenic tumors and the host immune system plays a crucial role in inhibiting tumor growth and metastasis (Cohen, 1973 and Cohen, 1985) [7, 8]. Potential risk group for metastases includes immune-compromised young dogs (Yang, 1988) [35]. Metastases were markedly reported to be more frequent in males than in female dogs. Subcutaneous tissue, skin, lymph nodes, eyes, tonsils, liver, spleen, oral mucosa, peritoneum, brain and bone marrow were the sites where metastases could be seen (Brown *et al*., 1981; Krouger *et al*., 1991; Moulton, 1978 and Tinnuci- Costa *et al*., 1997) [4, 17, 19, 30]. Extragenital lesions can occur in association or in isolation with the genital lesions (Richardson, 1981) [24].

Immunological studies have demonstrated that the tumor could be transplanted through barriers of major histocompatibility complexes (MHC) (Yang and Chandler, 1987) [34]. Serum samples screened from dogs with TVT were positive for the presence of immunocomplexes (Palker and Yang, 1985) [22]. Type I and II MHC antigens were not expressed by the tumor cells in the rapid growth phase, while 30% to 40% of cells in the initial regression phase expressed both the antigens. Such difference in the expression pattern of MHC antigens was thought to be responsible for the additional immune response in the host which accelerates the regression of the tumor (Yang, 1988) [35]. Different stages of tumor progression present different cell types. In progressive growth phase, tumor cells will be round with the presence of microvilli while regressing tumors present transitional cells rather than fusiform. T lymphocytic cells were abundant in regressing tumors (Hill *et al*., 1984 and Weir *et al*., 1987) [12, 32]. Investigations demonstrated that substances secreted by the lymphocyte infiltrate induces cellular differentiation responsible for the tumor's regression by inducing cellular differentiation (Yang, 1988; Yang *et al*., 1991 and Yang *et al*., 1976) [35, 36, 37].

7. Clinical presentation of a TVT

Male and female external genitalia are the primary locations of such tumor cells. In the male the tumor is most commonly located along the shaft of the penis. In many cases extrusion of the penis is necessary to visualize the tumor. In bitches the tumor is most commonly located in the vestibule of the vagina and can be visualized protruding through the lips of the vagina. The tumor ranges from 0.5 mm to more than 10 cm in diameter. They are usually presented as a cauliflower-like in appearance, being friable and are red to flesh colored.

8. Gross and microscopic findings

Initial lesions are superficially pink to red and 1-3 mm in diameter which may be pedunculated or dermoepidermal. Multiple nodule then fuses together forming larger, red, hemorrhagic and cauliflower-like friable masses. The nodular mass can range between 5 cm to 7 cm in diameter which then progresses deeper into the mucosa as multilobular subcutaneous lesions with diameters that can exceed 10 – 15 cm. Larger sized tumor can bleed easily which then ulcerate and become contaminated (Hoque, 2002) [13].

Cytological studies picture TVT cells as round to oval in shape containing mitotic figures, with chromatin clumping and one or two prominent nucleoli (Gonzalez *et al*., 2000 and Singh *et al*., 1996) [10, 26]. Presence of multiple clear cytoplasmic vacuoles is the most prominent cytological finding (Tella *et al*., 2004) [29].

Histological examination of TVTs usually reveals that the component cells grow in compact masses or confluent sheets. Sometimes, they grow in rows, cords, or loose in a delicate stroma. As the tumor mass increases, the cells become

irregular and gets tightly packed giving the appearance of fibroblasts (Calvet, 1982 and Kennedy *et al*., 1977) [5, 16]. Infiltration of lymphocytes, plasma cells and macrophages are quite predominant suggesting a role of immune mediated control. TVTs should be differentiated from mastocytomas, histiocytomas or malignant lymphomas before confirmation (Richardson, 1981) [24].

9. Diagnosis

Clinical sign and symptom varies according to the localization of the tumor. Hemorrhagic discharges are common in dogs with genital localization of the tumor cells. In males, localization of the lesion is cranially on the glans penis, preputial mucosa or on the bulbus glandis. Phimosis can be a complication if tumoral masses are seen protruding from the prepuce (Higgins, 1966) [11]. The discharge should not be confused with urethritis, cystitis, or prostatitis (Rogers, 1997) [25]. Regional lymph node involvement is frequent in males with large sized tumors.

In bitches the tumors are of similar gross appearance as in male dogs with localization in the vestibule and/or caudal vagina, protrusion from the vulva causes a deformation of the perineal region. Persistent haemorrhagic vulvar discharge may result in anaemia in the affected animal. The discharge can attract male dogs and owners can mistake this condition as estrous. Tumor localization in the uterus is infrequent (Aprea *et al*., 1994) [2].

In cases with extra genital localization of the tumor cells, diagnosis is difficult because appearance of clinical signs depends on the anatomical localization of the tumor such as epistaxis, sneezing, epiphora, halitosis and tooth loss, skin bump, exophthalmos, facial or oral deformation along with regional lymph node enlargement (Rogers, 1997) [25]. Definitive diagnosis is based on physical examination and cytological findings typical of TVT in exfoliated cells obtained from the tumor site by swabs, fine needle aspirations or imprints (Daleck *et al*., 1987; Moulton, 1978 and Richardson, 1981) [9, 19, 24].

10. Treatment

Several treatment regimes both invasive and non-invasive including surgery, immunotherapy, radiotherapy, biotherapy and chemotherapy have been applied for correction of TVT. Small localized TVTs can be surgically excised, but in cases of large invasive tumors the recurrence rate can be as high as 50 - 68% (Johnson, 1994; Rogers, 1997 and Weir *et al*., 1987) [14, 25, 32]. As reported, contamination of the surgical site with TVT cells could also act as a source of recurrence (Boscos and Ververidis, 2004) [3]. Transmissible venereal tumors were found to be radiosensitive and X-ray tube operating at voltages in the 100-500 kV range as well as cobalt has been used for treatment (Rogers, 1997 and Vermooten, 1987) [25, 31]. Biotherapy studies were also carried out for treatment purposes but with limited success. The intratumoral application of Calmette-Guérin's bacillus (BCG) was used for three weeks but reoccurrence rate was found to be higher [15]. Case recurrences have been established after immunotherapy using Staphylococcus protein A or BCG (Amber *et al*., 1990 and Rogers, 1997) [1, 25].

Chemotherapy has been proved to be the most effective and practical therapy, with vincristine sulfate being the most frequently used drug (Calvet, 1982) [5]. Vincristine administration schedule can be followed weekly at a dose of 0.025 mg/kg, IV (Cohen, 1985 and Johnson, 1994) [8, 14]. The involution of the lesions is gradual and complete remission of the tumoric lesion usually takes 2 to 8 injections (Calvet, 1982 and Daleck *et al*., 1987) [5, 9]. If cases are treated in the initial stages of progression a cure rate approaching 100% can be achieved. In chronic cases, longer periods of therapy are required, and the cure rate is much lower (Boscos and Ververidis, 2004) [3].

Vincristine is a cytostatic drug that causes myelosuppression and gastrointestinal effects resulting in leukopenia and vomition in 5 to 7% of the cases. Paresis is also among the side effect due to peripheral neuropathy (Withrow and McEwen, 1996 and Calvet, 1982) [5, 33]. Therefore, a complete white blood cell count is recommended prior to administration of the drug. If WBC count is below 4000 mm^3 further administration of the drug should be delayed 3 to 4 days and the dose rate for administration can be reduced to 25% of the initial dose. The most frequent complication of IV vincristine injection is the occurrence of local tissue lesions caused by extravasation of the drug resulting in the development of necrotic lesions with crusts.

Other chemotherapeutic agents indicated and validated for treatment include cyclophosphamide (5 mg/kg, PO, for 10 days as a single drug therapy or given in combination with prednisolone (3 mg/kg, for 5 days), weekly vinblastine (0.1 mg/kg, IV during 4 to 6 weeks), methotrexate (0.1 mg/kg, PO, every other day) or a combination of the above 3 drugs can also be prescribed. However, case reports have shown that there is no perceptible advantage in the combination of chemotherapy over vincristine injection alone (Brown *et al*., 1981; Richardson, 1981, Vermooten, 1987 and Yang *et al*., 1991) [4, 24, 31, 36]. Treatment regime for resistant cases include doxorubicin injection @30 mg/m^2, IV, with 3 applications every 21 days (Richardson, 1981 and Souza *et al*., 1998) [24, 28]. If the tumoral mass doesn't disappear by chemotherapy, electro-cauterization or cryocauterization can be of useful means (Rogers, 1997 and Vermooten, 1987) [25, 31]. Small remnant lesions can disappear spontaneously after 1 or 2 weeks after therapy. In patients not responding to chemotherapy radiotherapy has been reported to yield good results.

11. Conclusion

TVT is the most prevalent neoplastic disease of the external genitalia of the dog in tropical and sub-tropical regions. The etiology of TVT is clearly due to cell transplant from affected dogs. Clinical cases are mostly presented with the owner's mostly complaining with hemorrhagic discharge. Diagnosis is based on physical and cytological findings. Weekly IV vincristine injection has proved to be the most effective and practical therapy. Further experimental studies are necessary to investigate the changes in patency of the reproductive tract during vincristine treatment and its long term effects on spermatogenesis and fertility. Until sufficient information on fertility effects becomes available, clinicians and owners must balance the potential benefits to the patient. Immune modulation or immune therapy is yet to be validated before it becomes clinically available.

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