

## Pathomorphologic Characteristics of Non-Neoplastic Lesions in Bovine Urinary Bladders

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**Abstract:** Non-neoplastic epithelial and stromal changes might be prognostic in early phase of premalignant neoplastic developments of urinary bladder. In this regard, diagnosis and histological classification of these lesions give valuable knowledge for prevention and treatment in both human and veterinary medicine. In Turkey, bovine urinary bladder lesions have been encountered in great ratio even though the small numbers of cases have been observed in other animals. According to our great experiences and field-studies for years concentrating on the topic, inflammatory and neoplastic of pathologies in urinary bladders might be easily developed after long term Bracken fern-consuming cattle. In current study, non-neoplastic cases including mainly epithelial, stromal, vascular, and inflammatory characteristic lesions were identified and described separately. Degenerative, desquamative, cystic, hyperplastic, and metaplastic lesions were found prominently in urinary bladder epithelium. Consecutive lesions comprised stromal changes and vascular lesions characterized with circulatory problems. Accompanying those, remarkable mononuclear cell infiltrations were found in a lot of cases. In conclusion, such kind of non-neoplastic lesions at least should be considered as important as neoplastic lesions because the lesions can have a risk in course of premalignant neoplastic transformation.

**Keywords:** Cow, Histopathology, Non-neoplastic changes, Urinary bladder.

### Sığır İdrar Keselerindeki Non-neoplastik Lezyonların Patomorfolojik Özellikleri

**Özet:** Non-neoplastik epitelyal ve stromal değişiklikler, idrar kesesinin premalign neoplastik gelişimlerinin erken evresinde prognostik olabilir. Bu lezyonların tanısı ve histolojik sınıflandırması, hem insan hem de veteriner hekimlikte önleme ve tedavi için değerli bilgiler vermektedir. Türkiye’de, diğer hayvanlarda az sayıda olgu görülmesine rağmen sığır idrar kesesi lezyonlarına yüksek oranlarda rastlanmaktadır. Yıllara dayalı yeterli deneyimlerimiz ve saha çalışmalarımıza göre, uzun vadede eğrelti otu tüketen büyükbaş hayvanların idrar keselerinde yangısal ve neoplastik patolojiler kolaylıkla gelişebilir. Bu çalışmada, başlıca epitelyal, stromal, damarsal ve yangısal karakterli lezyonları içeren non-neoplastik olgular tanımlanmış ve ayrı ayrı açıklanmıştır. İdrar kesesi epitelinde dejeneratif, deskuamatif, kistik, hiperplastik ve metaplastik lezyonlar belirgin olarak bulundu. Ardışık lezyonlar stromal değişiklikler ve dolaşım problemleri ile karakterize damarsal lezyonları da içeriyordu. Bunlara eşlik eden, dikkate değer mononükleer hücre infiltrasyonları çok sayıda vakada bulundu. Sonuç olarak, bu tür non-neoplastik lezyonların en azından neoplastik lezyonlar kadar önemli olduğu düşünülmelidir, çünkü lezyonlar premalign neoplastik transformasyon sırasında bir risk oluşturabilir.

**Anahtar Kelimeler:** Sığır, Histopatoloji, Non-neoplastik değişiklikler, İdrar kesesi.

### Introduction

Many different tumor-like but non-neoplastic lesions of the urinary bladder are among the most misdiagnosed cases in human medicine (Wong-You-Cheong et al., 2006; Young, 2009). As in human cases, those focal or diffusely developed lesions in urinary bladder have mimicked the malignancy in also animals (Aydin and Ozkul, 1995; Peixoto et al., 2003). Similar to humans, focal or diffuse wall thickening can develop in too many non-neoplastic pathologic conditions in the bladder in case of bracken fern toxicity (Carvalho et al., 2006; Roperto et al., 2010). Both human (Wiener et al., 1979; Young, 2009) and animals (Peixoto et al., 2003)

epithelial non-neoplastic lesions, especially; von Brunn’s nests, cystitis cystica and cystitis glandularis, reactive papillary proliferation, papillary-polypoid cystitis are common in normal bladders and such proliferations may mimic the nested variant of urothelial carcinoma, particularly if the nests lie relatively deep in the lamina propria (Young, 2008). In human medicine, the molecular genetics and biomarker characterizations of several urinary bladder pathologies have been demonstrated to provide considerable advantage at last decade (Lopez-Beltran et al., 2002). In this course, several molecular alterations have been

found in association with intraepithelial lesions such as dysplasia and carcinoma in situ (CIS). However, their usage in routine clinical settings remains still controversial in humans (Reuter, 1999). The situation is almost same in veterinary medicine and there are still numerous unclarified hypothesis on the basis of molecular interactions in different source of urinary system cells in cattle (Keles et al., 2018; Ozkul et al., 2008; Yucel-Tenekeci et al., 2017).

In veterinary medicine, only a few studies (Carvalho et al., 2006; Roperto et al., 2010) have described the pathologic features of non-neoplastic bladder lesions of cattle. In this study, we aimed to illustrate the histopathological features and pathomorphological characteristics of bracken fern-associated non-neoplastic lesions in bovine urinary bladder.

## Materials and Methods

**Sample collection:** Totally, 216 urinary bladder samples belonging to cows older than 2 years of age including Holstein, Jersey, domestic black cattle, half or mixed culture breeds were used. These selected samples were provided from slaughterhouses in center and / its neighbors of several provinces (Trabzon, Ordu, Giresun, Samsun, Karabuk, Sakarya provinces) located in the Black Sea region of Turkey. The pastures in this area are often composed of bracken fern as result of our field observation. Also, fresh or digested bracken-fern herbals were found in ruminal ingredients in some of slaughtered cattle, so that a cross-check in direction to theconsumption of this plantwere provided.

**Macroscopical examinations:** For better fixation of the urinary bladder samples, mucosal surface was reversed and fixed in a 10% neutral buffered formalin. Lesion localizations and numbers were described as collum vesicae, corpus vesicae, vertex vesicae, and trigonum vesicae in collected samples. Macroscopical features including thickening of wall, vesicular or balloon like changes, distribution, shape and circumscription, of lesions as well as hyperemia and hemorrhage etc. were illustrated in a urinary template for each collected samples.

**Histopathological examinations:** Each described lesion collected from all samples were processed routinely in alcohol and xylol series. The samples were embedded in paraffin wax, and 5 µm thick sections were cut from paraffin blocks. After that,

these sections were stained with hematoxylin and eosin. The sections were examined and classified according to the established criteria for neoplastic and non-neoplastic urinary bladder lesions (Roperto et al., 2010; Volmar et al., 2003). Hematoxylin and eosin-stained slides were examined for architectural features, such as size, shape, and distribution of lesions. Cellular characteristics were also noted, including nuclear pleomorphism, prominent nucleoli, mitotic figures, and evidence of non-urothelial differentiation including squamous and glandular differentiation. The nature of the intervening stroma was searched, including desmoplasia, inflammation, and necrosis.

## Results

**Macroscopic findings:** Location of non-neoplastic lesions has been evaluated on lateral or ventral wall, neck and vertex of the urinary bladder. All of the abnormal changes such as wall thickness, hyperemia, hemorrhage, papillary or verrucoid structures and indurations were examined.

**Histopathological findings:** Histopathologically, lesions in the cow bladder were divided as epithelial, stromal, vascular, and inflammatory. All evaluated lesions were semi-quantitatively scored as no lesion (-), mild (+), moderate (++) and severe (+++). Results are given in Table 1 and then detailed according to the characteristics of findings.

**Urothelial lesions:** Histologically, lesions were described as hyperplasia characterized with increased numbers of the normal transitional cell layers which arranged either papillary (Fig. 1A) or nodular (Fig. 1B) in structure. There were few or no significant cytological abnormalities, although slight nuclear enlargement might focally present. In some cases, light to severe hydropic degeneration was observed in hyperplastic epithelium (Fig. 1C). Intraepithelial cysts (Fig. 1D) within the epithelial layers and epithelial desquamation (Fig. 1E) in the outer row of transitional epithelium were noticed in some cases with severe papillary hyperplasia. In the lamina propria, oval or round and generally smoothly contoured von Brunn's nests which a transitional cell aggregates with or without connection to the surface epithelium were found single or multiple in some cases (Fig. 1D). The epithelium in the von Brunn's nests were similar to the surface epithelium and exhibited hyperplasia, reactive urothelial atypia (including prominent nucleoli), and mitotic activity. Some of these nests

had central lumina, and this lesion was classified as cystitis cystica (Fig. 1F) and or into intestinal columnar mucin-secreting glands (goblet cells) were named as cystitis glandularis (Fig. 1G). Cystitis glandularis developments were seen both into papillary and nodular masses. There are two type of glandular hyperplasia were seen in the cases. In the first (non-intestinal) form of cystitis glandularis was characterized by glands lined by cuboidal to low columnar cells, which were themselves surrounded by a layer of transitional cells. In the second form of cystitis glandularis, the cells lining the glands in the intestinal-type cases were tall and columnar with abundant mucin. These cells may be admixed with goblet cells and the epithelium often closely resembles intestinal epithelium. The second type also named as glandular metaplasia or colonic

metaplasia (Fig. 1H) and characterized by the presence of epithelial cells of colonic type with a goblet cell appearance within the surface epithelium (flat pattern) or/and in association with cystitis cystica (endophytic pattern). Mucin-secreting metaplasia that shows a striking resemblance to intestinal mucosa, including a crypt-like architecture, has been designated intestinal metaplasia. Intestinal-type mucinous metaplasia may include focal or diffuse areas of the type of intestinal metaplasia consisting of goblet cells or colonic-type glands. Morphologically it has a villous or a tubulo-villous architecture with fronds lined by tall, pseudo-stratified, colonic-type epithelium whose nuclei are dark, elongated and in a basal position.

**Table 1.** Non-neoplastic epithelial, stromal, vascular, and inflammatory lesions\*.

Lesions (n:216)	No lesion (-)	Mild (+)	Moderate (++)	Severe (+++)
<b>EPITHELIAL</b>				
Hydropic degeneration	82	32	87	15
Epithelial desquamation	190	17	7	2
Intraepithelial cysts	124	65	23	4
Cystitis cystica	170	21	20	5
Cystitis glandularis	188	7	19	2
Papillary hyperplasia	55	69	89	3
Nodular hyperplasia	58	47	106	5
von Brunn nests	133	52	27	4
Metaplasia	202	14	0	0
<b>STROMAL (Spindle cells)</b>				
Fibrosis	123	64	27	2
Myxomatous stroma	180	16	17	3
<b>VASCULAR</b>				
Edema	180	34	2	0
Thrombosis	200	11	4	1
Hemorrhage	88	30	61	37
Erythrocyte exostosis	168	21	11	16
Neo-vascularization	79	36	94	7
<b>INFLAMMATUAR</b>				
Mononuclear cells	55	41	93	27

\*The numbers of animals with lesions are given in the columns.

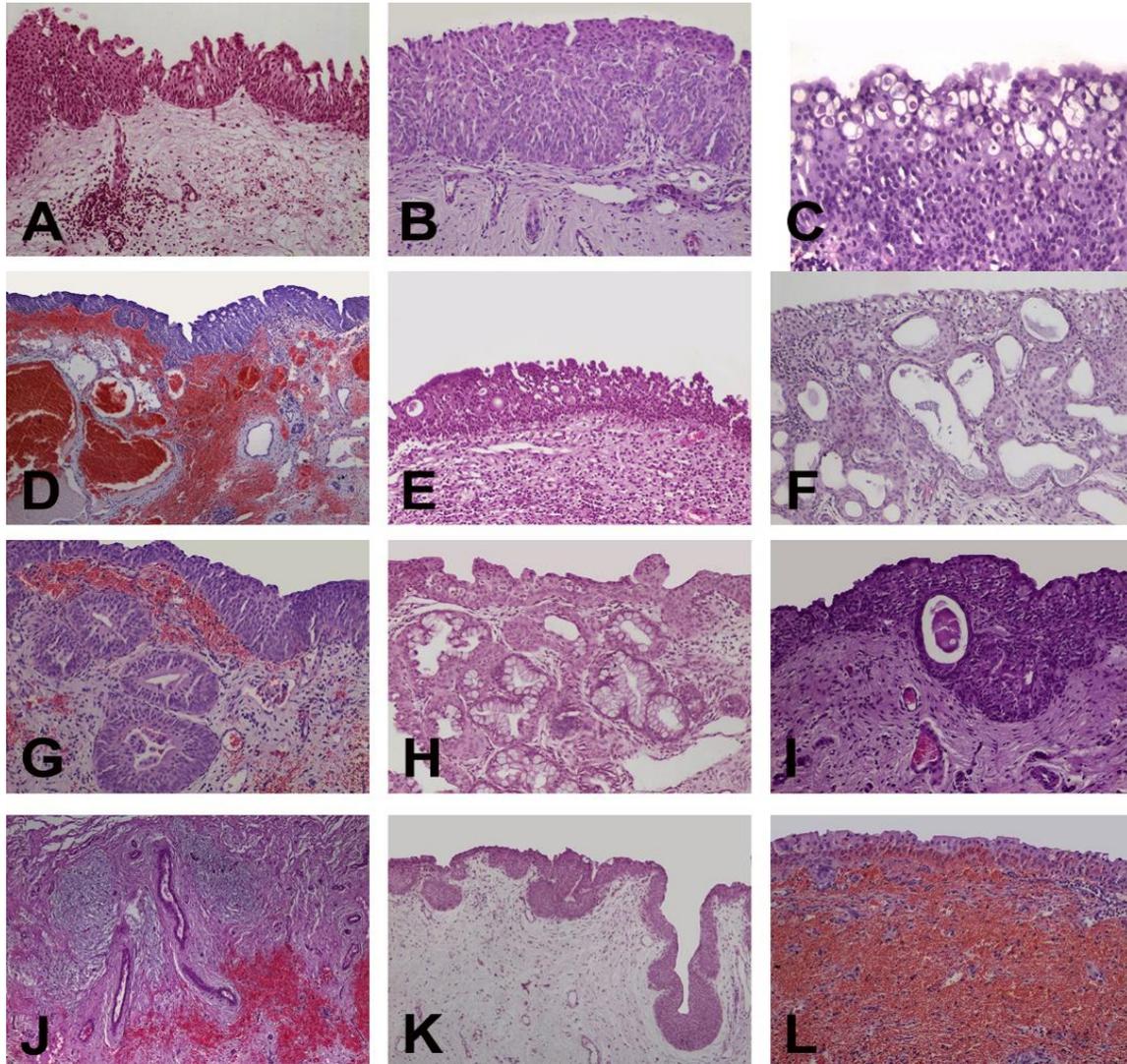
**Stromal lesions:** Herein, lesions were generally interested to spindle and/or star-like shape cells. Fibrosis, abnormal connective tissue deposition, was seen in dermis localized just below to most remote regions of the transitional epithel with focal or diffuse shape (Fig. 1I). Similar to fibrosis myxomatous stroma-myxomatous tissue components (Fig. 1J) were seen in some cases with similar to location and shape of fibrosis.

**Vascular lesions:** Submucosal edema (Fig. 1K) was noticed in some cases with different severity. In

some cases, newly formed and/or shaped vascular capillary clusters -neo-vascularization- (Fig. 1D) were observed. Although they are different from normal appearance, some of them opened to the blood circulation, and the other cleft shaped primitive capillaries were not opened the blood circulation. Thrombosis (Fig. 1D) was firmly stocked to the vessel wall, partially closed the lumen, and with layered view and a hyaline-like proteinaceous appearance viewed at the thrombotic mass. In the lesions were described as hemorrhage (Fig. 1L) red blood cell extravasations were seen between

connective tissue cells and elements. Although sometimes small amount of erythrocytes, sometimes dense erythrocyte extravasations were completely covered the underlying structures. Most of such severe bleeding cases erythrocyte exostosis (Fig. 1L) was detected between the associated transitional epithelial cells.

**Inflammatory changes:** Mononuclear cells were predominant. The cells were belonged to a vast majority of lymphocytes and a small number of macrophages and also a few and plasma cells were observed in the submucosal areas with varying intensity. These diffuse (Fig. 1A) and/or focal cell aggregates sometimes were observed in the style of lymphoid follicles.



**Figure 1.** Hematoxylin and Eosin stained urinary bladders. Magnifications are 10, 10, 20, 4, 10, 10, 10, 4, 4, 10, 4, and 10, respectively. The most prominent lesions were noted in the legends and the others were ignored in this section. **A.** Papillary hyperplasia, nodular hyperplasia, and mononuclear cells. **B.** Nodular hyperplasia. **C.** Hydropic degeneration and nodular hyperplasia. **D.** von Brunn's nests, intraepithelial cysts, neo-vascularization, thrombosis, and hemorrhage. **E.** Intraepithelial cysts, epithelial desquamation, and mononuclear cells. **F.** Cystitis cystica. **G:** Glandular metaplasia and hemorrhage. **H:** Colonic metaplasia and papillary hyperplasia. **I:** Fibrosis and nodular hyperplasia. **J:** Myxomatous stroma-myxomatous tissue components and hemorrhage. **K:** Edema, nodular hyperplasia, and von Brunn's nests. **L:** Hemorrhage and erythrocyte exostosis.

## Discussion

In the current study, we reached some major outcomes: (i) in non-neoplastic pathologies, urothelium was susceptible to bracken-fern

toxicants. Their pathologies were more predominant and common when compared to stromal pathologies; (ii) general vascular lesions were less common than urothelial pathologies even though neo-vascularization were found mildly in

numerous cases; (iii) there may not be any association with bracken fern toxication and its triggering effect of inflammation in each case.

Mucosal layers of urinary system have been consisting of multiple layers of transitional urothelium in several characteristics. Thus, the developed lesions might be different here. These are described pathologies as hyperplasia, von Brunn's nest hyperplasia, mullerianosis of urinary bladder, cystitis, papillary polypoid cystitis, cystitis cystica, malacoplakia, atypia, squamous metaplasia, pseudocarcinomatous proliferation in humans (Koren et al., 2006; Readal and Epstein, 2010; Sampson et al., 2007; Volmar et al., 2003; Wiener et al., 1979). In veterinary medicine, such kind of similar descriptions have also been found in cattle (Peixoto et al., 2003; Roperto et al., 2010). These changes as in human counterparts could be in flat, exophytic and endophytic form (Roperto et al., 2010). Sometimes there are only epithelial changes, but sometimes there may be stromal and vascular pathologies (such as vascular ectasia, inflammatory pseudotumor and myxoid stroma etc.)\_along with epithelial changes. In the current study, we, take into consideration such terminology; however, preferred to use classical descriptions in veterinary medicine. About classification of the non-neoplastic pathologies, at last decade, Young (2009) reported to categorize non-neoplastic human bladder lesions as follows: (1) pseudocarcinomatous proliferations of transitional epithelium; (2) glandular lesions; (3) papillary lesions; (4) spindle cell lesions and (5) miscellaneous others. To the best of our knowledge about veterinary counterpart of any classification, there have not been on non-neoplastic developments. According to our observation in the current study, we grouped bracken fern-associated non-neoplastic lesions in the bovine urinary bladder as: (1) epithelial lesions (hydropic degeneration, epithelial desquamation, intraepithelial cysts, cystitis cystica, cystitis glandularis, papillary hyperplasia, nodular hyperplasia, von Brunn's nests, metaplasia), (2) stromal lesions (especially spindle cell) (fibrosis, myxoid stroma), (3) vascular lesions (edema, thrombosis, hemorrhage, erythrocyte exostosis, neo-vascularization), and (4) inflammatory changes (mononuclear cell infiltrations).

About epithelial lesions, in human autopsy, these proliferative lesions, such as von Brunn's nests and cystitis cystica have been found in more than 90% of normal bladders (Wiener et al., 1979). In bovine cases in the present study, the absence of another lesion and the high rate of these macroscopically unobtrusive lesions was found to be compatible with human study. Therefore, we come to conclusion that urothelial pathologies were

more common than other pathologies. Even though focal or diffuse wall thickening may develop suitably to the such lesions; but, sometimes there may not give any macroscopic finding (Carvalho et al., 2006; Roperto et al., 2010). Therefore, it should be best to make a decision for classification of pathologies by considering such microscopic changes throughout all mucosa for human and veterinary cases. In epithelial micro-architecture, although solely the epithelial lesions can be present, the lesions can eventually be seen in a consecutive series of style as a part of chain of events. As described by Montironi et al. (2003), the event initiate as epithelial hyperplasia and develop atypical hyperplasia and can afterwards gain non-invasive papillary carcinoma, invasive carcinoma characteristics. Even, it can be metastasis to distant tissues due to high malignant potential (Montironi et al., 2003). In this situation, we agree to the postulate at the same way. The urothelial cells can cause hyperplasia, dysplasia, or metaplasia, and thereafter the cells can be undergone a malignant transformation. According to our thought, von Brunn's nests are also the next stage of nodular hyperplasia likely to be in other urothelial lesions. And it can be under experienced for malignant transformation in ongoing stages. These result can have been confirmed because such kind of cases, in previous studies, contained together both non-neoplastic-premalignant and malignant epithelial lesions (Keles et al., 2018; Ozkul et al., 2008; Yucel-Tenekeci et al., 2017). Regarding stromal changes, there have been found different topics suitably to situation and cellular type in human medicine. These have been known since long term as non-neoplastic stromal cells with atypia, postoperative spindle cell nodule, inflammatory pseudotumor (ancient terminology: pseudosarcomatous myofibroblastic proliferation), and hamartoma etc. (Harik et al., 2006; Nochomovitz and Orenstein, 1985; Proppe et al., 1984; Roth, 1980; Wick et al., 1988; Young, 2008). However, in veterinary terminology, there have not been important development at recent years. Aydin and Ozkul (1995) did not document any stromal changes in 131 urinary bladders with lesions of cattle and water buffalo even though the researchers made a classification in epithelial, inflammatory lesions and vascular disturbances. However, in the current study, we set an extra-category of these stromal changes including fibrosis and myxomatous stroma despite of being not lesions of a vast majority of them. We demonstrated stromal microarchitecture, in sometimes, might be also affected in addition to other cellular component of mucosa. On the other hand, we are not certain whether the stromal changes can be resourced spontaneously or after

interaction to vascular changes, epithelial lesions and inflammatory cells, not.

About inflammatory changes, Peixoto et al. (2003) stated that focal or diffuse inflammatory infiltration, mostly lymphocytes, can be found in neoplastic and non-neoplastic conditions. Therefore, the researchers took no simple correlation between inflammations and any neoplastic or non-neoplastic alterations. In this point, we share the same thoughts with the researchers. Our results also showed us inflammatory changes cannot be developed against any urothelial and/or stromal changes. However, the mononuclear cells can be related to action against or by means of chemicals compounds of bracken-fern herbal. These problematic should be needed to be more investigated in-vitro conditions prepared from bovine urothelial and stromal cells introducing reaction with toxicants well-described such as mainly ptaquiloside (a norsesquiterpenoid glycoside), quercetin, shikimic acid, and prunasin (Pamukcu at al., 1967; Pamukcu, 1974).

About vascular lesions and vessel alterations, Peixoto et al. (2003) reported that they can be developed in varying degree of the propria mucosa and accompanied by any epithelial lesions. According to our experience, in particular, hemorrhage should consider for evaluation of the non-neoplastic changes because small amount of erythrocytes or erythrocyte extravasations are completely covered the underlying structures. We believe that triggering of such kind of changes in bovine cases is again responsible for several toxicants of bracken-fern even though the changes are not mentioned in human counterparts at every case. However, according to our results, the observational frequency is indeed not enough when compared to epithelial lesions.

In conclusion, we believe that we gained a general point of view to non-neoplastic lesions of bovine urinary bladders. These lesions are again related to bracken-fern toxication under shed light of previous experience. The lesions have a risk because it is suitable for premalignant neoplastic transformation in terms of especially epithelial or urothelial changes. However, it needs to more clarification on the basis of molecular and genetic alterations comparing them and following developments in human and veterinary medicine.

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