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Case Report

CASE REPORT

Alveolar soft part sarcoma mimics prostate cancer metastasis

Daniel R. Principe[1,†], Nisha A. Mohindra[2], Hidayatullah G. Munshi[2] and Suneel D. Kamath[2,*]

[1]Medical Scientist Training Program, University of Illinois College of Medicine, Chicago, IL, USA, [2]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA.

*Correspondence address. School of Medicine, Northwestern University Feinberg, 676 N St. Clair St., Suite 850, Chicago, IL 60611, USA. Tel: (312) 695-2351; Fax: (312) 695-2772; E-mail: suneelkamath13@gmail.com

Abstract

A 61-year-old man presented to the oncology clinic with Gleason 9 (4 + 5) prostate cancer. Staging CT showed multiple nodules in both lungs. Since the lung lesions were too small for biopsy, he was started on anti-androgen therapy for suspected metastatic, hormone-sensitive prostate cancer. While his prostate-specific antigen decreased from 32 to <0.1 ng/ml, the multiple lung lesions showed no response on subsequent imaging. The patient presented during follow-up with severe right leg pain, at which time magnetic resonance imaging revealed a large, hyperintense mass in the femur. The mass was resected along with two lung nodules, with pathology demonstrating metastatic alveolar soft part sarcoma. This serves as an important reminder that lesions suspicious for metastases may be due to cancers of multiple primary origins, particularly if the pattern of metastasis is atypical or there is varied response to therapy.

INTRODUCTION

Prostate cancer is the second most common cancer worldwide, with 1 276 106 new cases in 2018 [1]. The metastatic spread of prostate cancer follows a well-described pattern with preferential involvement of the bone, followed by lymph nodes and visceral organs (e.g. lung, liver) [2]. Based on this pattern, nuclear medicine bone scan is the first test of choice to evaluate for metastatic disease, especially for patients with a serum prostate-specific antigen (PSA) of over 10 and/or a high histologic grade. In both localized and disseminated diseases, the foundation of first-line therapy is androgen suppression, often with a depot formulation of a gonadotropin-releasing hormone agonist (e.g. leuprolide). Additional androgen receptor-targeted agents or chemotherapy are added in the appropriate clinical settings, typically those with rapid PSA doubling times or high-volume metastatic disease. This approach has led to significant improvements in the prognosis of prostate cancer patients, with the current 5-year survival rate exceeding 98% [1].

Here, we describe a unique case of a patient presenting with hormone-sensitive prostate cancer with possible metastatic spread to the lungs. While androgen suppression led to a favorable response based on decreased serum PSA, the lung nodules showed no response. The patient soon re-presented with severe right thigh pain. Imaging revealed a large mass in the proximal right femur indicative of a soft tissue malignancy rather than a metastatic lesion. The patient subsequently underwent surgical resection of the leg mass and two isolated lung lesions. Histologic evaluation showed the leg mass and lung lesions to be alveolar soft part sarcoma (ASPS). Hence, this exceedingly rare case underscores the importance of including cancers of multiple primary etiologies in the differential

†Daniel R. Principe, http://orcid.org/0000-0003-4355-6597
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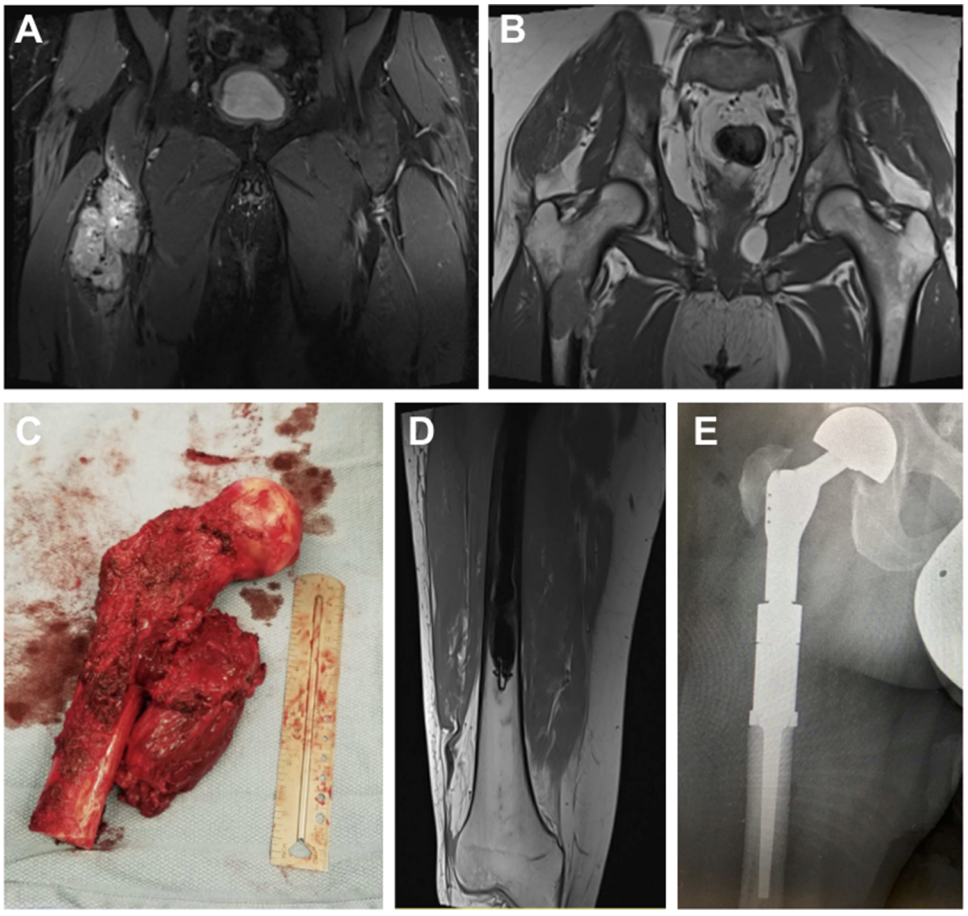

Figure 1: (**A**, **B**) Preoperative imaging revealing a large mass in the right leg. (**C**) Gross pathology of resected mass. (**D**) Post-operative imaging showing the absence of leg mass. (**E**) Imaging post reconstruction showing leg implant.

diagnosis, particularly when the known malignancy displays an atypical pattern of dissemination, or when multiple tumor sites show variable responses to therapy.

Case presentation

A 61-year-old man was referred for treatment of Gleason 9 (4 + 5) prostate cancer involving all 12 core biopsy specimens. CT imaging revealed locally advanced disease, as well as scattered pulmonary nodules of varying sizes (all <8 mm), concerning for possible metastatic spread. The patient refused biopsy of the lung nodules, and positron emission tomography/CT did not demonstrate metabolic uptake. He was started on oral abiraterone and leuprolide injections, and his PSA declined, remaining consistently below 0.1 ng/ml. This was paralleled by reductions in the primary tumor on subsequent imaging scans; however, his lung nodules did not respond to treatment and remained stable in size. Four months later, the patient complained of severe right thigh pain during a routine follow-up visit. On physical exam, a tender, palpable mass deep in the right thigh was appreciated.

Multiplanar magnetic resonance imaging of the right hip and leg utilizing T1-weighted and fluid-sensitive sequences revealed a T1 hypointense, T2 hyperintense bone lesion measuring 5.3 × 2.7 × 2.5 cm in the right femur at the level of the lesser trochanter, contiguous with a T1 hypointense, and T2 hyperintense soft tissue lesion in the anterior vastus intermedius muscle measuring 9.1 × 4.9 × 4.8 cm (Fig. 1a and b). The patient underwent total resection of the right thigh mass and implantation of a hip prosthesis (Fig. 1c–e), and left upper/lower lobe wedge resections to address the suspected pulmonary metastases. Both specimens stained focally positive for cytokeratin AE1/AE3, and negative for cytokeratin 7, 8, 18 and 20, Factor VII, HepPar-1, NKX3.1, PSA, prostatic specific acid phosphatase, prostein and prostate membrane antigen, excluding the possibility of a prostate cancer metastasis. FoundationOne next-generation sequencing found a Transcription Factor binding to immunoglobulin heavy chain Enhancer 3 (*TFE3*) rearrangement at Xp11.2. The *TFE3* rearrangement and histopathology were highly suggestive of ASPS. Based on these findings and the propensity of ASPS to originate in the extremities, the patient was diagnosed with primary ASPS of the right thigh with presumed pulmonary metastases.

DISCUSSION

Here, we present the first known case of a patient with both locally advanced prostate cancer and unrelated metastatic ASPS. This serves as an important reminder that lesions suspicious for metastases may not always arise from the known malignancy and that in the appropriate clinical context, an unrelated malignancy should be included in the differential diagnosis. Multiple primary malignancies are rare, accounting for as few as 3.8% of cancer patients [3]. However, the incidence of multiple primary malignancies is thought to be increasing. There are several reported cases of patients developing multiple primary cancers. In most cases, these are due to syndromes

such as Li Fraumeni [4]. However, these cancers often occur sequentially, with childhood cancer survivors displaying the highest risk of a second malignancy [4]. Our patient had no such syndrome and, based on the next-generation sequencing results of his tumor, hereditary testing was not indicated. Further, there have been no genetic or epidemiologic studies linking prostate cancer and ASPS. Also, these cancers share no clinically relevant risk factors, suggesting that the two simultaneous malignancies in our patient are likely sporadic in nature.

ASPS is a rare neoplasm accounting for <1% of soft tissue malignancies. It is unique in that it has indolent biology, but greater metastatic potential than other soft tissue sarcomas. Median overall survival is 11 years for patients without metastatic disease at diagnosis, but only 3 years for those with metastases [5]. These tumors most often manifest in adolescents and young adults, have a slight female predominance and commonly affect the extremities, as it was seen in our patient [5]. To date, there are no established treatment guidelines for ASPS, as it is largely refractory to cytotoxic therapy [6]. As a result, there are no curative intent strategies for disseminated disease. Emerging evidence supports the use of several tyrosine kinase inhibitors including pazopanib, sunitinib, cediranib, dasatinib or tivantinib to achieve long-term disease stability [6]. There are also supporting data for immunotherapy for ASPS, though this requires further study [7].

ASPS can be challenging to diagnose using traditional histopathologic examination alone. The oncogenic fusion of the Alveolar Soft Part Sarcoma Chromosomal Region Candidate Gene 1 (*ASPSCR1*) gene with *TFE3* is a characteristic molecular finding in alveolar soft part sarcoma. The encoded ASPSCR1-TFE3 fusion protein acts as an aberrant transcriptional transactivator that is stronger than the normal TFE3 protein, leading to deregulated transcription and oncogenesis [8]. Analogous *TFE3* gene fusions have also been observed in renal cancers, namely, transitional renal cell carcinoma (RCC) [9]. However, the molecular mechanisms through that aberrant TFE3 signaling appears to promote carcinogenesis are largely unclear, though recent evidence in transitional RCC appears to suggest that TFE3 may be a critical activator of the PI3K/AKT/mTOR pathway [9].

While one case of ASPS involving the prostate has been described [10], to our knowledge, ours is the first reported case of ASPS presenting simultaneously with a second unrelated malignancy. Interestingly, prostate cancer survivors have the highest relative risk of a second malignancy when compared to other cancers in men. In fact, between 1 and 8% of prostate cancer survivors will be diagnosed with a second malignancy [11–13]. This due to several factors, including the high annual incidence and prevalence of prostate cancer, median age at diagnosis (66 years old) and the 98% 5-year survival rate [1]. Therefore, when there are atypical patterns of behavior or inconsistent responses to therapy for known prostate cancer, we suggest further investigations to rule out the possibility of a second malignancy.

CONFLICT OF INTEREST STATEMENT

None declared.

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CONSENT

The patient provided fully informed, written consent to have his clinical information and imaging shared in this report. Additional information is available on request.

GUARANTOR

Daniel R. Principe.

AUTHOR CONTRIBUTIONS

D.P. consulted with the patient, assimilated patient information and drafted the manuscript. N.M. and H.M. consulted with the patient and edited the manuscript. S.K. was the main care provider, determined the overall treatment plan, assimilated patient information and edited the manuscript. All authors reviewed and approved of the final version of the manuscript.

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