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Clinical and therapeutic aspects of dogs with transmissible venereal tumor in nasal cavity: report of two cases

Aspectos clínicos e terapêuticos de cães acometidos com tvt em cavidade nasal: relato de dois casos

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ABSTRACT: Canine transmissible venereal tumor is a contagious neoplasm typically found on the external genital mucosa of dogs of both sexes; however, it can also occur in extragenital areas, such as the nasal cavity. It spreads through contact with damaged tissues or mucous membranes containing viable neoplastic cells, or through the hemolymphatic system. This study aimed to report two cases of canine transmissible venereal tumor in the nasal cavity of two intact male mixed-breed dogs. Both animals exhibited neoplasm in the nasal septum with oral involvement. Diagnosis in both cases was made through clinical and radiological assessments; the neoplasia was confirmed through cytological analysis. Radiological assessment showed retraction of the alveolar bone adjacent to the right premolars in the animal in Case 1, whereas in the animal in Case 2, it revealed an increase in volume in the dorsal portion of the skull, with radiopacity, extending to the frontal, incisive, and nasal bones, confirming lysis in these bones. Animal in Case 1 was subjected to chemotherapy with doxorubicin, however, it experienced recurrence in the oronasal region after some time of tumor remission, requiring treatment with vincristine and subsequent surgical resection. Considering Case 2, the animal responded well to treatment with vincristine sulfate. The animal in Case 1 was discharged 6 months post-procedure, whereas the animal in Case 2 had a good response to the treatment of choice. Clinical information on cases of canine transmissible venereal tumors in the nasal region is essential, mainly regarding therapeutic success, diagnosis, prognosis, and treatment duration.

KEYWORDS: Doggs; mucosa; neoplasia; TVT; vincristine.

RESUMO: O tumor venéreo transmissível canino é uma neoplasia contagiosa e é tipicamente observada na mucosa genital externa de cães de ambos os sexos, mas também pode ocorrer em áreas extragenitais, como a cavidade nasal. A disseminação ocorre através do contato de tecido lesionado, de mucosas com células neoplásicas viáveis ou através da via hemolinfática. O objetivo deste relato é descrever dois casos de tumor venéreo transmissível canino na cavidade nasal de dois cães machos, não castrados, sem raça definida. Os dois animais apresentavam neoplasia nos septos nasais com acometimento oral. Em ambos, o diagnóstico foi possível pela avaliação clínica, exame radiográfico e confirmação da neoplasia através do exame citopatológico. No primeiro caso o exame radiográfico constatou retração óssea em osso alveolar adjacente à pré-molares direitos, já no segundo havia aumento de volume, com radiopacidade na porção dorsal do crânio e extensão aos ossos frontal, incisivo e nasal, atestando então a lise dos mesmos. No caso 1, optou-se pelo tratamento quimioterápico com doxorrubicina, porém, após algum tempo da remissão do tumor, o animal apresentou recidiva na região oronasal, tendo que iniciar o tratamento com vincristina e posteriormente ressecção cirúrgica; já o caso 2, respondeu bem ao tratamento com sulfato de vincristina. O animal do caso 1 teve alta após 6 meses do procedimento e o animal 2 teve boa resposta com o tratamento de eleição. Informações clínicas em casos de TVTc nasais, principalmente sobre sucesso terapêutico, diagnóstico, prognóstico e duração do tratamento, são essenciais.

PALAVRAS-CHAVE: Cães; mucosa; neoplasia; tumor venéreo transmissível; vincristina.

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INTRODUCTION

Canine transmissible venereal tumor (TVT), Tasmanian devil facial tumor, and a type of neoplasia resembling leukemia exclusively affecting mollusks (*Mya arenaria*) are the only naturally transmissible malignant neoplasms in animals (Metzger; Goff, 2016). TVT was first reported by researcher Huzard in 1820 (Araújo, 2019), initiating a series of research studies on this subject. In 1904, this tumor was described in detail and named lymphosarcoma (Scarabello; Oliveira; Romariz, 2019; Araújo, 2019; Ortiz, 2021). The implantation of tumor cells occurs through contact with damaged tissues or mucous membranes containing viable neoplastic cells, or through the hemolymphatic system (Murchison *et al.*, 2014).

TVT is more frequent in dogs (Horta *et al.*, 2022) and is characterized as a highly contagious round cell tumor. It is transmitted through the implantation of tumor cells in susceptible individuals through mating, as well as through contact with contaminated environments or infected animals (Groth *et al.*, 2021; Ortiz, 2021; Conte *et al.*, 2022).

TVT in the nasal cavity has a higher incidence in male dogs (Ojeda *et al.,* 2018; Ignatenko *et al.,* 2020), and only 3.5% of dogs diagnosed with this neoplasm will exhibit nasal lesions (Huppes *et al.,* 2014). Its clinical presentation includes sneezing and bloody and/or purulent discharge, with potential involvement of adjacent bone structures, oronasal fistula formation, and facial asymmetry (Ignatenko *et al.,* 2020).

Diagnosis is based on clinical symptoms, medical history, physical examination, and definitive diagnostic methods such as cytology, slide imprint, or fine-needle aspiration (FNA) (Araújo, 2019; Souza *et al.*, 2020). Histopathological analysis, immunohistochemistry, and polymerase chain reaction are alternative diagnostic methods for cases with inconclusive cytological analysis, typically in poorly differentiated tumors (Setthawongsin *et al.*, 2018).

Vincristine sulfate is the most effective and commonly used antineoplastic chemotherapy for TVT cases (Horta *et al.*, 2022). However, the tumor may exhibit resistance to vincristine, which can be substituted with doxorubicin, thus initiating a new chemotherapy protocol (Huppes *et al.,* 2014). Radiotherapy, surgery, and immunotherapy are alternative therapies; however, antineoplastic chemotherapy has presented higher effectiveness in most cases (Tinucci; Castro, 2016).

In this context, this study aimed to report two cases of extragenital canine transmissible venereal tumor with similar clinical characteristics but distinct therapeutic responses. The cases described in the presented study presented similar clinical signs and macroscopic and radiological lesions.

CASE 1

A 6-year-old intact male mixed-breed dog, weighing 7 kg, was attended at the Prof. Dr. Ivon Macêdo Tabosa University Veterinary Hospital at the Federal University of Campina Grande, Campina Grande, Paraiba, Brazil. The medical history revealed an increase in volume in the nasal region, with a 40-day progression. Additionally, the animal experienced sneezing episodes accompanied by bloody nasal discharge.

The physical examination showed an increase in volume in the right nasal region (Figure 1A), with a firm and and adherent consistency, measuring approximately 3.2×2.5×3 cm, eliciting pain on palpation. Inspection of the oral cavity enabled the observation of an ulcerated, friable mass in the gum area, with a cauliflower-like appearance, draining a bloody discharge and exhibiting an oronasal fistula, with possible bone involvement (Figure 1B). No other abnormalities were observed in the animal.

Complementary exams were conducted, and no hematological abnormalities were found, as the levels were within the reference range (complete blood count, albumin, alanine aminotransferase - ALT, aspartate aminotransferase - AST, creatinine, gamma-glutamyl transferase – GGT, and total proteins). Evaluation of radiographic images in latero-lateral and ventral-dorsal projections of the cranial region indicated retraction of the alveolar bone adjacent to the right premolars (Figure 1C). A sample was collected for cytological analysis, showing a hypercellular sample composed mainly of round cells with clear to basophilic cytoplasm and numerous diffuse vacuoles. There was a high nucleus-to-cytoplasm ratio, with oval nuclei, homogeneous chromatin, and well-evident nucleoli. Anisocytosis, anisocariosis, atypical mitoses, red blood cells, leukocytes, and background bacteria were also present. The diagnosis was transmissible venereal tumor of the plasmacytoid type.

The dog was enrolled in a research project, with permission form signed by the guardian (protocol CEUA/CSTR no. 49/2021), and then a doxorubicin chemotherapy protocol was initiated. The choice to use doxorubicin was related to a research project in which the animal was enrolled at the same institution. Seven sessions of chemotherapy with doxorubicin were performed, with 21-day intervals between sessions. The dose used was 1 mg kg^{-1}, administered exclusively intravenously over a 30-minute period, not exceeding the cumulative dose of 180 mg m^{-2}, along with the intramuscular application of promethazine (0.5 mg kg^{-1}) 15 minutes

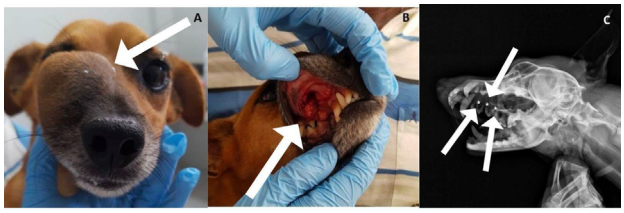

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Figure 1. Macroscopic aspects of a lesion in a 7-year-old male mixed-breed dog. (A) Increase in volume in the right nasal region, measuring approximately 3.2×2.5×3 cm. (B) Ulcerated, friable lesion in the gum area, draining a bloody discharge, with the presence of an oronasal fistula. (C) Radiographic image suggestive of retraction of the alveolar bone adjacent to the right premolars.

before each session. Echocardiographic monitoring was not performed due to the young age, low body weight, and good clinical condition of the animal, and the absence of echocardiogram equipment at the institution. Hematological analysis, including complete blood count, creatinine, ALT, and alkaline phosphatase (ALP), was conducted to monitor potential side effects of the antineoplastic drug. Material was collected at the end of each session for cytological analysis, focusing on monitoring tumor remission (Figure 2), which occurred after 147 days from the beginning of the chemotherapy protocol.

Oncological follow-up was carried out two months after tumor remission, when the animal exhibited an increase in volume in the nasal region with persistent oronasal fistula, emitting a foul odor. Samples from both sites were collected and sent for cytological examination, resulting in diagnosis of TVT. The treatment of choice was not administered due to the animal's enrollment in a research project; therefore, a chemotherapy protocol with intravenous administration of vincristine sulfate at a dose of 0.75 mg m^{-2} was initiated, with a 7-day interval between sessions, totaling five sessions. However, these sessions were not sufficient for complete remission. According to personal reasons of the guardian, it was not possible to continue with systemic chemotherapy, which was replaced with metronomic chemotherapy consisting of oral administration of cyclophosphamide (15 mg m^{-2}) every 24 hours for 30 days, with monthly hematological monitoring. However, this protocol was also ineffective.

Considering the neoplasm's resistance to chemotherapy, the oronasal fistula was surgically corrected for the comfort of the animal and the visible mass was excised. The metronomic chemotherapy protocol was resumed after the postoperative period. The animal underwent oncological follow-ups every two months. No recurrences were observed and the animal was discharged six months after the surgical procedure.

CASE 2

Case 2 involved a 9-month-old male mixed-breed dog with a clinical history of edema in face and nasal cavity, progressing for 4 months. The animal had been treated with azithromycin at a dose of 10 mg kg-1 orally administered every 24 hours for three days, which resulted in a clinical improvement, according to the guardian.

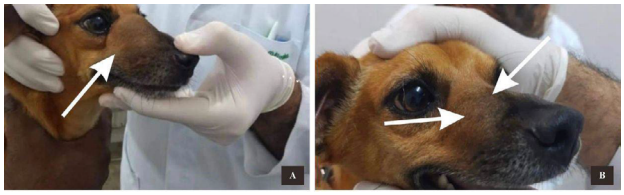

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Figure 2. Animal presenting an increase in nasal volume during treatment of transmissible venereal tumor (A) and the same animal after surgical remission of the neoplasm (B).

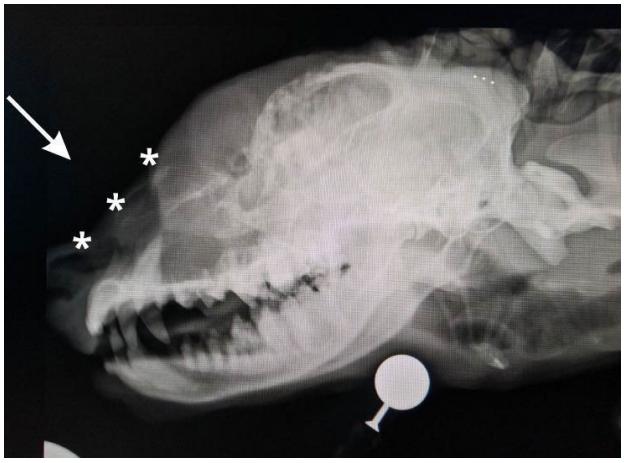
The clinical examination revealed body temperature of 40.3 °C (37.5 to 39.3 °C), with no abnormalities in other physiological parameters (heart and respiratory rates, capillary refill time, auscultation, lymph nodes, and abdominal palpation). The animal's body condition score was 1 (1-to-5 scale). The ocular mucous membranes were congested, with a purulent and bloody discharge. The hard palate exhibited an increase in volume.

The main lesion was in the nasal cavity, affecting the entire snout and showing hemorrhage. The lesion ascended to the frontal region, involving the ocular area, extending to the oral cavity. The primary clinical suspicion was an abscess due to the presence of a purulent discharge; an extragenital TVT was included as a differential diagnosis. Complementary tests were performed, including a complete blood count, skull X-ray, and cytology through FNA in the nasal region.

The radiological examination showed an increase in volume, with radiopacity, in the dorsal portion of the skull, extending to frontal, incisive, and nasal bones, indicating lysis in these bones (Figure 3).

The cytological analysis confirmed the presence of a plasmacytoid-type TVT, as the samples exhibited round cells with a moderate amount of cytoplasm and distinct vacuoles. A chemotherapy protocol was initiated, consisting of administering vincristine sulfate (dose of 0.5 to 0.75 mg m^{-2}) at weekly interval for 6 weeks. The dog was monitored through complete blood count tests and serum biochemical analysis before each session.

A new cytological analysis was conducted at the end of the treatment, indicating no further cellular evidence of TVT. The animal was subjected to a skull X-ray, which showed persistent bone lysis but the absence of volume increase in the dorsal-frontal part of the skull.



Source: author's collection.

Figure 3. Macroscopic aspects of a lesion in a 9-month-old male mixed-breed dog. Increase in volume, with radiopacity, in the dorsal part of the skull, extending to frontal, incisive, and nasal bones.

DISCUSSION

The two dogs in the reported cases exhibited facial deformity due to an increase in volume caused by transmissible venereal tumor (TVT); however, the tumor lesions were inside the nasal plane, making visual inspection and collection of material for cytological analysis challenging. These findings are consistent with the results reported by Ojeda; Mieres; Soto; Arnes *et al.* (2018), who described a nasal TVT with similar characteristics. Regarding clinical signs, one of the dogs presented frequent episodes of sneezing, and both dogs had significant nasal discharge, as described by Ignatenko *et al.* (2020).

Radiological assessments revealed bone involvement in both animals. The animal in Case 1 exhibited changes indicative of retraction in the alveolar bone adjacent to the right premolars. The animal in Case 2 exhibited changes indicative of bone lysis in the frontal, incisive, and nasal regions. Radiological exams are not specific for TVT diagnosis; however, imaging findings are a useful tool contributing to the choice of appropriate therapy in cases of extensive lesions with potential bone involvement (Joshi; Alam; Dimri, 2016).

Antineoplastic chemotherapy was initially chosen as treatment for Case 2 due to its well-documented efficacy in scientific literature. Vincristine sulfate is the drug of choice for TVT cases, acting on the cell cycle and consequently inducing apoptosis of neoplastic cells (Gonzalez *et al.*, 2000). Studies have reported a remission rate of up to 90% for malignancies; however, resistance to chemotherapy has been found is some cases, mainly attributed to mechanisms developed by P-glycoprotein (P-gp), a multidrug resistance protein 1 (MDR1) (Zandvliet *et al.*, 2015). Chemotherapy with doxorubicin was chosen for Case 1 because the animal was enrolled in a research project. Additionally, doxorubicin is the antineoplastic drug of choice to initiate a new chemotherapy protocol in cases of tumors resistant to vincristine (Das; Das, 2000). Furthermore, the cytological classification of TVTs (plasmacytoid cells) results in increased expression of P-gp, enhancing the potential for resistance to these chemotherapeutics (Gaspar *et al.,* 2010). However, P-gp expression is not the unique resistance mechanism that has been reported; this resistance pathway was not assessed in the animals of the present study.

TVTs resistant to therapeutic drugs typically exhibit neoplastic cells with a more aggressive potential, larger nucleoli, a higher propensity for metastasis (Amaral *et al.*, 2011), and overexpression of P-gp, which is a determining factor for cases of chemotherapy resistance, as it can recognize chemotherapy agents and transport them to the extracellular environment, reducing drug concentration within the cells (Binkhathlan; Lavasanifar, 2013). Doxorubicin and vincristine are some of the cytotoxic substances susceptible to P-gp (Maia; Rumjanek, 2004), potentially resulting in multidrug resistance (Tsujimura; Tanaka, 2012).

One of the reported cases presented a TVT resistant to the initially stablished chemotherapy protocols, requiring the inclusion of multimodal therapy, which included chemotherapy with intravenous administration of the maximum tolerated dose of doxorubicin, combined with intramuscular administration of promethazine, intravenous administration of vincristine sulfate, and metronomic chemotherapy with cyclophosphamide. Surgical correction of the fistula and excision of the mass were performed, although these procedures were not included in the therapy of choice because high metastasis rates (from 30 to 75%) occur due to surgical implantation of tumor cells through instruments or gloves that have had contact with the primary neoplastic lesion (Kunakornsawat *et al,* 2010). However, the animal does not fit into this statistic, as it is still in total remission due to the multimodal treatment applied.

CONCLUSIONS

Clinical information on canine transmissible venereal tumor (TVT) in the nasal region is still scarce, mainly regarding therapeutic success involving different treatment modalities in veterinary oncology. However, cases of nasal lesions with chemotherapy resistance are not well-described in the literature. Additionally, including TVT in the diagnosis for animals showing chronic clinical signs of nasal cavity diseases is important. A detailed documentation of these cases, including the use of multimodal therapy, is essential to support the veterinary literature.

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