Case Report

Metastasis in urothelial carcinoma mimicking prostate cancer metastasis in Ga-68 prostate-specific membrane antigen positron emission tomography-computed tomography in a case of synchronous malignancy

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ABSTRACT

Prostate cancer is the second most common cancer in man. It commonly presents with urinary symptoms, bone pain, or diagnosed with elevated prostate-specific antigen (PSA) levels. Correct staging and early diagnosis of recurrence by a precise imaging tool are the keys for optimum management. Molecular imaging of prostate cancer with Ga-68 prostate-specific membrane antigen (PSMA), positron emission tomography-computed tomography (PET-CT) has recently received significant attention and frequently used with a signature to prostate cancer-specific remark. However, this case will highlight the more cautious use of it. A 72-year-old male treated earlier for synchronous double malignancy (invasive papillary urothelial carcinoma right ureter and carcinoma prostate) presented with rising PSA (0.51 ng/ml) and referred for Ga-68 PSMA PET-CT, which showed a positive enlarged left supraclavicular lymph node. Lymph node biopsy microscopic and immunohistochemistry examination revealed metastatic carcinoma favoring urothelial origin. Specificity of PSMA scan to prostate cancer has been seen to be compromised in a certain situation mostly due to neoangiogenesis, and false positives emerged in renal cell cancer, differentiated thyroid cancer, glioblastoma, breast cancer brain metastasis, and paravertebral schwannomas. Understanding the causes of false positive will further enhance the confidence of interpretating PSMA scans.

Keywords: Dual malignancy, false positive, prostate cancer, prostate-specific membrane antigen positron emission tomography-computed tomography, urothelial carcinoma ureter

INTRODUCTION

Prostate cancer is the second most common cancer and sixth leading cause of cancer death in men worldwide.[1] Patients with prostate cancer commonly presents with urinary symptoms, bone pain, or diagnosed with raised prostate-specific antigen (PSA) incidentally.[2] Correct staging and early diagnosis of recurrence by a precise imaging tool is what required in cancer management.

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Cancer imaging is passing through a transition phase from morphological to molecular imaging in clinics. Similarly, in prostate cancer, many newer specific molecular targets for imaging have been recently identified. Prostate-specific membrane antigen (PSMA) is the preferred one among these; however, few case reports questioning its signature to prostate cancer have been published recently. Here, we present a first case report of PSMA expression in urothelial carcinoma mimicking prostate cancer metastasis on Glu-NH-CO-NH-Lys-(Axe)-[Ga-68(HBED-CC)] (Ga-68 PSMA) positron emission tomography-computed tomography (PET-CT) in a dual malignancy case.

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CASE REPORT

A 72-year-old male treated earlier with transurethral resection of prostate and the right open radical nephroureterectomy in 2013 for synchronous double malignancy (high-grade invasive papillary urothelial carcinoma right ureter and adenocarcinoma prostate Gleason 4+4) presented with rising PSA (0.59 ng/ml) with PSA doubling time of <6 months on routine follow-up. He was referred for Ga-68 PSMA PET-CT scan to our department to localize disease recurrence site. PET-CT scan revealed PSMA expressing enlarged left supraclavicular lymph node measuring 4.0 cm × 3.0 cm with SUVmax 4.9 [Figure 1] and no focal tracer uptake in the prostatic fossa. In the given clinical scenario of rising PSA, PET-CT finding favored recurrent prostate carcinoma. Biopsy from the left supraclavicular lymph node was performed and microscopic examination revealed metastatic poorly-differentiated carcinoma with focal necrosis [Figure 2]. Immunohistochemistry (IHC) examination revealed tumor cells express CK7 and GATA-3 strongly and diffusely while CK20 expression was focal and moderate however negative for prostate-specific acid phosphatase (PSAP) [Figure 3]. Overall, IHC profile favored metastatic urothelial carcinoma.

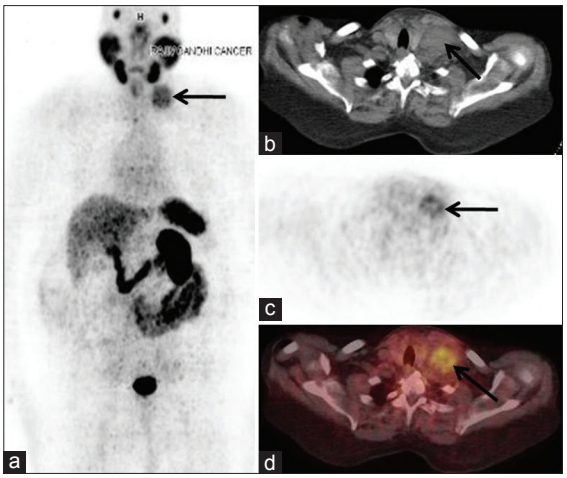

Figure 1: Ga-68 prostate-specific membrane antigen positron emission tomography-computed tomography scan, (a) maximum intensity projection; (b) axial computed tomography; (c) axial positron emission tomography; (d) fused positron emission tomography-computed tomography: Images show prostate-specific membrane antigen avid enlarged left supraclavicular lymphnode (black arrow)

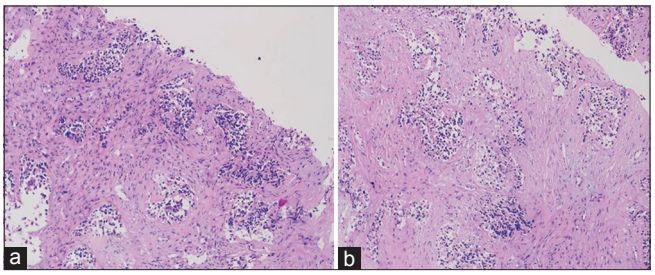

Figure 2: Core biopsy from the left supraclavicular lymphnode shows a tumor embedded in a fibrous stroma. The cells are arranged in irregular nests. (a) H and E, ×10; (b): H and E, ×20)

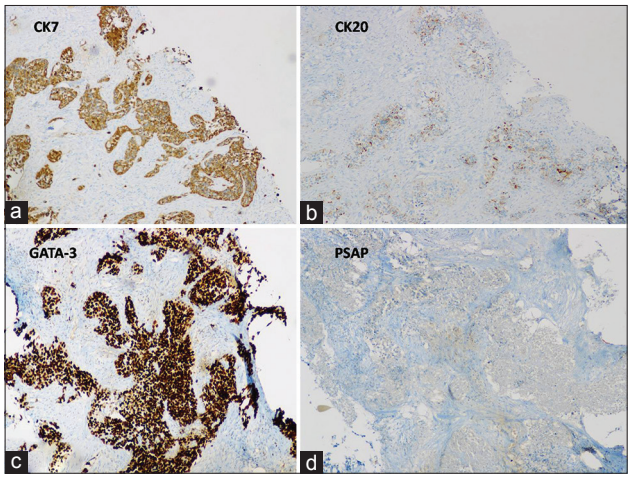

Figure 3: A tumor which is positive for CK7 (diaminobenzidine, ×20). (b) A tumor which is focally positive for CK20 (diaminobenzidine, ×20). (c) A tumor which strongly expresses GATA-3 (diaminobenzidine, ×20). (d) A tumor which is negative for prostate-specific acid phosphatase (diaminobenzidine, ×20)

DISCUSSION

Newer tracers in molecular imaging are paving a way for more tumor-specific armamentarium; however, a caution is required for their precision and exclusivity. These tracers need to prove them in various clinical scenarios before accepting them truly. PSMA has received a resurgence of attention after unsuccessful stories of PSA and PSAP in molecular imaging. PSMA is a type II membrane glycoprotein consisting of 750 amino acids (100–120 kDa), with a 19 amino acid intracellular component, a 24 amino acid intramembrane segment, and a large 707 amino acid extracellular component.[3] PSMA gene is located on chromosome 11.[4] PSMA exhibits folate hydrolase/glutamate carboxypeptidase II enzymatic activity; however, its precise role *in vivo* has not yet fully elucidated. *In vitro* its folate hydrolase activity has been associated with prostate carcinogenesis.[5] Certainly its expression is directly proportional to Gleason score and hormone resistant in prostate cancer but expression can be lost in poorly-differentiated tumor cell. PSMA is also expressed in salivary glands, duodenal mucosa, subset of proximal renal tubular cells, and subpopulation of neuroendocrine cells in colonic crypts small intestine.[6] Silver *et al.* also reported that renal cell carcinoma, bladder transitional cell carcinoma, and colonic adenocarcinoma cells do not exhibits PSMA expression however intratumoral and peritumoral capillary endothelial cells showed intense immunoreactivity.[6] Case reports of false-positive PSMA PET-CT have been published in renal cell cancer,[7] differentiated thyroid cancer,[8] glioblastoma,[9] breast cancer brain metastasis,[10] and paravertebral schwannomas[11] with expression limited to neovasculature endothelial cells in most.

In our case, the patient had synchronous malignancies in the right ureter and prostate and with rising PSA (0.59 ng/ml) and short PSA doubling time (<6 months), a more specific scan (^{68}Ga-PSMA) was performed which showed positive left supraclavicular lymph node, nonetheless biopsy with IHC

suggest metastatic urothelial carcinoma. GATA-3 is a sensitive and specific marker for urothelial carcinoma both in primary and nodal metastasis.[12] It expression is comparable to urothelial carcinoma associated markers CK7 and better than p63. CK20 is also positive in half of urothelial carcinoma. Because of suboptimal sensitivity of PSA for high-grade prostate carcinoma, PSAP IHC was used, but it was found negative. No further IHC such as PSMA was done due to financial constraints. In this case, most likely PSMA has been expressed on neovasculature of metastatic urothelial carcinoma cells and caused false-positive results on PET-CT. In our experience of over 150 cases of Ga-68 PSMA PET-CT since 2014, we have indeed seen PSMA expression in synchronous mucinous adenocarcinoma colon and metastatic lymph nodes from parotid gland carcinoma in one of each case as well.

CONCLUSION

PSMA PET-CT has received tremendous attention in molecular imaging, especially for the diagnosis of recurrence in treated prostate cancer patients. Being a very sensitive test, its use has grown in recent years despite few known limitations. This case report further highlights its vigilant use in differentiating prostate carcinoma with other solid cancers. Quantification values may be a key factor for differentiating false positive from true ones and should be a topic of research for the future.

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Conflicts of interest
There are no conflicts of interest.

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