Benign mimickers of prostatic adenocarcinoma

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The diagnosis of prostatic adenocarcinoma, especially when present in small amounts, is often challenging. Before making a diagnosis of carcinoma, it is prudent for the pathologist to consider the various benign patterns and processes that can simulate prostatic adenocarcinoma. A useful method of classifying benign mimickers is in relationship to the major growth patterns depicted in the classical Gleason diagram. The four major patterns are small gland, large gland, fused gland and solid. Most mimickers fit within the small gland category and the most common ones giving rise to false-positive cancer diagnosis are atrophy, post-atrophic hyperplasia, atypical adenomatous hyperplasia and seminal vesicle-type tissue. A number of other histoanatomic structures such as Cowper's gland, verumontanum mucosal glands, mesonephric glands and paraganglionic tissue may be confused with adenocarcinoma. Additionally, metaplastic and hyperplastic processes within the prostate may be confused with adenocarcinoma. Furthermore, inflammatory processes including granulomatous prostatitis, xanthogranulomatous prostatitis and malakoplakia may simulate high-grade adenocarcinoma. Atypical adenomatous hyperplasia (adenosis), a putative precursor of transition zone adenocarcinoma, has overlapping features with low-grade adenocarcinoma and may cause problems in differential diagnosis, especially in the needle biopsy setting. The pathologist's awareness of the vast array of benign mimickers is important in the systematic approach to the diagnosis of prostatic adenocarcinoma. Knowledge of these patterns on routine microscopy coupled with the prudent use of immunohistochemistry will lead to a correct diagnosis and avert a false-positive cancer interpretation.
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Prostatic adenocarcinoma is characterized by diverse architectural patterns and as such can be confused with other histological patterns and processes. Histoanatomic structures such as seminal vesicle, inflammatory and reactive conditions and pathophysiological processes including atrophy, hyperplasia and metaplasia have protean patterns which may simulate adenocarcinoma. Most of these lesions are readily recognized and easily separated from malignancy but they may present problems, especially when dealing with limited sampling in thin core needle biopsies. False-positive cancer diagnosis, albeit uncommon, may be rendered in some cases leading to serious clinical, psychological and medicolegal consequences. Prostatic biopsy pathology has been identified as a problem area which may lead to litigation.[1–3] In my own experience, the most likely patterns giving rise to false-positive malignant cells are atrophy, post-atrophic hyperplasia, atypical adenomatous hyperplasia (adenosis) and seminal vesicle.

In this paper, the differential diagnosis of prostatic adenocarcinoma will be discussed with emphasis on benign mimickers as outlined in Table 1. Prostatic intraepithelial neoplasia and other carcinomas may be confused with prostatic adenocarcinoma but these topics will not be addressed. The mimickers of other rare prostatic malignancies such as sarcoma will not be covered. The differential diagnosis of adenocarcinoma has been detailed in several recent reviews and monographs.[4–10]

A pattern-based approach to differential diagnosis

The utility of the now famous Gleason diagram extends beyond its role as a grading tool.[11,12] It is useful in a discussion of the protean architectural patterns that are important in diagnosing prostatic adenocarcinoma. Additionally, it provides a conceptual framework for discussing differential diagnosis. In the Gleason diagram, there are nine

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Table 1 Classification of benign mimickers of adenocarcinoma

Histoanatomic structures
  Seminal vesicle/ejaculatory
    duct
  Cowper's gland
  Paraganglion
  Verumontanum mucosal
    glands (hyperplasia)
  Mesonephric gland
    remnants (hyperplasia)

Atrophy
  Simple (lobular)
  Sclerotic
  Cystic
  Linear (streaming)
  Post-atrophic hyperplasia
    (partial atrophy)

Inflammation
  Usual prostatitis with
    preservation artifacts
  Granulomatous prostatitis,
    nonspecific
  Xanthogranulomatous
    prostatitis (xanthoma)
  Malakoplakia

Reactive atypia
  Inflammatory
  Ischemic
  Radiation

Metaplasia
  Mucinous
  Nephrogenic (adenoma)

Prostatic hyperplasia
  Basal cell hyperplasia
  Benign nodular hyperplasia,
    small gland pattern
  (Clear cell) cribriform
    hyperplasia
  Sclerosing adenosis

*Atypical adenomatous
hyperplasia (adenosis)*

patterns which can be lumped into four major architectural categories for discussion of differential diagnosis (see Figure 1 and Table 2).

The predominant pattern of adenocarcinoma is the small glandular one. This corresponds to Gleason patterns 1, 2, 3A, 3B and consists of separate acini which may be tiny, small or medium in size. Most benign mimickers enter the differential diagnosis of small acinar adenocarcinoma.

The second major pattern is the large glandular one. Medium to large simple acini and/or papillary and cribriform structures are seen. Central (comedo) necrosis involving round duct-like structures may also be identified. The large gland architecture includes Gleason patterns 3A, 3C and 5A.

The third major growth pattern of adenocarcinoma is fused glandular which comprises Gleason patterns 4A and 4B. The infiltrating coalesced glands may be either amphophilic (Gleason 4A) or clear (so-called hypernephroid; Gleason 4B). A few structures and benign processes simulate this fused gland pattern.

The final major pattern of adenocarcinoma is the solid one which consists of sheets, cords and single infiltrating cells and corresponds to a pattern 5B in the Gleason chart. Certain inflammatory lesions may be confused with solid adenocarcinoma.

A benign mimicker may in some situations simulate more than one major pattern of adenocarcinoma. For instance, reactive atypia involving small acini can be mistaken for small acinar carcinoma. However, if the atypia affects medium to large glands, then the differential diagnosis is with the large gland pattern of carcinoma.
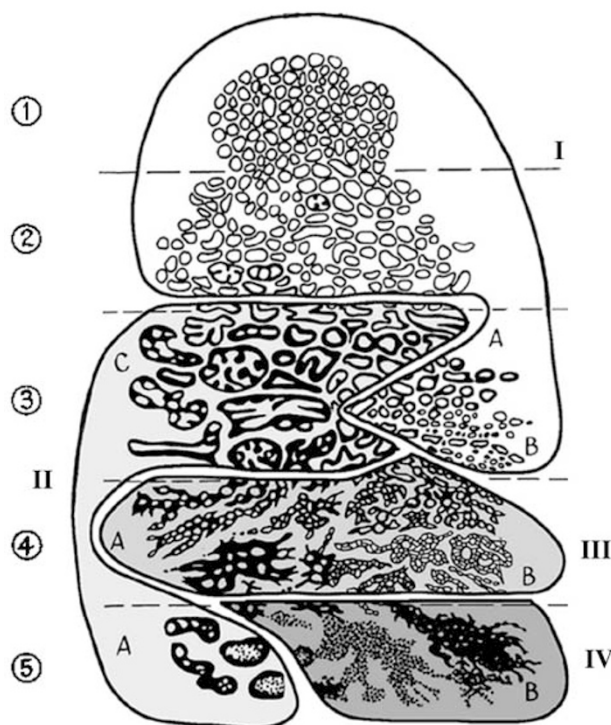

Figure 1 Gleason diagram divided into four major architectural patterns of prostatic adenocarcinoma. I—small gland pattern; II—large gland pattern; III—fused gland pattern; IV—solid pattern (see Table 2).

Table 2 Major growth patterns of adenocarcinoma

	Growth pattern	Gleason patterns	Descriptors
I	Small gland	1, 2, 3A, 3B	Tiny, small, medium, separate acini
II	Large gland	3A, 3C, 5A	Simple, papillary, cribriform, comedo
III	Fused gland	4A, 4B	Coalescing acini, amphophilic or clear (hypernephroid)
IV	Solid	5B	Sheets, cords, single cells

The benign mimickers and the corresponding patterns of adenocarcinoma that may be simulated are shown in Table 3. The discussion of these entities will follow this pattern-based approach.

Small Gland Pattern

Seminal vesicle
Seminal vesicle tissue may be present in transurethral resectates or in needle biopsies, usually unexpectedly, but sometimes as a result of specific sampling.[13,14] The seminal vesicle is characterized by a central lumen with branching glands surrounded by smooth muscle. Commonly, the end

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Table 3 Benign mimickers in relation to major growth patterns of prostatic adenocarcinoma

Small gland pattern	Large gland pattern
Seminal vesicle	(Clear cell) cribriform
Cowper's gland	hyperplasia
Atrophy	Adenoid cystic-like basal
Post-atrophic hyperplasia	cell hyperplasia
Reactive atypia	Reactive atypia
Mucinous metaplasia	
Nephrogenic metaplasia	
(adenoma)	Fused gland pattern
Basal cell hyperplasia	Paraganglioma
Benign nodular hyperplasia	Xanthogranulomatous
Sclerosing adenosis	inflammation (xanthoma)
Verumontanum	Malakoplakia
Mucosal gland	
hyperplasia	Solid pattern
Mesonephric gland	Usual prostatitis with crush
hyperplasia	artifacts
Atypical adenomatous	Idiopathic granulomatous
hyperplasia	prostatitis
	Signet ring-like change in
	lymphocytes and stromal
	cells

branching is complex with numerous small glands, resulting in the so-called adenotic pattern of seminal vesicle (Figure 2). This latter pattern can present problems, especially when the overall gland structure and central lumen are not recognized. Tangential sampling of adenotic areas in a needle biopsy may produce a small gland pattern causing confusion with small acinar carcinoma.[15] Helpful features to distinguish adenotic seminal vesicle include the presence of nuclear hyperchromasia and pleomorphism which at times is striking.[13,16] The degree of atypia is thought to increase with advancing age.[13] Atypical cells are found centrally within the acini and they are often more atypical than the nuclei of small acinar carcinoma (Figure 2). Mitoses are not identified. Small nuclear pseudoinclusions are commonly seen. In the cytoplasm, golden-brown lipofuscin pigment is usually identified, although the amount varies from case to case. When prominent, the diagnosis of seminal vesicle epithelium is easily supported.

It must be remembered however that lipofuscin pigment may be present in normal, hyperplastic, preneoplastic (PIN) and carcinomatous glands.[17–19] The presence of lipofuscin pigment in small acinar carcinoma however is rare. When the epithelial atypia and pigmentation are not prominent, a significant diagnostic challenge may result. In problematic cases, negative immunohistochemistry for prostatic-specific antigen (PSA) and prostatic acid phosphatase (PAP) helpful. Additionally, the 34βE12 stain shows basal cells in seminal vesicular glands which of course are absent in small acinar carcinoma.

Ejaculatory duct epithelium has a similar morphology to that of the seminal vesicle. Ejaculatory ducts however are surrounded by a band of loose
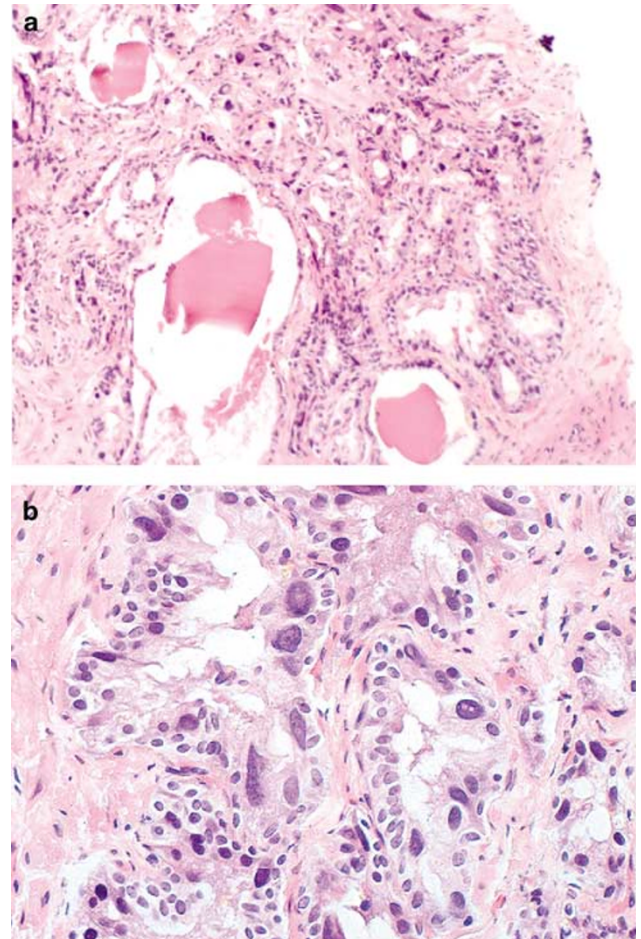

Figure 2 (**a**) Low-power photomicrograph showing seminal vesicle with dilated central glands and peripheral small 'adenotic' glands. (**b**) High-power photomicrograph of seminal vesicle glands showing nuclear atypia within luminal cells and focal cytoplasmic lipofuscin pigment.

fibrovascular connective tissue and lack the well-formed muscular wall of seminal vesicle. This distinction is of practical importance since the presence of carcinoma in ejaculatory duct tissue does not indicate extraprostatic disease whereas carcinomatous involvement of seminal vesicle proper indicates high stage disease (at least stage pT3b) and has adverse prognostic significance.

Cowper's gland
Cowper's glands, also referred to as the bulbourethral glands are paired periurethral structures located near the prostatic apex.[20,21] They are rarely sampled in prostatic specimens. Cowper's glands have a lobular configuration with a central duct surrounded by tightly packed round acini composed of cells with abundant mucinous cytoplasm (Figure 3). The nuclei are basally located and uniform. Sometimes, skeletal muscle, typical of the apical region, is present in the periglandular stroma. Cowper's glands are rarely confused with small
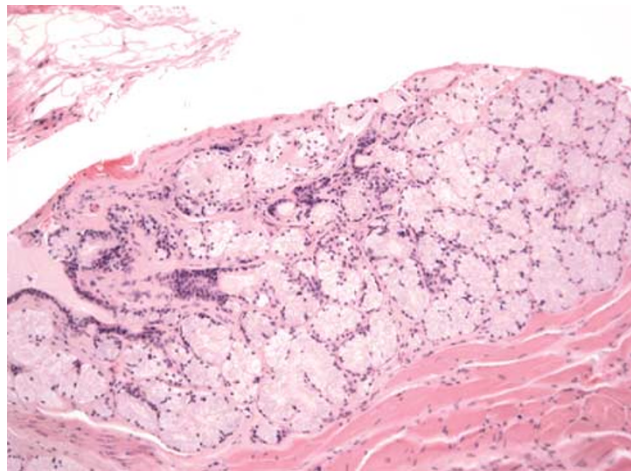
Figure 3 Cowper's gland. Note uniform collection of mucinous acini with excretory duct (left).
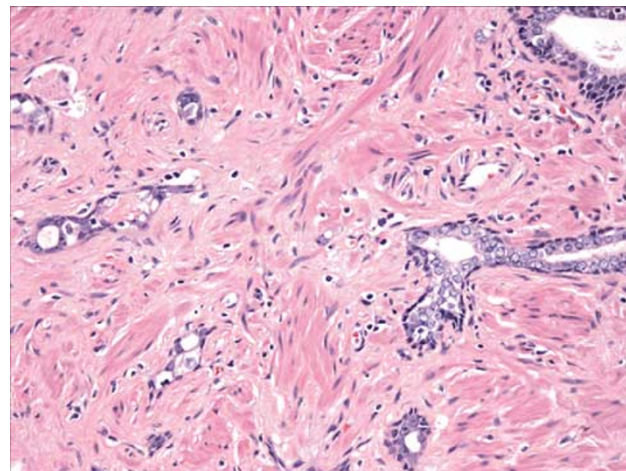

Figure 4 Atrophy in association with antiandrogen effects—note prominent basal cell layer and tiny irregular acini with pseudoinfiltrative growth pattern.

acinar carcinoma. The duct-acinar architecture, cytoplasmic mucin and lack of cellular atypia distinguish Cowper's glands from adenocarcinoma. In difficult cases, special stains for mucin (mucicarmine, PAS-D) may be employed. Cowper's glands show variable staining results for PSA and are negative for PAP.[20,21] The ductal cells exhibit high molecular weight keratin (34βE12) staining and in some cases attenuated cells around the periphery of the acini are also positive.[20] The latter cells may also exhibit smooth muscle actin positivity.[20,21] Another differential diagnosis of Cowper's glands is mucinous metaplasia of prostatic acini which is usually seen in association with atrophy.[22]

Atrophy
Atrophy of prostatic glands is a common process typically but not exclusively found in older patients. Atrophy may be seen in the young adult prostate and is commonly admixed with areas of nodular prostatic hyperplasia.[23] While common in the peripheral zone, atrophy may also be seen in the central and transition zones. Glandular atrophy is commonly associated with chronic prostatitis which may have an active component characterized by intraglandular neutrophils. Some recent evidence suggests that prostatic atrophy may be a manifestation of chronic ischemic disease, although many examples of atrophy are still considered idiopathic in nature.[24] Atrophy can also be the result of treatment with radiation and antiandrogens[25–30] (Figure 4). Treatment-associated atrophy is frequently extensive and severe and in the case of radiation may be associated with epithelial atypia.

Four main patterns of atrophy are recognized— lobular (simple), sclerotic, cystic and linear or streaming (Figure 5). Combined patterns are common. Lobular (simple) atrophy is characterized by small glands arranged in circumscribed (lobular) nests. The orderly architecture is best appreciated

on low power. In sclerotic atrophy, the small glands are distorted by dense collagenized stroma which results in sharply angulated and irregular shapes. The stroma often has an elastotic appearance similar to that seen in some breast conditions. At low power, the lobular architecture is usually evident and sometimes a central dilated duct is appreciated. The almost desmoplastic appearance of the stroma in sclerotic atrophy contrasts with low grade, small acinar carcinoma which incites little or no stromal response. In cystic atrophy, varying degrees of acinar dilatation are seen and usually other areas of more typical simple atrophy are found nearby. Occasionally, atrophy may have a linear, streaming pattern in which small dark acini are lined up in a row, seemingly permeating through stroma. This latter pattern is particularly prone to be overinterpreted as carcinoma.

Regardless of the architectural subtype of atrophy, the cytological features are similar. The cells are small, shrunken and dark. They have high nuclear to cytoplasmic ratios but the nuclei are uniform and lack nuclear membrane irregularity and chromatin abnormalities. Occasionally, small chromocenters are seen but prominent nucleoli are absent. Double layering of cells is often seen but in some instances it may be difficult to appreciate because of the marked secretory cell atrophy (Figure 6). In such cases, stains for high molecular weight keratin (34βE12) may be employed to highlight the basal cell compartment.[31]

The important features in separating atrophy from small acinar carcinoma are the low power maintenance of lobular architecture at least in part, uniform cytology and absence of prominent nucleoli. In some cases, especially when the atrophy is along the edge of a biopsy or when distortion or secondary inflammation is present, diagnosis may be difficult and special stains for high molecular weight keratin should be employed.
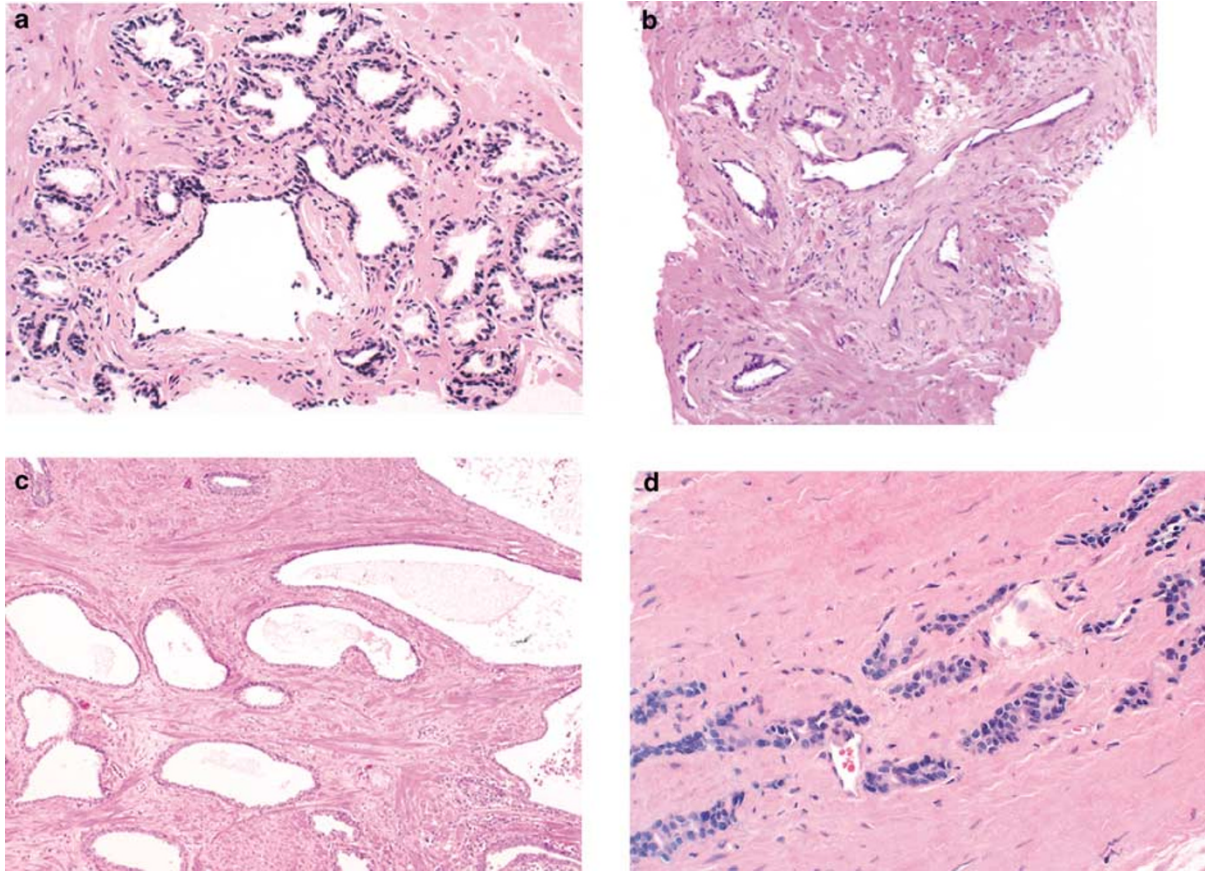
Figure 5 Patterns of atrophy. (**a**) Simple lobular; (**b**) Sclerotic; (**c**) Cystic; (**d**) Linear or streaming.

In a series of secondary reviews of prostatic pathology prior to definitive treatment, atrophy was a lesion in needle biopsies sometimes overinterpreted as adenocarcinoma.[32] It should be emphasized that carcinoma may have an atrophic appearance and as such may be under-interpreted as atrophy. Atrophic adenocarcinomas are composed of small dark acini usually with an irregular permeative pattern of growth. On close inspection, there is nuclear atypia and nucleoli are usually recognized at least focally. In some instances, 34βE12 staining may be required to distinguish the atrophic adenocarcinoma from atrophy.[33,34]

Atrophy associated with inflammation, especially active inflammation, may be particularly challenging and one should be cautious in diagnosing carcinoma in inflamed small gland foci. Additionally, in the setting of radiation, atrophy may be severe and may be associated with stromal fibrosis. This may result in architectural distortion which when coupled with cytological atypia typical of radiation effects can cause considerable diagnostic confusion. In such cases, high molecular weight keratin stains (34βE12) are useful to separate non-neoplastic atrophic glands from residual carcinoma.

Post-atrophic hyperplasia
Post-atrophic hyperplasia, also referred to as partial atrophy or hyperplastic atrophy is an uncommon histological process found in about 2–3% of prostatic needle biopsy cases.[35–38] It is usually found in the peripheral zone. In most cases, it is difficult to know if post-atrophic hyperplasia represents a normal or hyperplastic focus undergoing atrophy (partial atrophy) or secondary hyperplasia occurring in atrophic areas. Studies with proliferation markers however show increased proliferation in areas of post-atrophic hyperplasia, thus supporting the latter hypothesis.[39,40]

Post-atrophic hyperplasia consists of a combination of atrophic acini and ones that contain more abundant clear or amphophilic cytoplasm and appear hyperplastic (Figure 7). The lobular arrangement is usually maintained and there is often apparent budding of 'neoacini' lined by cuboidal cells with clear cytoplasm. A mixture of cells with atrophic and nonatrophic cytoplasm leads to a variety of irregular glandular shapes including stellate ones. Some nuclear enlargement may be seen and rarely, enlarged nucleoli are identified. The busy architecture of post-atrophic hyperplasia may cause diagnostic confusion with adenocarcinoma, however there is generally a maintenance of some
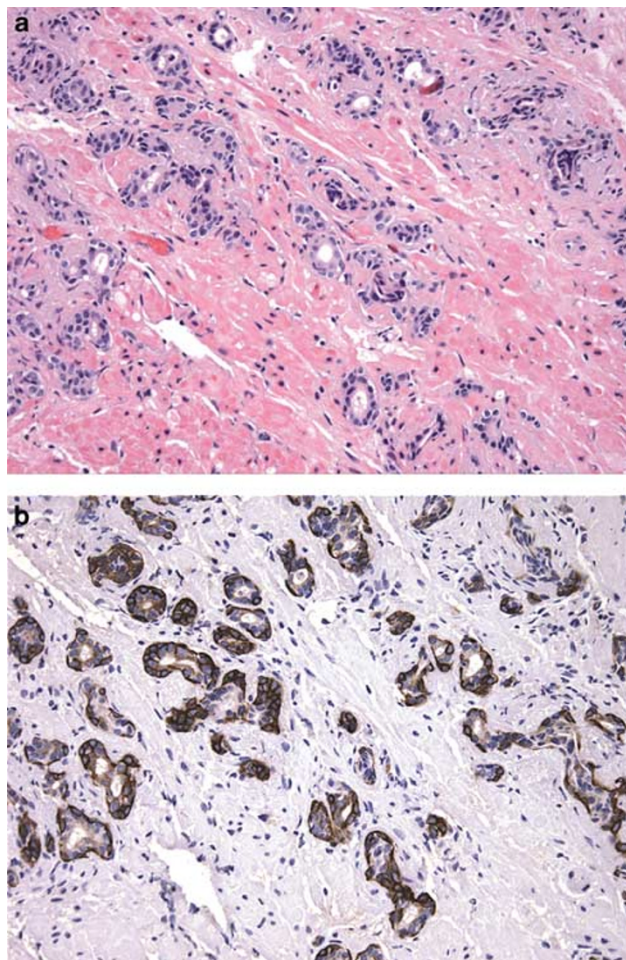
Figure 6 (**a**) Atrophy with pseudoinfiltrative growth pattern. (**b**) High molecular weight keratin stain showing prominent basal cell staining.

Figure 7 Post-atrophic hyperplasia. (**a**) Low-power photomicrograph showing mixture of shrunken atrophic glands and ones with more abundant clear cytoplasm. At the periphery there are some tiny apparent neoacini. (**b**) High-power photomicrograph showing admixture of small atrophic and hyperplastic glands—note absence of significant nuclear atypia.

degree of lobular architecture and basal cells are usually recognized, even at the H&E level. Caution should be exercised whenever there is an admixture of atrophic and nonatrophic acini, especially when a lobular pattern is not readily recognized. Prominent nucleoli in a significant number of cells are not typically found in post-atrophic hyperplasia. The prudent use of high molecular weight keratin (34βE12) immunostains is important in difficult cases. There is a discontinuous layer of basal cells in post-atrophic hyperplasia whereas in small acinar carcinoma, the basal cell layer is completely absent. In rare instances, luminal crystalloids and even small amounts of basophilic luminal mucus may be present in post-atrophic hyperplasia.

The early ideas of Franks and Laivag that atrophy and post-atrophic hyperplasia are involved in the pathogenesis of prostatic cancer were largely ignored until recently.[35,39] The common topographic association of prostatic carcinoma, atrophy and chronic inflammation is well known but most investigations had been focused on other putative precursors such as prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia
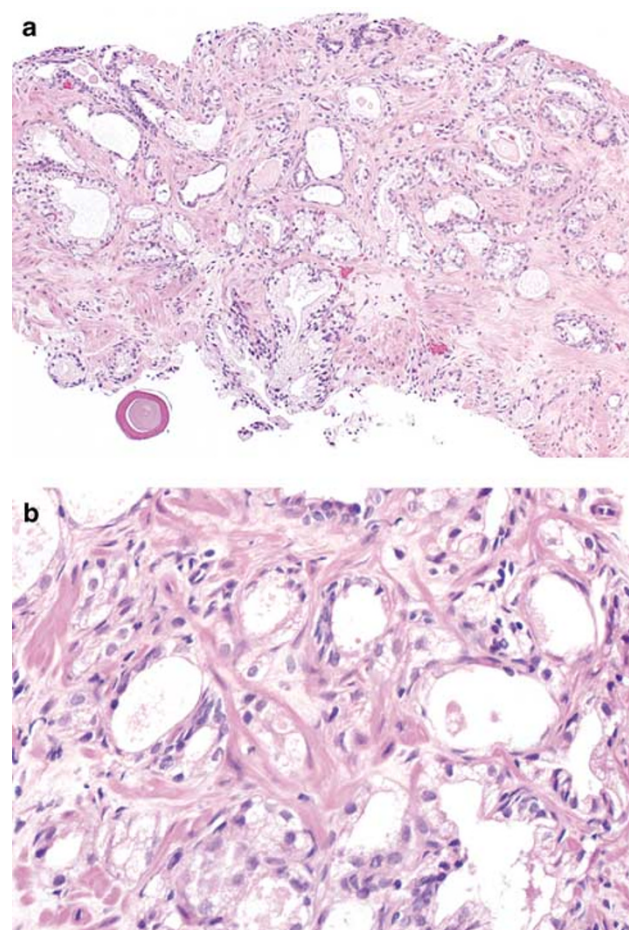
(adenosis). De Marzo and co-workers have recently identified a lesion which they refer to as proliferative inflammatory atrophy which may represent a precursor of adenocarcinoma.[40–42] This lesion is morphologically represented by areas of simple atrophy and/or post-atrophic hyperplasia in which there is superimposed chronic inflammation. Using immunohistochemistry, the above authors have identified areas of high cell proliferation in which there is increased staining of Π-glutathione s-transferase (GSTP1) and bcl-2 along with decreased staining of the cyclin-dependent kinase inhibitor p27. The findings suggest that the cells of the secretory compartment in proliferative inflammatory atrophy have an immature secretory phenotype similar to that seen in cells of high-grade PIN and carcinoma. The authors have identified areas of atrophy merging into high-grade PIN within the same glands. They suggest that proliferative inflammatory atrophy may give rise to carcinoma, either directly or through high-grade PIN as an intermediary step. Clearly, further investigations are required

to evaluate this hypothesis. It should be stressed however that proliferative inflammatory atrophy is a lesion which is not defined solely on the basis of the H&E morphology but requires immunohistochemical markers of proliferation and differentiation for identification.

Reactive atypia

Epithelial atypia may be seen in association with acute or chronic prostatitis and may sometimes be present in association with prostatic ischemia (infarction). Reactive atypia can be confused with adenocarcinoma[43–45] (Figure 8). The glands in most cases of reactive atypia are atrophic and there may be some associated basal cell or transitional cell hyperplasia. In some cases, especially in ischemia, the epithelium may have a squamoid appearance and frank squamous or transitional metaplasia may be present (Figure 9). Mild to moderate nuclear enlargement is seen and sometimes nucleoli are prominent. The nucleolar enlargement may actually exceed that of adenocarcinoma.

The low-power architecture, presence of basal cells and degree of cytological atypia usually allow separation of reactive lesions from adenocarcinoma. However, adenocarcinoma may be present in areas of prostatitis and ischemia and as such diagnostic caution should prevail.

A special situation of reactive atypia is radiation effects.[26,27] The degree of cytological atypia in irradiated prostates may be severe with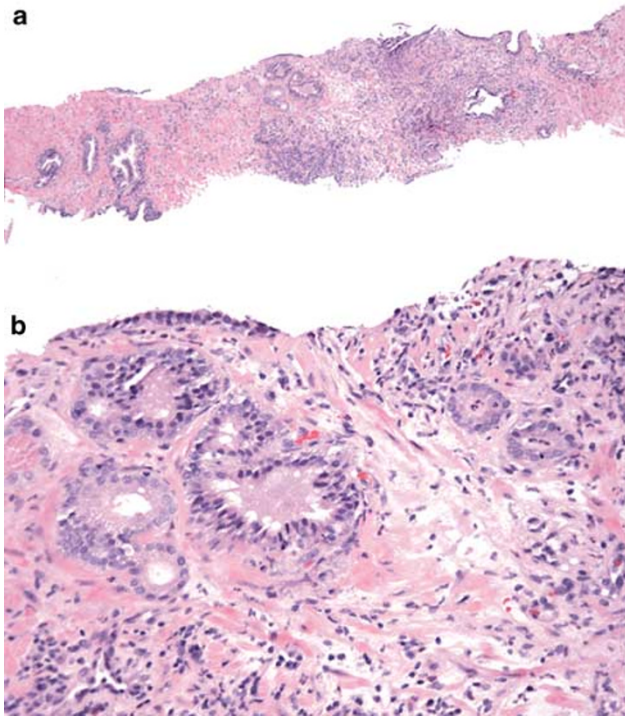 enlarged, hyperchromatic nuclei and prominent nucleoli. The low-power architectural arrangement of the atypical glands is helpful in separating radiation atypia from residual adenocarcinoma. Other radiation-associated changes include prominent atrophy, transitional cell and squamous metaplasia, stromal fibrosis, edema and changes within prostatic arteries. In difficult cases, immunohistochemistry for high molecular weight keratin (34βE12) is invaluable in resolving the differential diagnosis.

Mucinous metaplasia

Mucin-producing cells are sometimes identified within prostatic glands, usually atrophic ones.[22] As such, this process may enter the differential diagnosis of small acinar carcinoma. The lobular pattern of the associated atrophy usually points to the benign nature of this lesion (Figure 10). Individual mucous cells have a vacuolated appearance on H&E and highlighted by mucicarmine and PAS stains. When there is florid mucinous metaplasia, especially in an apical location, confusion with Cowper's (bulbourethral) glands may occur.[20,21]
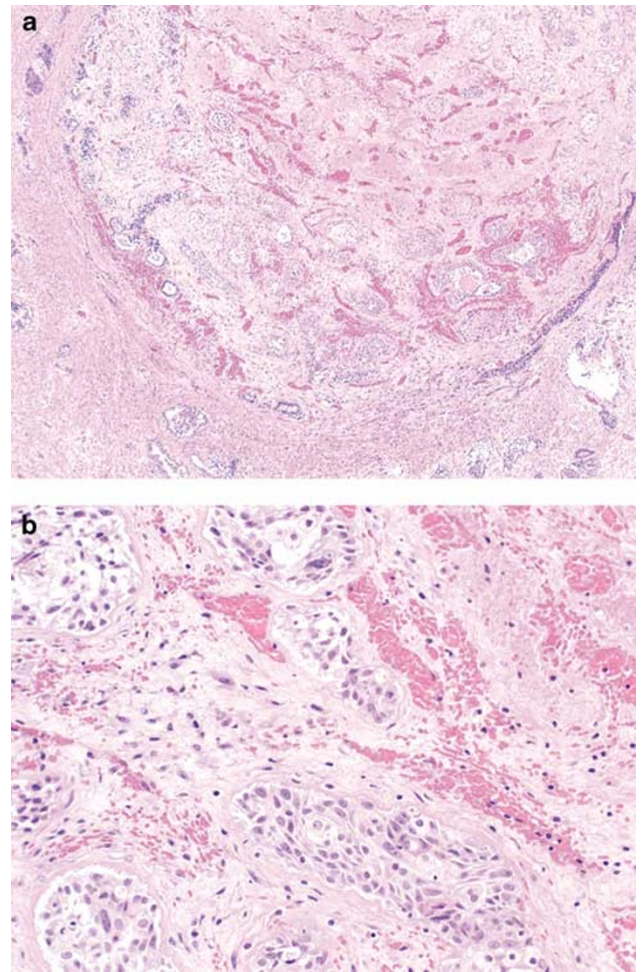

Figure 8 Active chronic prostatitis with reactive glandular atypia. (**a**) Low-power of needle biopsy. (**b**) High-power—note nuclear atypia in some glands.

Figure 9 Prostatic infarct with reactive atypia. (**a**) Low power. (**b**) High power showing glands at edge of infarcted area—note squamoid features and nuclear atypicality.
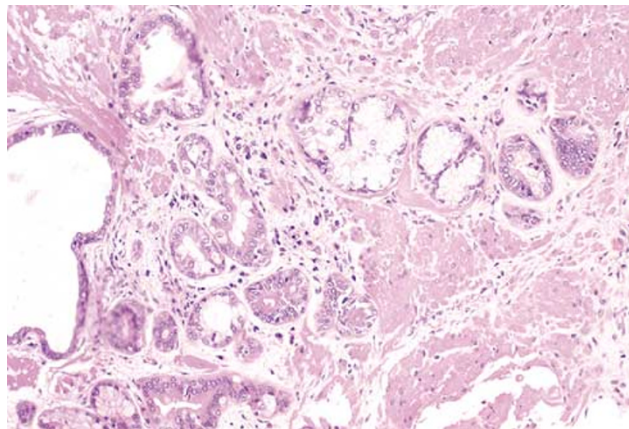
Figure 10 Atrophic prostate glands with focal mucinous metaplasia.

Nephrogenic metaplasia (adenoma)

Nephrogenic metaplasia (adenoma) is uncommonly encountered in the prostatic urethra, and subjacent prostatic tissue.[46–49] It may be present as an exophytic (papillary) lesion or as a flat or nodular abnormality. In most instances, there has been a previous history of trauma, instrumentation or transurethral resection. Problems can arise when a prior transurethral resection has revealed adenocarcinoma.

Nephrogenic metaplasia displays exophytic papillary and tubulocystic elements. The latter may have a pseudoinvasive growth pattern (Figure 11). The acini of nephrogenic metaplasia are usually small and the cells have scant cytoplasm. Sometimes they may have more abundant clear cytoplasm. At least focally, the tubules may display cystic change and sometimes hobnail cells are identified. Commonly, the adjacent stroma is both edematous and inflamed.

The small size of the acini, cystic dilatation and inflamed stroma separate nephrogenic metaplasia from small acinar carcinoma. High molecular weight keratin (34βE12) is positive in some but not all cases of nephrogenic metaplasia.[49] When positive, it is a helpful adjunctive test. The PSA and PAP stains are usually negative but there may be focal positivity of tubular cells and/or secretions.[49]

A recent study suggests that nephrogenic metaplasia (adenoma) is neither metaplastic nor neoplastic in nature.[50] Molecular studies in the setting of transplantation suggest that this lesion is truly nephrogenic in origin and results from the implantation of renal tubular cells at sites of prior urothelial injury with subsequent proliferation of epithelial elements.

Basal cell hyperplasia

Basal cell hyperplasia is typically seen as part of the spectrum of nodular hyperplasia usually in samples from the transition zone.[51–54] Recently, it has been
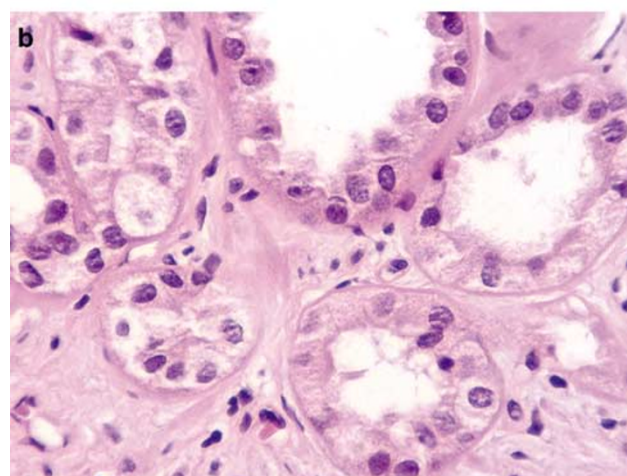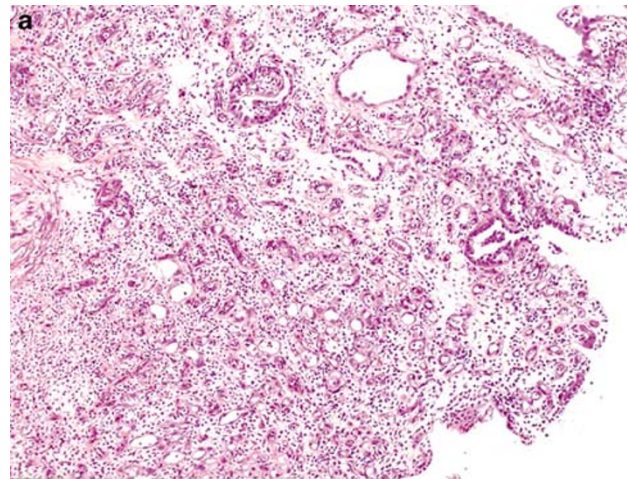

Figure 11 Nephrogenic metaplasia. (**a**) Low power. Note pseudoinfiltrative small tubules in an inflammatory background. (**b**) High power showing small acini with slight nuclear irregularity. This lesion may be confused with small acinar carcinoma.

recognized that basal cell hyperplasia may also affect the peripheral zone.[55] It is usually identified in transurethral resection specimens but may be encountered in needle biopsies (Figure 12). Basal cell hyperplasia may also occur in association with atrophy, usually in the setting of antiandrogen therapy.[28–30] Basal cell hyperplasia may be confused with adenocarcinoma.

Basal cell hyperplasia is usually characterized by nodular expansion of uniform round glands associated with a cellular stroma. It may be complete or incomplete.[15] There is a lack of secretory (luminal) cell differentiation in the complete form in which solid nests of dark-blue cells are present. In the incomplete form, there are residual small lumina lined by secretory cells with clear cytoplasm and these are surrounded by multiple layers of basal cells. In each type, the basal cells are dark and have scant cytoplasm and display round, oval or somewhat spindled hyperchromatic nuclei (Figure 12). Nucleoli are usually indistinct but in some
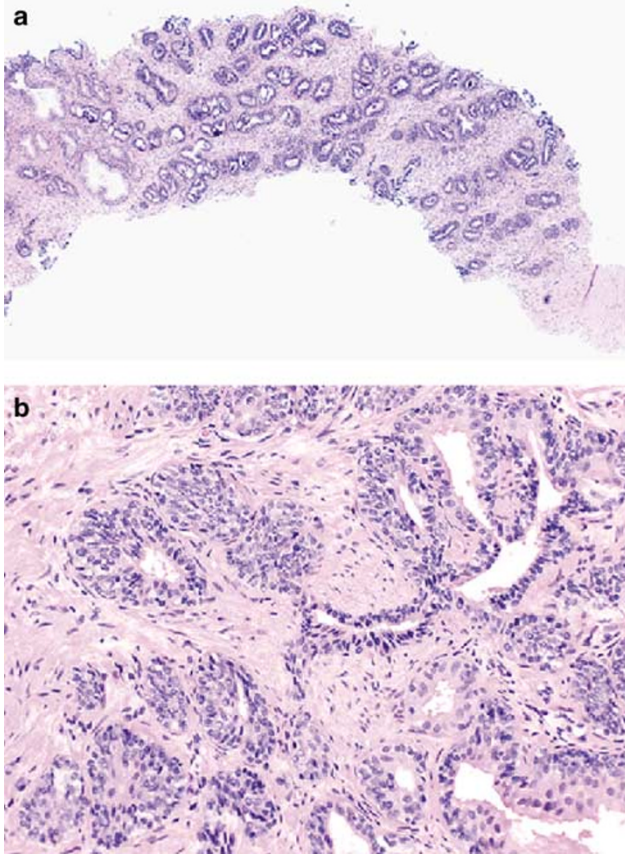
Figure 12 Basal cell hyperplasia in needle biopsy. (**a**) Low-power appearance showing prominent basophilic glands. (**b**) High-power photomicrograph showing budding and proliferation of small, uniform, dark basal cells.

examples of the so-called atypical basal cell hyperplasia, nucleoli may be more prominent.[53,56] Microcalcifications are present in up to half of the cases of basal cell hyperplasia. The adjacent stroma is often hypercellular and consists of proliferating fibroblasts and smooth muscle cells similar to those seen in usual nodular hyperplasia.

Basal cell hyperplasia is readily separated from adenocarcinoma in most cases, especially in transurethral resectate and prostatectomy specimens. The nodular arrangement, association with ordinary nodular hyperplasia, cellular uniformity and lack of prominent nucleoli serve to separate this condition from cancer. It may be more difficult however in small biopsies in which part of a focus of basal cell hyperplasia is only partially represented. In such cases, the distinction relies on the identification of uniform cytological and nuclear features and in some instances may require immunohistochemical staining for high molecular weight keratin $(34\beta E12)$.[52]

Benign nodular hyperplasia, small gland pattern
Benign nodular hyperplasia of prostate can have a variety of morphologies including predominantly stromal, mixed glandular and stromal, and predo-
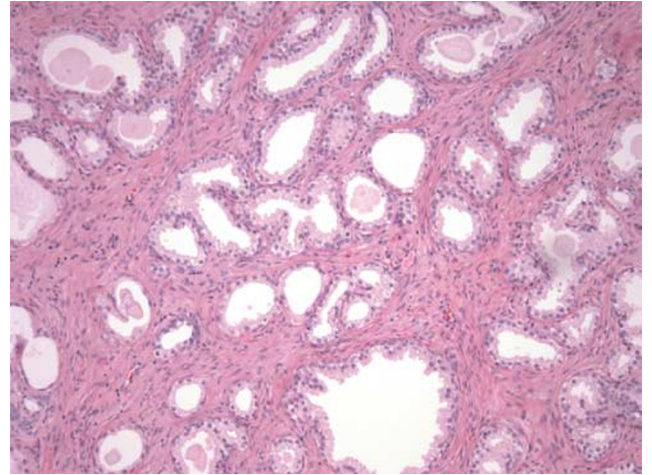

Figure 13 Small gland pattern of benign nodular hyperplasia. Note several small- to medium-sized, irregular acini embedded in a cellular stroma.

minantly glandular growth patterns.[9,15] The glandular elements usually consist of medium to large acini, often showing luminal papillae. Occasionally, areas of nodular hyperplasia are composed of mainly small to medium sized, closely packed acini with rounded lumens.

Usually basal cells are readily identified and small amounts of intervening cellular stroma are seen. The nodular circumscription, uniform architecture, presence of basal cells and intervening stroma serve to separate this proliferative pattern from low-grade (Gleason patterns 1, 2) adenocarcinoma (Figure 13).

It is probably more common for adenocarcinoma to mimic benign nodular hyperplasia than the converse. The pseudohyperplastic pattern of adenocarcinoma is composed of medium to large acini that may have a somewhat nodular appearance on low power.[57,58] This form of carcinoma can be deceptively bland and may only be suspected when there is a subtle disruption of the normal gland/stroma relationship on low power. This observation can be quite difficult in thin core biopsies. On higher power, there is an absence of basal cells and the typical nuclear features of adenocarcinoma are present. The cells comprising this lesion are usually high cuboidal to columnar cells with abundant apical, often clear cytoplasm. These cells resemble the appearance of the secretory cell compartment in benign nodular hyperplasia aside from their nuclear features. The $34\beta E12$ stain is invaluable in confirming a diagnosis of pseudohyperplastic adenocarcinoma.

Sclerosing adenosis
The term sclerosing adenosis of the prostate was first used by Young and Clement in 1987 to describe an unusual prostatic proliferative lesion which resembled to some extent sclerosing adenosis of breast.[59] There had been an earlier report in which

the term adenomatoid tumor was used.[60] Sclerosing adenosis is an uncommon lesion largely restricted to the transition zone and is generally an incidental finding in transurethral resectates or radical prostatectomy specimens. It is rarely seen in needle biopsies. A few series of sclerosing adenosis cases have been reported.[61–63]

Sclerosing adenosis is characterized by a more or less circumscribed proliferation of variably sized, often small glands embedded in a cellular and often edematous stroma (Figure 14). Sometimes the lightly basophilic stroma is recognized on low power. Tiny microacini, cords, solid clusters and single cells are seen. A double layer is present but may be difficult to appreciate with the H&E stain. The lining cells often have open nuclear chromatin with inconspicuous nucleoli although prominent nucleoli may be focally present. Glandular lumens may contain crystalloids or occasionally acid mucin. A characteristic feature is the present of a thick eosinophilic basement membrane around at least some glands.

Sclerosing adenosis is unique in that the basal cells in this condition undergo myoepithelial metaplasia and show coexpression of both high molecular weight cytokeratin and muscle-specific actin (HHF-35)[63] (Figure 14). S100 protein is also positive in these cells. The myoepithelial differentiation has been confirmed by electron microscopic studies.

The key features distinguishing sclerosing adenosis from adenocarcinoma include the variation in gland size and shape, thickened basement membranes and cellular stroma. Immunohistochemistry for high molecular weight keratin (34βE12) and actin can be used in problematic cases.

Verumontanum mucosal gland hyperplasia

Verumontanum mucosal gland hyperplasia is identified as an incidental finding in radical prostatectomy specimens.[64] In all, 14% of 30 radical prostatectomy specimens in one series contained one or more foci of hyperplastic verumontanum mucosal glands. This process is rarely encountered in needle biopsy specimens.[65] It is characterized by relatively uniform, closely packed, round glands containing numerous corpora amylacea which may have a red or orange-brown coloration (Figure 15). Basal cells are usually identified and there is a lack of nuclear features of malignancy. In particular, prominent nucleoli are not seen. Lipofuscin pigment may be present within the cytoplasm of
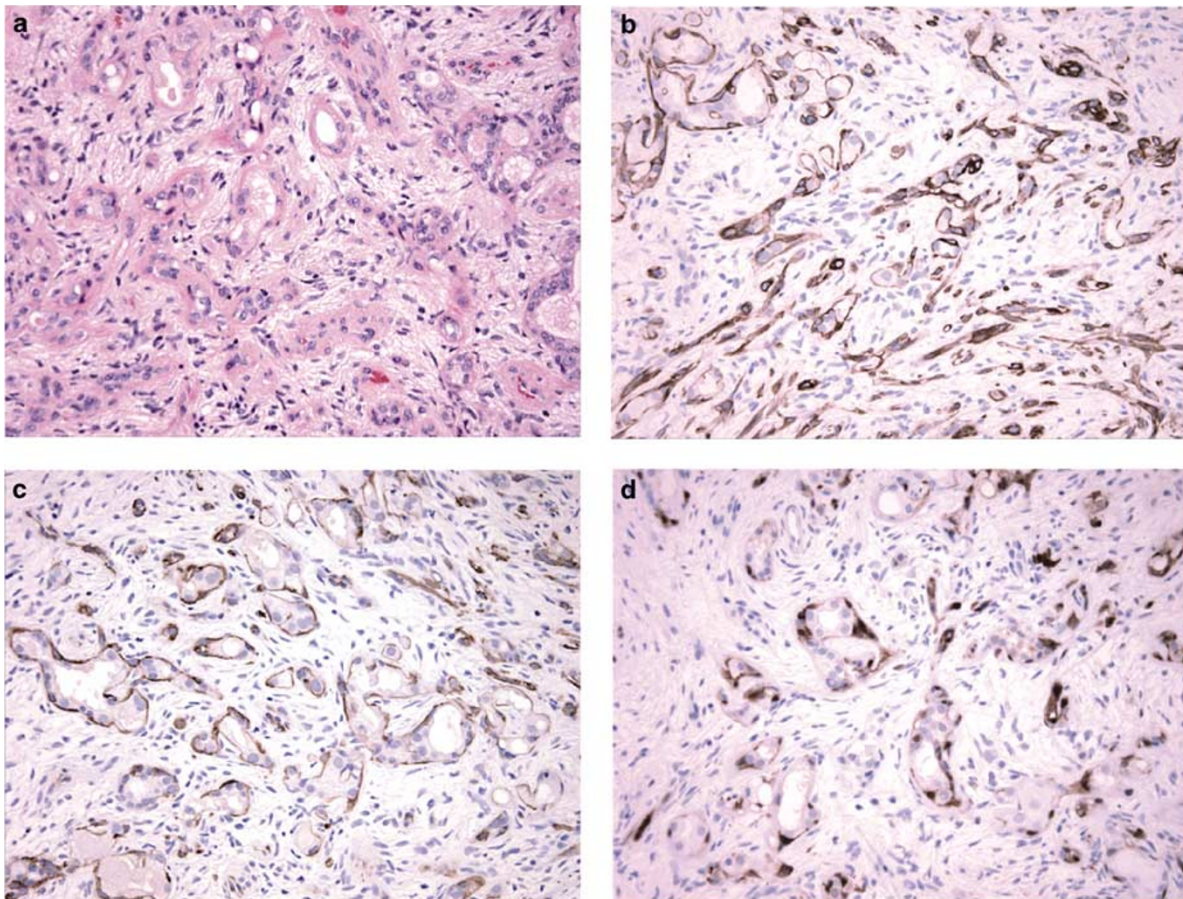

Figure 14 Sclerosing adenosis of prostate. (**a**) H&E appearance showing small glands with thick basement membranes embedded in cellular fibrous stroma. (**b**) High molecular weight keratin staining (34βE12) demonstrating positive basal cells. (**c**) HHF35 (muscle-specific actin) staining in basal cells indicating myoepithelial metaplasia. (**d**) S100 positivity in basal cells.

glandular cells. Prostatic urethral tissue is often seen nearby and islands of transitional cell epithelium may be present in or adjacent to the proliferating verumontanum glands. The suburethral location, acinar and cellular uniformity, basal cells and prominent corpora amylacea allow separation of this entity from low-grade adenocarcinoma. Recently verumontanum mucosal gland hyperplasia has been associated with atypical adenomatous hyperplasia in a radical prostatectomy series.[66]

Hyperplasia of mesonephric glands

Mesonephric gland remnants are rarely identified in prostatic specimens.[67–71] In a series of close to 700 transurethral resectates, 0.6% contained mesonephric remnants.[70] Mesonephric gland remnants occasionally undergo hyperplasia and may be confused with adenocarcinoma. Gikas *et al* identified two cases in transurethral resection specimens that were interpreted as adenocarcinoma which in one instance led to an unnecessary radical prostatectomy.[67] The hyperplastic mesonephric glands are typically small and may have an infiltrative appearance (Figure 16). Sometimes tubular dilatation, epithelial tufting and micropa-
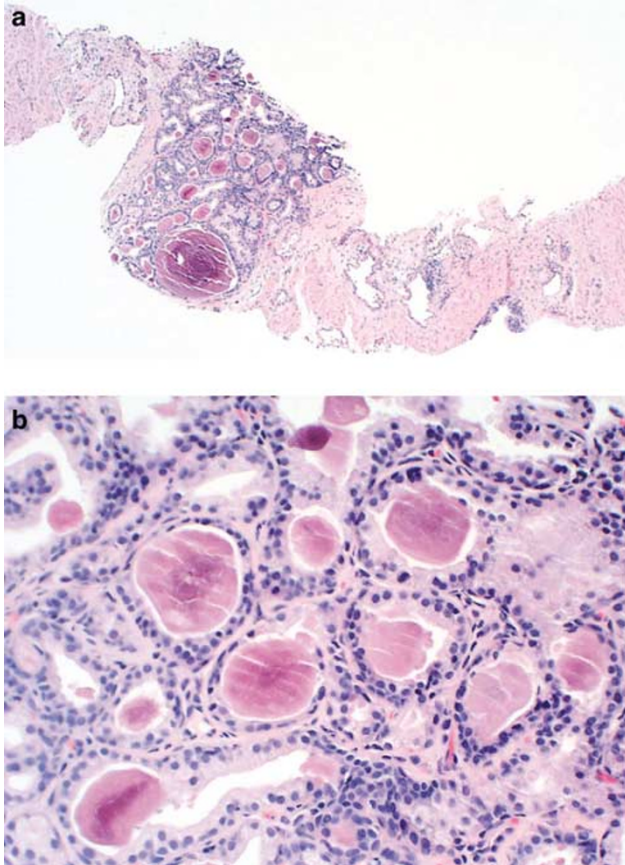
pillary formations are seen. They may demonstrate perineural spread and extraprostatic extension. Mesonephric glands are lined by a single layer of cuboidal cells. Typically, the small glands contain a dense eosinophilic luminal substance which contrasts with the loose granular eosinophilic material typical of small acinar carcinoma (Figure 16). Immunohistochemistry may be helpful in difficult cases. The glands of mesonephric hyperplasia stain negatively for PSA and PAP and often positively for high molecular weight cytokeratin (34βE12) in contrast to adenocarcinoma which lacks 34βE12 basal cells.

Atypical adenomatous hyperplasia (adenosis)

Atypical adenomatous hyperplasia (AAH) is a proliferative lesion characterized by crowded small acini, usually forming well circumscribed nodules which often simulate the small gland pattern of carcinoma.[72–78] While many authors use the term
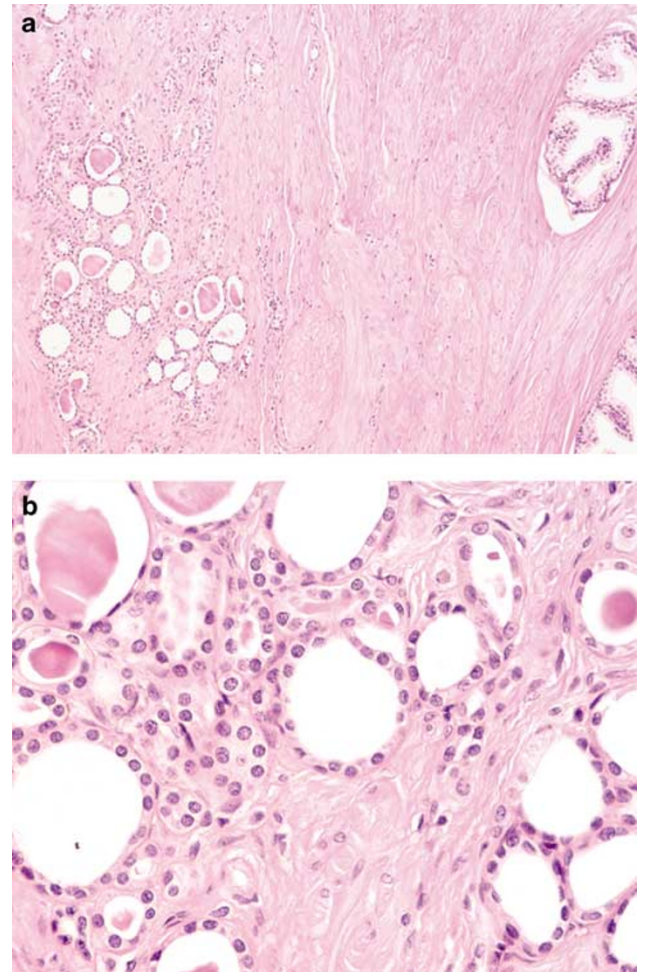

Figure 15 Verumontanum mucosal gland hyperplasia. (**a**) Low-power appearance in needle biopsy. (**b**) High-power appearance showing tightly packed small acini with prominent corpora amylacea.

Figure 16 Hyperplasia of mesonephric glands. (**a**) Low power. Note prostatic glands on right side and mesonephric glands on left. (**b**) High-power photomicrograph. Note small acini, some of which are cystically dilated and some containing colloid-like secretions.

'atypical adenomatous hyperplasia' others prefer the rubric 'adenosis'.[79–83] AAH is a well-defined entity but the term 'adenosis' has been used more loosely, even to the extent that some examples of adenosis have been interpreted by experts as adenocarcinoma.[84]

AAH has been identified in 1.5–19.6% of transurethral resectates and in up to 33% of radical prostatectomy specimens.[9] It is uncommon in needle biopsy specimens but occasionally occurs.[82]

Most evidence associating AAH with carcinoma is circumstantial.[9,75,78] AAH has a predilection for the transition zone and morphologically simulates low grade (Gleason 1, 2) carcinoma. Examples of small acinar carcinoma arising in relationship to AAH have been reported. Additionally, the age of patients with AAH is usually 5–10 years, less than those with carcinoma.

The basal cell-specific keratin stain shows a discontinuous pattern which is intermediate between the continuous pattern of normal prostate and the absence of basal cells in carcinoma.[8,74,85] Studies with tridiated thymidine, immunohistochemistry for proliferation markers (Ki67/M1B-1) and silver staining of nucleolar-organizer regions suggest that AAH has a proliferation rate between benign prostate hyperplasia and low-grade carcinoma.[86–88] Recent molecular and phenotypic studies suggest a possible linkage between AAH and carcinoma in the minority of cases.[89,90]

While circumstantial evidence exists, there is lack of proof of a relationship between AAH and adenocarcinoma.[9] It has been suggested that AAH is a precursor of some low-grade transition zone carcinomas but the lack of an increased prevalence of AAH in prostate glands with transition zone carcinoma argues against this hypothesis.[9] Clearly, there is less evidence linking AAH to carcinoma than there is for high-grade PIN and cancer.[9,75]

The major importance of AAH is its potential for being misdiagnosed as adenocarcinoma. Foci of AAH are usually less than 5 mm across and are characterized by a proliferation of relatively small uniform acini, often within or adjacent to typical hyperplastic nodules (Figure 17). Sometimes there is a prominent perinodular distribution of the abnormal glands. The low-power architecture is reminiscent of Gleason patterns 1 and 2 carcinoma. AAH usually has a pushing rather than infiltrating border but may show a limited degree of infiltration (Figure 18). Individual glands are closely packed but separate and show no evidence of fusion. They show some variation in size and shape and are lined by cuboidal to low columnar cells with moderate to abundant clear or lightly eosinophilic cytoplasm. Basal cells are usually recognized at least focally. The luminal borders are often irregular and somewhat serrated in contrast to the rigid borders that typify small acinar carcinoma. The lumens are often empty but may contain corpora amylacea and in some
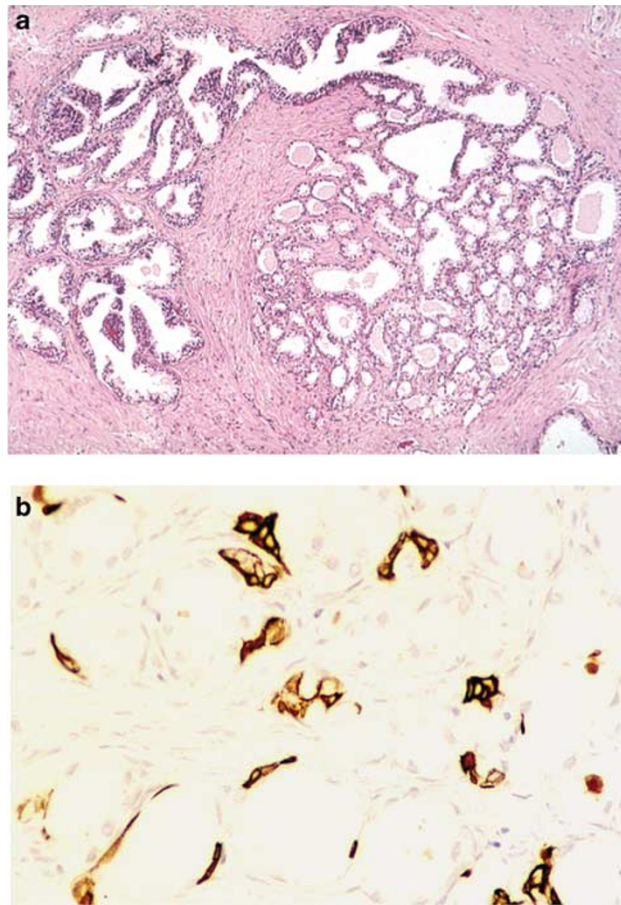
Figure 17 Atypical adenomatous hyperplasia (adenosis). (a) Low-power photomicrograph showing apparent budding of small regular acini off a parent duct. Note close relationship between the small gland proliferation and the benign overall nodule. (b) Discontinuous pattern of 34βE12 staining characteristic of atypical adenomatous hyperplasia (adenosis).

instances luminal eosinophilic crystalloids.[74,81] Occasionally, basophilic luminal mucus may be seen.[91,92] There is usually no stromal response but occasionally, a fibroblastic response is identified which leads to overlap with the pattern of sclerosing adenosis.[59–63]

The nuclei of atypical adenomatous hyperplasia are round to oval and there is uniform fine chromatin.[74] Nucleoli may be present but they are generally small. Uncommonly, enlarged nucleoli ($>1\,\mu$m) are identified in a subset of cells.[74]

By immunohistochemistry, the glands of AAH exhibit strong positivity for PSA and PAP and there is typically a discontinuous basal cell pattern with the 34βE12 stain (Figure 17).

The most important features in separating AAH from adenocarcinoma is the lack of significantly enlarged nucleoli and the presence of a fragmented basal cell layer. A comparison between high- and low-grade carcinoma is shown in Table 4.

From a clinical perspective, AAH should be considered as a benign lesion and patients followed
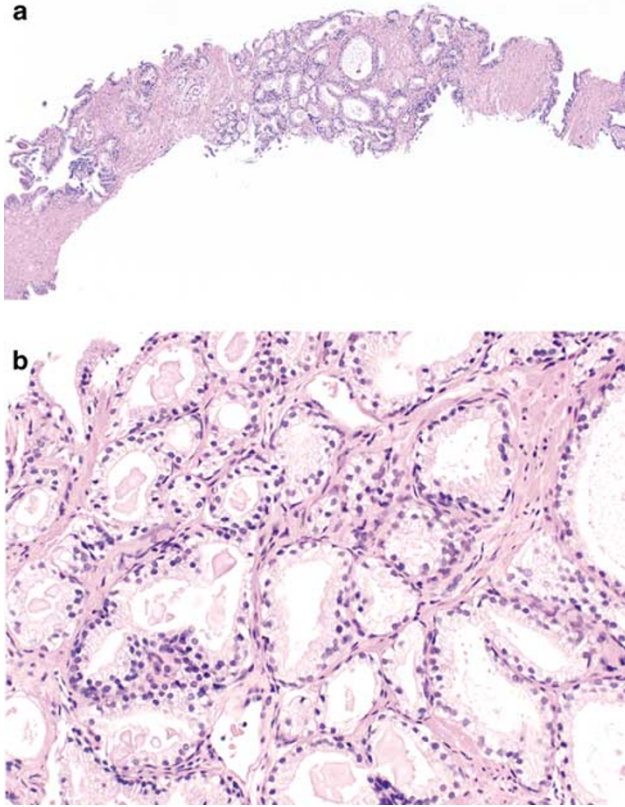
Figure 18 (**a**) Atypical adenomatous hyperplasia (adenosis) in needle biopsy. Note central proliferating small gland process. (**b**) High-power photomicrograph showing some variation in size and shape of small acini. Basal cells are maintained and there is no significant nuclear atypia.

Table 4 Atypical adenomatous hyperplasia *vs* well-differentiated adenocarcinoma

	Atypical adenomatous hyperplasia	Carcinoma (Gleason grades 1 and 2)
Architectural and associated features		
Low power	Circumscribed or limited infiltration	Circumscribed or limited infiltration
Lesion size	Variable	Variable
Gland size	Variable	Less variable
Gland shape	Variable	Less variable
Crystalloids	Infrequent	Frequent
Corpora amylacea	Frequent	Infrequent
Basophilic mucin	Infrequent	Frequent
Nuclear features		
Nuclear size variation	Less variable	Variable
Chromatin	Uniform/granular	Uniform or variable
Parachromatin clearing	Infrequent	Frequent
Nucleoli	Inconspicuous	Prominent
Basal cell layer		
H&E stain	Inconspicuous	Absent
HMWK (34βE12) stain	Fragmented	Virtually absent

Modified from Bostwick et al.[5]

conservatively. The term should not be used as a 'wastebasket' for small glandular lesions that are difficult to classify or for suspicious atypical small gland proliferations (atypical small acinar proliferation [ASAP], glandular atypia), just below the threshold of adenocarcinoma.[9]

Large Gland Pattern

Clear cell cribriform hyperplasia
Benign nodular hyperplasia occasionally displays areas of prominent cribriform glands. Rarely, the cribriform process dominates the histologic picture.[93,94] Cribriform hyperplasia is characterized by a crowded proliferation of complex glands without cytologic atypia. In most instances, the cribriform glands have clear cytoplasm and uniform round lumina. This lesion generally has a low-power nodular appearance and intervening cellular stroma is seen (Figure 19). The cells comprising the central cribriform areas are cuboidal to low columnar secretory-type cells with uniform round nuclei and clear cytoplasm. They lack nuclear atypia and nucleolar enlargement. Basal cells are prominently displayed around the periphery.

Cribriform hyperplasia enters the differential diagnosis of both prostatic intraepithelial neoplasia

and cribriform adenocarcinoma. The distinction of cribriform hyperplasia from cribriform carcinoma is based on the 'low power' nodularity, cellular stroma, presence of basal cells and lack of significant cytologic atypia.

Adenoid cystic-like basal cell hyperplasia
While most forms of basal cell hyperplasia are characterized by relatively small nests of basal cells, the incomplete form of basal cell hyperplasia may be composed of medium to large glands with a complex cribriform pattern, sometimes with cyst formation and squamous metaplasia.[9,52,95,96] Such a process rarely enters the differential diagnosis of cribriform carcinoma. Some of these cases have been termed adenoid basal cell tumor or even basal cell carcinoma (Figure 20). The presence of typical areas of basal cell hyperplasia, lack of significant infiltration and absence of cytological atypia favor adenoid cystic-like basal cell hyperplasia over cribriform carcinoma.

Reactive atypia in large glands
Medium to large glands may display reactive atypia in the setting of inflammation, ischemia and radiation.[9,43–45] Such processes may lead to glandular distortion and nuclear atypia which sometimes results in a pattern that may be confused with prostatic intraepithelial neoplasia (PIN) and large gland patterns of adenocarcinoma. The most helpful features to distinguish reactive atypia from
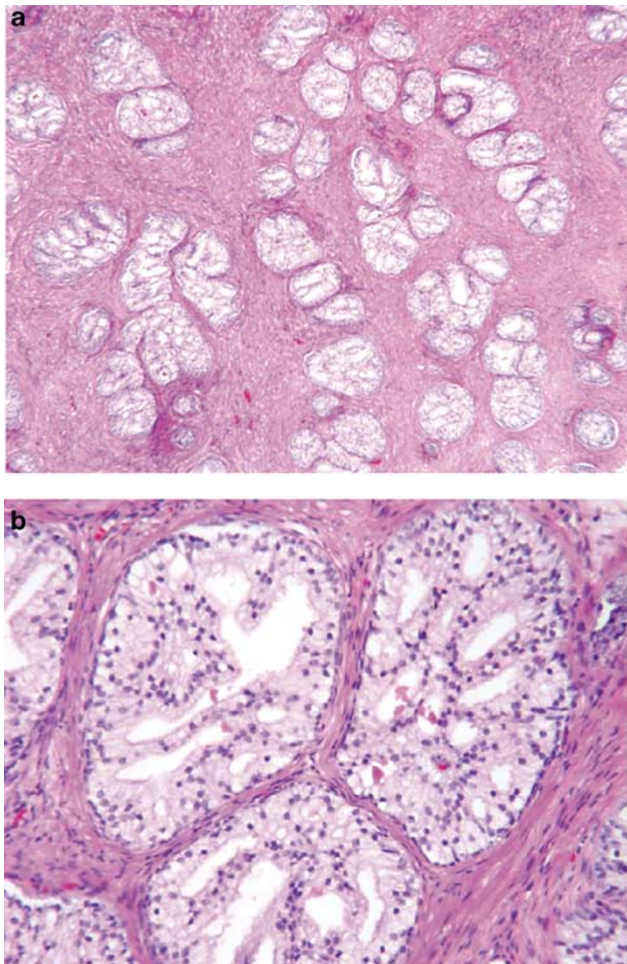
Figure 19 Clear cell cribriform hyperplasia. (**a**) Note low-power nodularity and uniform distribution of cribriform glands in cellular stroma. (**b**) High-power photomicrograph showing uniform cribriform glands with abundant clear cytoplasm. Basal cells are apparent. No significant nuclear atypia is seen.
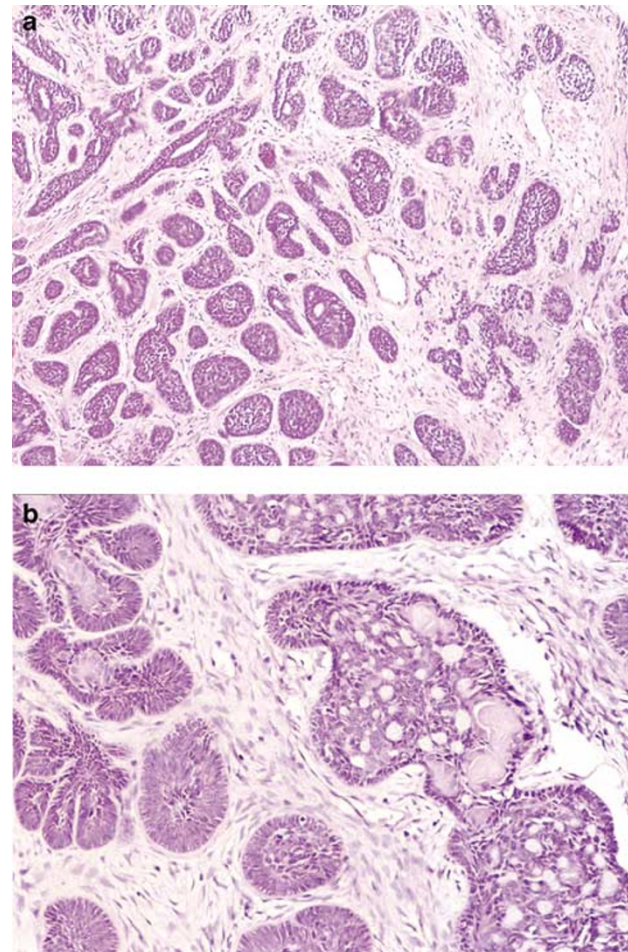

Figure 20 Adenoid cystic-like basal cell hyperplasia. (**a**) Low-power photomicrograph showing a rounded collection of large basaloid nests embedded in loose stroma. (**b**) Medium-power photomicrograph showing proliferation of basaloid nests and cribriform structures with focal dense amorphous material.

malignancy is the recognition of the associated inciting factor such as inflammation, infarction or radiation, and the maintenance of the basal cell compartment. The atypia associated with reactive conditions may result in nuclei that appear hyperchromatic and somewhat degenerate. In some cases, the nucleolar enlargement associated with the reactive state may be more prominent and more uniform than that seen with adenocarcinoma. The low-power architecture and presence of a residual basal cell layer sometimes requiring confirmation with the 34βE12 stain are the best clues to the benign nature of this condition.

Fused Gland Pattern

Paraganglion
Paraganglionic tissue may be encountered within prostatic and periprostatic tissue, usually the latter.[97–99] Paraganglia are characterized by small, solid

nests of cells with clear or amphophilic cytoplasm, often with a 'zellballen' arrangement. There is a delicate background network of capillaries. The nuclei are often hyperchromatic but nucleoli and other features of adenocarcinoma are not seen. The islands of paraganglionic tissue are separated by fibrous stroma. Paraganglionic tissue can simulate the fused gland pattern of adenocarcinoma (Gleason 4) (Figure 21). If the cytoplasm of the paraganglionic tissue is amphophilic, it may look like Gleason pattern 4A and if clear may look like Gleason pattern 4B. Cases in needles biopsies are quite rare. A more common issue is the overinterpretation of extraprostatic paraganglionic tissue in radical prostatectomy specimens leading to spurious overstaging of organ-confined cancer. Additionally, the interpretation of paraganglionic tissue as adenocarcinoma may lead to a grading inaccuracy. When a Gleason grade 3 tumor is encountered and accompanying paraganglionic tissue is interpreted as Gleason grade 4 tumor, the resultant score would be inaccurately
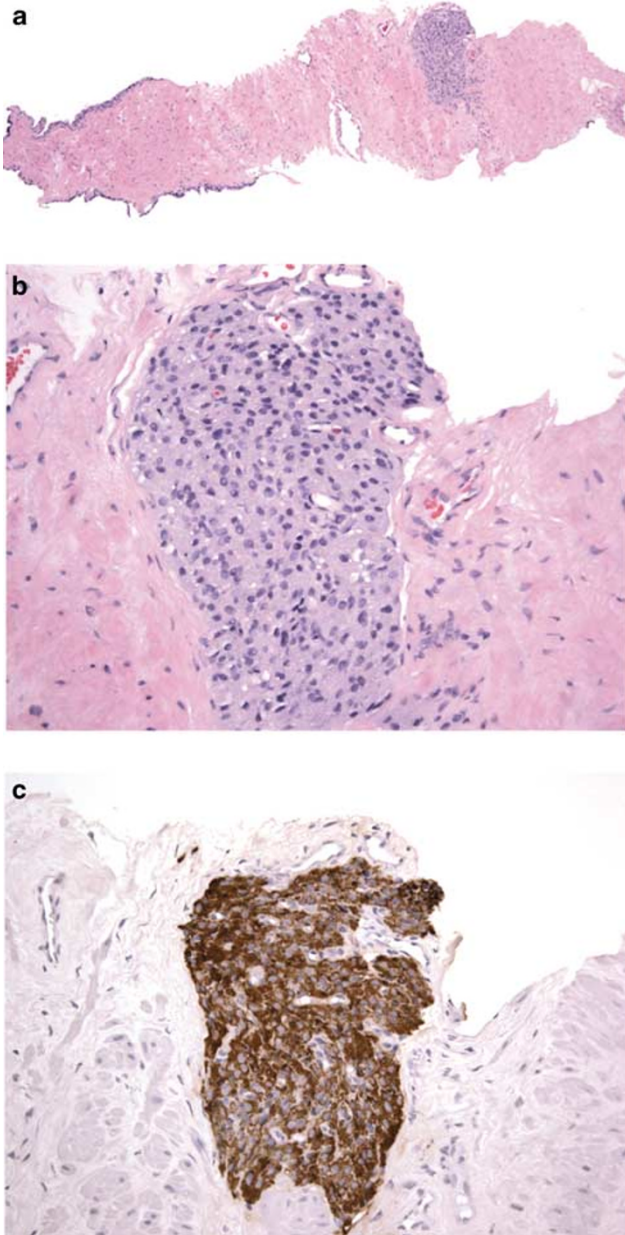
Figure 21 Prostatic paraganglion. (**a**) Needle biopsy showing solid amphophilic area. (**b**) High-power photomicrograph showing rounded amphophilic cellular mass without significant atypia. (**c**) Positive chromogranin stain.

recorded as 7 instead of the correct score of 6. In problematic cases, special stains determining prostatic origin (PSA, PAP) and stains for neuroendocrine cells (chromogranin, synaptophysin) should be employed (Figure 21).

Xanthogranulomatous prostatitis (xanthoma)
Collections of lipid-laden macrophages in the prostate may cause diagnostic confusion with the hypernephroid pattern of adenocarcinoma (Gleason 4B)[100,101] (Figure 22). Xanthomatous histiocytes usually have small uniform nuclei within incon-
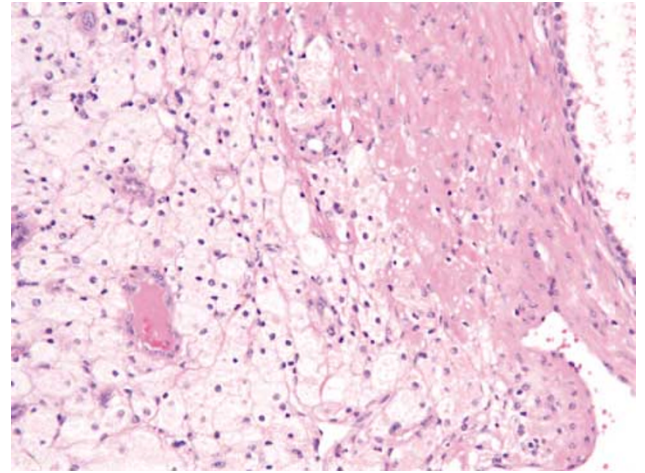

Figure 22 Xanthogranulomatous inflammation (xanthoma) of prostate. Note collection of uniform cells with small dark nuclei and abundant clear to foamy cytoplasm. This lesion may be confused with the hypernephroid pattern of prostatic adenocarcinoma (Gleason 4B).

spicuous nucleoli and are commonly admixed with other types of inflammatory cells. In some instances, there is almost a pure population of foam cells which can lead to considerable diagnostic confusion. The problem is compounded by the fact that some hypernephroid carcinomas do not show the typical nuclear features of malignancy. They may have small dark nuclei without prominent nucleoli. In rare cases, immunohistochemistry utilizing stains for epithelial and prostatic cells (cytokeratin, PSA, PAP) and histiocytes (CD68) is required to resolve the diagnostic confusion.

Malakoplakia
Malakoplakia of the prostate is a rare infiltrative lesion characterized by diffuse sheets of histiocytes, usually admixed with other inflammatory cells including lymphocytes, plasma cells and neutrophils.[102–106] In the early phase of malakoplakia when von Hansemann histiocytes predominate, the lesion may simulate carcinoma, especially Gleason pattern 4B. The lack of any acinar differentiation and admixed inflammatory infiltrate along with the typical Michaelis–Gutmann bodies will lead to a correct diagnosis (Figure 23). The absence of cytokeratins and prostatic epithelial markers along with the presence of CD68 staining may resolve difficult diagnostic problems.

Solid Pattern

Ordinary prostatitis
Occasionally, needle biopsies with prostatitis of the usual type may cause diagnostic problems.[107–109] This is especially true when there is poor preservation and mechanical (crush) artifacts (Figure 24). In some cases, immunohistochemical stains (keratins,
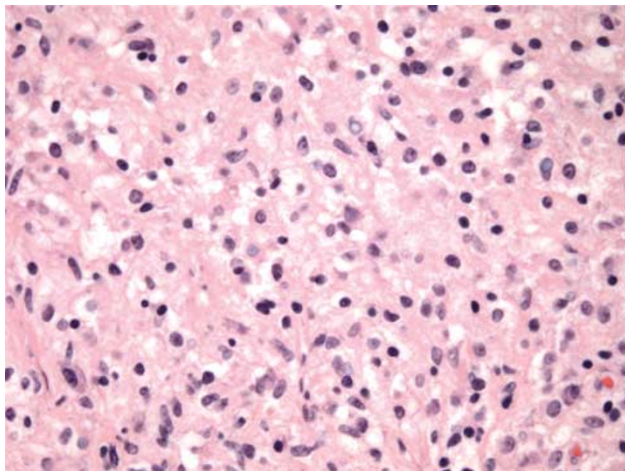
Figure 23 Prostatic malakoplakia—note sea of pink histiocytic cells (Von Hansemann cells) with occasional Michaelis–Gutmann bodies.
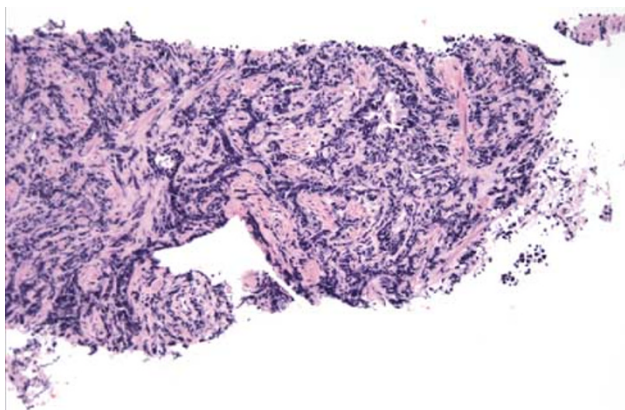

Figure 24 Crushed and inflamed prostatic tissue simulating solid carcinoma.

Figure 25 Nonspecific granulomatous prostatitis. (**a**) Low-power appearance in needle biopsy showing solid pattern. (**b**) High-power appearance showing admixture of histiocytes and lymphocytes.

leukocyte common antigens) are required in order to resolve a differential diagnosis.

Non-specific granulomatous prostatitis
Granulomatous prostatitis commonly results in a prostate gland that feels firm to hard and clinically simulates carcinoma.[110,111] In biopsy samples, especially needle biopsies, florid nonspecific granulomatous prostatitis may simulate carcinoma.[112,113] The association of the inflammation with ducts may not be seen and when the inflammatory process is diffuse, it may raise the suspicion of high-grade (Gleason 5) carcinoma (Figure 25). The problem is amplified if poor preservation or mechanical artifacts are present. The recognition of the inflammatory nature of the cells along with the association of giant cells and fibrosis are helpful features. In difficult cases, immunohistochemistry for cytokeratins, prostatic epithelial markers and lymphohistiocytic markers may be used (Figure 26). Granulomatous prostatitis associated with specific infections
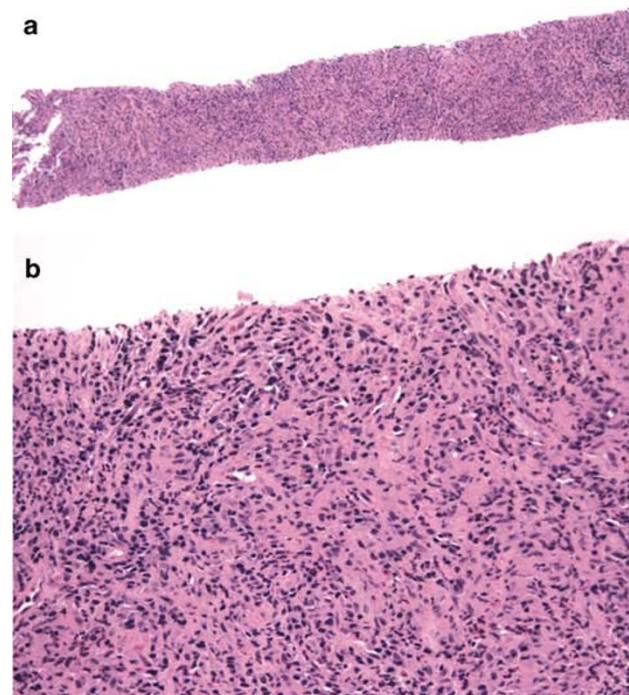
such as fungus and tuberculosis, BCG-associated granulomas and the procedural associated granulomas (palisading granulomas) do not usually cause problems in the differential diagnosis of adenocarcinoma.

Degenerative changes in lymphocytes and stromal cells
Lymphocytes and sometimes stromal cells may undergo degenerative changes which result in a signet ring-like morphology.[114–116] If the change is prominent, the pattern can resemble high-grade adenocarcinoma composed of individual signet ring cells (Figure 27). The artifactual signet ring-like pattern, while initially described in transurethral resectates, may be found in needle biopsies. In the series of 47 cases, these 'atypical' cells were prominent in three cases and rare in 11 cases.[115] It is very important to be aware of this phenomenon and not to overinterpret such cells as being malignant. In difficult cases, immunohistochemical stains can be used to confirm the nonepithelial nature of the cells.

Summary

There are a wide variety of patterns and processes that may be confused with one or more of the diverse patterns of prostatic adenocarcinoma. In general, recognition of this differential diagnosis coupled with careful routine microscopy will
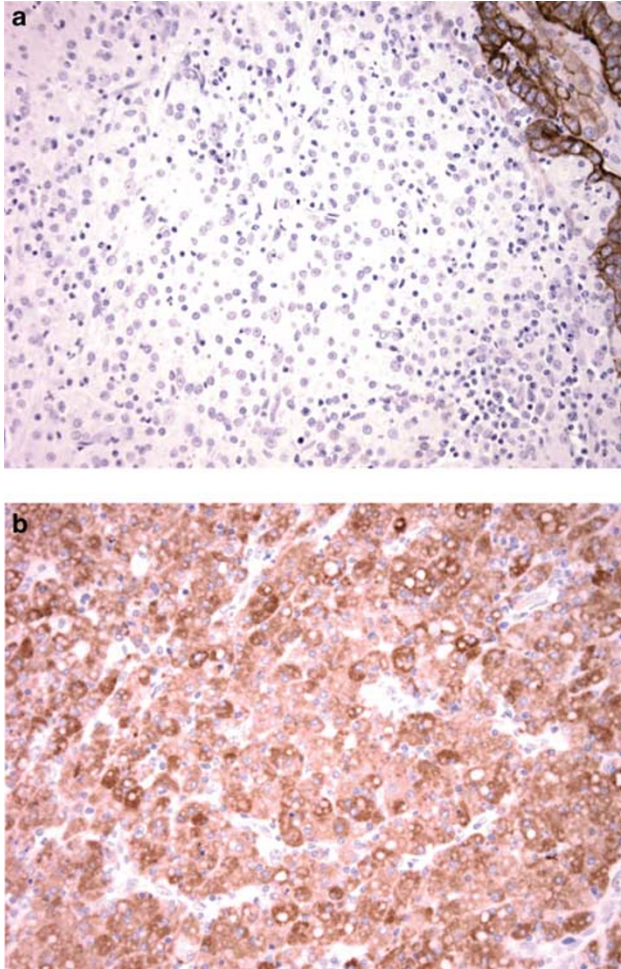
Figure 26 Granulomatous prostatitis (**a**) Immunohistochemistry for cytokeratin (CAM 5.2)—note positive glands (upper right) and negative staining of infiltrate. (**b**) Infiltrate stains positively for the macrophage marker, CD68.

Figure 27 Degenerative changes in lymphocytes and stromal cells simulating signet ring pattern of prostatic adenocarcinoma.

Table 5 Benign mimickers of adenocarcinoma: useful immuno-histochemical markers

Cytokeratins (general)
    AE1/AE3, Cam 5.2, MAK6
Basal cell markers
    $34\beta E12$, CK5/6, p63
Secretory cell markers
    Prostate-specific antigen (PSA), prostatic acid phosphatase
      (PAP), CD57
Neuroendocrine markers
    Chromogranin, synaptophysin
Lymphohistiocytic markers
    Leukocyte common antigen, CD56, CD68
Other markers
    α-Methylacyl-CoA racemase (P504S)

lead to a correct diagnosis. In some instances however, ancillary immunohistochemical studies aimed at identifying prostatic basal cells ($34\beta E12$, CK5/6, p63), prostatic secretory cells (PSA, PAP, CD57), neuroendocrine cells (chromogranin, synaptophysin) and inflammatory cells (LCA, CD68) may be required to resolve a diagnostic dilemma (see Table 5). The new marker α-methylacyl-CoA racemase (P504S) appears to be of value in supporting a diagnosis of adenocarcinoma, especially when one is dealing with small foci[117,118] (Figure 28).

Awareness of the differential diagnosis of prostatic adenocarcinoma is especially important in the context of diagnosing limited carcinoma in small biopsy samples. It is important to always be aware of the potential of false-positive cancer diagnosis when looking at prostatic biopsies and to utilize appropriate consultation and ancillary studies to arrive at a confident and correct diagnosis.
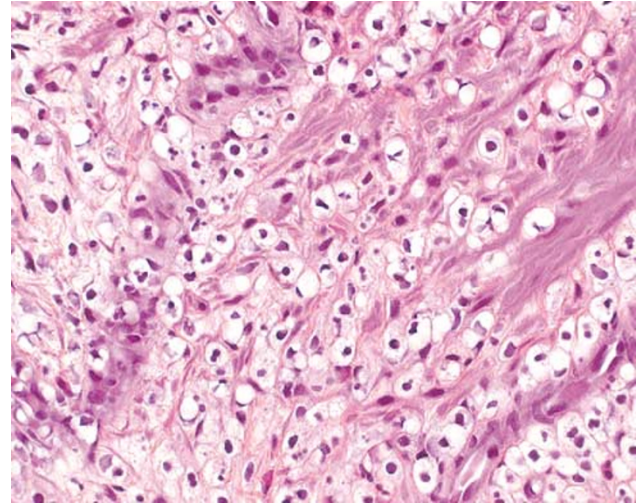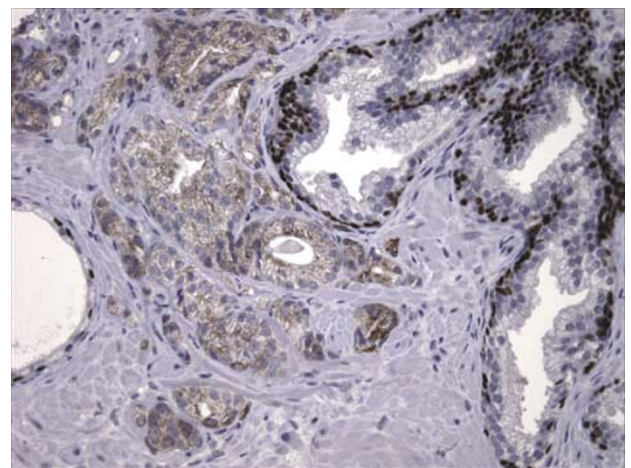

Figure 28 Small focus of adenocarcinoma stained with PIN cocktail (P504S + p63). Note non-neoplastic glands with prominent basal cells decorated with the nuclear stain, p63 (right). Centrally, there is an infiltrate of small glands lacking basal cells and staining positively for P504S. These markers are useful in the diagnosis and differential diagnosis of small foci of adenocarcinoma.

Acknowledgements

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