NEUROENDOCRINE TUMOUR OF THE PROSTATE: A RARE VARIANT

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ABSTRACT

About 95% of prostate cancers are adenocarcinomas. Neuroendocrine differentiation (NED) is seen in virtually all cases of prostatic carcinoma, mostly in a focal pattern. Extensive NED is associated to aggressive disease with a poor prognosis and most cases are diagnosed in advanced stages. We present a 79-year-old male who was admitted to our department with severe lower urinary tract obstructive symptoms and weight loss. On digital rectal examination, the prostate was fixed to the rectum with irregular margins. Serum prostate-specific antigen (PSA) level was 1.9 ng/ml. Transrectal ultrasound-guided prostate biopsies revealed small-cell carcinoma of the prostate. Multiple metastatic lesions in vertebral bones and iliac lymph nodes were detected by nuclear bone scan and abdominal computerised tomography CT. Thereafter, the patient was treated with cisplatin-based chemotherapy and palliative radiotherapy.

Keywords: prostate, prostate tumour, small-cell cancer.

INTRODUCTION

Cancer of the prostate (PCa) is one of the most important medical conditions facing the male population. In Europe, PCa is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering lung and colorectal cancer.[1] Furthermore, PCa is currently the second most common cause of cancer death in men.[2] In Turkey, PCa is the second common solid neoplasm after lung cancer in male population.[3]

Herein, we report a rare case of advanced stage pure small-cell prostate cancer, with diagnostic work-up and management.

CASE REPORT

A 79-year-old male admitted to our outpatient clinic with severe obstructive lower urinary tract symptoms and weight loss. His low urinary tract symptoms progressed particularly in the last six months. His medical history included presence of coronary artery disease and cholecystectomy for gallbladder stone twenty years ago. His International Prostate Symptom Score (IPSS) was 27 and quality of life (QoL) score was 6. Uroflowmetry showed obstructed urine flow with peak flow rate of 8.3 ml/sec, average flow rate of 4.1 ml/sec with total voided urine volume of 295 cc. Digital rectal examination (DRE) revealed a prostate including a stiff mass almost in all areas extending to the rectum with irregular margins. Serum prostate specific antigen (PSA) level was 1.9 ng/ml. Hypochromic anemia observed in complete blood count. Serum electrolytes and renal function tests were normal in blood biochemistry. Urine test was negative for urinary infection and for microscopic hematuria.

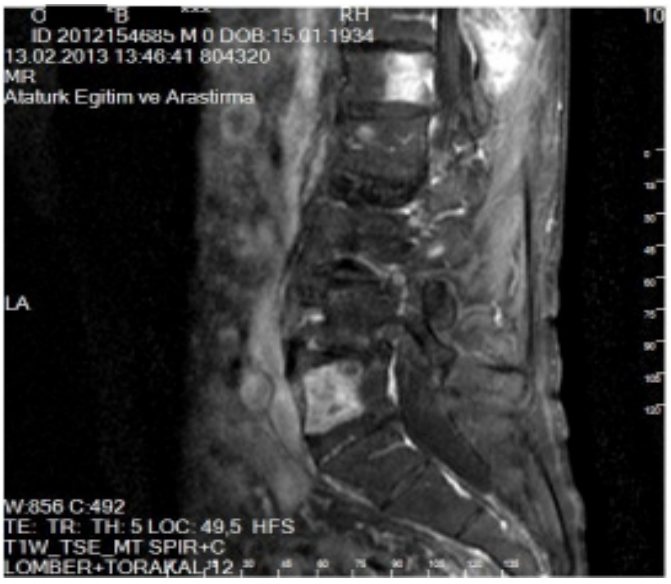

Figure 1. Abdominal computerised tomography showing multiple vertebral body metastases.

Urinary ultrasound showed normal kidneys without any hydronephrosis. We performed a 12-core transrectal ultrasound-guided prostate biopsy, and histopathological examination showed small-cell carcinoma of the prostate in all cores. Nuclear bone scan and abdominal computerised tomography (CT) demonstrated multiple vertebral metastatic lesions and enlarged iliac lymph nodes suggesting tumour metastasis (Figure 1). The thorax CT scan was within normal limits.

Patient was referred to the department of medical oncology and radiation oncology for further treatment. Cisplatin-based chemotherapy was administered with additional palliative radiotherapy for vertebral metastatic disease. During follow-up, serum creatinine levels elevated and the development of bilateral hydronephrosis detected on abdominal ultrasound as a consequence of local tumour infiltration of the ureters. Post-renal kidney failure was managed by inserting bilateral percutaneous nephrostomy. Currently, patient is on the sixth–month follow-up after the initial diagnosis.

HISTOPATHOLOGICAL EVALUATION

In histomorphologic examination, atypical cells with high nuclear-cytoplasmic ratio, having hyperchromatic granulations, hyperchromatic and irregular nucleus with fine granular chromatins invading the prostate gland was observed. Mitosis was a very common finding. Immunohistochemistry staining showed a diffuse positive staining of the tumour cells with synaptophysin, chromogranin and TTF-1 (Figures 2-5). Immunohistochemistry with Ki-67 staining was detected in more than 40% of the areas with tumour (Figure 6). No staining was observed by PSA. Due to WHO 2004 classification, these findings revealed a low differentiated neuroendocrine carcinoma of the prostate. The same histopathologic and immunuhistochemical findings were detected in all 12 cores of the prostate biopsy. Prostatic adenocarcinoma component was not observed in any of the cores.

DISCUSSION

Prostatic neuroendocrine differentiation has three distinct forms including focal neuroendocrine differentiation in prostatic adenocarcinoma, carcinoid tumour (well differentiated according to WHO classification) and small cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma according to WHO classification).[4] Poorly differentiated neuroendocrine

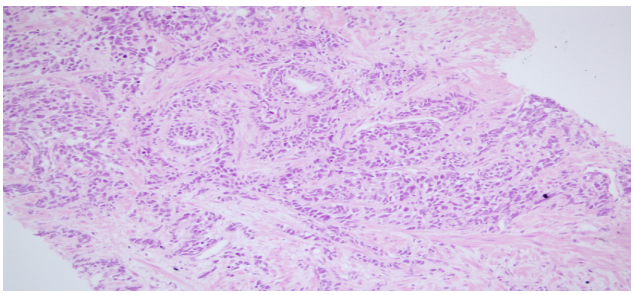

Figure 2. Atypical cells with pleomorphic nucleus invading the stroma between the prostate glands (H&E x200).

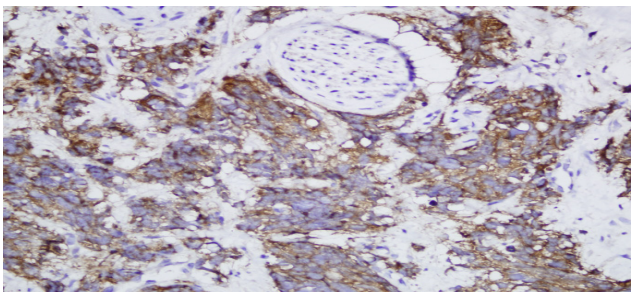

Figure 3. Diffuse chromogranin staining of tumour cells (x400).

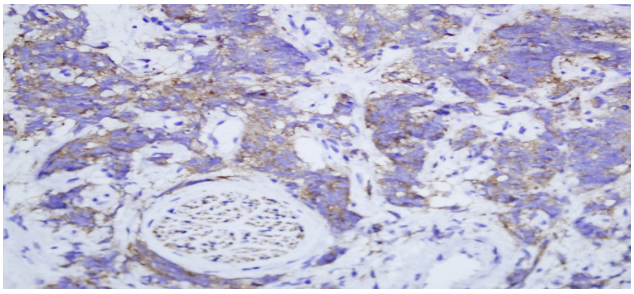

Figure 4. Diffuse positive staining of tumour cells with synaptophysin (x400).

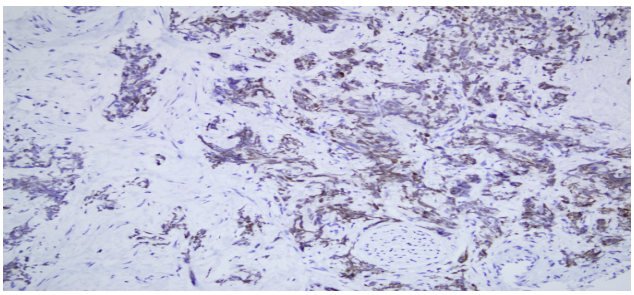

Figure 5. Diffuse positive staining of tumour cells with TTF-1 (x200).

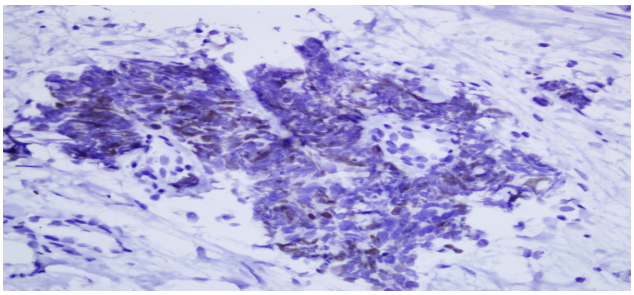

Figure 6. Diffuse positive staining of tumour cells with Ki-67 (x400).

carcinomas are detected up to 50% with prostatic adenocarcinoma.[4] However, in our patient, concurrent prostate adenocarcinoma was not detected in any of the 12 core prostate biopsies. In mixed tumours, neuroendocrine carcinoma components show positive staining with synaptophysin and chromogranin while they show negative staining for Papanicolaou (PAP) and PSA negative. Neuroendocrine carcinoma of the lung should be considered in differential diagnosis. In our case, immunohistochemical studies showed positive staining with TTF-1, which has a significant value in the differentiation from lung tumours.[5] In order to exclude the presence of lung cancer, a thorax CT was performed which revealed no lesion in the lung parenchyma. Therefore, our case was diagnosed as a primary prostate neuroendocrine tumour, which is a very rare entity.

Almost 95% of the prostatic neoplasms are adenocarcinomas.[6] Depending on the kind of technique used in detecting neuroendocrine cells, 10-100% of the prostate cancer tissues might involve neuroendocrine differentiation.[7,8] Histopathological forms include small-cell carcinomas,[9] carcinoids[10] and foci of neuroendocrine neoplastic cells in prostatic adenocarcinoma.[9,11] Extensive neuroendocrine differentiation (NED) is associated with hormone therapy refractory and aggressive disease.[12] This is of major importance because prostate cancers with NED have a poor prognosis (35% survival at 2 years) compared with cases where there are no neuroendocrine cells (97% survival at 2 years).[13,14]

Small-cell prostate cancer (SCPC) is a tumour with a tendency to systemically metastasise and thus has a poor prognosis. Even at the time of diagnosis, nearly 75% of patients are at advanced stage. SCPC has similar features with small-cell lung cancer.[15] It most commonly metastasises to the lymph nodes, liver, bone, lungs, pericardium, brain, rectum, and urinary bladder.[16] The number of patients reported is very limited in the literature. Therefore, the optimal therapy for SCPC has still to be defined. Extrapulmonary small-cell cancers are less sensitive to chemotherapy than pulmonary small-cell carcinomas. Although chemotherapy and radiotherapy may provide a cure in local disease, total treatment failure rate has been reported to be 84%.[17]

Elevated serum PSA is one of the most important tools in the diagnosis of prostate adenocarcinoma. However, in neuroendocrine tumours of the prostate, serum PSA levels might be within normal limits despite the patient having metastatic disease including systemic complaints such as weight loss, anemia and palpable tumour on DRE. In our case, serum PSA level was 1.9 ng/ml at the time of the diagnosis and our patient had multiple metastatic foci involving abdominal lymph nodes and vertebral bones. Therefore, DRE is very important in suggesting malignancy despite normal serum PSA levels as seen in our case.

CONCLUSION

In conclusion, neuroendocrine differentiation characterises the second phenotype by prevalence in comparison with prostate adenocarcinoma, but remains underdiagnosed. Neuroendocrine tumours cells are androgen-intensive and have a mitogenic effect on adjacent tumour cells. They are resistant to irradiation and chemotherapy. No standard therapeutic regimen exists, and the predicted survival is very short. Despite the fact PSA screening is highly valuable in detecting PCa; in highly aggressive PCa such as small-cell prostate cancer, serum PSA levels could be normal.

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