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CASE REPORT

Mixed adenocarcinoma and neuroendocrine prostate cancer: a case report

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Background: Neuroendocrine prostate cancer is rare but lethal. It is one of the most common extra pulmonary manifestations of small cell cancer.
Case presentation: Here we present a case report of a 53-year-old male who presents with a mixed adenocarcinoma and neuroendocrine prostate tumor on a background of previously normal prostate-specific antigen (PSA). His initial symptoms prior to diagnosis included decreased urine output and acute kidney injury (AKI).
Conclusion: Neuroendocrine tumor does not elevate the PSA level and hence is often a late finding with a poor prognosis. Special staining on histopathogy is required to reveal this diagnosis.

Keywords: *neuroendocrine*; *prostate cancer*; *prostate specific antigen*

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Neuroendocrine prostate cancer was first described approximately 40 years ago, but remains a poorly understood entity. Prostate-specific antigen (PSA) levels are unreliable markers of disease activity and may remain low despite advanced obstructive symptoms, thereby fostering a false sense of security among care providers. With this case report, we hope to highlight key clinical features of neuroendocrine prostate cancer.

Case report

A 53-year-old male with a previous history of minimal prostatic hypertrophic symptoms and benign exam initially presented with productive cough, shortness of breath, and fevers. After failing to improve with two rounds of oral antibiotics, a chest x-ray was performed and revealed bilateral multifocal pneumonia leading to admission to the hospital. On admission, he incidentally noted decreased urinary output for several days, and was found to have acute kidney injury (AKI) (creatinine 5.25 mg/dL, baseline 1.03 mg/dL), as well as a profound anemia with no significant bleeding site identified (Hgb 5.1 g/dL). Renal ultrasound revealed a right-sided hydronephrosis. Digital rectal exam was positive for a grossly irregular, firm, nodular prostate suspicious for aggressive prostate cancer. Due to AKI, a computed tomography (CT) urogram was not possible; however, urine cytology showed evidence of atypical cells and microscopic hematuria. Non-contrast CT scan of the abdomen and pelvis showed evidence of sclerotic bony lesions suggestive of metastatic disease. In addition, his PSA which 7 months earlier was 1.9 ng/mL had risen to 119.69 ng/mL. Biopsy was refused by the patient, his pulmonary symptoms resolved, and the patient was subsequently discharged and lost to follow-up for 2 months. He then presented to the emergency department with urinary retention and productive cough and dyspnea. At that time, he had progressed to bilateral hydronephrosis with obstruction despite routine self-catheterization and required bilateral nephrostomy placement. Prostate biopsy revealed concurrent small cell carcinoma (SCC) of the prostate and a minor component of high-grade adenocarcinoma, Gleason (3 + 4) (Figs. 1–3). Positron emission tomography (PET) scan showed evidence of metastasis to bone (Fig. 4), with the largest most hypermetabolic foci in the left scapula, left iliac wing and lymph nodes of the thorax and lung. CT scan showed mediastinal lymphadenopathy with a right middle lobe opacification concerning for post bronchial obstruction (Fig. 5). Transbronchial biopsy revealed small cell anaplastic carcinoma. He was immediately started on cisplatin and etoposide for the neuroendocrine component, as well as Lupron and Bicalutamide for the adenocarcinoma component.

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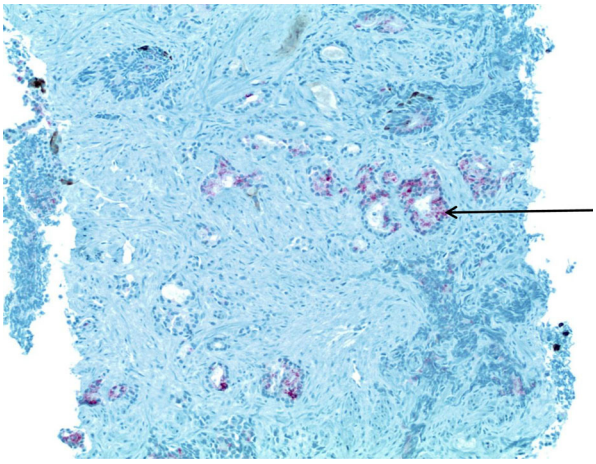

Fig. 1. Racemase stain (arrow) highlighting Gleason (3 + 4) adenocarcinoma.

Discussion

Neuroendocrine prostate cancer, also known as small cell cancer of the prostate, was first reported in 1977 (1). Extrapulmonary sites of small cell carcinoma account for approximately 11% of total small cell cancer presentations, with 3% of these presenting first in the prostate (2). In total, these cancers represent less than 1% of all prostatic cancers (3). It is one of the more common sites for extra pulmonary manifestation of small cell cancer with approximately 10% extra pulmonary cases noted to be in the prostate gland. An under recognized clinical condition, it has an overall poor prognosis as it is aggressive with early metastasis and is poorly responsive to chemotherapy regimens (4).

Presenting complaints are generally related to obstruction, with difficulty urinating and hematuria being especially common (5). Our patient presented with acute renal failure secondary to an obstructive uropathy and anemia with an Hb of 5.1 g/dL. PSA is an unreliable marker and can remain low unless the neuroendocrine

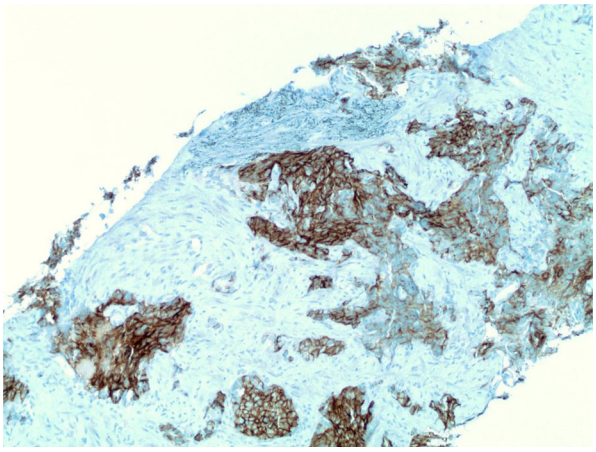

Fig. 2. CD-56 stain highlighting areas of small cell carcinoma (area stained brown is positive for CD-56).

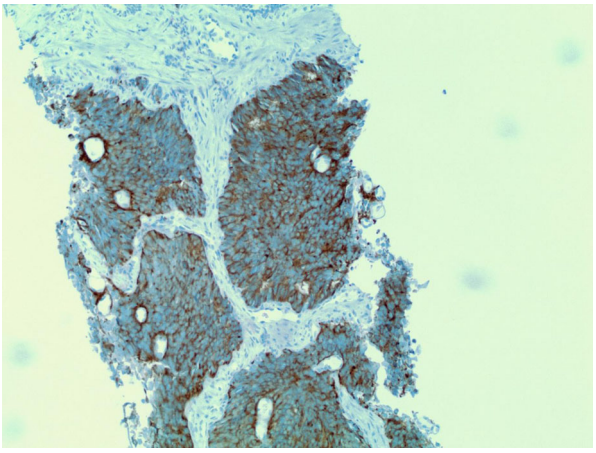

Fig. 3. Synaptophysin statin highlighting areas of small cell carcinoma (area staining brown is positive for SCC).

carcinoma is present along with another more common prostatic adenocarcinoma (5). Over the course of 7 months, this patient went from a benign prostate exam with a PSA of 1.9 ng/dL to a grossly abnormal exam and a PSA of 119.69 ng/dL, testifying to the aggressive nature of the disease process. Metastatic disease of the adenocarcinoma was present at the time of diagnosis (the bony metastases) and was the more likely cause of the PSA elevation.

The origin of small cell prostate cancer is largely unknown with some authors of the opinion that it is a dedifferentiation of an aggressive adenocarcinoma that can result in extensive and frequently terminal disease. Beltran et al. (6) indicate that neuroendocrine cells are responsible for hormonal therapy resistant prostate cancer, which allows some prostate adenocarcinomas to completely escape androgen blockade and become hormone refractory. Some authors have documented this as a dedifferentiation of a typical prostatic adenocarcinoma as the disease progresses, thus representing an aggressive and often terminal phase of this disease. In these situations, a neuroendocrine component has been found in 10–100% of prostate cancer cases (7, 8). A postulated competing theory is that the neuroendocrine component originates from malignant transformation of normal prostatic cells or even pluripotent epithelial cells, thereby causing unpredictable differentiation (9, 10). A third theory postulates that the origin of this type of malignancy is directly from stem cells, given its immunohistochemical features, low PSA levels, androgen receptor positivity and very high MIB-1 index (2). Postulates 2 and 3 might explain the presentation in our patient with a normal PSA less than a year before he was diagnosed with small cell prostate carcinoma. Immunohistochemistry can be useful in identifying this malignancy, with CD-56 staining positive in 92% of cases and synaptophysin positive in 85% of cases, which is helpful in discriminating

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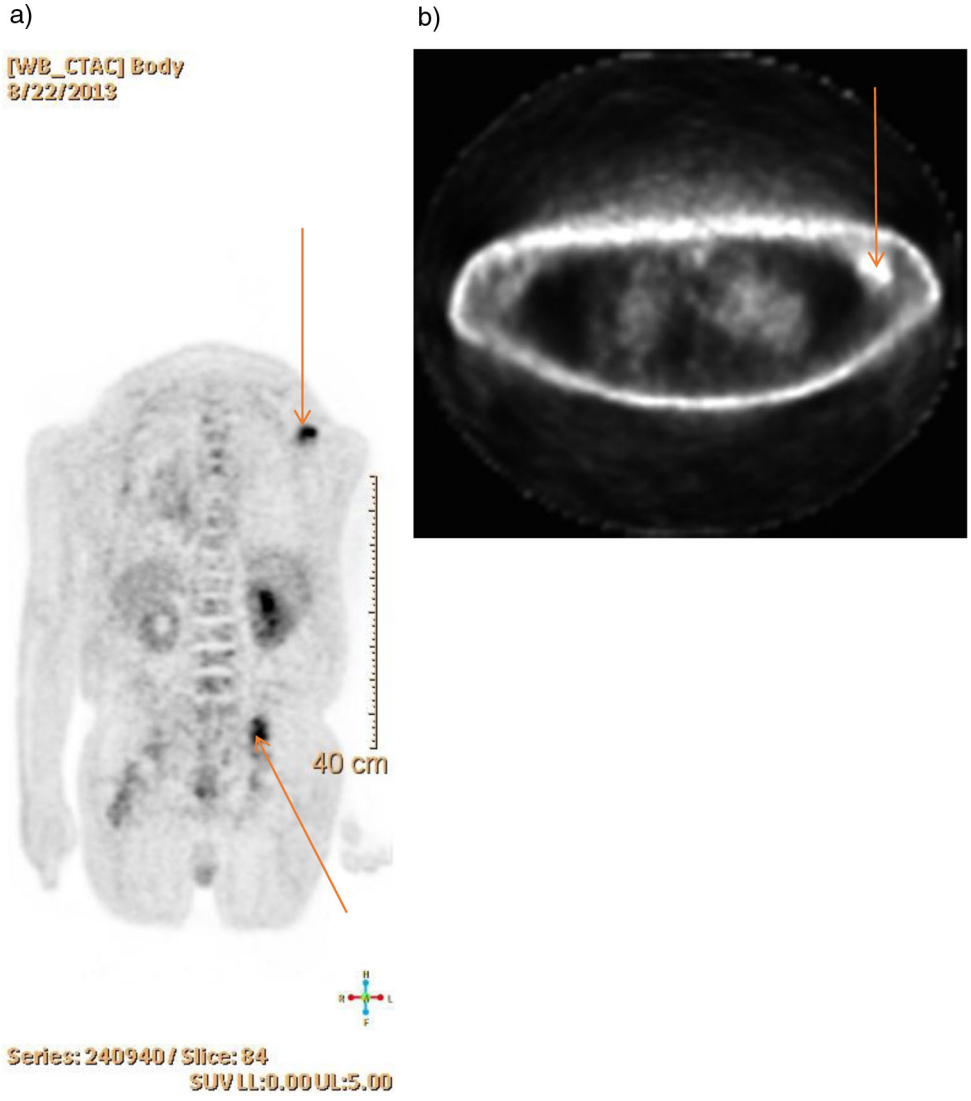

Fig. 4. (a) PET CT showing hypermetabolic lesions in L scapula and L Iliac wing suggestive metastatic disease (solid arrows). (b) PET CT in in coronal section showing hyper lucent lesion in L scapula; note the absence of PET CT findings in lung tissue which is pathognomonic of neuroendocrine tumors.

this tumor from poorly differentiated acinar adenocarcinoma (Gleason 5) (11).

The median overall survival time is approximately 13 months (12, 13). At the time of diagnosis, hyponatremia, non-genitourinary extrapulmonary small cell cancer, extensive disease, elevated serum lactate dehydrogenase (LDH), low serum albumin and older age at presentation are associated with poorer prognosis in these patients (12–14). One case with a mixed adenocarcinoma and neuroendocrine small cell carcinoma with extensive disease has been reported with remission up to 36 months with aggressive hormonal and chemotherapy (six cycles of etoposide, cisplatin 100 mg/m^2) and radiotherapy to pelvis and lymph nodes (15). Stein et al.'s retrospective study of 30 patients with prostate SCC revealed only one patient who remained in remission for 54 months post-chemo radiation therapy (5). No correlating factors were found. However, in that case the lung metastasis was of adenocarcinoma origin, which might explain the prolonged disease free period. However, our patient was noted to have small cell carcinoma on lung biopsy which is likely to have a negative effect on his overall prognosis.

Molecular characterization of this malignancy has revealed overexpression and amplification of the *AURKA* and *MYCN* (16, 17). Both in vivo and in vitro studies have shown promising results with Aurora Kinase inhibitor therapy (16); however, these are still at an experimental stage and not available to patients at this time.

Conclusion

Extrapulmonary SCC is a rare but often fatal etiology of prostate cancer with an overall bleak prognosis and no

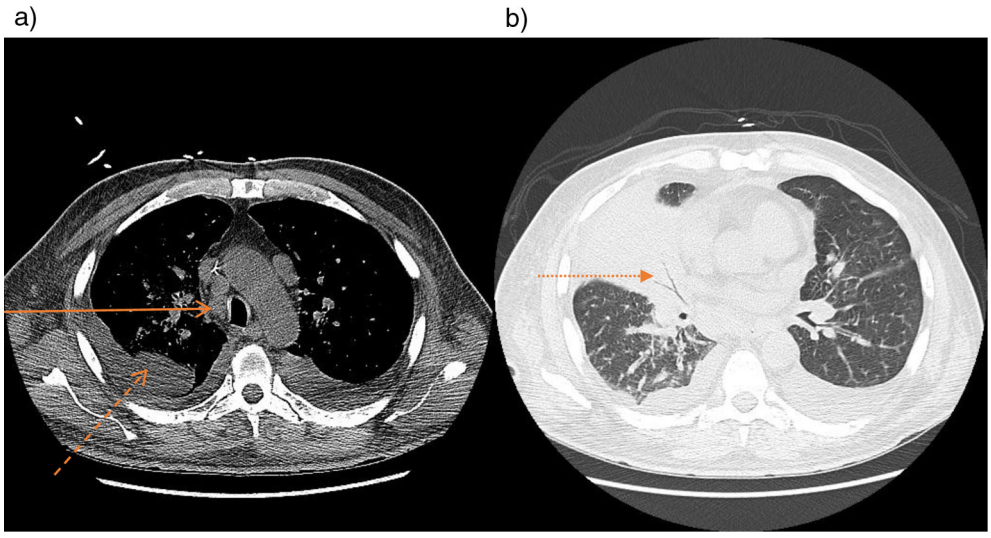

Fig. 5. (a) Represents a non-contrast CT scan (mediastinal window) with arrow showing paratracheal lymphadenopathy and (dashed arrow) showing R sided pleural effusion. (b) CT scan showing R sided opacification with concern for pneumonia vs. post bronchial obstruction and concern for malignancy (this was the lesion that was biopsied).

means for early detection. It is currently treated with chemo and radiation therapy and the treatment protocol often mimics that of small cell cancer of the lung. It is important for clinicians to remember that this aggressive form of prostate cancer is not detectable with PSA studies and there are no other early detection modalities available at this time. Additionally, these tumors often have features that make it arduous for surgical pathologists to identify it, thus making it a diagnostic dilemma for clinicians.

Conflict of interest and funding

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