UROLOGICAL PATHOLOGY

Benign mimics of prostate cancer

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Summary

The histopathological diagnosis of prostatic adenocarcinoma is challenged by the existence of numerous benign mimics. Most of these lesions have no clinical significance and many do not need to be reported. Their clinical relevance lies in the risk that they are misinterpreted as cancer. This review presents the histopathological features of benign mimics and discusses their distinction from cancer. The lesions that are most often misdiagnosed as cancer are atrophy and its variants, including simple atrophy, partial atrophy and post-atrophic hyperplasia. Benign proliferations are a group of lesions with crowded small glands with no or little nuclear atypia. The most problematic entity of this group is adenosis, which may have a more alarming architecture than some cancers. A diagnostic problem with atrophy and several of the benign proliferations is that the glands often have a discontinuous or absent basal cell layer. Hyperplastic and metaplastic lesions include basal cell hyperplasia. Basal cell hyperplasia may especially mimic prostate cancer with its small dark glands, variable nuclear atypia and a pseudoinfiltrative pattern, which may be present. The anatomical structure that most often causes diagnostic problems is the seminal vesicle. The mucosa of the seminal vesicle contains small acini, often with very pronounced nuclear atypia that may be misinterpreted as cancer. Pathologists need to be familiar with these mimics, as a false positive diagnosis of prostate cancer may lead to unnecessary radical treatment.

Key words: Prostate cancer; mimics; benign; differential diagnoses.

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INTRODUCTION

The histopathological diagnosis of prostate cancer differs in several ways from that of other cancers. While other organs

may harbour distinct tumours that are either palpable or easily visible by radiological techniques, prostate cancer is often diagnosed by core needle biopsies that are not directed at a specific target. Magnetic resonance imaging guided biopsies are now undertaken more frequently, but the specificity and sensitivity of this technique is far from perfect. Biopsies may thus contain either cancers or incidentally sampled benign lesions. In the vast majority of cases, the pathologist must ascribe a diagnosis almost entirely based on morphological findings, with little or no assistance from any clinical details. This is particularly challenging as the spectrum of prostate pathology includes a plethora of benign lesions that closely mimic prostatic adenocarcinoma. Most of these entities have no clinical significance, to the best of our knowledge, but the pathologist needs to recognise them in order to avoid reporting a false positive diagnosis of cancer. A false positive diagnosis of prostatic adenocarcinoma often has disastrous consequences for the patient, resulting in, for example, an unnecessary radical prostatectomy.

A series of 4192 consecutive prostate biopsies was prospectively reviewed by Oxley and Sen.¹ They found false negative and positive rates for the diagnosis of cancer to be 1.7% and 0.5%, respectively. Beltran *et al.* reviewed 1359 transurethral resection or needle biopsy specimens diagnosed between 1990 and 2003, from patients who had been diagnosed with prostate cancer and managed by watchful waiting.² A false positive diagnosis of prostate cancer was reported in 30 (2.2%) cases, with the correct diagnoses being adenosis, partial atrophy, prostatic intraepithelial neoplasia (PIN), seminal vesicle epithelium and hyperplasia. The spectrum of lesions misdiagnosed in transurethral resection of the prostate (TURP) specimens can differ from those of needle biopsy specimens, as the former mainly samples the transition zone, where adenosis, basal cell hyperplasia and sclerosing adenosis commonly occur.³

This review describes the spectrum of the benign mimics of prostate cancer, including lesions that can be found in needle biopsies and TURP specimens. Premalignant and malignant lesions that may be misinterpreted as adenocarcinoma with

stromal invasion, such as high grade PIN or intraductal carcinoma of the prostate are not included in the discussion.

ANATOMICAL STRUCTURES

In the vicinity of the prostate there are anatomical structures that may be sampled incidentally by either needle biopsies or transurethral resection. Seminal vesicles may be found in biopsies directed to the base of the prostate and occasionally Cowper's glands are sampled by biopsies from the apical region. Paraganglia are located immediately external to the prostate, often at the prostatic base. All these structures may be misinterpreted as cancer.

Seminal vesicles

The seminal vesicles are accessory glands located at the base of the prostate. Their function is to produce a secretion that, among other substances, contains seminogelin, a fibrinogen-like protein that polymerises after ejaculation.⁴ Both TURP specimens and core biopsies may include fragments of seminal vesicle mucosa and muscle wall. Core biopsies directed to the base of the prostate may inadvertently sample either the intra- or extraprostatic component of a seminal vesicle.

The mucosa of the seminal vesicle has a columnar to cuboid epithelium, with a basal cell layer that is

inconspicuous in haematoxylin and eosin (H&E) stained sections.^{5,6} In histological sections small gland-like structures are grouped around a larger, central lumen (Fig. 1A,B). Core biopsies from the seminal vesicles are often short because of fragmentation at the central lumen (Fig. 1A). Seminal vesicle epithelium often shows pronounced nuclear atypia that may lead to a false diagnosis of prostatic adenocarcinoma (Fig. 1B).^{7,8} The atypia of seminal vesicle epithelium is more severe than that seen in most prostate cancers. While atypia of this severity may occasionally be seen in prostate cancer, the tumour is high grade and largely lacks the acinar structure of seminal vesicle mucosa. The atypia of seminal vesicle epithelium bears some resemblance to the atypia seen after radiotherapy with randomly distributed large, hyperchromatic nuclei adjacent to apparently normal nuclei. The atypia often seen in seminal vesicle mucosa is not associated with malignancy and primary carcinoma of the seminal vesicle is exceedingly rare.^{9,10} Assessment of proliferative activity can be useful, as that of seminal vesicle epithelium is lower than that of benign prostate glands.¹¹ The nuclear chromatin is smudged and nucleoli are not as prominent as those seen in prostate cancer. Large yellow-brown lipofuscin pigment granules are often seen in the cytoplasm of seminal vesicle epithelium and this is an important diagnostic feature. This pigment differs from that seen in the cytoplasm of

Fig. 1 Anatomical structures. (A) Seminal vesicle. Fragmented needle biopsy with seminal vesicle mucosa and muscle wall. Small glands hanging along luminal structure in the ends of the fragments. (B) Seminal vesicle. Same case as A. Tightly clustered glands with plump, hyperchromatic nuclei and sticky luminal secretions. Lipofuscin pigment in cytoplasm. (C) Cowper's glands. Pale mucinous glands with obliterated lumina and small nuclei. Excretory ducts with scant cytoplasm. The glands and ducts are embedded in smooth and striated muscle. (D) Cowper's glands. Same case as C. Basal cells expressing actin HHF35 indicating myoepithelial differentiation. (A–C) H&E and (D) immunohistochemical staining for actin HHF35 (D).

benign prostate epithelium which is usually darker and brown-blue.

Deep to the mucosa of the seminal vesicle there is a thick layer of smooth muscle, which is often included in core biopsies that have sampled seminal vesicle tissue. The biopsy fragments often have mucosa at one or both ends, with smaller glands clustered below the surface epithelium. A thick muscle collar lies adjacent to these smaller glands and this pattern, seen at low power, is an important clue to the diagnosis. Occasional glandular structures may be seen in the muscle wall, and these are outliers of seminal vesicle mucosal glands. These glands should not be misinterpreted as prostate cancer invading the seminal vesicle, as their tinctorial features are similar to the glands of the mucosa, while malignant glands usually contrast with seminal vesicle epithelium.

The ejaculatory duct is a paired structure that extends from the base of the seminal vesicle to the verumontanum. The epithelium of the ejaculatory duct resembles that of the seminal vesicle and may show a similar degenerative atypia. It is difficult to distinguish between seminal vesicle and ejaculatory duct epithelium in biopsies. Hence, the recommendation is that these structures be reported as seminal vesicle or ejaculatory duct.¹²

When seen in a needle biopsy, seminal vesicle mucosa is occasionally misdiagnosed as prostate cancer. This is not surprising as small seminal vesicle acini with marked nuclear atypia may have a striking resemblance to prostatic adenocarcinoma. Clues to the correct diagnosis are the presence of pronounced nuclear atypia, which exceeds that of low grade prostate cancer, yellow cytoplasmic pigment and the characteristic architecture, with glands clustered along the mucosal surface next to a thick muscle layer. In difficult cases, immunohistochemistry is helpful in achieving a diagnosis. Seminal vesicle mucosa is negative for prostate specific antigen (PSA) and alpha-methylacyl-CoA-racemase (AMACR),¹³ while basal cells are positive for high molecular weight cytokeratin¹⁴ and p63.

Cowper's glands

Cowper's glands, also known as the bulbourethral glands, are paired mucinous glands located in the urogenital diaphragm, below the prostate. The role of the glands is to provide lubrication of the urethra by the secretion of alkaline mucin,¹⁵ and also to assist in the post-ejaculatory coagulation of the seminal vesicle secretions.¹⁶ The glands consist of lobulated groups of mucinous glands with thin excretory ducts.

Cowper's glands are occasionally found in needle biopsies directed to the apex of the prostate that pass through the pelvic floor. The glands are usually seen embedded in bundles of striated and smooth muscle, with no adjacent prostate glands (Fig. 1C). The secretory ducts may be misinterpreted as atrophic prostatic glands. The mucinous glands are small and rounded, and are lined by cells that are filled with pale, slate-blue mucin. As opposed to low grade prostate cancer, the glandular lumina are more or less obliterated. The nuclei are small, pyknotic and compressed by the mucin against the basement membrane. Cowper's glands may be negative for prostate specific markers such as PSA, although positive PSA staining has been reported.¹⁷ They have an inconspicuous myoepithelial basal cell layer that have positive immunorepression for traditional basal cell markers (p63 and high molecular weight cytokeratin) and for smooth muscle actin. It

should be noted that one report has claimed that high molecular weight cytokeratin stains were negative in most cases¹⁸ (Fig. 1D).

Cowper's glands may be mistaken for mucinous metaplasia; however, the latter is found in association with prostatic glands, mucinous metaplasia also has goblet cells and the glandular lumina show less obliteration than that seen in Cowper's glands. The distinction between the two entities has no clinical relevance as both are benign.

Paraganglia

Paraganglia are loosely grouped nests of neuroendocrine cells and smaller supporting cells. The neuroendocrine cells have bland looking nuclei with homogenous chromatin and cytoplasm that is either clear, amphophilic or basophilic, and finely stippled.^{19–21} Paraganglia are found mainly along the margins of the prostate and only rarely inside the gland.^{19,20} In a series of 100 radical prostatectomy specimens, paraganglia were found in eight cases, usually in or adjacent to the neurovascular bundle.²¹ They are occasionally seen in needle biopsies, where they may mimic high grade prostate cancer.^{19,20} As paraganglia are usually located immediately outside the prostate they may even be misinterpreted as extra prostatic extension of prostate cancer.²⁰ Identifying features of paraganglia are that the cell nests are mixed with capillary vessels and have a very bland looking nuclear morphology. If there is any doubt as to the diagnosis, an immunohistochemical stain for chromogranin A, synaptophysin or other neuroendocrine markers will be helpful, as neuroendocrine cells are strongly positive, while a PSA stain is negative.^{19–21}

HYPERPLASIAS AND METAPLASIAS

Hyperplasias and metaplasias in the prostate gland are frequently reactive processes arising as a response to tissue damage or treatment. Different forms of hyperplasias and metaplasias are often combined and there are often transitions between these lesions. In some cases there is no obvious cause for the epithelial changes and they may simply be a variant of normal histology.

Urothelial metaplasia

The ducts of the prostatic glands open into the prostatic urethra. The distal part of the duct is often lined with urothelium similar to that seen in the prostatic urethra.²² This differs from that of the urinary bladder by having a cuboidal or low columnar surface epithelium. Urothelium extends a variable distance into the ducts and here it is best considered as normal histology, rather than true metaplasia. When seen in the peripheral part of the prostate gland, some distance from the urethra, it may be a reactive process, but any relationship to the urethra is impossible to determine in TURP specimens or needle biopsies. Hence, what is sometimes called urothelial metaplasia may be normal or hyperplastic periurethral duct epithelium.

In urothelial metaplasia the nuclei are ovoid and perpendicular to the surface of the epithelium (Fig. 2A). The amount of cytoplasm is moderate and not scant, as seen in basal cell hyperplasia. The nuclei may have visible, pinpoint size nucleoli and coffee bean grooves, but lack atypia. The nuclei are often parallel to each other and seem to be streaming, giving the image of a school of herring. A cross section

Fig. 2 Hyperplasias and metaplasias. (A) Urothelial metaplasia. Streaming, parallel, oval nuclei with some pinpoint size nucleoli and nuclear grooves. (B) Basal cell hyperplasia. Small, round, dark glands. Some glands have an open lumen and prominent basal cell layer, while others look solid. (C) Basal cell hyperplasia with cribriform architecture and intraluminal mucin. (D) Clear cell cribriform hyperplasia. Large, pale glands with prominent basal cell layer. (A–D) H&E and (C) immunohistochemical staining for p63 and AMACR.

through a duct or gland with urothelial metaplasia may have a cloverleaf architecture, where the epithelium produces soft protrusions into the stroma. This feature differs from that of most cases of high grade PIN, where the epithelium protrudes into the lumen, while the boundary towards the stroma is smooth.

There is not always a clear distinction between urothelial metaplasia, squamous metaplasia and basal cell hyperplasia. Urothelial and squamous metaplasia appears to arise from basal cells and have the same immunohistochemical features.²³ Transitions between them may be seen and they frequently occur together in the same specimen. All three lesions are positive for high molecular weight cytokeratin and usually negative for PSA, although a weak reaction for PSA may be seen. Reporting of these lesions is not necessary, but the pathologist must be able to distinguish them from PIN or cancer.

Squamous metaplasia

Squamous metaplasia is commonly seen in the prostate and in early reports was noted along the edges of areas of prostatic infarction.²⁴ Squamous metaplasia is a reactive lesion and other common causes include inflammation, previous TURP, hormonal treatment or radiation therapy. After TURP, squamous metaplasia is seen lining the urethral cavity and in prostatic infarction it is found along the margins of areas with

coagulative necrosis.²⁴ After hormonal treatment with oestrogen, gonadotropin release hormone agonist, total androgen blockage or surgical castration, there may be quite an extensive squamous metaplasia. Squamous epithelium in the prostate is sometimes vacuolated with clear cytoplasm. There may be reactive atypia with some nucleolar prominence, which should not be misinterpreted as malignant.²⁵ It is important to use low power magnification to determine if an infiltrative pattern is present. Immunohistochemistry for PSA is usually negative and cannot be used to differentiate squamous metaplasia of the prostate from invasive non-prostatic squamous cell carcinoma.^{23,26}

Basal cell hyperplasia

Prostate gland epithelium has a luminal, secretory epithelium and a basal cell layer.²² The basal cells have ovoid, triangular or flattened nuclei that lie parallel to the basement membrane and are usually inconspicuous. The cytoplasm is normally scant, but activated basal cells may have a cytoplasmic clearing and more rounded nuclei.

In basal cell hyperplasia, the basal cell layer stands out with crowded, enlarged nuclei that tend to overlap each other.^{14,27–29} In cases of mild basal cell hyperplasia the basal cell layer may be slightly thickened and prominent. Basal cells tend to pile up to form a cap on one side of the gland. In more pronounced hyperplasia, the lumen may be seemingly

obliterated, giving the gland a solid appearance (Fig. 2B). In some glands a small and often eccentric lumen remains. It should be noted that luminal cells are at times difficult to identify in H&E stained sections, even when there is a clearly visible lumen.

The nuclei of the epithelial cells in basal cell hyperplasia are round or oval, and palisaded. While normal basal cells lie parallel with the basement membrane, hyperplastic basal cells are perpendicular. The nuclei may have granular and slightly hyperchromatic chromatin, which would be considered atypical in luminal cells (Fig. 2B). In cases where the basal nature of the cells is not obvious, immunohistochemistry can be helpful. Basal cell hyperplasia is positive for both p63 and high molecular weight cytokeratin, although the latter may be only weakly positive.

Hyperplastic basal cells have a scant cytoplasm. Together with the dark and enlarged nuclei this gives the glands a basophilic appearance (Fig. 2B), which makes them stand out from the normal prostate glands. The cells are small, round and surrounded by connective tissue arranged concentrically. Basal cell hyperplasia may occasionally be cribriform or contain intraluminal blue mucin, which further adds to the diagnostic difficulties (Fig. 2C).³⁰ Basal cells are generally reported to be negative for PSA, but may actually show a weak, patchy positivity.²⁷

Basal cell hyperplasia is usually encountered within nodules of benign prostatic hyperplasia in the transition zone of the prostate gland, but has also been reported in the peripheral zone.²⁹ In rare cases, glands with basal cell hyperplasia appear to be streaming between benign glands. This infiltrative pattern is normally a feature diagnostic of prostatic adenocarcinoma. However, pseudoinfiltrative glands of basal cell hyperplasia do not reach outside of the confines of nodules of benign prostatic hyperplasia and should be considered part of the hyperplastic process. On a needle biopsy, this architectural relationship may be difficult to assess, but the basaloid appearance of the seemingly infiltrating glands should favour a benign diagnosis.

Basal cell hyperplasia with nucleolar prominence was designated atypical basal cell hyperplasia.³¹ This terminology was problematic as the entity lacks clinical significance and there is no evidence of an increased risk of cancer. Basal cell adenoma is most likely a morphological variant of basal cell hyperplasia that has a rounded, circumscribed contour.³² The term florid basal cell hyperplasia has been used for exuberant proliferations of basaloid glands and these may be difficult to distinguish from basaloid carcinoma of the prostate.³³

Basaloid prostate cancer and adenoid cystic carcinoma are very rare malignant prostate tumours with a basal cell phenotype.^{27,34,35} As opposed to basal cell hyperplasia, both of these cancers have a truly infiltrating growth pattern. Diagnostic criteria that have been suggested for these tumours are the presence of extra prostatic extension, perineural invasion and a desmoplastic stromal response.^{35,36} Some of these tumours resemble adenoid cystic cancer of salivary glands, while others are solid. Only a small number of cases have been reported, which makes it difficult to predict the outcome, but these tumours are capable of locally aggressive spread and some cases have shown metastatic potential.^{36,37}

Basal cell hyperplasia is occasionally mistaken for PIN due to the presence of nuclear crowding, hyperchromasia and nucleolar prominence. However, the nuclear atypia in PIN is only seen in luminal cells, and in PIN there is more abundant

cytoplasm. Glands with PIN also tend to be larger, with an open lumen, while glands of basal cell hyperplasia are small and dark, with a more compact morphology.

Clear cell cribriform hyperplasia

Clear cell cribriform hyperplasia is found in the basal parts of the prostate and consists of large, cribriform glands lined by epithelium with pale staining cytoplasm (Fig. 2D). The basal cell layer tends to be prominent, possibly because it stands out against the pale luminal cell layer (Fig. 2D). The lesion is usually not seen together with inflammation or tissue damage and its pathogenesis is unclear. It may simply be a variant of normal histology in this part of the prostate. The clinical significance of clear cell cribriform hyperplasia lies in the risk of it being misinterpreted as high grade PIN, intraductal cancer or cribriform prostate cancer.³⁸ Importantly, the luminal cells of clear cell cribriform hyperplasia do not show any nuclear atypia.³⁸ The epithelial cells are uniformly pale throughout the thickness of the epithelium, while the cytoplasm of premalignant or malignant lesions tends to be darker, either at the periphery of the gland or along the luminal border. Glands of high grade PIN or cancer also have a significant nuclear atypia in at least some cells, especially near the periphery of the glands. There is no evidence that clear cell cribriform hyperplasia is malignant or premalignant, as evidenced by its non-infiltrative architecture, the preservation of a basal cell layer, the lack of nuclear atypia, the presence of a diploid DNA profile and its clinical course.³⁹

ATROPHY AND RELATED LESIONS

Prostatic atrophy in its different forms occurs in the majority of elderly men and can thus be considered part of the normal aging process. An international working group established a morphological classification of atrophy related lesions, including simple atrophy, simple atrophy with cyst formation, partial atrophy and post-atrophic hyperplasia.⁴⁰ These diagnoses are now commonly used in the literature, with perhaps the exception of simple atrophy with cyst formation. An alternative classification also included sclerotic atrophy, i.e., atrophy with a reactive stroma that distorts and compresses the atrophic glands.^{41,42}

Simple atrophy

Simple atrophy is a common lesion in the prostates of elderly men, with a reported prevalence of 85% in autopsy prostates.^{22,41} Simple atrophy may be difficult to differentiate from cancer, particularly when seen in needle biopsies. The pathogenesis of atrophy is unclear.⁴¹ The morphological appearance of atrophic glands suggests a slow cell turnaround interval. However, the paradox is that in reality these cells have a higher proliferation rate than that of non-atrophic benign glands, with reported proliferation indices of 2.75% and 0.35%, respectively.⁴³ It has been proposed that prostatic atrophy may be a precursor of prostate cancer, possibly with the involvement of inflammation.⁴⁴ The hypothesis that atrophy is related to inflammation with subsequent regeneration has led to the term proliferative inflammatory atrophy (PIA).⁴⁵ A problem with this terminology is that it is difficult to fit it into the current morphological classifications of atrophy. Although the role of atrophy in prostatic carcinogenesis is of great theoretical

Fig. 3 Atrophy. (A) Simple atrophy. Small glands lined by attenuated epithelium with small, monotonous, hyperchromatic nuclei. (B) Partial atrophy. Pale glands lined by cuboidal epithelium. Occasional small glands outside the lobular unit. (C) Post-atrophic hyperplasia. Multilobular proliferation of small, dark glands. Mild chronic inflammation in the background. (D) Post-atrophic hyperplasia. Central feeder duct surrounded by grouped dark glands. Subepithelial stromal degeneration within lobular units. Mild chronic inflammation in the background. (A–D) H&E.

interest, its main clinical significance is as a diagnostic pitfall.

Glands with simple atrophy are lined by a flattened epithelium (Fig. 3A).⁴¹ The glands appear darker than non-atrophic benign glands, both because the cytoplasm is scant and the nuclei hyperchromatic. The small, streaming, dark glands may closely mimic prostate cancer. However, the nuclei of simple atrophy are smaller and more monotonous than those of cancerous glands (Fig. 3A). Prostatic adenocarcinoma of atrophic type is a morphological variant of acinar adenocarcinoma, which may be remarkably similar to benign atrophy.⁴⁶ The glands of this cancer type are also lined by a thin epithelium and the architecture of the cancer may also closely resemble benign atrophy with parallel, tubular glands. In most cases, however, simple atrophy has a lobular arrangement and the glands do not infiltrate the stroma.⁴⁶ Another helpful feature is that the nuclei of atrophic glands are very small and monotonous when compared to malignant nuclei. Moreover, the atrophic type of prostate cancer is in most cases combined with usual, non-atrophic type acinar adenocarcinoma. The identification of areas of transition to non-atrophic cancer are obviously very helpful in establishing a diagnosis of cancer. Unfortunately, needle biopsies may occasionally sample the atrophic component of the tumour

only. In such cases the diagnosis can be very difficult, although immunohistochemical stains are usually helpful.

Partial atrophy

Partial atrophy is probably the benign lesion that is most frequently confused with prostate cancer in needle biopsies.⁴⁷ Partially atrophic glands have cuboidal epithelium with pale cytoplasm (Fig. 3B).^{42,48} The contour of the glands is often undulating, giving them a soft appearance.⁴⁹ Occasional partially atrophic glands may be round with a rigid contour, but more often the glands appear to be partially collapsed. The nuclei are usually somewhat enlarged when compared to those seen in simple atrophy and are pale with homogenous chromatin. Some nuclei are so pale that they may seem to fade away. Occasional visible nucleoli are often present,⁴⁹ but they are usually of pinpoint size and not as prominent as those seen in cancer (Fig. 3B). A few partially atrophic glands are often seen in isolation, outside of their lobular units (Fig. 3B). The diagnosis of partial atrophy can be difficult, especially when there are occasional scattered small glands or even seemingly isolated cells in the stroma. These cells may mimic macrophages but their nuclei resemble those of adjacent partially atrophic glands. In partial atrophy the

glands are loosely grouped together into a lobular unit, but this may not be apparent in tissue sections because of tangential cutting.

Although immunohistochemistry is generally helpful for the diagnosis of prostate cancer, the staining seen in partial atrophy may lead to a false positive diagnosis of cancer. Most partially atrophic glands are positive for basal cell markers, but some of the glands may have a fragmented basal cell layer with only scattered basal cells. Occasional glands may even be entirely negative for these markers.⁴⁸ A useful feature is that glands that are negative for basal cell markers appear similar to adjacent glands that are morphologically similar, but exhibit a preserved basal cell layer. Stains for AMACR are usually negative, but positive staining has been reported in 10% of cases.⁴⁸

The chronic inflammation that is often associated with glands showing simple atrophy or post-atrophic hyperplasia, is usually absent in partial atrophy.⁴⁸ The stromal background surrounding partially atrophic glands is strikingly clean and inert. A helpful diagnostic clue is the finding of simple atrophy in the vicinity of partial atrophy. A comparison of nuclear size and shape against these obviously benign glands often shows a similarity, as opposed to the contrasting cell populations seen when cancer infiltrates benign prostate tissue.

Post-atrophic hyperplasia

Post-atrophic hyperplasia is a proliferation of small glands with atrophic features. Similar to simple atrophy, post-atrophic hyperplasia is most often seen in the peripheral zone of the prostate.⁵⁰ The term suggests that the glands have first undergone atrophy and have then become hyperplastic, but little is known regarding the pathogenesis and evolution of the lesion. In one study, a high rate of post-atrophic hyperplasia was reported, with a prevalence in prostatectomy specimens and needle biopsies of 32% and 27%, respectively.⁵¹ Similar to other benign lesions of the prostate, the threshold for diagnosing this entity is obviously poorly defined.

Post-atrophic hyperplasia consists of a lobular group of small, dark glands lined with cuboid epithelium, often surrounding a central wider duct that has been described as a so-called 'feeder duct' (Fig. 3C,D).^{52,53} Post-atrophic hyperplasia is often seen in several lobular units within the same area, giving it a multilobular appearance. The glands are less tightly clustered than those seen in adenosis and usually have a darker, more basophilic appearance. Simple atrophy is often seen in the surrounding prostatic tissue. There is little or no nuclear atypia, although small nucleoli may be found. A sprinkle of chronic inflammatory cells is commonly seen in the stromal background. This is similar to simple atrophy, which contributes to the dark appearance of the lesion. The subepithelial stroma within the glandular lobules often appears to be somewhat degenerate, resembling the degenerative changes in the dermal connective tissue of actinic elastosis (Fig. 3D).⁵³ This phenomenon has been referred to as prostate elastosis and it has been suggested that it may be the result of arteriosclerotic ischaemia.⁵⁴ It has been suggested that post-atrophic hyperplasia may have a role in prostatic carcinogenesis,^{45,50} while others have failed to demonstrate a link to cancer.⁵¹ Similar to simple atrophy, the clinical importance of this entity is that it may mimic cancer on needle biopsy. Important clues as to the correct diagnosis are the lobular grouping of the glands, and the presence of a

relatively monotonous nuclear morphology. In addition, a degenerate stromal background, when present, is diagnostically helpful, as this does not occur in cancer. It is important to be aware that, in the situation that is similar to partial atrophy and adenosis, some glands in post-atrophic hyperplasia may have a fragmented basal cell layer or may even be entirely negative for basal cell markers.

BENIGN PROLIFERATIONS

Benign proliferations of the prostate are a group of lesions characterised by the clustering of small glands whose architecture mimics cancer. These lesions do not usually show nuclear atypia. Occasionally there may be a mild atypia, with slight nuclear enlargement and visible nucleoli.

Adenosis

In the early literature the term atypical adenomatous hyperplasia was proposed for this lesion,⁵⁵ but now the preferred designation is adenosis, which has the advantage of being more concise, without suggesting pre-malignancy or malignancy.

Adenosis consists of a nodular group of clustered small, pale staining glands with absent or mild nuclear atypia (Fig. 4A).^{56–58} Adenosis is usually found in the transition zone of the prostate gland in the setting of benign hyperplasia. It has been suggested that adenosis may be a precursor of low grade prostate cancer arising in the transition zone.⁵⁹ This hypothesis is supported by the morphological resemblance between adenosis and some prostate cancers. The clustering of small glands of adenosis and a marginal pseudo-infiltrative growth pattern seen in some lesions may indeed be suggestive of malignancy. In the 1990s, genetic mutations were reported in adenosis that were considered indicative of a relationship to carcinoma.^{60,61} These findings have not been repeated and there is no clinical evidence that adenosis actually evolves into cancer on follow-up. The current concept is that adenosis is considered to be a benign lesion and patients do not need to undergo repeat biopsies, unless there are clinical indications, such as an elevated serum PSA level.

Adenosis consists of a rounded but not encapsulated group of small glands. The glandular architecture may have a striking resemblance to prostate cancer, but unlike cancer there is little nuclear atypia and at least some of the glands have basal cells (Fig. 4A,B).^{56–58} In H&E stained sections, the basal cell layer is very difficult to visualise, but occasional basal cells can sometimes be identified. The diameter of the glands tends to decrease towards one end of the lesion, where the glands may become so small and crowded that they are very difficult to distinguish from cancer. There may be some pseudoinfiltration of the stroma and even seemingly solid strands of epithelium may be present. Adenosis is a lobular lesion, but it is not perfectly circumscribed. Glands sometimes seem to spill out from the focus of adenosis into the surrounding stroma and a few glands may even be located some distance from the body of the lesion. Recently, three dimensional reconstructions have demonstrated that the glands in adenosis show such an extensive branching that an acinar pattern is no longer obvious.⁶² An important clue to the diagnosis is that there is a gradual transition between large, obviously benign glands and small glands suspicious of

Fig. 4 Benign proliferations. (A) Adenosis. Tightly clustered pale glands. Gradual transition from larger, obviously benign glands to smaller glands along the periphery of the lesion. (B) Adenosis. Same case as A. Some glands have a fragmented basal cell layer while others are entirely negative for basal cells. (C) Sclerosing adenosis. A spindle cell proliferation compresses the glands. (D) Verumontanum mucosal gland hyperplasia. Small, clustered glands along duct-like structure. Numerous, dark corpora amylacea. (A,C,D) H&E and (B) immunohistochemical staining for p63 and AMACR.

cancer. This differs from foci of cancer where there are two contrasting glandular populations, with an abrupt transition between benign and malignant glands.

Despite the worrisome glandular architecture of adenosis, the cellular details, including the nuclear and cytoplasmic features, are very similar to those of benign glands. This is diagnostically helpful as malignant glands usually contrast with adjacent benign glands. Sometimes there is a subtle nuclear atypia with general nuclear enlargement and some nucleoli may be visible.^{56,58} However, the nucleoli are usually not as prominent as those seen in cancer and the nuclei have a more smoothly rounded contour.⁵⁶ A number of the usual diagnostic features of prostate cancer are not helpful if the differential diagnosis is adenosis. This includes glands that are packed back to back, intraluminal crystalloids, intraluminal mucin, medium size nucleoli and focal single cell invasion at the edge of the lesion.^{56,58} The diagnosis of adenosis is based on a combination of characteristic architectural features without pronounced nuclear atypia and the presence of basal cells in at least some of the glands.⁵⁸ Similar to prostate cancer, adenosis may be multifocal or diffuse.^{16,63} In some cases adenosis can be very difficult to differentiate from prostate cancer and a definitive diagnosis may not be possible.

Similar to the situation for post-atrophic hyperplasia, the prevalence of adenosis in TURP specimens and core biopsies depends on the distinguishing features utilised to differentiate

between it and prostate hyperplasia. Some observers may diagnose adenosis based on an increased number of small glands, while others would require a more distinct lesion with glandular crowding that is suggestive of cancer. Since the distinction between adenosis and prostate hyperplasia with an increased number of glands is unclear, the incidence of adenosis varies widely in the literature. Some have reported an incidence of 1.6–2.2% in TURP specimens^{57,64} while others have found it to be as high as 19.6%.⁶⁵

Because of the diagnostic difficulties outlined above, it is often necessary to perform immunohistochemical stains to rule out cancer. In adenosis there is usually a characteristic patchy distribution of basal cells (Fig. 4B). The basal cell layer is fragmented in some glands and absent in others. It is very important that such staining results not be over interpreted, as this would lead to a false positive diagnosis of cancer. The most important component of the diagnosis is always H&E based histology and immunohistochemical findings need to be carefully correlated with morphology. Positive staining for AMACR has been reported in 18% of cases of adenosis, but usually only focally.⁶⁶ Adenosis is typically seen in the transition zone and thus is often found in TURP specimens, but may also occasionally be seen in needle biopsy specimens. It is helpful to document the presence of adenosis in the pathology report, so as to inform pathologists, who may subsequently review the case, of details relating to the decision making process. However, it

should be clearly stated that it is a benign proliferation. It is potentially confusing for the urologist if adenosis is used as a stand alone diagnosis in the summary diagnosis in e.g., a needle biopsy report.

Sclerosing adenosis

Similar to adenosis, sclerosing adenosis is usually seen in the transition zone of the prostate. It is a rare entity reported in 1.9–2% of surgical prostate specimens.^{67,68} This lesion consists of small glands that are more or less compressed by proliferating stroma, often giving the glands a tapered profile (Fig. 4C). The glands are often surrounded by hyaline sheets and the stromal component has a spindle cell proliferation, in some cases with a myxoid appearance.⁶⁹ A unique feature of sclerosing adenosis is that S-100 protein and smooth muscle actin stains are positive, sometimes in the stromal cells and sometimes in the basal cells of the glands, indicating that the lesion is a myoepithelial metaplasia.^{69,70} Ultrastructural studies of sclerosing adenosis have confirmed myoepithelial differentiation of cells located between the basement membrane and the secretory cells and it has been suggested that they arise by metaplastic transformation of basal cells.^{67,71}

Cases with sufficient cellular atypia, so as to raise the suspicion of cancer, have been referred to as atypical sclerosing adenosis.⁷⁰ In a series of five cases of atypical sclerosing adenosis, immunohistochemistry demonstrated that all had an intact basal cell layer and were negative for AMACR.⁷⁰

Verumontanum mucosal gland hyperplasia

The term verumontanum mucosal gland hyperplasia was coined by Gagucas *et al.* and refers to a proliferation of glands in the posterior wall of the prostatic urethra, being seen in 14% of radical prostatectomy specimens.⁷² The lesion is located in the verumontanum area where it forms clusters of small glands draped along prostatic ducts, giving it the appearance of clinging bunches of grapes (Fig. 4D). The glands contain numerous orange-brown, calcified corpora amylacea that are often fragmented. Intraluminal mucin and crystalloids are not seen.⁷² The basal cell layer is preserved and is often quite conspicuous in H&E stained sections. Verumontanum mucosal gland hyperplasia is occasionally found in needle biopsies and may then be a differential diagnosis of prostate cancer.⁷³ Despite this, the lack of nuclear atypia, the conspicuous basal cell layer and the characteristic presence of corpora amylacea should rule out malignancy.

CONCLUSION

This review has listed and described a number of benign entities that may occur in prostate specimens. These lesions, in terms of our current understanding, have no clinical significance. However, the pathologist must be familiar with them in order to avoid diagnostic errors. It is a paradox that several of the lesions have a more alarming morphology than some prostate cancers. The key to a correct diagnosis is the understanding of the histology of the spectrum of benign lesions and the rational utilisation of immunohistochemical stains. Without such knowledge, the pathologist risks over diagnosing prostate cancer, which may lead to over treatment by radical surgery or radiotherapy.

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