De novo metastatic prostate cancer with neuroendocrine differentiation: A diagnostic dilemma

Somaye Barashki[1], Emran Askari[1], Mahmoudreza Kalantari[2], Hadis Mohammadzadeh Kosari[1], Kamran Aryana[1]

[1]Nuclear Medicine Research Center, Mashhad University of Medical Science, Mashhad, Iran
[2]Department of Pathology, Faculty of Medicine, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding author:
Dr. Kamran Aryana
Nuclear Medicine Research Center, Mashhad University of Medical Science, Mashhad, Iran
E-mail: aryanak@mums.ac.ir

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ABSTRACT
De novo metastatic prostate cancer with neuroendocrine differentiation (NED) at first presentation is extremely rare. A 65-year-old man (Gleason score 5+4, first assumed to be acinar adenocarcinoma), was referred for [^{99m}Tc]Tc-HYNIC-PSMA SPECT/CT due to low back pain. The PSA levels were 8 and <0.07 ng/mL at the time of diagnosis and prior to scintigraphy respectively. The scan revealed multiple non-PSMA-avid lesions throughout the skeleton, lung and liver, suggesting the possibility of NED or 2nd malignancy. Second-look and review of the pathology led to change of the diagnosis to mixed small cell neuroendocrine carcinoma-acinar adenocarcinoma. This case highlights the importance of PSMA imaging in suggestion of type of the tumor which as in our case, might alter the pathologic tissue diagnosis.

Keywords: Prostate cancer; Neuroendocrine differentiation; [^{99m}Tc]Tc-PSMA SPECT/CT

CASE PRESENTATION
A 65-year old man diagnosed with locally advanced prostate adenocarcinoma (Gleason score 5+4), was referred to our center due to low back pain. The patient underwent prostatectomy 4 months before referral. He also had undergone external beam radiation therapy (EBRT) as well as androgen-deprivation therapy (ADT). His preoperative CT-scan showed an ill-defined mass in the liver segment VIII (Figure 1C). Although PSA level was 8 ng/mL at the time of diagnosis, the physician decided to pursue a core-needle biopsy from the liver which was negative for malignancy. Whole body bone scan was also negative, demonstrating normal thoracic vertebra on his previous CT scan (Figures 1A and 1D). Despite surgery, EBRT and ADT, the patient reported worsening of his low back pain which prompted his clinician to request for [^{99m}Tc]Tc- HYNIC-PSMA SPECT/CT imaging. His PSA level was <0.07 ng/mL at the time of scintigraphy. Four hours after intravenous injection of 740 MBq of [^{99m}Tc]Tc-

HYNIC-PSMA, whole body scan and SPECT/CT was done, showing only mild irregular PSMA uptake throughout the skeleton (Figure 1B). Low dose CT component of the study revealed multiple lytic lesions throughout the skeleton, multiple small nodules in both lungs and a hypo-dense mass in the segment VIII of the liver (Figures 1E, 1F and Figure 2). The scan findings were suggestive of either non-PSMA-avid prostate cancer or a 2nd malignancy. To decide between the two possible diagnoses, a second review of pathology slides and immunohistochemical staining was performed. Histopathologic findings showed prominent Gleason 5, suggestive of neuroendocrine carcinoma (small cell subtype) and patchy cribriform Gleason 4 acinar adenocarcinoma (arrow) (Figures 3A and 3B). Immunohistochemical staining was focally and patchy positive for PSA, CK7, CK20 and AMACR in cribriform areas (Figures 3C-3F) and strongly positive for CD56, chromogranin A as well as synaptophysin in solid areas (Figures 3G-3I). These findings confirmed the diagnosis of de novo mixed small cell neuroendocrine carcinoma-acinar adenocarcinoma according to 2014 WHO classification [1]. While double carcinoma was not completely excluded at that time, the team decided to start chemotherapy for the patient, which was not successful. His interval abdomino-pelvic CT with contrast showed progression of his previously mentioned lesions (Figures 1G and 1H). Meanwhile, he had been scheduled for somatostatin receptor imaging and a repeat liver biopsy, which were not performed due to coagulopathy and patient clinical deterioration. The patient passed away 11 months after diagnosis.

DISCUSSION

De novo prostate cancer with neuroendocrine differentiation (PCaNED) is reported in 0.5 to 2% of all cases of prostate cancer. However, de novo metastatic PCaNED as first presentation is extremely rare with grave prognosis [2-5].

According to some reports PCaNED can present with locally invasive or metastatic disease at the time of presentation including visceral metastasis to the liver, lung, and predominantly lytic bone metastases [3, 6-7]. Various studies have shown the role of other nuclear medicine imaging methods, such as somatostatin receptor imaging, in the evaluation of PCaNED patients [8-10]. Some studies have also examined the role of somatostatin receptor therapy in PCaNED patients [11, 12]. Our patient was also a candidate for [^{68}Ga]Ga-DOTATATE PET/CT scan, but unfortunately, he passed away before the scan could be performed.

CONCLUSION

Although post-mortem autopsy was not performed in this case, the propensity to rapidly metastasize to the liver, the "5" component Gleason score, immunohistochemistry staining, low [^{99m}Tc]Tc-PSMA uptake (which has comparable sensitivity to [^{68}Ga]Ga-PSMA PET/CT), low PSA levels at diagnosis, rapidly progressive and resistant nature of the disease could all be explained by the presumptive diagnosis of neuroendocrine differentiation [13] and highlights the usefulness of PSMA imaging in prostate cancer.

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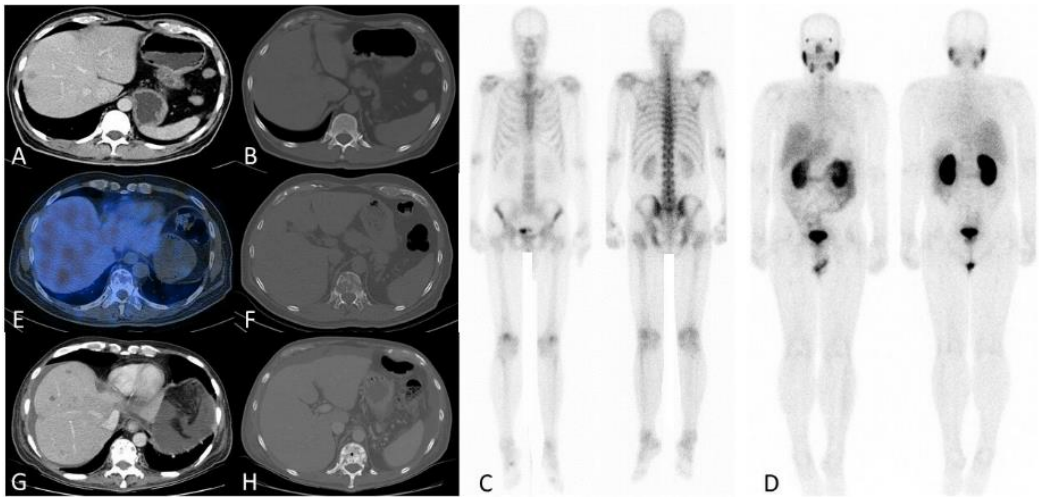

Fig 1. (A) Whole body bone scan; (**B)** Whole body [^{99m}Tc]Tc-HYNIC-PSMA scan; (**C** and **D)** CT scan from the liver and thoracic vertebra for initial staging; (**E)** SPECT/CT from the liver with no abnormal uptake; (**F)** CT component of the [^{99m}Tc]Tc-HYNIC-PSMA; (**G** and **H)** Post chemotherapy CT scan

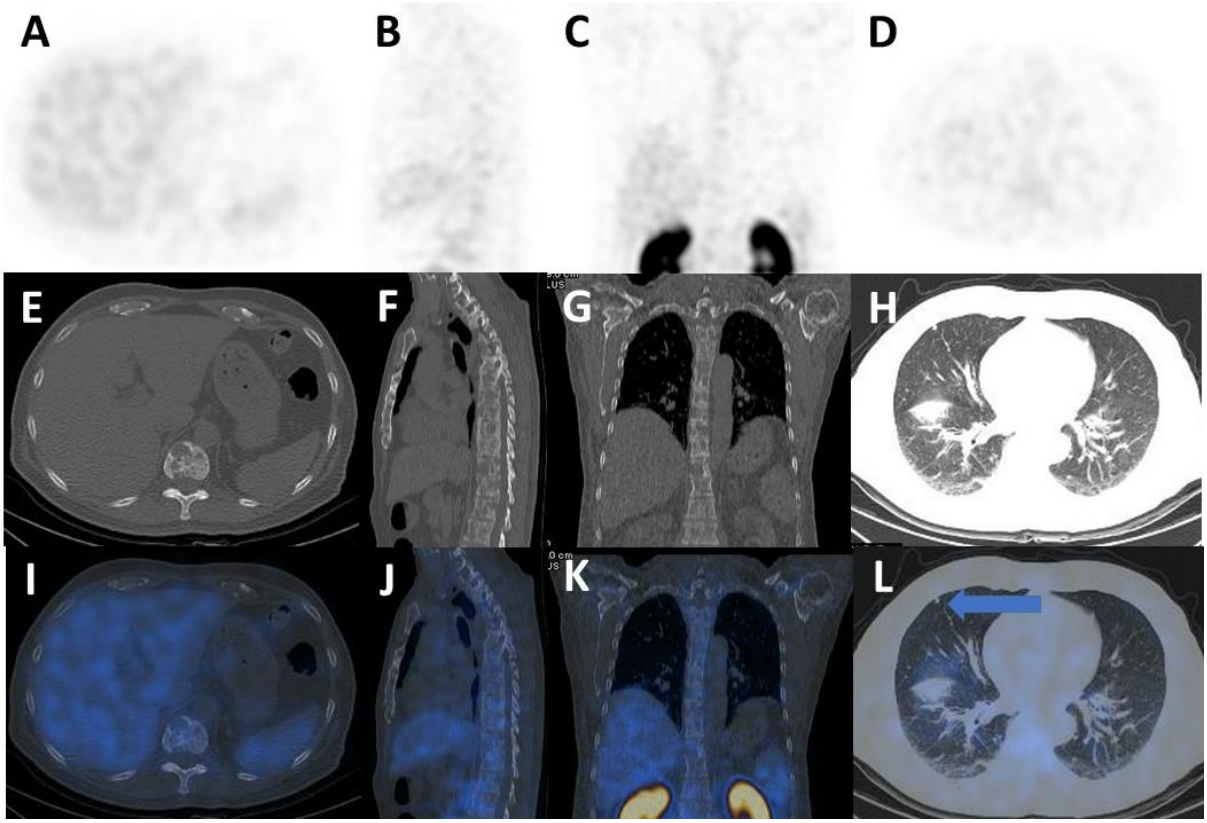

Fig 2. (A-L) SPECT, CT and fused SPECTCT images in axial, sagittal and coronal view from bone metastases as well as in axial view from lung metastasis

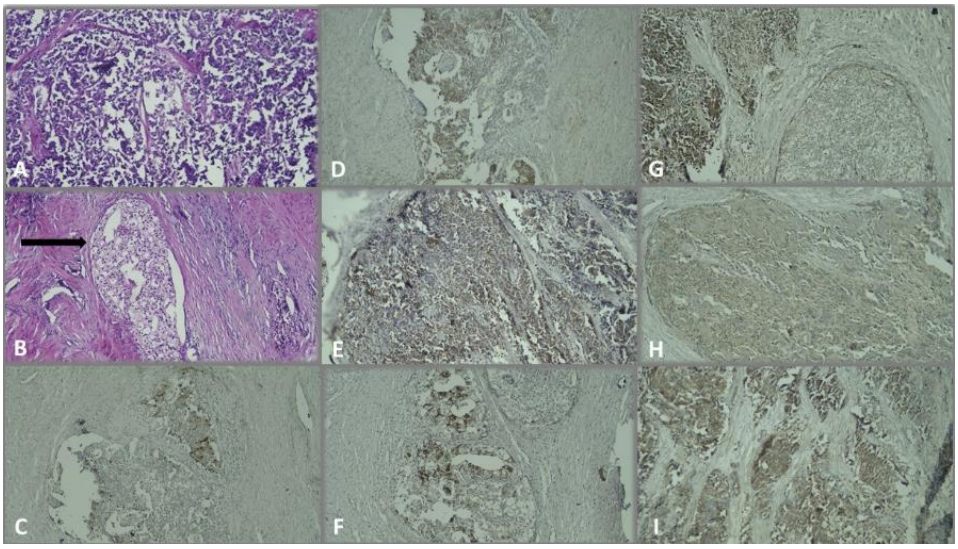

Fig 3. (A and **B)** Hematoxylin and Eosin staining; (**C-I)** Immunohistochemical staining for PSA, CK7, CK20, AMACR, CD56, chromogranin A and synaptophysin