Rare Case of Neuroendocrine Prostate Cancer detected on 68Ga – DOTANOC PET/CT.

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Abstract

Prostate cancer is the second most common malignancy and the fifth leading cause of cancer death among men worldwide. Prostatic acinar adenocarcinoma is the most common histological variant of diagnosed prostate cancer. Other less common histological variants of prostate cancer are classified as non-acinar carcinoma. These include neuroendocrine prostate cancer, sarcomatoid carcinoma, ductal adenocarcinoma, urothelial carcinoma, squamous and adenosquamous carcinoma, and basal cell carcinoma. Most of these non-acinar carcinoma variants of prostate cancer are aggressive and associated with poor prognosis.

Neuroendocrine tumors are characterized by the expression of somatostatin receptors (SSTRs). Positron emission tomography/computed tomography (PET/CT) using radiolabelled somatostatin-analogs like DOTANOC have been used to detect and stage these neuroendocrine tumors (NETs). These radiolabelled somatostatin analogs also provide the option of treatment of these tumors and have been used in Peptide Receptor Radionuclide Therapy (PRRT) of these tumors. We here report a case of metastatic neuroendocrine prostate cancer (NEPC) detected on 68Ga - DOTANOC PET/CT.

Introduction

Prostate cancer is the second most common malignancy and the fifth leading cause of cancer death among men worldwide [1]. It is a malignancy afflicting elderly men, other risk factors being family history and black race. The majority of men diagnosed with prostate cancer are asymptomatic at the time of diagnosis. However, prostate cancer may present with nonspecific lower urinary tract symptoms like haematuria. Other symptoms like frequency, urgency, nocturia, and hesitancy can also be seen; however, these are more commonly seen in benign conditions such as benign prostatic hyperplasia. Bone pain can also be a presenting complaint in case of patients diagnosed with metastatic skeletal disease at onset. Serum PSA level is a commonly used initial test in the diagnosis of prostate cancer. The possibility of prostate cancer increases with higher values of PSA levels. However, there is no single threshold value of PSA to decide the diagnosis of prostate cancer.

Moreover, raised PSA levels can also be seen in benign conditions like prostatitis. Digital rectal examination (DRE) is used to detect enlarged prostate, asymmetry, and prostate nodules, which guides further evaluation. Suspicious DRE findings, combined with PSA levels, help guide the clinician in deciding whether there is a need for a biopsy [2]. However, prostate cancer is not always detected on DRE and, hence, not a recommended standalone screening modality for prostate cancer [3]. Imaging modalities like transrectal ultrasonography (TRUS) and MRI have been used to improve the accuracy of prostate biopsies [4]. Positron emission tomography (PET) in conjunction with computed tomography (CT) and MRI are also being used now for imaging-guided biopsy of prostate lesions [5]. On biopsy, acinar adenocarcinoma is the most common variant of prostate cancer, accounting for more than 90% of the cases. Other non-acinar carcinoma histological variants account for 5-10% of cases of prostate cancer [6]. These histological variants include neuroendocrine prostate cancer (NEPC), sarcomatoid carcinoma, ductal adenocarcinoma, urothelial carcinoma, squamous and adenosquamous carcinoma, and basal cell carcinoma. After confirmation of prostate cancer on biopsy, imaging is undertaken for staging of the disease and deciding treatment modalities available for the patient. MRI is the recommended modality for locoregional evaluation and guiding biopsy in cases of prostate cancer [7].

CT and whole–body bone scans have been used for staging prostate cancer. However, now, prostate-specific membrane antigen (PSMA) PET/CT is being increasingly used in staging and response evaluation of adenocarcinoma prostate [8]. PET/CT has also been used in the staging of other non-acinar histologic variants of prostate cancer, NEPC is an aggressive variant of prostate cancer, and 18F - Fluorodeoxyglucose (FDG) and 68Ga - DOTANOC PET/CT have been used in the staging of these tumors. Depending on the Gleason score, stage, and condition of the patient in cases of adenocarcinoma prostate, surgical treatment options include radical prostatectomy, robotic or laparoscopic prostatectomy, and transurethral resection of
Radiotherapy is also used in treatment of prostate cancer either in the form of external beam radiotherapy including stereotactic radiotherapy, and brachytherapy. Adenocarcinoma variants of prostate cancer are androgen-dependent, and hormonal therapy treatment options like bilateral orchidectomy and anti-androgen therapy (ADT) drugs are also used. In metastatic stage IV cases of prostate cancer, chemotherapy is also used, the most widely used chemotherapy agent being docetaxel. When all treatment options are exhausted, then PRRT is an option for treatment in these patients.

**Case Presentation**

We report a case of biopsy-proven NEPC with nodal and skeletal metastases. The index case is a 65-year-old man who initially presented with complaints of haematuria. At initial presentation, serum PSA was raised (7.8 ng/mL), and DRE revealed an enlarged, hard, nodular prostate gland. TRUS-guided biopsy of the prostate confirmed the diagnosis of adenocarcinoma carcinoma of the prostate with a Gleason score of 8 (4 + 4). CT thorax and abdomen with whole body bone scan were negative for nodal and distant metastases. The patient did not want to undergo surgical treatment after initial staging and work up. He received a definitive dose of radiation therapy (RT) to local site. The patient was put on anti-androgen therapy (ADT) and was followed up with serum PSA levels. Approximately 18 months after RT, the patient came to outpatient with a complaint of bone pain. Serum PSA level was raised (168.2 ng/mL), and whole body bone scan revealed multiple skeletal metastases. CT thorax and abdomen confirmed skeletal metastasis in the form of sclerotic lesions involving multiple skeletal sites. Diagnosis of metastatic castration-resistant prostate cancer (mCRPC) was established in conjunction with biochemical tests, and the patient was started on docetaxel-based palliative chemotherapy at 75 mg/m², a total of six cycles at three week intervals. The patient responded well, symptoms of pain were alleviated, and PSA level came back within normal range. The patient was continued on ADT and kept on follow-up with serum PSA level monitoring. Again, after a period of approximately 12 months, the patient came back with complaints of haematuria and pelvic bone pain. DRE revealed a hard, nodular prostate; however, PSA level was within normal range (2.8 ng/mL). TRUS-guided biopsy was undertaken. Histopathology, in conjunction with IHC, confirmed the diagnosis of NEPC. 68Ga - DOTANOC PET/CT was conducted for staging of the disease after obtaining written consent from the patient. PET/CT study was analyzed, and standardized uptake values (SUVmax) were obtained. Findings (Figures 1A - 1G) revealed DOTANOC avid soft tissue lesion involving the entire prostate gland (SUVmax 67.4). Pelvic lymph nodes (SUVmax 50.1) and skeletal sclerotic lesions (SUVmax 27.5) were also noted with increased DOTANOC uptake. Background SUVmax value of 3.1 was noted. These findings established the diagnosis of stage IV NEPC. Subsequently, the patient received a cisplatin-based palliative chemotherapy regimen.

**FIGURE 1: 68Ga - DOTANOC PET/CT images of the patient**

(A) MIP; (B, D & F) axial view of CT; (C, E & G) axial view of 68Ga - DOTANOC PET/CT fusion. Image A shows DOTANOC uptake in the region of prostate (black arrow), pelvic lymph nodes (red arrow) and skeletal metastatic sites in region of left humerus and right femur (blue arrows). Images B & C reveal prostate mass with DOTANOC uptake suggesting somatostatin receptor expressing neoplastic disease (white arrows). Images D & E show bilateral iliac lymph nodes with DOTANOC uptake (white arrows). Images F & G shows sclerotic lesion involving sacrum with DOTANOC uptake (white arrows).

MIP: maximal intensity projection; 68Ga-DOTANOC PET/CT: 68Gallium labelled DOTANOC positron emission tomography/computed tomography.

**Discussion**
Prostate cancer is one of the most common malignancies and a leading cause of death in men worldwide. Adenocarcinoma, the most typical variant of prostate cancer, is androgen dependent; hence, surgical castration and ADT therapy like GnRH agonists and hormonal therapy with Abiraterone have been used in management. However, despite these treatment options, prostate cancer progresses and metastasizes within two to three years. These cases of prostate cancer are termed castration-resistant prostate cancer (CRPC). The emergence of CRPC is due to the development of resistance to therapy in cancer cells. The diagnosis of CRPC is not dependent only on the progression of symptoms. CRPC is defined as a documented rise in PSA > 2 ng/mL, PSA values > 25% above nadir, PSA elevation in three consecutive determinations at least one week apart, and/or radiological progression in castrated patients with serum testosterone levels < 50 ng/dL. CRPC may be due to primary resistance to ADT or acquired resistance when on ADT. This process is androgen-dependent, and androgen receptor (AR) plays a vital role in the development of CRPC. Multiple mechanisms have been proposed, including AR amplification and hypersensitivity, AR mutations leading to promiscuity, coactivators/corepressors, androgen-independent AR activation, and intratumoral and alternative androgen production. The cases of mCRPC are treated with taxane-based chemotherapy in addition to second-generation ADT like Abiraterone and Enzalutamide. Another response to bypass ADT and/or chemotherapy in prostate cancer is the transformation of histopathology from AR-expressing prostate adenocarcinoma to AR-negative poorly differentiated small cell neuroendocrine carcinoma histology, commonly referred to as NEPC. The transformation of histopathology from AR-expressing prostate adenocarcinoma to AR-negative poorly differentiated small cell neuroendocrine carcinoma histology is also referred to as NEPC. NEPC is an aggressive variant of prostate cancer that develops later as a mechanism of treatment resistance. It is characterized by down-regulation of PSMA expression with low or non-rising PSA levels. Most NEPC are a treatment-emergent response to therapy and termed as t-NEPC. Rarely NEPC can also occur as a primary form of prostate cancer with an incidence rate of 1%. Like other neuroendocrine tumors, NEPC is characterized by the expression of neuronal markers, including enolase 2, chromogranin A, and synaptophysin. Serum markers like chromogranin A and neurone-specific enolase are typically raised in NEPC. These also express SSTRs; hence, radiolabelled somatostatin analogs are used in imaging these tumors. The index case presented here in this article is a case of t-NEPC presenting as metastatic disease detected on 68Ga-DOTANOC PET/CT. NEPC is an aggressive type of mCRPC with a poor prognosis and very often presents with visceral metastases. Platinum-based palliative chemotherapy regimens with etoposide and taxanes have been used in treatment. Surgery and radiotherapy have also been used for clinically localized disease or palliation of individual metastatic sites.

Conclusions

mCRPC results as a treatment evasive response to ADT in cases of adenocarcinoma prostate. Another mechanism of developing resistance to therapy is neuroendocrine differentiation in these tumors with a resultant transformation of histology to neuroendocrine malignancy from that of adenocarcinoma. These treatment-emergent NEPCs are aggressive forms of mCRPC presenting with distant metastasis, associated with poor prognosis and survival rates. Treatment guidelines for NEPC are not clearly defined and mainly consist of platinum-based chemotherapy, which is effective for a short duration. This case study highlights the role of 68Ga-DOTANOC PET/CT imaging in detecting NEPC in a therapy resistant adenocarcinoma prostate.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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