Secondary mucinous carcinoma of the prostate after low dose rate brachytherapy

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Radiation induced malignancy (RIM) after treatment for prostate cancer is well documented after external beam irradiation, but less so in the setting of brachytherapy. We report a case of mucinous adenocarcinoma of the prostate, consistent with a RIM, which developed 12 years after low dose rate brachytherapy for low risk prostate adenocarcinoma. Diagnostic and therapeutic considerations of RIM are discussed. As long term survivors are followed in the community by primary care physicians and urologists, awareness of RIM as a potential late effect of brachytherapy is important to ensure that cases are diagnosed and managed appropriately.

Key Words: brachytherapy, prostate cancer, mucinous carcinoma, radiation-induced malignancies

Introduction

Increased screening with prostatic specific antigen (PSA) has led to the detection of many prostate cancers at an early stage, and successful treatments have increased the number of long term survivors. Since men often elect for radiotherapeutic management, it is expected that radiation induced malignancies (RIM), a rare late effect of treatment, will be encountered more often.

Permanent seed-implant brachytherapy offers excellent long term control for appropriately selected patients with localized prostate cancer.[1] The few reports of RIM following brachytherapy have involved secondary cancers arising in the bowel and bladder,[2] but to our knowledge, none has reported RIM cases arising from the prostate itself.

Mucinous carcinoma (MC) is a rare subtype of prostate cancer,[3-5] characterized by mucin comprising > 25% of tumor volume following complete resection. Similar to the predominant acinar subtype, MC of the prostate can stain positive for PSA and prostatic specific acid phosphatase (PSAP), although variations have been reported.[3] MC can also be associated with elevated serum PSA, and can demonstrate response to endocrine therapy.[5] Although early reports describe MC as an aggressive phenotype,[6] there have been more recent reports of good prognosis following surgical resection.[3,4]

In this article, we discuss a case of MC of the prostate, consistent with a RIM, occurring 12 years after low dose rate brachytherapy for adenocarcinoma of the prostate.

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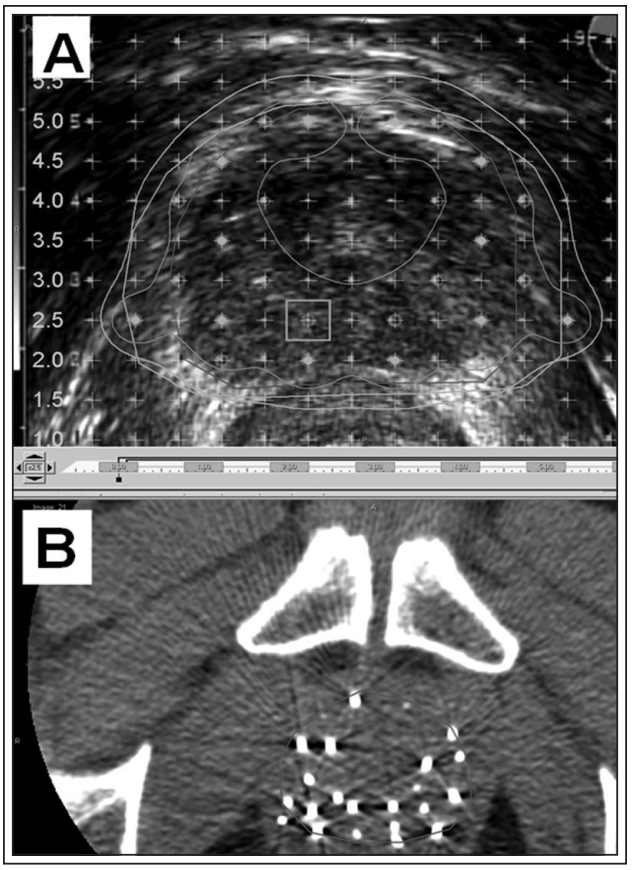

Figure 1. A) Planning ultrasound showing treatment volumes. Contours: orange = 216 Gy, blue = 144 Gy. **B)** Post-implant CT scan showing LDR iodine-125 transperineal brachytherapy implant of 140 x 0.334 mCu seeds, planned to deliver a modified peripheral dose (MPD) of 144 Gy, maintaining the periurethral dose to < 150% of the MPD.

Case report

A 62-year-old, previously healthy patient presented in 2004 with a slowly rising PSA, elevated at 5.9 ug/L. Digital rectal exam revealed an area of firmness in left lobe. Ultrasound showed a hypoechoic region in the left midzone of the prostate. Biopsy confirmed prostatic adenocarcinoma, positive in 2/9 cores (left lobe), Gleason score 3+3 = 6/10 without perineural invasion, lymphovascular invasion, or extracapsular extension. Bone scan and chest radiograph were negative for metastases. Clinical stage was T2a NX M0. In February 2005, he underwent treatment with low dose rate brachytherapy using an iodine-125 transperineal implant, which proceeded uneventfully, Figure 1. Prescription dose was 144 Gy. The prostate was palpably normal at all follow up examinations. PSA continued to decline, and was undetectable (< 0.02 ug/L) 10 years post-treatment.

The patient experienced gross hematuria September 2006, and again in December 2010. With each episode, ultrasound of the kidneys and bladder was normal. Cystoscopy identified a urethral stricture, and the hematuria resolved without intervention. In April 2011, the patient presented to the urologist with symptoms of urinary obstruction. Urethrotomy was recommended because it was felt that his problems were related to urethral stricture. During the procedure, no abnormalities were noted within the bladder cystoscopically, but a papillary growth was seen emanating from the left lobe of the prostate. This was resected, and the pathology was negative for malignancy. After the urethrotomy, the patient recovered well. Urinary function remained normal until late 2015, at which time his obstructive symptoms recurred, and gradually worsened to the point where a second procedure was recommended.

In September 2016, the patient consented to a repeat urethrotomy. The urologist saw a mild stricture within the urethral sphincter, and a proximal large prolapsing mass arising from the left apex of the prostate. Complete resection using laser was performed. No additional lesions were seen in the bladder. On pathology, the mass was a mucinous adenocarcinoma, with small areas of tumor cells floating in pools of mucin, Figure 2. Goblet cell metaplasia was present. Stains for CDX2 and cytokeratin 20 were positive. Stains for cytokeratin 7, PSA, and PSAP were negative. Pathology review of the patient's initial biopsy from September 2004, upgraded his initial prostate adenocarcinoma to Gleason 3+4 = 7/10.

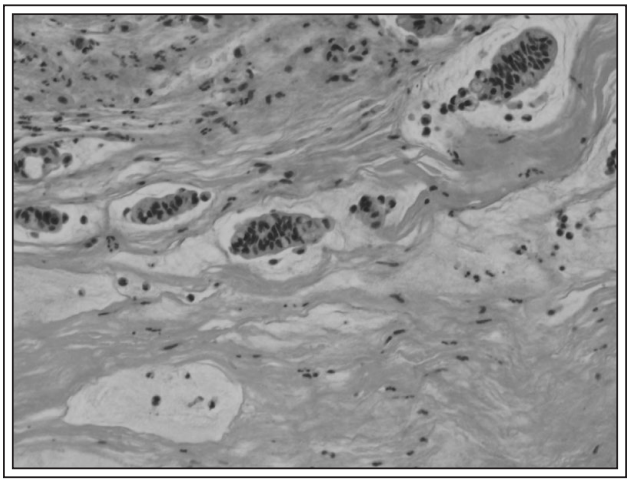

Figure 2. Pathology from September 2016 urethotomy & resection, showing mucinous adenocarcinoma.

Due to the pure mucinous morphology, the patient underwent investigation to rule out a colon or bladder primary malignancy. Tumor markers, including CEA (2.1 ug/L), CA 19-9 (8.5 kU/L), CA-125 (12.4 kU/L), and PSA (< 0.02 ug/L) were all normal. Magnetic resonance imaging of the pelvis was limited by brachytherapy-related changes, but did not show any lesions typical for a high Gleason score prostate cancer, nor any extraprostatic lesion. The seminal vesicles, bladder, and regional lymph nodes were normal. Cystoscopy at the time of urethrotomy did not identify any lesions within the bladder. Colonoscopy and positron emission tomography did not identify another primary malignancy. The diagnosis was hence deemed to be a primary mucinous adenocarcinoma of the prostate.

In February 2017, the patient underwent radical cystoprostatectomy with urethrectomy, ileal conduit urinary diversion, and bilateral pelvic lymph node dissection. Pathology showed multiple small foci of in situ mucinous adenocarcinoma involving the intraprostatic urothelium in sections from the right apex with a single focus of invasive mucinous adenocarcinoma, Figure 3. No conventional prostatic adenocarcinoma was identified. The margins were clear, and there was no extraprostatic or seminal vesicle invasion. Brachytherapy seeds and radiation-related changes were identified including reactive glandular atypia, fibrosis, and atrophy. The bladder urothelium was normal. There was no pelvic lymph node involvement. The final stage was pT2 pN0.

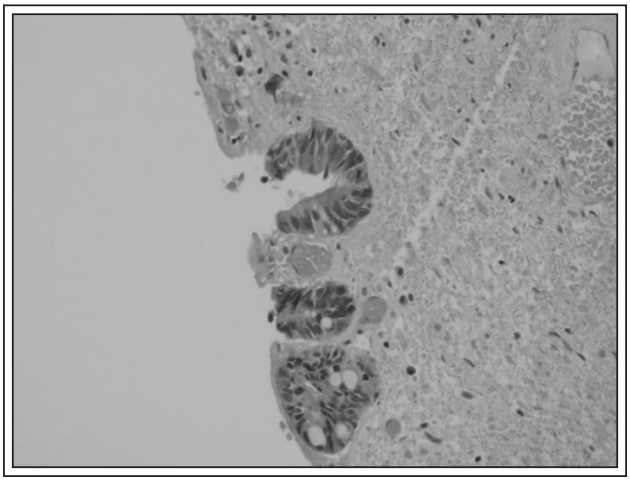

Figure 3. Pathology from February 2017 radical cystoprostatectomy showing a single focus of invasive enteric-type mucinous adenocarcinoma (0.2 cm), with multiple small foci of in situ disease involving the intraprostatic urothelium in sections from the right apex.

Discussion

MC of the prostate is a rare entity. The case reported here arose in the prostatic apex 12 years after prostate brachytherapy and may represent a brachytherapy-induced RIM. Work up including imaging, cystoscopy, and colonoscopy was negative for an alternate primary. More importantly, the presence of in situ disease supports the MC as prostatic in origin. The initial prostate adenocarcinoma in 2004 was screen-detected, and there were no symptoms to suggest an abnormality of the prostatic urethra. Therefore, this case met all of the criteria for RIM as defined by Cahan et al[7] including: 1) the tumor arose in the irradiated field, 2) sufficient time had passed in-between irradiation of the first and diagnosis of the second malignancy, 3) both tumors were different histologically, and 4) the tissue in which the second tumor arose was normal prior to the radiation exposure.

RIMs have been well-studied following irradiation of various cancer sites, and in non-cancer treatment settings. The incidence of RIM following external beam radiation for prostate cancer is reportedly low, less than 1% after 5 years, and 1%-2% after 10 years.[8] In the setting of brachytherapy, studies of RIM after prostate brachytherapy have addressed those arising in the bladder and rectum, for which the reported incidence is less than 1%.[2] A secondary malignancy arising from the prostate gland itself has not been previously reported to our knowledge.

Serum PSA is a key tool in the post-treatment setting for detecting prostate adenocarcinoma, but there are few studies correlating elevated PSA to the presence of MC, and of those studies, it is difficult to isolate the effect of any prior androgen deprivation therapy.[4] Moreover, the sensitivity of PSA in detecting recurrence is limited.[9] In the current case, PSA levels were consistently undetectable; a RIM that develops or progresses without biochemical evidence may be difficult to detect unless palpable on clinical examination or symptomatic to warrant investigations.

Although prior cases suggest MC of the prostate behaves aggressively,[6] more recent studies suggest that prognosis can be good following complete resection.[3,4] This may be related to the development of modern diagnostic, treatment, and surveillance techniques that enable early detection, and differentiation between different pathologies. For example, signet ring cell carcinoma is also a rare mucin-producing cancer that has poor prognosis, no reliable tumor markers, low response to endocrine therapy, and is now classified separately from MC.[5]

Given advances in detection and treatment, it is likely that we will continue to see more prostate cancer patients diagnosed with early stage disease. Many will be suitable for, and will choose, low dose rate brachytherapy. As such, it is reasonable to expect an increase in the number of patients developing second malignancies in the future, but reassuring that the absolute incidence of RIM has remained low.[2,10] While our case met all the criteria for a RIM,[7] we acknowledge that since MC is a rare tumor and brachytherapy for prostate cancer is a common procedure, the current case could have been a sporadic event, unrelated to prior brachytherapy.

The benefit of curative prostate brachytherapy is substantially greater than the absolute risk of a RIM. While RIM is rare, cases of suspected RIMs should be tracked to ensure their incidence remains low, and to inform brachytherapy decision-making in patients with localized prostate cancer. As long term survivors are followed in the community by primary care physicians, it is important to educate those responsible for follow up care to be aware of RIM, so that cases may be identified promptly and managed appropriately. □

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