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Original article

The macrostructure and microstructure of the urinary bladder and urethral mucosa in dogs with lower urinary tract diseases

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Abstract

The aim of the study was to assess the macrostructure and the microstructure of the bladder and urethral mucosa in dogs with lower urinary tract disease as well as to evaluate the usefulness of the WHO/ISUP grading of invasive and non-invasive tumours of the bladder and urethral mucosa. The study was carried out on 37 dogs of different breeds and of both sexes, from 9 months to 15 years old. An urethrocystoscopy and a histopathological evaluation of mucosal biopsies were carried out in all the studied dogs. Cystitis was the most common disease noted during urethrocystoscopy. Chronic active inflammation of the bladder was the most common inflammatory lesion diagnosed in the histopathological examination, while the transitional cell carcinoma was the most common tumour of the bladder. Urethrocystoscopy proved to be a very useful tool in the assessment of macroscopic lesions in the bladder and urethral mucosa in dogs. We also evaluated the type and extent of microscopic inflammatory lesions in the bladder and urethral mucosa using the modified Sydney scale. The WHO/ISUP scale is very helpful in the histopathological classification of canine invasive and non-invasive proliferative lesions in the bladder and urethra.

Key words: bladder, urethra, urethrocystoscopy, histopathology, dog

Introduction

The endoscopic examination is one of the best imaging techniques used to macroscopically assess the bladder and urethra (urethrocystoscopy). A biopsy of the bladder and/or urethral mucosa may be performed during urethrocystoscopy. Urethrocystoscopy may also be used to treat lesions and enables several procedures, such as electrocautery to control bleeding, electroresection of proliferative lesions, the extraction of ureteral, bladder or urethral calculi, endoscopic lithotripsy and foreign body retrieval. In addition, urethrocystoscopy is minimally invasive (Adamiak 2000, Holak et al. 2005, Kubiak et al. 2006). A histopathological assessment of the biopsy specimens obtained during urethrocystoscopy compliments

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the macroscopic assessment of the bladder and urethra (Cannizzo et al. 2001, Messer et al. 2005).

In veterinary medicine, in the majority of published research, cystitis in dogs is divided into an acute and chronic form. Every pathologist usually differently classifies changes in the histological examination of urinary bladder and urethra. There are large variations in the histopathological classification of the subtypes of cystitis. Madej et al. (2000) divided cystitis into two groups: *acute cystitis* and *chronic cystitis*. To acute cystitis include: *cystitis catarrhalis acuta, cystitis haemorrhagica*, *cystitis purulenta*, *cystitis fibrinosa*, *cystitis diphteroidalis.* Chronic cystitis is divided into: *cystitis follicularis* and *cystitis granulomatosa*.

Other veterinary pathologists divided cystitis in dogs also into acute and chronic form (Maxie and Prescott, 1993, Meuten 2002, Meuten et al. 2004, Im et al. 2007). Maxie and Prescott (1993) divided chronic cystitis into: *cystitis follicularis* and *cystitis polypoidalis.* While acute cystitis is divided into: *cystitis catharralis acuta*, *cystitis fibrionsa superficialis* and *cystitis difteroidalis*. Other histological division of cystitis in dogs applies Katkiewicz and Osińska (2009). They distinguished: *cystitis catharrhalis acuta* and *cystitis catharrhalis chronica*, *cystitis haemorrhagica acuta*, *cystitis eosnophlica*, *cystitis follicularis chronica*, *cystitis polypoidalis chronica.*

Hence, histopathologists use their own grading systems when assessing the microstructure of the urethra and bladder. For example, Katkiewicz and Osińska (2009) classified haemorrhagic and eosinophilic inflammation as signs of acute cystitis. They suggested that papules and nodules indicate chronic inflammation. According to Madej et al. (2000) catarrhal, haemorrhagic, purulent and necrotic processes reveal acute inflammation, while the presence of papules and granulomas indicate chronic inflammation. We used a modified Sydney scale to define the inflammatory lesions in the bladder and urethra.

Urethral and bladder tumours in dogs are divided into malignant and benign neoplasms, primary and secondary tumours and mesenchymal or epithelial tumours (Moulton 1978, Madej et al. 2000, Meuten et al. 2004, Katkiewicz and Osińska 2009). Patrick et al. (2006) divided urethral and bladder tumours in dogs according to WHO/ISUP classification used in human medicine. This human classification was considered to be directly applicable to canine urothelial tumours, and likely to be of value in future studies on the biological behaviour and treatment of such neoplasms (Patrick et al. 2006). There are research reports indicating the need to develop modification of classification system of urinary bladder and urethral tumors in dogs which will more correlate with biological behaviour of tumors and response to the applied treatment (Rocha et al. 2000, Sledge et al. 2015).

The aim of this study was to compare macroscopic and microscopic lesions in the bladder and urethral mucosa in dogs with lower urinary tract disease. In addition, we aimed to evaluate the usefulness of the WHO/ISUP grading of invasive and non-invasive tumours of the bladder and urethral mucosa and usefulness of modification of Sydney scale for cystitis and urethritis in dogs.

Materials and Methods

The study was carried out on 37 dogs of different breeds and both sexes from 9 months to 15 years old that had lower urinary tract symptoms and that were referred to the Gastroenterology Division for an urethrocystoscopy.

The animals underwent urethrocystoscopy based on the history, clinical examination, blood results, urinalysis and abdominal ultrasound.

The urethrocytoscopy was carried out using a 67 cm. long and 2.5 mm. wide Karl Storz 11274 AA1 uretero-renoscope and a 60 cm. long 5 mm. wide Sure fiberoscope. The biopsy specimens were obtained using Karl Storz 11275 ZE biopsy forceps or 1022.00A007 biopsy forceps. The urethral patency, ureteral abnormalities, the urine in the urinary bladder, ureteral ostia and the bladder and urethral mucosa were assessed. Based on macroscopic changes in the urethra and bladder mucous membrane found during urethrocystoscopy (degree of redness and edema, presence of mucosal ulcers, presence of petechiae), inflammatory lesions were classified as: severe, moderate, and mild degree.

The biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. The paraffin-embedded tissues were cut into 5 fm sections using a microtome. Sections were then deparaffined with xylene, placed on Super Frost + slides and stained with hematoxylin and eosin (HE) to assess pathological lesions. The histopathological analysis of the biopsy specimens was carried out using the OLYMPUS BX41 light microscope using 10x, 20x and 40x objective lenses.

The own's modification of Sydney scale was used to assess histopathological inflammatory lesions in the mucosa of the bladder and urethra. In this classification severity of inflammatory lesions (number of mononuclear cells), the activity of inflammation (neutrophil infiltration density) and presence of squamous metaplasia were assessed (Table 1.)

Table 1. Histological scale according to the author's modified Sydney scale.

Degree of inflammation – number of mononuclear cells		
0 points	normal	Single stromal mononuclear cells
1 point	mild	Few mononuclear cells in the stroma of the mucosa
2 points	moderate	A moderate amount of mononuclear cells
3 points	severe	Massive infiltration of mononuclear cells
Inflammatory activity – density of neutrophil infiltration		
0 points	normal	No neutrophils present
1 points	mild	Single neutrophils in the stroma of the mucosa
2 points	moderate	A moderate amount of neutrophils in the mucosa
3 points	severe	Massive infiltration of neutrophils in the mucosa
Squamous metaplasia		
0 points		none
1 points		mild
2 points		moderate
3 points		severe

Table 2. A detailed WHO/ISUP histopathological classification of the non-invasive proliferations in the bladder (2004).

Histological finding	
Normal urothelial epithelium	Mild lesions, previously classified as mild dysplasia, may be present
Hyperplasia of urothelial epithelium	Sessile hyperplasia
	Papillary hyperplasia
Flat epithelial atypia	Reactive (inflammatory) atypia
	Atypia of undetermined significance
	Dysplasia (low-grade intraurothelial neoplasia)
	Preinvasive neoplasia, CIS (high-grade intraurothelial neoplasia)
Papillary tumours	Papilloma
	Inverted papilloma
	Papillary urothelial neoplasm of low malignant potential
	Low grade papillary urothelial carcinoma
	High grade papillary urothelial carcinoma*

* If the lesion is invasive, the depth of the tumour invasion should be evaluated. It may reach the lamina propria or the lamina muscularis mucosae.

Two standard classifications used in humans were applied to assess neoplastic lesions in the bladder and urethra:

1) The World Health Organization/International Society of Urological Pathology (WHO/ISUP) histopathological grading of non-invasive proliferative bladder lesions (Table 2).

2) The WHO histopathological grading of invasive tumours of the bladder and upper urinary tract (Table 3).

The StatSoft Inc Statistica 10 software was used for statistical analysis. All the analyses were carried out with a 5% level of significance ($p<0,05$). The Spearman's rank correlation was used for non-parametric ordinal data, and the Chi square test of independence was used for non-parametric nominal data.

Table 3. Current WHO histopathological grading of invasive cancers of the bladder and upper urinary tract (2004).

Histological finding	
Transitional cell carcinoma	sessile
	with glandular differentiation
	with trophoblastic differentiation
	micropapillary
	microcystic
	with involvement of lymphatic endothelium
	lymphoma type
	sarcomatoid
	clear cell
	Giant cell
Squamous cell carcinoma	Papillary carcinoma
Adenocarcinoma	Intestinal type
	mucinous
	Signet ring
	Clear cell
	hepatoid
Small cell cancer	
Undifferentiated carcinoma	

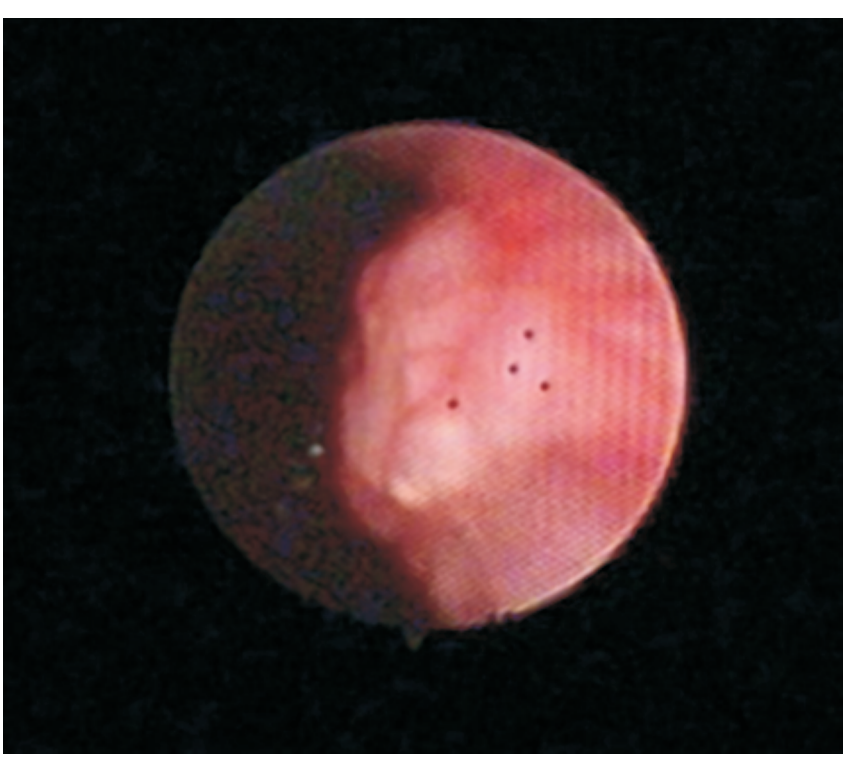

Fig. 1. A proliferative lesion in the lateral bladder wall.

Table 4. The macroscopic appearance of the lesions found in the urethra and ballder during the urethrocystoscopic examination in the studied dogs.

Endoscopic diagnosis	Macroscopic changes
Bladder and urethral inflammation	Inflammation of the entire urethra and bladder; the bladder was filled with cloudy urine containing fibrin strands in 28 cases; the mucosa was reddened; fragile and swollen with prominent blood vessels; there were numerous petechiae in the mucosa in four cases; there were numerous small ulcerations in the bladder mucosa in two cases.
Ectopic ureter	The bladder was filled with cloudy urine containing fibre strands; the right ureteral orifice was present in the bladder trigone while the left ureteral orifice was present in the neck of the bladder; the mucosa in the neck of the bladder was thickened; the mucosa of the body and apex was reddened and swollen with prominent blood vessels.
Bladder diverticulum	The urethral mucosa was slightly reddened; the bladder was filled with a small amount of clear urine; the mucosa in the fundus was reddened and fragile; a diverticulum could be seen in the apex of the bladder. The mucosa of this diverticulum had inflammatory lesions – it was reddened and oedematous.
Bladder and urethral calculi	Calculi were present in the urethra and bladder in one case. In three cases the calculi were limited to the bladder. The calculi were cream-coloured and round in three cases. They were yellow with sharp edges in one case. There was reddening and oedema at the site of the stone location.
Proliferative lesions in the urethra	Proliferative lesions were localised to the internal urethral orifice. They had a rough surface and caused urethral stricture. At the site of the proliferation, the mucosa was reddened, oedematous and fragile. Blood clots and fibrin strands were present inside the urethra.
Proliferative lesions in the urinary bladder	In seven cases, the proliferations were present in the bladder trigone. In two cases, they were localised in the neck of the bladder and there was a single case of a lesion in the apex of the bladder. The lesions were spherical with a smooth surface in two cases, while they had an irregular shape in five cases. The mucosa was reddened, fragile and swollen at the site of the lesions.

Results

The urethrocystoscopy revealed urethritis in 26 cases (70.2%), cystitis in 37 cases (100%), ectopic ureters in one case (2.7%), a bladder diverticulum in one case (2.7%), urinary calculi in four cases (10.8%), proliferative lesions in the bladder in seven cases (18.9%) (Fig. 1) and proliferative lesions in the urethra and bladder in three cases (8.1%). In case of proliferative lesions found during urethrocystoscopy in the urethra, all were located in the area of the internal urethra. However, in case of proliferative lesions diagnosed during urethrocystoscopy in bladder, 7 cases were located in the bladder trigone area, in 2 cases the lesions were located in bladder neck area and in 1 case the lesions were located in bladder apex area. The macroscopic lesions found in the urethra and bladder during the urethrocystoscopy in the studied group of dogs are presented in Table 4.

The following lesions were diagnosed based on the WHO/ISUP histopathological grading of non-invasive proliferative bladder lesions and the WHO histopathological grading of invasive tumours of the bladder and urethra: hyperplasia in the bladder epithelium in four cases (10.8%), reactive urothelial atypia in three cases (8.1%), urothelial dysplasia in two cases (5.4%), transitional cell carcinoma of the bladder in ten cases (27%) (Fig. 2) and urethral transitional cell carcinoma in two cases (5.4%).

Based on the histopathological assessment of the bladder and urethral mucosa using the own modified Sydney scale, the following lesions were diagnosed: chronic active cystitis in six cases (16.2%), chronic active urethritis in three cases (8.1%), chronic active cystitis with squamous metaplasia in one case (2.7%), chronic inactive urethritis in one case (2.7%), chronic inactive haemorrhagic cystitis in two cases (5.4%).

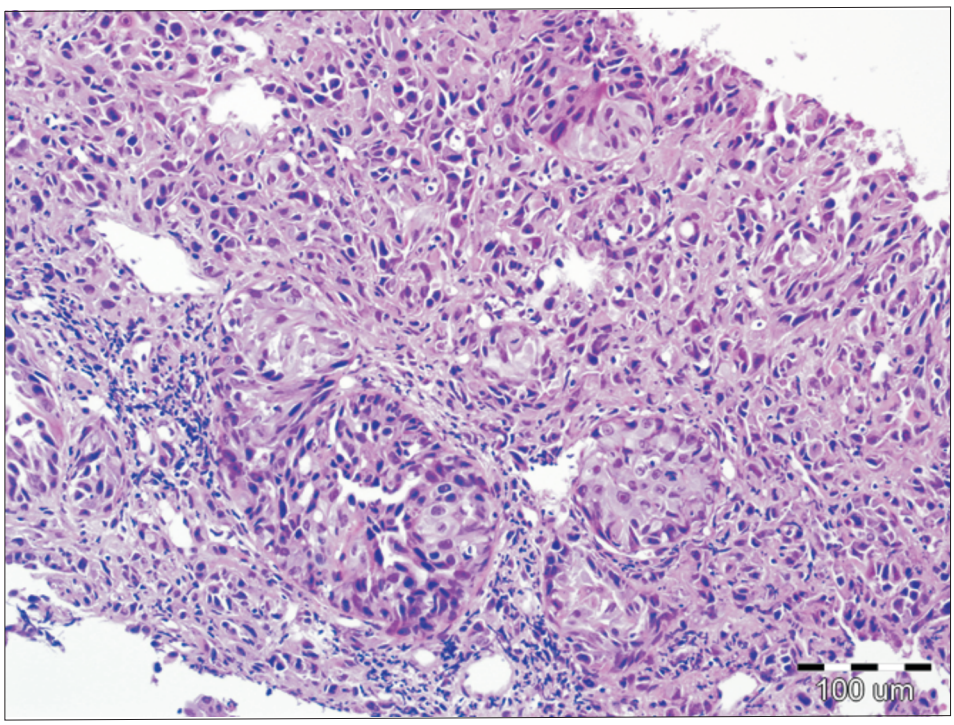

Fig. 2. A high-grade invasive urothelial carcinoma in the bladder (G3) infiltrating the mucosa, HE staining.

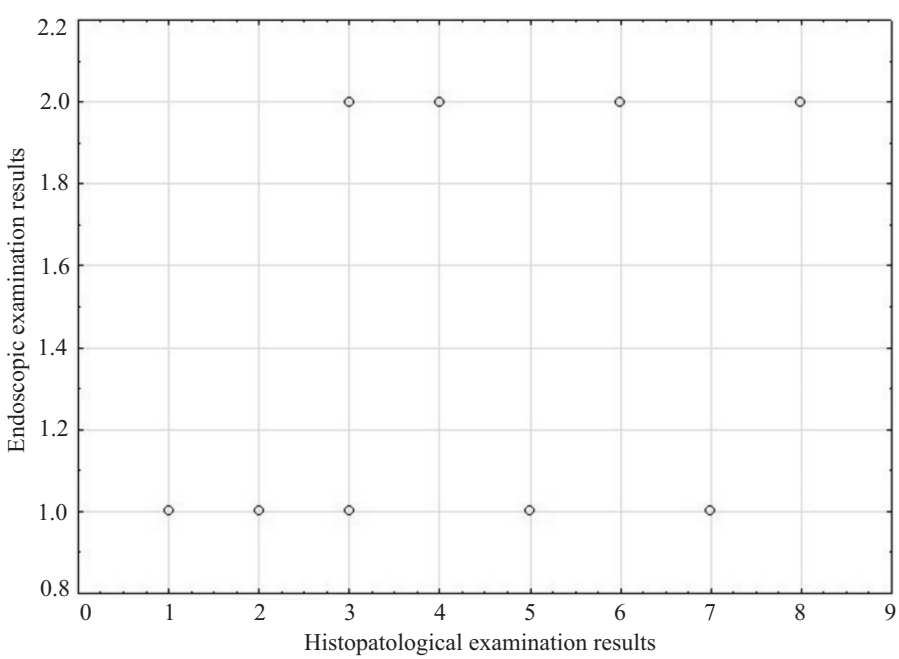

Fig. 3. A comparison of the histopathological examination of the biopsy specimens with the urethrocystoscopic findings.
NOTE: There may be multiple representations of single points on the scatterplot, which may affect the general appearance of the plot.

The inflammatory lesions in the urinary bladder and urethra were graded using a seven point Sydney scale (median 3.08 points; ± 1.5). A score at 1 – 3 points indicated advancement of inflammation (mean 1.77 points; ± 0.6), a score at 0 – 2 points indicated activity of inflammation (mean 1.15 points; ± 0.8), 0 or 2 points indicated squamous metaplasia (mean 0.15 points; ± 0.6). In six cases (16.2%), a definitive diagnosis could not be obtained because the biopsy samples were too small.

There was a correlation between the results of the urethrocystoscopy and the histopathologic examin-

ation of the biopsy samples obtained from the bladder and urethra (Spearman's rank correlation coefficient Rs=0.829, p<0.001; Fig. 3).

Discussion

Urethrocystoscopy is one of the best tool to diagnose pathologic lesions in the urethra and urinary bladder. This method enables the diagnosis of various diseases in the lower urinary tract, which cannot be detected otherwise. An endoscopic examination of the urethra and urinary bladder also enables the examination of their interior surface. In addition, a biopsy sample may be obtained from a chosen location for the histopathological analysis (Adamiak 2000, Cannizzo et al. 2001, Messer et al. 2005, Kubiak et al. 2006, Holak et al. 2007).

In order to enable a complete visualisation of the bladder wall in our study, the bladder was inflated with air or a warm saline solution (0.9% NaCl). Messer et al. (2005) and Biewegna et al. (1985) recommend the use of a sterile 0.9% NaCl solution at body temperature to inflate the bladder. Similarly, Holak et al. (2007) recommended the use of a saline solution at room temperature rather than insufflation using carbon dioxide as carbon dioxide damages the endoscope hindering assessment of the bladder mucosa. Furthermore, carbon dioxide is converted to carbonic acid, which irritates the bladder mucosa. Cannizzo et al. (2001) also found that warm 0.9% NaCl provided better visualisation of the interior surface of the bladder. We found that inflation using air provided better visualisation than 0.9% NaCl. Saline may mix with residues of bloody or cloudy urine hampering the optical clarity of the images.

The macroscopic assessment of the urethral and bladder mucosa may reveal mucosal inflammation in the urinary bladder and/or urethra, tumours in the bladder and/or urethra, ectopic ureters, calculi in the bladder or urethra, urethral atrophy, bladder or urethral trauma, urethral stricture, urethral foreign bodies or bladder diverticula (Biewegna et al. 1985, Adamiak 2000, Cannizzo et al. 2001, Messer et al. 2005, Kubiak et al. 2006, Holak 2007). The macroscopic evaluation of the bladder and urethra led to a more frequent diagnosis of reddening, oedema and mucosal fragility (suggesting inflammation). Proliferative lesions were diagnosed less frequently. Calculi, bladder diverticula and ectopic ureters were diagnosed least often. Holak et al. (2007) also found that mucosal inflammation was the most common lesion seen in a macroscopic examination of the bladder and urethra. On the other hand, Martinez et al. (2003) found that proliferative lesions in the bladder were more common than mucosal inflammation. However, the high incidence of proliferative lesions in their study could have been a result of a small sample size (eight dogs) and the inclusion criteria, where dogs with suspected inflammatory mucosal polyps in the bladder were included in the study.

The final diagnosis can often be based on a histopathological examination of the biopsy specimens of the bladder and urethra. There should be enough biopsy specimens collected during the cystoscopy to ensure the reliability of the histopathological examination. In our study, a histopathological examination of the specimens could not be performed in 16.2% of the dogs, which had mucosal inflammatory lesions in the bladder and/or urethra, due to the small size of the specimens. The bladder and urethral mucosa is tough and it may be difficult to obtain a large sample using biopsy forceps. Similar observations were made by Martinez et al. (2003).

Using own's modification of Sydney scale we found that chronic active inflammation of the bladder and/or urethra occurred most frequently. Chronic inactive mucosal inflammation and haemorrhagic inflammation of the urethra and/or bladder occurred much less frequently. Using the modified Sydney scale, we were able to determine the degree of inflammation in the bladder and urethra. That was particularly useful in squamous metaplasia, which is a benign lesion. Patients diagnosed with this condition may be monitored frequently in order to diagnose a neoplastic lesion at an early stage (McKenney JK 2007).

The Sydney scale is used to assess inflammatory changes in gastric mucous membrane in human and veterinary medicine (Dixon et al. 1996, Rzeszutko et al. 2006, Day at al. 2008). This system includes endoscopic and histologic image of gastric mucous membrane. Histological description includes: etiological part, morphological part and topographic part.

In endoscopic examination of urinary bladder in dogs, it is possible to describe changes such as: reddening of mucous membrane, fragility of mucous membrane, swollen of mucous membrane, presence of erosions of mucous membrane, like in gastric mucous membrane. The own's modification of Sydney scale was used to assess histopathological inflammatory lesions in the mucosa of the bladder and urethra. In this classification severity of inflammatory lesions (number of mononuclear cells), the activity of inflammation (neutrophil infiltration density) and presence of squamous metaplasia was assessed.

Microstructural lesions in the bladder and/or urethral mucosa also include proliferative lesions, which are usually malignant (Norris et al. 1992, Valli et al. 1995, Katkiewicz and Osińska 2009). Classification of transitional cell carcinoma in humans is based

primarily on the classification of the World Health Organization and the International Society of the Urological Pathology (WHO/ISUP) 1998, which was adapted in 2004 (Grignon 2009). Conducted studies evaluate the use of this classification in veterinary medicine, mainly in dogs, due to similarities between morphology, biological behaviour and response to chemotherapy of the bladder cancer in humans and in dogs (Patrick et al. 2006, Knapp et al. 2015).

Presently, the WHO/ISUP scale is not widely used in veterinary medicine to grade non -invasive proliferative lesions in the bladder and urethra (Epstein JI et al. 1998). Similarly, the WHO histopathological grading of invasive tumours of the bladder and upper urinary tract is rarely used in veterinary pathology (Eble et al. 2004).

The study shows correlation to morphological aspects between hyperplasia at urothelium in humans and dogs. There is no data on the prognostic application of the histological classification (Patrick et al. 2006). Patrick et al. (2006) had the same difficulty in distinguishing fibroepithelial polyps from polypoid cystitis , both of which commonly showed a varying degree of inflammation. Diagnosis relied heavily on whether the mass appeared histologically to consist of a solitary lesion with a single attachment to the mucosa (polyp), or multiple lesions (polypoid cystitis). Urinary bladder polyps, unlike polypoid cystitis, are rare in man; they appear, however , to be more common in dogs (Patrick et al. 2006).

Using these grading scales, we found that the transitional cell carcinoma was the most common proliferative lesion (57% of the cases) in the bladder and urethra. Valii et al (1995) and Sapierzyński et al. (2007) also found a high incidence of TCC when using the above mentioned grading scale (42% and 91%, respectively). Bladder adenocarcinomas were the most common type of tumour (28.7%) reported by Katkiewicz and Osińska (2009). However, they did not use the aforementioned classification system.

In conclusion, we found that urethrocystoscopy is very useful in the macroscopic evaluation of mucosal lesions in the urinary bladder and the urethra in dogs. Urethrocystoscopy enables precise localisation and collection of specimens from the mucosa for further histopathological assessment. In addition, we found that the microscopic assessment of the mucosal inflammation in the bladder and/or urethra using the modified Sydney scale enabled a more precise diagnosis of the type of inflammation. Using the modified Sydney scale, we evaluated the degree of metaplasia as well as the inflammatory intensity and activity which influence the choice of therapy. The modified WHO/ISUP histopathological grading of non-invasive proliferative bladder lesions and the WHO histopathological grading of invasive tumours of the bladder and upper urinary tract were useful in the diagnosis of the types of proliferative lesions and the degree of invasion in the bladder and urethra in dogs.

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