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Testicular and Bladder Metastases From Prostate Adenocarcinoma 18 Years After Definitive Treatment Despite Undetectable Prostate-Specific Antigen and Negative Prostate-Specific Membrane Antigen Positron Emission Tomography

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Abstract

Secondary tumors of the prostate commonly metastasize to the lymph nodes, bones, and lungs. While the prostate is the most frequent primary source of secondary testicular malignancies, the latter occurs rarely and is usually detected as a mass on examination or ultrasonography.

We describe an instance of a 71-year-old patient with a history of T4bN1 Gleason 8 prostatic adenocarcinoma treated with a radical prostatectomy followed by adjuvant radiotherapy, and androgen deprivation therapy (ADT), who remained disease free on follow-up studies for a period of 18 years, until he was evaluated in June of 2024 with right sided orchialgia. His workup, including multiple testicular ultrasounds, was benign, and the patient ultimately underwent a radical orchiectomy for unrelenting pain. Pathologic staining was positive for AE1/AE3 and strongly positive for NKX3.1, with focal CA9 and scant CDX2 positivity without any positivity of placental alkaline phosphatase (PLAP), overall suggestive of metastatic carcinoma of prostatic origin. 10 months later, the patient presented with recurrent urinary tract infections (UTIs) and hematuria in association with abnormal cytology and positive fluorescence in situ hybridization (FISH) testing. Initial cystoscopy and bladder biopsies were benign. Surveillance imaging demonstrated asymmetrical thickening of the inferior left bladder wall, and repeat cystoscopy revealed a 3 cm calcified mass at the bladder neck. Tumor pathology demonstrated poorly differentiated adenocarcinoma with focal nuclear staining of NKX3.1, once again consistent with metastatic prostatic carcinoma.

This is a rare example of metachronous metastasis to unusual genitourinary structures in a patient with prostate adenocarcinoma 18 years after primary treatment despite a low to undetectable prostate-specific antigen (PSA) and negative surveillance prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging.

Categories: Urology, Oncology, Anatomy
Keywords: bladder metastasis, genitourinary oncology, metachronous metastasis, nkx3.1, prostate adenocarcinoma, psma pet/ct, secondary bladder tumor, testicular metastasis, undetectable psa

Introduction

Prostatic adenocarcinoma is one of the most frequently diagnosed noncutaneous malignancies in men and a leading cause of cancer related death. Its metastatic behavior is well characterized. In an autopsy study of 1,589 men with prostate cancer, hematogenous metastases most often involved bone (90%), followed by lung, liver, pleura, and adrenal glands [1]. The testes and the urinary bladder are rarely mentioned in descriptions of this usual pattern.

Secondary tumors of the testis are uncommon in both surgical and autopsy material [2], and the incidence figures most often quoted in the literature derive from older series without a uniform denominator [3]. Nonetheless, when metastasis to the testis does occur, the prostate is the leading primary site. In the largest multinational series, comprising 157 metastatic solid tumors to the testis, prostate accounted for 34% of cases, followed by kidney (20%) and colorectum (9%), and a testicular mass or nodule was the presenting finding in most patients [4]. A pooled analysis of nonhematopoietic secondary testicular tumors in the indexed literature reached a similar conclusion, with prostate accounting for 38.8% of cases [5-7]. These two types of data should be interpreted differently: Autopsy series largely capture terminal, widely disseminated disease, whereas surgical and clinical series reflect diagnostic evaluations in living patients, and outcome data from both span all primary sites rather than prostate cancer specifically.

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The urinary bladder is likewise an unusual site of recurrence once the prostate has been removed. Although the prostate is the second most frequent source of secondary bladder tumors, most such cases represent direct extension from an intact gland rather than true metastasis after radical prostatectomy [8]. In the only published series specifically addressing bladder metastasis after radical prostatectomy, three of four patients presented with intermittent gross hematuria, and only one had an elevated prostate specific antigen (PSA) [7].

This last observation is central to the present case. After definitive treatment, serum PSA is the cornerstone of surveillance, and biochemical recurrence typically precedes clinical or radiographic progression. Prostate-specific membrane antigen (PSMA) is a transmembrane protein overexpressed by most prostate adenocarcinomas, and PSMA positron emission tomography (PET) is the most sensitive imaging modality currently used to localize recurrent disease. However, PSA production depends on intact androgen receptor (AR) signaling, and PSMA expression is frequently reduced or lost in tumors that undergo neuroendocrine transformation. A subset of prostate cancers that become AR independent or dedifferentiated, often termed aggressive variant prostate cancer, may therefore progress with a low to undetectable PSA and a negative PSMA PET, leaving clinicians without the markers they ordinarily rely upon to detect recurrence.

The clinical importance of these lesions lies less in their frequency than in their capacity to be misinterpreted. Metastatic carcinoma involving the testis may closely simulate a primary testicular neoplasm, and in a series of 26 nonincidental cases the primary tumor was unknown at the time of diagnosis in 62%. Similarly, prostatic adenocarcinoma presenting as a solitary bladder mass has been misdiagnosed as muscle invasive bladder cancer (urothelial carcinoma invading the detrusor muscle, which is typically treated with radical cystectomy), resulting in referral for cystectomy. We describe a patient who developed metachronous testicular and bladder metastases (that is, metastases arising at separate time points rather than simultaneously) from prostate adenocarcinoma 18 years after definitive treatment with radical prostatectomy, adjuvant radiotherapy, and androgen deprivation therapy (ADT) (pharmacologic suppression of testosterone), and we review the diagnostic and management considerations raised by this presentation [9].

Case Presentation

A 71-year-old male patient presented to the office with acute right sided testicular pain. His past urologic history is significant for T4bN1 Gleason 8 high-risk prostate cancer diagnosed 18 years prior to presentation and treated with radical prostatectomy followed by post-operative radiation to the prostatic bed and pelvic lymph nodes, in addition to adjuvant hormonal therapy for four years with viadur implants and casodex. The patient responded exceedingly well and his PSA has remained low to undetectable on serial testing to the present date, without a rising trend. He suffered from postoperative side effects, including intermittent bothersome lower urinary tract symptoms like incontinence and incomplete emptying, as well as erectile dysfunction, for which he underwent a malleable prosthetic implantation. Periodic PSMA PET scans were obtained every few years and negative for disease.

At Month 0, he presented to the office with right sided testicular pain. On exam the patient had a tender right testicle without any skin changes, edema or palpable discrete mass. A scrotal ultrasound was obtained (Figure *1*), which showed bilateral thickening of the tunica albuginea, greater on the right with multiple internal microcalcifications. There was no evidence of an intratesticular mass. He was treated empirically for epididymo-orchitis; however, his pain persisted. At Month 3, a repeat ultrasound was obtained and stable when compared to his prior study. Ultimately, given his unrelenting pain with no identifiable cause, the decision was made to undergo a right radical orchiectomy. Serum testicular tumor markers (alpha fetoprotein, beta human chorionic gonadotropin, and lactate dehydrogenase) were not obtained prior to surgery, as there was no sonographic or clinical concern for a testicular mass at the time. The radical orchiectomy was completed through a standard inguinal incision and the testicle appeared normal on gross examination. Pathology revealed testicular parenchyma distorted by atrophic tubules mixed with additional tubular structures with anastomosing and cribriform architecture composed of cells with abundant clear cytoplasm, distinct cell borders, and nuclei, which ranged from round and small to large and multinucleated with occasional mitotic features. The specimen was sent to the Cleveland Clinic for an expert opinion and further identification of the clear cell origin of proliferation. Their findings revealed the specimen stained positive for AE1/AE3 and negative for placental alkaline phosphatase (PLAP), which support a diagnosis of metastatic carcinoma. Additionally, the neoplastic clear cells demonstrated strong nuclear positivity for NKX3.1, a prostate specific transcription factor used in pathology to identify prostate cancer [10]. This staining was localized to the neoplastic epithelial cells rather than to the surrounding non-neoplastic Sertoli cells. There was focal positivity in the neoplastic cells for CA9 and trace reactivity for CDX2. Taken together, these findings supported a diagnosis of metastatic carcinoma suggestive of prostatic origin. Given the clear cell morphology and focal CA9 expression, metastatic clear cell renal cell carcinoma (RCC) was considered in the differential diagnosis. PAX8 and RCC marker immunostains were not performed; however, cross sectional imaging demonstrated no renal mass, and subsequent right retrograde pyelography, ureteroscopy, and renal pelvis biopsies were benign. Additional immunohistochemistry for PSA, PSMA, AR, and neuroendocrine markers was not performed on this specimen. A PSMA PET was obtained following the diagnosis and was negative for any abnormal radiotracer uptake.

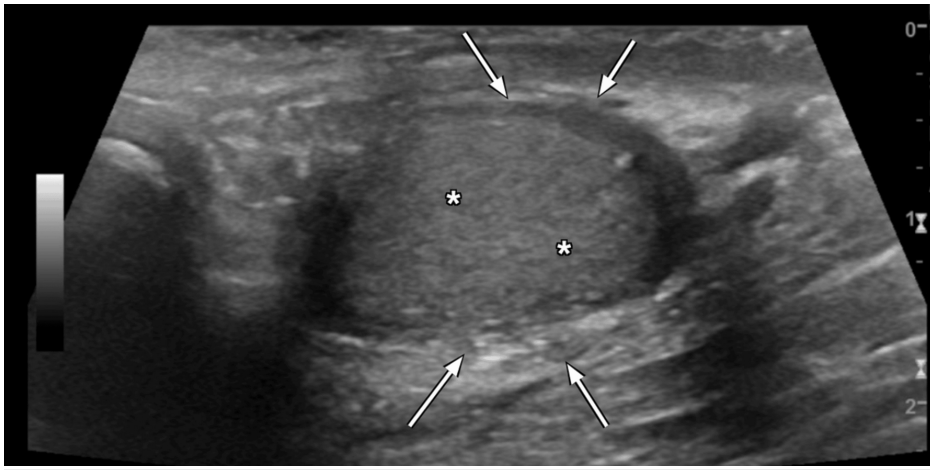


FIGURE 1: Grayscale scrotal ultrasound of the right testis at presentation. The testicular parenchyma is homogeneous without a discrete intratesticular mass or focal lesion (asterisks). Arrows indicate the tunica albuginea along the superior and inferior margins, which appears mildly thickened. Depth markers at the right denote 1 cm increments. A repeat study three months later was unchanged.

At Month 10, the patient began having recurrent culture-proven urinarty tract infections (UTIs). He persisted to have blood on his urinalyses, which prompted a cytology and office cystoscopy. Cytology revealed atypical urothelial cells, and cystoscopy was negative for tumors. Repeat cytologies continued to be atypical and a fluorescence in situ hybridization (FISH) analysis found four or more morphologically abnormal cells with aneuploidy of chromosomes 3, 7, or 17, or biallelic deletion of 9p21 in at least 12 cells. These findings raised concern for an undetected urothelial carcinoma in situ, invasive urothelial carcinoma or high grade noninvasive papillary urothelial carcinoma. The patient was taken for a cystoscopy, right retrograde pyelogram, ureteroscopy, and renal pelvis biopsies with bladder biopsies. There were no obvious tumors identified at the time. Pathology for both bladder and renal pelvis biopsies came back benign. The patient was taken again to the operating room for a cystoscopy, which this time revealed a 3 cm calcified lesion on the left side of the bladder neck. Because his bladder neck was contracted from his history of prostatectomy with radiation therapy, a resectoscope could not be safely passed. The lesion was, therefore, removed piecemeal with cold cup biopsy forceps through a rigid cystoscope until no visible tumor remained at the bladder neck. Subsequent follow up cystoscopy and imaging confirmed no residual lesion. Tumor pathology revealed poorly differentiated adenocarcinoma with focal nuclear reactivity to NKX3.1 within the tumor cells, consistent with prostatic origin.

Discussion

Epidemiology and pattern of spread

Prostatic adenocarcinoma is the most frequent primary source of secondary testicular tumors, yet the absolute incidence remains low. The apparent paradox of a common tumor rarely seeding an anatomically adjacent organ has been attributed to the relatively low scrotal temperature and the barrier function of the blood testis interface, although neither explanation has been established experimentally.

Four routes of spread to the testes have been proposed: back venous spread, back lymphatic spread, arterial embolization, and spread by direct luminal spread along the vas deferens. The evidence at autopsy for back venous spread from the prostate to the axial skeleton has been extended by analogy to the scrotal contents [1]. None of these mechanisms have been proved and their relative contribution is unknown. In our patient these patterns of spread are informative but not conclusive. The two areas of metastasis occur in the lower genitourinary system at separate timepoints. This seems more likely to represent locoregional spread either through the vas deferens, urethra, or retrograde venous and lymphatic pathways rather than hematogenous spread throughout the body, given the lack of distant metastasis to the bones, nodes, or viscera.

Furthermore, metastasis in the setting of a discordantly low or negative PSA is suggestive of an aggressive-variant or neuroendocrine prostate cancer. These variants often present with a loss of ARs leading to downregulation of PSA expression in relation to tumor burden. This can happen over time and is frequently driven by AR gene alterations. However, this mechanism remains a hypothesis in our patient. Immunohistochemistry for PSA, PSMA, and AR, as well as for neuroendocrine markers, such as chromogranin A, synaptophysin, CD56, and INSM1, was not performed on either the testicular or the

bladder specimen, so loss of tissue PSA, PSMA, or AR expression and neuroendocrine differentiation could not be confirmed. The poorly differentiated morphology of the bladder lesion, together with a low to undetectable serum PSA and a negative PSMA PET despite biopsy proven metastases, is consistent with, but not diagnostic of, an AR independent or dedifferentiated phenotype. We consider this an important limitation of this report, and in similar cases such staining should be obtained whenever tissue is available, as it may clarify tumor biology and influence the choice of systemic therapy.

Clinical presentation

In review of the existing literature, reported cases fall under three categories: incidental finding in a bilateral orchiectomy specimen excised as a means of androgen deprivation, palpable testicular mass in setting of known prostate cancer, and testicular mass as the first manifestation of an occult prostatic primary [8], the latter particularly challenging to diagnose. Beyond these primary categories, secondary testicular involvement can present deceptively. For example, metastasis on a background of low, suppressed or undetectable serum PSA, after radical prostatectomy or (radio)therapy, while on ADT, has been reported at times more than 10 years after treatment of low risk disease [7,8,11,12]. The second is the presentation mimicking infectious or inflammatory scrotal disease, for which multiple case reports note a period of treatment for epididymo-orchitis before the diagnosis was made [13]. Both presentations show that a normal or down trending PSA does not exclude metastasis, and secondary symptoms in the context of prostate cancer should always be carefully evaluated.

Imaging

Sonographic findings are nonspecific: a heterogeneous, hypoechoic intratesticular lesion with increased Doppler flow is indistinguishable from a primary germ cell tumor. Ultrasound establishes the lesion but not its origin.

PSMA PET has improved detection of atypical metastatic sites, including isolated testicular recurrence [14], but physiologic epididymal uptake limits specificity. Among 114 patients with PSMA PET and scrotal ultrasound within 100 days, 24 (21%) had scrotal uptake yet metastasis was confirmed in only five, all with focal, unilateral, intense uptake; 16 of 17 patients with mild focal uptake had a normal ultrasound. Uptake intensity, maximum standardized uptake value (SUV_{max}), laterality, and restaging indication predicted true metastasis [15,16]. Ultrasound correlation is, therefore, essential.

Our patient illustrates the opposite and arguably more consequential problem: a false negative PSMA PET. PSMA expression is heterogeneous, and a minority of prostate cancers, particularly poorly differentiated, PSA nonsecreting, and neuroendocrine tumors, show low or absent PSMA expression; neuroendocrine differentiation has been shown experimentally to suppress PSMA expression. In this setting, ^{18}F fluorodeoxyglucose (FDG) PET/CT can identify metabolically active disease that is not PSMA avid, and FDG positive, PSMA negative disease has been associated with poor outcomes in advanced prostate cancer. A small-volume disease like microscopic testicular deposit without a sonographic mass may also fall below the spatial resolution of PET, and lesions at the bladder neck can be obscured by urinary excretion of PSMA radiotracers. Therefore, in a patient with high-risk disease and new genitourinary symptoms despite a low to undetectable PSA and a negative PSMA PET, FDG PET/CT and early tissue sampling should be considered.

Bladder metastases in a patient with history of prostatectomy

Post-prostatectomy metastasis to the bladder is rare and, in this patient, was associated with hematuria and irritable urinary symptoms rather than an elevated PSA. Further complicating diagnosis is the fact that lower urinary tract symptoms after surgery and pelvic radiation are common and easy to attribute to common side effects such as bladder neck contractures, radiation cystitis, and/or infection. Additionally, urine cytology and UroVysion FISH were developed for the detection of urothelial carcinoma, but neither is specific for it. FISH detects aneuploidy of chromosomes 3, 7, and 17 and loss of 9p21, alterations that reflect the genomic instability shared by many high-grade carcinomas rather than a urothelial lineage. A poorly differentiated prostatic adenocarcinoma involving the bladder neck could therefore shed aneuploid cells into the urine and produce a positive result. Radiation-induced urothelial atypia is a recognized cause of atypical cytology after pelvic radiotherapy and should be considered as an alternative explanation, but it is less likely to account for the multichromosomal aneuploidy detected in multiple cells in our patient. In retrospect, the persistently abnormal cytology and FISH were most plausibly explained by the bladder neck metastasis, which was not apparent on the initial cystoscopy, and these results justified continued evaluation of the bladder until a lesion was identified. Of note, calcified lesions in an area of previous irradiation, such as the bladder neck, can easily be confused with a stone, an encrusted suture, or a radiation change [17]. It is important to differentiate this disease from a primary bladder malignancy, or less likely metastatic malignancy, as the management approaches are different. For example, metastatic prostatic adenocarcinoma has been confused with urothelial carcinoma invading muscle leading to referral for radical cystectomy.

Pathology and differential diagnosis

Metastases to the testes infiltrate the interstitium with relative sparing of seminiferous tubules and frequent

lymphovascular invasion. Paratesticular structures were involved in 48% of cases and intratubular growth, which mimics germ cell neoplasia in situ, in 11% [4].

Immunohistochemistry is crucial and often the deciding factor in pin-pointing a malignancy's site of origin. Prostatic origin is supported by NKX3.1, PSA responsivity, prostatic acid phosphatase, PSMA, AR, ERG, and prostein with pancytokeratin; germ cell tumor is excluded by negative SALL4, OCT3/4, CD30, and CD117, and sex cord stromal tumors by negative inhibin and Melan A [9,17]. Clear cell morphology with CA9 expression, as seen in our patient, should also prompt consideration of metastatic clear cell RCC, the second most common source of testicular metastasis [4], for which PAX8 and RCC marker are the most useful discriminating stains. These stains were not performed in our case, which we acknowledge as a limitation. However, the absence of a renal mass on cross sectional imaging and PSMA PET, the benign right retrograde pyelogram, ureteroscopy, and renal pelvis biopsies, and the later development of an NKX3.1 positive adenocarcinoma at the bladder neck, all argue against a renal primary.

Two pitfalls warrant emphasis. Prostatic markers are not silent in normal testis: NKX3.1 stains Sertoli cells strongly and diffusely, and prostein stains Leydig cells and rete testis epithelium, so both require a broader panel and attention to which cell type is staining. Confirming that NKX3.1 staining is localized to the neoplastic epithelial cells rather than to non-neoplastic Sertoli cells is therefore necessary to establish true prostatic origin [18]. In our patient, strong nuclear NKX3.1 positivity was confirmed within the neoplastic clear cells rather than the surrounding Sertoli cells, and the subsequent bladder lesion showed nuclear NKX3.1 reactivity within the tumor cells as well. Moreover, it is important to recognize that a malignant Leydig cell tumor is a mimicker of Gleason 5 + 5 adenocarcinoma; steroidogenic factor 1 resolves the differential and belongs in the panel for high grade solid morphology [19,20].

Management and prognosis

There are no guidelines that specifically address the management of testicular or bladder metastasis from prostatic adenocarcinoma, and the evidence consists entirely of case reports and small series. Radical inguinal orchiectomy is the standard approach, undertaken for diagnostic certainty and symptom control, with systemic therapy directed by the patient's castration status and overall disease burden.

Whether orchiectomy confers oncologic benefit as metastasectomy is unresolved. A castration resistant patient maintained on enzalutamide demonstrated a further significant PSA response after excision of a testicular deposit [18], whereas another patient achieved an undetectable PSA after orchiectomy, only to have a PSA rise five months later with PSMA avid iliac nodal disease subsequently identified, with no durable advantage [21]. Testicular involvement typically occurs in the context of disseminated disease, present concurrently or previously in 77% of patients in the largest series, and disease specific mortality among those with follow up was 53% [4]. That figure spans all primary sites and should not be presented as prostate specific. While historical cases estimated a median survival of 12 months following the diagnosis of testicular metastasis from prostate cancer, more recent reports document survival beyond two years without biochemical relapse, indicating that the overall prognostic impact remains poorly defined.

Conclusions

In conclusion, this case is an example of how seemingly benign symptoms, namely, testicular pain and recurrent UTIs, in a gentleman with a history of high-risk locally advanced prostate cancer can be signs of metastasis. Furthermore, this case highlights an incidence where a low to undetectable PSA and negative PSMA PET surveillance imaging may pose a diagnostic challenge to detecting progression of disease in a patient with suspected AR independent prostate cancer. In patients with high-risk disease, physicians should be diligent to work-up atypical new symptoms, taking care to rule out disease progression, particularly once treatment of more common issues, such as epididymitis/orchitis in our patient, doesn’t resolve the issue. Lastly, this case demonstrates the importance of continued close follow up for patients with high-risk, locally advanced prostate cancer, as even a long disease free period doesn’t omit the risk of progression in the future.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Zuhair Chaudhry, Jessica Cronberg, Patrick Hurley, Todd Campbell

Acquisition, analysis, or interpretation of data: Zuhair Chaudhry, Jessica Cronberg, Patrick Hurley, Todd Campbell

Drafting of the manuscript: Zuhair Chaudhry, Jessica Cronberg, Patrick Hurley, Todd Campbell

Critical review of the manuscript for important intellectual content: Zuhair Chaudhry, Jessica Cronberg, Patrick Hurley, Todd Campbell

Supervision: Patrick Hurley, Todd Campbell

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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