Neuroendocrine Tumors of the Prostate and Molecular Features

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Introduction

Prostate cancer is the third most common carcinoma among men. According to the American Cancer Society's estimate, 1 in 7 men will be diagnosed with prostate cancer during their lifetime. Prostate cancer is the second leading cause of cancer death in American men, behind only lung cancer. About 1 man in 38 will die of prostate cancer [1]. The World Health Organization (WHO) currently divides neuroendocrine (NE) tumors into conventional prostatic adenocarcinoma, carcinoid tumor (WHO's well-differentiated neuroendocrine tumor), small cell carcinoma, large cell neuroendocrine carcinoma, and paraganglioma. Recently, the working committee for the Prostate Cancer Foundation has proposed a classification of NE differentiation in prostate cancer [2]. According to this committee, the NE differentiation in prostate carcinoma can be divided into usual prostate adenocarcinoma with NE differentiation, adenocarcinoma with Paneth cell NE differentiation, carcinoid tumor, small cell carcinoma, large-cell neuroendocrine carcinoma (LCNEC), and mixed (small or large) NE carcinoma–acinar adenocarcinoma.

Endocrine Differentiation Within Adenocarcinoma

Normal prostate glands contain NE cells randomly scattered within the epithelial cells. On microscopic examination, these are small cells resting on the basal cell layer and in between the secretory cells. These cells may have a bright granular eosinophilic cytoplasm on hematoxylin and eosin staining (Fig. 1). A variety of peptide hormones like serotonin, histamine, chromogranin A, calcitonin, vasoactive

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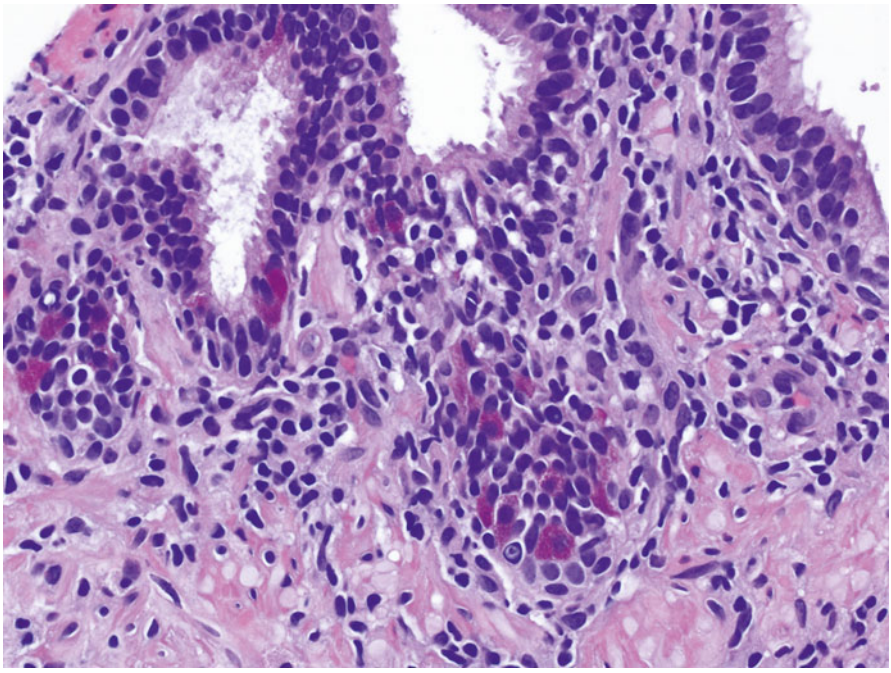

Fig. 1 Benign prostatic glands with scattered neuroendocrine cells having bright, granular eosinophilic cytoplasm

intestinal peptide, and bombesin/gastrin-releasing peptide besides others are secreted by these cells [3–5]. Prostate is the organ in the genitourinary system with the highest number of NE cells.

Usual prostate adenocarcinoma with NE differentiation is defined as the usual acinar or ductal adenocarcinoma of the prostate in which NE differentiation is demonstrated by immunohistochemical (IHC) stains (synaptophysin, chromogranin, and CD56) alone [2]. All prostate cancers can show focal NE differentiation [6, 7]. Majority show only rare or sparse single NE cells demonstrated by NE markers immunohistochemically (Fig. 2). Most of the studies have not shown any prognostic relationship in tumors exhibiting focal NE differentiation [8–10]. Hence, it is not recommended to routinely use IHC stains to detect NE differentiation in a typical prostatic adenocarcinoma.

Carcinoid Tumor

Carcinoid tumor is defined as a well-differentiated NE tumor occurring in the prostate gland that meets the diagnostic criteria for carcinoid tumor elsewhere (Fig. 3). It should not be closely associated with usual prostatic adenocarcinoma and should

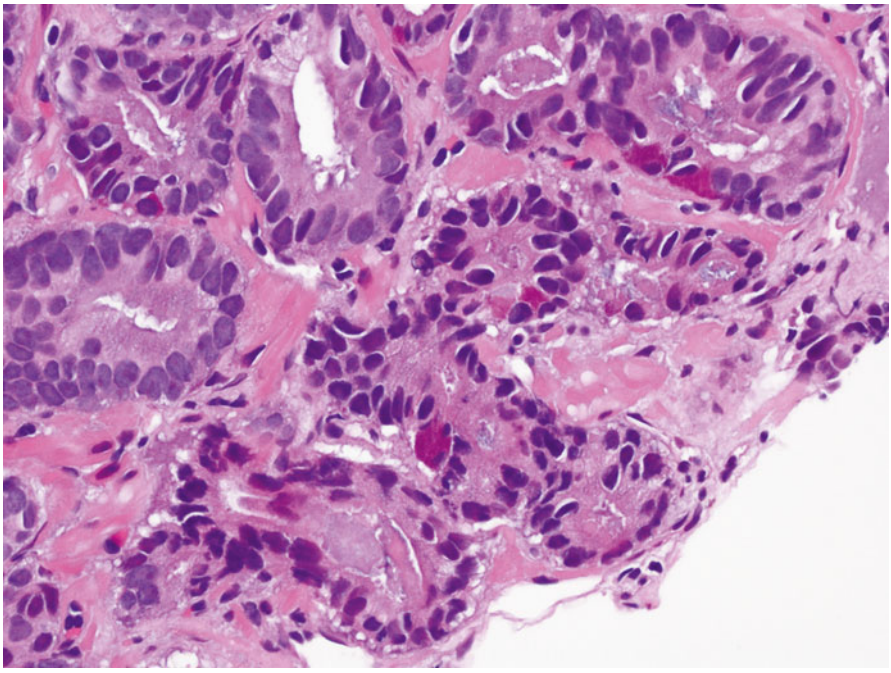

Fig. 2 Prostatic adenocarcinoma, Gleason score 6 (3 + 3) with scattered neuroendocrine cells having bright, granular eosinophilic cytoplasm

not arise from the urethra or extend from the bladder [2]. It is an extremely rare tumor of the prostate gland. These tumors are diffusely positive for NE markers synaptophysin, chromogranin, and CD56 and are negative for PSA (Figs. 4 and 5). Proliferation marker Ki67 is reported to be low (<5–20 %). Carcinoid tumors have to be differentiated from "carcinoid-like tumors" that most commonly include the usual acinar prostatic adenocarcinoma with an organoid appearance and focal neuroendocrine immunoreactivity. The "carcinoid-like tumor" is usually strongly positive for prostate-specific antigen (PSA), whereas carcinoid tumor is negative for PSA. Carcinoid tumors occur in younger patients including children as compared to the prostatic adenocarcinoma patients and may be associated with multiple endocrine neoplasia IIB syndrome [11, 12].

Small Cell Carcinoma

Small cell carcinoma is a high-grade neuroendocrine tumor that is histologically identical to small cell carcinoma of the lung [13]. On microscopic examination, the tumor cells exhibit lack of prominent nucleoli, nuclear molding, crush artifact, high nuclear-to-cytoplasmic ratio, and indistinct cell borders (Fig. 6). There is brisk

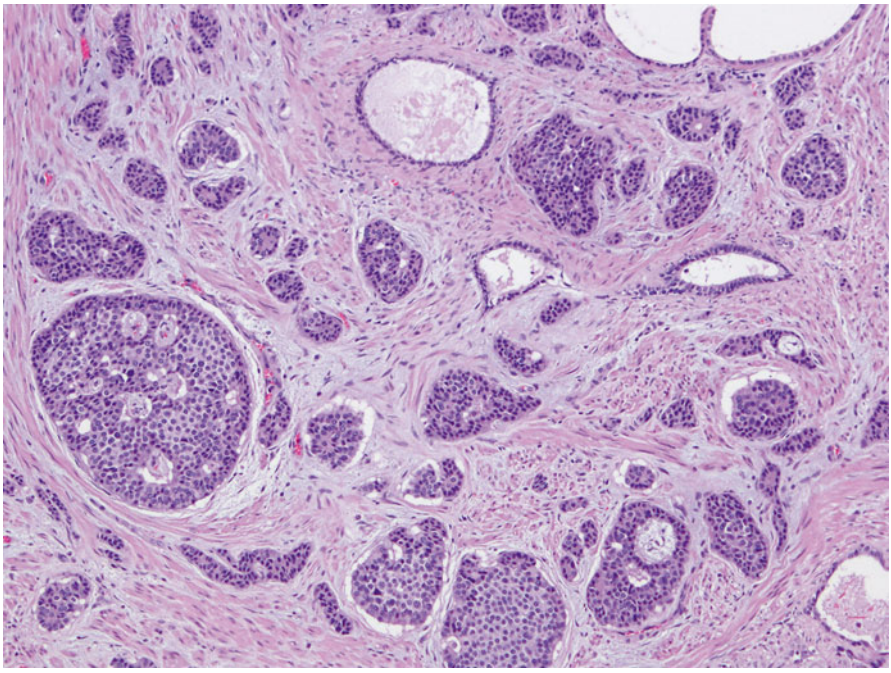

Fig. 3 Carcinoid tumor of the prostate showing tumor cells exhibiting little cytologic variability

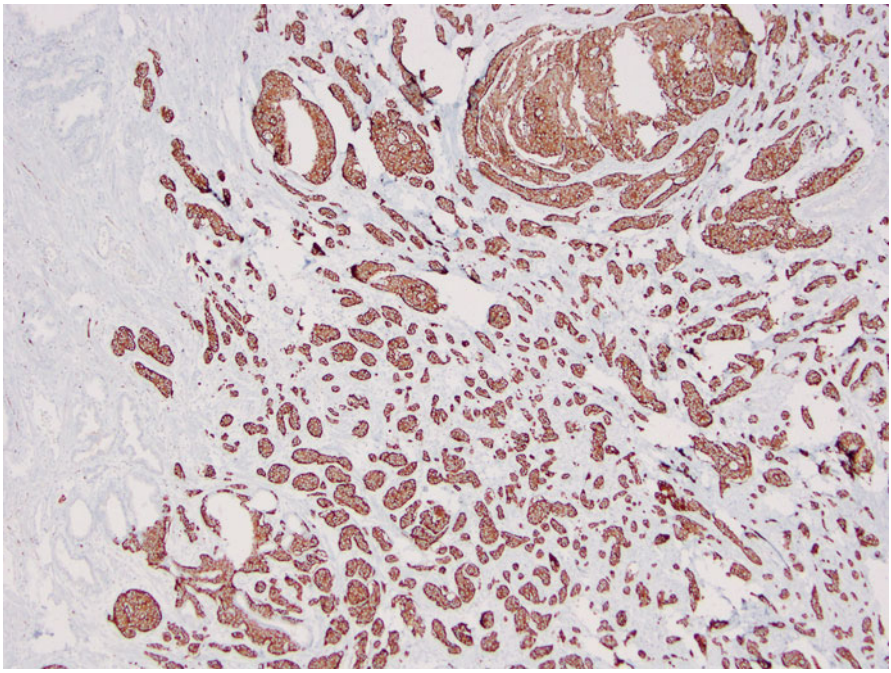

Fig. 4 Synaptophysin with strong positivity in the carcinoid tumor to the right and negative staining in the benign prostate glands to the left

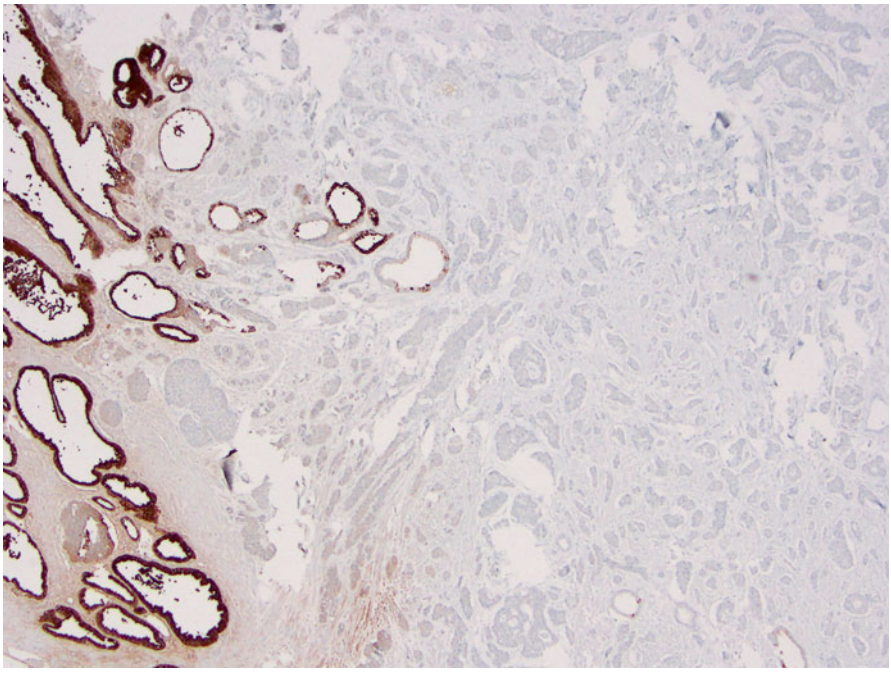

Fig. 5 PSA with no staining in the carcinoid tumor to the right and strong staining in the normal prostatic glands to the left

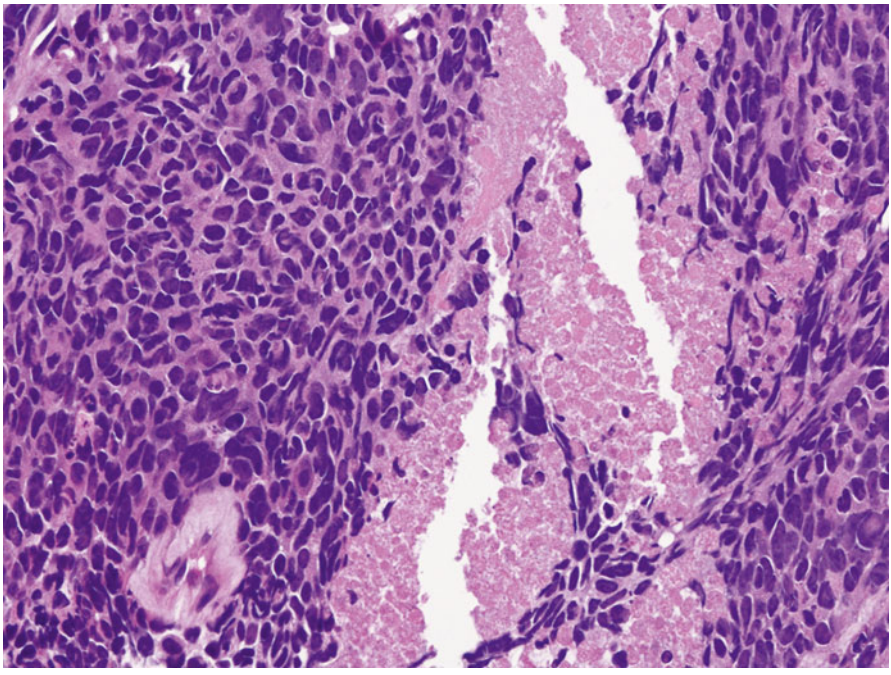

Fig. 6 Small cell carcinoma of the prostate admixed with necrosis

mitotic activity with numerous apoptotic bodies. Proliferation marker Ki67 is usually positive in >80 % of the tumor cell nuclei. Geographic foci of necrosis are frequently present in prostatectomy specimens. Morphologic variations include intermediate cell type with open chromatin and small visible nucleoli, tumor giant cells, and Indian filing [14]. Almost 90 % of the tumors express NE markers synaptophysin, chromogranin, and CD56 [14, 15]. Prostate-specific markers PSA and prostein are positive in about 17–25 % of cases [14, 15]. Immunohistochemical stain TTF1 is reported to be positive in >50 % of cases, making it difficult to distinguish prostate from a lung primary [14–16]. Fluorescence in situ hybridization (FISH) testing for TMPRSS2 and ERG (ETS-related gene) gene fusion is relatively specific for prostatic origin and is present in approximately 50 % of the small cell carcinomas of the prostate [17, 18].

Approximately half of small cell carcinomas have previous history of a hormonally treated acinar prostatic adenocarcinoma. As the small cell component predominates, serum PSA levels fall. Small cell carcinomas account for majority of prostatic tumors with clinical evidence of ACTH or antidiuretic hormone production. Patients with emergence of small cell carcinoma during progression of prostatic adenocarcinoma usually present with visceral metastasis. The median cancer-specific survival of patients with small cell carcinoma of the prostate according to the SEER database from 1973 to 2004 was reported to be 19 months. Two- and 5-year survival rates were reported to be 27.5 % and 14.3 %, respectively [19].

Small cell carcinoma of the prostate is treated aggressively with chemotherapy and radiation. Metastatic small cell carcinoma is treated with platinum-based combination chemotherapy [20, 21].

Paraganglioma

Paragangliomas of the prostate are extremely rare tumors with only seven cases reported in the literature. Paragangliomas are slow-growing usually benign tumors thought to arise from the extra-adrenal chromaffin cells. The tumor is composed of small nests (zellballen) or clusters of round cells surrounded by fibrous trabeculae. The tumor cells have abundant, granular, eosinophilic cytoplasm and are uniform and mostly round. The nuclei have a salt-and-pepper appearance, with occasional nuclear pleomorphism. Histopathological features associated with malignant behavior of the tumor are confluent tumoral necrosis, vascular invasion, capsular invasion, and increased mitotic activity. However, presence of metastases is the only currently widely accepted criterion to define malignant paraganglioma. On needle core biopsies, paragangliomas may be misdiagnosed as prostatic adenocarcinoma due to rarity of these tumors. However, this can be avoided if attention is paid to the morphologic features and utilizing pertinent immunohistochemical stains. Paragangliomas may stain like prostatic adenocarcinoma with PIN4 immunostaining which is a cocktail

of AMACR, p63, and high molecular weight cytokeratin (HMWCK) exhibiting no staining with basal cell markers p63 and HMWCK. However, these tumors are negative for prostate-specific markers like PSA and prostate-specific acid phosphatase and are strongly positive for chromogranin and synaptophysin [22]. Immunostain S100 highlights the sustentacular cells that surround the nests of tumor cells.

Clinical presentation is variable and depends if the tumor is functional or nonfunctional. Functional tumors may present with symptoms of catecholamine overproduction such as hypertension, headaches, sweating, tachycardia, or anxiety. These symptoms may be precipitated by micturition. Nonfunctioning tumors may present with hematuria, obstructive symptoms, or a palpable nodule [23, 24]. Nonfunctioning tumors may not be clinically detected until at advanced stage. Of the reported five cases of nonfunctioning prostatic paraganglioma, two were surgically unresectable. Paragangliomas are treated either surgically or by radiation. Radiation is used as a palliative treatment in bone metastasis.

Adenocarcinoma with Paneth Cell-Like NE Differentiation

The working committee of the Prostate Cancer Foundation has proposed adenocarcinoma with Paneth cell-like NE differentiation as one of the subtypes of prostate cancer with NE differentiation. This tumor subtype is composed of typical adenocarcinoma of the prostate containing varying proportions of cells with prominent eosinophilic cytoplasmic granules on microscopic examination. These Paneth cell-like foci stain positive for NE markers [2]. Paneth cell-like NE differentiation is usually associated with lower-grade conventional adenocarcinoma. The current recommendation of the working committee is not to assign a Gleason score to these tumors and to add a comment to the generally favorable prognosis of this morphologic variant based on the limited data available [25].

Large-Cell Neuroendocrine Carcinoma (LCNEC)

LCNEC is a recently described entity which is included in the recent 4th edition of the WHO classification of the neuroendocrine tumors of the prostate. This is an aggressive, high-grade NE tumor that is composed of large nests with peripheral palisading and large foci of necrosis. The tumor cells have prominent nucleoli, abundant cytoplasm, and a high mitotic rate. Ki67 stains usually >50 % of the tumor cell nuclei. These tumors are diffusely positive for NE markers and usually negative for PSA.

LCNEC of the prostate is rare and usually represents progression from prior typical prostate adenocarcinoma after long-standing androgen deprivation therapy [26]. In a study by Evans et al., patients had a mean survival of 7 months and rapid

metastases. It can also be present in association with small cell carcinoma and prostate adenocarcinoma.

Mixed NE Carcinoma: Acinar Adenocarcinoma

This subgroup is defined by the working committee as a biphasic carcinoma that is composed of a mixture of NE carcinoma (small cell or large cell) and usual conventional acinar adenocarcinoma [2]. Both the components should be distinct and recognizable. Most of the cases encountered are mixed small cell carcinoma–acinar adenocarcinoma where the patients usually have metastatic castration-resistant disease. It is a high-grade and aggressive tumor. The working committee recommends that the percentage and grade of the acinar component be provided when reporting these tumors.

Molecular Features

Approximately half of the usual prostatic adenocarcinomas and small cell carcinomas of the prostate have fusion of the androgen-responsive gene transmembrane serine 2 (TMPRSS2) with ETS-related genes in particular estrogen-regulated gene (ERG), both of which are located on chromosome 21 [17, 18, 27]. This fusion can be detected by fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction. The overexpression of ERG in these cases can also be detected immunohistochemically. However, small cell carcinomas with TMPRSS2-ERG rearrangements are not reliably positive for ERG protein by IHC [17], requiring the use of FISH for confirmation. This fusion when present helps to distinguish small cell carcinoma of the prostate from other small cell carcinomas.

Prognostic value of TMPRSS2-ERG gene fusion is hotly debated with most studies indicating an unfavorable outcome. In prostate cancer, overexpression of ERG and loss of PTEN (phosphatase and tensin) homolog deleted on chromosome 10 are two common events involved in the molecular pathogenesis of this disease [27, 28]. PTEN is a tumor suppressor gene, whose disruption leads to activation of downstream components of the phosphatidylinositol-3-kinase pathway. Besides upregulation of ERG and loss of PTEN, other molecular alterations identified in small cell prostate cancer include loss of androgen receptor (AR) and androgen-regulated protein expression and loss of tumor suppressor genes p53 and RB1. Loss of RB1 may be a useful potential therapeutic target [29]. p53 mutation leads to Aurora kinase A (AURKA) overexpression which is critically important for rapid proliferation and aggressive behavior of small cell prostate cancer and is considered to be a viable therapeutic target [30]. Molecular alterations such as PLK1 upregulation and c-MYC PCDH-PC, EZH2, IL-6, MIF, FAK, Siah2, and c-Kit overexpression in small cell prostate cancer are other potential therapeutic targets.

Abbreviations

AR	Androgen receptor
AURKA	Aurora kinase A
ERG	Estrogen regulated gene
HMWCK	High molecular weight cytokeratin
IHC	Immunohistochemical
LCNEC	Large-cell neuroendocrine carcinoma
NE	Neuroendocrine
PSA	Prostate-specific antigen
PTEN	Phosphatase and tensin
TMPRSS2	Transmembrane serine 2
WHO	World Health Organization

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