Small Cell Carcinoma of Prostate: A Case Report of a Patient With a Normal PSA and a Giant Prostate Volume

Alan Hasigov¹, ², ³, Jean Paul Ndamba Engbang², ³, ⁴, Tamerlan Tlatov¹, Aleksandre Ephiev¹, ³
¹Republican Oncology Center, Vladikavkaz, Russia
²Republican Clinical Hospital, Vladikavkaz, Russia
³North-Ossetian State Medical Academy, Vladikavkaz, Russia
⁴Faculty of Medicine and Pharmaceutical Sciences, The University of Douala, Douala, Cameroon

*Corresponding author(s): Jean Paul Ndamba Engbang, Faculty of Medicine and Pharmaceutical Sciences, The University of Douala, BP 2701 Douala, Cameroon
Email: jean_pen@yahoo.ca, jpauleng@gmail.com
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ABSTRACT

Neuroendocrine differentiation (NED) in prostate cancer (PCa) implies the presence of a malignant neoplasm of the prostate with the neuroendocrine component. NED is a common feature of prostatic adenocarcinomas. There are three types of NED: pre-existing NED, therapy-induced NED and radiotherapy-induced NED. Pure neuroendocrine prostate cancer (NEPC) and a small cell PCa represent rare and aggressive tumors, such as primary carcinoids, which are also very rare. The most common clinical symptoms of small cell carcinoma are dysuria and urinary tract irritation. DRE, Trans-rectal ultrasound sonography, Abdomen scans, magnetic resonance imaging (MRI) scan and bone scintigraphy to know the prostate volume, its structure the presence or not of metastasis. In contrast to prostatic adenocarcinoma, PSA is an unreliable tumor marker for small cell prostate carcinoma and is usually normal, even when there is metastatic disease. The confirmation of SCC of the prostate relies mainly on pathological findings (morphological features and Immunohistochemical staining). The treatment for patients remains surgery and/or systemic chemotherapy but depends on the stage of the disease. We describe the case of a patient with small cell carcinoma of the prostate characterized by a normal PSA and a giant prostate volume.

Keywords: small cell carcinoma, giant prostate, PSA, chemotherapy.

INTRODUCTION

Neuroendocrine cells (NEC) are scattered in prostatic glands in all anatomic zones and comprise less than 1% of the benign prostatic glandular epithelium. These cells are a small subset of cells and have a unique function in regulating the growth of prostate cells [1, 2]. Neuroendocrine differentiation (NED) in prostate cancer (PCa) implies the presence of a malignant neoplasm of the prostate with neuroendocrine components (NEC). About 10% of untreated usual prostate adenocarcinoma shows focal NED [3]. De novo NE tumors of the prostate, which are composed of exclusive NE tumor cells without history of prostate adenocarcinoma, are very rare but aggressive [2, 4]. According to the 2004 WHO
classification, NED in prostate cancer occurs in 3 forms: Focal NED in conventional prostate adenocarcinoma, Carcinoid tumor, and Small cell NE carcinoma. Although that classification is simple and it is based on the standard for all neuroendocrine tumors (NETs), it does not reflect unique aspects present in PCa. Recently, Epstein et al. proposed a new morphological classification of prostate cancer with NED. The proposed classification is as follows: (I) usual prostate adenocarcinoma with NED; (II) adenocarcinoma with Paneth cell-like NED; (III) carcinoid tumor; (IV) small cell carcinoma; (V) large cell NE carcinoma; (VI) mixed NE carcinoma-acinar adenocarcinoma [5]. Their major symptoms are signs of bladder outlet obstruction and signs of metastatic disease-like bone pain neurologic signs, hydronephrosis or abdominal pain [6].

In contrast to prostatic adenocarcinoma, PSA is an unreliable tumor marker for small cell prostate carcinoma and is usually normal, even in the presence of metastatic disease [7]. Transrectal sonography, CT scan, MRI and bone scintigraphy are usually used to know the prostate volume, its structure, and the presence or not of metastasis [7]. NE cells in the prostate are immunohistochemically positive for CgA, Syn, CD56 etc., but negative for prostate specific antigen (PSA), AR and Ki67 because they appear to be non-proliferative and postmitotic cells [2]. For many researchers, systemic chemotherapy with etoposide and cisplatin may be the treatment of choice in the metastatic SCC [8, 9]. We are presenting a case of a patient with a Small cell carcinoma of the prostate, a normal PSA, and a giant prostate volume. The informed consent from the patient for this study was obtained.

CASE PRESENTATION

In April 2016, a 58-year-old male patient presented with a 2 to 3-month history of complaints of difficulty in urinary-voiding, difficulty evacuating his rectum, pelvic pain, periodic hematuria, general weakness, weight loss.

On the digital rectal examination (DRE) the prostate was significantly enlarged, firm, with irregular contours, juts out into the lumen of the colon by ½ its diameter; the mucosa on the prostate with limited mobility, the pelvic wall infiltrated. PSA total - 0.38 ng / ml, the ratio of free and bound PSA (F / T) - 26.3%. Transrectal ultrasound scan of the prostate gland revealed a prostate volume of 686 cm3, heterogeneous structure, rough contours, the seminal vesicles and the border of the bladder were not differentiated.

Whole abdomen CT found Hepatosplenomegaly, signs of portal hypertension. Prostatic 115x100x115mm mass, hilly contours, heterogeneous structure, intimate contact with the rear bottom wall of the bladder with symptoms of infection and spread to the mouth of the left ureter and rectum, seminal vesicles increased, merging with the prostate and were not clearly differentiated. Lymphadenopathy – para-rectal, para-vascular - 18-68 mm (right paravesical conglomerate enlarged lymph nodes (LN) - 68x55 mm (20-49mm right-left 42-84mm), para-aortic, para-caval to 42 mm. Left pyelocalyceal cysts (pelvis-30mm, calyx-10mm, ureter-12mm).

Bone scintigraphy (bone scan) – Did not find a pathological accumulation of the radiopharmaceutical. In the multi-slice computer tomography (MSCT) of the chest, pathological changes were not found. The histology of the tumors revealed adenocarcinoma in biopsies complexes, with morphological features that do not allow to exclude adenocarcinoma with neuroendocrine differentiation. Recommended immunohistochemistry (IHC) (Figure 3). IHC found in tumor cells, the expression of CK18, synaptophysin, AR, P504S; in single cells the expression of chromogranin A, TTF1, p63. The expression of CK5 / 6 SK5 / 14, PSA was not detected in tumor cells. Ki67 proliferative index was equal to 70% of the tumor cells. Conclusion: that conforms to the prostate small cell (neuroendocrine) G3 cancer.

The Multi-Disciplinary Team recommended that the patient should receive chemotherapy in the Republican Oncology Center. He was counseled and consented for six cycles of chemotherapy (Cisplatin 75 mg / m2 and etoposide 120mg / m2, every 21 days). The patient tolerated and responded well to treatment. The MRI scan 3 months after his initial diagnosis showed some slight improvement in the lymph nodes. He would continue his treatment with a regular Oncology and urology follow-ups as well as further CT scans, and blood tests.

DISCUSSION

Normal prostate tissue consists of three types of epithelial cells: basal cells, luminal cells, and neuroendocrine (NE) cells. Unlike basal cells and luminal cells, NE cells constitute only <1% of total epithelial cells, and their physiological role remains unclear [10]. NED is a common feature of prostatic adenocarcinomas. Pure neuroendocrine prostate cancer (NEPC) and a small cell PCa represent rare and aggressive tumors, such as primary carcinoids, which are also very rare [4]. Detection of small cell carcinoma (SCC) at an early stage of prostate cancer is very rare but is often found in PCa patients treated with first and second line ADT that complicates the cell of origin giving rise to these tumors [1]. The originality of our presented case is that the pathology appeared without any history of early treatment of PCa that means it is not a therapy-induced, nor RT-induced NED. The second aspect is the giant volume of the tumor.

Clinical signs presented by our patient were difficulty in urinary-voiding, the difficulty of rectum evacuation, pelvic pain, periodic hematuria, general weakness and weight loss. For Umar et al, the major symptoms are signs of bladder outlet obstruction in 50% of patients and signs of metastatic disease-like bone pain neurologic signs, hydronephrosis or abdominal pain in 33% of patients [6]. In China, reporting of 26 cases, Guo A et al found that the common clinical symptoms for these cases were dysuria and urinary tract irritation. Occasionally, there was hematuria, which might be due to the invasion into the bladder or the urinary tract [11]. Huang et al described symptoms of urinary difficulty, bone pain, and gross hematuria [12]. Cecen et al presented a case with no complaints of urinary symptoms at first admission [8]. The disease can be silent and its only manifestation might be symptoms associated with metastasis. For this reason, most patients are diagnosed when SCCP is at an advanced stage [8].

The origin of SCC is controversial. A theory suggests that small cell carcinomas of the prostate arise from amine precursor uptake decarboxylation cells of local endodermal origin. Another theory proposes that small cell of prostatic carcinomas arise from dedifferentiation of prostatic adenocarcinomas, suggesting that small cell carcinomas are part of a spectrum of prostatic adenocarcinomas rather than a separate disease entity [8]. Currently, the most accepted theory suggests that SCC has its own stem cell origin and does not derive from dedifferentiated adenocarcinoma or from benign neuroendocrine cells of the prostatic epithelium. This hypothesis is based on the discovery of the lack of typical immunohistologic characteristics of prostatic epithelial cells (PSA expression and androgen receptor positivity) and their
high elevated index of MIB-1 as compared to the dedifferentiated adenocarcinomas [12].

Digital rectal examination (DRE) contribute significantly to the diagnosis of SCC. For Cecen et al case, a rectal digital examination of the prostate revealed an enlarged irregular prostate with right-side nodule [8]. Sahoo et al detected a hard nodular enlargement of prostate more in the right side, strongly suspicious of neoplasia [9]. Concerning some Chinese cases, Guo reported that DRE indicated grade III prostate enlargement or the prostate was homogeneously enlarged with the disappearance of the central sulcus [11]. Our case confirmed that description of the prostate, as such we found a prostate significantly irregularly enlarged.

In our case, like in many others in the literature, PSA was normal. It is commonly accepted that NE tumor cells are AR- and PSA- negative and prostatic acid phosphatase-positive [13]. In contrast to prostatic adenocarcinoma, PSA is an unreliable tumor marker for small cell prostate carcinoma and is usually normal, even when there is metastatic disease [7]. SCPC cases have normal levels of PSA and prostatic acid phosphatase (PAP). Combined type tumors have an elevated level of PSA and PAP that may be used for assessment of treatment response [14]. Guo et al revealed that among the 21 patients with pure SCC, serum PSA levels in 18 cases (85.7%) were normal and only elevated in three (14.3%) cases. For the five mixed cases, three (60.0%) had an elevation, and the other two (40.0%) had serum PSA levels in the normal range [11]. Thus serum PSA level is not an appropriate marker for SCC of the prostate [11]. A study suggested that carcinoembryonic antigen is a more reliable marker, increases, and decreases in antigen levels are found with disease progression and regression, respectively. Neuron-specific enolase has also been proposed as a prognostic indicator; high levels suggest a poor prognosis [7].

For the diagnosis of this affection, imagery can play an important role. They often use transrectal sonography, CT scan, MRI, and bone scintigraphy to know the prostate volume, its structure the presence or not of metastasis. SCPC is a tumor with a tendency to systemically metastasize. Whereas mixed small cell carcinomas and adenocarcinomas usually are aggressive recurrences of a primary adenocarcinoma; because of its aggressive nature, pure small cell carcinoma of the prostate is often associated with early metastatic disease [7]. Even at the time of diagnosis, almost 75% of patients are at the advanced stage. It most commonly metastasizes to the lymph nodes, liver, bone, lungs, pericardium, brain, rectum, and urinary bladder [9]. In addition, small cell prostate cancers have been reported to produce paraneoplastic syndromes associated with the production of adrenocorticotropic hormone [7]. In 5 cases, Brownback et al revealed that approximately 3/5 patients developed liver metastases, 2/5 patients had bone metastases, and 1/5 patients developed carcinomatous meningitis [15].

Trans-sectional ultrasound scan of the prostate gland revealed a prostate volume of 686 cm³. Whole abdomen CT concerning that prostatic, showed a mass size of 115x100x115mm. We didn’t find this prostate size in the literature. Demitats found a prostate size of 50±43±50mm [14]. Sahoo revealed gross enlargement of the prostate of 117 cm³ [9]. The prostate size was not mentioned by many authors. That kind of giant prostate with normal PSA confirms the originality of our case.

The confirmation of SCC of the prostate relies mainly on pathological findings. In our case, the histology found adenocarcinoma, with morphological features not allowing to exclude adenocarcinoma with neuroendocrine differentiation. Microscopically, SCC cells are consistently round or short-spindle-shaped, arranged in a flaky or nest-like pattern. The cells only contain a small amount of cytoplasm, with the nuclei barred and darkly colored. The nucleolus is obscured and mitotic figures are frequently observed. Necrosis is also common [11]. SCC may occur in pure form (50-60% of cases), but it may also occur adjacent to or concomitantly with conventional adenocarcinoma in other cases, it is estimated that 40 to 50% of SCC cases have a history of prostatic adenocarcinoma [16]. Other authors confirmed that only about 35% of reported cases are pure SCC [17]. Guo et al, among the 26 cases reported in China, revealed that 21 cases were pure SCC (80.8%) [11].

SCC represents a heteroge-neous immunophenotype and their origin may be from multipotent stem cells in the prostate (CD44+). Immunohistochemically, SCC shows strong chromogranin and synaptophysin positive expression in the majority of cases (61% and 89%); 17% and 24% of cases are positive for PSA and PSAP; 24% and 35% of cases are positive for basal cell markers, p63 and HMWCK respectively [18]. Immunohistochemical staining of SCC cells for NSE, Syn, CGa, and CD56 is usually carried out for diagnosis. Combined use of these four markers often results in a definitive diagnosis. Moreover, PSA, PAP, and P504S expression are rare in SCC and a CK-positive staining pattern in SCC is characteristically dot-like. This can be used to differentiate SCC from the poorly differentiated acinar adenocarcinoma [11]. In the presented case, IHC found in tumor cells, the expression of CK18, synaptophysin, AR, P504S; in single cells the expression of chromogranin A, TTF1, p63. The expression of CK5/6, S5C/14, PSA was not detected in tumor cells. Ki67 proliferative index was equal to 70% of the tumor cells.

Our patient received in the scheme cisplatin 75 mg / m2 and etoposide 120mg / m2, every 21 days. Currently, there are no established guidelines for the treatment of SCC of the prostate due to the small number of cases. Although SCC is a hormone-independent tumor, and endocrine therapy is not effective for SCC. That is why SCC of the prostate is more sensitive to chemotherapy, which is recommended as the first-line treatment for the cases confirmed by biopsy [11]. But, there’s no consensus on that question. Some clinicians thought that SCC of the prostate should be treated as any other small cell carcinoma with systemic chemotherapy alone while others include ADT [16]. In some reports, it has been proposed that surgery is the first choice for early and confined lesions [19]. However, most SCC cases are already in advanced stages when diagnosed and some others with gross prostate, as in our case, it is difficult to achieve the best outcome with surgery for such advanced cases. For many researchers, systemic chemotherapy with etoposide and cisplatin may be the treatment of choice in the metastatic SCC [8, 9].

CONCLUSION

SCC of prostate cancer is rare. This histological type is often characterized by a PSA, which might be normal, despite the presence of metastases. The case presented here, help to understand that, all that precedes an important element that concerns the giant volume of the prostate can be added. All these permits in the understanding why, although there is not yet a consensus, many authors agree that chemotherapy is the reference treatment for this type of prostate cancer.

CONFLICT OF INTEREST

There is no conflict of interest.
Figure 1. MSCT of the pelvic organs. Prostate tumor occupying the pelvic cavity, infiltrating the front wall of the rectum, the bladder neck. A pair of a right-vesical conglomerate of enlarged lymph nodes 68x55 mm.

Figure 2. A-MSCT of the abdominal cavity: secondary paraaortic, paracaval, or iliac lymphadenopathy. B-MSCT of the abdomen and pelvis: Prostate tumor occupying the pelvic cavity, infiltrating the front wall of the rectum, the bladder neck. Secondary para-aortic lymphadenopathy.
Figure 3. (A) Tumor tissue in forms of nests and strands relatively to monomorphic cells with hyperchromatic nuclei (B) SCC showed immunoreaction with synaptophysin (C) SCC showed immunoreaction with chromogranin A (D) SCC nonreactive with PSA (E) Proliferation index Ki67 - 70%

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