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Case Report

Case Series: "Silent" Spinal Epidural Metastases in Metastatic Castrate-Resistant Prostate Cancer

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Abstract
Introduction: Spinal epidural metastases (SEM) are an uncommon phenomenon and traditionally occur as a preterminal event in heavily pre-treated patients. The introduction of novel anti-androgen therapies, such as enzalutamide and abiraterone acetate, has greatly improved the survival of patients with metastatic prostate cancer but may be changing the pattern of disease. ***Case Presentation:*** Four patients diagnosed with metastatic castrate-resistant prostate cancer (CRPC) were commenced on enzalutamide prior to chemotherapy. Baseline scans in all patients demonstrated extensive bony disease and lymph node involvement. All patients experienced a moderate initial PSA response to treatment (median PSA at baseline 53.5 ng/mL to median nadir 24.5 ng/mL). In all four cases, clinical presentation of spinal cord compression was unexpected with no prodromal neurological symptoms, PSA levels either stable or slowly rising, and CT scans and whole-body bone scans showing stable disease at other metastatic sites. Whole-spine MRI on presentation of neurological deficits showed epidural and dural metastases on the background of stable bone disease. Spinal cord compression occurred at a median of 11.4 months after starting enzalutamide. ***Conclusion:*** Clinicians should be aware of this change in the pattern of CRPC in patients treated with novel anti-androgen therapy. Onset of "silent" spinal cord compression due to SEM rather than bone metastases, can occur relatively early with minimal warning despite stable disease on PSA and standard imaging. Differential

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progression in nontraditional sites suggests that research into the androgen microenvironment in a wide range of tissue sites should be undertaken, and may explain why prostate cancer metastasizes preferentially to bone and lymph nodes.

Introduction

Spinal epidural metastases (SEM) secondary to castrate-resistant prostate cancer (CRPC) are an uncommon phenomenon – usually presenting in heavily pre-treated patients and often as a preterminal event [1, 2]. The inclusion of CYP17 inhibitor abiraterone [3, 4] and novel androgen receptor antagonist enzalutamide [5, 6] into the anti-prostate cancer armamentarium has greatly impacted on the overall survival of patients with CRPC but may be changing the pattern of disease. Less common sites of metastatic disease have been noted [7, 8] and may be due to multiple factors, including molecular escape mechanisms, phenotypic reprogramming in response to treatment, and epigenetic-mediated resistance [9–11]. In a longitudinal analysis of 41 genome-wide copy number variation profiles pre- and posttreatment, it was demonstrated that disease progression after androgen receptor-targeted therapy was associated with a dramatic change in the genotype and phenotype of the disease [12]. In comparison, those that were treated with standard chemotherapy had very little change [12].

The therapeutic landscape of prostate cancer contains to develop rapidly with novel therapeutic approaches beyond chemotherapies and hormonal therapies such as the use of antibody-drug conjugates [13], bone-targeting agents [14], immunotherapies [15], and microbiome-based therapeutics being investigated [16]. In this era of molecularly targeted therapy and the evolution of disease response to newer treatments, noninvasive methods of diagnosing and monitoring disease response and progression are pertinent. Here, we describe four cases of early malignant spinal cord compression secondary to SEM in patients receiving enzalutamide before traditional chemotherapy and discuss strategies to improve outcomes for this cohort of patients.

Case Series

Case 1

A 72-year-old man was diagnosed with de novo metastatic prostate cancer involving only bone in 2011 and commenced on leuprorelin. Four years later, he received enzalutamide with initial response before changing to abiraterone plus prednisone due to biochemical progression. There was an initial incomplete PSA response (Fig. 1a) followed by a rise. He remained asymptomatic, and whole-body bone scan (WBBS) and CT of the chest, abdomen, and pelvis showed no significant change so abiraterone was continued. Six weeks later, he presented with sudden onset of unsteady gait and a sensory deficit without increase in bone pain. An MRI scan demonstrated thoracic cord compression at T5 to T7 due to a 6-cm-long intraspinal mass (Fig. 2a). Despite urgent radiotherapy, he had progressive neurological deficits and died a few weeks later.

Case 2

A 64-year-old man presented with widespread bone metastases and a PSA of 500 μg/mL and was treated with goserelin, bicalutamide, and denosumab with an incomplete PSA response (PSA 190 μg/mL). On biochemical progression (PSA 390 μg/mL), enzalutamide was

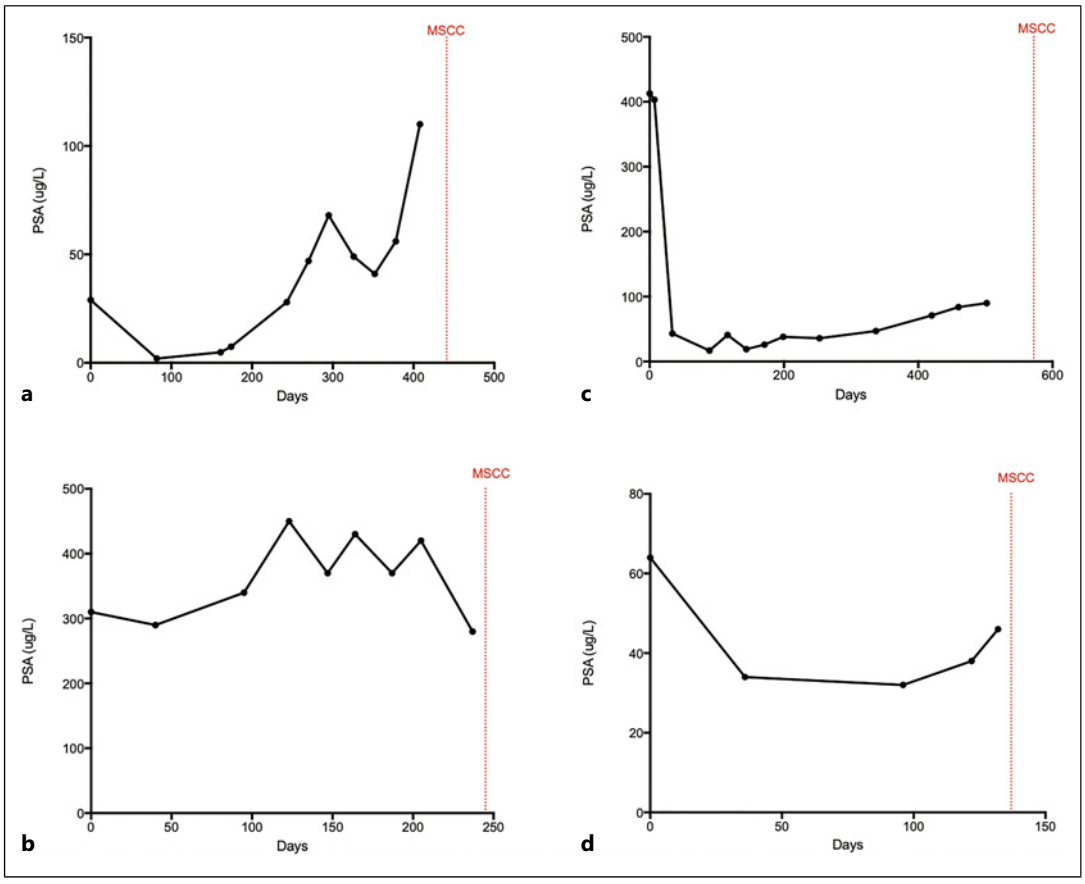

Fig. 1. Time to MSCC – case 1 (**a**); case 2 (**b**); case 3 (**c**); case 4 (**d**). The x-axis represents the number of days since starting enzalutamide. The y-axis represents PSA level. The plots indicate the PSA level on a specific day. Red dotted line indicates the day of spinal cord compression diagnosis.

commenced in August 2014. The PSA fluctuated over a 6-month period (Fig. 1b) but he remained well with no pain, and WBBS and CT of the chest, abdomen, and pelvis showed stable bone metastases. Without an increase in bone pain and in the presence of a falling PSA, he developed rapid onset of ataxia and sensory changes in the lower limbs and whole spine MRI showed an epidural mass extending over multiple levels (Fig. 2b). MRI brain showed an extra-axial mass lesion in the anterior aspect of left middle cranial fossa. He was treated with radiotherapy to the spine and brain and was commenced on docetaxel with good clinical and biochemical response.

Case 3

A 72-year-old man was diagnosed with de novo metastatic prostate cancer involving bone and lymph nodes when the PSA was over 3,000 μg/mL, and was commenced on goserelin and bicalutamide with good initial effect (PSA nadir 2.5 μg/mL). He was switched to enzalutamide due to biochemical progression after 6 months and the PSA fell from over 400 ng/mL to 17 μg/mL (Fig. 1c). PSA rose slowly over 12 months to 96 μg/mL. Despite having no bone pain or other symptoms and a serial WBBS showing stable disease, he presented with sudden onset lower limb weakness and whole-spine MRI demonstrated spinal cord compression at

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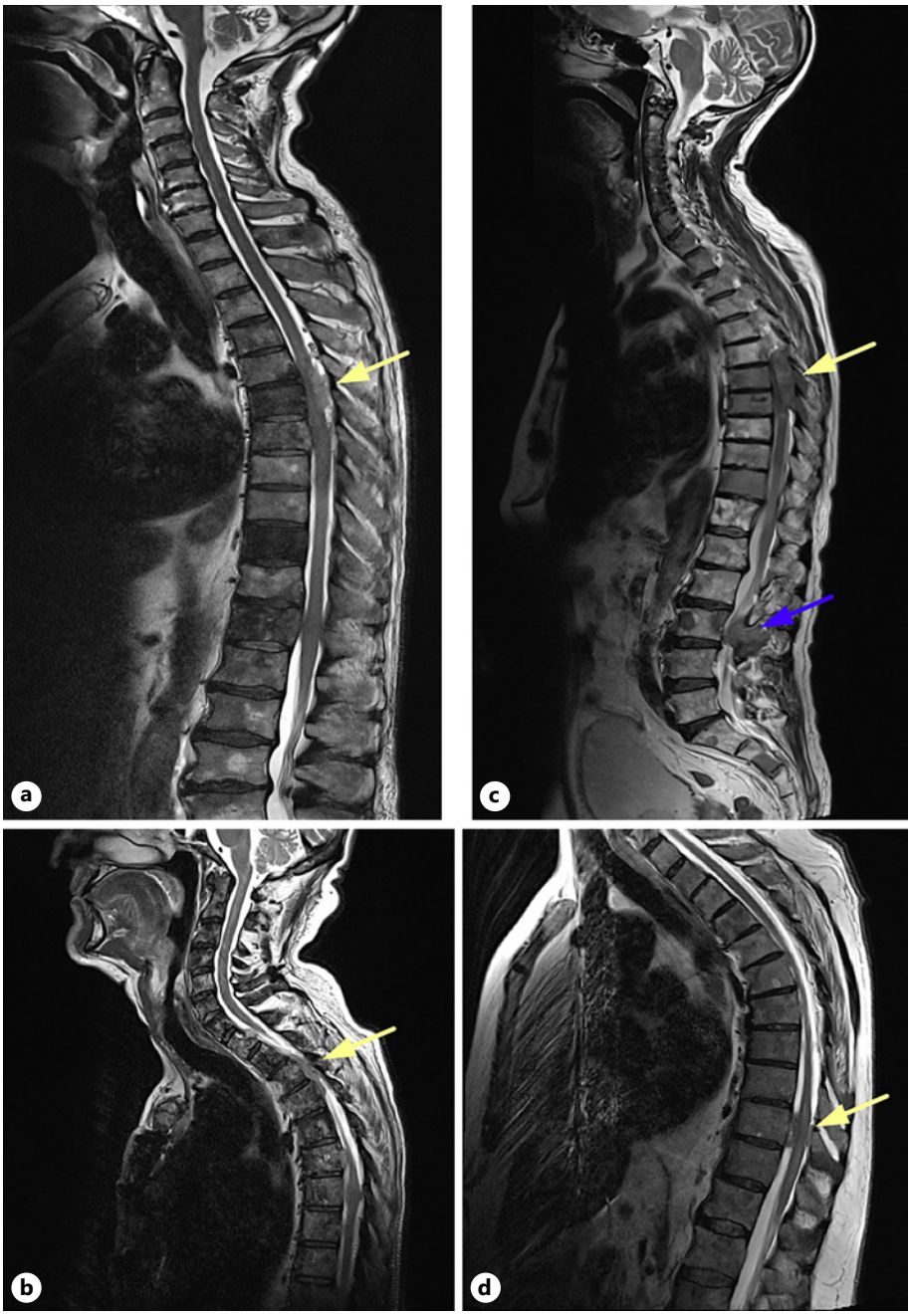

Fig. 2. Sagittal T2 weighted sequence MRI spine. **a** Low T2 signal soft tissue mass involving spinal cord and CSF space at T6 level (yellow arrow) on the background of extensive vertebral body metastatic disease. **b** Low T2 signal soft tissue mass at T7 level with extensive epidural space extension, spinal canal stenosis, and spinal cord compression (yellow arrow). **c** Large soft tissue mass centered on epidural space in T7 and T8 causing severe cord compression (yellow arrow). A soft tissue mass extending into posterior epidural space at L3 level (blue arrow). **d** Large epidural mass at T10 level causing complete canal block (yellow arrow).

T7 and T8 due to a large epidural soft tissue mass (Fig. 2c). He received urgent radiotherapy but remained paraplegic. The cancer otherwise remained relatively stable with no additional therapy but 12 months later he passed away secondary to complications of the paraplegia.

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Case 4

A 77-year-old man was diagnosed with early prostate cancer in 2008 and was treated with goserelin only. In January 2013, he developed bone and lymph node metastases and he was commenced on enzalutamide with a fall in PSA from 64 μg/mL to 34 μg/mL (Fig. 1d). In April 2015, he developed mild back pain but with no neurological signs or symptoms. PSA had risen slightly but recent standard imaging showed stable metastases. However, because of the previously described cases, an MRI spine was performed which showed a T10 epidural mass with cord compression (Fig. 2d). The patient was treated with urgent radiotherapy and then commenced on docetaxel with good disease control.

Discussion

Our case series exemplifies a change in the clinical pattern of metastases of CRPC in the presence of potent androgen axis inhibition. In these patients, spinal cord compression occurred relatively early in the course of the disease and occurred directly from epidural metastases rather than bone metastases.

A post hoc analysis of the PREVAIL study, which used enzalutamide before docetaxel in CRPC, showed that nearly one-quarter of patients with radiographic progression had a non-rising PSA, and that subset of patients had a worse survival compared to those with progression associated with a rising PSA [17]. The authors concluded that a disease monitoring strategy should include imaging and not rely entirely on serial serum PSA measurement to assess disease progression. Our series goes further to show that catastrophic spinal cord compression may occur "silently" in patients treated with novel androgen receptor axis-directed therapy (ARDT) despite no or minimal rise in PSA, no progression on standard imaging, and no increase in bone pain or prodromal neurological symptoms.

Patients in our series are defined by (1) incomplete or short-lived initial response to ARDT; (2) stable or slow rise in PSA while on therapy; (3) apparent stable metastases in "traditional" sites of bone and lymph node, and (4) the relative absence of pain or neurological symptoms or signs before the sudden onset of spine cord progression. Spinal cord compression occurred at a median of 11.4 months after starting ARDT.

An important clinical message of our series is that imaging beyond standard WBBS and CT may be necessary to monitor disease progression. In patients fulfilling the criteria as we have described, there should be a high index of suspicion for epidural or leptomeningeal metastases leading to early imaging even in the absence of classic symptoms. The increasing availability and role of next-generation imaging such as MRI with gadolinium enhancement and 68Ga-PSMA-11 PET/CT may also increase sensitivity in assessing for early progression that may be missed on conventional imaging [18].

Long before the introduction of the potent ARDT, spinal cord compression was usually due to progression in known bone metastases, and was preceded by warning symptoms such as increasing back pain [19]. The clinical presentation of dural metastasis was rare, which contrasted with autopsy findings that reported a much higher incidence. In 2003, a review of 16,280 prostate cancer cases at MD Anderson revealed only 19 cases diagnosed with dural metastases [20]. Before 2008, patients diagnosed with dural metastases were usually heavily pre-treated, had significantly higher PSA with heavy disease burden and clear progression of disease at other sites [1]. More recent series have also confirmed that the majority of dural metastases have occurred earlier in the disease course with prolonged exposure to ARDT [21].

Poor drug distribution and low central nervous system (CNS) penetrance of drugs are unlikely to be major contributory mechanism, given that enzalutamide crosses the blood-brain barrier and can cause convulsions through an off-target mechanism [10]. Clinically,

enzalutamide lowers the threshold for seizures and causes cognitive changes in a small proportion of patients [6]. Despite the CNS penetrance of this agent, the anticancer effect of enzalutamide was overcome in the epidural sites but not in the bone and lymph node, suggesting that drug distribution is not the cause.

One hypothesis for the differential progression in the CNS, compared to traditional sites of metastases is that there are diverse androgen environments in different body tissues which may lead to different levels of cancer control [22]. Investigation of this question may shed light on why prostate cancer preferentially metastasizes to bone and lymph nodes and may suggest new therapies for resistant disease. It is possible that some tissue types, such as the leptomeninges and other CNS sites, may be "androgen-deprived." Nadig et al. [23] have suggested that totipotential stem cells, normally present in prostate acini, adapt in an androgen-deprived environment to assume neuroendocrine differentiation and result in the progression of this aggressive variant of prostate cancer.

We hypothesize that traditional sites of bone and lymph node provide an environment which favors hormone-sensitive prostate cancer even in the presence of androgen axis suppression. It is known that hormone-dependent prostate cancer can suppress the growth of hormone-independent cancer. Wright et al. [24] showed that androgen receptor activation in patients with hormone-sensitive prostate cancer cells repressed an intrinsic neuroendocrine differentiation process in these cells.

It is possible that the bone or nodal environment is relatively "androgen-rich," which allows the persistence of hormone-dependent cancer even in the presence of ARDT which, in turn, suppress the outgrowth of resistant cancer clones at those sites. Relatively "androgen-poor" sites (which may include the dura) would not have a "suppressive" hormone-dependent cancer cell population, allowing resistant cells to grow unfettered through the pressure of ARDT. Such a hypothesis would also explain the predilection for bone and lymph node for metastases of hormone-sensitive cancer. In this case series, we describe a change in the expected clinical course of CRPC with epidural metastases occurring relatively early in the disease process, in a subset of patients described as those with an incomplete or poor initial response to treatment, stable disease in the "traditional" sites of the bone and lymph node, and with stable or slowly rising PSA.

In an era where upfront use of ARDT is becoming more commonplace in the sequencing of treatment for prostate cancer, we believe that recognition of this emerging clinical pattern will allow clinicians to have a high index of suspicion and undertake early MRI assessment for spinal cord compression in the absence of classic symptoms and signs. Further research into the escape mechanisms and development of SEM in patients treated with ARDT is required. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534685).

Statement of Ethics

Written informed consent was obtained from the patients of case 2 and case 4 for publication of the details of their medical case and any accompanying images. Written informed consent was obtained from the next of kin of the patients of case 1 and case 3 for publication of the details of their medical case and any accompanying images. This study protocol was reviewed and the need for approval was waived by the Nepean Blue Mountains Local Health District (NBMLHD) Human Research Ethics Committee in accordance with local guidelines.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Author Contributions

Dhanusha Sabanathan (D.S.), Andrew O. Parsonson (A.O.P.), John J. Park (J.J.P.), and Howard Gurney (H.G.) made substantial contributions to the conception, design, acquisition, analysis, and interpretation of data for the work; were involved with drafting the work and revising it critically for important intellectual content; provided final approval of the version to be published; and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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