

Unusual Presentation of *De Novo* Case of Prostate Adenocarcinoma with Diffuse Neuroendocrine Differentiation

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Abstract

The interest regarding neuroendocrine prostate cancer has widened in the last few years as many of these cases were seen coinciding with the accelerated utilization of androgen deprivation therapy, and thus the possible association between androgen deprivation therapy and neuroendocrine prostate cancer was hypothesized. Even though, androgen deprivation therapy is considered to be the main culprit associated with neuroendocrine prostate cancer, there have been few rare cases that had no prior history of androgen deprivation therapy use in their past. We report here an unusual presentation of *de novo* case of prostate adenocarcinoma with diffuse neuroendocrine differentiation. An elderly male of 59-year-old presented to our clinic with an enlarged lymph node on left side of neck. Physical examination showed soft abdomen and no visceromegaly, spine was non tender. An excisional biopsy of the lymph node was sent for histopathological examination depicting diffuse effacement of the lymph node architecture by a metastatic tumor comprised of cribriform glands. Immunohistochemical markers were applied to delineate the primary site which showed that the tumor was negative for CK7 and CK20, however prostate specific antigen and prostatic specific acid phosphatase displayed diffuse positivity. In addition, since many cells showed nuclear molding therefore synapophysin and chromgranin were also applied and both of them displayed extensive granular cytoplasmic positivity. Based on these findings a final diagnosis of metastatic prostatic adenocarcinoma with diffuse neuroendocrine differentiation was rendered. Later on, Trans rectal ultrasonography biopsy was performed from all six lobes which showed Grade 5 (Gleason score 4+5) tumor in five out of 6 cores. These tumor cells also displayed strong cytoplasmic staining for synaptophysin and chromogranin highlighting their neuroendocrine differentiation. Only few such cases have been reported in literature and information regarding its clinicopathological features and disease outcome are limited. Our case was a challenging and insightful to add to the literature regarding this rare presentation of prostate cancer.

Keywords: Prostate Cancer; Cervical Lymphadenopathy; Metastasis; Neuroendocrine

Introduction

Prostate cancer is the most common malignant tumor among men, worldwide [1]. The vast majority of prostate adenocarcinomas are of acinar types, however some rare variants also exist. Neuroendocrine tumors (NETs) of the prostate comprise < 1% of all prostatic adenocarcinomas and are distinguished by the presence of neurosecretory granules [1]. These tumors have characteristic morphological and immunohistochemical features along with biological behavior that makes them distinct from conventional prostatic adenocarcinomas [1]. Neuroendocrine tumors of prostate are broadly categorized into four subtypes, prostate adenocarcinoma with neuroendocrine differentiation, carcinoid tumor, Small cell neuroendocrine carcinoma and Large cell neuroendocrine carcinoma [2]. Till date, most of the published cases of NETs actually represent those forms of cancer that progressed from prior typical adenocarcinoma after undergoing a long duration of androgen deprivation therapy (ADT). Moreover, neuroendocrine cells and neuroendocrine prostate cancer (NEPC) are said to be lacking in androgen receptors and as such are thought to be hormone refractory. In a nutshell, NEPC are considered aggressive that are associated poor prognosis [1,2]. The interest regarding neuroendocrine prostate cancer has widened in the last few years as many of these cases were seen coinciding with the accelerated utilization of ADT, the use of more and more potent ADT regimens and thus the possible association between ADT and NEPC was hypothesized [3]. Even though, ADT is considered to be the main culprit associated with NEPC, there have been few rare cases that had no prior history of ADT use in their past [4,5].

We report here an unusual *de novo* case of Prostate adenocarcinoma with diffuse neuroendocrine differentiation. To our knowledge, previously only few such cases have been reported worldwide and information regarding its clinicopathological features and disease outcome are limited.

Case Report

A 59-year-old male presented to surgical department with an enlarged lymph node on left side of neck, beside this he had no fever, loss of appetite, weight loss or urological symptoms. Furthermore, he had no complaints of flank pain, gross hematuria or any kind of bone pain. The systemic enquiry regarding central nervous system, cardiovascular system, respiratory and gastrointestinal system was unremarkable. There was no history of medical comorbidities or TB (Tuberculosis) contact in past. Moreover, there was no previous history of urological surgery. Family history was negative for malignancy. He was an ex-smoker of 10 - 15 cigarettes daily for 28 years. On examination, he had a single, non tender, firm to hard nodule that measured approximately 1.9 cm. Physical examination showed soft abdomen having no visceromegaly. There was clear entry of air in chest and spine was non tender. No other palpable lymph nodes were found elsewhere.

In surgical ward initial evaluation by DRE (Digital rectal exam) and PSA (prostatic specific antigen) was not done as he had no urological symptoms. An excisional biopsy of the lymph node was performed to rule out suspected TB or other chronic disease and specimen was sent for histopathological examination. Microscopic examination of the lymph node showed diffuse effacement of the lymph node architecture by a metastatic tumor comprised of cribriform glands (Figure 1). Immunohistochemical (IHC) markers were applied to delineate the primary site. On IHC, the tumor was negative for CK 7 and CK20, however PSA and PSAP displayed diffuse positivity. In addition, since many cells showed nuclear molding therefore synapophysin and chromgranin were also applied and both of them displayed extensive granular cytoplasmic positivity (Figure 1). Based on these findings a final diagnosis of metastatic prostatic adenocarcinoma with diffuse neuroendocrine differentiation was rendered. Further laboratory investigations were sent which showed raised PSA of 85.90 ng/mL. Hemoglobin was 10.2 g/dL, platelets 191000/mm³, alkaline phosphate 212 U/L (slightly raised). His sputum culture test was also done for ruling out TB, that came out to be negative. His Chest XRay was normal. After these findings he was referred to urology department for further management. Shortly thereafter, patient developed lower urinary tract symptoms. Digital rectal examination showed right firm and mildly enlarged prostate. Trans rectal ultrasonography biopsy of prostate was performed from all six lobes which showed Grade group 5 (Gleason score 4+5) tumor in five out of 6 cores (Figure 2). These tumor cells also displayed strong cytoplasmic staining for synapophysin and chromgranin (similar to the stains results for the cervical lymph node biopsy) highlighting their neuroendocrine differentiation.

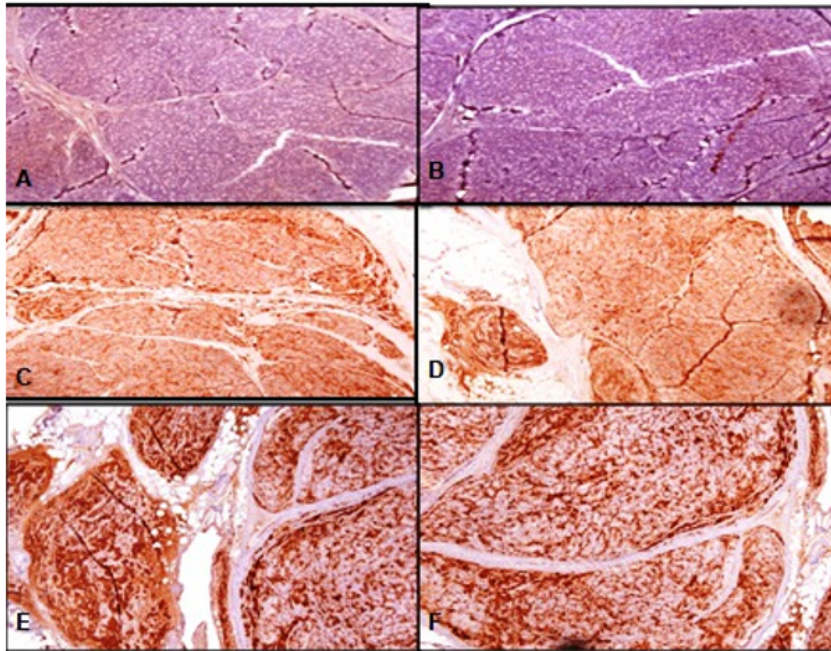


Figure 1: (A and B) Showing CK7 and CK 20 negativity, C and D showing PSA and PSAP positivity, E and F showing synaptophysin and chromogranin positivity on immunohistochemical staining (A-F, 20X).

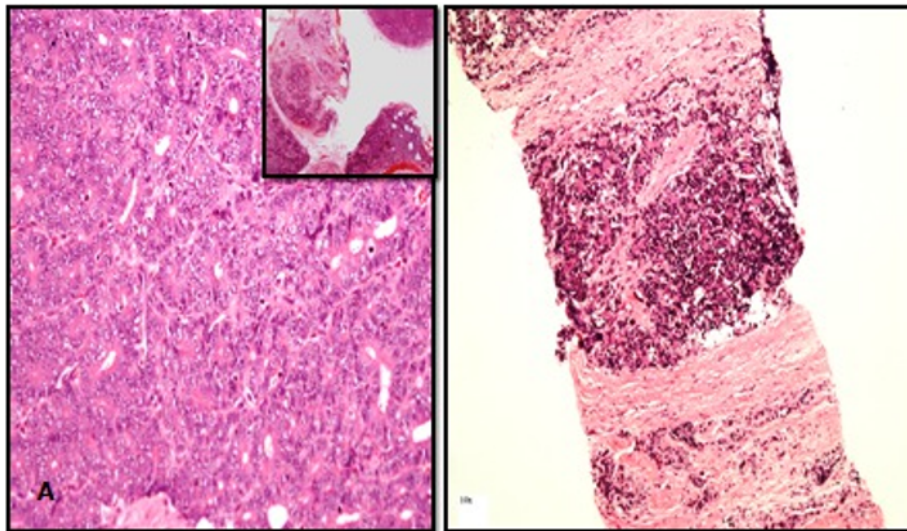


Figure 2: A. Lymph node showing effaced architecture by a glandular tumor. Inset shows residual lymphoid tissue at the periphery (20X). B. TRUS biopsy showing Grade group 5 (Gleason score 4+5) tumor (10X).

The patient had a computed tomography (CT) scan of the neck, chest and abdomen and pelvis to work up metastatic spread if any. The CT demonstrated adenopathy within the supraclavicular region only with no other sites of metastasis (Figure 3 and 4). Bone scan was negative for bone metastasis. This case was discussed in multidisciplinary team meeting, following which orchiectomy was planned. We discussed with him the available treatment options. Due to economical restraints of the patient he opted for orchiectomy. His consent was taken to share information in this case report. After orchiectomy his PSA dwindled to 6.36 ng/ml. After 8 months of follow up he developed obstructive lower urinary tract symptoms for which channel Trans Urethral Resection of Prostate was done to relieve his obstructive urinary symptoms. His disease remained stable over 18 months of follow up.



Figure 3: Computed tomography abdomen showing no visceral metastasis.



Figure 4: Computed tomography pelvis showing no pelvic metastasis.

Discussion

The current report describes a unique case of prostatic adenocarcinoma in which enlarged cervical lymph node was the primary presentation. Histopathology report showed a diagnosis of prostatic adenocarcinoma with neuroendocrine differentiation. The clinical course was stable in our case for 18 months of initial diagnosis. After this he was lost to follow up but on contact with the family members he died of unknown cause.

Majority of prostatic cancers are adenocarcinomas which express androgen receptors. A subset of cases, accounting for almost 10% of adenocarcinomas show neuroendocrine differentiation, whereas pure neuroendocrine carcinomas (NECs) of prostate are even rarer [3,5]. Previous literature is sparse regarding neuroendocrine tumors (NET) of the prostate. Racquel, *et al.* [3] and other similar other case report studies described that NETs of the prostate present at an advanced age just like conventional prostatic adenocarcinomas [4]. Our reported case had an age of 59 years similar to previous few case reports. Most of the patients as documented in previous studies, present with lower urinary tract symptoms analogous to traditional adenocarcinoma [4]. However, our case was distinctive in the sense that patient came to clinical attention as a result of enlarged cervical lymph node, and it was only after histopathological and radiological work up that prostate was identified as the primary site of carcinoma.

According to literature, cases of NETs of prostate arise from conventional adenocarcinoma as a result of androgen deprivation and castration resistant tumor. Moreover, proportion of NE differentiation increases in response to androgen deprivation therapy (ADT) and with time passage these tumors undergo trans differentiation leading to expression of NE markers [1]. A previous study by Lin, *et al.* on prostate-derived xenografts concluded that NE differentiation in prostate cancer can evolve directly from adenocarcinoma via an adaptive response to prolonged androgen withdrawal through changes at genetic level [2]. Although previous case reports have signified the importance of trans differentiation in preexisting adenocarcinoma, our case was unique in a sense that it presented with *de novo* NE differentiation. It was as depicted by diffuse staining by synaptophysin and chromogranin in metastatic as well as primary histopathology sample from the prostate. It's an interesting and important fact in our case that patient had received no prior medical or surgical treatment for prostatic cancer. Wei, *et al.* had also described a case of *de novo* mixed neuroendocrine-acinar adenocarcinoma of prostate [3]. Except for a few published case reports, we have no authentic knowledge regarding the biological behavior of adenocarcinomas with extensive NE differentiation in contrast to focal NE differentiation as proposed by WHO classification of NE tumors of prostate [4]. A recent update by Samson has hinted that adenocarcinomas with extensive NE differentiation do not neatly fit into any of the current categories as illustrated by WHO. As a result authors fit such cases improperly into the already established categories of NE tumors by WHO. Furthermore, some new authors have tried accommodating these tumors under vague terminologies. According to Samson such unique cases should be reported as "Prostate adenocarcinoma with diffuse NE differentiation" so as to separate them from more common focal NE differentiation [5].

NE differentiation in prostate is correlated with an aggressive clinical outcome and increased recurrence along with metastasis [6]. In our knowledge, the only case previously reported of prostatic adenocarcinoma with extensive NE differentiation similar to ours had a particularly dismal patient outcome with multiple site of metastasis and death of the patient within 01 year of initial diagnosis. Our patient only presented with a metastatic lymph node. We had discussed his case in MDT (Multi-disciplinary team) meeting. We discussed with patient the options to start either anti androgen therapy (medical castration) in form of medication (Goserelin acetate and bicalutamide) or to undergo surgical castration (sub capsular orchiectomy). As he was a poor driver so he opted for the cheaper option of surgical castration (sub capsular orchiectomy). After orchiectomy his PSA level reduced to 6.36 ng/ml. After 8 months of follow up he developed obstructive lower urinary tract symptoms for which channel Trans Urethral Resection of Prostate was done. Our patient died after 18 months of the initial diagnosis [7,8]. It's interesting here that he had fairly stable disease for 18 months in contrast to previously few reported cases having dismal initial course of the disease. Till to date, no consensus has been reached regarding standard treatment of such tumors but it has been proposed that these tumors might benefit from somatostatin and peptide analogues [8-10].

Conclusion

In older age patients a cervical lymph node can be the first presentation of metastatic prostatic cancer. We propose that correct identification based on histopathological and immunohistochemically analysis is important in order to predict patient prognosis. Aggressive treatment options can be initiated from the beginning so that patient's outcome and survival could be improved.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initial would not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of Interest

None.

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