MICROSCOPIC HEMATURIA

Gina C. Guzman, MD, DBIM, FALU, ALMI
Second Vice President and Medical Director

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Munich RE

Case Presentation

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60 year male looking for $2,000,000 of Term Life insurance. No admitted medical history. No APS. Review of the lab results reveal:

Blood Urea Nitrogen (BUN)	22 mg/dL	(7.85 mmol/L)
Creatinine	0.8 mg/dL	(70.7 umol/L)

All the rest of the chemistries are normal.

<u>Urinalysis</u>

Heme moderate

RBC = 25 per HPF

WBC = 0 per HPF

Protein/Creatinine = 0.03

Cotinine Heavy

What do you think? What's wrong here? Can you make an offer?

Discussion Questions

Munich RE

What do you think? What's wrong here?

Can you make an offer?

60 year old Male Smoker with Microscopic Hematuria

Microscopic Hematuria: ≥ 3 RBCs per HPF on a UA with microscopy

Gross hematuria: Blood in the urine that can be seen with the naked eye

Discussion Questions

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Are there any clues from this history that suggest a particular diagnosis?

60 year old Male Smoker with Microscopic Hematuria

Risk Factors for Urinary Tract Malignancy in Patients with Microhematuria

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- **Male Gender**
- **Age > 35 years**
- Past or current **smoking** history – risk correlates with the extent of exposure
- Occupational exposure to chemical or dyes (benzenes, aromatic amines)
  - Printers, painters, chemical plant workers
- History of gross hematuria (clots generally lower tract source)
- History of urologic disorder or disease (e.g. chronic cystitis, chronic UTI)
- History of irritative voiding symptoms
- History of pelvic irradiation
- History of exposure to known carcinogenic agents (e.g. cyclosphosphamide)

American Urological Association (AUA) Best Practice Guideline May 2012

Discussion Questions

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What are the most common causes of microscopic hematuria?

Major Causes of Hematuria by Age and Duration

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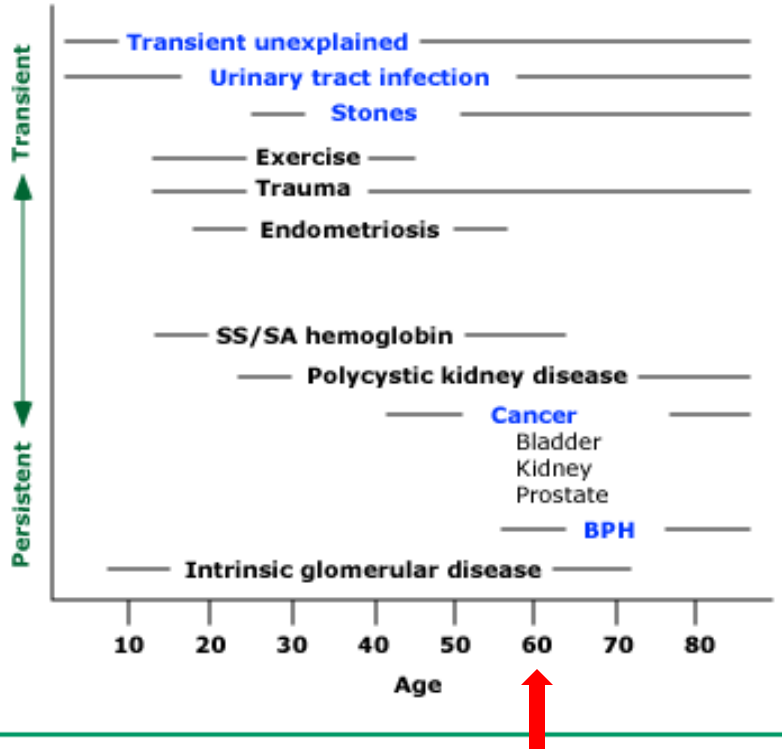
UpToDate.

Major causes of hematuria by age and duration



Schematic representation of the major causes of hematuria in relation to the age at which they usually occur (horizontal axis), transience or persistence (vertical axis), and frequency (blue implies more frequent).
BPH: benign prostatic hyperplasia.

9-15% of normal people have “benign” transient hematuria
(J Urol 1989;141(2):350
JAMA 1986 Jul 11;256(2):224-9)

Causes of Hematuria

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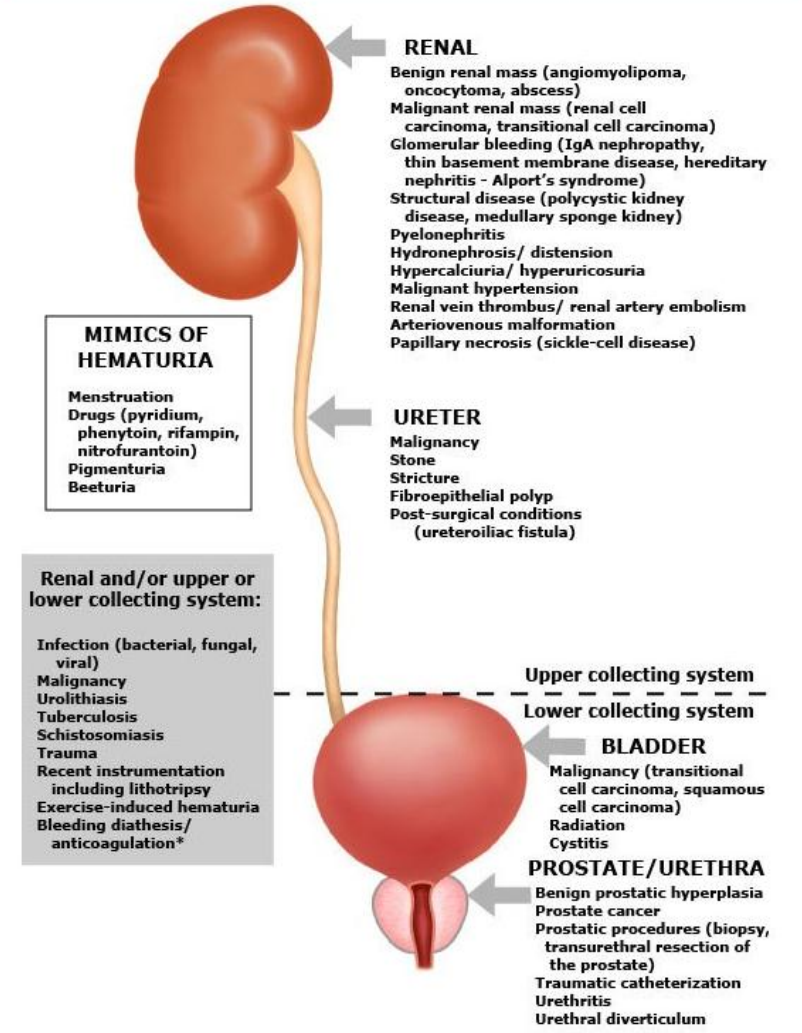
Causes of hematuria



* Hematuria may not be attributed solely to alterations in coagulation or platelet function until competing causes have been ruled out.
Courtesy of Michael Kurtz, MD.

Discussion Questions

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Can an APS or medical history help distinguish between the various causes of microscopic hematuria?

Differential Diagnosis by History

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- Pyuria, dysuria, hematuria – suspect UTI
- Unilateral flank pain – think stones
- Older men with LUTS – think BPH
- Recent URI – possible post-infectious GN, IgA nephropathy
- Recent strenuous exercise – exercise induced hematuria
- Family History of renal disease, hereditary nephritis, PCKD, sickle cell disease
- Bleeding disorder history?
- Medications
- Travel to places endemic for Schistosomiasis or TB?

Case (continued)

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The applicant goes to his physician for evaluation. He is asymptomatic and complete physical exam including blood pressure reading is normal. A repeat urinalysis confirms microscopic hematuria with 50 RBCs per HPF. Urine culture is negative. He is referred to Urology.

What is the appropriate work-up for unexplained persistent hematuria?

American Urological Association (AUA) Guideline

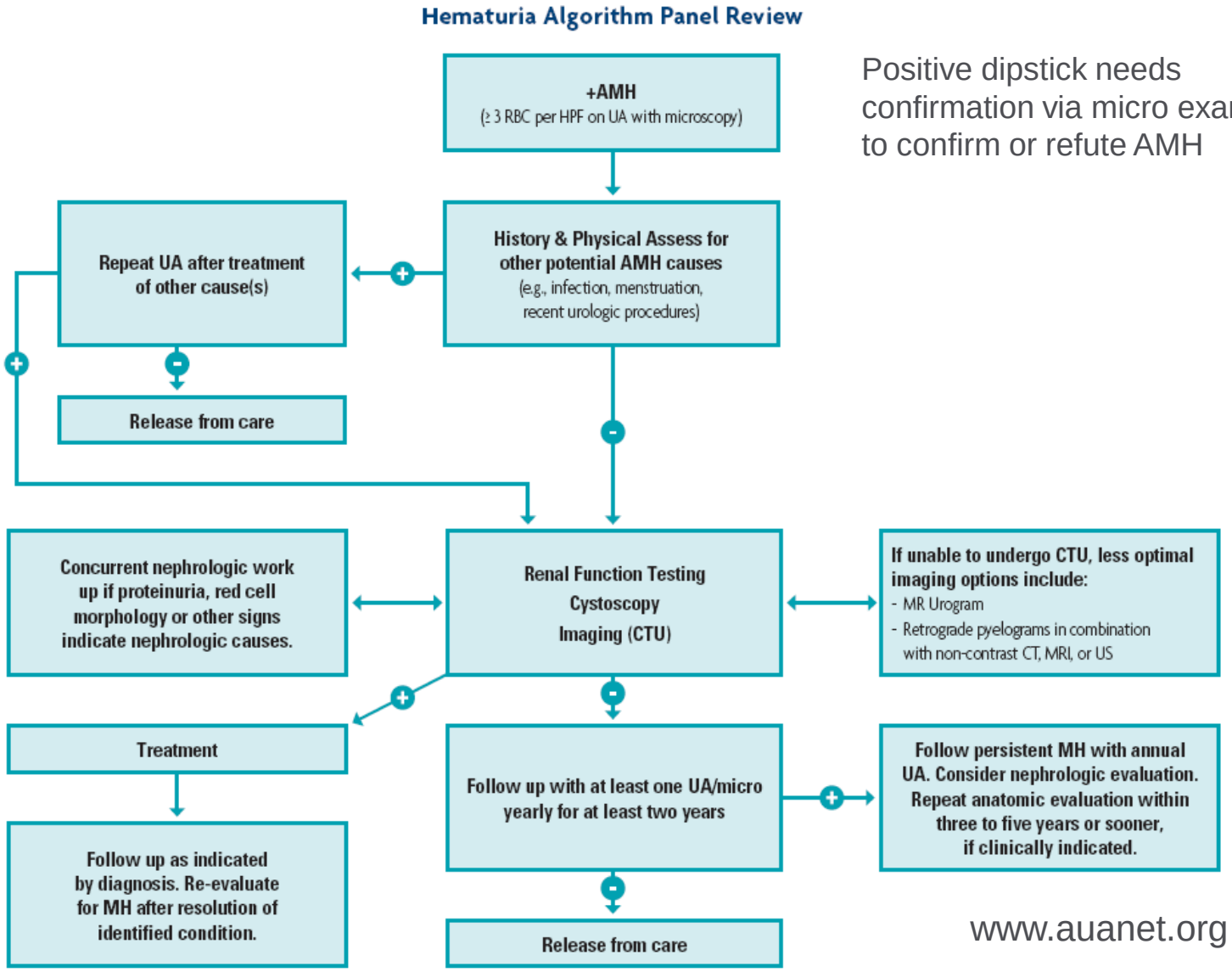
DIAGNOSIS, EVALUATION and FOLLOW-UP OF ASYMPTOMATIC MICROHEMATURIA (AMH) IN ADULTS: AUA GUIDELINE

Rodney Davis, J. Stephen Jones, Daniel A. Barocas, Erik P. Castle, Erick K. Lang, Raymond J. Leveillee, Edward M. Messing, Scott D. Miller, Andrew C. Peterson, Thomas M.T. Turk, William Weitzel

Approved by the AUA Board of Directors May 2012

www.auanet.org

AUA Guideline Algorithm (2012) for Asymptomatic Microhematuria (AMH)



Positive dipstick needs confirmation via micro exam to confirm or refute AMH

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Complete Urological Workup

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- **Urine culture** to r/o UTI
- **Cystoscopy** – gold standard
  - All patients ≥ age 35; physician's discretion for < age 35
  - All patients with risk factors for GU tract malignancies
  - All cases of gross hematuria or blood clots
- **MDCT urography** is the preferred imaging modality vs. IVP
  - Sensitivity 100% vs. 61%
  - r/o tumors of the kidney and evaluate upper tracts
  - 130 patients with renal pelvic cancer, 51% also had bladder cancer (Am J Surg Path 2004;28(12):1545)

Urine Cytology and Biomarkers

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- Urine cytology and urine biomarkers are NOT recommended as part of routine w/u for AMH, but may be helpful for persistent AMH with negative w/u
- **Urine cytology**
  - Consider as an “adjunct” test; less sensitive than cystoscopy (11-76% vs 90+%)
  - Higher sensitivity for high grade TCC bladder and Tis (>90%); false positives are RARE
  - Not great for low grade and upper tract lesions; 65-95% false NEG rate
- **Urine biomarkers** identify proteins, antigens, or genetic alterations associated with cancer cells (over 30 reported for use, only few commercially available)
  - FISH (fluorescent in situ hybridization), NMP-22 (nuclear matrix protein)
  - None have sufficient sensitivity to replace cystoscopy for screening

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May 2012

A single positive urinalysis with microscopy for AMH is enough to warrant a complete urological examination (entire urinary tract).

"Urinary tract conditions that cause bleeding are often 'silent' and present with few symptoms until the disease is advanced or causes more serious symptoms" - Dr. Rodney Davis, panel chair

www.auanet.org

Discussion Questions

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So do these new AUA guidelines mean that every one of our insurance cases that show microscopic hematuria needs to be POSTPONED for this complete urological evaluation?

NO!

MAYO CLINIC

ORIGINAL ARTICLE

Stratifying Risk of Urinary Tract Malignant Tumors in Patients With Asymptomatic Microscopic Hematuria

Ronald K. Loo, MD; Stephen F. Lieberman, MD; Jeff M. Slezak, MS; Howard M. Landa, MD; Albert J. Mariani, MD; Gary Nicolaisen, MD; Ann M. Aspera, MD; and Steven J. Jacobsen, MD, PhD

Objective: To identify patients who could safely avoid unnecessary radiation and instrumentation after the detection of microscopic hematuria.
Prospective cohort study: 2630 patients referred to urologists for full evaluation of AMH (west coast USA)

 ■ Mayo Clin Proc. 2013;88(2):129-138

Results

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- Of 2630 patients, 55 (2.1%) had a neoplasm detected and 50 (**1.9%**) had a pathologically confirmed urinary tract cancer
- Multiple other studies have confirmed low prevalence of urinary tract cancer in those with AMH (0.43%, 5%, 13%)
- Prevalence of urinary tract cancer in the general population is low (0.01% - 3%)

- **Age > 50**, **male sex**, and **gross hematuria** were the strongest predictors of cancer

- **Conclusion:** A considerable portion of patients could avoid extensive evaluations

Major Causes of Hematuria by Age and Duration

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UpToDate.

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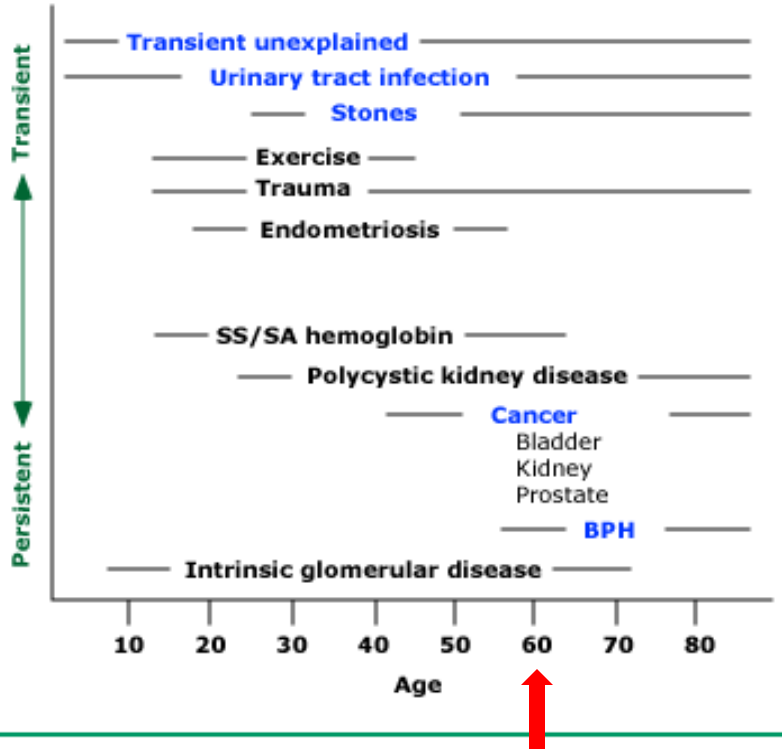

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Case (continued)

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A cystoscopy done in the urologist's office reveals a single small 1 cm papillary lesion. He is scheduled for TURBT (transurethral resection of bladder tumor). Pathology from his TURBT reveals low grade transitional cell carcinoma of the bladder with no invasion of the submucosa or lamina propria. There is no muscular propria present in the specimen.

What is the stage of his bladder cancer?

TNM staging system for bladder cancer

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TNM staging system for bladder cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)*	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Low grade transitional cell carcinoma of the bladder with no invasion of the submucosa or lamina propria

TNM staging system for bladder cancer

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Anatomic stage/prognostic groups			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

Discussion Questions

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Is there any significance with the lack of muscular propria in the specimen?

Importance of Accurate Staging

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- Disease-appropriate therapy is based on accurate staging
- In the **absence of muscularis propria** in the specimen, data suggests 20-40% will either have residual tumor and/or unrecognized muscle invasive disease (J Urol 2001;166;490)
- For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed for re-staging (BJU Int 2006;97:1199)

Bladder Cancer "Numbers"

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- > 73,500 new cases/year in the USA (2012 NCI data)
- ~14,900 deaths/year
- Second most common malignancy of the urinary system (#1 prostate)
- *70-75% nonmuscle invasive*, 20% muscle invasive, 5% metastatic
- 3x M > F
- > 90% are diagnosed in patients ≥ 55 years old
- ≥90% **Urothelial (transitional cell) carcinoma** (TCC) USA/Europe
  - <10% Non-urothelial (SCC (5%), adenoCA (1%), small cell (neuroendocrine), sarcoma, pheochromocytoma, melanoma, lymphoma)
  - *Up to 75% SCC in certain endemic regions for schistosomiasis

Discussion Questions

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Is he considered “high-risk” or “low-risk” for disease recurrence?

How would his risk change if there were multiple papillary tumors?

Risk for Progression (vs. Recurrence)

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- **LOW RISK**
  - Low grade, Stage Ta disease
  - ≤ 3 small lesions (≤ 3 cm), papillary appearance with a thin stalk
  - If recurrent, long interval between recurrences
- **HIGH RISK**
  - High grade, Stage T1 and higher
  - > 3 lesions or any tumor > 3 cm in diameter, sessile, or with thick stalk
  - Incomplete resection
  - Diffuse Tis or Tis associated with papillary tumors
  - Two or more recurrences in a given year

Bladder Tis – a unique subtype of nonmuscle invasive TCC

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- Commonly associated with irritative voiding symptoms (frequency, urgency, dysuria)
- Flat, erythematous, “velvety” lesions, sometimes difficult to visualize
- Can be patchy, diffuse
- Considered *High grade*, non-invasive tumors
- Consider “ominious” due to occult, multicentric nature, difficulty in diagnosis
- The majority are associated with other high-grade nodular tumors (Ta, T1), only 3-5% occur in isolation; > 5% associated with urothelial cancers within ureter/intrarenal collecting system
- **The presence of Tis, especially if diffuse, is associated with a high frequency for recurrence and progression to invasion (up to 83% if left untreated)** J Urol 1995;153:564

Discussion Questions

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What risk factors can he eliminate to decrease his risk of recurrence?

Stop Smoking!

- Cigarette smoke is responsible for 50% of urothelial cancer in both men and women
- Risk correlates with extent of exposure
- Smoking cessation decreases risk, but ^ risk remains even after 20 years (JAMA 2011;306(7);737. Int J Cancer. 2000;86(2):289)
  - > 30% decrease at one to four years
  - 60% decrease at 25 years
- Must encourage all smokers to stop!

Discussion Questions, cont.

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What is the appropriate treatment and follow-up?

Bladder Cancer Treatment

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		Surgery	Intravesical therapy / chemo	
Ta	**Noninvasive** papillary			
Ta Low Grade	Single	TURBT	+/- Single dose intravesical BCG or mitomycin C	
	Multiple or recurrent	TURBT	*Induction* Rx x 6-8 weeks	*+/- Maintenance* over 36 mo (24 mo if mito C)
Ta High Grade	Single	TURBT	*Induction* Rx x 6-8 weeks	*Maintenance*
	Multiple or recurrent	Consider cystectomy	vs. repeat Induction	
T1 +/- Tis	**Invades lamina propria**	TURBT	*Induction* Rx x 6-8 weeks	*Maintenance*
	Multiple or recurrent	Consider cystectomy		
T2	**Invades muscularis propria**	Radical Cystectomy	+/- neoadjuvant cisplatin-based chemo	

Intravesical Immunotherapy and Chemotherapy

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- **Bacillus Calmette-Guerin** (BCG)
  - Live, attenuated strain of *Mycobacterium bovis*, first used as a TB vaccine
  - Widespread use since 1970s
  - Triggers an inflammatory host response, release of cytokines
  - First line treatment for high-grade disease (Ta, T1,Tis)
  - Dose: weekly x 6 weeks, then maintenance over 36 months
- **Mitomicin C**
  - Chemotherapeutic agent
  - Antibiotic that inhibits DNA synthesis
  - Dose: weekly x 8 weeks; then monthly x 1 year

Surveillance Recommendations

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- Absolutely required!
- Recurrent disease can develop ANYWHERE in the GU tract
- Repeat **cystoscopy** with **urine cytology** q 3 months x 1 year, q 3-6 months x 4 years, then yearly, progressively declining as time passes
- **MDCT** q 1-2 years for at least 5 years (assess upper tracts) for low-risk; lifelong for high-risk disease

Case (continued)

He remains compliant with routine bladder cancer surveillance recommendations. At year number two, however, a routine surveillance urinary cytology comes back POSITIVE for atypical cells. Repeat cystoscopy is clear without any visualized lesions.

What are the next diagnostic steps to rule out recurrent disease?

MDCT to assess upper tracts

Biopsy of "normal" urothelium

Selective cath of the ureters with **urine cytology from each ureter**

Urine biomarkers

URINE CYTOLOGY WITH REFLEX FISH REPORT

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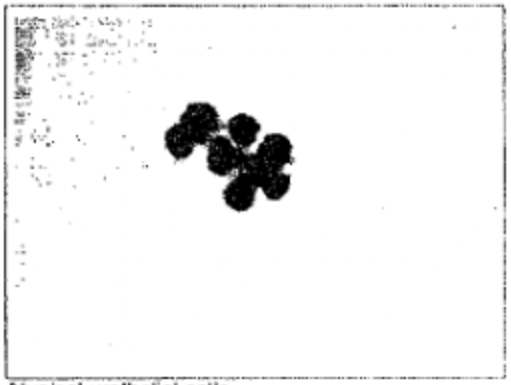
PATHOLOGIST'S ANALYSIS

Cytology Diagnosis:

Urine, Random Void

- **Atypical urothelial cells present(few)**
- **Squamous cells present.**



Atypical urothelial cells

Comments:

ICD-9 Code: 599.71

Gross:

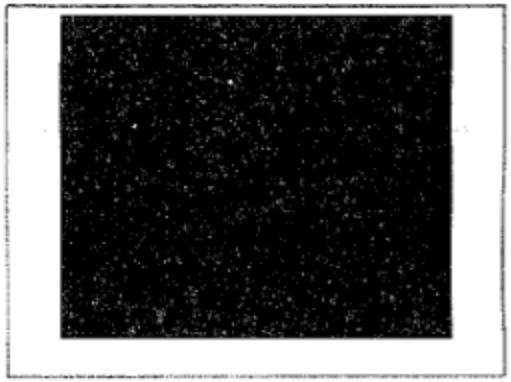
Received is 80 ml yellow fluid of voided urine in one tube with PreservCyt added. The specimen was processed into one slide.

FISH (UROVYSION) ANALYSIS

Result:

- **Negative for aneuploid cells in this urine specimen. 25 or greater urothelial/epithelial cells were evaluated.**

Fluorescent Micrograph:



Discussion Questions, cont.

Munich RE

What if the repeat cystoscopy revealed a recurrent papillary tumor?

If this was removed by another TURBT and the pathology confirmed a similar non-muscle-invasive bladder tumor,

would his prognosis be worse than if this lesion never recurred?

Ta tumors, like all bladder tumors, have a high rate of recurrence after TURBT, but the risk of stage progression, particularly for low-grade papillary Ta tumors, remains LOW (less than 5%) Urol Clin North Am 1992;19:435