CASE REPORT

Painful testicular metastasis from prostate adenocarcinoma

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SUMMARY

A 60-year-old man presented with unilateral testicular pain and urinary frequency. His presenting prostate-specific antigen (PSA) was 100 ng/mL, and a biopsy revealed Gleason 4+4 prostate adenocarcinoma. The significance of his initial PSA was somewhat complicated by possible prostatitis and early initiation of bicalutamide. PSA rose on two occasions prior to radiotherapy but coincided with a flare of testicular pain on one of these. Whole-body staging diffusion-weighted MRI scan was negative. He was treated with 3 years of androgen deprivation therapy (ADT) and radical radiotherapy. PSA fell to undetectable levels on ADT. Twelve months following completion of ADT, PSA rose to 3.6 ng/mL. No disease recurrence was noted on restaging MRI pelvis. The patient was well, except for persistent testicular symptoms, which failed to resolve following multiple antibiotics. Testicular tumour markers were negative. Ultrasound findings were consistent with chronic epididymitis. A right orchidectomy was performed for symptomatic relief, confirming metastatic prostate adenocarcinoma.

BACKGROUND

On review of the literature, it is clear that while clinically relevant and symptomatic testicular metastases from prostate cancer are rare, they are certainly not uncommon, particularly in autopsy series. As such, we must consider them as a possible cause for rising prostate-specific antigen (PSA) both at diagnosis and indefinitely thereafter, and most importantly, in the context of recurring testicular symptoms.

This case documents a metastatic deposit in the testicle of a patient originating from a previously treated adenocarcinoma of the prostate. This is a rare finding, and carries a very important educational message. This patient had a rising PSA and progressively worsening pain in his testicle along with a palpable mass but was diagnosed as having chronic epididymo-orchitis. Only following an orchidectomy performed for pain relief purpose was the metastasis diagnosed on pathology. Following orchidectomy, this patient has had no further testicular symptoms.

CASE PRESENTATION

A 60-year-old patient presented with an episode of right-sided testicular pain and urinary frequency. He worked as a farmer and was married with three adult children. He had never smoked and drank

seven units of alcohol per week. His father died of bladder cancer at the age of 73 years, and his mother as a result of cardiovascular disease at the age of 83 years. His medical history was significant only for mild hypertension, appendectomy and tonsillectomy as a child and an umbilical hernia.

His PSA was 100 ng/mL. On digital rectal examination, a very small area of nodularity was noted towards the apex of the prostate gland on the right side. Both sides of the gland were noted to be modestly tender. Urine cultures were negative at this time. A transrectal ultrasound-guided biopsy revealed extensive Gleason 4+3 prostate adenocarcinoma, with a single core of Gleason 4+4. Two weeks following this biopsy, and 1 week following commencement of bicalutamide 50 mg daily therapy, he developed an acute episode of presumed epididymo-orchitis, for which he was treated with ciprofloxacin. Examination revealed unilateral testicular tenderness. Following 4 weeks of antibiotic and approximately 6 weeks of bicalutamide, the PSA dropped to 9 ng/mL and symptoms of testicular pain resolved. The presenting PSA of 100 ng/mL was thus attributed to inflammation/prostatitis. A bone scan was negative for bony metastatic disease.

At this point, this patient was referred to our institution; the significance of his initial PSA was somewhat unclear, and had been complicated by possible prostatitis and treatment with bicalutamide. We elected to discontinue bicalutamide and observe his PSA level while continuing ciprofloxacin antibiotic for a further 6 weeks. Our rationale was that, if the PSA remained low, we could reasonably assume that the initial PSA of 100 ng/mL was misleading, and if the PSA increased rapidly, we would restage him with further imaging. We additionally performed an MRI, which showed T3b disease, with bilateral involvement of the seminal vesicles.

Five weeks after stopping the bicalutamide, the PSA was measured at 13 ng/mL but this coincided with a flare of his testicular symptoms and was thus felt to be likely unrepresentative of prostate cancer disease activity. The decision was made to proceed with a plan to treat with 3 years of androgen deprivation therapy (ADT) and radical radiotherapy. Five weeks later and just prior to initiation of ADT, his PSA was measured at 35 ng/mL. This was at a time of relative resolution of testicular symptoms. Treatment was briefly stalled while an MRI whole body was organised. This imaging revealed no evidence of metastasis, and his PSA rise was once again attributed to an unusual case of prostatitis/orchitis.

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Figure 1 There is a focal area of hypoechogenicity within the right testis, which measures 1.6 cm in maximum dimension.

He completed 3 years of ADT, with intensity-modulated radiotherapy delivered after 6 months of hormonal therapy. He was treated with 70 Gy to his prostate and 55 Gy to his pelvic nodes, both in 35 fractions of radiotherapy. His PSA fell to undetectable levels (<0.04 ng/mL) while on ADT.

Six months following completion of ADT, the PSA was measured at 1.8, at 12 months it was 3.6 and at 18 months it measured 4.7. No disease recurrence was noted on restaging with MRI pelvis. The patient was well, except for persistent and worsening right testicular pain and swelling, which failed to resolve entirely following multiple courses of antibiotics prescribed for chronic epididymitis. These episodes were dealt with by the general practitioner, and to our knowledge, positive urine cultures were not detected at any point.

An ultrasound of the testis displayed a persistent 16 mm area of hypoechogenicity within the right testis along with swelling of the right epididymis (figures 1 and 2). Appearances were consistent with chronic epididymitis with ongoing cyst formation associated with multiple foci of calcification within the right epididymis. Antibiotics were prescribed and a repeat ultrasound

Figure 2 The right epididymis contains multiple small cysts and small foci of calcification in keeping with an appearance of chronic orchitis.

was organised at a 4–6 weeks' interval. Alfafetoprotein (AFP) and human chorionic gonadotrophin (HCG) were negative at 7 and <2 ng/mL, respectively.

The patient requested an orchidectomy due to extreme testicular discomfort. He was reviewed by the urological surgeons with a view to such, who agreed that this was an appropriate next step. He proceeded to radical inguinal orchidectomy without the scheduled repeat ultrasound.

Sections of the testis show infiltration of the testicular parenchyma by tumour displaying glandular pattern. The tumour was diffusely positive for PSA and cytokeratin AE1/AE3 and negative for CD117, CD30, placental alkaline phosphatase (PLAP), cytokeratin (CK) 7 and CK20. No other malignancy of intratubular germ cell neoplasia was seen. The morphological appearances and immunohistochemistry were consistent with metastatic adenocarcinoma of prostate origin.

OUTCOME AND FOLLOW-UP

This patient's PSA was 4.7 ng/mL just prior to orchidectomy and measured 0.06 ng/mL 3 months postoperatively. A very slow rise in PSA was seen for 2 years following removal of the metastasis. PSA doubling time then rapidly rose to 3 months. Restaging with CT and bone scan were performed with a PSA of 9 ng/mL. Four small bony metastatic deposits led to initiation of ADT. Within 12 months, he became castrate resistant and was commenced on abiraterone. He continues on this with an undetectable PSA and stable disease on imaging 3.5 years later with no further testicular symptoms.

A painful testis is most common due to infection or injury. Testicular torsion must be considered in the acute presentation of a tender, swollen unilateral testis particularly among young boys. A sexually transmitted infection is the most common cause of epididymo-orchitis in young men. In the elderly, infection in the form of orchitis or epididymo-orchitis is the most common finding. Patients typically present with fever and dysuria paired with a painful, erythematous and swollen epididymis and/or testis.

Tumours of the testis present as a lump or swelling, 'dragging' sensation around the testis or with pain. In this case, the differential included a primary testicular cancer or a secondary metastasis from either the prostate or another, undiagnosed site of malignancy.

DISCUSSION

The most common metastatic sites of prostate carcinoma are bone, lung and liver. Testicular metastases are very rare, and are most likely to be incidental findings in 2%–4% of orchidectomies for the purpose of surgically castrating patients with known metastatic disease.¹ Secondary neoplasms of the testis have been reported with an incidence of 0.02%–2.5% on autopsy.² The reason for such a low incidence of metastases to the testis would seem to be that the low temperature of the scrotum presents unfavourable conditions for establishment of metastatic tumours.³ Routes of metastatic spread to the testis are discussed controversially. Overall, there are four proposed mechanisms for the spread of the lesions to the testis: a retrograde venous extension, a retrograde lymphatic extension, arterial embolism and through the lumen of the vas deferens.⁴

Most cases of prostate carcinoma in the literature describe other metastatic sites besides the testis, for instance in the skeletal system or disseminated locations.⁴ The first reported case of local metastasis was described in 1935. In a large autopsy study of patients older than 40 years, 19316 routine autopsies were

Table 1 Cases of prostate adenocarcinoma with testicular metastases

Author	Journal	Year of publication	Number of cases	Time of diagnosis—localised or metastatic	Initial PSA (ng/mL)	Relapse PSA (ng/mL)	Treatment	Evolution/outcomes
Campara <i>et al</i>	<i>Med Arch</i>	2016	1	Localised	Not known	'Gradual rise' over 9 years	Left orchidectomy for symptomatic mass.	Unknown
Zhang <i>et al</i> ¹²	<i>Oncol Lett</i>	2016	1	Localised	>100	N/A	Bilateral orchidectomy (done as surgical castration—incidental finding).	Stable with no signs of disease at 24 months
Sampathrajan <i>et al</i> ¹³	<i>J Clin Diagn Res</i>	2015	1	Metastatic	225.49	Unknown	Bilateral orchidectomy (done as surgical castration—incidental finding).	Not discussed
Kusaka <i>et al</i> ¹¹	<i>Case Rep</i>	2014	1	Metastatic	137	Undetectable postoperatively on ADT	ADT initially followed by right inguinal orchiectomy for symptomatic mass.	Stable with no signs of disease at 12 months
Kwon <i>et al</i> ⁹	<i>Korean J Urol</i>	2011	1	Localised	0.347	Unknown	Initial prostatectomy. Right inguinal orchidectomy due to symptomatic mass.	Stable with PSA 0.3 1 month postoperatively
Janssen <i>et al</i> ⁸	<i>Anticancer Res</i>	2010	1	Localised	2.07	Undetectable	Prostatectomy, RT for suspected recurrence followed by bilateral orchidectomy as surgical castration.	Stable with no signs of disease at 24 months
Erlianti Rahardjo <i>et al</i>	<i>Asian J Surg</i>	2010	1	Metastatic	40	Unknown	TURP and bilateral orchidectomy as part of surgical castration.	One year post-treatment alive with high PSA but refusing further treatment/investigation
Smaali <i>et al</i> ¹⁰	<i>Urology</i>	2010	1	Localised	Zhang 150	35	ADT and RT initially. Then right orchidectomy for symptomatic mass.	Unknown
Haupt <i>et al</i> ¹	<i>Int J Clin Exp Pathol</i>	2009	1	Localised	Unknown	Unknown	ADT followed by surgical castration (bilateral orchidectomy).	Unknown
Haupt <i>et al</i> ¹	<i>Int J Clin Exp Pathol</i>	2009	1	Localised	Unknown	Unknown	ADT, RT to bony mets and then bilateral orchidectomy as surgical castration.	Unknown
Manikandan <i>et al</i> ¹⁶	<i>Int J Urol</i>	2006	1	Metastatic	1100	11	ADT followed by unilateral orchidectomy for symptomatic mass.	Stable on ADT 4 years postoperatively
D'Amico <i>et al</i>	<i>Int Urol Nephrol</i>	1995	1	Localised	Unknown	Unknown	Right orchidectomy for symptomatic mass.	Unknown
Weitzner ¹⁸	<i>Cancer</i>	1973	15	Five had testicle as only site of metastases	N/A	N/A	Thirteen had incidental orchidectomy; two had unilateral orchidectomy.	Eight alive, seven dead (six died of disease)
Moskovitz <i>et al</i>	<i>Urol Int</i>	1987	1	Metastatic	Not known	Not known	TURP and bilateral orchidectomy as part of surgical castration.	Not known
Marble ¹⁷	<i>J Urol</i>	1960	1	Localised	Unknown	Unknown	ADT and then bilateral orchidectomy as surgical castration.	Died 2 years postorchidectomy

ADT, androgen deprivation therapy; mets, metastasis; N/A, not applicable; PSA, prostate-specific antigen; RT, radiotherapy; TURP, transurethral resection of the prostate.

performed from 1967 to 1995.⁴ Bubendorf *et al* analysed the reports from the 1589 patients with prostate cancer: 35% of them had haematogenous metastases, most frequently involving the bone (90%), lung (46%) and liver (25%); metastases in the testes were found in 0.5% only (5). Nevertheless, prostate cancer is the most common tumour which metastasises to the testis (15%); infrequently lung tumours, melanomas, colon, pancreatic or kidney tumours also spread to the testis.³ In another prospective autopsy study of male subjects with malignant neoplasms, six were shown to have metastatic deposits within the testis (2.5%). These were metastases from carcinoma of the prostate (two cases), melanoma (two cases), bronchial carcinoma (one case) and pleural mesothelioma (one case). In an American study published in 1971, of 22 cases of secondary carcinoma of testis, the primary tumours were malignant melanoma in nine cases, lung cancer in three cases and prostate cancer in two cases.⁵ In a number of more recent studies for the cases of metastatic carcinomas to the testis, the most frequent primary sites were prostate, followed by lung, kidney, colon and stomach.^{6,7}

Case studies and series relating to testicular metastases from prostate primaries have been summarised in table 1.

Most reports on single cases involve patients previously treated curatively for confined disease with prostatectomy^{8,9} or radiotherapy.¹⁰ A smaller number do document cases of patients who had testicular metastases at presentation.^{11,12} Some cases describe incidentally discovered testicular metastases, diagnosed incidentally following radical orchidectomy for the purposes of surgical castration.¹³ In most instances, testicular secondaries

are unilateral, with rare bilateral involvement.^{14–16} A number of older and larger case series do comment on presentation, with Marble reporting 7 of 30 patients had a palpable testicular mass at presentation,¹⁷ while only 2 of 15 patients in a series by Weitzner had palpable disease on presentation.¹⁸

This patient was incorrectly felt to have chronic infection, and his testicular metastasis was diagnosed only through pathology. While the ordering of AFP and BHCG tumour markers suggests

Learning points

- ▶ Testicular metastases from prostate cancer are clinically rare, but as noted from autopsy series, not pathologically uncommon.
- ▶ There is a need for proper evaluation of rare metastatic sites such as the testis or the epididymis for accurate staging and early detection of possible metastasis in the setting of an elevated prostate-specific antigen level.
- ▶ Orchidectomy provides lasting symptomatic relief and providing treatment for the underlying malignancy in patients with testicular metastases.
- ▶ In any patient with a previous or current malignancy and a persistently painful testis that fails to respond to antibiotic treatment, early consideration must be given to potential malignancy while acknowledging that infection is a likely diagnosis.

that consideration was given to a testicular primary, there was no thought given to the possibility that the unusual PSA pattern could be attributed to a testicular metastasis. Indeed, no link was made between recurrent and progressively painful 'epididymo-orchitis' and prostate cancer, other than the fact that the inflammatory effects of the former complicated the diagnosis of the latter.

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