

Integrative Tumor Board: Transitional Cell Carcinoma of the Bladder

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Case Review

- In this case, we are presented with a 70 year old male retired insurance executive, 35 pack-year smoker, with no other environmental exposure risks, but with a history of lithotripsy for renal stones, and with non-invasive papillary transitional cell carcinoma (TCC) in the right ureter and bladder (at least 2 sites). The patient presented with hematuria, right flank pain, urinary urgency and dysuria.
- Bladder biopsy has been obtained, the right ureter has been stented, and imaging studies (CT and bone scan) show right adrenal prominence and a questionable nodule in the bladder dome. Renal function studies are normal, but with suggestion of right collecting system obstruction. Right total nephrectomy has initially been recommended.

Background

- About 5% of all urothelial cancers develop in the upper urinary tract, in the ureter or renal pelvis. 40-70% of these tumors appear to be associated with cigarette smoking (1).
- Occupational carcinogens (e.g. aniline dyes), analgesic abuse, stone disease, and Balkan nephropathy are considered additional risk factors. Cytogenetic studies revealed that the most frequent aberration is the partial or complete loss of chromosome 9 (2;3).
- Approximately 20-50% of patients with upper urinary tract (UUT) TCC have bladder cancer at some point on their course, whereas the incidence of UUT TCC after primary bladder cancer is 0.7-4%. Grade and stage of the disease have the most significant impact on survival (4).

Smoking

- There is convincing evidence that cigarette smoking status, frequency and duration substantially increase the risk of urothelial cancer (5;6) . Certain individuals are now thought to have genotypes which increase their risk for urothelial cancer after tobacco exposure (7).
- One meta-analysis found suggestive evidence that continued smoking constitutes a moderate risk factor for recurrence and death, and that stopping smoking could favorably change this (8). The current patient should be counseled to avoid further active or passive smoking.

Imaging

- Correct tumor staging is imperative for proper treatment planning for this patient. This patient has received appropriate conventional imaging. However, does he have only local disease, multifocal disease, or metastatic disease? What is the nature of the “prominent” right adrenal gland? Are any lymph nodes normal by size criteria, but yet involved with tumor?
- Few studies have addressed the role of FDG-PET (positron emission tomography) in bladder cancer. Because of its renal excretion, FDG has not been a useful tracer for the detection of primary bladder tumors.
- However, PET scans can be useful for identifying sites of disease not found by conventional imaging, In particular, PET may identify unsuspected pelvic, para-aortic, mediastinal, or supraclavicular nodal metastasis, sometimes sparing the patient inappropriate surgery.
- In urothelial cancer, the role of PET is still being defined, but it has a high positive predictive value and can be used for problem solving in patients with indeterminate findings on conventional imaging (9).
- Based on our own experience with over 30 PET scans in patients with transitional cell carcinoma, we would encourage this patient to have a PET scan to better stage his disease -- even though PET is currently expensive and not reimbursed by Medicare. The main focus would be on defining unknown sites of disease outside the bladder or ureter.

Urological Surgery

- The current standard treatment of transitional cell carcinoma of the ureter in patients who have a normal contra lateral kidney is nephroureterectomy with removal of a cuff of bladder. (10). Removal of the entire ureter and bladder cuff is considered to be important because if a stump of ureter is left as many as two thirds of patients will have recurrence in the stump. (11). Such recurrence can be difficult to detect unless retrograde pyelography or ureteroscopy is done. (12).
- Fortunately, tumors occur concurrently on the opposite side in less than 2% of these patients, (13) but all who have upper tract transitional cell carcinoma need to be followed closely for subsequent bladder cancer which will occur in one third to one half of patients (10;11).
- With advances such as improved ureteroscopy, laser surgery, and the advent of more effective topical treatments, the standard treatment of nephroureterectomy is being challenged. (14). Key in the decision to use less aggressive surgery is the location, grade, and stage of tumor. (15). Location is important because these

tumors tend to “seed” downstream. Recurrence in the lower ureter or ureteral stump and bladder is frequent, but higher recurrence is not. Therefore, the distal ureter may be resected with the expectation of good results, but resection of a section of proximal ureter is not done.

- Tumor grade was not specified in this patient. The results of endoscopic resection of low-grade tumors, which are almost invariably papillary and non-invasive, is good. High-grade tumors carry a much worse prognosis, and are more likely to have a flat configuration, invade, metastasize, and have associated carcinoma in situ. The muscular wall of the ureter is very thin when compared with that of the bladder. Invasion of muscle is therefore more dangerous in the ureter, so tumors that are high grade or lamina-propria invasive are best treated with standard nephroureterectomy.
- Assuming this patient had a noninvasive, low grade tumor in the distal ureter and a low grade bladder tumor near the ureteral orifice, less-aggressive surgery should be at least considered. One option would be to resect the bladder tumor and ureteroscopically biopsy and fulgurate or cauterize the base of the tumor with electrocautery or laser. I like to do an excisional biopsy of the ureteral orifice as well, which will result in vesicoureteral reflux. With multifocal transitional cell carcinoma the patient would then be a candidate for intravesical therapy to reduce the risk of tumor recurrence. With reflux such topical therapy would also benefit the lower ureter. A single postoperative dose of chemotherapy such as Thiotepa 30mg in 15cc reduces seeding at the time by 20% (16).

Immunotherapy

- Currently the most effective treatment for superficial bladder cancer is immunotherapy with Bacillus Calmette-Guerin. Comparative randomized clinical trials have shown BCG to be superior to chemotherapy (17), and unlike chemotherapy, BCG also reduces the risk of disease progression (18). Maintenance BCG using instillations weekly for 3 weeks at 3, 6, 12, 18, 24, 30 and 36 months following the standard 6 week induction is shown to be superior to induction alone, and in patients with papillary transitional cell carcinoma 75% of patients would be expected to remain free of tumor recurrence for 10 years (19).
- The efficacy of BCG can be significantly improved with the addition of high dose vitamins. In my double-blind randomized clinical trial comparing recommended daily allowance vitamins versus RDA plus high doses of vitamins A, B6, C, E and Zinc (Oncovite, Mission Pharmacal) tumor recurrence was reduced by a highly significant 40% with Oncovite in patients receiving BCG (20). The benefit was highest in patients who had low grade, noninvasive tumors, but was also evident in patients with high grade disease. O'Donnell (personal communication) has recently confirmed the benefit of high dose vitamins in patients given combination BCG and interferon as well.

Chemotherapy

- Although superficial urothelial cancer can often be controlled by local surgery and immunotherapy, disease spread to nodes outside the pelvis, or to distant organs, has generally been incurable. However, combination chemotherapy has proven of benefit in palliating symptoms and prolonging survival in responding patients with advanced disease (21).
- In general, about 65% of patients treated with advanced disease have >50% tumor shrinkage, and about 15% have complete disappearance of disease with multi-year survival. Further, newer drug combinations using the agents cisplatin, gemcitabine, and paclitaxel are proving effective with less toxicity (22).
- Similar to the proven benefit of adjuvant chemotherapy in breast and colon cancers, recent data suggest survival benefits from brief, peri-operative courses of chemotherapy in urothelial cancer (23).

Follow Up

- Because of the propensity of patients with urothelial cancer to have disease relapse and multifocality, they need lifelong periodic follow-up with interim history, physical examination, urine cytology, cystoscopy, and other appropriate studies (24).

Summary

- The current patient needs to finalize tumor grading and staging to assess how much urothelium is affected by the cancer and to thoroughly exclude muscle invasive disease, early lymph node involvement, or metastases.
- If his disease is focal and superficial within the urothelium, primary treatment could be transurethral resection and topical immunotherapy, administered into the bladder and ureters.
- If disease penetrates muscle in the ureter or bladder, or if there is any evident pelvic nodal involvement, perioperative chemotherapy and surgical resection should be considered.
- If metastatic disease is documented and the patient has adequate organ function and is not too debilitated, initial multi-drug chemotherapy would be standard, often with need for concurrent nutritional support. A three-to-six week trial of chemotherapy is usually sufficient to see if the tumor will respond. If the patient has advanced disease but responds nicely to chemotherapy, he could be treated to “best response” then followed in remission. There is an approximately 15% cure rate with chemotherapy.

- If the patient does not respond to chemotherapy within six-to-eight weeks, the tumor is likely resistant to the drugs chosen and the treatment should stop or possibly change to other drugs.
- No matter what the tumor stage or primary treatment used, the patient should stop smoking, have careful follow-up, and consider lifestyle and nutritional measures as discussed here by other contributors.

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