A case of urothelial carcinoma *in situ* of the bladder in local dog in Bali, Indonesia

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ABSTRACT

Urothelial carcinoma is a malignant neoplasm of the urinary tract arising from the transitional epithelium. Its clinical manifestations often overlap with non-neoplastic conditions, such as urinary tract infections, thereby presenting a diagnostic challenge for clinicians. Differentiating from others condition is important, as the treatment and prognoses vary significantly. This case report presented a 4-year-old female local dog, weighing 11.55 kg in BVC Animal Hospital with a primary complaint of hematuria. Clinical, hematological, and serum biochemical evaluations revealed no significant abnormalities. Ultrasonographic examination identified a hypoechoic mass measuring 0.31 × 0.85 cm located within the lumen and thickening of urinary bladder wall. Cytological assessment was performed via urine

catheterization. The cytological specimen demonstrated a population of cells with anisocytosis, anisokaryosis, and a high nucleus-to-cytoplasm ratio, raising suspicion of a malignant tumor. Consequently, biopsy was performed via cystotomy to establish a definitive diagnosis. Prior to release the histopathological results, post-cystotomy the dog was treated with cefadroxil as antibiotics at 20 mg/kg BW b.i.d for 14 days, carprofen as anti-inflammatory at 2 mg/kg BW s.i.d. for 5 days, and tramadol as analgesics at 2 mg/kg BW b.i.d. for 5 days. Histopathological examination showed a non-encapsulated tumor with well-defined demarcation in the mucosa. The tumor consists of a dense population of epithelial tumor cells without evidence of invasion, confirmed the diagnosis of non-invasive, non-papillary urothelial carcinoma (*in situ*). The patient was managed palliatively with the administration of piroxicam at 0.3 mg/kg BW s.i.d as monotherapy. Until day 190, the dog showing a stable disease. To the best of the authors' knowledge, this is the first documented case of canine urothelial carcinoma in Indonesia.

Keywords: bladder cancer, dog, palliative therapy, transitional cell carcinoma

1. Introduction

Transitional cell carcinoma, now referred to as urothelial carcinoma, is a malignant tumor originating from the transitional epithelium and commonly occurs in the urinary tract of dogs. This malignancy may arise in the renal pelvis, urethra, or urinary bladder. Although urothelial carcinoma has a relatively low incidence, comprising less than 2% of all diagnosed cancers, it is estimated to affect approximately 10,000 dogs annually worldwide (1,2). Urothelial carcinoma is characterized by local invasiveness and a high potential for metastasis. Approximately 14% of cases demonstrate distant metastases, 16% involve lymph node metastasis, and 10% present with both lymph node and distant metastases (3). Among the various regions of the urinary tract, the urinary bladder is the most common site for this neoplasm.

Diagnosing urothelial carcinoma presents a significant clinical challenge due to its nonspecific clinical manifestations, which often resemble those of urinary tract infections (4). In certain instances, the clinical signs may even improve temporarily with the administration of antibiotics, potentially leading to misdiagnosis (5). Clinical signs may include dysuria, hematuria, stranguria, pollakiuria, urinary

incontinence, and abdominal discomfort (6,7,8). Abdominal ultrasonographic (USG) examination may yield imaging findings that overlap with other conditions such as benign polyps or cystitis (9). Differentiating urothelial carcinoma from these other conditions is critical, as treatment approaches and prognoses vary significantly. Therefore, definitive diagnosis requires further confirmation through cytological and histopathological examinations (1,10). Similar diagnostic challenges have also been reported in human medicine, where bladder cancer is frequently misdiagnosed as cystitis in its early stages (11). Cytology is a commonly employed diagnostic method; however, its sensitivity and specificity depend on the collection technique used. Histopathological evaluation of tissue biopsies obtained via cystoscopy, cystotomy, or catheterization remains the gold standard for diagnosis (12). This case report presents urothelial carcinoma *in situ* of the bladder in a female local dog in Bali, Indonesia, and provides a comprehensive overview of clinical evaluations including ultrasonography, cytology, hematology, and histopathology.

2. Case Presentation

A 4-year-old female local dog weighing 11.55 kg was presented by its owner to BVC Animal Hospital, Pererenan, Indonesia, with a primary complaint of hematuria. The dog's appetite and water intake remained normal, and no other clinical signs were reported. The dog appeared alert and generally responsive. Clinical examination revealed a rectal temperature of 38.6°C, with heart rate and respiratory rate within normal limits. There were no signs of dehydration, as indicated by a capillary refill time < 2 seconds and normal skin tent. Fecal consistency was also normal. Examination of the superficial lymph nodes showed no signs of enlargement or abnormalities. The dog was found to be experiencing hematuria.

Table 1. Hematology examination result

Parameter	Results	Reference range*
WBC (10^3/µL)	13.7	6-17
Lymphocytes (10^3/µL)	2.9	0.8-5.1
Mid (10^3/µL)	1.8	0-1.8
Granulocytes (10^3/µL)	9	4-12.6
RBC (10^6/µL)	7.59	5.5-8.5
Hemoglobin (g/dL)	18.4	11-19
Hematocrit (%)	53.8	37-55
MCV (fL)	71	62-72
MCH (pg)	24.2	20-25
MCHC (g/dL)	34.2	30-38
Platelet (10^3/µL)	243	200-490

Plateletcrit (%)	0.206	0.100-0.500

Note: WBC=White blood cell; RBC=Red blood cell; MCV=Mean Corpuscular Volume; MCH=Mean Concentration Hemoglobin; MCHC=Mean Corpuscular Hemoglobin Concentration. *Reference range: CC-3200Vet® Hematology Analyzer.

Hematological and biochemical blood examinations were conducted to assess the general health status of the animal. Blood samples were collected via the saphenous vein and subsequently placed into EDTA tube and plain tube. The sample collected with EDTA tube was then analyzed using hematology analyzer (CC-3200Vet®, Shenzhen Licare Biomedical Technology Co., Ltd., China). For the plain tube, the serum was collected then analyzed using biochemical analyzer (SMT-120VP®, Chengdu Seamaty Technology Co., Ltd.). The results of the hematology and biochemical analyses are presented in Table 1 and Table 2, respectively. The hematology and blood biochemistry results showed no abnormalities.

Table 2. Serum biochemistry result

Parameter	Results	Reference range*
Albumin (g/L)	30.8	23-40
Total Protein (g/L)	66	49-82
Globulin	35.2	19-45
Albumin/Globulin ratio	0.87	-
Total bilirubin (µmol/L)	0.4	0-15
GGT (U/L)	< 2	0-10
AST (U/L)	20	13-50
ALT (U/L)	35	10-109
ALP (U/L)	48	17-212
Total Bile Acids (µmol/L)	1.62	0-17
Lipase (U/L)	35	0-216
Lactate Dehydrogenase (U/L)	45	40-400
Creatine Kinase (U/L)	116	52-368
Creatinine (mg/dL)	0.82	0.32-1.4
Uric Acid (µmol/L)	<10.00	0-60
Urea (mmol/L)	3.6	2.9-10

Urea/Creatinine ratio	50	16-219
Glucose (mg/dL)	98.41	74.06-143.08
Total Cholesterol (mmol/L)	2.98	2.84-8.27
Triglycerides (mmol/L)	0.8	0-1.13
Total CO_2 (mmol/L)	17.3	12-27
Calcium (mmol/L)	2.15	1.98-3
Phosporus (mmol/L)	1.23	0.81-2.19

Note: GGT=Gamma-Glutamyl Transferase; AST=Aspartate Aminotransferase; ALT=Alanine Aminotransferase; ALP=Alkaline Phosphatase.*Reference range: SMT-120VP® Chemistry Analyzer.

Ultrasonographic examination was performed to assess the internal structure of the urinary bladder, including both the lumen and the wall. First, the animal positioned in dorsal recumbency, then examination was conducted using the EMP G30 Portable Veterinary Color Doppler Ultrasound System (Shenzhen Emperor Technology Co., Ltd., China) equipped with a micro-convex probe operating at a frequency of 8 MHz.

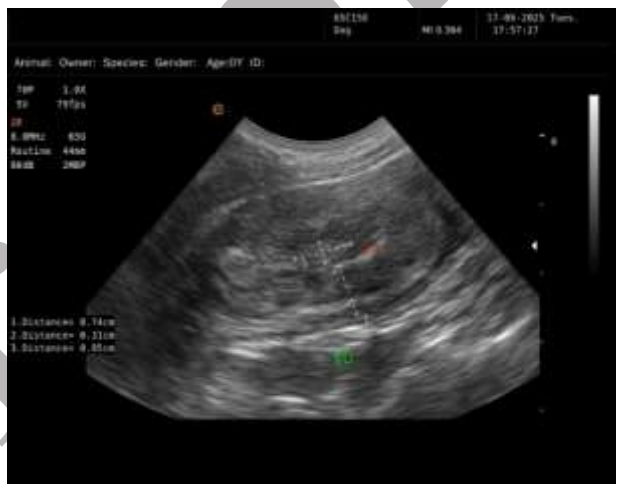

Figure 1. A noticeable thickening of the urinary bladder wall and the presence of a hypoechoic mass was detected within the lumen of the urinary bladder.

The examination results revealed a thickening of the urinary bladder wall measuring 0.74 cm, with a hypoechoic mass measuring 0.31 × 0.85 cm located within the lumen of the urinary bladder (Figure 1).

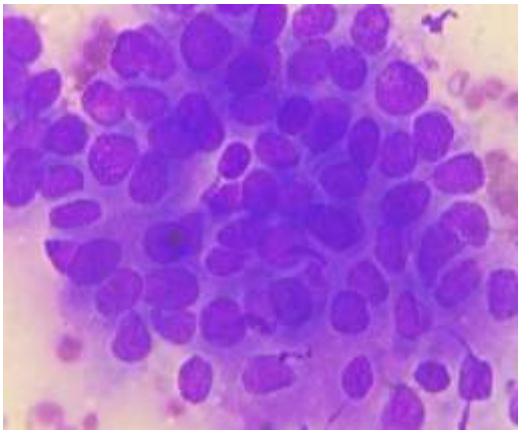

Figure 2. Cytological smear showing epithelial cells suspected to be neoplastic (Diff-Quik stain, 1000×).

As tumor mass was suspected based on USG examination, urine sample was collected via catheterization to further assess the malignancy potential. The collected sample was immediately expelled onto a glass slide, stained using the Diff-Quik, and examined microscopically at 1000× magnification. The cytological results demonstrated a population of epithelial cells with a high nucleus-to-cytoplasm ratio, slightly irregular nuclear contours and borders, cytoplasmic homogeneity, and mild anisocytosis and anisokaryosis (Figure 2). Based on these findings, it was concluded that the hypoechoic mass observed in the ultrasonographic examination was suspected to be a malignant tumor.

Due to the cytological findings indicating a potential malignant tumor, biopsy was performed to confirm the diagnosis. The biopsy was conducted on the thickened urinary bladder tissue via cystotomy. A small portion of tissue was excised, placed in 10% neutral buffered formalin, and subsequently sent to the Pathology Laboratory at the Primate Study Center, IPB University, Indonesia for diagnostic confirmation by a veterinary pathologist. Prior to release of biopsy results, therapeutic management following the cystotomy procedure included the administration of antibiotics, anti-inflammatory drugs, and analgesics. Cefadroxil as antibiotic was administered at 20 mg/kg body weight (BW) b.i.d. for 14 days, carprofen as anti-inflammatory at 2 mg/kg BW s.i.d. for 5 days, and tramadol as analgesic at 2 mg/kg BW b.i.d. for 5 days.

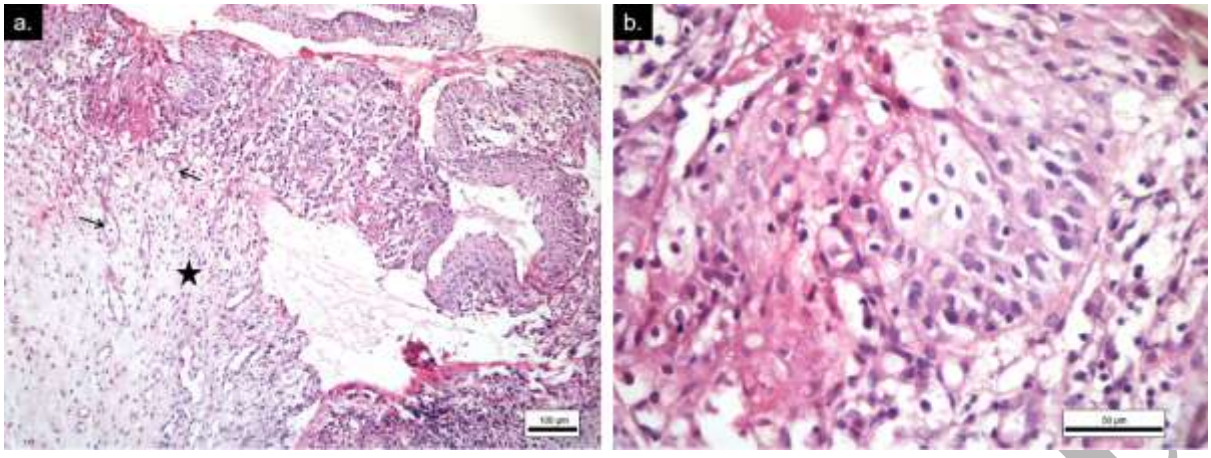

Figure 3. Microphotograph of urothelial carcinoma *in situ* of the bladder. (a) A non-encapsulated tumor with well-defined demarcation was seen extensively in the mucosa. Coagulative and lytic necrosis, edema, and infiltration of lymphocytes and neutrophils are observed in the submucosa (star). Several neovascularization also observed (arrow). (b) The tumor consists of a dense population of epithelial tumor cells with prominent nucleoli. A mild degree of anisocytosis and anisokaryosis is present (Hematoxylin-Eosin 100× and 400× magnification).

After two weeks, the biopsy results confirmed that the thickened urinary bladder tissue was diagnosed as non-invasive, non-papillary urothelial carcinoma (*in situ*). Well-demarcated tumor cells were observed in the mucosal layer. The tumor consisted of epithelial cells of varying sizes, with round to oval nuclei containing 1-2 prominent nucleoli. Mitoses were observed at a rate of 3-5 per five high-power fields (HPF). Tumor cytoplasm exhibited vacuoles or Melamed-Wolinska bodies. The submucosa was infiltrated by mild neutrophilic and lymphocytic inflammatory cells, with areas of coagulative and lytic necrosis, as well as edema. Several neovascularization was also noted. No evidence of tumor cell invasion into the submucosa or serosa was detected (Figure 3). Clinical staging was performed and revealed no involvement of regional or juxtaregional lymph node (N0) and no distant metastasis (M0). The dog in this case was treated with piroxicam at a dosage of 0.3 mg/kg BW s.i.d. as monotherapy. Until day 190, the dog showed stable disease, as evidenced by the stable tumor mass size and improvement in clinical signs (no hematuria was present).

3. Discussion

Urothelial carcinoma of the urinary bladder is frequently diagnosed in dogs. Although urothelial carcinoma has a relatively low incidence, comprising less than 2% of all diagnosed cancers, it is estimated to affect approximately 10,000 dogs annually worldwide (1,2). This malignant tumor has a

multifactorial etiology, with several potential risk factors identified, including female sex, history of ovariohysterectomy or orchiectomy, breed, obesity, exposure to flea or tick control products as well as other insecticides and herbicides, exposure to cyclophosphamides, and living in industrial areas (3). Breeds susceptible to developing this tumor include Scottish Terriers, Fox Terriers, West Highland White Terriers, Beagles, Collies, and Shetland Sheepdogs (5). It has been documented that urothelial carcinoma occurs between 4 and 16 years of age, with an average onset around 9 to 10 years (13). For dogs at risk of developing urothelial carcinoma, limiting exposure to chemicals, flea control agents, and providing vegetables in the diet at least three times per week are important recommendations to inform owners (1). In this case, urothelial carcinoma was diagnosed in an intact female local dog. To the authors' knowledge, this article represents the first reported case of canine urothelial carcinoma in Indonesia.

Urothelial carcinoma can metastasize to lymph nodes, lungs, or even bone. Knapp et al. (14) reported the most frequent sites of metastasis in 137 dogs with urothelial carcinoma necropsied at Purdue University as follows: lung (50%), regional lymph nodes (29%), thoracic nodes (12%), bone (15%), liver and kidney (7%), adrenal gland and skin (6%), spleen and heart (4%), gastrointestinal (2%), brain (1.5%), and other nodes (1%). Typically, the tumor arises in the trigone area of the bladder, and in males, it may also involve the prostate gland (15). Tumor occurrence in the trigone is attributed to urine accumulation in this area, which may lead to prolonged exposure of transitional epithelium to toxins or carcinogens present in the urine (16). In diagnosing urothelial carcinoma, cytological examination generally has low sensitivity; therefore, histopathology remains the gold standard for definitive diagnosis. Nonetheless, cytology can assist in the preliminary assessment of the malignancy potential of transitional cells (1). Cytological samples are commonly obtained via urinary catheterization. Cystocentesis may be performed, but it is less recommended and should be done cautiously to prevent tumor cell seeding into the abdominal cavity (17). The cytology results in this report suggested a malignant tumor. Biopsy was performed for further diagnostic confirmation.

The 2004 World Health Organization (WHO) classification of urinary bladder urothelial carcinoma, which categorizes tumors as either papillary or non-papillary and as invasive or non-invasive, has been applied in veterinary medicine for classifying tumors in domestic animals (13). Histopathologically, neoplastic cells exhibit round to oval nuclei that are generally large with prominent nucleoli. Urothelial carcinoma is also characterized by the presence of Melamed-Wolinska bodies, cytoplasmic vacuoles that are either empty or occasionally contain eosinophilic material (1). In this case report, histopathology showed no signs of tumor cell infiltration into the submucosa or serosa, and the tumor in the mucosa did not form papillae. Therefore, this case was classified as non-invasive, non-papillary urothelial carcinoma, also referred to as urothelial carcinoma *in situ*. In advanced stages, histopathology of urothelial carcinoma may reveal secondary projections or branching "villi" of the tumor (14). According

to Rasteiro et al. (18), urothelial carcinoma *in situ* is very rarely reported. This form is likely attributed as an early neoplastic transformation of the transitional epithelium (16). Immunohistochemical staining for uroplakin III, CK7, or CK20 is commonly used as a marker for urothelial carcinoma in dogs (18).

The hematological and biochemical profiles in this case showed no abnormalities and were generally within normal limits. Nagata (19) reported similar hematology and blood biochemistry parameters of dog with urinary bladder urothelial carcinoma, showing only a slight increase in blood urea nitrogen (49 mg/dL). A retrospective study conducted by Norris et al. (8) showed that dogs with bladder tumor showed hematological abnormalities such as neutrophilia (13%, 14/107), neutrophilia with left shift (7%, 7/107), non-regenerative anemia (5%, 5/107), and regenerative anemia (3%, 3/107). While the serum biochemistry showed increased in ALP (27%, 29/105), ALT (17%, 18/105), urea (13%, 14/105), creatinine (9%, 9/105), phosphorus (8%, 8/105), calcium (5%, 5/105), globulin (4%, 4/105), and creatine kinase (4%, 4/105).

In general, the prognosis of urothelial carcinoma is poor, with most patients surviving less than one year despite treatment (20). Therefore, therapy is primarily aimed at improving the patient's quality of life. Common treatment options include chemotherapy and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (12,16,21,22). The role of surgery in treating urothelial carcinoma in dogs remains debated, as most tumors arise in the trigonal bladder region where resection is rarely feasible. Even when tumors outside the trigone are excised with clear margins, recurrence is common due to field effect in the bladder urothelium (23). Several case reports have described the administration of the NSAID piroxicam as providing a favorable response and improving patient quality of life. A study by Knapp et al. (21), who documented 34 dogs treated with piroxicam as monotherapy at 0.3 mg/kg BW s.i.d., reported a median survival time of 181 days, including two cases of complete remission, four cases of partial remission, 18 dogs showing stable disease, and the rest showing progressive disease. Therapy with this NSAID generally well tolerated, with gastrointestinal toxicity reported in six dogs and kidney papillary necrosis in two dogs (12). Piroxicam is typically combined with other chemotherapeutic agents such as mitoxantrone, carboplatin, or doxorubicin to induce tumor remission (16, 22).

In this case, we performed monotherapy with piroxicam. Using that therapy, the disease in this case tends to be stable until day 190, above median survival time reported by Knapp et al. (21). According to the literature, an alternative of NSAID, firocoxib, has also been reported as an effective single-agent therapy for urothelial carcinoma, improving patients' quality of life (24). Unfortunately, firocoxib was unavailable, precluding its use in this case. Nevertheless, this case highlights the importance of ancillary tests in diagnosing urothelial carcinoma, as its clinical presentation can overlap with non-neoplastic conditions such as urinary tract infections. This case remains important to raise awareness of urothelial carcinoma in veterinary medicine, particularly in Indonesia where such cases are rarely reported.

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Authors' Contribution

Study concept and design: P.S.S., W.M.N.

Acquisition of data: P.S.S., W.M.N.

Analysis and interpretation of data: I.W.N.F.G., I.B.O.W.

Drafting of the manuscript: P.S.S.

Critical revision of the manuscript for important intellectual content: I.M.K., I.A.D.K.D.

Ethics

Not applicable

Conflict of Interest

All of the authors declared that there is no competing of interest exists.

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Data Availability

All of the data has been included in the manuscript

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