# Prognostic Significance of Paneth Cell-like Neuroendocrine Differentiation in Adenocarcinoma of the Prostate

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**Abstract:** The prognostic significance of Paneth cell-like neuroendocrine differentiation in adenocarcinoma of the prostate has not yet been established. We studied 36 cases of adenocarcinoma of the prostate showing Paneth cell-like neuroendocrine differentiation, including needle biopsy specimens (n = 27), radical prostatectomies (n = 8), and transurethral resection specimens (n = 1). Paneth cell-like neuroendocrine cells (NECs) were observed as either patchy isolated cells or diffusely involving glands or nests. With Gleason pattern 3, a patchy pattern of NECs was seen in 18/19 cases with only 1/19 (5.3%) case showing diffuse NECs. All the 4 Gleason pattern 4 cases had patchy NECs. Of the 21 cases with Gleason pattern 5, 18 (85.7%) had diffuse NECs with the remaining 3 exhibiting patchy NECs. Radical prostatectomy was performed in 16/36 (44.4%). Tumor was organ confined in 10/16 cases (62.5%). Extraprostatic extension (EPE) with positive surgical margins was seen in 6/16 cases (37.5%). In 4 cases, seminal vesicles were positive for cancer. Pelvic lymph nodes were free of tumor in all cases. The actuarial prostate specific antigen progression-free risk at 5 years and 7 years was 92% and 80%, respectively. Only 2 patients progressed after radical prostatectomy and they both had Gleason score 7 cancer with extraprostatic extension and seminal vesicle invasion. Of the 16 radical prostatectomy cases, 8 (50%) had a Gleason pattern 5 component either on needle biopsy or at radical prostatectomy, with nests, cords, or single cells containing Paneth cell-like neuroendocrine differentiation. Five of these 6 cases with Gleason pattern 5 and available follow-up information had no evidence of progression with mean and median follow-ups of 46 months. Radiation therapy either as monotherapy or combined with hormonal therapy was used to treat patients in 13/36 cases. Overall only 2 patients progressed, one with clinical T2 and the other T3 disease. Of the 5 cases with Gleason pattern 5 composed in part or totally by NECs treated by radiation therapy, all are without evidence of recurrence with a mean and median follow-up of 47 and 45 months, respectively. Of the remaining 5 cases with available follow-up treated with watchful waiting, hormone therapy, or cryotherapy, 4 had Gleason pattern 5 tumor with NECs. Of these 4 cases, 3 had no progression with a mean and median follow-up of 42.5 and 60.5 months, respectively. Despite the cells' bland histologic appearance, strictly applying the Gleason grading system one would have to assign a Gleason pattern 5 to these foci with no glandular differentiation. The current study demonstrates that applying the Gleason score to these foci does not accurately reflect their clinical behavior. In cases with Paneth cell-like NECs, only the conventional adenocarcinoma component should be assigned a Gleason score. In cases in which the entire tumor is composed of Paneth cell-like cells and areas of the tumor lack glandular differentiation, the tumors should not be assigned a Gleason score and a comment should be provided as to the generally favorable prognosis of this morphologic pattern of neuroendocrine differentiation.

**Key Words:** neuroendocrine, prostate cancer, gleason grading, Paneth cell-like cells

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Tumors of the prostate with neuroendocrine differentiation represent a heterogeneous group of entities. Neuroendocrine differentiation in the prostate ranges from focal neuroendocrine cells (NECs) in otherwise conventional adenocarcinoma to carcinoid tumor to small cell carcinoma.[10]

Small cell carcinomas of the prostate are rare tumors, which behave in a very aggressive fashion. Patients often present with metastases at the time of diagnosis and survival is usually very short, typically less than 2 years after diagnosis.[16,19,21,23] Primary carcinoid tumors within the prostate are even less common. The majority of prostatic tumors that morphologically resemble carcinoids are acinar adenocarcinomas with bland cytology that express neuroendocrine markers, and yet also express prostate specific antigen (PSA) and prostate specific acid phosphatase (PSAP). These tumors are best regarded as acinar adenocarcinomas with neuroendocrine differentiation rather than true carcinoid tumors. The few true carcinoid tumors that have been reported have a better prognosis that small cell carcinoma, yet there are insufficient data on the true behavior of these lesions.[25]

It is important to distinguish small cell carcinoma and carcinoid of the prostate from ordinary adenocarcinoma of the prostate with neuroendocrine differentiation. Neuroendocrine differentiation in the prostate may be

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unapparent on hematoxylin and eosin (H&E)-stained sections, detectable only by the use of immunoreactivity. NECs may also be visible on routine H&E-stained slides, where the NECs resemble Paneth cells in the small intestine. These cells, characterized by small eosinophilic cytoplasmic granules, are not true Paneth cells as they stain with neuroendocrine markers and are uniformly negative for lysozyme.[3,9] Paneth cell-like NECs are occasionally observed in the normal prostate, high-grade prostatic intraepithelial neoplasia (HGPIN) and adenocarcinoma. The prognostic significance of Paneth cell-like neuroendocrine differentiation in adenocarcinoma of the prostate has not yet been established.[1,17,18,22]

## MATERIALS AND METHODS

We studied 36 cases of adenocarcinoma of the prostate showing Paneth cell-like neuroendocrine differentiation, including needle biopsy specimens (n = 27), radical prostatectomies (n = 8), and transurethral resection specimens (n = 1). After a needle biopsy diagnosis of cancer with NECs, another 8 radical prostatectomies were performed but the slides were not available for review; these cases were analyzed for pathologic stage and follow-up information. Cases were retrieved from the consultation files (n = 27) and in-house pathology files of The Johns Hopkins Hospital (n = 9) for the time interval between 1994 and 2005.

Histologic slides were reviewed and regraded using the Gleason grading system, ignoring the Paneth cell-like features and grading tumors solely on their architectural pattern. The pattern of neuroendocrine differentiation was also classified as patchy or diffuse based on the distribution of the NECs and recorded separately for each Gleason grade pattern. In cases with patchy staining, one could have a discordant situation in which all the tumor glands or nests had a few NECs, yet the overall percentage of tumor cells with neuroendocrine differentiation was very limited. To accurately indicate the extent of NECs in radical prostatectomy and transurethral resection specimens, both the percentage of glands or nests containing any NECs along with the overall percentage of NECs within the entire tumor were recorded. To indicate the extent of NECs in needle biopsy cases, we recorded the percentage of glands or nests with NECs along with the overall percentage of NECs for the core involved by cancer. In the core involved by tumor showing neuroendocrine differentiation, the total length of cancer (including cancer without NECs) was also noted.

Immunohistochemical stains for chromogranin (Clone LK2H10, Ventana) and synaptophysin (Polyclonal, Cell Marque) were performed in 19/36 cases (53%) based on the availability of unstained slides.

Clinical follow-up was carried out in 34/36 cases (93.9%) by directly contacting the urologist using a structured clinical questionnaire. The mean follow up time was 29 months (range: 1 to 180 mo). Patients with no evidence of progression after radical prostatectomy were defined as having a postoperative PSA level of $< 0.2$ ng/mL with no evidence of local recurrence or metastasis.

## RESULTS

### Clinicopathologic Features

The mean age of the patients was 65.5 years (range: 48 to 76 y). A family history of prostate adenocarcinoma existed in 6/36 cases (16.6%). The stage was T1 in 5 cases (13.8%), T2 in 19 cases (52.7%), T3 in 8 cases (22.2%), and unknown in 4 cases (11.1%). Information on stage was obtained from radical prostatectomy specimens in 16/36 (44.4%) patients and from clinical evaluation in 17/36 (47.4%) patients who did not undergo radical prostatectomy.

Cancers containing Paneth cell-like NECs were conventional in 31 cases (86.1%), pure ductal adenocarcinoma in 1 case (2.7%), and conventional adenocarcinoma with ductal features in 4 cases (11.1%) (Figs. 1–4). For the 8 radical prostatectomy specimens with NECs, the mean percentage of cancer glands involved by NECs is displayed in Table 1. One TUR specimen had 80% of the nests/glands with some neuroendocrine differentiation and overall 80% of the tumor cells in the case were NECs. Data for the extent of NECs in needle biopsies are depicted in Table 2. The cores involved by NECs tended to have limited cancer with a median length of cancer measuring 2.5 mm. Cases with $> 50\%$ NECs per core with NECs had $< 1$ mm of cancer on the involved core.

Paneth cell-like NECs were observed either as patchy isolated cells or diffusely involving glands or nests. With Gleason pattern 3, a patchy pattern of NECs was seen in 18/19 cases with only 1/19 (5.3%) case showing diffuse NECs (Figs. 1, 2). All of the 4 Gleason pattern 4 cases had patchy NECs (Fig. 3). Of the 21 cases with Gleason pattern 5, 18 (85.7%) had diffuse NECs

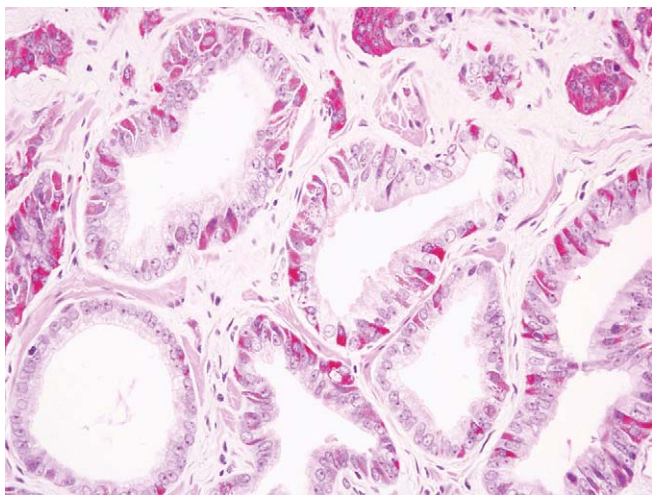

**FIGURE 1.** Gleason pattern 3 adenocarcinoma with patchy distribution of NECs with red neuroendocrine granules.

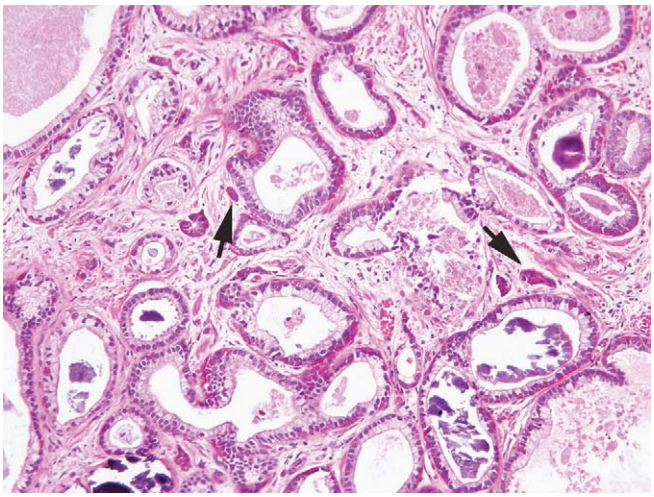

**FIGURE 2.** Gleason pattern 3 adenocarcinoma showing a patchy distribution of NECs with eosinophilic granules. Note adjacent small nests of Gleason pattern 5 exhibiting a diffuse distribution of NECs (arrows).

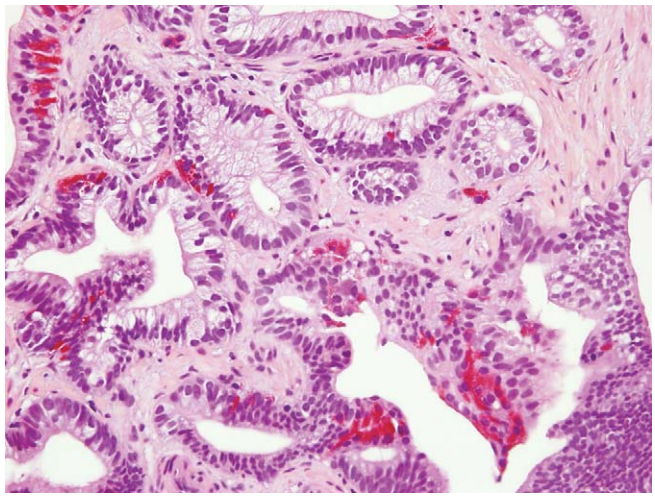

**FIGURE 4.** Ductal adenocarcinoma with patchy distribution of NECs.

with the remaining 3 exhibiting patchy NECs (Figs. 2, 5–7). All of the Gleason pattern 5 cases with NECs, except for 2, also had adenocarcinoma of the prostate with Gleason patterns 3 or 4 or ductal differentiation elsewhere in the case. One of the 2 cases with pure Gleason pattern 5 composed of NECs had focal PSA immunochemistry, with the other case having no tissue available for immunohistochemistry. Paneth cell-like NECs were uniformly positive for neuroendocrine markers chromogranin and synaptophysin on immunohistochemical stains (Fig. 7).

## Treatment and Prognosis

Radical prostatectomy was performed in 16/36 (44.4%) cases. Tumor was organ confined in 10/16 cases (62.5%). Extraprostatic extension with positive surgical margins was seen in 6/16 cases (37.5%). In 4 cases, seminal vesicles were positive for cancer. Pelvic lymph nodes were free of tumor in all cases. The actuarial PSA progression-free risk at 5 and 7 years was 92% and 80%, respectively. Only 2 patients progressed after radical prostatectomy and they both had Gleason score 7 cancer with extraprostatic extension and seminal vesicle invasion. One of these patients had additional adverse features, including ductal differentiation and positive margins. Of the 16 radical prostatectomy cases, 8 (50%) had a Gleason pattern 5 component either on needle biopsy or at radical prostatectomy, with nests, cords, or single cells containing Paneth cell-like cells. Five of these 6 cases with Gleason pattern 5 and available follow-up information had no evidence of progression with mean and median follow-ups of 46 months.

Radiation therapy either as monotherapy or combined with hormonal therapy was used to treat patients in 13/36 cases. Overall, only 2 patients progressed, one with clinical T2 and the other T3 disease. Of the 5 cases with Gleason pattern 5, composed in part or totally by NECs, all are without evidence of recurrence after radiation with a mean and median follow-up of 47 and 45 months, respectively.

Of the remaining 5 cases with available follow-up treated with watchful waiting, hormone therapy, or cryotherapy, 4 had Gleason pattern 5 tumor with NECs.

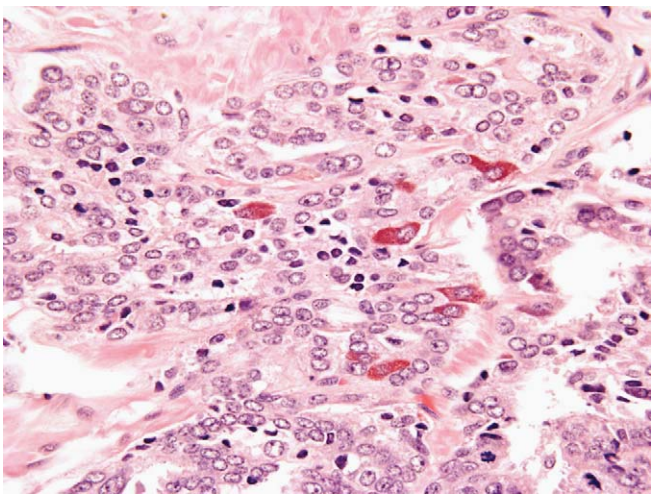

**FIGURE 3.** Gleason pattern 4 with patchy NECs.

**TABLE 1.** NECs in Radical Prostatectomy Specimens

| | Percent Glands/Nests With NECs | Overall Percent NECs |
|---|---|---|
| Mean (%) | 15.7 | 15 |
| Median (%) | 30 | 1.5 |
| Range (%) | 1–100 | < 1–100 |

**TABLE 2.** NECs in Needle Biopsy Specimens

| | Percent Glands/Nests With NECs/Involved Core | Overall Percent NECs/ Involved Core |
|---|---|---|
| Mean (%) | 41 | 19.4 |
| Median (%) | 10 | 2 |
| Range (%) | 1–100 | < 1–100 |

Of these 4 cases, 3 had no progression with a mean and median follow-up of 42.5 and 60.5 months, respectively.

## DISCUSSION

Endocrine cells in the prostate were first documented by Feyrter in 1951.[12]

They have a common origin with the luminal cells, arising from endodermal-derived prostate stem cells.[4,22] As opposed to luminal cells that are considered the proliferative compartment, NECs in prostate are considered terminally differentiated cells without proliferative activity.[4] It is believed that they play a physiologic role in the maintenance of homeostasis and regulation of the prostatic fluid.[17]

Prostatic NECs are more abundant in the major ducts and more sparsely present in acinar tissue. Two types of NECs can be distinguished: ''open'' cell type with a flash-shaped form and slender extensions reaching the lumen and ''closed'' cell type that lacks luminal extensions. Dense core granules within these cells store and secrete a variety of endogenously active substances, including serotonin, chromogranin, somatostatin, calcitonin, gastrin-releasing peptide, α-human chorionic gonadotrpin, thyroid-stimulating hormone-like peptide, parathyroid hormone-related protein, cholecystokinin, and others.[1,2,4,16,24]

NECs are androgen insensitive, lacking the androgen receptors seen in luminal cells. Some authors speculate that this property could make them potentially immortal and less susceptible to radiation and hormone therapy, potentially conferring on them a survival advantage.[4,17] A number of clinical studies suggested that NECs might play a role in prostate cancer development or progression stimulating the growth of the surrounding carcinoma cells in a paracrine fashion through an androgen-independent pathway.[4,13,20]

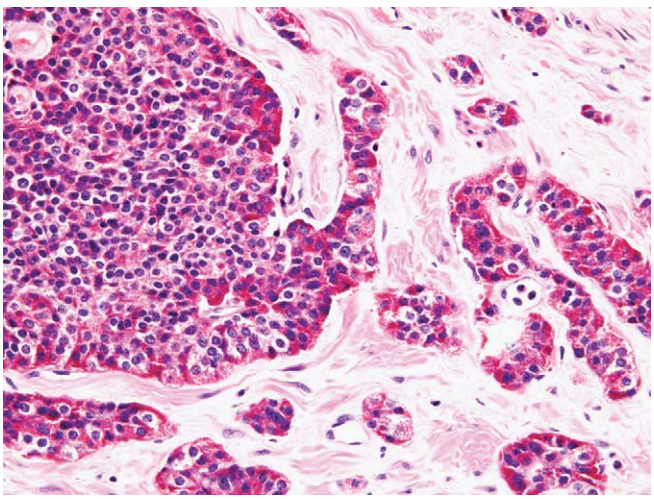

**FIGURE 5.** Carcinoid-like growth pattern of Gleason pattern 5, with solid nests of NECs.

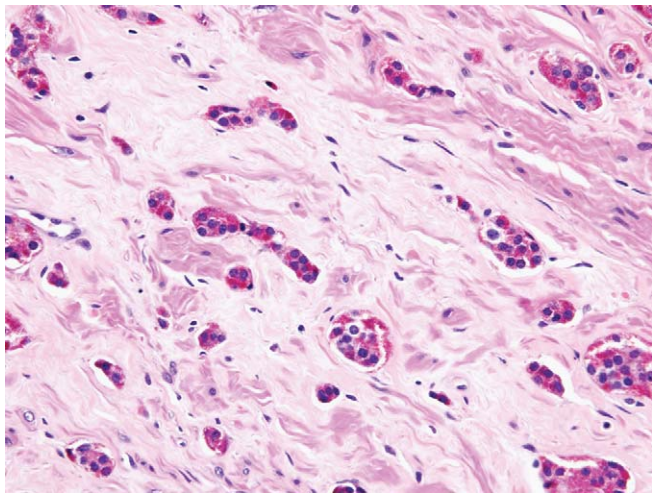

**FIGURE 6.** Gleason pattern 5 with individual or cords of cells with neuroendocrine granules.

Previous studies have shown controversial results regarding the prognosis of focal neuroendocrine differentiation as demonstrated by immunohistochemistry in otherwise typical adenocarcinoma of the prostate. Some reports have shown a negative effect on prognosis although others have shown little or no relationship to prognosis.[1,2,4,6,7,13,15,17] Whereas prior studies evaluated the prognostic significance of neuroendocrine differentiation based on immunohistochemical markers, the significance of Paneth cell-like differentiation has not been evaluated.

Paneth cell-like NECs are positive for neuroendocrine markers and negative for lysozyme, making them distinct from the true Paneth cells of the small intestine.[3,9,15,22,24] Electron microscopy studies reveal, within the cytoplasm of Paneth cell-like cells, dense core neurosecretory granules.[24]

The most common pattern seen in the current study with Paneth cell-like change was patchy NECs in malignant glands. In addition to the common finding of patchy NECs in malignant glands, NECs were also seen as single cells, cords, or nests of cancer cells with no luminal differentiation. Although by the Gleason system these were graded as pattern 5, their bland cytology, typically limited nature, and frequent association with lower grade conventional adenocarcinoma raised questions as to whether this unique histology should not be diagnosed as high grade. Their association with ordinary adenocarcinoma in all but 2 cases argues against designating these foci as carcinoid tumor. One of the 2

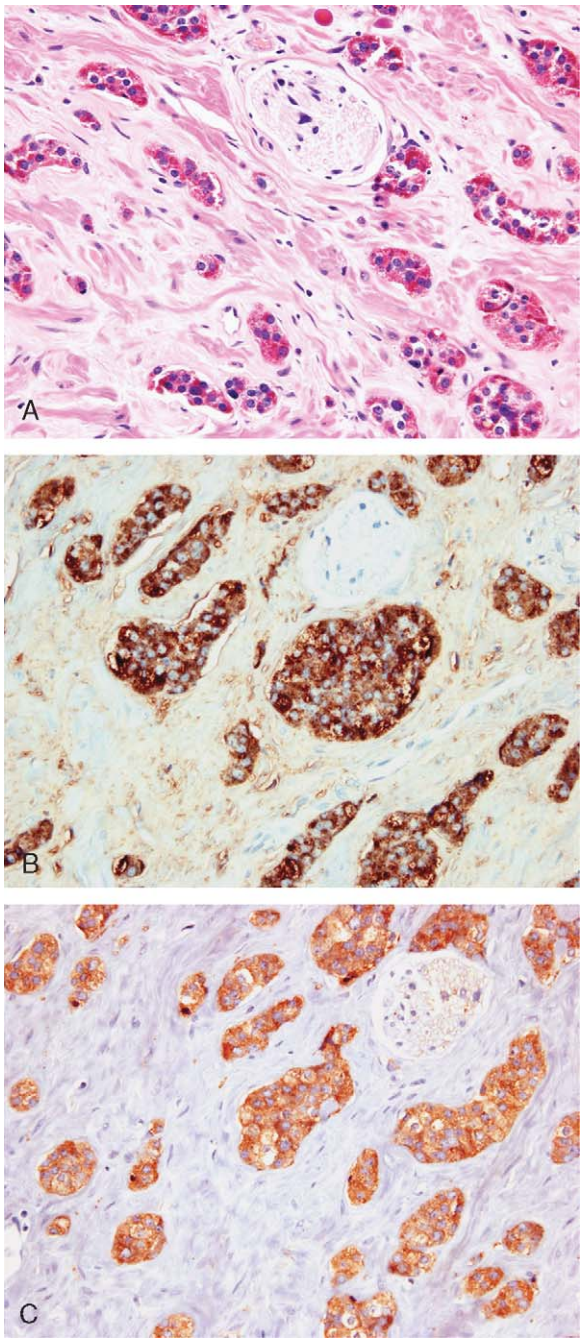


**FIGURE 7.** A, Small nests of cells with diffuse distribution of neuroendocrine cells, Gleason pattern 5. B, Intense cytoplasmic chromogranin immunostaining in the nests of cells with eosinophilic granules. C, Intense cytoplasmic synaptophysin immunoreactivity in nests of cells with eosinophilic granules.

cases with pure Gleason pattern 5 composed of NECs had focal PSA immunochemistry further supporting that these are variants of adenocarcinoma of the prostate and not carcinoid tumors. Most cases with a high percentage of NECs were small foci of cancer such that

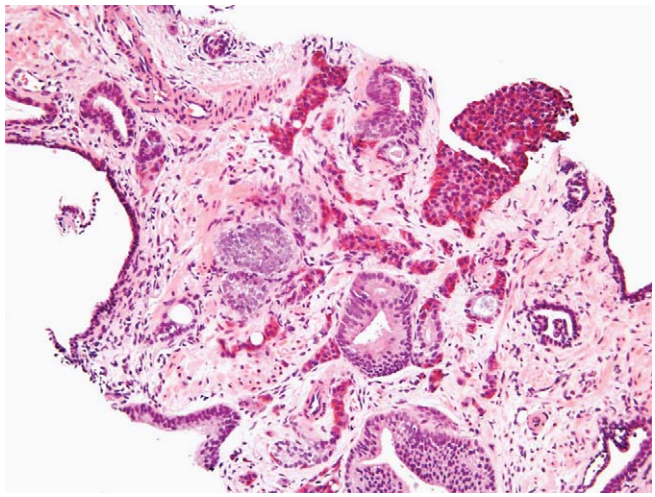

**FIGURE 8.** Small focus of adenocarcinoma, Gleason pattern 5 composed entirely of NECs with eosinophilic granules.

it is unusual to have a lot of prostate cancer with a majority of the cells being NECs.

Although we did not compare the prognosis after radical prostatectomy for cases with NECs to a control population without NECs owing to the limited number of cases with NECs, we were able to conclude that the presence of NECs on needle biopsy or within radical prostatectomy specimens did not invariably indicate aggressive tumor. Cases with NECs had organ confined cancer in 62.5% of cases with only 31.2% of cases having positive margins. In only 4 cases, seminal vesicles were positive for cancer. Pelvic lymph nodes were free of tumor in all cases. The postoperative course was also very favorable with an over 90% actuarial PSA progression-free risk of 5 years. The prognosis seemed to be driven by conventional parameters independent of NECs. The only 2 patients who progressed after radical prostatectomy had Gleason score 7 cancer with extraprostatic extension and seminal vesicle invasion, with one also having ductal differentiation and positive margins.

This study brings to attention the potential problem that could arise in grading tumors with Paneth cell-like changes, when areas of the tumor consist of isolated cells or cords of cells resembling a carcinoid tumor. Despite the cells' bland histologic appearance, strictly applying the Gleason grading system one would have to assign a Gleason pattern 5 to these foci with no glandular differentiation (Fig. 8). The current study demonstrates that applying the Gleason score to these foci does not accurately reflect their clinical behavior. In cases with Paneth cell-like NECs, only the conventional adenocarcinoma component should be assigned a Gleason score. In cases in which the entire tumor is composed of Paneth cell-like cells and areas of the tumor lack glandular differentiation, the tumors should not be assigned a Gleason score and a comment should be provided as to the generally favorable prognosis of this morphologic

pattern of neuroendocrine differentiation. From a practical standpoint, one should not use, without further explanation, the diagnostic term "prostatic adenocarcinoma with neuroendocrine differentiation" to denote Paneth cell-like change in an adenocarcinoma, as we have seen such cases misconstrued by clinicians as small cell carcinoma.

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