

Case Report

Prostate cancer metastatic to bilateral testicles: case report and literature review

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Abstract: Purpose: Hormone-refractory prostate cancer (PCa) has a high incidence of metastasis with common secondary site locations. Our case report describes a rare metastatic site of PCa infiltrating bilateral testicles in the absence of definitive radiologic evidence. Materials and Methods: Following the patient's consent and IRB exemption, we report the clinical, radiological, and pathological presentation of the patient treated at our institution. We also conducted an inclusive literature review of PCa with bilateral testicular metastases. Results: Our patient is a 54-year-old male who presented to the emergency room with lower urinary tract symptoms and failure to void. A full workup including digital rectal examination, PSA (580 ng/ml), and a transrectal ultrasound (TRUS) biopsy performed afterward revealed an adenocarcinoma of the prostate. The metastatic workup at presentation was negative. After failure to comply with treatment guidelines, the patient was referred back to us with bilateral testicular masses. Without clear evidence of the origin of the masses, bilateral orchiectomy was performed, and pathological analysis confirmed it was metastatic prostate adenocarcinoma. Post-orchiectomy, the patient was again lost to follow up. Three years later the patient returns and placed in palliative care. Conclusions: This case report highlights that PCa can have a highly variable course and progression can occur in the absence of adherence to treatment. Any evidence of disease relapse and clinical suspicion of metastasis should be investigated, especially in patients with advanced and metastatic disease or poor adherence to surveillance protocol.

Keywords: Prostate cancer, metastasis, testicles, hormone-refractory

Introduction

Prostate Cancer (PCa) is the most common cancer in men worldwide. With aggressive cancer, metastasis is not uncommon. Prostate cancer often metastasizes to the bones, lungs, liver, and brain. The testes are proven to be a rare site of distant metastasis from solid organ tumors and the incidence of secondary neoplasms is less than 2.5% in autopsy studies [1].

The most common primary malignancies in such cases, in descending order of incidence, are the prostate, GI tract, kidneys, bladder, and lung tumors [2]. Testicular metastasis of PCa is rare with only about 200 cases reported and bilateral involvement is exceedingly rare [3, 4]. When testicular metastasis does occur from the prostate, it presents as palpable unilateral mass with rare involvement of the epididymis [5]. It is hypothesized that the testes are an

unfavorable site for metastasis due to their low temperature in the scrotum [6]. There are four proposed mechanisms in which prostate cancer could metastasize to the testes. They include an arterial embolism, via the lumen of the vas deferens, retrograde venous extension, and retrograde lymphatic extension [1].

Here we report a case of a patient with a high-grade prostate adenocarcinoma without definitive radiologic evidence of metastatic disease at presentation. However, a year after completing radiation therapy and androgen deprivation therapy (ADT), he presented with bilaterally palpable testicular masses. Surgical excision and histology confirmed prostatic origin of metastasis in bilateral testicles. Surgical excision of both testicles not only confirmed his diagnosis of metastatic prostate adenocarcinoma, but also provided the benefits of castration in the patient.

Case

The following case received IRB exemption (STUDY00001046), and the patient gave written informed consent for documentation of his case. A 54-year-old male patient presented to the emergency room on secondary to urinary retention, which was preceded by seven days of weak stream and difficulties emptying his bladder. He reported bothersome lower urinary tract symptoms (LUTS) for the past 6 months, both obstructive and irritative symptoms including straining, urgency, and frequency. A digital rectal exam was significant for an enlarged, firm prostate with bilateral nodules. PSA was 580 ng/ml. He was noted to be in acute urinary retention and a Foley catheter was placed at the time of this PSA. A repeat PSA was 220 ng/ml after transitioning the patient from self-intermittent catheterizations to dual therapy with tamsulosin and finasteride. He denied a history of GU malignancies, UTIs, or kidney stones. A transrectal ultrasound (TRUS) biopsy revealed adenocarcinoma of the prostate with a Gleason score of 4+5=9 with perineural invasion and extra-prostatic extension. A staging CT scan and bone scan were obtained. The CT revealed multiple small para-aortic, pelvic, and inguinal lymphadenopathy smaller than staging criteria. The bone scan revealed questionable cervical lesions followed up to be degenerative changes on CT spine.

Options were discussed, and given no definitive metastatic disease, he elected to proceed with radiation therapy and androgen deprivation therapy. After receiving a course of external beam radiation and one dose of androgen deprivation therapy, PSA receded to 11.5 ng/ml. He was then lost to follow up despite the initial treatment plan of continuing androgen deprivation therapy two years after radiation.

One year after completing his radiation course, he was re-referred for bilateral testicular masses and hydroceles noted on exam. An ultrasound revealed a heterogeneous 2 × 1.6 cm hypoechoic nodule in the right testicle with vascularity and two hyperechoic, heterogeneous nodules in the left testicle with a large hydrocele (**Figure 1A-D**). These lesions were concerning for a metastatic process given his history of high-risk PCa.

Restaging CT and bone scan were obtained revealing mild interval increase in retroperito-

neal lymphadenopathy. PSA was 9.29 ng/ml. Testicular tumor markers of AFP, HCG, and LDH were obtained and within normal limits. Given poor compliance to previous androgen deprivation and bilateral testicular masses, the patient elected to proceed with bilateral orchiectomy. Histologic examination confirmed poorly differentiated prostatic adenocarcinoma. The tumor cells were poorly differentiated with pleomorphic nuclei, macronucleoli, and lack of glandular formation. Nests of tumor cells infiltrated and surrounded atrophic seminiferous tubules. Tumor cells were also identified completely filling seminiferous tubule lumens, mimicking a primary intratubular germ cell neoplasia (**Figure 2A and 2B**). The PSA immunohistochemical stain confirmed prostatic origin of tumor cells while negative placental-like alkaline phosphatase ruled out germ cell origin (**Figure 2C and 2D**). After his surgery, the patient missed his post-operative appointments and again was lost to follow up post-operatively. He was re-referred again and had presented now approximately three years after initial presentation for follow up. PSA at this visit was 7.67 ng/ml and testosterone confirming castration <8 ng/dl.

The patient continued to show signs of progression. Four months later, his PSA continued to rise 14.8 ng/ml. CT scan was consistent with disease progression along with concern for metastasis to the mediastinum, lungs, liver, adrenal gland, and inguinal lymph nodes. FNA biopsy of left inguinal lymph node confirmed metastatic prostate carcinoma. Bone scan showed no definite evidence of new metastatic disease. He was started on palliative docetaxel and a follow up CT scan revealed a clinical response in those metastatic sites.

Discussion

Metastatic tumors to the testes are very rare and are usually found incidentally on autopsy. A blood-testis barrier has been proposed, allowing the testicles to be the immune privileged site of spermatogenesis. When metastasis is suspected, PCa is the most likely culprit, followed by the malignancies of the lung and gastrointestinal tract [1]. In the case of metastatic cancers, it has also hypothesized that blood-testis barrier decreased the penetrance and effect of chemotherapeutic agents and thus reducing the efficacy of treatment [7]. Radiological evaluation to appraise tumor origin poses a challenge as prostatic metastasis

Metastatic prostate cancer to testicles

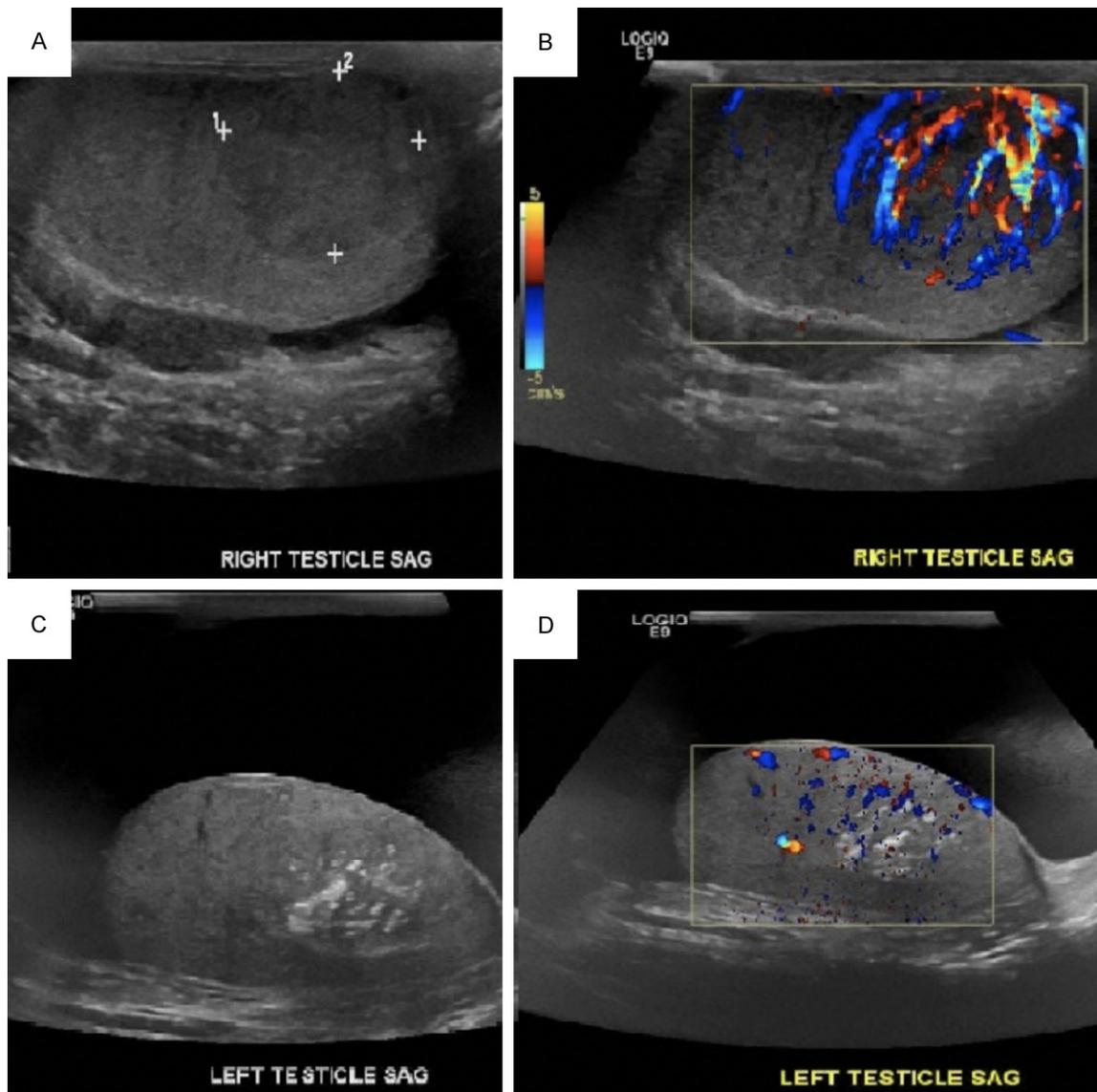


Figure 1. Testicular ultrasound. A, C. Ultrasound imaging of bilateral testicles with findings concerning for metastatic lesions to both testicles. B, D. Ultrasound with doppler sonography for blood flow visualization.

can mimic primary testicular tumors, such as mixed germ cell tumor [8].

Current literature reports there are approximately 200 cases of PCa metastasizing to the testes [3]. Case reports suggest that testicular metastases can present asymptotically at approximately 6 years after the diagnosis of PCa [9]. Initial treatment options in the palliative management of PCa include castration, typically through medical androgen deprivation therapy. Surgical castration was widely used historically in PCa [10, 11]. Although there are several proposed mechanisms of testicular

metastasis from prostatic adenocarcinoma, further research is needed to establish the implications of testicular metastases of PCa and delineate treatment strategies.

Of the approximately 200 cases that describe the rare phenomenon, the occurrence of bilateral testicular metastasis is exceedingly uncommon. Here, we summarize the 16 case reports totaling 17 events (Table 1). Our addition to the literature is only the 18th documented case. Of the patient that presented with bilateral metastasis, the average age was 69 years old with a range from 56 to 81. Our case is the

Metastatic prostate cancer to testicles

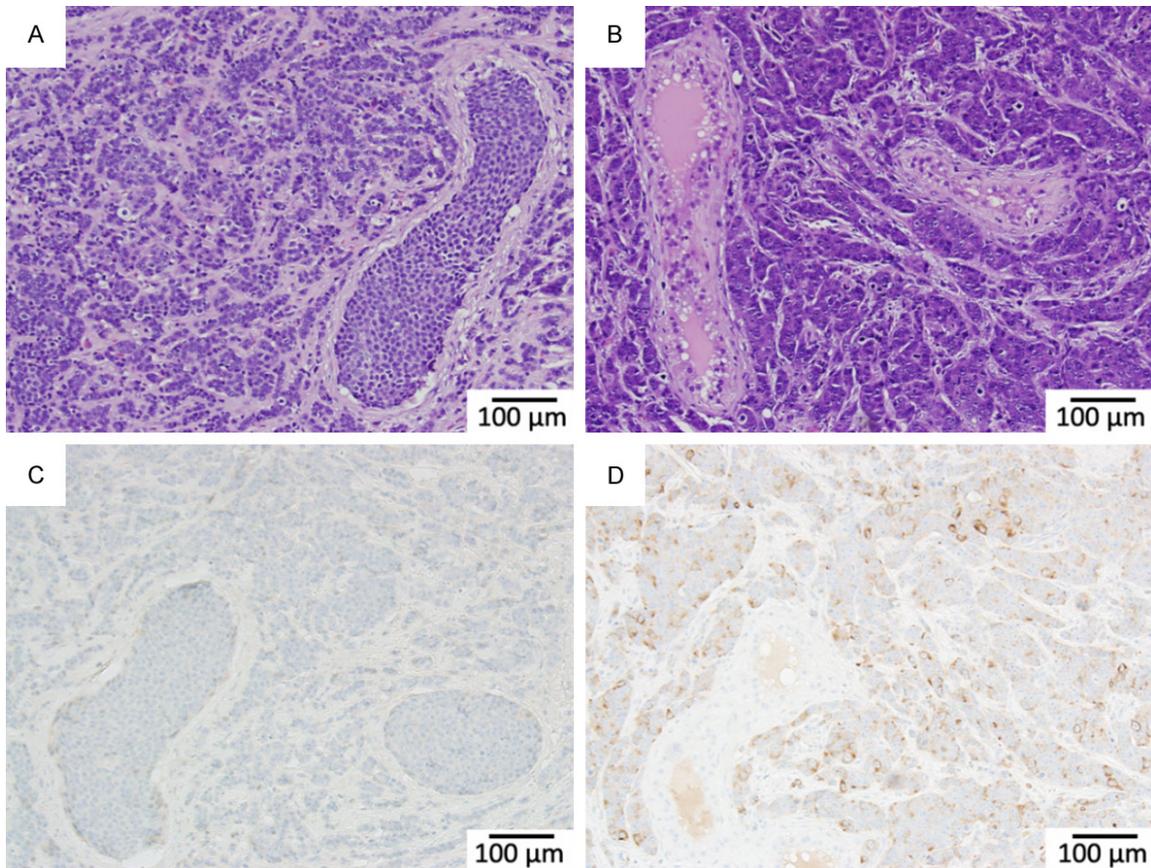


Figure 2. Abnormal growth in testes is of prostatic origin. A, B. H&E stained testes tissue revealed poorly differentiated cells with absence of glandular structure. Colonies of tumor cells invaded atrophic seminiferous tubule lumens. C. Immunohistochemical staining for placental-like alkaline phosphatase was negative, denying tumor germline origin. D. Immunohistochemical staining for PSA confirmed prostatic origin of invasive cells.

youngest on record to present with bilateral testicular metastasis. Ten of the patients had an adenocarcinoma of the prostate and three with castrate-resistant PCa (CRPCa). Nine of the patients presented with bone involvement as was seen with our patient. Two patients were also found to have lymph node involvement, one with metastasis to his seminal vesicle, and one with PCa found in his epididymis. The average time from initial diagnosis to testicular involvement was found was 4.1 years with a range from 0-15. Our patient presented with testicular lesions one year after initial PCa diagnosis. Due to the rare nature of bilateral involvement, several cases were inaccessible outside of the abstract on PubMed and the data was left “unknown”. In addition to the findings in the table, two other cases should be noted. The first reported a patient with bilateral epididymal lesions from PCa metastasis were found; however testicular involvement

was negative [12]. The second case described bilateral seminal vesicle involvement and a single testis involved [13].

Our case is unique in that on admission our patient had no significant evidence metastatic PCa on radiologic imaging who subsequently presented with bilateral testicular metastasis within 18 months of diagnosis. His prostate biopsy showed a particularly aggressive pattern of Gleason 4+5 PCa with perineural invasion and extra-prostatic invasion. He also had a very high PSA of 580 ng/mL on initial presentation and 220 ng/mL post-dual therapeutic intervention. With the high risk of micro-metastasis in this patient, the patient elected to pursue treatment with curative intent with radiation and adjuvant androgen deprivation. Early evidence of high-risk disease, inconsistent follow up, and failure to complete adequate androgen deprivation therapy were likely

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Table 1. Literature review of all bilateral testicular metastasis from prostate cancer

Manuscript Title	Age at initial PCa workup	PCa Staging at time of testes involvement	Other Metastatic sites	Time from initial diagnosis (Years)
Bilateral testicular metastasis from prostatic adenocarcinoma mimicking an intertubular pattern of seminoma and expressing Rhamm [14]	56	CRPC (Gleason 7)	Bone	0.83
Bilateral testicular metastases from prostatic carcinoma [15]	56	Adenocarcinoma (Gleason 3+3)	Bone	7
Case report of metastatic prostate cancer to testicles: An ominous sign of advanced disease [16]	56	Adenocarcinoma (High Grade)	Bone	5
Bilateral testicular metastases from prostate carcinoma: Gray scale and color doppler sonographic findings [11]	60	Adenocarcinoma	Bone, Seminal vesicles	15
Bilateral testicular metastases and filariasis in prostatic adenocarcinoma [17]	71	Adenocarcinoma (Gleason 3+4)	Bone, Lymph nodes	0
A rare case of isolated castrate resistant bilateral testicular metastases in advance prostate cancer [18]	72	CRPC (Gleason 4+5)	Bone, Lymph nodes	3
Testicular and epididymal metastasis from prostate carcinoma: A rare manifestation of common disease [19]	75	Adenocarcinoma (Gleason 5+3)	Epididymis, Bone	0
Prostatic carcinoma with bilateral testicular metastasis: A case report [20]	77	Adenocarcinoma	N/A	0
Bilateral testicular metastasis from prostatic adenocarcinoma [21]	78	Adenocarcinoma (Gleason 4+4)	Bone	6
Symptomatic bilateral testicular metastasis from carcinoma of the prostate [22]	78	CRPC	Bone	1
Prostate cancer with solitary metastases to the bilateral testis [23]	81	Adenocarcinoma (Gleason 4+3)	N/A	8
Metastases to the spermatic cord, epididymis and testicles from carcinoma of the prostate-five cases [24]	2 patients, both unknown	Unknown	Unknown	Unknown
Bilateral testicular metastasis of cancer of the prostate [25]	Unknown	Adenocarcinoma	Unknown	Unknown
Bilateral testicular metastasis of an adenocarcinoma of the prostate [26]	Unknown	Adenocarcinoma	Unknown	Unknown
Silent testicular metastasis from carcinoma of the prostate [27]	Unknown	Unknown	Unknown	Unknown
Metastatic carcinoma to the testis: A clinicopathologic analysis of 26 nonincidental cases with emphasis on deceptive features [2]	Unknown	Unknown	Unknown	Unknown

The table is listed in order from youngest patient reported to oldest, followed by unknown. Stage of PCa at time of metastasis, other metastatic locations, and time from initial PCa diagnosis is also provided.

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factors in the patient's rapid recurrence and progressive disease. He also showed signs of early castrate resistant disease with an undetectable testosterone and continued rise in his PSA. His eventual continued progression required to use of palliative treatment options and chemotherapeutics to slow his cancer's progression.

Conclusion

In conclusion, this case highlights that PCa can have a highly variable course and progression. Special attention should be paid to the treatment of patients. Given the slow but potentially aggressive growth and progression of PCa, patients should be counselled on the importance of adherence to surveillance schedules. While common areas of recurrence and metastasis exist, metastasis to rare sites can occur, including the testicle as we presented. Any evidence of disease and clinical suspicion of metastasis should be worked up, especially in patients with factors that put them at risk for advanced and metastatic disease or poor adherence to surveillance protocols.

Disclosure of conflict of interest

None.

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