Case Report

Clinicopathologic correlation is essential for diagnosis of metastatic aggressive variant prostate carcinoma: A series of two cases

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Abstract

A subset of patients with castrate resistant prostate cancer, may evolve into androgen receptor-independent phenotype, clinically characterized by low serum levels of prostate-specific antigen and rapidly progressive disease course, referred to as aggressive variant prostate carcinoma (AVPCa). Essentially, a clinical diagnosis, the increasing incidence has highlighted the need to identify potential targeted therapy options which needs tissue from primary or metastatic site. We present a series of 2 metastatic carcinomas of prostate origin with clinical features and molecular signature of AVPCa. The biopsies of metastatic sites revealed a carcinoma with squamous and neuroendocrine differentiation in one case and the second case showed an adenocarcinoma with neuroendocrine differentiation. Both tumors were negative for prostate-specific markers and positive for neuroendocrine markers. The morphologic heterogeneity and inconsistent immunohistochemistry of AVPCa at the site of metastasis emphasizes the role of interdisciplinary diagnostic approach to confirm prostate origin in this subset of tumors.

Keywords: Aggressive variant of prostate carcinoma, castrate resistant prostate cancer, clinical features, metastatic castrate-resistant prostate cancer, pathologic features

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INTRODUCTION

Aggressive variant of prostate carcinoma (AVPCa) is a subtype of metastatic castrate-resistant prostate cancer (mCRPC) that occurs in the setting of relatively low prostate-specific antigen (PSA) levels.[1] Since procurement of biopsies from metastatic sites can be technically challenging, diagnosis of AVPCa has been based on clinical criterion.[1] More recently, collaborative efforts and clinical trials have made biopsies and subsequently genomic analysis of mCRPC feasible leading to identification of a molecular signature of AVPCa (alterations in RB, Tp53 and/or phosphatase and tensin homolog [PTEN]) which can be detected with ease using immunohistochemistry.[1] These efforts are centered on biopsy results, thereby, increasing the number of biopsies from metastatic sites.

We present two cases of mCRPC with the molecular signature of AVPCa to highlight its morphologic

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heterogeneity, limited role of immunohistochemistry, and importance of clinical correlation in establishing the diagnosis of primary prostate origin.

CASE REPORTS

Case 1 [Table 1]

A 52-year-old man presented with abdominal pain, dysuria, and pain in his chest. Computed tomography (CT) of his abdomen and pelvis found a 9.4 cm prostate mass that extended to the bladder and posterior pelvic wall. Significant retroperitoneal lymphadenopathy including a soft-tissue mass (5.2 cm) posterior to the left common iliac vein was identified. PSA was 261 ng/mL. Nuclear medicine bone scintigraphy revealed multiple abnormal areas of skeletal uptake. Biopsy of prostate revealed an acinar adenocarcinoma, Grade Group 5. The patient was started on docetaxel and androgen deprivation therapy (ADT). His PSA initially declined to 0.51 ng/ml but 5 months later rose to 2.54 ng/mL and he transitioned to CRPC. He was then started on enzalutamide. After 6 months of therapy, PSA started rising again along with radiographic progression of disease. An image-guided fine-needle aspiration (FNA) and needle core biopsy of an iliac crest mass was performed to help guide therapy. FNA showed a small cell neuroendocrine carcinoma while needle core biopsy showed keratinizing squamous cell carcinoma (immunoreactive for CK903, p40, and p63) in addition to small cell neuroendocrine carcinoma (immunoreactive for pan cytokeratin, CD56, synaptophysin, and chromogranin) [Figure 1]. Tumor was negative for PSA, prostatic acid phosphatase (PSAP), and NKX3.1 with focal expression for AMCAR. Patient then received 5 cycles of carboplatin and etoposide along with palliative radiation therapy, but again developed radiographic progression. The evaluation for molecular signature revealed loss for PTEN, p53 mutation, and intact nuclear staining for Rb. The treatment was changed to three cycles of cabazitaxel and carboplatin. The patient died 27 months after his initial diagnosis.

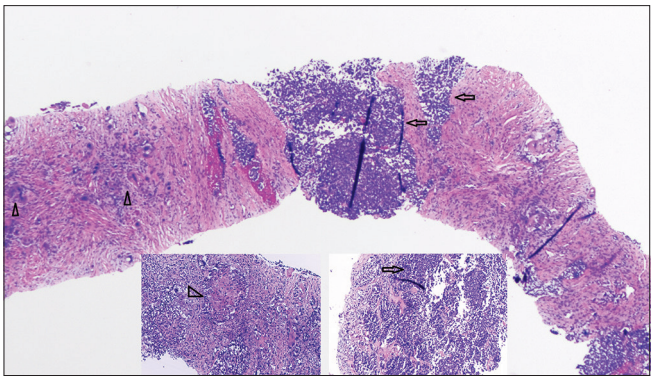

Figure 1: Case 1, iliac crest, needle core biopsy showing metastatic carcinoma with neuroendocrine carcinoma (arrow) and squamous cell carcinoma (arrow head) (H and E, original magnification, ×10). Inset left-high power image of the malignant squamous component (H and E, original magnification, ×200). Inset right-high power image of the neuroendocrine component (H and E, original ×200)

Case 2 [Table 2]

A 59-year-old male presented to his urologist with a complaint of difficulty urinating, PSA of 7.1 ng/ml and an outside diagnosis of prostate adenocarcinoma. CT of chest, abdomen, and pelvis revealed several sclerotic lesions, slight distention of the bladder, and a right lung base nodule. Nuclear medicine scintigraphy showed multiple areas of uptake in the axial and appendicular skeleton. The patient was started on ADT and enzalutamide. In the setting of worsening diffuse pain but a stable (<2 ng/mL) PSA, a repeat imaging 8 months later revealed increased extraosseous soft-tissue disease. Biopsy showed metastatic carcinoma with infiltrating tumor present in solid nests and dilated tubular pattern [Figure 2]. Tumor cells showed moderate pleomorphism, molding, and coarse chromatin with occasional macronucleoli. Tumor was positive for broad-spectrum keratin, thyroid transcription factor-1, and synaptophysin (inset, [Figure 2]). Tumor was negative for NKX3.1, GATA3, CD 56, and chromogranin. There was loss of PTEN and RB with wild type p53. The patient was switched to chemotherapy (carboplatin and docetaxel) which he received over the next 6 months. The patient died 18 months after his initial diagnosis.

DISCUSSION

ADT is the mainstay of systemic therapy for patients with advanced prostate cancer, however, despite significant responses, nearly all patients ultimately progress and

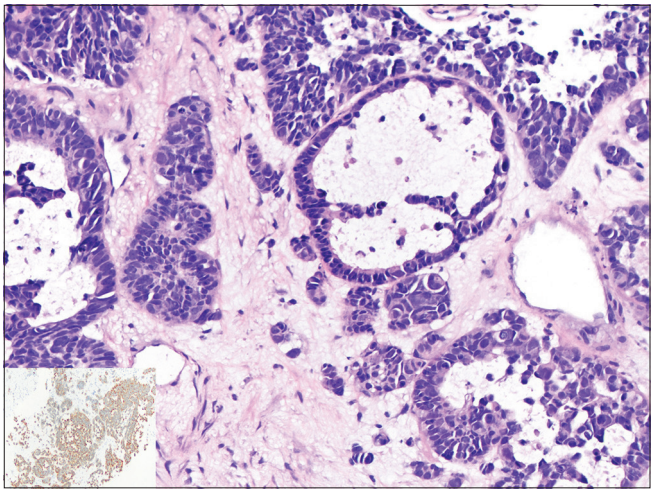

Figure 2: Case 2, thoracic vertebra, needle core biopsy showing a metastatic carcinoma with neuroendocrine features and large/dilated glandular pattern (inset – synaptophysin positivity) (H and E, original ×200)

Table 1: Clinicopathological details of the three cases of aggressive variant of prostate carcinoma

	Case 1	Case 2
Age at diagnosis (years)/race	54/African American	59/Caucasian
Grade group of acinar adenocarcinoma at the time of diagnosis	GG5	NA
Presentation		
PSA at diagnosis	261 ng/ml	7.1 ng/ml
Multiple and diffuse osseous metastasis	Present	Present
Enlarged abdominal lymph nodes	Present	No
Initial therapy	Leuprolide and docetaxel	Leuprolide and enzalutamide
Time to initial radiographic progression (PSA at that time)	10 months (2.5 ng/ml)	16 months (0.20 ng/ml)
Biopsy	Iliac crest	T8
Histologic diagnosis	Metastatic carcinoma with squamous and neuroendocrine differentiation	Metastatic adenocarcinoma with neuroendocrine differentiation
IHC		
Positive	Neuroendocrine component - CD56, synaptophysin, chromogranin Squamous component - CK903, p63, p40	Synaptophysin
Negative	PSA, PSAP, NKX3.1	CD56, NKX3.1
IHC for molecular signature (PTEN/RB/p53)	Loss of PTEN and p53	Loss of PTEN and RB
Follow-up	Deceased 27 months after diagnosis	Deceased 18 months after diagnosis

PSA: Prostate-specific antigen, IHC: Immunohistochemistry, ERG: ETS related gene ; RB: Retinoblastoma gene/protein; PSAP: prostate specific acid phosphatase

develop castration resistance.[2,3] Despite castrate levels of testosterone, most CRPC tumors remain dependent on androgen receptor (AR) signaling resulting from AR gene amplification, intratumoral androgen production, and constitutive activation of AR.[2] Patients with CRPC are therefore treated with highly potent AR pathway enzyme inhibitors such as abiraterone acetate and AR antagonists such as enzalutamide. While these drugs improve survival and quality of life, patients with CRPC will ultimately develop disease that will evade these therapies and become less dependent on AR signaling (i.e., "androgen indifferent") and are referred to as AVPCa,[5] As per original diagnostic criteria, AVPCa is characterized by bulky lytic bone metastasis, frequent visceral metastasis without significant PSA elevation and histologic evidence of small cell neuroendocrine carcinoma.[1] However, it is now known that many AVPCa do not show typical morphology of neuroendocrine carcinoma and may show additional features which include poorly differentiated pattern with solid sheets of tumor cells, squamous differentiation, and even sarcomatous change.[6] In order to identify the primary site of origin for a metastatic tumor, pathologists rely primarily on morphological clues with support of immunohistochemical stains. However, AVPCa with divergent differentiation loose expression of prostate-specific markers including PSA, PSAP, and even the novel NKX3.1. Some aggressive forms may not even express neuroendocrine markers.[7] Besides, morphologic and immunohistochemical features of metastatic squamous cell carcinoma or neuroendocrine carcinoma are not organ specific. Alpha methylacyl CoA racemase, prostate-specific membrane antigen and a positive ETS- related gene break apart fluorescence *in situ* hybridization test have been reported to be better at identifying the prostate origin, however, with variable results.[7] More recently combined alterations in RB, Tp53 and/or PTEN have been identified as a potential clinical predictor of AVPC's responsiveness to a taxane plus platinum chemotherapy regimen.[4]

In order to improve patient selection and guide the treatment of AVPCa, oncologists are increasingly requesting biopsies of the metastatic sites. Our case series highlight that histological features other than that of small acinar pattern of prostate adenocarcinoma, divergent histologic differentiation in addition to neuroendocrine carcinoma and lack of expression for prostate-specific markers pose a challenge in excluding malignancies from other organs.

Awareness of this emerging entity, strong clinical suspicion, and interdisciplinary diagnostic approach is required to confirm prostate origin in this subset of tumors.

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Conflicts of interest

There are no conflicts of interest.

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