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Advances in prostate pathology

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Comparison of benign, premalignant and malignant lesions of the prostate in routine and consultation material

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Due to recent improvements in the diagnosis of prostatic diseases pathologists are confronted with an increase in prostatic specimens as well as an increase in the spectrum of prostatic diseases that have to be differentiated. In the past few years, various diagnostic methods have been added to the clinical routine: determination of serum prostate specific antigen (PSA), transrectal ultrasound and the ultrasound guided systematic high-speed punch biopsy technique. Suspicious lesions can now be detected very early and are clarified by an increasing number of prostate biopsies.

Prostatic intraepithelial neoplasia

The most decisive recent addition to the diagnostic spectrum has taken place by morphological definition of the preneoplasia "prostatic intraepithelial neoplasia" (PIN). PIN has to be regarded as the most important precursor of carcinoma, especially of high-grade carcinomas, preceding carcinoma by at least 10 years (1,2). In a very high proportion PIN and carcinoma are detected simultaneously. Therefore the diagnosis of isolated PIN without carcinoma should force the urologist to follow the patient up closely by means of serum PSA controls and repeated punch biopsies.

Atypical adenomatous hyperplasia Atypical small acinar proliferations

In recent years, the large group of atypical microglandular proliferations, which is often difficult to differentiate clearly from adenocarcinoma, has been further characterized by the definition of two additional diagnostic entities: atypical adenomatous hyperplasia (AAH) of the anterocentral zone and atypical small acinar proliferations (ASAP) which is encountered mainly in the peripheral zone of the prostate (2-6). Their role as putative precursors of carcinoma are still under debate.

Routine

The impact of these clinical and histopathological innovations on daily routine pathology is analyzed in two ways: i) By analyzing the proportion of the most common groups of prostatic diseases (benign prostatic hyperplasia, prostatitis, preneoplasia, and carcinoma) spanning a period of 8 years. For this purpose we studied our complete routine material of prostatic specimens from the years 1991, 1993, 1995, 1997 and 1998. ii) Problems for the pathologist in dif-

ferential diagnosis of the different prostatic diseases are evaluated by analysis of the uropathological consultation service, which has been increasingly used at the Institute of Pathology, Singen, since 1989.

The number of prostatic specimens sent in for histological analysis increased from 1,026 in 1991 to 3,367 in 1998. This increase is mainly explained by an enormous increase in the number of biopsy cases, from 593 in 1991 to 2,491 in 1998, representing 58% of the complete prostatic material in 1991 and 74% in 1998. Most noticeable was the increase in the number of carcinomas diagnosed. Their number increased from 259 in 1991 to 1,316 in 1998, with an increase in the proportion of high-grade carcinomas from 59.1-70.4% of all carcinomas. Furthermore, we noticed a 14-fold increase in the number of PIN. The high-grade PIN lesions were combined with carcinoma in 30.3% of the cases with a predominance of high-grade carcinoma in 20.1%. There was a twofold increase in the diagnosis of AAH. In 13.8% AAH was combined with carcinoma, mostly with low-grade carcinoma (10.7%)

Consultation

Analysis of diagnostic problems was carried out in the consultation service for pathologists. Between 1989 and 1998, 2,333 prostatic specimens were sent in for consultation, mainly due to uncertainties in the diagnosis of carcinomas, especially low grade carcinomas. The following problems were most commonly discussed: i) differentiation of sclerosing adenosis from well-differentiated adenocarcinoma; ii) principal difficulties in differentiation of AAH from PIN; iii) differentiation of AAH from well-differentiated adenocarcinoma; iv) differentiation of high-grade PIN and cribriform high-grade carcinoma; v) difficulties in differentiation of low- and high-grade carcinomas, especially in the intermediary zone between Gleason grade 3+3=6 and Gleason grade 3+4=7 carcinomas; and vi) in 1998, differentiation of ASAP from low-grade carcinoma represented a major problem in 21% of the consultation cases.

Conclusion

In conclusion, we have noticed a massive increase in the frequency of prostate biopsies during the last 8 years. Within the histological diagnostic spectrum, there is a shift to PIN and high-grade carcinoma. The number and percentages of cases with benign prostatic hyperplasia and prostatitis are almost unchanged.

As a consequence of these recent improvements in the diagnosis of prostatic diseases, pathologists are confronted with problems in differential diagnosis, which are mainly concentrated on the diagnosis and differential diagnosis of low-grade carcinoma. In 1998, the newly introduced diagnostic entity of ASAP represented quite an important differential diagnosis. In a strikingly high number of these atypical small acinar lesions, suspicious but not diagnostic for carcinoma, especially in those with distinct cytological atypias, an association with carcinoma of the prostate exists. Therefore, as in the case of high-grade PIN, patients with the diagnosis of ASAP without the evidence of carcinoma should be controlled by future biopsies.

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Morphogenetic concepts of normal and abnormal growth in the human prostate

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Benign prostatic hyperplasia and prostate cancer are multifactorial disease processes, involving a growing number of biochemical, genetic and epigenetic factors. The present review focuses on current morphogenetic factors implicated in normal and abnormal growth in the human prostate.

Benign prostatic growth

The cellular diversity of basic cell types making up the prostatic epithelium (secretory luminal cells, basal cells and endocrine-paracrine cells) suggests the existence of pluripotent stem cells, presumably located in the basal cell layer. This concept derives from a series of biological properties of basal cells, including: i) their differentiation potency to give rise to secretory luminal and endocrine cells; ii) their proliferative function in normal and hyperplastic conditions; iii) their androgen independence; and iv) their ability to respond to circulating androgens, which is required for the differentiation process to secretory luminal cells (1, 2). Currently, two functional compartments can be defined within the prostatic epithelial cell system. The proliferation compartment is androgen independent and consists of basal cells. The secretory epithelium constitutes the differentiation compartment, which is androgen dependent but which has a limited proliferative capacity (2). The growth rate within the proliferation compartment is regulated by a network of growth factor receptors (e.g., EGF-R, p185^{Srbu}, p180^{e-3}) and Bcl-2, preventing basal cells from androgen dependent programmed cell death (1). Differentiation processes within the prostatic epithelial cell system involve a delicate balance between circulating androgens and estrogens. The phenotypic change from basal cells to secretory luminal cells is triggered by androgens, while estrogens block this process, leading to basal cell hyperplasia (1). The age-related decrease of androgens in the aging male, together with stromal derived growth

factors may increase androgen gene expression in the basal cell layer (proliferation compartment), making basal cells more sensitive to the low levels of bioavailable androgens. This hormonal imbalance results in glandular hyperplasia by accelerating the differentiation process from basal cells to secretory luminal cells (1, 2).

Premalignant lesions

High-grade prostatic intraepithelial neoplasia (HGPIN) is considered to be the most likely precursor of peripheral zone cancer (3). This premalignant condition reflects severe proliferation and differentiation disorders within the prostatic epithelial cell system. The basal cell layer loses its proliferation function, whereas secretory luminal (dysplastic) cells acquire increased proliferative activity (1). These premalignant proliferation disorders are associated with aberrant expression of growth factor receptors (p185^{erbB-2}, p180^{erbB-3},

c-met) and tumor suppressor genes (nm23 Hi) restricted to basal cells in normal and hyperplastic conditions (1). In addition, the apoptosis suppressing Bcl-2 oncoprotein is overexpressed in approximately 20% of HGPIN, which is associated with markedly decreased levels of the nuclear androgen receptor in the dysplastic epithelium (1). This abnormal Bcl-2 process induces severe differentiation disorders by protecting the differentiation compartment from apoptotic cell death. The resulting increased life span of the transformed cells, together with the high proliferation rate, provides an environment in which genetic instability can occur. The most common numerical alterations detected in HGPIN so far include the loss of 8p, 10q, 16q, 18q and the gain of chromosomes 8q and 7, indicating that genes on these chromosomes may play a role in early phases of prostatic cancerogenesis (4). While virtually all phenotype and genotype data support the premalignant nature of HOPIN, the role of atypical adenomatous hyperplasia as a precursor of transition zone cancer is less well established. In particular, the morphogenesis of small acinar adenocarcinoma remains poorly understood (5).

Pathogenesis of stromal invasion

Adhesive interactions in premalignant lesions do not differ significantly from those encountered in benign prostate tissue. Dramatic changes occur during early stromal invasion when the transformed epithelium loses basal cell differentiation (6). This process is associated with the loss of a number of hemidesmosome-forming proteins and associated adhesive molecules, including collagen VII, 33 and $\gamma 2$ subchains of laminin 5, and $\alpha 6 \beta 3$ integrins. Being retained in benign acini and HOPIN, it is quite clear that the loss of these hemidesmosome-forming proteins represents a key step in the progression of HGPIN to early invasive cancer. It is well established that common prostatic adenocarcinoma produces newly formed basement membranes to invade the host tissue (6). Invasive tumor cells are separated from the stroma by distinct periacinar and pericellular basement membrane and express associated integrins that mediate attachment to these basement membrane-like matrices. This particular tumor-host relation is maintained through the various stages of the disease, including high-grade lesions, metastases and therapy-induced changes. Recent *in situ* hybridization analysis also suggests that the basement membrane-forming process increases with tumor progression. Neoplastic basement membrane differ from their normal counterparts in their differential susceptibility to pepsin treatment, and lack hemidesmosome-associated laminin 5, collagen VII and type IV collagen $\alpha 5$ and $\alpha 6$ chains. Their functional significance for the process of stromal invasion has also been demon-