Foamy Gland Carcinoma of the Prostate in Needle Biopsy

Incidence, Gleason Grade, and Comparative α-Methylacyl-CoA Racemase vs. ERG Expression

Joshua I. Warrick, MD and Peter A. Humphrey, MD, PhD

Abstract: Foamy gland carcinoma is a variant of prostatic acinar adenocarcinoma characterized by abundant, foamy cytoplasm, frequently showing small, pyknotic nuclei. The incidence and Gleason grade of foamy gland carcinoma in a large prostate needle biopsy series have not been established. Foamy gland carcinoma may be deceptively benign appearing and missed on needle biopsy. Immunohistochemical staining for basal cells and α-methylacyl-CoA racemase (AMACR) can support a diagnosis of foamy gland carcinoma, but the sensitivity of AMACR for foamy gland carcinoma has been reported to be lower than that for usual acinar carcinoma. The utility of ERG immunohistochemistry in the diagnosis of foamy gland carcinoma has not been explored. The aim of this study was to characterize the incidence and Gleason grade of foamy gland carcinoma in a large consecutive series of prostate needle biopsy cases. We also assessed ERG expression in foamy gland carcinoma, in comparison with AMACR expression, to determine whether ERG expression provides added diagnostic value beyond AMACR expression. We evaluated a consecutive series of 476 prostatic adenocarcinoma needle core biopsy cases for presence, linear extent, and Gleason grade of foamy gland carcinoma. A selected block from each case containing foamy gland carcinoma was evaluated for AMACR and ERG expression by immunohistochemistry. Of the 476 cases, 17% contained a foamy gland carcinoma component, with 2% of the cases showing pure foamy gland carcinoma. Two cases of pure foamy gland carcinoma had a total linear extent of <3 mm. The majority (80%) of cases had a Gleason score $3+3=$ score of 6. Sensitivity of AMACR for foamy gland carcinoma was 92%, and sensitivity of ERG was 42%. No AMACR-negative case was ERG positive. Low AMACR expression was detected in 24 of 72 cases (33%), and of these cases ERG was positive in 5 (21%). In summary, foamy gland carcinoma features are relatively common in prostate needle core biopsies, the foamy gland carcinoma is admixed with usual acinar carcinoma in the majority of cases, and is usually not of high Gleason grade, although 20% are Gleason score 7 or greater. ERG immunohistochemistry did not provide added value beyond AMACR expression in most cases, suggesting that it need not be initially utilized in addition to basal cell markers and AMACR when immunohistochemistry is needed to substantiate a diagnosis of foamy gland malignancy. This is an important consideration in this era of cost-consciousness in application of immunohistochemistry. Sensitivity of AMACR for foamy gland carcinoma was comparable to that seen in studies of usual acinar carcinoma and is an excellent marker for foamy gland carcinoma of the prostate. ERG immunohistochemistry could be considered in a second round of immunostaining of select difficult cases of foamy gland carcinoma with low AMACR expression.

Key Words: prostate, adenocarcinoma, foamy gland, immunohistochemistry, ERG

(*Am J Surg Pathol* 2013;37:1709–1714)

Foamy gland carcinoma is a variant pattern of prostatic acinar adenocarcinoma first described by Epstein and Nelson,[1] characterized by abundant, foamy cytoplasm.

In this original series, the majority of cases showed small, pyknotic nuclei and a high Gleason score. Owing to the minimal nuclear atypia in many cases, foamy gland pattern carcinoma may be deceptively benign appearing and accounts for a large percentage of prostatic carcinoma cases misdiagnosed as benign on needle biopsy.[2,3] Immunohistochemistry can be an important diagnostic tool in confirming a diagnosis of foamy gland carcinoma, but α-methylacyl-CoA racemase (AMACR), which is expressed in 90% of usual acinar adenocarcinomas,[4–6] has been reported to be expressed in only 68% of foamy gland carinomas.[7] The discovery of *TMPRSS2:ERG* gene rearrangement in approximately 50% to 70% of prostatic carcinomas,[8–10] the correlation of the gene fusion with ERG protein expression, and the subsequent development of a highly specific antibody have generated considerable interest in ERG immunostains as an aid in detecting prostatic carcinoma.[11–16] *ERG* gene rearrangement has been identified in foamy gland carcinoma,[17] but ERG protein expression has not been evaluated in foamy gland carcinoma. Of particular interest would be an analysis that addressed whether ERG immunohistochemistry might provide additional value beyond AMACR immunohistochemistry in supporting a diagnosis of adenocarcinoma. Specifically, as AMACR is

From the Department of Pathology and Immunology, Washington University School of Medicine, Saint Louis, MO.

Present address: Joshua I. Warrick, MD, Department of Pathology, University of Michigan, 1301 Catherine st., Ann Arbor, 43109, MI.

Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Correspondence: Peter A. Humphrey, MD, PhD, Department of Pathology and Immunology, Washington University School of Medicine, Campus Box 8118 660, South Euclid Ave., St Louis, MO (e-mail: humphrey@wustl.edu).

negative in 32% of foamy gland carcinomas, would ERG immunohistochemistry be of diagnostic value in these cases?

The incidence and Gleason grade of foamy gland carcinoma have been characterized in prostate glands from radical prostatectomy specimens,[18] but the incidence in needle biopsy has not been reported, and the Gleason grade in a series of consecutive needle biopsy cases has not been determined. The purpose of this study was to characterize the incidence and Gleason grade of foamy gland carcinoma in a large consecutive series of prostate needle biopsy cases. We also assessed ERG expression in foamy gland carcinoma, in comparison with AMACR expression, to determine whether ERG expression provides added diagnostic value beyond AMACR expression.

MATERIALS AND METHODS

Case Selection

A total of 476 consecutive prostate needle core biopsies were identified by a computerized database search of the surgical pathology archives of Barnes-Jewish Hospital, diagnosed over a 2-year period. The slides with the cores were reviewed by J.I.W., who documented the number of cases with foamy gland carcinoma, the linear extent of foamy gland carcinoma, and Gleason grade according to a modification of the International Society of Urological Pathology guidelines,[19] with the modification being that all cribriform carcinomas were graded as pattern 4.[20,21] The diagnosis of foamy gland carcinoma was confirmed by P.A.H. in all cases.

Immunohistochemistry

For each case a representative block was selected, and 2 consecutive 5-μm-thick sections were cut from formalin-fixed, paraffin-embedded tissue blocks and mounted on positively charged slides. Separate slides were then stained with ERG (Ventana Medical Systems, Tucson, AZ; clone EPR3864, catalog #790-4576) and AMACR (P504S; Cell Marque, Rocklin, CA; clone 13H4, catalog #504R-10) antibodies. The immunohistochemical staining for ERG was performed with a Benchmark XT automatic immunostainer (Ventana Medical Systems). Antigen retrieval was accomplished with heat-inducted epitope retrieval and cell conditioning 1 standard (CC1 standard, 1 mM EDTA-Tris–based buffer pH 8.0) for 60 minutes. The prediluted antibody was then applied and incubated for 16 minutes at 37°C. Detetion was achieved with the ultraview Universal DAV Detection kit (catalog #760-500; Ventana). Immunostaining for AMACR was performed using Venta Ultra automated stainer (Ventana Medical Systems). Slides were incubated at 37°C with Cell Marque's P504s (AMACR) prediluted antibody for 28 minutes. The slides were then rinsed and counterstained with Ventana's hematoxylin and Ventana's bluing reagent.

Evaluation of Immunohistochemistry

Slides stained with AMACR were evaluated for intensity and proportion of carcinoma cells stained. Intensity score was rated 0 (noncircumferential staining), 1+ (focal apical granular staining), 2+ (diffuse weak cytoplasmic staining), or 3+ (strong, cytoplasmic and luminal staining). Proportion was rated with respect to percentage of positively stained cells, as follows: 0 (< 5% cells stained), 1+ (5% to 25% of cells stained), 2+ (26% to 50% of cell stained), 3+ (51% to 75% of cells stained), and 4+ (76% to 100% of cells stained). The intensity and proportion scores were added to give an overall score, with 7 being the highest possible. All scores > 0 were considered AMACR positive. ERG staining was assigned scores for intensity and proportion, as has been previously described,[22] with intensity score ranging from 0 to 3+ and proportion score ranging from 0 to 4+. The immunoreactive score was calculated as the product of the intensity and proportion scores, with a maximum possible score of 12. All scores > 0 were considered ERG positive. Upon completion of review of all hematoxylin and eosin (H&E) slides, immunohistochemistry for AMACR and ERG was reviewed, along with the corresponding H&E slides to confirm staining applied to the cancer foci of interest. The association between ERG status of foamy gland carcinoma and adjacent usual acinar carcinoma was evaluated with the Fisher exact test using the Stats package in the R programming language.[23]

RESULTS

Percentage of Cases Involved by Foamy Gland Carcinoma, and Linear Extent of Foamy Gland Carcinoma

Of 476 consecutive prostate cancer cases diagnosed on needle biopsy, 17% (81 cases) contained a foamy gland carcinoma component. Cases of pure foamy gland carcinoma accounted for 2% (10/476) of all cases. Of the 81 foamy gland carcinoma cases, 12% (10/81) were pure. The remaining cases (88%, 71/81) contained both foamy gland and usual acinar carcinoma. In pure foamy gland carcinoma cases, linear extent of carcinoma ranged from 2 to 19 mm. Average linear extent was 9.8 mm (SD 6.9 mm). Of the cases with both a foamy gland component and a usual acinar carcinoma component, linear extent of the foamy gland component ranged from 1 to 38 mm. The average linear extent of the foamy gland component in mixed cases was 8.2 mm (SD 7.5 mm). Total linear extent of cancer in 2 cases of pure foamy gland carcinoma was < 3 mm (both 2 mm in linear extent).

In total, 122 slides contained foamy gland carcinoma from the 81 cases. Average linear extent of foamy gland carcinoma was 6 mm (SD 4 mm; range, 1 to 20 mm) per slide. Slides in which foamy gland carcinoma represented the entire prostate cancer on the slide accounted for 45% (55/122) of slides. Of the slides containing only foamy gland carcinoma, linear extent of cancer measured < 3 mm in 13% (7/55 slides; 2 mm linear extent in 6 slides, 1 mm linear extent in 1 slide). In all slides containing foamy gland carcinoma, the foamy gland component accounted for 7% to 100% of total cancer (median 83%).

TABLE 1. Foamy Gland Carcinoma Gleason Scores

Gleason Score	% (No. Cases/No. Evaluated)
3+3 = 6	80 (65/81)
3+4 = 7	14.5 (12/81)
4+4 = 8	2.5 (2/81)
4+5 = 9	1.5 (1/81)
5+3 = 8	1.5 (1/81)

Histomorphologic Findings

The majority (80%, 65/81) of foamy gland carcinomas had a Gleason grade of 3+3 = score of 6. Gleason scores of the foamy gland component of the 81 cases are presented in Table 1. H&E-stained sections of various Gleason patterns are presented in Figure 1. Of all foamy gland carcinoma cases, 68% (55/81) showed areas of small, pyknotic nuclei. Of the pure foamy gland carcinoma cases, 70% (7/10) showed areas with small, pyknotic nuclei.

Immunohistochemistry

After obtaining deeper sections, 72 carcinomas with a foamy gland component had sufficient tissue for immunohistochemical studies. Of these, 92% (66 cases) were AMACR positive. Median AMACR score was 6 (range, 0 to 7). Of the AMACR-positive cases, 33% (22/66 cases) showed low AMACR staining (sum score <6). Of the 72 evaluable cases, 42% (30 cases) were ERG positive. Of the ERG-positive cases, 80% (25/30) had a product score of 12, and the remaining product scores were 8, 6, 6, 4, and 2. None of the AMACR-negative cases were ERG positive. Of the low AMACR staining cases, 21% (5/24) were ERG positive.

Expression status of ERG and AMACR tended to be uniform across the cancer specimen on a given slide. Three foamy gland cancers (4%, 3/72) showed different expression statuses from an adjacent usual acinar carcinoma. In 2 of these, the usual acinar carcinoma was $AMACR^+/ERG^+$, whereas the foamy gland cancer was $AMACR^+/ERG^-$. In the third case, the usual acinar carcinoma was $AMACR^+/ERG^+$, whereas the foamy gland carcinoma was $AMACR^-/ERG^-$. Two cases (3%, 2/72) showed distinct foamy gland populations demonstrating different expression statuses. In 1 case, one population was $AMACR^+/ERG^+$, whereas the other was $AMACR^+/ERG^-$. In the other case, one population was $AMACR^+/ERG^+$, whereas the other population was $AMACR^-/ERG^-$. In both cases, the ERG product score assignment was 6. Of the remaining 93% (67/72) of cases evaluated with immunohistochemical analysis, the entire cancer specimen on the slide showed the same AMACR and ERG expression status. Both foamy gland carcinoma and usual acinar carcinoma were present on the evaluated slide in 64% (46/67) of these cases and showed the same expression status for AMACR and ERG. The association between ERG status of foamy gland cancer and adjacent usual acinar carcinoma in these cases was highly statistically significant ($P < 0.001$, Fisher exact test). Images of $AMACR^+$, ERG^+, and ERG^- foamy gland carcinoma are presented in Figure 2.

DISCUSSION

The current study is the first to our knowledge to characterize a consecutive series of foamy gland carcinomas diagnosed on prostate needle core biopsy. The results demonstrate that foamy gland carcinoma is relatively common on needle biopsy, with foamy gland features identified in 17% of cancer cases. It is noteworthy that this incidence is similar to the 15% to 23% incidence of foamy gland carcinoma features described in the whole prostate gland at radical prostatectomy.[18] Thus, in prostatic adenocarcinoma in both needle biopsies and radical prostatectomy cases, one can anticipate encountering foamy gland features on a regular basis.

We also characterize Gleason grade in this series of foamy gland carcinomas in needle biopsy, which is the largest reported series to date. The finding that the majority of cases in the present series were of Gleason grade 3+3 = score of 6 is somewhat surprising, considering that the majority of foamy gland carcinomas in the whole gland are reported to be of a higher grade, with the largest study showing the majority to be Gleason score 3+4 = score of 7 at radical prostatectomy.[18] As is a common problem in prostate pathology, this may represent a clinical sampling issue, in which a prostate gland contains a Gleason grade 3+4 = 7 carcinoma, but only the pattern 3 component is sampled by needle biopsy. Higher-grade foamy gland carcinomas did comprise a significant minority, at 20%, of all foamy gland carcinomas in needle biopsy, substantiating the existence of Gleason pattern 4 and 5 foamy gland carcinoma in needle core tissue[24] and establishing the incidence of this finding. Another potential basis for the difference in Gleason grades in needle biopsy tissue compared with that in radical prostatectomy prostate tissue is that these were different patient populations, and there could have been a selection bias for higher-grade carcinomas in foamy gland carcinoma patients who underwent radical prostatectomy.

Our study also found that pure foamy gland carcinomas were relatively uncommon, representing only 2% of all prostate adenocarcinomas diagnosed on needle biopsy. These 10 cases of pure foamy gland carcinoma, which comprised 12% of all foamy gland carcinomas in needle biopsy, showed a linear extent as small as 2 mm, which could be easily missed, as previously reported.[2,3,25] For smaller and/or pure foamy gland carcinoma, it would be diagnostically advantageous to search for areas where nuclear atypia and nonpyknotic nuclei were present. Not all foamy gland carcinomas in this series had pyknotic nuclei, similar to previous reports,[1,18,24] and thus examination of both the foamy gland adenocarcinoma component and the commonly admixed nonfoamy usual acinar adenocarcinoma for nuclear enlargement and prominent nucleoli is a recommended diagnostic approach.

AMACR expression as assessed by immunohistochemical analysis has been shown to be approximately 90% sensitive for usual acinar–type adenocarcinomas of the prostate.[4–6] The largest series evaluating AMACR expression in foamy gland carcinoma showed AMACR immunostaining to have decreased sensitivity compared with

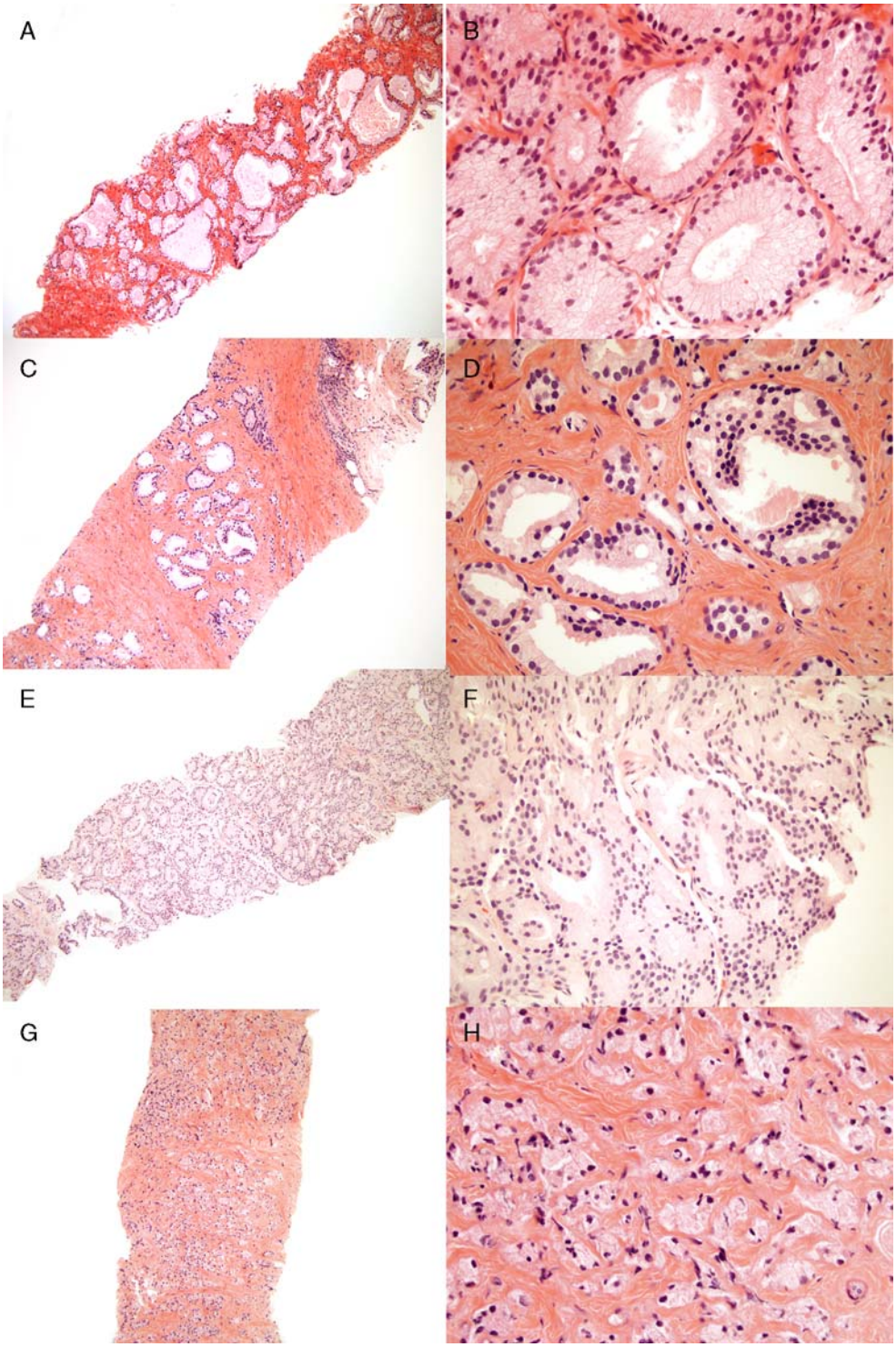

FIGURE 1. H&E-stained sections of prostate needle cores showing foamy gland carcinomas of varying Gleason scores, all of which contain abundant, foamy cytoplasm. A and B, Gleason grade 3 + 3 = score of 6 with well-formed glands, (C and D) Gleason grade 3 + 4 = score of 7 with focal cribriform pattern, (E and F) Gleason grade 4 + 4 = score of 8 with complete cribriform pattern, and (G and H) Gleason pattern 5 with infiltrating single cells.

usual acinar carcinoma, with expression in only 68% of cases.[7] In contrast, we found 92% of the foamy gland carcinomas to be AMACR positive, representing sensitivity equivalent to that seen in usual acinar carcinoma. The basis for this difference is unclear. The previous study used similar criteria for AMACR positivity as the present study,

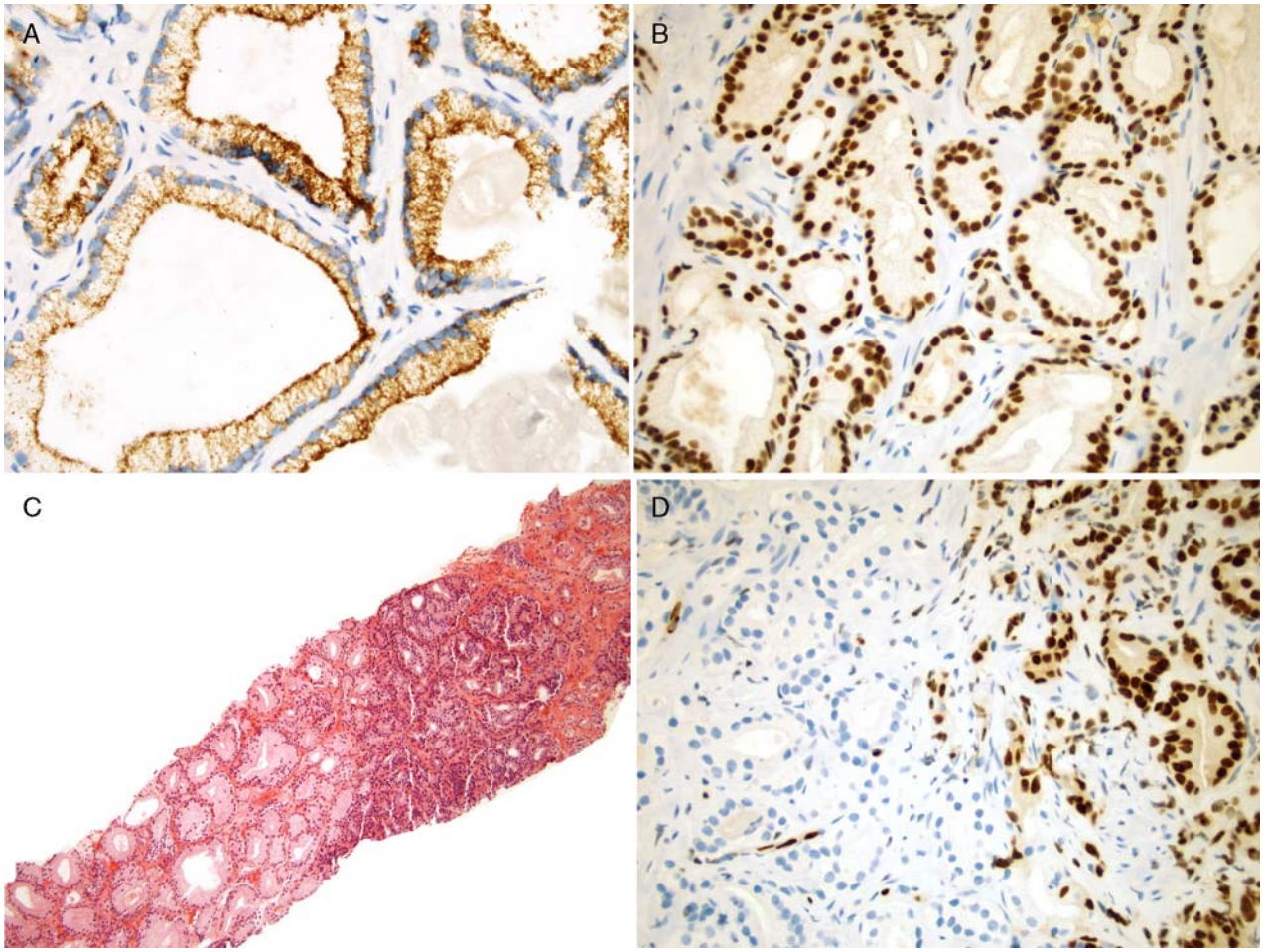

FIGURE 2. Immunohistochemical analysis result showing strong luminal and cytoplasmic AMACR expression in this foamy gland carcinoma (A), and strong, diffuse nuclear expression of ERG (B). H&E-stained section showing foamy gland carcinoma (lower left) with adjacent usual acinar carcinoma (upper right) (C), and different ERG expressions in adjacent foamy gland carcinoma (lower left, ERG^-) and usual acinar carcinoma (upper right, ERG^+) (D).

although staining in a cancer focus was interpreted with consideration of background staining (eg, if background benign prostate showed moderate staining, moderate staining in cancer was considered negative).[7] Our AMACR immunostain was well optimized, and background staining was not observed. Thus, we do not believe that differing criteria for AMACR positivity account for the difference in reported AMACR expression.

ERG protein, which is a highly selective marker for prostatic neoplastic cells, has diagnostic potential in detecting prostatic adenocarcinoma and has been tested in the diagnosis of limited prostate cancer,[22] for the assessment of atypical glands suspicious for carcinoma,[26] and for detection of metastatic prostatic carcinoma.[14] ERG protein expression is related to the *TMPRSS2-ERG* gene fusion. Fusion genes resulting from rearrangements involving members of the ETS family of transcription factors, including ERG, are one of the most common known molecular abnormalities in prostate cancer and have been identified in ~50% of prostate cancers identified using prostate-specific antigen screening.[8–10] The most common such rearrangement involves fusion of the androgen-upregulated *TMPRSS2* with the ETS gene *ERG*, with resulting androgen-driven overexpression of the ERG protein product. Detection of ERG expression by immunohistochemistry has been shown to be sensitive and specific for *TMPRSS2-ERG* rearrangements,[11–16] although a limitation of the use of ERG immunostaining in the diagnosis of prostatic carcinoma is that the sensitivity is modest at 50% of all prostatic carcinomas. Studies of *TMPRSS2:ERG* rearrangements in foamy gland carcinomas have shown it to be present in 29% of foamy gland carcinoma cases by fluorescence in situ hybridization.[17] We found 42% of foamy gland carcinomas in the present study to be ERG positive by immunohistochemistry, but none of the AMACR-negative cases was ERG positive, suggesting that ERG is unlikely to be of utility in cases showing negative AMACR staining. In our study, ERG expression was seen in several cases with low AMACR expression. ERG immunohistochemistry offers potential value in difficult cases of foamy gland carcinoma that show weak or focal AMACR expression. In this era

of cost-consciousness in application of immunohistochemistry, immunostains for basal cell markers and AMACR should be the first immunostains ordered, when immunohistochemistry is needed to support a histologic diagnosis of foamy gland adenocarcinoma. In the one third of cases that are low AMACR expressors, ERG may be beneficial in only around 20% of cases; therefore its use should be limited to low AMACR expressors where there is substantial need for confirmation of malignancy.

In summary, foamy gland carcinoma is a fairly common finding on needle biopsy and is most often Gleason grade 3 + 3 = score of 6, although 20% of cases have high-grade pattern 4 or 5. Foamy gland carcinoma is admixed with usual acinar adenocarcinoma in the vast majority of cases and is rarely found in pure form in needle biopsy. A search for the admixed usual acinar component can be of diagnostic value, as nuclear atypia in this component is greater than that seen in the foamy gland component, which often has pyknotic nuclei. Sensitivity of AMACR and ERG detection by immunohistochemistry in foamy gland carcinoma is similar to that seen in usual acinar carcinoma. Confirmatory immunohistochemistry with AMACR and basal cell markers is sufficient in most cases of foamy gland carcinoma, with ERG immunohistochemistry utility limited to cases with weak or focal AMACR staining.

REFERENCES

1. Nelson RS, Epstein JI. Prostatic carcinoma with abundant xanthomatous cytoplasm. Foamy gland carcinoma. *Am J Surg Pathol*. 1996;20:419–426.
2. Carswell BM, Woda BA, Wang X, et al. Detection of prostate cancer by alpha-methylacyl CoA racemase (P504S) in needle biopsy specimens previously reported as negative for malignancy. *Histopathology*. 2006;48:668–673.
3. Wolters T, Van der Kwast TH, Vissers CJ, et al. False-negative prostate needle biopsies: frequency, histopathologic features, and follow-up. *Am J Surg Pathol*. 2010;34:35–43.
4. Hameed O, Sublett J, Humphrey PA. Immunohistochemical stains for p63 and alpha-methylacyl-CoA racemase, versus a cocktail comprising both, in the diagnosis of prostatic carcinoma: a comparison of the immunohistochemical staining of 430 foci in radical prostatectomy and needle biopsy tissues. *Am J Surg Pathol*. 2005;29:579–587.
5. Kunju LP, Chinnaiyan AM, Shah RB. Comparison of monoclonal antibody (P504S) and polyclonal antibody to alpha methylacyl-CoA racemase (AMACR) in the work-up of prostate cancer. *Histopathology*. 2005;47:587–596.
6. Kunju LP, Rubin MA, Chinnaiyan AM, et al. Diagnostic usefulness of monoclonal antibody P504S in the workup of atypical prostatic glandular proliferations. *Am J Clin Pathol*. 2003;120:737–745.
7. 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.
8. Clark JP, Cooper CS. ETS gene fusions in prostate cancer. *Nat Rev Urol*. 2009;6:429–439.
9. Van Leenders GJLH, Boormans JL, Vissers CJ, et al. Antibody EPR3864 is specific for ERG genomic fusions in prostate cancer: implications for pathological practice. *Mod Pathol*. 2011;24:1128–1138.
10. Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science*. 2005;310:644–648.
11. Furusato B, Tan S-H, Young D, et al. ERG oncoprotein expression in prostate cancer: clonal progression of ERG-positive tumor cells and potential for ERG-based stratification. *Prostate Cancer Prostatic Dis*. 2010;13:228–237.
12. Park K, Tomlins SA, Mudaliar KM, et al. Antibody-based detection of ERG rearrangement-positive prostate cancer. *Neoplasia*. 2010;12:590–598.
13. Braun M, Goltz D, Shaikhibrahim Z, et al. ERG protein expression and genomic rearrangement status in primary and metastatic prostate cancer-a comparative study of two monoclonal antibodies. *Prostate Cancer Prostatic Dis*. 2012;15:165–169.
14. Falzarano SM, Zhou M, Carver P, et al. ERG gene rearrangement status in prostate cancer detected by immunohistochemistry. *Virchows Arch*. 2011;459:441–447.
15. Miettinen M, Wang Z-F, Paetau A, et al. ERG transcription factor as an immunohistochemical marker for vascular endothelial tumors and prostatic carcinoma. *Am J Surg Pathol*. 2011;35:432–441.
16. Fine SW, Gopalan A, Leversha MA, et al. TMPRSS2-ERG gene fusion is associated with low Gleason scores and not with high-grade morphological features. *Mod Pathol*. 2010;23:1325–1333.
17. Han B, Mehra R, Suleman K, et al. Characterization of ETS gene aberrations in select histologic variants of prostate carcinoma. *Mod Pathol*. 2009;22:1176–1185.
18. Hudson J, Cao D, Vollmer R, et al. Foamy gland adenocarcinoma of the prostate: incidence, Gleason grade, and early clinical outcome. *Hum Pathol*. 2012;43:974–979.
19. Epstein JI, Allsbrook WC Jr, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol*. 2005;29:1228–1242.
20. Epstein JI. An update of the Gleason grading system. *J Urol*. 2010;183:433–440.
21. Epstein JI, Cubilla AL, Humphrey PA. *Tumors of the Prostate Gland, Seminal Vesicles, Penis, and Scrotum*. Washington, DC: American Registry of Pathology; 2011.
22. Yaskiv O, Zhang X, Simmerman K, et al. The utility of ERG/P63 double immunohistochemical staining in the diagnosis of limited cancer in prostate needle biopsies. *Am J Surg Pathol*. 2011;35:1062–1068.
23. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2011.
24. Zhao J, Epstein JI. High-grade foamy gland prostatic adenocarcinoma on biopsy or transurethral resection: a morphologic study of 55 cases. *Am J Surg Pathol*. 2009;33:583–590.
25. Arista-Nasr J, Martinez-Benitez B, Camorlinga-Tagle N, et al. Foamy gland microcarcinoma in needle prostatic biopsy. *Ann Diagn Pathol*. 2008;12:349–355.
26. He H, Magi-Galluzzi C, Li J, et al. The diagnostic utility of novel immunohistochemical marker ERG in the workup of prostate biopsies with "atypical glands suspicious for cancer". *Am J Surg Pathol*. 2011;35:608–614.