Partial Atrophy on Prostate Needle Biopsy Cores: A Morphologic and Immunohistochemical Study

Wenle Wang, MD, PhD, Xinlai Sun, MD,† and Jonathan I. Epstein, MD*‡§*

Abstract: Partial atrophy is the most common benign mimicker of prostate cancer on needle biopsy. Of 3916 prostate needle core biopsy cases received in our consultation service over a period of 3 months (March 1, 2007 to May 31, 2007), 170 cases (4.3%) with partial atrophy were diagnosed as atypical glands by outside pathologists and prospectively identified. We supplemented our material with 108 cases of partial atrophy sent to our consultation service in 2006 from a single institution, which frequently uses a triple cocktail stain [p63, high molecular weight cytokeratin (HMWCK), α-methyl acyl-Coa racemase (AMACR)]. The morphologic features of the 278 cases and immunohistochemistry of 236 cases (198 with prostate cocktail and 38 with only basal cell makers) were analyzed. Forty-eight of 278 (17.3%) partial atrophy cases were mixed with postatrophic hyperplasia. Enlarged nuclei were visible in 43/278 (15.5%) cases, with prominent nucleoli seen in 58/278 (20.9%) cases (30 cases associated with nuclear enlargement). Of 198 cases with a prostatic cocktail stain, 48 (24.2%) had a cancer pattern for both basal cells and AMACR (p63−, HMWCK−, and AMACR+), 14 (7.1%) had a cancer pattern for basal cells (p63−, HMWCK−, and AMACR−), 89 (44.9%) had a cancer pattern for AMACR (p63+, HMWCK+, and AMACR+), and 47 (23.7%) had a totally benign pattern (p63+, HMWCK+, and AMACR−). Of the 198 cases using the cocktail stain, 136 (68.7%) had positive basal cell staining. The percentage of basal cells labeled with the combination of p63/HMWCK was: < 5% in 42 (21.2%) cases, 5% to 75% in 58 (29.3%) cases, and > 75% in 36 (18.2%) cases. An additional 38 cases immunostained only for p63 and/or HMWCK was negative in 2 (5.2%) cases, < 5% (13.1%) in 5 cases, 5% to 75% in 19 (50%) cases, and > 75% in 12 (31.6%) cases. In conclusion, partial atrophy is a benign mimicker of adenocarcinoma both as a result of its routine morphologic features and its immunohistochemical profile. Recognition of the classic morphology of partial atrophy on routine hematoxylin and eosin-stained sections is critical to avoid misdiagnosing partial atrophy as adenocarcinoma.

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

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

Key Words: prostate, adenocarcinoma, atrophy, partial atrophy, immunohistochemistry, AMACR, p63, high molecular weight cytokeratin

(*Am J Surg Pathol* 2008;32:851–857)

Although partial atrophy is one of the most common benign mimickers of prostate cancer on needle biopsy, it was only first described in 1992 and further studied in 1998 by Epstein et al.[10,17] Recognized as a distinct pattern of atrophy, partial atrophy still remains a diagnostic dilemma for pathologists. It was the current authors' impression before formally studying this issue that the increased use of immunohistochemistry, in particular the utilization of the triple cocktail stain for basal cell markers and α-methyl acyl-Coa racemase (AMACR), rather than making the diagnosis of partial atrophy easier, led to more confusion in its distinction from adenocarcinoma of the prostate. The current work reports on the largest series of partial atrophy with more detailed evaluation of both its nuclear features on routine hematoxylin and eosin (H&E) stained sections and its immunohistochemical profile using basal cell markers and AMACR, including many cases labeled with the triple cocktail stain.

MATERIALS AND METHODS

Two populations were analyzed for morphologic and immunohistochemical features. One hundred and seventy cases of partial atrophy on prostatic needle core biopsies were sent in consultation to 1 of the authors over a 3-month period (March 1, 2007 to May 31, 2007) as "atypical, suspicious for carcinoma." These cases represented 4.3% of the 3916 prostate needle biopsy specimens received in our consultation service during this time period. We supplemented our material with 108 cases of partial atrophy sent in consultation to our service in 2006 from a single institution where triple prostate cocktail stains are frequently performed. Cases were included only if there were no atypical glands or adenocarcinoma on the same core. Although the nature of the fixative was typically not provided, the vast majority appeared fixed in formalin based on the observed morphology.

Immunohistochemical stains were performed by the outside institutions in 236/278 (84.9%) of the cases. Immunostains for prostate triple cocktail [p63, high molecular weight cytokeratin (HMWCK), and AMACR]

were performed on 198 cases with immunostains only for basal cell markers (HMWCK and/or p63) performed on 38 cases. We classified the immunostaining pattern seen with the triple cocktail into 4 categories: (1) cancer pattern with both basal cells and AMACR (p63−, HMWCK−, and AMACR+); (2) cancer pattern with basal cells (p63−, HMWCK−, and AMACR−); (3) cancer pattern with AMACR (p63+, HMWCK+, and AMACR+); and (4) totally benign pattern (p63+, HMWCK+, and AMACR−). AMACR immunoreactivity in partial atrophy was further characterized as diffuse cytoplasmic versus luminal and evaluated for intensity compared to adjacent benign glands (negative, 0; weakly positive, 1+; moderately positive, 2+; and strongly positive, 3+). Stains for AMACR were interpreted as negative if it was similar to the background benign glands. The percentage of the circumferential area of all the glands in question where basal cells were seen with basal cell markers was recorded as 0, < 5%, 5% to 75%, and > 75%.

The extent of AMACR positivity and extent of basal cell staining between the 1 institution with 108 cases and the mixture of consults from other institutions was compared using the χ^2 test (STATA Corporation, College Station, TX). As there was no difference in the extent of basal cell staining and extent of AMACR staining between 2 groups (data not shown), the data were combined.

RESULTS

Of 3916 prostate needle core biopsies received in our consultation service over a period of 3 months (March 1, 2007 to May 31, 2007), 170 cases (4.3%) with partial atrophy were diagnosed as atypical glands by outside pathologists and prospectively identified. Of the 170 cases, 145 had 1 core involved, 21 had 2 cores involved, and 4 had 3 cores involved with partial atrophy. An additional 108 cases of partial atrophy sent in 2006 from a

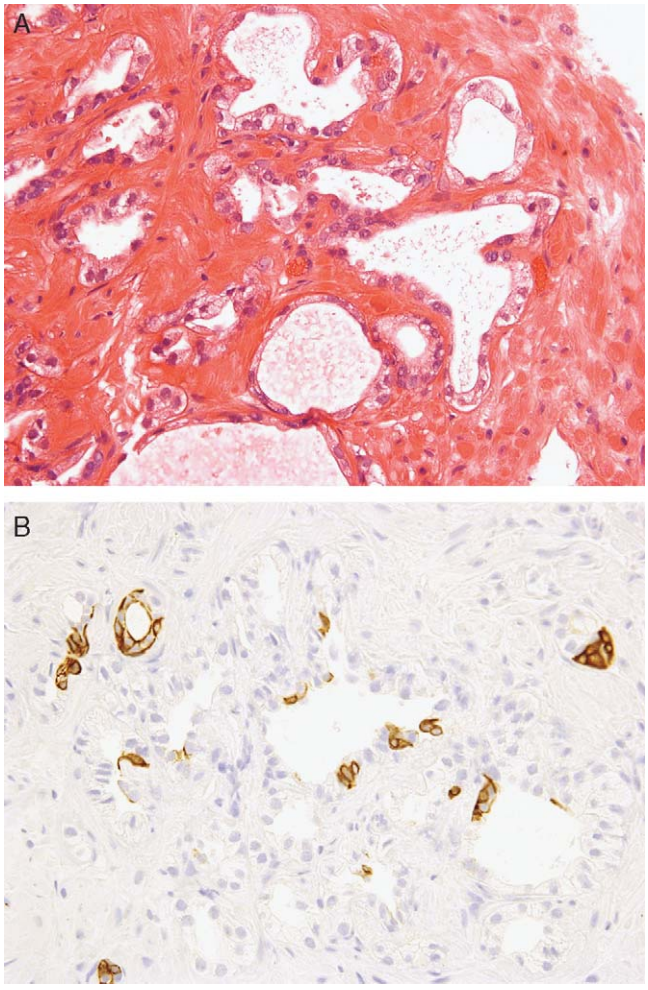

FIGURE 1. A, Glands of partial atrophy with subtle infolding of lumina border. Cells have scant apical cytoplasm with abundant pale cytoplasm laterally. Nuclei are small without obvious nucleoli. B, Patchy stain for HMWCK with some glands negative.

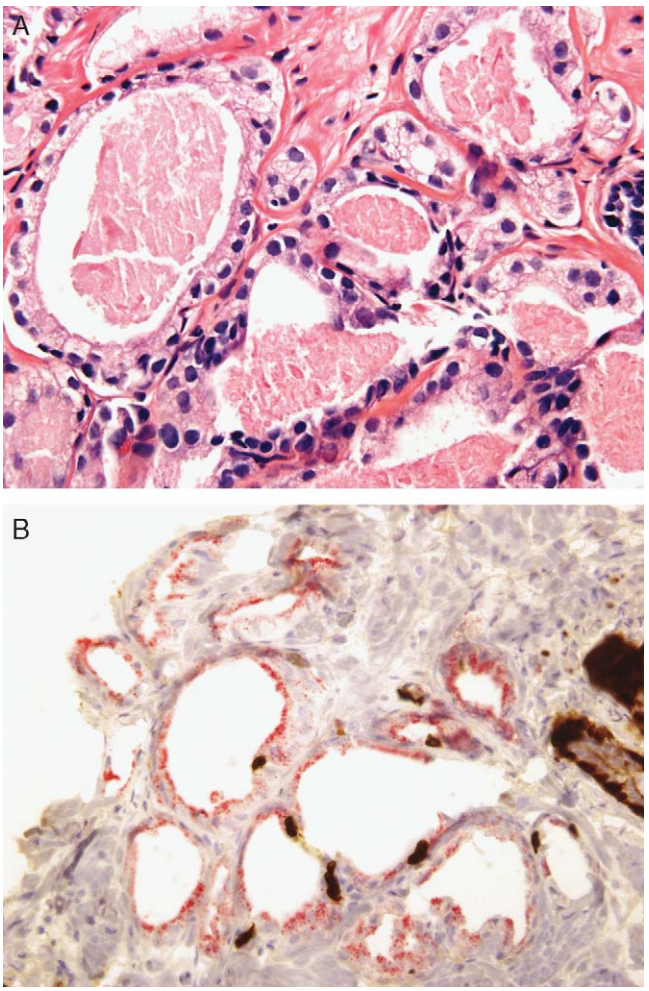

FIGURE 2. A, Crowded glands of partial atrophy with PAH. B, Triple cocktail stain showing patchy labeling for p63 and HMWCK with moderate positivity for AMACR.

single institution as atypical were also reviewed. Patient's age ranged from 39 to 86 years (mean and median of 61).

Partial atrophy lacked a basophilic appearance at low magnification as the nuclei were more spaced apart with lateral pale eosinophilic cytoplasm (Fig. 1). Although most cases of partial atrophy consisted of glands that were separated by a modest amount of stroma, a few cases had glands that were more crowded with back-to-back glands (Fig. 2). Glands had benign features characterized by undulating luminal surfaces with subtle papillary infolding (Fig. 3). In glands with partial atrophy, nuclei in areas reached the full height of the cytoplasm, in contrast to adenosis, which has abundant cytoplasm. In 48/278 (17.3%) of partial atrophy cases, there was an intimated mingling with postatrophic hyperplasia (PAH) (Fig. 4). Enlarged nuclei were visible in 43/278 (15.5%) cases, with prominent nucleoli seen in 58/278 (20.9%) cases (30 associated also with nuclear enlargement) (Figs. 5, 6). In none of the cases was nucleolar size as large as seen in some prostatic adenocarcinomas (Table 1).

Immunohistochemistry was performed at the referring institutions in 236 cases (84.9%) with the results summarized in Table 2. Of 198 cases with a triple cocktail stain, 48 (24.2%) had a cancer pattern for both basal cells and AMACR (p63 −, HMWCK −, and AMACR +), 14 (7.1%) had a cancer pattern for basal cells (p63 −, HMWCK −, and AMACR −), 89 (44.9%) had a cancer pattern for AMACR (p63 +, HMWCK +, and AMACR +), and 47 (23.7%) had a benign pattern (p63 +, HMWCK +, and AMACR −) (Figs. 6–8). Of the 198 cases using the cocktail stain, 136 (68.7%) had positive basal cell staining. The percentage of basal cells labeled with the combination of p63/HMWCK was: < 5% in 42 (21.2%) cases, 5% to 75% in 58 (29.3%) cases, and > 75% in 36 (18.2%) cases. An additional 38 cases immunostained only for p63 and/or HMWCK was negative in 2 (5.2%) cases, < 5% (13.1%) in 5 cases,

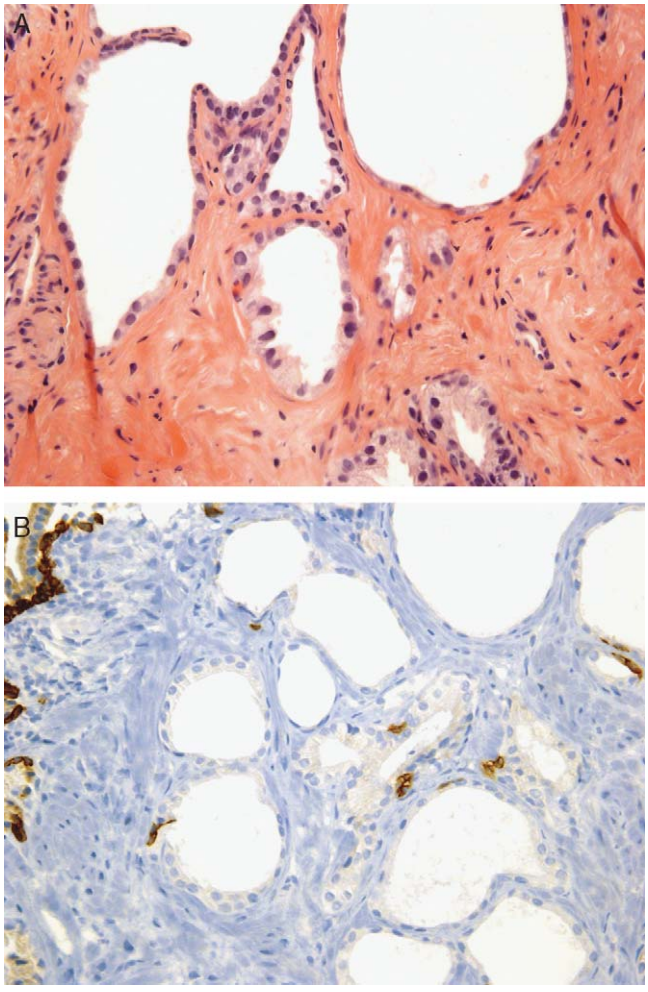

FIGURE 3. A, Partial atrophy ruffling of luminal border (center). B, Patchy stain for HMWCK with majority of glands negative and positive glands only having a rare positive basal cell.

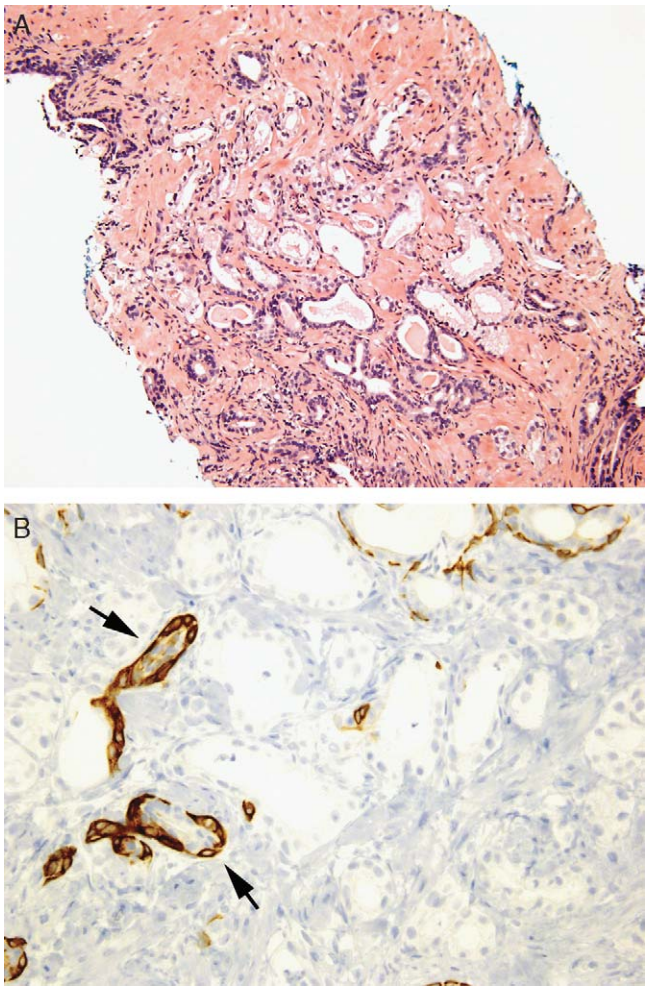

FIGURE 4. A, Partial atrophy (center) merging with PAH (below). B, Mostly negative for HMWCK in partial atrophy with only rare scattered positive cells in contrast to circumferential staining in PAH glands (arrows).

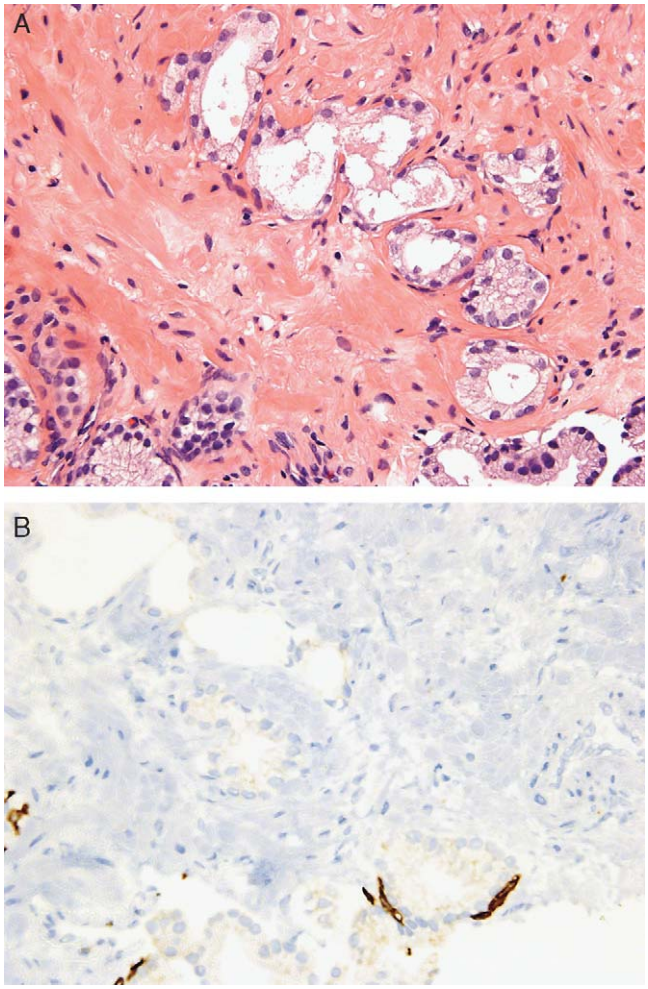

FIGURE 5. A, Enlarged nuclei with visible nucleoli in partial atrophy. B, Patchy stain for HMWCK with a few positive glands demonstrating only rare positive basal cells.

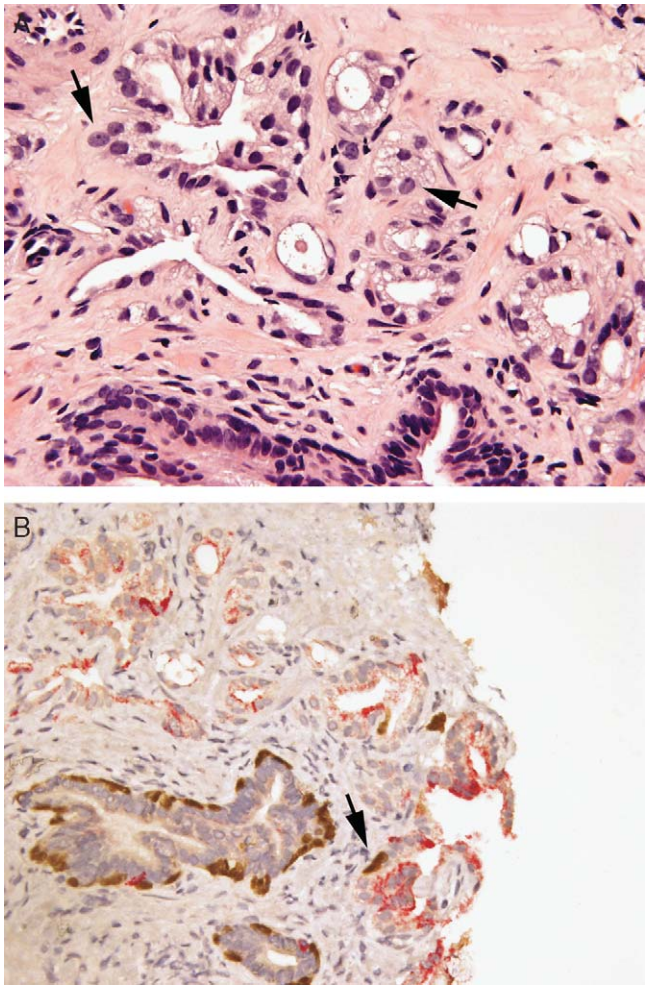

FIGURE 6. A, Enlarged nuclei with visible nucleoli (arrows) in partial atrophy. B, Triple cocktail stain showing patchy labeling for p63 and HMWCK (arrow) with moderate positivity for AMACR. Note PAH glands (lower left) without AMACR.

5% to 75% in 19 (50%) cases, and > 75% in 12 (31.6%) cases (Figs. 1B, 3B, 4B, 5B).

DISCUSSION

Prostatic needle core biopsy remains the single most important tool for diagnosing prostate adenocarcinoma. Prostate atrophy is widely recognized as a benign mimicker of prostatic adenocarcinoma, reported as early as 1936 by Moore.[3,4,6,8,9,13,15,16–19] Atrophy in the prostate gland can begin in men as young as in their 20s, although it is more characteristically seen in older man.[7] Prostatic atrophy can be either diffuse or focal, with diffuse atrophy typically resulting from androgen deprivation. The terminology for focal atrophy has until recently been poorly characterized and inconsistent. In a recent consensus paper, focal atrophy was categorized into 4 distinct subtypes: (1) simple atrophy, (2) simple atrophy with cyst formation, (3) PAH, and (4) partial atrophy.[5]

Before the recognition of partial atrophy, PAH was the form of atrophy that was most often cited as a mimicker of prostate cancer. PAH appears basophilic at low power with its basophilic appearance owing to scant cytoplasm both apically and laterally. At low magnification, one merely sees the nuclear outline of the gland. In contrast, partial atrophy lacks the basophilic appearance of PAH as the nuclei are more spaced apart. Whereas PAH does not currently seem to pose as significant a diagnostic dilemma for pathologists, the presence in partial atrophy of crowded glands with scant pale cytoplasm is less readily recognized as atrophy and is

TABLE 1. Morphologic Features of Partial Atrophy

Features	Present
Mixed with PAH	58/278 (17%)
Nuclear enlargement	43/278 (15.5%)
Nucleoli	58/278 (20.9%)

TABLE 2. Immunohistochemistry

	Basal Cell Markers				AMACR+ Location		AMACR+ Extent		
Stain and Patterns	**0%**	**< 5%**	**5%-75%**	**> 75%**	**Cytoplasmic (%)**	**Luminal (%)**	**1 (%)**	**2 (%)**	**3 (%)**
Prostate cocktail (198)									
p63 –, HMWCK –, and AMACR+ (48)	48 (24)				38 (79)	10 (21)	20 (42)	16 (33)	12 (25)
p63 –, HMWCK –, and AMACR – (14)	14 (7)								
p63+, HMWCK+. and AMACR+ (89)		30 (15)	42 (21)	17 (9)	60 (67)	29 (33)	45 (51)	39 (44)	5 (5)
p63+, HMWCK+, and AMACR – (47)		12 (6)	16 (8)	19 (10)					
Total AMACR+ (137)					97 (71)	40 (29)	65 (47)	55 (40)	17 (13)
Total p63, HMWCK (198)	62 (31)	42 (21)	58 (29)	36 (18)					
Basal cell markers only (38)	2 (5)	5 (13)	19 (50)	12 (32)					

more difficult for pathologists to distinguish from adenocarcinoma.

In addition to a classic low power basophilic appearance, glands of PAH are commonly arranged in a lobular distribution with in some cases atrophic acini surrounding a dilated central acinus. Some of these lesions resemble normal appearing resting breast lobules, and in the past were referred to by some authors as lobular atrophy. Another feature of PAH that is not seen in cancer is associated sclerotic or elastotic fibrosis. Partial atrophy lacks the elastotic and sclerotic collagen characteristic of PAH and is not as lobular. In 17.3% of our cases, partial atrophy merged with PAH, which could help in diagnosing the focus as benign.

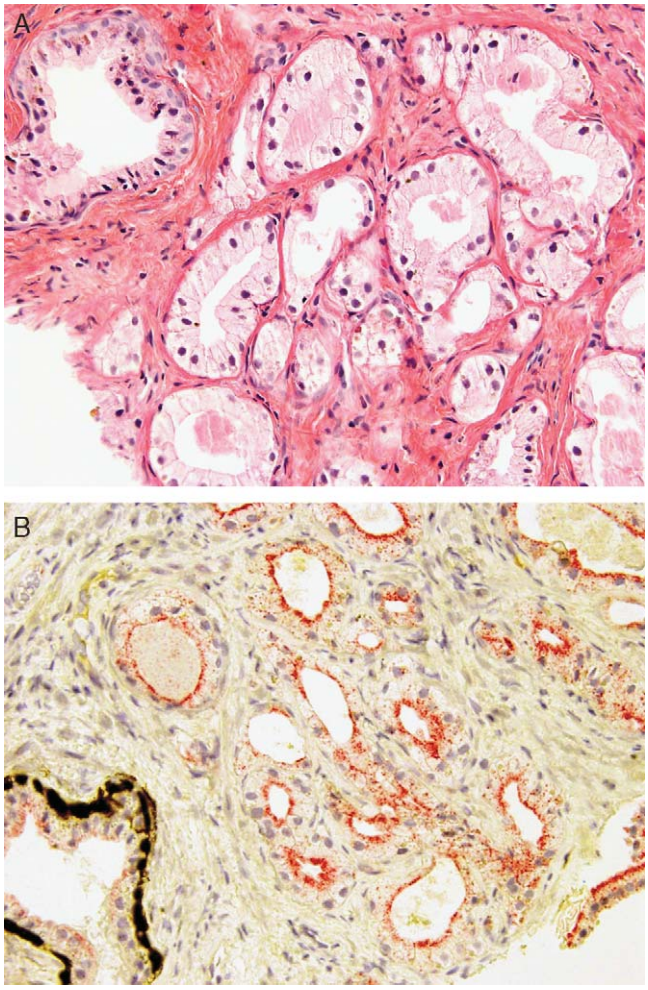

FIGURE 7. A, Partial atrophy with pale cytoplasm with lipofuscin granules. B, Partial atrophy with cancer immunostaining pattern (p63 –, HMWCK –, and AMACR+).

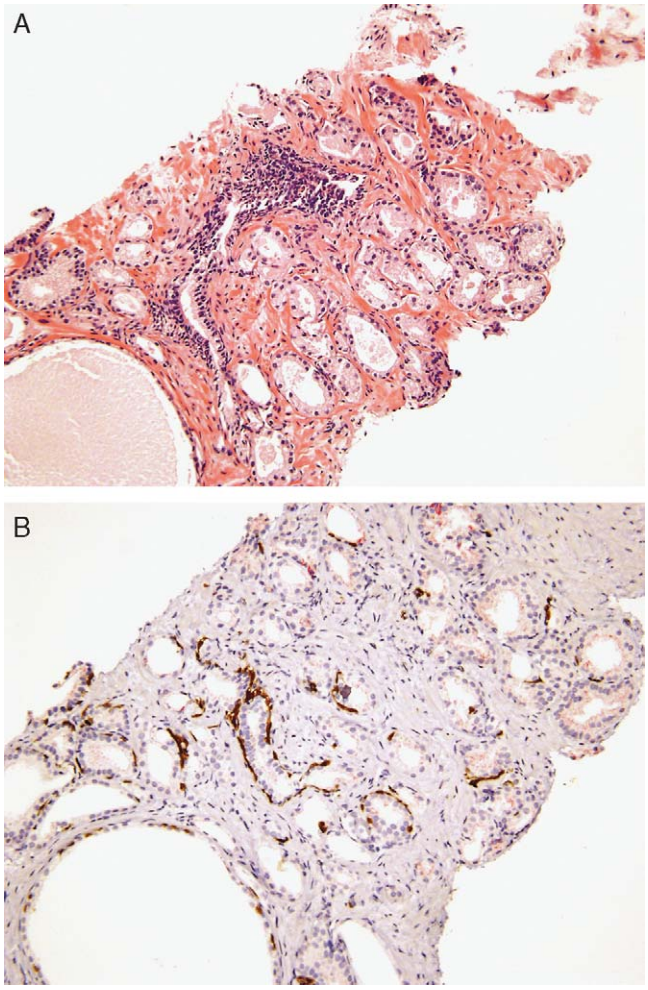

FIGURE 8. A, Low power of partial atrophy mimicking prostate cancer. B, Triple cocktail stain showing patchy labeling for p63 and HMWCK with weak positivity for AMACR.

The key to recognize partial atrophy is that the glands have benign features, including subtle papillary infolding. Although some of the glands within a focus of partial atrophy may have straight luminal boarders, others have a slight undulating luminal surface. In contrast, most carcinomas have the majority of their glands with straight, even luminal borders. The other critical feature to recognize is that the glands are partially atrophic with nuclei in areas reaching the full height of the cytoplasm. The nuclear features in partial atrophy tend to be relatively benign, although our study highlights that 15.5% of cases have some enlarged nuclei with 20.9% cases having small but prominent nucleoli. In our original paper on this subject published in 1998 on 51 cases, 25.4% of cases were noted to have frequent nucleoli.[17] There was no comment in either this or in our subsequent paper on partial atrophy on the presence of enlarged nuclei in partial atrophy.[10] Although visible nucleoli is an important criterion for the diagnosis of adenocarcinoma, enlarged nuclei is also a feature more commonly present in carcinoma as opposed to benign glands and its presence in partial atrophy further mimics prostate cancer. A distinguishing feature is that the nucleoli in partial atrophy never reach the size seen in some prostatic adenocarcinomas. Atrophic prostate cancers have either: (a) a truly infiltrative process with individual small atrophic glands situated between larger benign glands, (b) the concomitant presence of ordinary less atrophic carcinoma, or (c) greater cytologic atypia than is seen in partial atrophy. Atrophic prostate cancers typically also lack the pale cytoplasm of partial atrophy. The key features, morphologic features, differentiating partial atrophy from prostate cancer are outlined in Table 3.

In recent years, several immunohistochemical markers, including p63, HMWCK, and AMACR have become common tools to aid in the diagnosis of challenging prostate cases, with AMACR positive in 80% to 100% of prostatic adenocarcinomas and HMWCK/p63 negative in virtually all prostate cancers.[2,11,12,14,20] It is recognized that partial atrophy can have some glands with a lack or decreased basal cells.[1,10,17] Whereas in our 1998 study on this topic, all 12 cases studied had patchy HMWCK staining, in 2005 we found that 13% of 117 cases were negative for basal cell markers. No description on the extent of basal cell staining in the positive cases was noted in either paper.[10,17] In the current study, 27.1% (62 + 2/198 + 38) of the total of 236 cases with immunostains for basal cells lacked any basal cells. An additional 23.7% (47 cases) had focal (< 5%) staining. This focal staining often consists of just a few scattered basal cells, which to some observers could be interpreted as not being definitively positive.

In the first paper to describe AMACR in partial atrophy, we previously studied only 19 cases with positive staining seen in 15 (79%) cases. No mention on the intensity of the staining was noted.[10] The current study highlights that with the triple stain only 23.7% of cases had a classic benign staining pattern (p63 +, HMWCK +, and AMACR −) with 24.2% having the classic cancer staining pattern for both basal cells and AMACR (p63 −, HMWCK −, and AMACR +), with the remaining cases having mixed benign/cancerous staining patterns for basal cells and AMACR. A total of 137 of 198 (69%) exhibited some AMACR immunoreactivity. However, in contrast to the strong AMACR staining seen with many prostate cancers, partial atrophy exhibited strong AMACR reactivity in only 13% of cases with 50% showing weak staining. Partial atrophy differs from PAH that uniformly labels with basal cell markers and uncommonly expresses AMACR. Our results are likely not representative of all partial atrophy cases because cases with a classic benign staining pattern would more likely not be sent for consultation. Another weakness of the current study is that the immunostaining was performed in multiple different institutions, where the exact methods of staining cannot be determined. However, this could also be considered a strength of the study in that it reflects results from multiple institutions and hence a more generalized representation, rather than a paper published from a single academic institution which typically would have a specialized interest in urologic pathology. Regardless of any potential selection bias, our findings emphasize that triple stains of partial atrophy are particularly misleading for cancer and that the diagnosis is primarily established on the routine H&E-stained sections.

In conclusion, partial atrophy is a benign mimicker of adenocarcinoma both on routine morphology and on immunohistochemical stains. Immunohistochemistry can help confirm the diagnosis if basal cells are demonstrated, yet it must be recognized that basal cells may be very focal, labeling only a couple of cells in a few of the glands. Negative basal cell staining is still consistent with the diagnosis. AMACR stains are also potentially misleading,

TABLE 3. Features Distinguishing Adenocarcinoma and Partial Atrophy

Features	Partial Atrophy	Adenocarcinoma
H&E-stained sections		
Infiltrative	Not common	Common
Mixed with PAH	May be with PAH	Rarely, coincidentally
Cytoplasm	Pale	Often basophilic
Luminal boarder	Ruffled	Typically straight
Blue intraluminal mucin	Absent	Often present
Pink intraluminal secretion	Rarely present	Often present
Nuclear enlargement	Yes, minimal	Yes, can be marked
Nucleoli	Yes, small	Yes, can be large
Immunohistochemistry		
Basal cell makers	Often patchy negative in some cases	Negative
AMACR	Negative in some cases negative to strongly positive most cases with moderate-weak intensity	Positive in 80% cases most moderate-strong

as it is often positive in partial atrophy. Recognizing the H&E features of partial atrophy is still the most critical aspect in preventing a misdiagnosis of adenocarcinoma. Despite partial atrophy being well recognized as a distinct pattern of atrophy, it remains a particularly difficult lesion for pathologists on prostate needle biopsy and additional reports on this topic will hopefully increase the awareness of this lesion's morphologic and immunohistochemical profile.

REFERENCES

1. Adley BP, Yang XJ. Alpha-methylacyl coenzyme A racemase immunoreactivity in partial atrophy of the prostate. *Am J Clin Pathol*. 2006;126:849–855.
2. Chan TY, Mikolajczyk SD, Lecksell K, et al. Immunohistochemical staining of prostate cancer with monoclonal antibodies to the precursor of prostate-specific antigen. *Urology*. 2003;62:177–181.
3. Cheville JC, Bostwick DG. Postatrophic hyperplasia of the prostate. A histologic mimic of prostatic adenocarcinoma. *Am J Surg Pathol*. 1995;19:1068–1076.
4. Cina SJ, Silberman MA, Kahane H, et al. Diagnosis of Cowper's glands on prostate needle biopsy. *Am J Surg Pathol*. 1997;21:550–555.
5. De Marzo AM, Platz EA, Epstein JI, et al. A working group classification of focal prostate atrophy lesions. *Am J Surg Pathol*. 2006;30:1281–1291.
6. Frauenhoffer EE, Ro JY, el-Naggar AK, et al. Clear cell cribriform hyperplasia of the prostate. Immunohistochemical and DNA flow cytometric study. *Am J Clin Pathol*. 1991;95:446–453.
7. Gardner WA Jr, Culberson DE. Atrophy and proliferation in the young adult prostate. *J Urol*. 1987;137:53–56.
8. Gaudin PB, Epstein JI. Adenosis of the prostate. Histologic features in needle biopsy specimens. *Am J Surg Pathol*. 1995;19:737–747.
9. Gaudin PB, Wheeler TM, Epstein JI. Verumontanum mucosal gland hyperplasia in prostatic needle biopsy specimens. A mimic of low grade prostatic adenocarcinoma. *Am J Clin Pathol*. 1995;104:620–626.
10. Herawi M, Parwani AV, Irie J, et al. Small glandular proliferations on needle biopsies: most common benign mimickers of prostatic adenocarcinoma sent in for expert second opinion. *Am J Surg Pathol*. 2005;29:874–880.
11. Jiang Z, Woda BA, Rock KL, et al. P504S: a new molecular marker for the detection of prostate carcinoma. *Am J Surg Pathol*. 2001;25:1397–1404.
12. Jiang Z, Wu CL, Woda BA, et al. P504S/alpha-methylacyl-CoA racemase: a useful marker for diagnosis of small foci of prostatic carcinoma on needle biopsy. *Am J Surg Pathol*. 2002;26:1169–1174.
13. Jones EC, Clement PB, Young RH. Sclerosing adenosis of the prostate gland. A clinicopathological and immunohistochemical study of 11 cases. *Am J Surg Pathol*. 1991;15:1171–1180.
14. Luo JH, Yu YP, Cieply K, et al. Gene expression analysis of prostate cancers. *Mole Carcinog*. 2002;33:25–35.
15. Moore R. The evolution and involution of the prostate gland. *Am J Pathol*. 1936;12:599–624.
16. Oppenheimer JR, Kahane H, Epstein JI. Granulomatous prostatitis on needle biopsy. *Arch Path Lab Med*. 1997;121:724–729.
17. Oppenheimer JR, Wills ML, Epstein JI. Partial atrophy in prostate needle cores: another diagnostic pitfall for the surgical pathologist. *Am J Surg Pathol*. 1998;22:440–445.
18. Sebo TJ, Bostwick DG, Farrow GM, et al. prostatic xanthoma: a mimic of prostatic adenocarcinoma. *Hum Pathol*. 1994;25:386–389.
19. Young RH. Tumor-like lesions of the prostate gland. *Am J Surg Pathol*. 1995;104:607–610.
20. Zhou M, Jiang Z, Epstein JI. Expression and diagnostic utility of alpha-methylacyl-CoA-racemase (P504S) in foamy gland and pseudohyperplastic prostate cancer. *Am J Surg Pathol*. 2003;27:772–778.

