INTRODUCTION
Pathologists are understandably concerned about failing to diagnose a malignant neoplasm. It is arguably as important, however, for them to recognize benign but deceptive lesions that mimic cancers. Overinterpretation of such pseudomalignant lesions may lead to unnecessary, radical surgery with attendant functional disability and even potential mortality. In this lecture we will explore some of the lesions of the prostate that are commonly confused with cancers. Time constraints prevent further exploration of these interesting and important lesions at other sites of the male genitourinary tract, however, there are a number of excellent reviews for those who wish to investigate this topic in greater depth and at additional genitourinary tract locations.\textsuperscript{1-11}

PSEUDOMALIGNANT LESIONS OF THE PROSTATE
The prostate is often sampled and the source of a number lesions that mimic cancers. Because these lesions tend to preferentially affect different prostatic zones, it is useful to review the anatomy of the prostate according to the McNeal model.\textsuperscript{12,13}
The prostate is a pyramidal shaped organ with its base oriented superiorly and its apex inferiorly. The urethra enters the prostatic base and has a sharp angulation at the verumontanum, with the proximal segment bent anteriorly. There are four major prostatic zones; the central zone is a wedge-shaped segment of the gland with its base at the prostatic base and its apex terminating at the verumontanum at the angulation of the prostatic urethra; it comprises about 25% of the glandular prostate but is less commonly the site for prostatic carcinoma based on its size. The ejaculatory ducts penetrate the prostatic central zone and run within it to terminate at the verumontanum. The transition zone is a small dumbbell-shaped segment that surrounds the proximal prostatic urethra; it represents about 5% of the gland-bearing portion of the prostate, but disproportionate numbers of primary carcinomas develop within it. The peripheral zone comprises the majority of the glandular prostatic volume (70%) and envelopes the posterior portion of the gland with lateral wings along either side. The majority of prostatic carcinomas, and especially the clinically relevant ones, develop in the peripheral zone. The anterior fibromuscular stroma comprises the anterior aspect of the prostate, from superior to inferior aspects but terminating at the level of the urethra; it lacks glandular tissue.

Atrophy

Atrophy is said to be the benign lesion of the prostate that is most commonly misinterpreted as adenocarcinoma. This appears to be especially the case with a lesion that is designated “partial atrophy,” with the more classic form of atrophy, now termed “post-atrophic hyperplasia” according to a consensus paper, posing less of a diagnostic problem.
Atrophy is common and may be seen at any age but increases in frequency in older men. The peripheral zone of the prostate is preferentially involved, where atrophy is invariably an incidental finding in prostatic biopsies or resections. It is associated with chronic prostatitis, ischemia, hormonal deprivation therapy, and radiation treatment. The former two result in focal atrophy whereas the latter two produce diffuse atrophic changes. The biologic significance of atrophy is not clear, with arguments both supporting and refuting its possible role as a precursor to prostate cancer, particularly atrophy associated with inflammation (so called “proliferative inflammatory atrophy” [PIA])\(^{17,18}\). For instance, one recent study found that atrophy on an initial prostate biopsy was associated with a reduced risk of cancer,\(^ {19}\) whereas others considered atrophy a plausible precursor based on its linkage to inflammation and consequent oxidative cellular damage as well as its disproportionate frequency in proximity to cancer.\(^ {17,20,21}\) Because there is no consensus concerning the association of atrophy with cancer, it is not necessary to document its presence in biopsy reports.

A recent paper proposed a consensus classification of atrophy, recognizing four categories: simple atrophy, simple atrophy with cyst formation, post-atrophic hyperplasia, and partial atrophy.\(^ {14}\) Because the first two groups, definitionally, have normal-sized glands with shrunken cytoplasm, they are not frequently misinterpreted as carcinoma and will not be considered here.
Post-atrophic hyperplasia was often formerly termed lobular or sclerotic atrophy. It consists of lobular arrangements of small glands with shrunken cytoplasm, typically centered on a large duct. The scant cytoplasm causes a basophilic appearance at low magnification. The immediately surrounding stroma may be sclerotic and chronically inflamed, and the prostatic glands are often angulated. At high magnification, the nuclei of the atrophic secretory cells are crowded but have bland cytological features. A basal cell layer is present but often compressed and therefore relatively inconspicuous.

Post-atrophic hyperplasia may be confused with atrophic prostatic adenocarcinoma.\textsuperscript{22-24} The low power appearance of the latter may mimic post-atrophic hyperplasia, showing an apparently lobular arrangement of atrophic glands in the limited sampling afforded by a needle biopsy. However, there are non-atrophic glands with the typical features of usual prostatic adenocarcinoma (nuclear enlargement, nucleomegaly, darker cytoplasm, luminal crystalloids, absence of basal cells) that permit the correct diagnosis. Atrophic adenocarcinoma may also have an invasive growth pattern of shrunken glands with the usual cytological features of prostatic adenocarcinoma. This variant is less problematic since the low power appearance is alarming. If the distinction of post-atrophic hyperplasia from atrophic adenocarcinoma is in doubt (mostly on needle core biopsies), immunostains for basal cells and racemase are useful since basal cells are present in post-atrophic hyperplasia whereas they are absent in atrophic adenocarcinoma, with racemase being positive in about two-thirds of the latter\textsuperscript{25} (more intensely so, in my experience, in the non-atrophic glandular component).
Pseudomalignant Prostatic Lesions

Partial atrophy is perhaps the single most common benign prostatic lesion to be misinterpreted as carcinoma. It represents a lobular to partially disorganized arrangement of glands with scant apical cytoplasm and abundant, lightly-staining lateral cytoplasm. The latter causes a pale appearance at low magnification, similar to that of many low-grade prostatic adenocarcinomas. The poorly organized lobular arrangement of many cases and the limited sampling afforded by needle biopsy cause concern for adenocarcinoma. This concern is further enhanced by nuclear enlargement and nucleolar prominence in 15% and 20% of cases, respectively. Additionally, immunostains are not an always reliable means of resolving the differential diagnosis of partial atrophy versus adenocarcinoma in a significant proportion of cases. In one study of partial atrophy on needle biopsy specimens, only 24% of cases had the expected benign immunophenotype (positive for basal cells and negative for racemase), whereas basal cells were absent by immunostaining in almost one-third of cases and racemase was positive in close to 70%. This, therefore, is a differential diagnosis that may largely rely on careful light microscopic analysis of routine H&E stains.

There are several key light microscopic features that, collectively, allow the accurate diagnosis of partial atrophy. Despite that a lobular pattern may not be appreciable in all cases, partial atrophy lacks an overtly infiltrative pattern, unlike most prostatic adenocarcinomas. The cytoplasm is pale, which contrasts with the more darkly staining cytoplasm of many adenocarcinomas. A key feature is that the luminal border in partial atrophy is at least focally ruffled, unlike the straight luminal border typical of adenocarcinoma and the contour of the glands is also often undulating. The “stunted”
apical cytoplasm contrasts with the usually more abundant apical cytoplasm of adenocarcinoma. Furthermore, “blue” (acidic) mucin is lacking and “pink” intraluminal secretions are rare, unlike the frequent presence of these features in adenocarcinoma. Although nuclear and nucleolar enlargement are seen in up to 20% of cases, the prominent enlargement of these structures that occurs in some adenocarcinomas is not seen. Occasional glands involved by partial atrophy may have foci that show complete atrophy, with scant lateral cytoplasm. Additionally, glands of partial atrophy and complete atrophy may admix. A positive reaction for basal cell markers, although not always seen, indicates a benign process. These are lesions that have glands with a variable appearance; some glands are more worrisome than others. The fundamentally similar nuclear morphology of the clearly benign glands compared to the worrisome glands provides reassurance that both are benign.

**Sclerosing adenosis**

Sclerosing adenosis is a rare lesion of the transition zone mostly seen in older men. It is therefore usually detected in TUR specimens rather than needle biopsies and consists of a circumscribed proliferation of small glands, nests, and individual cells that are intimately admixed with a spindle cell stroma. The acini, nests, and single cells may be surrounded by a thick basement membrane, in contrast to prostatic adenocarcinoma. In occasional cases, the glands my contain luminal crystalloids and, occasionally, acidic mucin. A distinctive and diagnostically important feature is the myoepithelial differentiation of the basal cell layer, which therefore stains for S-100 protein and muscle-specific actin as well as high molecular weight cytokeratin. Although most cases
Pseudomalignant Prostatic Lesions

have bland cytological features, infrequent examples may show cytological atypia in the form of nuclear enlargement and nucleolar prominence (termed “atypical sclerosing adenosis”); these cases nonetheless have the other features of more usual sclerosing adenosis and the patients had a benign follow-up.

Because of the small nests and individual cells that are seen in sclerosing adenosis, the chief differential diagnostic consideration is high-grade adenocarcinoma. Features of sclerosing adenosis that contrast with those of high-grade adenocarcinoma include its circumscription, generally bland cytological features, prominent associated spindle cell stroma, presence of thick pericellular basement membrane, and transition zone predominance. Confirmation can be obtained by positivity for myoepithelial markers.

Atypical adenomatous hyperplasia (AAH)/adenosis

This is a lesion that occurs mostly in the transition zone, the periurethral area, or the prostatic apex. It is common and found in about 20% of TUR specimens at a mean age of 65-70 years. We still do not know the biologic significance of AAH/adenosis, and this deficiency is reflected in the variable nomenclature.

On microscopic examination, there is a circumscribed nodule of variably sized glands with abundant, pale cytoplasm. The larger glands have papillary infoldings or undulating borders but some of the smaller glands have straight luminal edges that typify prostatic adenocarcinoma. The smaller, more concerning glands, at least in my experience, tend to be placed at the periphery of the focus of AAH/adenosis. The glandular secretory cells
Pseudomalignant Prostatic Lesions

have bland cytological features but often their acini lack a discernable basal cell layer, although basal cells may be identified in otherwise similar glands that are close by. Basal cell markers show a discontinuous and patchily absent basal cell layer, providing reassurance of the benign nature of the lesion. Immunostains for racemase may be positive in AAH/adenosis and are, therefore, not very helpful in the differential diagnosis with prostatic adenocarcinoma.35

The chief differential of AAH/adenosis is with low-grade adenocarcinoma. Helpful features include, in AAH/adenosis: the presence of larger glands with papillary luminal infoldings (in contrast to the small glands with straight borders in carcinoma); the fact that AAH/adenosis has pale or clear cytoplasm (whereas adenocarcinomas may have more densely staining cytoplasm); inconspicuous to medium-sized nucleoli in AAH/adenosis; the rare occurrence of acidic mucin in AAH/adenosis; and the occurrence of basal cells in AAH/adenosis.

(Clear cell) Cribriform hyperplasia

This is a distinctive and incidental lesion of the transition zone that is mostly found in TUR specimens of patients with prostatism.36,37 It consists of a circumscribed proliferation of glands with a complex, cribriform architecture whose cells often, but not always, have clear or at least pale cytoplasm. In contrast to adenocarcinomas having cribriform glands, there is an intact (and often conspicuous) basal cell layer in clear cell cribriform hyperplasia and the nuclear features are bland, with the latter feature also contrasting with cribriform PIN/intraductal adenocarcinoma. The clear to pale cytoplasm
of clear cell cribriform hyperplasia also contrasts with the denser cytoplasm that typifies higher-grade adenocarcinoma and PIN. Ploidy studies and follow-up support its benign nature.  

**Basal cell hyperplasia**

Basal cell hyperplasia is mostly a transition zone lesion that is seen in about 10% of TUR specimens, although it rarely occurs in the peripheral zone where it is more apt to be sampled by needle biopsy. Some cases are secondary to antiandrogen therapy. At low magnification there is a nodular pattern of darkly stained glands having peripheral cuffs of proliferated basal cells with (“incomplete basal cell hyperplasia”) or without (“complete basal cell hyperplasia”) residual lumens. Psammomatous calcification occurs in about one-half of the cases. An adenoid-cystic-like pattern may develop in some glands, with the development of a cribriform growth of cells around eosinophilic to lightly basophilic material. Cytological atypia of the basal cells may also be seen; this usually takes the form of mild nuclear enlargement with nucleolar prominence. Some striking examples of atypia arise secondary to radiation treatment; in these cases the basal cells may show prominent nuclear enlargement, pleomorphism, hyperchromasia and nucleolar prominence. Despite such features, this is a benign lesion.

Basal cell hyperplasia may be confused with high grade PIN. Contrasting features include the small acinar appearance of basal cell hyperplasia, with PIN occurring in normal-sized glands; the frequently solid nests formed by basal cell hyperplasia, with PIN glands having residual lumens; the flat to round lesional cells in basal cell hyperplasia, with PIN
showing columnar and stratified cellular profiles; the bland cytological features of residual secretory cells in basal cell hyperplasia, with PIN having secretory cells with nuclear enlargement, hyperchromasia and nucleolar prominence; and the fact that the lesional cells in basal cell hyperplasia are positive for p63 and high molecular weight cytokeratin, but not those of PIN.

Another important differential for basal cell hyperplasia is its distinction from basal cell carcinoma. Contrasting features include confinement of basal cell hyperplasia to the prostate, whereas basal cell carcinoma may extend outside of the gland, especially involving the bladder neck; the nests and glands of basal cell hyperplasia are relatively uniform in size and shape, whereas those of basal cell carcinoma are often more irregular; basal cell hyperplasia is not necrotic, with basal cell carcinoma sometimes having central necrosis; no perineural invasion is seen in basal cell hyperplasia, but it may be found in basal cell carcinoma; basal cell hyperplasia does not induce a stromal reaction, whereas desmoplasia is frequent in basal cell carcinoma. Some cases of basal cell hyperplasia may develop an adenoid-cystic like pattern; in contrast to true adenoid cystic carcinoma of the prostate, which is a very rare entity usually considered to be a variant of basal cell carcinoma, adenoid cystic-like hyperplasia is transition zone predominant, often multifocal, has a lobular arrangement and close association with nodular hyperplasia, does not form large cribriform glands and lacks invasive growth patterns and perineural invasion. Psammomatous calcifications, hyaline globules, and cytologically bland, non-keratinizing squamous metaplasia also favor basal cell hyperplasia.
Nephrogenic adenoma

Nephrogenic adenoma is a classic pseudomalignant lesion that may occur in the prostatic urethra (hence its inclusion in this discussion of prostatic pseudomalignancies), although its most common location is the urinary bladder. Most patients have a history of prior procedures (cystoscopy, catheterization), infection, or urinary stones. Molecular studies support that nephrogenic adenoma is a true nephrogenic proliferation that derives from shed renal tubular cells that ectopically implant in distal sites. It is likely that “favorable soil” is created by the predisposing conditions mentioned above. Those that develop in the prostatic urethra may extend into the underlying prostatic stroma, thereby creating confusion with prostatic adenocarcinoma.

A variety of patterns, including tubular, papillary, cystic, and diffuse may be seen. Most characteristic is the formation of small tubules with cuboidal, biscuit-shaped cells, sometimes having apically protruding nuclei (“hobnail cells”). Some case may show rare signet ring-type cells amid the usually tubules. Many tubules have laterally attenuated cytoplasm, as often seen in the regenerating tubules of the kidney following an episode of acute tubular necrosis. Those with cystic change may show a glassy, colloid-like secretion in the cystic spaces. A characteristic and diagnostically helpful finding, reported in 20-65% of cases, is a thickened, and hyalinized basement membrane around the tubules and nests, similar to that seen in cases of sclerosing adenosis. Mitotic figures are very rare to absent, and the stroma often has a granulation tissue-like quality, with numerous vessels and mixed inflammatory cells. About 20% of the cases are multifocal.
A more recently described variant that may also occur in the prostatic urethra has been termed “fibromyxoid” type. In these cases, the nephrogenic adenoma is dominated by a stroma that varies from myxoid to fibrous and that contains occasional spindle shaped cells. The typical immunohistochemical staining features of nephrogenic adenoma (see below) and the association of the fibromyxoid pattern with more characteristic foci permit diagnosis of this variant.

Nephrogenic adenoma is positive for cytokeratins and, in about 60% of cases, for AMACR (racemase). Secretions in the lumens of its tubules may be positive for PSA and prostatic acid phosphatase and high molecular weight keratin stains may be negative. These reactions, coupled with the extension into the prostatic stroma, nucleolar prominence and blue-tinged luminal secretions may give rise to a false diagnosis of adenocarcinoma. Helpful differentiating features include the occurrence of multiple architectural patterns in many nephrogenic adenomas, whereas adenocarcinomas are limited to glandular patterns; the flattened to hobnail cell profiles in nephrogenic adenoma, which contrast with the cuboidal or columnar profiles with straight luminal edges in adenocarcinoma; the prominent peritubular basement membrane in areas of many nephrogenic adenomas, a finding absent in adenocarcinoma; the inflamed stroma of nephrogenic adenoma, which contrasts with the normal stroma seen in adenocarcinoma; and the “hard,” colloid-like secretions present in nephrogenic adenomas with cystic change, in contrast to the “loose” amorphous glandular secretions characteristic of adenocarcinoma. Cytoplasmic (not luminal) positivity for PSA and prostatic acid
Pseudomalignant Prostatic Lesions

phosphatase points to adenocarcinoma, whereas PAX2, PAX8 and CK7 immunostaining supports nephrogenic adenoma.$^{49}$

Verumontanum mucosal gland hyperplasia (VMGH)

Crowded small glands occur in and around the verumontanum and may cause confusion with adenocarcinoma.$^{50,51}$ This lesion is termed verumontanum mucosal gland hyperplasia, but it is arguable if it is a true hyperplasia or simply a normal finding. VMGH, unlike prostatic adenocarcinoma, has an investing layer of basal cells peripheral to the secretory cells and shows a distinctive, brown-orange, colloid-like secretion and corpora amylacea in the lumens of some of the glands.

Seminal vesicle and ejaculatory duct (SV/ED)

When either the seminal vesicle or ejaculatory duct is sampled on needle biopsy of the prostate, it may be misinterpreted as adenocarcinoma. This is most apt to occur in biopsies directed at the prostatic base. Significant cytological atypia of the lining cells occurs in both of these structures; there are nuclear pleomorphism, hyperchromasia, and nuclear pseudoinclusions. Actually, all of these features should prompt consideration of SV/ED because most prostatic adenocarcinomas lack such findings to the same degree. In some cases, the lobular arrangement of the atypical glands around a larger duct helps with the recognition of SV/ED. The presence of conspicuous cytoplasmic lipofuscin provides evidence of SV/ED but should not be considered specific since lipofuscin also may be seen in prostatic adenocarcinoma as well as non-neoplastic prostate,$^{52}$ although not usually to an equivalent extent as in SV/ED. Additionally, SV/ED has an investment
of basal cells that may be demonstrated with p63 and high molecular weight cytokeratin immunostains, unlike prostatic adenocarcinoma. Also, SV/ED is negative for both PSA and prostatic acid phosphatase, unlike the great majority of prostatic adenocarcinomas.

Mesonephric remnant hyperplasia

Hyperplasia of mesonephric remnants\(^\text{53}\) may be misinterpreted as adenocarcinoma, leading to unnecessary prostatectomy. This lesion is rare and invariably an incidental finding, mostly in TURP or radical prostatectomy specimens. The average age is 60 years. The anterior fibromuscular stroma and the region near the prostatic base are most commonly affected, but other foci may be involved.\(^\text{53}\) The usual finding is a lobular proliferation of small glands with colloid-like secretion, although cystic change and a more disorganized arrangement may also be seen. Less frequently small glands admix with spindle cells. Immunostains for PAX8 are positive and PSA are negative, helping with the distinction from prostatic adenocarcinoma. On the other hand p63 is negative, and 34\(\beta\)E12 and AMACR variable, possibly causing additional simulation of prostatic adenocarcinoma.
References

Pseudomalignant Prostatic Lesions


