Uncommon presentation of prostate cancer with neuroendocrine differentiation


ABSTRACT

Neuroendocrine differentiation (NED) in prostate cancer has gained in importance due to its prognostic and therapeutic implications. Some authors have related NED degree with poor cellular differentiation, disease progression and androgen-independence.

Objective: The case of a patient diagnosed with prostate cancer in remission with neuroendocrine differentiation and multiple metastatic disease is presented.

Clinical case: The 78-year-old patient presented with prostate adenocarcinoma, Gleason 4+4, 79ng/ml initial PSA and positive scintiscan in May, 2003 (T2bN0M1). He received anti-androgen hormonal treatment and underwent orchietomy. Patient went into clinical remission with 0.0ng/ml PSA in June 2004 and so antiandrogen was suspended. In January 2008, patient presented with intestinal obstruction and 1.7ng/ml PSA. He underwent exploratory laparoscopy which revealed hepatic nodules and prostate-dependent pelvic mass infiltrating bladder and rectum. Diversion colostomy was performed. Progression was not favorable and the patient died 5 days later. Post-mortem histopathological report stated prostate adenocarcinoma, Gleason 5+5, significant neuroendocrine differentiation and rectum and bladder invasion.

RESUMEN

La diferenciación neuroendocrina en el cáncer de próstata ha cobrado importancia por las implicaciones pronósticas y terapéuticas. Algunos autores han relacionado el grado de diferenciación con pobre diferenciación celular, progresión e independencia a andrógenos.

Objetivo: Presentar el caso de un paciente con diagnóstico de cáncer de próstata en remisión, con diferenciación neuroendocrina y enfermedad metastásica múltiple.

Caso clínico: Paciente del sexo masculino de 78 años de edad que cursó con adenocarcinoma de próstata, Gleason 4+4, antígeno prostático específico inicial de 79ng/mL y gamagrama óseo positivo en mayo de 2003 (T2bN0M1). El paciente recibió tratamiento hormonal con fármacos antiandrogénicos y se le practicó orquiectomía. Presentó remisión del cuadro clínico, documentada por medio de: antígeno prostático específico de 0.0 ng/mL en junio 2004, lo que motivó suspender el tratamiento antiandrogénico. En enero de 2008 ingresó al servicio por presentar obstrucción intestinal, la determinación de antígeno prostático específico fue de 1.7 ng/mL. Se le practicó laparotomía exploradora encontrando nódulos hepáticos, masa en pelvis dependiente de próstata con infiltración a vejiga y recto. Se le realizó colostomía derivativa. La evolución no fue favorable y falleció
Discussion: Prostate cancer patients with high NED marker levels (chromogranin A) appear to have poor prognosis and can present with poorly differentiated, hormone-resistant tumors. In long-term anti-androgen treatment there is an elevation of neuroendocrine cells, suggesting that hormonal deprivation accelerates the process.

Conclusions: Neuroendocrine differentiation is related to poor prostate cancer prognosis.

Key words: Neuroendocrine differentiation, chromogranin A, prostate cancer, Mexico.

- BACKGROUND
Prostate cancer (CaP) is the most frequently diagnosed malignant neoplasia in men. Its natural history is mainly influenced by factors such as clinical stage and tumor differentiation grade. Prognosis is good, with or without treatment, when CaP is detected in the early stages and is low grade, unlike advanced stage CaP with a high differentiation grade.

Neuroendocrine differentiation (NED) has become more important due to its prognostic and therapeutic implications. Neuroendocrine (NE) cells have a regulatory function in growth, cellular differentiation and other biological processes. Chromogranin A is very useful in the characterization of neuroendocrine tumors. The degree of NED has been associated with poor cellular differentiation, disease progression and androgen-resistance.

- CLINICAL CASE
The patient is a 78-year-old man with a family history of CaP (father), a history of high blood pressure of 3-year progression, smoking and serious alcoholism. He sought medical attention at the emergency room for intense abdominal pain, abdominal distension and constipation, all of 48-hour progression. Patient presented with obstructive urinary symptomatology of 5-year progression, an IPSS of 25 points and initial PSA of 79 ng/ml. During physical examination the distended abdomen was painful upon palpation, but with no signs of peritoneal irritation. Digital rectal examination (DRE) revealed empty rectal ampulla and grade III prostatic growth of soft consistency with T2b staging. Ultrasound-guided transrectal prostate biopsies were carried out reporting prostate adenocarcinoma with Gleason 4+4=8 in 9/9 fragments. Bone scintiscan was positive for metastatic disease in L1-L5 and sternum. Treatment was initiated with maximum androgen blockade with simple bilateral orchiectomy and the anti-androgen, flutamide.

Obstructive symptomatology deteriorated into acute urinary retention (AUR), requiring transurethral resection of the prostate (TURP). Histopathological report stated adenocarcinoma, Gleason 3+4=7 and control PSA of 2.7 ng/ml.

Patient discontinued follow-up for 3 years until current hospital admittance for intestinal obstruction associated with macroscopic hematuria.

Intestinal obstruction was managed conservatively but it persisted. Abdominal tomography was ordered which showed images suggestive of metastatic disease in liver and retroperitoneum as well as an obstructive, heterogeneous prostate with increase in volume.

Obstructive symptoms persisted and patient showed clinical decline. Exploratory laparotomy was performed revealing enlarged mesenteric lymph nodes, multiple...
hepatic nodules, tumor mass in the iliac fossa with infiltration into the bladder and rectum. There was almost total obstruction of the rectal opening and so diversion colostomy was carried out.

After surgery, there was progressive general deterioration resulting in cardiac failure, renal insufficiency, respiratory insufficiency, abdominal distension and refractory shock. The patient responded poorly to treatment with vasoactive amines and died 4 days later.

Autopsy report described poorly differentiated prostate adenocarcinoma with a Gleason 5+5 pattern and neuroendocrine differentiation (NED) with bladder and rectum invasion. It also reported metastases to periaortic, peritrachael-bronchial and peripancreatic lymph nodes, liver, gall bladder, lung, vertebra and rib.

**DISCUSSION**

Neuroendocrine cells have been identified in up to 92% of prostatic tissue. However, it has been observed that higher levels of NED markers in CaP patients may be due to tumors that are poorly differentiated, hormone resistant and with poor prognosis. Since NED is more frequently seen in poorly differentiated tumors, some authors question its association with poor prognosis considering them to be independent factors. A greater number of neuroendocrine cells have been observed after hormone deprivation and long-term androgen blockade (since this can reduce enzyme degradation of neuroendocrine products), suggesting that hormone deprivation may speed up the NED process.

**CONCLUSIONS**

Neuroendocrine differentiation in prostate cancer is associated with poor prognosis, tumor differentiation grade and clinical stage. It is also thought that androgen blockade can activate disease progression, extension and dissemination (from the increase in the number of neuroendocrine cells). The relation observed among neuroendocrine differentiation, metastasis and disease extension is debatable.

Therefore it is necessary to continue to analyze the direct association between prostate cancer and neuroendocrine differentiation in order to establish early therapeutic strategies and to predict prognosis.

**BIBLIOGRAPHY**