J. Comp. Path. 2021, Vol. 182, 9–14

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NEOPLASTIC DISEASE

# Histological Characterization of Feline Bladder Urothelial Carcinoma

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## Summary

Urothelial (transitional cell) carcinoma (UC) is the most common type of bladder cancer in humans, dogs and cats, although the incidence in cats is comparatively low. This retrospective study details the histopathological features of UC of the urinary bladder in 38 samples from 35 cats. Of the 38 samples, eight had a papillary architecture and in nine the tumour cells formed tubular or acinar structures. Tumour cell invasion of the bladder wall varied from confinement within the lamina propria or submucosa to transmural or extending to the serosa. The tumour stroma varied from sparse to abundant, with a scirrhous, myxomatous or mucinous appearance in eleven cases, three cases and one case, respectively. The degrees of tumour cell necrosis and inflammation were highly variable. We confirm that the histopathological features of bladder UC in cats have many similarities to the corresponding tumours in dogs and humans.



*Keywords:* cat; comparative pathology; histology; transitional cell carcinoma

Human urinary bladder cancer (UBC) is among the 10 most common cancer types in the world, representing 2.1% of all cancer deaths (Bray *et al*, 2018). More than 90% of UBC cases are urothelial carcinoma (UC), formerly known as transitional cell carcinoma (TCC). The incidence of UBC varies significantly between geographical regions due to differing exposure to risk factors (Richters *et al*, 2019). UBC comprises ~2% of all malignancies in dogs, with UC being the most common type (Meuten and Meuten, 2017). In contrast, UBC occurs much less frequently in domestic cats, with studies placing it at frequencies of 0.38–0.56% of all feline malignancies (Wimberly and Lewis, 1979; Shida *et al*, 2010). UC is the most common type of malignancy in the feline bladder (80/119 cases; 67%) (Engle and Brodey, 1969; Caywood *et al*, 1980; Schwarz *et al*, 1985; Walker *et al*, 1993; Wilson *et al*, 2007; Meuten and Meuten, 2017). Speculation on the lower incidence in cats relative to dogs and humans has considered the lower quantities of tryptophan metabolites excreted in feline urine (Brown and Price, 1956), the composition of some species-specific flea or tick treatments (Kvamme, 2012) and potential underdiagnosis, as UCs often occur in geriatric cats with concurrent diseases (Meuten and Meuten, 2017).

In contrast to dogs, very few studies have been published on urinary bladder UC in cats. Two retrospective studies that reviewed the clinical findings, treatments and outcomes in cohorts of cats with urinary bladder UC did not extend their analysis to the histopathological features (Wilson *et al*, 2007; Griffin *et al*, 2020). Four retrospective studies that focussed on the histopathology of feline UC or UBCs only included small numbers of cases (3-10 cats) and were published over 30–40years ago (Wimberly and Lewis, 1979; Schwarz *et al*, 1985; Brearley *et al*, 1986; Patnaik *et al*, 1986), with two more recent studies focussing on the pathology of

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0021-9975/$ - see front matter
https://doi.org/10.1016/j.jcpa.2020.11.001

UC in captive-bred fishing cats (*Prionailurus viverrinus*) (Sutherland-Smith *et al*, 2004; Landolfi and Terio, 2006).

The present retrospective study includes archived formalin-fixed, paraffin wax-embedded tissue samples from cats that were submitted between 2009 and 2020 to VPG Histology (formerly Bridge Pathology) in the UK. The histopathology database was searched to identify cats with urinary bladder samples that had a histopathological diagnosis of UC or TCC and 38 samples from 35 individuals (two cats had more than one sample submitted) were found. The signalment and a summary of the key histopathological findings in each of the 38 cases (samples) are provided in Table 1. The available follow-up information for 14 cats is provided in Supplementary Table 1.

The typical histological presentation of feline UC was that of an alteration of the normal urinary bladder architecture due to the presence of an unencapsulated, moderately to densely cellular neoplastic mass. Ulceration or erosion of the epithelium was reported in 11/38 cases (Table 1). The tumours formed either papillary finger-like exophytic growths into the lumen of the bladder (8/38 samples) (Fig. 1) or non-papillary, sessile growths (27/38 samples) (Table 1). In humans, urinary tract UC is divided into two main subgroups, invasive or non-invasive. These tumours can have a variety of growth patterns but, most commonly, are papillary or solid. The papillary pattern is usually low grade and is associated with multifocality and local recurrence but with a lower risk of progression. The papillary subtype has also been well reported (Meuten and Meuten, 2017) in dogs but is not officially recognized in cats, possibly due to the paucity of cases relative to the number in dogs. Nevertheless, other studies of feline urinary bladder UC have used the WHO classification and reported the cases as 'papillary, infiltrating carcinomas' (40–80% of cases) or 'non-papillary, infiltrating carcinomas' (20–30% of cases) (Wimberly and Lewis, 1979; Patnaik *et al*, 1986; Landolfi and Terio, 2006). In our cohort, we had eight cases with papillary formations and which could therefore be grouped under the papillary subtype.

All samples that were of sufficient size to be assessed (30/38 cases) were invasive and thus were classified as high grade (Meuten and Meuten, 2017). These cases had histological features similar to those of high-grade (grade 3) urinary bladder UC of humans according to the WHO 1973 and 2004/2016 classification systems (Compérat *et al*, 2019) and were consistent with previous reports of urinary bladder UC in cats (Wimberly and Lewis, 1979; Brearley *et al*, 1986). When highly invasive neoplasms extended widely throughout the surrounding submucosa and muscularis layers, some had neoplastic cell infiltration of lymphatics, blood vessels or nerve bundles (Table 1).

The individual neoplastic cells were typically polygonal with small to moderate amounts of eosinophilic to amphophilic cytoplasm and usually distinct, although sometimes not well-defined, cell borders. Three of the 38 samples (cases no. 5, 9 and 33) showed occasional neoplastic cells with a large clear intracytoplasmic vacuole that resulted in an eccentric nucleus, consistent with signet ring cell formation or Melamed–Wolinska bodies (Fig. 2). The mitotic rate was highly variable between cases, with reports of bizarre mitoses including tripolar mitoses (Table 1).

The neoplastic cells were arranged in a variety of patterns, including papillae, cords, islands and nests that infiltrated the underlying submucosa or muscularis propria. In some cases, the neoplastic cells formed occasional tubular or acinar structures (Fig. 3 and Table 1). A variant of UC seen in humans has divergent glandular differentiation, in which the neoplastic cells form, almost exclusively, acini or small- to medium-sized tubules (Cheng *et al*, 2019). This variant requires differentiation from primary adenocarcinoma of the bladder, an extension of a prostatic adenocarcinoma (Huang *et al*, 2004) or an adjacent bowel malignancy. In 9/38 of our samples, the neoplastic cells formed tubular, tubule-like or a combination of tubular and acinar structures. As these structures were not the predominant cell type, they may not justify classification as 'UC with glandular differentiation'. However, we believe that it is crucial to mention glandular structures in pathological reports of UC in cats, as metastases may show a similar pattern. Of note, a previous study of feline UC classified 2/5 cases with 'scattered islands of cells with glandular structure' as 'glandular variants of transitional cell carcinoma' (Wimberly and Lewis, 1979) and it might be worth introducing this subclassification to the diagnosis of feline UC. Focal or multifocal areas of necrotic tumour cells were present in 20/38 samples (Fig. 2 and Table 1). The presence of necrosis, most commonly mild, was reported in 24% of canine UC cases examined in a recent study (de Brot *et al*, 2019), which is similar to our cohort of feline cases in which most cases (10/20) were graded as mild. In contrast, large areas of necrosis were seen in 6/10 cases of UC in fishing cats (Landolfi and Terio, 2006).

The stroma associated with the neoplastic cells varied from sparse to abundant, with a range of morphologies, including mucinous, myxomatous or markedly scirrhous (desmoplastic) (Table 1). Desmoplasia is a stromal response to invasive carcinoma that has been reported in human UC (Cheng *et al*, 2019), and we observed this change in 11/38 samples in our

**Table 1**
**Patient signalment and histopathological features of urothelial carcinoma in cats**

| *Case no. (Animal ID)*[†] | *Breed* | *Sex* | *Age (years)* | *Histopathological features* | *Tumour invasion* | *Maximum no. mitoses per high-power field (×400)* | *Necrosis* | *Stroma* | *Inflammation* | *Margins* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 (1) | DSH | FN | 18 | P | NA | 6 | – | 1 | 1 | – |
| 2 (2) | DSH | F | 11 | – | 2 | 1 | – | 2 | 3 | – |
| 3 (3) | DLH | MN | 8 | – | 3 | 3 | 3 | 3, S | 4 | C |
| 4 (4) | DSH | FN | 14 | – | 1 | 3 | – | 1, S | 1 | UC |
| 5 (5) | DSH | MN | 17 | – | 1 | 12* | 1 | 1, S | 1 | C |
| 6 (6) | DSH | FN | 15 | P | NA | 2* | 1 | 1 | 1 | – |
| 7 (5) | DSH | MN | 17 | T | 1 | 2 | – | 1 | 3 | C |
| 8 (7) | DSH | FN | 10 | – | NA | 6 | 3 | 1 | 2 | – |
| 9 (8) | DSH | F | 12 | P | 2 | 6 | – | 3, S | 3 | PM |
| 10 (5) | DSH | MN | 19 | T | 1 | 5 | – | 2 | 3 | C |
| 11 (9) | U | M | 12 | U | 2 | 2 | – | 2, My | 1 | PM |
| 12 (10) | DSH | FN | 13 | U | 3 | 3 | 2 | 3, S | 1 | C |
| 13 (11) | DSH | FN | 14 | T, U | 3 | 2 | 1 | 2, Mu | 1 | UC |
| 14 (12) | DSH | MN | 19 | – | 2 | 4 | 3 | 3, My | 3 | UC |
| 15 (13) | DLH | FN | 16 | P, U | 2, B | 7* | 3 | 3, S | 3 | C |
| 16 (14) | DSH | MN | 12 | U | 1 | 1 | – | 2 | 1 | – |
| 17 (15) | DSH | FN | 17 | NA | NA | 1 | 1 | 1 | 1 | – |
| 18 (16) | DSH | F | 13 | – | NA | 6 | 1 | 2 | 2 | – |
| 19 (14) | DSH | MN | 12 | – | 1 | 3 | – | 2 | 2 | C |
| 20 (17) | DSH | M | 11 | T, U | 2, B | 2 | – | 3 | 2 | UC |
| 21 (18) | DSH | FN | 13 | P | 2 | 2 | 1 | 3S | 1 | UC |
| 22 (19) | DSH | MN | 20 | P, T, U | 2, N | 56 | – | 3 | 4 | UC |
| 23 (20) | DSH | U | 11 | U | 2, L | 1 | – | 3S | 1 | C |
| 24 (21) | DR | FN | 13 | – | 2 | 3 | – | 2 | 1 | C |
| 25 (22) | DSH | MN | 14 | T | 2 | 1 | 2 | 2 | 4 | C |
| 26 (23) | DSH | MN | 16 | – | 1 | 13 | 1 | 2 | 1 | C |
| 27 (24) | DSH | MN | 18 | – | 2 | 3* | – | 1 | 1 | C |
| 28 (25) | DSH | MN | 14 | T | 3, B | 2 | 1 | 3, My | 2 | C |
| 29 (26) | DSH | FN | 16 | – | 1 | 1 | 3 | 2 | 1 | – |
| 30 (27) | DSH | FN | 14 | U | 2 | 1 | – | 2, S | 1 | UC |
| 31 (28) | DSH | FN | 12 | – | 1 | 7 | 2 | 2 | 3 | UC |
| 32 (29) | BB | MN | 14 | U | 2 | 4 | 1 | 2, S | 2 | UC |
| 33 (30) | DSH | FN | 14 | P, T | 1 | 2* | 1 | 2 | 3 | UC |
| 34 (31) | DLH | FN | 4 | U | 2 | 2 | 1 | 3, S | 2 | UC |
| 35 (32) | DSH | MN | 13 | – | 1 | 8 | 2 | 1 | 2 | UC |
| 36 (33) | DSH | U | 15 | P | NA | 3 | – | 1 | 1 | – |
| 37 (34) | DSH | FN | 5 | – | NA | 3 | 1 | 1 | 1 | – |
| 38 (35) | DSH | FN | 13 | T | NA | 1 | – | 2 | 3 | – |

Tumour invasion categories: NA, sample too small for analysis, 1, lamina propria or submucosa; 2, muscularis; 3, transmural; B, vascular invasion; L, lymphatic invasion; N, nerve bundle invasion.
Necrosis categories: 1, mild focal; 2, moderate multifocal, 3, extensive multifocal; -, absent.
Stroma categories: 1, sparse; 2, moderate; 3, abundant; Mu, mucinous; My, myxomatous; S, scirrhous.
Inflammation categories: 1, none; 2, mild; 3, moderate; 4, severe.
Margins categories: C, clear, UC, unclear; PM, post-mortem case and margins not assessed; -, margins not present.
Breeds: BB, British Blue; DLH, Domestic Longhair; DR, Devon Rex; DSH, Domestic Shorthair.
Sex: F, female; FN, female neutered; M, male; MN, male neutered; U, unknown.
Histopathological features: P, papillary growths; T, tubules or acini; U, ulceration.
[†]38 tumour samples from 35 cats.
*Bizarre mitoses.

study. Desmoplasia has also been reported in other studies of UC in cats (Wimberly and Lewis, 1979; Patnaik *et al*, 1986). Some human cases can have a pseudosarcomatous morphology due to the degree of desmoplastic response. In three of our samples, the stroma was myxomatous. UC with myxoid features has been rarely reported in humans (Tavora and Epstein, 2009). A fibromyxoid stroma was common in canine UC and a strong indicator of muscle invasion in a recent study (de Brot *et al*, 2019). Three of our cases with myxomatous stroma had tumour cell invasion of the muscle (Table 1). The cellular inflammatory response to the neoplasm, when present, was variable (Table 1). In agreement with a previous

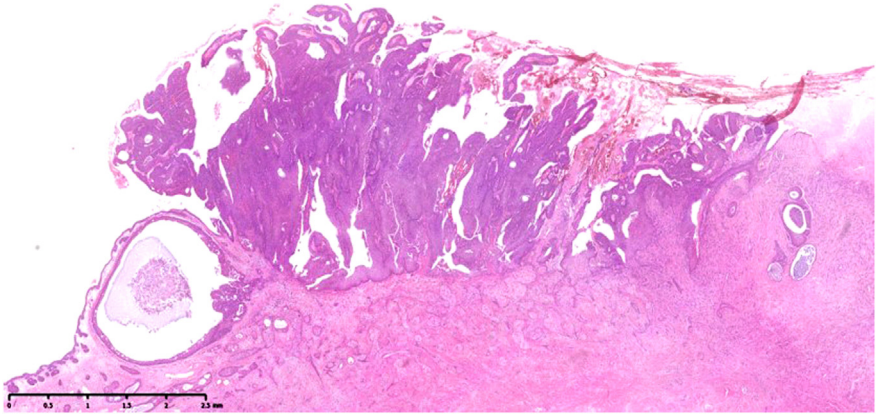

Fig. 1. Cat, urinary bladder, urothelial carcinoma. Papillary exophytic growths into lumen of bladder of a 13-year-old neutered female Domestic Shorthair cat (case no. 21). HE. Bar, 2.5 mm.

report (Brearley *et al*, 1986), the cellular infiltrate consisted predominantly of lymphocytes, with fewer plasma cells and neutrophils (Fig. 3).

Where clear tumour margins were assessable in the sample (Table 1), changes in the urothelium adjacent to the neoplasm ranged from hyperplasia to dysplasia, as has been reported by others (Brearley *et al*, 1986; Patnaik *et al*, 1986). Dysplastic changes were present in the epithelium of 4/38 samples in addition to the UC (cases no. 16, 21, 24 and 33). Multiple coexisting tumours often arise in humans before symptoms become apparent, with individual tumours not necessarily sharing the same histological appearance (Cheng *et al*, 2019). In our cohort, the bladder of 6/35 cats was sampled repeatedly by fine-needle aspirate or biopsy, although not all samples were submitted to VPG Histology for assessment. The multifocal and recurrent nature of bladder cancer in humans has been explained by the 'field cancerization' effect, whereby cells in the normal bladder epithelium contain mutations caused by environmental exposures, including chemical carcinogens, infectious agents and chronic inflammation. For example, concurrent infection of the urinary tract has been reported in >70% of cats with UC (Meuten and Meuten, 2017; Griffin *et al*, 2020). In our cohort, 4/14 cases for which information was available had cystitis, bladder crystals or stones at the time of investigation. Interestingly, there are conflicting reports in humans of a potential causal link between urinary tract infections and the development of bladder cancer (Jiang *et al*, 2009; Vermeulen *et al*, 2015). Nevertheless, the initial molecular changes may progress to histologically visible lesions such as foci of hyperplasia or dysplasia and eventual carcinoma *in situ* or cancer (Czerniak *et al*, 2016).

The highly recurrent nature of UC in cats is highlighted by the two cases in which the tumour had

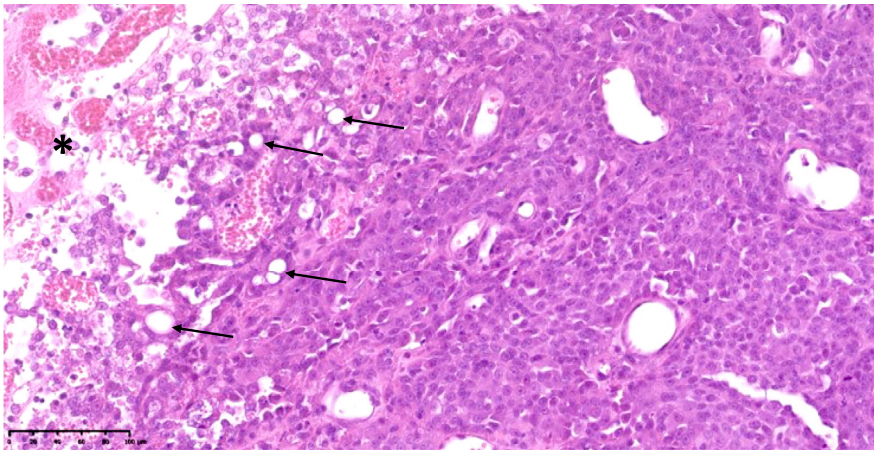

Fig. 2. Cat, urinary bladder, urothelial carcinoma. Necrosis (asterisk) and neoplastic cells with signet ring appearance (arrows) in bladder of a 14-year-old neutered female Domestic Shorthair cat (case no. 33). HE. Bar, 100 µm.

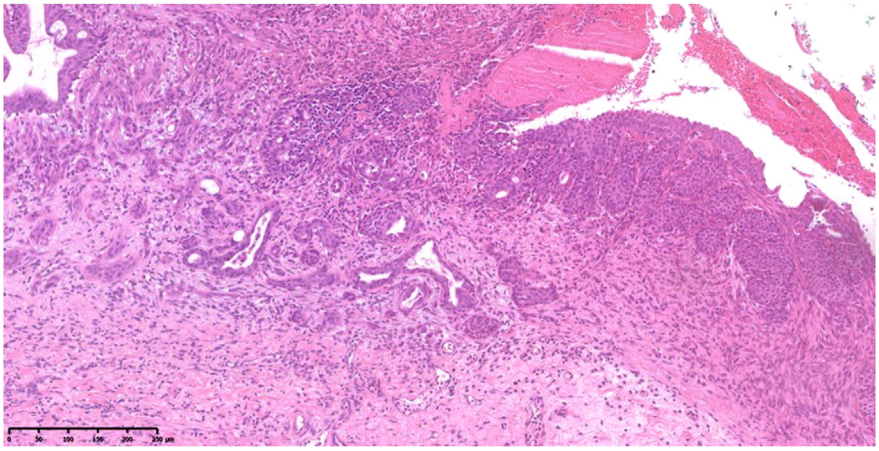

Fig. 3. Cat, urinary bladder, urothelial carcinoma. Neoplastic cells form tubular or acinar structures in bladder of a 14-year-old neutered female Domestic Shorthair cat (case no. 33). HE. Bar, 250 μm.

been surgically removed but had recurred in less than 1 year (animal IDs no. 5 and 14). Similarly, in another study all three cases of feline urinary bladder UC samples had arisen from recurrent lesions (Schwarz *et al*, 1985). Others found evidence of metastasis, typically to the regional lymph nodes or lungs, at the time of diagnosis of the urinary bladder UC in 12–50% of cases (Schwarz *et al*, 1985; Sutherland-Smith *et al*, 2004; Griffin *et al*, 2020). The prognosis in canine UC is strongly associated with the tumour–node–metastasis (TNM) stage at the time of diagnosis, with advanced TNM stage associated with decreased survival (Mutsaers *et al*, 2003). However, there is no corresponding prognostic information for cats as TNM staging is not usually considered in the histopathological evaluation of feline UC.

It is important to note that although our cohort is larger than any previous reports of the histopathological changes in feline urinary bladder UC, our study has limitations. Firstly, as most of the samples were urinary bladder biopsies, we cannot comment on other aspects of the disease such as the presence or absence of multiple independent lesions or metastasis. Secondly, with cases from a single institution, there is always a risk of inadvertent sample bias (eg, sampling technique) and interpretation. Thirdly, due to incomplete availability of clinical results (only limited clinical data were available for 14/35 animals) we are unable to draw any firm conclusions as to whether a particular histopathological observation is associated with the presence of metastasis, survival or outcome. Nevertheless, it is noteworthy that three cats (cases no. 28, 30 and 33; animal IDs 25, 27 and 30, respectively) (Supplementary Table 1) with invasive or highly proliferative tumours (transmural with vascular invasion in case no. 28) that received treatment with meloxicam, vinblastine or mitoxantrone after surgical resection, did not have the worst prognosis. This finding suggests that such histological features might not inevitably be associated with a poor prognosis and that the choice of treatment may be a more important determinant of prognosis. More cases require to be investigated to confirm this hypothesis. Thus, a large-scale, multicentre prospective study on feline urinary bladder UC, with histopathology and full clinical history, is needed to fully understand this disease and to identify risk factors, prognostic factors and the most effective treatments.

## Acknowledgments

We thank the submitting vets who provided clinical data and follow-up for these cases, Deepthi Chandy (VPG Histology) for valuable laboratory assistance and Mark Bennett (VPG Histology) for critical reading of the manuscript.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

## Conflict of Interest Statement

The authors declare no potential conflicts of interest with respect to the research, authorship or publication of this article.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcpa.2020.11.001.

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[ *Received, May 12th, 2020*
*Accepted, November 2nd, 2020* ]