Bladder cancer will grow anywhere: report of a urothelial carcinoma drop metastasis to the vagina and literature review

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Urothelial carcinoma is the 2nd most common cancer of the urinary tract and accounts for the majority of cases of bladder cancer. Metastases are not infrequently encountered, increasing with disease stage and are most commonly seen in the bones and lungs. Many other sites have been described including the omentum, liver, and ovaries. An extremely rare site of metastatic disease however is within the vagina. Here we present a case of a probable vaginal "drop metastasis" from previously treated urothelial carcinoma in the ureter and bladder.

Key Words: urothelial carcinoma, bladder cancer

Introduction

Urothelial carcinoma (UC) is the 2nd most common cancer of the urinary tract and will account for an estimated 16,390 deaths in the United States this year[1] and represents 90% of the cases of bladder cancer.[2] Approximately one quarter of patients present with metastases to either regional lymph nodes or distant sites.[2] Recurrence rates, whether local or distant, are very high, reinforcing the need for surveillance many years beyond primary treatment. While metastases most often occur in the bones or lungs,[2] UC has the ability to metastasize almost anywhere, with documented cases including the liver, ovary, uterus, vagina, omentum, submandibular gland, and skin.[3,4] Recurrences from intraoperative tumor spillage have also been reported, lending to the adage, "Bladder cancer can grow on carpet". Here we report the 8th case of UC spreading to the vagina via implantation from presumed urine pooling.

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Case report

An 86-year-old female with a history of urothelial carcinoma (UC) presented to the emergency room (ER) with vaginal bleeding in July 2015. She had a history of high grade urothelial carcinoma of the left ureter, treated with left nephroureterectomy in 2002. She was found to have synchronous non-invasive low grade UC and carcinoma in situ (CIS) of the bladder, and as such underwent BCG therapy. Surveillance was unremarkable until 2009 when she was noted to

have redness of the bladder. Biopsy was negative, but washings were positive for right upper tract high grade urothelial carcinoma, which was successfully treated with BCG/Interferon a-2b x 6. For the next 6 years, she continued to have normal surveillance studies. In 2014 she had a positive fluorescence in situ hybridization (FISH) test (23/25 abnormal nuclei) and cytology showed rare atypical urothelial cells. Cystoscopy was negative, so she was continued on routine surveillance.

In the ER, she reported vaginal spotting for a few months that had become more persistent recently, however she denied hematuria. She had not experienced vaginal bleeding since menopause at age 52. She reported urinary incontinence, though no continuous leakage suggestive of a vesicovaginal fistula. Cystoscopy and a CT urogram showed no abnormalities or evidence of fistula. Repeat cystoscopy and CT urogram 3 months later were again negative, however vaginoscopy showed papillary appearing lesions on the posterior vaginal wall, Figure 1. At that time, her urine cytology returned with "atypical cells" and FISH was positive (14/25 abnormal nuclei). She was referred to gynecologic oncology where a vaginal biopsy was performed and showed metastatic non-invasive high grade papillary UC carcinoma that appeared as "droplets" in the vaginal canal. The cells were strongly staining for the transcription factor GATA3 confirming the diagnosis of metastatic urothelial carcinoma.

Given her recurrent disease within the vagina, she had multiple treatment options. The lesions represented metastatic disease, though not by the conventional definition. Options, including radical surgery were discussed, as were more creative solutions. She opted for a less invasive treatment course and first underwent laser ablation of several small (2 mm-3 mm) polypoid vaginal lesions on the sidewall and apex of her vagina. Most recently she finished the six treatments of local chemotherapy via a docetaxel soaked tampon inserted vaginally for 60 minutes. Follow up cystoscopy showed new flat red patches in the bladder while concurrent vaginoscopy showed new papillary lesions on her vaginal wall, Figure 1. Biopsies were CIS of the bladder and high grade noninvasive urothelial carcinoma of the vagina. She was recently restarted on local chemotherapy with intravesical gemcitabine plus docetaxel, to reduce any chance of continued seeding from her bladder, and intravaginal docetaxel.

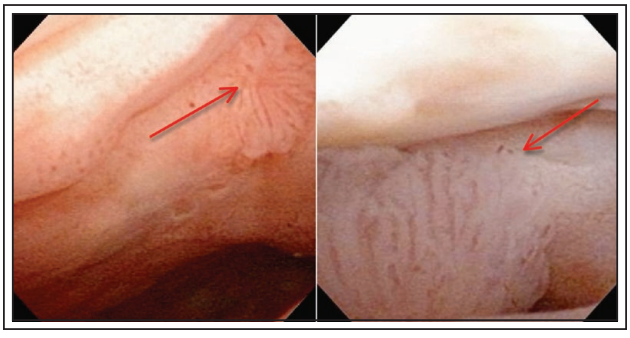

Figure 1. (Left) Papillary growth (arrow) on vaginal wall on initial vaginoscopy and (Right) papillary growth seen on vaginal wall (arrow) on follow up vaginoscopy. Both were confirmed to be high grade urothelial carcinoma upon resection.

Discussion

Metastatic UC to the vagina is exceedingly rare with our report representing the 8th case of vaginal implantation of UC. Furthermore, only 15 prior cases of metastatic vaginal UC have been reported within the literature. The pathogenesis of implantation was first described by Noordzij et al[5] when he described shed tumor cells infiltrating downstream tissues outside of their normal territory. Frequent instrumentation, including surveillance cystoscopy, intravesical therapy, and transurethral resection of bladder tumor (TURBT) are thought to contribute to many of the cases.[3,6] Others have suggested it may be the result of voiding dysfunction, urine pooling due to labial adhesions[7] or sequela from excision of a urethral tumor.[3]

Implantation of UC is well accepted within urology. The instillation of mitomycin C into the bladder following TURBT is standard of care and is performed in an effort to prevent reimplantation of floating tumor cells. Therefore, it follows that women who experience pooling of urine within the vagina and who have concurrent UC, may be at risk for implantation of tumor cells within the vagina. Our patient had normal vaginal anatomy, but suffered from chronic urinary incontinence, likely resulting in mild pooling and frequent contact of urine with her vaginal epithelium, suggesting a possible mechanism by which spread occurred. There was no evidence either clinically or radiographically of a vesicovaginal fistula.

The presentation of UC within the vagina has ranged from isolated urothelial tumors to those surrounded by diffuse bladder type urothelial cells covering the typical squamous cells of vagina.[3,8] In addition, there have been six reports of primary vaginal UCs.[6] Implantation of such tumors have led some to speculate that since both urothelium and mullerian epithelium are derived from the urogenital sinus, the vagina may provide a unique atmosphere where UC may be able to spread in a "drop" metastasis fashion.[8]

TABLE 1. **Cases of vaginal metastases due to "drop" implantation**

Case	Author	Age at diagnosis	Initial presentation	Tumor grade	Years to vaginal metastasis from initial presentation	Vaginal presentation	Vaginal UC grade	Vaginal recurrence	Time to vaginal recurrence
1	Noordzij et al	73	bladder	high grade	9	physical exam	high grade	no	none
2	Ralph et al	70	bladder	high grade	14	vaginal bleeding	"invasive, poorly differentiated"	yes	18 months
3	Kasai et al	81	bladder/ urethra	high grade	1	vaginal bleeding	high grade	unknown	unknown
4	Okada et al	57	bladder	high grade	17	vaginal bleeding	"invasive G3"	yes	unknown
5	Mondaini et al	72	bladder	high grade	8	physical exam	high grade	yes	24 months
6	Ogiso et al	81	bladder	high grade	7	physical exam	high grade	yes	16 months
7	Ohgaki et al	68	renal pelvis	high grade	3	CT	high grade	unknown	unknown
8	This case	73	ureter	high grade	13	vaginal bleeding	high grade	yes	4 months

Metastatic spread via lymphatics or vasculature accounts for only three of the recorded vaginal UC cases.[3] The outcomes of these were worse as they included multiple metastases or highly invasive tumors.[9] Other reports have found synchronous UC within the urinary tract and vagina.[3] Most women with vaginal metastases present well after UC within the bladder (average – 9 years) and recurrence is common, often occurring within the first 18 months, Table 1. While direct extension of UC into the vagina is not uncommon, spread in the fashion described here is, but does highlight the importance of a pelvic exam in women with a history of bladder cancer, especially those with symptoms of recurrence.

Conclusion

Our report of a vaginally implanted UC represents the 8th such case within the literature and highlights the resilience of UC. Our patient's chronic incontinence supports an implantation theory, especially in light of her recently positive urine cytology and FISH studies. While this presentation is rare, our findings accentuate the importance of a thorough pelvic exam in females with a history of UC and substantiate the claim that "Bladder cancer can grow on anything". □

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