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INTRAVESICAL ADMINISTRATION OF CYTOSTATIC IN A DOG WITH URINARY BLADDER CARCINOMA - CASE STUDY

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Abstract

A 9-year-old spayed female mixed Pit Bull Terrier of 33.2 kg was referred with a complaint of stranguria, pollakiuria, hematuria, and abdominal pain of 5 weeks duration, not responding to treatment. The results of physical examination were unremarkable. A abdominal ultrasound revealed a large mass on the wall of the urinary bladder. The regional lymph nodes and the other abdominal organs present normal sonographical features. Thoracic radiography showed no evidence of metastatic disease. Blood samples have been taken for biochemistry work, CBC and urine samples. The dog underwent a cystoscopy, histopathological examination of the retrieved specimen reveal $T_2N_0M_0$ TCC (muscle-invasive transitional cell carcinoma). Due to the mass location on the wall of the bladder, surgery was not an option. Considering the result of the investigation, chemotherapy treatment has been applied: intravesical every 2-week cycle consisted of alternating epirubicin and 5-fluorouracil and intravenous holoxan. The treatment was well tolerated with no occurrence of any side effects. The abdominal ultrasound was repeated every 1 month and showed no progression of the disease.

Key words*: carcinoma, chemotherapy, cystoscopy.*

INTRODUCTION

Bladder cancer is one of the leading lethal cancers worldwide. Although urinary bladder cancer is reported to comprise only 2% of all reported cancers in dogs, bladder cancer affects tens of thousands of dogs every year worldwide.Transitional cell carcinoma (TCC), also referred to as urothelial carcinoma, is the most common form of urinary tumour in dogs, a malignant tumour that develops from the transitional epithelial cells that line the bladder. This tumour invades into the deeper layers of the bladder wall including the muscle layers. As the cancer enlarges in the bladder, it can cause obstruction to the flow of urine from the kidneys to the bladder or from the bladder to the outside of the body. Canine TCC also has the ability to spread to lymph nodes and to other organs in the body (lung, liver, others). TCC most frequently is found in the bladder, but can also develop in the kidneys, ureters, prostate, and urethra. Canine TCC is usually a high grade invasive cancer (Fulkerson, 2015). Problems associated with TCC include obstruction, distant metastases in > 50% of affected dogs, and clinical signs that are troubling both to the dogs and to their owners. Risk factors for TCC include exposure to older types of flea control products and lawn chemicals, obesity, female sex, and a very strong breed-associated risk.

This knowledge is allowing pet owners to take steps to reduce the risk of TCC in their dog.

The diagnosis of transitional cell carcinoma (TCC) can be made by histopathology of several tissue biopsies obtained with the help of cystoscopy or surgery. Studies showed that percutaneous aspirates and biopsies should be avoided due to the risk of tumour seeding. TCC is most commonly located in the trigone region of the bladder making impossible a complete surgical resection.

Although TCC is not usually curable in dogs, multiple drugs have activity against it, Regardless of clinical stage, systemic chemotherapy, having shown efficacy in bladder cancer, remains the standard approach for most of these dogs.

The appropriate treatment of patients with superficial bladder cancer requires the assessment of multiple variables, including

accurate clinical evaluation, understanding the natural history of the disease, pharmacology of the drugs currently used, and the expected efficacy of each drug (Badalament, 2017).
The treatment of superficial bladder cancer has three principal objectives: eradication of existing disease, to provide prophylaxis against tumour recurrence, and to avoid deep invasion into the muscle layers of the bladder. Almost every drug imaginable has been instilled into the bladder to treat superficial bladder cancer. However, five chemotherapeutic drugs (doxorubicin, mitomycin C, epirubicin, holoxan and fluorouracil) have widespread usage. Epirubicin is an anthracycline derivative of doxorubicin. Its antitumour effects are similar to doxorubicin, with a more favourable toxicity profile. In a study by Burk et al. (1989) involving 911 patients, no systemic toxicity was noted; chemical cystitis occurred in 15% and seemed to be related to drug oncentration.
Efficacy of intravesical chemotherapy can be measured in terms of tumour reduction, recurrence or progression (Lammet al., 1996).

MATERIALS AND METHODS

A 9-year-old spayed female mixed Pit Bull Terrier of 33.2 kg was referred with a complaint of stranguria, pollakiuria, hematuria, and abdominal pain of 5 weeks duration, the dog was not responding to treatment of classic cystitis. The results of physical examination were unremarkable and the lymphnodes were not enlarged or painful.
Then, urine samples have been taken for urine chemistry, sediment and cytology. The result came back with the following results: increased turbidity, increased RBC, increased WBC. The papillary tumours were characterized histologically by multiple papillae of spindle cells supported by thin, fibrovascular stroma and solid sheets of ovoid to round cells separated by similar stroma.
We also found presence of bacteria in sampled urine and most important neoplastic squamous cells.
A abdominal ultrasound revealed a large urethral mass extending to the trigone of the bladder, also affecting the inner bladder wall. The regional lymph nodes and the other abdominal organs were sonographically normal. Thoracic radiography showed no evidence of metastatic disease.
The owner elected for cystoscopy and histopathology of tissue biopsies (Figure 4). Blood biochemistry and CBC have been performed before anesthesia, the result being in normal limits.
The dog was premedicated for anesteshesia using Diazepam (0.2 mg/kg) and Butorphanol (0.2 mg/kg), Propofol (4 mg/kg) used for induction followed by endotracheal intubation using a 10 mm endotracheal tube and maintained with Isoflurane 2.5% and 100% oxygen. The dog was positioned in dorsal recumbency (Figure1).

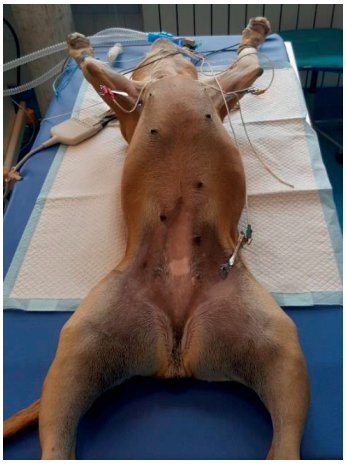

Figure 1. The dorsal recumbency postion for the procedure

For this procedure we used a Storz Hopkins forward-oblique telescope 30˚, 4 mm diameter and length 30 cm and a double action jaws, flexible biopsy forceps (Figures 2, 3).

Figure 2. Instruments for cystoscopy and biopsy samples

Figure 3. Monitor and modular camera control system

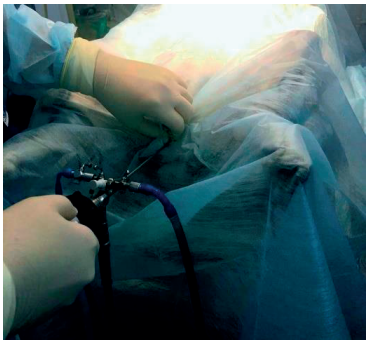

Figure 4. Undergoing the procedure

Inside the bladder, we tried to find areas with thickened or ruptured bladder wall or mass lesions within the urinary tract and take several biopsy samples for histopathological examination (Figures 5a, 5b, 5c).

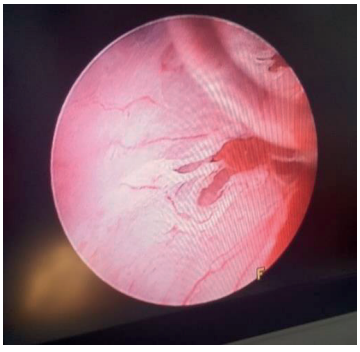

Figure 5a. Ruptured bladder wall

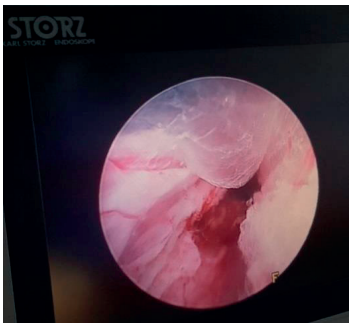

Figure 5b. Mass lesions inside the bladder wall

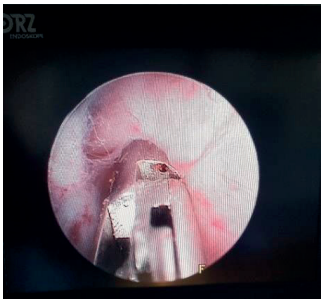

Figure 5c. Bladder biopsy sampling

Fluids have been provided during the procedure (Lactate Ringer) at 3 ml/kg/h rate. For the whole cystoscopy procedure, the heart rate, respiratory rate, concentration of CO_2 in expired gas, pulse, oxygen saturation and non-invasive blood pressure were measured. All the parameters were in normal limits during the procedure and the recovery period (Figure 6).

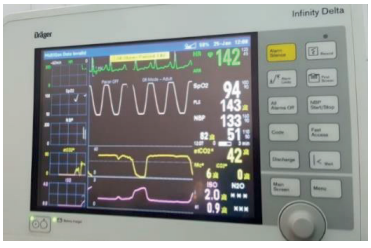

Figure 6. Vital sign monitor

RESULTS AND DISCUSSIONS

Pathological examination of retrieved specimen revealed to be Canine Transitional Cell Carcinoma. Due to the mass location on the bladder wall, surgery was not an option.
Consequently, treatment with intravesical chemotherapy has been applied: Epirubicin

alternated with 5-fluorouracil every 2 weeks and Holoxan i.v. Specific hepatic protective medication has been provided, such as liver enzymes and nutritional supplement for dogs suffering from cancer to greatly improve the animal's well-being during the treatments.

The chemotherapy was instillated using a semi-rigid urinary, sterile catheter, after eliminating and emptying the bladder and the dog had to walk and not urinate for 45-50 minutes. The dosage for Epirubicin was of 7 mg-3.5 mL, 5-fluorouracil was 4.5 mL both intravesical, and Holoxan intravenously 140 mg-3.5 mL.

The treatment was well tolerated with no occurrence of any side effects. We rechecked the blood chemistry, CBC and the abdominal ultrasound when the patient came for consultation after chemotherapy, as described in the tables below (Tables 1 and 2) and ultrasound pictures (Figures 7-10).

Table 1. Biochemistry results on different consults

Parameter	Reference interval	Day 1	Day 16	Day 60	Day 98	Day 125
GLU mg/dL	70-143	98	98	104	102	101
CREA mg/dL	0.5-1.8	1.2	1.1	1.0	1.9	1.5
BUN mg/dL	7- 27	13	11	12	16	15
TP g/dL	5.2-8.2	6.7	6.2	6.1	6.9	6.6
ALT U/L	10-100	37	61	79	70	75
ALKP U/L	23-212	74	64	82	65	77
CA mg/dL	7.9-12.0			10.1	10.9	11.1
ALB g/dL	2.2-3.9			3.2	2.8	3.3
Glob g/dL	2.5-4.5			2.9	4.1	4.4
GGT U/L	0-7			0	0	0
TBYL mg/dL	0.0-0.9			<0.1	0.2	0.3
AMYL U/L	500-1500			449	760	880
LIPA U/L	200-1800			436	524	613

Table 2. CBC results on different consults

Parameter	Reference interval	Day 1	Day 16	Day 60	Day 98	Day 125
HCT %	37.0-55.0	51.7	45	51.8	42.5	48.7
HGB g/dL	12.0-18.0	17.8	16.4	15.8	14.8	14.0
MCHC g/dL	30.0-37.5	34.4	36.4	30.5	34.8	35.2
WBC K/µL	5.50-16.90		5.90	5.29	4.50	3.91
GRANS K/µL	3.30-12.0	9.60	4.40		11.70	10.9
% GRANS		80.0	74.6		83.6	
L/M	1.1-6.3	2.4	1.5		2.3	1.8
% L/M		20	25		16	14
PLT	175-500	354	268		480	
RBC M/µL	5.50-8.50			7.22		
MCV fL	60.0-77.0			71.7		
MCH pg	18.5-30.0			21.9		
RDW %	14.7-17.0			15.3		
% RETIC				0.2		
RETIC K/µL	10.0-110.0			14.2		
% NEU				64.9		
% LYM				23.5		
% MONO				8.5		
% EOS				2.4		
% BASO				0.7		
NEU K/µL	2.00-12.0			2.86		
LYM K/µL	0.50-4.90			1.04		
MONO K/µL	0.30-2.00			0.38		
EOS K/µL	0.10-1.49			0.11		
BASO K/µL	0.00-0.10			0.03		
MPV fL				13.8		
PDW %				22.8		
PCT				0.61		

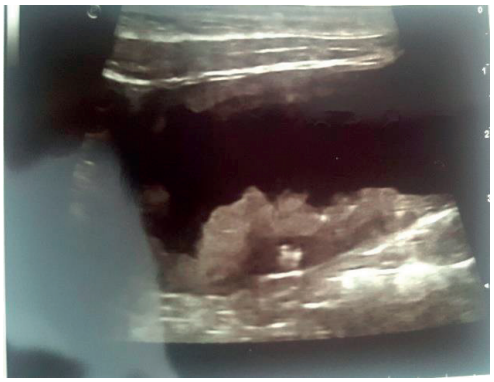

Figure 7. Longitudinal section with evidence of tumor formation in the middle region of the bladder and loss of parietal stratification

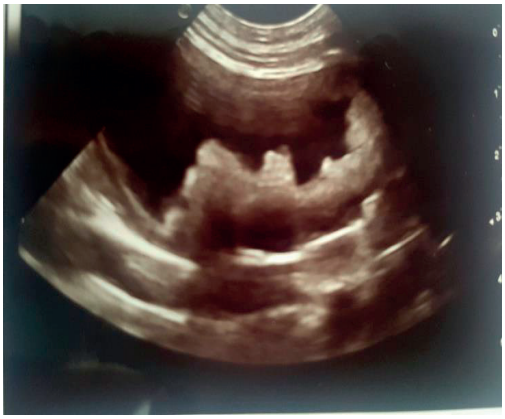

Figure 8. Longitudinal section of the middle and bottom region of the bladder and highlighting the tumor mass with irregular contour and broad-base in the middle region

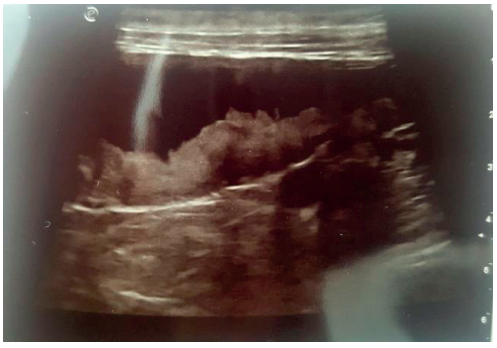

Figure 9. Longitudinal section of the middle region and neck of the bladder with highlighting the extension to the neck of the bladder

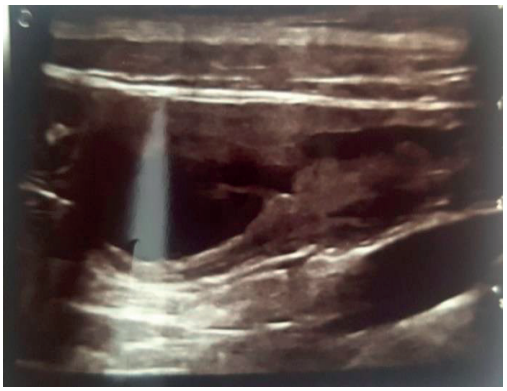

Figure 10. Longitudinal section with the highlighting of the tumor formation with regular contour and the tendency to reduce the size of the implantation base towards the bladder neck

The ultrasound examination was performed with the animal in the dorsal decubitus using a MyLab device and a 7.5 MHz microconvex probe.

After preparing the ventral abdominal region by trimming and applying the ultrasound gel, the bladder was examined both in the longitudinal section and in the cross-section, sequentially, starting from the neck of the bladder to the deep region.

As we can see in the pictures above, in the lumen of the bladder, a mass of increased size measuring18.3 mm thick and 27.4 mm length, was observed, occupying approximately 55% of the lumen with irregular appearance and large implantation base, with a strong infiltrative character in the deep parietal layers which causes the loss of the normal stratification of the wall in the region middle towards the neck of the bladder.

Subsequent examinations performed during the specific treatment revealed the tendency of localization of the tumour mass, with the obvious reduction up to size of 5.1 mm thick and 14.4 mm length with the reduction of occupied intralumenal space.

The aggressive infiltrative character of the formation, respectively the modification of the deep structure of the bladder wall was maintained throughout the ultrasonographic monitoring but with a clear reduction of the affected area.

CONCLUSIONS

The purpose of this study was to determine the antitumoural activity of 2 chemotheraphy agents administered intravesical, Epirubicin and 5-fluorouracil, in combination with Holoxan administered i.v. The study results provide evidence that this specific combination of drugs is more effective than either drug alone. It is not possible to know whether the Epirubicin and 5-fluorouracil enhanced the effects of the Holoxan or whether the Holoxan administered i.v. enhanced the effects of the Epirubicin, just that the combination resulted in a favourable remission rate.

Antibiotic treatment may cause reduction or temporary resolution of clinical signs. The urinary tract signs with TCC closely mimic those of a urinary tract infection.

Finding abnormal epithelial cells in urine and thickened bladder wall or mass lesions within the urinary tract also increases suspicion for TCC. Histopathological examination provides a definitive diagnosis of TCC and characterization of the different pathological types of TCC. Tissue biopsies from the bladder can be obtained by cystoscopy, and with this procedure the operator can visually inspect the urethra and bladder wall and obtain biopsies using this method.

In dogs with confirmed or suspected TCC, evaluation should include an assessment of overall health and tests to determine tumour stage, as this information will be used in planning treatment. This includes a complete blood count (CBC), serum biochemistry profile, urinalysis with or without urine culture, thoracic radiography, abdominal ultrasonography, and urinary tract imaging. Urine should be collected by free catch or catheterization; cystocentesis should be avoided as it could lead to tumour seeding.

When using ultrasonography to monitor changes in TCC masses, however, it is essential to have the same operator for performing each examination, to standardize the dog's position, probe position, and data collection, and to have a similar level of bladder distension for each ultrasound examination visit.

The main of TCC treatment in dogs continues to be systemic medical therapy which usually consists of chemotherapy. Although medical therapy is not usually curative, remission or stable disease (lack of progression) can be accomplished with several different drugs, and most treatments are well tolerated.

The best results often occur in dogs that sequentially receive multiple different treatment protocols over the course of their disease, like in our case.

Epirubicin appears to have the greatest level of antitumour activity against canine TCC, especially when combined with 5-fluorouracil.

Future studies with a larger population of dogs undergoing this approach and treatment should be performed to assess whether this strategy may be successful in dogs with Transitional Cell Carcinoma in the urinary bladder.

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