NYU Langone Health

Department of Urology Case of the Month

Carcinoma in Situ of the Bladder

CASE PRESENTATION

Prior to referral to NYU Langone, a 65-year-old male presented to an outside urologist with severe urinary urgency and urge incontinence refractory to medical therapy, resulting in the need to wear diapers. His urine cytology was negative, but his fluorescence in situ hybridization (FISH) analysis was positive. He underwent in-office cystoscopy, with "suspicious findings." White light cystoscopy (Figure 1) and random bladder and prostatic urethral biopsies were performed under general anesthesia. All biopsies were negative for any malignancy. The patient also had negative CT and MRI urograms. He denied any history of hematuria, dysuria, kidney stones, flank pain, or any other genitourinary surgeries. His father had prostate cancer. The patient's PSAs were normal. He tried multiple anticholinergic medications and alpha blockers, with no change in his urgency. He had COVID-19 in March 2020, with worsening of his urinary symptoms at that time.

The patient was referred to NYU Langone—Brooklyn for a second opinion.

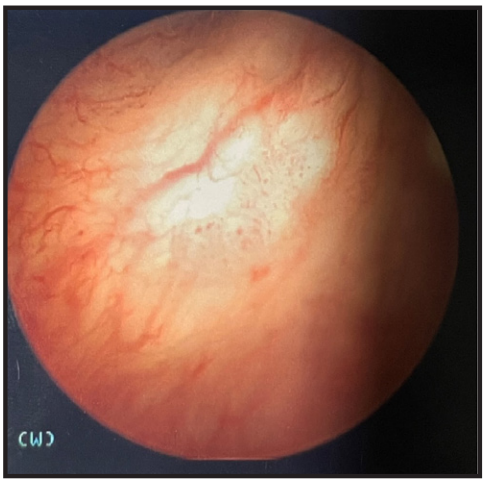

Figure 1. White light view of right lateral bladder wall.

MEDICAL HISTORY AND PHYSICAL EXAMINATION

- **Past medical history:** coronary artery disease with cardiac stents, atrial fibrillation, hypertension, type 2 diabetes mellitus, and thrombocytopenia
- **Past surgical history:** cardiac catheterization, cholecystectomy, cardiac artery bypass graft x3 vessels and then 2 cardiac stents, retinal detachment surgery
- **Social history:** never smoker
- **Review of systems:** noncontributory

- **Medications:** ASA 81 mg, glipizide 10 mg, labetalol 200 mg, metformin 1000 mg, Xarelto 20 mg, silodosin 8 mg, torsemide 20 mg and Vascepa 1 g
- **AUA symptom score:** 22
- **Quality of Life (QoL) score:** 5
- **Sexual Health Inventory for Men (SHIM) score:** 5
- **Physical examination**
  - Blood Pressure: 132/76
  - Heart rate: 87
  - Height: 5' 8"
  - Weight: 248 lb (112.5 kg)
  - Head, eyes, ears, nose, and throat (HEENT): normocephalic, pupils equal and reactive to light and accommodation (PERLA), extraocular movements intact (EOMI)
  - Neck: no masses, normal range of motion, no thyromegaly
  - Abdomen: obese with large pannus and no organomegaly, soft, not tender and not distended, no masses, + reducible left inguinal hernia
  - Back: no costovertebral (CVA) tenderness
  - Genitalia: uncircumcised penis with normal foreskin, glans, and meatus; testes both descended, with no masses or tenderness; prostate enlarged at 50 grams, no nodules, symmetric, and not tender
  - No rectal masses
- **Laboratory values**
  - Urinalysis: 3+ glucose, trace + blood, negative nitrite and trace leukocytes; microscopic examination showed 0-2 RBC/HPF, 5 WBC/HPF, with few bacteria and epithelial cells
  - Urine cytology: suspicious for malignant cells; favor high-grade urothelial neoplasm

MANAGEMENT

Because of the positive bladder cytology, blue light cystoscopy was performed (Figure 2).

Cysview (hexaminolevulinate HCl) was instilled in the bladder 1 hour prior to the surgery. Under white light, there was a red velvety area on the left lateral wall suspicious for tumor. Following blue light visualization, there was subsequent enhancement of the lesion, which was resected. Under white light inspection, the remainder of the bladder was normal. However, the right lateral wall had a suspicious area that turned pink on blue light imaging. The suspicious area was then mapped in blue light and resected in normal white light. The specimens were sent as tumor. Then, deep resection biopsy of the right prostatic urethra was performed x2 and sent as separate specimens. After the resection, blue light visualization confirmed the suspicious area had been completely resected. The edges and base of the bladder resection were fulgurated, with excellent hemostasis. The ureteral orifices were both lateral and were effluxing clear urine after the resection. It should be noted that on blue light cystoscopy, none of the suspicious areas coincided with the prior clearly visualized random biopsy sites. The patient tolerated the procedure well and was transferred to the post-anesthesia care unit (PACU) in stable condition.

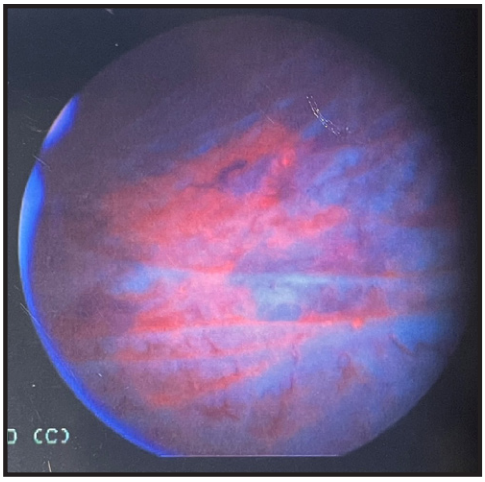

Figure 2. Blue light cystoscopy image of right lateral bladder wall.

FINAL DIAGNOSIS

The final pathology showed:

1. Bladder, right lateral wall, transurethral resection
   - High grade urothelial carcinoma, suspicious for superficial lamina propria invasion
   - Urothelial carcinoma in situ (CIS)
   - Muscularis propria present and uninvolved by tumor
2. Bladder, left lateral wall, transurethral resection
   - Denuded urothelial mucosa with cystitis cystica and chronic inflammation
   - Muscularis propria present
3. Prostatic urethra, transurethral resection
   - Benign fibromuscular tissue, urothelial mucosa not present

Note: The neoplastic cells were positive for GATA3 (performed on B1). Parts 2 and 3 were reviewed at the genitourinary pathology conference on January 12, 2021, with consensus opinion reflected in the diagnoses above.

FOLLOW-UP

After adequate healing, the patient was placed on TICE BCG 50 mg intravesical weekly for 6 weeks and he tolerated the treatment well. Three months after the Bacillus Calmette-Guérin (BCG) instillations, the patient again underwent blue light cystoscopy and bladder biopsies, which showed no recurrence of the CIS of the bladder. He is currently receiving maintenance therapy with BCG per AUA guidelines. Three months after he finished the 6-week induction phase of BCG, his urgency and urgency incontinence disappeared.

COMMENT

The American Cancer Society's estimate for bladder cancer in 2021 is 83,730 new cases, predominating in men, with 64,280 cases compared to 19,450 cases in women, and about 17,200 deaths, again predominating in men, with 12,260 deaths compared to 4,960 deaths in women. Bladder cancer is the fourth most common cancer in men. Nine out of ten cases of bladder cancer occur in individuals over the age of 55, with the average age at diagnosis at 73 years. The chance that a male will develop bladder cancer over his lifetime is 1 in 27, compared to 1 in 89 in women.[1] Caucasians have a higher incidence of bladder cancer than African Americans or Hispanic Americans. Risk factors for bladder cancer include smoking, industrial chemical exposure to aromatic amines, use of pioglitazone (Actos), aristolochic acid dietary supplement, arsenic in drinking water, and chronic bladder irritation from catheters, stones, schistosomiasis, and pelvic radiation.[2] Non-muscle invasive cancers account for about 50% of all bladder cancer.[1] Traditionally, bladder cancer is diagnosed with a combination of urinalysis, white light cystoscopy, imaging with CT scan pre and post contrast, and a delayed urogram. Blue light cystoscopy has been shown to assist in the detection of non-muscle-invasive bladder cancer.

After bladder instillation, Cysview interacts with the heme biosynthetic pathway of rapidly proliferating malignant cells, causing an intracellular accumulation of photoactive porphyrins (PAP). This preferential accumulation does not occur in normal cells. After instillation of Cysview in the bladder for 1 hour, there is sufficient accumulation of PAPs. Under blue light illumination between 375 nm and 440 nm, the neoplastic cells fluoresce a bright pink. This enhanced visualization of the tumor tissue not only can improve detection but also can allow for a complete resection of all of the malignant tissue.[3] In Daneshmand et al., 26 of 63 patients (41%) confirmed to have CIS, the CIS was detected only by blue light cystoscopy in 9 of the 26 (34.6%).[4] In a meta-analysis of photodynamic diagnosis of non-muscle-invasive bladder cancer, Burger et al. found that blue light cystoscopy enabled the detection of 40.8% more CIS lesions and that in 26.7% of the patients CIS was detected only by blue light cystoscopy. This meta-analysis concluded that hexaminolevulinate blue light cystoscopy significantly improved the detection of bladder tumors and thus reduced recurrence of the non-muscle-invasive bladder cancer at 9 to 12 months.[5] As a result of these overall findings, the AUA guidelines now recommend the use of blue light cystoscopy in the management of non-muscle-invasive bladder cancer.

Cysview is approved for use with the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) System as an adjunct to white light cystoscopy.

Cysview should not be used in patients with porphyria, gross hematuria, or known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid. False positive fluorescence can occur in the setting of inflammation, infection, cystoscopic trauma, scar tissue, previous bladder biopsy, tangential imaging of the bladder wall, and recent intravesical immunotherapy or chemotherapy.

FINAL THOUGHTS

Blue light cystoscopy with hexaminolevulinate bladder instillation enhances the detection and resection of bladder cancer. In particular, it significantly enhances the detection of CIS missed by traditional white light cystoscopy and bladder biopsies, as in the patient discussed here, and should become part of the armamentarium of the urologist.

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