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Original contribution

Prostatic atrophy: its spatial proximity to carcinoma and intraepithelial neoplasia based on annotation of digital slides☆,☆☆

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Summary Whether atrophy is a precursor to high-grade prostatic intraepithelial neoplasia (HGPIN) and cancer is controversial. A virtual slide set comprising 48 prostatectomy cases was used to investigate associations among the amounts and spacing of these entities. Foci of atrophy without inflammation (A), atrophy with inflammation (AI), cancer (by patterns), and HGPIN were digitally annotated. Atrophy's proximity to cancer and HGPIN was assessed with two measurements: abutment (touching) or nearness (≤2 μm without touching). Area sums per specimen were computed for A, AI, cancer, and HGPIN. Abutment rates of AI and A foci to cancer were 23% versus 21% (p = NS); for nearness, 29% of AI foci were near to cancer versus 12% of A ($P = .0001$). Abutment or nearness of A and AI to HGPIN were in the 1.4% to 2.4% range. When A, AI, or HGPIN abutted cancer, it was disproportionately to Gleason grade 3 cancer foci even after adjusting for the lesser frequency of higher-grade cancer foci. Area sums of A, AI, or (A + AI) per specimen showed no correlations with those of HGPIN, and mostly negative ones with area sum and with tumor volume of cancer. In conclusion, atrophy with inflammation showed some preferential spatial association to cancer, although area sums of atrophy with or without inflammation correlated negatively with those of cancer. These divergent spatial associations suggest that atrophy and inflammation in biopsy specimens may have clinical relevance. The frequency of inflammatory atrophy (AI) merging with HGPIN was far less than reported previously, weakening the theory that AI gives rise to HGPIN.

1. Introduction

Atrophy of the prostatic secretory layer of epithelium is the most ubiquitous microscopic finding in the adult prostate, noted in up to 94% of biopsy cases [1], and classifiable into 4 subtypes with good agreement among pathologists [2]. Controversy has arisen regarding the causative relationships

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between atrophy and high-grade prostatic intraepithelial neoplasia (HGPIN) and between atrophy and invasive cancer. An additional category of atrophy with inflammation and increased proliferation, called proliferative inflammatory atrophy (PIA) has been posited as a precursor to HGPIN or cancer [3]. In 2000, Putzi and De Marzo, in a small series of 14 radical prostatectomy cases, found that 42.5% of HGPIN lesions merged with PIA, whereas cancer did not merge with PIA [4]. Other studies by Billis et al using prostatectomy [5–7] or needle biopsy [8] tissue have asserted that atrophy [6] or inflammatory atrophy [5,7,8] lack a topographic relation to cancer [8] or to both HGPIN and cancer [5–7]. To determine whether these entities share topographic relationships, we used a series of virtual radical prostatectomy slides to annotate and measure digitally the proximity of foci of atrophy, HGPIN, and cancer. This novel approach allows more precise measurements than in prior studies using ink pen and point count [5–7].

2. Materials and methods

2.1. Study group

The source for this study was a virtual slide set comprising 48 prostatectomy cases that we used previously [9,10] from the University of Colorado Denver Hospital. Those papers were paired case-control studies comprising equal numbers of men with prostate-specific antigen (PSA) failure (defined as a rise to 0.2 ng/mL or more) and without failure. Exclusion criteria were a history of receiving cryotherapy, radiotherapy, or androgen deprivation before failure, or a predominant Gleason grade of 5. All men had postoperative drops in PSA levels to undetectable. Most had Gleason score 7 cancer, with >95% in the 6-8 range, the range in which outcome varies the most.

2.2. Digital assessment

Prostates were completely sampled at 4- to 6-mm intervals at all contributing sites. Patients' entire whole-mount slide sets were re-reviewed. Those slides containing cancer (average ± SD per case, 8.0 ± 4.3) were digitally scanned as virtual slides using a ScanScope XT (Aperio Technologies, Vista, CA). We previously [9] used ImageScope software (Aperio) to annotate all foci of 9 histologic patterns in a non-overlapping manner, using a different color for each pattern. For the purpose of this analysis, the patterns were grouped according to International Society of Urologic Pathology (2005) criteria [11]. Gleason grade 3 comprised all single, separate small acini, medium single acini with open undulated or stellate lumens, and mucinous (colloid) carcinoma without fused acini. Grade 4 comprised fused, ragged small acini (in rare cases, with mucinous stroma), (micro)papillary ones consisting of medium to large spaces with stromal cores or cells bridging across the acinus, and cribriform cancer. Grade 5 comprised individual infiltrating or sheet-like cells lacking lumen formation.

Three different colors were used to annotate atrophy without inflammation (designated "A," of all subtypes [2]), atrophy with inflammation (AI, consistent with proliferative inflammatory atrophy), and HGPIN. The frequency of abutment of these three types of area to the 3 grades of cancer was recorded. When these three features did not abut cancer, the distances between them and the cancer were measured using Aperio ImageScope's Scale Axes/Grid function. Nearness was defined as encircled areas whose outlines were ≤2 μm of each other without touching. Foci that were further apart were excluded from these two categories but were accounted for by the area sum: defined as the sum of all annotated areas of a given type (cancer grade 3, grade 4, grade 5, A, AI, HGPIN), for the whole specimen. The frequencies of abutment and nearness of atrophy without inflammation to HGPIN, and of atrophy with inflammation to HGPIN, were also assessed.

2.3. Statistical analyses

Data on total tumor volume, serum PSA, and gland volume were log-transformed, and the Pearson test was used to assess correlation with annotated area sums. Area sums of annotated foci were not normally distributed, so the Spearman correlation coefficients were used. For the ordinal variables of stage and Gleason score, Spearman correlation coefficients were used. For proximity of annotated areas to other annotated areas, the percentage of these foci abutting (or, near without touching) others was tested by χ^2 test or Fisher exact test when zero values were present. Statistical significance was set at $P < .05$.

3. Results

The mean percentage of prostatic tissue with both types of atrophy was 59.2 ± 27.0% (range 7.4%-96.4%). Among 230 slides, a total of 1163 foci of atrophy without inflammation (A), 402 of atrophy with inflammation (AI), and 363 of HGPIN were observed.

Table 1 shows the frequency of abutment or nearness of foci of A and AI, to cancer or HGPIN, and the frequency of HGPIN's abutment or nearness to cancer. AI did not abut cancer more frequently than A did (23% vs 21%, $P = .31$) but nearness (≤2 μm) of AI to cancer was more frequent than nearness of A to cancer (29% vs 12%, $P = .0001$). HGPIN foci abutted cancer in 75% of foci, far exceeding atrophy's abutment to cancer. Abutment or nearness of HGPIN to A or AI were all very low, ranging from 1.4% to 2.4% of atrophic foci. Of 363 HGPIN foci, 8 (2.2%) abutted inflammatory atrophy and 6 (1.7%) were near inflammatory atrophy.