

REVIEW OF CANINE TRANSMISSIBLE VENEREAL TUMOUR (TVT) IN DOGS

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INTRODUCTION

Transmissible Venereal tumour (TVT) also known as stickers sarcoma (Sticker, 1904) transmissible venereal tumour, venereal granuloma, canine condyloma or infectious sarcoma (Madewell and Theilen, 1987; Nielsen and Kennedy, 1990 and Roger, 1997). Canine transmissible venereal Sarcoma (TVS) (Yang, 1988) is the most notable among the three recognized transmissible tumours in domestic animals. It is a naturally occurring contagious round cell neoplasia of dogs. It is a well characterized sexually transmitted neoplasm commonly affecting the external genitalia in dogs (Brown et al., 1980; Richardson, 1981 and Cohen, 1985). TVT is primarily located in the mucous membrane of the external genitalia of either sex. This tumour is unique in oncology, because it was the first tumour to be transmitted experimentally. This was achieved by the Russian Veterinarian, Nowinsky in 1876 according to Epstein and Bennett (1974) and Yang, et al (1991). Canine transmissible venereal tumour (CTVT) is virtually the only tumour transmitted by cell transplantation under natural conditions (Yang, 1988). Viable CTVT cells can be transmitted to susceptible animals and transfer, in a given dog, to other mucous membranes (e.g. the oral cavity) spontaneously through injured skin, or mucosa during coitus, licking, fighting/ biting, sniffing or scratching (Stubbs and Furth, 1934). In addition to the genital system (Higgins, 1966), CTVT can occur any where on the body including the skin, oral and nasal cavities, conjunctiva and even the anal mucosa (Nielsen and Kennedy, 1990, Calvert, 1984; Harmir, 1986; Amber and Adeyanju, 1986; Adeyanju et al., 1987 and Betamuzi and Bittegeko, 1991)

gluteal region, maxilla gingival, dorsal skin of thorax (Gurel et al., 2002). TVT can be experimentally transmitted to wolves, Jackals, Coyotes and red foxes (Madewell and Theilen, 1987; Nielsen and Kennedy, 1990 and Roger, 1996). Recent research in Australia which revealed the existence of a newly emerged tumour in Tasmanian Devils (Devils are an endangered marsupial species) that appears to be caused by transmissible cancer cells, in this case by biting (Claudio et al., 2006). The tumour is recognized in all dog breeds in various part of the world, especially in tropical and sub tropical zones (Gurel, et al., 2002). Due to the nature of transmission by sexual contact, free roaming, sexually active dogs in region with poorly enforced leash laws are at greatest risk for contracting this disease. Although, CTVT does not often metastasized, it has been reported in the regional lymph nodes, liver, pancreas, spleen, lung, kidney, ocular cavity and brain (McLeod and Lewis, 1972; Oduye et al., 1973; Adams and Slaughter, 1970; Prier and Brodey, 1963, Yang, 1987, Perez et al., 1998, Ferréira et al., 2000). CTVT transplantability in animal model showed that tumour cell differentiation and, in turn, spontaneous regression could be induced. (Yang, 1988 and Angell, 2000).

DISTRIBUTION

CTVT was first described over 100 years ago in Europe. It now has a world wide distribution at the present time. There are enzootic areas in many parts of the world. The disease is mostly seen in free roaming, sexually active dogs in tropical and sub tropical countries (Gurel et al., 2002), particularly in the cities and rural parts of the Southern United States, Central and South America, South East Europe, Ireland, Japan,

China, the far East, Middle East and parts of Africa (Rust, 1949; Higgins, 1966 and Idowu et al., 1984). In Japan, it is the most common tumour in dogs (Tateyama et al., 1986) It is common in South west France, where it appears in an enzootic form in some areas (Barski and Cornefert-Jensen, 1966) but it is unknown in Sweden and is rare in Denmark and Great Britain (Moulton, 1990).

In one report, 1% of the adult dogs admitted to the University Hospital in Kabete, Kenya had CTVS (Rottcher and Frank, 1972). The condition is enzootic in Puerto Rico (Rust, 1949) and in Bahamas where it is the most common tumour of dogs (Higgins, 1966) It is also common in Papua New Guinea (Rust, 1949). The prevalence has varied with time in the United States (Karlson and Mann, 1952), being high in New York and Philadelphia during 1910-1919 but has decreased by 1950-1959; the tumour is occasionally found in Ohio, Kansas, Michigan, Minnesota and California and has been common around Chicago (Moulton, 1990). The prevalence was reported as 11% in Kenya (Kimeto and Mugeru, 1974), 32% in Sri Lanka (Wettimuny and De, 1975), 10% in the former USSR (Osipov and Golubera, 1976) and 10% in Maryland, USA (Thacher and Bradley, 1983).

In India, it is the most common tumour of dogs owing to uncontrolled breeding practice, (Singh et al., 1991). The prevalence of CTVT in Punjab was 23.5% (Singh, 1993) to 28.6% (Gandotra et al., 1993) of the total number of tumours in canine patients.

A similar prevalence of 28.6% was reported by Choudhary and Mohan-Rao (1990). The ignorance of the stud owners and lack of stringent legislation for monitoring the sexual health of dogs are the main causes of the wide spread distribution of this disease throughout the country. While working in the different parts of India, the authors have come across clinical cases of CTVS in the desert of Rajasthan; arid zones of Haryana, Madhya Pradesh, Bihar and Bengal; Sub-Himalayan Uttar Pradesh, Bihar and Bengal; the East and West coasts, Chotnagpur and Gondwana plateau; and in the Himalayan cities of Nainital, Missouri and Darjeeling. This is suggestive of a homogenous distribution of the

neoplasm, irrespective of the diversified altitudes and climates. In rural areas, it is more predominant, possibly because of the sylvan habitat and lack of adequate Veterinary services.

At Ibadan, Western Nigeria, Idowu (1985) treated fifteen dogs of different breeds, sexes and ages between March, 1981 and December, 1982 using Cryosurgery. Amber et al (1987) reported 47 cases within 2 years in Ahmadu Bello University Veterinary Teaching Hospital, (ABUVTH), Zaria, Northern, Nigeria. In another report, Amber, et al (1990) recorded 48 TVT cases at (ABUVTH), Zaria, Nigeria within 21 months. At the University of Nigeria, Veterinary Teaching Hospital, Nsukka, Nigeria, TVT cases constituted 11% of canine surgical cases reported from 1985 to 1995 (Eze and Idowu, 2002). A 4.8% TVT prevalence rate among canine cases in Government owned veterinary clinic, in Imo state, Nigeria has also been reported (Eze and Okoli, 2006).

TRANSMISSION AND AETIOLOGY

TVT was the first reported neoplasm to be successfully transplanted (Epstein and Bennett, 1974; Yang, et al., 1991). This was done by Nowinsky (1876) who succeeded in transplanting the tumour from one dog to another by rubbing the excised tumour on the scarified genital mucosa of a susceptible dog. CTVT is virtually the only tumour transmitted by cell transplantation under natural conditions (Yang, 1988). Viable CTVT cells can transmit to susceptible animals spontaneously through injured skin or mucosa during coitus, licking of the external genital (prepuce, penis, vulva and vagina), fighting, biting or other types of contact, sniffing, scratching (Stubbs and Furth, 1934 and Bloom, 1954). The violent exertions associated with coitus in dog render both sexes prone to genital injury and so susceptible to transplantation of the tumour cells (Feldman, 1929). Occurrence in dogs is also more in countries where the population of stray dogs is high. The growth generally appears within 2 to 6 months of first mating. Das et al (1986) described this tumour as a "naturally occurring allograft".

This animal model showed that tumour cell differentiation and in turn, spontaneous regression could be induced (Yang, 1988). Experimentally, Karlson and Mann (1952) succeeded in passing the tumour through 40 generations of dogs over a period of 17 years. Of the 564 dogs involved, 68% developed tumours and there were no changes in the histopathology of tumour during the passage. Transmission of the venereal tumour occurs only by transplantation of viable tumour cells and not by a virus that transforms cells in a susceptible host (Rust, 1949). The tumour cannot be produced with cells that have been frozen heated, treated with glycerin or desiccated and it has been reported that cell-free filtrates do not transmit it (De Monbreum and Goodpasture, 1934 and Das and Das, 2000).

Oncogenic viral particles have never been seen in the tumour cells with the electron microscope (Murray et al., 1969 and Moulton, 1990). However, some authors have claimed transmission with cell-free filtrates (Ajello, 1960) and C-type particles have been reported to be associated with this tumour (Sapp and Adams, 1970), which would suggest that the agent may be a type C-retrovirus.

SEASON, AGE, BREED AND SEX SUSCEPTIBILITY

Idowu (1983) reported that the disease is enzootic in Nigeria. In Nigeria, studies on distribution pattern of TVT in two areas of Eastern Nigeria, Nsukka and Owerri show that the disease is endemic and not influenced by season (Eze and Idowu, 2002, Eze and Okoli, 2006). Venereal tumours are most common during the period of maximum sexual activity in dogs and the animals are particularly at highest risk when females exhibit the signs of oestrous. Dogs of any breed, age or sex are susceptible (Kimeto and Mugeru, 1974 and Betamuzi, 1992). In a retrospective study, of TVT in Texas by Kenita et al (1998), sixteen of 29 dogs studied were neutered but the surgical procedure was performed within the previous 12 months, often after clinical signs of TVT

were present. However, the author observed a case of TVT in neutered local where surgical procedure had occurred over five years before clinical signs of TVT were observed at the University of Nigeria Veterinary Teaching Hospital, Nsukka Nigeria.

Although dogs over one year of age are at high risk in endemic areas (Bashford et al., 1905), CTVT in most common in dogs 2 to 5 years old (Pandey et al., 1977; 1989 and Das et al., 1991). The mean ages and ranges of the affected dogs were 4.4 (Brodey and Rosze, 1967), 4.5 (Brown et al 1980), 3.9 (1.10) (Calvert et al., 1982) 4.1 (2-7) (Thacher and Bradley, 1983) and 3.9 (1-13), (Singh et al., 1996) years. In most studies of spontaneously occurring TVT, there has been no clear sex or breed predisposition (Brown et al., 1980; Thrall, 1982 and Calvert, 1982). On the other hand vulvar or vaginal tumours in dogs other than CTVS showed a higher prevalence in the age group of 10-11 years (Thacher and Bradley, 1983; Kydd and Burnie, 1986 and Owen, 1991). Kenita et al (1998) reported six of 29 cases with extra genital involvement of tumours where two of these had nasal TVT, and five cases (including those of the nasal cases) had evidence of metastasis confirmed with cytological evaluation. In another report, Gurel et al (2002) demonstrated eight extra genital cases of CTVT between 1997 to 2000 at Faculty of Veterinary Medicine, Istanbul, Turkey. Georgia et al (1996) also reported that metastasis of TVT in the eye, penis, lymph nodes and (nodules in the subcut) in the inguinal area in a six year old intact Brazilian terrier. The tumour has never been found in virginal females.

The role of TVT in the pathogenesis of urinary tract infection (UTI) in dogs has been investigated. Obliteration of the urethral orifice by the tumour, possibly leading to urine retention, was thought to be the main reason for high incidence of urinary tract infection among dogs with TVT (Betamuzi and Kristensen, 1996) The most commonly isolated causes of UTI in dogs are *Escherichia coli*, *Staphylococcus* species, *Proteus* species, *Klebsiella* species and *Streptococcus* species (Bush, 1984). *E. coli* is the bacteria most commonly isolated.

Moulton (1990), Aiello (1980) and Singh et al (1996) found females to be more susceptible than males. Naturally occurring disease may be more common in females because one infected male often mates with numerous females, both in kennels and in free range. However, Osipor and Golubera (1976), Brown et al (1980) and Boscos (1988) reported more cases in male dogs. Hamir (1985) and Pandey et al (1989) reported that metastasis is mostly observed in adult male dogs.

The tumour is reported to be strictly host specific for the dog and fox (Rust, 1949). However, the occurrence of this disease in related canidae may not have been noticed. There is no heritable breed related prevalence of this tumour (Karlson and Mann, 1952; Betamuzi, 1992).

CLINICO PATHOLOGICAL FEATURES

Fallon and Swayne (1984) presented a diagnostic dilemma of CTVT, probably because of primary genital tumours and the various areas involved. In the male dog, the tumour is usually located on the caudal part of the glans penis, from the crura to bulbus or the area of the glans penis and occasionally on the prepuce (Das et al., 2000; Karlson and Mann, 1952 and Weiss, 1974). In the bitch the neoplasm is usually found in the posterior part of the vagina, often at the junction of the vestibule and the vagina.

At the University of Texas, the tumour has been diagnosed to be present at the lip of vulva. Again, some times, it is seen surrounding the vagina, it may protrude from the vulva (Das et al., 2000 and Moulton, 1990). The gross appearance of the tumour on the external genitalia of both sexes appear initially as small hyperaemic papule that later progresses to nodular, papillary multilobulated cauliflower like or pedunculated proliferation measuring up to 15cm in diameter. The mass is firm but friable, and the superficial part is commonly ulcerated and inflamed (Brown et al., 1980).

It is also described as well circumscribed, unencapsulated expansile, densely cellular mass on the dermis, submucosa and subcutaneous connective tissue. The tumor cells are situated in a fibrovascular network of the skin. During rapid tumour growth, the colour is bright red owing to is

extensive vascularization. The tumour often oozes a serosanguinous or simple haemorrhagic fluid and eventually becomes ulcerated with a necrotic appearance. The continuous discharge from the external genitalia, soiling the floor, carpet and even clothes, is a nuisance for the owner. The bloody discharges may be confused with oestrous, urethritis or cystitis and in the male with prostatic. In older dogs, the differential diagnosis must also include urinary bladder and urethral neoplasms (Gordon et al., 1979). Phimosis or paraphimosis may complicate the cases in the male (McLeod and Lewis, 1972).

According to Das and Das (2000) there are a few cases on record where this neoplasm has caused actual mechanical obstruction to the flow of urine or has produced dystocia at whelping (Kenita et al., 1998). A number of bacteria which are important in urinary tract infection (UTI) were isolated from the external genitalia of dogs with TVT (Betamuzi and Kristensen, 1996). There is therefore strong indication that dogs with TVT are at high risk of contracting UTI compared to those without TVT, or extra genital lesions without any genital involvement. CTVS may also develop at extra genital sites, even when there are no genital lesions, for example, on the skin or in and around the mouth (Mulligan, 1949; Higgins, 1966; Stookey, 1969; Broadhurst, 1974 and Das et al., 2000).

Higgins (1966) suggested that many of the cutaneous sites where these tumours are found represent lesions caused by biting, and scratching, common in stray dogs, which predispose the skin to implantation of the tumour. He observed scars in the skin above subcutaneous tumours suggestive of previous wounds. Skin tumours were found on the back, flank, neck, head and limbs of dogs; they were usually up to 6cm in diameter, raised above the surface, often ulcerated and bleeding.

Metastatic Lesions

CTVT does not often metastasize as the tumour is generally considered a benign tumour (Madewell and Theilen, 1987; Neilsen and Kennedy, 1990; Roger, 1997; Gurel et al.,

2002). However, metastases may occur in some of the cases and lesions may some times be observed in extra genital region of some animals. The incidence of metastasis is quite low and occurs in 5 % or less of the cases (Gurel et al., 2002; Karlson and Mann, 1952, Adams and Slaughter, 1970, Oduye et al., 1973 and Moulton, 1990).

Metastasis also occasionally occurs to the inguinal lymph nodes (Adams and Slaughter, 1970; Oduye et al., 1973; Idowu, 1977; Das et al., 1986; Yang, 1987; Ayyappan et al., 1994 and Gurel, et al., 2002), the external iliac lymph nodes (Adams and Slaughter, 1970, Yang, 1987) cutaneous sites (Feldman, 1984; Das et al., 1989; Gandotra et al., 1993 and Ayyappan et al., 1994). Metastatic growth of this tumour has been recognized in the tonsils (Rottcher and Frank, 1972), orbit (Barron et al., 1963; Higgins, 1966; Adams and Slaughter, 1970 and Das and Sahay, 1989), brain (Adams and Slaughter, 1970; Madewell and Theilen, 1987; Neilson and Kennedy, 1990; Roger, 1996 and Hamir, 1985), other internal organs such as the spleen, liver, Kidney (Madewell and Theilsen, 1987; Neilson and Kennedy, 1990; Roger, 1996 and Harmir, 1985), adenohipophysis (Manning and Martin, 1970), as well as maxillary bone of the nose (Kimeto and Mugeru, 1974 and Harmir, 1985).

According to Das et al (2000) and Gordon et al (1979), tumours on the lips are similar to other lesions on the genitalia, but those in the mouth and on the tonsil appear more diffuse and bright red in colour. Orbital growth of the tumour may cause blindness (Das et al., 1986 and Moulton, 1990).

Das et al (2000) and Dass and Sahay (1989) found metastasis in about 7% of dogs with CTVS. Many of the reported cases of metastasis are actually mechanical extension of the growth or either auto-or hetero- transplantation to the skin, cervix, uterus and fallopian tubes from the tumour on the external genitalia. As in humans (Batson, 1942 and Das et al., 2000) the functional anatomy of the longitudinal vertebral venous sinuses in dogs provides the pathway for tumour metastasis to the cerebral

dural sinuses from primary sites in the pelvic and abdominal cavities. This system provides a bypass around the canal portal and pulmonary systems and so may serve as a partway for tumour metastasis (Worthman, 1956).

Histological Features

These were studied in considerable detail early in the twentieth century, firstly by Bashford et al (1905), who came to the conclusion that CTVS was not a sarcoma but an infective granuloma, and the following year by Sticker (1906), who erroneously called it 'Contagious Lymphoma'.

De monbreum and Goodpasture (1934) and Rust (1949) described this neoplasm as lymphosarcoma, Jackson (1944) described it as a tumor of the neuro-ectodermal cells or an aortic body tumor, Muligan (1949) described it as a histiocytoma; while Nanta et al (1949) described it as an infective granuloma. According to Orkin and Schwartzman (1960) and Moulton (1990) this tumor was not morphologically similar to a histiocytoma, a mastocytoma, an aortic body tumor or a seminoma. Following eletromicroscopic studies, Hernanderz-Jauregui et al (1973), Cockril and Beasley (1975) and Kennedy et al (1977) have suggested that it is a tumor of reticuloendothelial origin.

Moulton (1990) described it as a round cell sarcoma while Duncan and Prasse (1979) defined it as an undifferentiated round cell neoplasm of reticuloendothelial origin the histological result present similar findings irrespective of the location of the mass. In one report, According to Gurel et al (2002), the histology of the specimen excised from the gingiva revealed large areas of erosion, and inflammatory cell infiltration, mainly neutrophils were noted in some parts of the mucosa.

It was noted that the basal cells of the stratified squamous epithelium had formed papillary projection towards the muscular layer Atypical tumoral cells, round or polygonal in shape, with large nuclei that contain Unique nucleoli and a slight pinkish cytoplasm infiltrated throughout the sub-mucosal layer the majority of cells were hyperchromatic and numerous mitotic figures were seen. A fine stromal fibrovascular network proliferated between these cells. Similar findings

were observed from the biopsies excised from the nasal regions. In some area, focal necroses with haemorrhage were also present. Various stages of mitosis were prominent.

In another study, the tissue had a sheet-like arrangement with moderate to large amounts of cytoplasm and large nuclei (Fallon and Swayne, 1984). Georgia et al (1996) described their own Histological examination as round cells containing a large nuclei and a pale cytoplasm containing few small, clear round vacuoles. In another study with 11 tumors diagnosed histologically, Gonzalez et al (1999) confirmed other reports thus: uniform populations of large cells, round or oval in shape with scant but well defined cytoplasm, arranged in compact groups. The nuclear chromatin was fine and diffusely distributed and the nuclei which were ovoid and large, contained prominent centrally placed nucleoli cells groups were surrounded by small numbers of delicate collagen fibres. Small areas of focal lymphocyte infiltration were seen around blood vessels. Marchal et al (1997) on the other hand characterized TVT by compact sheets of round or polyhedral cells with a large, round, central nucleus usually containing a single prominent nucleolus.

Cytogenetic Features

There is a remarkable aberration in the numbers and morphology of the chromosomes of the constituent cells of CTVS (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 CTVS, there are usually oncogenes, which occasionally cause malignant diseases, such as transmissible venereal tumour (TVT) in dog (Katzir et al., 1985; 1987) and human breast carcinoma. The P53 tumour suppressor protein plays a central role in the maintenance of genomic integrity (Young Ki and Chul Joong, 2002).

Inactivation of P53 tumour suppressor gene by the point mutation and translocation events has been associated with a large number of human neoplasms (Hainaut et al., 1997). Recently, similar mutations have occurred within the canine cancer types including thyroid carcinoma (Devdee et al., 1994), mammary tumours (Van Leeuwen, 1996), osteosarcoma (Johnson et al.,

1998), circumanal gland adenoma (Mayr et al., 1997) and lymphoma (Veldhoeno et al., 1998). It is suggested that the vast clinical knowledge concerning the identification and treatment of canine and the apparent similarity of P53 inactivation in the tumours of some cancer patients identifies canine P53 as a potential target for anticancer therapy in the dog (Vedhoen and Milner, 1998).

Sequence analysis of canine LINEY elements and P53 gene in canine transmissible venereal tumour, indicates that the insertion of a truncated LINE 1 element upstream of the e mye gene may be the genetic event specific for the tumourigenesis of TVT disease (Young Ki and Chul Joong, 2002). It also showed that mutation of P53 gene at coden 316 in the TVT tissues although it wasn't existed from exon 3 to 8 of where there commonly occurred mutations in the human but it may be one of the etiological reasons for the development of TVT. In another study, Chu et al (2000), used the same PCR method to confirm the existence of CTVT cells using primers designed to cover the sequence between 5' end e-mye near the first exon and 3' end outside the LINE gene. The authors showed that only CTVT samples were positive for this sequence; samples from other tumors and normal tissues were negative. The same report showed that the sequence PCR products indicated that CTVT from Taiwan and other countries exhibited over 98% sequence homology thus; reconfirms that, worldwide all CTVT cells are very similar hence the probability of being from the same origin.

IMMUNOPHENOTYPE/HISTOCHEMICAL CHARACTERIZATION

Few attempts have been made to define the TVT immunophenotype. Laging and Kroning (1989) and Bacchi and Negrette (1990) did not find cytokeratin in the cytoplasm of TVT cells, while Sandusky et al (1987) found that Vimentin was immuno histochemically expressed but not S 100 protein, K and ? light chains, cytokeratin or neuron- specific enolase (NSE). The exact cytogenetic origin of this tumor also remained unknown for a long time. Mozos et al (1996) discovered lysozyme ad alpha-1 antitrypsin immunoreactivity, which

supported the hypothesis of a histiocytic immuno phenotype for TVT. Similarly, Marchal et al (1997) in their own study with fourteen specimens of neoplastic tissues collected from dogs of different ages, breeds and sexes showed that the expression of lysozyme by all the TVTs, and of the ACM, antigen by 11 out of the 14 tumours studied, is strongly suggestive of a histiocytic origin. Mozos et al (1996) were of the view that the four negatives they recorded may have been due to over fixation of the tissue. Lysozyme immuno reactivity was characterized by Moore (1986a) in normal canine tissues. Its distribution in dogs has generally been found to be similar to that described in humans and Lysozyme has also been found in macrophages, myeloid leukocytes and epithelial cells from exocrine glands as well as known or suspected canine histiocytic disorders such as systemic histiocytosis malignant histiocytosis and granulomatous panniculitis (Moore, 1986b). Whereas, in canine cutaneous histiocytoma, which is a Langerhans cell tumour (Moore et al., 1996), lysozyme expression has been found to be variable (Moore, 1986b and Sandusky et al., 1987) or even absent (Marchal et al., 1995). In all this staining techniques could be used in the differential diagnosis with lymphomas (Mozos et al., 1996).

Immunity

Specific circulating antibodies to antigens from the venereal tumour have been demonstrated in dogs bearing the tumour (De monbreum and Goodpasture, 1934; McKenna and Prier, 1966; Adams and Chineme, 1967 and Powers, 1968) and these antibodies are believed to be associated with the mechanism of natural regression that commonly occurs with this tumour. Complete regression is accompanied by the development of resistance to further successful implantation and growth of the tumour cells. Spontaneous regression is due to the formation of IgG in the sera of dogs after a period of (40 days) of tumour growth (Cohen, 1985). The antibody can be demonstrated on the cell surface membrane by direct immuno fluorescence (Epstein and Bennett, 1974), complement fixation and erythrocyte rosette formation (Cohen, 1978).

Spontaneous regression of experimentally transplanted CTVS is well-documented (Karlson and Mann, 1952; Stookey, 1969, Yang and Jones, 1973) and spontaneous regression of naturally occurring tumour has been alluded to by Higgins (1966). However, spontaneous regression is not recorded in most reports of naturally occurring CTVS (Rust, 1949; Cotchin, 1954; Prier and Johnson, 1964; Cohen, 1978; Brown et al., 1980; Laging and Kroning, 1989 and Singh et al., 1996). Spontaneous regression usually starts within 3 months after the implantation of the tumour and that the chance of self regression is remote in naturally occurring CTVS if the age of the tumour is over 9 months. (Das and Das, 2000). It seems reasonable to assume that failure on the part of the host to produce a sufficient amount of antibody may predispose to wide spread metastasis (Adams and Slaughter, 1970).

Newborn puppies from 'immune' dams (mothers with antibody to the tumour) show a longer latent period for tumour development and the neoplasm in these puppies are smaller and show more rapid spontaneous regression (Moulton, 1990). The biology of transplantation immunology and histocompatibility typing CTVS has also been investigated by Epstein and Bennett (1974). Neither chemotherapy nor radiotherapy, as currently used for CTVT, would be expected to abolish the host immune response, which plays a role in spontaneous regression of CTVT (Gonzalez et al., 2000). Diagnosis of CTVT is based on environmental history, clinical and cytological findings. Biopsy for histological examination is the most reliable method for diagnosis. If there is doubt about the histological diagnosis, a definitive diagnosis can be made by chromosome analysis and transmission studies (Karlson and Mann, 1952; Makino, 1963; Murray et al., 1969 and Yang, 1987). Histochemical and electron-microscopic studies will also help to detect CTVS (Hernander Jauregui et al., 1973 and Mozos et al., 1996).

RADIOGRAPHIC FEATURES

Radiography is not a popular diagnostic method in CTVT. However, radiography and Rhinoscopy have been used to examine the features of organs with metastatic lesion. In one

study, where nasal passages were involved, radiological features included (1) enlargement of the left palatine feature. (2) displacement to the right of the rostral aspect of the vomer bone (3) soft tissue density in the left nasal passages, with some radiolucent areas and (4) two metallic foreign bodies in the left caudal nasal cavity. Rhinoscopy (Needlescope ® - Dynamics) detected a 2x3cm mass inside the nasal cavity against the medial nasal septum and bilateral haemorrhagic mucosa (Fallon and Swayne, 1984).

TREATMENT

The ultimate goal of the treatment of the tumour is complete cure, which may be achieved by surgical excision, radiotherapy, immunotherapy and or chemotherapy. The high incidence of regression under natural conditions indicates that caution must be used in interpreting the effect of any therapeutic agents (Moulton, 1990).

Surgical Excision

Three principal type of surgery are used. They include the traditional type (Enblock excision or Debulking), electrosurgical excision, and cryosurgery. Recurrence following traditional surgery is not uncommon (Karlson and Mann, 1952; Prier and Johnson, 1964 and Brodey and Roszel, 1967) and was recorded in 22% (Rottcher and Frank, 1972); 68% (Idowu, 1989), 12% (Dass and Sahay, 1989), 38% Pandey et al., 1989) and 18% (Gandotra et al., 1993) of cases. Recurrence was minimal when orchidectomy or ovario-hystereomy was practiced along with chemotherapy (Pandey et al., 1989). Besides, surgery is impracticable in cases of generalized canine transmissible venereal tumour. If the tumour is resectable, electro-surgical excision or cryosurgical treatment as described by Idowu (1985) is desirable. This is because the tumour is easily transplanted to surgical wounds when using traditional operative methods. In fact, the author has witnessed recurrence of cases at the University of Nigeria Teaching hospital (UNVTH) following thermocautery surgical excision method.

An autochthonous vaccine supplemented with levamisol may also be used to prevent recurrence of tumour following surgical excision (Pandey et al., 1997, 1989 and Panchbhai et al., 1990). During

operations on male dogs, care should be taken not to damage the urethra of the penis. If the urethral orifice is involved, an indwelling catheter should be used until the area is healed (Das and Das, 2000). In cryosurgery, frozen nitrogen is tied to the mass after some time, the tumours mass becomes necrotic, and the colour becomes bluish and eventually falls off leaving behind a raw ulcer which heals eventually.

Radiotherapy

Radiotherapy has been reported to be effective against CTVS (Osipor and Golubera, 1976) but necessitates chemical immobilization of the dog during the radiotherapy (Boscos, 1988) with specialized personnel and equipment. Thrall (1982) applied a dose of 10GY (1000 rad) in each treatment and obtained complete regression in most cases following 1 to 3 treatments. Radiation treatment is often associated with complications. Acute adverse effects of radiation include dermal erythaemia, ulceration, mucositis, radiodermatitis, alopecia and excessive pigmentation and late development of other tumour types at the radiation site (Mcknight et al., 2000). However, Kenital et al (1998) noted no adverse reactions to treatment with radiation.

Immunotherapy

For immunotherapy, the generalized form of CTVS may be treated with transfusions of whole blood or serum from a recovered animal or a homogenate of the tumour may be used as an autochthonous vaccine (Bergell and Sticker; 1907, Crile and Beebe, 1908; Prier and Johnson, 1964, Power; 1906), but the results were variable. Beebe and Tracy (1907) used various bacterial toxins to treat CTVS case; comparatively satisfactory results were obtained from killed suspensions of chrombacterium pordigiosum alone or in combination with other organisms. Carteaude (1975) and Bennett et al (1975) also claimed an apparent positive effect from injecting bacteria toxins. In Zimbabwe, locally applied low dose of inter luekin 2 therapy has been found very effective against transplanted and spontaneous tumours in veterinary cancer patients especially transmissible venereal tumour in dogs.

Chemotherapy

Antimitotic agents, such as cyclophosphamide, methotrexate, vincristine sulphate, vinblastine or doxorubicin, are preferred chemotherapeutic agents for treating this tumour (Boscos, 1988). Chemotherapy of CTVS has been attempted using cyclophosphamide (Pandey et al., 1989 and Das et al., 1991a), methotrexate (Das et al., 1991a), Cyclophosphamide and prednisone (Hernandez Jauregni, 1974), vinblastine and doxorubicin (Calvert et al., 1982), but the responses were variable. Lawrence and John (1977) used combination chemotherapy with cyclophosphamide, methotrexate and vincristine to prevent metastasis of the tumour after surgery. Wasecki and Mazur (1977) and Singh et al (1996) observed almost complete recovery using Vinblastine intravenously at the dose rate of 0.1mg /kg body weight on 4 to 6 occasions at weekly intervals. Transient side effects, such as anorexia, vomiting or diarrhea, were found after the commencement of treatment.

Calvert et al (1982) observed complete remission of a tumour in a dog that had failed to respond to Vincristine, after further treatment with doxorubicin given intravenously at a dose of 30mg /m² surface area three times at weekly intervals.

Calvert et al (1982), Tuntivonich (1983), Idowu (1984), Das et al (1991b), Maiti et al (1995) and Singh et al (1997) found that vincristine sulphate at the rate of 0.025 mg/kg body weight intravenously at weekly intervals on 3 to 4 occasions is the most effective, safe and convenient chemotherapeutic agent, giving a better survival time even in CTVS patient with extra genital metastasis. Thus, it would appear that CTVS can be considered as a neoplasm amenable to chemotherapy with vincristine sulphate alone. The better response reported to the single drug vincristine or vinblastine than to combined chemotherapy may be due to their being less myelosuppression (Theilen and Made well, 1987), no opposite synergy (Bender and Hamel, 1991) non -development of resistance to all antineoplastic drug (Kanem and Winick, 1988) and no immuno suppression by methotrexate (Horton, 1990). Savatsis et al (1999) however, observed transient

deterioration of semen characteristics following treatment with Vincristine sulphate which returned to normal 15 days later. These changes were attributed to a direct effect of vincristine on the extragonadal spermatozoal reserve contained in epididymis and ductus deferens.

Combined Therapy

Combined treatments that have proven most effective for TVT are radiation and chemotherapy, particularly with vincristine as a single agent. Surgery is not considered an effective therapy for this tumour (Ogilvie and Moore, 1995 and Boscos, 1988). Lawrence and John (1977) used combination chemotherapy with cyclophosphamide, methotrexate and vincristine to prevent metastasis of the tumour after surgery. In other studies, combination chemotherapy yielded satisfactory results using cyclophosphamide, methotrexate and vincristine in clinical cases of CTVS without major ill effects or recurrence (McAfee and McAfee, 1977; Brown et al., 1980; Das et al., 1991 and Hoque et al., 1995). Complete and sustained remission of the tumours including the extra genital metastatic growths was observed (Das and Das, 2000).

CONTROL

Control of CTVT is difficult because stray dogs serve as reservoir. Dog owners and breeders should carefully examine all males and females before mating and should also prevent mingling of valued /priced dogs with strays (Rust, 1949). Careful examination of animals in breeding kernels before mating, with a view to avoid breeding affected animals and enforcement of dog licensing laws, controlling the pool of potentially infected, ownerless dogs roaming wild and sustained campaign of sterilization will control the incidence of the disease in countries where both these factors have been in operation, the incidence of the disease has fallen and the disease is rare (Head, 1967).

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