MIMICKERS OF ADENOCARCINOMA OF THE PROSTATE

MIMICKERS OF GLEASON SCORE 2 TO 6 ADENOCARCINOMA

Adenosis

There are several mimickers of Gleason 2 to 6 adenocarcinoma (Table 7.1). One of the most common lesions that may be confused with carcinoma is adenosis.1–7

The other commonly used term for adenosis is atypical adenomatous hyperplasia (AAH). We prefer the term adenosis, as prefacing adenomatous hyperplasia with atypical has adverse consequences both in terms of practical patient management and in our theoretical framework of this entity. As outlined in the following text, there are very little data in support of a relation between adenosis and carcinoma. By designating these lesions as atypical, many patients will be subjected to unnecessary repeat biopsies. Conceptually, as has happened in the past, use of the term atypical adenomatous hyperplasia will result in this entity being considered with prostatic intraepithelial neoplasia (PIN) as precursors to carcinoma of the prostate. Whereas there is strong evidence that PIN is a precursor to some prostate cancers, this evidence is lacking in adenosis.

There is a wide spectrum in the literature in terms of the reported incidence of adenosis on transurethral resection of the prostate (TURP), ranging from 2.2% to 19.6%.8 The reason for this broad range is different thresholds for diagnosing a focus of crowded glands as adenosis. Included within the lower threshold are prostate specimens with foci of crowded glands, which could be considered a minimal example of adenosis, although they do not closely mimic adenocarcinoma. Crowded benign glands that have absent or patchy staining for basal cell markers and/or positive racemase immunoreactivity are one of the more frequent mimickers of prostate cancer.9 At the other extreme, seen in 1.6% of benign TURPs performed at The Johns Hopkins Hospital, adenosis closely mimics adenocarcinoma of the prostate. The diagnosis of adenosis should be restricted to cases with a sufficiently atypical growth pattern that one has to seriously consider the diagnosis of low-grade cancer. This gradual spectrum within adenosis from a crowded focus of obviously benign glands
to lesions that share similar features, yet more closely resemble cancer, supports the concept that adenosis is a hyperplastic rather than neoplastic lesion. Because adenosis preferentially occurs within the transition zone, it is more frequently seen on TURP as an incidental finding than on needle biopsy. However, in approximately 0.8% of needle biopsies, adenosis may be identified. This incidence is infrequent enough that many pathologists do not consider it in the differential diagnosis of small glandular lesions on needle biopsy. However, the frequency of adenosis on needle biopsy is sufficiently high that there is a good chance that one will see this lesion in one's practice with the potential to overdiagnose it as adenocarcinoma.

The distinction of adenosis from low-grade adenocarcinoma is based on architectural and cytologic features (Table 7.2). In order to minimize
misdiagnoses, the constellation of histologic features seen in a lesion should outweigh the significance of any one diagnostic feature (eFigs. 7.1 to 7.115). At scanning magnification, adenosis is characterized by a lobular proliferation of small glands (Figs. 7.1 to 7.5). In contrast, low-grade carcinoma has a haphazard, irregular, infiltrative growth pattern. Despite the overall lobular pattern seen in adenosis, 19% of cases reveal minimal infiltration of glands into the surrounding stroma (Fig. 7.4).

Probably the most important differentiating feature of adenosis seen on hematoxylin and eosin (H&E) stain is that within a nodule of adenosis there are elongated glands with papillary infolding and branching lumina typical of more benign glands, yet in their nuclear and cytoplasmic features, they look similar to the adjacent small glands suspicious for carcinoma (Figs. 7.6 and 7.7). Another common feature seen is the budding off of glands of adenosis from obviously benign glands. Glands of adenocarcinoma, even in the unusual case when the tumor is fairly lobular, shows a pure population of small crowded glands without benign architectural features that do not merge in with adjacent larger benign glands.

At higher power, adenosis is typically composed of small glands with pale to clear cytoplasm, as opposed to some carcinomas, which have more amphophilic cytoplasm (Figs. 7.7 to 7.9). In order for this feature to be diagnostically useful, the cytoplasm of benign prostate glands should appear pale or clear on routinely stained slides. A diagnosis of carcinoma should not be rendered based on what appears to be either a few individual cells or poorly formed glands within a nodule that is otherwise (text continues on p. 137)
FIGURE 7.2  Medium magnification of Figure 7.1 with small glands merging in with more recognizably benign glands.

FIGURE 7.3  Higher magnification of Figure 7.1 with some glands showing recognizable basal cells (arrows). Note adenosis may contain small visible nucleoli.
FIGURE 7.4  Adenosis which appears circumscribed in some areas (right) yet somewhat more infiltrative in others (top). Note admixture of more benign–appearing glands with papillary infolding and branching adjacent to smaller crowded glands.

FIGURE 7.5  Well-circumscribed nodule of adenosis containing benign-appearing glands with papillary infolding and branching mixed with smaller crowded glands resembling cancer.
FIGURE 7.6  Medium magnification of Figure 7.5 where small glands of adenosis share identical nuclear and cytoplasmic features to adjacent more benign–appearing gland.

FIGURE 7.7  Higher magnification of Figure 7.5 of adenosis showing occasional glands with recognizable basal cell layer (arrows). Note small but visible nucleoli.
**FIGURE 7.8** Well-circumscribed nodule of adenosis.

**FIGURE 7.9** Adenosis with some visible nucleoli. Note corpora amylacea (same case as Fig. 7.8).
typical of adenosis. Occasional single cells or poorly formed glands are not uncommon in a nodule of adenosis and probably represent tangential sections of small glands (Table 7.3).

Usually, adenosis has been described as having totally bland-appearing nuclei without nucleoli. This is generally valid; most (60%) lesions contain no or at most rare prominent nucleoli. In the other 40%, fairly prominent (>1.6 microns) nucleoli are present, which should not lead to the diagnosis of carcinoma (Fig. 7.9).10

In another study, 18% contained nucleoli larger than 1 micron.1 Only huge nucleoli (>3 microns) are incompatible with a diagnosis of adenosis. In contrast, the majority (70%) of foci of low-grade adenocarcinoma have occasional or frequent large nucleoli. The remaining low-grade carcinomas have either no prominent or at most rare prominent nucleoli. These findings emphasize that, although nucleoli are generally helpful in differentiating adenosis from adenocarcinoma, there is overlap between the two entities.

The luminal contents also may be useful in this differential diagnosis. Corpora amylacea are commonly seen in adenosis and are rare in carcinoma. Only 2% of cases of adenosis contain blue intraluminal secretions visible on H&E-stained sections, a feature common in low-grade carcinomas. It is not helpful to perform special stains for mucin. Despite earlier studies’ claims that acid mucin was diagnostic of carcinoma, a later work found that 54% of foci of adenosis contained acid mucin secretions.11 Crystalloids are intraluminal structures that have been touted as distinguishing adenosis from carcinoma. However, 18% to 39% of foci of adenosis contain crystalloids, sometimes in great number (Fig. 7.10). Crystalloids should not be used to differentiate adenosis and carcinoma (Table 7.3).

The presence of basal cells is the one feature seen in adenosis that is typically not seen in carcinoma. Although basal cells may be difficult to identify within many of the glands, a flattened basal cell layer can be seen in at least some of the glands. As long as the glands with a basal cell layer are otherwise identical to the glands where a basal cell layer cannot be identified, then the entire lesion is benign. It is important to distinguish basal cells from adjacent fibroblasts. Although fibroblasts have elongated,
pointed, hyperchromatic nuclei, basal cell nuclei that are recognizable in routine sections have a more cigar-shaped ovoid contour with chromatin similar to that of the overlying secretory cells (Fig. 7.7). Basal cells may sometimes be apparent as a cluster of cells with scant cytoplasm polarized at the edge of a gland. In foci of glandular crowding where all of the features are typical of adenosis and there is no cytologic atypia, adenosis can be diagnosed without immunohistochemical stains even if basal cells are not visible on routine sections.

In cases where the architectural pattern favors adenosis yet there are visible nucleoli, the diagnosis can be clarified using immunohistochemistry for basal cells. The use of a basal cell specific antibodies to high molecular weight keratin or p63 is helpful since some glands will show a thin rim of keratin immunoreactivity beneath the cuboidal or columnar secretory cells. As few as 10% of the glands in a nodule of adenosis may be labeled with antibodies to basal cell markers, although usually more than half of the glands will show some staining. The stain is also patchy within a given gland, with sometimes only one to two basal cells identified (Figs. 7.11 and 7.12). If some glands suspicious for adenosis lack high molecular weight cytokeratin or p63 immunoreactivity, yet are otherwise indistinguishable from adjacent glands that demonstrate basal cell immunoreactivity, the absence of a basal cell layer in some glands should not be used to diagnose the lesion as carcinoma. Some of the variability in basal cell immunoreactivity within adenosis and other lesions may be caused by tissue fixation because more uniform immunoreactivity has been observed in frozen tissue. In addition to the patchy staining in adenosis, another
FIGURE 7.11  Crowded glands of adenosis on needle biopsy. Note admixture of more benign–appearing glands with papillary infolding.

FIGURE 7.12  Adenosis may contain only patchy basal cells around a minority of the glands with immunostains for basal cell markers. However, the negatively stained glands are identical to those that show a patchy basal cell layer (same case as Fig. 7.11).
immunohistochemical pitfall in the interpretation of these lesions is that they express racemase, a marker preferentially expressed in prostatic adenocarcinoma. In one study, 10% of cases demonstrated focal racemase positivity with 7.5% showing diffuse immunoreactivity.13

Adenosis often appears to be multifocal. In a few cases on TURP, foci are so numerous that, if misdiagnosed as carcinoma, they would be classified as stage T1b, leading to unwarranted radical therapy. The distinction between adenosis and low-grade adenocarcinoma in even a single focus may be critical, because diagnosis of even a single focus of carcinoma on TURP in a relatively young man may lead to aggressive surgery.

The diagnosis of adenosis on needle biopsy is more difficult, since it is more difficult to appreciate the architectural pattern on needle biopsy. Adenosis on needle biopsy appears as a relatively well-localized nodule of closely packed glands with pale to clear cytoplasm (Figs. 7.11 to 7.13). In only 7% of foci is the entire lobular lesion visualized on needle biopsy.3 In 45% of foci, one edge of the nodule can be appreciated and is circumscribed, yet the other side is not visible because the lesion is bisected by one edge of the needle biopsy. The remaining 48% of foci are transected in the middle of the nodule of adenosis such that the lesion extends to both edges of the needle biopsy. Although in these cases assessment of circum- scription is difficult, in all but a few cases foci of adenosis occupy a small portion of the core length, uncommonly measuring more than 3 mm of the core length. Other than not having an entire nodule available for evaluation, the histologic features of adenosis on needle biopsy are the same as
on TURP. On needle biopsy, due to the limited number of glands in question, basal cell specific antibodies must be interpreted with caution. Because basal cell staining may be patchy in adenosis, negative staining in a small focus of glands is not necessarily indicative of malignancy. However, if some of the glands within a crowded glandular focus on needle biopsy demonstrate a basal cell layer, then adenosis can be diagnosed. Because of the difficulty in diagnosing adenosis on needle biopsy, it is useful to verify the diagnosis with high molecular weight cytokeratin or p63 antibodies. In the evaluation of a nodule of adenosis, it is difficult to determine where the smaller crowded glands, where one is considering the diagnosis of cancer, end and the more obviously benign glands begin, because the small glands of adenosis merge in with the surrounding more recognizable benign glands. In contrast, with cancer, one should be able to identify each gland in question as malignant based on cytologic and/or architectural differences compared to adjacent benign glands. Whereas the immunohistochemical staining pattern in adenosis shows a few glands with patchy basal cell staining, cancer glands are negative and adjacent benign glands show circumferential complete basal cell immunoreactivity (Figs. 7.14 to 7.21).

Although adenosis mimics carcinoma, there is no conclusive evidence suggesting that patients with adenosis have an increased risk of harboring or developing adenocarcinoma of the prostate. In one series of adenosis, 14% of the transurethral resection (TUR) specimens examined also contained incidental foci of adenocarcinoma of the prostate. This is similar to the reported frequency of incidental adenocarcinomas found in (text continues on p. 145)
FIGURE 7.15  Adenocarcinoma mimicking adenosis. Multiple prominent nucleoli (arrows) raise the question of adenocarcinoma (same case as Fig. 7.14).

FIGURE 7.16  All of the atypical glands are negative for high molecular weight cytokeratin. Only positive glands are entrapped benign glands, which stain uniformly in contrast to patchy basal cell staining seen with adenosis (same case as Fig. 7.14).
FIGURE 7.17 Adenocarcinoma mimicking adenosis, although the small glands do not merge in with the more obvious benign glands at the top.

FIGURE 7.18 At higher magnification, the small crowded glands have slightly enlarged nuclei relative to the benign glands at the top (same case as Fig. 7.17).
FIGURE 7.19  All of the small glands are negative for high molecular weight cytokeratin diagnostic of carcinoma (same case as Fig. 7.17).

FIGURE 7.20  Adenosis.
TURs performed for clinically benign disease. Prior reports of transitions between adenosis and carcinoma were not verified with the use of basal cell specific antibodies and may have been adenosis with foci of individual cells, minimal infiltration, or visible nucleoli. Another argument that has been raised to suggest that adenosis is a precursor to prostate cancer is that the two entities share certain morphologic features. Several studies have shown that adenosis may contain acid mucin, crystalloids, nucleoli, racemase, and have a patchy basal cell layer. Rather than proving a relation between adenosis and carcinoma, these findings demonstrate that any one of these features, by itself, is not specific for carcinoma. For example, acid mucin may be seen in atrophy a patchy basal cell layer in clear cell cribriform hyperplasia, racemase in partial atrophy, and nucleoli in basal cell hyperplasia.9,11,14,15 None of these lesions is considered a precursor to prostate cancer. The interpretation of these features must be made in the context of the totality of a lesion’s architectural and cytologic features. Those studies suggesting a higher risk of carcinoma in men with adenosis have defined it differently, including many examples of what most authorities would call carcinoma.16 Adenosis is closer to benign prostatic hyperplasia than carcinoma in terms of its proliferation rate.17,18 There have been a limited number of studies looking at the genetic findings in adenosis. Qian et al.,19 using fluorescence in situ hybridization (FISH) analysis, demonstrated chromosomal anomalies in only 9% of cases of adenosis as compared to 55% of carcinomas. There was also no relationship between the chromosomal anomalies seen in adenosis and matched foci.
of carcinoma. In another study by the same group, Cheng et al.\textsuperscript{20} noted allelic imbalances in 7 of 15 (47\%) cases of adenosis. A subsequent study by Doll et al.,\textsuperscript{21} however, found allelic imbalances in only 12\% of cases of adenosis. One potential difference between the two studies was that the cases with foci of adenosis in the study by Doll et al.\textsuperscript{21} lacked associated carcinomas. Also, Doll et al.\textsuperscript{21} used the more stringent allelic imbalance criteria of a 50\% reduction of allelic intensity in adenosis samples as compared to the patient-matched normal samples, whereas Cheng et al.\textsuperscript{20} used a 30\% reduction criterion. Bettendorf et al.,\textsuperscript{22} using comparative genomic hybridization, found that adenosis uncommonly had allelic imbalances and concluded that adenosis is not closely linked to prostatic carcinoma. These cumulative results suggest that genetic alterations in adenosis may be infrequent.

In a more recent study by Cheng et al.,\textsuperscript{23} \textit{TMPRSS2-ERG} gene fusion (see Chapter 19), a common chromosomal rearrangement that occurs early in the development of invasive adenocarcinoma of the prostate and is present in 50\% of adenocarcinomas and in 20\% of high-grade prostate intraepithelial lesions, were assessed in adenosis by FISH and immunohistochemistry techniques. None of the 55 prostatic adenosis specimens that were investigated showed evidence of \textit{TMPRSS2-ERG} alteration by either technique.\textsuperscript{23} Similar results were also found by our group.\textsuperscript{24} Formalin-fixed, paraffin-embedded tissue sections of adenosis from cases of prostate biopsies ($n = 30$), TURPs ($n = 12$), and radical prostatectomies ($n = 3$) were analyzed using immunohistochemistry for ERG. None of the foci of adenosis were positive for ERG protein expression. In comparison, in 40 cases of Gleason score 6 adenocarcinoma on a tissue microarray, 22 (55\%) were positive for ERG protein. The findings in both studies support the notion that adenosis is not a precursor lesion of adenocarcinoma. Moreover, it suggests that immunohistochemistry for ERG expression could be a useful tool to differentiate adenosis from adenocarcinoma.\textsuperscript{24}

The most critical issue in terms of patient management is whether patients with adenosis on histologic examination are at increased risk of subsequently being diagnosed with adenocarcinoma. In the only study to address this issue, Renedo et al.\textsuperscript{25} studied 24 men with foci of adenosis compared to 61 men with benign prostatic hyperplasia. Men with adenosis were followed on average 6.5 years. There was no difference in the subsequent development of adenocarcinoma between the two groups. When diagnosing adenosis, we include the following statement, “Adenosis, although mimicking cancer, has not been shown to be associated with an increased risk of prostate cancer.”

**DIFFUSE ADENOSIS OF THE PERIPHERAL ZONE**

We have observed a group of typically younger patients with multiple foci of small, nonlobular, crowded, but relatively bland acini on needle
biopsy as well as in prostatectomy specimens.\textsuperscript{26} The architectural pattern can mimic low-grade adenocarcinoma especially in the subset of cases that may display rare acini with cytologic atypia. It is unclear whether this architectural pattern, which we have termed \textit{diffuse adenosis of the peripheral zone} (DAPZ), is simply a crowded glandular variant of normal prostate morphology or whether it represents a precursor or a risk factor for the development of prostatic carcinoma. Men with DAPZ tend to be younger (mean age: 49 years; range: 34 to 73 years) than the average age of men with prostate cancer. We evaluated 60 such cases on needle biopsy. Over half of the men on rebiopsy cases (57\%) were subsequently diagnosed with carcinoma. Although the majority of tissue sampled in a typical DAPZ case had no cytologic atypia, in two-thirds of cases there were admixed rare foci of atypical glands with prominent nucleoli comprising less than 1\% of submitted tissue. Patients with a subsequent diagnosis of carcinoma were more likely to have had DAPZ with focal atypia. DAPZ should be considered a risk factor for prostate cancer and that patients with such finding should be followed closely and rebiopsied (Fig. 7.22).\textsuperscript{26}

\textbf{FIGURE 7.22} Four needle core biopsies from the same patient with DAPZ. All cores demonstrate small, crowded acinar foci with minimal cytologic atypia in a nonlobular distribution throughout the biopsies. Inset shows minimal nuclear enlargement yet no prominent nucleoli.
ATROPHY

Typically considered to be a process affecting the elderly, atrophy has been demonstrated in at least 70% of 19- to 29-year-old men. Atrophy may result in prostatic induration or give rise to a hypoechoic lesion on transrectal ultrasound and may be biopsied as a lesion suspicious for cancer.

There are distinct histologic variants of atrophy, which can be classified as simple atrophy, postatrophic hyperplasia (PAH), and partial atrophy. At low magnification, glands of simple atrophy appear basophilic, which reflects relative lack of cytoplasm both apically and laterally compared to normal epithelium. Simple atrophy glands are of relatively normal caliber and are generally spaced apart in a configuration similar to that of normal epithelium. In simple atrophy with cyst formation, the acini are rounded and appear cyst-like. Many of the acini in this pattern are arranged in a back-to-back configuration with little intervening stroma. Simple atrophy does not pose diagnostic difficulties.

PAH also often appears basophilic at low power. It consists of acini that are small and mostly round that are arranged in a lobular distribution. Often, these acini appear to be surrounding a somewhat dilated “feeder” duct (Figs. 7.23 to 7.25). Many of these lesions frequently resemble normal-appearing resting breast lobules and are referred to by some authors as lobular atrophy. The lesions appear hyperplastic because the close packing of multiple small acini suggests that there is an increase in their number compared to normal tissue. PAH glands have a much higher proliferation rate than nonatrophic benign glands, and in some cases,
FIGURE 7.24  Sclerotic atrophy. Note occasional nucleoli (arrow).

FIGURE 7.25  PAH with central dilated acinus surrounded by sclerosis and smaller atrophic glands.
mitotic figures can be identified (Figs. 7.26 and 7.27). Although the
glands may appear infiltrative, they appear invasive as a patch not as indi-
vidual glands infiltrating in between larger benign glands. The basophilic
appearance of glands of atrophy is due to their scant cytoplasm and
crowded nuclei such that at low magnification one is merely seeing a

![Image of Postatrophic hyperplasia.](image1)

**FIGURE 7.26** Postatrophic hyperplasia.

![Image of Higher magnification of Figure 7.26 showing atrophy with occasional nucleoli and a mitotic figure (arrow).](image2)

**FIGURE 7.27** Higher magnification of Figure 7.26 showing atrophy with occasional nucleoli and a mitotic figure (arrow).
nuclear outline of the gland (Figs. 7.28 and 7.29, eFigs. 7.116 to 7.149). Longitudinal tangential sections of atrophic glands results in cords of cells that can further mimic cancer (Fig. 7.30, eFigs. 7.150 to 7.152). In some cases, there may be associated fibrosis, which gives the atrophic glands a more infiltrative appearance that has been termed in the past as **sclerotic**
atrophy (Fig. 7.31). Whether one uses the term postatrophic hyperplasia or merely benign prostate tissue with atrophy in one’s diagnostic reports is a matter of personal preference.

Compared to atrophy, gland-forming adenocarcinomas of the prostate typically have a greater amount of cytoplasm so that at low magnification,
the neoplastic glands are not as basophilic. Atrophy’s very basophilic appearance is distinctive even when compared to adenocarcinoma with very amphophilic cytoplasm (Fig. 7.32). Atrophy may show enlarged nuclei and prominent nucleoli, although not the huge eosinophilic nucleoli seen in some prostate cancers. Although prominent nucleoli are more common in atrophic glands associated with inflammation, we have also seen prominent nucleoli in atrophy without inflammation. Furthermore, the inflammation associated with atrophy may be trivial and chronic in nature but still give rise to significant nuclear atypia. In deciding whether an atypical focus represents carcinoma, the presence of atrophic cytoplasm should, in general, make one cautious in diagnosing carcinoma. When there are concerns as to whether a focus represents PAH or adenocarcinoma, immunohistochemistry with antibodies to high molecular weight cytokeratin or p63 can be performed to resolve the issue, as PAH uniformly labels with basal cell markers (Fig. 7.33). As opposed to partial atrophy (see the following text), PAH uncommonly expresses racemase.31,32

Rarely, carcinoma with an atrophic appearance may be present on needle biopsy. The diagnosis of carcinoma in these cases is made on (a) a truly infiltrative process with individual small atrophic glands situated between larger benign glands; (b) the concomitant presence of ordinary, less atrophic carcinoma; and (c) greater cytologic atypia than is seen in benign atrophy (see Chapter 6).31

Another variant of atrophy, the most common mimicker of prostate cancer that causes confusion with carcinoma, is “partial atrophy”9,33

FIGURE 7.32 Atrophy (right) contrasted amphophilic cancer (left).
Partial atrophy may still retain the lobular pattern of PAH, or as seen in Figures 7.34 and 7.35, have more of a disorganized diffuse appearance. Partial atrophy lacks the basophilic appearance of fully developed atrophy (simple atrophy, PAH) as the nuclei are more spaced apart (Figs. 7.36 to 7.38). The presence of crowded glands with pale
cytoplasm may lead to an overdiagnosis of low-grade adenocarcinoma. At higher power, however, the glands have benign features characterized by undulating luminal surfaces with papillary infolding. Most carcinomas have more straight, even luminal borders. In addition, the glands are partially atrophic with nuclei in areas reaching the full height of the
cytoplasm. The nuclear features in partial atrophy tend to be relatively benign without prominent nucleoli, although nuclei may appear slightly enlarged with small nucleoli. One should hesitate diagnosing cancer when the nuclei occupy almost the full cell height and the cytoplasm has the same appearance as surrounding more obvious benign glands. As with...
adenosis, partial atrophy typically has a patchy basal cell layer and express racemase (Fig. 7.39).9

There is emerging data that atrophy and associated inflammation are linked with prostate carcinogenesis.34 However, the hypothesis is that these factors are involved in the initiation of prostate cancer and are not proximately related to cancer by the time atrophy is identified on needle biopsy. Atrophy of all morphologic types are very common on needle biopsy and are not associated with an increased risk of cancer or PIN on subsequent biopsy.35

**BASAL CELL HYPERPLASIA**

A spectrum of basaloid lesions ranging from hyperplasia to carcinoma exists in the prostate. Basal cell hyperplasia may resemble prostate acini seen in the fetus, accounting for the synonyms “fetalization” and “embryonal hyperplasia” of the prostate.

The most common form of basal cell hyperplasia consists of tubules or glands with piling up of the basal cell layer.36–38 Although they are often overlooked, small glands with basal cell hyperplasia are not uncommonly found focally within nodules of benign prostatic hyperplasia (Fig. 7.40). Glandular-stromal nodules in which a majority of glands show basal cell hyperplasia may also be identified. In these cases, there is usually no confusion with carcinoma given the well-circumscribed nature of the lesion, the abundant stroma, as well as the intermingling of the glands of basal cell hyperplasia with normal glands.

Basal cell hyperplasia may be more florid in some cases, whereby it may be confused with prostatic adenocarcinoma (eFigs. 7.202 to 7.240).
In some cases of florid basal cell hyperplasia, the basal cell proliferation still retains a lobular configuration. In other instances, the lobular configuration may either be lost or not appreciated because of the fragmented nature of the TUR specimen (Figs. 7.41 and 7.42). Even at low magnification, basal cell hyperplasia can be distinguished from carcinoma by its very basaloid appearance. The glands appear basophilic at low power due to multilayering of the basal cells that have scant cytoplasm. In contrast, gland-forming adenocarcinomas of the prostate almost always have more abundant

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<th>Table 7.4 Features of Basal Cell Hyperplasia Not Typically Seen in Carcinoma</th>
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<tr>
<td>• Multilayering of cells</td>
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<td>• Cells with scant cytoplasm</td>
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<td>• Glandular lumina with atrophic luminal cytoplasm</td>
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<td>• Pseudocribriform glands</td>
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<td>• Well-formed lamellar calcifications</td>
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<td>• Intracytoplasmic eosinophilic globules</td>
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<td>• Positivity for high molecular weight cytokeratin and p63</td>
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AMACR, alpha-methylacyl-coenzyme A racemase.
cytoplasm resulting in a more eosinophilic appearance to the glands at low magnification. Within basal cell hyperplasia, there is piling up of the nuclei within the lumen ranging from a double cell layer in a few glands, to three to four cells thick in other glands, to solid nests of epithelium (Figs. 7.43 and 7.44). Basal cell hyperplasia may reveal focal cribriform and more commonly pseudocribriform glands. Pseudocribriform hyperplasia consists
of back-to-back small round glands of basal cell hyperplasia rather than a solid nest of cells with punched out lumina that characterize true cribiform glands (Fig. 7.45).\(^{39}\) Adjacent to cribiform and pseudocribiform basal cell hyperplasia are usually more typical individual glands of basal cell hyperplasia. Basal cell hyperplasia is also one of the few prostatic entities that
contain intraluminal calcifications (Fig. 7.46). These calcifications consist of well-formed lamellar calcifications. Carcinomas rarely contain calcifications, and when present, usually consist of fine calcified grains usually within central necrosis in high-grade cancers or intraductal carcinoma (eFigs. 7.241 to 7.244). Another unique feature seen within the cells of basal cell hyperplasia
is the presence of intracytoplasmic eosinophilic globules (Fig. 7.47, eFigs. 7.245 to 7.252). Squamous features can also be seen in a minority of cases of basal cell hyperplasia, which tend to have more prominent fibrous stroma between the basaloid nests than normal prostatic stroma. With the exception of basal cell hyperplasia with squamous features, basal cell hyperplasia lacks an associated desmoplastic response. In between the glands of basal cell hyperplasia is relatively unremarkable smooth muscle or on occasion a minimally myxoid stroma.

Basal cell lesions are preferentially located in the transition zone and are usually seen on TURP. Basal cell hyperplasia less frequently occurs in the peripheral zone, where it can be sampled on needle biopsy (eFigs. 7.253 to 7.268). A unique difficulty of recognizing basal cell hyperplasia on needle biopsy is that the lobular growth pattern often seen on TURP or enucleation is not apparent when nodules of basal cell hyperplasia are transected on needle biopsy. In a series of basal cell hyperplasia seen on needle biopsy, the most common patterns were either individual glands or solid nests. The presence of solid nests of cells helps to rule out adenocarcinoma. However, basal cell hyperplasia with retention of glandular lumina further mimics cancer. Although occasionally adenocarcinomas of the prostate appear to consist of glands with multilayering, the multilayered glands typically occupy only a minority of the cancerous glands. In contrast, all of the glands in basal cell hyperplasia have multilayering. Glands of basal cell hyperplasia also tend to have more atrophic cytoplasm than adenocarcinoma. Other potential worrisome features that can be seen in basal cell hyperplasia on needle biopsy include cribriform and pseudocribriform formation, prominent nucleoli, mitoses, and an infiltrative pattern between benign prostate glands.
If by light microscopy there is difficulty in distinguishing basal cell hyperplasia from prostatic adenocarcinoma, utilization of immunohistochemistry with a basal cell specific antibody can differentiate between the two lesions (Figs. 7.48 and 7.49). On the average, over 80% of the glands of basal cell hyperplasia are immunoreactive with these antibodies and
often the staining is very intense.12,37,42,43 Racemase is typically negative in basal cell hyperplasia.38,41

Basal cell hyperplasia may have prominent nucleoli but is otherwise identical to ordinary basal cell hyperplasia15,44 (Fig. 7.48, eFigs. 7.269 to 7.276). In the past, these cases were referred to as atypical basal cell hyperplasia. As these lesions are not associated with an adverse prognosis, we have dropped the word atypical so as not to cause undue concern for clinicians or patients. The enlarged nucleoli in general are seen diffusely throughout the lesion. In some cases of basal cell hyperplasia with prominent nucleoli, nuclei are seen undermining the overlying secretory cells that are cytologically normal. Other features usually attributable to carcinoma that may be seen in basal cell hyperplasia with prominent nucleoli are nuclear hyperchromasia, rare mitotic figures, nuclear enlargement, individual cell necrosis, necrotic intraluminal secretions, and blue-tinged mucinous secretions. Basal cell hyperplasia with prominent nucleoli is distinguished from acinar adenocarcinoma by the multilayering of its nuclei, solid nests, and atrophic cytoplasm. There is no known association between basal cell hyperplasia showing prominent nucleoli and either acinar adenocarcinoma or basal cell carcinoma. Distinguishing basal cell hyperplasia with prominent nucleoli from PIN is more difficult (see Chapter 5).

When a well-formed distinct nodule of basaloïd nests is formed, the term basal cell adenoma or adenoid basal cell tumor is sometimes employed, although it is preferable to consider these lesions as more pronounced examples of basal cell hyperplasia (eFig. 7.277).37,45,46

COLONIC MUCOSA

Rarely, distorted fragments of colonic mucosa on transrectal biopsies of the prostate can be confused with adenocarcinoma of the prostate (Fig. 7.50, eFigs. 7.278 to 7.286).47 In addition to the distorted architecture, features mimicking prostate cancer include (a) blue-tinged intraluminal mucinous secretions, (b) prominent nucleoli, (c) mitotic activity, (d) extracellular mucin, and (e) infrequently adenomatous changes of the rectal tissue. Immunohistochemical results further mimic prostate cancer with negative stains for the basal cell markers and positive stains for racemase. Diagnostic clues to recognizing that these foci are distorted rectal fragments are the presence of (a) lamina propria in the focus, (b) the rectal tissue located on a detached fragment of tissue, (c) associated inflammation, (d) goblet cells, and (e) muscularis propria. Assessing the colonic mucosa can also be helpful in diagnosing limited prostate cancer on biopsy. In some cases, the H&E stain is so basophilic that the colonic mucosa has a blue hue, such that the significance of blue-tinged mucinous secretions in atypical prostatic glands is not as discriminatory as in cases where the H&E stain is not as basophilic.
COWPER GLANDS

Initially, Cowper glands were identified on TUR as a potential pitfall in the diagnosis of prostate cancer. Subsequently, it was noted that they may be sampled on needle biopsy. Cowper glands particularly resembles foamy gland carcinoma, which typically has bland cytology (Figs. 7.51 and 7.52, eFigs. 7.287 to 7.300). The presence of glands in skeletal muscle may further mimic cancer if the lesion is not recognized as Cowper glands. The diagnosis of Cowper glands rests on the recognition of a noninfiltrative lobular pattern of a dimorphic population of ducts and mucinous acini in Cowper glands with the caveat that the ducts may not be obvious in all foci. Cowper glands have distended rounded cells that are expanded to the point that glandular lumina are often totally or subtotally occluded. In contrast, foamy gland cancers lack globoid cells and have well-formed open lumina often with dense pink secretions. The presence of abundant mucin-filled cytoplasm also distinguishes this lesion from carcinoma. Although prostate cancer cytoplasm may contain neutral mucinous secretions, they lack abundant intracytoplasmic mucin.

In difficult cases where ducts in Cowper glands may not be obvious, immunohistochemistry with a panel of antibodies may be useful. Prostate-specific acid phosphatase (PSAP) is negative in all cases, although the abundant cytoplasm of the acinar cells may stain focally with prostate-specific antigen (PSA) in a heterogeneous “clumped” fashion. Ductal epithelium fails to react with either antibody. High molecular weight
FIGURE 7.51  Cowper gland. Note muscle (left) and dimorphic pattern with scattered atrophic ducts among acini lined by mucinous cells.

FIGURE 7.52  Cowper gland with mucin-filled ovoid goblet cells almost occluding the lumina of the acini.
Mesonephric remnant hyperplasia in the prostate is a very rare benign mimicker of prostate adenocarcinoma that is identical to the lesion seen in the female genital tract (Fig. 7.53). They are negative for PSA and prostate-specific acid phosphatase (eFigs. 7.301 to 7.308).

The anatomic location and histologic spectrum and their immunohistochemical profile using current prostatic diagnostic markers have been addressed in a recent series from our group. The latter included 10 cases of mesonephric remnant hyperplasia involving the prostate and periprostatic tissue, including 8 cases seen in radical prostatectomy specimens and 2 TURP specimens performed for obstruction. One patient underwent prostatectomy because of the misdiagnosis of mesonephric remnant hyperplasia on TUR as carcinoma. Patients ranged in age from 48 to 70 years (mean age: 60 years). The distribution of prostatic mesonephric hyperplasia was concentrated in two areas: (a) the anterior fibromuscular stroma and adjacent anterolateral periprostatic tissue (75%) and (b) the base posteriorly and posterolaterally either within or exterior to the prostate and around the seminal vesicle (50%). Histologic patterns observed included in order of frequency: small- to medium-sized acini or tubules with a lobular distribution (all cases); cysts either in clusters or scattered containing secretions; small or ill-formed glands with an infiltrative growth;
glands with papillary infoldings or micropapillary tufts; and two cases exceptionally displayed nodules of ill-formed small glands intermixed with spindle cells, mimicking sclerosing adenosis or Gleason pattern 5 prostate cancer. Most cases had florid hyperplasia and harbored three or more growth patterns. All cases were negative for PSA. High molecular weight cytokeratin was diffusely positive in almost half of the cases and showed focal immunoreactivity in the remaining cases. Except for occasional focal positivity seen in 4 of 7 cases, p63 was largely negative. Racemase was also focally positive in 4 of 7 cases. Importantly, small glands with an infiltrative growth pattern, the most difficult pattern to distinguish from cancer, were negative or only focally positive for high molecular weight cytokeratin, negative for p63, and only focally positive for racemase. All cases examined in the study were diffusely positive for PAX8, a marker that is very helpful in the differential diagnosis especially in cases where basal cell marker and racemase expression may overlap with that of prostate cancer. Lack of PSA is another helpful distinguishing feature.  

NEPHROGENIC ADENOMA  
Nephrogenic adenoma can rarely affect the prostatic urethra. Extension of small tubules of nephrogenic adenoma into the underlying prostatic fibromuscular stroma can lead to the misdiagnosis of low-grade prostatic adenocarcinoma in TUR specimens and rarely on prostate biopsies. As this lesion is mainly associated with the prostatic urethra, it is discussed in Chapter 18.

RADIATION ATYPIA  
Radiation changes in benign prostate glands can mimic adenocarcinoma of the prostate. This subject is discussed in Chapter 14 along with other manifestations of therapy-related morphologic changes.

SEMINAL VESICLES  
The incidence of TUR material containing seminal vesicle epithelium in our institution is approximately 3%. There are differences in the literature as to the clinical significance of resecting seminal vesicle epithelium. In one study, there was a high incidence of postoperative epididymitis, whereas there was no significant morbidity in another study. Although the overdiagnosis of seminal vesicles as carcinoma is less likely in TUR material given the greater amount of tissue to evaluate, there are some instances where seminal vesicle epithelium is composed of closely packed glands resembling adenocarcinoma (Figs. 7.54 to 7.56, eFigs. 7.309 to 7.323). Occasionally, seminal vesicles sampled on needle biopsy can also be a source of overdiagnosing prostatic adenocarcinoma. The recognition of seminal vesicle rests on appreciating its architectural as well as
FIGURE 7.54 Seminal vesicles on biopsy with lumen toward right and outpouchings of seminal vesicles surrounding lumen.

FIGURE 7.55 Seminal vesicle on needle biopsy. Note lumina of seminal vesicle (top) with outpouchings off of seminal vesicle (bottom).
FIGURE 7.56 Seminal vesicle epithelium with scattered markedly atypical hyperchromatic degenerative-appearing nuclei. Note abundant lipofuscin pigment.

cytologic features. Seminal vesicles are characterized by a central large dilated lumina with numerous small glands clustered around the periphery. Often, the glands appear to bud off from the central lumen. Although on needle biopsy it may be difficult to recognize the architectural pattern of seminal vesicles due to the limited tissue, certain features may be present. A common finding on needle biopsy of the seminal vesicle is the dilated irregular lumen of the seminal vesicle seen at the edge of the tissue core, where the core has fragmented as it entered the seminal vesicle lumen. Surrounding this dilated structure are clusters of smaller glands (Fig. 7.55). Recognition that the small glands suspicious for carcinoma are all clustered around this dilated glandular structure is the first step in not overdiagnosing seminal vesicle epithelium as carcinoma. Verification that one is dealing with seminal vesicle epithelium can readily be accomplished at higher magnification examination. Seminal vesicle epithelium characteristically have scattered cells showing prominent nuclear atypia. These nuclei are markedly enlarged with bizarre shapes and have marked hyperchromasia that often obscures nuclear details (Fig. 7.56). Despite these pleomorphic features, these nuclei lack mitotic activity. The atypia appears degenerative in nature, similar to that which is seen with radiation atypia. The common finding within seminal vesicles of markedly atypical nuclei present within well-formed glandular structures differs from prostate cancer in which gland-forming well- to moderately differentiated carcinomas have only slight to moderate nuclear atypia. Even in poorly differentiated prostatic carcinoma that lacks glandular
differentiation, one rarely sees the severe atypia that is present within scattered seminal vesicle epithelial cells. Prominent globular golden brown lipofuscin granules are typical of seminal vesicle epithelium. Benign prostate tissue, high-grade PIN, and rarely carcinoma may contain lipofuscin pigment, but it differs in that the granules are smaller and more red-orange or blue (eFigs. 7.324 to 7.328). If there still exists questions as to whether the lesion is seminal vesicle epithelium or prostatic adenocarcinoma, immunohistochemistry for high molecular weight cytokeratin will label basal cells surrounding seminal vesicle epithelium, whereas basal cells are absent in prostate adenocarcinoma. Although not commonly used in practice, antibodies to MUC6 label seminal vesicle ejaculatory duct epithelium and are negative in prostate cancer. Caution must be used with immunohistochemistry using antibodies to PSA and PSAP, because it may label seminal vesicle tissue.

**VERUMONTANUM MUCOSAL GLAND HYPERPLASIA**

Gagucas et al. reported the presence of a distinctive small acinar proliferation in radical prostatectomy specimens involving the verumontanum and adjacent posterior urethra. This lesion, termed *verumontanum mucosal gland hyperplasia* (VMGH), is a potential mimic of adenocarcinoma and should be included in the differential diagnosis of small acinar proliferations of the prostate (Fig. 7.57, eFigs. 7.329 to 7.339). Similar lesions may be rarely encountered in prostatic needle biopsy specimens.

![Figure 7.57](image) VMGH on needle biopsy with crowded glands with gray-green intraluminal concretions.
The verumontanum is situated along the posterior prostatic urethral wall and is the point at which the utricle and ejaculatory ducts merge with the prostatic urethra. The mimicry of adenocarcinoma that is produced by VMGH is particularly evident at low magnification. Here, the small size and crowded nature of verumontanum mucosal glands may simulate low-grade prostatic adenocarcinoma. Further confusion with carcinoma may arise from the presence of VMGH in multiple cores or from extensive involvement (i.e., >50%) of a single biopsy core. The glands of VMGH lack the infiltrative and haphazard arrangement of the glands typically found in prostatic adenocarcinoma. Moreover, the glands of prostatic adenocarcinoma are often found infiltrating between benign prostatic glands, a feature that is absent in VMGH. In addition, VMGH is characteristically identified adjacent to and often contiguous with urothelium. Contents of these mucosal glands are sufficiently distinct to allow discrimination from prostatic adenocarcinoma. Unlike prostatic adenocarcinoma, corpora amylacea are a feature typical of VMGH. Also, in VMGH, one characteristically finds distinctive brown-orange-green concretions. Verumontanum mucosal glands are immunophenotypically similar to prostatic acini; thus, the secretory cells of these mucosal glands stain positively with antibodies to PSA, whereas the basal cells stain with antibodies to high molecular weight cytokeratin and p63.

MIMICKERS OF GLEASON SCORE 7 TO 10 ADENOCARCINOMA

Clear Cell Cribriform Hyperplasia

One of the mimickers of Gleason score 7 to 10 adenocarcinoma is clear cell cribriform hyperplasia, which occurs within the transition zone and is mostly seen in TURP specimens removed for urinary obstructive symptoms and rarely seen on needle biopsy (Table 7.5). It is considered by some to be a cribriform variant of benign prostatic hyperplasia (BPH).

<table>
<thead>
<tr>
<th>Entity</th>
<th>Predominant Mode of Sampling</th>
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<tbody>
<tr>
<td>Nonspecific granulomatous prostatitis</td>
<td>TURP = Needle</td>
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<tr>
<td>Paraganglia</td>
<td>TURP = Needle</td>
</tr>
<tr>
<td>Clear cell cribriform hyperplasia</td>
<td>TURP &gt; Needle</td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>TURP &gt;&gt; Needle</td>
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<tr>
<td>Xanthoma</td>
<td>Needle &gt; TURP</td>
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<tr>
<td>Signet ring cell lymphocytes</td>
<td>TURP</td>
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TURP, transurethral resection of the prostate.
Although its classification within a conceptual framework is unresolved, it remains useful from the practical standpoint to consider it as a distinct entity, because it may be confused with either PIN or adenocarcinoma of the prostate.

In its most readily recognized form, clear cell cribriform hyperplasia is composed of numerous cribriform glands separated from one another by a modest amount of stroma in a pattern of nodular hyperplasia. In florid cases, the glands infiltrate the stroma more diffusely and can have back-to-back glands (Figs. 5.20 and 5.21, eFig. 7.340 to 7.362). If it were to be misdiagnosed as adenocarcinoma, it would be classified as cribriform Gleason score 4 + 4 = 8. The epithelial cells have distinctive clear cytoplasm and small bland nuclei with inconspicuous or small nucleoli. Around many of the glands of clear cell cribriform hyperplasia is a strikingly prominent basal cell layer, consisting of a row of cuboidal darkly stained cells beneath the clear cells (Fig. 5.22). The basal cells may form small knots at the periphery of some of the glands. Occasionally, the basal cells may have small nucleoli. The basal cell layer may be incomplete and in some glands may be invisible in routine sections. Tangential sections can also result in the appearance of occasional nests of clear cells without cribriform architecture or basal cells. Although usually unnecessary, immunostains for high molecular weight cytokeratin can highlight the basal cell layer.

The distinction between clear cell cribriform hyperplasia and cribriform PIN may be difficult (see Chapter 5). The distinction between clear cell cribriform hyperplasia and infiltrating cribriform carcinoma is easier. The presence of basal cells around some of the glands in clear cell cribriform hyperplasia rules out carcinoma, even though some glands with identical nuclear and cytoplasmic features may not have an apparent basal cell layer. The glands in clear cell cribriform hyperplasia lack cytologic atypia, in contrast to infiltrating cribriform carcinoma. Also, it is uncommon to see cribriform carcinoma unaccompanied by small infiltrating neoplastic glands.

Clear cell cribriform hyperplasia is uncommon, and its natural history is unknown. Although 3 of 25 reported cases were associated with adenocarcinoma of the prostate, there were no areas of transition from clear cell cribriform hyperplasia to carcinoma of the prostate. Taking into account prostate cancer’s high incidence in elderly men, it is felt that clear cell cribriform hyperplasia is unrelated to adenocarcinoma of the prostate.

**NONSPECIFIC GRANULOMATOUS PROSTATITIS**

One of the principle entities that can be confused with high-grade prostate cancer is nonspecific granulomatous prostatitis (NSGP). Although discussed in general in Chapter 4, it is discussed here in the context of its differentiation from adenocarcinoma. NSGP can closely mimic cancer clinically. In a series of cases on needle biopsy, prostatic carcinoma was
suspected or considered prior to biopsy in 55% of cases.\textsuperscript{64} PSA levels greater than 4 ng/mL were seen in 84% of NSGP and digital rectal exam was frequently abnormal.

Although most cases of NSGP seen on needle biopsy do not histologically resemble prostate cancer, 4% of cases can closely resemble cancer. These cases of NSGP consist of sheets of epithelioid histiocytes, some with prominent nucleoli with abundant granular cytoplasm (Figs. 7.58 and 7.59, eFigs. 7.363 to 7.370). Reactive cribriform nonneoplastic prostatic glands further mimicking cancer may be seen in 7% of NSGP cases on biopsy. The key feature to avoid a misdiagnosis of cancer is to recognize the other inflammatory cells in NSGP, such as scattered neutrophils, lymphocytes, plasma cells, and eosinophils. The presence of scattered multinucleated giant cells may also aid in the diagnosis of NSGP. However, despite its name, approximately 50% of cases of NSGP lack multinucleated giant cells on needle biopsy.\textsuperscript{64} In contrast, most adenocarcinomas of the prostate lack an associated inflammatory component.\textsuperscript{65} Although it may be difficult to appreciate on needle biopsy specimens, NSGP initially is localized around ruptured ducts and acini. As seen in Figure 7.59, the epithelioid cells are not present diffusely throughout the needle biopsy core but surround an acinus or duct with attenuated partially disrupted epithelium. If this were carcinoma, the epithelioid cells would show no relationship to acini and ducts but would infiltrate throughout the core.

If there are difficulties in distinguishing NSGP from poorly differentiated adenocarcinoma, immunohistochemistry can be utilized. These

![Image](image-url)
epithelioid cells will be negative for PSA, PSAP, and pancytokeratin and positive for various histiocytic markers. Just as isolated architecturally atypical glands can be seen on H&E stains in a heavily inflamed prostate, there may be focal architectural abnormalities when evaluating sections labeled with PSA, PSAP, or pancytokeratin. Out of context, focal collections of individual immunoreactive epithelial cells may be suspicious for cancer. However, these foci are localized and the vast majority of epithelioid cells are negative for epithelial markers indicating that these areas represent ruptured ducts and acini.

PARAGANGLIA

Paraganglia have been identified in 8% of radical prostatectomies. They are usually present in the posterolateral soft tissue exterior to the prostate. Uncommonly, they may be found in the lateral prostatic stroma or in the bladder neck smooth muscle. Rarely, paraganglia may be seen on TURP or on needle biopsy where their distinction from carcinoma must be made. They consist of clusters of clear or amphophilic cells with fine cytoplasmic granules and a prominent vascular pattern, often intimately related to nerves (Fig. 7.60, eFigs. 7.371 to 7.376). Nucleoli are occasionally prominent, and when present, nuclear atypia is usually degenerative in appearance as seen in endocrine lesions. Paraganglia are situated in smooth muscle, not admixed with benign prostate glands. Although this lesion closely mimics high-grade adenocarcinoma of the
prostate, the highly vascular setting and degenerative atypia are clues to prevent a misdiagnosis. Also before diagnosing a small focus of high-grade carcinoma on TURP or needle biopsy, where the atypical focus appears entirely extraprostatic, paraganglia should be considered in the differential diagnosis. Verification of the diagnosis can be accomplished with positive immunostaining for neuroendocrine markers diffusely and S100 labeling sustentacular cells and negative reactivity for PSA and PSAP.

**SCLEROSING ADENOSIS**

Lesions with the morphology of sclerosing adenosis were first reported in 1983 as an adenomatoid prostatic tumor. The preferred term is *sclerosing adenosis* as their histogenesis is unrelated to adenomatoid tumors seen elsewhere. In one series, sclerosing adenosis was found in approximately 2% of prostatic specimens. In most cases, lesions are discovered incidentally in TURs performed for urinary obstructive symptoms. Usually, only one or two small foci are present, although in one report, as many as 10 prostatic chips contained the lesion. As with any lesion seen on TUR, true multifocality as opposed to multiple sections through a single lesion cannot be distinguished. Very rarely, sclerosing adenosis may be seen on needle biopsy. The major differential diagnosis rests between sclerosing adenosis and adenocarcinoma. Sclerosing adenosis consists of a mixture of well-formed glands, single cells, and a cellular spindle cell component (Fig. 7.61, eFigs. 7.377 to 7.403).
There are several features that should prevent a misdiagnosis of malignancy:

1. Adenocarcinomas of the prostate composed of an admixture of glands, poorly formed glandular structures, and single cells would be assigned a high Gleason score (7 or 8). Prostatic adenocarcinomas with these scores are only rarely seen as limited foci within a TURP. The finding of only one or several small foci of a cellular lesion suspicious for high-grade carcinoma should prompt a consideration of sclerosing adenosis or paraganglia. Furthermore, although sclerosing adenosis may be minimally infiltrative at its perimeter, the lesion is still relatively circumscribed in contrast to high-grade prostate adenocarcinoma.

2. The glandular structures in sclerosing adenosis resemble those seen in ordinary adenosis. They are composed of cells with pale to clear cytoplasm and relatively benign-appearing nuclei. In many of the glandular structures, a basal cell layer can be identified on H&E-stained sections that may be focally prominent and contains dense amphophilic cytoplasm. This contrasts to carcinoma where basal cells are absent.

3. Sclerosing adenosis contains a dense spindle cell component that is typically lacking in adenocarcinomas (Figs. 7.61 and 7.62) the stromal cells are plump fusiform cells with amphophilic cytoplasm. The stroma occasionally displays a characteristic myxoid appearance. Usually, adenocarcinomas of the prostate show no apparent stromal response or at most a hypocellular fibrotic reaction.

FIGURE 7.61 Sclerosing adenosis with mixture of well-formed glands and cellular spindle cell proliferation.
4. A rather unique feature of sclerosing adenosis is the presence of a hyaline sheath–like structure around some of the glands (Figs. 7.62 and 7.63). The glands in ordinary adenocarcinoma lack such a collarette and have a “naked” appearance as they infiltrate the stroma.

5. The relatively bland cytology may also help in distinguishing sclerosing adenosis from adenocarcinoma, although some nuclei within sclerosing adenosis may be moderately enlarged and contain prominent nucleoli.

These light microscopic features are classic for sclerosing adenosis, and it is usually not necessary to perform immunohistochemistry to clarify the diagnosis. However, immunohistochemistry is definitive in difficult cases. Ordinary adenocarcinomas of the prostate of all grades lack basal cells. Sclerosing adenosis contains a basal cell layer around most of the glandular structures as well as among the individual cells and cords of cells. The basal cells within sclerosing adenosis, however, are distinctive in their immunophenotypical staining and differ from ordinary basal cells. Ordinary basal cells of the prostate show no myoepithelial cell differentiation. They lack staining for muscle-specific actin and ultrastructurally do not show contractile elements. Within sclerosing adenosis, the basal cells show muscle-specific actin positivity and may also show S100 positivity consistent with myoepithelial cell differentiation (Fig. 7.64).⁶⁹,⁷²,⁷³ The dense spindle cell component in sclerosing adenosis also shows partial staining with keratin and muscle-specific actin and occasionally S100 consistent with myoepithelial cell differentiation.⁷³ Ultrastructural examination of several of these
FIGURE 7.63  Sclerosing adenosis with hyaline sheath around some of the glands (arrow). Note cellular stroma in between glands.

FIGURE 7.64  Sclerosing adenosis with positivity for muscle-specific actin in basal cells and focally in intervening stroma.
cases has verified their myoepithelial differentiation.\textsuperscript{70} There is no known association between sclerosing adenosis and adenocarcinoma of the prostate.

**SIGNET RING LYMPHOCYTES**

TURP specimens may frequently show aggregates of degenerated lymphocytes with a signet ring cell appearance.\textsuperscript{74} This finding results from thermal injury and is not seen in needle biopsy or open prostatectomy specimens. Only rarely are these changes so prominent to be confused with signet ring cell carcinoma (Fig. 7.65, eFigs. 7.404 to 7.407).

**XANTHOMA**

Although rare, prostatic xanthoma can be a source of diagnostic confusion, particularly with small tissue fragments such as those obtained from needle biopsies (Fig. 7.66, eFigs. 7.408 to 7.428).\textsuperscript{75,76} Most cases contain only one focus of prostatic xanthoma, which are 0.5 mm or smaller. Exceptionally, xanthomas may range up to 2.5 mm. Xanthoma cells have small uniform, benign-appearing nuclei; small inconspicuous nucleoli; and abundant vacuolated, foamy cytoplasm with no mitotic figures. Although most xanthomas are arranged in a circumscribed solid nodular pattern, xanthomas can form cords and individual cells infiltrating the prostatic stroma, further mimicking high-grade prostate carcinoma. Careful attention to morphology with adjunctive use of CD68 (positive) and CAM5.2 (negative) immunohistochemical stains are helpful in the diagnosis of prostatic xanthoma, especially in difficult cases with an infiltrative pattern.

![Figure 7.65](image_url)  
*Figure 7.65* Signet ring lymphocytes.
FIGURE 7.66 Xanthoma.

REFERENCES


