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Castration-Resistant Prostate Cancer Presenting as Bulky Lymphadenopathy: A Case without Bone Metastasis

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Patient: Male, 75-year-old
Final Diagnosis: Metastatic prostate cancer
Symptoms: Urine retention
Clinical Procedure: None
Specialty: Oncology • Urology

Objective: Unusual clinical course

Background: Prostate cancer (PCa) tends to spread most often to the regional lymph nodes and then to the skeleton. The prevalence of bone metastases is more than 80% in patients with metastatic PCa. Non-regional lymph node (NRLN) metastasis is defined as cancer cells spreading to lymph nodes distant from the primary tumor and often signals a more advanced stage of cancer. We are reporting such a rare case of NRLN without skeletal metastasis in PCa.

Case Report: We report a rare case of persistently elevated PSA >20 ng/mL after the treatment of localized PCa in the past. A workup by PSA positron emission tomography (PSMA-PET) scan showed the presence of bulky retroperitoneal massive lymphadenopathy, a type of NRLN metastasis, in the absence of bone metastasis. The patient was then treated with abiraterone plus docetaxel, leading to a decrease in PSA levels from 21 ng/mL to 2.42 ng/mL. The PSMA-PET scan also showed significant shrinkage of lymphadenopathy, marking a favorable response.

Conclusions: Castration-resistant PCa typically metastasizes to bone, but our case presents a rare occurrence of bulky NRLN metastasis without skeletal involvement. The use of PSMA-PET imaging and genetic testing can help identify this atypical metastatic pattern. Early recognition is crucial, as it enables more accurate diagnosis and prompt treatment decisions and improves outcomes through timely intervention and personalized therapeutic strategies.

Keywords: Prostate • Bone Metastasis • Carcinoma of Prostate • Lymphadenopathy

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Introduction

Prostate cancer (PCa) is currently the second most common malignancy in men in the United States, after non-melanoma skin cancer [1,2]. The most common metastatic sites for PCa are the bones, followed by distant lymph nodes, liver, and lung [3,4]. It is prudent to have an accurate knowledge of the metastatic sites in patients presenting with PCa, to plan staging and additional diagnostic procedures. Distant lymph node metastasis, or non-regional lymph node (NRLN) involvement, occurs in approximately 10% of PCa cases, and spread typically follows a route from the pelvic lymph nodes, often leading to bone metastasis [5,6]. Compared with metastasis to regional lymph nodes, NRLN is less common and more aggressive, with a potentially poorer prognosis [7].

We report a case of advanced PCa that presented as massive lymph node metastasis, without any evidence of bony metastasis.

Case Report

We present this case of a 75-year-old man with a past medical history of hypertension, osteoporosis, and hyperlipidemia who was found to have persistently elevated prostate-specific antigen (PSA) >20 ng/mL after treatment of localized PCa in the past. He initially received a diagnosis of PCa in 2014, after a tissue biopsy confirmed a Gleason score of 4+3 (grade 3) in 5 of the 12 cores, placing him in the unfavorable intermediate-risk category of PCa. At the time of initial diagnosis, bone and computed tomography (CT) imaging confirmed no metastasis. He opted for external beam radiation therapy, along with androgen deprivation therapy with leuprolide. Subsequently, he had a good response to the treatment, with PSA<0.1 mg/dL.

Following treatment and resolution, he was closely monitored at regular intervals with PSA levels. After 3 years of treatment, in 2018, the PSA was noted to be steadily increasing over time, at >21 ng/mL. A positron emission tomography (PET) scan and bone scan were ordered, to rule out metastatic disease. The bone scan was negative for any bony involvement. The CT and PET scan revealed several bulky paraaortic lymph nodes (**Figures 1A, 1B, 2A, 2B**). The persistent rising levels of PSA after initial treatment, combined with the atypical metastatic pattern of extra-pelvic NRLN, prompted the oncologist to have a high clinical suspicion of neuroendocrine prostate carcinoma (NEPC). A CT-guided retroperitoneal lymph node biopsy was performed, showing metastatic malignant neoplasm with crush artifact that favored poorly differentiated carcinoma of the prostate. On immunohistochemistry, the sample was shown to be AE1/AE3 positive, while P-504S (AMACR) was focally positive. Tumor markers CD56, synaptophysin, NKX3, PSA, and TTF-1 were all negative, thus ruling out NEPC. The final diagnosis was confirmed as poorly differentiated prostate adenocarcinoma with retroperitoneal lymph node metastasis and no other distant metastasis, including no bony spread. Based on National Comprehensive Cancer Network guidelines for metastatic castration-resistant PCa and the patient not having been exposed to prior docetaxel, he was deemed a candidate for novel hormone therapy and systemic therapy. He was treated with abiraterone 1000 mg orally per day plus docetaxel 75 mg/m^2 intravenous infusion for 6 cycles, leading to a decreased PSA level up to 2.42 ng/mL, and a subsequent

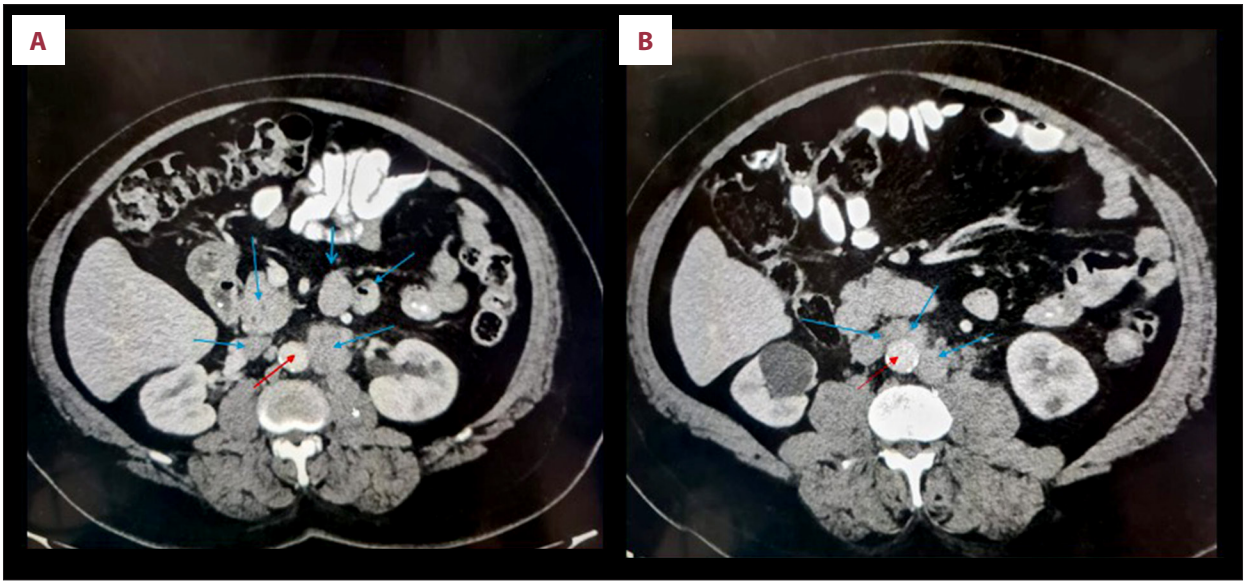

Figure 1. (**A, B**) Computed tomography scan section depicting the retroperitoneal adenopathy as shown by blue arrow; the red arrow marks the aorta.

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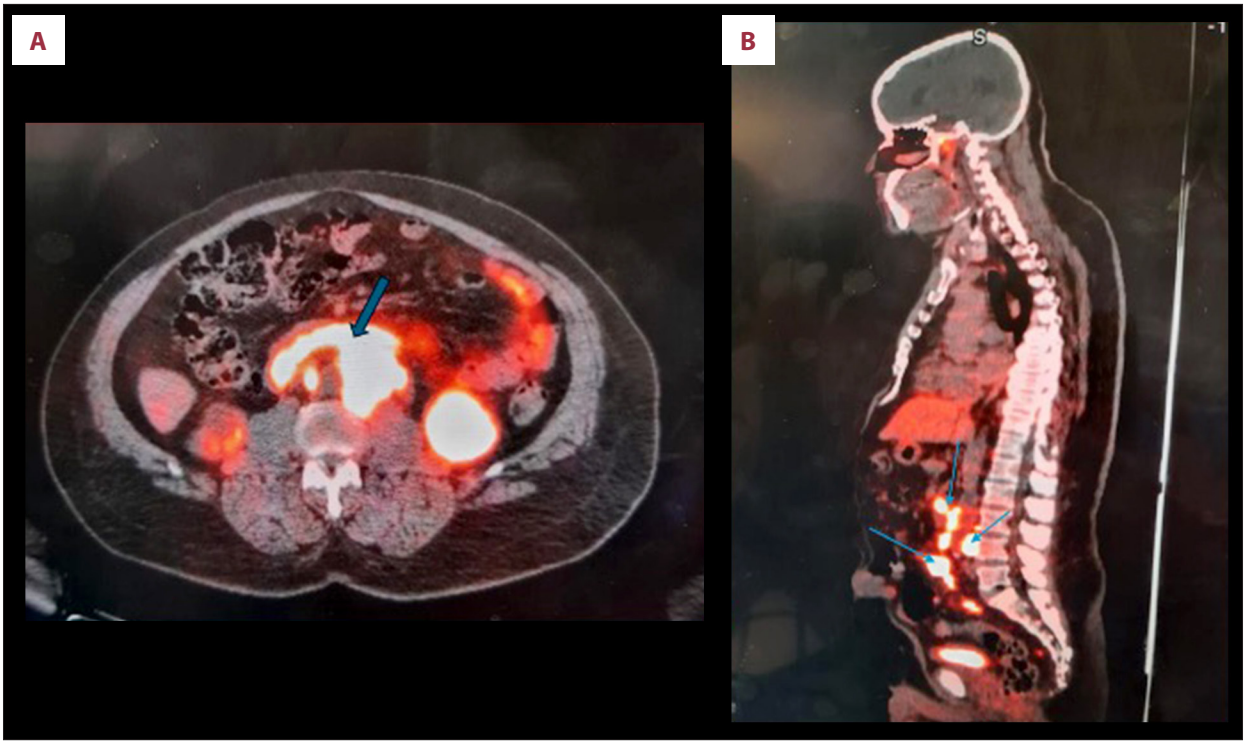

Figure 2. (**A, B**) Positron emission tomography scan section showing increased standardized uptake value by retroperitoneal lymph nodes in the abdominal area as marked by blue arrow.

PSMA-PET scan showed significant shrinkage and decreased uptake in lymph nodes.

Discussion

PCa is the most common cancer among men in the United States, after non-melanoma skin cancer, affecting 43% of men aged between 65 and 74 years of age, according to the Centers for Disease Control. The incidence rate in 2023 was 112 per 100 000 men. It has been found that about 30% of all men >50 years of age harbor PCa, but only 9% develop clinically evident disease [8]. PCa typically presents as a localized disease, with only about 5% of cases, in patients aged 75 to 79 years, presenting as metastatic disease [9]. The therapeutic outcome and prognostic relevance of PCa are mainly determined by the presence of metastasis at the time of diagnosis. As supported by several studies, 90% of PCa will metastasize to the bone, followed by the lung (46%), liver (25%), pleura (21%), and adrenal glands (13%) [8,10]. In 5% to 12% of cases of PCa, regional lymph node metastasis is noted with clinically organ-confined cancer [11]. However, in about 15% of the cases, metastasis occurs to sites other than the bones and localized lymph nodes [12]. NRLN metastasis, including the retroperitoneal lymph node, is an atypical site for metastasis [13], as seen in our patient, and we need to elucidate the etiopathogenesis to understand the prognostic implications. The favorable 5-year overall survival rate is about 99% for localized PCa, whereas only 28% of distantly metastatic PCa show 5-year survival in the United States [14].

Various theories have been proposed for describing the mechanisms of metastasis, including migration from the primary site, hematogenous spread, tumor milieu at the metastatic site, angiogenesis role, and extravasation to the target organ [15]. Many years ago, Paget et al [16] proposed the theory of "seed and soil", which can be applied to PCa, with prostate cells (seeds) in the blood, migrating to bones (soil) through the hematogenous route [17,18]. More recently, Mengmeng et al demonstrated that epithelial-mesenchymal transition and anoikis resistance are key mechanisms driving tumor cell metastasis [19]. Additionally, they highlighted that various components of the tumor microenvironment and their complex interactions with cancer cells are closely involved in distant metastasis. Also, the contributing factors for the high incidence of bone metastasis can be the interaction between metastatic PCa cells and the bone microenvironment, involving the production/release of chemokines [20]. LuCaP 23.1, LNCaP, C4-2, and IGR-CaP1 are the cell lines adopted in xenograft PCa models to understand the underlying molecular mechanisms of metastasis [21]. Androgen receptor expression plays a pivotal role as knockdown of its expression impacts androgen receptor-mediated transcription and cell growth in androgen-resistant (androgen-independent) PCa cell lines [22].

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For lymph node metastasis, the role of vascular endothelial growth factor (VEGF) VEGF-C and VEGF-D, along with their receptors, are the major mediators of the process called tumor lymph angiogenesis [23]. Involvement of para-aortic lymph nodes is considered as distant metastasis and includes these tumors in the M1 category [5]. Retroperitoneal lymph node involvement is an atypical presentation of PCa usually resulting from the lymphatic spread of nodal metastases in an ascending manner [24].

In the literature search, we came across an unusual case presentation of supraclavicular lymph node involvement in advanced PCa, without the involvement of regional lymph node and bone metastasis [25]. Vinjamoori et al [12] studied atypical presentations of PCa (10 years of experience at a single institution) and reported supradiaphragmatic lymphadenopathy in 3 of 26 patients, without osseous metastasis. As reported by Cho et al [26], 26 patients were identified with supradiaphragmatic lymph node involvement in metastatic PCa, with 35% of them without any bony metastasis. However, a case of massive retroperitoneal lymphadenopathy without bone metastasis is a rare occurrence.

Saitoh et al [27] retrospectively analyzed 476 cases with lymph node involvement at autopsy and commented on 2 distinct lymph node metastatic patterns. While type 2 metastatic patterns featured direct skip metastasis to the paraaortic lymph nodes, without involving the pelvic lymph nodes, type 1 metastatic patterns involved simultaneous metastases of both the pelvic and paraaortic lymph nodes and were continually invasive. In type 2 cases, some metastases may have progressed by the vertebral vein bypass route and may have been connected to a hematogenous pattern of spread. PCa cells can easily access the lower spine through a venous system that connects to the lower spine, and metastasis to the abdominopelvic lymph nodes is achieved through a vertical pathway through the internal iliac nodes, a possible explanation for our case [5].

Atypical metastasis in PCa, which is rare and aggressive, underscores the importance of early and accurate detection. Studies support the use of PSMA-PET/CT as the preferred diagnostic modality for identifying NRLN metastasis, with it providing higher sensitivity than conventional imaging in detecting metastatic spread [28,29]. Additionally, genetic testing plays a growing role in predicting metastatic potential. Three tissue-based genomic tests (Oncotype DX, Prolaris, and Decipher) are currently available to assess the risk of metastasis [30]. Oncotype DX, a biopsy-based test, uses reverse transcription polymerase chain reaction to analyze the expression of 17 genes in tumor RNA. While there is substantial evidence supporting its ability to identify aggressive PCa or high-risk histology, its utility in predicting distant metastasis is still evolving and requires further validation.

NEPC is one of the differential diagnoses to be kept in mind, especially in the clinical scenario in which patients have steadily rising PSA levels on treatment and progression to the castration-resistant variant. Although NEPC constitute <1% of all prostate tumors, it is known for one of the most aggressive clinical courses and poor prognosis [31]. NEPC is an aggressive variant of PCa with a high propensity for distant and unusual sites of metastasis [4]. Multiparametric magnetic resonance imaging (MRI) is the standard modality of choice for initial local tumor staging, and PET/CT and PET/MRI are preferred for distant extra-prostatic (node, metastasis) sites, biomedical relapse, and assessment of treatment response with androgen deprivation therapy [32]. Immunohistochemically, they are identified by markers, mainly neuron-specific enolase, synaptophysin, and chromogranin A [33]. Our patient had recurrence despite androgen deprivation therapy, and thus, we needed to rule out possible neuroendocrine origin. Synaptophysin and CD56 were evaluated and were negative. In contrast, AE1/AE3, which indicates epithelial origin, was positive, thus favoring primary metastatic prostate adenocarcinoma.

Our case report highlights an important fact, that even when bone is the primary metastatic site, up to 20% of patients of PCa can have an atypical site of metastasis, including massive lymphadenopathy, hence making thorough imaging modalities an integral part of advanced PCa management [34].

Conclusions

PCa commonly affects elderly men, with bone and local pelvic lymph nodes being the usual site of presentation. An atypical presentation can pose a diagnostic and treatment challenge for physicians. Thus, accurately understanding the characteristics of PCa metastasis could help medical oncologists predict the prognosis of PCa and provide treatment decisions for these patients. We present a rare case of massive isolated retroperitoneal para-aortic lymphadenopathy as a feature of metastatic PCa with no evidence of bony metastasis. PSMA-PET/CT and genetic tests, such as Oncotype DX, can be valuable in diagnosing and predicting metastasis in such atypical presentations. Recognizing this unusual metastatic pattern is crucial for reducing diagnostic delays and improving patient outcomes by enabling earlier treatment initiation.

Informed Consent

Consent for publication of this report was obtained from the patient.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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