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Histologic Variants of Acinar Prostate Carcinomas: Clinicopathologic Importance

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Abstract

Acinar carcinoma comprises more than 90% of prostatic adenocarcinomas and is characterized by a small gland proliferation with an infiltrative growth pattern. The numerous, variably-defined histological variants of prostatic adenocarcinoma can prove to be diagnostic challenges and show prognostic differences when compared to the usual acinar carcinoma, thus emphasizing the importance in accurate recognition.

Variants of acinar prostatic adenocarcinoma include the atrophic, pseudohyperplastic, microcystic, foamy gland, mucinous (colloid), signet ring-like cell, pleomorphic giant cell, and sarcomatoid variants. The atrophic, pseudohyperplastic, microcystic, and foamy gland variants can be challenging to diagnose due to their deceptively benign appearance. While the atrophic, pseudohyperplastic, microcystic, and foamy gland variants usually present as low-grade malignancies (Gleason score 6-7), the mucinous (colloid), signet ring-like cell, pleomorphic giant cell, and sarcomatoid variants often present as high-grade malignancies (Gleason score >7) and are usually associated with a worse prognosis.

Small cell carcinoma is not considered as a variant of acinar carcinoma, is classified under neuroendocrine tumors, and is recommended not to be assigned a Gleason score. Small cell carcinoma is often preceded by a diagnosis of acinar adenocarcinoma, rarely presents as a de novo tumor, and, as in other organs systems has an aggressive clinical course.

In this review article, we discuss variants of prostatic acinar carcinomas and briefly discuss small cell carcinoma. Awareness of variants of acinar prostate carcinoma and their clinicopathologic features is essential to rendering an accurate diagnosis and clinical management of patients with these tumors.

Key words prostate, acinar carcinoma, histologic variants, clinicopathologic importance

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Introduction

Prostate cancer is the most common cancer and the second most common cause of cancer death in men in USA [1]. Most prostate cancers are adenocarcinomas categorized as acinar adenocarcinoma or ductal adenocarcinoma. The incidence of adenocarcinoma is variable among races in different countries, with the highest reported incidence in North America, Australia, and Scandinavian countries [2]. Acinar carcinoma comprises more than 90% of prostatic adenocarcinomas and is characterized by a small gland proliferation with an infiltrative growth pattern. When assessing for the possibility of acinar adenocarcinoma of the prostate in biopsy or transurethral resection of prostate (TURP) specimens, a simple triad of the "three toos": too small glands, too crowded glands with back- to- back arrangement, and too clear glands is useful in screening and identifying carcinoma (**Figure 1A**). When any of the "three toos" is seen, one must consider the possibility of prostatic adenocarcinoma. To confirm the diagnosis of carcinoma, an additional three important diagnostic features should be present, which are: (1) nuclear enlargement, (2) prominent nucleoli and, (3) lack of basal cells (**Figure 1B**) [2].

Features that can aid in the diagnosis of prostate cancer include the presence of intraluminal crystalloids, pink amorphous secretions, and intraluminal acid mucin, although these features are not considered pathognomonic of acinar adenocarcinoma as they may be seen in numerous carcinoma mimickers. Common adenocarcinoma mimickers include atypical adenomatous hyperplasia (adenosis), sclerosing adenosis, basal cell hyperplasia, and clear cell cribriform hyperplasia [2]. Features including collagenous micronodules (mucinous fibroplasia), glomerulation, circumferential perineural invasion and glands involving fat are pathognomonic for the diagnosis of prostate cancer.

The most important prognostic and predictive factors for prostate cancer include TNM stage, Gleason grade, and serum PSA level. In this review article, we review the histologic variants of acinar prostate carcinomas, their morphologic characteristics, and clinicopathologic features. The WHO classification of epithelial prostate tumors included acinar carcinoma in addition to morphologic variants of acinar carcinoma and other epithelial prostate tumors (**Table 1**) [3]. Although small cell carcinoma is categorized as a neuroendocrine tumor in the WHO classification, we briefly touch on small cell carcinoma in this article because this tumor is often preceded by a diagnosis of acinar adenocarcinoma (**Table 2**).

Atrophic variant

Atrophic variant adenocarcinoma is characterized by malignant glands with atrophic features. It is characterized by cytoplasmic volume loss similar to that seen in benign atrophy [4-7]. By comparison, the usual variant of acinar adenocarcinoma demonstrates a moderate amount of cytoplasm. The atrophic variant can be seen following radiation or androgen deprivation therapy, or in a sporadic setting [4-7]. The glands are oval to round and typically small with virtually all cases showing atrophic malignant glands intermixed with the malignant glands of the usual acinar variant of adenocarcinoma. No cases of pure atrophic pattern adenocarcinoma have been reported to date [5]. An infiltrative arrangement of glands displaying loss of cytoplasmic volume, macronucleoli, and nucleomegaly are seen in **Figures 2A** and **2B**. The incidence of sporadic atrophic variant of adenocarcinoma is approximately 2% in needle core biopsy specimens [5] and approximately 16% in radical prostatectomy specimens, with few reported cases in TURP specimens [4].

The proportion of the atrophic tumor comprised of glands with atrophic features is variable, averaging 16-25% of the total

adenocarcinoma showing glands with atrophic features [5, 6]. The reported range is broad, 10-90% in needle biopsy cases [5] and 1-70% in radical prostatectomy cases [5, 6]. Thus, pure atrophic pattern of adenocarcinoma should not be diagnosed in needle biopsy cases, as recognition and discrimination from benign atrophy can serve as a diagnostic dilemma.

When considering the differential diagnosis, it is imperative to distinguish between the atrophic pattern of adenocarcinoma and benign atrophy. The most reliable features supporting a diagnosis of atrophic variant of adenocarcinoma over benign atrophy remain to be infiltrative growth pattern, nuclear atypia, and the diffuse absence of basal cells [4-6]. Additional features include the presence of intraluminal pink secretions, intraluminal wispy blue mucin, and intraluminal crystalloids; however, these findings have been shown to be detected in only a minority of atrophic variant adenocarcinoma cases [3], limiting their diagnostic utility.
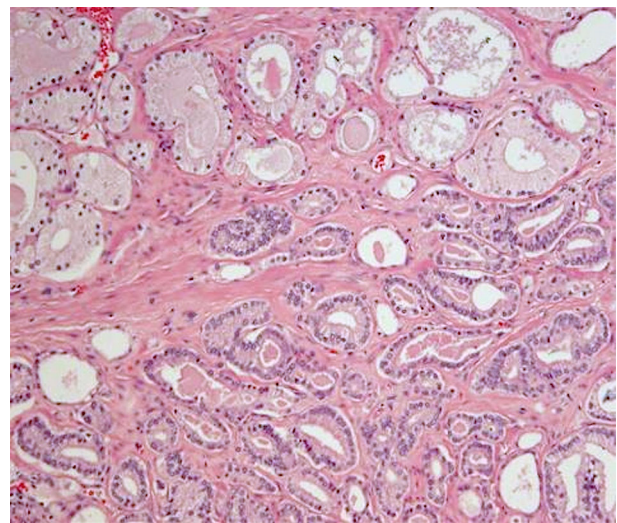
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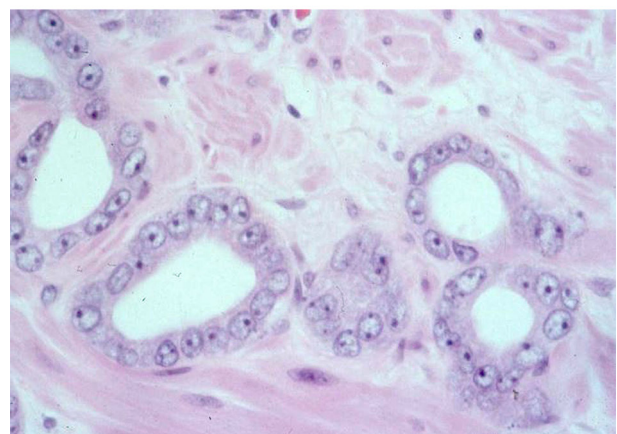
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Figure 1. The "three 'toos" of acinar adenocarcinoma. A: The "three 'toos" (too small glands, too crowded glands with back- to- back arrangement, and too clear glands) as seen in this figure are useful in screening and identifying carcinoma. (Hematoxylin and eosin stain, 40X magnification). B: To confirm the usual variant of acinar adenocarcinoma, a diagnostic triad is required: enlarged nuclei, prominent nucleoli, and lack of basal cells. (Hematoxylin and eosin stain, 400X magnification).

Table 1. World Health Organization classification of Epithelial Tumor of Prostate.

Glandular neoplasms	ICD-0*
Acinar adenocarcinoma	8140/3
Atrophic	-
Pseudohyperplastic	-
Microcystic	-
Foamy gland	8480/3
Mucinous (colloid)	8490/3
Signet ring-like cell	8572/3
Pleomorphic giant cell	-
Sarcomatoid	-
Prostatic intraepithelial neoplasia, high grade	8148/2
Intraductal carcinoma	8500/2
Ductal adenocarcinoma	8500/3
Cribriform	8201/3
Papillary	8260/3
Solid	8230/3
Urothelial Carcinoma	8120/3
Squamous neoplasms	-
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Basal cell carcinoma	8147/3

* International Classification of Disease for Oncology; Modified from WHO Classification of Tumours of the Urinary System and Male Genital Organs 4th edition [3].

Perineural invasion may also be seen. A potential pitfall in the differential diagnosis of atrophic pattern of adenocarcinoma versus benign atrophy includes the potential for immunophenotypic overlap. Up to 6-23% of cases of benign atrophy are negative for basal cell markers [8-13]. AMACR can show overexpression in up to 4% of cases of benign atrophy [14, 15] and 10-79% of cases of partial atrophy [8, 9, 12, 16]. These findings show that benign atrophy may show a malignant phenotype consisting of AMACR overexpression and basal cell loss.

Other diagnostic challenges are posed by atrophic pattern of acinar carcinoma. Atrophic pattern of adenocarcinoma may resemble the microcystic variant of acinar adenocarcinoma, which may also have lining tumor cells showing loss of cytoplasmic volume resembling atrophic features [5, 6, 17]. Identification of nuclear atypia within malignant glands in the atrophic variant can be challenging due to nuclear compression. AMACR expression has also been found to be diminished in the atrophic variant compared to cases of usual acinar adenocarcinoma, with positivity rates of 70% and 90% respectively [14]. Still, similar to the usual acinar variant of adenocarcinoma, there is complete loss of basal cells in all atrophic pattern adenocarcinoma glands as seen by immunohistochemistry using antibodies directed against high-molecular-weight cytokeratins and p63 [6].

Atrophic pattern adenocarcinoma is predominantly a Gleason pattern 3 carcinoma but may show Gleason pattern 4 in the usual acinar component in up to 13% of cases [6]. The proliferation index of atrophic pattern adenocarcinoma (4%), as determined by Ki-67 immunolabeling, is similar to that of the usual acinar adenocarcinoma (5%) with rare identification of mitoses [6, 16]. The presence of atrophic features in adenocarcinoma is unlikely to be of prognostic significance as adenocarcinomas with and without atrophic change do not differ in Gleason grade or pathologic stage

Table 2. World Health Organization classification of Neuroendocrine Tumors of the Prostate.

Tumors type	ICD-0*
Adenocarcinoma with neuroendocrine differentiation	8574/3
Well-differentiated neuroendocrine tumor	8240/3
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3

* International Classification of Disease for Oncology; Modified from WHO Classification of Tumours of the Urinary System and Male Genital Organs 4th edition [3].

[6, 18].

Pseudohyperplastic variant

The pseudohyperplastic variant can simulate the appearance of usual epithelial hyperplasia often seen in benign prostatic hyperplasia and accounts for a large percentage of needle biopsy cases misdiagnosed as benign prostate [19, 20]. The incidence in needle biopsy cases is 2% [21], 11% in radical prostatectomy cases [22], and 3% of TURP cases [21]. This variant demonstrates branching, papillary infoldings, luminal undulations, and cystic dilatation with a predominantly nodular configuration (see Figure 3A). A minority of cases may show an infiltrative component [21].

The tumor may be present in the transition and/or peripheral zone. In radical prostatectomy cases, there is almost always an associated usual small acinar adenocarcinoma component, although in needle core biopsy cases, up to 90% of the adenocarcinoma may be pseudohyperplastic [19]. The nuclei are rounded, without stratification, and typically show prominent nucleoli. Nuclear atypia may be minimal in some cases, particularly in cases with foamy cytoplasmic features [16, 20]. Intraluminal crystalloids, pink amorphous secretions, and wispy blue mucin are seen in a minority of cases [16, 19, 21].

The differential diagnosis includes crowded benign glands, usual glandular hyperplasia of the prostate, and ductal adenocarcinoma. Findings useful in establishing a diagnosis of malignancy include
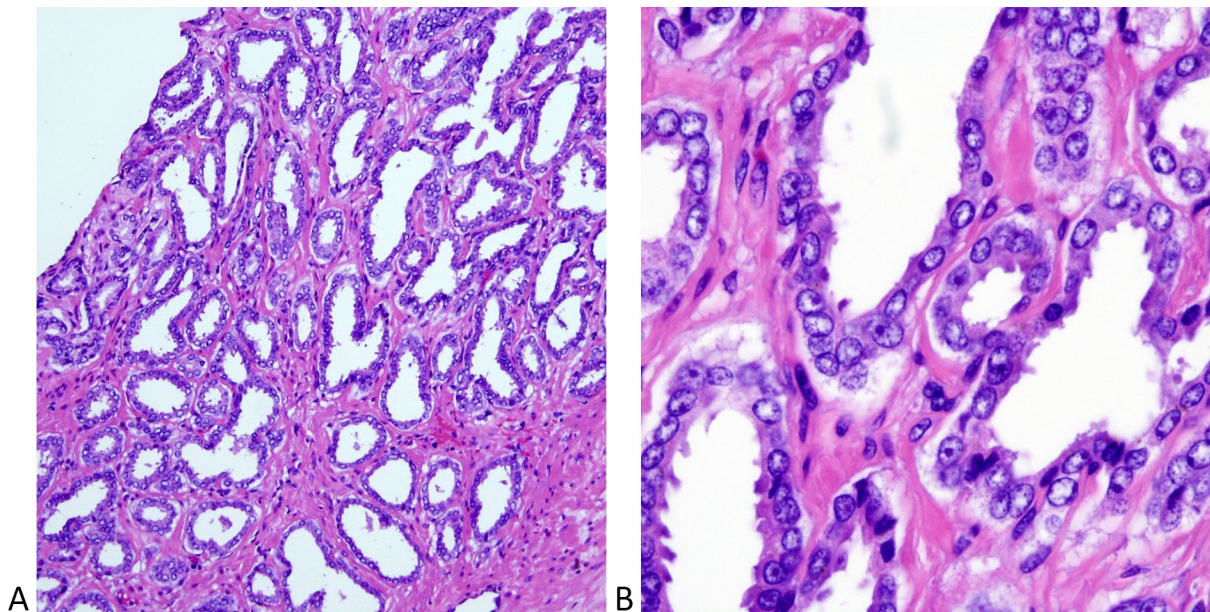

Figure 2. Atrophic variant of acinar adenocarcinoma. A: Atrophic variant of acinar adenocarcinoma consisting of crowded, round to irregular and angulated glands with scant cytoplasm, mimicking benign atrophy. (Hematoxylin and eosin stain, 40X magnification); B: Higher magnification image showing the cytologic features observed in this example of atrophic variant of prostatic adenocarcinoma including enlarged nuclei, prominent nucleoli, and lack of basal cells. Note scanty cytoplasm different from classic acinar carcinoma. (Hematoxylin and eosin stain, 200X magnification).

Table 3. Histologic features of Variants of Usual Acinar Adenocarcinoma of the Prostate.

Tumors type	Pattern	Gleason score	Differential diagnosis
Atrophic	Atrophic with loss of cytoplasm	6 (3+3)	Atrophy
Pseudohyperplastic	Cystically dilated medium to large-caliber glands that can mimic benign hyperplasia with papillary infoldings and luminal undulations; nuclei round with prominent nucleoli and without pseudostratification	6 (3+3)	Benign crowded glands Benign glandular hyperplasia Ductal adenocarcinoma
Microcystic	Cystically dilated medium-caliber glands with round profiles and flat luminal cell lining mimicking benign cystic atrophy	6 (3+3) in majority with approximately 36% showing Gleason score 7	Benign cystic atrophy of transition zone Cystic hyperplasia of transition zone
Foamy	Tumor cells with foamy/xanthomatous cytoplasm and small, pyknotic appearing nuclei, often admixed with non-foamy gland carcinoma	7 (most common 60%), 6 (32%), 9-10 (5%), 8 (3%)	Cowper's glands Histiocytes
Mucinous (Colloid)	Individual glands, fused glands, cribriform nests floating in extracellular mucin pools or lakes (at least 25% for mucinous carcinoma). Mucinous carcinoma cannot be made on biopsies.	7 or 8	Metastasis
Signet ring-like cell	Tumor cells with empty vacuoles lacking intracellular mucin; at least 25% of tumor cells composed of signet ring-like cells	9-10	Metastasis
Pleomorphic Giant Cell	Giant, bizarre, anaplastic tumor cells with pleomorphic nuclei with no spindle cell component	9-10	Sarcomatoid carcinoma with marked nuclear pleomorphism Tumors with osteoclast-type or trophoblastic giant cells Metastasis
Sarcomatoid	Biphasic neoplasm with tumor cells showing epithelial and sarcomatoid differentiation; sometimes display mixture of sarcomatoid component and typical adenocarcinoma	Epithelial component usually showing high Gleason score (9-10)	Metastasis (urothelial or GI tract)
Small cell carcinoma	Small to medium sized, round to oval cells with minimal cytoplasm, finely dispersed nuclear chromatin, no distinct nucleoli, numerous apoptotic cells and high mitotic rate	Not assigned	Large cell neuroendocrine carcinoma (rare) Metastasis

glandular crowding, nucleomegaly, prominent macronucleoli, and transition to usual acinar adenocarcinoma. A search for adjacent typical acinar adenocarcinoma is essential. As seen with cases of atrophic variant adenocarcinoma, pure pseudohyperplastic adenocarcinoma should not be diagnosed in needle biopsy cases and one should maintain a low threshold for performance of immunohistochemistry in such cases concerning for this variant. AMACR expression is seen in 70-83% of cases [23] without the presence of basal cells in concerning glands by immunostaining (**Figure 3B**). While detected in only a minority of cases, perineural invasion by pseudohyperplastic glands, when present, can aid in the diagnosis. The papillary growth pattern of pseudohyperplastic adenocarcinoma may be mistaken for the papillae of ductal adenocarcinoma of the prostate. However, the neoplastic epithelial lining is typically pseudostratified with

elongated nuclei in ductal adenocarcinoma [24], whereas the lining cells of pseudohyperplastic adenocarcinoma papillae do not show stratification and have rounded, basally located nuclei.

Pseudohyperplastic adenocarcinomas are Gleason pattern 3 tumors within the prostate [25] and may metastasize [21]. The prognosis of patients with pseudohyperplastic adenocarcinoma is uncertain, but likely favorable. There is no significant difference in prognosis by pathologic stage for cases with and without hyperplastic features [21].

Microcystic variant

Microcystic acinar adenocarcinoma exhibits intermediate-sized glands with cystic dilatation. On average, the glands are 10 times the size of usual acinar adenocarcinoma and show rounded
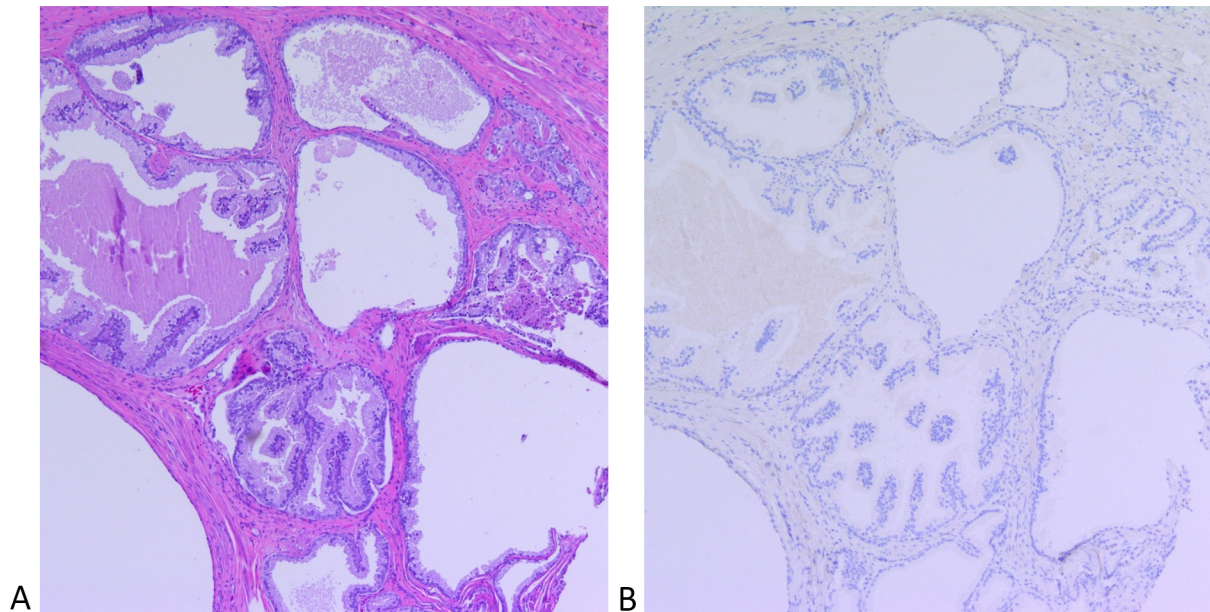
Figure 3. Pseudohyperplastic variant of acinar adenocarcinoma. A: Pseudohyperplastic variant of acinar adenocarcinoma composed of medium to large-sized glands showing dilatation and papillary infoldings with a deceptively benign appearance. A focus usual acinar adenocarcinoma (arrow) is seen adjacent to the malignant glands of pseudohyperplastic variant adenocarcinoma. (Hematoxylin and eosin stain, 40X magnification); B: An immunohistochemical for p63 demonstrates a complete lack of staining for basal cells in usual acinar carcinoma (arrow) and pseudohyperplastic carcinoma focus (open arrow) indicating these glands to be malignant in nature. (Hematoxylin and eosin stain, 40X magnification).

profiles and a flat luminal cell lining, simulating benign cystic atrophy of the prostate (**Figure 4A**). Up to 11% of usual acinar adenocarcinomas exhibit microcystic foci in radical prostatectomy cases [8]. AMACR expression is seen in almost all cases (96%), with the dilated glands lacking basal cells (**Figure 4B**) [16, 17].

The differential diagnosis includes cystic hyperplasia and cystic atrophy of the transition zone [26]. Findings useful in establishing a diagnosis of malignancy within microcystic glands include nuclear atypia, AMACR overexpression, lack of basal cells, and adjacent small acinar adenocarcinoma. Ductal adenocarcinomas of the prostate may also show cystic dilatation of the malignant glands, which can occasionally be seen microscopically and macroscopically [27, 28]. However, they differ from microcystic acinar adenocarcinomas in that the cysts are typically large (5-10 mm) and show intracystic papillae [16, 27]. In contrast, the malignant glands of microcystic acinar adenocarcinoma range from 0.4 to 0.9 mm, and typically have a flat malignant lining layer [17].

The assigned Gleason pattern is 3 for microcystic adenocarcinoma. While this is largely a low-grade adenocarcinoma, up to 36% of radical prostatectomy cases harbor Gleason pattern 4 elsewhere within the prostate [17], demonstrating that presence of only microcystic adenocarcinoma in a prostate needle biopsy specimen may indicate high-grade pattern 4 in the whole gland that was not sampled at the time of the biopsy. Uncommonly, the microcystic adenocarcinoma glands have been reported to invade into periprostatic adipose tissue [7], leading to a higher pT tumor classification. Microcystic acinar adenocarcinoma exhibits intermediate-sized glands with cystic dilatation. On average, the glands are 10 times the size of usual acinar adenocarcinoma and show rounded profiles and a flat luminal cell lining, simulating benign cystic atrophy of the prostate (**Figure 4A**). Up to 11% of usual acinar adenocarcinomas exhibit microcystic foci in radical prostatectomy cases [8]. AMACR

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Foamy gland variant

Foamy gland adenocarcinoma is typically found as a component of acinar adenocarcinoma (16-22% of cases) [29] and can be deceptively benign-appearing due to a lack of nuclear atypia [29-33]. Clinically, the mean age at diagnosis is 65 years (range 50-78 years) [31] and the preoperative PSA levels resemble those of patients with non-foamy gland carcinomas [32]. Morphologically,
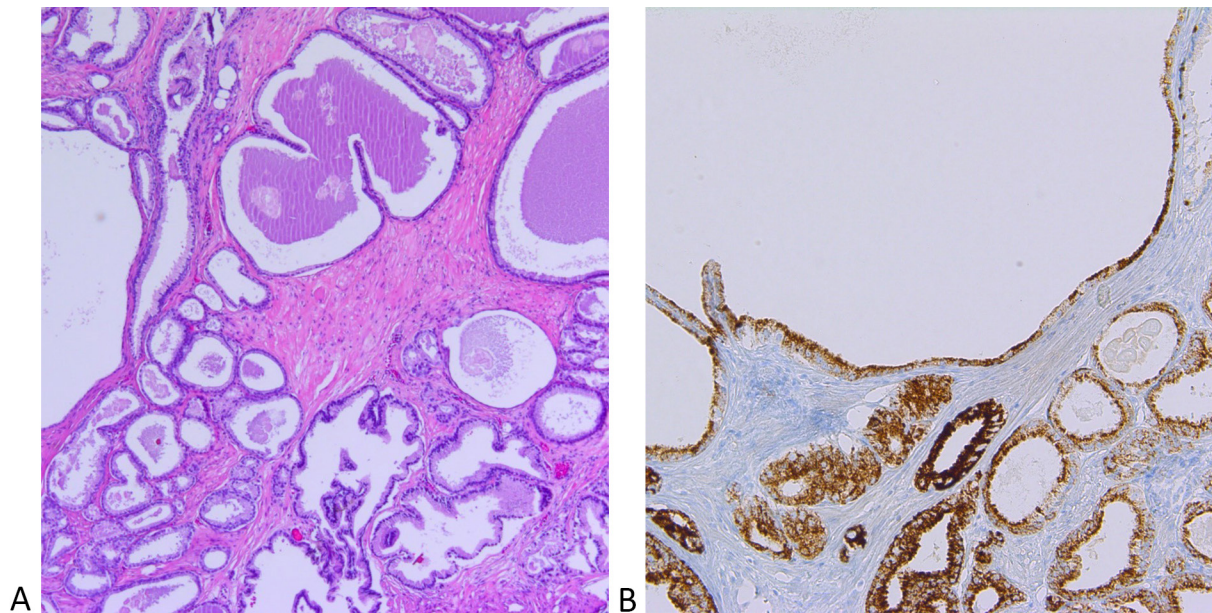
Figure 4. Microcystic variant of acinar adenocarcinoma. A: Cystically dilated glands with rounded profiles and flat luminal linings simulating benign glands with cystic change. Few admixed small malignant glands of the usual acinar adenocarcinoma with abundant cytoplasm and intraluminal mucin (arrow) are seen. (Hematoxylin and eosin stain, 40X magnification); B: AMACR (racemase) and p63 double stain shows intense racemase cytoplasmic staining and lack of p63 basal cell staining within the glands of the microcystic variant of acinar adenocarcinoma (arrow) as well as acinar carcinoma. (Immunohistochemical stain, 100X magnification).

the foamy gland variant is characterized by abundant foamy/ xanthomatous cytoplasm (**Figure 5**), often admixed with a non-foamy gland carcinoma component in 17% of needle biopsy cases [34], and 13-23% of radical prostatectomy cases [29]; they are rarely found in pure form. The foamy appearance of the cytoplasm is due to the presence of numerous intracytoplasmic vesicles lacking lipid or neutral mucin [35]. The nuclei are often pyknotic, without nuclear enlargement or prominent nucleoli, however up to 33% of cases show numerous prominent nucleoli with a Gleason score of 7 (16%) or above (52%) [36]. Immunohistochemical studies demonstrate AMACR to be an excellent diagnostic marker for foamy gland carcinoma with AMACR overexpression rates
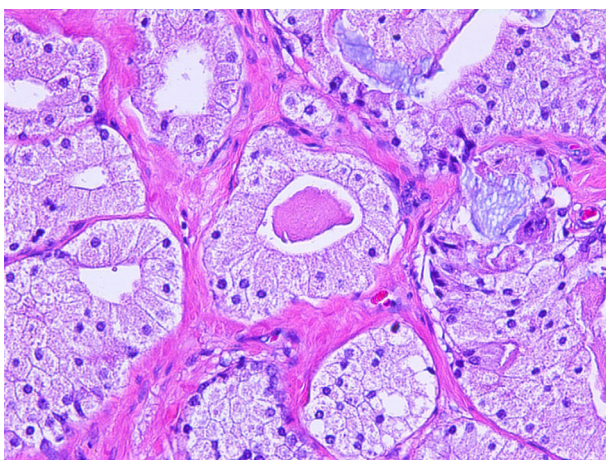

Figure 5. Foamy gland variant of adenocarcinoma seen here characterized by nests of cells with abundant xanthomatous cytoplasm, small pyknotic nuclei, and eosinophilic luminal secretions. (Hematoxylin and eosin stain, 200X magnification).

of up to 92% [29]. Basal cells are absent. TMPRSS2-ERG gene fusion is seen in 29% of foamy gland adenocarcinomas [37]. ERG protein expression by immunohistochemistry is detected in 42% of cases [33] but does not provide added diagnostic value beyond detection of AMACR in most cases.

The differential diagnosis includes benign prostatic glands, which can have foamy cytoplasm, as well as foamy macrophages, such as those seen in prostatic xanthomas [34, 35] and granulomatous prostatitis. Positivity for pan-cytokeratin, PSA, PAP, and NKX3.1, and negativity for CD68 can aid in confirmation of foamy gland carcinoma when foamy histiocytes are a consideration. Of note, rare cases of foamy gland high-grade prostatic intraepithelial neoplasia [38], intraductal foamy gland carcinoma [31], and foamy gland change in ductal adenocarcinomas of the prostate [39] have been reported. Androgen deprivation therapy can also induce cytologic changes in prostatic adenocarcinoma cells producing a similar appearance to foamy gland carcinoma with cytoplasmic vacuolization and nuclear pyknosis [40].

The lack of nuclear atypia in foamy glands can create diagnostic difficulties in establishing a malignant diagnosis, particularly in needle biopsy tissue. In contrast to the previously discussed deceptively benign-appearing prostatic adenocarcinomas, high grade foamy gland adenocarcinomas are seen more frequently and observed with Gleason pattern 7 assigned as the most common Gleason score (60%), followed by Gleason score 6 (32%), Gleason score 8 (3%), and Gleason score 9-10 (5%) [29]. Foamy gland carcinoma has a similar prognosis as non-foamy gland adenocarcinoma following prostatectomy [29].

Mucinous (Colloid) variant

Mucinous adenocarcinoma is defined as a tumor of which at least 25% has extracellular mucin pools. When mucin is confined within the lumen without spilling into the stroma, it does not qualify as a mucinous carcinoma component. Tumors from other primary

sites should be excluded with immunohistochemical confirmation of prostate origin. Because of the minimum 25% mucinous carcinoma volume requirement, this diagnosis can be made reliably only upon sampling of the entire tumor on radical prostatectomy specimens. When evaluating needle biopsy specimens, tumors with this morphology may be more appropriately described as adenocarcinoma with a "mucinous carcinoma component". Due to this requirement, approximately only 0.2% of prostatic adenocarcinomas are diagnosed as mucinous adenocarcinoma in radical prostatectomy specimens [41-43]. These tumors have no specific epidemiological features.

Mucinous adenocarcinoma is composed of individual glands, fused glands, and cribriform nests floating in large mucin pools and lakes, with the individual tumor cells showing the usual cytologic features of acinar adenocarcinoma. Collagenous micronodules may be present [44] but intracytoplasmic mucin is generally not seen. To determine the grade, the mucin must be ignored, and the usual Gleason criteria must be applied to the underlying architecture. Immunohistochemical studies show positive immunoreactivity for prostate-specific markers and ERG similar to usual acinar adenocarcinoma [45].

Most cases of mucinous adenocarcinoma are assigned Gleason scores of 7 or 8. Early reports found these to be aggressive tumors [41, 46], however more recently published data suggests that they may have better prognosis than that indicated by the assigned Gleason score [47, 48]. According to a Surveillance, Epidemiology, and End Results Program (SEER) database study, mucinous adenocarcinomas were found to have a similar survival to that of usual adenocarcinomas but superior to those of other adenocarcinoma variants [48].

Signet ring-like cell variant

Signet ring-like cell variant of prostate carcinoma was so named because the signet ring cell formation in the prostate is usually due to the presence of intracytoplasmic vacuoles, rather than intracytoplasmic mucin. Signet ring cell tumors with intracytoplasmic mucin positive with mucin stains, such as PAS, Alcian blue or mucicarmine stains, are more likely to originate from the bladder or other metastatic sites, such as stomach, colon or rectum. The major differential diagnostic consideration of prostatic signet ring-like cell carcinoma is metastasis or secondary involvement of signet ring cell carcinoma from the gastrointestinal or urothelial tract, which are positive for mucin stains and negative for prostate-specific markers. Signet ring-like cell carcinoma requires at least 25% of tumor cells be composed of signet ring-like cells (**Figure 6**). Additionally, to make a diagnosis of true signet ring-like cell carcinoma of the prostate, vacuoles must be seen in single isolated tumor cells of Gleason pattern 5. Hormone treated prostate cancers frequently produce signet ring-cell distortion and superficially resemble signet ring-like cell variant of prostate carcinoma. Therefore, hormone treated prostate cancer should be excluded before making a diagnosis of primary signet ring-like cell carcinoma of prostate.

Signet ring-like cell carcinoma of the prostate is rare, with an estimated incidence of 30 cases per 100 000 cases of prostate cancer [49]. Clinically, the presentation is similar to conventional acinar prostatic adenocarcinoma [16, 50-53], however this is a highly aggressive tumor, with a mean survival of 29 months [49]. Patients treated with a combination of surgery and hormonal therapy tend to have superior outcomes [49, 52, 54].

Pleomorphic giant cell variant

An exceptionally rare variant with few cases reported is pleomorphic giant cell variant of adenocarcinoma. This variant contains giant, bizarre, anaplastic cells with pleomorphic nuclei lacking a malignant spindle cell component (**Figure 7**). Clinically, the mean patient age at diagnosis is 65 years (ranging from 45 to 77 years), with most patients having a history of conventional prostate cancer being treated with hormonal or radiation therapy prior to the diagnosis of pleomorphic giant cell adenocarcinoma being rendered. Morphologically, there is marked pleomorphism involving up to 70% of the tumor including the possible presence of atypical mitoses. Admixed conventional adenocarcinoma with a Gleason score of 9 or 10 is present in almost all cases of pleomorphic giant cell adenocarcinoma [55, 56]. Cases are reported to be DNA aneuploid and immunoreactive for cytokeratins using AE1/AE3 and/or CAM 5.2 antibodies. Staining for conventional prostate markers may be negative, with approximately 50% of cases positive for PSA in the conventional prostate carcinoma component (1-100%) [55, 56].

The differential diagnosis should include sarcomatoid carcinoma exhibiting occasional pleomorphism and tumors with spindle cells,
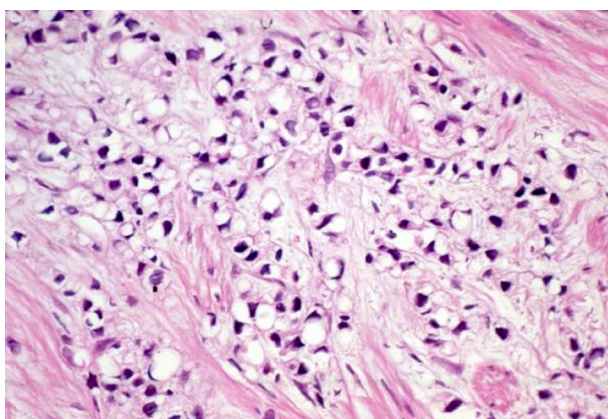

Figure 6. Signet ring-like cell variant. Diffuse infiltration by cords of discohesive round cells with intracytoplasmic vacuoles causing peripheral displacement of nuclei. This carcinoma is usually of high grade (Gleason pattern 5). (Hematoxylin and eosin stain, 200X magnification).
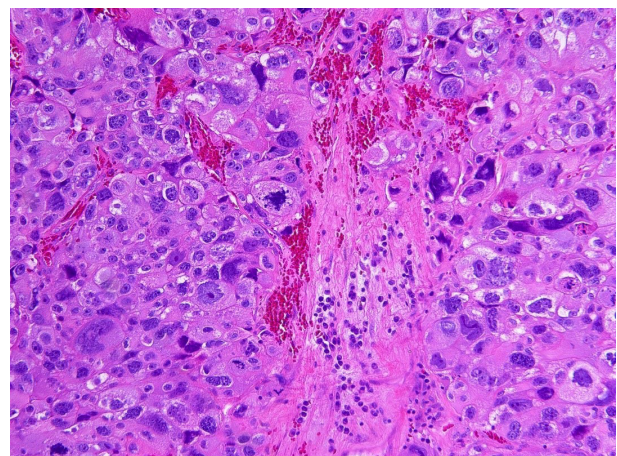

Figure 7. Pleomorphic giant cell variant prostatic adenocarcinoma showing giant, bizarre, anaplastic tumor cells with significant nuclear pleomorphism and atypical mitotic figures. No spindle cell component is seen. (Hematoxylin and eosin stain, 200X magnification).

osteoclast-type or trophoblastic giant cells. High grade urothelial carcinoma is also an important diagnostic consideration, and urothelial markers such as GATA3 should be performed prior to rendering a diagnosis of pleomorphic giant cell carcinoma of the prostate. These tumors have an extremely aggressive disease course.

Sarcomatoid variant

Sarcomatoid carcinoma (also known as "carcinosarcoma") is a biphasic malignant neoplasm exhibiting epithelial and sarcomatoid differentiation. Clinically, these tumors present in older men (median age 68 years) [57, 58]. Approximately half of patients have a history of acinar adenocarcinoma treated with radiation and/or hormonal therapy [58, 59]. Morphologically, some cases display a mixture of a sarcomatoid component and typical adenocarcinoma. Recent molecular studies have shown that both elements are of the same clonal origin [60]. The epithelial component is usually adenocarcinoma with a variable but relatively high Gleason score [57, 58] that shows immunoreactivity for cytokeratin, PSA, and PAP. Sarcomatoid components include homologous sarcomatoid components including leiomyosarcoma, liposarcoma, angiosarcoma, and heterologous components with osteosarcoma, chondrosarcoma, rhabdomyosarcoma, and other multiple heterologous lines of differentiation with frequent immunopositivity for various mesenchymal markers [57, 58]. Sarcomatoid carcinomas tend to have a dismal prognosis, regardless of treatment, showing a 5-year cancer-specific survival rate of 40% [57].

Small cell carcinoma

Small cell carcinoma is classified as a separate tumor category in WHO classification, within the neuroendocrine tumors. The discussion of small cell carcinoma in this review is included because small cell carcinoma is often preceded by a diagnosis of acinar adenocarcinoma and rarely presents as a de novo tumor [2]. More than half of small cell carcinomas are associated with a conventional prostatic adenocarcinoma [2, 61, 62]. As in other systems, small cell carcinoma has an aggressive clinical course, however, treatment with chemotherapeutic regimens like those used for pulmonary small cell carcinoma has resulted in a prolonged survival, particularly in patients with only regional lymph node spread [61-66]. These tumors tend to metastasize early to pelvic lymph nodes, lung, and liver, with less commonly reported locations including omentum, vocal cord, temporal bone, axillary lymph node, and peripheral soft tissue [67]. Due to the unique clinicopathologic features of small cell carcinoma, which are typically distinct from those of Gleason pattern 5 acinar adenocarcinoma, these tumors should not be assigned a Gleason score [25].

   The histologic and immunohistochemical features are similar to those seen in lung and other extrapulmonary sites including hyperchromatic nuclei and prominent nuclear molding (**Figures 8A and 8B**), and immunoreactivity for neuroendocrine markers (synaptophysin, chromogranin and CD56). These malignancies can rarely be associated with sarcomatoid and squamous carcinoma components [61]. The cells of some tumors contain dense core neurosecretory granules and show positive immunoreactivity for synaptophysin, chromogranin, and CD56 as well as TTF-1 (50%) [68], and CD44 (100%) [67]. CD44 has been found to be negative in most small cell carcinomas of non-prostate origin [68]. A significant subset is frequently negative for prostate tissue markers such as P501S, PSA, and PAP [67].

   Small cell carcinoma may be difficult to differentiate from crushed non-small cell carcinoma. If prostatic markers such as
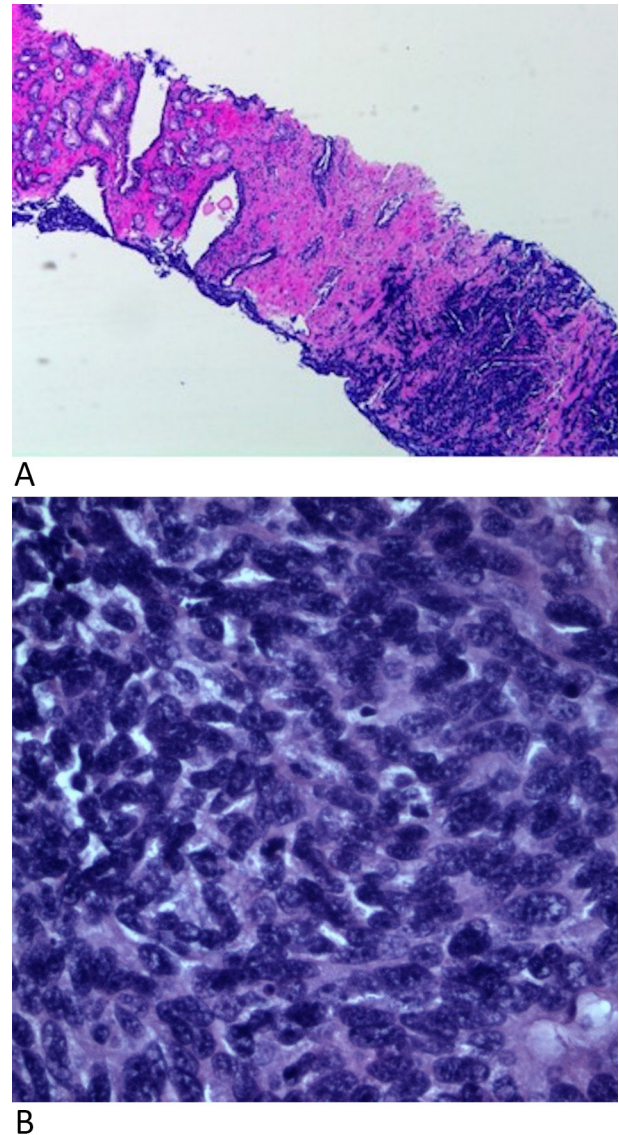
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B

Figure 8. Small cell carcinoma of the prostate. A: Small cell carcinoma (right) consisting of tumor cells with hyperchromatic nuclei and nuclear molding with a focus of usual acinar adenocarcinoma (left). (Hematoxylin and eosin stain, 40X magnification); B: Small cell carcinoma showing small round, oval, or spindle cells with hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm with nuclear molding. Few mitotic figures are also seen. (Hematoxylin and eosin stain, 400x magnification).

PSA and PAP are strongly and diffusely positive, a diagnosis of small cell carcinoma should not be made and should instead be interpreted as non-small cell carcinoma. Small cell carcinoma is typically negative or focally, weakly positive for PSA and PAP and positive for neuroendocrine markers.

Conclusion

It is important to differentiate the histologic variants of prostate acinar adenocarcinoma from benign prostate lesion mimickers and potential metastatic tumors. Important benign mimickers that may be misinterpreted as a variant of acinar adenocarcinoma include lesions such as benign atrophy, benign prostatic hyperplasia, and cystic atrophy. These benign mimickers can be problematic

when attempting to differentiate them specifically from the atrophic, pseudohyperplastic, and microcystic variants. Benign prostatic glands with foamy features, prostatic xanthomas, and granulomatous prostatitis can cause diagnostic confusion with the foamy gland variant of acinar adenocarcinoma. Although variants such as the mucinous, signet ring-like cell, pleomorphic giant cell, and sarcomatoid variants may not present as diagnostic challenges when evaluating for the presence of malignancy, it is important to rule out involvement by metastatic carcinomas, most commonly of bladder or colonic origin, which will often require the use of immunostains. Additionally, some variants of acinar adenocarcinoma show prognostic differences, further illustrating the importance of accurate recognition. While the atrophic, pseudohyperplastic, microcystic, and foamy gland variants typically show no prognostic difference, the mucinous, signet ring-like cell, pleomorphic giant cell, and sarcomatoid variants are usually higher-grade tumors and are associated with a worse prognosis. Small cell carcinoma of the prostate is not considered a true variant of acinar adenocarcinoma and is not assigned a Gleason score, but is often preceded by a diagnosis of acinar adenocarcinoma and has an aggressive clinical course. A foundational diagnostic awareness of these histologic variants, as well as of their clinicopathologic features, is essential in rendering an accurate diagnosis.

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