Canine Transmissible Venereal Tumor: A Review

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Abstract

Canine transmissible venereal tumor (TVT) is a commonly occurring tumor of dogs affecting both sexes. It is common in dogs which have an uncontrolled sexual behavior with incidence ranging from 2 to 43 percent of all tumors in temperate climates. The etiology appears to be cell transplant from affected to unaffected dogs. The pathogenesis, gross and microscopic findings, diagnosis, prognosis and therapies have been reviewed. Gross findings of small nodule like lesions which bleed is the most consistent clinical finding. Smears made from the tumor reveal round cells with vacuoles and mitotic figures. The tumor is many times self limiting and vincristine sulfate is currently considered the most effective therapy. The use of vincristine sulfate in male dogs must balance the potential benefits to the patient and the interest in using the animal for breeding as vincristine sulfate impairs the semen quality. Immune therapy of TVT is still to be validated for clinical use.

Transmissible venereal tumor (TVT), also known as infectious sarcoma, venereal granuloma, transmissible lymphosarcoma or Sticker tumor is a benign reticulo-endothelial tumor of the dog that mainly affects the external genitalia and occasionally the internal genitalia. As it is usually transmitted during coitus (Tella et al., 2004) it mainly occurs in young, sexually mature animals (Rogers, 1997).It is transplanted during coitus with intact viable cells across major histocompatibility complex (MHC) barriers within the same species (Mukaratirwa and Gruys, 2003) and even to other members of the canine family, such as foxes, coyotes and jackals (Higgins, 1966). Laboratory transplantation of TVT from one dog to other using viable cells is also possible (Yang and Jones, 1973). TVT cells contain an abnormal number of chromosomes ranging from 57 to 64 and averaging 59, in contrast to the normal 78 of the species. Metastasis of TVT is uncommon, only occurring in puppies and immuno-compromised dogs. The uniqueness of TVT lies in the fact that this 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. In other words, the the tumor behaves like a parasite. This kind of tumor developed only in the dog, probably because during coitus there is extensive abrasive abrasions and bleeding of the penile mucosa and vagina, making transplantations of the tumor easy. Because TVT can be easily transplanted investigations on various aspects of tumor biology have been done to provide clues to similar phenomenon that occur in other animal and human tumors. Thus TVT has been studied extensively. A very interesting aspect that has attracted attention of TVT is the role of the host's immune response during the progressive and regressive stages of the tumor. The capacity of immunologic response of the host has a main role in the expansion of such tumors (Cohen, 1973) with an increase in severity seen in immunologically compromised animals. In this review some known facts of TVT have been reviewed.

INCIDENCE

TVT has continued to be a serious problem around the world (Moulton, 1961) occurring at same frequencies in both male and female dogs (Smith and Washbourn, 1998). It is estimated to be more prevalent in temperate climates (Ndirty et al., 1977; Withrow and McEwen, 1989; Rogers, 1997). A large number of reports have been produced in India (Pandey and Dhawedkar, 1977; Chaudhary and Rao, 1982; Nayak et al., 1987; Padile et al., 1988; Das et al.,1989; Pandey et al., 1989; Das and Sahay,1990; Chauhan et al.,1991; Das et al., 1991; Tiwari et al., 1991; Dinesh et al., 1993; Gandotra et al ., 1993; Hoque et al., 1995; Maiti et al., 1995; Jain et al., 2002 a, 2002b). It is commonly observed in dogs that are in close contact with one another, or in stray and wild dogs that exhibit unrestrained sexual activity (Cangul, 2003). In India TVT is known to be the most frequently reported tumor in dogs ranging from 23-43 % of the total number of tumors in canine population (Gandotra et al., 1993; Chaudhary and Rao, 1982). Uncontrolled sexual behavior and a large stray dog population appear to be one

reason for such a high incidence of TVT. An age related incidence has been shown for TVT (Higgins, 1966; Pandey et al., 1997; Thakur and Bradley, 1983) with the tumor being common at 2-5 years of age.

PATHOGENESIS

Canine TVT was initially described by Novinsky in 1876, who demonstrated that the tumor could be transplanted from one susceptible host to another by inoculating it with tumoral cells (Richardson, 1981). Some workers attributed this neoplasia to be because of viral agents (Cockril and Beasly, 1975), however, the tumor could not consistently be transmitted by cell free extracts (DeMonbreun and Goodpasture, 1934; Calvet,1983) and oncogenic viral particles have never been seen in the tumor cells with the electron microscope (Moulton, 1990). The current consensus view is therefore that the abnormal cells of the neoplasm are the vectors of transmission. The exfoliation and transplantation of neoplastic cells during physical contact provide the main mode of transmission onto genital mucosa, and also onto nasal or oral mucosa, during mating or licking of affected genitalia, respectively (Cohen, 1985; Johnston, 1991). The loss of mucosal integrity favors transmission (Vermooten, 1987).

TVTs can either grow slowly and unpredictably for years or be invasive and eventually become malignant and metastasize (Lombard and Cabanie, 1968; Moulton, 1978). Metastases have been reported in less than 5 - 17 % of cases (Richardson, 1981; Rogers, 1997). They have been described in subcutaneous tissue, skin, lymph nodes, eyes, tonsils, liver, spleen, oral mucosa, hypophysis, peritoneum, brain, and bone marrow (Moulton,1978,) Although, spontaneous remission has been described in experimental transplantation it has not been confirmed in natural cases (Richardson,1981; Vermooten,1987).

Differences in cell types have been found between stages of tumor progression. Tumors in progressive growth have round cells with microvilli while regressing tumors present transitional rather fusiform cells.

Moreover, regressing tumors have a high number of T lymphocytes (Hill et al., 1984). It is thought that substances secreted by the lymphocyte infiltrate are responsible for the tumor's regression by inducing cellular differentiation (Yang, 1988, Yang et al., 1991). A recent study suggested the role of hyaluronan in the growth of the tumor. This study also emphasized that the modulation of stromal cells that occur during the regression of TVT is similar to that occurring during wound healing (Mukaratirwa et al., 2004).

GROSS AND MICROSCOPIC FINDINGS

Initial lesions are superficial pink to red and 1-3 mm in diameter. Then, multiple nodules fuse together forming larger, red, hemorrhagic, cauliflower-like, friable masses. The masses can be 5 cm to 7 cm in diameter which then progress deeper into the mucosa as multilobular subcutaneous lesions with diameters that can exceed 10 - 15 cm. Tumors bleed easily and while becoming larger, normally ulcerate and become contaminated (Hoque, 2002). Cytologically, TVT cells have a very distinct appearance. They are round to oval in shape and often contain mitotic figures, with chromatin clumping and one or two prominent nucleoli (Singh et al., 1996; Gonzalez et al., 2002). Perhaps the most striking cytological finding, however, is the presence of multiple clear cytoplasmic vacuoles (Tella et al., 2004). Histological examination of TVTs usually reveals that the component cells grow in compact masses or confluent sheets. Sometimes, however, they grow in rows, cords, or loose in a delicate stroma. As the tumor mass increases, the cells become tightly packed and irregular in shape and fibroblasts appear, perhaps an indication of the transformation of tumor cells (Kennedy et al., 1977; Calvet et al., 1982).

There is frequently an infiltration of lymphocytes, plasma cells and macrophages (Tella et al., 2004) which suggest a role of immune mediated control. TVTs should be differentiated from mastocytomas, histiocytomas or malignant lymphomas (Richardson, 1987).

DIAGNOSIS

Clinical signs vary according to the localization of the tumors. Dogs with genital localization have a hemorrhagic discharge. In males, lesions usually localize cranially on the glans penis, on preputial mucosa or on the bulbus glandis. Tumoral masses often protrude from the prepuce (Higgins, 1966) and phimosis can be a complication (Mc Envoy, 1987). The discharge can be confused with urethritis, cystitis, or prostatitis (Rogers, 1997). The involvement of regional lymph nodes is frequent in males with large tumors.

In bitches the tumors are of similar gross appearance as in male dogs and can be localized in the vestibule and/or caudal vagina, protruding from the vulva and frequently causing a deformation of the perineal region. Only very rarely, however, do they interfere with micturition. A considerable hemorrhagic vulvar discharge may occur and can cause

anemia if it persists. The discharge can attract males and the condition of the bitch can be mistaken for estrus by the owners. Infrequently, TVTs can localize in the uterus (Aprea et al ., 1994). In cases with extra genital localization of the TVT, clinical diagnosis is usually more difficult because TVTs cause a variety of signs depending on the anatomical localization of the tumor, e.g., sneezing, epistaxis, epiphora, halitosis and tooth loss, exophthalmos, skin bumps, facial or oral deformation along with regional lymph node enlargement (Rogers, 1997).Exfoliative vaginal cytology has been one means of diagnosing TVT in the bitch (Erunal-Maral et al., 2000).

Definitive diagnosis is based on physical examination and cytological findings typical of TVT in exfoliated cells obtained by swabs, fine needle aspirations or imprints of the tumors (Richardson, 1981; Moulton, 1978,). There is marked aberrations in the numbers and morphology of the chromosomes of the constituent cells of TVT (Idowu, 1977; Theilen and Madewell, 1987). The normal number of chromosomes in the somatic cells of dogs is 78, of which all but two are acrocentric chromosomes. In TVT there are usually 58-59 chromosomes with 13-17 metacentric and 42 acrocentric chromosomes (Wright et al., 1970). One interesting observation in animals suffering from TVT is that they develop polycythemia (Cohen, 1985). Therefore, this may be diagnostic (Withrow and Mc Ewen, 1989) but this still needs to be validated. In dogs, TVT grows progressively for a few months and then usually regresses spontaneously. A long interspersed nuclear element (LINE) insertion is found specifically and constantly in the 5' end of the TVT cell c-myc gene, outside the first exon. The rearranged LINE-c-myc gene sequence has been used with polymerase chain reaction (PCR) to diagnose TVT. However, in TVT cells, the total length of the inserted LINE gene is not constant. (Liao et al., 2003).

PROGNOSIS

Immunological studies have clearly demonstrated that TVT is antigenic in the dog and an immune response against the tumor plays a major role in determining the course of the disease (Mizuno et al., 1994). In most adult dogs the tumor regresses spontaneously after a period of logarithmic growth, and the development of tumor immunity prevents successive occurrences (Powers, 1968). In contrast, the tumor progresses to ulceration and metastasis in the immunologically incompetent or compromised host (Cohen, 1973). Nevertheless, metastases have been reported in occasional cases (Ferreira et al., 2000). The biological behavior of canine TVT can be estimated by the demonstration of AgNORs (Harmelin et al., 1995). The poor prognosis in TVT is due to an increase of the AgNORs in the nucleus of TVT cells.

TREATMENT

The management of TVT has not been very easy. Several treatments including surgery, radiotherapy, immunotherapy, biotherapy and chemotherapy have been applied for TVT. Surgery has been used extensively for the treatment of small, localized TVTs, although the recurrence rate can be as high as 50 - 68% in cases of large invasive tumors (Rogers, 1997; Weir et al., 1987). Contamination of the surgical site with TVT cells is also a source of recurrence (Boscos and Ververidis, 2004).Methods to prevent recurrence subsequent to surgery include excision along with cauterization (Hoque, 1995), electrosurgical or cryosurgical excision (Idowu, 1985; Rao et al., 1993; Hoque et al.,1995) or chemotherapy subsequent to surgical excision. Transmissible venereal tumors are radiosensitive and orthovoltage as well as cobalt have been used for this purpose (Weir et al., 1987).

Immunotherapy studies have also been reported. There are reports to show that generalized form of TVT may regress following transfusion of whole blood or serum from a recovered animal or after treatment with tumor homogenate used as an autocthonius vaccine (Prier and Johnson, 1964; Powers, 1968). A very few paramunity activators have been tried in TVT. The intra-lesional application of Calmette-Guérin's bacillus (BCG) was used for three weeks with sporadic success (Johnston, 1991). Recurrences have been described after immunotherapy using Staphylococcus protein A, BCG or a vaccine made from tumoral cells (Amber et al., 1990; Rogers, 1997). Biotherapy has unfortunately also resulted in a high rate of recurrence (Richardson, 1981; Vermooten, 1987, Amber et al., 1990). Parvovirus vaccine has been shown to prevent experimental tumor transplantation when the vaccine was inoculated simultaneously with the tumor (Yang, 1987), but the routine use of this vaccine is not reported. Paramunity activators are given with the intention of enhancing the non-specific immune reactivity to the host, and this non-specific immunity is both humoral and cellular (Mayr, 1981). Since humoral and cellular immunity is known to play an important role in the regression of TVT (Cohen, 1980; Mizuno et al., 1994) paramunity activators are expected to be effective in both prophylaxis and treatment of this tumor. Local injection of interleukin-2 has been tried for immunotherapy with 32% success(Otter et al., 1999).The

mechanism how IL-2 causes regression of the tumor is not clear.

Chemotherapy has been shown to be the most effective and practical therapy, with vincristine sulfate being the most frequently used drug (Calvet et al., 1982; Nak et al., 2005). Vincristine, is (Boscos and Ververidis, 2004) administered weekly at a dose of 0.5 to 0.7 mg/m^2 of body surface area or 0.025 mg/kg, IV (Cohen, 1985; Singh et al., 1996). The involution of the lesions is gradual, although it is particularly noticeable and significant at the beginning of the treatment. Complete remission usually takes 2 to 8 injections (Calvet et al 1982) and occurs in more than 90% of the treated cases. A cure rate approaching 100% (Boscos and Ververidis, 2004) is achieved in cases treated in the initial stages of progression, especially in cases of less than 1 year duration, and independent of the presence or not of metastases (Boscos et al., 2004).

In cases of longer duration, longer periods of therapy are required, and the cure rate is lower (Boscos and Ververidis, 2004). Side effects can be expected. Cytostatic agents, such as vincristine, can cause myelosuppression and gastrointestinal effects resulting in leucopenia and vomiting in 5 to 7% of the patients. Paresis has also been described as a side effect due to peripheral neuropathy (Calvet et al., 1982; Withrow and Mc Ewen, 1996). A complete white blood cell count is, therefore, recommended prior to each administration. When the white blood cell count is below 4,000 mm^3 further administration should be delayed 3 to 4 days and the dose of vincristine can be reduced to 25% of the initial dose (Calvet et al., 1983). The most frequent complication of vincristine treatment is the occurrence of local tissue lesions caused by extravasation of the drug during IV application resulting in the development of necrotic lesions with crusts.

Other chemotherapeutic agents indicated for TVT treatment include cyclophosphamide (5 mg/kg, PO, for 10 days as a single drug therapy or given in association with prednisolone, 3 mg/kg, for 5 days); also, 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 3 drugs. However, there is no apparent advantage in the combination of chemotherapy over using vincristine alone (Richardson, 1981; Vermooten, 1987; Yang et al., 1991; Singh et al., 1996).

Resistant cases can be treated with doxorubicin, 30 mg/m^2, IV, with 3 applications every 21 days (Richardson, 1981; Souza et al., 1998). When total disappearance of the tumor cannot be achieved by chemotherapy, electro-cauterization or cryo-cauterization can be useful (Rogers, 1997, Vermooten, 1987). After therapy, small remnant lesions can disappear spontaneously after 1 or 2 weeks (unpublished observations). In cases that fail to resolve with chemotherapy, radiotherapy has been reported to yield good results (Boscos et al., 2004). The tumor immunity plays a role in tumor regression after modest chemotherapy (Gonzalez et al., 2000).

EFFECTS OF VINCRISTINE TREATMENT ON SPERMATOGENESIS

Spermatogenesis can be temporarily or permanently altered by the administration of cytotoxic drugs (Rosenthal, 1981; Daleck et al., 1995). Drug-altered spermatogenesis may not return to normal for one or more spermatic cycles (Freshman, 1989). It is known that vincristine reduces human fertility (Mc Envoy, 1987). Studies in laboratory animals have shown that vincristine damages the DNA of germ cells thereby reducing the rate of development of these cells (Zhang and Sun, 1992). Vincristine can cause cytoplasmic protein precipitation, which in turn interferes with microtubule formation (Rosenthal, 1981). Little information is available on the long-term effects of vincristine on male dog fertility and most of the studies only have described semen quality during treatment (Mc Envoy, 1987)

Conflicting reports evidence that the semen quality may or may not regain after vincristine treatment of male dogs (Saratsis et al., 2000; Gobello and Corrada, 2002) and point out that the gonadal response to treatment varies among individuals.

CONCLUSIONS

TVT is the most prevalent neoplasia of the external genitalia of the dog in tropical and sub-tropical areas. The etiology of TVT is now known to be cell transplant from affected dogs. The most frequent owner's complaint is the hemorrhagic discharge. Diagnosis is based on typical physical and cytological findings. Weekly IV vincristine administration has been shown to be the most effective and practical therapy. Further experimental studies, carried out in larger groups of dogs, are necessary to investigate the changes in semen quality 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

and the interest in using the animal for breeding. Immune modulation or immune therapy is yet to be validated before it becomes clinically available.

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