Small cell-like change in prostatic adenocarcinoma and intraductal lesions – neuroendocrine or not?

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Abstract

Background: Small cell-like change in prostatic neoplasia (both invasive adenocarcinoma and intraepithelial lesions) is described in three previous reports. None of them to date proved to be associated with overt prostate neuroendocrine carcinoma.

Case presentation: We report findings from a radical prostatectomy of 80-year-old patient (adenocarcinoma GG5 pT3b with 10% involvement of the gland) with small cell-like change in intraductal carcinoma and in the invasive component. An additional 3.5-mm focus of poorly differentiated carcinoma was observed (PSA, TTF1, chromogranin and CD56 negative; synaptophysin positive in scattered cells; and a Ki67 label index of 50%).

Conclusion: Our case expands the data accumulated on small cell-like change in prostate neoplasia. As most of other reported cases, there was no expression of neuroendocrine markers or high proliferative index in small-cell like areas. On the other hand, for the first time, a transition morphology between acinar adenocarcinoma and neuroendocrine carcinoma was observed in a prostate with small cell-like change.

Keywords: Prostate, Adenocarcinoma, Neuroendocrine tumors

Background

Small cell like change in prostatic neoplasia (both invasive adenocarcinoma and intraepithelial lesions) is described in three previous reports. None of them to date proved to be associated with overt prostate neuroendocrine carcinoma.

Case presentation

An 80-year-old patient sought urologic assistance due to an elevated serum Prostate Specific Antigen (PSA) level (17.5 ng/mL). His previous medical history was unremarkable. A systematic biopsy was performed (and evaluated by other Pathology Laboratory) with diagnosis of GG5 adenocarcinoma. The treatment option was for a radical prostatectomy with retroperitoneal lymphadenectomy. The prostatectomy specimen showed a usual acinar adenocarcinoma GG5 with pT3b stage and 10% involvement of the gland. Nineteen retroperitoneal lymph nodes were identified – all of them negative for malignancy.

Two unusual findings were observed in the prostatectomy specimen. First, apical and mid-gland right-anterior zone showed small cell aggregates within invasive component and in intraductal carcinoma with a cribriform morphology (consistent with intraductal carcinoma of the prostate). In intraductal lesions, these small cells with bland cytology and monotonous appearance were placed in the center of glands (Figs. 1 and 2). A clear transition between small cells and usual acinar adenocarcinoma could be recognized (Fig. 3). Rosette formation was easily recognized (Figs. 2 and 4). These areas mirror what has been named in literature as small cell-like change in prostatic neoplasia (see discussion below). Basal cell markers proved that
this change was observed both in invasive and intraepithelial lesions (Fig. 5). PSA expression was markedly reduced or absent in this small cell-like foci, in contrast with diffuse expression in most areas of the high-grade prostate carcinoma. Additional immunostains showed no expression of neuroendocrine markers (chromogranin, synaptophysin, CD56 and TTF1). The glands with intraductal carcinoma showed Ki67-positive cells in periphery and no expression in the center of the gland with small cell aggregates (Fig. 6). Ki67-positive cells could be easily identified also within the invasive tumor but not in the small cell-like areas.

The second peculiar finding was 3.5-mm focus of poorly differentiated carcinoma within an extensive area of GG5 adenocarcinoma in mid-gland at right anterior zone, thus, in the vicinity of small cell-like areas in intraductal lesions. At HE sections, this area raised concern for a possible coexistence of neuroendocrine carcinoma.
(Fig. 7). Immunostains showed overlapping features of both usual acinar adenocarcinoma and neuroendocrine carcinoma: markedly reduced PSA expression; absent expression of neuroendocrine markers (chromogranin, CD56 and TTF1); only scattered positive synaptophysin positive cells; and a Ki67 labelling index of 50% in hot spot areas (see discussion) (Fig. 8). The pathology report was signed with a comment on this focus describing the overlapping features between both entities and emphasizing that a minute / incidental finding of neuroendocrine carcinoma is not an expected presentation of this tumor. After 3 months of follow up, the patient is alive with no evidence of biochemical or clinical recurrence.

**Discussion**
In 1997, Reyes and colleagues described unusual variants of high-grade intraepithelial prostatic neoplasia (HGPI
One of these cases was a dense cribriform intraductal lesion (more akin to the current diagnosis of intraductal carcinoma of the prostate) with what was called "small cell neuroendocrine HGPIN". The center of the intraductal proliferation showed bland and monotonous proliferation of small cells. The reported case showed expression of neuroendocrine markers (chromogranin, synaptophysin, and neuron-specific enolase) by immunohistochemistry and had neuroendocrine-type granules at electron microscopy (Reys et al. 1997).

In 2013, Lee and colleagues described seven cases of what they named small cell-like change (SCLC) in high-grade intraepithelial prostatic neoplasia and intraductal carcinoma. Five cases had coexisting prostatic invasive adenocarcinoma and four showed small cell-like change in the invasive tumor. Rosette-like formations (as seen in the present case) were noted within some involved ducts in three cases. Despite resemblance of small cell carcinoma, no lesion expressed the most commonly used neuroendocrine markers chromogranin and synaptophysin. Focal expression of TTF1 was focal in three out of four tested cases (Lee et al. 2013).

These findings were expanded in a series of 11 eleven cases by Kryvenko and colleagues. All had HGPIN or intraductal carcinoma with small cell-like change. Again, rosette formation was also a consistent feature. In nine cases with high-grade invasive carcinoma, SCLC was observed in invasive component or intraductal carcinoma. In two cases, it has observed in intraductal lesions away from low-volume GG1 adenocarcinoma. Expression of synaptophysin, chromogranin, and serotonin were seen in only 2/11 cases, but at least focal expression of TTF1 was documented in 6/11 cases. In four cases, electron microscopy was performed and did not show any evidence of neuroendocrine granules (Kryvenko et al. 2017).

Accurate diagnosis of true prostatic neuroendocrine carcinoma is crucial for proper management (Lotan et al. 2020). Neuroendocrine carcinoma of the prostate may occur in pure forms (41%) or mixed with adenocarcinoma (59%) (Conteduca et al. 2019). Small cell neuroendocrine carcinoma largely predominates among neuroendocrine carcinomas of the prostate and comprises 1–5% of all prostate malignancies (if mixed cases with adenocarcinoma are included) (Fine 2018). It may arise de novo (54%) or present in the setting of androgen deprivation therapy (46%) (Conteduca et al. 2019). Although neuroendocrine differentiation is well known as a form of tumor progression during hormonal blockade, only about 10% of castration-resistant prostate cancer are neuroendocrine carcinomas (Shah et al. 2004). The diagnosis of neuroendocrine carcinoma implies high risk of visceral metastasis (common at the time of diagnosis) and poor survival. Recommended treatment include...
**Fig. 6** Immunophenotype of small cell-like change in intraductal carcinoma. Absent expression of PSA (A: PSA, 100x) and absent expression of chromogranin (B: chromogranin, 100x). Synaptophysin expression was not observed in small cell-like change in intraductal carcinoma, however, focal expression was observed in usual acinar adenocarcinoma in the vicinity (C: Synaptophysin, 100x). CD56 expression was not observed in small cell-like change in intraductal carcinoma, however, scattered cells were positive in usual acinar adenocarcinoma in the vicinity (D: CD56, 400x). Ki67-positive cells are easily seen in the periphery of intraductal carcinoma, but no expression was detected in small cell-like areas (E and F: Ki67, 400x).

**Fig. 7** A minute 3.5-mm focus of poorly differentiated carcinoma. A solid proliferation with numerous apoptotic bodies and nuclei alternating prominent nucleoli or stippled chromatin. Hematoxylin and eosin stain: A (40x), B (100x) and C, D and E (400x)
cisplatin-based chemotherapy with etoposide with same recent series suggesting combination with consolidative surgery or radiotherapy (Fine 2018).

To date, no cases of small cell-like change showed association with concurrent or subsequent neuroendocrine carcinoma. Therefore, this finding is believed to do not bring any relevant prognostic information. The presented case showed a small focus of carcinoma with overlapping features between adenocarcinoma and neuroendocrine carcinoma. The current WHO Classification of tumors states that is not unusual to see some carcinomas with transition morphology between both entities since the neuroendocrine pathway is a known way of alternative growth in hormone-dependent prostate adenocarcinoma. In difficult cases, the diagnosis of neuroendocrine carcinoma is favored by decreased and absent expression of PSA, expression of neuroendocrine markers (at least one positive in 88%) and TTF1 (in 50% of all cases), and a proliferative index higher than 50% (Epstein and Netto 2014) (Moch et al. 2016). Based on morphology and immunophenotype, the focus of interest may be labeled as transition zone not qualifiable as overt neuroendocrine carcinoma. Acinar adenocarcinoma of the prostate typically has a proliferative index lower than 50% and neuroendocrine carcinoma usually will have a proliferative index higher than 70% (Epstein and Netto 2014).

Fig. 8 Immunophenotype of a 3.5-mm focus of poorly differentiated carcinoma. Ki67 with proliferation index of about 50% (Ki67: A, 100x, and B: 400x). Weak to absent expression of PSA (C: PSA, 100x) and synaptophysin expression in scattered cells (D: Synaptophysin, 100x).
Our case expands the data accumulated on small cell-like change in prostate neoplasia. As most of other reported cases, no high proliferation of neuroendocrine markers expression was observed in our case. On the other hand, for the first time, a transition morphology between acinar adenocarcinoma and neuroendocrine carcinoma was observed in a prostate with small cell-like change. This report may call attention to this uncommon lesion and may stimulate further evaluation of the potential biologic associations of small cell-like change in the prostate.

Antibodies used in the present report
AMACR (13H4, Dako)
CD56 (123C3, Dako)
Chromogranin (Polyclonal, Dako)
Ki67 (MIB-1, Dako)
High Molecular Weight Cytokeratin (34βE12, Dako)
P63 (DAK-p63, Dako)
PSA (Polyclonal, Dako)
Synaptophysin (SY38, Dako)
TTF1 (8G7G3/1, Dako)

Abbreviations
AMACR: alpha-methylacyl-CoA racemase; CD56: Cluster of differentiation 56; HE: Hematoxylin and eosin stain; HGPIN: High-Grade Prostatic Intraepithelial Neoplasia; PSA: Prostate Specific Antigen; TTF1: Thyroid transcription factor 1; WHO: World Health Organization

Acknowledgements
None.

Authors’ contributions
DAA conceived the idea. DAA was the major contributor to the writing of the manuscript. DAA and MFS diagnosed the case. MSF was a major contributors for critically revising the manuscript for important intellectual content. The authors read and approved the final manuscript.

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Funding
This work has no funding sources.

Availability of data and materials
Supplementary data is available upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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