Canine transmissible venereal tumor in the genital area with subcutaneous metastases in the head - case report.

Tumor venéreo transmissível canino na região genital com metástase subcutânea na cabeça – relato de caso.

Priscila D. Lopes¹*, Ana C.A.A. dos Santos², José E.S. Silva³*

¹Universidade Estadual Paulista, FCA V, Departamento de Patologia Animal, Jaboticabal, São Paulo, Brasil
²Faculdade de Ciências Agrárias de Andradina, FCA V, Andradina, São Paulo, Brasil
³Universidade Estadual Paulista, FMVA, Departamento de Fisiopatologia Clínica e Cirúrgica, Araçatuba, São Paulo, Brasil

Resumo: O tumor venéreo transmissível canino tem sido frequente em clínicas e hospitais veterinários, principalmente em populações de cães errantes e/ou sem raça definida, em fase sexual ativa. O presente estudo descreve o relato de um cão, sem raça definida, com três anos de idade. O animal apresentava uma massa tumoral na região do pênis e prepúcio e uma massa subcutânea, de aspecto rígido e indolor, sem ruptura da integridade estrutural na cabeça. Foi realizada anamnese, exame físico e citológico, sendo diagnosticado tumor venéreo transmissível canino. O tratamento instituído foi a quimioterapia associada a ivermectina. O tumor na região genital regrediu após quatro semanas de tratamento, porém na região subcutânea da cabeça não houve alteração, sendo indicada a excisão cirúrgica, seguida de quimioterapia e substâncias imunomoduladoras. Após um ano de tratamento o animal retornou ao hospital veterinário para avaliação, sem apresentar recidivas.

Palavras-chave: Ivermectina, neoplasia, rescisão cirúrgica, Sticker, vincristina

Introduction

Canine transmissible venereal tumor (TVT), also called Sticker tumor is a tumor that develops mainly in the external genitalia of dogs of both sexes, but the implementation may occur in extra-genital areas, especially in the conjunctiva mucosae, such as the oral cavity and nasal (Amaral et al., 2012). Metastasis occurs in less than 5% of cases, being observed in lymph nodes, spleen, skin and subcutaneous regions (Das e Das, 2000; Nak et al., 2005).

The TVT occurs primarily in young dogs, sexually active and stray animals, being more common in males than in females (Boscos e Ververidis, 2004). The tumor is transmitted by means of allogeneic transplantation, where viable tumor cells are transferred from one dog to another through intercourse, licks or even through the act of sniffing. This explains the primary cases that occur in the oral mucosa and nasal (Purohit, 2008; Stockmann et al., 2011; Behera et al., 2012).

In the male, the tumor is observed the penis and prepuce, and in females the affected sites are the vulva and vagina (Nak et al., 2005). Solitary or multiple tumor masses, which are ulcerated, hemorrhagic, friable and irregular in appearance similar to a “cauliflower” can be observed macroscopically. Tumor size ranges from millimeters to several centimeters with dark red to grayish pink coloration (Das e Das, 2000; Purohit, 2008). Large cells, round or oval indistinct contours are observed histologically. Another feature of this neoplasm is the presence of inflammatory cells and mitotic figures. The nucleus is round or oval, centrally located, variable size with coarsely granular chromatin with one or two prominent nucleolus. The cytoplasm is slightly basophilic and multiple vacuoles, small and light, that often accompany cell board (Stockmann et al., 2011).

The diagnostic of TVT is done considering the history of the animal, gross lesions and the cytological
examination by fine needle aspiration or smear per impression and histopathology (Das e Das, 2000; Amaral et al., 2004). The cytological examination is a complementary test, with a simple, quick, minimally invasive and cost-effective method, directing thereby the appropriate type of treatment for the animal. The tumor may be confused with mastocytoma, histiocytoma and lymphoma, and should emphasize the importance of differential diagnosis (Amaral et al., 2007).

Spontaneous healing can occur in dogs with TVT, since the immunity of the animal would fight tumor cells, otherwise the animal should be subjected to treatment with radiotherapy, chemotherapy, immunotherapy and surgical excision (Andrade et al., 2009; Lapa et al., 2012). Postoperative recurrence can occur in 12-68% of cases. The treatment of choice for TVT is chemotherapies and radiation therapies. Today many agents and chemotherapy protocols, such as cyclophosphamide, vincristine sulfate, vinblastine, doxorubicin and methotrexate are used, these drugs being used as a single agent or combined with each other. Immunotherapy has been adopted in the case of immunosuppressed animals, using substances that act on the immune system (Das e Das, 2000).

The most effective, safe and convenient therapy in clinical practice is the use of vincristine as a single agent, but its extensive use in the TVT treatments, combined with the existence of malignant neoplasm characteristics, has increased the number of applications of the drug. The use of vincristine in resistance has been correlated with the overexpression of a protein molecule of the plasma membrane, called P-glycoprotein (Pouliot et al., 1997). The molecule is expressed in various tissues such as kidney, liver, colon, brain, lung, peripheral blood, normal bone marrow. Tumors derived from tissues expressing high amounts of P-glycoprotein exhibit intrinsic resistance to chemotherapy (Gaspar et al., 2010), since this molecule acts as a carrier the membrane, functioning as an efflux pump dependent on the energy generated by ATP hydrolysis, resulting in a range transport of drug into the extracellular medium, thus reducing its concentration to levels just lethal (Korystov et al., 2004; Gaspar et al., 2010). Some studies have shown that the combination of vincristine sulfate with ivermectin has shown beneficial, since this antiparasitic used as substrate the P-glycoprotein, and thereby decrease the amount of the molecule in the tissue, thereby potentiating the antitumor treatment and slowing treatment resistance (Andrade et al., 2009).

**Case report**

This study reports the case of an animal of the canine species, mixed breed, male, 3 years old, weighing 11.5 kg that had free access to the street. The dog was treated at the Veterinary Hospital the Faculdade de Ciências Agrárias de Andradina - SP (FCAA) having a crumbly dough in the penis region and prepuces that bled easily, ulcerated and had like a “cauliflower” appearance. The head had a rigid and painless mass without disruption of structural integrity, measuring 5x7 cm, ulcerated not extending from the upper eyelid and zygomatic region to the region of the temporal bone in the skull, focusing on the right antimere (Figure 1A). It was confirmed by x-ray and ultrasound that was no involvement of other local or internal organs.

The vital parameters were within normal animals. On cytological examination, performed by printing the tumor mass was observed the presence of round cells with large nuclei, prominent nucleolus and frequent mitotic figures confirming the clinical diagnosis of canine transmissible venereal tumor (TVT). Then was performed a radiograph to know the boundaries of the tumor (Figure 1B).

The treatment was the administration once a week, for four weeks, the following drugs: initial administration of 50 mL of saline solution 0.9% and 0.26 ml of vincristine (respecting the calculation dose/m²) intravenously, respectively. Ivermectin subcutaneous (400 µg /kg) was then given. During the 5º week the tumors

Figure 1- Physical characteristics of canine transmissible venereal tumor. (A) Radiographic view of the skull, observe the area of radiopacitity at the level of the frontal bone; (B) Mass starting in eyelid-zygomatic region, extending to the region of the parietal bone in the skull.
of the penis and prepuce regressed, however there was no tumor regression of the head, indicating surgical excision was needed.

Surgery was performed through a semi-lunar incision caudal to the tumor, and other midline incision of the skull to the base of the nose, followed by exposure to dilatation and delineation of the tumor (Figure 2A), which reached from the subcutaneous tissue to the bony parts. The skin suture was performed with nylon string by the Wolf technique for the reduction of dead space which was compromised by the loss of tissue. Macroscopically, the tumor presented itself lobulated and encapsulated, with friable masses.

After surgery a seroma formed that was controlled with punches and ice packs for five days. Furthermore, five-week treatment with chemotherapy cyclophosphamide (50 mg/m²) and immunomodulators interferon-α (10 IU / kg daily) and levamisole (0.2 mg / kg three times per week) was prescribed. The animal was seen weekly for five months and after one year the patient returned to the veterinary hospital. During this period, the dog showed no recurrence (Figure 2B).

Discussion

The TVT is a cancer that affects mainly stray dogs, mixed breed, with a mean age of three to eight years, i.e., their active sexual cycle, being intercourse the main form of transmission. The tumor is often found in the genital regions, but can occur in other extragenital regions (Das e Das, 2000; Stockmann et al., 2011). In this present case report suggests that the first site of the tumor was the external genitalia of a male dog, which then resulted in subcutaneous metastases in the head, forming a rigid mass without breaking skin. The cases of metastases are rare, their occurrence more in males and immunosuppressed dogs (Bocos e Ververidis, 2004; Stockmann et al., 2011).

The treatment of choice for the TVT is vincristine as a single agent applications being performed weekly for six weeks, which is not suitable, since this drug is neurotoxic, and cause gastrointestinal lesions, myelosuppression and lesions at the site of application (Souza et al., 2000; Silva et al., 2007; Gaspar et al., 2009). However, resistance to chemotherapy has been an inconvenience during treatment requiring more sessions chemotherapy to cure the TVT. One of the causes of resistance to treatment is by overexpression of P-glycoprotein in various tissues, which carries several drugs into the extracellular medium, thus interfering in the treatment (Pouliot et al., 1997; Koryostov et al., 2004). Many studies have demonstrated that the administration of vincristine associated with ivermectin has shown satisfactory results, due to synergy between these two drugs (Lapa et al., 2012). The antiparasitic in question uses the P-glycoprotein as a substrate for metabolism, these being excreted by kidney, biliary and intestinal route. Thus, the protocol used in the case of vincristine, association with ivermectin was effective in eliminating cancer of the penis and prepuce the animal since the amount of chemotherapy applications has been reduced to four weeks, a significant finding because promoted a decrease the number of administrations, faster recovery patient and reduced cost of treatment. This finding also corroborates other authors (Drinyaev et al., 2004; Andrade et al., 2009; Lapa et al., 2012).

Although the protocol used have been effective in curing tumors in the genital region of the dog, on the other hand it was not effective in eliminating the TVT subcutaneous head. Second Gaspar et al. (2010), the non primary tumor masses have higher expression of P-glycoprotein. It is believed that for this reason, the subcutaneous tumor was more resistant to treatment with chemotherapeutic associated with ivermectin. Moreover, it appears that the location and the biological characteristics of the tumor, such as cytomorphology and the tumor cell population, were instrumental in a tumor with greater malignancy, hindering thereby the treatment (Amaral et al., 2007; Gaspar et al., 2007). In this case, we opted for surgical resection, followed by sessions with chemotherapy and immunomodula-
tors. The use of chemotherapy after surgical resection of the tumor is indicated in an attempt to prevent the recurrence of neoplastic tissue (Das & Das, 2000; Eze et al., 2007).

The recurrence rate after surgery and the difficulty in obtaining a complete excision in some locations, surgery becomes a bad option in many cases. In the case of TVT metastatic, the surgery is useless, besides being an invasive and traumatic procedure with high risk of scar deformation (mainly electro dissection) (Souza et al., 2000). The surgical procedure is usually adopted in emergency cases where the tumor has increased in size. In the present study, the subcutaneous tumor was difficult to locate due to its proximity to the eye region. However, treatment of drugs associated with the surgical procedure resulted in clinical cure no recurrence of the tumor, noting that the use of immunomodulators and chemotherapeutic in that case was an effective alternative.

**Conclusion**

Treatment associating vincristine with ivermectin was effective, as an alternative in cases of resistance to use with conventional antineoplastic treatment using vincristine sulfate alone. However, this treatment was not effective in curing subcutaneous tumor in the head. It is believed that the location and biological characteristics may have hindered treatment in this region. Having adopted a more invasive protocol for the cure of subcutaneous tumor, surgical removal followed by chemotherapy showed satisfactory results because all possible remaining TVT cells were destroyed, and consequently there was no occurrence of tumor recurrence after one year of treatment.

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