

Atypical Transitional Epithelial Cells

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Evaluation of urine sediment is useful when confirming a normal urine sample or diagnosing inflammation, infection, crystalluria, or neoplasia. Some sediment findings have multiple potential causes and must be considered in context of sample collection method, presenting complaint, physical examination findings, imaging, and results of other laboratory and diagnostic results.

Transitional epithelial cells line the urinary tract from the renal pelvis to the proximal urethra and are typically seen in low numbers in urine sediments. In many cases, large numbers or aggregates of transitional epithelial cells in wet-mount urine sediment preparations should prompt additional investigation (**Figure 1**).

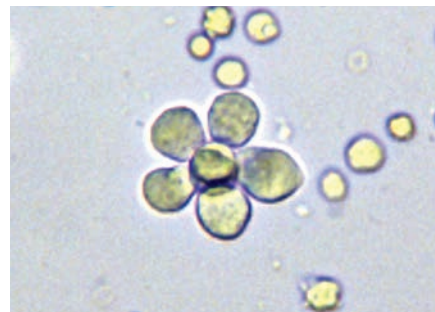
Atypical epithelial cells may have larger-than-normal nuclei, coarsely clumped chromatin, large and prominent nucleoli, variable size and shape of nuclei and cells, multiple nuclei per cell, increased mitosis, and other features. Cellular atypia is not only seen with neoplasia but can also be seen with hyperplasia associated with inflammation, infection, or in response to mechanical trauma.

When atypical epithelial cells are observed in a urine sediment wet-mount preparation, it is helpful in many cases to prepare a dry-mount urine cytologic specimen for further evaluation, as thorough assessment of cell morphology is often not possible using low magnification and a wet-mount preparation. A dry-mount urine sediment cytologic specimen can also be easily shipped to a commercial laboratory for evaluation by a pathologist as needed.

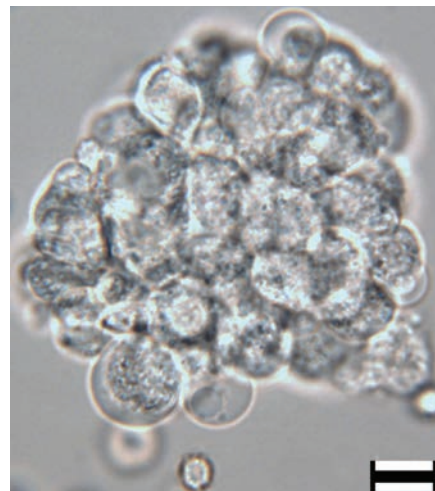
In the following cases, atypical transitional epithelial cells or aggregates of epithelial cells were identified in the wet-mount urine sediment preparation, and additional cytologic preparations were pursued. In two of the cases, urine sediment dry-mount preparations were made. For the other two cases, additional techniques were used to collect a representative sample.

Examination of exfoliative cytology obtained by urinary catheterization or fine-needle aspirate are relatively noninvasive and inexpensive methods for obtaining specimens from the urethra or urinary bladder mucosa.¹⁻³ There is a low risk for seeding neoplastic cells into the peritoneum or body wall with fine-needle aspiration (FNA), but some recommend the use of urinary catheterization to avoid this complication,⁴ especially in patients with an operable bladder mass.

FNA = fine-needle aspiration



Unstained urine sediment wet mount, original magnification 200×. An unusual flower-shaped aggregate of transitional epithelial cells is shown.



1 Unstained urine wet mount, 500× magnification, bar = 10 μm. A large, dense aggregate of epithelial cells is pictured. Observation of a large number of epithelial cells, especially in aggregates or sheets in urine, is abnormal. To better evaluate cell morphology and identify features of atypia, a dry mount cytologic preparation is very helpful.

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Case 1

A 5-year-old, spayed hound crossbreed was presented for a 1-year history of pollakiuria and intermittent inappropriate urination in the house. Urinalysis was conducted (Table, page 88); radiographs disclosed urolithiasis.

Ask Yourself



- What characteristics of atypia are present?
- Could the atypical features be explained by additional findings in the urine sediment dry-mount?
- What could be the underlying cause of the atypia?

Diagnosis

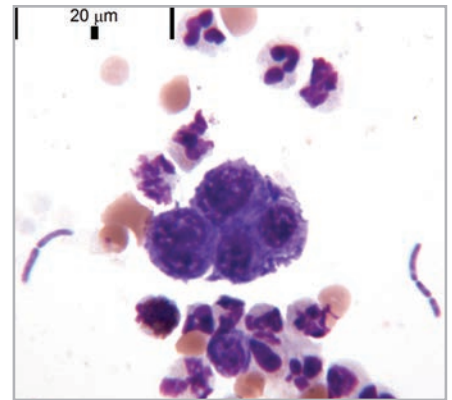
Urolithiasis with bacterial cystitis with transitional cell hyperplasia

Interpretation

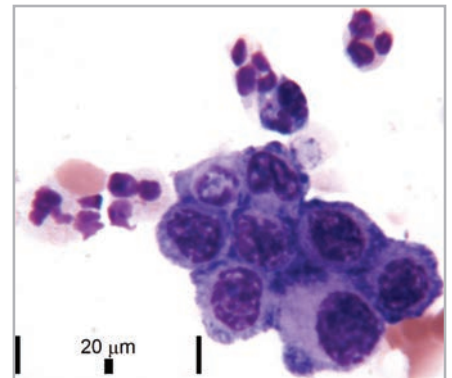
This patient's transitional epithelial cell atypia was associated with cystoliths and bacterial infection. The patient had hyperplasia of the bladder epithelium caused by underlying mechanical trauma from cystoliths and irritation caused by inflammation and infection associated with the cystoliths.

Several oval, radiopaque uroliths were identified on radiography; no urinary tract masses were visible on ultrasonography.

This case illustrates the importance of exercising caution and not over-interpreting cellular atypia in the presence of infection and inflammation, which induces reactive epithelial hyperplasia with cytologic changes that may mimic malignancy.



Wright-Giemsa–stained urine sediment, dry-mount, 1000× magnification. An aggregate of epithelial cells is present in the center. Multiple neutrophils are present above and below the epithelial cells. Extracellular bacilli are at the far left and right.

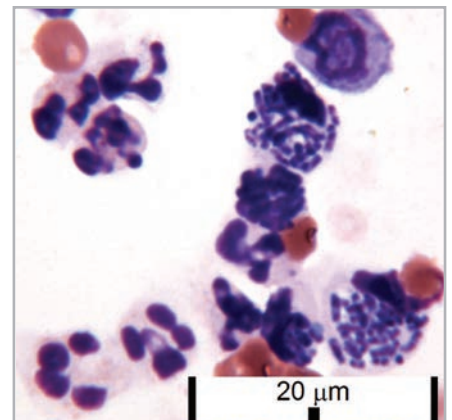


Wright-Giemsa–stained urine sediment, dry-mount, 1000× magnification. A small aggregate of epithelial cells is present with 4 neutrophils.

Did You Answer?



- Large nuclei with high nucleus:cytoplasm ratio, variable nuclear size, coarsely clumped chromatin, and cells with 2 nuclei.
- Yes; the inflammation and infection are potential causes of hyperplasia and associated cytologic atypia.
- Many neutrophils are seen, and some contain a large number of bacilli. The neutrophilic inflammation and bacterial infection suggest that the atypical epithelial cells are present as a result of reactive hyperplasia.



Wright-Giemsa–stained urine sediment, dry-mount, 1000× magnification. Several neutrophils are present; 2 of the neutrophils contain many intracellular bacilli. One epithelial cell is present at the top right.

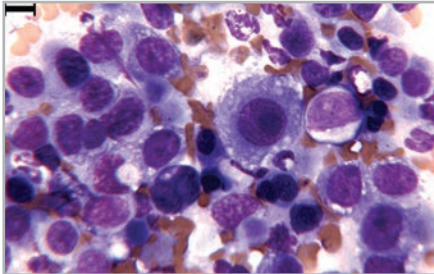
FNA = fine-needle aspiration

Case 2

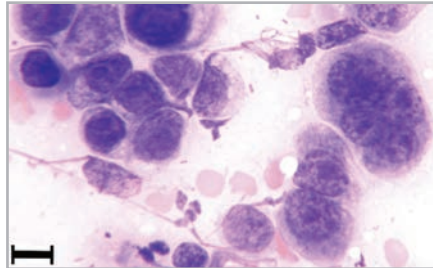
A 12-year-old, spayed greyhound was presented for anorexia, vomiting, and stranguria. The patient was azotemic, and thickening of the bladder trigone area was identified by ultrasound. Urinalysis was pursued (Table, page 88).

The transitional cells in the urine sediment dry-mount cytology were moderately to highly atypical; however, pyuria and bacteriuria were also present. This confounded diagnosis of neoplasia by urinalysis as infection can induce hyperplasia with cytologic changes that mimic malignancy.

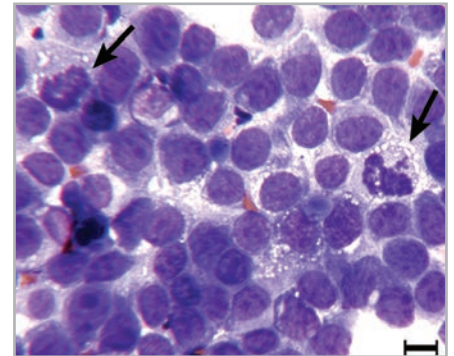
Because urinalysis results were equivocal and a discrete bladder mass was not visualized, FNA of the bladder trigonal thickening was performed to further investigate potential transitional cell carcinoma versus the less likely consideration of hyperplasia secondary to the infection.



Wright-Giemsa–stained FNA of bladder thickening, 500× magnification, bar = 10 μm. Moderately to markedly atypical epithelial cells with mildly increased neutrophils. The neutrophil at the top center contains phagocytized bacilli.



Wright-Giemsa–stained FNA of bladder thickening, 500× magnification, bar = 10 μm. Markedly atypical epithelial cells and neutrophils.



Wright-Giemsa–stained FNA, 500× magnification, bar = 10 μm. Markedly atypical epithelial cells with mitotic cells at the top left and center right (arrows).

Diagnosis

Transitional cell carcinoma with secondary neutrophilic inflammation and bacterial infection

Interpretation

With the improved cytologic detail provided by the FNA, the atypical cellular features were more reliably assessed. Although infection was present, the cytodiagnosis of transitional cell carcinoma was made based on the consistently high degree of epithelial cell atypia in the aspiration sample.

The decision to perform FNA in this case was based on multiple factors, including the client's wishes for palliative care, patient's general health status, disease extent and location (bladder trigone), and overall prognosis. Because prognosis was unlikely to be affected by seeding along the needle tract, FNA was performed to provide additional diagnostic information in this case.

Ask Yourself

- What characteristics of atypia are present?

Did You Answer?

- Very large nuclei with high nucleus-to-cytoplasm ratio; cells with multiple nuclei; variation in nuclear and cell sizes and shapes; crowded nuclei; coarsely clumped chromatin; mitotic figures that are sometimes abnormal; and large, prominent nucleoli of variable number, size, and shape.

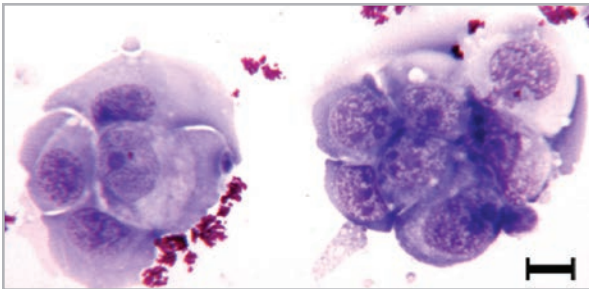
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Case 3

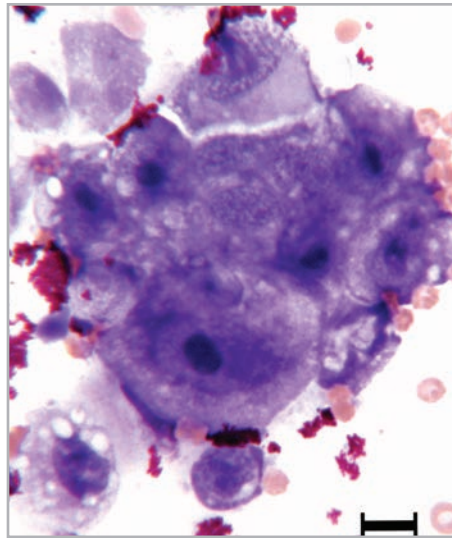
A 10-year-old, castrated Cairn terrier was presented for gross hematuria. Urinalysis confirmed hematuria and disclosed increased atypical epithelial cells (Table, page 88). Imaging disclosed an apical bladder mass, which was further evaluated by exfoliative (traumatic) catheterization cytology.

Ask Yourself

- What traits of atypia are present?
- Are there additional findings in the urinalysis that could provide a specific cause for the atypia?



Wright-Giemsa–stained urine sediment, dry-mount, 500× magnification, bar = 10 μm. Aggregates of markedly atypical epithelial cells with multiple features of malignancy are shown. The granular magenta material is lubricant used with catheterization. This artifact may obscure cytologic detail in some cases.



Diagnosis

Transitional cell carcinoma

Interpretation

Results of urinalysis showed no evidence of inflammation or infection that would induce reactive hyperplasia of the epithelial cells or explain the presence of atypical epithelial cells in the urine sediment. Coupled with the clinical presentation, this was consistent with transitional cell carcinoma.

Diagnostic imaging may aid in the diagnosis of transitional cell carcinoma in patients with atypical epithelial cells in the urine sediment and help exclude urolithiasis or document a urinary tract mass. Abdominal imaging of this patient disclosed an apical bladder mass. Given the mass location, this patient was considered a candidate for aggressive medical therapy and surgical removal. Preoperative evaluation included cytology of the mass.

Exfoliative catheterization was chosen in lieu of FNA to avoid seeding cancer cells along the needle tract (peritoneum, body wall, subcutaneous tissue). For this patient with an apical bladder mass, the cytologic finding of marked epithelial cell atypia without infection, inflammation, or cystic calculi was diagnostic for transitional cell carcinoma. The diagnosis was confirmed histopathologically.

Did You Answer?

- Very large nuclei with high nucleus-to-cytoplasm ratio; cells with multiple nuclei; variation in nuclear and cell sizes and shapes; crowded nuclei; coarsely clumped chromatin; and large, prominent nucleoli of variable number, size, and shape.
- There was no evidence of inflammation or infection in this case, which might indicate a hyperplastic process.

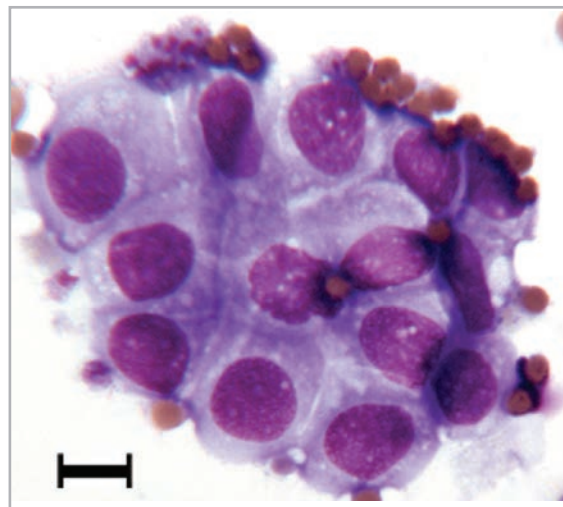
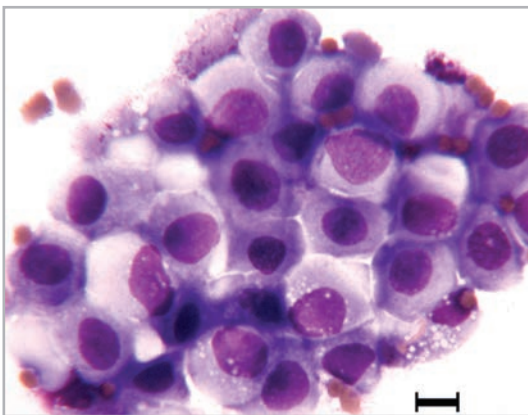
Case 4

A 4-year-old, castrated domestic shorthaired cat was presented for anorexia, anuria, and apparent abdominal pain. On bladder palpation, the patient voided urine and resisted additional palpation. Following appropriate analgesic administration, cystocentesis was performed and urinalysis results were available (Table, next page).

Ask Yourself



- What traits of atypia are present?
- Given the many struvite crystals and hematuria, what additional diagnostics may be warranted?



Wright-Giemsa–stained urine sediment dry-mount, 500× magnification, bar = 10 μm. Mildly atypical epithelial cells in sheets are pictured associated with numerous erythrocytes.

Diagnosis

Feline lower urinary tract disease (FLUTD) with transitional epithelial cell hyperplasia

Interpretation

The mild epithelial cell atypia represents reactive hyperplasia associated with idiopathic cystitis and FLUTD. Culture and imaging did not show underlying infection or anatomic abnormality, although abundant hyperechoic material consistent with marked crystaluria was present.

It is unusual to observe large sheets of epithelial cells in urine sediment. Dry-mount cytology permits thorough evaluation of cytomorphology and optimally preserves cells for evaluation by a pathologist at a reference laboratory.

Did You Answer?



- There is mild atypia, indicated by increased nuclear size with mild variation of nuclear sizes and shapes.
- Abdominal imaging and urine culture are indicated.

Table > Urinalysis Physical and Chemical Results Values with asterisk (*) are outside reference interval or value

Parameter	Case 1	Case 2	Case 3	Case 4	Reference Interval or Value
Collection method	Cystocentesis	Free catch	Free catch	Cystocentesis	
Color	Brown*	Light yellow	Light yellow	Red-orange*	Yellow to amber
Clarity	Cloudy*	Slightly hazy	Clear	Hazy*	Clear or slight haze
USG	1.025	1.016	1.018	1.034	Usual: 1.020–1.050 (range, 1.001–1.070)
pH	8.5*	6.0	6.0	7.0	5.5–7.5
Dipstick protein	4+*	2+*	2+*	2+*	Negative to trace, depending on USG
Glucose	Neg	Neg	Neg	Neg	Negative
Ketones	Neg	Neg	Neg	Neg	Negative
Bilirubin	Neg	Neg	Neg	Neg	Negative to 1+, depending on species and USG
Hemoprotein	4+*	4+*	1+*	3+*	Negative
Casts/LPF	None	Rare granular	Rare granular	None	0–1 granular or hyaline/LPF
Epithelial cells/LPF	5–10*	Many*	5–10*	Occasional sheets*	0–5/LPF
WBC/HPF	TNTC*	20–25*	0–2	3–5*	0–3
RBC/HPF	TNTC*	20–25*	5–10*	50–100*	0–5
Bacteria/HPF	Many bacilli*	Occasional bacilli*	None	None	Depends on collection method
Crystals	Occasionally amorphous	None	None	Many struvite*	Depends on crystal type

HPF = high-power field (40× magnification), LPF = low-power field (<10× magnification is LPF), TNTC = too numerous to count, WBC = white blood cell, RBC = red blood cell, USG = urine-specific gravity

Conclusion

Dry-mount cytology of the urine sediment is useful in-house to permit more accurate visualization of atypical cells. Urine sediment dry-mount cytology is also particularly helpful when a pathologist's second opinion is desired about atypical cells identified during urinalysis.

Cytology prepared in this way is indefinitely stable, so the opportunity for cytodiagnosis based on a urine sample is not lost on account of delay associated with transport to the outside diagnostic laboratory.

A common difficulty encountered when interpreting transitional epithelial cell atypia is the mixed-cell population, which refers to observation of inflammation with concurrent cytologic atypia suggestive of malignancy.

Secondary infection is common with transitional cell carcinoma and may be a confounding factor when attempting cytodiagnosis. Transitional cell carcinoma with secondary infection may be cytologically similar to cystitis-induced hyperplasia. In some cases, repeated cytology after resolution of the infection and inflammation, sampling of the mass itself by exfoliative catheterization or FNA, or histopathology may be required for definitive diagnosis.

In this series, all of the patients presented with lower urinary tract signs and atypical transitional cells as part of their urine sediment findings. However, underlying causes, treatment, and prognosis varied. The series underscores the need to evaluate atypical transitional epithelial cells in light of the patient's signalment,

presenting complaint, physical examination findings, other clinical pathology data, and imaging. ■ **cb**

References

1. **Examination of the urine sediment.** Wamsley HL. In Valenciano AC, Cowell RL (eds): *Cowell and Tyler's Diagnostic Cytology and Hematology of the Dog and Cat*, 4th ed—St. Louis: Mosby Elsevier, 2014, pp 402-430.
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4. **Needle-tract implantation following US-guided fine-needle aspiration biopsy of transitional cell carcinoma of the bladder, urethra, and prostate.** Nyland TG, Wallack ST, Wisner ER. *Vet Radiol Ultrasound* 43:50-53, 2002.