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REVIEW ARTICLE

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Differential diagnosis of glandular proliferations in the prostate

A conventional and immunohistochemical approach

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Abstract A variety of small acinar lesions of the prostate can mimic prostate cancer in punch biopsies and in transurethral resection material. The first part of this review deals with differential diagnostic problems of the central and transition zone, including atypical adenomatous hyperplasia of the prostate, atrophic processes, sclerosing adenosis, basal cell hyperplasia, and low-grade adenocarcinoma. The second part deals with differential diagnostic problems in the peripheral zone: prostatic intraepithelial neoplasia, postatrophic hyperplasia, Cowper's glands, seminal vesicles, and ductal and intraductal carcinoma. Finally, atypical and small acinar proliferations are described. Diagnostic perspectives are discussed.

Key words Atypical small acinar lesions · Prostate cancer · Immunohistochemistry

Introduction

Pathological examination is the most important diagnostic method in diseases of the prostate. Punch biopsies from the periphery and transurethral resection material from the central and transitional parts may reveal benign lesions, atrophic and inflammatory processes and carcinoma. The differential diagnostic spectrum of pathology of the prostate is wide, with a variety of microglandular changes in the central and transition zone [6a]. These range from definitively benign processes and the questionably precancerous atypical adenomatous hyperplasia (AAH) to low-grade prostatic carcinomas. In the peripheral area, the differential diagnosis for the predominantly high-grade carcinoma is mainly high-grade prostatic intraepithelial neoplasia (PIN) [49]. In addition, there are atypical small acinar proliferations (ASAP) that cannot be integrated into any of the well-established diagnostic entities [1, 16, 22, 41].

The relevant glandular proliferations of the central, transitional and peripheral zones of the prostate are discussed here with reference to the related carcinomas.

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Central and transition zone

Benign prostatic hyperplasia

Benign stromoglandular hyperplasia of the prostate develops centrally, leading to compression of dorsal and posterior areas by increasing volume. Hyperplasia develops with diffuse and nodular fibroleiomyomatous proliferations and the growth of glandular nodules with micro- and macroglandular appearances. The glands are lined by a secretory epithelium with frequent papillary infoldings. There is a continuous basal cell zone. The secretory epithelium is characterized immunohistochemically by expression of prostate-specific antigen and the basal cells, by expression of keratin with high molecular weight, e.g. clone 34β-E 12 [7, 35].

Clear cell and cribriform hyperplasia are variants of typical benign hyperplasia, which may suggest the differential diagnostic diagnoses of clear cell microglandular or cribriform carcinoma. They are localized in the peripheral areas of the organ, but may extend to the central and transition zone with increasing volume. The detection or lack of basal cells is crucial in differential diagnosis. Generally, carcinomas lack basal cells, whereas hyperplastic lesions contain them. Intraductal spread of carcinomas with residual basal cells may occasionally cause diagnostic difficulty. Attention must be paid to cytological features in these cases, especially prominent nucleoli, which are not found in hyperplastic processes [35].

Atrophy

In elderly patients, atrophic glands, sometimes with cystic dilatation, can be found in transurethral resection

Table 1 Differential findings of prostatic partial atrophy (PPA) and prostatic carcinoma (PC) with / without atrophy according to Oppenheimer et al (48).

	PPA	PC / atrophic pc
Architecture	Localized lesion	More infiltrative appearance Atrophic PC associated with nonatrophic PC
Cytology		
Nuclear / cytoplasmic ratio	High, owing to cytoplasmic atrophy	High, owing to increase in nuclear size
Nucleus	Normal size but irregular elongated appearance	Enlarged, oval/round
Nucleoli	Visible, but smaller than in PC	Larger than in PA
Crystalloids	Absent	Frequent
Mucin	Absent	Frequent

(TUR) material from the central and transition zone. They are covered by a single layer of atrophic secretory epithelium with preserved basal cell layer. In contrast to hyperplastic glands with flat and relatively clear cell epithelium, the atrophic glands appear dark with strongly eosinophilic cytoplasm. Franks' [26] sclerosing variant of glandular atrophy has been regarded as differential diagnosis to prostatic carcinoma for years. The possibility of immunohistochemical detection of basal cells has opened an easy solution for this problem. However, atypical atrophy is an important mimic of carcinoma with atrophic patterns. Recent morphological analyses have shown that prostatic carcinomas may contain a high proportion of atrophic glands with enlarged nuclei and prominent nucleoli in close vicinity to usual glandular carcinoma (Gleason score 4–6 or 7) [17, 23]. A diagnostic pitfall may be partial atrophy in needle cores. Partial atrophy may be confused with low-grade adenocarcinoma because of the presence of foci of crowded glands, irregular nuclei and visible nucleoli [48]. For differential findings from adenocarcinoma see Table 1.

Sclerosing adenosis

Another, although rare, glandular proliferation in TUR material is sclerosing adenosis. This is a microglandular proliferation with myoepithelial differentiation and a sclerosing stromal component with spindle cells. There is no biological relationship to carcinoma. However, there are morphological similarities. The differential diagnosis versus carcinoma is supported by immunohistochemical detection of myoepithelial differentiation with demonstration of muscle-specific antigen and S-100 protein. The sclerosing adenosis consists of well circumscribed foci with a nodular pattern. In the periphery, however, the border may become blurred, mimicking stromal invasion. Immunohistochemical detection of basal cells is important in the differential diagnosis versus carcinoma. As a rule, carcinomas do not induce stromal sclerosis. Scattered small, centrally located nucleoli may occasionally be found in sclerosing adenosis. Prominent eccentric nucleoli, which are typical of carcinomas, do not occur. The immunohistochemical findings and the sclerosing component allow a clear distinction both from atypical adenomatous hyperplasia and from basal cell hyperplasia [31, 53].

Basal cell hyperplasia

The basal cell function is independent of androgen stimulation. Basal cell proliferation and hyperplasia are induced under the influence of estrogens or androgen deprivation. Recent studies have revealed that certain basal cell populations are also reactive to circulating androgens. In this case, however, no hyperplasia develops but there is an increase in the differentiation of basal cells to secretory cells, i.e., the glandular part of benign prostate hyperplasia (BPH) [5, 6]. In normal and in regulated hyperplastic situations (BPH), the basal cell layer comprises the proliferative compartment. In order to maintain this proliferative compartment, the mitochondrial oncoprotein bcl-2, which acts as a suppressor of programmed cell death, is expressed exclusively in the basal cells. In secretory cells that are prone to programmed cell death, bcl-2 is not expressed [5, 6, 6b, 7]. The histological pattern of activated and hyperplastic basal cells may be solid, tubular, cribriform, or mixed. Mostly, secretory luminal cells are found within these glands, with a positive reaction to prostate-specific antigen (PSA), in contrast to the PSA-negative basal cells. Nuclei of activated and hyperplastic basal cells may contain small, centrally located nucleoli [21]. The surrounding stroma is frequently hyperplastic and hypercellular. Basal cell hyperplasia is most frequently found in pre-existing glandular and ductal structures, mainly in hormonally treated prostatic cancers. In TUR material of BPH, newly formed glandular complexes with basal cell hyperplasia are found. They may have cribriform or tubular structures and usually do not contain secretory cells. The differential diagnosis versus low-grade carcinoma is straightforward. Carcinoma lacks the dense stromal cellularity of basal cell hyperplasia, and the nuclei and cyto-

plasm of basal cell hyperplasia stain distinctly darker than those of central low-grade carcinoma. In cases in which differential diagnosis is difficult, the immunohistochemical detection of high-molecular-weight cytokeratin in basal cell hyperplasia and of PSA in carcinoma may be helpful. Basal cell carcinoma is a very rare entity, which can be differentiated from basal cell hyperplasia by capsule penetration, perineural invasion and metastases [20, 21, 30].

Atypical adenomatous hyperplasia

High-grade PIN is regarded as a precursor of peripheral high-grade carcinoma, but no similar relationship of atypical adenomatous hyperplasia (AAH) to low-grade central carcinoma has been proven [10, 12, 32]. AAH is localized in the central or transitional zone of the prostate and corresponds to newly formed microglandular nodules, mostly found in the vicinity of typical glandular nodules of BPH [49]. In punch biopsy material from the peripheral zone, AAH is diagnosed in less than 1% compared with those cases in which the high-speed biopsy needle reaches the central areas. In TUR material from the central zones, AAH can be found in up to 20% [1, 9, 10, 12, 13, 24, 25, 28, 29].

The microacinar glands of AAH are distinctly smaller than the large glands of BPH (Fig. 1a). They develop from typical nodules of BPH without transition. The microacinar glandular proliferations are closely packed, almost "back to back," similar to the situation in carcinoma. Occasionally, they are separated by fibrous bands. The border to the surrounding stroma is somewhat blurred. The differential diagnosis versus low-grade carcinoma can be facilitated by application of high-molecular-weight cytokeratin clone 34βE12 (Fig. 1b). However, in some cases of AAH basal cells may be completely lacking. In these cases, cytological criteria are helpful. As a rule, nuclear and nucleolar enlargement is not a prominent feature in AAH, although small to medium-sized nucleoli may occasionally be observed. Crystalloids are frequently found in microglandular carcinomas (up to 75%) and are much less frequent in AAH. Intraluminal mucin production is a frequent finding in microglandular carcinomas, but is only very rarely encountered in AAH. The histological and cytological peculiarities of AAH and low-grade carcinomas are given in Table 2. There are some overlapping features [10, 12, 35, 39, 40, 42].

With the uncertain discrimination of AAH from carcinoma, an intensive discussion has developed about the preneoplastic character of AAH. Cell kinetic data for AAH give values between those for BPH and for low-grade carcinoma with a very low proliferative activity [15, 34, 37, 54]. This is restricted to the basal cells, like bcl-2 expression. Most authors do not exclude transition of AAH to invasive well-differentiated low-grade carcinoma, but as this event is regarded as very rare, the preneoplastic character of AAH does not seem to be established. Epstein [24, 25] and Gaudin and Epstein [28, 29] categorically deny a preneoplastic character of AAH and have emphasized the benign character of AAH in numerous publications. They refer to this microglandular lesion as adenosis rather than AAH, which is the term most uropathologists prefer [13]. As in other organs, especially the breast, central low-grade prostatic carcinoma can certainly develop de novo at the border of or within hyperplastic nodules. In 10–20% of therapeutic TURs for urinary obstruction caused by BPH, these carcinomas can be diagnosed histologically and are called incidental carcinomas. The incidence of AAH in therapeutic TUR material varies between 4% and 15%. At autopsy, there is an incidence of 15% even in prostates without carcinoma. In combination with a latent prostatic carcinoma the incidence is doubled. This is also true for combinations with low-grade carcinomas in TUR material. As the prognostic significance of central low-grade carcinoma is less than that of peripheral high-grade carcinoma, the question of whether atypical adenomatous hyperplasia is a precursor lesion of low-grade carcinoma is of minor importance. In our opinion, the progressive loss of basal cells in AAH can be regarded as evidence for the development of microglandular low-grade carcinoma from such lesions. Therefore, AAH cannot be excluded as a precursor of well-differentiated low-grade central carcinoma of the prostate [39, 40].

Glandular and intraglandular proliferations in the peripheral zone

For the evaluation of suspicious lesions in the peripheral zone, punch biopsy is the diagnostic method of choice. The staging of carcinoma can be confirmed morphologically on the radical prostatectomy specimen. Glandular changes in the peripheral zone include glandular atrophy similar to changes in central areas, glands with basal cell hyperplasia similar to that described in the central zone, very rarely, clear cell cribriform hyperplasia with inflammatory and reactive changes, mainly basal cell hyperplasia, and prostatic intraepithelial neoplasia and the variety of prostatic carcinomas.

The differential diagnosis of basal cell hyperplasia and clear cell cribriform hyperplasia versus carcinoma has already been described for the central region. Basal cell hyperplasia following chronic destructive prostatitis may present differential diagnostic difficulties versus carcinoma, especially in cases with prominent nucleoli. An intact basal cell layer can be detected immunohistochemically in such cases. The most important differential diagnosis of prostatic carcinoma is prostatic intraepithelial neoplasia (PIN).

PIN lesions

The most important differential diagnosis of prostatic carcinoma in diagnostic punch biopsies is prostatic intraepithelial neoplasia (PIN) [8]. Whereas AAH consists of

Table 2 Differential findings in atypical adenomatous hyperplasia (*AAH*), atypical small acinar proliferations (*ASAP*) and low-grade prostatic carcinoma (*PC*).

	AAH	ASAP	Low-grade PC
Definition	Atypical adenomatous hyperplasia	Atypical small acinar proliferations	Prostatic carcinoma, Gleason score 2–6, WHO subgroups I b – IIa
Localisation	Mainly transitional zone	Mainly dorso-peripheral zone	Antero-central zone frequently (incidental PC), dorso-peripheral zone rarely
Histology	Primary disturbances of histoarchitecture Well defined proliferation of densely packed glands without epithelial infoldings. Lobular growth. Placed between larger benign partly atrophic glands. Often in the periphery of a node of BPH	Circumscribed micro-glandular proliferation, clear cell pattern frequently combined with prostatitis adjacent atrophy and high grade PIN	Circumscribed or limited infiltration of moderately large to small glandular proliferations
Crystalloids	Infrequent	Infrequent	Frequent
Corpora amylacea	Frequent		Infrequent
Mucin	Infrequent	Frequent	Frequent
Cytology	Cytology almost identical with that of neighbouring benign glands	In more than 50% cellular atypias and nuclei with nucleoli exist	Variable cellular and nuclear atypias
Secretory cells (cytoplasm)	Inconspicious	Inconspicious	Atypical (tumor) cells
Nucleus	Size less variable	Moderately enlarged with variation in size	Enlarged with variation in size
Nucleolus	Mean diameter <1 μm	Mild enlargement	Prominent nucleoli (1.0 –3.0 μm) in central location within nucleus
Basal cells	Inconspicuous mostly only scattered basal cells visible	Inconspicious but scattered	Absent
Basal cell layer	Intact to fragmented	Intact to fragmented	Absent
Immunohistochemistry Basal cells (basal cell cytokeratin 34ßE12)	mostly positive	occasionally negative	Negative
Secretory cells (PSA)	Positive	Positive	Positive tumor cells
Consequences	Wait and see	Repeat biopsy	Surgical therapy

newly formed small glandular complexes, in PIN structural alterations within preexisting prostatic glands and ducts occur. In normal and hyperplastic glands there is a regulated mechanism of proliferation and differentiation with restriction of the proliferative compartment to the basal cell layer, the secretory glands being a product of differentiation without proliferative activity. In prostatic intraepithelial neoplasia this process has reversed with atypically differentiated basal cells moving into the luminal layers of the secretory cells and thereby disturbing the proliferative pattern [5, 6]. The nuclei mostly show prominent solitary nucleoli, which may be in an eccentric location [34, 37]. Immunohistochemically, the basal cell layer is often fragmented, as shown by cytokeratin 34βE-12 [6, 7].

It is essential in the work-up of punch biopsies to choose a low-power view for the first survey. Characteristically, the glands of PIN are much larger than those of carcinoma. The epithelium is basophilic, resulting in a darker aspect than benign glands. This is intensified by

the shift in nucleus/cytoplasm relation in favour of the nucleus. The growth pattern can be papillary, flat, cribriform, or tufting [8]. The surrounding stroma is loose and by no means as highly cellular as in basal cell hyperplasia or as sclerotic as in sclerosing adenosis.

Based on the grades of cytological alterations, especially, the frequency and size of nucleoli, three, and more recently two, grades of atypia have been differentiated. Low-grade PIN is characterized by minimal cytological deviations and is of minor differential diagnostic importance versus carcinoma. According to the consensus conference, low-grade PIN is regarded as of no diagnostic or therapeutic significance [44]. High-grade PIN, however, is considered to be a precursor of prostatic carcinoma [8] with transition from PIN to carcinoma with increasing and complete loss of basal cells having been demonstrated.

To the urologist, the diagnosis of PIN poses the problem that it implicates a precancerous lesion but does not justify operation (radical prostatectomy). Owing to the high coincidence with invasive carcinoma (60%), rebiopsy should be recommended when a diagnosis of high-grade PIN is made. In about half of the cases, the carcinoma is confirmed upon rebiopsy [8, 39, 40].

Foamy cell carcinoma

This recently described type of prostatic carcinoma with xanthomatous cytoplasm has also certain similarity to papillary high grade PIN. The cytoplasm in foamy gland carcinoma, however, is larger and very clear. This should not be confused with the usually dark aspect of PIN [47].

Postatrophic hyperplasia

These changes can be found in the vicinity of hyperplastic nodules but mostly in the periphery of the prostate. Small atrophic gland complexes are encountered with focal regenerative epithelial activation forming intraductal pseudopapillary buds. The proliferating cells are primarily basal cells. In larger glands, differentiation towards secretory cells may occur. The nuclei of these glandular buddings are very dark and may exhibit small to medium-sized nucleoli. Therefore, misinterpretation as microglandular carcinoma is possible. Immunohistochemical examination of basal cells can be helpful in differential diagnosis (Fig 2a, b). Atrophy-associated glandular changes may also follow healed inflammation [14, 35].

Cowper's glands

In punch biopsies, Cowper's glands can be found. The differential diagnosis includes clear cell low grade carcinomas, foamy gland carcinoma, mucinous metaplasia, and the atypical small acinar proliferations described below. Immunohistochemistry may be helpful in finding the correct diagnosis [16, 18, 22, 52].

Ductal and intraductal prostatic carcinoma

The growth patterns of PIN lesions can mimic several types of prostatic carcinoma. Papillary high-grade PIN must be separated from papillary adenocarcinoma of the prostate (previous terminology endometrioid carcinoma). Papillary ductal adenocarcinoma of the prostate develops within large ducts and commences by intraductal spread. In these cases, residual basal cells can be detected immunohistochemically [55]. Similar problems may occur in development and intraductal spread of cribriform carcinomas. The proof of vascularized stromal axes in carcinomas is often difficult, but may be decisive in differential diagnosis versus PIN. Crystalloids and mucin production, which are quite typical for carcinomas, are rather rare in PIN. Necrotic debris is very rare in PIN, but typical for carcinoma. After a thorough search, small foci of invasive carcinoma are often found in the vicinity of larger areas of PIN [8, 9, 39, 40].

Seminal vesicles

Parts of the seminal vesicles and of the ampullae of the ejaculatory ducts can give rise to differential diagnostic problems if they are encountered in punch biopsies. It is important to look for high amounts of lipofuscin that are typical for this epithelium, which may exhibit very variable nuclei. If attention is paid only to nuclear variation, high-grade PIN or carcinoma may be misdiagnosed.

Atypical small acinar proliferations

Punch biopsies from the periphery of the prostate may also show ill-defined glandular changes that cannot be classified among the above-mentioned entities [16, 22]. They are descriptively named atypical small acinar proliferations (ASAP) and consist of small foci of glands lined by a single-layered mostly clear cell epithelium. The basal cell layer can be fragmented or lacking completely in immunohistochemical staining for cytokeratin 34βE-12 (Fig. 3a, b). Cellular atypia with enlarged nuclei and prominent nucleoli may be found in up to 80% of the cases, as well as intraluminal mucin and an infiltrative growth pattern (67%). Crystalloids are rare. There is often concomitant inflammation. Bostwick's group [16, 41] has found high-grade PIN in the vicinity of more than 40% of such lesions. The aspect is sometimes similar to AAH with the difference of the peripheral location. In conclusion these lesions cannot be clearly defined as benign or malignant. Control biopsies should be performed similar to the diagnosis of PIN. Bostwick's group [16, 41] has differentiated three groups of atypical microglandular proliferations: benign, uncertain, and suggestive of carcinoma. In 41–60% of these patients with ASAP, on repeat biopsy at short-term follow-up adenocarcinomas were found. The follow-up should not rely on a single biopsy but on sextant biopsies, because in 14–23% of cases carcinomas are located in the contra-

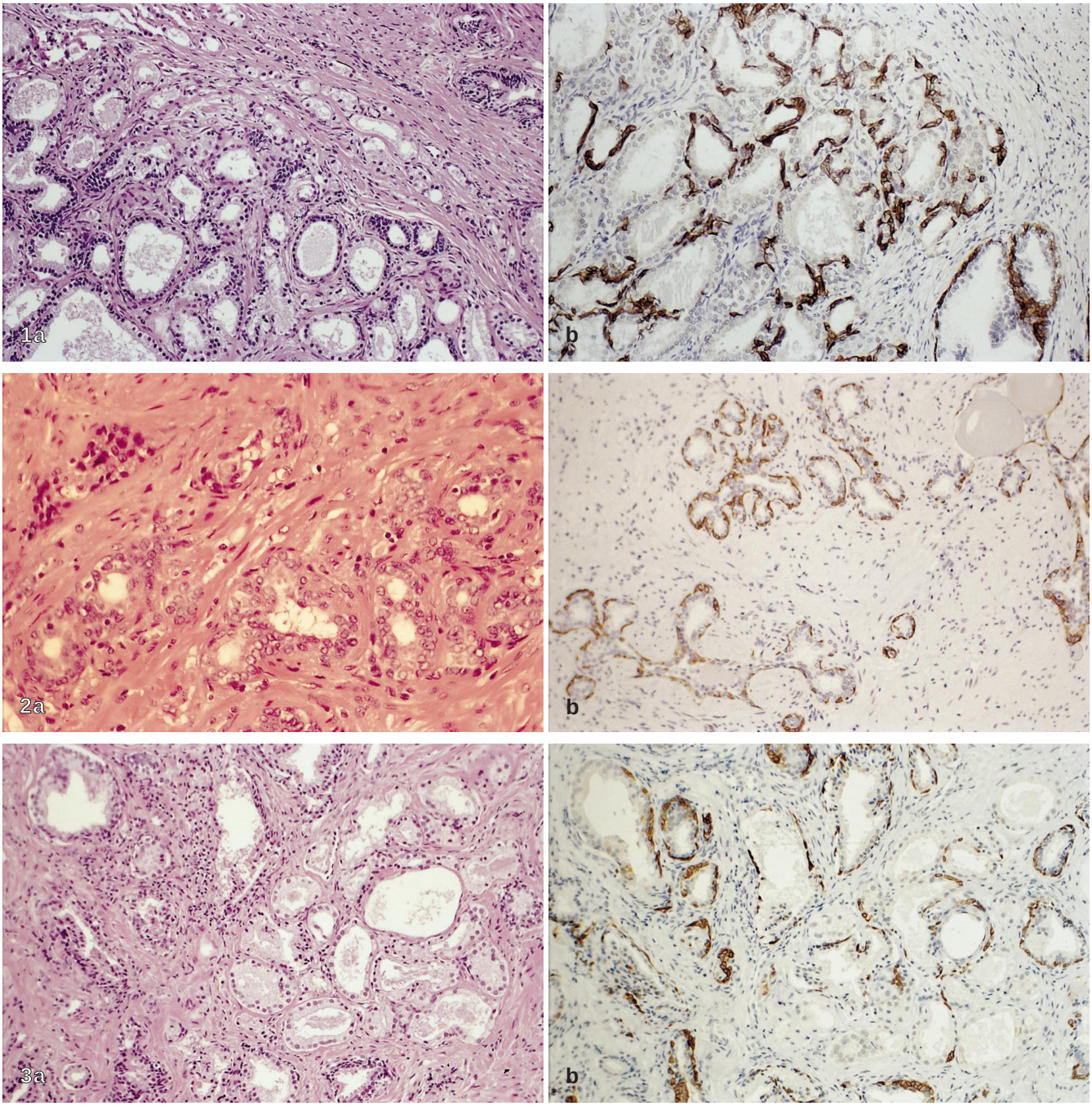

Fig. 1 **a** Atypical adenomatous hyperplasia (AAH) mimicking infiltrating carcinoma. Haematoxylin-eosin **b** Fragmented basal cell layer of the tumour glands. All glands demonstrating at least some basal cells. Immunohistochemical staining with cytokeratin 34βE12

Fig. 2 **a** Postatrophic hyperplasia with dark and clear nuclei and small to medium sized nucleoli mimicking microglandular carcinoma. Haematoxylin-eosin **b** Intact basal cell layer. 34βE12 Immunohistochemical staining

Fig. 3 **a** Atypical small acinar proliferation (ASAP) with intraluminal mucin and with enlarged nuclei and nucleoli mimicking adenocarcinoma. Haematoxylin-eosin **b** Fragmented basal cell layer. Some glands are negative for cytokeratin staining 34βE12

lateral side of the prostate [22]. In control biopsies following the diagnosis of ASAP with a benign character, carcinoma was found in 22%. In comparison with high-grade PIN, ASAP serves as another great predictor of a future diagnosis of carcinoma in needle biopsy (18%). In 45% of cases with ASAP, low-grade carcinomas (Gleason score 4–7) have been found in the vicinity. Therefore, special attention should be paid to small foci of adenocarcinoma in the neighbourhood of atypical small acinar proliferations. ASAP is identified in 1.5–5.0% of needle biopsies, as against high-grade PIN in 2.0–16.5% and carcinoma in 28.0–45.0% [16, 22]. One of the most important differential diagnoses is prostatic adenocarci-

noma, mostly of low-grade malignancy on the one hand and high-grade PIN, basal cell hyperplasia, atrophy and postatrophic hyperplasia of the seminal vesicles on the other [22]. As in AAH, in ASAP the atypical glands are newly formed, in contrast to the pre-existing glands in high-grade PIN without an infiltrative pattern. Further differential diagnoses include mesonephroid hyperplasia or mesonephroid remnants, which are characterized by atrophic secretory glandular structures with scanty cytoplasm and colloid-like intraluminal secretions [2]. Immunohistochemistry reveals positive reactions for cytokeratin clone 34βE-12 and negative reaction for PSA. In contrast, atypical small acinar proliferations express PSA and are often negative for cytokeratin clone 34βE-12 (Fig. 3a, b).

Dundor has recently written that "ASAP is not a diagnostic entity but it is a valid diagnostic category" [22]. ASAP is of great clinical importance because in a high percentage of patients prostatic adenocarcinoma is found in a short follow-up period [22]. At the moment the diagnosis of ASAP is mostly based on observer-dependent criteria rather than valid objective variables. Therefore, further studies similar to the study of Montironi et al. [45] should be initiated.

Histologic effects of radiation and hormonal therapy on glandular proliferations in the prostate

Radiation therapy

Irradiated benign glands show different degrees of atrophy. A pseudoinfiltrative pattern exists, resembling sclerotic atrophy. The atrophic epithelium often shows marked atrophic atypia with nuclear enlargement and prominent nucleoli. Usually more than one layer of cells exists, but sometimes there is only one. Such cases may be misinterpreted as adenocarcinoma [11], and immunohistochemistry is often helpful in demonstrating basal cells with sometimes atypical nuclei. PSA expression is often negative, whereas prostatic carcinoma usually is positive [33, 36]. In contrast to prostatic adenocarcinoma, radiation therapy does not significantly alter the architectural and cytological features of PIN. Slight changes are characterized by a diminution in the number of neoplastic glands, sclerosis of the stroma as well as vacuolization, pleomorphic nuclei with a decrease in the number and finally granular cytoplasm. These changes are more intense in nonneoplastic glands [27, 33, 36]. The PSA expression pattern is heterogeneous. The basal cell cytokeratin expression for 34βE12 is negative. The differential diagnosis to nonneoplastic glandular proliferations sometimes seems to be very difficult. The effect of irradiation on ASAP is unknown.

Hormone therapy

Basal cell hyperplasia and/or squamous/transitional cell metaplasia with reduction of secretory activity of the luminal cells and up to glandular atrophy are well documented reactions in nonneoplastic glands [33, 38]. Vacuolated cytoplasm and pyknotic nuclei are further characteristics [33]. In recent years so-called total androgen blockade and/or androgen deprivation have been used as pre- or postoperative therapy [57, 58], and finasteride, a 5α-reductase inhibitor, is used to treat prostatic hyperplasia as well as prostatic carcinoma [3, 19, 27]. In comparison with conventional hormone therapy the effect is less intense [19]. PIN also shows involution changes with decrease in the number of PIN foci. The effect of finasteride does not differ significantly in nonneoplastic prostatic tissue [19].

The effect of hormonal therapy on prostatic adenocarcinoma is well known. Hormonal sensitive carcinomas show a reduction of tumour volume, loss of glandular architecture, nuclear condensation with pyknosis and loss of nucleoli. The cytoplasm is clear, sometimes xanthomatous or foamy. The effect of finasteride may be similar to that of total androgen blockade therapy [3, 19, 27]. Immunohistochemically the reaction of basal cell cytokeratin 34βE12 is negative. The expression of PSA is positive in individual cancer cells. The expression of the proliferation marker MIB-1 has decreased or is negative [33, 34]. Nothing is known about the effects of hormone therapy on ASAP glands.

Diagnostic perspectives

Plan embedding of punch biopsies is essential in routine diagnostic work-up in order to achieve the best quality of histological sections. Good haematoxylin-eosin staining on thin section is important for assessment of cytological details. Histochemical, immunohistochemical, and molecular pathological methods may yield valuable additional information. The detection of prostate specific antigen and basal cell labelling by cytokeratins 1, 5, 10, 14 (34βE-12) should be standard. Proliferation markers such as Ki67/MIB-1 or PCNA can yield interesting additional information for serial studies as well as silver stainable nucleolar organizing regions [54]. These methods are not appropriate for routine studies, however, since the proliferative activity of all prostatic lesions except high-grade PIN and high-grade carcinomas is very low. Expression patterns of apoptosis-suppressing oncoprotein bcl-2, tumour suppressor gene *p53*, and E-cadherin are not predictive except in some cases of high-grade PIN and high-grade carcinomas. So far, these markers are used to support the preneoplastic character of high-grade PIN [46].

DNA cytometry has been successfully applied for the differentiation of low- and high-grade carcinomas but is not an appropriate method for evaluation of prostatic microglandular proliferations, since euploid DNA patterns predominate even in low-grade carcinomas. Discrimination of atypical adenomatous hyperplasia and low-grade carcinomas is not possible by this method.

There are differences in staining for growth factor receptors like erbB-2 and erb-B3 between high-grade PIN

and high-grade carcinomas and prostatic epithelium without malignant transformation. So far, this technique cannot be used in routine diagnosis. The same is true for detection of the androgen receptor [46].

Cytogenetic and molecular pathological studies have shown that chromosomal deletions are most frequently located on the Y chromosome (7q, 8p, 10q, 13q, 16q, and 16p). These appear to be the locations of the tumour suppressor genes for prostatic carcinoma. DNA amplifications on chromosome 7 (8q and 11q) indicate a location of possible oncogenes. Detection of polysomy in carcinomas indicates a poor prognosis. Amplification of androgen receptor genes indicates hormone resistance. None of these methods allows discrimination of benign from malignant lesions, and they are not appropriate for routine diagnostic use so far [43, 50, 51, 56].

Evaluation of prostatic lesions is still based upon basic histological methods. All the lesions described can be diagnosed from haematoxylin-eosin stained paraffin sections. Immunohistological methods are necessary in under 10%.

This survey of benign and malignant glandular lesions is justified by the relatively high rate of misinterpretations revealed by recent analyses of routine diagnoses [400].

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