Large cell differentiation of metastatic prostate cancer after androgen deprivation therapy

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PATEL R, FAIENA I, GELTZEILER J. Large cell differentiation of metastatic prostate cancer after androgen deprivation therapy. *Can J Urol* 2015;22(2): 7752-7754.

We present a case of a 75-year-old male with a history of high risk prostate cancer who underwent androgen deprivation therapy and palliative radiation treatments for his disease. Subsequently, he presented with gross hematuria and severe lower urinary tract symptoms. A palliative transurethral resection of the prostate (TURP) at that time, demonstrated large cell differentiated neuroendocrine carcinoma with metastasis to the lung. We review the limited literature on this rare form of disease and present current treatment strategies.

Key Words: large cell neuroendocrine tumor, prostate cancer, hormone refractory prostate cancer, neuroendocrine differentiation

Introduction

Prostate cancer is the most common malignancy in men, with an incidence of 220,800 new cases per year.[1] More than 95% of primary prostate cancers are adenocarcinomas. The rest are compromised of neuroendocrine tumors, interlobular acinar, ductal, clear cell, and mucinous carcinomas. Among neuroendocrine tumors, small cell carcinoma is the most common. In comparison, large cell neuroendocrine prostate cancer (LCNEPC) has only been reported in a few case reports.[2] Here, we describe a case of LCNEPC with metastasis to the lungs and review the literature related to the rare form of this disease.

Accepted for publication February 2015

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Case report

Our subject is a 75-year-old male who is an established patient that was being followed for minor nocturia and hesitancy. Beginning in 2005, annual prostate cancer screening with digital rectal exams and PSA was initiated. Starting PSA was 1.54 ng/mL, with subsequent yearly values ranging from 1-2 ng/mL. He was last seen in 2009 with a PSA of 2.04 ng/mL and subsequently lost to follow up until 2012. A repeat PSA at that time was 7.5 ng/mL. The patient then underwent a 12 core transrectal ultrasound guided biopsy of his prostate, showing Gleason 9 (5+4) in 3 cores, Gleason 8 (5+3) in 2 cores, and (3+5) in 1 core. With these findings, he was started on complete androgen deprivation therapy (ADT) with biclutamide and a GnRH agonist. Subsequent bone scan exhibited abnormal uptake compatible with metastatic malignancy in his right posterior hip/

acetabulum and distal femur. Palliative radiation therapy, 30 Gy in 10 fractions, was initiated in April 2013. An additional bone scan in 2013 showed mild progression of disease in the distal femur and no abnormal uptake in the hip. In response to his treatments, his PSA had dropped to 0.1 ng/mL.

In 2014, he presented to the hospital with severe lower urinary tract symptoms and gross hematuria. He was started on continuous bladder irrigation and antibiotics for a concurrent urinary tract infection. The patient also underwent a CT scan of the chest, abdomen and pelvis due to an abnormal chest x-ray, and was found to have a lobulated pleural mass in the right upper lobe. This was biopsied and found to be a high grade neuroendocrine carcinoma, with intermediate to large cell features based on histological and immunohistochemical staining (synaptophysin, TTF1).

He subsequently underwent a cystoscopy, clot evacuation and bladder fulgeration with plans for a palliative transurethral resection of the prostate (TURP). During the procedure, he was found to have extension of his prostate cancer into the bladder neck, with more prominence on the left. The prostate chips, see Figure 1, showed a high grade neuroendocrine carcinoma with intermediate to large cell features, similar in morphology to the lung biopsy. The cells showed positive staining for synaptophysin, as seen in Figure 2, chromogranin A (CgA), and CD56. Serum PSA at this time was < 0.01 ng/mL.

A diagnosis of metastatic prostate adenocarcinoma with large cell neuroendocrine differentiation was made, and the patient was commenced on a platinum-vp16 chemotherapy regimen. At the time of this report, the patient remains well and will continue on the chemotherapy region.

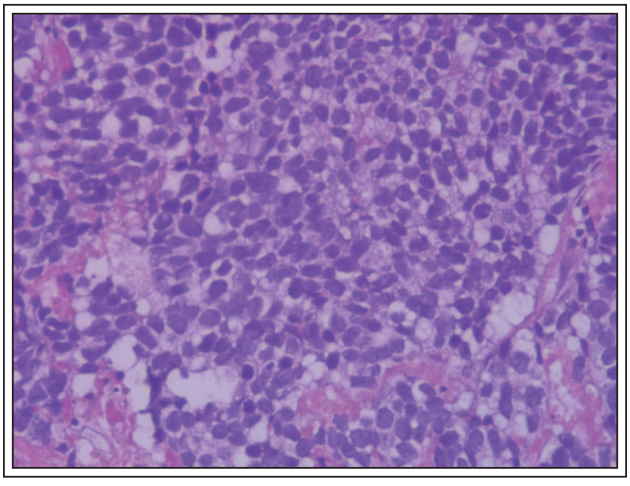

Figure 1. High power magnification view showing high grade neuroendocrine carcinoma with intermediate to large cell features.

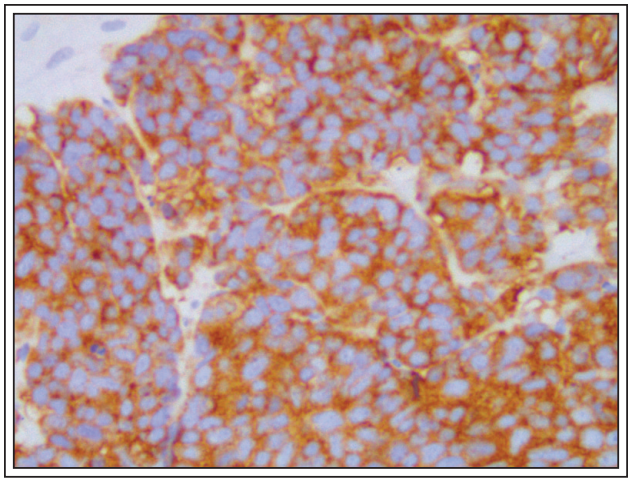

Figure 2. High power magnification view showing diffusely positive synaptophysin immunohistochemical stain.

Discussion

LCNEPC is a rare variant of prostate cancer, described only in a handful of case reports.[2] Histopathologic features of the LCNEPC seen in this patient mirror those defined by Travis et al.[3] The pathologic features include: a) cells of large size, polygonal shape and low nuclear to cytoplasm ratio, b) nuclei with coarse chromatin and frequent nucleoli, c) high mitotic activity with multiple areas of necrosis, and d) immunohistochemical evidence of neuroendocrine differentiation - synaptophysin, chromogranin, CD56. While the primary cancer in this patient matched all criteria, in previous case reports, a wide spectrum of differentiation was seen.[2] In addition, LCNEPC has usually developed in the setting of long term ADT, demonstrating clonal selection which results in growth of androgen-insensitive cells because of lack of androgen receptors.[4] Neuroendocrine differentiation may then further contribute to the emergence of hormone refractory prostate cancer (HRPC). This differentiation is increased in high grade and high stage localized tumors, and even more so in androgen deprived tumors.[5] With the introduction of novel androgen-receptor targeted drugs, the incidence of neuroendocrine differentiated tumors should theoretically increase. Therefore, targeting neuroendocrine cells in HRPC may provide a novel approach to treatment.

Platinum has been studied in small cell neuroendocrine lung cancer, where it has been established as a first line treatment option.[6] Thus, clinical trials have been conducted to assess response in patients with neuroendocrine differentiation utilizing neuron-specific enolase (NSE) and CgA. CgA, in patients with androgen-insensitive tumors, appears to increase with the incidence of distant metastasis.[7] Culine et al have reported a 50% decrease in serum levels with cisplatin and docetaxel treatment.[8] Further studies have included regimens with gemcitabine, docetaxel, doxorubicine, cisplatin and carboplatin with variable success, demonstrating partial responses and 10%-50% serum decrease in PSA, CgA or NSE levels.[9] Despite these promising results, survival outcomes have been poor; previous case reports and trials have reported a survival of 12 month or less.[8] Since current LCNEPC treatments are based on small cell neuroendocrine therapy, the poor survival and possible improvement in serum markers highlight the need for further study. In addition, it becomes important to investigate the possibility of mixed neuroendocrine and adenocarcinoma within tumors. Perhaps the optimal therapy would be a combination of hormone and platinum-based therapy, depending on the clinical scenario and further study into LCNEPC.

Conclusion

Neuroendocrine differentiation of prostate cancer is generally associated with aggressive tumors with poor prognosis and long term hormone treatment. The case presented here demonstrates the possibility that the treatment of an adenocarinoma of the prostate with ADT may have resulted in clonal selection of LCNEPC. Currently, treatment options are limited to platinum-based therapies, a regimen resulting from studies of neuroendocrine tumors in other sites. Further investigation, and clinical trials are necessary to develop new and more effective treatment strategies, as well as the etiology of LCNEPC in the setting of ADT. □

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