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Prostate cancer with Paneth cell–like neuroendocrine differentiation has recognizable histomorphology and harbors *AURKA* gene amplification^{☆, ☆☆, ☆☆☆}

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Summary

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Aurora kinase A (*AURKA*) gene amplification has been documented in 67% of hormone-naïve prostate cancer cases that progress to a highly aggressive variant of castrate-resistant disease, clinically referred to as “neuroendocrine” prostate cancer, “small cell” prostate carcinoma, or “anaplastic” prostate cancer. Therefore, *AURKA* amplification is a potential prognostic biomarker that may help to identify patients with prostate cancer who are at high risk for developing castrate-resistant disease with clinical features of small cell carcinoma. Furthermore, *AURKA* inhibitors are currently being tested in clinical trials. In a previous study, we found *AURKA* amplification in 6 cases of prostate cancer with Paneth cell-like cells. This morphologic pattern has been suggested to represent low-grade neuroendocrine differentiation (NED) with generally favorable prognosis. We sought to investigate the frequency of *AURKA* amplification and the histologic characteristics of prostate cancer with Paneth cell-like NED. Twenty-five cases from 172 prostatectomies were evaluated for the presence of 18 morphologic features and *AURKA* amplification. Most prostate cancers with Paneth cell-like NED had macronucleoli (92%), basophilic appearance (88%), perineural invasion (72%), and nuclear stratification (76%). The frequency of *AURKA* amplification was 45%, present throughout the examined tumor nodule including areas without Paneth cell-like cells. When histologically similar cases with and without *AURKA* amplification were compared, this gene alteration was associated with larger extent of Paneth cell-like NED identified at magnification $\times 20$ ($P = .015$), higher percentage of Paneth cell-like NED throughout the tumor nodule ($P = .033$), ductal features ($P = .02$), and higher overall Gleason grade ($P = .039$). *AURKA* amplification was not associated with age, serum prostate specific antigen, or tumor stage. The high frequency of *AURKA* amplification (45%) in localized prostate cancer with Paneth cell-like NED and its potential prognostic significance warrant further investigation.

Keywords

Paneth cell-like; Neuroendocrine differentiation; *AURKA* amplification; *MYCN* amplification; Prostate cancer

1. Introduction

Primary or de novo small cell carcinoma of the prostate is rare, and most cases present as a component of mixed tumors with conventional adenocarcinoma [1]. In contrast, neuroendocrine differentiation (NED) in prostate cancer is common and increases with tumor grade and stage, especially in the setting of androgen deprivation therapy [1-4]. Shifting toward a neuroendocrine phenotype without androgen receptor signaling is 1 proposed mechanism by which prostate cancer develops resistance to the effects of hormonal therapy [2]. In recent studies, Aurora kinase A (*AURKA*) and N-Myc (*MYCN*) genes have been found to be significantly overexpressed and amplified in a highly aggressive variant of advanced castrate-resistant prostate cancer with NED as well as in their matched hormone-naïve primary tumors [2,5]. This aggressive subtype has been clinically referred to as “neuroendocrine” prostate cancer [2,5,6], “small cell” prostate cancer, or “anaplastic” prostate cancer [7]. The importance of these findings is that *AURKA* and *MYCN* amplifications in prostate cancer may represent prognostic biomarkers of tumors that will progress to a particularly aggressive phenotype after androgen deprivation therapy. Clinical features include rapid progression of the disease with visceral metastases in the setting of

low (< 10 ng/mL) or modestly rising prostate-specific antigen (PSA) and/or elevated neuroendocrine serum markers (chromogranin A > 5× upper limit of normal, neuron-specific enolase (NSE) >2× upper limit of normal) [6,7]. Currently, AURKA inhibitors are being tested in clinical trials for treatment of patients with this variant of advanced castrate-resistant prostate cancer.

In the prostate, the presence of Paneth cell-like cells, which contain eosinophilic cytoplasmic inclusions, has been documented in benign prostatic glands, prostatic intraepithelial neoplasia, and prostate cancer [8]. These distinct cells express neuroendocrine markers and lack lysozyme [8]. Although they do appear histologically more like intestinal neuroendocrine cells and not like intestinal Paneth cells, the term *prostate cancer* with “Paneth cell-like” change or NED has long been used [9,10]. Based on 1 study, it has been suggested that prostate cancer with Paneth cell-like NED has relatively favorable prognosis, and Gleason score should be assigned only to areas of conventional adenocarcinoma [11]. However, long-term follow-up is lacking in most cases, and histologic and molecular characterization of prostate cancer with Paneth cell-like NED has not been methodically performed. In light of recent molecular advances in prostate cancer, in particular, the discovery of potential prognostic biomarkers of aggressive disease, we sought to investigate *AURKA* and *MYCN* amplifications and morphologic features of prostate cancer with Paneth cell-like NED.

2. Materials and methods

2.1. Pathologic evaluation

Formalin-fixed, paraffin-embedded tissue of 172 radical prostatectomy (RP) specimens from 4 institutions was available for the study. Collection of archival material at each collaborating institution was performed in compliance with institutional guidelines and under institutional review board– approved protocols. One hundred sixty-three of these specimens corresponded to consecutive RP specimens from 3 institutions of the Early Detection Research Network processed from 2007 to 2012 as previously described [12]. Hematoxylin and eosin (H&E)–stained slides were reviewed for the presence of Paneth cell-like cells. Three study pathologists (M. M. S., B. D. R., and J. M. M.) evaluated 18 morphologic features of prostate cancer (Fig. 1 and Table 1) and the percentage of cells with eosinophilic cytoplasmic granules in tumor nodules with Paneth cell-like NED. The extent of Paneth cell-like cells was assessed at magnification ×20 in the area with most cells containing the characteristic cytoplasmic eosinophilic granules. When there was a discrepancy among the 3 pathologists regarding morphologic features, a majority opinion was honored. For continuous variables (ie, percentage of Paneth cell-like cells), the median was considered.

2.2. Fluorescence in situ hybridization

To assess *AURKA* and *MYCN* amplifications, a locus-specific probe for each gene plus a reference probe located at 10q25 (BACRP11431P18) were used as previously described [5,13]. Amplification was defined as the presence of four or more copies of gene-specific signals (red) compared to two reference signals (green). *ERG* gene rearrangement was also

assessed using a dual-color break-apart interphase fluorescence in situ hybridization (FISH) assay as previously described [14,15].

2.3. Statistical analysis

Prostate cancer with Paneth cell-like NED was divided into 2 groups based on *AURKA* amplification status (ie amplified versus nonamplified), and their morphologic and clinical features were compared accordingly. Fisher exact test was used to evaluate association between categorical variables. Wilcoxon rank-sum test was performed to compare continuous variables (eg, age). For all statistical test, $P < .05$ was considered statistically significant.

3. Results

3.1. Common morphologic features of prostate cancer with Paneth cell-like NED

Paneth cell-like NED was identified in 25 prostate cancers from 172 RP cases. Of these, 16 cases were identified in 163 consecutive RP specimens from the Early Detection Research Network, the frequency of prostate cancer with Paneth cell-like NED being 9.8%. Among 18 morphological features evaluated (Fig. 1 and Table 1), macronucleoli (23/25), basophilic appearance (22/25), nuclear stratification (19/25), and perineural invasion (18/25) were seen in most tumors with Paneth cell-like NED. Other common features included scattered crushed nuclei (13/25) and angulated glands (9/25) (Table 1).

3.2. Extent of Paneth cell-like NED

The extent of Paneth cell-like NED in prostate cancer cases was focal with uneven distribution. Some cases demonstrated scattered Paneth cell-like cells, whereas others featured areas with aggregates of these cells. The overall percentage of Paneth cell-like neuroendocrine cells in the tumor nodules ranged from less than 1% to 10% in this series. Of 25 cases, 15 had less than 1% of cells exhibiting Paneth cell-like NED within the tumor nodule. When assessed at 1 high-power field (magnification $\times 20$) in the area containing the most Paneth cell-like cells, the extent ranged from less than 1% to 40% (Table 2).

3.3. Gleason score and Paneth cell-like NED

When Gleason score was assigned only to the conventional adenocarcinoma component of prostate cancer cases with Paneth cell-like NED, most cases (20/25) had overall Gleason grade 7. There were 2 cases each with Gleason grades 6 and 8 and 1 case with Gleason grade 9.

When Gleason grade was assigned to prostate cancer including areas with Paneth cell-like NED, the percentage of Paneth cell-like cells at both magnification $\times 20$ and within a tumor nodule was positively associated with Gleason grade ($P = .032$ and $P = .028$, respectively).

3.4. Gene alterations

ERG gene rearrangement was present in 14 of 25 cases of prostate cancer with Paneth cell-like NED (56%), a similar frequency previously documented in unselected cohorts of primary prostate cancer [14,16]. *AURKA* amplification was identified in 45% (10/22) of

assessable cases. Such gene amplification was present throughout the tumor nodule including areas without Paneth cell-like NED. Only 1 (5%) of 21 assessable cases demonstrated *MYCN* amplification, which also had concurrent *AURKA* amplification (Fig. 2). To verify if *AURKA* amplification was present independent of the aforementioned morphologic features, FISH assay was performed on 15 cases with similar histomorphology but without Paneth cell-like NED. Only 1 (7%) of 15 cases showed gene amplification (Fisher exact test, $P = .0136$).

3.5. Association of *AURKA* status with other parameters

Prostate cancer with concurrent Paneth cell-like NED and *AURKA* amplification was significantly associated with larger extent of Paneth cell-like NED assessed at magnification $\times 20$ (Fisher exact test, $P = .015$), higher percentage of Paneth cell-like NED in the tumor nodule ($P = .033$), presence of ductal features ($P = .02$), and higher overall Gleason grade ($P = .039$). *AURKA* amplification was not correlated with *ERG* status, age, serum PSA, or tumor stage (Table 3).

3.6. Paneth cell-like NED is not present in benign prostate tissue

Although we did not identify Paneth cell-like NED in benign prostate tissue of RP cases from the study, we evaluated 2 prostate needle biopsies that contained benign prostatic glands with Paneth cell-like cells. These biopsies were not related to the RP cases and did not contain concurrent cancer. *AURKA* amplification was not present in these benign cells with characteristic eosinophilic granules (not shown).

3.7. A case of prostate cancer with Paneth cell-like NED with swift clinical progression

We have recently observed a case in consultation from a patient with metastatic castrate-resistant prostate cancer, whose initial prostate biopsy in 2011 showed prostatic adenocarcinoma with diffuse Paneth cell-like NED involving 20% of 1 of 5 cores. At the outside institution, Gleason grade was not assigned, and a note in the report read that this morphologic pattern had a generally favorable prognosis (Fig. 3). Despite androgen deprivation therapy, the patient progressed to castrate-resistant disease within only 2 years after initial diagnosis, developing osseous and lymph node metastases. A retroperitoneal lymph node biopsy showed metastatic high-grade prostatic carcinoma with extensive NED (Fig. 3). Unfortunately, molecular assays were not feasible due to lack of archival pathology material.

4. Discussion

In recent studies [2,5], we identified *AURKA* and *MYCN* gene amplifications as potential biomarkers that may predict the development of aggressive prostate cancer with NED, in the setting of hormonal deprivation therapy. *AURKA* amplification was present in 67% of primary (hormone naive) prostate cancer from patients that eventually progressed to castrate-resistant disease with highly aggressive clinical features [6]. Concurrent *MYCN* amplification was noted in 70% of these tumors. In contrast, both gene amplifications were observed in only 5% of an unselected cohort of 169 localized prostate cancers [2]. This current study stemmed from the observation that *AURKA* amplification was present in the 6

cases of prostate cancer with Paneth cell–like NED that were used as controls for low-grade NED in our previous work [2].

Paneth cell–like cells in prostate cancer can be readily identified on H&E stain and are considered to be a distinctive form of NED expressing chromogranin, synaptophysin, serotonin, and neuron-specific enolase [10,11,17]. In the first large cohort, Adlakha and Bostwick [17] identified 30 prostate cancers with Paneth cell–like NED by evaluating 300 serially sectioned radical prostatectomy specimens (10%), demonstrating that it is more prevalent than commonly believed. As discussed in their study, the prevalence could have been underestimated due to the focal and patchy nature of Paneth cell–like cells. The variability in the distribution of these cells was also observed in our study, which extent ranged from less than 1% to 10% with a median of 0.5% in tumor nodules. This focal presence can be easily overlooked unless carefully evaluated on H&E stain, especially in those tumors with features that hint at the presence of Paneth cell–like cells (see below). When systematically searched, we found Paneth cell–like NED in 25 prostate cancers from 172 RP specimens, 16 of which were identified in 163 consecutive prostatectomies (9.8%), essentially the same frequency described by Adlakha and Bostwick [17].

We noted that prostate cancer with Paneth cell–like NED frequently exhibits recognizable features including macro-nucleoli, basophilic appearance, nuclear stratification, peri-neural invasion, scattered crushed nuclei, and angulated glands, features that can prompt pathologists to search for cells with the characteristic eosinophilic granules in the cytoplasm of tumor cells. Although all these morphologic features are common in prostate cancer, we often observed their presence to be concurrent in tumors with Paneth cell–like NED. In particular, most cases (>75%) in our series showed macronucleoli, basophilic appearance, and nuclear stratification.

A compelling observation is that among 25 cases of prostate cancer with Paneth cell–like NED, 45% (10/22) of assessable cases harbored *AURKA* amplification, which was present throughout the tumor nodule including areas without Paneth cell–like cells. This frequency is significantly higher than 5% observed in an unselected cohort of localized hormone-naïve prostate cancer and closer to 67% *AURKA* amplification detected in primary tumors from patients who progressed to an aggressive form of castrate-resistant prostate cancer with clinical features of small cell carcinoma [2,5,6]. Furthermore, *AURKA* gene amplification was associated with the presence of ductal features ($P = .02$), larger extent of Paneth cell–like NED ($P = .033$), and higher overall Gleason grade ($P = .039$). For comparison, we also assessed the frequency of *AURKA* amplification in prostate cancers with similar morphologic features (ie, macronucleoli, basophilic appearance, nuclear stratification, etc) but lacking Paneth cell–like change. Among the 15 cases that were assessed, *AURKA* amplification was detected only in 1 case (7%) ($P = .0136$). These findings further support that the presence of conspicuous Paneth cell–like NED in prostate cancer is associated with *AURKA* amplification ($P = .015$).

Among the prostate cancer cases with Paneth cell–like NED, only 1 case demonstrated *MYCN* amplification, which was concurrent with *AURKA* amplification. We have previously demonstrated that *AURKA* and *MYCN* cooperate to induce a neuroendocrine phenotype in

prostate cells and often show concurrent amplification in both hormone-naïve prostate cancer and metastases from patients that progress to an aggressive castrate-resistance prostate cancer with clinical features of small cell carcinoma. It is possible then that *MYCN* amplification may play a later role in the biology of prostate cancer with Paneth cell-like NED or that its true frequency is not represented in this study given the relatively small number of cases.

Prostate cancer with Gleason pattern 5 composed in part or totally of Paneth cell-like neuroendocrine cells has been previously reported to have a more favorable prognosis over a mean of 46-month follow-up when compared to tumors with conventional Gleason pattern 5 [11]. Thus, it has been suggested to grade only the conventional adenocarcinoma component but not the areas with Paneth cell-like NED [11]. Described above (last section of Results) is a recent consult case from a patient with metastatic castrate-resistant prostate cancer with extensive NED, whose initial prostate biopsy, only 2 years before, showed prostatic adenocarcinoma with diffuse Paneth cell-like NED (Fig. 3). This example illustrates that cases of prostate cancer with Paneth cell-like NED have the potential to progress to an aggressive disease within a short period. Because of lack of archival material, we were not able to determine the status of *AURKA* amplification in this case. However, the clinical course is similar to cases that, harboring *AURKA* amplification, progress to an aggressive form of castrate-resistant prostate cancer [2,6].

One of the limitations that we encounter in the present study is that the significance of *AURKA* amplification in prostate cancer has been extrapolated from our previous data on hormone-naïve tumors that have progressed to an aggressive subtype of castrate-resistant disease with NED [2]. It is possible that this gene alteration, when present in prostate cancer with Paneth cell-like NED, may not carry similar prognostic value. Therefore, outcome studies of patients with prostate cancer with Paneth cell-like NED and *AURKA* amplification are needed.

In summary, we illustrate that prostate cancer with Paneth cell-like NED has a recognizable histomorphology and a high frequency of *AURKA* amplification (45%). The presence of this gene alteration is enriched in prostate cancer with conspicuous Paneth cell-like cells. Significant clinical implications of *AURKA* amplification in prostate cancer have been previously described [2]. Therefore, prostate cancer with Paneth cell-like NED that harbors *AURKA* amplification should be best viewed for now as having uncertain clinical behavior. The predictive role of *AURKA* amplification in determining the biologic potential of these cases warrants further exploration.

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Fig. 1.

Representative photomicrographs illustrating 18 morphologic features assessed in prostate cancers with Paneth cell-like NED. A, Tumor with basophilic appearance, nuclear stratification, cribriform morphology, and macronucleoli (inset, original magnification $\times 400$). B, Basophilic appearance, nuclear stratification, and dense pink secretion. C, Angulated glands with scattered crushed nuclei. D, Prostate cancer with foamy cytoplasm and blue-tinged mucin. E, Prostate cancer with crystalloids. F, Tumor with basophilic appearance and ductal features. G, Prostate cancer with perineural invasion and

extraprostatic extension. H, Basophilic appearance, nuclear stratification and intraductal spread. I, Prostate cancer with mucinous fibroplasia (collagenous micronodules). J, Prostate cancer with glomerulations. (All hematoxylin and eosin images at magnification $\times 200$ with exception of inset and C.)

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Fig. 2. *AURKA* amplification is associated with prostate cancer featuring conspicuous Paneth cell-like NED. A and B, Tumor glands with basophilic appearance, macronucleoli, and rare cells with eosinophilic granules in the cytoplasm. *AURKA* amplification is not present (inset). C, Angulated tumor glands with conspicuous Paneth cell-like cells. *AURKA* amplification is present (inset). D, Tumor glands with cribriform morphology and nuclear stratification. Paneth cell-like cells are readily identified. *AURKA* amplification is present (inset). E and F, Prostate cancer with ductal features and numerous Paneth cell-like cells. *AURKA*

amplification is present (inset). G, Prostatic adenocarcinoma with abundant Paneth cell-like NED. *AURKA* amplification is present (inset). H, Area of perineural invasion with characteristic tumor cells containing large eosinophilic cells in the cytoplasm. *AURKA* and *MYCN* amplifications are present (inset). (All hematoxylin and eosin images at magnification $\times 400$.)

Fig. 3.

A case of prostatic adenocarcinoma with Paneth cell-like NED that progressed to metastatic castrate-resistant prostate cancer with NED, within a 2-year period. A, Prostate needle biopsy with initial diagnosis of adenocarcinoma (original magnification $\times 100$). B, Higher magnification ($\times 400$) of tumor demonstrates extensive Paneth cell-like NED. C, Retroperitoneal lymph node biopsy demonstrates metastatic prostate cancer with NED (the patient had clinical presentation of metastatic castrate-resistant prostate cancer with small cell-like clinical features) ($\times 100$). D, Higher magnification shows a poorly differentiated adenocarcinoma, composed of sheets of tumor cells with variable amounts of basophilic cytoplasm and prominent nucleoli. Chromogranin A (CGA) immunohistochemistry is diffusely positive in tumor cells (inset, $\times 400$).

Table 1

Morphologic features sought for in 25 cases of prostate cancer with Paneth cell-like NED

Morphologic features	n (%)
Macronucleoli (magnification $\times 20$)	23 (92%)
Basophilic appearance	22 (88%)
Nuclear stratification	19 (76%)
Perineural invasion	18 (72%)
Dense eosinophilic secretion	13 (52%)
Scattered crushed nuclei	13 (52%)
Blue-tinged mucin	10 (40%)
Angulated glands	9 (36%)
Crystalloids	8 (32%)
Cribriform morphology	7 (28%)
Ductal features	7 (28%)
Extraprostatic extension	6 (24%)
Intraductal spread	5 (20%)
Foamy cytoplasm	3 (12%)
Mucinous fibroplasia (collagenous micronodules)	1 (4%)
Signet ring-like cell features	1 (4%)
Glomerulations	1 (4%)
Comedonecrosis	0 (0%)

Abbreviation: NED, neuroendocrine differentiation.

Table 2

Clinicopathological features of 25 cases of prostate cancer with Paneth cell-like NED

Variable	n
Age (y)	
Range	50-84
Median	64
Prebiopsy PSA (ng/mL)	
Range	1.4-19
Median	5.6
Pathologic stage	
T2c	12
T3a	12
T3b	1
Overall Gleason grade	
<7	2
7	20
>7	3
% of Paneth cell-like cells in tumor nodule	
Range	0.1%-10%
Median	0.5%
% of Paneth cell-like cells at magnification ×20	
Range	0.1%-40%
Median	2

Abbreviations: NED, neuroendocrine differentiation; PSA, prostate-specific antigen.

Table 3

Characteristics of prostate cancer with Paneth cell-like NED versus *AURKA* amplification status (total assessable cases, 22)

	No amplification (n = 12)	Amplification (n = 10)	<i>P</i>
% of Paneth cell-like NED at magnification $\times 20$ (mean $\pm$ SD)	3.4 $\pm$ 8.5	17.8 $\pm$ 14.0	.015
% of Paneth cell-like NED in tumor nodule (mean $\pm$ SD)	0.6 $\pm$ 1.4	2.9 $\pm$ 4.0	.033
Ductal features, no./total (%)	1/12 (8)	6/10 (60)	.020
<i>ERG</i> rearrangement, no./total (%)	8/12 (67)	5/10 (50)	0.666
<i>MYCN</i> amplification, no./total (%)	0/11 ^a (0)	1/10 (10)	
Age (mean $\pm$ SD)	61.5 $\pm$ 6.2	66.1 $\pm$ 10.2	.306
Prebiopsy PSA (mean $\pm$ SD)	6.8 $\pm$ 4.6	6.4 $\pm$ 4.8	.651
Gleason grade			.039
6	1	0	
7	11	7	
8	0	2	
9	0	1	
Pathologic stage			1.000
T2c	6	5	
T3a	6	4	
T3b	0	1	

^a Of 12 cases without *AURKA* amplification, 11 were available for *MYCN* FISH.