Morphologic Spectrum of Neuroendocrine Tumors of the Prostate
An Updated Review

Jing Hu, MD, PhD; Bo Han, MD, PhD; Jiaoti Huang, MD, PhD

Context.—The incidence of neuroendocrine tumors of the prostate increases after hormonal therapy. Neuroendocrine tumors possess a broad spectrum of morphologic features and pose challenges in the pathologic diagnosis and clinical management of patients.

Objective.—To present a brief updated summary of neuroendocrine tumors of the prostate with an overview of their histopathologic and immunohistochemical profiles and differential diagnoses.

Data Sources.—Literature review, personal experience in the daily practice of pathologic diagnosis, and laboratory research.

Conclusions.—Our understanding of neuroendocrine tumors of the prostate classification and diagnosis continues to evolve. These advances benefit the risk stratification and management of prostate cancer.

Prostate cancer (PCa) is the most common noncutaneous malignancy and the fifth leading cause of death in men worldwide, with 1,276,106 new cases and 358,989 deaths estimated in 2018.1 Histologically, the majority of PCas are classified as acinar type (conventional) adenocarcinoma, composed of tumor cells with luminal differentiation including the expression of prostate-specific antigen (PSA) and androgen receptor (AR).2 In contrast, neuroendocrine (NE) tumors of the prostate are rare.3 In 2016, the World Health Organization reclassified prostatic NE tumors into 5 groups as follows: usual adenocarcinoma with NE differentiation, adenocarcinoma with Paneth cell–like NE differentiation, carcinoid tumor, small cell NE carcinoma (SCNC), and large cell NE carcinoma (LCNC).4

Neuroendocrine tumors of the prostate can arise de novo but much more commonly occur after androgen deprivation therapy for prostate adenocarcinoma.5 So far, androgen deprivation therapy remains the frontline treatment for patients with advanced and metastatic PCas.6 However, patients invariably relapse with the more aggressive castration-resistant PCAs.7 Notably, most cases of castration-resistant PCAs have morphologic features of adenocarcinoma, and AR signaling is still active and critical at this stage of the disease. Based on this notion, newer agents have been developed to inhibit intratumoral androgen synthesis (eg, abiraterone) or more effectively inhibit AR signaling (eg, enzalutamide). Despite their proven efficacy, resistance to these drugs occurs quickly, and more importantly, a significant portion of the patients with late-stage castration-resistant PCAs eventually develop highly aggressive NE tumors, most of which are classified as SCNC.2

At present, morphology remains the gold standard for pathologic diagnosis of NE tumors while immunohistochemical (IHC) studies are contributory in certain cases. Although the 2016 World Health Organization classification has provided an excellent framework for the diagnosis of NE tumors of prostate, these tumors still pose diagnostic challenges for pathologists because of their subtle morphologic features and variations within each of the entities.

NE CELLS IN BENIGN PROSTATE

The epithelial components of prostate glands include 2 main types of epithelial cells: luminal cells and basal cells, which can be easily identified and distinguished using light microscopy.8 A third and minor cell type, the NE cells, is also present in prostate glands.9 Neuroendocrine cells comprise no more than 1% of the total epithelial cell population and are scattered as individual cells or small nests among the more abundant basal and luminal cells. Two types of NE cells can be identified ultrastructurally: the open type and the closed type.8 The open-type NE cells have cell bodies that extend to the glandular lumen, whereas the closed type rest on the basal cell layer and are not in contact with the glandular lumen. Neuroendocrine cells in mice are enriched in the proximal prostatic urethra but are usually...
not found in the main portions of the prostate lobes. In human prostate, the transition zone and peripheral zone have more abundant NE cells than the central zone, suggesting their potential involvement in benign prostatic hyperplasia and PCs, respectively. Neuroendocrine cells cannot be easily identified on hematoxylin-eosin–stained sections but are identifiable by electron microscopy. Ultrastructurally, the NE cells show elongated cell bodies, with dendritelike branches extending between other epithelial cells, and intracytoplasmic dense-core secretory granules. Immunohistochemistry is a more practical method to highlight NE cells in prostate glands. Neuroendocrine cells do not express luminal differentiation markers AR or PSA and are positive for NE markers including chromogranin A (CgA), synaptophysin (SYN), and neural cell adhesion molecule 1 (CD56).

The function of NE cells in the prostate is largely unknown. Immunohistochemical studies also have identified a variety of products in these cells including serotonin, histamine, CgA, calcitonin, neuron–specific enolase, and neural cell adhesion molecule 1. These products may participate in the regulation of the prostate epithelium and sperm function.

**USUAL PROSTATE ADENOCARCINOMA WITH NE DIFFERENTIATION**

The term usual prostate adenocarcinoma with NE differentiation refers to cases of typical adenocarcinoma (Figure, A), acinar or ductal type, in which focal NE cells are appreciable by IHC stains (Figure, B). Histologically, prostate adenocarcinoma is composed of neoplastic proliferation of luminal cells and the loss of basal cells. The number of NE cells varies from case to case, but generally comprises no more than 1% of the entire tumor cell population. As mentioned above, NE cells in adenocarcinoma are not easily identified in hematoxylin-eosin–stained sections, and IHC is usually required. The detection of NE cells depends on the sensitivity and specification of the antibodies against NE markers. Commonly used markers include CgA and SYN. CgA is the most commonly used marker and is considered sensitive and specific. Ultrastructurally, NE cells in PCs are morphologically different from those in normal prostate glands. Normal NE cells usually exhibit irregular dendrite-like processes, whereas NE cells in PCs may lack the typical neuronlike morphology.

It has been reported that the number of NE cells is positively correlated with tumor grade, and is particularly high in patients treated with hormonal therapy. However, the clinicopathologic significance of NE cells in prostate adenocarcinoma is still uncertain. Most studies have not found any prognostic significance of focal NE differentiation. Kardoust Parizi et al analyzed a total of 16 studies and concluded that the prognostic significance of NE tumor cells was weak and not useful clinically. Detection of NE cells by IHC in cases without histopathologic features of NE tumor is not necessary and the diagnostic term of prostate adenocarcinoma with NE differentiation is not recommended.

**ADENOCARCINOMA WITH PANETH CELL–LIKE NE DIFFERENTIATION**

Adenocarcinoma with Paneth cell–like NE differentiation is defined as typical adenocarcinoma of the prostate containing varying proportions of cells with prominent eosinophilic cytoplasmic granules on routine light micros-
more of the NE markers (SYN, CgA, CD56). Thyroid transcription factor 1 (TTF-1) is often positive in SCNC, regardless of the primary site of origin. We and others have reported that SCNCs are positive for CD44, which is rare in adenocarcinoma. We also identified forkhead box A2 (FOXA2) as a sensitive and specific molecular marker that may be extremely valuable in the pathologic diagnosis of SCNC. Most cases of SCNC showed strong expression of FOXA2, whereas only rare cases of adenocarcinoma were positive for FOXA2. A series of publications revealed that serine/arginine repetitive matrix 4 (SRRM4) promotes adenocarcinoma transition to NE tumors. SRRM4 detection by in situ hybridization is highly sensitive in SCNC.

Despite the unique histologic features and clinical courses of SCNC, SCNC and adenocarcinoma share certain important molecular features. Approximately half of prostate adenocarcinoma cases harbor erythroblast transformation–specific transcription factor (ETS) arrangement by FISH detection. Several studies revealed that a similar proportion of ETS transcription factor ERG (ERG) arrangements exists in SCNC. Importantly, in cases of mixed SCNC with adenocarcinoma, there was perfect concordance with regard to the TMPRSS2-ERG fusion status between the adenocarcinoma loci and the NE loci. These findings suggest that SCNC may share a common origin with adenocarcinoma in cases with mixed histology.

In a previous publication, mixed NE tumors (adenocarcinoma mixed with SCNC, adenocarcinoma mixed with carcinoid tumor, and adenocarcinoma mixed with LCNC) were proposed to be their own separate diagnostic entity: mixed NE carcinoma–acinar adenocarcinoma. In reality, carcinoid tumor and LCNC are exceedingly rare and most of the so-called NE tumors (or NE carcinoma) of the prostate are SCNCs. We prefer the more straightforward term of SCNC and also specify whether it is pure or mixed with conventional adenocarcinoma.

Although most cases of SCNC arise in patients who have been treated with hormonal therapy for prostatic adenocarcinoma, some patients can develop SCNC as a primary tumor in the prostate. De novo SCNC is rare and comprises no more than 1% of PCa cases. Small cell NE carcinoma is...
highly aggressive and often leads to early and multiple visceral metastases. However, the results of our recent clinical study found that there is no preferential metastatic patterns for the 2 histologic types (adenocarcinoma versus SCNC). Hormonal therapy is ineffective in treating SCNC. Chemotherapy has been used with very limited efficacy.

LARGE CELL NE CARCINOMA

Large cell NE carcinoma was newly included as a type of NE tumor of the prostate in the 2016 World Health Organization classification of prostate tumors. This term describes a high-grade tumor that shows NE differentiation but cannot be classified as SCNC. The tumor cells of LCNC grow as solid sheets, ribbons, or nests with focal microscopic necrosis in the center and areas of peripheral palisading. In contrast to SCNC, the tumor cells of LCNC tend to be large, with a polygonal shape and abundant cytoplasm. The nuclei contain coarse chromatin and prominent nucleoli. An electron microscopic study observed abundant cytoplasmic secretory granules. Pure LCNC is extremely rare. Most LCNC cases appear to be mixed NE tumors that also contain a component of adenocarcinoma. Fernandes et al reported a case with mixed small cell carcinoma–LCNC. Tumor cells of LCNC express one or more NE markers (SYN, CgA, or CD56), with variable expression of PSA, PAP, CK7, and CK20. The LCNCs are usually negative for AR, Ki-67 labeling index often exceeds 50%.

High-grade NE carcinoma has a broad spectrum and mainly includes SCNC and LCNC. There are cases with typical morphologic features that can be confidently classified as one of the above 2 entities. However, a more common and more challenging scenario encountered by pathologists in their routine practice is to have cases that are not typical for either entity. It is our belief that interobserver variability leads to additional challenges, as a small subset of patients with PCa die from pure AR-centric NE tumors,5,65,66 but this may underestimate the true incidence. Our recent study of metastatic tumors in patients who have been extensively treated suggest that a subset of patients with PCa die from pure AR-negative NE tumors,5,65,66 but this may underestimate the true incidence. Our recent study of metastatic tumors in patients with metastatic SCNC contains only 7 cases. Only 1 case was otherwise specified.

DEFINING PROSTATE ORIGIN OF METASTATIC SCNC

Neuroendocrine tumors can arise from many different organs and share common morphologic features and molecular alterations irrespective of organ of origin. For example, carcinoid tumors of the prostate are morphologically similar to carcinoid tumors arising in other organs. Similarly, the diagnostic criteria for SCNC of the prostate are identical to those of pulmonary small cell carcinoma. We emphasize that morphology should be the gold standard in the diagnosis of SCNC, the most common form of NE tumors of the prostate. Immunohistochemical study can provide supportive evidence to aid in the diagnosis. However, the diagnosis should not rely upon IHC studies, as there are significant variations from case to case in terms of IHC patterns.

It is generally difficult to determine the origin of metastatic SCNC. Clinical and radiologic findings are usually the most important evidence in determining the primary site of metastatic SCNC. However, expression of CD44 appears to be tissue specific for SCNC. Prostatic SCNC expresses CD44 in a distinct membranous pattern, whereas SCNC of nonprostatic origin is rarely positive for CD44. Expression of AR and PSA in SCNC would also suggest prostate origin, whereas PAP is less useful because it is also expressed in NE tumors of hindgut origin. Genomic rearrangement of the ERG gene occurs with similar frequency (~50% of cases) in adenocarcinoma and SCNC of the prostate. Although negative results are not useful, positive ERG rearrangement by FISH confirms prostate origin.

CHALLENGING ISSUES

The true incidence of SCNC in the recurrent and metastatic setting remains unknown. This is because biopsy is usually not done at this stage of the disease. Tumor heterogeneity leads to additional challenges, as a small biopsy may not represent the entire tumor and many patients have multiple metastases. Autopsy studies suggest that a subset of patients with PCa die from pure AR-negative NE tumors, but this may underestimate the true incidence. Our recent study of metastatic tumors in patients who have been extensively treated suggest that
approximately 17% of such tumors have a SCNC component.

The transformation from adenocarcinoma to SCNC after androgen deprivation therapy is a very intriguing phenomenon. Because adenocarcinoma contains both luminal-type and NE tumor cells, an unresolved but critical issue is to determine if SCNC arises from the former (transdifferentiation) or the latter (clonal expansion). Because it is almost impossible to study this in the tumor tissue of patients longitudinally, most studies have used model systems, and an increasing body of cell culture-, genomics-, and morphology-based studies appears to support the transdifferentiation model. Withdrawal of androgen from the culture media induces reversible NE differentiation of LNCaP cells with morphologic changes and expression of NE markers. Transformation from adenocarcinoma to SCNC after castration of the mouse has been reported in a patient-derived xenograft model.

It was observed that the morphologic transformation is accompanied by gradual loss of luminal transcription signature and a corresponding increase in the NE transcription signature. However, the above findings do not rule out the clonal expansion model. Small cell NE carcinoma often harbors specific genetic alterations such as those involving RB transcriptional corepressor 1 (RB1), P53, and MYCN. We have demonstrated loss of P53 in NE cells as a potential molecular basis for the development of SCNC.

For practicing pathologists, consistent nomenclature in pathology reports is very important in transmitting accurate information to clinicians for proper management. We would like to suggest the following principles: (1) Morphology should always be considered the gold standard in pathologic diagnosis of PCa with NE differentiation. (2) Carcinoid tumor and LCNC are exceedingly rare, and diagnosis of these entities should be made only when a tumor has perfect morphology and IHC profile. (3) Current literature supports the notion that besides conventional adenocarcinoma, SCNC occurs frequently in the recurrent and metastatic setting and may be diagnosed using the same criteria as those used in diagnosing SCNC of other organs. (4) Immunohistochemical studies may help to distinguish between SCNC and high-grade adenocarcinoma in some cases, but their value is generally overstated. (5) Conventional adenocarcinoma often contains scattered NE cells, which vary in abundance from case to case. If a case is morphologically adenocarcinoma, the presence of a NE cell component revealed by IHC staining should not change the diagnosis. The term adenocarcinoma with NE differentiation for such cases is discouraged because it can be mistaken by clinicians as being equivalent to SCNC, which is treated differently. (6) We also think that the commonly used term NE carcinoma is too vague and can be confusing. A pathologist would wonder if this is equivalent to SCNC or whether it is some other high-grade carcinoma with NE differentiation.

In this article, we present a brief update of the well-established entities in the spectrum of NE tumors of the prostate with an overview of their histopathology, IHC characteristics, and differential diagnoses. It is well recognized that a significant number of patients will develop SCNC after failing hormonal therapy; this remains incurable at the moment. Although the clinicopathologic significance of NE tumors of the prostate has come to be better appreciated, a lot more needs to be learned to combat this deadly disease. Future research should integrate morphology, IHC, molecular biology, and genomics as well as clinical and radiologic studies.

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