Journal of Cellular Biochemistry, Supplement 16I:73–75 (1992)

# Cytology

**Myron R. Melamed, MD**

New York Medical College, Valhalla, New York 10595

**Abstract** Exfoliative cytology is a relatively sensitive, highly specific technique for the detection and diagnosis of bladder cancer, and for monitoring conservative treatment. Cytologic diagnosis is based on cellular changes in DNA content, chromatin structure, and metabolic activities which are characteristic of cancer cells and can be recognized in desquamated isolated cells or cell clusters. The cytologic techniques are most effective in identifying low stage flat or papillary carcinoma, but not cytologically benign papillomas or ulcerating invasive cancers that do not easily shed cancer cells. With the growing number of pathologists who, in recent years, have become skilled cytopathologists, urinary tract cytology has developed into an essential diagnostic tool for the urologist. 

**Key words:** bladder cancer, cytology, cytopathology, urinary tract, urothelium

Exfoliative cytology now has a well-established, major role in detecting bladder cancer and in monitoring treatment. It is most sensitive and useful in patients with known or suspected superficial tumors, and has proved effective in monitoring local ablative treatment by transurethral resection or intravesical Bacillus Calmette-Guerin (BCG).

In its early stages, carcinoma of the urinary bladder is defined histologically by the presence of cancer cells within an otherwise unremarkable urothelium (flat carcinoma *in situ*), or in papillary epithelium (focal or diffuse non-invasive papillary carcinoma). The cancer cells that make up these early neoplastic lesions can also be recognized out of context, *e.g.*, within the exfoliated epithelium of the urinary sediment. Like the cells of other carcinomas, the light microscopic appearance of bladder cancer cells is due primarily to three types of nuclear change: (1) increased DNA content resulting in nuclear hyperchromasia and enlargement; (2) structural chromatin abnormalities which account for textural nuclear changes and irregular nuclear membranes; and (3) increased proliferation and metabolic activity associated with more prominent nucleoli and changes in cytoplasmic staining. Of course, there may be other cellular changes, including changes in cytoplasmic staining or configuration due to altered differentiation, changes in cell surface antigens, and loss of intercellular desmosomes and tight junctions.

Cells of benign papilloma cannot be differentiated from normal urothelium; however, the sensitivity of cytology for carcinoma increases with increasing grade. Overall, cytological sensitivity is variously reported at 50–60% for a single specimen, increasing to 80–90% for multiple examinations [1]. Specificity approaches 100%. Thus, for purposes of cancer detection in a patient suspected of or at high risk for bladder cancer, a series of 3 or more urine cytology specimens can be a very useful diagnostic tool. Since current evidence suggests that carcinoma *in situ* requires many months or even years to progress to invasion, sequential cytologic examinations at regular 3–6 month intervals are a potentially valuable means of detecting incipient carcinoma in the urinary bladder, as they are, for example, in cervical cancer.

Normal urinary sediment is sparsely cellular. Exfoliated urothelial cells are few and they come almost entirely from the bladder where the urothelium is alternatively stretched and relaxed as it distends and contracts. The superficial cells that shed spontaneously are relatively large, 20–40 $\mu$m in diameter, usually with one or two smoothly contoured round or oval nuclei, and abundant, lightly staining amphophilic

cytoplasm. Deeper cells are smaller, with less cytoplasm but with similar-appearing nuclei. They are found in catheterized or cystoscopic irrigation specimens, and are dislodged mechanically. They may be found singly or in small clusters.

Inflammation or irritation increases epithelial cell exfoliation and substantially increases overall cellularity, including leukocytes, histocytes, and erythrocytes in varying numbers. The appearance of the exfoliated cells is also changed. Most now come from the deeper layers of the epithelium and exhibit "reactive" changes, that is, changes in cytologic morphology and staining that reflect the increased metabolic and proliferative activity of an injured and regenerating epithelium. The resting nuclei of exfoliated superficial cells of the normal bladder have very delicate chromatin structure and inconspicuous nucleoli. The nuclei of reactive urothelial cells are slightly larger, with more coarsely textured chromatin, increased nuclear staining intensity, and prominent chromocenters or visible nucleoli. The cytoplasm also stains more intensely, due to increased RNA and protein. Mitoses are rare. Reactive epithelial cells are quite commonly shed in small groups as well as singly.

Cells shed from most carcinomas of the urinary tract resemble the exfoliated cells of poorly differentiated epidermoid carcinoma. They are smaller than the normal superficial urothelial cells, more closely approximating the size of cells in the deeper epithelial layers. As summarized above, they have increased nuclear DNA content (aneuploidy) and abnormal chromatin structure, evidenced by nuclear hyperchromasia, increased nuclear/cytoplasmic ratio, coarsely textured chromatin staining, and irregular, even angular, nuclear configuration. The cells shed from carcinoma *in situ* are typically single and relatively uniform. The epithelium of carcinoma *in situ* is intact, and while there are occasional red blood cells present, there is no significant inflammation. With invasion there is ulceration, inflammation, and bleeding so that malignant cells are found against a background of many inflammatory and degenerating cells, as well as many red blood cells. There is also variability in size, shape, and staining characteristics of the exfoliated malignant cells, which frequently form clusters with a characteristic structure.

The sensitivity of cytology, particularly in cases of *in situ* or early invasive carcinoma, is due to the disproportionately greater shedding of malignant cells as compared to benign epithelial cells. This is due, in part, to the increased proliferation of tumor cells but is also due to the fact that intercellular junctions are fewer than normal and are poorly formed. Hence the cells of a carcinoma are loosely coherent and readily dislodged. In some specimens from patients with limited areas of carcinoma, there may be a surprising number of malignant cells present. If carcinoma or carcinoma *in situ* is suspected, for example, during follow-up of patients treated by conservative surgery or intravesical BCG but cannot be documented by voided urine cytology, it is sometimes useful to obtain a bladder irrigation specimen. The turbulent irrigating fluid will dislodge epithelial cells from both normal and malignant areas of bladder urothelium that do not shed well spontaneously. It must be remembered, however, that advanced invasive carcinoma involving a bladder wall that is ulcerated and surfaced by inflammatory tissue cannot be expected to shed malignant cells either spontaneously or with vigorous irrigation.

Squamous and adenocarcinoma of the bladder are uncommon in the United States, accounting for perhaps 10% of cases. Squamous carcinoma is very common, however, in areas of Egypt and sub-Saharan Africa where bilharziasis is endemic. Squamous cancers are recognized in cytologic specimens by the presence of at least a few malignant cells showing densely eosinophilic cytoplasm and markedly hyperchromatic condensed nuclei, sometimes with squamous "pearls" present. There is usually a background of leukoplakia, *e.g.*, anucleated, squamous cells. Adenocarcinoma is much more difficult to recognize. While the cells that are shed are clearly malignant, they seldom show the prominent nucleolus of adenocarcinoma of other origins, nor do they shed in organoid cell groups.

Carcinomas of the urothelium of the upper urinary tract are quite similar to those of the bladder; cells shed by these carcinomas are recognized by the same cytologic features described above. However, malignant cells are few in voided urine specimens, and the sensitivity of cytologic diagnosis is much less than that for the bladder. Carcinoma of the upper urinary

tract should be suspected when malignant cells are found in voided urine but not in bladder irrigation specimens. The diagnosis can be confirmed by irrigation or brushing of the ureter and renal pelvis to obtain cells for cytologic examination. The same approach may be used to evaluate urethral specimens for possible carcinoma involvement.

In summary, exfoliative cytology is a clinically useful detection and diagnostic technique, particularly in cases of suspected flat or papillary carcinoma that are *in situ* or superficially invasive. Diagnostic cytologic criteria are well established and there is a growing number of pathologists skilled in the use of this technique. The applications of exfoliative cytology in following patients with bladder tumors which have been treated conservatively are well established, as are their limitations in identifying low grade tumors (papillomas) that shed benign cells, or ulcerating invasive carcinomas that are not shedding cancer cells.

## REFERENCE

1. Koss LG, Deitch D, Ramanathan R, Sherman AB: Diagnostic value of cytology of voided urine. Acta Cytol 29:810–816, 1985.