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Case report

Synchronous metastatic prostate cancer and male breast cancer while on testosterone replacement therapy: Case report

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ABSTRACT

Introduction: Testosterone replacement therapy (TRT) can improve quality of life for men with hypogonadism. However, it is generally avoided in patients with a history of prostate cancer or breast cancer as there is uncertainty about risks. This case illustrates an example of synchronous metastatic prostate cancer and male breast cancer following TRT.

Presentation of case: A 72-year-old man with previously treated intermediate-risk prostate adenocarcinoma experienced a gradual rise in prostate-specific antigen (PSA) while self-administering testosterone replacement. He was later found to have recurrent metastatic prostate cancer and prior to initiating androgen deprivation therapy (ADT), he was also diagnosed with male breast cancer. His treatment has consisted of continued ADT for metastatic castration-sensitive prostate cancer (mCSPC) as well as surgical resection of his breast cancer.

Discussion: ADT plays a role in treatment of male breast cancer and prostate cancer. TRT remains relatively contraindicated in patients with a history of these malignancies, but the evidence supporting this recommendation is somewhat limited.

Conclusion: This case highlights the potential risk for synchronous recurrent prostate and new male breast cancer following TRT. Further studies are needed to better elucidate the increased risks of these malignancies with TRT.

1. Introduction

Testosterone replacement therapy (TRT) can be used to treat symptomatic primary hypogonadism with the benefits of increased energy, libido, mobility, and potentially decreased risk of bone density loss and metabolic syndrome [1]. For men with a history of prostate cancer, common practice is to avoid prescribing TRT due to concern for the risk of recurrence [2]. There is inconsistent evidence whether TRT truly increases the risk of de novo prostate cancer, and there is also uncertainty regarding risk of prostate cancer progression with long-term TRT [3]. For men with hypogonadism and low risk factors for prostate cancer, a randomized clinical trial found no increased incidence of high-grade prostate cancer after an average of 22 months of follow-up [4]. TRT is also avoided in men with a history of breast cancer, but the evidence remains limited due to the rare occurrence of male breast cancer [5].

This case illustrates a unique presentation of synchronous metastatic prostate cancer and male breast cancer following TRT. To our knowledge, there have been no previous reported cases of simultaneous male breast cancer and recurrent, metastatic prostate cancer following TRT. This work has been reported in line with the SCARE criteria [6].

2. Presentation of case

A 72-year-old Caucasian man with previously treated stage pT2cN0R0 intermediate-risk (Gleason 4 + 3 = 7) prostate adenocarcinoma was seen in initial consultation in late 2023 for progressive increase in prostate-specific antigen (PSA) values following use of TRT with over-the-counter testosterone enanthate. His other past medical history included well-controlled type 1 diabetes mellitus, hypertension,

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and primary hypogonadism. Pertinent family history included prostate cancer in the patient's father and paternal grandfather but no family history of breast or ovarian cancer.

For his initial diagnosis of prostate adenocarcinoma in 2015, he underwent robot-assisted laparoscopic radical prostatectomy and lymphadenectomy with negative margins. Prior to this, he had used over-the-counter testosterone enanthate in 2010 but stopped when diagnosed with prostate cancer in 2015. Post-prostatectomy, the patient followed with his urologist once every few months for a total of 1 year. Post-operative PSA nadir was undetectable (<0.1 ng/mL) in late 2016. Due to his persistent symptoms from hypogonadism, he elected to restart TRT with testosterone enanthate injections 250 mg/mL every 7–10 days against medical advice. As a result, his PSA began to gradually increase in 2017. After his prostatectomy, he was concerned about urinary frequency and erectile dysfunction, and he eventually underwent penile implant placement in late 2018. Imaging in 2019 and 2021 was suggestive of local recurrence and nodal metastases, so he was offered salvage intensity modulated radiotherapy (IMRT) but declined. At the time, he also elected to continue TRT against medical advice. Outside Piflufolastat F-18 prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and computed tomography (CT) scan in 2023 demonstrated high PSMA uptake at the vesicourethral anastomosis, several avid retroperitoneal and pelvic lymph nodes, and a focal 1 cm region of sclerosis in the left superior pubic ramus, all consistent with recurrent metastatic castration-sensitive prostate cancer (mCSPC) (Fig. 1). The PSMA PET CT scan report mentioned low level of PSMA uptake in the right breast, initially thought to be related to asymmetric gynecomastia. He continued to take TRT after his metastatic diagnosis despite re-counseling, and his PSA reached a peak of 244 ng/mL in late 2023 prior to eventual discontinuation on initial consultation. For mCSPC, he started androgen deprivation therapy (ADT) with bicalutamide lead-in to leuprolide, and a second-generation anti-androgen, darolutamide, was added per standard of care in early 2024.

Prior to the initiation of ADT and approximately 3 weeks after initial consultation, the patient reported a non-tender lump behind his right nipple. Ultrasound and mammography were obtained showing high-risk features. Breast biopsy showed grade 2 invasive ductal carcinoma with mucinous features that was estrogen receptor (ER) positive, progesterone receptor (PR) positive, and human epidermal growth factor receptor 2 (HER2) negative. Germline genetic testing was negative for BRCA1 or BRCA2, and an extended panel was also non-contributory. Notably, he did not have a family history of breast cancer. He underwent right central partial mastectomy and sentinel lymph node mapping and excision approximately 1 month after diagnosis that resulted in a 2.2 cm pT2N0 invasive ductal carcinoma with clear margins and 0 out of 1 negative lymph nodes. Biomakers from the surgical pathology showed ER positivity of 95 %, PR 2 %, HER-2 negative, and Ki-67 10 %. OncotypeDx recurrence score was 19, indicating <1 % benefit for adjuvant chemotherapy.

Currently, he continues ADT with darolutamide twice daily and leuprolide every 3 months for mCSPC. He also routinely follows every 3–6 months for invasive ductal carcinoma of the breast and is scheduled to undergo breast radiation later in 2024.

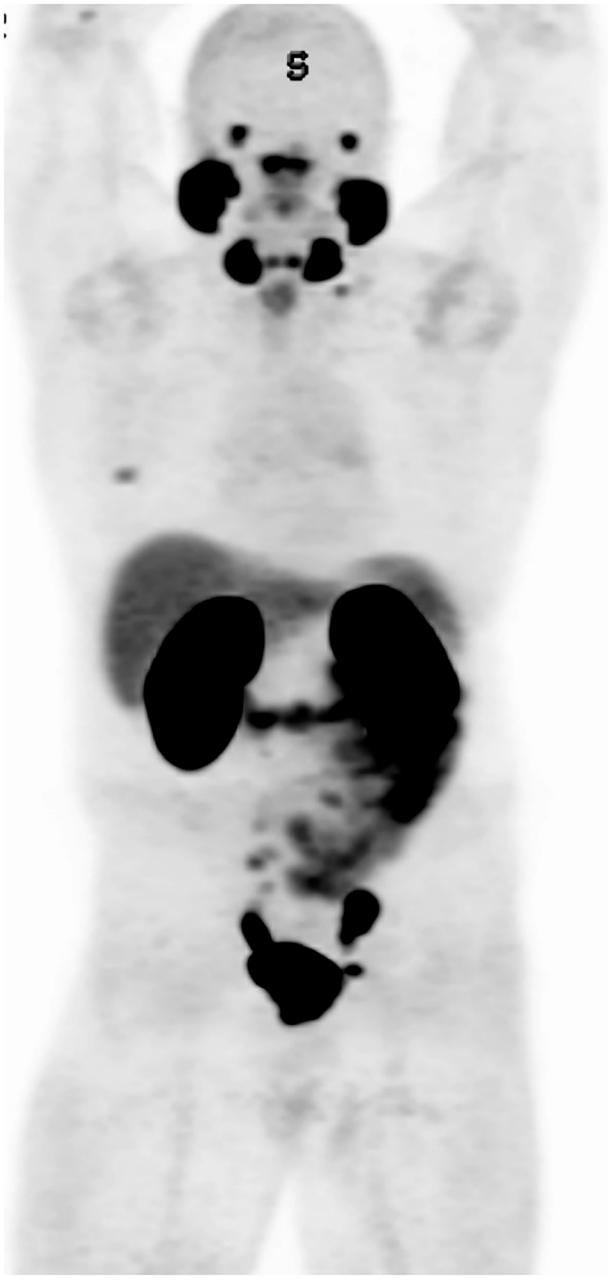

Fig. 1. Image of PSMA PET CT scan. The scan shows high PSMA uptake at the vesicourethral anastomosis, several avid retroperitoneal and pelvic lymph nodes, and focal 1 cm region of sclerosis in the left superior pubic ramus. There was also mention of low level of PSMA uptake in the right breast, initially incorrectly thought to be related to asymmetric gynecomastia.

3. Discussion

This report illustrates a case of recurrent metastatic prostate cancer and new male breast cancer following TRT. Despite significant concern with utilizing TRT in patients with a history of prostate cancer, evidence suggests that the risk of recurrent disease is relatively low [1]. Studies with relatively small numbers of patients (<100) found evidence of biochemical recurrence between 1 and 4 % among men previously treated for prostate cancer, including those that were intermediate-to-high risk [3]. Our patient initially was diagnosed with intermediate-risk prostate cancer (Gleason 4 + 3 = 7), so he likely would have had a similar risk of recurrence to the patients in these studies. Nevertheless, our patient had demonstrable evidence of recurrent metastatic disease likely due to continued use of TRT.

Likewise, TRT is contraindicated for use in men with history of breast cancer, but there is limited data on the association of TRT with development of breast cancer partially due to the rarity of male breast cancer [5]. In a systematic review of all published studies of TRT and association of male breast cancer, only 4 cases of breast cancer in cisgender males were identified, limiting the ability to associate TRT with development of male breast cancer [7]. On the other hand, a nationwide study of breast cancer risk in transgender people on hormone treatment in the Netherlands, showed a risk of breast cancer in transgender men, albeit lower than that of cisgender women [8].

ADT remains an important backbone in the treatment of metastatic

prostate cancer [9]. Long-term ADT for mCSPC eventually precipitates castration-resistant disease [10]. One approach under investigation is bipolar androgen therapy (BAT), which couples alternating periods of testosterone suppression with ADT followed by periods of testosterone supplementation. It is postulated that BAT may extend the overall duration of ADT response and re-sensitize castration-resistant clones to subsequent anti-androgen therapies [11,12]. In our patient's case, however, his use of TRT was not concordant with BAT protocol, as he self-administered testosterone for an extended duration of time without the use of ADT.

ADT, including leuprolide, also plays a role in treatment of men with breast cancer based on retrospective studies [13–17]. Pre-clinical studies have suggested that gonadotropin-release hormone receptor, a target of leuprolide, inhibits breast cancer proliferation and metastasis [18]. Use of leuprolide for men with both prostate and breast cancer is not well-studied. One case report reported a diagnosis of male breast cancer approximately 15 months after initiating concurrent radiation therapy and ADT with leuprolide, but this was felt to be related to resistance to leuprolide [19]. After diagnosis of breast cancer, the patient started aromatase therapy with anastrozole after declining adjuvant chemotherapy following modified radical mastectomy. In this case study, genetic testing revealed a rare BRCA2 mutation (K1025E variant) with a known family history of breast cancer in the patient's daughter, whereas for our patient, neither of these risk factors were present. Given the evidence from retrospective studies on use of leuprolide for male breast cancer and its guideline-recommended use for prostate cancer, ADT continued to be indicated for our patient.

4. Conclusion

TRT is generally avoided in patients with a history of prostate and breast cancer. Evidence remains uncertain about the magnitude of risk of these malignancies with TRT. This case highlights the potential risk for developing synchronous recurrent prostate cancer and male breast cancer. Future research is needed to ascertain how much this risk is increased, if at all, and whether TRT can ever be safely used with a prior history of prostate cancer or breast cancer.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Ethical approval was granted by the UCLA Institutional Review Board IRB #23–000376.

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Author contribution

Justin J. Cheng – data curation; analysis and interpretation of data; original draft; review & editing; final approval of version submitted.

John Shen – conceptualization, data curation; methodology; original draft; review & editing; final approval of version submitted.

Yashila Suresh – analysis and interpretation of data; original draft; review & editing; final approval of version submitted.

Nelli Akopyan – data curation; analysis and interpretation of data; review & editing; final approval of version submitted.

Nimmi Kapoor – conceptualization, design; data curation; methodology; supervision; original draft; review & editing; final approval of version submitted.

Guarantor

Justin J. Cheng.
John Shen.
Yashila Suresh.
Nelli Akopyan.
Nimmi S. Kapoor.

Conflict of interest statement

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