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CASE REPORT
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Transmissible Venereal Tumor in a Border Collie Bitch with MDR1 Mutation - Successful Treatment with Lomustine

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ABSTRACT

***Background*:** The multidrug resistance (MDR1) gene is responsible for encoding P-glycoprotein (P-gp), a transmembrane efflux pump of intracellular xenobiotics that regulates the distribution, absorption, and elimination of substances in the body. If a mutation occurs, the protein becomes non-functional or partially functional, resulting in higher bioavailability and lower hepatic, renal and intestinal elimination of drugs transported by this route, increasing the risk of toxicity. This report concerns a case of transmissible venereal tumor (TVT) in a Border Collie bitch, with a mutated MDR1 gene, who received an alternate treatment with lomustine.

***Case*:** A 2-year-old intact Border Collie bitch, weighing 19.8 kg, whit history of vaccination, deworming, parasite control treatments up-to-date, progestogen use and access to the streets, was treated at the Veterinary Hospital of the State University of Northern Paraná (HV-UENP), Bandeirantes, PR, Brazil. The main complaint was a reddish wound present in the vaginal region for 2 weeks, with active bleeding and abnormal odor. On physical examination, a "cauliflower" lesion was observed in the vulva, with bleeding upon manipulation and foul odor. Through palpation of the vaginal canal, the presence of a rough and firm lesion, friable upon touch was established, with characteristics similar to the vulvar lesion. The suspicion of TVT was confirmed by cytological examination via vaginal canal swab, fine needle aspiration (Fna) and vulvar imprint. Due to the patient's race, testing for the MDR1 mutation was requested and returned positive for the MDR1 gene mutation (homozygosity); for this reason, the use of 3 sessions of lomustine [Citostal® at a dose of 70 mg/m^2, orally every 21 days] was prescribed, since animals carrying this mutation are sensitive to conventional TVT treatments. The patient showed complete remission, confirmed by negative vaginal cytology after the 3rd session of the established chemotherapy treatment.

***Discussion*:** TVT is a highly prevalent clinical condition, characterized by the development of highly vascularized masses of friable consistency affecting mucosal regions, especially the genitals of dogs. TVT transmission happens when viable tumor cells implant themselves onto the mucosa surface or injured membranes. This process can occur through intercourse, biting, or licking the affected area, facilitating the spread between healthy and contaminated individuals. The MDR1 gene mutation, characterized by the deletion of 4 base pairs, can be found in several dog breeds, with a higher prevalence in the collie lineage and grazing breeds. Given this genetic predisposition, testing for the MDR1 gene mutation was indicated for the patient in order to provide a safer treatment, since the 1st-choice antineoplastic drug, vincristine sulfate, is absorbed and excreted by P-gp. The homozygous mutation of the MDR1 gene indicated the need to modify the conventional treatment, opting for lomustine or, alternatively, reducing the usual doses of vincristine sulfate. It is important to note that other medications for TVT treatment, such as doxorubicin and vinblastine, should be prescribed cautiously, as animals may be sensitive to these medications. It is possible to conclude that: an individualized approach in the treatment of the canine border collie patient, diagnosed with TVT and carrying the homozygous mutation of the MDR1 gene was effective, with the use of 3 sessions of lomustine resulting in complete remission confirmed through cytological examination, after the last session.

Keywords: TVT, ABCB1-1 Δ, homozygosity, lomustine, P-glycoprotein, chemotherapy, neoplasia.

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INTRODUCTION

The multidrug resistance gene (MDR1), also known as ABCB1-1 Δ, is the gene responsible for encoding P-glycoprotein (P-gp) [13,18], acting on the transport of substances from the intracellular to the extracellular environment, in addition to being responsible for the absorption, distribution and excretion of several drugs in the body, involving energy expenditure [9,12,13]. Mutations in this gene result either in a defunct P-gp, or one with reduced capabilities, which hinders excretion or increases uptake of drugs mediated by this way [12].

Transmissible venereal tumor (TVT) is a contagious neoplasm that mainly affects medium-sized dogs, aged between 1 and 15 years, with an average age of 7 years [15]. The highest incidence occurs in bitches, the most frequently affected location being the vagina (53% of cases), vulva (33%) and extra-genital region (14%) [7]. Antineoplastic chemotherapy is the preferred treatment option due to its less invasive nature compared to surgical procedures [2,5,8].

This paper describes individualized conduct, based on research of the MDR1 genetic mutation in a Border Collie bitch, who received care at the Veterinary Hospital of the State University of Northern Paraná (HV-UENP), diagnosed with TVT and treated with lomustine.

CASE

A 2-year-old intact Border Collie bitch, weighing 19,8 kg, was treated at HV-UENP, with the main complaint being a vaginal lesion, which persisted for 2 weeks, with bleeding and foul odor.

The bitch resided in a rural area with unrestricted access to properties in the region and was in contact with other uncastrated canines with no documented health history. Moreover, the patient had received a 2-month course of progestogen.

During the physical examination, a lesion with a "cauliflower" aspect was identified in the vulvar region (Figure 1), with bleeding upon handling, an abnormal odor, and did not appear painful to the touch. In addition, the local touch examination verified the involvement of the vaginal canal.

After observation, a sample was collected from the region with a vaginal brush, fine needle aspiration (Fna) and local "imprint" for cytological evaluation, confirming the diagnosis of TVT. Screening tests, including blood count and serum biochemistry (Alanine Aminotransferase, Alkaline Phosphatase, urea and creatinine), showed no changes. Additionally, genotyping was conducted, and the blood sample was collected in an EDTA tube before being sent to the VETPAT® Laboratory for PCR examination. The result indicated a positive finding for the MDR1 mutation in a homozygous state.

As the patient had an MDR1 mutation (homozygous), the 1st-choice antineoplastic chemotherapy protocol for TVT treatment, with intravenous vincristine sulfate, was replaced by lomustine[1] [Citostal® at a dose of 70 mg/m^2 orally every 21 days, totaling 3 sessions]. Preceding each session, clinical and complementary tests (blood count and serum biochemistry) were performed to monitor the tumor as well as hematological, hepatic and renal functions.

Before starting the stipulated treatment, the initial lesion showed progression, an increase in mass and the presence of myiasis. Thus, the larvae were manually removed and Nitenpiram[2] [Capstar® 57mg, oral single dose] was prescribed, in addition to local cleaning with 0.9% saline solution every 12 h. At the time of the 1st antineoplastic chemotherapy session, the biochemical and hematological exams were within the species' normal values. However, the lesion had

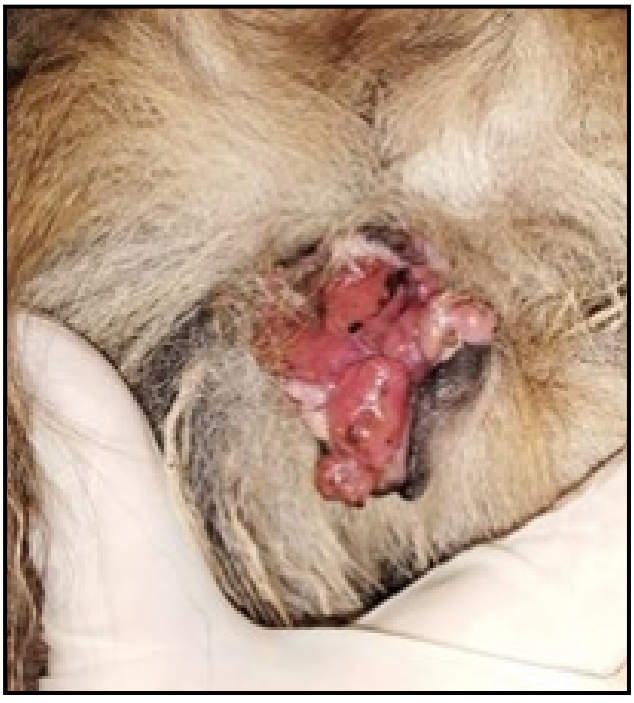

Figure 1. A 2-year-old intact Border Collie bitch, weighing 19.8 kg, in her 1st visit at HVE-UENP. There is a "cauliflower" lesion on the dorsal edge of the vulva, with signs of bleeding identified by clots attached to the hair of the perivulvar region.

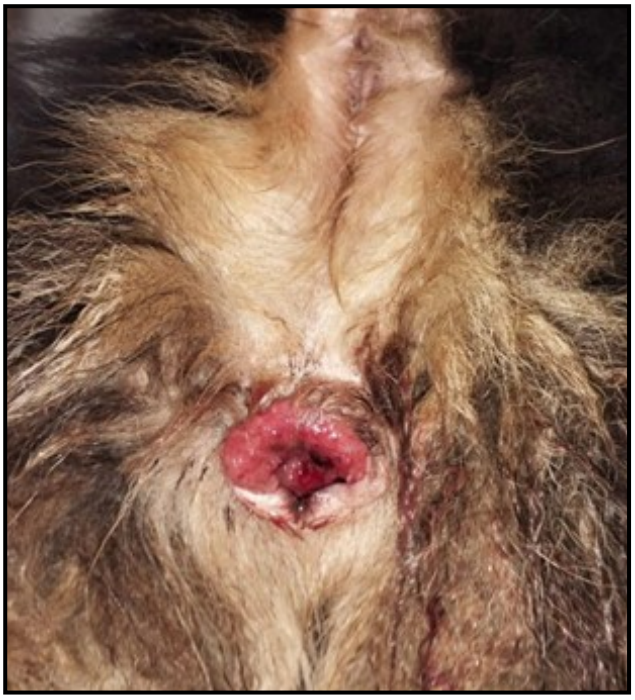

Figure 2. A 2-year-old intact Border Collie bitch with primordial lesion affecting the entire vulva, except for the right ventral and lateral portion. Before antineoplastic chemotherapy.

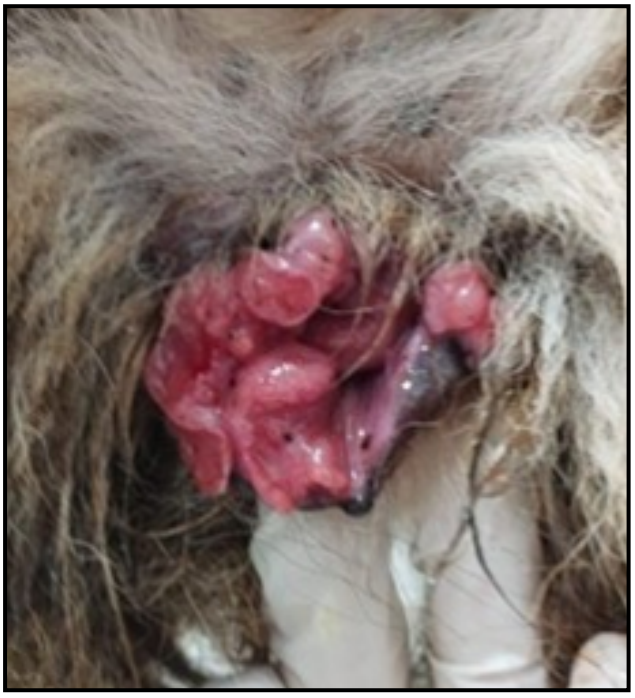

Figure 3. A 2-year-old intact Border Collie bitch after 21 days of the 1st session of antineoplastic chemotherapy with lomustine (70 mg/m^2). Partial tumor regression is observed.

enlarged, affecting the entire vulvar border except for the right ventral and lateral portions (Figure 2).

After 21 days, the animal returned for the 2nd session, there was a partial reduction in the vulvar lesion and clinical and hematological examinations did not indicate side effects (Figure 3). At 42 days after the start of treatment, the 3rd session was performed after the exclusion of hematological changes, when a total reduction of the patient's lesion was observed (Figure 4). Finally, at 63 days of treatment, a sample was collected for cytological examination, and a local tumor remission was observed, with a fibrotic region remaining in the vulvar genital mucosa.

DISCUSSION

TVT is a highly prevalent communicable disease in dogs, especially females, with more frequent involvement of the vagina (53% of cases), followed by the vulva (33%) and extragenital cases (14%) [7]. Transmission of TVT occurs through the implantation of viable tumor cells on the surface of the mucosa or injured membranes, which may occur through intercourse, biting, or licking of the affected area between healthy and contaminated individuals [3].

The clinical signs described in the literature are: bloody vaginal discharge with abnormal odor; morphologically, the tumor has a cauliflower-like appearance, with easy bleeding due to its high vascularity [1,6,9,20]. These characteristics were observed in the patient during care.

Diagnostic suspicion is considered by associating anamnesis and physical examination, in which the patient's contact with wandering dogs and the presence of the signature lesion were respectively identified. Cytological examinations, using a vaginal brush, FNAB and "imprint", resulted in the TVT diagnosis for the aforementioned patient [19].

TVT is frequently diagnosed without requiring histopathological analysis, as cytopathology reveals a characteristic morphological appearance. Other round cell tumors, such as lymphoma, mastocytoma, plasmacytoma, histiocytoma and melanoma, should be considered as differential diagnoses, although they are rarely confused in cytopathology [11].

As the patient belongs to the border collie breed, the MDR1 mutation investigation was requested, due to the increased susceptibility of this breed to adverse effects of 1st-line antineoplastic chemotherapy (vincristine sulfate). The Polymerase Chain Reaction (PCR) indicated the mutated gene in the patient. Although the mutation can be found in several dog breeds, collies and herding dogs are the most frequently mentioned in scientific literature [14,16,18].

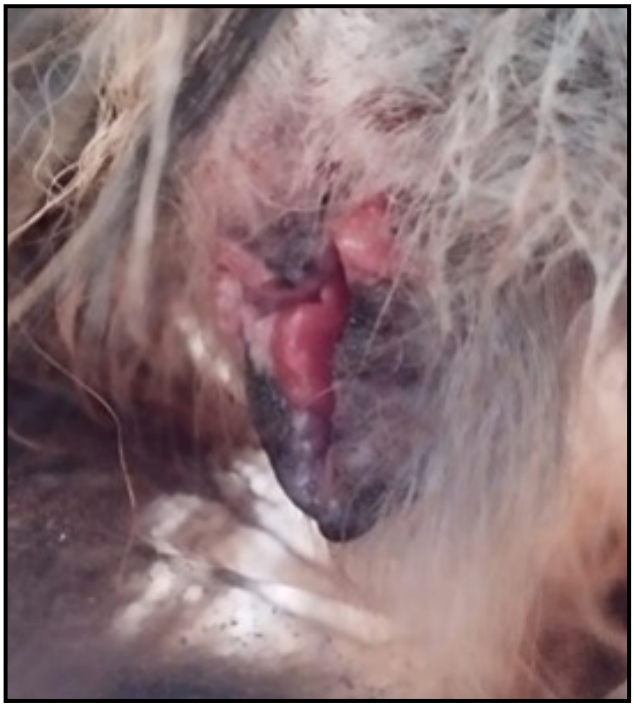

Figure 4. A 2-year-old intact Border Collie bitch after 42 days of the 1st session of antineoplastic chemotherapy with lomustine (70 mg/m^2). Complete tumor regression is observed, with depigmented areas.

This mutation is associated with dominant or recessive alleles and may manifest as either heterozygous or homozygous. Studies have shown that canines carrying mutant dominant alleles exhibit functional P-gp, regardless of homozygous or heterozygous traits. In the homozygous case, both copies of the gene are mutated, while in the heterozygous, the individual has 1 normal copy of the gene and 1 mutant copy; however, the phenotype associated with the mutation usually manifests itself due to the dominant nature of the mutation. In another scenario, dogs with the recessive mutation require the condition of homozygosity for the mutant trait to manifest, meaning they must inherit 2 copies of the mutant gene to present a drug-sensitivity phenotype. Conversely, non-mutated dogs possess a fully functional P-gp [13]. In the case of the present article, the patient was observed to have a homozygous mutation, making her P-gp completely non-functional.

P-gp plays a crucial role in protecting the body against toxicity associated with drugs that rely on this protein to be excreted. Among such drugs, the antineoplastic agents vincristine sulfate and doxorubicin (recommended for treatments of canine TVT) are mentioned [14]. As a component of the blood-brain barrier, P-gp is essential to avoid neurotoxicity [12,13,18] and may, in dogs with a non-functional P-gp, result in the stimulation of the vomiting center, manifesting emesis [14]. Therefore, the bitch in question would have a higher risk of excessive toxicity when taking vincristine sulfate or doxorubicin, since both drugs are actively transported by the P-gp pump [10,12]. In addition, the individual variability of each patient is also responsible for the sensitivity to certain drugs and doses [13].

The antineoplastic chemotherapy protocol used in the treatment of TVT includes the administration of intravenous vincristine sulfate as a 1st choice and intravenous doxorubicin in resistant cases [4,17]. However, side effects may be exacerbated in patients carrying the MDR1 mutation. Therefore, due to the patient's greater susceptibility to adverse effects resulting from a non-functional P-gp, we opted for the use of lomustine[1] [Citostal® at a dose of 70 mg/m^2 orally every 21 days, for a total of 3 sessions] until complete remission. Before each session, clinical and complementary examinations (blood count and serum biochemistry) were performed to certify the safety of the subsequent application, given possible side effects.

Although there are few studies on the efficacy of lomustine in treating canine TVT, its prescription is based on the fact that this antineoplastic agent acts on other round-cell tumors, such as lymphoma and mastocytoma. In another case, 3 sessions of lomustine were used in the treatment of vincristine sulfate-resistant TVT, being effective in achieving total remission without the occurrence of side effects [4], similar to what occurred with the patient of the present report.

It can be concluded that the patient with TVT was effectively treated, with a complete remission after 3 sessions of lomustine [Citostal®]. This case highlights the importance of individualized therapy, as the patient had the homozygous mutation of the MDR1 gene, thus avoiding aggravated side effects.

MANUFACTURERS

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