Cytologic Detection of Urothelial Lesions
ESSENTIALS IN CYTOPATHOLOGY SERIES

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Cytologic Detection of Urothelial Lesions

With 131 Illustrations in Full Color
To our families and friends for their love and support, and to the legacy of the late George L. Wied, M.D., FIAC.
Dr. Rosenthal and Dr. Raab correctly place urinary cytology in the backwater of the field, noting the difficulties many of us encounter when assessing urinary specimens or washes of the urinary tract. For a variety of reasons, these specimens are saved for the end of the day, cause the most trouble and frustration, and are the least successful from the standpoint of the pathologist, the urologist, or the patient.

This book represents, in keeping with the philosophy behind the series, Essentials in Cytopathology, a systematic description of microscopic findings in urinary specimens, whether normal, reactive, or neoplastic, accompanied by an extensive collection of photomicrographs (in color) illustrative of the full range of lesions. Drawing upon their personal collections and the diagnostic resources of several major cytologic laboratories, they have assembled examples of the common diagnostic entities in the field plus an assortment of confounding circumstances, which contribute to the difficulties presented by urinary specimens. Handy tables accompany the photographs, offering help where needed. This is particularly relevant because the subtlety of urinary cytology defies the dependable diagnostic categorization obtained with samples from other sites.

Reading this book set me to thinking about the evolution of texts in pathology from exhaustive narratives about visual concepts accompanied by relatively few black and white photographs or drawings in black and white or rarely with added color. Many of us can recall when colored photomicrographs were not available and when they became available but were not affordable. Now, it is unusual...
to find black and white photographs in medical texts, electron micrographs aside. Young physicians, having extensive experience with digital cameras and computers with Photoshop, will feel comfortable with this illustrated book whether beginning their studies in cytology or reviewing urinary cytology in preparation for their board examinations. Even experienced cytotechnologists and cytopathologists may find the illustrations and guidelines useful in the murky waters of urinary cytology, thanks to Dr. Rosenthal and Dr. Raab.

Jerry Waisman
February 20, 2005
Series Preface

The subspecialty of cytopathology is 60 years old and has become established as a solid and reliable discipline in medicine. As expected, cytopathology literature has expanded in a remarkably short period of time, from a few textbooks prior to the 1980s to a current library of texts and journals devoted exclusively to cytomorphology that is substantial. *Essentials in Cytopathology* does not presume to replace any of the distinguished textbooks in Cytopathology. Instead, the series will publish generously illustrated and user-friendly guides for both pathologists and clinicians.

Building on the amazing success of *The Bethesda System for Reporting Cervical Cytology*, now in its second edition, the series will utilize a similar format including minimal text, tabular criteria and superb illustrations based on real-life specimens. *Essentials in Cytopathology* will, at times, deviate from the classic organization of pathology texts. The logic of decision trees, elimination of unlikely choices and narrowing of differential diagnosis via a pragmatic approach based on morphologic criteria will be some of the strategies used to illustrate principles and practice in Cytopathology.

Most of the authors for *Essentials in Cytopathology* are faculty members in The Johns Hopkins University School of Medicine, Department of Pathology, Division of Cytopathology. They bring to each volume the legacy of John K. Frost and the collective experience of a preeminent cytopathology service. The archives at Hopkins are meticulously catalogued and form the framework for text and illustrations. Authors from other institutions have been
selected on the basis of their national reputations, experience and enthusiasm for cytopathology. They bring to the series complementary viewpoints and enlarge the scope of materials contained in the photographs.

The editor and authors are indebted to our students, past and future, who challenge and motivate us to become the best that we possibly can be. We share that experience with you through these pages, and hope that you will learn from them as we have from those who have come before us. We would be remiss if we did not pay tribute to our professional colleagues, the cytotechnologists and preparatory technicians who lovingly care for the specimens that our clinical colleagues send to us.

And finally, we cannot emphasize enough throughout these volumes the importance of collaboration with the patient care team. Every specimen comes to us as a question begging an answer. Without input from the clinicians, complete patient history, results of imaging studies and other ancillary tests, we cannot perform optimally. It is our responsibility to educate our clinicians about their role in our interpretation, and for us to integrate as much information as we can gather into our final diagnosis, even if the answer at first seems obvious.

We hope you will find this series useful and welcome your feedback as you place these handbooks by your microscopes, and into your bookbags.

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Note: All figures are stained by the Papanicolaou method unless otherwise stated. H & E is hematoxylin and eosin stain.
Cytologic Detection of Urothelial Lesions

Introduction

This second volume in the Springer-Verlag series, Essentials in Cytopathology, addresses a very difficult and often frustrating area of cytodiagnosis. Unlike gynecological cytology, urinary tract cytologic testing is not intended for the general population. Symptomatic patients, usually hematuria, or those who are at risk for bladder cancer are suitable candidates for morphologic examination of their urine.

The intent of the authors is to present a simple approach to dealing with cellular samples from the urinary tract. Rather than attempting to diagnose the lowest grade lesions as definitive entities, we have placed them in an indeterminate category, along with reactive/atypical changes to infection and therapy. Thus, the clinician is notified that the sample is not normal, but is not forced to “find the lesion”. On the other hand, we emphasize the importance of identifying the high grade lesions, as these are life threatening to the patient, and demand careful and directed management to control or eradicate the tumor(s). The need for frequent surveillance of the patient with high grade urothelial carcinoma creates a long term partnership between the cytopathologist and the urologic oncologist. We emphasize the importance of direct and clear communication between the partners since the patient becomes a lifetime candidate for recurrent or new urothelial lesions.
Background

In the U.S., an estimated 56,500 new cases of bladder cancer are detected annually, with approximately 12,600 deaths. These figures may seem insignificant when compared with the incidence and death rates of carcinoma of the lung (169,400 new cases, 154,900 deaths). What is significant is the biologic behavior of most urothelial lesions of the urinary tract, including the ureters and renal pelves. Generally speaking, 5-year survival rates encompass too short a time to tell the full natural history of these tumors, which can easily span 15–20 years. This long survival rate can be attributed to effective chemotherapy and good patient management, but also to the often indolent nature of this unique neoplasm. Although 70% of bladder tumors are superficial or only minimally invasive, and theoretically curable, 50–70% of these patients will have “recurrent” or new tumors, up to a third of which are of higher grade and/or stage. The remaining 30% initially present with muscle invasion or distant metastases.

Synchronous or metachronous tumors may arise in the urothelium of the urinary tract, and can vary in stage and grade when they occur simultaneously. Thus, the clinician and patient are faced with a long-term commitment to control an unpredictable neoplastic process. Obliteration of a low grade tumor in one site provides no guarantee that another tumor, perhaps of higher grade, will not occur in another area.

Cytology plays an important role in the management of these patients. Cystoscopy can visualize and locate papillary lesions of the urinary bladder for biopsy, but lesions of the urethra, ureters, and renal pelves are not as accessible. Radiographic demonstration of a “filling defect” can provide only putative evidence that a tumor is present. Therefore, urinary cytology may be relied upon to indicate if a neoplasm is actually present. The decision to remove a kidney because of suspected ureteral or calyceal tumors or divert the collecting system into an ileal loop or neo-bladder based on cytologic findings places a grave burden of responsibility upon cytologists.

Thus, in order to establish criteria for diagnosing low grade urothelial lesions in the upper urinary tract (ureters and renal pelves)
the cytologist must refine diagnostic criteria to distinguish the low grade papillary lesions from benign/reactive atypias. By comparing cytologic specimens derived from bladders that contain histologically proven low grade neoplasms, the cytologist can apply the same criteria to the diagnosis of upper tract lesions, even though the “normal” epithelium has more atypia in the upper tract than the bladder. However, most of the upper tract low grade lesions will not shed diagnostic material unless the sample is obtained after vigorous washing (barbatage).

Although all types of urinary tract lesions, benign and malignant, can be diagnosed theoretically by cytology, only the most common diagnostic problems will be addressed herein. The ambitious student is referred to the referenced works for a more complete discussion. One of the most important factors in becoming proficient in urinary cytology is to effectively communicate with the urologists who submit cytologic specimens. A lesion of the upper tract should never be diagnosed unless the radiographic findings are reviewed with the urologist and the cytologic findings are considered in light of available evidence. Such close collaboration will not only corroborate the cytologic diagnosis, but will provide the urologist with an understanding of the difficulties and problems involved in rendering a reasonable diagnosis. The overwhelming majority of low grade tumors are not life threatening, allowing time for repeat studies to follow the lesion’s development and confirm initial impressions.

**Suggested Reading**


Anatomic Considerations

The urinary tract can be divided into three regions: the kidney; the calyces, pelves and ureters (upper collecting system or upper tract); and the bladder and the urethra (lower collecting system or lower tract). From an exfoliative cytology standpoint, the kidneys are rarely of concern, for the tumors of the renal parenchyma are infrequently recovered in urinary specimens. Renal tumors are currently diagnosed pre-operatively either by their radiologic characteristics or by a Fine Needle Aspirate (FNA). Coverage of this topic is beyond the scope of this volume.

Normal Urothelial Histology and Cytology

The majority of the collecting system is lined by urothelium (transitional epithelium). Variable areas of the bladder and urethra may be lined by glandular epithelium (simple columnar), especially in the trigone and the dome of the bladder (the vestigial urachus); paraurethral glands, which provide lubrication for the urethra, might also be a source of glandular epithelium from that area. Cystitis cystica or glandularis, arising in Brunn’s nests in the bladder mucosa, may shed groups of atypical glandular cells not to be confused with those cells of an adenocarcinoma of the bladder or prostate. In addition, the prostate and accessory sex glands are lined by
columnar epithelium. Therefore, if glandular cells are seen within a urine sample, these sources should be considered.

The urothelium is a unique mucosa, specialized for the urinary tract for its ability to expand and contract, and as a barrier against the toxic urine. This stratified epithelium is morphologically intermediate between cuboidal and squamous, hence its old name, “transitional”. When contracted, the bladder is lined by a layer 4–5 cells thick with the basal cells assuming a cuboidal shape; the intermediate cells, polygonal; and the surface cells round and large, and often binucleate. When the bladder is distended, the mucosa may be only 2–3 layers thick and the intermediate and surface cells may appear flattened.

The surface cells, the largest ones found in cytologic samples, have abundant cytoplasm, the luminal surface of which may appear thickened (Fig. 1.1). The nuclei of these superficial cells, often called umbrella cells, because of their position over more than one intermediate or basal cell (Fig. 1.2), may have prominent nucleoli, and may be multinucleated (Fig. 1.3).

The physiologic role of the urothelium is fascinating, and as unique as its cytologic appearance. The purpose of the urinary epithelium is to provide a barrier between the blood and the usually hypertonic toxic urine, which contains the majority of wastes from the body. The plasma membranes of the surface of umbrella cells are thicker than most other cell membranes. This rigid trilaminar membrane, the so-called “asymmetric unit membrane” is composed of a unique family of proteins, uroplakins. Interdigitating cell junctions permit great distension of the epithelium without damage to the integrity of the mucosal surface. The epithelium is connected to a basement membrane that appears invisible by light microscopy. The basal layer may be deeply indented by strands of underlying connective tissue which contain capillaries.

The histology of the other parts of the urinary tract, the ureters, pelves and calyces, and urethra, is essentially identical to the bladder, except that the size of the cells is smaller. Cross section of a contracted ureter reveals large mucosal folds that flatten if the ureter distends.

Columnar cells are infrequently present, but their identity is readily recognized as the cellular features are the same as any other benign columnar cell (Figs. 1.4, 1.5). Their origin may be in
glandular remnants in the dome or trigone of the bladder. Urothelial cells on the surface of an hyperplasia may also appear to be columnar (Figs. 1.6, 1.7). Any atypia needs to be assessed in the context of accompanying inflammation, as from cystitis cystica/glandularis or suspicion of glandular neoplasia, based on history and cytologic features.

Squamous epithelium (Figs. 1.8, 1.9) can occur as a result of metaplasia or as a congenital area, especially within the trigone of women. The distal portion of the penile urethra is lined by squamous epithelium. In females, vaginal contamination during a voided urine collection (Fig. 1.10) can be a source of benign and neoplastic squamous and glandular epithelium (see Chapter 5).
Figure 1.1. Normal Umbrella Cells—bladder washing: The thickened unilateral aspect of the cytoplasmic boundary is a manifestation of the asymmetric unit membrane whose purpose is to prevent toxic urine from entering the blood stream. In addition to the thickened asymmetric membrane, the frothy perinuclear cytoplasm is also characteristic of benign urothelial cells. Chromatin is fine and uniform in texture and distribution. (600x)
Figure 1.2. Benign Urothelial Cells—catheterized urine: Clusters of benign urothelial cells are admixed with squamous cells. Several acute inflammatory cells are seen in the background. The urothelial cells are seen in two main clusters, one cluster of which is smaller than the second. Cytoplasmic vacuolization and variability in nuclear size and shape is observed. Although the cytoplasm appears to be homogeneous, the nuclear cytoplasmic ratio is not increased. In catheterized specimens, these clusters represent benign or reactive urothelial cells. (600x)