NKX3.1 Identifies Prostatic Origin of Dural Metastasis in the Setting of Negative Prostate-Specific Antigen Stain

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Abstract

No clear guidelines exist for the appropriate diagnostic workup of an intracranial mass suspected to be a metastasis from unknown primary origin. Dural metastasis from prostatic origin is very rare. Patients with a known history of metastatic prostate cancer who present with a newly discovered lesion on brain imaging require neurosurgical biopsy to confirm diagnosis prior to initiating treatment. Intracranial metastasis from prostate cancer is rare, and dural metastasis is rarer than intraparenchymal metastasis. Current consensus guidelines support immunohistochemical staining with classic markers such as prostate-specific antigen (PSA) to identify prostatic origin. However, PSA detection of prostate metastases declines with higher Gleason scores and in patients undergoing androgen deprivation therapy. NKX3.1 is another stain that is highly sensitive and specific for prostate. Our patient was a 54-year-old man with a history of metastatic prostate cancer who presented with new-onset seizures. Brain imaging revealed a dural-based lesion with surrounding vasogenic edema and midline shift. The patient underwent resection of the lesion, which was stained with multiple cancer markers. Prostate-specific antigen was negative, but NKX3.1 was positive indicating a prostatic origin for the mass. He underwent a craniectomy to remove the lesion and was given steroids. However, he succumbed to his illness several months later. Here, we document the first report to our knowledge of a patient with prostate metastasis to the dura that is PSA negative, but NKX3.1 positive.

Keywords

prostate adenocarcinoma, dural metastasis, immunohistochemical stain, brain biopsy

Introduction

Prostate adenocarcinoma is the most common cancer diagnosed in adult men in the United States and third most common cancer diagnosed in adult men in the world after lung and colorectal cancers. Prostate cancer infrequently metastasizes to the brain, but when it does, it is usually in the setting of widespread metastasis.¹ A large study in M.D. Anderson showed that dural metastasis from prostate cancer is very rare, occurring in 32 of 16 208 patients, whereas intraparenchymal metastasis occurred in 103.¹ Biopsy is often required in patients with prostate cancer and brain lesions. Prostate-specific antigen (PSA) and prostate-specific antigen phosphatase have been used as histological markers for primary prostate adenocarcinoma; however, these antigens are poorly expressed on the surface of well-differentiated and metastasized tumors.² *NKX* genes represent a family of homeodomain transcription factors.³ NKX3.1 is a negative regulator of epithelial cell growth in prostate tissue; aberrant expression of this gene is associated with prostate tumor progression.⁴ It

has recently been shown to be a highly sensitive and specific marker for metastatic prostate adenocarcinoma.⁴ Here, we report a case of NKX3.1-positive and PSA-negative prostate cancer metastatic to the intracranial dura.

Case Description

The patient is a 54-year-old Caucasian man with a history of castration-resistant prostate cancer after transurethral

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Figure 1. Imaging of brain metastasis. The noncontrast brain computed tomography (CT) shows a mildly hyperdense extra-axial mass the in right frontal region with severe surrounding vasogenic edema, mass effect, and right to left midline shift (A). The postcontrast CT shows the mass to be avidly enhancing (B). The axial T2 sequence shows the mass to have a heterogeneous T2 hypersignal with mass effect and parenchymal edema (C). The mass contains foci of susceptibility artifacts suggesting hemorrhagic changes (D). The mass shows avid enhancement after contrast injection, with dural tail (E).

resection of the prostate 4 months prior to his neurologic presentation with Gleason score 5 + 4 on androgen deprivation therapy (enzalutamide, bicalutamide, and leuprolide). Serum PSA on discharge was 6.37 ng/mL. He had known metastasis to the right pelvis after stereotactic radiation therapy to the pelvis but was without known brain or meningeal metastasis. He presented to the emergency department with first-time seizures. He was in his usual state of health until a week prior to presentation when he received his leuprolide shot after which he reported feeling slow. His wife reports that at the time he was confused with slurring of speech. The day prior to presentation, he developed mild left facial droop and atypical left-hand movements followed by a bilateral tonic-clonic seizure for 2 minutes and postictal confusion and drowsiness lasting 5 minutes. On arrival to the emergency department, he was hemodynamically stable and afebrile with a physical examination notable for mild left facial droop, mild left upper extremity, and lower extremity weakness. Serum PSA was elevated at 137.61 ng/mL. Computed tomography scan of the head revealed a dural-based extra-axial mildly hyperdense right frontal enhancing lesion causing significant vasogenic edema with right to left midline shift of 12 mm (Figure 1A and B). No bony involvement was noted. Magnetic resonance imaging of the brain revealed a large dural-based lesion along the right frontal convexity with marked mass effect and susceptibility artifact (Figure 1C-E).

Differential at the time included atypical meningioma, hemangiopericytoma, or metastatic disease. Levetiracetam and corticosteroids were started, and the patient had an electroencephalogram. He underwent a tumor resection; pathological evaluation revealed poorly differentiated glandular malignancy with marked anaplasia and elevated mitotic index as well as abundant tumor necrosis (Figure 2A-E).

The tumor formed large glandular structures lined by columnar cells that were piled up and markedly atypical, exhibiting numerous mitotic figures. Immunohistochemical staining with prostatic markers PSA and erythroblast transformation-specific-related gene was negative. Lung markers cytokeratin 7

(CK7) and thyroid transcription factor 1 and colorectal markers CK20 and CDX2 were also used to stain the mass, which were all negative. However, NKX3.1 stained strongly positive, indicating the primary origin was prostatic. Following surgery, the patient showed significant improvement from his preoperative symptoms. He had no further seizures following surgery and his dysarthric speech and facial asymmetry were mostly resolved. He was discharged home with a steroid taper. Two months later, he developed new neurological symptoms and the family decided to place him in hospice care without further diagnostic evaluation. He died several days later.

Discussion

The presence of a solitary intracranial dural mass with malignant appearance on radiological imaging often raises the question of whether the cancer is primary or a metastasis. In individuals with metastatic prostate cancer, dural metastasis is included in the differential diagnosis. The most common intracranial sites for metastasis are the leptomeninges, cerebrum, and cerebellum.⁵ Metastasis to the dura is rare.¹ Our patient had a large dural-based lesion along the right frontoparietal convexity. For cancers of unknown primary site, the Spanish Society for Medical Oncology guidelines state the use of CK7 and CK20 first to further stratify adenocarcinomas.⁶ For CK7, CK20-negative tumors, staining with PSA, indicate a prostate primary.^{6,7} In a recent 2014 study of 39 samples of distant prostate metastases (mostly osseous), PSA was found to be the best marker for prostate metastasis (97% sensitivity), while the combination prostate-specific membrane antigen and prostein detected 100% of PSA-negative metastases.³ Another study of 349 cases showed that the sensitivity of NKX3.1 staining for prostate metastasis is 98.6% and specificity is 99.7%.⁴ A large study of 225 primary prostatic adenocarcinomas stratified by Gleason score demonstrated that 14 of 150 carcinomas of Gleason score 8, 9, and 10 failed to stain with the PSA marker, while a recent study of prostate cancer metastases reported a detection rate of 100% for the NKX3.1 marker.^{8,9} Also, androgen deprivation therapy is

Figure 2. Histopathology of brain metastasis. A, The prostatic adenocarcinoma metastasis presented as a dural-based mass. B, The metastasis was comprised of aggregates of poorly differentiated malignant cells. C, Numerous mitotic figures were noted. D, Prostate-specific antigen staining was negative. E, There was strong nuclear positivity for the NKX3.1 marker.

known to decrease PSA positivity.⁴ There have been no large studies to date on the immunohistochemical staining patterns of prostate metastases to the dura. Nevertheless, it is reasonable to posit that dural metastases may exhibit higher Gleason scores, the very situation in which negative PSA staining has been observed.⁸ Our patient had a high Gleason score of 9 and was on androgen deprivation therapy. His CK7, CK20, and PSA were negative, while the NKX3.1 stain exhibited strong positive staining of tumor cells. The use of NKX3.1 as a sensitive and specific marker for prostate cancer has only been recently described. A large survey in 2010 included staining of 69 metastatic prostate cancers with NKX3.1, 68 (98%) of

which were positive, and out of 340 other tumors of nonprostatic origin, only 1 stained NKX3.1.⁴ This is the first case that reports the utility of NKX3.1 staining in diagnosing prostate metastasis to the brain. In conclusion, staining NKX3.1 should be considered in the evaluation of a patient with a known history of prostate cancer who presents with a new brain tumor.

Authors' Note

Informed consent was obtained from the patient to publish a case report manuscript.

Declaration of Conflicting Interests

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