

## Follicular cystitis in a dog: First case report described in Brazil

[Cistite folicular em cão: primeiro relato de caso descrito no Brasil]

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### ABSTRACT

A 2-year-old English bulldog presented history of recurrent lower urinary tract disease, refractory to treatment. The Complete Blood Count revealed lymphopenia, hyperproteinemia, and hyperglobulinemia, while urinalysis indicated leukocyturia and bacteriuria. On the abdominal ultrasound, the bladder had a focal wall thickening in its cranial portion, as well as irregular echogenicity and internal margins. A bladder surgical biopsy was performed, indicating the presence of follicular cystitis. Clinical signs disappeared after treatment with a combination of amoxicillin and clavulanic acid, NSAIDs, supplementation with cranberry extract associated with cat's claw (*Uncaria tomentosa*). Clinical follow-up 12 months after surgery showed remission at all clinical signs. Follicular cystitis in dogs was reported only once worldwide, this case report is the first in Brazil; thus, it may be considered in the differential diagnosis for patients with refractory and recurrent lower urinary tract disease.

Keywords: ultrasound, canine, urinary bladder, inflammation

### RESUMO

Um Bulldog Inglês de 2 anos apresentou história clínica de doença recorrente do trato urinário inferior, refratária ao tratamento. O hemograma revelou uma discreta linfopenia, hiperproteinemia e hiperglobulinemia. Já a urinálise apontou leucocitúria e bacteriúria. Na ultrassonografia, a bexiga apresentava espessamento focal da parede da bexiga em porção cranial, ecogênica e margens internas irregulares. A biópsia cirúrgica da bexiga foi compatível com cistite folicular. Os sinais clínicos desapareceram após o tratamento com uma combinação de amoxicilina - ácido clavulânico, AINEs, suplementação alimentar de extrato de cranberry associado a unha de gato (fitoterápico da planta *Uncaria tomentosa*). O acompanhamento, 12 meses após a cirurgia, confirmou que o cão estava livre de sinais clínicos. A cistite folicular foi relatada apenas em 1 cão no mundo, sendo esse considerado o primeiro relato no Brasil. Essa enfermidade deve ser considerada um diferencial para pacientes com doença refratária do trato urinário inferior de longa data.

Palavras-chave: ultrassonografia, canino, vesícula urinária, inflamação

### INTRODUCTION

Follicular cystitis is a rare and nonspecific inflammatory disease of the bladder, it was first described in humans by Cruveilhier in his treaty dated 1856 apud Schlomovitz (1942). That etiology is not yet fully understood; however, studies show that inflammatory processes and bacterial infections have been considered

influential in its etiopathogenesis (Zaharopoulos, 2002; Somvanshi *et al.*, 2012; Ediz *et al.*, 2017).

In humans, follicular cystitis is also uncommon and mainly affects women, due to the higher incidence of chronic urinary diseases. Clinical presentations are nonspecific and variable, and common symptoms reported include dysuria, pollakiuria, hematuria and recurrent urinary tract

infections (Zaharopoulos, 2002). Follicular cystitis has also been reported in buffaloes in India and in cattle and buffaloes in Turkey (Somvanshi *et al.*, 2012). A report in dog has been described in the United Kingdom (Sul *et al.*, 2014). The aim of this study was to report the first case of canine follicular cystitis in Brazil, with a focus on clinical, diagnostic, and therapeutic aspects.

### CASE REPORT

A 2-year-old neutered female English Bulldog was referred for veterinary nephrology service with history of recurrent pollakiuria, hematuria, abnormal urine odor, and frequent licking of the perineal region. In investigations prior to referral, no specific cause was identified to justify the persistence of recurrent urinary infections, despite treatment with NSAIDs (non-steroidal anti-inflammatory drugs) and several treatments with antibiotics. The dog had full immunization and had no travel history. On clinical examination palpable stiffening on the dorsal vulvar surface with the presence of erythema without other significant abnormalities was observed. Laboratory screening performed with complete blood count, serum biochemistry analysis, abdominal ultrasound, serology, and polymerase chain reaction (PCR) for

leishmaniasis, hemoparasitosis test (snap 4DX, IDEXX®) and urinalysis with urine culture collected via cystocentesis. Complete blood count revealed lymphopenia, and serum biochemistry hyperproteinemia and hyperglobulinemia.

Tests to detect hemoparasitosis (in vitro diagnostic for the detection of *Dirofilaria immitis* antigen, antibody to *Anaplasma phagocytophilum*, antibody to *Anaplasma platys*, antibody to *Borrelia burgdorferi*, antibody to *Ehrlichia canis*, and antibody to *Ehrlichia ewingi*) and leishmaniasis were negative. Urine examination revealed a urinary density of 1,044, leukocyturia (3+ dipstick test and microscopic examination of urine with >3 leukocytes/high-power field (HPF)), bacteriuria (microscopic examination of urine 0-3 bacteria/HPF) and normal urinary creatinine protein ratio (0.14; reference < 0.20)

Abdominal ultrasound suggested a subjective impression of focal thickening of the bladder wall in its cranial portion, measuring 1.15cm in thickness with echogenicity and irregular internal margins. Heterogeneous anechoic content with large amount of suspended echoic points and hyperechoic sediment promoting posterior acoustic shadow (Figure 1).

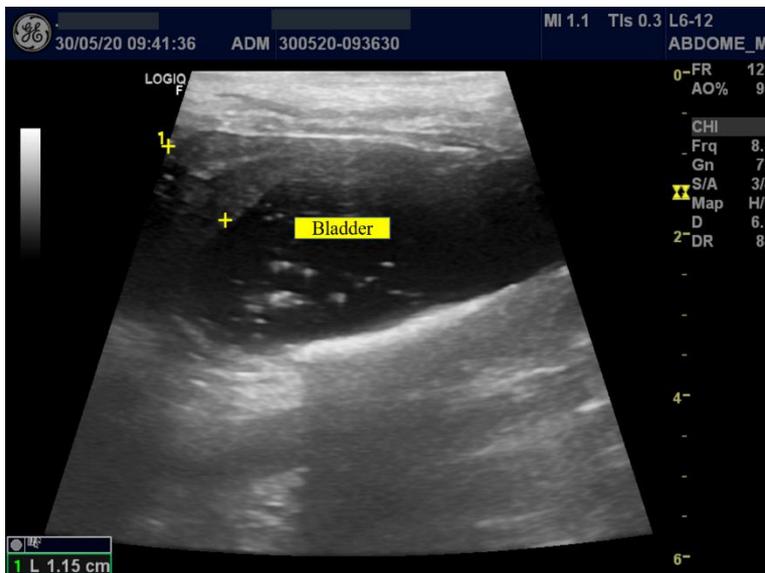


Figure 1. Ultrasonography of the bladder shows focal thickening of the bladder wall in its cranial portion (1.15 cm thick) with irregular echogenicity and internal margins. In addition to a heterogeneous anechoic content with many echoic points in suspension and hyperechoic sediment promoting posterior acoustic shadow.

### Follicular cystitis...

Based on physical examination and ultrasound findings, the diagnosis of a mass-like formation in focal topography of the bladder wall and vaginal hypertrophy associated with chronic vaginitis was obtained. Differential diagnosis consisted of polyps, cysts, tumors, or granulomas. The next day, the patient was referred for exploratory abdominal surgery through a midline ventral celiotomy and biopsy cystotomy.

Cystotomy was performed and a small structure was observed covering the entire bladder mucosa lining, with abundant vascularization and erythema. Two full-thickness sections of the bladder wall were collected for histopathological and microbiological analysis. The procedure of ovariohysterectomy was also performed since a portion of the uterus had multiple adhesions to the bladder wall.

Histopathological analysis revealed nodular masses within the bladder wall, corresponding to lymphoid aggregates of variable size with activated germ centers (Figure 2A and 2B). There was a moderate to perivascular interstitial inflammatory infiltrate comprising lymphocytes and plasma cells (Figure 2C) in the submucosa, that also had mild edema and contained moderate multifocal areas of hemorrhage with congested, dilated blood vessels containing marginal neutrophils (leukostasis) (Figure 2A). Lymphocytes were also present in the overlying mucosa (exocytosis) (Figure 2D). These findings led to the diagnosis of diffuse chronic follicular cystitis. Aerobic culture and antimicrobial sensitivity of the bladder specimen were consistent with *Proteus sp* (286.000 UFC/mL) infection with amoxicillin-clavulanic acid susceptible.

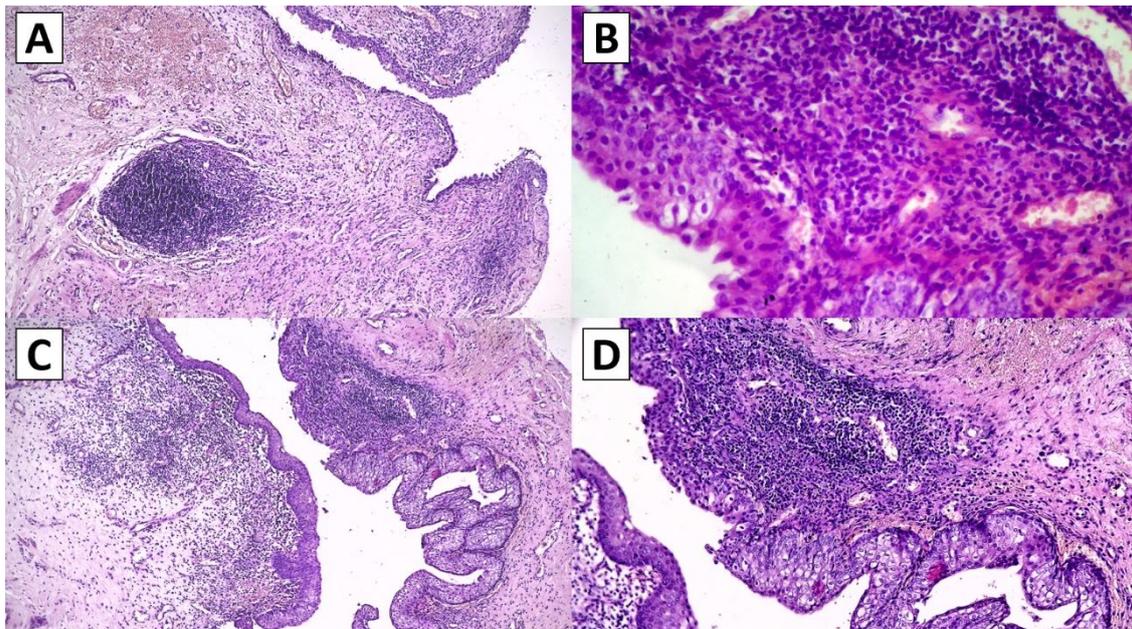


Figure 2. Histopathological sections showed an intense multifocal to coalescent inflammatory infiltrate in the bladder lamina propria (A and B), consisting of lymphocytes and plasma cells (B), sometimes forming lymphoid aggregates (C and D). Hemorrhage and edema foci were observed, and neoplastic cells or microorganisms were absent. Hematoxylin and eosin (H&E), Magnification: 400× (Figure 2A,2C and 2D) and 600X (2B).

Histopathological diagnosis was of moderate diffuse chronic follicular cystitis. Aerobic culture and antimicrobial sensitivity of the bladder specimen were consistent with *Proteus sp* infection with amoxicillin-clavulanic acid susceptible.

The patient was initially treated with amoxicillin-clavulanic acid 20mg/kg (BID, orally for three weeks); meloxicam 0.1mg/kg (SID, orally for one week); supplementation of 10mg/kg cranberry extract associated with cat's claw (from

*Uncaria tomentosa* plant; BID, orally for four weeks) with resolution of clinical signs.

After 30 days, the patient was re-evaluated and the tutor reported presence of hematuria, but with no strong urine odor. A new urinalysis was performed and revealed a urinary density of 1,044, hematuria (3+ dipstick test and urine microscopic examination >3 erythrocyte/high-power field (HPF) without leukocyturia, and negative uroculture. It was indicated return to supplementation of 10mg/kg cranberry extract associated with cat's claw, with subsequent resolution of clinical signs.

A new clinical re-evaluation was performed 60 days after surgery and the patient did not present any of the clinical signs previously reported and it received medical discharge. An annual follow-up was suggested.

Follow-up 12 months after surgery confirmed that the patient had not clinical signs and it enjoyed good quality of life.

## DISCUSSION

Follicular cystitis is a rare inflammatory disease that leads to non-specific symptoms in the urinary tract (Somvanshi *et al.*, 2012; Sul *et al.*, 2014; Ediz *et al.*, 2017). In humans, the disease mostly affects adult females (Marsh *et al.*, 1974; Blanco *et al.*, 2007). Ediz *et al.* (2017) states that the disease should be particularly considered in women over 50 years old with a recurrent history of urinary infections and hematuria. In veterinary medicine, however, there is only one report of the disease in a female dog, being the present study the second report in the species, and, unlike humans, both are young adults (Sul *et al.*, 2014).

The female dog had a history of recurrent urinary infections and clinical signs such as hematuria, pollakiuria and abnormal urine odor compatible with urinary tract disease. Recurrent urinary tract infections (UTI) or hematuria (microscopic or macroscopic) may be present in the history of patients, and in humans, irregular use of antibiotics in cystitis treatment is also described (Ediz *et al.*, 2017). In a study carried out by Marsh *et al.* (1974), human follicular cystitis affected 35% of patients with chronic UTI and, although the etiology of follicular cystitis has not

been fully elucidated, it is known that inflammatory reactions are dominant. This exposure to chronic irritation within the bladder is considered an important factor in the disease development (Blanco *et al.*, 2007; Ediz *et al.*, 2017).

Vasoactive and inflammatory mediators released after urothelium involvement play an important role in chronic inflammatory cystitis and factors such as toxins, allergens and stress can trigger and/or perpetuate bladder inflammation (Theoharides *et al.*, 2001). Thus, it is considered a multifactorial condition involving epithelial dysfunction, neurourothelial interactions and chronic inflammation (Sant *et al.*, 2002). The intense lymphocytic infiltration and consequent formation of germinal follicles observed in histopathology may contribute to the local antibacterial defenses with immunoglobulins production. This is a possible explanation for the increase in the patient's serum globulins. In these cases, more details about the type and cause of inflammation are obtained through the proteinogram. It is noteworthy that a large part of the data is extrapolated from the medical literature due to the reduced number of specific subsidies reported in patients in veterinary medicine (Sul *et al.*, 2014).

Despite the reported symptoms, the patient had hematology and serum biochemistry levels without many noteworthy changes, which is usually observed in human patients, where the literature reports that there is limited contribution of blood analysis to the diagnosis. The evaluation of urine samples from humans with follicular cystitis demonstrates the frequent presence of white blood cells (Blanco *et al.*, 2007; Ediz *et al.*, 2017). Similarly, in the patient from this report, there was an important presence of leukocyturia, which may suggest similarity in the disease pathogenesis.

Imaging methods can contribute more to differential diagnoses than to effectively diagnosing follicular cystitis. A definitive diagnosis occurs by histological evaluation, as mentioned in humans, and in this species, it is routinely obtained through cytoscopy (Ediz *et al.*, 2017). The lesion is histologically characterized by a germinal center of lymphocytic infiltration located in the bladder lamina propria (Blanco *et al.*, 2007; Ediz *et al.*,

2017). Recognition of malignant lymphoid structures is important for the differential diagnosis, although follicular lymphoma is rarely found in the bladder. Granulomas may be similar; however, they are histiocyte-rich formations (Ediz *et al.*, 2017). All differential factors described above were ruled out in this report by imaging and histopathology studies.

Somvanchi *et al.* (2012) describe cases of follicular cystitis in buffaloes from India. Histological samples were obtained from slaughterhouses, and despite the macroscopic appearance of tumors, neoplasms were not microscopically detected. Microscopic findings frequently found were simple, nodular, or papillary hyperplasia, averaging 59%, followed by focal or diffuse hemorrhage (43%), edema (39%) and lymphoid cell aggregates in the lamina propria (20%) (Somvanchi *et al.*, 2012), demonstrating a possible under diagnosis of the disease in veterinary medicine.

Sul *et al.* (2014) describe the follicular cystitis in the first time in a 4-year-old female Cavalier King Charles Spaniel. In the case report, they observed that the patient has vaginal hypertrophy and thickening of the urinary bladder wall, both findings were found through ultrasound evaluation by our group. These findings may indicate a common sign of the disease, although it is not pathognomonic. In addition, the appearance of the urinary bladder mucosa during surgical intervention may alert to a possible case of follicular cystitis, even though definitive diagnosis requires histopathology (Sul *et al.*, 2014). Therefore, the recommendation of bladder biopsy in cases of recurrent urinary disease is encouraged because even in the absence of macroscopic abnormalities, microscopic follicles can be found. The histopathological finding of nodular masses in the bladder wall with lymph node aggregates and germinal centers confirms the case of follicular cystitis. This finding is found even in human and dog biopsies, as found by our group and Sul *et al.* (2014), these demonstrates similarity of the disease between these species.

The treatment of follicular cystitis can be challenging and, although surgical resection has been used in humans, it is only performed in cases where massive infiltrative disease develops. Typically, patients are treated similarly

to other chronic urinary pathologies until a definitive diagnosis is made (Blanco *et al.*, 2007). Antimicrobial therapy was based on a urine culture result with antimicrobial susceptibility testing. In addition, non-steroidal anti-inflammatory, herbal supplement (cranberry and "cat's claw") was used. The use of antibiotics, prednisone and vitamin A has been described in humans (Blanco *et al.*, 2007) where treatment is similar to other types of chronic cystitis, oriented towards inflammation cause and suppression (Ediz *et al.*, 2017). Therefore, antibiotic therapy and suppressive treatment can be planned in patients with a recurrent history of UTI (Blanco *et al.*, 2007; Ediz *et al.*, 2017).

Multimodal treatment was recommended due to the complex pathophysiological cascade of follicular cystitis. Therefore, the choice of cranberry extract supplementation comes from its prophylactic effects on UTI. The consumption of cranberry extract prevents urinary tract infections in women (Stothers, 2002) and, there is evidence, although scarce, for the benefit of cranberry in dogs as well (Chou *et al.*, 2016). Chou *et al.* (2016) investigated the efficiency of cranberry extract, *in vitro* and *in vivo*, in preventing UTI in dogs with a history of disease recurrence. Authors noted that using the extract daily during the 6-month follow-up prevented urinary infections (based on clinical and laboratory evaluation). The study describes that the cranberry extract, in the *in vitro* tests, was not able to inhibit the growth of *E. coli* in culture medium and anti-adherent activity of *E. coli* was observed in Madin-Darby canine kidney (MDCK) cell cultures. These findings suggest that UTI prevention occurs by blocking bacterial adhesion in the uroepithelium. Therefore, the use of cranberry for UTI prophylaxis is a better therapeutic resource than the use of low-dose antibiotics, as the prolonged use of these drugs increases the risk of antimicrobial resistance (Howell e Foxman, 2002).

*Uncaria tomentosa* or "cat's claw" as it is popularly known, is widely used in traditional Peruvian medicine. Its bark and roots are used in preparations for the treatment of various general conditions and inflammatory diseases including urinary tract diseases. The major activities of this plant are attributed to the presence of three main fractions: polyphenols, alkaloids and quinovic acid glycosides (Heitzman *et al.*, 2005; Dietrich

et al., 2015). Dietrich et al (2015) evaluated the anti-inflammatory effects of "cat's claw" on cyclophosphamide-induced hemorrhagic cystitis in mice. The fraction tested, with quinovic acid glycosides, reduced nociceptive behavior and decreased visceral sensitivity in the pelvic region suggests analgesic action, which may be mediated by the modulation of inflammatory responses. Due to the empirical use and the effects described by Dietrich et al (2015), the formulation containing "cat's claw" extract was used as a supporting treatment. In our study, we observed that occurred an improvement in the clinical signs associated with cystitis. This observation may be the result of the sum of treatment (traditional and phytotherapy), therefore, we do not recommend using only herbal treatment as a therapy.

Although follicular cystitis follows a course adjacent to malignant pathologies, in terms of prognosis it is extremely harmless and without any risk of malignant transformation. However, the diagnosis can be delayed as the cause is not fully known and, therefore, there is no specific treatment identified. Thus, molecular and genetic studies are needed to better understand this disease pathophysiology.

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