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Mucinous adenocarcinoma of the prostatic urethra following a remote history of primary brachytherapy for prostate cancer

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Abstract

Secondary malignancies are a known, albeit uncommon, complication of radiation for prostate cancer, either in the form of external beam radiotherapy or seed-implant brachytherapy. Of these secondary malignancies, mucinous adenocarcinoma of the prostatic urothelium is an extremely rare clinical entity that has only once been reported in the literature. We report the case of an 80-year-old gentleman who initially underwent low-dose brachytherapy for low-risk prostate cancer 18 years ago. He subsequently developed recurrent gross hematuria and obstructive voiding symptoms. He underwent cystoscopy and transurethral resection of a large tumor from within the prostate. Final pathology of the tumor revealed a mucinous adenocarcinoma. Further immunostaining revealed this is likely to have originated from the prostatic urothelium. Given his age, comorbidities, and no clear data demonstrating that aggressive extirpative surgery provides a clinical benefit, we elected to undergo surveillance. Clinicians should be aware of mucinous adenocarcinoma of the prostatic urethra as an extremely rare, radiation-induced malignancy. Once a diagnosis is made, extirpative surgery is an option for localized disease, although prognosis remains poor.

Keywords

Mucinous adenocarcinoma, prostatic urethra, urology

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Introduction

Secondary malignancies are a unique complication for patients undergoing radiotherapy for prostate cancer. Studies show that for patients who receive radiation, either in the form of external beam radiotherapy or seed-implant brachytherapy, there is a statistically significant increase in the risk of developing a secondary malignancy.[1] Histologically, these secondary malignancies are commonly urothelial or squamous cell carcinomas when originating from the bladder and adenocarcinomas from the colon.

Mucinous adenocarcinoma of the prostate and prostatic urethra is an extremely rare histologic variant. It has only once been reported as a secondary malignancy from prostate radiotherapy. Small case series have reported on this entity as a primary malignancy, providing the only data that clinicians have to guide treatment. In this article, we discuss a case of mucinous adenocarcinoma of the prostatic urethra, occurring 18 years after low-dose brachytherapy for low-risk prostate adenocarcinoma.

Case report

The patient is an 80-year-old gentleman with past medical history significant for hypothyroidism, chronic prostatitis, and prostate cancer. He was originally diagnosed with

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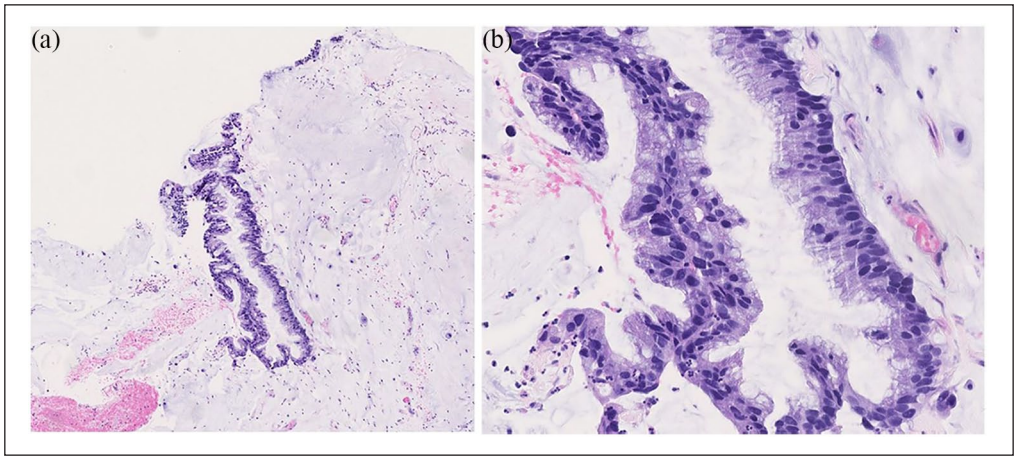

Figure 1. A (a) 4× low magnification and (b) 20× high magnification image of the pathologic specimen demonstrating the atypical glandular epithelium floating in pools of extracellular mucin, consistent with a mucinous adenocarcinoma.

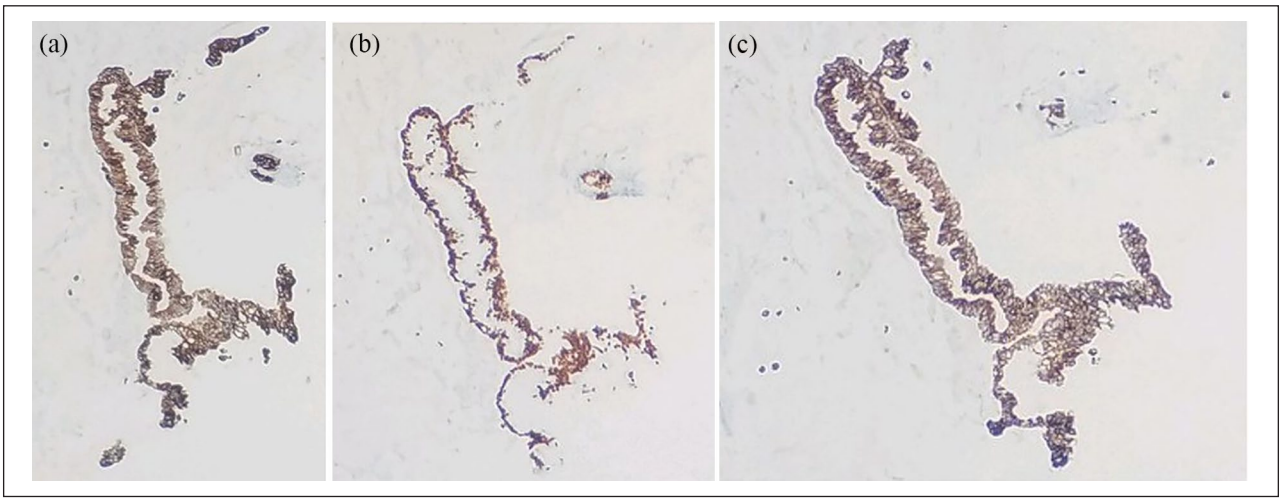

Figure 2. Immunohistochemical staining of the pathologic specimen, demonstrating positive staining for (a) CK-7, (b) CK-20, and (c) CD-X2.

prostate cancer 28 years ago, in 1992. He initially elected to undergo watchful waiting. His PSA (prostate-specific antigen) rose in 1995, leading to a repeat biopsy, which was negative for malignancy. In 2001, 9 years after the initial diagnosis, his PSA increased to 7.5 ng/mL. A repeat biopsy demonstrated a single focus of Gleason 3 + 3 = 6 (Grade Group 1). He decided to undergo low-dose brachytherapy for definitive therapy. A total of 87 seeds were placed in July 2001, with an activity per seed of 0.391 and total activity of 34.0 mCi. The total brachytherapy dose amounted to 144 Gy. Over the following 4 years his PSA slowly declined, finally reaching a nadir of less than 0.1 ng/mL in December 2005. His PSA was monitored annually thereafter and remained undetectable.

In 2011, he developed gross hematuria. A cystoscopy was performed at that time and was negative for lesions or masses. In April 2019, he again developed recurrent episodes of gross hematuria. Of note, he denied mucosuria. He underwent another cystoscopy, where there was an atypical papillary lesion within the prostatic urethra that was whitish in appearance and friable. A biopsy was performed. The lesion consisted of atypical glandular epithelium floating in pools of mucin, consistent with a mucinous adenocarcinoma (Figure 1(a) and (b)). The tumor was immunoreactive for cytokeratin-7 (CK-7), cytokeratin-20 (CK-20), and caudal type homeobox 2 (CD-X2) (Figure 2(a)–(c)). It was negative for p63. At the time, his PSA was undetectable, less than 0.01 ng/mL. A computed tomography (CT) abdomen/pelvis was performed to rule out a separate primary malignancy. Imaging was unremarkable. He was subsequently referred to our institution for further management. A re-resection was performed in November 2019. Intra-operatively, there was a

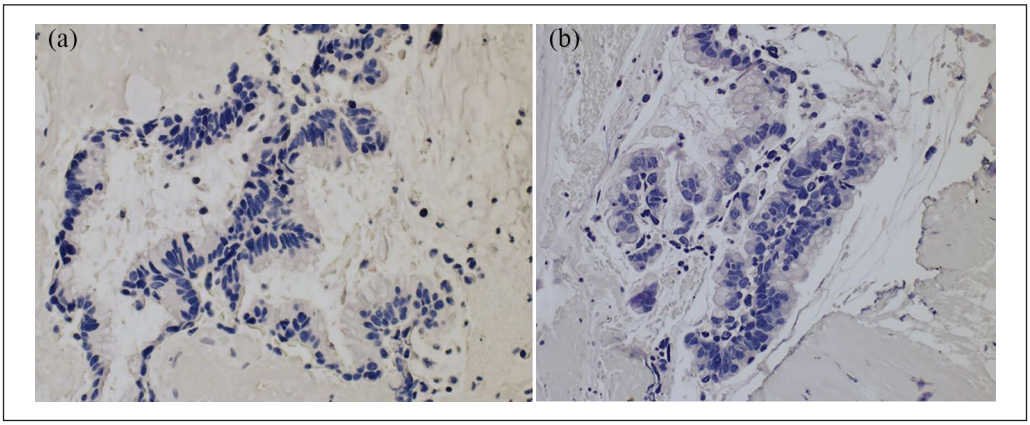

Figure 3. Immunohistochemical staining of the pathologic specimen, demonstrating negative staining for (a) PSA and (b) PSAP.

large, lobulated tumor along the right lobe of the prostate with overlying mucous. This was resected. Final pathology once again demonstrated mucinous adenocarcinoma, similar in appearance to the initial biopsy. To better understand the origin of the tumor, immunostains for racemase, PSA, and prostatic specific acid phosphatase (PSAP) were performed (Figure 3(a) and (b)). All markers were negative. To rule out colon cancer, he underwent a colonoscopy and random biopsies. Final pathology was negative for invasive cancer. As of 22 January 2020, his PSA remains <0.01 ng/mL. After presenting this case to our institutional tumor board, followed by a discussion with the patient, we agreed to forego radical resection. Instead, as he was an elderly comorbid gentleman, we agreed to pursue conservative management. The patient will undergo surveillance cystoscopy and cross-sectional imaging, with the possibility of repeat transurethral resection if the tumor causes significant bladder outlet obstruction.

Discussion

Mucinous adenocarcinomas involving the prostate are rare variants of disease that pose a diagnostic and therapeutic dilemma for physicians. When this tumor is of true prostatic origin, it is either considered to be a variant of the more common acinar adenocarcinoma or strictly a mucinous adenocarcinoma. By definition, it is considered a variant when there is extravasated mucin in less than or equal to 25% of the tumor specimen.[2] Conversely, it is considered a pure mucinous adenocarcinoma when there is extravasated mucin in more than 25% of the specimen. If the tumor originates from urethra, then it may grow only from within the prostatic urethra or invade from within the bladder. A third possibility is that the tumor has metastasized or spread directly to the prostate from a separate primary source, most commonly the colon. A colonoscopy and cross-sectional imaging can usually determine whether a primary colorectal malignancy is present. However, differentiating prostatic from urethral sources can be particularly challenging, as the tumors can appear similar on cystoscopy. Nevertheless, there is evidence that immunostaining can aid in the diagnosis. One study found that focal positivity of both CK-7 and CK-20 was highly suggestive of urothelial origin.[3] This, in combination with a negative PSA and PSAP, is very suggestive of urethral origin. On the contrary, when only CK-7 or CK-20 is positive, or both are negative, there is limited clinical utility in distinguishing the carcinomas. Therefore, when reviewing the immunostaining of the mucinous adenocarcinoma resected from this case, it is likely of prostatic urethral origin.

Mucinous adenocarcinoma of prostatic urethral origin was first reported by Tran and Epstein[4] in 1996. Two patients were included in this small series. Neither had an elevated PSA. Neither had evidence of metastatic disease, and a gastrointestinal malignancy work-up was negative. One patient underwent a radical prostatectomy. The other patient underwent a simple prostatectomy but no further definitive therapy for several years, at which point the tumor had progressed locally to an advanced stage. Both died of disease within 5 years of follow-up. This same group followed up with a larger series of 15 patients in 2007. In Osunkoya and Epstein,[5] all patients presented with obstructive symptoms, normal PSA, unremarkable cross-sectional imaging, and negative colonoscopies. Five patients underwent radical prostatectomy, two a cystoprostatectomy, one a pelvic exenteration, and seven a transurethral resection of prostate (TURP). Radiation was also given in several cases. Follow-up of this cohort revealed that eight patients died of their disease, four of those who had received radical resection and four who received TURP.

Another case was reported in 2019 by Solakhan et al.[6] This was a 77-year-old man who initially presented with bothersome lower urinary tract symptoms (LUTS). He did not have an elevated PSA. He underwent a TURP, and on pathologic examination was found to have urethral mucinous adenocarcinoma of the prostate. Radiotherapy and hormonotherapy were started, but he progressed shortly thereafter, with metastases to bone, pelvic lymph nodes, and lung. He subsequently failed a trial of gemcitabine, before finally responding to a metastatic colon cancer regimen of

chemotherapy plus panitumumab. Contrasting these reports, other groups have reported elevated PSA values in their isolated cases.[7,8] In Ortiz-Rey et al.,[7] the patient underwent two TURPs, but eventually succumbed to the disease 40 months after diagnosis. In Adley et al.,[8] the patient underwent a radical prostatectomy, but was found to have local recurrence and widespread metastases within 4 months of surgery. Common to these cases and the select few others that exist is the common immunohistochemical profile, which is positive for CK-20 and CK-7 and negative for PSA and PSAP.[4,5,7–10] However, also common in all of these cases is the generally poor prognosis despite aggressive resections.

Only one case in the literature, Murchison et al.,[11] has reported on a radiation-induced mucinous adenocarcinoma of the prostate. Interestingly, just as in our case, this patient underwent low-dose brachytherapy for what today would be considered low-risk prostate cancer. This was a 62-year-old man with clinical stage T2a Gleason 6 prostate cancer who underwent definitive low-dose brachytherapy. After therapy, his PSA declined and was undetectable 10 years out from treatment. However, as in our case, the patient began experiencing gross hematuria, first 2 years from initial treatment, and then at 6 years. A work-up with cystoscopy was negative at that time. 12 years after therapy, he underwent another cystoscopy for obstructive voiding symptoms. A large prolapsing mass was found arising from the left apex of the prostate. The mass was resected, and pathology revealed mucinous adenocarcinoma. The tumor stained positive for CD-X2 and CK-20. It stained negative for CK-7, PSA, and PSAP. Serum PSA and other tumor markers were undetectable and normal, respectively. His metastatic work-up, which include colonoscopy and positron emission tomography (PET) CT, was negative. The patient underwent a radical cystoprostatectomy with urethrectomy and ileal conduit. Final pathology revealed in situ mucinous adenocarcinoma involving the prostatic urethra with negative margins, no extraprostatic or seminal vesicle invasion, no bladder involvement, and no pelvic lymph node involvement. There is no report on post-operative follow-up. It is important to note that while the authors suggested this tumor arose from the prostate, the final pathology and immunostaining would suggest that it in fact originated from the prostatic urethra, as in this case and the previously mentioned series.

It remains unclear at this time which systemic therapies should be given once metastases develop. Series have reported using hormonal therapy, chemotherapy, and targeted molecular inhibitors, but there is little data to support their efficacy. Given that this tumor is of urethral origin and does not express PSA, it is unlikely to be driven by androgen signaling pathways. Thus, androgen deprivation therapy is unlikely to be of clinical utility. There are, however, histologic similarities to mucinous colorectal cancer. As such, some clinicians suggest relying on colorectal literature to guide treatment. Specifically, data have shown that there is some efficacy when using chemotherapeutic regimens such as FOLFOX, FOLFIRI, and XELOX for mucinous colorectal adenocarcinoma.[12] Furthermore, there are data suggesting that targeting the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway with epidermal growth factor receptor (EGFR) inhibitors provides oncologic efficacy in mucinous colorectal adenocarcinoma.[12] Indeed, when using these colorectal regimens for mucinous adenocarcinoma of the bladder, case reports have shown a clinical response.[13] Therefore, in the absence of strong clinical evidence, clinicians will have to rely on case reports, draw from the colorectal literature, and maintain a shared decision-making process with the patient, to guide management of this rare malignancy.

Conclusion

Mucinous adenocarcinoma of the prostatic urethra is a rare clinical entity. It is exceedingly rare as a primary malignancy, but even more so as one induced by the effects of radiation. Only one previous case believed to be the result of radiation has been reported in the literature. With no follow-up for this one patient, we can only rely on the limited series that have been reported on primary tumors. Most patients have undergone radical resection either with a radical prostatectomy or cystoprostatectomy. Fewer have elected for conservative transurethral resection. Regardless of treatment modality, it appears that prognosis is very poor. It would seem reasonable in patients who are elderly and with additional medical comorbidities that conservative management is an acceptable strategy.

Declaration of conflicting interests

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Ethical approval

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Informed consent

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