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MEETING REPORT

Rodolfo Montironi · Erik Alexander
David G. Bostwick

Prostate pathology case study seminar

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Abstract Great strides have been made in the past decade in our understanding of the pathology of the prostate. Diagnostic criteria have been proposed, debated, and refined for a number of entities, including prostatic intraepithelial neoplasia, atypical adenomatous hyperplasia, basal cell proliferations, postatrophic hyperplasia, verumontanum mucosal gland hyperplasia, and numerous new variants of prostatic adenocarcinoma such as ductal adenocarcinoma, mucinous carcinoma, signet ring cell carcinoma, and lymphoepithelioma-like carcinoma. This report presents a series of case studies in prostate pathology which illustrate some of the contemporary issues which confront the pathologist and urologist.

Key words Prostate · Prostatic intraepithelial neoplasia · Atypical adenomatous hyperplasia · Basal cell proliferations · Postatrophic hyperplasia · Verumontanum mucosal gland hyperplasia · Stromal hyperplasia with atypia · Duct adenocarcinoma · Mucinous adenocarcinoma · Androgen deprivation · Finasteride

Introduction

This communication is an abbreviation of a slide seminar held at the University of Ancona, Ancona, Italy, in February 1996. It was the purpose of the course to draw attention to a number of aspects of prostate pathology that have been the subject of recent discussion in the literature.

R. Montironi (✉)
Institute of Pathological Anatomy and Histopathology,
University of Ancona, Nuovo Ospedale Regionale,
Via Conca, I-60020 Torrette di Ancona, Italy
Fax: (39) 71-889985

E. Alexander
Department of Urology, Mayo Clinic, Rochester, Minnesota, USA

D.G. Bostwick
Department of Pathology and Laboratory Medicine,
Mayo Clinic, Rochester, Minnesota, USA

Case 1

History

A 70-year-old man presented with urinary obstructive symptoms, including weak stream, abdominal straining, and terminal dribbling. The serum prostatic specific antigen (PSA) concentration was 4 ng/mL. Benign nodular hyperplasia was diagnosed. The patient underwent simple prostatectomy, and the surgical specimen was totally submitted for microscopic evaluation as whole mount tissue sections.

Pathologic findings

The transition zone of the prostate and the periurethral region showed glandular and stromal nodules typical of nodular hyperplasia. Macroscopically, the verumontanum was prominent and elongated, impinging on the lumen of the distal third of the prostatic urethra (Fig. 1A).

Microscopically, there was a microacinar proliferation at the verumontanum where the ejaculatory ducts and utricle empty into the urethra immediately subjacent to the urothelium. The acini were closely packed and lined by a benign cuboidal-to-columnar epithelium with small nuclei and inconspicuous nucleoli (Fig. 1B). The cytoplasm was eosinophilic, amphophilic, or clear, with well-defined borders. Basal cells were present in most of the acini. Eosinophilic corpora amylacea with concentric laminations and orange-red concretions were common. The columnar cells showed intense immunoreactivity for PSA antigen, and the basal cells expressed high-molecular-weight keratin. Interglandular stroma was minimal.

Diagnosis

Verumontanum mucosal gland hyperplasia (VMGH).

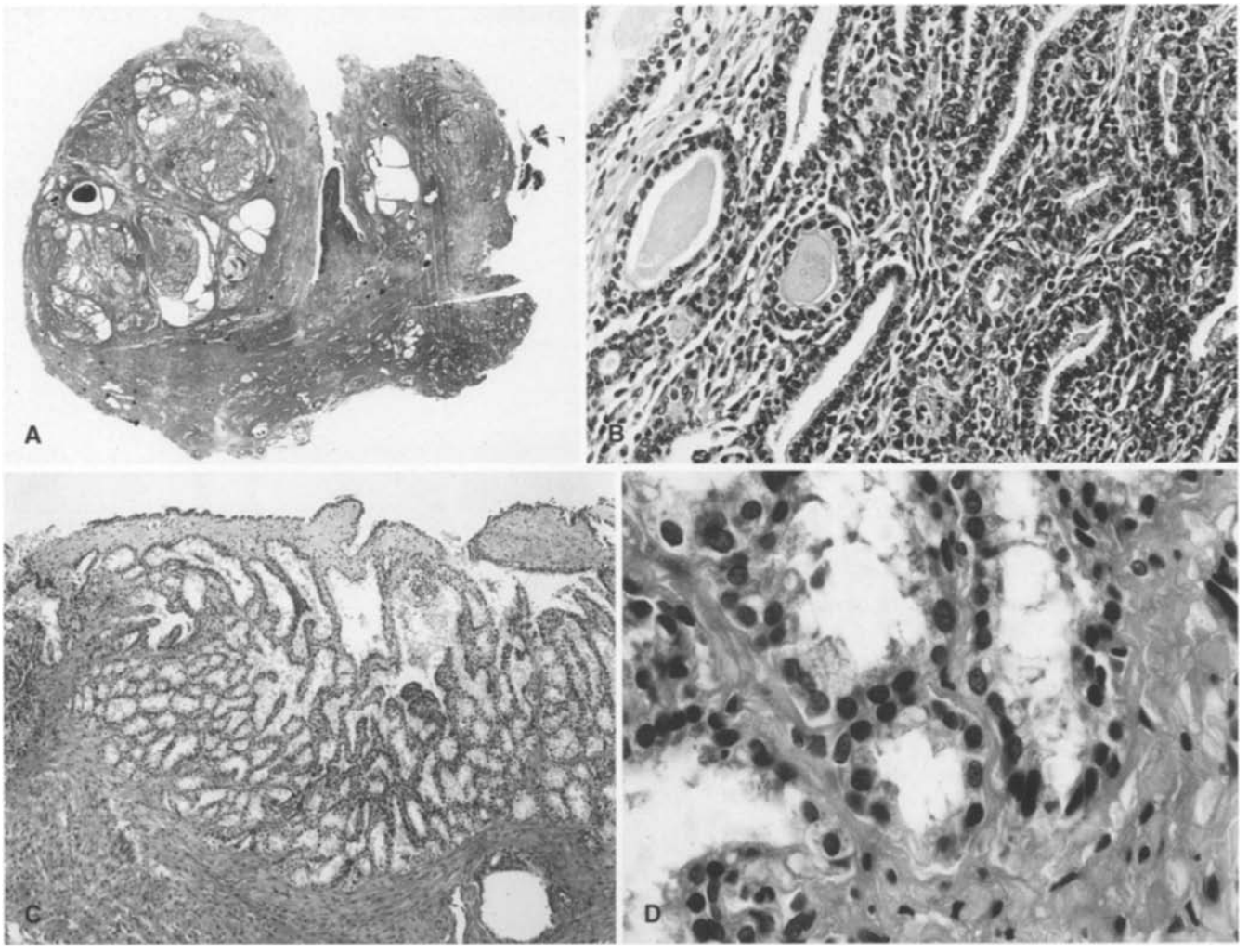


Fig. 1A–D Verumontanum mucosal gland hyperplasia (VMGH). **A** The verumontanum forms an elongate mass protruding into the urethral lumen. There is also prominent nodular hyperplasia. **B** The acini are lined by a benign epithelium with small nuclei and inconspicuous nucleoli. **C** Another case of VMGH in which there is a suburothelial collection of benign acini. **D** The nuclei are hyperchromatic, but there is no atypia or nucleolomegaly

Discussion

The verumontanum is an elevated ridge on the posterior wall of the distal third of the prostatic urethra. To the urologist, it represents an important cystoscopic landmark which resides just proximal to the external striated sphincter. The prostatic ducts of the verumontanum are typically lined by columnar epithelium with basal cells, but occasionally show urothelial metaplasia. Within this ridge is the utricle, a structure flanked by the distal portion of each ejaculatory duct.

Proliferative lesions of the verumontanum and associated tissues include prostatic ductal adenocarcinoma (adenocarcinoma with endometrioid features), prostatic urethral polyps, and VMGH [3, 4, 7]. Prostatic ductal adenocarcinoma is distinguished by tall pseudostratified epithelium arranged in long papillae, large cribriform glands, or single glands, and is not likely to be confused with benign verumontanum mucosal glands; however, it may be histologically confused with peripheral zone adenocarcinoma which occasionally contains similar features but lacks large duct or urethral involvement. Urethral polyps are distinctly polypoid, often lined by urothelium, contain stroma, and histologically resemble prostatic glands. VMGH is a newly described lesion characterized by microglandular proliferation that occurs exclusively in the verumontanum and adjacent posterior urethra where the ejaculatory ducts and utricle empty into the urethra [3]. The lack of recognition of this process reflects the relative rarity of the verumontanum in biopsy material, as this portion of the urethra is generally avoided in needle sampling. During transurethral resection of the prostate, the verumontanum is usually not removed. In our experience, the distinction between normal verumontanum mucosa and VMGH may be arbitrary and quantitative rather than qualitative (Fig. 1C, D).

VMGH may be mistaken for low-grade adenocarcinoma, particularly in prostatic needle biopsy specimens [1–6]. Both may be small and consist of crowded glands. Confusion with carcinoma may also arise from the presence of VMGH in multiple cores or from extensive involvement of a single biopsy core. However, the glands

of VMGH lack the infiltrative and haphazard arrangement of the glands typically found in prostatic adenocarcinoma. Moreover, cancer glands often infiltrate between benign prostate glands, a feature that is absent in VMGH. Finally, VMGH is characteristically adjacent to and often contiguous with the urothelium. At high magnification, the cytologic features and luminal contents of these mucosal glands are sufficiently distinct to allow discrimination from low-grade adenocarcinoma, and are similar to surrounding benign prostatic glands. In difficult cases, antibodies to high-molecular-weight cytokeratin may be useful in distinguishing these two lesions; adenocarcinoma lacks a high-molecular-weight-immunoreactive basal cell layer, whereas it is usually intact in VMGH.

Case 2

History

A 76-year-old man with urinary obstructive symptoms underwent needle biopsy of the prostate.

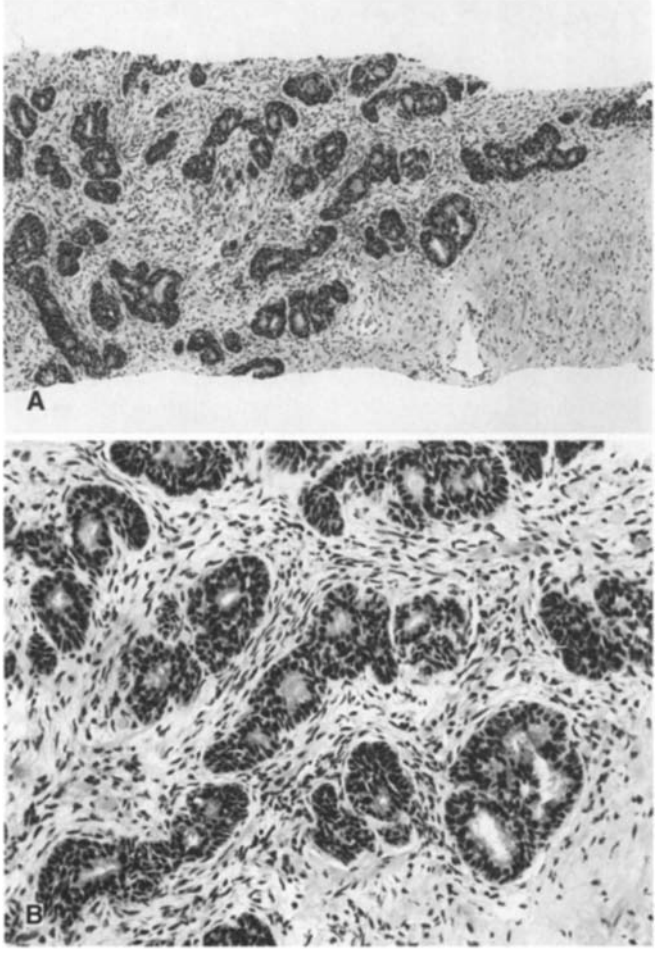


Fig. 2A, B Basal cell hyperplasia forming a circumscribed nodule (basal cell adenoma)

Description

At the tip of one needle core, there was a circumscribed aggregate of benign acini composed chiefly of hyperplastic basal cells, varying from small, solid nests to larger open cystically dilated glands (Fig. 2A). The basal cells were plump with large nuclei, scant cytoplasm, and inconspicuous nucleoli (Fig. 2B). Stroma traversed the nodule and was focally condensed, but there was no cytologic atypia. Basal cells stained intensely with high-molecular-weight keratin 34β-E12, whereas less than 50% of the cells stained with PSA and PAP.

Diagnosis

Basal cell adenoma. (Discussion follows report on case 3.)

Case 3

History

An 87-year-old man with urinary obstructive symptoms underwent transurethral resection of the prostate (TURP). Three months later, he underwent liver needle biopsy.

Description

The lesion consisted of basaloid cell nests of various sizes that infiltrated a myxoid or fibrotic stroma (Fig. 3 A, B). The cell nests were frequently large and round, with peripheral basaloid cells exhibiting elongated nuclei, often with palisading (Fig. 3C). Nucleoli were inconspicuous. Cell crowding was prominent, with multiple luminal spaces of various sizes. Pale amorphous material was seen in the lumina in hematoxylin-and-eosin-stained sections. The cells were similar to those in basal cell adenoma except for mild nuclear enlargement. Variable immunoreactivity with high-molecular-weight 34β-E12 was present. Rare scattered cells with PSA and PAP immunoreactivity were observed. The liver biopsy revealed predominately crushed cells, although some fragments contained malignant cells identical to those in the prostatic specimen (Fig. 3D).

Diagnosis

Adenoid cystic/basal cell carcinoma of the prostate.

Discussion of cases 2 and 3

The spectrum of benign basal cell proliferations in the prostate is divided into three patterns of benign basal cell hyperplasia, including typical basal cell hyperplasia,

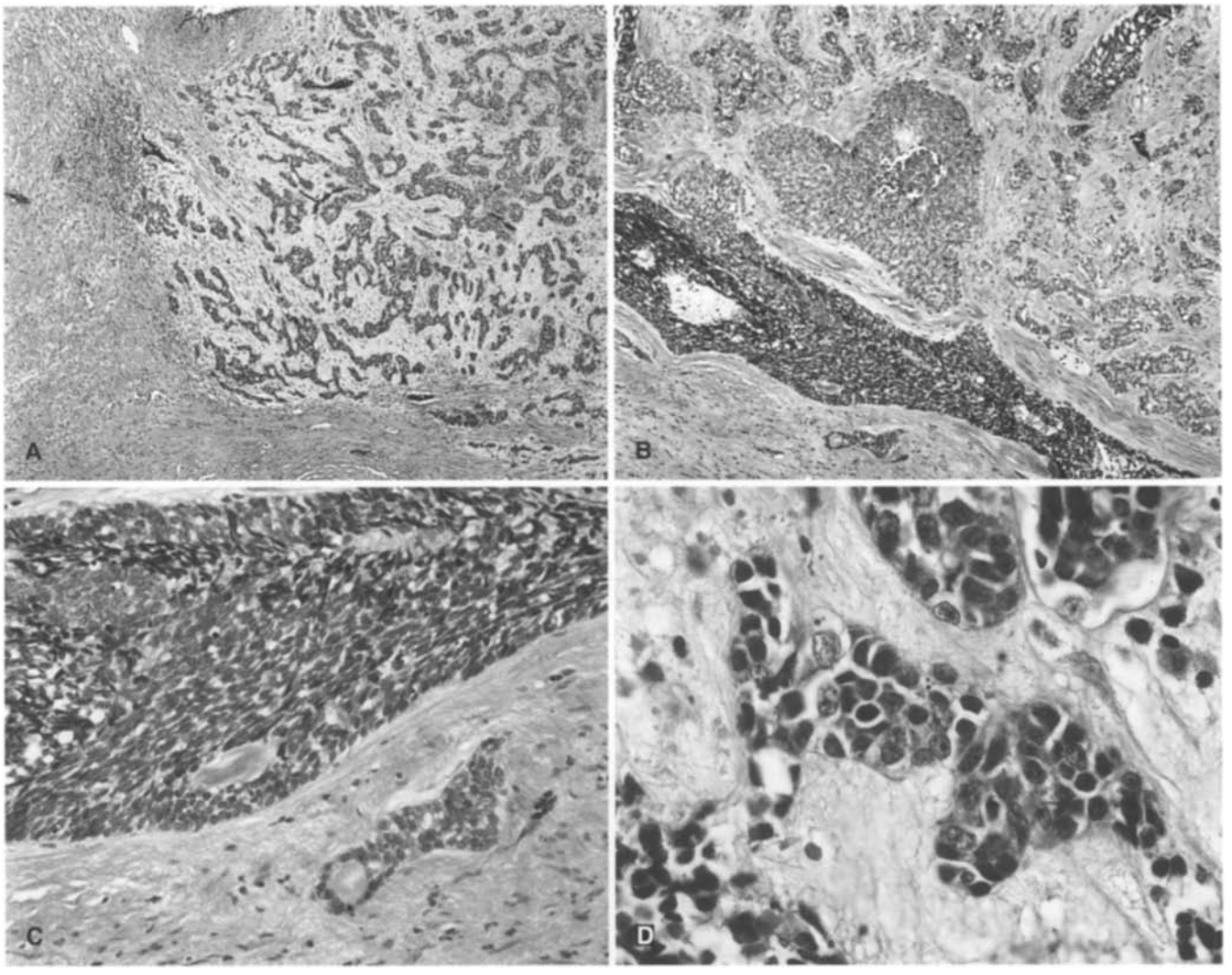


Fig. 3A–D Adenoid cystic/basal cell carcinoma of the prostate. **A** At scanning magnification, the cell nests are irregular in size, shape, and distribution. **B** Large basal cell aggregates are surrounded by smaller cell clusters; note necrosis in one of the large masses. **C** Basal cell proliferation, with closely packed cells with scant cytoplasm. **D** Liver metastasis, consisting of small nests of malignant cells with large hyperchromatic nuclei and scant cytoplasm

atypical basal cell hyperplasia, and basal cell adenoma [8, 12]. Adenoid cystic/basal cell carcinoma is considered the malignant counterpart of basal cell hyperplasia. Light-microscopic findings usually suffice to separate basal cell proliferations from other lesions. Immunohistochemical staining with antibodies directed against high-molecular-weight keratin 34β-E12 is useful in confirming the presence of basal cells in equivocal cases. Some basal cell proliferations may be mistaken for high-grade prostatic intraepithelial neoplasia (PIN) and carcinoma due to the presence of significant cytologic abnormalities, including nuclear and nucleolar enlargement [8, 9]. These cases are often a source of diagnostic confusion, particularly in small samples such as needle biopsy specimens.

Basal cell hyperplasia consists of two or more cells in thickness at the periphery of prostatic acini. A minimum of two basal cells in thickness is required for diagnosis, although this is an arbitrary criterion [8, 9, 12]. Basal cell hyperplasia sometimes appears as small nests of cells surrounded by a few concentric layers of compressed stroma, often associated with chronic inflammation. The nests may be solid or cystically dilated and occasionally are punctuated by irregular round luminal spaces, creating a cribriform pattern. Basal cell hyperplasia frequently involves only part of an acinus, and sometimes protrudes into the lumen, retaining the overlying secretory cell layer; less commonly, there is symmetric duplication of the basal cell layer at the periphery of the acinus. The cells in basal cell hyperplasia are enlarged, ovoid or round, and plump, with large pale nuclei, finely reticular chromatin, and a moderate amount of cytoplasm. Nucleoli are usually inconspicuous, less than 1 μm in diameter, although they are enlarged in atypical basal cell hyperplasia (see below). Basal cell hyperplasia is occasionally associated with atypical adenomatous hyperplasia [8].

Atypical basal cell hyperplasia is identical to basal cell hyperplasia except for the presence of large promi-

nent nucleoli; in one study, the mean nucleolar diameter was 1.96 μm with a maximum of 4.8 μm [8, 9]. A morphologic spectrum of nucleolar size is observed in basal cell proliferations, and only those with more than 10% of cells exhibiting prominent nucleoli are considered atypical. There is no apparent clinical significance of atypical basal cell hyperplasia other than as a diagnostic pitfall.

Basal cell adenoma consists of a large, round, usually solitary circumscribed nodule of acini with hyperplastic basal cells and peripherally condensed stroma. Prominent calcific debris is often present within acinar lumens. Multiple basal cell adenomas (basal cell adenomatosis) invariably arises in association with nodular hyperplasia and appears to be a variant of basal cell hyperplasia [8].

Cribriform hyperplasia, including clear-cell cribriform hyperplasia, consists of a benign proliferation of acini with a distinctive cribriform pattern, sometimes forming a nodule. The cells in such acini have pale to clear cytoplasm, small uniform nuclei, and inconspicuous nucleoli [8, 9, 12].

The rarest neoplastic basal cell proliferation in the prostate is adenoid cystic/basal cell carcinoma (adenoid basal cell tumor; adenoid cystic-like tumor), with fewer than 50 documented cases, and most with little or no clinical follow-up [10, 11, 13–18]. The age, presenting symptoms, and clinical findings are similar to typical acinar adenocarcinoma. Almost all reported cases were confined to the prostate at presentation, and follow-up has not extended beyond 6 years after diagnosis. Serum PSA and PAP concentration is not usually elevated. Adenoid cystic/basal cell carcinoma of the prostate is histologically similar to adenoid cystic carcinoma or basal cell carcinoma at other sites. The criteria for distinguishing these lesions have recently been refined, and the malignant nature of cases previously reported as adenoid cystic carcinoma has been questioned [8, 9, 18]. There have been no documented metastases from these tumors, although the case described herein displayed liver metastases; we are aware of two other cases with histologic documentation of metastases.

Adenoid cystic/basal cell carcinoma is histologically similar to basal cell hyperplasia and basal cell adenoma, but the tumor involves large areas of the prostate with no circumscription [18]. It shows varying proportions of two distinct architectural patterns: adenoid cystic carcinoma [8, 18] and basal cell carcinoma [8, 18]. The adenoid cystic pattern consists of irregular clusters of crowded basaloid cells punctuated by round fenestrations, many of which contain mucinous material; the findings are virtually identical to those in salivary gland adenoid cystic carcinoma, including a propensity for perineural invasion. The basaloid pattern consists of variably sized round basaloid cell nests with prominent peripheral palisading. These patterns are usually intimately admixed [18]. These tumors are expansive, extending into the stroma of the prostate and often accompanied by a myxoid matrix. Adenocarcinoma may be adjacent, but has not been reported in direct contact with adenoid cystic/basal cell carcinoma.

Case 4

History

A 64-year-old man with urinary obstructive symptoms underwent TURP (case courtesy of Dr. James Williams, Mayo Clinic, Scottsdale, Arizona).

Description

The specimen contained typical nodular hyperplasia as well as multiple typical stromal nodules in the transition zone with increased cellularity and nuclear atypia interspersed with benign glands. In the cellular areas, the stromal nuclei were large, hyperchromatic, and occasionally multinucleated or vacuolated, with inconspicuous nucleoli (Fig. 4A, B); scattered bizare cells were present. There were no mitotic figures and no necrosis.

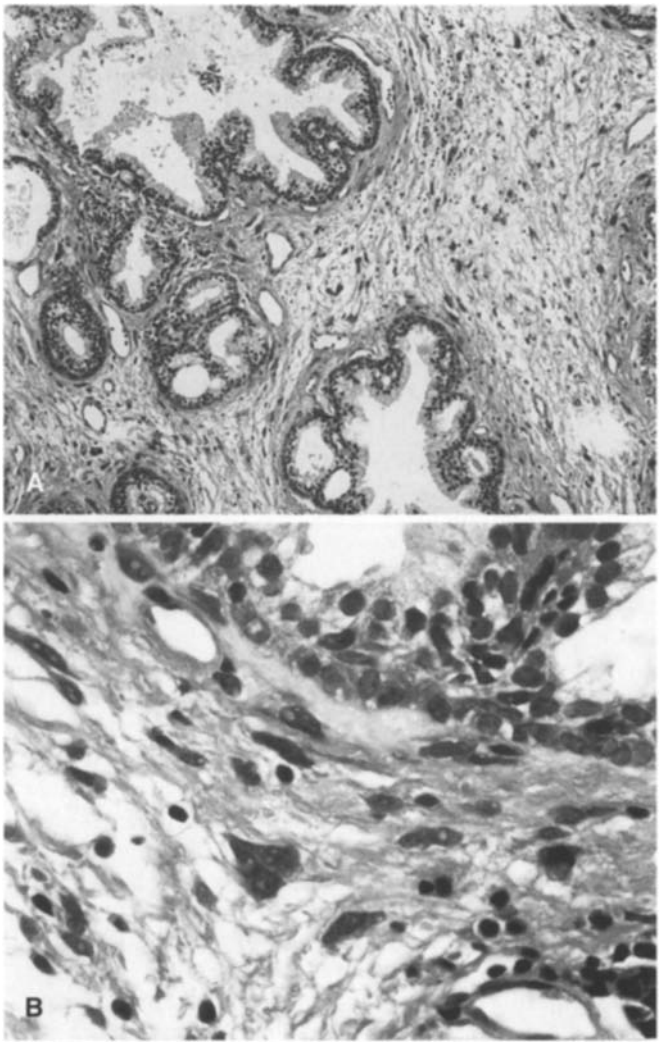


Fig. 4A, B Stromal hyperplasia with atypia. **A** The stroma surrounding these benign acini contains numerous enlarged cells. **B** The stromal nuclei are enlarged and hyperchromatic, but lack mitotic figures. They often appear smudged

Diagnosis

Stromal hyperplasia with atypia (stromal hyperplasia with bizarre nuclei).

Discussion

Stromal hyperplasia with atypia consists of stromal nodules in the transition zone with increased cellularity and nuclear atypia [21, 26]. These may appear as solid stromal nodules (often erroneously referred to as atypical leiomyoma) or with atypical cells interspersed with benign glands. Stromal nuclei are large, hyperchromatic, and rarely multinucleated or vacuolated, with inconspicuous nucleoli. There are no mitotic figures and no necrosis. Stromal hyperplasia with atypia has no malignant potential, and the atypical cells are considered degenerative.

The differential diagnosis of stromal hyperplasia with atypia includes phyllodes tumor, leiomyoma, and sarcoma. Phyllodes tumor of the prostate is a rare lesion which should be considered a neoplasm rather than atypical hyperplasia due to the frequent early recurrences, infiltrative growth, and potential for extraprostatic spread in some cases. Important diagnostic clues include diffuse infiltration, variably cellular stroma surrounding cysts, and compressed elongate channels which often have a leaf-like configuration [20, 22, 24, 27, 28, 31, 33]. Prostatic phyllodes tumor exhibits a spectrum of histologic features similar to its counterpart in the breast. It may be subdivided into low-grade, intermediate-grade, and high-grade groups, but even low-grade tumors may recur [20]. High-grade prostatic phyllodes tumor has a high stromal-epithelial ratio, prominent stromal cellularity and overgrowth, marked cytologic atypia, and increased mitotic activity. A sarcomatous component may arise within a low-grade tumor over time, invariably after multiple recurrences over many years [20, 35]. Phyllodes tumor may also arise in the seminal vesicles as a supraprostatic retrovesicular mass, but is separated from its prostatic counterpart by the absence of PSA and PAP immunoreactivity in the epithelium.

Other diagnostic mimics of stromal hyperplasia with atypia include leiomyoma [25, 30, 32], fibroma, leiomyosarcoma, and other sarcomas [19, 34, 35]. Leiomyoma and fibroma are often confused with nodular hyperplasia, and the distinction may be impossible in biopsy or transurethral resection specimens. Leiomyoma is defined as a circumscribed solitary smooth muscle nodule greater than 1 cm in diameter [23, 25, 29, 30]. It is histologically identical to leiomyoma occurring in the uterus and other sites, and consists of a proliferation of benign smooth muscle cells with a variable amount of collagen. Fibroma is a similar nodule composed of collagen with few fibroblasts; fibroma may be indistinguishable from a pure stromal nodule of nodular hyperplasia. Some authors have questioned the existence of these tumors, preferring to consider them within the spectrum of nodular hyperplasia. Unlike stromal hyperplasia with atypia, they lack cytologic abnormalities.

Variants of leiomyoma include cellular leiomyoma, atypical leiomyoma, and leiomyoblastoma [29]. The cellular variant is distinguished by increased cellularity, whereas the atypical (symplastic; bizare) variant contains multinucleated giant cells with smudged nuclear detail, probably representing degenerative changes. Mitotic figures are rare or absent.

Primary sarcoma of the prostate such as leiomyosarcoma is also a diagnostic consideration, but this tumor consists of a monophasic densely cellular proliferation of spindle cells which lacks the intimate association with the epithelial component of stromal hyperplasia with atypia. Sarcomatoid carcinoma is a concern when an overtly malignant spindle cell component is present, but is distinguished by the presence of a malignant epithelial component or evidence of epithelial differentiation within the neoplastic spindle cells.

Case 5

History

A 73-year-old man presented with urgency and urge incontinence. His medical history included partial cystectomy 5 years previously for adenocarcinoma thought to be arising in the bladder. Digital rectal examination showed diffuse bilateral induration of the prostate; serum PSA was 4 ng/mL. Biopsy of the central zone was obtained with ultrasound guidance.

Description

The prostate biopsy showed extensive acinar adenocarcinoma. The cancer cells contained enlarged nuclei, inconspicuous nucleoli, and cytoplasmic vacuoles which stained with Alcian blue and periodic acid–Schiff (Fig. 5A, B). Immunohistochemical studies for PSA and PAP were negative in the cancer cells and positive in the uninvolved benign prostatic ducts and acini.

Sections of the previous bladder specimen revealed adenocarcinoma with identical morphologic, histochemical, and immunohistochemical findings.

Diagnosis

Involvement of the prostate by urinary bladder adenocarcinoma simulating prostatic adenocarcinoma. (See report on case 6 for discussion.)

Case 6

History

A 61-year-old man with a prior history of gastric adenocarcinoma presented with urinary obstructive symptoms. He had a history of gastric adenocarcinoma diagnosed 3 months before by biopsy; gastrectomy was not per-

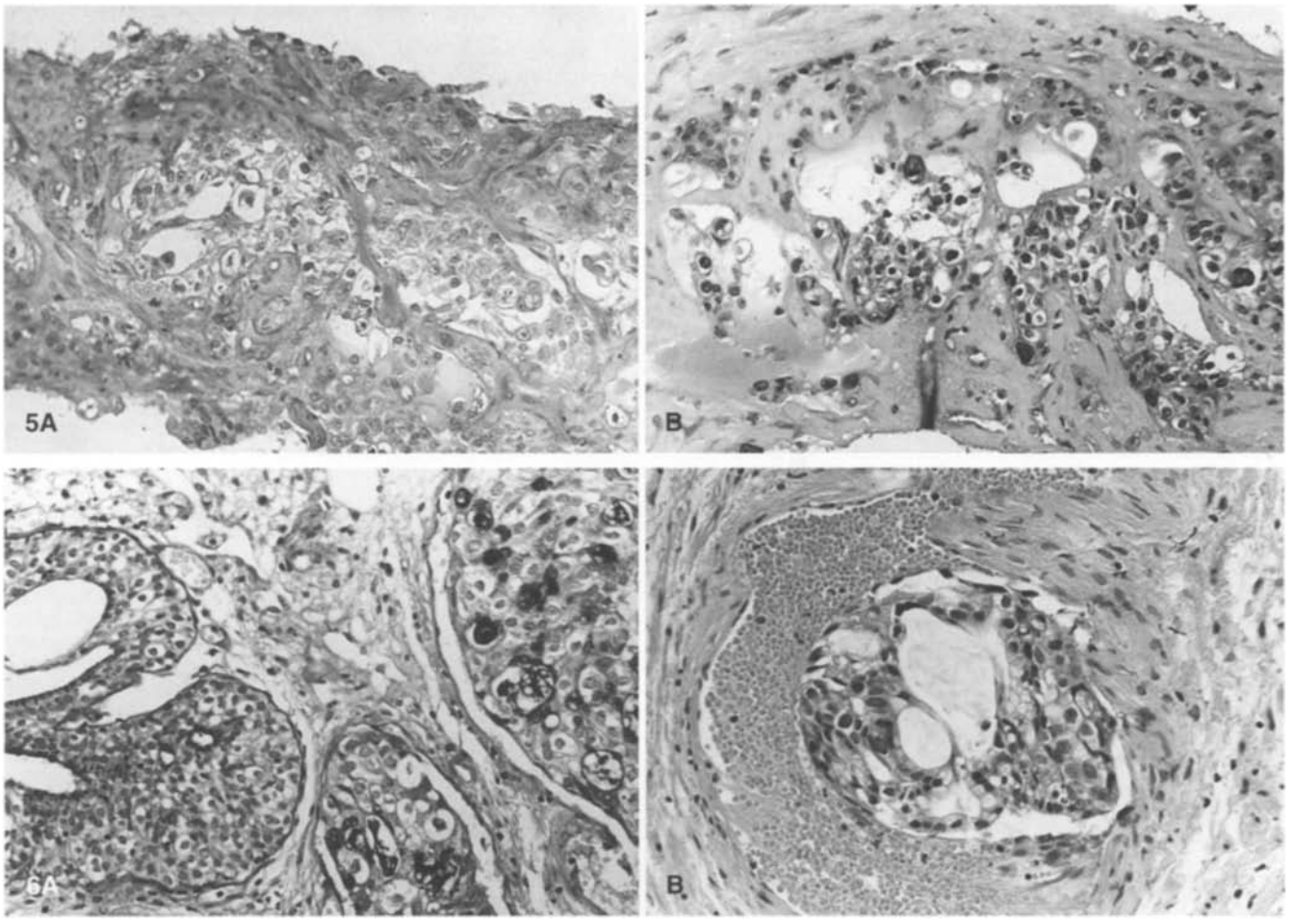


Fig. 5A, B High-grade adenocarcinoma of the bladder with secondary involvement of the prostate

Fig. 6A, B Gastric adenocarcinoma metastatic to the prostate. **A** Periodic acid–Schiff stain (after diastase digestion) reveals moderate amount of mucin within cancer glands (appears as *dark amorphous material*). **B** Vascular invasion by adenocarcinoma was prominent

formed because the cancer was too advanced. Serum PSA was 3 ng/mL. Stenosis of the proximal tract of the urethra was found at cystoscopy, and transurethral resection was performed.

Description

The transurethral resection specimen contained a diffuse infiltrate of mucinous adenocarcinoma with vascular invasion in all the chips (Fig. 6A, B). The mucous was mainly cytoplasmic and stained with Alcian blue and periodic acid–Schiff, indicating the presence of acid and neutral mucins. Immunohistochemical studies for PSA and PAP were negative in the cancer cells and positive in the benign and hyperplastic prostatic acini. The urothelium of the prostatic urethra was normal.

The prostatic adenocarcinoma was identical to the gastric adenocarcinoma.

Diagnosis

Metastatic mucinous adenocarcinoma to the prostate, gastric primary.

Discussion of cases 5 and 6

The prostate is occasionally involved by tumors arising in other organs, usually due to contiguous spread. Urothelial carcinoma of the bladder is the cancer that most commonly secondarily involves the prostate. Colorectal adenocarcinoma also may invade the prostate by contiguous spread, but this is invariably clinically apparent due to the bulkiness of the cancer; histologically, it may resemble prostatic ductal adenocarcinoma [37]. Rarely, primary adenocarcinoma may arise in the bladder and secondarily involve the prostate, as in case 5. Immunohistochemical studies with PSA and PAP are usually helpful in separating prostatic and bladder adenocarcinomas, although prostatic cases are occasionally unreactive, especially when of high grade, and bladder adenocarcinoma is occasionally weakly reactive. The correlation of clinical and pathologic findings is useful.

Metastases to the prostate as in case 6 are extremely rare, with involvement at autopsy in 0.5–2.2% of men

dying of malignancies [36, 43]. The most common is squamous cell carcinoma of the bronchus, accounting for almost half of all prostatic metastases [36, 43]. Malignant melanoma accounts for 27% of metastases, with an incidence at autopsy of 1.1% among patients with malignant melanoma [38–43]. Grignon et al. described an unusual case of tumor-to-tumor metastasis of malignant melanoma to prostatic adenocarcinoma [39]. Other metastases to the prostate arise from a variety of sites [38, 42], including pancreatic carcinoma [38] and goblet cell carcinoid of the appendix [41]. One documented case of metastatic carcinoma to the prostate from clinically inapparent carcinoma of the stomach was reported by Alberts and Stephenson [36].

Case 7

History

A 66-year-old man underwent radical retropubic prostatectomy for clinical stage T3a+bNOMx adenocarcinoma (extra-prostatic extension without metastases). For 3 months prior to surgery, he received androgen deprivation therapy [goserelin acetate (Zoladex) and leuprolide (Lupron)] in an effort to reduce the size of the tumor.

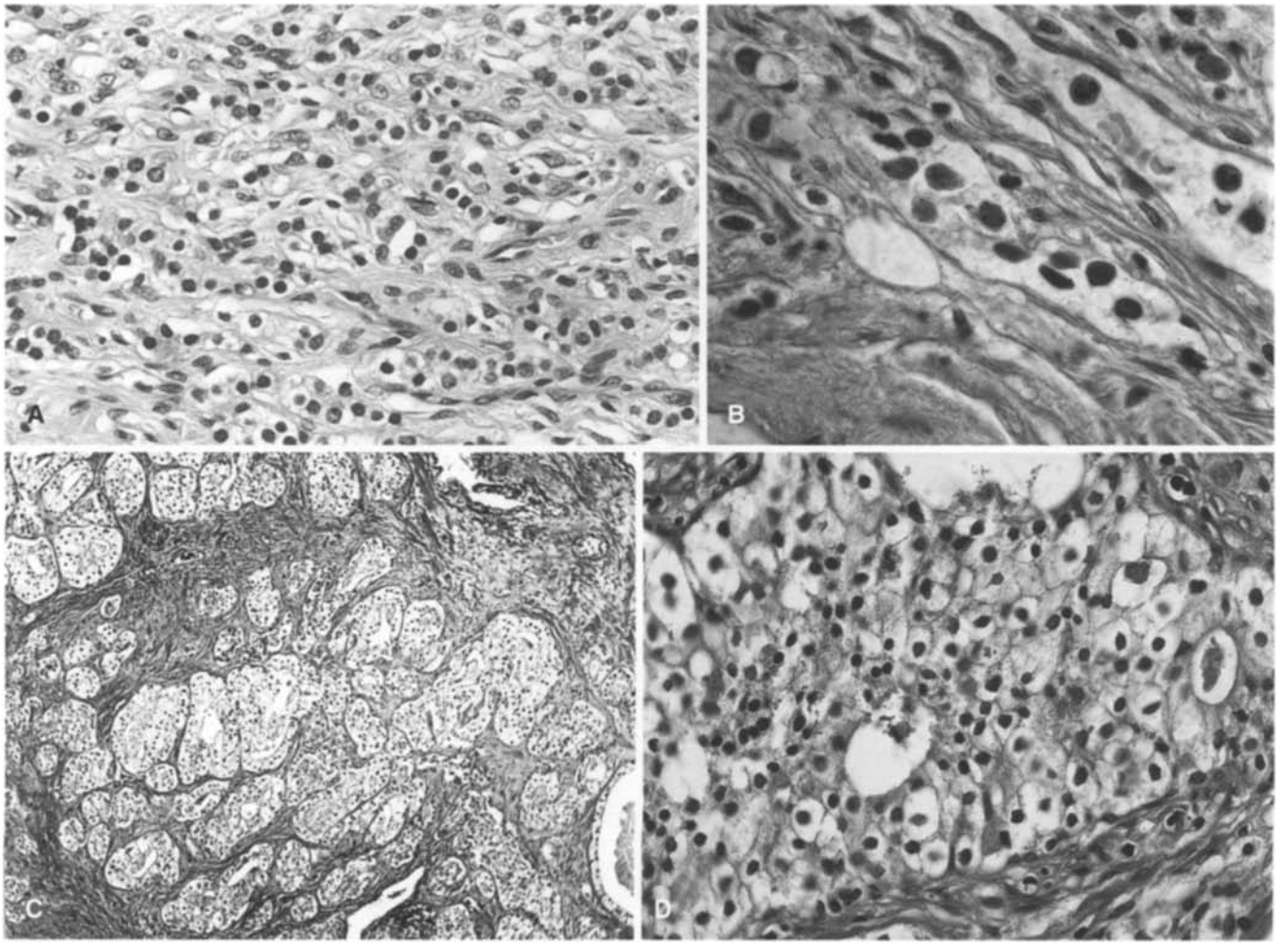
Description

Androgen-deprived cancer consists of shrunken neoplastic acini and areas of individual infiltrating tumor cells separated by abundant interglandular connective tissue (Fig. 7A, B). The cancer cells have shrunken pyknotic nuclei, condensed chromatin, inconspicuous nucleoli, cytoplasmic clearing and enlargement by coalescence of vacuoles, and rupture of cell membranes. Apoptotic bodies are easily identifiable in all epithelial cell layers.

Diagnosis

Residual prostatic adenocarcinoma with androgen deprivation effect.

Fig. 7A–D Androgen deprivation therapy effect in prostatic adenocarcinoma. **A** The acini are randomly scattered and closely packed. **B** Characteristic cytologic changes include nuclear and nucleolar shrinkage, hyperchromasia, and cytoplasmic clearing. **C,D** Another case of adenocarcinoma following treatment. The cancer forms irregular aggegates and masses, with cells punctuated by small dark nuclei



Discussion

The histologic changes in adenocarcinoma following therapy such as androgen deprivation or radiation therapy often present a significant diagnostic challenge, particularly in biopsy specimens. The clinical history is invaluable in such cases [44–52].

Androgen deprivation is used for preoperative tumor shrinkage and treatment of prostatic hyperplasia, and may be effective for cancer prophylaxis, although this remains speculative. Androgen deprivation of normal, hyperplastic, and dysplastic epithelial cells causes acceleration of programmed cell death of single cells (apoptosis), with fragmentation of DNA, emergence of apoptotic bodies, and inhibition of cell growth [49]. Characteristic pathologic changes occur in the prostate after androgen deprivation therapy. Benign acini show marked lobular and acinar atrophy, epithelial vacuolation, basal cell hyperplasia, squamous metaplasia, transitional metaplasia, and acinar rupture with extravasation of secretions. Similar changes occur in malignant acini (Fig. 7C, D). Androgen deprivation therapy also causes a marked reduction in the presence and extent of high-grade PIN. The "uncoupling" of the architectural and cytologic pattern in carcinoma is vexing due to the presence of small shrunken nuclei within malignant acini, particularly in lymph nodes submitted for frozen section evaluation. Immunohistochemical studies for PSA, PAP, and high-molecular-weight keratin 34β-E12 are useful in identifying carcinoma following therapy. No differences occur in expression of neuroendocrine differentiation markers [44, 49, 50, 52].

For about 12 months after radiation therapy, needle biopsy is of limited value due to the delayed manifestation of tumor cell death [45]. After this period, however, biopsy is the best method for assessing local tumor control. If prostatic carcinoma is not histologically ablated by radiotherapy after 12 months, it is probably biologically active. No definitive method exists for assessment of tumor viability after irradiation. Cancer grading after radiation therapy has yielded conflicting results, with some observers noting no difference from pre-therapy grade and others finding a substantial increase in grade. There may also be a shift toward aneuploid DNA content in up to 31% of pretreatment diploid tumors, indicating increasing histologic and biologic tumor aggressiveness. Despite conflicting results, most investigators recommend grading of specimens after therapy, recognizing that the biologic significance of grade may be different than in untreated cancer [45, 47].

All forms of hyperthermia for nodular hyperplasia result in sharply circumscribed hemorrhagic coagulative necrosis which soon organizes with granulation tissue. When delivered transurethrally, laser thermocoagulation and microwave hyperthermia does not usually involve the peripheral zone or neighboring structures, presumably due to differences in tissue perfusion [46]. Coagulation necrosis is greater in areas of predominantly epithelial nodular hyperplasia rather than predominantly stromal hyperplasia and the dense fibromuscular tissue of the bladder neck. Confluent coagulation necrosis occurs when multiple laser lesions are created in a single transverse plane.

Cryosurgical ablation refers to freezing of the prostate. Multiple cryoprobe needles filled with circulating liquid nitrogen transform the prostate into an iceball, resulting in substantial tissue destruction and death of cancer cells. Following cryosurgery, the prostate shows typical features of repair, including marked stromal fibrosis and hyalinization, basal cell hyperplasia with ductal and acinar regeneration, squamous metaplasia, and stromal hemorrhage and hemosiderin deposition. Coagulative necrosis is present between 6 and 30 weeks of therapy, but patchy chronic inflammation is more common. Focal granulomatous inflammation is associated with epithelial disruption due to corpora amylacea. Dystrophic calcification is infrequent, and usually appears in areas with the greatest reparative response. Atypia and PIN are not seen in areas that otherwise show changes of post-cryoablation therapy. Biopsy after cryosurgery may reveal no evidence of recurrent or residual carcinoma; in other cases, the tumor appears unchanged, with no change in grade or definite evidence of immune response [51].

Phytotherapy refers to the use of plant extracts for treatment of nodular hyperplasia. This therapy is popular in Germany and some other countries, and has been shown to improve micturition and urinary flow rate. The use of Sabal extract, one type of phytotherapy, reduces stromal edema, mucoid degeneration, and intraglandular congestion in the setting of nodular hyperplasia, but has no influence on benign or neoplastic epithelium [48].

Case 8

History

A 57-year-old man with benign prostatic hyperplasia (BPH) received therapeutic doses of finasteride (5-α-reductase inhibitor) daily for 6 months. The prostate shrank in volume by 20%. There was no clinical relief of urethral obstruction (no change in the urinary flow rate), so prostatic adenectomy (simple prostatectomy) was performed.

Description

The adenectomy specimen showed a reduction in prostate size by 20% and an increase in the stroma/epithelial and the stroma/lumen ratios with respect to untreated BPH. The ducts and acini were variable in size, and some ducts and acini retained a bistratified epithelium similar to that of untreated BPH (Fig. 8A–C). The secretory cells had shrunken nuclei, condensed chromatin, and inconspicuous nucleoli. Apoptotic bodies were occasionally present in the epithelial cells and in the lumina, but there were no mitotic figures. After treatment, there

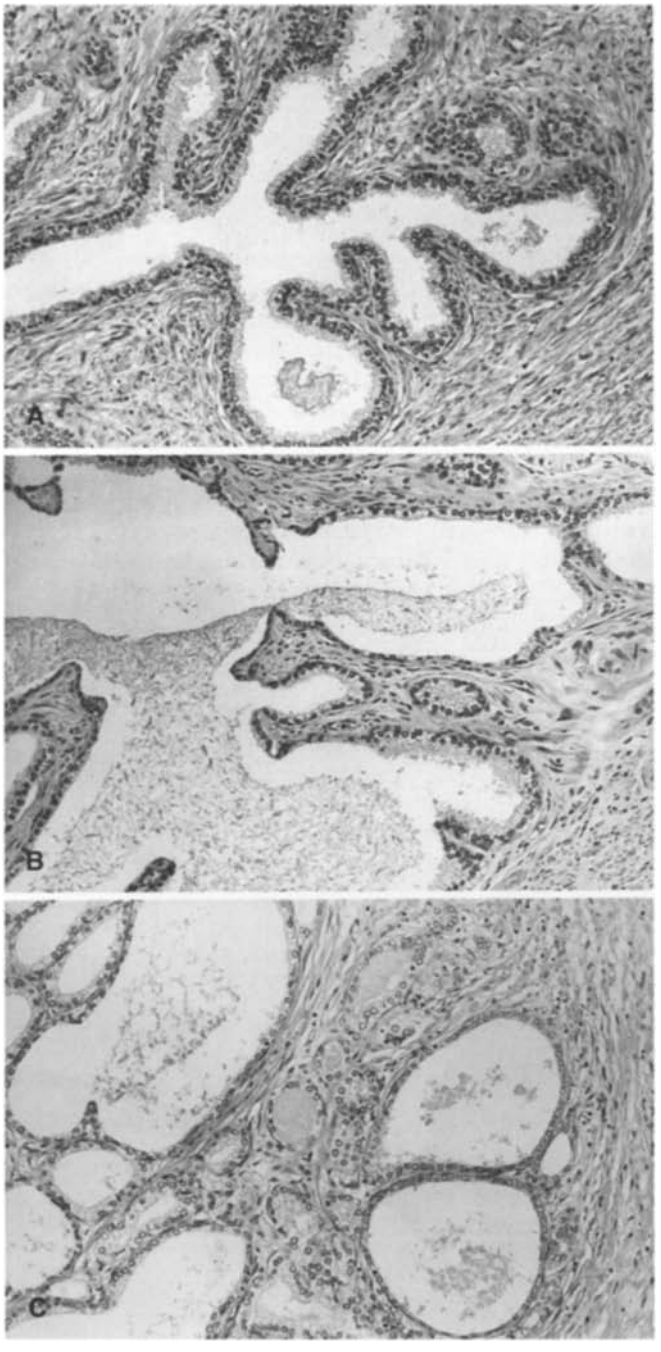


Fig. 8A–C Hyperplastic prostatic epithelium after finasteride treatment. Architectural and cytologic changes are minimal (see text)

was some secretory cell cytoplasmic clearing and basal cell layer prominence. Scattered clusters of small acini were present and contained a mixture of round, regular and irregular contours. In these small acini, the secretory cells appeared as cuboidal or columnar cells with pale cytoplasm, round basal nuclei with uniform granular chromatin, and inconspicuous or mildly enlarged nucleoli. The basal cell layer was often inconspicuous by routine light microscopy. Focal squamous metaplasia, urothelial metaplasia, and stromal nodules of primitive mesenchyme were seen mainly in the periurethral region.

Diagnosis

Morphological change in BPH following chronic treatment with the 5-α-reductase inhibitor (finasteride) in a patient who failed to respond.

Discussion

The androgen primarily responsible for the development of BPH is dihydrotestosterone, which is converted from testosterone by 5-α-reductase. Selective inhibition of 5-α-reductase may be an effective treatment for BPH [60].

The findings in this patient treated for 6 months with finasteride are particularly prominent in the epithelium [54, 55, 57]. However, the effect on the ducts and acini was not homogeneously distributed within the individual lobules as well as among them, contrary to the results of total androgen ablation [58, 61]. This morphological observation is in agreement with the experimental study by Cohen et al. [54] involving canine hyperplastic prostates treated with steroid 5-α-reductase inhibitors. Juniewicz et al. [56] investigated the prostate of beagle dogs and observed that finasteride induced "incomplete atrophy".

Finasteride acts by blocking 5-α-reductase, thus reducing hormonal stimulation of the epithelial prostate component [60]. The lack of mitotic figures in the ducts and acini indicates that there is no growth of the epithelial component as a result of this treatment. This is in agreement with a recent study published by Bologna et al. [53], who assessed the effects of finasteride on the growth rate of the androgen-responsive human prostate carcinoma cell line LnCaP. Since apoptotic bodies were present in our study, the apoptotic phenomenon was probably triggered by the finasteride treatment as a way to eliminate cells. This phenomenon has been described in normal, preinvasive, and invasive human prostate lesions after total androgen ablation [57–59]. Tuttle et al. [62] investigated the effect of 5-α-reductase inhibition on growth characteristics in the non-androgen-dependent human prostate cancer line PC-3 and found that finasteride caused apoptosis. In an experimental study, Cohen et al. [54] noted a net increase in prostatic cell death in canine BPH. They suggested that more cell death occurred after castration than with inhibitors of 5-α-reductase.

Finasteride treatment created clusters of small acini morphologically similar to postatrophic hyperplasia and atypical adenomatous hyperplasia [59].

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