Diffuse Adenosis of the Peripheral Zone in Prostate Needle Biopsy and Prostatectomy Specimens

Tamara L. Lotan, MD and Jonathan I. Epstein, MD*† ‡*

Abstract: We have observed a group of typically younger patients with multiple foci of small, nonlobular, crowded, but relatively bland acini on needle biopsy and in prostatectomy specimens. It is unclear whether this architectural pattern, which we have termed diffuse adenosis of the peripheral zone (DAPZ), is simply a crowded glandular variant of normal prostate morphology or whether it represents a risk factor for the development of prostatic carcinoma. We studied 60 cases of DAPZ on needle biopsy in our consult practice from 2001 to 2007. Cases, on average, showed 72% of cores involved by DAPZ. Average patient age was 49 years (range: 34 to 73) and the average prostate specific antigen (PSA) level at the time of biopsy was 5.2 ng/mL (n = 42). Forty-three (72%) men had available clinical follow-up with 35 (81%) patients undergoing rebiopsy and 8 (19%) followed with serial PSA measurements. Patients who were rebiopsied after DAPZ diagnosis had higher PSA levels than those who were followed by PSA levels alone (6.2 vs. 3.1 ng/mL, $P = 0.04$). Of the rebiopsied cases, 20 (57%) were subsequently diagnosed with carcinoma, with an average of 15 months elapsed between initial biopsy and carcinoma diagnosis. Although the majority of tissue sampled in a typical DAPZ case had no cytologic atypia, in 65% of cases there were admixed rare foci of atypical glands with prominent nucleoli comprising $< 1\%$ of submitted tissue. Patients with a subsequent diagnosis of carcinoma were more likely to have had DAPZ with focal atypia, although this did not reach statistical significance (70% vs. 36%, $P = 0.08$). We histologically confirmed the carcinoma diagnosis in 18/20 cases. In 12/14 radical prostatectomies, we were able to review the slides. Eleven had Gleason score $3+3=6$ adenocarcinoma in addition to background DAPZ; 9 showed peripheral zone organ-confined cancer, and 2 had focal extraprostatic extension. In one case of DAPZ misdiagnosed as cancer on biopsy, no carcinoma was found at prostatectomy. DAPZ is a newly described and diagnostically challenging mimicker of prostate cancer seen in prostate needle biopsies from typically younger patients. Our findings suggest that DAPZ should be considered a risk factor for prostate cancer and that patients with this finding should be followed closely and rebiopsied.

From the Departments of *Pathology; †Urology; and ‡Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD.

Correspondence: Jonathan I. Epstein, MD, Department of Pathology, 401 N. Broadway St, Rm 2242, The Johns Hopkins Hospital, Baltimore, MD 21231 (e-mail: jepstein@jhmi.edu).

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Although current American Cancer Society guidelines recommend prostate cancer screening begin at age 50, prostate specific antigen (PSA) screening may begin as early as age 40 in African-Americans and men with a strong family history.[15] Young men also are biopsied as a result of increased serum PSA levels or an abnormal digital rectal examination discovered when they are worked up by urologists for other urologic symptoms. Consequently, in our consult practice we are seeing increasing numbers of needle biopsies in younger men, where the spectrum of benign and atypical acinar proliferative lesions and the risk of cancer associated with these lesions is less well-described.[9,13,14]

Recently, we have observed a group of typically younger patients with multiple foci of small, nonlobular, crowded, but relatively cytologically bland acini on needle biopsy and prostatectomy specimens. In contrast to usual adenosis, these foci are widespread, seen predominantly in the peripheral zone, and arranged in a nonlobular distribution. In contrast to prostatic adenocarcinoma or atypical glands suspicious for carcinoma, the vast majority of these foci display little-to-no cytologic atypia. Informally, we have referred to these cases as "funny looking prostates." However, it is unclear whether this architectural pattern, which we have more formally termed diffuse adenosis of the peripheral zone (DAPZ), is simply a cellular variant of normal prostate morphology in this age group or whether it represents a risk factor for the subsequent development of prostatic carcinoma. In this study, we characterized and obtained clinical follow-up on 60 cases of DAPZ identified in our consult files over the last 6 years.

MATERIALS AND METHODS

Sixty cases of DAPZ on prostate needle biopsy were prospectively collected over a 6-year period from the consultation files of one of the authors from 2001 to 2007. The vast majority was referred to resolve a diagnostic dilemma (carcinoma vs atypia). An average of 9 needle core biopsies (range: 2 to 17) were submitted for each case

and 55% of cases were accompanied by immunohistochemical stains for high molecular weight keratin, p63, and/or α-methyl acyl coenzyme-A racemase (AMACR) performed on at least 1 block. The percentage of involved cores was calculated for each case. Although the majority of tissue submitted from a patient with DAPZ had no cytologic atypia, more than half of the cases had rare foci of atypical glands with prominent nucleoli. Serum PSA level at the time of initial biopsy and after therapy were obtained where available. In patients with a subsequent diagnosis of cancer, diagnostic biopsy specimens or radical prostatectomy specimens were obtained, when possible, for histologic confirmation. Log rank test was used to evaluate whether there was any significant difference between PSA levels of patients who were rebiopsied compared with those who were not rebiopsied, or between patients whose subsequent biopsies showed benign changes versus those with subsequent carcinoma. Fisher exact test was used to calculate whether the proportion of DAPZ cases with focal cytologic atypia was significantly higher among patients with a subsequent diagnosis of carcinoma compared with those with a subsequent benign diagnosis.

RESULTS

Clinical

The mean age of the patients was 49 years, with 89% of the patients 55 years or less (range: 34 to 73 y). For the 42 patients where it was available, the average PSA level at the time of biopsy was 5.2 ng/mL, with a range from 0.5 to 30.8 ng/mL.

Histology

The 60 cases of DAPZ on prostate needle biopsy were all characterized by diffusely abnormal glandular architecture, without significant cytologic atypia. All biopsies showed multiple foci of small and crowded acini seen throughout the submitted material, interspersed with normal or atrophic glands. On average, 72% of submitted cores were involved by this process, (range: 38% to 100%) (Fig. 1). In contrast to typical adenosis, the foci of DAPZ did not show a lobular architecture, but were diffusely arranged (Fig. 2). Unlike most prostatic carcinomas or foci of atypical glands suspicious for carcinoma, most DAPZ foci showed only minimal cytologic atypia (Fig. 3). Additionally, the cytoplasm in these foci was predominantly pale and delicate, similar to surrounding benign glands. However, 65% of cases showed rare focal cytologic atypia comprising $< 1\%$ of submitted tissue. These foci were characterized by rare glands with prominent nucleoli, which we would diagnose as "atypical foci suspicious for adenocarcinoma" in a different context (Fig. 4).

Immunohistochemistry

Immunohistochemical stains for high molecular weight keratin, p63, and/or AMACR were reviewed where available (55% of cases) and showed the foci of DAPZ to have an intact, though often patchy, basal cell layer (Fig. 5). AMACR staining was variable in these foci (similar to the staining seen in usual-type adenosis).[3]

Clinical Follow-up

Forty-three (43) (72%) of the DAPZ cases had available clinical follow-up. Of the cases without follow-up, 12 were confirmed lost to follow-up and 5 were recent DAPZ diagnoses (within the last year). Mean follow-up was close to 3 years (range: 2 mo to 6 y). Rebiopsy was performed in 35/43 cases (81%) with available clinical follow-up, and 8 (19%) were followed with serial PSA measurements. Patients who were rebiopsied had higher PSA levels on average than those who were followed by PSA levels alone (6.2 vs 3.1 ng/mL, $P = 0.04$), but were of similar age (48.5 vs 52.3 y). Of the rebiopsied cases, 20 (57%) were subsequently diagnosed with carcinoma, 5 (14%) were subsequently diagnosed as atypical acinar proliferation suspicious for carcinoma, 1 (3%) was diagnosed with high-grade prostatic intraepithelial neoplasia, and 9 (26%) were diagnosed as benign.

There was no difference in initial PSA values in patients with DAPZ and a subsequent diagnosis of carcinoma compared with those having a subsequent benign or atypical diagnosis ($P = 0.23$). Patients with DAPZ with focal atypical glands on the original biopsy were more likely to have carcinoma on repeat biopsy than DAPZ without cytologically atypical foci (70% vs 36%, $P = 0.076$), although this finding did not reach statistical significance. The mean interval between the initial DAPZ biopsy and the diagnosis of carcinoma was 15 months. We were able to obtain slides of either the needle biopsy or subsequent radical prostatectomy specimen and histologically confirm the diagnosis of carcinoma in 18/20 (90%) patients. On needle biopsy, all of the carcinomas were Gleason score $3+3=6$ with the exception of one $3+4=7$ case. Definitive treatment included radical prostatectomy (n = 13), brachytherapy (n = 3), external beam radiation (n = 1), active surveillance (n = 1), or unknown therapy (n = 2). For the 10 patients with carcinoma and available posttherapy serum PSA levels, none showed evidence of biochemical recurrence (mean follow-up: 45 mo; range: 28 to 77 mo). One patient with a subsequent diagnosis of carcinoma (treatment unknown) was found to have widely metastatic disease.

Findings at Radical Prostatectomy

Twelve (12) radical prostatectomy specimens from patients diagnosed with DAPZ were reviewed. All showed DAPZ interspersed throughout the peripheral zone, involving roughly between 30% and 90% of sections from this region (Fig. 6). There was minimal to no involvement of the transition zone. Prostatic adenocarcinoma was present in 11 of the 12 radical prostatectomy specimens, often interspersed with DAPZ (Fig. 7). Tumor was confined to the peripheral zone in all cases. All cases were Gleason score $3+3=6$, although 2 cases showed tertiary pattern 4 carcinoma. Nine cases (81%) were

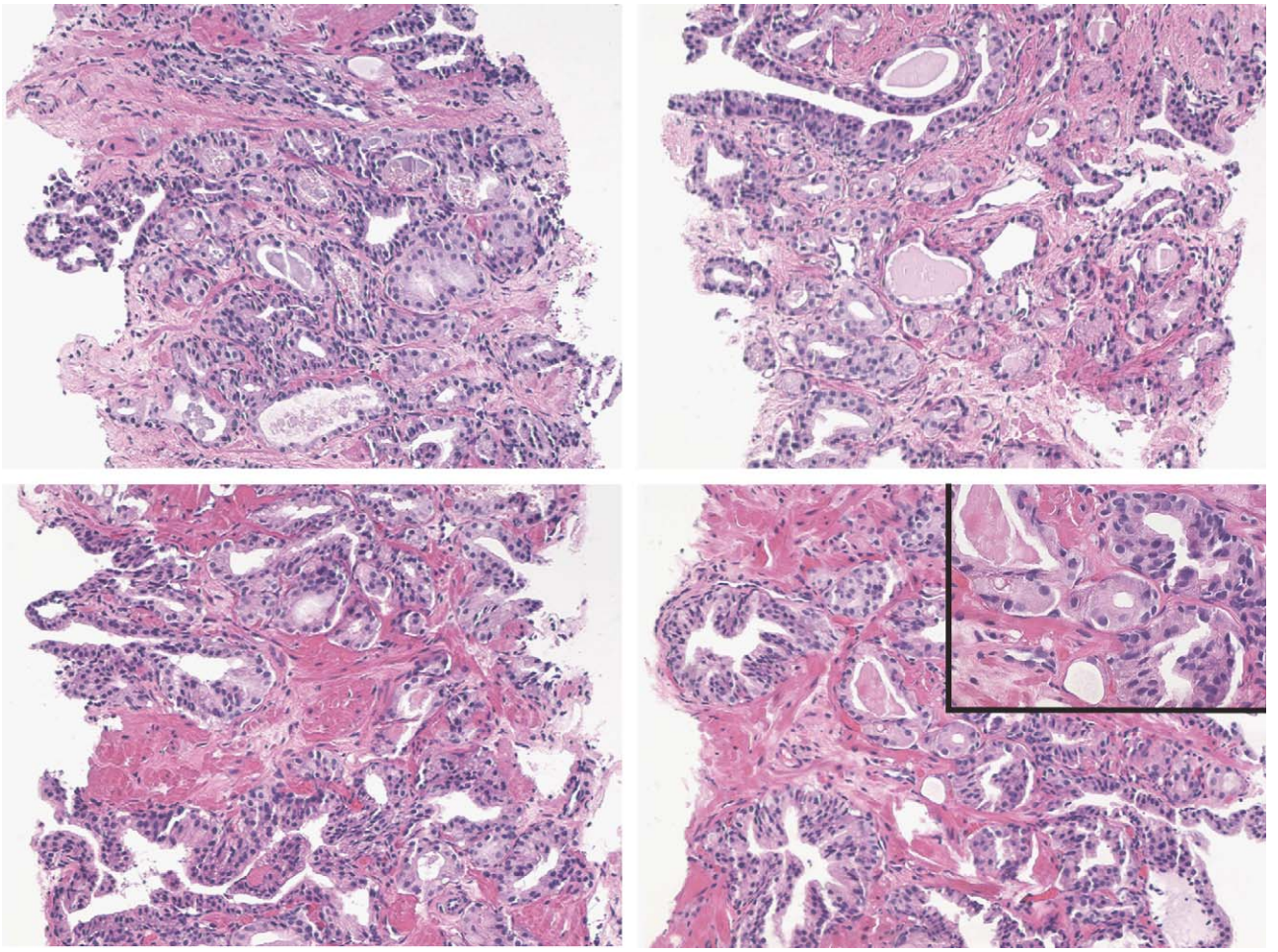

FIGURE 1. Four needle core biopsies from the same patient with DAPZ. All cores demonstrate small, crowded acinar foci with minimal cytologic atypia (inset) in a nonlobular distribution throughout the biopsies.

organ confined with 2 cases having focal extraprostatic extension. In 1 case originally diagnosed as DAPZ, the follow-up needle biopsy was misdiagnosed as carcinoma and the subsequent prostatectomy was negative for tumor with extensive DAPZ (Fig. 8).

DISCUSSION

DAPZ is a newly described and diagnostically challenging entity on prostate needle core biopsies. Typically seen in younger patients, the key to recognizing DAPZ is the presence of multiple foci of small, crowded acini throughout the majority of needle cores from a given patient. In contrast to traditional adenosis, these foci are present predominantly in the prostatic peripheral zone, rather than the transition zone and do not display a lobular configuration.[5,10] Furthermore, although typical adenosis is often multifocal where a few foci may be seen on biopsy, DAPZ consists of innumerable foci of small, crowded acini present diffusely throughout the biopsy.[1] In contrast to most foci of ''atypical glands suspicious for adenocarcinoma'' (also known as ''atypical small acinar proliferations''), DAPZ is a diagnosis resulting from *architectural*, not *cytologic* atypia.[4,7,11] Although there are multiple foci of small crowded glands on each core from a typical DAPZ patient, the vast majority of these foci do not display significant cytologic atypia, in contrast to what would be seen in a focus of atypical glands suspicious for adenocarcinoma. The crowded acini in DAPZ typically have relatively small, normochromatic nuclei with inconspicuous nucleoli. Although more than half of DAPZ cases do have rare glands showing true cytologic atypia, these foci typically comprise $< 1\%$ of submitted tissue. Also in contrast to the usual diagnosis of ''atypical glands suspicious for carcinoma,'' DAPZ occupies large areas of multiple biopsy cores. The diffuse presence of small, crowded acini without cytologic atypia throughout the needle biopsies should raise the pathologist's threshold for the diagnosis of carcinoma.[6] Diagnosing carcinoma on a small focus of crowded

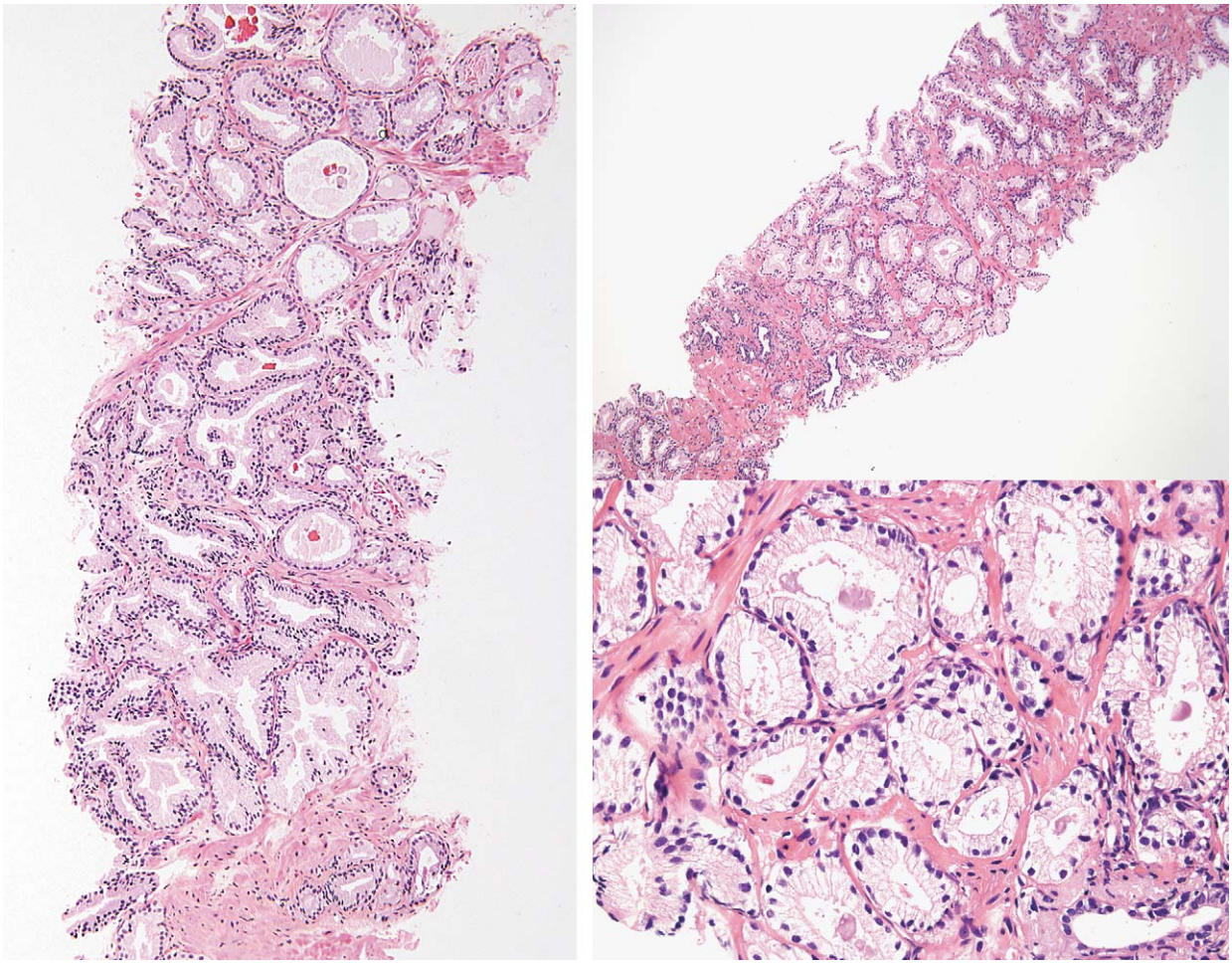

FIGURE 2. Needle core biopsies from 2 different patients showing changes of DAPZ.

glands without atypia in the setting of DAPZ is problematic because if any small focus of DAPZ in a case is called cancer, then all of the DAPZ in that case should be diagnosed as cancer. It would, however, be distinctly unusual for extensive carcinoma to be present on biopsy without cytologic atypia.

Initially, because of the typically young age of the patients, we questioned whether DAPZ was merely a crowded glandular variant of normal prostate morphology in young men mimicking cancer or a finding associated with an increased risk of cancer. The results of the current study indicate that DAPZ is associated with an increased cancer risk on rebiopsy and is therefore not likely a morphologic variant of normal prostatic histology. Perhaps the best analogy to DAPZ in another organ system is florid usual-type ductal hyperplasia in the breast, an entity often seen in young patients and associated with a 1.5 to 2-fold increase in risk of breast cancer.[8,16] In contrast to atypical ductal hyperplasia, which is associated with a 5-fold increase in cancer risk, florid usual-type hyperplasia shows minimal cytologic atypia and simply represents a more widespread and dramatic variant of usual ductal hyperplasia.[8] As with florid usual ductal hyperplasia, DAPZ may arise in part from an altered hormonal milieu, which may be more common in younger patients.[16]

The risk of prostatic adenocarcinoma on rebiopsy after a diagnosis of DAPZ is close to 60%, a risk that is nearly 3 times higher than the typical risk of 17% to 18% after a benign 12-core prostate needle biopsy.[7] There are a number of caveats to the interpretation of the cancer risk after a diagnosis of DAPZ, the most important of which is the relatively small sample size of the current study. Additionally, because the average PSA level of patients who underwent rebiopsy in our study was higher than the PSA levels of those who were not rebiopsied, it is possible that our results are biased by patient selection for rebiopsy and that the true risk of cancer after a DAPZ diagnosis is somewhat lower than we have observed. However, even if all of the men in our study who did not have a repeat biopsy underwent rebiopsy and had a benign diagnosis, the risk of cancer after a DAPZ

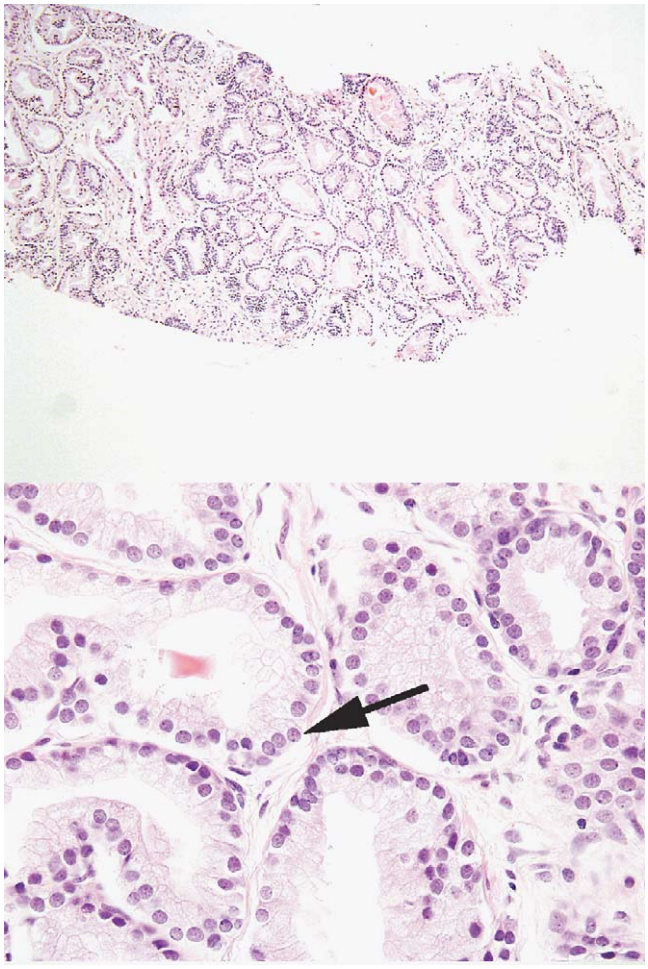

FIGURE 3. Most cases of DAPZ show minimal cytologic atypia in the crowded acinar foci, with small, normochromatic nuclei, and inconspicuous nucleoli (arrow).

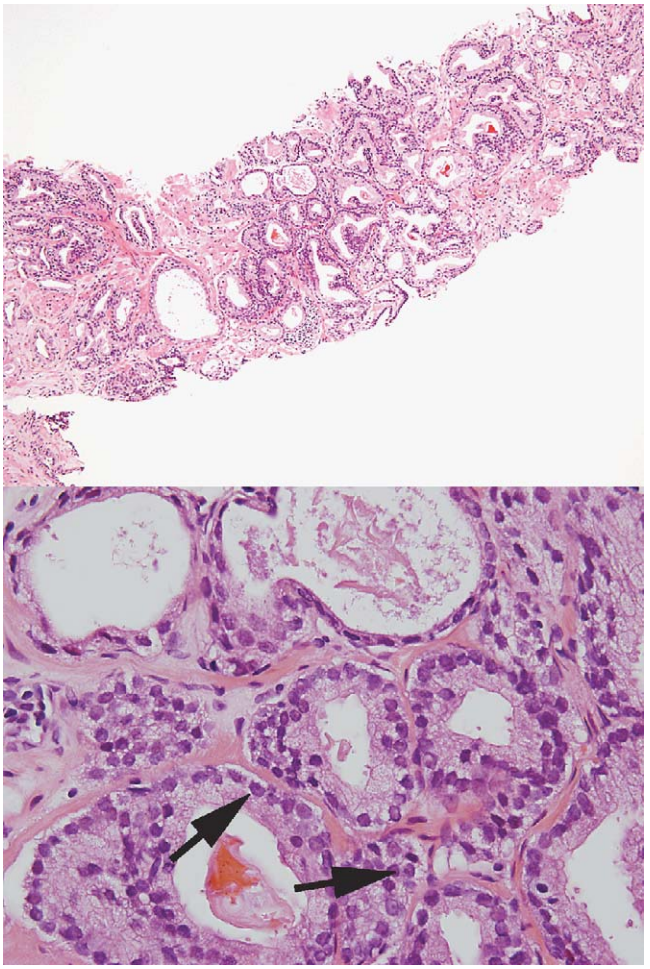

FIGURE 4. Rare foci of atypical glands suspicious for carcinoma were present in DAPZ cases. These foci showed slightly hyperchromatic nuclei with prominent nucleoli (arrows).

diagnosis would still be close to 50%. An additional selection bias in our study is that we have studied DAPZ in a population of young men who had an initial abnormality in serum PSA or digital rectal examination that led to a biopsy in the first place. There may be a large population of men with DAPZ and normal PSA levels that do not undergo biopsy, and these men may not have an associated increased risk of cancer. However, mildly elevated serum PSA levels in the 4 to 10 ng/mL range, as seen in the current study, are not associated with a > 50% risk of cancer on repeat biopsy as seen in the current study population, suggesting that DAPZ is responsible for at least some of the cancer risk.[12]

On the basis of the current data, we would suggest that the increased cancer risk associated with DAPZ is significant enough to warrant rebiopsy of these patients within 3 to 6 months of the initial biopsy to exclude the possibility of an unsampled prostatic adenocarcinoma. This recommendation is similar to the current recommendations for rebiopsy after a diagnosis of atypical glands suspicious for adenocarcinoma.[2,7] However, there are several advantages to carving the entity of DAPZ out from that of "atypical glands suspicious for carcinoma." First, the 2 entities are morphologically distinct in that biopsies from DAPZ patients are filled with multiple foci of small crowded glands, most of which show only minimal cytologic atypia, rather than a single focus showing significant atypia in the background of normal morphology. In addition to identifying patients in need of repeat biopsy, an equally important reason to recognize DAPZ as an entity is to sensitize pathologists to distinguish this lesion from prostatic adenocarcinoma. In contrast to the case with 1 or 2 foci of "atypical glands suspicious for carcinoma," the pathologist who is unfamiliar with DAPZ may be tempted to diagnose widespread carcinoma, rationalizing that there cannot be so many atypical foci without it representing cancer. We

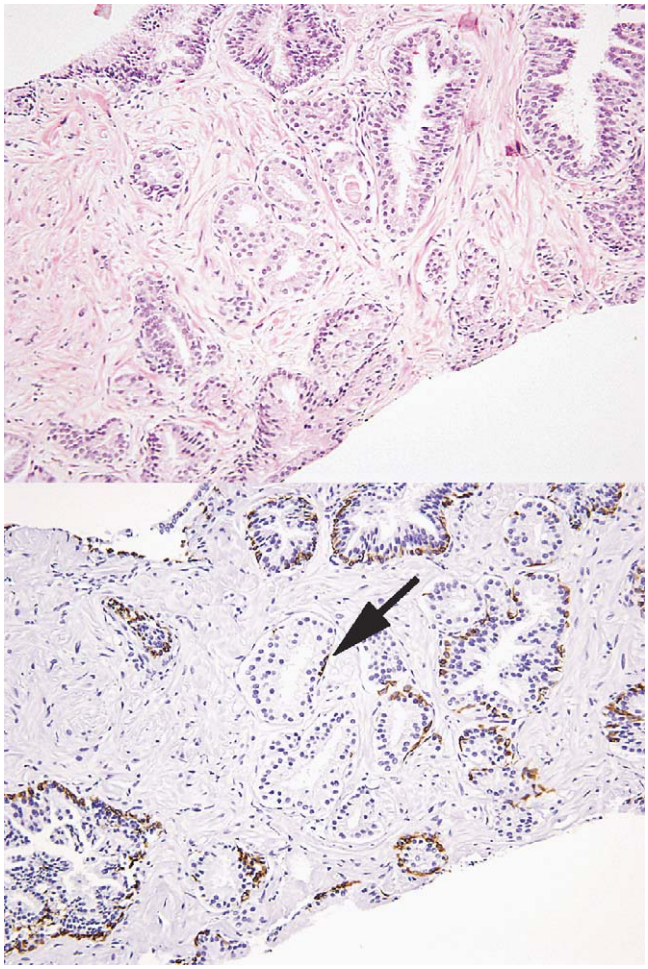

FIGURE 5. Immunostaining for cocktail of high molecular weight keratin and p63 reveals a patchy basal cell layer in crowded small acinar foci (arrow).

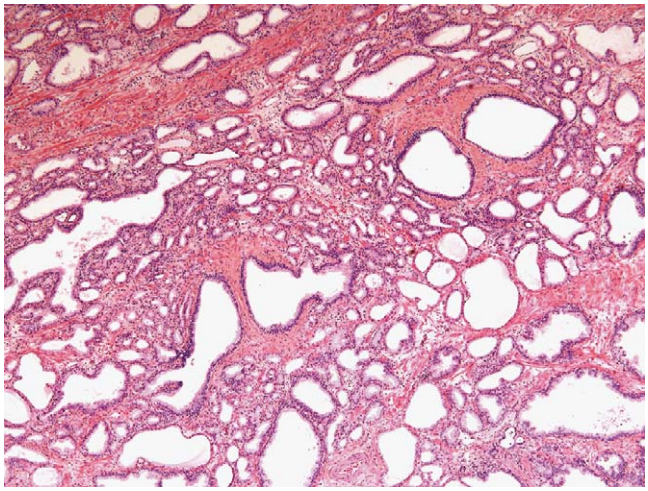

FIGURE 6. Radical prostatectomy specimen from patient with DAPZ showed varying numbers of nonlobular and crowded small acinar foci interspersed throughout normal prostatic glands in the peripheral zone.

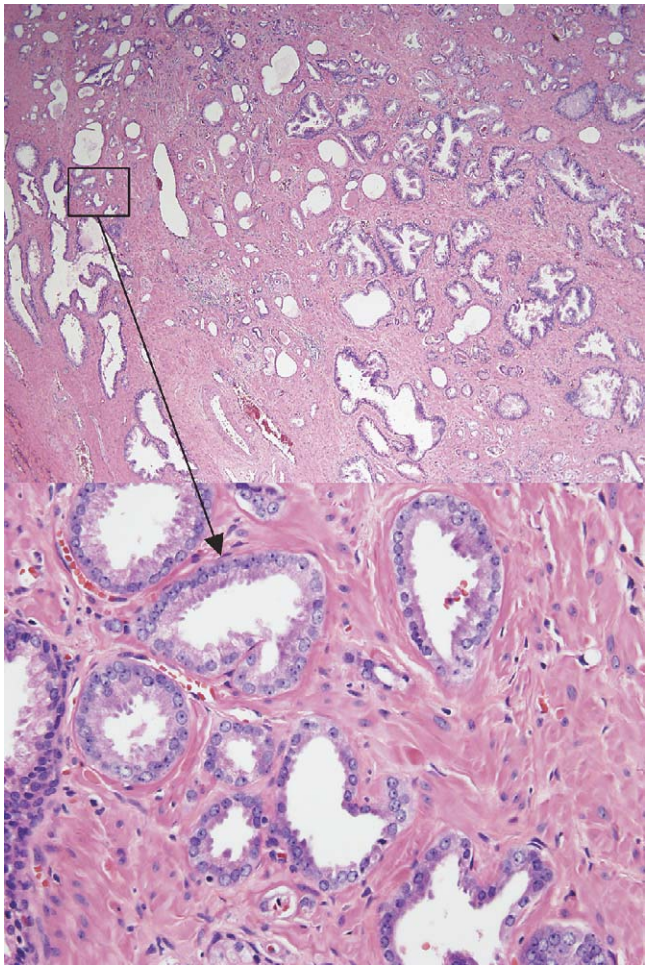

FIGURE 7. Small focus of Gleason score 3+3 = 6 adenocarcinoma in a radical prostatectomy from a DAPZ patient. Most of the specimen consisted of changes of DAPZ with minimal cytologic atypia. However, small, unequivocal foci of prostatic adenocarcinoma were intermingled with changes of DAPZ (bottom panel).

have seen at least 1 case of DAPZ that was misdiagnosed as carcinoma on needle biopsy and resulted in a radical prostatectomy, which did not show any carcinoma. Recognition of this process as a defined entity will increase its diagnosis, enhance our ability to further study this lesion, and allow us to gain greater insight into its biologic significance.

Overall, DAPZ is a newly described and diagnostically challenging entity on prostate needle biopsies from young patients which seems to be associated with an increased risk of prostatic adenocarcinoma on rebiopsy. It is essential to consider the background prostatic morphology when entertaining a diagnosis of prostatic adenocarcinoma in a case of DAPZ, and to avoid overinterpretation of needle biopsies with multiple foci of crowded, diffusely distributed but cytologically benign glands.

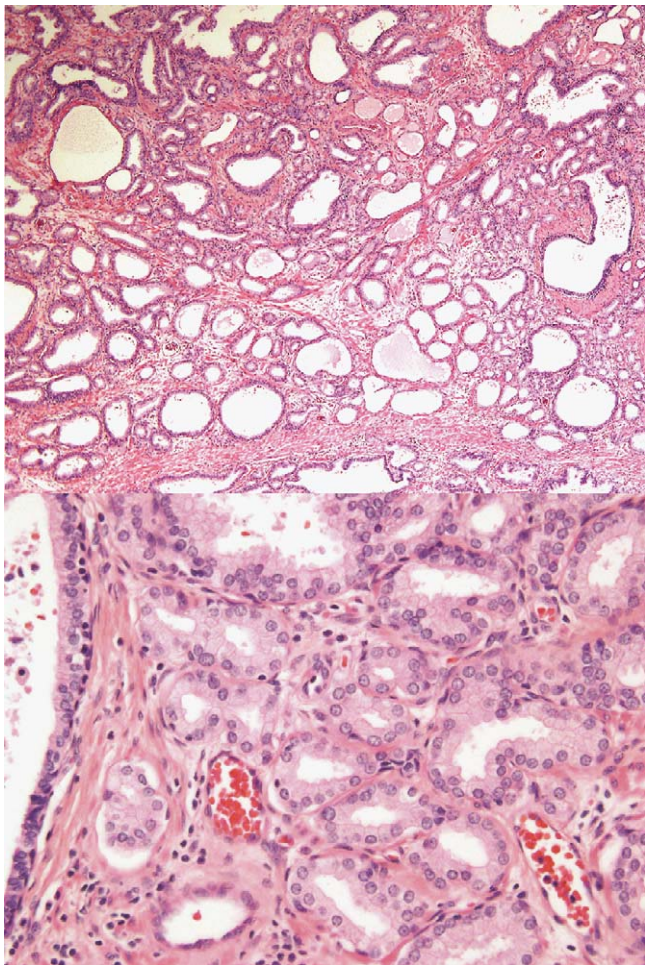

FIGURE 8. Radical prostatectomy from DAPZ patient incorrectly diagnosed with carcinoma on needle biopsy showed no carcinoma, only changes of DAPZ with minimal cytologic atypia and patchy basal cells (not illustrated) distributed throughout.

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