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ORIGINAL ARTICLE

Small cell-like glandular proliferation of prostate: a rare lesion not related to small cell prostate cancer

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Abstract Small cell-like change (SCLC) is a rare prostate lesion which has been described in only two previous studies (total of eight cases). Its relation to possible neuroendocrine differentiation remained unclear. We evaluated 11 SCLC cases with immunohistochemistry and electron microscopy. SCLC was characterized by crowded hyperchromatic small nuclei with scant cytoplasm, rosette-like structures, finely granular chromatin with indistinct nucleoli, and lack of mitoses, apoptoses, and necroses. In nine cases, SCLC was admixed with high-grade cancer, and in two cases, it represented a separate intraductal process, spatially remote from a low-volume Gleason score 6 (grade group 1) cancer. Only 2/11 SCLC labeled for synaptophysin, chromogranin, and serotonin, although 6/11 were at least focally positive for TTF1. Staining for NKX3.1 and pancytokeratin was typically weak, focal, and markedly reduced compared to the adjacent cancer. SCLC was positive for ERG in 1/8 and for racemase in 6/10 cases, again typically in a focal and weak fashion. There was no immunoreactivity with CD56, p63, or HMWCK. Ki-67 highlighted only rare nuclei (<1 %). No neuroendocrine granules were demonstrated by electron microscopy in four cases that showed no immunoreactivity for neuroendocrine markers. In summary, SCLC is more frequently found in high-grade prostate cancer, but it may also be encountered as a noninvasive lesion in Gleason score 6 (grade group 1) cancer. Importantly, it does not appear to indicate neuroendocrine differentiation. The low-grade cytology, the lack of mitoses and apoptoses, and the minimal Ki-67 reactivity are findings to support its discrimination from a small cell carcinoma.

Keywords Prostate · Cancer · Intraductal · Small cell-like

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Introduction

The accumulated pathologic and clinical knowledge of small cell carcinoma of prostate supports its distinct profile in the classification of primary prostate cancer (PCa). Small cell carcinoma has been primarily characterized by its neuroendocrine differentiation and its aggressive nature [1, 19, 22]. Recently, it appears that there is an increasing recognition, resulting in increasing incidence of this type of carcinoma of the prostate, particularly in men who have undergone prior androgen deprivation treatment for high-grade PCa [15, 22]. The treatment of small cell carcinoma differs from that of usual PCa and requires adding platinum-based chemotherapy to resection and/or radiation [19]. Thus, both overdiagnosis

and underdiagnosis are critical in avoiding overtreating patients with modalities resulting in significant morbidity or undertreating a highly aggressive malignancy. Small cell carcinoma of the prostate is not assigned a Gleason grade in current practice, in contrast to Gleason's original suggestion to interpret it as pattern 5 [3, 5, 9].

Small cell-like change (SCLC) is an unusual and rare prostatic glandular proliferation. SCLC has been described in only two previous reports [12, 17]. The initial description by Reyes et al. suggested an unusual histologic type of high-grade prostatic intraepithelial neoplasia (HGPIN) [17], but subsequently it has been described as a ductal lesion in association with PCa and even in specimens without an invasive PCa [12]. However, this lesion and its relationship with PCa remain poorly understood and its significance has not been addressed in the most recent 2014 International Society of Urological Pathology (ISUP) recommendations and contemporary grading system of PCa [3, 4, 12, 17]. In this report, we studied SCLC in 11 PCa cases and conducted a detailed immunohistochemical and ultrastructural analysis in order to better characterize this lesion and clarify its nature.

Materials and methods

We studied 11 patients who demonstrated PCa and SCLC and who underwent radical prostatectomy (n = 7), cystoprostatectomy (n = 1), and prostate biopsy (n = 3). The cases were identified through a search of the files of high volume urologic pathology practices from four academic centers. SCLC lesion was characterized by distinct areas of small cell-like formations demonstrating morphology resembling HGPIN, intraductal carcinoma (IDC-P), or invasive PCa according to previously published descriptions [12, 17]. PCa was graded according to the 2014 ISUP modification of Gleason grading system and assigned a corresponding grade group [3, 9, 16]. Unstained slides from one representative block with SCLC were subjected to immunohistochemistry panel evaluation at the University of Miami Miller School of Medicine or at the participating institutions (Table 1). To examine the possibility of neuroendocrine differentiation in SCLC, we additionally performed electron microscopy on formalin-fixed, paraffin-embedded tissue in four samples with SCLC that did not stain for neuroendocrine markers using a method described by Wang and Minassian [21]. In brief, the areas of interest were identified on H&E slides and were matched to the corresponding paraffin blocks. Under a dissecting microscope, these areas were cut out and placed into glass vials with 100 % xylene. After overnight xylene exposure and rehydration, the tissue was fixed for 1.5 h in glutaraldehyde fixative. After post fixation with osmium tetroxide and staining with uranyl acetate, the tissue was infiltrated with propylene oxide epoxy mixture and embedded in pure epoxy. Thin sections were stained with lead citrate and examined with a transmission electron microscope. One case was studied ultrastructurally at the Massachusetts General Hospital (MKS) and three cases at the Henry Ford Hospital (SRW).

Results

The clinicopathological features and the immunohistochemical profile of 11 patients with SCLC are summarized in Table 2. In six prostatectomies, SCLC was seen within PCa nodules with Gleason score 3 + 4 = 7 (grade group 2) (n = 1), 4 + 3 = 7 (grade group 3) (n = 3), and 4 + 5 = 9 (grade group 5) (n = 2) PCa. In three needle biopsies, SCLC was present in the cores with Gleason score 3 + 4 = 7 (grade group 2) (n = 1), 4 + 3 = 7 (grade group 3) (n = 1), and 5 + 4 = 9 (grade group 5) (n = 1) PCa. In two patients who underwent radical prostatectomy and cystoprostatectomy, SCLC was seen in the ducts remote from the low-volume Gleason score 3 + 3 = 6 (grade group 1) PCa.

SCLC demonstrated similar morphology, both in cases where it was admixed with and where it was seen separated from the PCa, involving the central parts of larger, cribriform glandular formations. At low-power magnification, the central aspects of the proliferations were filled with dark-blue smaller cells, forming rosette-like or cribriform structures (Figs. 1a–f and 2a). Peripheral cleft-like spaces separated the SCLC from the usual-appearing, larger neoplastic cells. At higher power magnification, the lack of cytoplasm was easily appreciated in the SCLC (Figs. 2b). In contrast to the larger cells with prominent nucleoli characteristic of usual PCa carcinoma, SCLC was composed of noticeably smaller and hyperchromatic monomorphic nuclei (typically two to three times smaller than the usual PCa nuclei). The cells of SCLC were densely packed, mimicking the molding effect seen in small cell carcinoma. However, no mitosis, apoptosis, or necrosis was seen in these areas. The chromatin was finely granular without the presence of easily identifiable nucleoli; however, small indistinct nucleoli were only seen at a very high-power magnification (Fig. 2b).

The immunohistochemistry results were comparable between the cases. Ki-67 nuclear labeling index was minimal, with either occasional positive cells or no labeling at all (Fig. 2c). Although pancytokeratin and NKX3.1 showed focal positivity in the SCLC foci, the staining intensity was much lower, typically involving only rare and scattered cells, compared to the strong and diffuse staining seen in the usual appearing carcinoma and in the benign prostate glands (Fig. 2d). Similarly, the racemase staining was also quite focal and weak, compared to the usual appearing carcinoma (Fig. 1b, d, f). TTF1 showed quite variable expression and labeled from 0 up to 90 % of the nuclei in SCLC admixed with invasive high-grade cancer. In the two cases of SCLC

Table 1 Description of antibodies

Antibody	Clone	Dilution	Manufacturer
PIN-4	13H4-34BE12-D5/16	RTU	Dako and BIOCARE
Synaptophysin	27G12	RTU	Leica
Chromogranin A	5H7	RTU	Leica
Ki-67	MM1	RTU	Leica
TTF1	SPT24	RTU	Leica
NKX3.1	Polyclonal	1:25	BIOCARE
Serotonin	Polyclonal	RTU	Leica
Cytokeratin cocktail	34BE12-AE1/3-CAM	1:50/1:200/1:1500	Dako/Becton Dickinson
ERG	EP111	RTU	Dako
CD56	CD564	RTU	Leica

RTU ready to use (prediluted by manufacturer)

spatially remote from the Gleason score 3 + 3 = 6 (grade group 1) PCa, the labeling for TTF1 involved 5–10 % of the nuclei (Fig. 2e). In two cases (cases 1 and 7), the usual-appearing PCa also focally labeled positively for TTF1. All of the studied lesions were negative for CD56. Only 2 of 11 (18 %) cases exhibited positive staining for synaptophysin, chromogranin A, and serotonin (Fig. 2f). In six of nine (67 %) cases of SCLC adjacent to high-grade cancer (cases 1, 3, 5, 7, 9, and 11), there were foci of usual-appearing PCa that labeled for neuroendocrine markers. ERG protein immunoreactivity was present in one SCLC case, which was similar to the reactivity in the usual-appearing PCa in the same case. In the other seven cases that were evaluated, neither the SCLC nor the usual-appearing PCa was labeled for the ERG protein.

Electron microscopy performed in four specimens (cases 1, 4, 5, and 7) did not reveal the typical neuroendocrine granules, which are expected in cases with neuroendocrine differentiation. Other cytoplasmic organelles such as mitochondria, endoplasmic reticulum, and nuclear constituents were well visualized. As expected, the cells with SCLC exhibited less voluminous cytoplasm, but there was more apparent wrinkling and irregularities of the nuclear membranes.

Discussion

In this study, we demonstrate that SCLC, which is an infrequent lesion seen in PIN-like or cribriform glandular formations, which are often admixed with PCa, does not demonstrate features suggestive of neuroendocrine differentiation or small cell carcinoma of the prostate. Thus, we confirm that this lesion should not be considered as part of the spectrum of small cell carcinoma of the prostate. At low-power magnification, the morphology of small cell-like change is notably distinct and easily catches the attention on visual examination. Similarly, at high-power magnification, there is minimal cytoplasm, and in all cases of SCLC in this study, there were prominent rosette-like structures, rather than solid sheet growth, which is more typical of small cell carcinoma. SCLC also did not demonstrate mitoses, apoptotic cells, or necrosis. In 2 of 11 cases, SCLC was seen spatially separated from a low-volume Gleason score 3 + 3 = 6 (grade group 1) disease, which would qualify for insignificant PCa [8, 10]. In a series by Lee et al., in a cystoprostatectomy case with HGPIN and a biopsy case with IDC-P, SCLC was even recorded without invasive carcinoma. Thus, it appears that SCLC can be seen in a wide spectrum of scenarios spanning from HGPIN to IDC-P seen in PCa with low and high Gleason score. Consequently, it is important to recognize that this pattern does not represent a form or a variant of small cell carcinoma (or small cell carcinoma differentiation), particularly in limited biopsy specimens.

SCLC represents a rare proliferation, which indeed may be erroneously misdiagnosed as small cell carcinoma of the prostate. Unlike the ominous prognosis of the latter, the clinical significance of SCLC is currently unknown, but likely does not indicate adverse clinical significance other than the one conveyed by the standard PCa pathological parameters, most notably the cancer grade and the stage. Although most of the observed SCLC lesions in this study were part of high-volume high-grade PCa, in two cases, SCLC lesions were found spatially separate from the coexisting low-volume low-grade PCa. One prior study has correctly suggested that such areas should not be graded, in contrast to the rest of the PCa, which should have a Gleason score assigned [12]. Indeed, only two previous studies have addressed the SCLC. Reyes et al. described unusual variants of HGPIN in 1997 and illustrated this finding as "small cell neuroendocrine HGPIN" in a single case in their series [17]. In their experience, SCLC expressed neuroendocrine markers immunohistochemically and the ultrastructural analysis of that case demonstrated neurosecretory-type granules. Although Reyes et al. demonstrated immunohistochemically presence of basal cells in the SCLC in their case and labeled it as HGPIN, the analysis of the illustrated photomicrographs reveals expanded ducts filled with dense cribriform proliferations, amidst areas of high-

Table 2 Patient characteristics and small cell-like change immunoprofile

Case #	Age	Specimen	Morphologic pattern	Synaptophysin	Chromogranin A	Ki-67	TTF1	NKX3.1	Serotonin	Cytokeratin cocktail	ERG	CD56	PIN-4		
													Racemase	p63	HMWCK
1	64[a]	RP	IDC-P, PCa	−	−	<1 %	+	+(d)	−	+(d)	+	−	+	−	−
2	81[b]	RCP	IDC-P	+	+	0 %	+	+(d)	+	+(d)	−	−	+	−	−
3	61[a]	RP	IDC-P, HGPIN	+	+	<1 %	+	+(d)[c]	+	+(d)	−	−	n/a	n/a	n/a
4	66[a]	RP	IDC-P	−	−	<1 %	−	+(d)	−	+	−	−	+	−	−
5	64[a]	RP	IDC-P	−	−	<1 %	−	+(d)	−	+(d)	−	−	+	−	−
6	67[b]	RP	PIN	−	−	0 %	+	+	−	+	−	−	−	−	−
7	44[a]	RP	IDC-P	−	−	<1 %	+	+(d)	−	+(d)	−	−	+	−	−
8	71[a]	RP	IDC-P, HGPIN	–[c]	–[c]	0 %[c]	+[c]	+(d)[c]	–[c]	+(d)[c]	n/a	–[c]	–[c]	–[c]	–[c]
9	68[a]	Bx	IDC-P	−	−	0 %	−	+	−	+	−	−	+	−	−
10	67[a]	Bx	IDC-P	–[c]	–[c]	0 %[c]	–[c]	n/a	–[c]	+(d)[c]	n/a	n/a	–[c]	–[c]	n/a
11	74[a]	Bx	HGPIN	–[c]	–[c]	<1 %[c]	–[c]	n/a	–[c]	+(d)[c]	n/a	–[c]	–[c]	–[c]	–[c]

RP radical prostatectomy, *RCP* radical cystoprostatectomy, *Bx* biopsy, *HMWCK* high molecular weight cytokeratin, *IDC-P* intraductal carcinoma of the prostate, *PCa* invasive prostatic adenocarcinoma, *HGPIN* prostatic intraepithelial neoplasia, *n/a* not available, (*d*) decreased stain intensity and extent compared to usual acinar carcinoma and benign prostate glands

[a] Small cell-like change in invasive and/or intraductal carcinoma

[b] Small cell-like change in ducts spatially remote from Gleason score 3 + 3 = 6 cancer

[c] Stain performed at the original institution

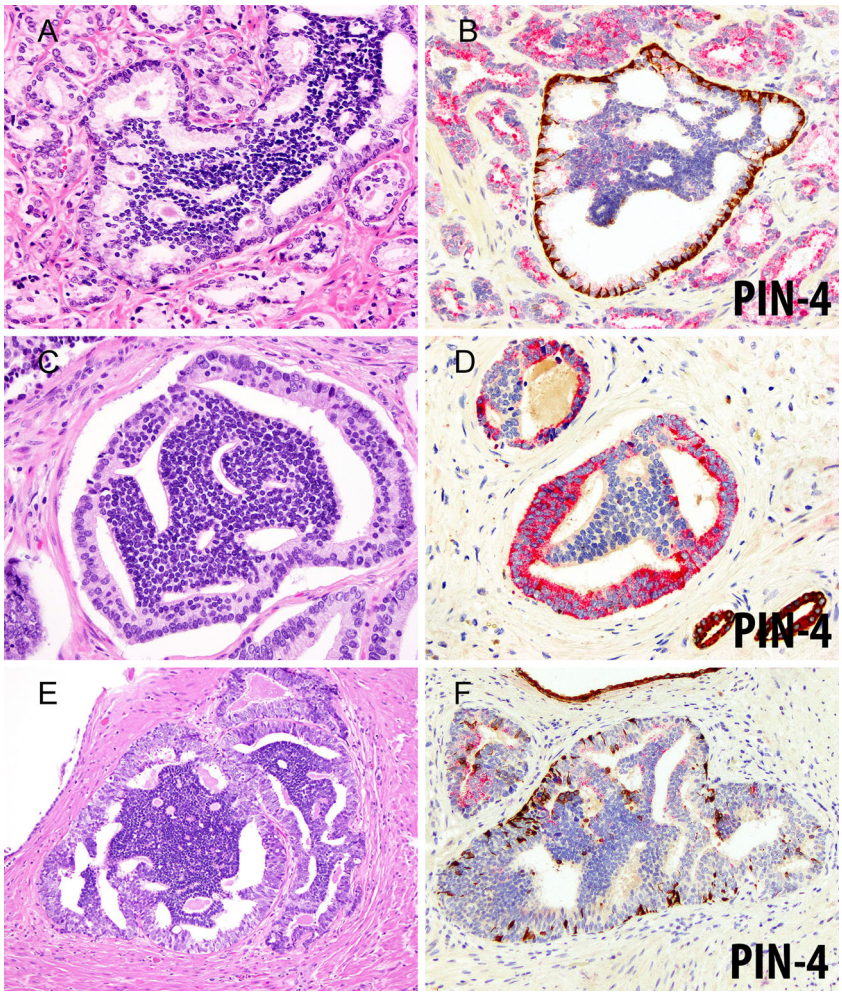

Fig. 1 **a** Small cell-like change (SCLC) in intraductal carcinoma adjacent to invasive acinar carcinoma with corresponding PIN-4 immunostain (**b**). **c** SCLC in invasive carcinoma confirmed by PIN-4 immunostain (**d**). **e** Low-power magnification of a duct spanning SCLC remote from a low-volume Gleason score 3 + 3 = 6 (grade group 1) acinar adenocarcinoma with corresponding PIN-4 immunostain (**f**)

grade cancer. In a more recent study in 2013, Lee et al. interpreted these findings as IDC-P and we concur with their interpretation [12]. This terminological discrepancy between the studies may be explained by the fact that the contemporary criteria for IDC-P were published nearly 10 years later after Reyes et al. report [6]. Lee et al. described seven cases from an expert consultation service, demonstrating SCLC in HGPIN, IDC-P, and invasive carcinoma [12]. In six of seven cases in this series, SCLC was negative for neuroendocrine markers, such as synaptophysin and chromogranin, but EM evaluation was not performed. They interpreted the constellation of the morphologic and the immunohistochemical features against true neuroendocrine differentiation. The authors also commented on the presence of SCLC in two cases associated with HGPIN—one admixed with IDC-P and invasive cancer and another showing only HGPIN in a cystoprostatectomy for urothelial carcinoma.

Two cases in our study in which SCLC was spatially remote from low-volume Gleason score 3 + 3 = 6 (grade group 1) disease deserve separate discussion. In one case, SCLC qualified as IDC-P because of the dense cribriform growth and distention of the preexisting ducts (case 2, using the criteria by Go and Epstein) [6]. In the other case, SCLC was quite limited and showed no duct expansion and likely it would have been better described as HGPIN (case 6). There was no high-grade cancer in both cases, in contrast to the other examples of IDC-P [6]. Neither necrosis nor high-grade cytology was a part of SCLC in these cases, similar to the cases admixed with higher grade PCa. IDC-P in usual-appearing tumors is thought to represent a spread of high-grade PCa within preexisting ducts, and therefore, it would be expected to label with the usual PCa markers (e.g., NKX3.1 or racemase). However, IDC-P with SCLC in our and Lee et al. series had only architectural features (i.e., dense cribriform proliferations expanding the preexistent prostatic ducts), but not cytological or immunohistochemical findings of usual-appearing IDC-P. Finally, SCLC in these two cases was ERG-negative. Morais et al. recently characterized a sequential change in ERG expression and PTEN loss in IDC-P and invasive cancer, concluding that ERG expression is the first molecular change in IDC-P [14]. Therefore, one possibility is that these spatially remote foci of SCLC in cases with Gleason score 6 (grade group 1) disease could represent *precursor-like* IDC-P lesions [13]. This is postulated solely based on the

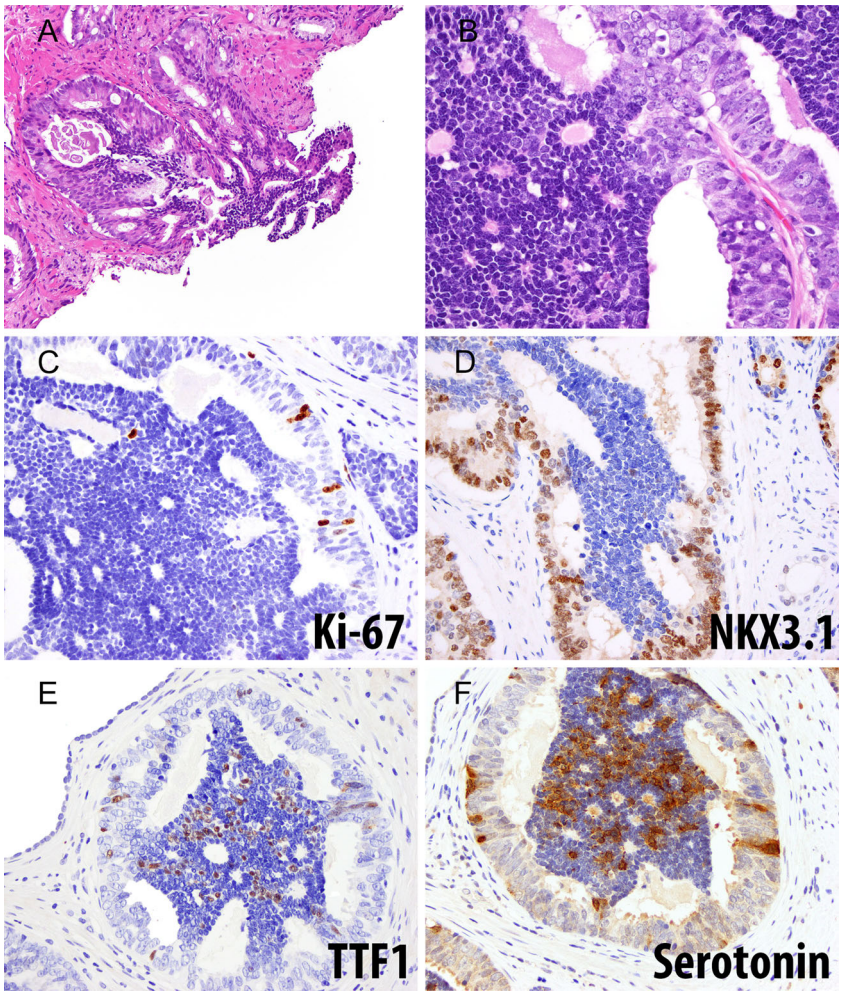

Fig. 2 **a** Small cell-like change (SCLC) in intraductal carcinoma on needle biopsy confirmed by PIN-4 stain (not shown). **b** Monomorphic cells of SCLC arranged in sheets with rosette-like structures without noticeable mitoses or apoptoses. Contrast with usual neoplastic cells is obvious. **c** Ki-67 nuclear labeling index of <1 % in small cell-like change. **d** Prostate-specific marker NKX3.1 is nearly absent in this focus of SCLC. **e** SCLC with patchy TTF1 immunoreactivity. **f** SCLC with serotonin immunoreactivity

architectural pattern of the SCLC. These intraductal foci were however ERG-negative, which argues against the possibility of intraductal spread of cancer. As only a subset of IDC-P is ERG-positive, the significance of ERG-positive HGPIN remains currently debated [7].

We also performed electron microscopy in four cases of SCLC that did not label for neuroendocrine markers immunohistochemically. Although we used formalin-fixed, paraffin-embedded tissue, and no fresh tissue was available for electron microscopy, we have used this method in the past with good results in visualization of microstructures (e.g., thanatosomes) [11]. We did not identify any evidence of neuroendocrine differentiation at ultrastructural level in SCLC. In two cases positive for synaptophysin, chromogranin, and serotonin, and negative for CD56, the SCLC focus was either too small to perform electron microscopy (case 2) or exhausted for prior diagnostic evaluation (case 3). Taken together with the immunohistochemical and ultrastructural findings, our results argue against the classification of SCLC as a neuroendocrine lesion, despite the focal positivity for a subset of neuroendocrine markers and TTF1. This staining pattern remains difficult to fully explain, but may be analogous to the usual PCa, for which labeling for neuroendocrine markers may be documented without a true small cell carcinoma morphology, with unknown clinical significance [1].

It is important to distinguish between SCLC and true small cell carcinoma of the prostate, which was originally described by Wenk et al. in 1977, in a report of PCa with ectopic ACTH production [23]. Small cell carcinoma of prostate demonstrates a frequent history of prior therapy for usual acinar prostatic carcinoma, particularly androgen deprivation [15]. Therefore, a growing number of men with long-term follow up after treatment of earlier-detected PCa, and likely with improved recognition, contribute to an increased incidence of small cell carcinoma in contemporary patients. Mechanisms of its development remain incompletely understood; however, one hypothesis is that small cell carcinoma may represent "escape" of a subpopulation of cells with neuroendocrine differentiation during the course of androgen deprivation treatment [15]. Rendering the diagnosis of small cell carcinoma rests primarily on histologic features [1, 2, 15, 22]. The criteria for diagnosing small cell carcinoma of the prostate

are not different from small cell carcinoma in the other organs. These include dense crowded proliferation of cells with scant cytoplasm, indistinct cell borders, *large* nuclei with "salt and pepper" speckled chromatin, and inconspicuous nucleoli. Frequently encountered and sought after findings include numerous mitoses and apoptotic cells. Although classic Gleason grading regarded small cell carcinoma as pattern 5, small cell carcinoma is not assigned a Gleason pattern in the contemporary practice [3, 5, 9].

The immunoprofile of small cell carcinoma shows reactivity for one or more neuroendocrine markers (e.g., CD56, chromogranin A, synaptophysin), but prostate-specific markers (e.g., PSA, NKX3.1, prostein) are often lacking or minimally preserved [18, 22, 24]. The Ki-67 nuclear labeling index is usually above 90 % of the cells. Mitoses and apoptotic cells are not as common in high-grade acinar adenocarcinoma as compared to small cell carcinoma. It should be specifically noted that high-grade acinar PCa may exhibit some labeling for neuroendocrine markers, as seen in our cohort of high-grade cancers (67 %, 6/9) [1]. For such cases in our practice (typically when immunohistochemistry is performed elsewhere), we comment that this is not a rare finding and that its significance is unknown. Most importantly, the immunohistochemical labeling for neuroendocrine markers by itself is *not sufficient to establish a* definitive diagnosis of small cell carcinoma. Thus, Ki-67 and TTF1 are among the markers most useful for the diagnosis of small cell carcinoma in conjunction with the appropriate morphology [2]. A recent study suggested loss of cyclin D1 expression may also represent a useful marker in identifying prostatic small cell carcinoma [20].

In addition to differential diagnosis with a small cell carcinoma, intraductal spread of urothelial carcinoma could be considered. By H&E light microscopy, SCLC is characterized by the presence of usual appearing prostatic glandular neoplastic cells surrounding a central cluster of cells with SCLC. Intraductal spread of urothelial carcinoma typically has only sparse atrophic prostatic cells surrounding it. Immunohistochemically, our and prior studies demonstrated that although SCLC often has a decreased expression of pancytokeratin and prostatic markers (e.g., NKX3.1), it does not express markers typically seen in urothelial carcinoma (e.g., p63, HMWCK). Ki-67 nuclear labeling index is also higher in urothelial carcinoma, particularly high-grade tumors.

Potential limitations of this study include its retrospective and multiinstitutional nature and the limited number of cases included, as well as the incomplete patient follow-up. Despite this being the largest series of these unusual cases reported to date, it would still have been difficult to identify the clinical significance of SCLC as other confounding variables, such as Gleason score (grade group), stage, and tumor volume significantly varied between the patients and may have had a stronger influence on the observed outcomes.

In summary, SCLC is a rare lesion that can be seen in a spectrum of preneoplastic and neoplastic prostate conditions ranging from intraductal proliferations unassociated with invasive cancer to IDC-P and high-grade cancer. Low-grade cytology and lack or minimal Ki-67 nuclear labeling index support its discrimination from true prostatic small cell carcinoma. It appears that its underlying pathogenetic mechanism is not related to neuroendocrine differentiation, and, therefore, the focal expression of TTF1, the decreased immunoreactivity with prostatic and epithelial markers, and the limited positivity for neuroendocrine markers in some cases should not be considered as evidence of small cell carcinoma differentiation. Although it remains speculative if per se SCLC imparts any clinical significance, we believe that its presence should be documented and that the usual-appearing adenocarcinoma should be graded in this infrequent scenario, by assigning a Gleason pattern combination with a corresponding grade group. This is particularly important for limited biopsy specimens, as SCLC can be occasionally seen in cases with low-volume and low-grade (insignificant) disease.

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