MORPHOMETRIC STUDY OF SCLEROSING ADENOSIS-A LESION THAT MIMICS PROSTATE ADENOCARCINOMA

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Abstract: *Adenocarcinoma of the prostate is the most common malignant neoplasm of the organ, which, from architectural point of view, is represented by small, large, fused glands and solid type. A common problem of differential diagnosis of small glands adenocarcinoma is represented by sclerosing adenosis, a pseudoneplasic lesion. Differentiation of these two entities is based, in addition to architectural and immunohistochemical features, on the nuclear changes in prostatic epithelial cells. In this study we aimed to assess nuclear morphometric features of epithelial cells in sclerosing adenosis (33 cases) compared with cases diagnosed with Gleason grade 1 and 2 adenocarcinoma (69 cases). Parameters evaluated were represented by the nuclear area, perimeter, maximum diameter, minimum diameter, mean diameter and elongation. Morphometric analysis revealed significantly higher values of nuclear parameters in adenocarcinomas compared with sclerosing adenosis cases (p <0.05). In conclusion, nuclear morphometry, proved useful in the discrimination of the two histopathological entities.*

INTRODUCTION

Sclerosing adenosis is an uncommon pseudoneoplasic lesion composed of small crowded glands in a dense fusiform stroma, continuous basal cell layer but difficult to appreciate with the routine staining and distinct immunohistochemical profile. It was first described in 1987 by Young and Clement as prostatic proliferative lesions similar to the histopathological entity described in the mammary gland.(1) Sclerosing adenosis is a less frequent histopathological entity, usually located in the transitional zone. The lesion is occasionally diagnosed on the prostate transurethral resection fragments and extremely rare on biopsy, due to location.(2) This benign lesion does not require specific treatment and aggressive therapy for a false positive diagnosis of cancer would have damaging consequences for the patient. Low grade prostate adenocarcinoma is represented by Gleason grade 1 or 2 malignant neoplasic proliferation of cancer acinar, characterized microscopically by small crowded glands architecture, large nuclei, prominent nucleoli and absence of basal cell layer. Gleason grade 1 adenocarcinoma of the prostate gland consists of small-medium glands of uniform appearance and minimal stromal invasion while adenocarcinoma Gleason grade 2 shows infiltrative margins and slight variability in gland size compared to the first grade.(3,4)

From morphological point of view, the cell nucleus is a complex structure with compartmenting characteristic having the role in maintaining cell functions.(5,6,7,8) Cancerous cell is characterized by changes of nuclear parameters, consisting in increasing nuclear volume, increase the number of the nucleoli, shape and chromatin modification, heterochromatin organisation with growth nucleo-cytoplasmic ratio. One of the quantitative nuclear parameters methods of study is nuclear morphometry with preoperative predictive and prognostic role, not only in prostate cancer but also in other cancers.(9,10,11,12,13)

PURPOSE

The aim of this study is to assess nuclear morphometric features of epithelial cells in sclerosing adenosis (33 cases) compared with cases diagnosed with Gleason grade 1 and 2 prostatic adenocarcinoma (69 cases).

MATERIALS AND METHODS

Morphometric study was performed over a period of four years and included two groups of patients. The first was composed of 33 cases of sclerosing adenosis of the prostate (aged between 63 and 84 years) and the second of 69 cases of prostatic adenocarcinoma with 1 and 2 Gleason grade (aged 52 and 86).

There has been studied prostatic tissue excised by transurethral resection of the prostate. Histopathology exam and nuclear measurements were performed in the Clinical Service of Pathology, Saint Apostle Andrew Emergency County Hospital of Constanța. Tissue fragments were fixed in 10% formalin, included in paraffin, sectioned and stained with hematoxylin-eosin.

For a detailed evaluation as epithelial component, we used the semiautomatic morphometry method. For this purpose, we used Hematoxylin-eosin stained microscopic preparations. Measurements were taken using Nikon microscope equipped with digital camera Nikon image pickup DN 100 pixel resolution of 1280 to 1024, connected to the computer morphometry program Lucia Imaging Laboratory Net - Net Eclipse Software. For each case we measured 100 nuclei, 10 nuclei by 10 different fields. Nuclear contour was traced at a magnification of 400 Previously, the software was calibrated for the goal that has been used. Unit of measurement was μm.

Values thus obtained were registered by the computer program into tables with calculating the average and standard deviation for each parameter. The following parameters were assessed: nuclear area (NA) in μm2 and standard deviation (dst. NA), nuclear perimeter P (μm) and standard deviation (dst. P), elongation factor and the standard deviation (E and dst. E), average diameter (DEQ), maximum diameter (Dmax) and standard deviation (dst. Dmax), minin diameter (Dmin) and standard deviation of the minimum diameter (Dmin dst).

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Statistical analysis of data was performed using Microsoft Office Excel 2007 and statistical software MedCalc for Windows healthcare. For data processing we used student test (t-test). Results were considered statistically significant at a p value <0.05. In order to establish correlations between morphometric parameters, we determined the Pearson correlation coefficient (r), which falls within the range (-1, +1). Values close to ± 1 show a strong correlation (strong), while values close to 0 reflect a weak correlation.

RESULTS

In terms of histopathology, Gleason grade 1 adenocarcinoma cases were represented by a proliferation of crowded glands, small size, the absence of basal cells and intraluminal crystalloids arranged in a well defined node. Gleason grade 2 adenocarcinomas were composed of a cluster of small glands and stroma environments absent or minimal between them, absent basal cell arranged as a node with infiltrative margins. The absence of basal cells has been demonstrated, in difficult cases, with anti-high molecular weight cytokeratin 34βE12.

Table no. 1. Morphometric values of nuclei of epithelial cells in sclerosing adenosis

Nuclei of sclerosing adenosis group	NA (μm²)	Deq (μm)	Dmax (μm)	Dmin (μm)	E	P (μm)
Minimum value	32,14	6,4	7,61	5,7	1,33	18,97
Maximum value	69,5	8,79	10,14	7,61	1,31	26,8
Mean value	48,39	7,78	9,06	6,81	1,31	23,83
Standard deviation	9,23	0,71	0,94	0,7	0,11	2,38

Table no. 2. Morphometric values of nuclei in small gland adenocarcinomas

Nuclei of adenocarcinoma group	NA (μm²)	Deq (μm)	Dmax (μm)	Dmin (μm)	E	P(μm)
Minimum value	49,88	7,97	8,24	6,71	1,06	24,27
Maximum value	138,48	13,23	15,31	11,54	1,57	41,6
Mean value	70,46	9,38	10,98	8,16	1,38	28,97
Standard deviation	16,85	1,06	1,34	0,98	0,12	3,33

Table no. 3. Comparison of nuclear parameters between adenocarcinoma with the small glands and sclerosing adenosis

Morphometric parameter	Type of lesion		t-test
	Small glands adenocarcinoma	Sclerosing adenosis	p value
Mean value of nuclear area (μm²)	70,46	48,39	p<0,0001
Mean value of mean diameter (μm)	9,38	7,78	p<0,0001
Mean value of maximim diameter (μm)	10,98	9,06	p<0,0001
Mean value of minimum diameter (μm)	8,16	6,81	p<0,0001
Mean value of elongation	1,38	1,31	p=0,0077
Mean value of perimeter (μm)	28,97	23,83	p<0,0001

Sclerosing adenosis cases were represented by a proliferation of small and medium sized glands with basal cell layer of continuous or inaparent sometimes arranged as a relatively well-circumscribed nodule or slightly infiltrative edges. Glands are arranged in a fusiform stroma and in some cases are surrounded by a characteristic hyaline halo, features regarded useful in making differential diagnosis according to the literature.(14)

Cells showed clear or slightly eosinophilic cytoplasm and nuclei were apparently benign appearance. Following nuclear quantitative measurements of adenocarcinoma cases we obtained the results summarized in table no. 1. Values of nuclear morphometric analysis in sclerosing adenosis cases were highlighted in table no. 2.

DISCUSSIONS

In prostatic pathology, a major problem of differential diagnosis of sclerosing adenosis of the prostate is with low-grade adenocarcinomas, and in difficult cases there are required special techniques to distinguish the morphological entities.

In prostate adenocarcinomas, the nuclear size ranged from values of NA appropriate to benign lesions (49.88 μm²) to the hyperchromic and increased volume (up to 138.48), with an average of 70.46. This feature showed a high degree of nuclear polymorphism. This has been seen in other studies, according to which pleomorphism is characteristic of high-grade tumors.(15) Among the parameters evaluated, nuclear area predicts survival and is part of no. 3 group of survival factors.(8) Lower values of the parameters obtained Aragona in 1989, when used as predictors for well-differentiated adenocarcinomas, values greater than 28 μm² for NA, average diameter of 5 mm, and the presence of more than 5% of the cell diameter greater than 6.16 μm.(16)

There is no consensus regarding the standard values for the parameters evaluated nuclear prostatic lesions. The variability of the published data can be explained by the fact that the prostate is a heterogeneous organ histological, and studies compared different regions with different morphological features.(17,18) In his study, Buhmeida (2000) calculated that the nuclear areas are defining in differentiating atypical lesions on biopsy. According to this study, benign lesions are characterized by a nuclear area of less than 27 μm², values over 39 μm² betray the possible existence of malignant cells and the values in malignant neoplasia exceed 52 μm².(19) The values obtained are smaller than that obtained in the present study, however, different pieces of the study, represented by biopsy, which is a very small amount of tissue. Similar values for nuclear area adenocarcinomas were obtained from Jose D. Debes et al in 2005, but this study had a minimum diameter smaller value.(20)

Following the determination of correlations between parameters evaluated to small gland adenocarcinomas, we found that there is a strong correlation between NA with P (r = 0.9903, p <0.0001), NAwith Deq (r = 0.9965, p <0.0001), NA with Dmax (r = 0.9228, p <0.0001), NA with Dmin (r = 0.9186, p <0.0001).

Elongation did not correlate with the nuclear area of adenocarcinomas (R = 0.09370, p = 0.4438). My results are similar to those found by Wang in 1992, in which the elongation factor is not significantly different between benign and malignant lesions, while all other parameters are useful in discriminating the two types of lesions.(21)

Elongation factor (E) is an invariant shape descriptor size form factor reflecting the shape of nuclei and for nuclei of round shape is 1. Its value increases for the ellipsoidal shape of the nucleus. The value is represented by the ratio Dmax / Dmin and is associated with nuclear irregularity index. It has proven prognostic significance in several studies conducted since 1982 by Diamond et al (22) until Epstein et al in 1994.(23)

The evaluation of nuclei of the epithelial cells of the glandular component 33 cases of sclerosing adenosis, we obtain a value of the nuclear area ranging from 32.14 to 69.5 with an

average of 48.39. Calculation of Pearson correlation coefficient, revealed a strong correlation between NA and P ($r = 0.9383$, $p < 0.0001$), NA and Deq ($r = 0.9848$, $p < 0.0001$), NA and Dmax ($r = 0.8489$, $p < 0.0001$), NA and Dmin ($r = 0.7375$, $p < 0.0001$). The only factor that did not correlate with the nuclear area was elongation ($r = 0.07236$, $p = 0.6890$). My results are similar to those found by Wang in 1992, the elongation factor was not significantly different between benign and malignant lesions, while all other parameters are useful in discriminating the two types of lesions.(21) Another study with the similar results on elongation factor was conducted by Taboga et al. in 2003.(24)

Application of student test (t-test) showed that between nuclear parameters of sclerosing adenosis and adenocarcinoma with the small glands the differences are statistically significant ($p < 0.05$) as shown in table no. 3.

In this sense, the quantitative morphometric method is useful in differential diagnosis of the lesion simulating an adenocarcinoma with malignant neoplasia. Although sclerosing adenosis is a lesion that mimics the architecture of an acinar adenocarcinoma, an important criterion in differentiating of the two diseases is the lack of nuclear atypia.(25,26) According to the literature, in sclerosing adenosis mild atypia has been described.(1) Currently, such cases are classified as atypical sclerosing adenosis, such as the study of Cheng in 2010.(27)

CONCLUSIONS

Nuclear parameters recorded higher values in cases diagnosed with adenocarcinoma. Also, between the parameters, nuclear area was correlated with other factors, except elongation. In conclusion, nuclear morphometry, with histopathological study on common stains, proved useful in the discrimination of the two histopathological entities, some of them with prognostic significance.

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