Small-cell neuroendocrine carcinoma as a variant form of prostate cancer recurrence: A case report and short literature review

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Abstract

**Background:** Small-cell neuroendocrine carcinoma has been recognized as a rare histologic variant occurring in only 0.5% to 2% of prostatic primary tumors. However, recent autopsy studies suggest development to this phenotype in up to 10% to 20% of the cases with hormone-refractory disease.

**Case Presentation:** A case of conventional adenocarcinoma before androgen-ablation therapy but showing progression to small-cell neuroendocrine carcinoma at the recurrence. The immunohistochemistry of the tumor showed strong positive staining for progastrin-releasing peptide (ProGRP), a carboxy terminal region common to 3 precursors for gastrin-releasing peptide, but almost negative staining for chromogranin-A and prostate-specific antigen. Combination chemotherapy based on cisplatin and etoposide was effective for controlling the tumor progression for 7 months, and the serum ProGRP level correlated well to the clinical course. Neither objective nor subjective responses were observed to somatostatin analogue therapy performed in the late stage of disease.

**Conclusions:** The present case reminds the urologist that small-cell neuroendocrine carcinoma may be a variant form of disease recurrence during androgen ablation in advanced prostate cancer. A strategic approach for this phenotype evaluating serum neuroendocrine markers, such as ProGRP, should be taken when serum prostate-specific antigen does not reflect the disease state. This approach would allow one to choose alternative therapies targeting neuroendocrine cells other than androgen ablation. © 2006 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; Small-cell carcinoma; Neuroendocrine marker; Progastrin-releasing peptide

1. Introduction

Prostate cancer with neuroendocrine features is recently attracting attention because peptide growth factors produced from the neuroendocrine cells act under an androgen-deprived milieu and are involved in androgen independence [1,2]. The neuroendocrine differentiation in the prostate comprises a broad spectrum, from scattered or focal neuroendocrine cells often observed in conventional adenocarcinoma as well as in benign prostatic epithelium to extensive neuroendocrine carcinoma. Despite the equivocal biologic value of the focal neuroendocrine differentiation in prostate cancer, extensive distribution of neuroendocrine cells, such as small-cell carcinoma, distinctly behaves as malignancy. Considering that prolonged pressure of androgen ablation would result in propagation of the neuroendocrine phenotype through processes of transdifferentiation or clonal selection [3-5], we need to be aware of the possibility of neuroendocrine carcinoma developing during androgen-ablation therapy. In this report, we present a case of small-cell carcinoma as a recurrent form of advanced prostate cancer treated with androgen-ablation therapy, and a short review of the literature to argue the necessity of a strategic approach for this variant phenotype.

2. Case presentation

A 69-year-old man was admitted to our institution because of difficulty in urinating and severe gross hematuria. The patient had been under treatment with androgen-ablation therapy consisting of a luteinizing hormone-releasing hormone analogue and bicalutamide for 10 months after the diagnosis of locally advanced prostate cancer (clinical
stage, T3b N0 M0). At the initial diagnosis, the serum prostate-specific antigen (PSA) level was 60.16 ng/mL, and pathologically the prostatic tumor was poorly differentiated adenocarcinoma, Gleason score 4 + 5 = 9 (Fig. 1). Abdominal computerized tomography (CT) revealed bilateral hydronephrosis, and an enlarged prostatic tumor infiltrating the urinary bladder wall and periprostatic area, but no metastases were found in the lymph node or bone. Laboratory examinations at the tumor recurrence showed a normal serum PSA value (0.07 ng/mL), and highly increased serum progastrin-releasing peptide (ProGRP) (12,900 pg/mL) and neuron-specific enolase (NSE) values (37.5 ng/mL). The normal range of the ProGRP and NSE is set at <46 pg/mL and 10 ng/mL, respectively.

To circumvent obstructive renal failure and control intractable gross hematuria, we performed ileal conduit urinary diversion, and simultaneously conducted needle and excision biopsies of the recurrent prostatic tumor. Pathologically, the recurrent tumor almost entirely consisted of small-cell neuroendocrine carcinoma with distinctive immunohistochemical findings of positive staining for ProGRP, NSE, synaptophysin, and thyroid transcription factor-1 but was almost negative for PSA and chromogranin-A (Fig. 2). These immunohistochemical characteristics were totally different from those in specimens obtained before androgen-ablation therapy, which contained few foci suggestive of neuroendocrine carcinoma (i.e., they were immu-

Fig. 1. Prostatic tumor before initial therapy was diagnosed as poorly differentiated adenocarcinoma (A) (hematoxylin-eosin). The tumor included Gleason 5 component, and immunohistochemistry showed few neuroendocrine features and completely negative staining for ProGRP (B) (magnification ×200 for A and B).

Fig. 2. Prostatic tumor at recurrence was entirely occupied by small-cell phenotype (A) (hematoxylin-eosin), and immunohistochemically positive for ProGRP (B) and scarcely positive for chromogranin-A (C) (magnification ×200 for A–C).
nohistochemically scattered positive for NSE but completely negative for ProGRP, synaptophysin, and thyroid transcription factor-1) (Fig. 1, Table 1). The patient was treated with combined chemotherapy consisting of cisplatin and etoposide [6], and the androgen-ablation therapy with a luteinizing hormone-releasing hormone analogue alone was continued after the small-cell component was identified. The measurement of serum ProGRP, NSE, and PSA levels closely monitored the clinical course. The chemotherapy was effective for controlling the tumor progression, which was determined by the decrease of serum neuroendocrine markers and abdominal CT for 7 months. However, thereafter, the tumor rapidly progressed, and cancerous cachexia appeared, accompanied by increased serum ProGRP and NSE levels (Fig. 3). Abdominal CT revealed metastases to liver, paraaortic lymph nodes, and bones. The bone lesions showed radiologically lytic changes. When the disease was considered resistant to the chemotherapy, somatostatin analogue injection (octreotide acetate, 100 μg every 12 hours for 2 weeks) was attempted to relieve abdominal symptoms, but neither objective nor subjective effects were observed. The serum ProGRP and NSE levels correlated subtly to the disease state, and fluctuation of ProGRP level was larger than that of NSE level, but serum PSA level remained in the normal range to the last follow-up (Fig. 3). The patient died 12 months after the diagnosis of small-cell neuroendocrine carcinoma, with an extremely high level of serum ProGRP (103,000 pg/mL) and NSE (416 ng/mL).

### 3. Discussion

The present case reminds the urologist that small-cell neuroendocrine carcinoma may be a variant form of disease recurrence during androgen-ablation therapy in advanced prostatic adenocarcinoma. The measurement of serum neuroendocrine markers, especially ProGRP, should be useful for diagnosing and monitoring the patient’s clinical course. In addition, ProGRP had an advantage over NSE because it reflected the disease state in a larger fluctuation of serum levels, although the tumor showed strong expression of both proteins by immunohistochemical analysis.

### Table 1

<table>
<thead>
<tr>
<th>Markers</th>
<th>Before MAB</th>
<th>At recurrence</th>
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<tbody>
<tr>
<td>PSA</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>TTF-1</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>CgA</td>
<td>−</td>
<td>−/+</td>
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<tr>
<td>ProGRP</td>
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<td>+</td>
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<td>NSE</td>
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<tr>
<td>Syn</td>
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<td>+/−</td>
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<tr>
<td>CD56</td>
<td>−</td>
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<td>S100a</td>
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CgA = chromogranin-A; + = extensively positive; +/− = focally positive; −/+ = scattered positive; − = negative; MAB = maximum androgen blockade; Syn = synaptophysin; TTF-1 = thyroid transcription factor-1.

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Fig. 3. Prospective monitor of serum neuroendocrine markers revealed that the serum ProGRP and NSE levels correlated subtly to the disease status, and fluctuation of the ProGRP level was larger than that of the NSE level. Platinum-based chemotherapy (blue squares) controlled tumor progression for 7 months. Short arrows indicate octreotide acetate treatment. ALP, alkaline phosphatase.
Small-cell neuroendocrine carcinoma of the prostate is a highly aggressive tumor, presenting early metastasis to soft tissues and bone without a commensurate with serum PSA level. The review of the literature showed 3 patterns of small-cell carcinoma: (1) 35.4% of cases presented pure small-cell carcinoma; (2) 17.7% of cases presented combined adenocarcinoma; and (3) approximately half the cases (46.9%) presented recurrence with small-cell carcinoma from conventional adenocarcinoma, as observed in our case [7–9]. A pluripotent stem cell, which can differentiate also into a prostatic epithelium, has been speculated as an origin of the small-cell neuroendocrine phenotype [10]. After recognition of the small-cell phenotype, in these cases, survival is less than 1.5 years [11].

The small-cell phenotype has been recognized as a rare entity with a low incidence of 0.5% to 2% of prostatic primary tumor. However, some autopsy studies revealed that the propagation of this phenotype is a more frequent event than previously thought among cases developing into a hormone-refractory disease stage. Turbat-Herrera et al. [12] reported 8 cases with neuroendocrine differentiation ranging from pure small-cell to mixed adenocarcinoma-small-cell phenotype among 69 (11.6%) prostate carcinoma cases. Tanaka et al. [13] found 4 cases with predominant composition of its phenotype of 20 cases (20.0%), Shah et al. [14] reported 3 of 30 (10.0%) cases, but they stated this as a low frequency.

Although the autopsy studies may include selection bias when the cases were registered and the vast majority of men who die of prostate cancer do not have very low PSA levels, these reported proportions of small-cell neuroendocrine phenotype cannot be disregarded by urologists treating cases of hormone-refractory disease having a heterogeneous nature. Furthermore, we reported 7 cases with the small-cell phenotype, 4 of which had been simply diagnosed as poorly differentiated carcinoma or Gleason pattern 5 until their immunohistochemical review, which indicates also the possibility that more small-cell neuroendocrine carcinomas lurk among the metastatic prostate cancer initially diagnosed as conventional adenocarcinoma [15]. Bostwick [16] recommended immunohistochemical staining in cases with a solid Gleason 5 pattern suggestive of neuroendocrine carcinoma.

A wide variety of secretory products are detected within the neuroendocrine cells, and the representative neuroendocrine tissue markers currently used in the pathologic diagnosis in addition to PSA and thyroid transcription factor-1 are shown in Table 1. Thyroid transcription factor-1 is a nuclear homeodomain transcription factor, which shows high sensitivity for small-cell carcinomas of the lung and some rates for extrapulmonary sites [17]. Chromogranin-A is a pan-neuroendocrine marker, and its serum level is considered the most useful for determination of neuroendocrine differentiation [18]. Chromogranin-A is likely to be expressed in the well-differentiated neuroendocrine carcinoma rather than the poorly differentiated one and often shows negative expression in the small-cell phenotype [19]. Prostatic small-cell neuroendocrine carcinoma showed similarity to small-cell lung carcinoma in morphologic features [8].

A recent tissue micro-array analysis by Shah et al. [14] revealed that its phenotype showed an expression pattern of some genes resembling that of small-cell lung carcinoma. Furthermore, our previous immunohistochemical analysis with the established neuroendocrine markers in small-cell neuroendocrine carcinoma revealed that 85.7%, 71.4%, and 50.0% of the cases showed positive staining for ProGRP, chromogranin-A, and NSE, respectively. ProGRP was the most sensitive marker, and cases with positive staining for chromogranin-A always showed positive staining for ProGRP [15]. Although NSE and chromogranin-A are current mainstay serum neuroendocrine markers for the clinical evaluation of small-cell carcinoma, these backgrounds encourage the advantage and validity of using serum ProGRP, the most sensitive and specific tumor marker for small-cell lung carcinoma, to diagnose and monitor that of prostatic origin [20,21]. Only a limited number of cases of prostatic small-cell carcinoma monitored by serum ProGRP measurements have been reported [22–25].

Whether the androgen-ablation therapy should be continued or not in patients whose tumors undergo neuroendocrine transdifferentiation, is a crucial matter. In our case, the androgen-ablation therapy was continued as an excuse to treat the adenocarcinoma cells, and the other treatment modalities were added to control the neuroendocrine component, but there is no definitive clinical evidence to support our choice. The present case was not given local treatment such as irradiation or surgery combined with systemic therapy, but the local control of localized small-cell carcinoma is recommended for palliative benefit or opportunity to prolong survival [26,27]. However, considering the presence of the neuroendocrine features associated with progression to lethal metastatic disease in locally aggressive androgen-independent disease, systemic therapy is indispensable, and the local treatment should remain an option according to the disease extent [28,29]. Papandreou et al. [9] advocated that the combination chemotherapy based on cisplatin and etoposide with or without doxorubicin caused higher toxicity related to the patient’s outcome. They reported that the response rate was 61%, median time to progression and overall survival time were 5.8 months and 10.5 months, respectively, and severe hematologic side effects were unavoidable (100%). Nevertheless, by introducing this regimen during the early stage of neuroendocrine disease, durable control of the disease could be expected, which contributes to the patient’s quality of life and some extension of survival in individual cases [6]. Alternatively, new agents based on the biology of neuroendocrine cells such as somatostatin analogues, neuropeptide antagonists, or inflammatory cytokines, like interleukin-6, are being investigated in clinical and laboratory settings [30]. Unfortunately, the present case did not show any re-
sponses to the somatostatin analogue therapy. However, recent trials using a somatostatin analogue in combination therapy not only for small-cell carcinoma but also hormone-refractory prostate cancer have attained some success without major adverse effects [31-33]. A strategic approach to prostatic small-cell neuroendocrine carcinoma evaluating serum neuroendocrine markers is necessary as well as the histologic confirmation when serum PSA does not reflect the disease state or when atypical visceral metastases are found. This approach would make possible a more objective staging of disease and allow one to choose cytotoxic chemotherapy or new treatment modalities targeting neuroendocrine cells other than androgen ablation for patients with advanced prostate cancer.

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References