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Frequencies of different nuclear morphological features in prostate adenocarcinoma

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Abstract Diagnosis of prostate adenocarcinoma is primarily based on morphological analysis. Nucleomegaly, prominent nucleoli, and hyperchromasia constitute current nuclear diagnostic parameters but are seen in benign conditions, vary with Gleason grade, and pose diagnostic challenge in well-differentiated tumors with accompanying inflammation or equivocal architectural features. In such cases, other pleomorphic nuclear features such as variation in size and shape, irregular contours, nuclear membrane infoldings, and nonuniform chromatin, which are not incorporated in formal evaluation, may prove helpful. Our aim was to study different nuclear morphological features of prostate adenocarcinoma (including currently practiced ones) and highlight their variation with Gleason grades. We examined 84 cases of prostate adenocarcinoma using oil immersion microscopy where necessary. Commonest Gleason pattern observed was grade 4a accounting for 42.8% of cases. Nuclear enlargement (moderate to marked in 93.8%), nucleolar enlargement (62.1%), and nonuniform chromatin distribution (100%) could serve as useful diagnostic features but did not vary with tumor differentiation. Pleomorphism (moderate in 58.6%), nuclear overlapping (62.8%), nuclear membrane infoldings (66.2%), and irregular contours (frequent in 94.5%) were significant diagnostic features that increased in frequency and extent with increasing grade and could be used to differentiate low-grade from high-grade tumors. Worsening of nuclear morphology with advancing tumor grades indicated that nuclear anaplasia accompanies poor architectural differentiation. Coexistence of pale and dark nuclei signified variable chromatin density of no diagnostic significance.

Keywords: Prostate adenocarcinoma; Nuclear morphology; Gleason grades

1. Introduction

Prostate carcinoma is the second most common malignant tumor and sixth leading cause of cancer-related deaths in males, accounting for 903 500 new cases and 258 400 deaths in 2008 [1]. Despite recent advances in molecular genetics, light microscopic evaluation of architectural and cytologic features on needle biopsy remains the gold standard for diagnosis of prostate adenocarcinoma [2-5]. However, approximately 18% to 28% [6-9] of clinically significant cancers are missed on primary biopsy, and to overcome this problem, efforts have always been made to study ongoing morphological changes and devise ancillary techniques that could help in early detection of prostate carcinoma, differentiate it from benign mimics, and predict its biologic behavior.

Nuclei have been center of research for decades. Nuclear atypia of malignancy is morphological expression of ongoing genetic and epigenetic changes in carcinogenesis [10-13]. Most of the published textbooks and journal articles describe nuclear atypia of prostate adenocarcinoma in terms of prominent nucleoli, nucleomegaly, and hyperchromasia [2-5,8]. Although regarded as significant diagnostic features [2-5,8], these are nonspecific and often seen in many benign conditions such as atrophy, basal cell hyperplasia, and in reactive atypia caused by acute or chronic prostatitis, infarction, and irradiation [8,9,14]. In addition, appearance of nucleoli, nuclear size, and chromasia are often influenced

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by differences in fixation, processing, section thickness, and staining [3,4,8,15]. Diagnosing carcinoma alone on these features is an extremely difficult task especially when architectural features are equivocal or difficult to assess because of scanty tissue in small biopsy specimens. In such cases, analysis of additional features such as variation in nuclear size and shape, irregular nuclear contours with indentations, undulations and folds of nuclear membrane, nonuniform chromatin texture, as well as changes in size, shape, and number of nucleoli, which are of great value in diagnostic evaluation of other tumors [16-20], are likely to help. Because prostate carcinoma shows variable degrees of differentiation, another concern is variation of nuclear morphology in different tumor grades. Many researchers have studied changes in nuclear size, shape, contours, chromatin, nuclear cytoplasmic ratio, and nucleoli and found significant changes in different Gleason grades, but most of them used morphometry, [21-30], which is difficult to use in routine practice because of complexity of image analysis. Some articles address morphological changes but consider only few characteristics such as variation in nuclear size, shape, chromatin distribution, and nucleoli [9,31,32].

Our aim was to determine frequencies of different nuclear morphological features in prostate adenocarcinoma and highlight their variation with different Gleason grades. This knowledge will be extremely useful in the evaluation of low-grade tumors, tumors with equivocal architectural features, presence of confounding factors such as inflammatory atypia, and in very small biopsies and cytology preparations devoid of sufficient architectural details.

2. Material and methods

This study was done at the Department of Histopathology, Pakistan Institute of Medical Sciences, after approval by regional research and training monitoring cell. From September 2010 to February 2011, 84 cases of prostate adenocarcinoma were selected by nonprobability consecutive sampling. These included 9 needle biopsies, 64 transurethral resections, and 11 prostatectomy specimens. Patients receiving radiotherapy, hormones, or chemotherapy were excluded from the study to avoid confusion with radiation and drug-induced atypia. Each case was subcategorized into primary, secondary, and tertiary Gleason grades (where applicable). To reduce statistical errors, each tumor with similar primary and secondary grades was analyzed as single case. Hematoxylin and eosin–stained sections with a thickness of 3 to 5 μm were first examined at low (×100) and high (×400) powers and then at oil immersion microscopy (×1000). Analysis of nuclear enlargement, pleomorphism (variation in nuclear size and shape), nuclear overlapping, prominent nucleoli, chromatin appearance, chromatin distribution pattern, nuclear membrane infoldings and thickening, and nuclear contours was done in comparison with benign glands in the specimens to reduce variability caused by differences in fixation, section thickness, and staining. Nucleomegaly and pleomorphism were subcategorized as mild, moderate, or marked; nuclear overlapping and membrane infoldings as absent, focal, or frequent; nuclear contours as uniform or nonuniform; and chromatin appearance as (1) light or pale (hypochromatic and vesicular), (2) dark (dense hyperchromatic and coarse chromatin), or (3) a combination of these. Nucleoli were designated as “prominent nucleoli” when seen easily on low power and as “visible nucleoli” when seen on high power. Statistical analysis was done using SPSS package program (version 17; SPSS Inc, Chicago, IL, USA).

3. Results

Mean age was 71.1 ± 10.6 years with an age range of 51 to 101 years. Commonest Gleason pattern observed was grade 4a accounting for 42.8% of cases. Nucleomegaly, pleomorphism, nonuniform chromatin distribution, and irregular nuclear contours were constant features in all cases, but their degree varied with Gleason grades. Normal prostate acinar cell nuclei were small, roughly equal to, or slightly larger than a small lymphocyte nucleus or a mature red blood cell. Nuclei were round or slightly angulated with regular contours, uniform dark chromatin, and occasionally observed tiny nucleoli. In prostate carcinoma, nuclei were 2 or more times enlarged. Largest nuclei seen were even greater than nuclei of vascular smooth muscle cells (Fig. 1). Nuclear enlargement and pleomorphism of mild to moderate degree were seen in grade 1 and 2 tumors and of mild to marked degree with bizarre nuclei in grade 3 to 5 tumors. An exception was grade 4b tumors that showed hyperchromatic mildly enlarged nuclei with minimal pleomorphism but irregular borders (Figs. 2 and 3). Tumors of all grades showed irregularly distributed chromatin with alternating areas of clearing, dense condensation with prominent chromocenters and vacuoles or bubbles. Contours were irregular with bumps and indentations. However, this feature was more pronounced in nuclei depicting hyperchromasia or coarse chromatin. Nuclear overlapping was observed in 91 (62.8%) cases, most of which belonged to grade 3 to 5 category. Nuclear membranes were irregularly thickened showing infoldings in 96 (66.2%) cases (Fig. 4). Both low- and high-grade tumors showed prominent nucleoli, which in many cases were multiple, eosinophilic, and often marginated (Fig. 5). Of the cases, 67.6% showed a combination of 2 types of nuclei (Fig. 6); one type, “light or pale nuclei,” had markedly enlarged round to ovoid nuclei showing minimal pleomorphism, vesicular irregularly distributed chromatin, large prominent and often multiple eosinophilic nucleoli, irregularly thickened nuclear membrane, irregular contours, and nuclear overlapping. Because of vesicular chromatin, these nuclei appeared pale with prominent eosinophilic nucleoli and fulfilled the commonly designated term *prostate carcinoma looks back at you*. These were observed in both low- and high-grade tumors. The other type of nuclei