Case – Foamy high-grade prostatic intraepithelial neoplasia: A false positive for prostate cancer on mpMRI?

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Introduction

The introduction of multi-parametric magnetic resonance imaging (mpMRI) of the prostate, and specifically the introduction of diffusion weighted imaging (DWI), has significantly impacted the diagnosis of prostate cancer and the management of clinically localized prostate cancer. Indeed, its localizing ability has now opened up opportunities to target focal lesions in partial gland ablation therapy as a treatment option for localized prostate cancer.

With negative predictive rates of mpMRI approaching 90% in certain series,[1] mpMRI has the ability to discriminate between clinically significant intermediate-to-high risk prostate cancer and low risk indolent disease. However, false positives can occur. In recent studies, lesions observed on MRI were classified as tumor on targeted biopsy in 47.6% to over 94% for tumors larger than 0.5 ml in volume.[2,3]

Herein we present a case of a rare non-cancer, but putatively pre-malignant prostatic histology that was found on biopsies directed at a category 5 PIRADS v2 (Prostate Imaging Reporting and Data System) lesion.

Case report

A 65-year-old man was referred to our center with a history of an elevated PSA (7.6 ng/mL) and one prior negative systematic biopsy at a local clinic. He is otherwise relatively healthy with a past medical history of gastroesophageal reflux disease, hyperlipidemia, and benign prostatic hyperplasia. His medications include tamsulosin, omeprazole, and simvastatin.

Due to his prior negative systematic biopsy and a subsequent rise in his PSA to 11 ng/mL, he was sent for a standard multiparametric prostate MRI (mpMRI) based on evidence-based guidelines.[4,5] The mpMRI, completed December 2015, demonstrated a 103 mL prostate, moderate hyperplasia of the transition zone (TZ) with a prominent median lobe, and a large PIRADS 5 lesion. Specifically, the lesion demonstrated T2 homogeneous low signal changes, marked restriction on ADC (ADC value of <700 mm^2/s) and was bright on the calculated high b-

value (1400 s/mm^2) DWI images. It extended from the mid-gland to the apex of the left peripheral zone (PZ) with some sparing of the left mid gland anterior PZ. The lesion also extended to involve the adjacent left TZ. The lesion measured 1.8 x 4.1 x 3.5 cm (Figure 1). The prostatic capsule appeared to be intact. No definite focus of tumor was seen in the right peripheral zone. The remainder of the MRI was normal – seminal vesicles, pelvic lymph nodes, bladder and bowel.

In January 2016, he underwent a transrectal ultrasound-guided (TRUS) biopsy. Because the lesion was visible on ultrasound (Supplementary Figure 1), cognitive real-time targeted and systematic biopsies were obtained. A total of 15 cores were taken, 13 during the systematic biopsy and 2 from the lesion itself. Extensive high-grade prostatic intraepithelial neoplasia (HG PIN) was identified on all the left sided cores, the right lateral cores and the targeted cores. A comment regarding "foamy HG PIN" was noted in the pathology report and applied specifically to the left-sided cores (Figure 2).

He was then discussed at our multidisciplinary rounds, attended by our uropathologists, radiologists, and urologic oncologists. By this time, his PSA remained elevated (9.88 ng/mL). Review of the pathology from the TRUS-guided biopsy of the left-sided lesion was remarkable for extensive HG PIN characterized by cells with abundant pale, foamy cytoplasm. Immunohistochemical staining confirmed the presence of a discontinuous basal cell layer in the involved glands, confirming a diagnosis of foamy gland HG PIN. Importantly, the involved glands were not completely filled or distended by the foamy cells nor did they show dense or loose cribriform or micropapillary architecture, marked nuclear atypia or comedo-type necrosis that would have suggested a diagnosis of intraductal carcinoma with foamy features. Foamy gland HG PIN is a known pathological entity, however its appearance on MRI is unknown. The consensus was to proceed with a repeat targeted biopsy, with the understanding that if similar findings were again noted, he would be placed on PSA surveillance

In October 2016, he underwent a targeted fusion biopsy using the Artemis MR fusion device platform (Eigen, California). A total of 3 cores were taken from the lesion, and the pathology again demonstrated extensive HG PIN with foamy gland features. No intraductal carcinoma with foamy gland features or invasive adenocarcinoma with foamy gland features or of usual acinar type was identified. He was again discussed at our multidisciplinary rounds. The consensus of the group was that, as he had been extensively biopsied, we should proceed with PSA surveillance and follow-up biopsies when clinically indicated.

Discussion

HG PIN is a putative precursor of invasive prostatic adenocarcinoma. It can have a variety of histological appearances including flat, tufted micropapillary and cribriform architecture.[6] Epstein and colleagues reported a case of foamy gland HG PIN identified in a radical prostatectomy specimen adjacent to known Gleason 3+3=6 prostate adenocarcinoma.[7] Morphologically, foamy gland HG PIN is characterized by bland nuclei and abundant xanthomatous cytoplasm with a distinct foamy appearance. Unlike foamy gland adenocarcinoma

of the prostate, foamy gland HG PIN has enlarged glands, lined by foamy cells with papillary infolding and a preserved, but discontinuous layer of basal cells as demonstrated by immunohistochemical staining for high-molecular weight cytokeratin. Foamy gland HG PIN is a rare finding that pathologists should not be confused for intraductal carcinoma with foamy gland features or invasive foamy gland prostatic adenocarcinoma. The latter is a rare variant of prostatic adenocarcinoma as described by Nelson and Epstein in 1996 and again by Zhao and Epstein in 2009.[8,9]

While the histology of foamy gland HG PIN has been previously reported, this is the first documentation of an apparently unique appearance of foamy gland HG PIN on mpMRI. On T2-weighted imaging, the area was hypointense, confined to the prostate and >1.5 cm in size, while on DWI, it showed marked hypointensity on ADC and marked hyperintensity on high b-value DWI; in keeping with a PIRAD 5 lesion. Despite thorough sampling by multiple image-guided needle biopsies directed at the lesion no invasive adenocarcinoma was identified.

We recognize that the ultimate support for the above conclusion would come from the histologic examination of a radical prostatectomy specimen from this patient, however this is obviously not possible in the absence of a diagnosis of invasive prostatic adenocarcinoma. Bacterial prostatitis, mycobacterial granulomatous prostatitis, malacoplakia, gland atrophy and necrosis have been noted to have imaging criteria on mpMRI that overlap with those of prostate carcinoma.[10] Several of these mimics have been shown to have histologic features similar to cancer, with increased cellularity, reduced loose supporting stroma or increased vessel density. Langer et al described that ADC and T2 were inversely related to the percentage area of nuclei and cytoplasm and positively related to volume of luminal space.[11] One hypothesis for foamy gland HG PIN to mimic prostate cancer on MRI may be the presence of the abundant cytoplasm characteristic of this entity.

This rare manifestation of HG PIN can be challenging to diagnose histologically and it is not to be confused with or treated as invasive foamy gland adenocarcinoma or classic acinar-type adenocarcinoma.

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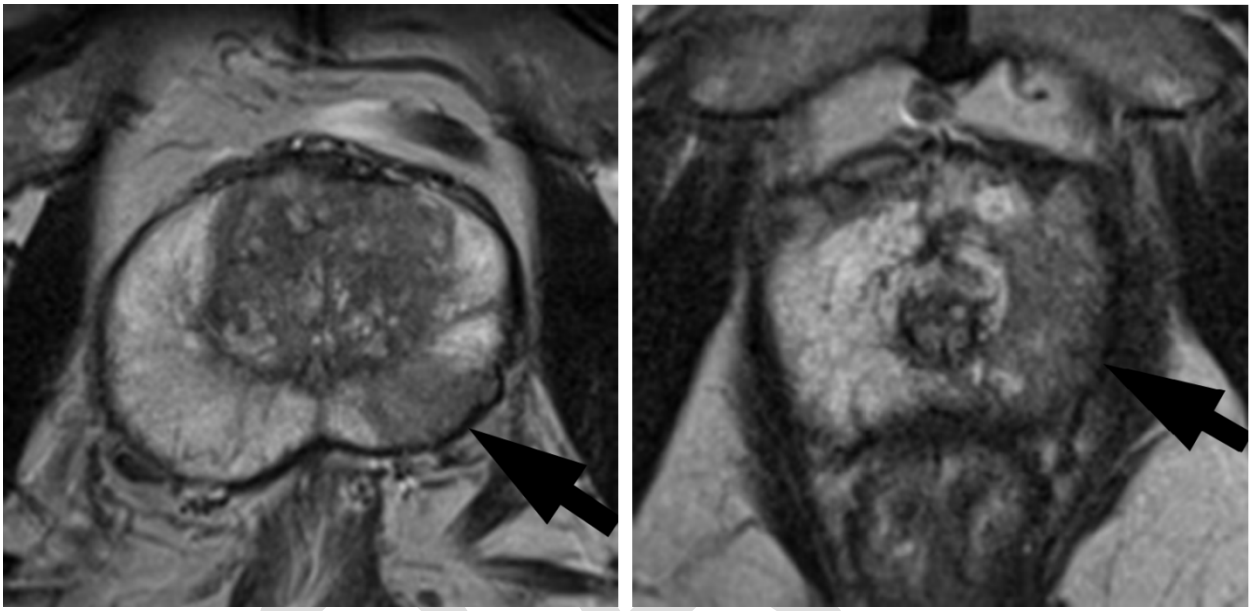
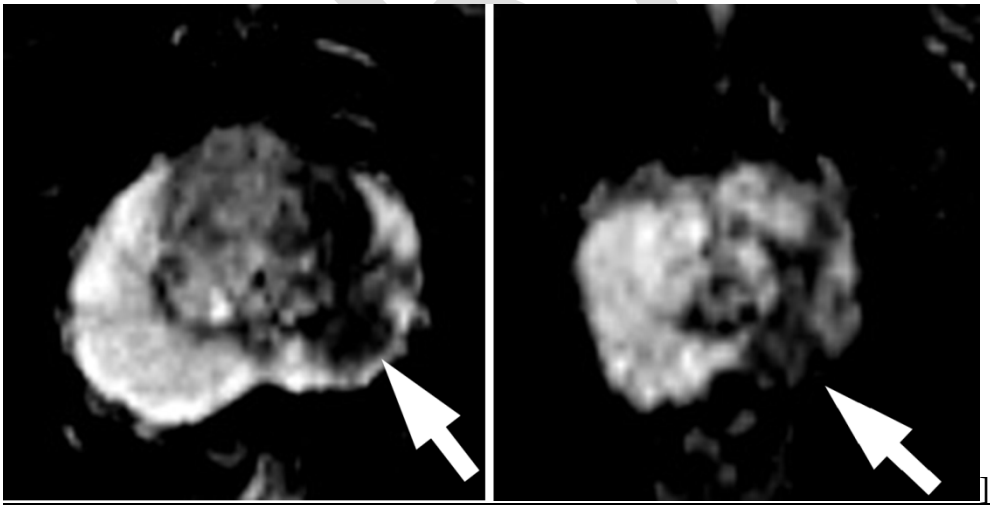
Figures and Tables

Fig. 1. mpMRI findings of foamy PIN. ***(A, B)*** Axial T2-weighted fast spin-echo MR image (TR/TE, 4140/97). ***(C, D)*** Corresponding axial apparent diffusion coefficient (ADC) map (TR/TE, 4800/70; b values100,400,800, 1000mm/s^2).

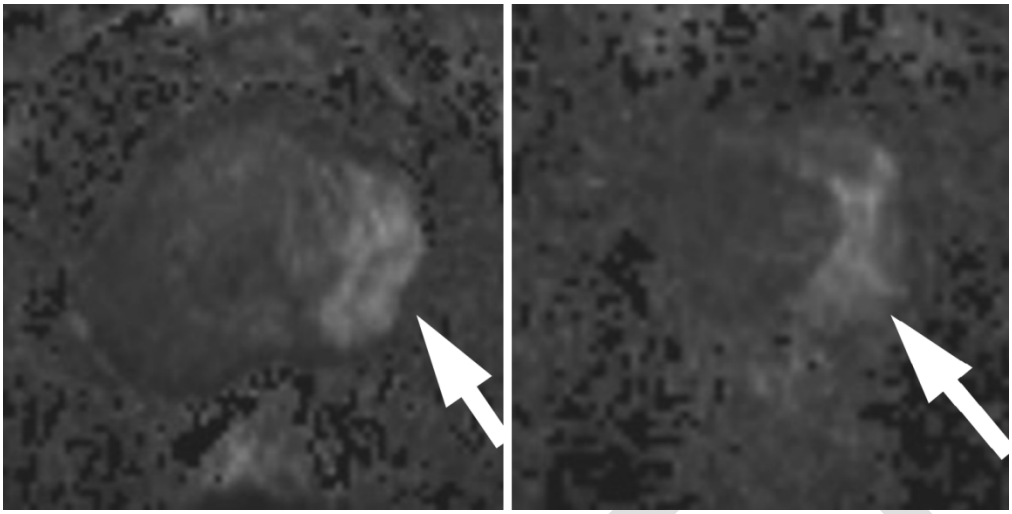
(A)



(B)



(C)



(D)

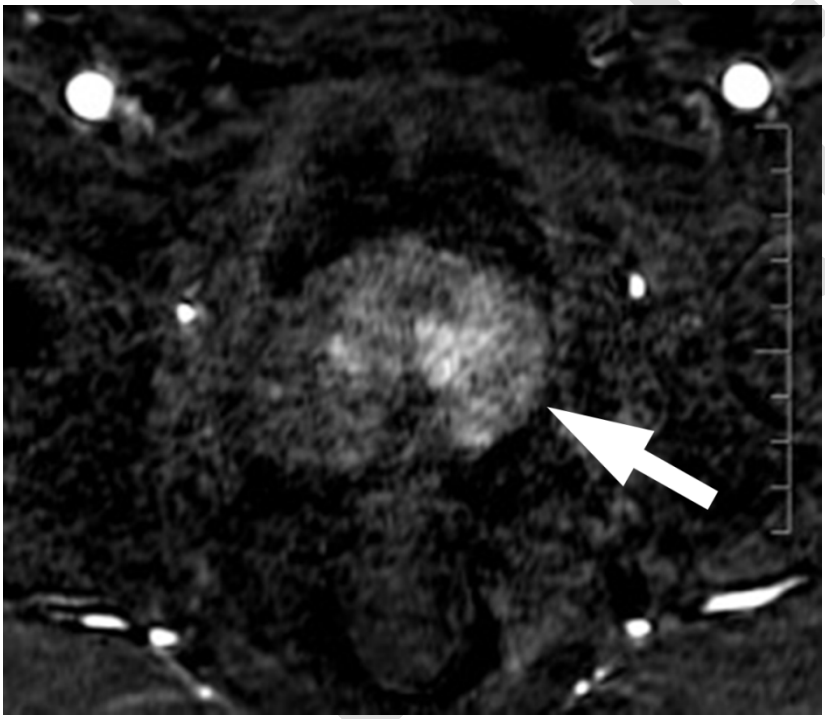
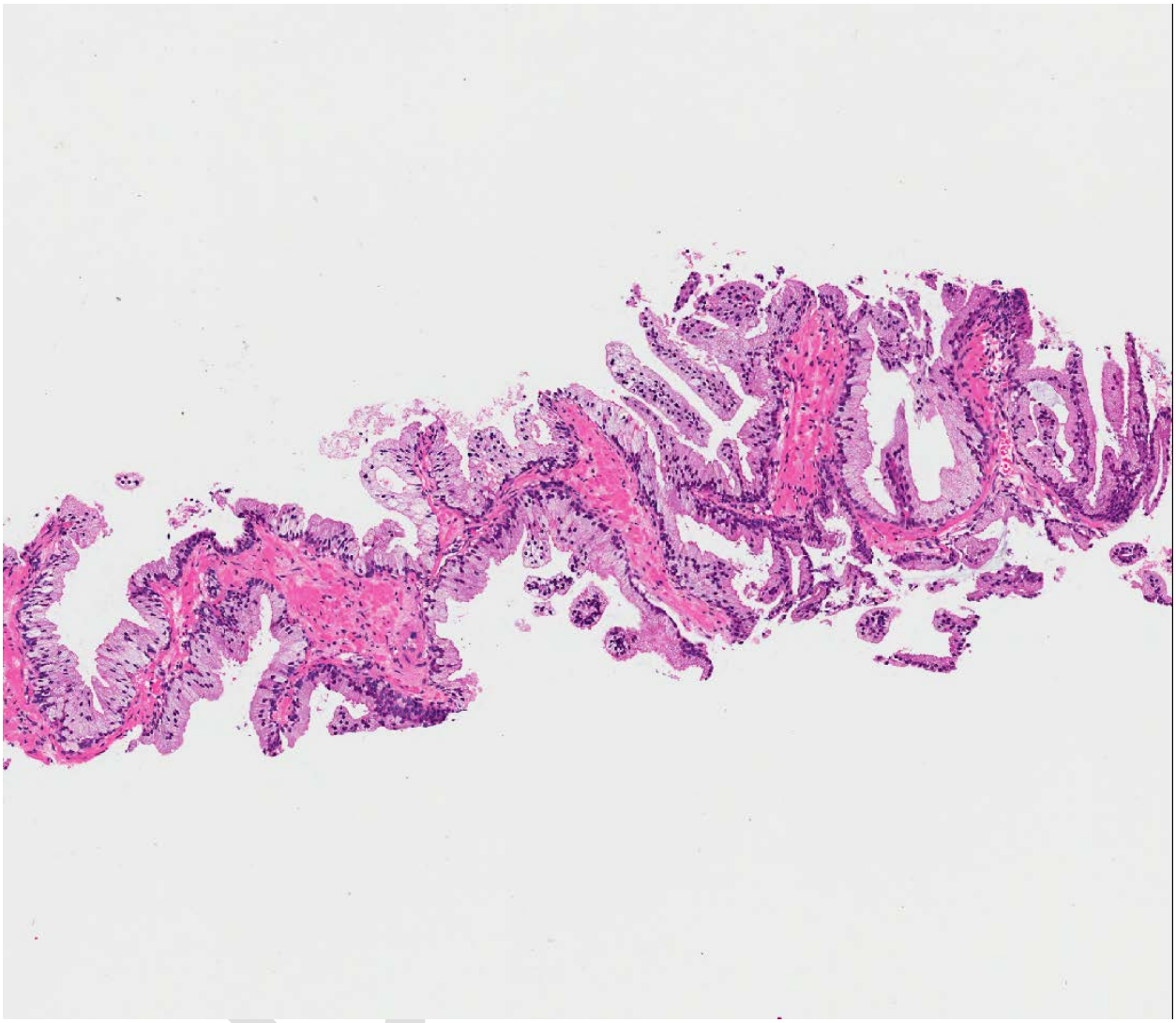
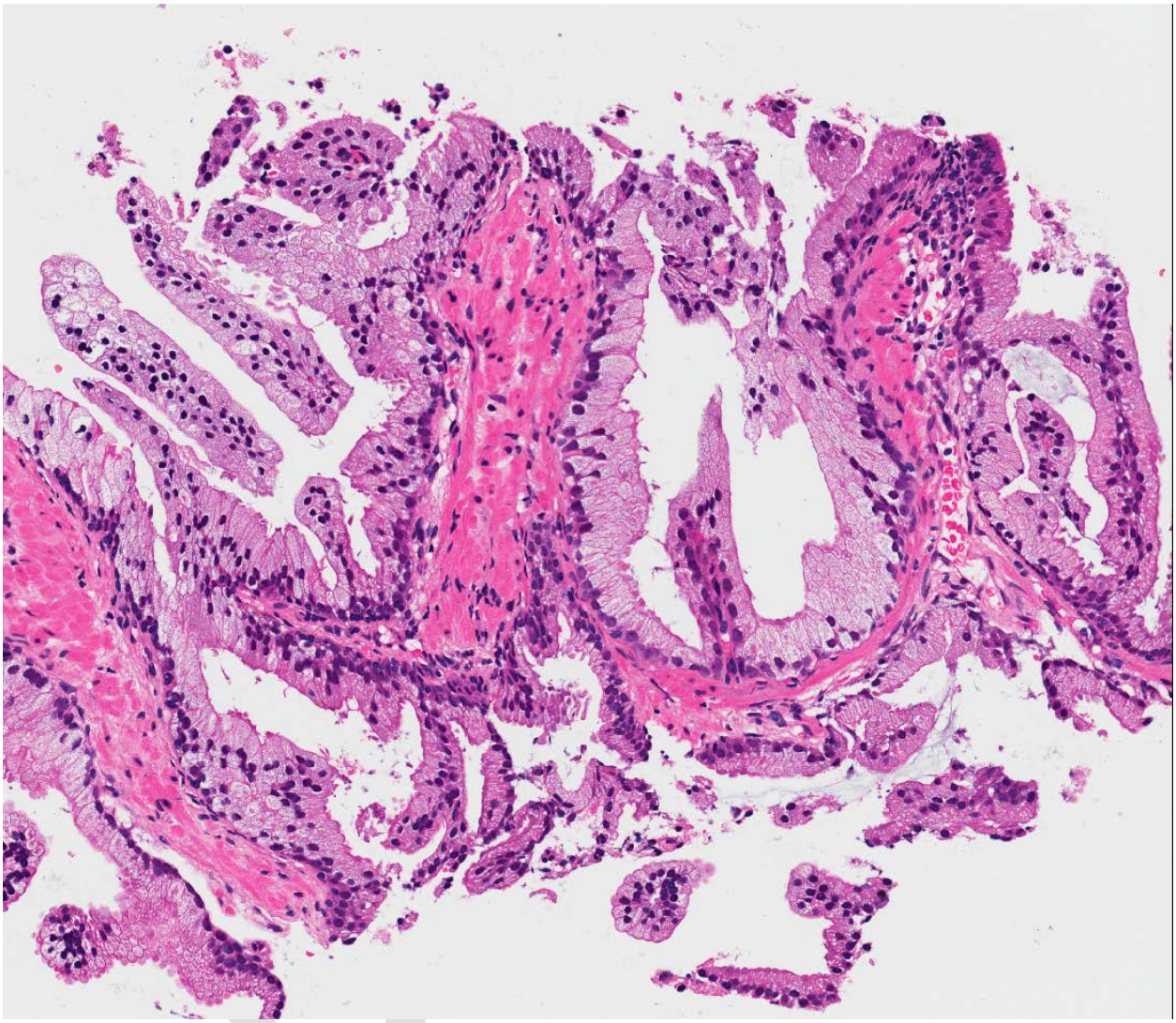


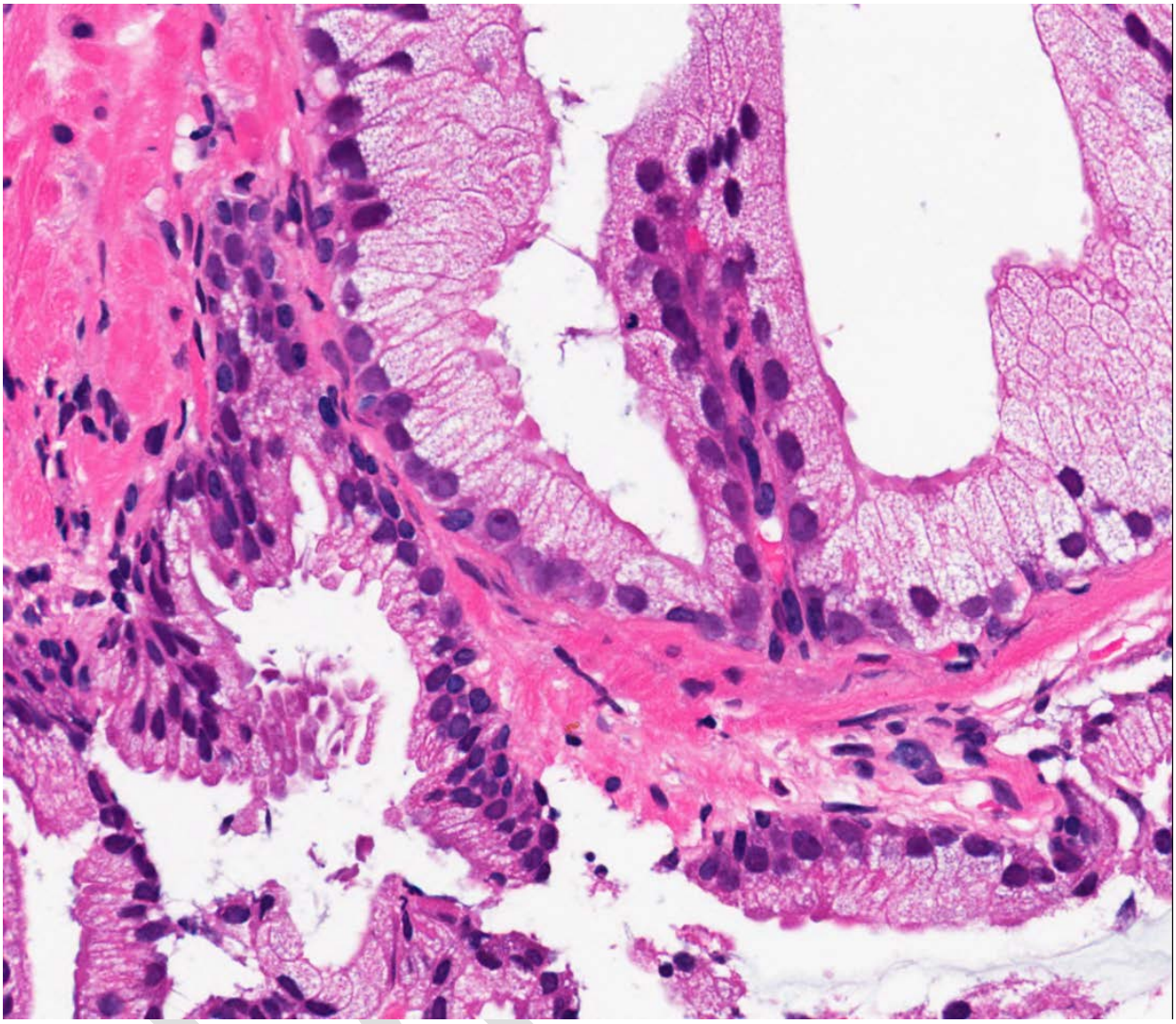
Fig. 2. Classic histologic features of Foamy High-Grade PIN. ***(A)*** Low magnification (50x) overview of a biopsy core from the "left MRI nodule" in the original biopsy performed in January of 2016. The core is extensively involved by foamy gland high-grade prostatic intraepithelial neoplasia (HG PIN).



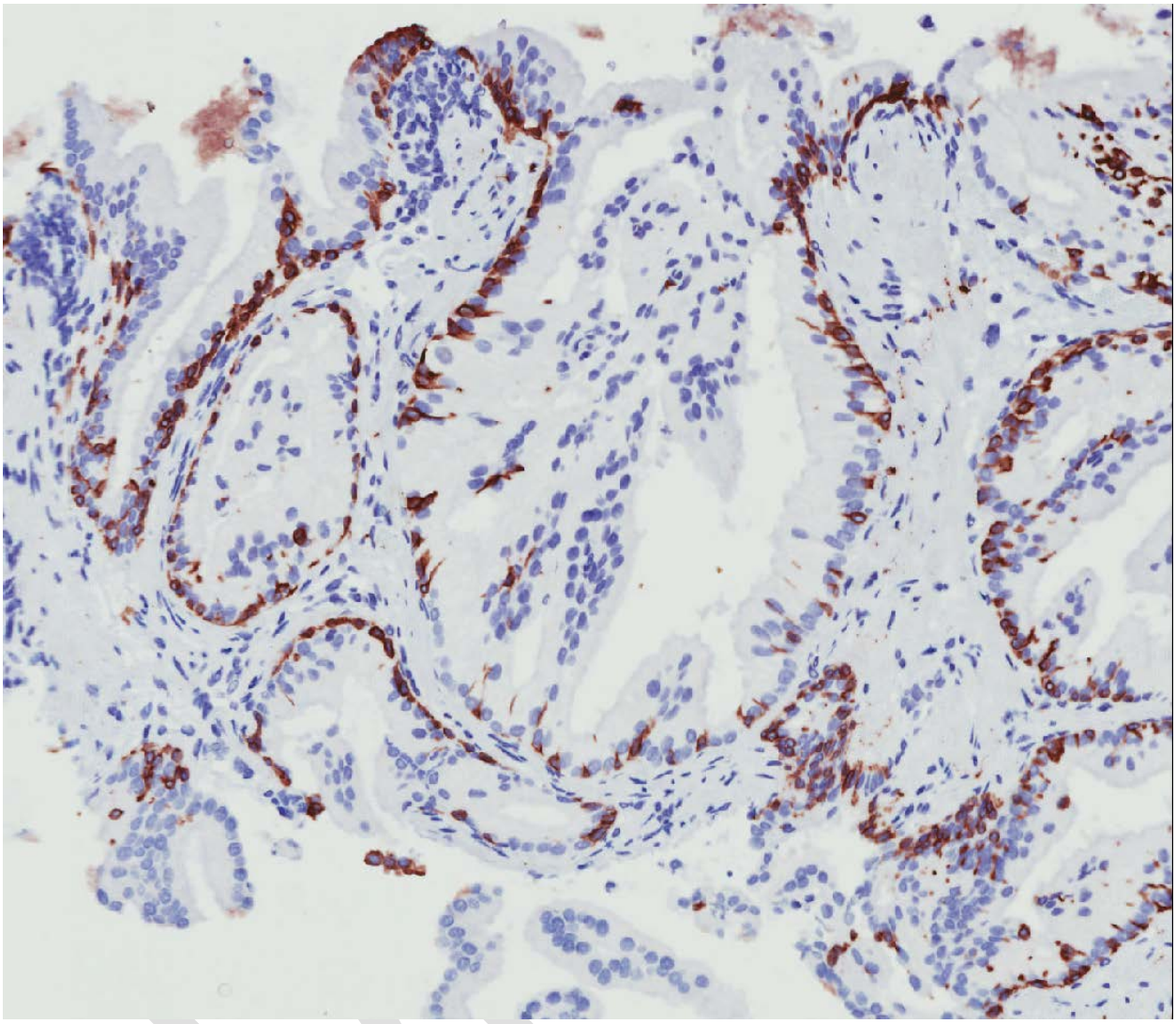
(B) Medium magnification (100x) micrograph showing prostatic glands lined by cells with abundant xanthomatous cytoplasm with a distinct foamy appearance and uniform nuclei. Papillary infolding is apparent, however the involved glands are not completely filled by the foamy cells.



(C) High magnification micrograph (400x) showing the presence of cells with macronucleoli within the foamy gland HG PIN.



(D) Immunohistochemical staining with high molecular weight cytokeratin (34βE12) demonstrates the presence of a discontinuous layer of basal cells (200x).



Supplementary Fig. 1. Representative transrectal ultrasound Images from January 2016 biopsy ***(A, B)*** Transverse transrectal ultrasound (TRUS) images of the prostate showing hypoechogenicity and increased Doppler signal at the sites identified on magnetic resonance imaging (MRI). On MRI-TRUS fusion at time of biopsy, the site of abnormality on TRUS corresponded to the site of abnormal signal on multiparametric MRI.