Laboratory Case Report

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Neuroendocrine differentiation of prostatic adenocarcinoma – an important cause for castration-resistant disease recurrence

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Abstract

Background: Neuroendocrine differentiation of prostatic carcinoma is a rare entity associated with metastatic castration-resistant disease. Among useful biomarkers of neuroendocrine differentiation, chromogranin A, serotonin, synaptophysin and neuron-specific enolase stand out, while total prostate-specific antigen (PSA) levels are often low or undetectable.

Case presentation: We report a case of prostatic adenocarcinoma recurrence after a 6-year disease-free follow-up, in which increased serum chromogranin A levels and undetectable total PSA provided a prompt indication of neuroendocrine transformation, confirmed through immunohistochemical evaluation.

Conclusions: Neuroendocrine differentiation is a relevant cause of prostatic adenocarcinoma recurrence, and

awareness of this entity is crucial due to its underdiagnosis and adverse prognosis.

Keywords: carcinoma; castration-resistant (D064129); cell transformation; neoplastic (D002471); neuroendocrine (D018278); prostate (D011467); prostatic neoplasms.

Introduction

Neuroendocrine prostatic carcinoma is a rare and underdiagnosed histologic subtype. Despite the low incidence rate of primary neuroendocrine prostatic carcinoma (which represents under 1% of all prostate cancers at diagnosis), 30–40% of patients who develop metastasized castration-resistant disease have neuroendocrine differentiation, with histologic transformation occurring due to an adaptive response to androgen deprivation [1, 2].

Among useful biomarkers for detection of neuroendocrine differentiation, chromogranin A, serotonin, synaptophysin and neuron-specific enolase stand out [2, 3]. Total prostate-specific antigen (PSA) levels are low or undetectable, and androgen receptors are negative, a finding that denotes the androgen independency of this histologic type [1].

Neuroendocrine prostatic carcinoma detection is of uttermost importance due to its association with advanced disease and dismal prognosis. Both elevated serum levels and immunocytochemical positivity for chromogranin A were positively associated with disease refractoriness to anti-androgenic therapy and negatively associated with survival [4, 5].

Case presentation

We report the case of a 64-year-old male diagnosed in April 2011 with invasive prostatic adenocarcinoma of acinar type, with a Gleason Score of 7 (3+4) – corresponding

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Figure 1: Cytological and histopathological characterization of the case.

(A) Histology of prostatic biopsy showing invasive adenocarcinoma of acinar type, Gleason 3 + 4 (with cribriform pattern 4). Hematoxylin-eosin, 200× magnification. (B) FNA cytology of iliac adenopathy showing aggregation of small epithelial cells with an hyperchromatic nucleus. Diff-Quik, 400× magnification. (C) FNA immunocytochemistry for cytokeratins 8/18 showing strong and diffuse staining, 400× magnification. (D) FNA tumor cells showing immunoexpression of synaptophysin. 400× magnification.

to a Grade Group 2 in the most recent 2016 World Health Organization classification. He underwent interstitial brachytherapy with ^{125}I in May 2011 and was kept under bi-annual surveillance in our institution. In September 2017, a biochemical relapse was detected (a total PSA of 5.73 ng/mL following a 0.15 ng/mL nadir); therefore, the patient was proposed for re-staging.

The pelvic magnetic resonance imaging (MRI) performed in February 2018 revealed no evidence of local recurrence but identified a right external iliac adenopathy with 16 mm greater diameter. The prostate biopsy performed a week later revealed a histologic pattern compatible with recurrence of acinar adenocarcinoma (Figure 1A), and prostate-specific membrane antigen positron emission tomography (PSMA-PET) performed the following month revealed hypercaptation foci in different lymph nodes.

These findings, together with increasing values of total PSA (which had reached a value of 15.7 ng/mL in May 2018), motivated the institution of anti-androgenic therapy with goserelin and bicalutamide.

In June 2018, fine-needle aspiration (FNA) biopsy of the iliac adenopathy identified in the pelvic MRI was performed. The analysis of the obtained sample revealed cytological and immunocytochemical profiles compatible

with adenocarcinoma of the prostate with neuroendocrine differentiation (Figure 1B–D).

In August 2018, total PSA dropped to 0.53 ng/mL, a result that was confirmed in the received specimen and in a new sample. Determination of neuroendocrine markers revealed an increase in serum chromogranin A

Figure 2: Evolution of total PSA values showing a prolonged nadir followed by biochemical recurrence detected in 2017.

The red square shows the chromogranin A serum level on August 28, 2018.

(1825 ng/mL), compatible with the histological transformation for neuroendocrine prostatic carcinoma (Figure 2). Neuron-specific enolase was within reference values.

Results and discussion

Acinar adenocarcinoma of the prostate often shows focal immunoexpression of neuroendocrine markers such as chromogranin, synaptophysin or CD56. For this reason, it is generally not recommended to stain for these markers in an otherwise classical acinar adenocarcinoma [6, 7]. Although some studies report conflicting results, it is important to consider the possibility of neuroendocrine differentiation in the differential diagnosis of a prostatic adenocarcinoma recurrence, given its adverse prognosis and underdiagnosis. The origin of this neuroendocrine trans-differentiation is also a matter of discussion, with some authors suggesting a putative origin in pre-existing neuroendocrine cells in the prostatic gland, and others stating that it results from a true differentiation of adenocarcinoma due to epithelial plasticity [8–10].

The so-called treatment-related neuroendocrine prostate cancer is androgen-receptor independent and emerges in the late stages of castration-resistant prostate cancer treatment. This cancer subtype has its specific molecular features [11]. The incidence of this cancer subtype is rising due to wide access and use of androgen receptor inhibitors for prostate cancer treatment. Thus, it is imperative to uncover novel therapies for these patients, who present with this aggressive subtype, often as disease recurrence [12].

The presented case illustrates that, in face of a low or undetectable total PSA and a high clinical suspicion of prostate cancer recurrence, determination of neuroendocrine markers allows a prompt and non-invasive initial diagnostic orientation, while also providing relevant information for therapy selection and prognostic evaluation of these patients.

In conclusion, all medical specialists involved (namely urologists, oncologists, radiologists, anatomic pathologists and clinical pathologists) must be aware of this tumor entity. In fact, only a multidisciplinary and timely approach will allow the clinical team to initiate an appropriate therapy and achieve the best possible outcomes for these patients.

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References

1. Komiya K, Yasuda A, Watanabe Y, Fujiuchi T, Tsuzuki H. Fuse: the prognostic significance of loss of the androgen receptor and neuroendocrine differentiation in prostate biopsy specimens among castration-resistant prostate cancer patients. *Mol Clin Oncol* 2013;1:257–62.
2. Epstein JI, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am J Surg Pathol* 2014;38:756–67.
3. Santoni M, Conti A, Burattini L, Berardi R, Scarpelli M, Cheng L, et al. Neuroendocrine differentiation in prostate cancer: novel morphological insights and future therapeutic perspectives. *Biochim Biophys Acta* 2014;1846:630–7.
4. Berruti A, Mosca A, Porpiglia F, Bollito E, Tucci M, Vana F, et al. Chromogranin A expression in patients with hormone naïve prostate cancer predicts the development of hormone refractory disease. *J Urol* 2007;178:838–43.
5. Taplin ME, George DJ, Halabi S, Sanford B, Febbo PG, Hennessy KT, et al. Prognostic significance of plasma chromogranin A levels in patients with hormone-refractory prostate cancer treated in Cancer and Leukemia Group B 9480 study. *Urology* 2005;66:386–91.
6. Berruti A, Vignani F, Russo L, Bertaglia V, Tullio M, Tucci M, et al. Prognostic role of neuroendocrine differentiation in prostate cancer, putting together the pieces of the puzzle. *Open Access J Urol* 2010;2:109–24.
7. Parimi V, Goyal R, Poropatich K, Yang XJ. Neuroendocrine differentiation of prostate cancer: a review. *Am J Clin Exp Urol* 2014;2:273–85.
8. Zou M, Toivanen R, Mitrofanova A, Floch N, Hayati S, Sun Y, et al. Transdifferentiation as a mechanism of treatment resistance in a mouse model of castration-resistant prostate cancer. *Cancer Discov* 2017;7:736–49.

9. Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyrta J, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. *Nat Med* 2016;22:298–305.
10. Li Y, Donmez N, Sahinalp C, Xie N, Wang Y, Xue H, et al. SRRM4 drives neuroendocrine transdifferentiation of prostate adenocarcinoma under androgen receptor pathway inhibition. *Eur Urol* 2017;71:68–78.
11. Akamatsu S, Inoue T, Ogawa O, Gleave ME. Clinical and molecular features of treatment-related neuroendocrine prostate cancer. *Int J Urol* 2018;25:345–51.
12. Choi SY, Ettinger SL, Lin D, Xue H, Ci X, Nabavi N, et al. Targeting MCT4 to reduce lactic acid secretion and glycolysis for treatment of neuroendocrine prostate cancer. *Cancer Med* 2018:1–8. [Epub ahead of print].

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