Solitary recurrence of castration-resistant prostate cancer with low or undetectable levels of prostate specific antigen salvaged with local ablative radiation therapy: A case report

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Abstract. Prostate cancer recurrences are usually first detected by increased levels of prostate specific antigen (PSA), and systemic therapy is often initiated if distant metastasis is confirmed. However, low or nearly undetectable levels of PSA in the modern era of ultrasensitive PSA assay may be difficult to interpret in patients with a history of prostate cancer. Deciding whether to initiate additional systemic therapy in limited indolent metastatic disease while balancing the quality of life of the patient and ensuring the oncologic control of the disease may be challenging. In the present study, the case of a biopsy-confirmed solitary spine recurrence of prostate cancer with nearly undetectable but persistent levels of PSA (0.05 ng/ml) is reported. Treatment of the recurrence with local ablative radiotherapy improved the pain experienced by the patient, and reduced his levels of PSA to undetectable limits (<0.05 ng/ml). Repeated imaging analysis, PSA assay and clinical assessment demonstrated durable control of the disease without the requirement for additional systemic treatments. The present case highlighted the importance of initiating appropriate work-up according to the clinical scenario. Local treatment for solitary or oligometastatic recurrence of prostate cancer may enhance the effectiveness of current therapeutic strategies and benefit certain patients.

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Introduction

The cancer-specific survival rates for patients with prostate cancer remain high, despite the fact that this type of cancer is the most common non-cutaneous malignancy, and the second leading cause of cancer-associated mortality in men in USA (1). According to Siegel *et al* (1), the 5-year relative survival rate for prostate cancer in the USA between 2003 and 2009 was 99% for all stages. There were ~233,000 new cases of prostate cancer diagnosed in the USA in 2014 (1). Close surveillance of survivors of prostate cancer is important, with physical examination and prostate specific antigen (PSA) testing being currently considered the standard of care to detect potential recurrences. For patients with prostate cancer that present an average risk of recurrence, the National Comprehensive Cancer Network recommends conducting a digital rectal examination every year, and measuring the levels of PSA every three-six months for the first five years following treatment, and annually thereafter. More intense monitoring every three months may be indicated for patients with high risk of recurrence, nodal involvement or distant metastasis at presentation (2). In the present study, a case of symptomatic solitary recurrence of prostate cancer that occurred while the patient was receiving androgen deprivation therapy (ADT), and presented with low/undetectable serum levels of PSA, is reported.

Case report

A 74-year-old Caucasian male with a history of prostate cancer presented to the University of Texas, Southwestern Medical Center (Dallas, USA) with worsening back pain. The patient had undergone radical prostatectomy (RP) with pelvic lymph node dissection four years earlier. Pathological analysis demonstrated Gleason score 8 disease (4+4 with tertiary grade 5) at stage pT3b, with involvement of seminal vesicles, perineural invasion, extracapsular extension and negative margins. None of the pelvic lymph nodes (0/2 nodes on the right side and 0/4 nodes on the left side) were involved. Six months following surgery, the levels of PSA of the patient increased to 1.0 ng/ml, with a doubling time of 1.7 months.

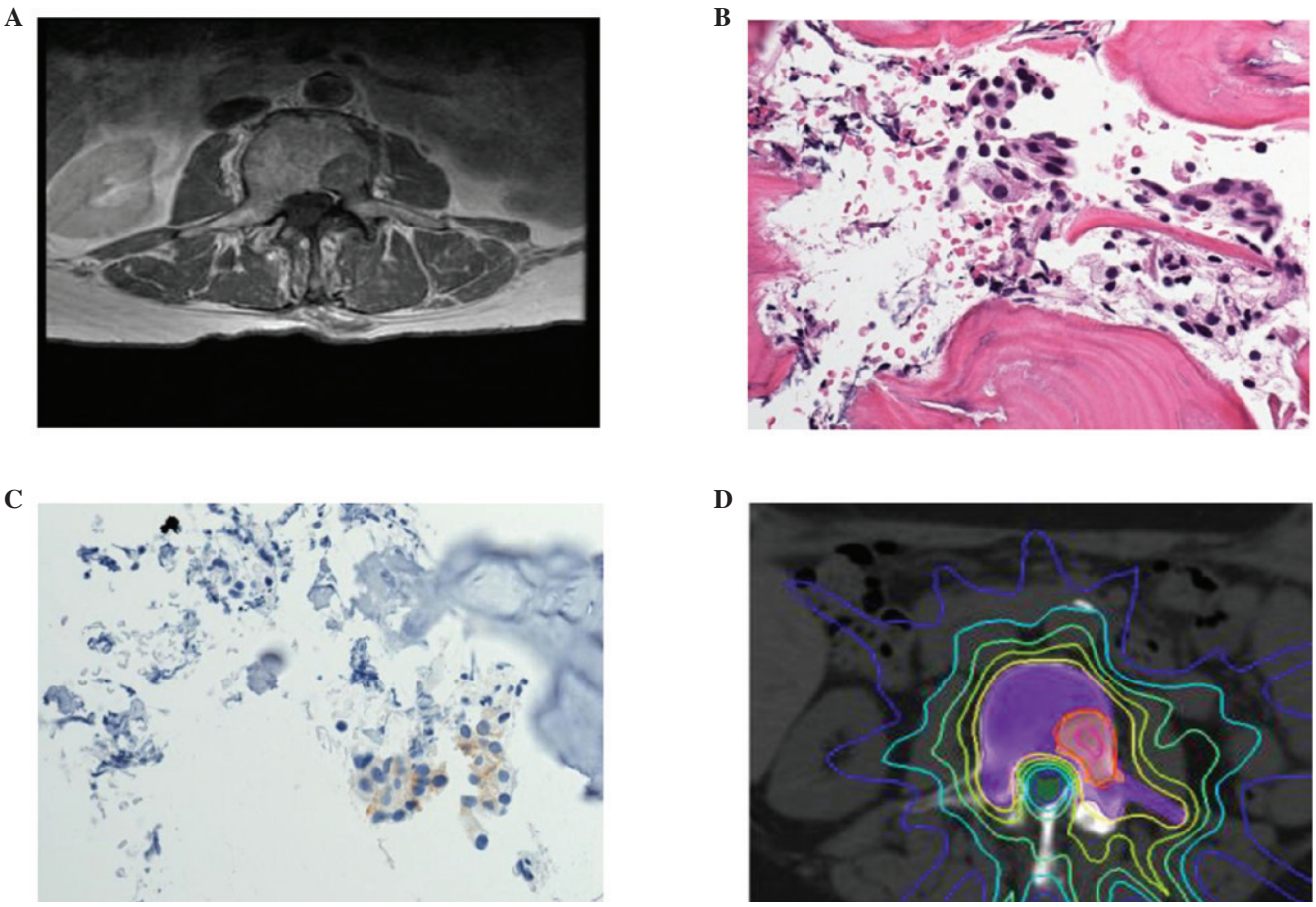

Figure 1. (A) Axial lumbar magnetic resonance imaging at the level of the L3 vertebral body, prior to the administration of SBRT. (B) Pathological analysis of the L3 vertebral body specimen obtained by biopsy, demonstrating metastatic adenocarcinoma consistent with primary prostate cancer (hematoxylin and eosin stain; magnification, x400). (C) Immunohistochemistry for prostate specific antigen (magnification, x400). (D) Axial view of the SBRT plan, delivering 20 Gy to the gross target and 14 Gy to the involved spine. SBRT, stereotactic body radiotherapy.

Work-up was not conclusive for metastatic or regional disease recurrence.

The patient underwent salvage radiation therapy (RT) with 6,662 cGy to the prostatic fossa and 4,500 cGy to the pelvic lymph nodes, in addition to short-term neoadjuvant therapy and concurrent ADT, consisting of leuprolide acetate depot every three months and daily bicalutamide. One month subsequently to the completion of RT, the levels of PSA of the patient reduced to 0.2 ng/ml. However, five months later, his levels of PSA increased to 2.84 ng/ml, and his levels of testosterone were 455 ng/dl. Thus, the patient was considered to present biochemical failure, and salvage ADT was consequently initiated. Following treatment, the levels of PSA of the patient declined, and were maintained at a nadir of 0.07 ng/ml. However, one year later, the patient presented with worsening back pain, numbness and burning sensation radiating to his left anterior thigh and knee, which was consistent with radiculopathy in the lumbar levels 3 and 4. The patient rated the level of pain as 9/10, which was unresponsive to pregabalin and hydrocodone, although the addition of tramadol reduced the pain to a level of 4/10. Magnetic resonance imaging (MRI) of the lumbar spine identified a 2.1x2.8 cm sclerotic lesion in the left L3 vertebral body that extended to the pedicle (Fig. 1A), which was suggestive of metastatic disease, and possibly responsible for the symptoms experienced by the patient. However, bone scan did not reveal any lesion. PSA analysis was then repeated, and the levels of PSA detected were 0.05 ng/ml, while the levels of testosterone were 2.5 ng/dl. These findings would have been considered as undetectable PSA prior to the era of ultrasensitive PSA assay, particularly due to the nadir levels of PSA exhibited by the patient while receiving ADT.

Based on this presentation, concerns about the etiology of the L3 lesion were raised, and a biopsy of the L3 lesion was then performed. Routine pathological and immunohistochemical analysis was performed using a Ventana BenchMark detection system and the following antibodies: Polyclonal rabbit anti-human PSA (#760-2506) and monoclonal mouse anti-human PSA (ER-PR8) (#760-4271; all from Ventana Medical Systems, Inc., Tucson, AZ, USA). Pathological analysis of the specimen demonstrated it to be a well-differentiated adenocarcinoma of the prostate, with focally positive PSA staining, thus confirming recurrent prostate cancer (Fig. 1B and C). Neuroendocrine features were not observed. With the confirmation of symptomatic solitary metastatic disease, the L3 lesion was then treated using stereotactic body RT (SBRT), with 2,000 cGy to 86% gross tumor volume and 1,400 cGy to 97% planning treatment volume (PTV) (Fig. 1D). The pain experienced by the patient subsequently improved to a level of 2/10, without requiring an increase in pain medications, and the levels of

PSA immediately reduced to undetectable levels (<0.05 ng/ml) two weeks following SBRT, and remained undetectable during the subsequent three measurements conducted at six months post-therapy. Subsequent clinical examination and imaging studies, including lumbar MRI performed at eight months post-SBRT, did not provide any radiographical evidence of disease progression in the site subjected to SBRT treatment or novel metastatic disease. Following completion of SBRT, no systemic therapy additional to leuprolide acetate has been administered to the patient to date.

The present retrospective case study was approved by the Ethics Committee of the University of Texas, Southwestern Medical Center (#STU 052012-019).

Discussion

PSA is generally a reliable biomarker with a high negative predictive value for detecting recurrence of prostate cancer in patients that had been previously subjected to RP (3). Ultrasensitive PSA testing methods enable the prediction of biochemical recurrence-free survival following prostatectomy (4). The threshold for biochemical failure subsequent to RT has evolved over time (5). However, recurrence of prostate cancer with low or undetectable levels of PSA has been previously reported (6-9), and therefore, low levels of PSA alone should not discard the possibility of recurrence of prostate cancer in a suspicious clinical setting.

Possible explanations for low or undetectable levels of PSA in the context of metastatic disease include technical limitations (10), effectiveness of the treatment (11,12) and biological characteristics of the tumor (7,8,13). The sensitivity of serum PSA assays has remarkably improved over the years, and false negative errors have become less likely with the modern detection methods currently available (4). A clinically detectable lesion suggestive of metastasis generally implies sufficient tumor burden possible to detect by serology. However, the patient of the present case report was on ADT at the time of recurrence, which may have reduced the levels of PSA and masked the detection of an increase in the levels of this marker. Furthermore, previous pathological reviews of prostatectomy-derived specimens demonstrated an inverse correlation between the Gleason score and the PSA content in prostate cancer, suggesting reduced PSA production in cases of high grade, de-differentiated prostate cancer (13). Previous retrospective studies have demonstrated that de-differentiated prostate cancer, which exhibits neuroendocrine features, may progress without increased levels of PSA in <3% of all cases of recurrent prostate cancer, which often appear to be more aggressive (7,8). However, in the present case, the pathological analysis did not detect these features, but demonstrated a well-differentiated adenocarcinoma with focally positive PSA. Intralesional heterogeneity, resulting in certain tumor tissues not expressing PSA, may have contributed to the low levels of PSA detected in the patient of the present study. This tumor heterogeneity may be due to the effect of the ADT treatment or the biology of the tumor. Previous literature reviews demonstrated that the majority of cases of recurrent prostate cancer without detectable levels of PSA displayed pathological confirmation of PSA on immunohistochemical stain (14). In the present case, it is conceivable that the recurrent cancer cells may have acquired novel mutations that prevented the secretion of PSA, resulting in false-negative PSA serology.

The current standard of care for recurrent prostate cancer following salvage RT is ADT, which is considered to be a non-curative treatment (15,16). Furthermore, PSA^- prostate cancer may be less sensitive to hormones, and responds unfavorably to salvage hormonal therapy (17). Since hormonal therapy markedly affects the quality of life of patients, limited ADT is often recommended for biochemical failure following definitive therapy (18). The majority of salvage treatments for castration-resistant prostate cancer provide a marginal improvement on survival (19), highlighting the importance of contemplating the quality of life of the patients while treating prostate cancer (20). In the present case, the lack of requirement for additional second line hormonal therapies following local ablative therapy was beneficial for the patient.

Traditionally, local therapy such as RT is generally reserved for symptomatic palliation (21,22). SBRT enables precise delivery of ablative radiation to the target, with minimum dose to the surrounding normal tissue, using image guidance and immobilization devices (23). SBRT has been previously used to treat spine metastasis in a cooperative group setting (Radiation Therapy Oncology Group #0631) (24). In order to account for microscopic extension of the tumor cells when treating spine metastasis by SBRT, the clinical target volume (CTV) must include the gross tumor volume defined by imaging, and the contiguous bone marrow cavity, including the two pedicles. The posterior element of the vertebra should be included in the CTV only if it is directly involved by the gross tumor. Due to the minimum motion of the spine and the use of daily image guidance, there is no margin for set-up errors in the PTV in spine SBRT.

SBRT has also been previously used to treat oligometastasis or disease that is non-responsive to systemic therapy (25-27). A recent phase II SBRT trial combining erlotinib in patients with oligometastatic non-small cell lung cancer who had failed first time treatment with chemotherapy, demonstrated an alteration in the pattern of failure experienced by the patients, and a marked delay in disease progression when subjected to SBRT, compared with historic controls (progression-free survival, 2-4 vs. 14.7 months; overall survival, 9 vs. 20.4 months) (28). A previous preliminary report from the Eastern Cooperative Oncology Group E3805 study indicated that the addition of docetaxel to ADT improves survival in patients with metastatic prostate cancer (29). While the benefits of local treatment of oligometastatic recurrence in castrate-resistant prostate cancer are unclear, consideration for such treatment has been suggested in the hormone-sensitive setting (30), and it has been proposed that local treatment may complement the effects of systemic therapy. Prostate cancer is generally a slow-growing tumor, and long-term survival may be achieved by early detection, effective surgery and advancements in systemic therapy (31). Nonetheless, disease progression in prostate cancer tends to occur at sites of tumor bulk, and castration-resistant clones may be present at the early stages of the disease (15,32). Application of local therapy such as SBRT may enable longer disease control, by complementing the effects of systemic therapy. Therefore, SBRT may possess a potential curative

role in certain subgroups of patients with metastatic prostate cancer, and should be considered in cases of oligometastasis.

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