Educational Case: Bladder Urothelial Cell Carcinoma TNM Stage, Prognosis and Management

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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 UTB1.4: Staging of Bladder Cancer. Relate stage of bladder cancer to prognosis and therapy, including the role of BCG, in the treatment of low-stage tumors.

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

Patient Presentation

A 71-year-old man presents to his primary care physician with dark red-colored urine on several occasions over the past month. The patient is a retired custodian with a past medical history of hypertension, high cholesterol, and a 50-pack year smoking history. There is no other relevant social, occupational, or family history.

Diagnostic Findings, Part I

His vital signs are a temperature of 98.7 F, a blood pressure of 130/82 mm Hg, respiratory rate of 16/minute, and heart rate of 70 beats per minute. When asked about medications, he is taking chlorothiazide 500 mg/day, atorvastatin 10 mg/day, and a daily multivitamin. The patient denies any recent travel. Physical examination including a genitourinary examination reveals no abnormalities. Medical history reveals no recent illnesses, no allergies, and no trauma. He denies any pain with urination as well as any flank pain. No changes in diet are noted with no recent consumption of beets, blackberries, or rhubarb.

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Questions/Discussion, Part 1

What Is the Clinical Differential Diagnosis for This Patient?

The patient presents with repeated episodes of asymptomatic dark red-colored urine. There are several possibilities for cause of dark colored urine. These may be innocuous and benign such as ingestion of certain foods or prescription or over the counter medications; or they may be indicative of a pathology. A careful history of comorbidities, drug audit, diet and other symptoms followed by required investigations helps to narrow the differential diagnosis and determine the cause.[2]

The most common abnormal color of urine seen is red or red-brown, as seen in this patient. When seen in females of reproductive age-group, it may be due to menstrual blood contamination. However, in the patient described, other causes need to be considered. The dietary causes include eating beets, rhubarb, blackberries, or foods containing certain food colorings that may be excreted in the urine. A number of medications can also result in dark red, brown, or orange colored urine. Some of these include antibiotics (eg, rifampicin), analgesics and muscle relaxants (eg, phenazopyridine, chlorzoxazone, ethoxazene, phenazopyridine), anthraquinone laxatives (eg, senna and cascara), purgatives (eg, phenolphthalein), iron and chelation agents (eg, deferoxamine mesylate, iron sorbitol), levodopa, and anticoagulants like phenindione (where it may be important to differentiate from hematuria) to name a few. Red colored urine may also be seen in porphyrias, especially congenital erythropoietic porphyria and porphyria cutanea tarda.[2,3] However, lead intoxication porphyrinuria does not cause red colored urine. These can be excluded in this patient as well.

The most common pathological cause of dark red-colored urine is hematuria. Hemoglobinuria and myoglobinuria may also produce pink, red, or red-brown colored urine. Hematuria can occur with neoplastic and non-neoplastic pathologies affecting the kidney and urinary tract including trauma (eg, injury or calculi). Renal and bladder cancer are 2 important causes of asymptomatic hematuria and should be considered here due to the asymptomatic, episodic presentation, age of the patient, and 50-pack year smoking history. Other causes of hematuria include kidney or bladder infection, glomerular pathology (eg, membranous nephropathy, IgA nephropathy, non-IgA mesangioproliferative glomerulonephritis, focal glomerulosclerosis), and other mild glomerular abnormalities. Glomerular hematuria can be ruled out here due to absence of dysmorphic red blood cells on urinalysis.[3] Patients suffering from bleeding disorders and patients on anticoagulants may also present with episodic hematuria. Hematuria may also be seen in healthy young person undertaking excessive exercise (marathon runners), in whom bleeding originates from the bladder mucosa. Rare parasitic infections of the bladder wall, for example, *Schistosoma haematobium* may also cause hematuria.[2,3]

Hemoglobinuria may be seen in any cause of hemolysis, for example, acquired or hereditary hemolytic anemia, glucose-6-phosphate dehydrogenase deficiency, sickle cell disease; malaria, *Clostridium welchii* toxin, brown spider bite; and certain prescription medications that cause oxidative hemolysis. Massive crush injury may lead to myoglobinuria. All 3 of these conditions are easily detectable on reagent strip testing; however, further evaluation is necessary for absolute differentiation and also exact cause.[3]

Other causes of dark colored (yellow-brown or green-brown) urine include the presence of bile pigments, chiefly bilirubin. On shaking the urine specimen, a yellow foam may be seen, which distinguishes bilirubin from a normal, dark, concentrated urine. Bilirubinuria is unlikely to cause episodic dark colored urine and may be seen along with jaundice, and therefore can be excluded in this patient. Causes of bilirubinuria include acute viral hepatitis, drug-induced cholestasis, acute alcoholic hepatitis, and exposure to potentially hepatotoxic drugs or toxins, where a positive test for bilirubinuria may be an early indication of liver damage. Other conditions like congenital hyperbilirubinemias that may cause dark colored urine can be excluded in this patient.[3]

Based on the clinical picture, a urinalysis is warranted as the next step in management of the patient.

Diagnostic Findings, Part 2

A routine urinalysis with microscopy is done at the physician's office and a urine sample is sent for cytological examination. The results are summarized in Table 1. A renal ultrasound done in the office shows that both kidneys are of normal size with no evidence of any masses or stones.

Table 1. Urinalysis and Urine Cytology Results of the Patient.

Urine Dipstick test Findings	
Test	Patient's findings
Specific gravity	1.015
pH	Acidic
Leukocytes	Negative
Blood/Hemoglobin	Positive
Nitrites	Negative
Ketones	Negative
Bilirubin	Negative
Urobilinogen	Normal
Proteins	Negative
Glucose	Negative
URINE Microscopy	
RBCs	15-20/hpf
WBCs/Pus Cells	Not seen
Casts	Not seen
Crystals	Not seen
URINE cytology	
Atypical urothelial epithelial cells in small clusters of 3-8 cells	

Abbreviations: RBC, red blood cells; WBC, white blood cells.

Questions/Discussion, Part 2

Given the Findings in the Urinalysis, What Is the Most Likely Diagnosis in the Patient?

Urinalysis confirms hematuria, and urine cytological examination reveals suspicious atypical urothelial epithelial cells in small clusters of 3 to 8 cells. The most common presentation of urothelial carcinoma is painless hematuria. Urinalysis with atypical urothelial cells suggests neoplasia of the bladder epithelial lining.

What Would Be the Next Step in Management of a Patient of Suspected Urothelial Cancer?

The patient should be referred to an urologist for further management. Current guideline recommendations suggest imaging and cystoscopy for the confirmation of a suspected urothelial carcinoma. Cystoscopy examination by urologist allows for the visualization of the bladder wall for the identification of either suspicious erythema or papillary lesions. Initial cystoscopy is commonly performed in office with a subsequent follow-up transurethral resection of the bladder tumor (TURBT) performed under anesthesia. Cystoscopy evaluation should elicit information on site, size, number, and appearance of the bladder wall for the lesion under investigation. Computed tomography (CT) urography may be performed for papillary tumors that cause filling defects due to obstruction. Bladder ultrasound may be performed to identify intraluminal masses but should not replace cystoscopy or CT urography. However, since the diagnosis of a bladder tumor cannot be made on imaging alone, cystoscopy is required.[4]

Diagnostic Findings, Part 3

White light cystoscopy shows a single raised red flat, granular, velvety lesion in the lower part of the trigone area. Two more suspicious areas of hyperemia are seen on the posterior wall. A cold cup biopsy forceps is used to take punch biopsy samples from the lesion. Additional biopsies include the hyperemic area samples, left lateral wall, right lateral wall, base, dome, and trigone of the bladder. The prostatic urethral lining appears normal. Computed tomography urogram and abdominal CT scan shows no other lesions in the ureters, renal pelvis, and the rest of the urinary tract. No enlarged perivesicular lymph nodes or other nodes including inguinal, hypogastric, obturator, and external iliac, or presacral lymph node group are noted.

Questions/Discussion, Part 3

What Is the Urologic Diagnosis for the Lesion Observed at Cystoscopy and CT?

The flat, red, velvety, and granular lesions seen on white light cystoscopy suggest carcinoma in situ (CIS). In contrast, papillary lesions have projections of finger-like papillary structures extending from the bladder mucosa into the lumen.[5] Although the CT scan did not reveal any lymph node involvement, it does not rule out local invasion or small nodal metastases. All lesions on cystoscopy suggesting abnormal bladder lining, such as flat red velvety lesions, papillary lesions, or sessile solid lesions, require biopsy and histological evaluation. All adequate urinary bladder biopsies should include muscularis propria to provide assessment of deep invasion.

A provisional diagnosis of bladder CIS is made based on the painless hematuria, urinalysis, cystoscopy, and CT findings, to be confirmed by biopsy.

Describe the Biopsy Findings as Depicted.

There is partial denudation of the bladder mucosa near the edges of the lesion, along with normal mucosa showing reactive changes only and no atypia (Figure 1A). Atypical hyperplastic urothelium with high-grade urothelial dysplasia is seen. Mucosa shows sessile micropapillary folds with intact basement membrane. There is cellular disarray and cellular piling (Figure 1B). Mucosal cells show atypical hyperplastic urothelium (Figure 1C) and large hyperchromatic nuclei, irregular nuclear chromatin, and prominent nucleoli. An atypical mitotic figure is seen (Figure 1D). The basement membrane is intact in all biopsies with no invasion of the lamina propria. No invasion of muscularis propria is seen (not pictured).

Based on the Histology Shown What Is the Patient's Diagnosis?

The histopathology suggests a noninvasive lesion with full thickness cytological atypia and dysplastic changes. Coupled with the cystoscopy findings of mucosal reddening and granularity and based on the histopathology features, a final diagnosis of urothelial CIS (Tis, N0, M0) is made as no lymph node (N) involvement or metastasis (M) are seen.

How Is Pathology Correlated to Staging of the Urothelial Cancer?

TNM classification system proposed by American Joint Committee on Cancer (AJCC) in 2017 for bladder cancers[6,7] is summarized in Table 2. The 2017 revised staging criteria are based on anatomy of progression and predict prognosis more closely. In order to confirm the diagnosis and determine the extent of the disease, a TURBT is done. The goal of TURBT is to resect all of the visible tumor in order to correctly identify the clinical stage and grade of disease and obtain samples that includes bladder muscle.

Noninvasive papillary lesions or Ta (Stage 0a) have a relatively low risk for progression to invasive disease; however, their biologic behavior is dependent on the grade of the papillary lesion.[8] Nearly 75% of the noninvasive papillary tumors detected are Ta (Stage 0a). The rest 25% have invasion into lamina propria or pT1 (Stage I). T1 tumors tend to be friable and therefore bleed easily causing the symptom of hematuria early in the disease. They have a tendency to recur; and
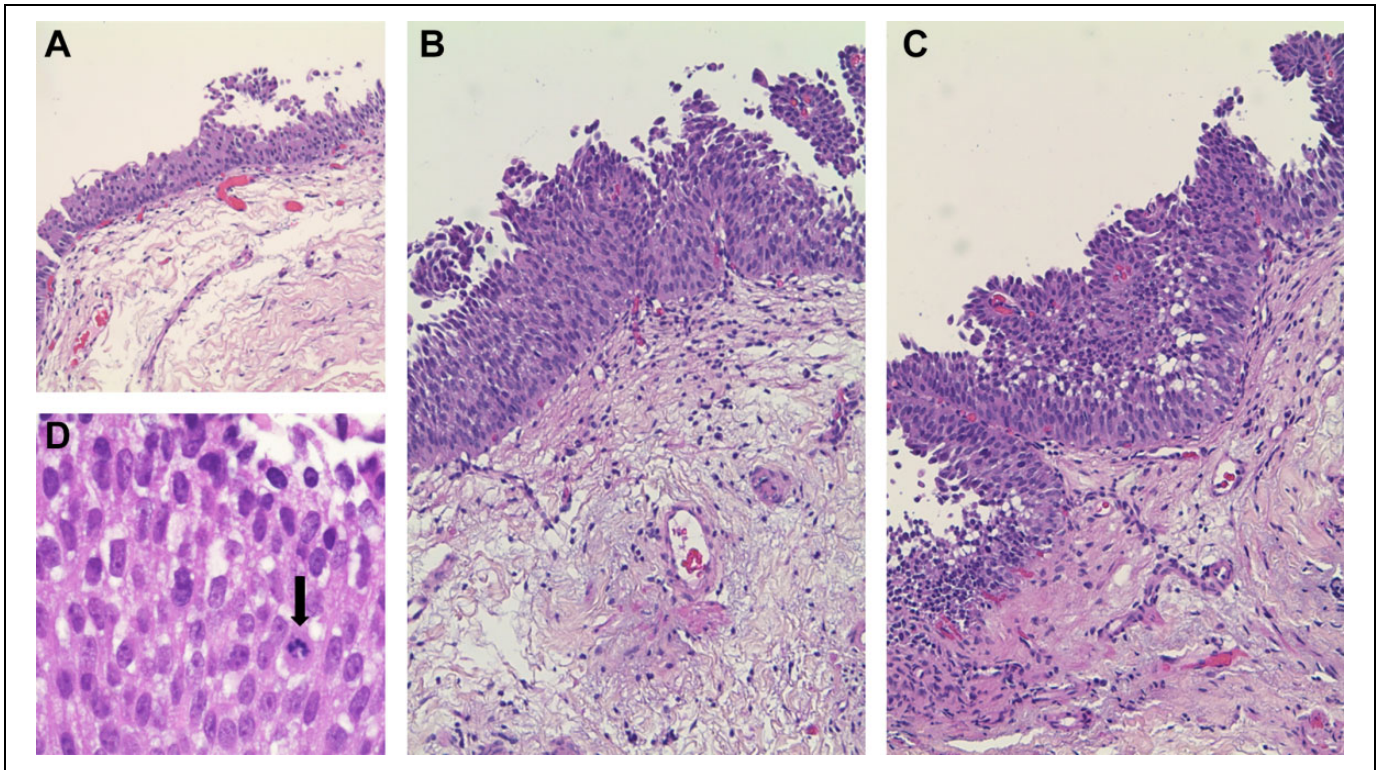
Figure 1. A biopsy of urothelial carcinoma with exfoliation and denudation of the bladder mucosa is shown. The basement membrane is intact in all biopsy samples with no invasion into the lamina propria. A, Shows normal reactive urothelium. There is no cellular atypia in this part of the biopsy. ×10 magnification. B, Shows atypical hyperplastic urothelium with high-grade urothelial dysplasia. There is cellular crowding and atypia. ×10 magnification. C, Shows bladder carcinoma in-situ. The section shows atypical hyperplastic urothelium with high-grade urothelial dysplasia, along with sessile papillary projections. ×10 magnification. D, Shows a higher magnification of carcinoma in-situ, hyperplastic urothelium with vesicular nuclei, prominent nucleoli, along with cellular crowding and atypia. One atypical mitosis is also seen (Arrow) ×40 magnification.

Table 2. TNM Classification System Proposed by American Joint Committee on Cancer (AJCC) in 2017 for Bladder Cancers.

If Tumor is . . .	Node is . . .	And Metastatic invasion is . . .	Then Stage would be . . .
Ta: Noninvasive papillary carcinoma	N0	M0	*0a*
Tis: Urothelial carcinoma in situ: "flat tumor"	N0	M0	*0is*
T1: Tumor invades lamina propria (subepithelial connective tissue)	N0	M0	*I*
T2: Tumor invades muscularis propria	N0	M0	*II*
pT2a*: Tumor invades superficial muscularis propria (inner half)	N0	M0	*II*
pT2b*: Tumor invades deep muscularis propria (outer half)	N0	M0	*II*
T3: Tumor invades perivascular tissue	N0	M0	*III*
pT3a*: Tumor invades perivesical soft tissue microscopically, *pT3b**: Tumor invades perivesical soft tissue macroscopically (extravesical mass), *T4a*: Extravesical tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina	N0	M0	*IIIA*
T1-T4a	N1†	M0	*IIIA*
T1-T4a	N2†, N3†	M0	*IIIB*
T4b: Extravesical tumor invades pelvic wall, abdominal wall	Any N	M0	*IVA*
Any T	Any N	M1a†	*IVA*
Any T	Any N	M1b	*IVB*

* *pTNM*: Pathological Classification: microscopically determined on biopsy and pathology review of resected surgical specimens.
† *N1*: Single regional lymph node metastasis (perivesical, obturator, internal and external iliac, or sacral lymph node); *N2*: Multiple regional lymph node metastasis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis); *N3*: Lymph node metastasis to the common iliac lymph nodes.
‽ *M1a*: Distant metastasis limited to lymph nodes beyond the common iliacs; *M1b*: Non-lymph-node distant metastases, microscopically confirmed.

between 31% and 78% of these tumors will recur, either at the same stage of the initial tumor or at an advanced stage.[9] A flat lesion occupying the full thickness of the mucosal layer (Tis) without basement membrane invasion is considered carcinoma in-situ or Stage 0is by TNM staging. All flat CIS urothelial lesions (Tis) are considered high grade and should be investigated for the characteristic genetic mutations and histopathologic features of nuclear and cellular atypia.[8,10] Histopathologic examination from TURBT of the lesion would show a flat lesion with full thickness cytological atypia and an intact basement membrane.

A T2 lesion is considered invasive because it disrupts the basement membrane and infiltrates the muscularis layer of the bladder wall and is divided into pT2a (tumor invading superficial inner half of the muscularis propria) or pT2b (tumor invading deep, to the outer half of the muscularis propria) based on the extent of muscularis invasion. Invasion of the muscularis decreases the 5-year survival to about 30%, and therefore has prognostic significance and is separated as Stage II. Additionally, the depth of invasion is not only the most important determinant of prognosis, it is also important in treatment of localized bladder cancer. Further, muscle-invasive disease (T2) is defined by the depth of malignant extension into the detrusor muscle, and perivesical tissue involvement defines T3 disease.[6,7] Therefore, cystectomy, rather than TURBT, is the option for differentiating the correct stage II tumors. Extravesical invasion into the surrounding organs (ie, the prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall) delineates T4 disease. The depth of invasion is the most important determinant of prognosis and treatment of localized bladder cancer. T3 and T4 lesions invade perivesicular fat and adjacent structures, and are classified as stage IIIA invasion beyond the bladder wall; and subsequent development of regional (T1-4a) and/or distant metastases (T4b), stage IIIB and IV, respectively.[6,7]

Discuss the Genetic Mutations and Their Correlation With the Pathobiology and Invasive Potential of the Bladder Carcinoma?

Urothelial cancers have 2 distinct types of biological behaviors. According to the "two-pathway theory"; the papillary pathway (70%-75%) includes papillary hyperplasia, which may progress to the low-grade, nonmuscle invasive bladder cancer (NMIBC). Nonmuscle invasive bladder cancer may progress to high-grade papillary lesions or recur but seldom invade the muscularis propria. However about 20% of high-grade papillary NMIBC invade muscularis propria.[8] Invasion into the lamina propria bodes for worse prognosis, however invasion of the muscularis propria (detrusor muscle), leads to a major decrease in survival and reduced (30%) 5-year mortality rate.[8] The nonpapillary pathway, flat dysplasia, and/or CIS (25%-30%), as seen in this patient (Figure 1) are the precursors of most muscle invasive bladder cancer (MIBC) and have a rapid progression and high metastatic potential and a high

mortality.[10] Loss of heterozygosity on chromosome 9p or 9q leading to deletion of *CDKN2A* is the most common alteration and may be seen in both papillary (exophytic) and flat (endophytic) bladder cancer morphology.[11,12] Fluorescence in situ hybridization a molecular diagnostic technique to detect chromosomal del 9p(21) abnormality in urine samples from patients with atypical, suspicious, and negative cytopathology. It is approved by the United States Food and Drug administration and has been shown to have a high sensitivity and specificity and therefore is of value for surveillance or screening of bladder cancer.[13] Studies report that the test is more sensitive than urine cytology for the detection of all stages and grades of bladder cancer.

The papillary pathway is characterized by gain of function oncogene mutation of *FGFR3* which encodes fibroblast growth factor receptor 3 and regulates RTK/RAS/RAF/MAPK and PI3K/Akt/mTOR pathways. *FGFR3* is associated with low recurrence and good prognosis.[10] In a minority of cases, *HRAS* may be mutated instead. Both of these mutations lead to sustained hyperplasia resulting in genomic stable, low-grade, non-muscle invasive tumors. Co-occurrence of telomerase reverse transcriptase mutations are thought to prevent recurrence and protect genomic integrity.[10,14] Loss of *CDKN2A* is seen in over 90% of *FGFR3* mutant papillary tumors, and homozygous deletion of *CDKN2A* leads to high-grade, nonmuscle invasive tumors (Figure 2). High-grade, nonmuscle invasive tumors share some genomic alterations with muscle invasive tumors.[12]

Nonpapillary pathway gives rise to flat lesions that characteristically have loss of function mutations in tumor suppressor genes *TP53, RB,* and *PTEN*.[15] The *TP53* and *RB* mutation positive tumors commonly progress to muscle invasive high-grade urothelial carcinoma.[8] However, even the low-grade urothelial tumors that acquire further mutations, deregulation, or loss of *TP53* and *RB* pathways may lead to progression to higher grade carcinoma.[10-12,14] *TP53* has a central role in muscle-invasive bladder cancer and may occur along with *RB* mutation. Despite the low incidence of *RB* loss, RB1 pathway is dysregulated in large number of tumors and along with *CDKN2A* loss, promotes genomic instability.[10,16,17] *EGFR* family genes may also be overexpressed in high-grade CIS and muscle invasive tumors. *PTEN* downregulation is seen in metastatic disease and loss of both *PTEN* and *TP53* predict poor survival.[10,11,16] Overexpression of many growth factor pathways including epidermal growth factor, vascular endothelial growth factor, and HER2/neu have been identified as prognostically relevant. However, the discussion of all molecular subtypes in relation to prognosis is beyond the scope of this narrative. Minoli et al[10] provide a more complete discussion if additional information is desired.

As suggested by epidemiological data, environmental carcinogens (eg, cigarette smoking, industrial chemicals, DNA altering agents, irradiation, and constant irritation by parasitic infection) have an important role in development of bladder cancers.[8] The high burden of somatic mutations of oncogenes and tumor suppressor genes that include genes involved in cell cycle regulation, chromatin regulation, DNA repair, and
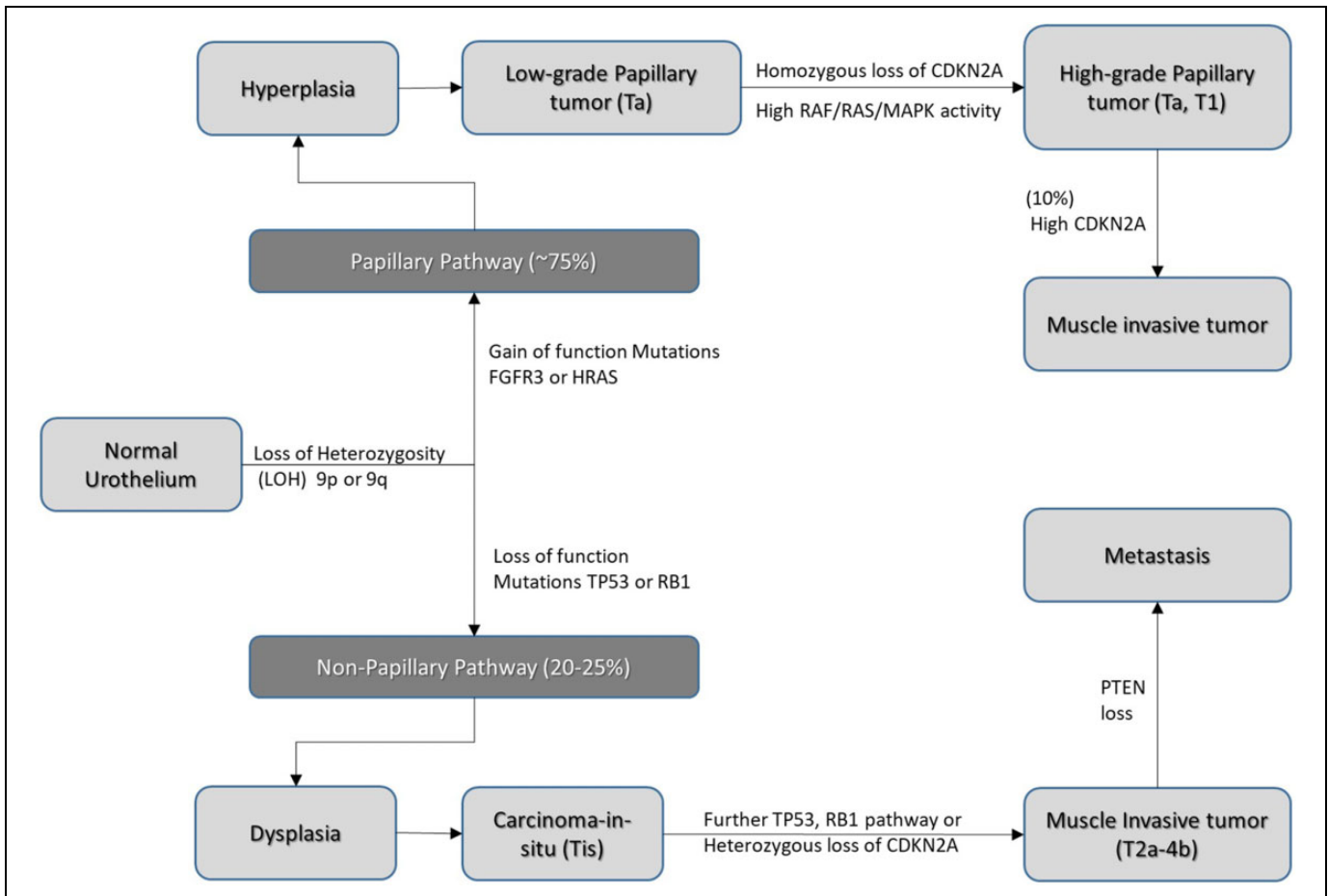
Figure 2. Simplified molecular changes for development of bladder cancer according to the "two pathway," papillary and nonpapillary pathways theory. Of the muscle invasive bladder cancers (MIBC) nearly 50% progress to metastatic disease. Only 10% to 20% of the nonmuscle invasive bladder cancers (NMIBC) progress to muscle invasive tumors. The various molecular changes are shown in the pathway.

growth factor signaling pathways suggest a relationship.[10] Additional ongoing research is looking to fully understand not only their biologic and clinical significance but also identify therapeutic targets to ensure more effective management.

What Is the Relationship of Staging to Prognosis of Bladder Cancer?

The prognosis of bladder cancer closely relates to the staging at diagnosis and largely involves the T-stage of the lesion. The TNM staging system translates to a numbered staging from I to IV (Table 2) which relates to identified 5-year survival rates. Tumors on the TNM staging system identified as superficial (Tis and Ta) or Stage I (T1) both have a 5-year survival rate of over 90%. T2 tumors invading the muscularis propria are equivalent to Stage II tumors with a 5-year survival rate of 70%. Tumors invading through the bladder wall, T3 tumors, equate to a Stage III bladder cancer with a 5-year survival of 35% to 50%. Tumors invading the nearby pelvic structures, lymph nodes, or distant metastasis, TNM Stage T4 or Stage IV, all have a 5-year survival rate of 10% to 20%.[18] Tumor

grade also plays a role in the prognosis of urothelial carcinoma with better prognosis in low-grade tumors. High-grade papillary lesions have a mortality rate of 25%. The majority of lesions remain the same grade postdiagnosis with less than 10% of low-grade lesions reclassified to high-grade or muscle invasive tumors.[10] However, many NMIBC tumors may recur after excision. Up to 75% of high-grade papillary NMIBC (T1) tumors recur with 33% of these experiencing further progression upon recurrence as compared to Ta tumors.[19] Risk factors for progression (and not recurrence) were age <70 years at diagnosis although mortality is high for >70 years of age. T1 tumors, female gender, and black race predicted higher risk of progression and mortality as compared to Ta tumors.[19]

How Does the Staging of the Bladder Cancer Correlate With Management of Bladder Cancer?

The stage of bladder cancer, especially presence or absence of muscle invasion, is one of the most important factors in determining the treatment options. According to the 2020 NCCN Guidelines for urothelial carcinoma, treatment is divided into 2

categories according to nonmuscle-invasive disease (Ta, T1, and Tis) and muscle-invasive disease (≥T2 disease).[9] Management of bladder cancer is based on the findings of the biopsy and TURBT specimens. Attention is given to histology, grade, and depth of invasion. Estimates of probability of recurrence and progression to a more advanced stage are based on these observations. Additional considerations include patient bladder function, comorbidities, and life expectancy at diagnosis.

What Is the Current Management of NMIBC?

Nonmuscle invasive bladder cancer are managed based on a risk stratification done following the TURBT. It relies on tumor stage and size, pathological grade, associated CIS (if any), lymphovascular invasion, or presence of aberrant histology (eg, adenomatoid or squamous cell carcinoma, and so on). The patients are categorized as low (primary, solitary, Ta, LG, < 3 cm, no CIS), intermediate (between the category of low and high risk), or high risk with any of the following (T1 tumor, HG tumor, associated CIS), or all of the following (multiple and recurrent and greater than 3 cm in size Ta low-grade tumors).[4] Low-risk or Low-grade (Ta) stage 0a, NMIBC papillary carcinoma, is treated with TURBT followed by intravesical chemotherapy to prevent recurrence.[20] These patients are treated by a single postoperative instillation of intravesical chemotherapy followed by surveillance for >5 years and normally no adjuvant intravesical treatment. Intermediate risk patients are given a single instillation of intravesical chemotherapy, followed by induction and 1 year of maintenance intravesical therapy with bacillus Calmette-Guérin (BCG) or chemotherapy (mitomycin or doxorubicin). This is followed by life-long surveillance. High-risk patients undergo TURBT in 4 to 6 weeks for restaging. Based on the new stage, the patient is either managed by intravesical BCG or radical cystectomy. High-grade (Ta) stage 0a is treated with TURBT followed by intravesical BCG. Recurrent NMIBC in the same or different location in the bladder is usually treated with the same strategy as the initial tumor. If there are multiple recurrences, cystectomy may be recommended.[20] Stage 0is bladder cancer, flat noninvasive tumor (Tis), is treated with TURBT and BCG therapy. Stage I bladder cancer has invasion into the lamina propria or the subepithelial connective tissue layer. Low-grade stage I tumors are treated with TURBT and risk-based intravesical BCG or chemotherapy. If there is high-grade stage I bladder cancer, or if there are multiple tumors, radical cystectomy is the treatment of choice.[4,9,20]

What Is the Current Management of MIBC?

Management of MIBC is also based on stage and if the patient is a surgical candidate for radical cystectomy. Stage II and III can be managed either with combined cisplatin and radical cystectomy or a combined modality (TURBT and chemoradiation). Stage II bladder cancer has invaded the muscle layer of the bladder wall and is treated with chemotherapy and radical cystectomy, as well as removal of nearby lymph nodes in many cases. Stage III bladder cancer has grown outside of the bladder and into nearby tissues and is treated with chemotherapy followed by radical cystectomy. Radiation therapy may also be used on the tumor or nearby lymph nodes before and/or after the cystectomy. Stage IV bladder cancer has invaded the pelvic or abdominal wall, nearby lymph nodes, or metastasized to distant tissues. The initial treatment is chemotherapy with or without radiation and possibly radical cystectomy. Stage IV metastatic disease treatment is with platinum-based chemotherapy, for example, methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Gemcitabine and cisplatin (GC) can also be used as a second line choice. Checkpoint inhibitors targeting the programmed cell death-1 protein (PD-1) or its ligand (PD-L1) is the preferred option for patients who are refractory to platinum-based chemotherapy regimens. However, Stage IV bladder cancer is difficult to cure so the goal of treatment is mainly to slow the progression of the disease.[9]

Discuss the Basis of BCG Immunotherapy and Its Role in Low-Stage and Recurrent Bladder Cancer?

The BCG vaccine, originally used for tuberculosis, has been shown to decrease recurrence and progression (up to 37% compared to no BCG therapy) of MIBC when compared to chemotherapy. The efficacy of BCG treatment was empirically determined. Intravesical BCG is frequently used in the management of recurrent and superficial urothelial carcinoma and is the most effective therapy.[21,22] Several BCG strains are used and may have variable potential clinical effects on the bladder tumors.[23] Presenting clinical features, tumor stage, and grade are the most important predictors for response to BCG therapy as opposed to markers like FGFR3 or TP53 and so on. The exact mechanism of BCG's antitumor effect is not fully known; however, it induces a stimulation of the immune system. The positive effects of BCG on progression and recurrence come from both a direct effect on tumor cells as well as a robust immune response.[24] There are 3 key steps in the BCG mediated antitumor effect: (1) Bacillus Calmette-Guérin induces expression of fibronectin allowing for the attachment and internalization on tumor cells; (2) This elicits the immune response against the infected cells via macrophages, T-cells, and granulocytes. Bacillus Calmette-Guérin increases the MHC Class I response, enhancing the antigen presentation and antitumor response. Cytokines, including interleukins, TNF-alpha, and IFN, assist in the antitumor process but may also cause adverse clinical responses to BCG instillation; (3) Cell-mediated immunity plays a major role in the overall antitumor effect of BCG via CD4+ and CD8+ T lymphocyte activity. Humoral immune responses have a lesser role in this antitumor activity. Instillations are completed in 3 week increments or longer, allowing adequate time for the immune-mediated effects to take place. Typical treatment courses involve an initial instillation during TURBT followed by scheduled maintenance therapy to prevent or manage recurrence.[21,25] Patients receiving BCG may be divided into 3 groups depending on their response to the induction of therapy including BCG relapse, BCG-

refractory, and BCG-intolerant. Bacillus Calmette-Guérin relapse constitutes recurrence of disease after 3 months for papillary tumors and 6 months after CIS. It may be further considered as early (less than 1 year), intermediate (1 to 2 years), or late (greater than 2 years) following treatment. These patients experiencing relapse are more likely to progress with their disease. Bacillus Calmette-Guérin-refractory patients are defined as persistent disease following an induction course of BCG treatment. Those who are BCG-tolerant are patients who are unable to tolerate one full induction course of BCG. This leads to a high likelihood of tumor recurrence due to the inability to adequately treat but does not have the same prognosis as a true BCG failure. Because of variable responses, other mechanisms of immunotherapy are currently being investigated. As the science progresses, BCG is unlikely to remain as mainstay therapy for bladder cancer treatment.[26]

Teaching Points

- The most common presentation of urothelial carcinoma is painless hematuria. A urine microscopic evaluation showing atypical urothelial cells is suggestive of, but not specific for, neoplasia of the lower urinary tract.
- There are 2 types of urothelial lesions, papillary and flat, arising from 2 different genetic mutation pathways. Gain of function mutations in FGFR3 and HRAS lead to the initiation of the papillary pathway. Loss of function mutations in TP53 or RB1 cause the transformation of normal urothelium along the nonpapillary pathway.
- The TNM staging system is used to stage bladder cancer based and determines the treatment approach. It is based on the degree of tumor invasion (T), extent of lymph node involvement (N), and whether or not the cancer has metastasized (M).
- Overall, low-grade papillary lesions have a 98% 10-year survival rate; whereas high-grade papillary carcinoma has a mortality rate of 25%. Low-grade papillary lesions frequently recur after excision, but less than 10% of cases progress to muscle invasive disease.
- All flat lesions can be considered high-grade tumors, with 28% progressing to muscle invasive disease, and have a 7% mortality rate.
- Low-grade papillary lesions are treated with a diagnostic transurethral resection. Treatment for papillary lesions with high risk of recurrence or progression consists of Bacille Calmette Guerin (BCG) therapy initiated postresection.
- Flat lesions, carcinoma in situ, are all treated with resection and BCG. Tumors invading muscularis propria and tumors that are refractory to BCG treatment are treated with radical cystectomy.
- Bacillus Calmette-Guérin therapy is used in low-grade and localized lesions. Bacillus Calmette-Guérin is an attenuated strain of *Mycobacterium bovis* which causes direct tumor lysis and a chronic inflammatory response to stimulate immune mechanisms to destroy the tumor.

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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. Aycock RD, Kass DA. Abnormal urine color. *South Med J*. 2012;105:43-47.
3. Riley R, McPherson R. Basic examination of urine. In: McPherson R, Pinkus M, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 23rd ed. Elsevier; 2017:442-443.
4. Babjuk M, Böhle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol*. 2017;71:447-461.
5. Lenherr SM, Crosby EC, Cameron AP. Cystoscopic findings: a video tutorial. *Int Urogynecol J*. 2015;26:921-923.
6. Cornejo KM, Rice-Stitt T, Wu CL. Updates in staging and reporting of genitourinary malignancies. *Arch Pathol Lab Med*. 2020;144:305-319.
7. Magers MJ, Lopez-Beltran A, Montironi R, Williamson SR, Kaimakliotis HZ, Cheng L. Staging of bladder cancer. *Histopathology*. 2019;74:112-134.
8. Netto G, MA. The lower urinary tract and male genital system. In: Kumar V, Abbas A, Aster J, Robbins S, eds. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed. Elsevier; 2021:953-983.
9. Flaig TW, Spiess PE, Agarwal N, et al. Bladder cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2020;18:329-354.
10. Minoli M, Kiener M, Thalmann GN, Kruithof-de Julio M, Seiler R. Evolution of urothelial bladder cancer in the context of molecular classifications. *Int J Mol Sci*. 2020;21:5670.
11. McConkey DJ, Choi W. Molecular subtypes of bladder cancer. *Curr Oncol Rep*. 2018;20:77.
12. Meeks JJ, Carneiro BA, Pai SG, et al. Genomic characterization of high-risk non-muscle invasive bladder cancer. *Oncotarget*. 2016;7:75176-75184.
13. Caraway NP, Khanna A, Fernandez RL, et al. Fluorescence in situ hybridization for detecting urothelial carcinoma: a clinicopathologic study. *Cancer Cytopathol*. 2010;118:259-268.
14. Al Hussain TO, Akhtar M. Molecular basis of urinary bladder cancer. *Adv Anat Pathol*. 2013;20:53-60.

15. Knowles MA, Hurst CD. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. *Nat Rev Cancer*. 2015;15:25-41.

16. Fantini D, Seiler R, Meeks JJ. Molecular footprints of muscle-invasive bladder cancer in smoking and nonsmoking patients. *Urol Oncol*. 2019;37:818-825.

17. Isharwal S, Hu W, Sarungbam J, et al. Genomic landscape of inverted urothelial papilloma and urothelial papilloma of the bladder. *J Pathol*. 2019;248:260-265.

18. Hahn NM.Cancer of the bladder and urinary tract. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 20thed, McGraw-Hill Education; 2018.

19. Chamie K, Litwin MS, Bassett JC, et al. Recurrence of high-risk bladder cancer: a population-based analysis. *Cancer*. 2013;119: 3219-3227.

20. 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.

21. Böhle A, Brandau S. Immune mechanisms in bacillus Calmette-Guerin immunotherapy for superficial bladder cancer. *J Urol*. 2003;170:964-969.

22. Kamat AM, Li R, O'Donnell MA, et al. Predicting response to intravesical bacillus Calmette-Guérin immunotherapy: are we there yet? A systematic review. *Eur Urol*. 2018;73:738-748.

23. Mukherjee N, Wheeler KM, Svatek RS. Bacillus Calmette-Guérin treatment of bladder cancer: a systematic review and commentary on recent publications. *Curr Opin Urol*. 2019;29: 181-188.

24. Wołącewicz M, Hrynkiewicz R, Grywalska E, et al. Immunotherapy in bladder cancer: current methods and future perspectives. *Cancers (Basel)*. 2020;12:1181.

25. Fuge O, Vasdev N, Allchorne P, Green JS. Immunotherapy for bladder cancer. *Res Rep Urol*. 2015;7:65-79.

26. Kamat AM, Flaig TW, Grossman HB, et al. Expert consensus document: consensus statement on best practice management regarding the use of intravesical immunotherapy with BCG for bladder cancer. *Nat Rev Urol*. 2015;12:225-235.