Androgen-deprivation therapy in the management of neuroendocrine prostate cancer

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Abstract

Background: Prostatic neuroendocrine carcinomas comprise <1% of all prostate neoplasms, and ~200 cases have been reported in the literature. We undertook this study to describe the experience in the management of prostatic neuroendocrine carcinoma with androgen-deprivation therapy (ADT).

Methods: We designed a retrospective, descriptive and observational study. In patients with suspicion of prostate cancer, transrectal ultrasonography-guided biopsy (TRUS) or transurethral resection of prostate (TURP) was carried out during the period from January 2000 to December 2007. Patients were selected by anatomopathological diagnostic study of neuroendocrine carcinoma including pure and mixed variants. Characteristics analyzed were age, clinical stage, prostate-specific antigen (PSA), imaging studies, treatment and survival.

Results: Ten cases were included with a median age of 66.5 years. Symptoms at diagnosis were associated with metastasis to other organs, one with bone metastasis, and presenting pain in 100% of the cases. A suspicious rectal digital examination was detected in 100% of the patients. In three (30%) patients, PSA was suspicious for prostate cancer. The extension studies showed bone, locoregional, lung and hepatic metastases. In six (60%) patients mixed variant was documented (acinar adenocarcinoma and neuroendocrine carcinoma) with a median survival of 11.6 months. In four patients (40%), pure neuroendocrine carcinoma was documented with a median survival of 7 months.

Conclusions: Prostatic neuroendocrine carcinoma is uncommon, aggressive and represents a prostatic neoplasia without PSA expression. In advanced disease, very low response is reached with ADT.

Key words: prostate cancer, prostatic neuroendocrine carcinoma, prostate-specific antigen, androgen-deprivation therapy.

Introduction

Prostate cancer constitutes the second cause of death in males worldwide and its incidence continues to rise. Neuroendocrine variant form of prostate carcinoma represents 5% of prostate neoplasias and is infrequent and very aggressive. Currently, <200 cases have been reported in the world literature.

Neuroendocrine carcinoma (NEC) of the prostate, also called small cell carcinoma, is infrequent and may present itself mainly in its pure or mixed form. It is associated with acinar adenocarcinoma of the prostate. Early diagnosis is difficult because obstructive urinary symptomatology is not characteristic as is the case in conventional prostate cancer. Frequently the prostate specific antigen (PSA) is within normal limits for the patient’s age; however, diagnosis is made due to symptoms originating in other organs secondary to distant metastasis. Digital rectal examination, in addition to being a key step in the examination of all patients, in these cases in particular constitutes the main tool of diagnostic suspicion.

Material for histological study is obtained from transrectal biopsy, transurethral resection of the prostate or laparascopic or open radical retropubic prostatectomy. Definitive diagnosis can be made by immunohistochemistry or by a confirmatory characteristic pattern.

Based on the experience of NEC in other body sites, use of systemic chemotherapy has become normal therapeutic behavior and, in prostate cancer is associated with total androgen blockade (TAB) and radiation therapy, being the best option at present.

At present we know that these patients have a poor prognosis with a reported overall survival of 7 months. Few series have
been published worldwide; therefore, we consider it to be important to present the experience in our institution

**Materials and Methods**

We present the experience from the Oncology Hospital, Centro Medico Nacional Siglo XXI, IMSS, Mexico City in managing NEC of the prostate. Study design was retrospective, descriptive and observational.

We conducted a review of medical records of all patients with suspected prostate cancer who underwent transrectal biopsy or transurethral resection of the prostate between January 2000 and December 2007, selecting patients with pathological diagnosis of pure or mixed variant NEC of the prostate.

Specimens were reviewed by the urology group of the hospital and diagnosis was made by direct observation of a characteristic pattern or use of immunohistochemistry (IHC) with chromogranin A and synaptophysin (CRG-SPT).

We analyzed age, clinical stage and functional status using the Eastern Cooperative Oncology Group (ECOG) classification, PSA, laboratory studies, IHC diagnostic methods, treatment and survival. For statistical analysis, $\chi^2$ and Fisher exact test were applied.

**Results**

There were 10 cases with histopathological report of NEC of the prostate included in the period previously mentioned. Average age of presentation was 66.5 years (range: 57-77 years), adverse functional state in the majority of the patients documented according to ECOG was as follows: functional value of II in 1 patient (10%), III in 5 patients (50%) and IV in 4 patients (40%). Survival according to functional state is shown in Figure 1.

Clinical symptomatology observed at the time of diagnosis in this group of patients was closely associated with metastatic invasion to other organs, with the main symptom being bone pain. In the majority of the cases, the bone pain presented in the lumbodorsal spine and was present in 100% of the cases. Lymphedema was also documented in one or both upper extremities in 6 patients (60%), secondary to obstruction due to lymph node activity and abdominal pain in 3 patients (30%), of which one presented with lower GI bleeding and two presented with ascites.

Rectal digital examination was fundamental, with a suspicious digital examination and in advanced stage in all patients, documenting clinical T4 in 9 patients (90%) and T2c in one patient, which is what precipitated the scrutiny and diagnosis.

PSA behaved very differently from that found in conventional prostate cancer. It is noteworthy that only in three patients (30%) was it suspicious for prostate neoplasia with their PSA values being >50 ng and in 6 patients (60%) normal reference values for age were found.

Chest x-ray was positive for bilateral metastasis in three patients (30%), abdominopelvic CAT scan was positive for regional node activity in 80% of the patients and 2 (20%) patients presented multiple hepatic metastatic activity, making it impossible to perform the study in two cases due to the initial adverse functional state according to ECOG. Likewise, bone scan was performed in all patients and was positive in 9 patients (90%) in multiple areas (cervical, dorsal, lumbar, costal arches and pelvic girdle) (Figure 2) and being normal in only one patient, with all patients staged as initial clinical stage IV.

Material for histopathological study was obtained in 7 patients (70%) by means of transrectal biopsy and in 3 patients (30%) the diagnosis was made by transurethral resection of the prostate.

In 6 patients (60%) the mixed variant was documented (acinar adenocarcinoma + neuroendocrine carcinoma) and in 4 (40%) patients, NEC in its pure form, making it necessary to perform IHC with CRG A and SPT in 5 patients (Figure 3).
Initial treatment consisted of TAB in all patients without the possibility of offering systemic chemotherapy to any of these patients due to an adverse ECOG classification and concomitant renal insufficiency for which palliative therapy was opted for in 2 patients.

Up to the time of this study, all patients died due to their disease. A factor directly related to survival was the PSA value because in three patients this value was >50 ng and the three patients responded to TAB with a nadir of 3-10 ng reported 3 months after the start of the blockage, reaching an overall survival of 12.3. Patients with a PSA of <50 ng/ml did not respond adequately to starting TAB and their overall survival was 8.7 months (Tables 1 and 2). Another prognostic factor was the pure variant of NEC, and those patients had an average survival of 7 months. Those who presented with a mixed variant reached an average survival of 11.6 months (Figure 4).

### Table 1. Clinical stages and presentation of patients at the time of diagnosis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>ECOG</th>
<th>PSA</th>
<th>Chest x-ray</th>
<th>CAT</th>
<th>Bone scan</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>2</td>
<td>4.5</td>
<td>N1</td>
<td>Regional adenopathies</td>
<td>Normal</td>
<td>T2c N1 M0</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>3</td>
<td>&gt; 150</td>
<td>N1</td>
<td>Development of nodes and obstructive uropathy</td>
<td>METS in C2-C3 and anterior costal ribs</td>
<td>T4 N1 M1b</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>3</td>
<td>0.37</td>
<td>Bilateral METS</td>
<td>Multiple liver METS Bilateral adenopathy</td>
<td>Multiple METS in lumbar and thoracic spine</td>
<td>T4 N1 M1c</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>3</td>
<td>69</td>
<td>Normal</td>
<td>NR</td>
<td>METS in left femur</td>
<td>T4 Nx M1b</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>4</td>
<td>5</td>
<td>Bilateral METS</td>
<td>Regional adenopathies</td>
<td>Cervical and thoracic METS</td>
<td>T4 N1 M1c</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>4</td>
<td>99.8</td>
<td>Bilateral METS</td>
<td>Regional adenopathies</td>
<td>Cervical and dorsolumbar METS</td>
<td>T4 N1 M1c</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>4</td>
<td>1.39</td>
<td>Normal</td>
<td>Regional adenopathies and liver METS</td>
<td>METS cervical spine, hip and right femur</td>
<td>T4 N1 M1c</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>3</td>
<td>3.7</td>
<td>Normal</td>
<td>Multiple regional adenopathies</td>
<td>METS cervical spine and right costal ribs</td>
<td>T4 N1 M1b</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>4</td>
<td>4.5</td>
<td>Normal</td>
<td>NR</td>
<td>METS to cervical and thoracic spine</td>
<td>T4 Nx M1b</td>
</tr>
<tr>
<td>10</td>
<td>77</td>
<td>3</td>
<td>12</td>
<td>Normal</td>
<td>Regional adenopathies</td>
<td>METS to thoracic spine</td>
<td>T4 N1 M1b</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen (ng) expressed in ng/ml; CAT, computerized abdominopelvic tomography; TNM, tumor-node-metastasis; N1, normal, NR, not reported; METS, metastasis.
Prostate cancer usually presents in patients >50 years of age with a high incidence in subjects >70 years of age. It is the most common malignancy in males and is the second cause of death due to cancer in males in the U.S., ranking only after lung cancer. Mexican epidemiological information indicates that cancer of the prostate and malignant tumors in general are ranked in second place as causes of death. Since 1999, prostate cancer has become the second cancer with the greatest mortality rate with an estimated >3500 deaths/year. There are no reports in the Mexican literature on the behavior of prostate NEC in our environment.

The clinical course of patients with prostate cancer remains difficult to predict. Variables such as histopathological grade and clinical stage are correlated with the biological behavior of these tumors and are considered to be the best prognostic parameters. Neuroendocrine cells can be found in benign prostatic ducts as well as adenocarcinoma, but their functional role is not as clear. The majority of the prostate carcinomas with neuroendocrine differentiation are adenocarcinomas with disperse neuroendocrine cells. Pure small-cell anaplastic carcinomas of the prostate are rare but highly aggressive and represent <1% of all prostatic tumors.

In contrast to pure adenocarcinoma of the prostate, PSA is not a useful tumor marker for small-cell lineage and is usually present in normal values, even with metastatic disease.

Table 2. Histopathological analysis, treatment and survival of patients with neuroendocrine prostate cancer

<table>
<thead>
<tr>
<th>Case</th>
<th>Dx method</th>
<th>HPR</th>
<th>IHC method</th>
<th>Initial Tx</th>
<th>Survival after diagnosis (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TRB</td>
<td>Poorly differentiated acinar adenocarcinoma GL: 5+4 (9) with areas of neuroendocrine differentiation</td>
<td>NR</td>
<td>BAT/RT</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>TRB</td>
<td>Poorly differentiated acinar adenocarcinoma GL: 4+4 (8) with areas of differentiation present in 100% of studied material</td>
<td>NR</td>
<td>TAB/palliative RT</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>TUPR</td>
<td>Poorly differentiated acinar adenocarcinoma GL: 5+4 (9) with neuroendocrine component in &gt;30% of studied material</td>
<td>CMG-SNF</td>
<td>TAB</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>TRB</td>
<td>Poorly differentiated acinar adenocarcinoma GL: 5+5 (10) with neuroendocrine differentiation in &gt;40% of studied tissue</td>
<td>NR</td>
<td>TAB/palliative RT</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>TRB</td>
<td>Poorly differentiated adenocarcinoma with areas of neuroendocrine component in both lobules</td>
<td>CMG-SNF</td>
<td>TAB</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>TUPR</td>
<td>Undifferentiated carcinoma with extensive areas of neuroendocrine carcinoma</td>
<td>CMG-SPT</td>
<td>TAB</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>TRB</td>
<td>Undifferentiated carcinoma with neuroendocrine characteristics</td>
<td>CMG-SPT</td>
<td>TAB</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>TUPR</td>
<td>Acinar adenocarcinoma with GL: 4+3 (7) in 98% of studied material with areas of neuroendocrine carcinoma</td>
<td>NR</td>
<td>TAB</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>TRB</td>
<td>Acinar adenocarcinoma with GL: 5+5 (10), in 80% of submitted material with areas of neuroendocrine differentiation</td>
<td>CMG-SPT</td>
<td>TAB</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>TRB</td>
<td>Undifferentiated carcinoma with extensive areas of neuroendocrine carcinoma</td>
<td>NR</td>
<td>TAB</td>
<td>3</td>
</tr>
</tbody>
</table>

Dx, diagnosis; HPR, histopathological report; IHC, immunohistochemistry; BAT/RT, total androgen block/radiotherapy; TRB, transrectal biopsy; NR, not reported; TUPR, transurethral prostate resection; CMG-SPT, chromogranin-synaptosin.

Discussion

Prostate cancer usually presents in patients >50 years of age with a high incidence in subjects >70 years of age. It is the most common malignancy in males and is the second cause of death due to cancer in males in the U.S., ranking only after lung cancer.

Mexican epidemiological information indicates that cancer of the prostate and malignant tumors in general are ranked in second place as causes of death. Since 1999, prostate cancer has become the second cancer with the greatest mortality rate with an estimated >3500 deaths/year. There are no reports in the Mexican literature on the behavior of prostate NEC in our environment.

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In contrast to pure adenocarcinoma of the prostate, PSA is not a useful tumor marker for small-cell lineage and is usually present in normal values, even with metastatic disease.

The clinical presentation at the time of diagnosis in most cases begins with asthenia, fatigue, and weight loss associated with bone pain at metastatic sites. It is uncommon to find obstructive lower urinary symptoms in physical examination with fixed prostate and a PSA within normal range for age.

In our series, all patients presented clinical stage IV disease and a clinical picture characterized by bone and abdominal pain, which reflected distant metastatic dissemination, coinciding with reports in the literature.

In recent years, an increasing number of studies related to prostate cancer with neuroendocrine differentiation have been published. At least one focus of neuroendocrine differentiation
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is present in all conventional prostate adenocarcinomas; however, one must not confuse the fact of having neuroendocrine cells in normal prostate tissue and malignant degeneration of these cells, which gives this neoplasm its aggressive characteristics.

Neuroendocrine activity is one of the factors involved in the progression of a state of hormone dependence to a hormone-independent prostate cancer. The neuroendocrine component of prostate cancer is hormone-independent and therefore does not produce PSA. The continued use of androgen ablation therapy may cause hyperactivation of the neuroendocrine system in the prostate tissue in patients with mixed tumors (adenocarcinoma and neuroendocrine carcinoma). The products of the neuroendocrine system can act as factors that inhibit apoptosis in neoplastic cells and thus induce androgen independence and disease progression. There are neuroendocrine markers such as serum CRG A and neuron-specific enolase (NSE), which increase when prostate cancer becomes hormone-refractory.

Histologically, small cell carcinoma of the prostate is characterized by a pattern similar to small cell carcinoma of the lung. Three theories to explain this histogenesis have been proposed. The first one suggests that small cell carcinoma of the prostate arises from an amino precursor in response to cellular decarboxylation, which originates in local cells of endodermic origin. Another theory proposes that small cell prostate carcinoma arises from the differentiation of prostate adenocarcinoma, suggesting that small cell carcinomas are part of a spectrum of the adenocarcinomas themselves and not a different entity.

Due to the histological similarities between small cell carcinoma of the lung and prostate and to the paraneoplastic syndromes similar in both tumors, the most accepted opinion is that small cell carcinoma of the prostate originates in totipotential stem cells of the prostate, which have the ability to differentiate into carcinomas of neuroendocrine or epithelial types.

The majority of these tumors with neuroendocrine differentiation can be revealed by means of IHC. In a study by Wenle et al. of 95 patients, positivity was reported in 75% of the patients for CRG A, 84% for SPT, 85% for NSE, and 92% for CD56. However, in some cases no reactivity is found to any specific marker. In these cases the diagnosis is established by the typical morphology of these tumors. In our series, in five patients IHC was performed and was positive for CRG-SPT.

Whereas mixed small cell carcinomas with adenocarcinoma generally have aggressive recurrences of a primary adenocarcinoma, the pure small cell carcinoma frequently is associated with early metastatic disease due to its aggressive nature. As with adenocarcinomas, small cell tumors appear in the periphery of the prostate and, therefore, cause few urinary symptoms. Occasionally the disease is characterized by its metastatic pattern to organs such as the liver, bone, lung, CNS and pericardium and, locally, to lymph nodes of the pelvis, rectum and bladder.

Active chemotherapeutic agents for pulmonary cancer (vincristine, doxorubicin, and cyclophosphamide) are less effective on its prostatic homologue, and there are few cases where complete transitory remission has been found. When the presentation is a mixed tumor with adenocarcinoma, treatment also includes TAB.

Survival is 5-17.5 months. Despite different treatment modalities, in our series overall survival in patients with pure form was 7 months. These data reflect the poor prognosis and also that no treatment method has been clearly established.

Although the reasons for the poor prognosis in this histologic subtype are not well defined, active neuroendocrine cellular products such as growth factor and lack of androgenic receptors in neuroendocrine cells can be included.

Wu studied 14 cases of prostate carcinoma resistant to hormonal treatment. High levels of CRG A were detected in 10, whereas the PSA was normal and NSE was not identified. Early detection of high levels of CRG A in the serum may be an indicator to change to a more aggressive therapy. Jiborn et al. suggested that androgenic ablation therapy may increase the selection and progression of neoplastic neuroendocrine cells.

Tumors with neuroendocrine differentiation may be a therapeutic target. Some analogues and antagonists of neuroendocrine hormones such as somatostatin, bombesin, and serotonin have been studied in vitro and in vivo. Somatostatin is an inhibitor of neuroendocrine hormone secretion. Recently, analogues of long-acting somatostatin in clinical trials in combination with other agents for hormone-independent prostate cancer have been used.

These studies have shown that somatostatin analogues in combination with standard androgen ablation produces objective clinical responses and symptomatic improvement in patients with hormone-refractory prostate cancer.

In conclusion, NEC of the prostate represents <1% of all prostate tumors and is a rare, aggressive, silent tumor usually diagnosed at advanced stages.

Despite treatment with systemic chemotherapy or TAB, the prognosis of small cell carcinoma of the prostate is poor, with the average survival being ~7 months.

In the era of PSA we must not ignore the existence of cancer of the prostate and, therefore, cannot depend solely on this tumor marker to suspect this neoplasm.

References