Educational Case: Urothelial Carcinoma: An Overview of Pathologic Diagnosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Primary Objective

Objective UTB1.3: Diagnosis and Surveillance of Urothelial Carcinoma. Describe the typical clinical presentation of urothelial carcinoma and the advantages and limitations of urine cytology in the diagnosis and surveillance of urothelial carcinoma.

Competency 2: Organ System Pathology; Topic UTB: Bladder; Learning Goal 1: Bladder Neoplasia.

Secondary Objectives

Objective UTB1.1: Urothelial Carcinoma. Compare and contrast the different precursor lesions of urothelial carcinoma in terms of architecture, cytologic features, molecular–genetic changes, and propensity for invasion/progression.

Competency 2: Organ System Pathology; Topic UTB: Bladder; Learning Goal 1: Bladder Neoplasia.

Objective UTB1.2: Risk Factors for Urothelial Carcinoma. Relate the risk factors for urothelial carcinoma to general principles of carcinogenesis.

Competency 2: Organ System Pathology; Topic UTB: Bladder; Learning Goal 1: Bladder Neoplasia.

Objective CYP1.2: Categorizing Diagnostic Certainty. Compare and contrast the degree of diagnostic certainty applied to general categorization in cytologic diagnosis.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 1: Cytologic Diagnosis.

Patient Presentation

A 71-year-old male presents to a urology clinic with dysuria and urinary urgency. His symptoms began 2 weeks ago, and he is urinating every 2 to 3 hours, an increase from his baseline of every 5 to 6 hours. He denies any additional symptoms, including hematuria and flank pain. He has a history of coronary

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artery disease and no prior surgeries. The patient quit smoking 5 years ago with a 25 pack-year smoking history and denies additional alcohol and drug use. The patient has no personal or family history of cancer. The patient is afebrile, and physical examination with rectal exam is within normal limits.

Diagnostic Findings, Part 1

At initial presentation, 2 urinalysis specimens showed micro-hematuria and were negative for bacteria and inflammatory cells. Urine cytology revealed atypical urothelial cells.

Questions/Discussion Points 1

Discuss the Differential Diagnosis of Hematuria and the Preliminary Working Diagnosis

Gross hematuria is when blood is visible in the urine, while microscopic hematuria is defined as 3 or more red blood cells per high-power field in a urine specimen. Hematuria can arise from anywhere along the urinary tract, including the kidney, ureter, bladder, prostate, and urethra. Etiologies include glomerular disease, neoplastic processes, calculi, trauma, and infections such as urethritis, prostatitis, and pyelonephritis. Other less common causes include uretero-arterial fistulas, hemorrhagic cystitis, and urethral strictures. Elements crucial to distinguishing between these etiologies include urinary symptoms, the presence and location of pain, fever, recent trauma, prior obstruction, and radiotherapy or family history. Unilateral flank pain is highly suggestive of calculi but may also be present in malignancy. Findings suggestive of infection include fever, dysuria, and white blood cells and bacteria in the urine.[2] This patient's microhematuria with dysuria and lack of flank pain suggests a diagnosis of benign prostatic hyperplasia or malignancy.

What Are the Patient's Risk Factors for Urothelial Carcinoma?

This patient's main risk factors for urothelial carcinoma (UC) of the bladder include smoking history, gender, and age. Smoking is the most significant risk factor for UC, contributing to approximately 50% of tumors (population attributable risk: 0.50, 95% CI: 0.45-0.54 in men and 0.52, 95% CI: 0.45-0.59 in women).[3] Aromatic amines from cigarette smoke are renally cleared and exert their carcinogenic effect on the urinary tract. Both cigarette smoking and environmental exposure to tobacco smoke have been shown to contribute significant risk. The second largest contributor is occupational exposure to aromatic amines in industries involving processing paint, dye, metal, and petroleum products. However, occupational exposures have decreased in recent years due to increased safety measures. Water intake is associated with decreased risk, likely due to the dilution of potential carcinogens in the urinary tract. Additional risk factors include male gender, white race, first-degree relative with UC, arsenic exposure, schistosomiasis, and chronic urinary tract inflammation or dilation, such as in chronic urinary retention. However, female gender and black race are associated with reduced survival.[4]

What Systems Are Used to Classify the Pathology Identified on Urine Cytology? What Are the Advantages of the Paris System for Reporting Urine Cytology?

The original criteria for the cytomorphological description of cancer cells in urine cytology were established by Drs Papanicolaou and Marshall in 1947. Dr Leopold Koss expounded upon urine cytology by describing the features used in the classification system and recognizing the limited utility of urine cytology in diagnosing low-grade urothelial carcinoma (LGUC). Numerous reporting systems have been suggested, but none gained broad acceptance. The Paris System (TPS) for Reporting Urine Cytology, published in 2016, addressed numerous pitfalls of the previous reporting systems by focusing on the diagnosis of high-grade urothelial carcinoma (HGUC). The Paris System divides specimens into the following categories: negative for HGUC, atypical, suggestive of HGUC, HGUC, low-grade urothelial neoplasia, and other malignancies.

The Paris System acknowledges the limitations of urine cytology in the diagnosis of LGUC. Although urine cytology has a greater than 95% specificity for HGUC, the sensitivity is highly limited, especially for LGUC. As a result, TPS focuses on detecting high-grade lesions. Although a negative urine test under these criteria does not exclude the possibility of a low-grade lesion, the low risk of progression of LGUC combined with the limited sensitivity of urine cytology for such lesions increases the clinical value of the cytology results.[5,6]

Another significant limitation of most reporting methods is the high frequency of indeterminate diagnosis. An atypical diagnosis has limited clinical significance due to its ambiguous determination of risk. The Paris System focuses on reducing the reporting of this category.[5] Early studies indicate that levels of atypical results decreased by 40% after TPS was implemented, greatly improving risk stratification.[7] Additionally, most reporting methods have a significant degree of interobserver variability, and applying the focused criteria of TPS decreases the prevalence of this issue. Recent studies have demonstrated that the application of TPS has resulted in an increase in specificity, accuracy, positive predictive value, and interobserver reproducibility.[8] In addition to providing guidance to pathologists, these improvements increase the clinical utility of urine cytology for urologists.

What Features Distinguish Urothelial Lesions on Urine Cytology According to The Paris System?

Negative for High-Grade Urothelial Carcinoma. Groups of urothelial cells are considered normal unless they meet criteria for atypia. Normal urothelial and squamous cells are the most common cellular elements observed (Figure 1). This category does not rule out LGUC. Rather, it is designed to denote the absence of a high-grade lesion.
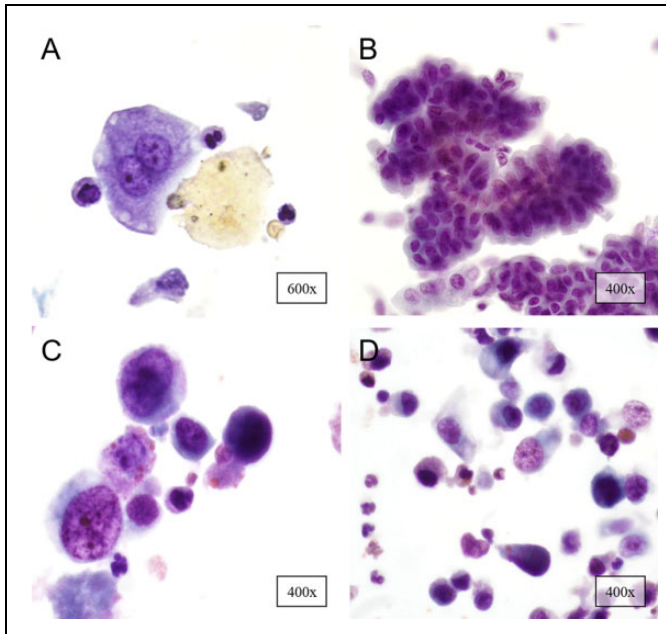
Figure 1. Urine cytology findings of (A) normal, (B) low-grade urothelial carcinoma, (C) suspicious for high-grade urothelial carcinoma, and (D) high-grade urothelial carcinoma specimens according to The Paris System for reporting urine cytology.

Atypical Urothelial Cells. The nuclear to cytoplasmic (N:C) ratio must be above 0.5. One of the 3 minor criteria must also be met: hyperchromasia, irregular nuclear membranes, and irregular clumpy chromatin. The hyperchromasia must be distinguishable from the surrounding benign urothelial cells but is not required to be as severe as in suspicious for high-grade urothelial carcinoma (SHGUC). This category denotes a risk of UC that is lower than that in SHGUC (8%-35% vs 50%-90% risk of malignancy).[5] Clinical follow-up is generally like that of negative for high-grade urothelial carcinoma (NHGUC).

Suspicious for High-Grade Urothelial Carcinoma. This category requires an N:C ratio of 0.5, moderate to severe hyperchromasia, and one of the following minor criteria: marked irregular nuclear membranes and irregular clumpy chromatin. This diagnosis can be made based on a single cell meeting the above criteria.[9]

High-Grade Urothelial Carcinoma. A cytologic diagnosis of HGUC requires a minimum of 5 to 10 cells meeting all major criteria: N:C ratio greater than 0.7, moderate to severe hyperchromasia, marked irregular nuclear membranes, and coarse chromatin. Additional features, such as nuclear pleomorphism, eccentric nuclei, mitotic figures, apoptotic bodies, prominent nucleoli, and enlarged nuclei, are commonly observed but are not required for diagnosis.[5]

Low-Grade Urothelial Neoplasm. The presence of fibrovascular cores warrants a diagnosis of LGUN. The term neoplasm is substituted for carcinoma due to the presence of fibrovascular cores in low-grade lesions other than LGUC. Although morphological characteristics of LGUC, such as nuclear enlargement, nuclear membrane irregularity, and nuclear elongation, are frequently seen in negative specimens, fibrovascular cores are rare, increasing the confidence of a low-grade diagnosis. As a result, while TPS focuses on the diagnosis of high-grade lesions, a diagnosis of LGUN may be reported alongside NHGUC if fibrovascular cores are observed.[5]

Other: Primary and Secondary Malignancies. Primary bladder cancers other than UC are rare and include squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Secondary bladder cancers represent less than 10% of bladder cancers and are most commonly a result of direct invasion from the gastrointestinal tract, prostate, uterus, and cervix.[5]

Describe the Molecular Pathways Responsible for Low-Grade and High-Grade Urothelial Carcinoma and Their Effect on Disease Prognosis

Low-grade and high-grade UCs develop as a result of mutations in different molecular pathways. Mutations in the MAPK and PI3K pathways are associated with low-grade lesions, while mutations affecting the G1/S cell cycle transition are responsible for high-grade tumors. Noninvasive low-grade papillary UC usually results from mutations in fibroblast growth factor receptor 3 and HRAS. These two proteins lie upstream of the MAPK, PI3K, and mTOR pathways, which regulate cell proliferation, differentiation, and protein synthesis. Although these mutations appear to be mutually exclusive, at least one of these mutations can be identified in 82% of nonmuscle invasive bladder cancer. Mutations in p110, a subunit of PI3K, have also been associated with low-grade papillary carcinomas.

High-grade lesions are most commonly associated will cell cycle dysregulation, especially at the G1/S checkpoint. Loss-of-function mutations in p53, which normally suppresses cell cycle progression, are associated with a worse prognosis. Decreased p53 functionality can also result from inactivating mutations in p14, an upstream modulator of p53 activity. High-grade lesions can also result from a mutation in the retinoblastoma (RB) pathway. These alterations include mutations involving the RB protein and decreased levels of cyclin D1 and E1.[10,11]

What Ancillary Tests Are Used Alongside Urine Cytology?

Due to the low sensitivity of urine cytology, ancillary testing is frequently used to increase detection rates. Fluorescence in situ hybridization, or UroVysion, is used due to the aneuploid nature of UC. Probes target the centromeres of chromosomes 3, 7, and 17 as well as the 9p21 locus to detect aneuploidy. However, care must be taken while interpreting results to ensure tetrasomic cells from the mitotically active sections of the upper urinary tract are not interpreted as positive for malignancy. ImmunoCty/uCyt+ is an antibody-based assay used to
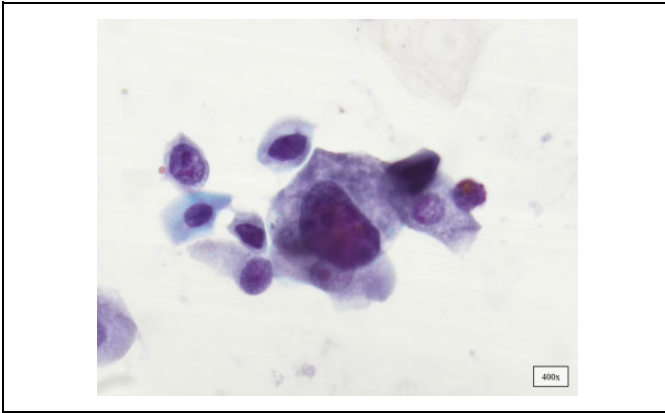
Figure 2. Patient's urine cytology specimen from the second clinical visit showing urothelial cells with a nuclear to cytoplasmic ratio of greater than 0.7, moderate hyperchromasia, and irregular nuclear membranes.

increase the sensitivity of cytology results. The presence of high-molecular-weight glycosylated carcinogenic embryonic antigen and bladder cancer-mucin-like antigens on five or more cells is considered a positive. This test also increases the detection of LGUC as such cancers often express these surface markers. However, the specificity of this test is significantly lower than that of urine cytology alone, as conditions such as benign prostatic hyperplasia and bladder calculi may cause falsely positive results.[9]

When Is the Use of Urine Cytology Recommended in Patient Workup and Screening?

The American Urology Association (AUA) guidelines recommend the use of urine cytology as a screening tool for patients at intermediate and high risk for nonmuscle invasive bladder cancer in cases where initial surveillance cystoscopy was negative for a tumor. For intermediate-risk patients, cytology should be used as an adjunct to cystoscopy every 3 to 6 months for 2 years and every 6 to 12 months for an additional 2 years followed by annual screening. In high-risk patients, these intervals are shortened to 3 to 4 months, 6 months, and annually, respectively. These recommendations are based on the sensitivity and specificity of urine cytology. Although urine cytology sensitivities are suboptimal, their use as a supplemental screening tool in intermediate- to high-risk patients is warranted based on the high risk of disease progression for these patients. The use of cytology is not recommended in patients with a history of low-risk cancer and normal cystoscopy due to the low sensitivity of urine cytology for low-grade lesions.[12]

The use of cytology in conjunction with cystoscopy in the workup of gross hematuria is warranted. However, the AUA does not recommend the use of urine cytology in the initial workup of asymptomatic hematuria due to its low sensitivity. Yet, it does not preclude the use of urine cytology as an adjunctive test following an initial negative workup in patients at high

risk for UC. Due to the high false-negative rate, a negative urine cytology result does obviate the need for a full workup.[13]

Diagnostic Findings, Part 2

Two months later, the patient returned to the clinic presenting with hematuria, difficulty maintaining a urinary stream, and persistent dysuria and urgency. Urine cytology showed 6 cells with an N:C ration of 0.7 or greater, moderate hyperchromasia, and irregular nuclear membranes (Figure 2). On cystoscopy, a left lateral wall mass with papillary projections was observed. Biopsies of the lateral and posterior walls revealed invasive high-grade papillary UC.

Questions/Discussion Points 2

Discuss the Clinical Presentation of Bladder Cancer. How Are the Patient's Laboratory Results Interpreted and What Is the Definitive Diagnosis?

The patient's cytology results meet the criteria for high-grade UC, and surgical pathology results demonstrate the presence of invasive UC. Urothelial carcinomas represent approximately 90% of all primary bladder tumors.[10] This patient's presentation, with hematuria, dysuria, and weak urinary stream, is consistent with the typical symptoms of UC. The most common symptoms of bladder cancer are hematuria, voiding symptoms, pain, and constitutional symptoms. Hematuria is the most common presenting symptom, with gross hematuria more suggestive of cancer than microscopic hematuria. Approximately 20% of patients presenting with gross hematuria are diagnosed with bladder cancer, although estimates for microscopic hematuria are less than 10%. Voiding symptoms, such as frequency, urgency, and dysuria, as seen in this patient, are most frequent in patients with carcinoma in situ. Pain and difficulty maintaining urinary stream are common in locally advanced or metastatic disease due to urethral obstruction. In advanced or metastatic disease, constitutional symptoms may also be present.[14] The patient's cytology findings of 4 cells with an N:C ration of 0.6, moderate hyperchromasia, and irregular nuclear membranes are suspicious for high-grade urothelial carcinoma. The biopsy taken during cystoscopy confirms a diagnosis of invasive high-grade papillary UC.

Discuss the Classification of Noninvasive Papillary Urothelial Carcinoma. What Is the Prognosis and Progression of Each Lesion?

Papillary urothelial lesions are classified according to the system proposed by the World Health Organization (WHO) and International Society for Urologic Pathologists (ISUP) in 1989. (This system was republished in 2004 and adopted by the WHO in 2016.) This system divided noninvasive urothelial lesions into the categories of urothelial papilloma, papillary urothelial neoplasm of low malignant potential, low-grade papillary UC, and high-grade papillary UC (Figure 3).[15]
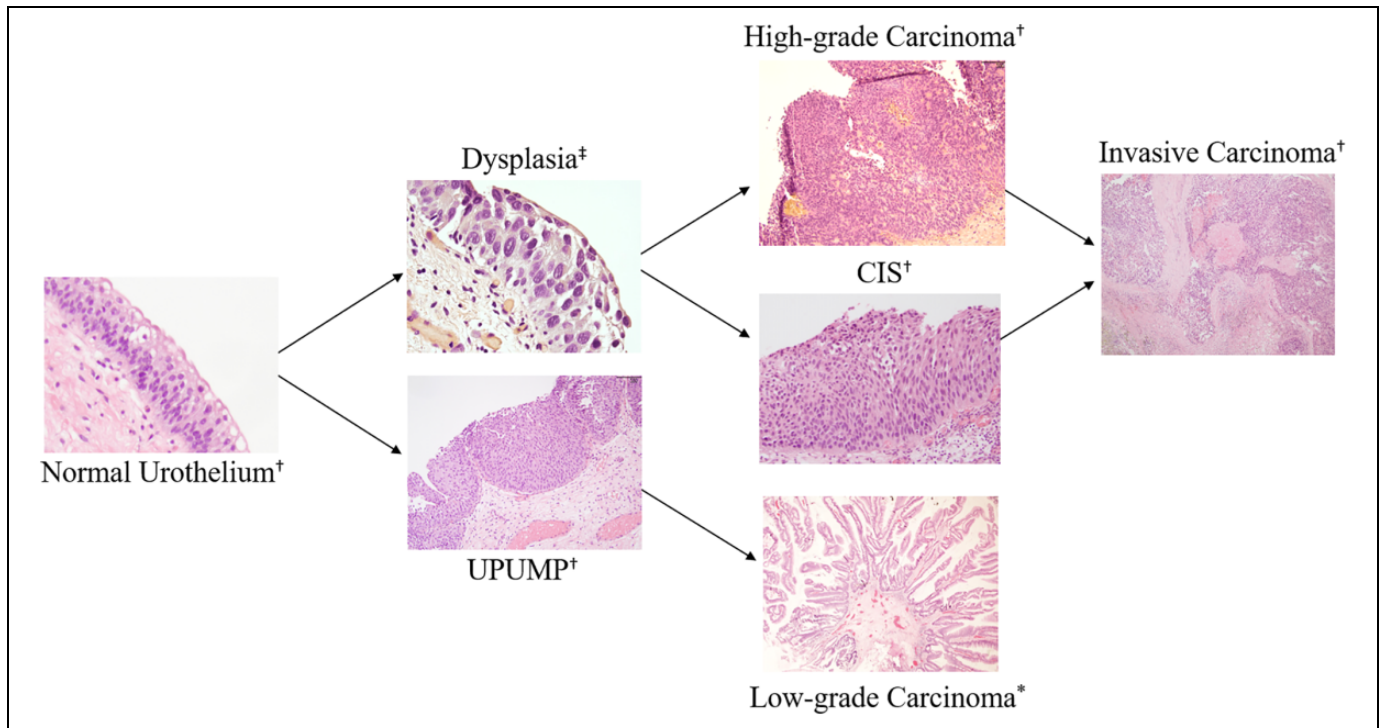
Figure 3. Schematic of the major pathways for the progression of urothelial carcinoma demonstrating the distinct pathogenesis of high-grade and low-grade urothelial lesions. *×20. †×40. ‡×100. CIS, carcinoma in situ; UPUMP, urothelial proliferation of uncertain malignant potential.

Urothelial Papilloma (Exophytic and Inverted). Exophytic urothelial papillomas are benign lesions that appear as nonbranching papilla lined by normal urothelium on histology. Papillary cores with dilated lymphatics as well as eosinophilic and vacuolated cytoplasm are common, but atypical cells are not observed. These lesions have a favorable prognosis and rarely progress to high-grade lesions, although recurrence is common. Inverted papillomas invaginate into the bladder wall but do not invade the muscular layer. Normal urothelial cells with mild to absent atypia are observed.[10] Similar to exophytic papillomas, the prognosis is favorable with rare progression to UC, and inverted papillomas have a lower rate of recurrence.[16]

Papillary Urothelial Neoplasm of Low Malignant Potential. Papillary urothelial neoplasm of low malignant potential appears similar to a papilloma on histology with hyperplasia of the urothelial layer.[10] These lesions frequently recur and infrequently progress to low-grade papillary urothelial carcinoma (LGPUC) or HGUC, although stage progression is rare.[17]

Low-Grade Papillary Urothelial Carcinoma. On histology, LGPUC shows fused and branching papilla with minimal loss of polarity. Cytologically, enlarged nuclei with mild pleomorphism, inconspicuous nucleoli, and occasional mitosis can be observed. Low-grade papillary urothelial carcinoma has a high recurrence rate, but disease progression is rare.[10]

High-Grade Papillary Urothelial Carcinoma. High-grade papillary urothelial carcinoma (HGPUC) shows fused and branching papillae on histology. Cytologically, cells have moderately to severely pleomorphic, hyperchromatic nuclei with multiple prominent nucleoli and frequent mitosis.[10] There is a high risk of progression, and metastatic disease is common at initial presentation. In specimens with high- and low-grade components, the WHO recommends describing the lesion based on the highest grade component. However, the minimum percentage of the high-grade component required to declare the sample HGPUC remains unclear.[18]

How Are Flat Urothelial Lesions Classified?

Flat urothelial lesions are classified according to WHO/ISUP 2016 classification system, which designates lesions as reactive urothelial atypia, urothelial atypia of unknown significance, urothelial dysplasia, and urothelial carcinoma in situ (CIS). Reactive urothelial atypia, commonly associated with inflammatory states, appears as enlarged rounded nuclei without nuclear polymorphism. Mitosis and prominent nucleoli may be observed, but the chromatin remains fine. Carcinoma in situ is identified by nuclear hyperchromasia, significantly enlarged nuclei, course chromatin, and loss of cellar polarity. Since CIS frequently maintains abundant cytoplasm, the N:C ratio may not be increased. Although noninvasive papillary UC is technically a carcinoma in situ, it should not be labeled as such, as urothelial CIS and papillary UC behave as distinct diseases. Interpretations of urothelial atypia of unknown significance and urothelial dysplasia have poor interobserver
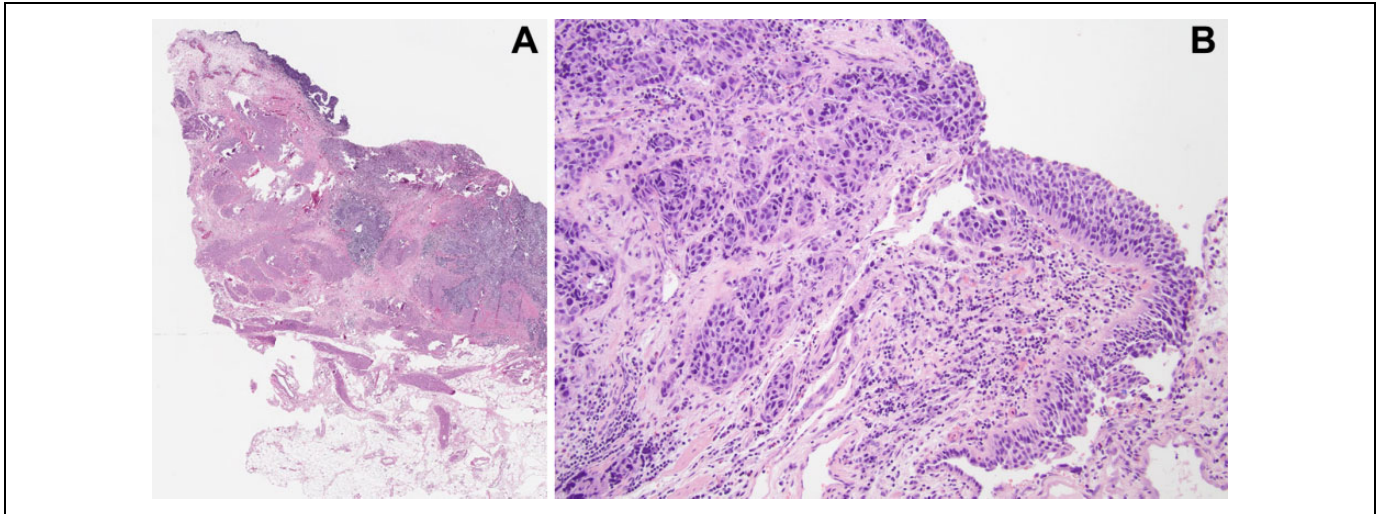
Figure 4. Postoperative surgical pathology bladder specimen from the patient's cystectomy. A, Slide scan demonstrating invasive urothelial cells in the deep muscle sparing the adventitia. B, High-power (×40) image of invasive urothelial cell nests.

reproducibility. As a result, the phrase "flat urothelial atypia cannot exclude early flat neoplasia" is frequently used for lesions of both categories. These lesions encompass all specimens falling between the criteria for reactive urothelium and urothelial CIS.[10]

What Are the Histological Subtypes of Invasive Urothelial Carcinoma?

Typical UC appears as irregularly distributed nests of urothelial cells which are often surrounded by fibrotic, inflammatory, myxoid, or desmoplastic stroma. Invasion into the muscularis propria is diagnostic of malignancy. Invasive UC has numerous histomorphological variants. Awareness of the variants is crucial in preventing misdiagnosis and in diagnosing metastasis, as secondary lesions frequently maintain the differentiation of the primary tumor. Squamous differentiation is estimated to account for 60% of UC and is identified by the presence of keratinization or intercellular bridges. Glandular differentiation, accounting for an additional 10% of UC, is identified by the presence of tubular or enteric glands. These variants, while common, have limited clinical significance, although recent studies suggest that squamous differentiation may affect the efficacy of chemotherapy and radiation. Several rare variants can be deceptively benign, such as nested, microcystic, tubular, and inverted patterns, which can appear like von Brunn's nests, cystitis cystica, benign glandular proliferation, and inverted papillomas respectively.[10,19]

Diagnostic Findings, Part 3

The patient received neoadjuvant chemotherapy and a radical cystectomy for the treatment of muscle-invasive UC. Postoperative surgical pathology of the bladder shows nests of urothelial cells beyond the muscularis propria, confirming the

Table 1. TNM Staging of Bladder Urothelial Carcinoma.

Stage	Extent of tumor
Tis	Carcinoma in situ
Ta	Noninvasive papillary lesions
T1	Invasion of the lamina propria
T2	Invasion of the muscle (T2a = superficial, T2b = deep)
T3	Invasion of the perivesical fat (T3a = microscopic, T3b = macroscopic)
T4	Extending into perivesical organs (T4a = prostate, uterus, or vagina, T4b abdominal or pelvic wall)
N	Lymph node involvement (N0 = no nodes N1-3 = nodal involvement)
M	Metastasis

Abbreviations: M0, no metastasis; M1, metastasis.

diagnosis (Figure 4). Follow-up imaging showed no signs of nodal or systemic metastasis.

Questions/Discussion Points 3

Discuss the Staging and Treatment of Urothelial Carcinoma. What Is the Patient's TNM Stage and What Is the Most Appropriate Treatment?

The pathologic staging of invasive UC follows the TNM system (Table 1). The deep muscle invasion without invasion into the adventitia, nodal involvement, or metastasis in this patient is consistent with a stage T2b tumor. Nonmuscle invasive UC (≤T1) is treated with transurethral resection of the bladder tumor followed by localized immunotherapy. However, prophylactic cystectomy is performed in high-risk cases, such as in patients with a large tumor, lymphovascular invasion, or a previously partially resected T1 tumor. Muscle invasive lesions are typically treated with neoadjuvant chemotherapy followed by radical cystectomy.[14] The classification of a tumor as

organ-confined or nonorgan-confined is the most significant prognostic for the success of radical cystectomy (hazard ratio: 1.80, 95% CI: 1.26-2.57). Additional prognostic factors include patient age, lymphovascular invasion, and nodal involvement. Patients with locally advanced disease, especially those invading adjacent organs, are typically treated with chemotherapy as in metastatic disease.[20]

Metastatic UC is treated with cisplatin or carboplatin-based chemotherapy regimens, with non-platinum-based regimens available for those unable to receive platinum-based therapy. Second-line treatments involve the use of immunotherapy drugs, predominantly those targeting programmed cell death-1 protein or its ligand (PD-L1). While second-line chemotherapy agents have not been Food and Drug Administration approved for use in metastatic UC, clinical trials are currently in progress to evaluate the efficacy of second-line chemotherapy regimens in the treatment of patients unable to receive immunotherapy.[21]

Teaching Points

- The most common presenting symptoms of UC are hematuria, voiding symptoms, pain, and constitutional symptoms in patients with a smoking history or occupational carcinogen exposure.
- The four criteria used to classify urine cytology specimens are N:C ratio, hyperchromasia, coarse chromatin, and nuclear membrane irregularities.
- The Paris System for Reporting Urine Cytology emphasizes the detection of HGUC over LGUC and reduces the prevalence of atypical diagnosis.
- High-grade and low-grade urothelial carcinomas involve different molecular pathways, resulting in different disease course and prognosis. Low-grade lesions involve MAPK and PI3K mutations, while high-grade lesions result from cell cycle dysregulation at the G1/S checkpoint. Efforts to detect UC are focused on the more rapidly progressive high-grade carcinomas.
- Urine cytology is recommended in the workup of gross hematuria and microscopic hematuria after an initial negative workup and for the screening of intermediate- and high-risk patients.
- Papillary lesions are classified as urothelial papilloma, papillary urothelial neoplasm of low malignant potential, low-grade papillary UC, and high-grade papillary UC.
- There are many variants of invasive UC that can be easily mistaken for other diagnoses and may affect treatment.

Declaration of Conflicting Interests

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References

1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. *Acad Pathol*. 2017:4. doi:10.1177/2374289517715040
2. Avellino GJ, Bose S, Wang DS. Diagnosis and management of hematuria. *Surg Clin North Am*. 2016;96:503-515. doi:10.1016/j.suc.2016.02.007
3. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet C. Association between smoking and risk of bladder cancer among men and women. *JAMA*. 2011;306:737-745. doi:10.1001/jama.2011.1142
4. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*. 2013;63:234-241. doi:10.1016/j.eururo.2012.07.033
5. Barkan GA, Wojcik EM, Nayar R, et al. The Paris system for reporting urinary cytology: the quest to develop a standardized terminology. *J Am Soc Cytopathol*. 2016;5:177-188. doi:10.1016/j.jasc.2016.04.005
6. Vandenbussche CJ. A review of The Paris System for reporting urinary cytology. *Cytopathology*. 2016;27:153-156. doi:10.1111/cyt.12345
7. Cowan ML, Rosenthal DL, Vandenbussche CJ. Improved risk stratification for patients with high-grade urothelial carcinoma following application of The Paris System for reporting urinary cytology. *Cancer Cytopathol*. 2017;125:427-434. doi:10.1002/cncy.21843
8. Glass R, Rosca O, Raab S, et al. Applying The Paris System for reporting urine cytology to challenging cytology cases. *Diagn Cytopathol*. 2019;47:675-681. doi:10.1002/dc.24166
9. Xing J, Reynolds JP. Diagnostic advances in urine cytology. *Surg Pathol Clin*. 2018;11:601-610. doi:10.1016/j.path.2018.06.001
10. Goldblum JR, Lamps LW, McKenney JK, Myers JL. Bladder. In: Rosai J, ed. *Rosai and Ackerman's Surgical Pathology*. 11th ed. Elsevier; 2018:1066-1096.
11. Solomon JP, Hansel DE. The emerging molecular landscape of urothelial carcinoma. *Surg Pathol Clin*. 2016;9:391-404. doi:10.1016/j.path.2016.04.004
12. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol*. 2016;196:1021-1029. doi:10.1016/j.juro.2016.06.049
13. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol*. 2012;188:2473-2481. doi:10.1016/j.juro.2012.09.078
14. DeGeorge KC, Holt HR, Hodges SC.Bladder cancer: diagnosis and treatment. *Am Fam Physician*. 2017;96:507-515.

15. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The world health organization/international society of urological pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Am J Surg Pathol*. 1998;22:1435-1448. doi:10.1097/00000478-199812000-00001

16. Picozzi S, Casellato S, Bozzini G, et al. Inverted papilloma of the bladder: a review and an analysis of the recent literature of 365 patients. *Urol Oncol*. 2013;31:1584-1590. doi:10.1016/j.urolonc.2012.03.009

17. Jaworski D, Szylberg Ł, Gzil A, Stawinski P, Kasperska A, Marszałek A. Diagnostic difficulties in cases of papillary urothelial neoplasm of low malignant potential, urothelial proliferation of uncertain malignant potential, urothelial dysplasia and urothelial papilloma: a review of current literature. *Ann Diagn Pathol*. 2019; 40:182-188. doi:10.1016/j.anndiagpath.2017.12.007

18. Reis LO, Taheri D, Chaux A, et al. Significance of a minor high-grade component in a low-grade noninvasive papillary urothelial carcinoma of bladder. *Hum Pathol*. 2016;47:20-25. doi:10.1016/j.humpath.2015.09.007

19. Amin MB. Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. *Mod Pathol*. 2009; 22:E15. doi:10.1038/modpathol.2009.26

20. Mitra AP, Quinn DI, Dorff TB, et al. Factors influencing post-recurrence survival in bladder cancer following radical cystectomy. *BJU Int*. 2011;109:846-854. doi:10.1111/j.1464-410x.2011.10455

21. Weiss J, Notohamiprodjo M, Bedke J, Nikolaou K, Kaufmann S. Imaging response assessment of immunotherapy in patients with renal cell and urothelial carcinoma. *Curr Opin Urol*. 2018;28: 35-41. doi:10.1097/mou.0000000000000463