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MANAGMENT OF CANINE TRANSMISSIBLE VENEREAL TUMOR, RETROSPECTIVE STUDY OF FIVE CASES[1]

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ABSTRACT

Tumors are the most common fatal disorders observed in animals. Nearly 16 to 24% of dogs deaths are associated with tumors. For many years, the surgical excision of tumors in animals was the only treatment technique. Canine transmissible venereal tumor (TVT), also known as transmissible venereal sarcoma and Stricker's sarcoma, is a naturally occurring, horizontally transmitted infectious histiocytic tumor of dogs usually spread by coitus, but it may also be spread by licking, biting and sniffing tumor-affected areas. It has been observed occasionally in other canids, such as foxes, coyotes and jackals. It has also been known as infectious sarcoma, venereal granuloma, canine condyloma, transmissible sarcoma and transmissible lymphosarcoma. One of the goal of this study was to examine the method of treatment that is most effective.

Key words: transmissible venereal tumor, dogs, treatment

[1] original scientific paper

INTRODUCTION

The evolution of veterinary surgical oncology is closely related to the latest advances in human medicine. Advances in diagnostic methods, anesthesiology, supportive therapy, the education of surgeons, and the multidisciplinary principle of treating patients suffering from tumors have led to encouraging results. The latest findings on the molecular biology of tumors, immunology and virology suggest hope that unknown factors will be resolved soon for the treatment of diseased tumor diseased patients.

Although TVT has a worldwide distribution, its prevalence is highest in tropical and subtropical areas, particularly in the southern United States, Central and South America, southeast Europe, Ireland, Japan, China, the Far East, the Middle East and parts of Africa (Rogers, 1997.; Das and Das, 2000.). In enzootic areas, where breeding is poorly controlled and there are high numbers of free-roaming sexually active dogs, TVT is the most common canine tumor (Rogers, 1997.; Das and Das, 2000.; Gurel et al., 2002.; Higgins, 1966.). TVT is very frequent in the Republic of Macedonia. One of the reasons for this situation in the country is the relatively large population of stray dogs that are the reservoir of this tumor.

Because TVT is primarily spread by coitus, free-roaming, sexually intact mature dogs are at greatest risk (Das and Das, 2000.). Dogs of any breed, age, or sex are susceptible (Rogers, 1997.; Das and Das, 2000.; Cohen, 1985.). No heritable breed-related predisposition has been found (Das and Das, 2000.; Cohen, 1985.). In endemic areas, although dogs over 1 year of age are at high risk, TVT is most common in dogs 2 to 5 years of age (Das and Das, 2000.). The most common sites of involvement are the external genitalia, but other sites that can be affected through licking or sniffing include the nasal and oral cavities, subcutaneous tissues and the eyes (Rogers, 1997.; Das and Das, 2000.; Gurel et al., 2002.; Mukaratirwa and , 2003.; Cohen, 1985.; Rogers et al., 1998.; Papazoglou et al., 2001.; Brandao et al., 2002.; Albanese et al., 2002.). Spontaneous regressions occur and have been associated with immune responses against the tumor. Hence immunosuppression of any cause may be a risk factor for the development and maintenance of TVT and may predispose to widespread dissemination. When spontaneous regressions occurs, it usually starts within 3 months after implantation but rarely after 9 months (Cohen, 1985.).

TVT usually remains localized, but metastasis occurs in 5% to 17% of cases to draining regional lymph nodes (i.e. inguinal, iliac, tonsils), subcutaneous tissue, skin, eyes, oral mucosa, liver, spleen, peritoneum, hypophisis, brain

and bone marrow (Das and Das, 2000.; Rogers et al., 1998.; Pereira et al., 2000.; Ferreira et al., 2000.; Kang et al., 2004.). Because TVT is also transmitted by licking, sniffing and biting, many cases of reported metastases may instead actually be spread of the growth by mechanical extension or autotransplantation or heterotransplantation. Spontaneous regression can occur within 3 to 6 months of implantation, but the chance of self-regression is remote if the tumor is present for over 9 months (Das and Das, 2000.).

The archetypical TVT patient is a sexually intact young adult dog either living in or having travelled to an area endemic for TVT, with a history of contact (coitus, sniffing, licking or biting) withdogs of similar signalment (Rogers, 1997.; Das and Das, 2000.; Cohen, 1985.; De Lorimier and Fan, 2007.). The primary lesions are usually on the external genitalia. In the male, the tumor is usually located on the caudal part of the penis, requiring caudal retraction of the penile sheath for visualization (Das and Das, 2000.; Cohen, 1985.). Occasionally, it is on the prepuce. In the bitch, the tumor is usually in the posterior vagina or vestibule (Das and Das, 2000.; Cohen, 1985.). Tumors appear initially as small 1 to 3 mm hyperemic papules that progress by fusing together into nodular, papillary, multilobulated cauliflower-like or pedunculated proliferations up to 10 to 15 cm in diameter. The mass is firm but friable, with an ulcerated inflamed surface. The tumor often oozes a serosanguineous or hemorrhagic fluid. Clinical signs vary according to the location of the lesions. Lesions often causes chronic signs of discomfort or hemorrhagic discharge from penile sheath or vulva for weeks to months prior to diagnosis, which can result in anemia (Das and Das, 2000.; Cohen, 1985.; De Lorimier and Fan, 2007.). Lesions can predispose to ascending bacterial urinary tract infections but rarely interfere with micturition (Batamuzi and Kristensen, 1996.). Extragenital lesions cause a variety of signs, depending on anatomic location, such as sneezing, epistaxis, epiphora, halitosis, tooth loss, exophthalmos, skin masses, facial deformation and regional lymph node enlargement.

A presumptive diagnosis of TVT can be obtained based on history, clinical sings and physical findings in dogs with the classic presentation. Definitive diagnosis is based on cytologic examination of cells obtained by swabs, or imprints of the tumors or histologic examination of a biopsy from the mass. TVT is described as a discrete (or round) cell tumor. TVT has a characteristic morphologic appearance on cytopathology and is often diagnosed without need for histopathology. Exfoliative cytology demonstrates uniform discrete round to polyhederal-shaped cells with moderately abundant pale blue cytoplasm and an eccentrically located

nucleus with occasional binucleation and mitotic figures (Mukaratirwa and Gruys, 2003.; Cohen, 1985.). Single or multiple nucleoli are often observed, surrounded by clumped chromatin. The most characteristic feature is the presence of numerous discrete clear cytoplasmic vacuoles.

TVT will respond to many forms of therapy, however, chemotherapy is the most effective. Single-agent vincristine (0,5 to 0,7 mg/m² intravenous [IV], once weekly for 3 to 6 treatments) obtains a complete and durable response in 90% to 95% of treated dogs (Rogers, 1997.; Das and Das, 2000.; Rogers et al., 1998.; Papazoglou et al., 2001.; Brandao et al., 2002.; Gonzales et al., 2000.; Scarpelli et al., 2010.). Other single-agent and combination multiagent protocols employing cyclophosphamide, vinblastine, methotrexate and prednisolone have not demonstrated superiority to vincristine alone (Amber et al., 1990.; Singh et al., 1996.). Resistant cases can be treated with DOX (25 to 30 mg/m² IV, every 21 days for 3 treatments) (Rogers, 1997.).

Surgery can be an effective treatment for small localized TVT, however, surgery has an overall recurrence rate of 30% to 75% (Idowu, 1984.; Amber and Henderson, 1982.). Marginal surgical excision is not effective and it can be difficult to obtain wide surgical margins in the areas in which TVT typically appears (Idowu, 1984.; Amber and Henderson, 1982.). In addition, tumor transplantation into the surgical wound by contamination from instruments or gloves may also cause postoperative tumor recurrence.

MATERIALS AND METHODS

In this study, 5 dogs with TVT were treated, aged 2 to 5 years. The dogs are treated in the Veterinary Clinic "Dameski Veterina" from Prilep in the period from 01.09.2016 until 01.11.2017.

Commercial preparations in this clinical study were used:

1. Chlorhexidine digluconate (Pliva Sept Blue, Pliva, Zagreb, Croatia)
2. Xylazine 2% (Xyla, Interchemie, Netherlands)
3. Ketamine (Ketamine 10%, Alfasan International B.V., Netherlands)
4. Propofol (Propofol 1%, Fresenius Kabi, Austria)
5. Amoxicillin (Biocillin – 150 LA, Interchemie, Netherlands)
6. Vincristine Sulfate (VinCristine Sulfate, 2mg/2mL, Hospira, USA)

7. 0,9% saline (Sodium Chloride, Alkaloid, Macedonia)
8. Monofilament absorbable suture (Monosyn 2-0, 3-0, B.Braun, Spain)

Regarding the breeds, 2 dogs were Sharplaninec, one Samoyed, one Serbian hound and one was a mixed breed. Three of them were female and two males. The first female was a Sharplaninec, 5 years old, the second female was Samoyed, 3 years old and the third female of a mixed breed 3 years old. One of the males was Sharplaninec, aged 4 years and the other Serbian hound was 2 years old. The average age of the treated dogs is 3,4 years.

For all dogs the premedication was performed with xylazine in a dose of 0,25 – 0,5 mg/kg IV, while induction of anesthesia was performed with ketamine at a dose of 3-5 mg/kg IV and a propofol in dose from 1 to 5 mg/kg IV. Dogs were placed in a dorsal recumbency and a wide excision of the tumor was performed. Reconstruction of the mucous membrane of the vagina, preputium and penis was done with a resorptive monofilament, 2-0 or 3-0, depending the size of the dog.

After the surgery, all dogs were postoperatively receiving chemotherapy once a week for five weeks with vincristine sulphate at a dose of 0,5mg/m², IV. Patient control was performed every week when the chemotherapy with vincristine sulphate was applied, until the fifth week of the last administration. The samples taken from the removed tumors were fixed in 10% neutral formalin. The molding was performed in the form of paraffin blocks. From each paraffin block with microtome we obtained samples from tumor with a thickness of 4 microns. After the routine dewaxing procedure, all samples are colored by the H&E stain. The whole procedure was performed at the Pathology and Cytology Laboratory at the Clinical Hospital Bitola.

From one of the females, Samoyed, was taken vaginal swab, which was fixed with methyl alcohol and then colored with Gimza. This preparation was made in the Veterinary clinic "Dameski Vetrina", Prilep.

RESULTS

Treatment of dogs with TVT is complex and can not be successful unless combined therapy is performed. It is necessary to be careful in assessing

which treatment will be the best choice for a complete remission of the tumor. Patients who have TVT can be treated with excision surgery, chemotherapy, radiotherapy, immunotherapy or a combination of one of these ways. Surgical excision in the treatment of TVT is no longer applicable because this method is not effective if it is not combined with other treatment and relapses in a high proportion (between 18 and 60%) are reported.

All the cases in this study were surgically treated, with the removal of the tumor mass, which was easily accessible in all cases and all tumors were generally solitary. All operated dogs after that were treated for 5 weeks with chemotherapeutic vincristine sulphate, once weekly at a dose of 0,5mg/m^2,IV and all cases ending with complete remission and regression of the tumor. In all the controls that were performed after each application of chemotherapeutic vincristine sulphate, there was no recurrence of macroscopically visible tumor in all dogs and the same finding was found at last control that was performed after the fifth application of the vincristine sulphate.

DISCUSSION

Chemotherapy in this disease provides excellent results and can achieve up to 100% remission, as was the case with our patients. Trials with antineoplastic drugs made in the 1950s showed that antimitotic agents are a great choice for treating TVT. A whole range of chemotherapy has been studied in the treatment of TVT such as cyclophosphamide, methotrexate, cyclophosphamide with prednisolone, vinblastine with cyclophosphamide or methotrexate, vincristine, vincristine with doxorubicin, cyclophosphamide with methotrexate and vincristine. Vincristine, which was found to be a drug of choice for the treatment of TVT is included in protocols for the treatment of this disease from the eighties of the last century (Amber et al., 1990.; Das et al., 1991a.; Das et al., 1991b.). Many studies suggested that treatment only with vincristine sulphate is better than other combined chemotherapy (Das and Das, 2000.). Therefore the intravenous use of vincristine sulphate in a dose of 0,5mg/m^2 once a week and two week after complete remission of the tumor is a medication of choice, regardless of the size of the tumor, the present metastases and the duration of the disease. With this treatment, the dogs are fully recovered, without any influence on their behavior and

without reducing their reproductive ability. Side effects, such as partial anorexia and mild depression, may occur in less than 20% of treated dogs and these changes occur usually 1-2 days after the use of vincristine sulphate. In our examination none of the owners of the treated dogs noticed or reported any side effect. Chemotherapy with vincristine sulphate can cause temporary leucopenia, which occurs in less than 2% of cases. In males who are treated with vincristine sulphate, sperm may temporarily be with worse quality. The quality of sperm returns to normal within 15 days of the last application of vincristine sulphate (Gobello et al., 2002.).

In any case, before starting chemotherapy with vincristine sulphate, it is necessary to assess the general health of the animal and control it during the treatment. We also did with the dogs in our study and started chemotherapy when it was determined that the animals are in good and stable health.

Only surgical excision in the treatment of TVT in dogs is no longer applicable because of the high percentage of recurrences (50 to 68%) due to transplantation of tumor cell into the surgical wound (Panchbhai et al., 1990.). In male dogs, should be care not to damage the urethra and if the tumor is affected urethra, a catheter should be used which should remain until the complete healing of the dog (Das and Das, 2000.). The same should be considered in females, if the tumor is affected by the urethra, it is necessary to set up a catheter during the surgery. Nowadays, surgical excision is recommended for treating TVT in dogs, although, as in our case, with a combination with chemotherapy. This combination proved to be very effective in many cases where the percentage of remission is very high.

CONCLUSION

Canine TVT is the oldest known malignant tumor that is contagious and is primarily spread by coitus. This tumor can be easily diagnosed in veterinary clinics based on the history, clinical signs and cytological characteristics that are sufficient to establish an accurate diagnosis. Biopsy and histological examination can be of great help, especially when we have atypical cases.

According to our study and results, which largely overlap with other studies of this disease, TVT can be cured almost in all cases by combined treatment

of excision surgery, when the tumor is solitary, and with three to five cycles of chemotherapy with vincristine sulphate at dose of 0,5mg/m², IV. This therapy gave excellent results and complete remission of the tumor in all five treated dogs.

TVT is difficult to control in countries where is a large population of stray dogs, which are reservoirs of this infectious tumor. In any case, in order to control this tumor disease, is necessary, males and females dogs, to be examined before being mating, by a veterinarian doctor and exclude diseased dogs from the breeding process and prevent mating with stray dogs. With one continuous control of dogs before coitus and control and reduce the stray dog population, TVT cases can be greatly reduced.

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