Diagnosis of Prostate Cancer in Core Needle Biopsy: A 3-step Approach

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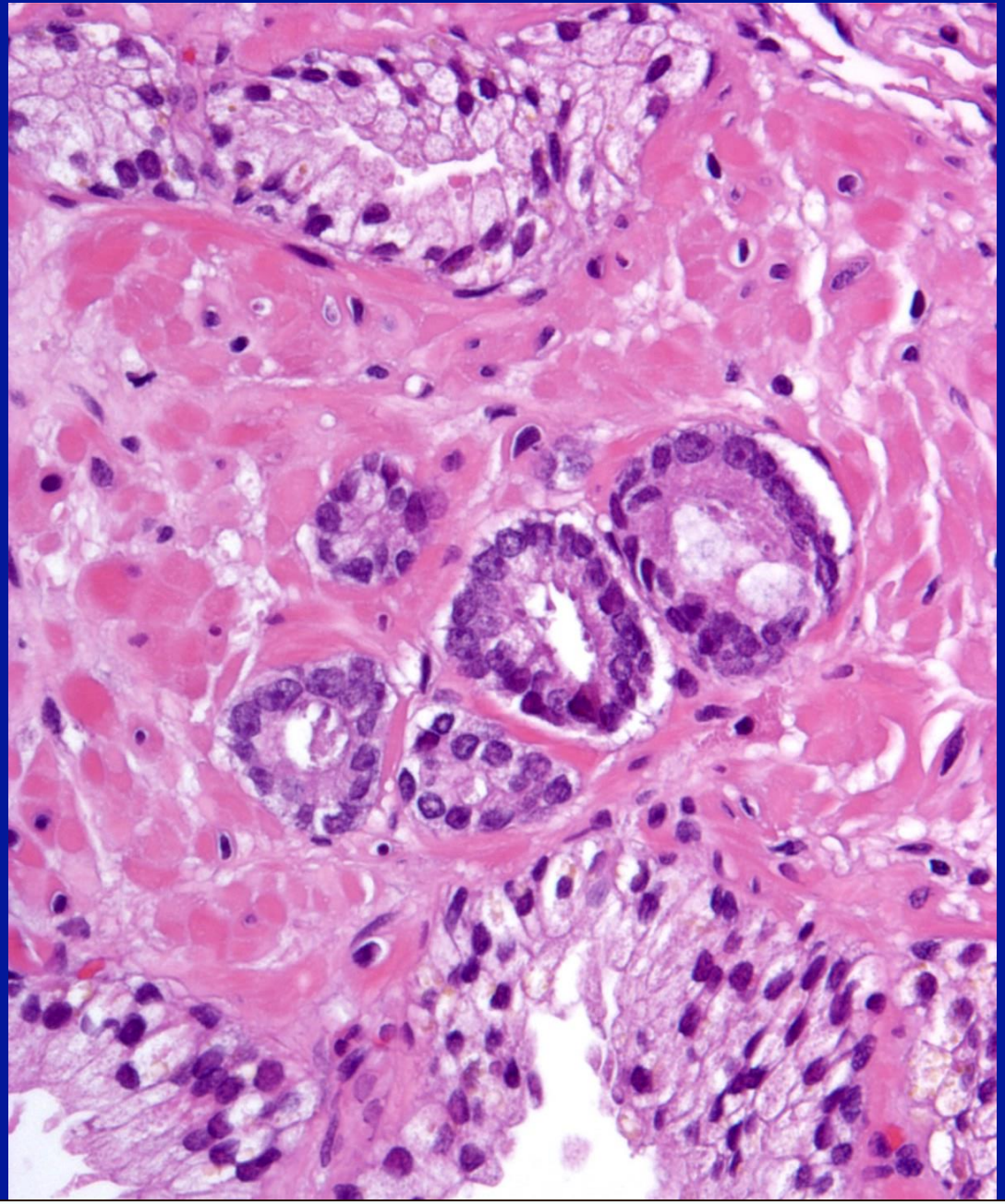


Case 1

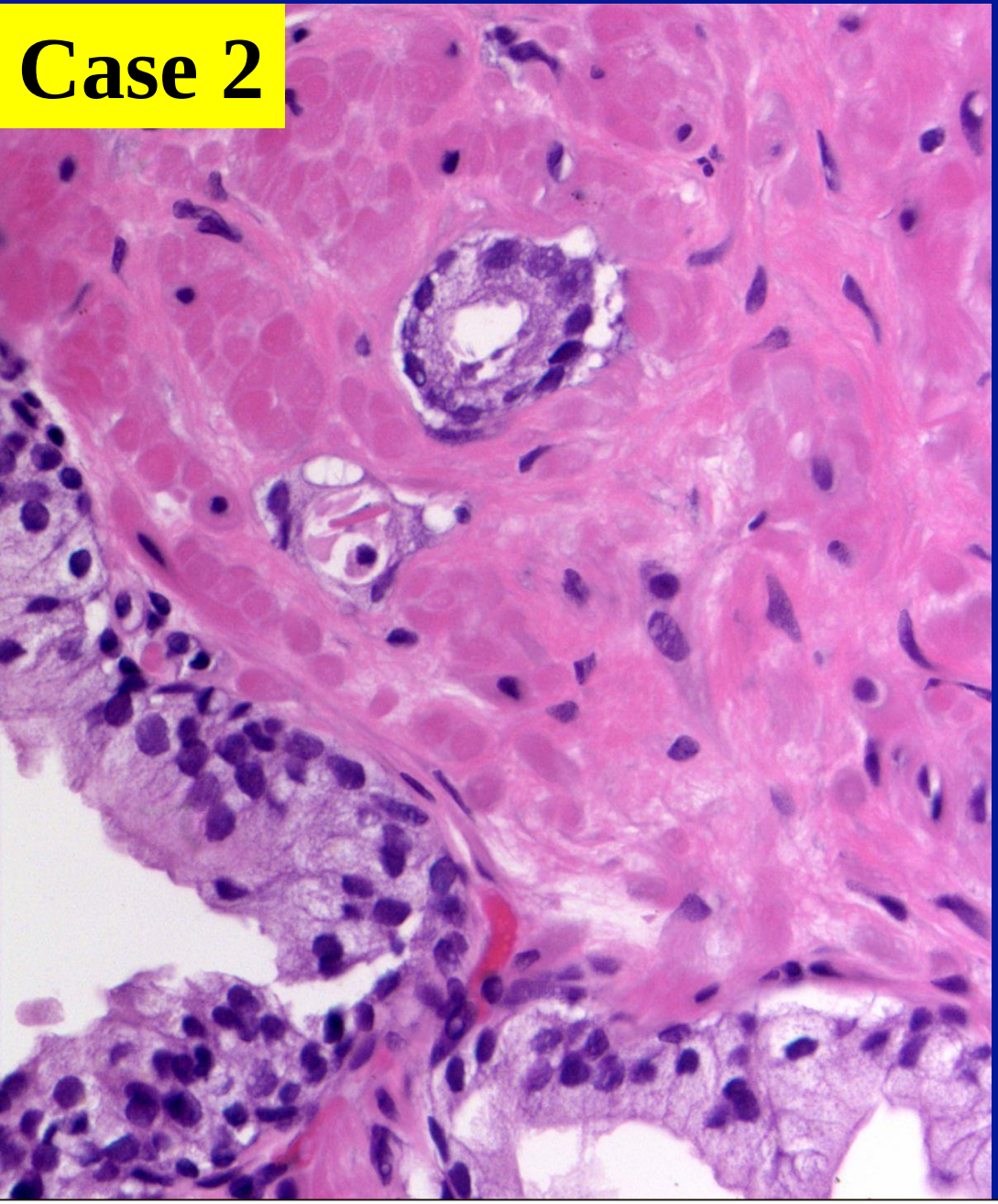
a. Adenocarcinoma, Gleason score 3+3=6

b. ATYP (ASAP)

c. Benign atrophy

60 year old male, elevated PSA - 5 ng/ml

Case 2



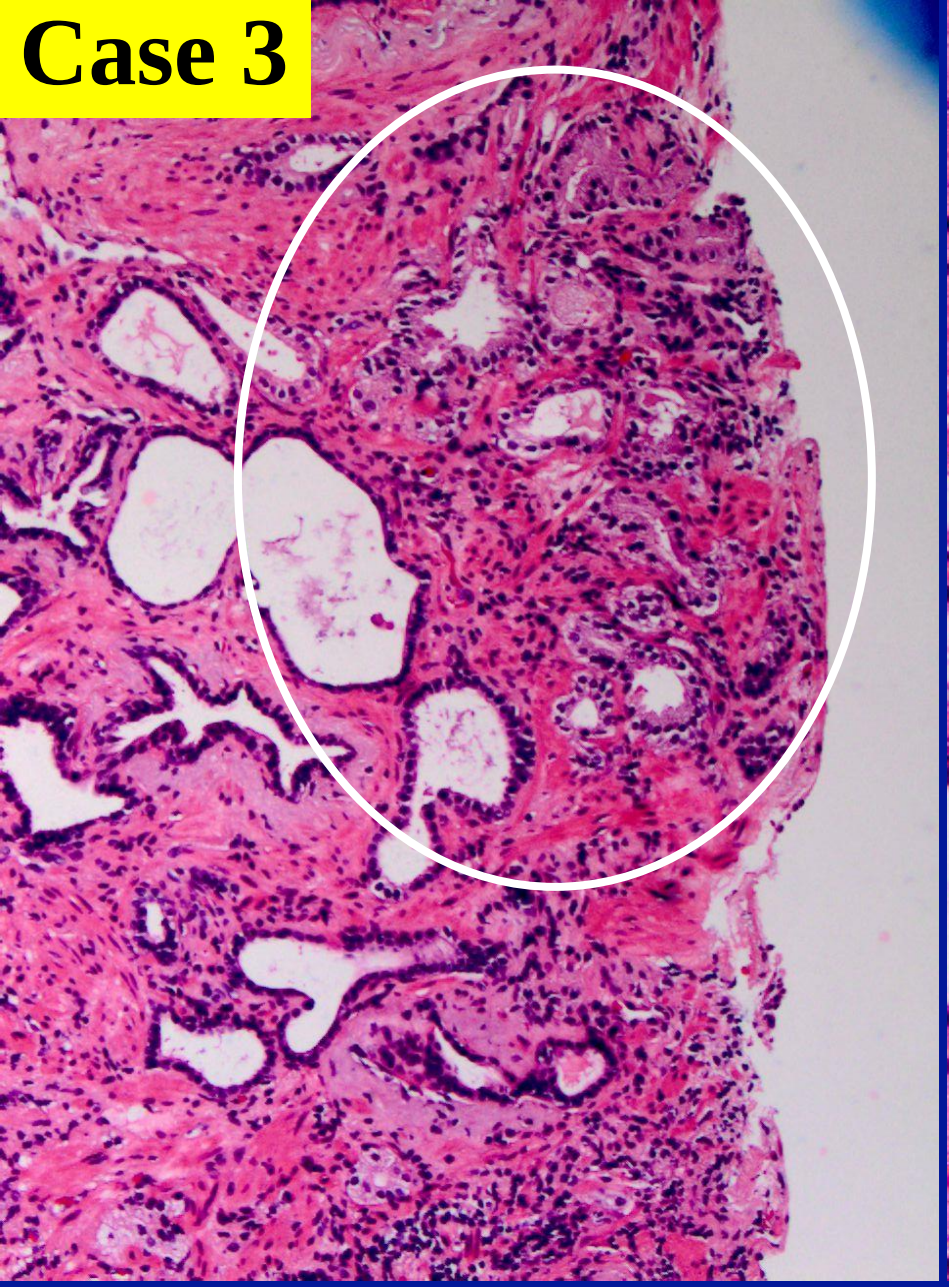
a. Benign atrophy

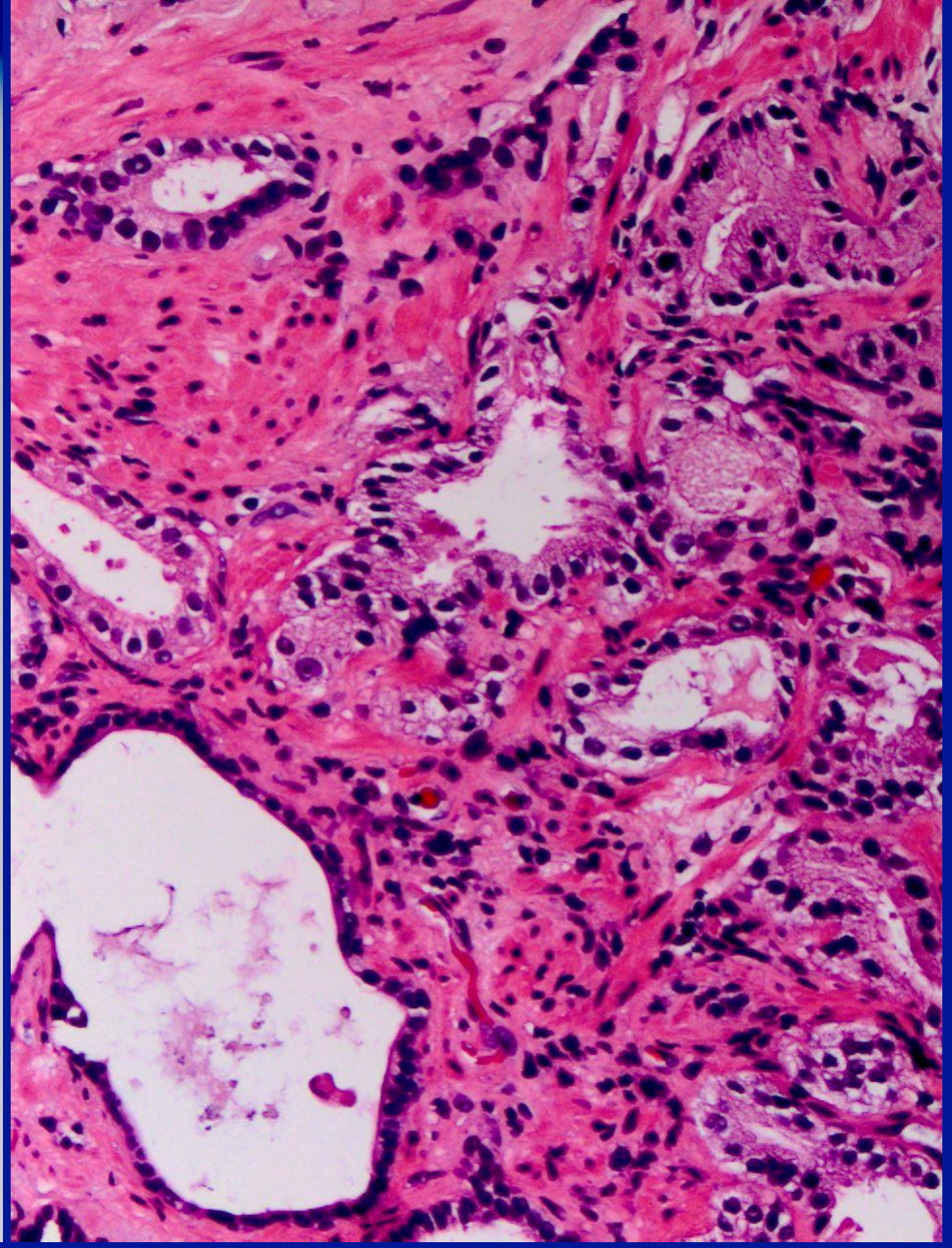
b. ATYP(ASAP)

c. Adenocarcinoma, Gleason score 3+3=6

55 year old male, elevated PSA- 4.5 ng/ml

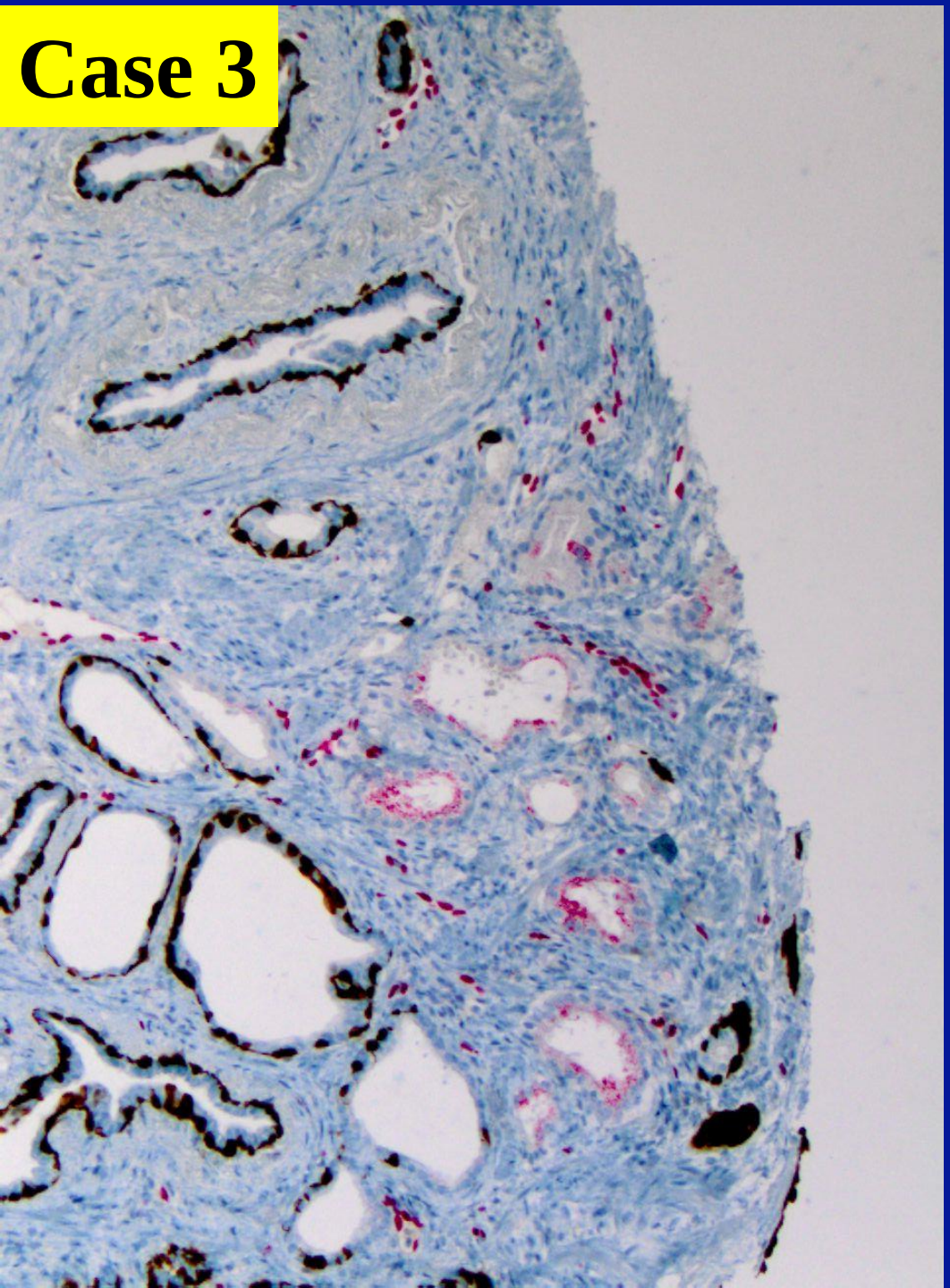
Case 3





70 year old male, PSA 6 ng/ml, normal DRE

Case 3



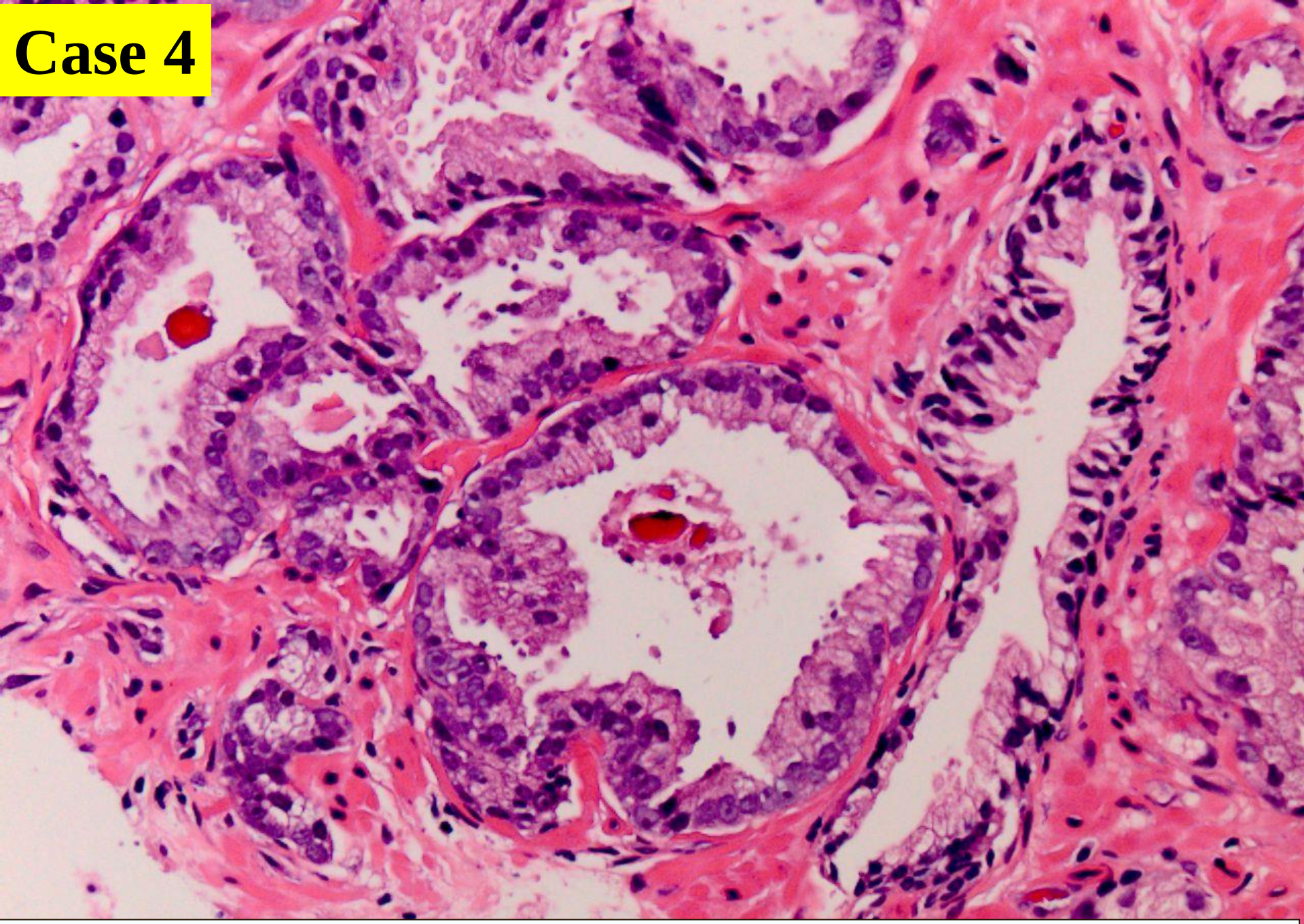
a. Benign adenosis

b. ATYP(ASAP)

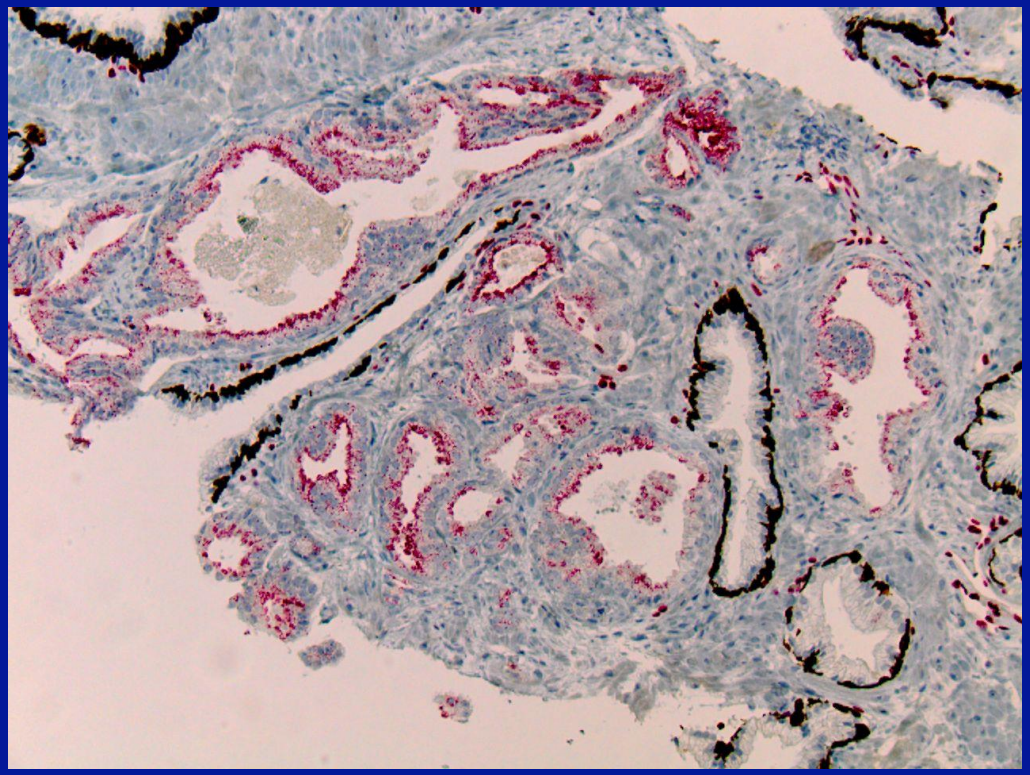
c. Adenocarcinoma, Gleason score 3+3=6

PIN4

Case 4



58 year old male, elevated PSA 5.5 ng/ml

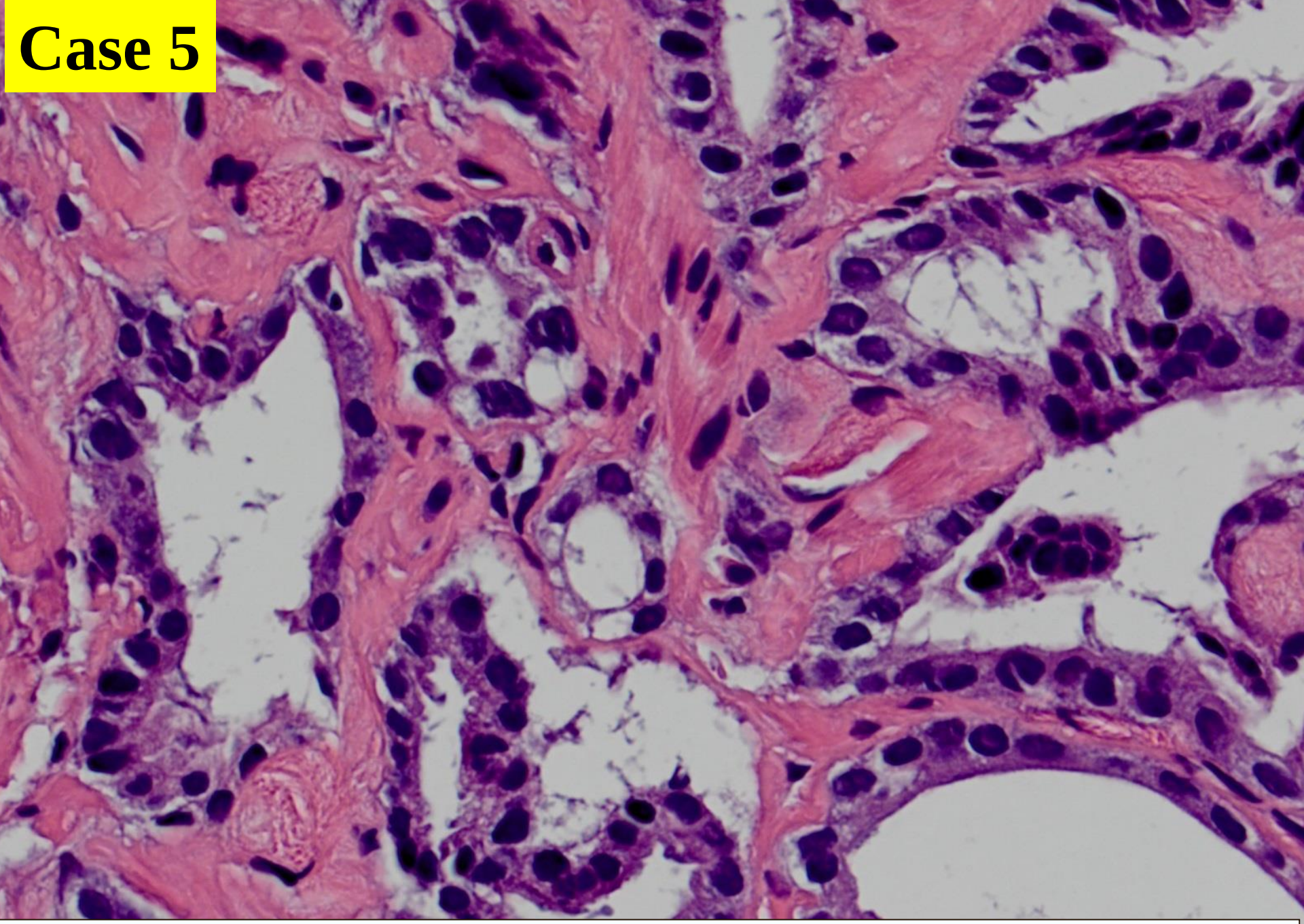


PIN4

a. Benign prostate hyperplasia

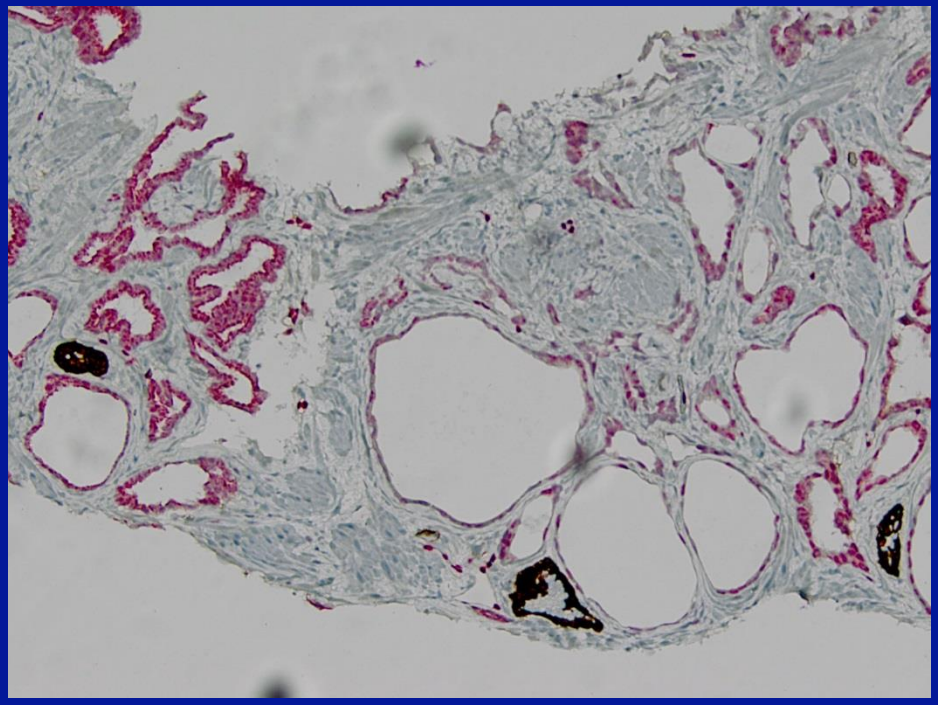
b. ATYP(ASAP)

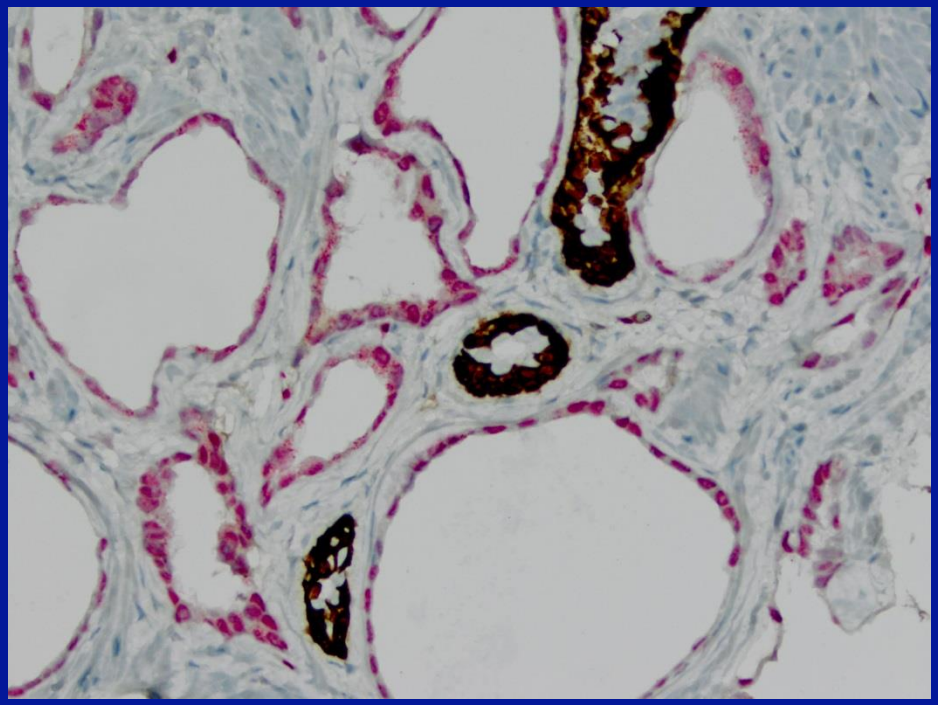
c. Adenocarcinoma with pseudohyperplastic features, Gleason score 3+3=6



61 year old male, elevated PSA 8 ng/ml

Case 5





PIN4-ERG

a. Partial atrophy

b. ATYP(ASAP)

c. Adenocarcinoma with atrophic features, Gleason score 3+3=6

Diagnosis of Prostate Cancer (PCa) in Prostate Biopsy: Critical Issues

- Recognize PCa (limited amount, subtle histological variations that mimic benign lesions) and avoid under-diagnosis (false negative)
- Recognize benign mimics of PCa and avoid over-diagnosis (false positive)
- Recognize features of a lesion that are borderline to classify (ATYP)

Histological pattern of cancer	Benign condition they may mimic
Foamy gland carcinoma	Cowper's glands Mucinous metaplasia Xanthoma
Atrophic carcinoma	Benign atrophy
Pseudohyperplastic carcinoma	Benign prostatic hyperplasia (BPH)
Microcystic adenocarcinoma	Cystic atrophy
PIN-like adenocarcinoma	Prostatic intraepithelial neoplasia (PIN)

Diagnosis of Prostate Cancer (PCa) in Prostate Biopsy: Critical Issues

- Recognize PCa (limited amount, subtle histological variations that mimic benign lesions) and avoid under-diagnosis (false negative)
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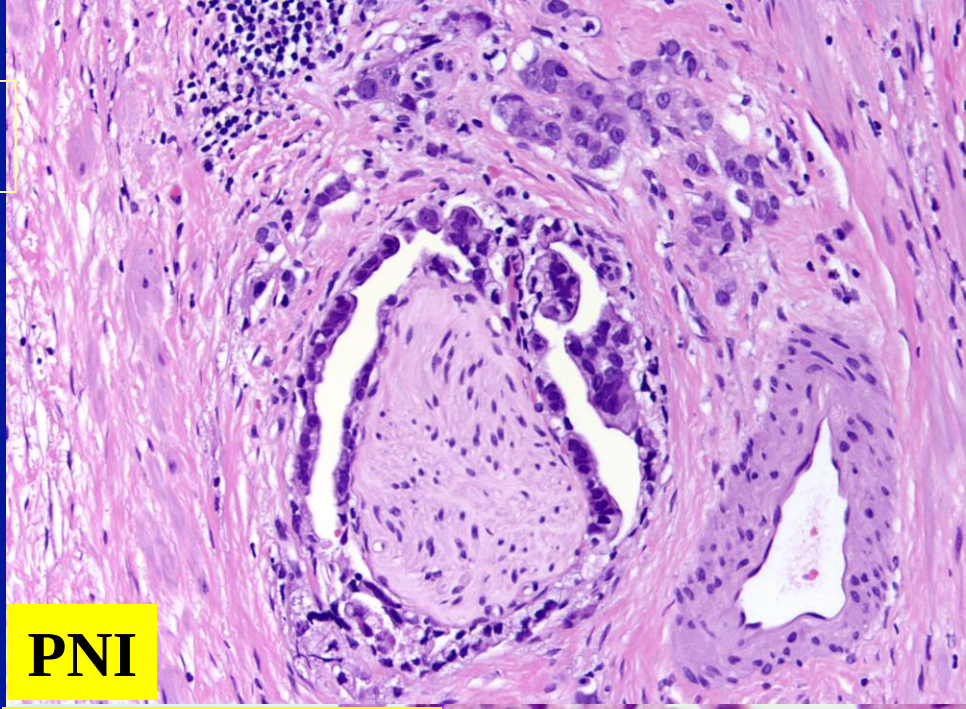
- Recognize features of a lesion that are borderline to classify (ATYP)

Histological findings specific for, therefore diagnostic of, limited PCa in prostate biopsy

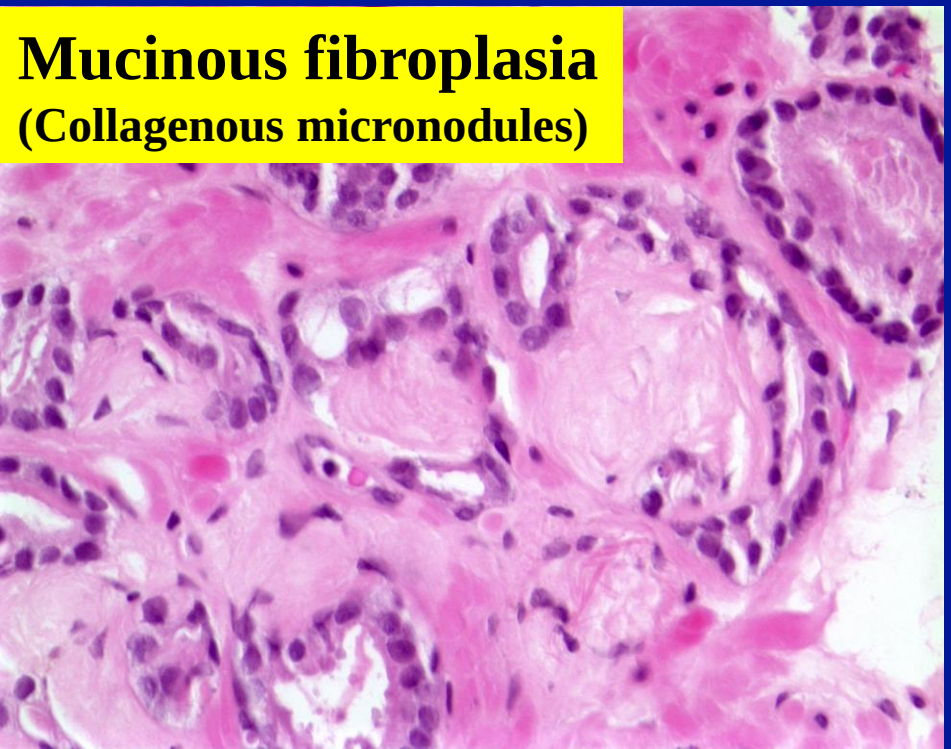
PCa specific features in NBX

PNI- 2-11%
Mucinous fibroplasia- 1-2%
Glomeruloid Structures- 3%

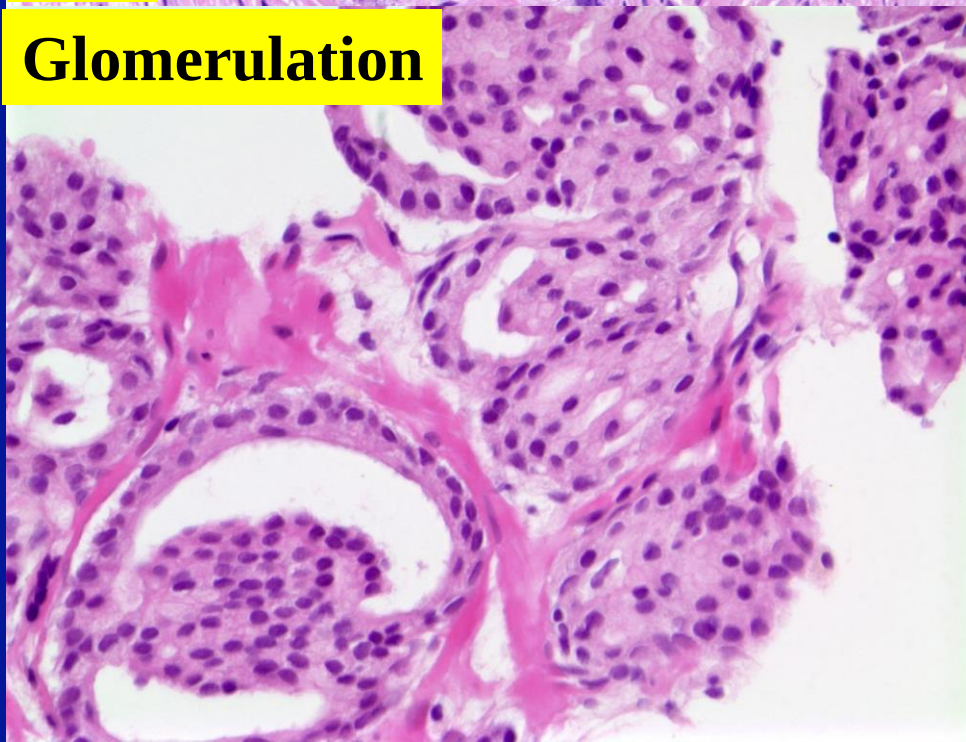


PNI

Mucinous fibroplasia
(Collagenous micronodules)



Glomerulation



Diagnosis of Limited PCa in Prostate Biopsy

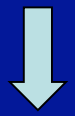
A 3-step Approach

Low power screening for architectural atypia:

Benign glands as reference

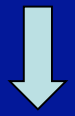
-Haphazard or infiltrative glands
-Glandular crowding
-Darker or foamy glands

Benign glands as reference



High power exam for cytological atypia:

-Nuclear enlargement
-Hyperchromasia
-Prominent nucleoli



Rule out benign conditions that may cause architectural/cytological atypia

Histological Criteria for Diagnosis of Limited PCa in Prostate Biopsy

Major

Architectural

Infiltrative pattern

Loss of basal cells

Nuclear atypia

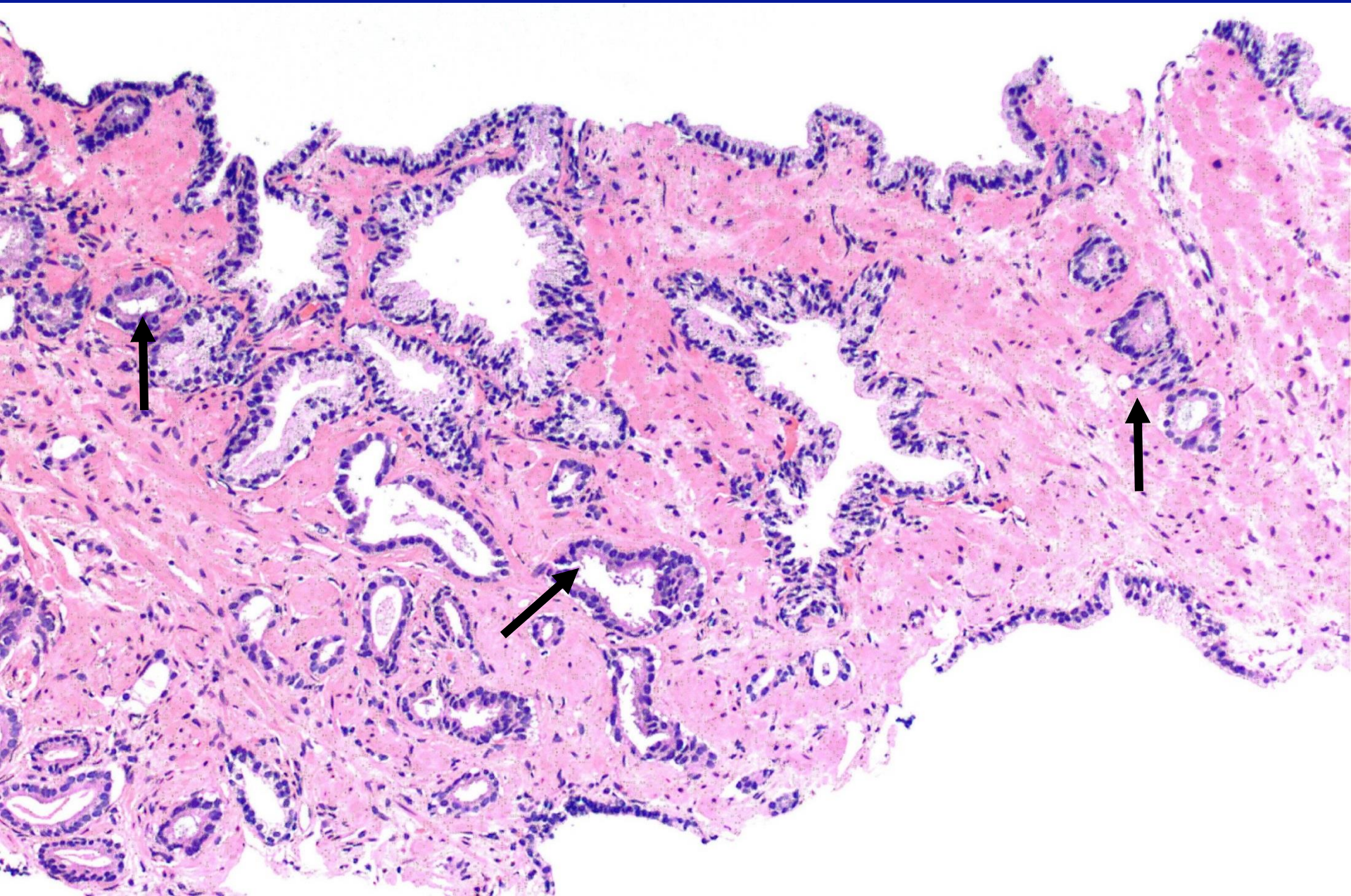
Nuclear enlargement
Prominent nucleoli
Hyperchromasia

Minor

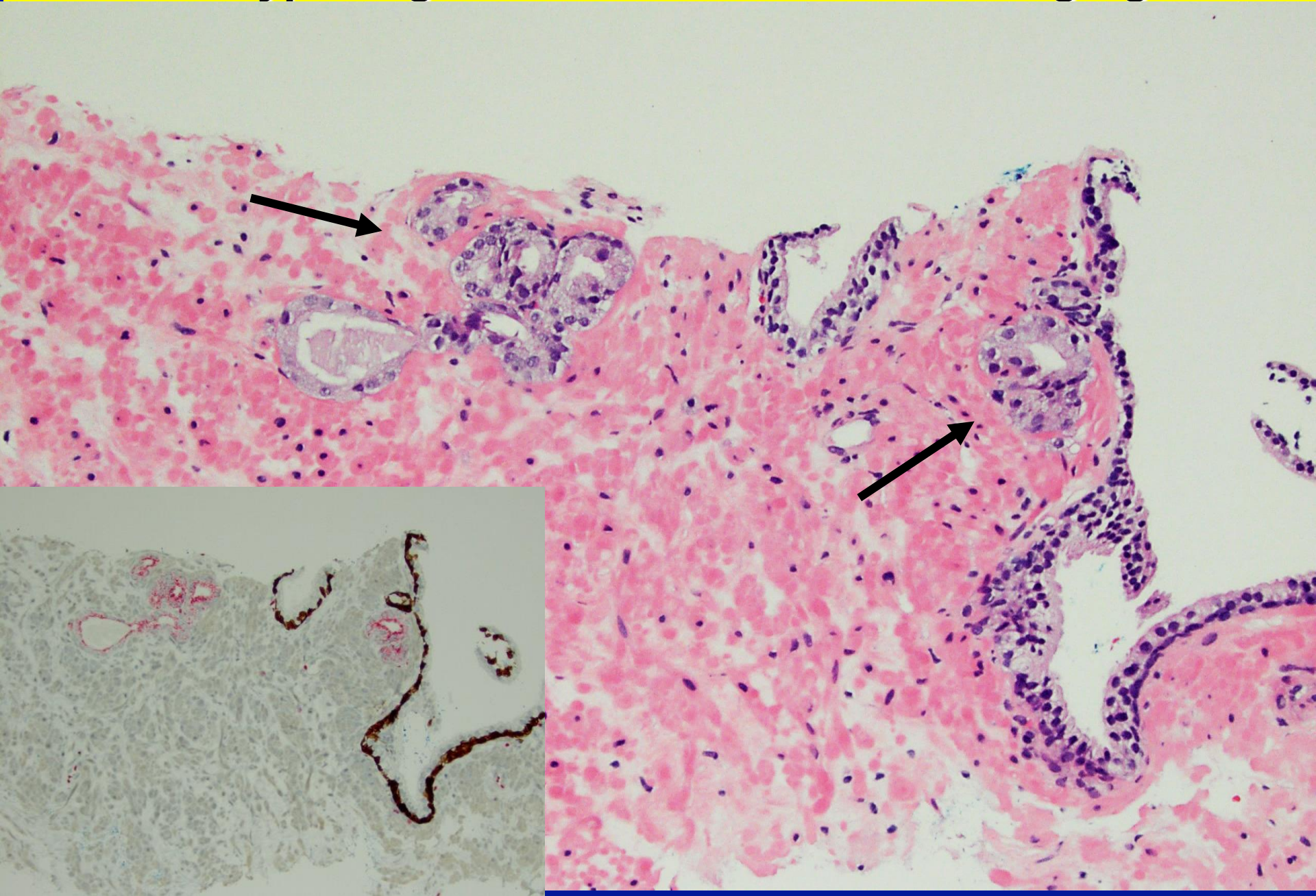
Intraluminal blue mucin
Pink amorphous secretions
Mitotic figures
Crystalloids
Adjacent HGPIN
Amphophilic cytoplasm

Algaba 1996

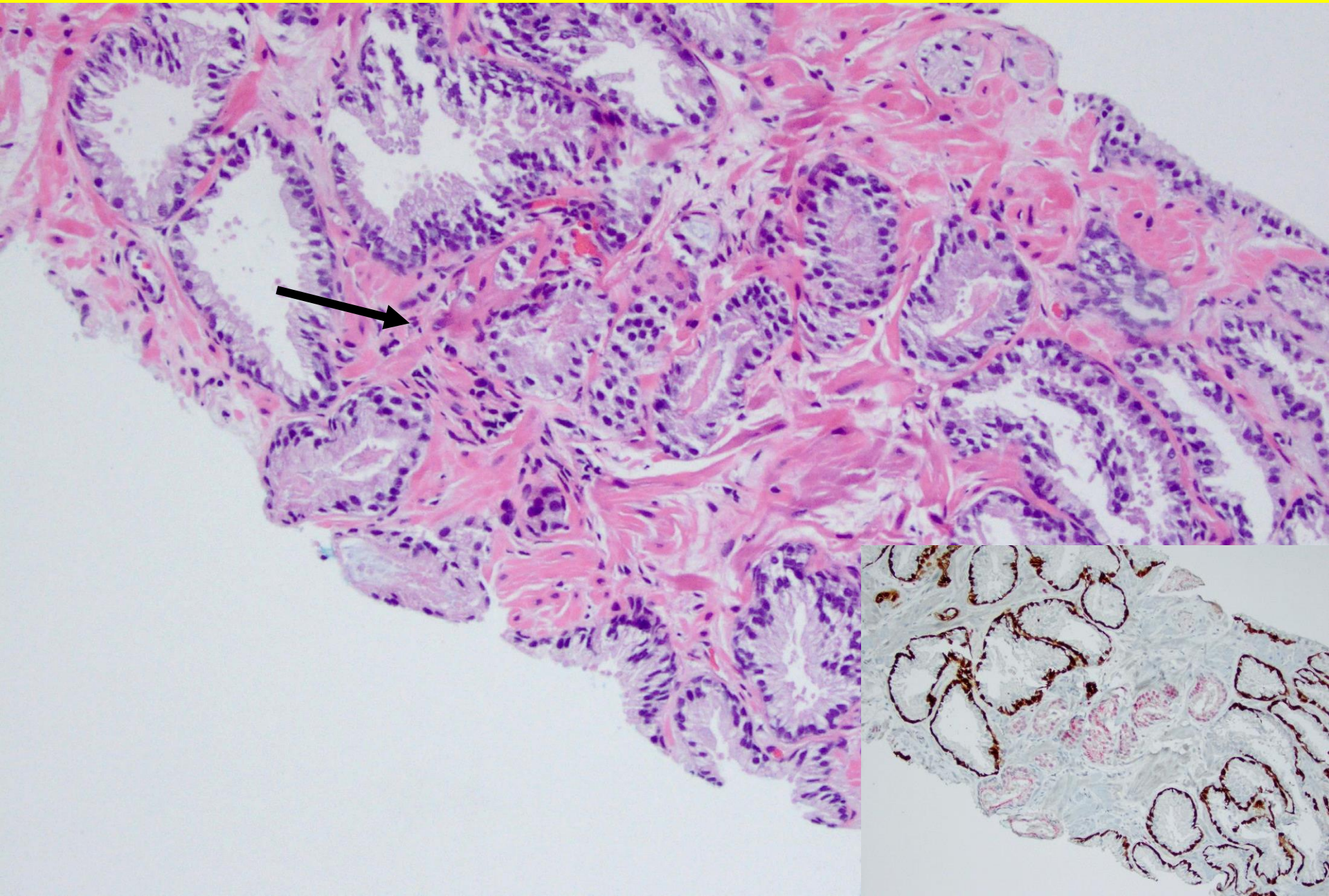
Abnormal Architectural Patterns in PCa
"Infiltrative Growth Pattern"



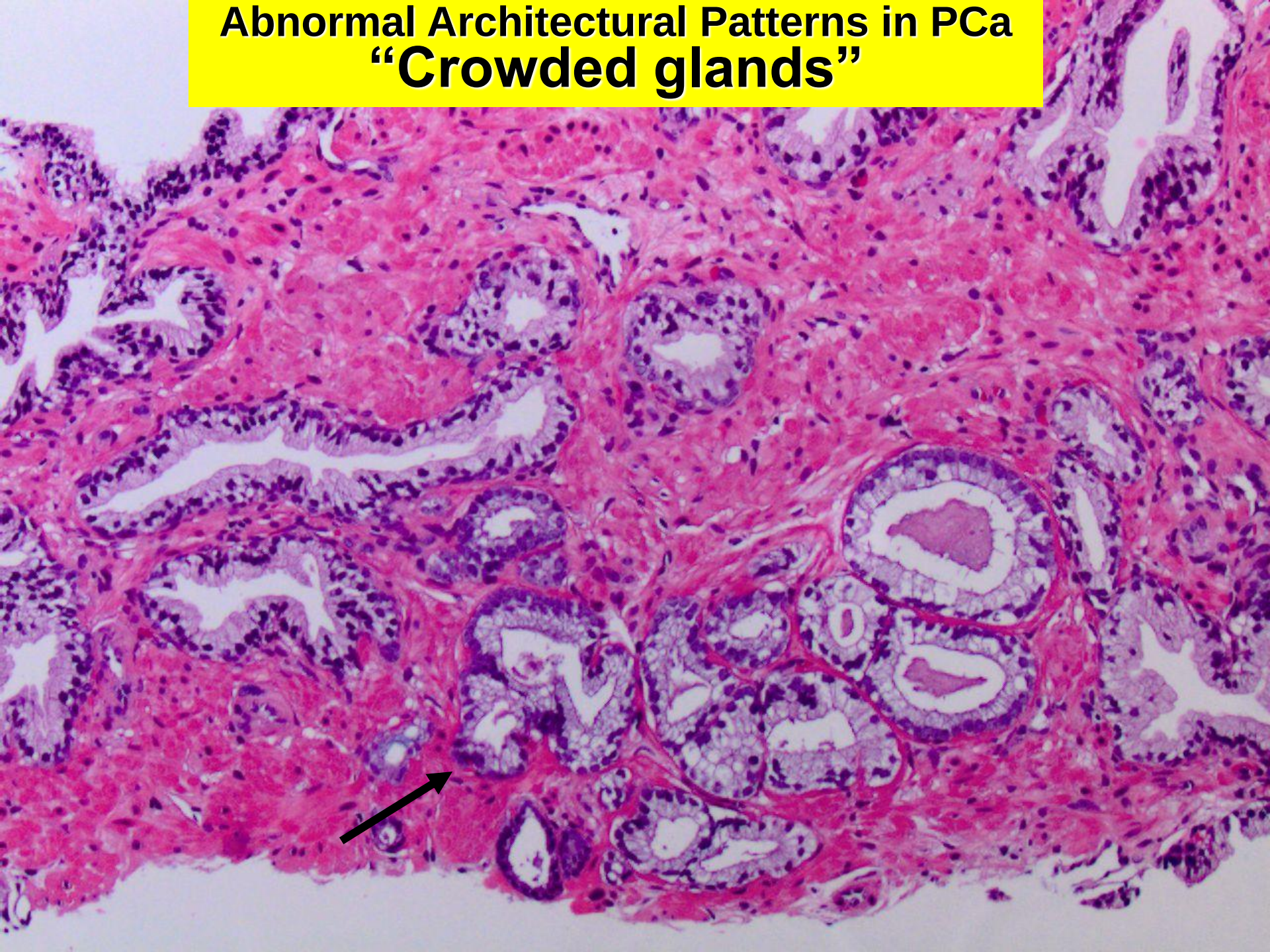
Infiltrative Architectural Patterns in PCa
"Small atypical glands on both sides of benign gland"



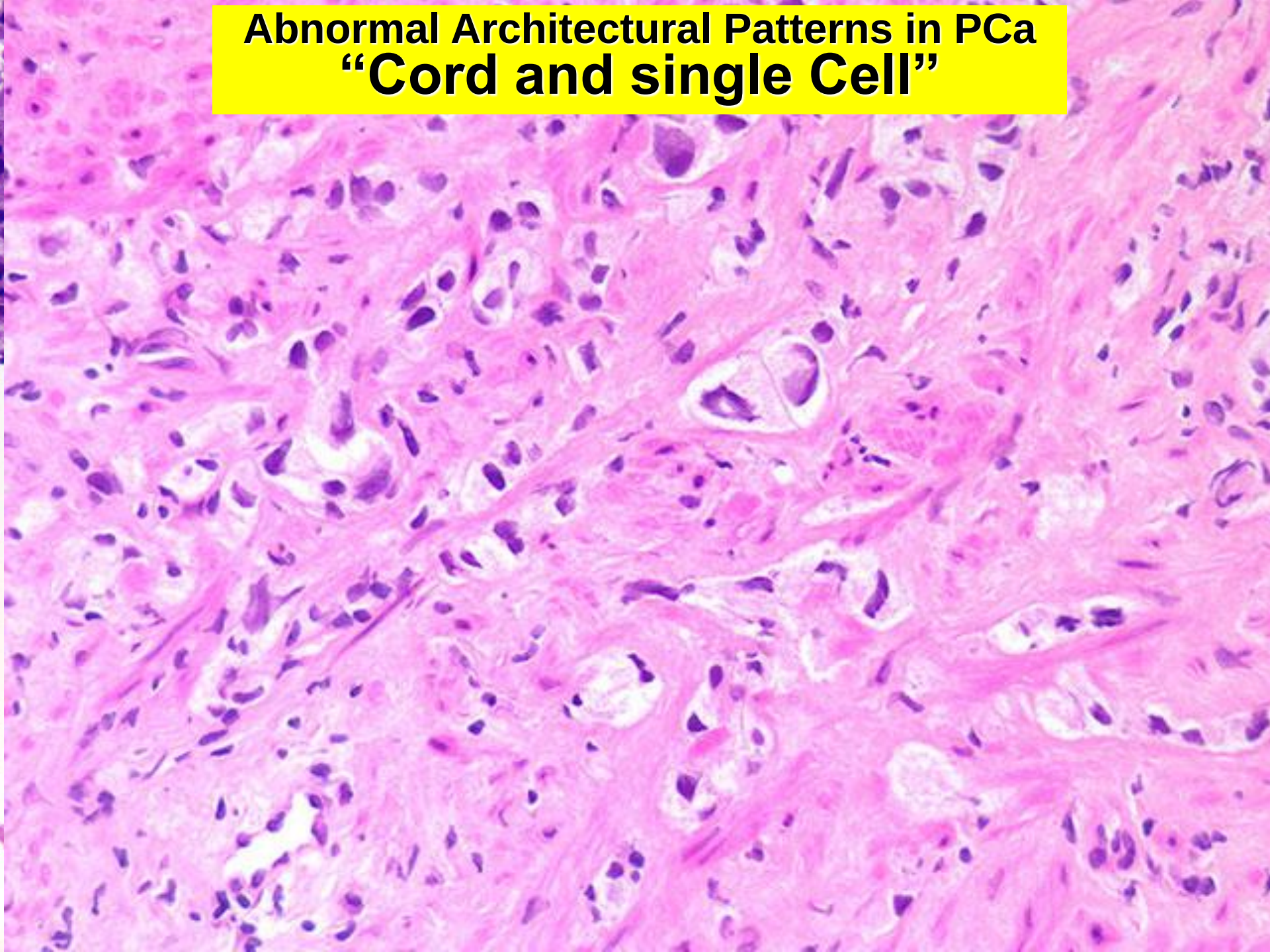
Infiltrative Architectural Patterns in PCa
"Row of atypical glands growing across core width"

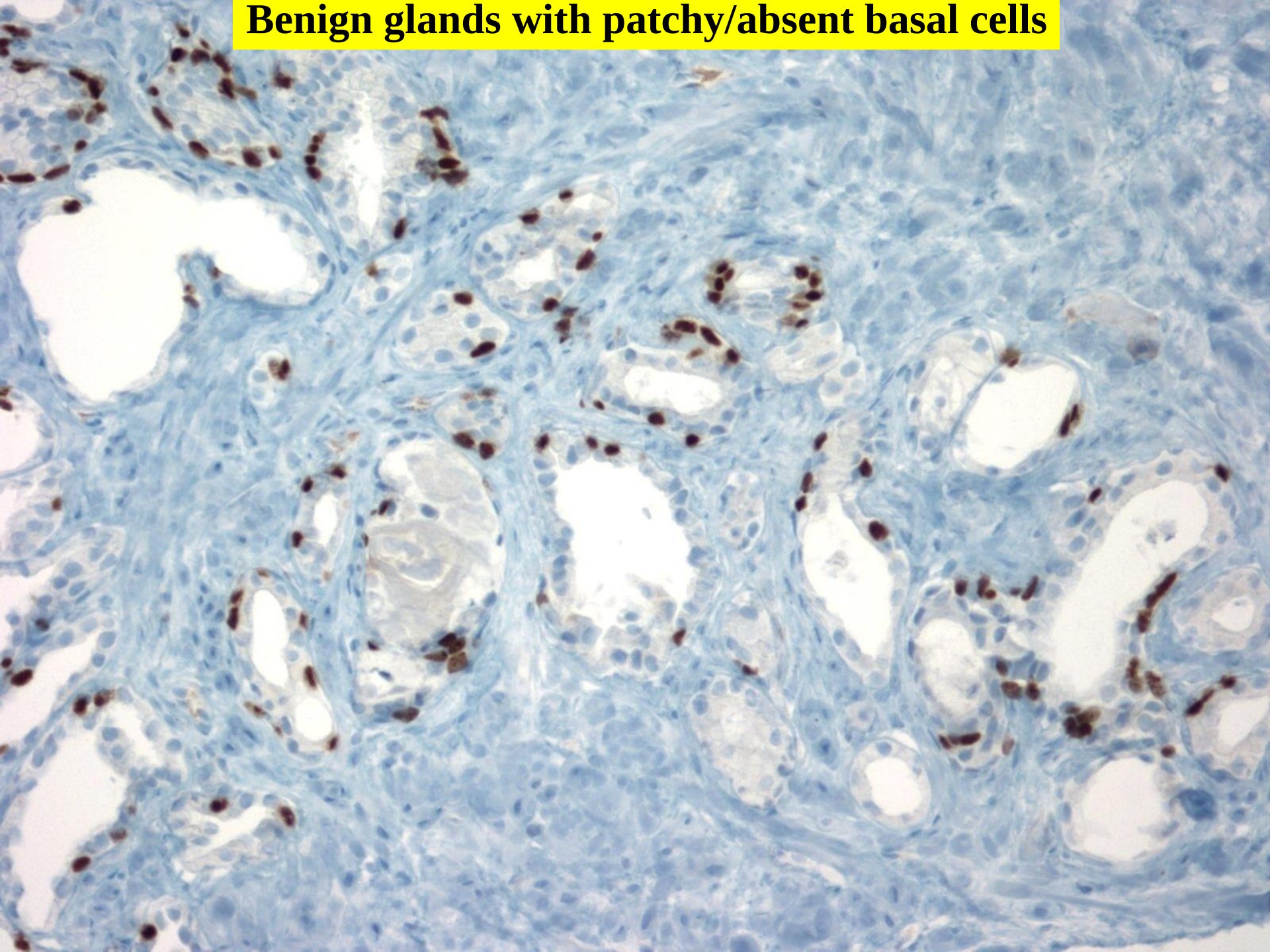


Abnormal Architectural Patterns in PCa
“Crowded glands”

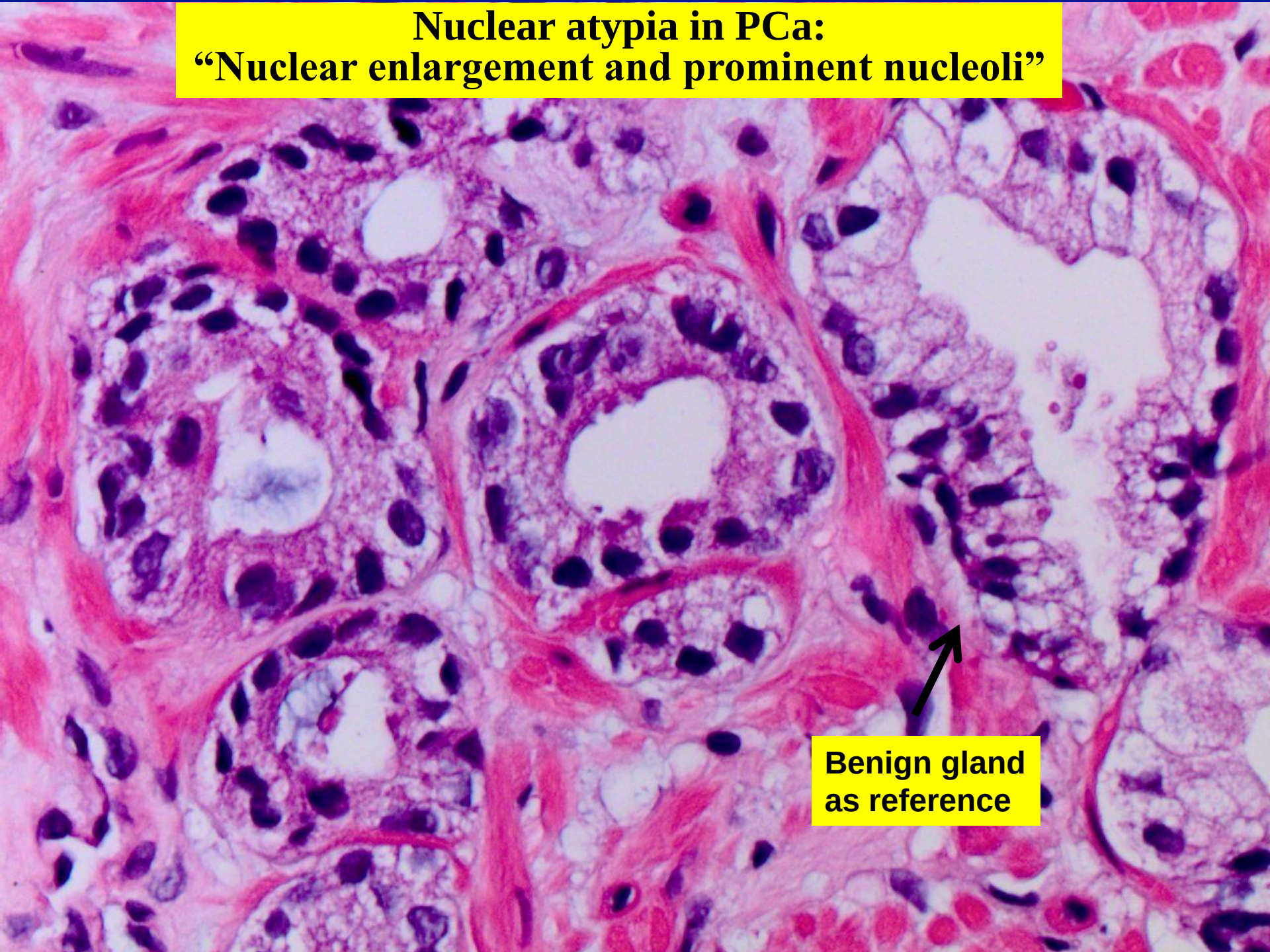


Abnormal Architectural Patterns in PCa
“Cord and single Cell”

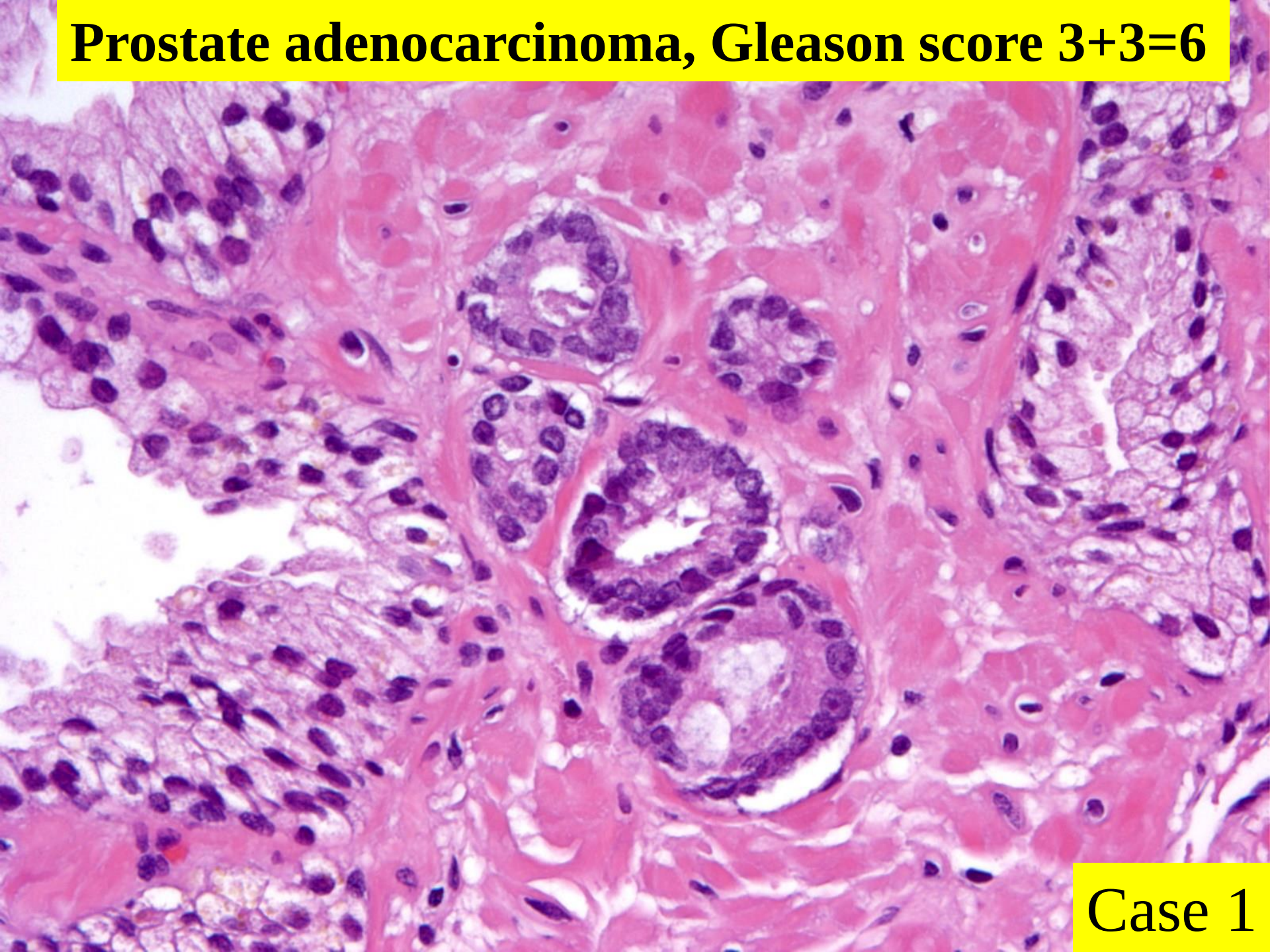



Benign glands with patchy/absent basal cells

Nuclear atypia in PCa:
"Nuclear enlargement and prominent nucleoli"



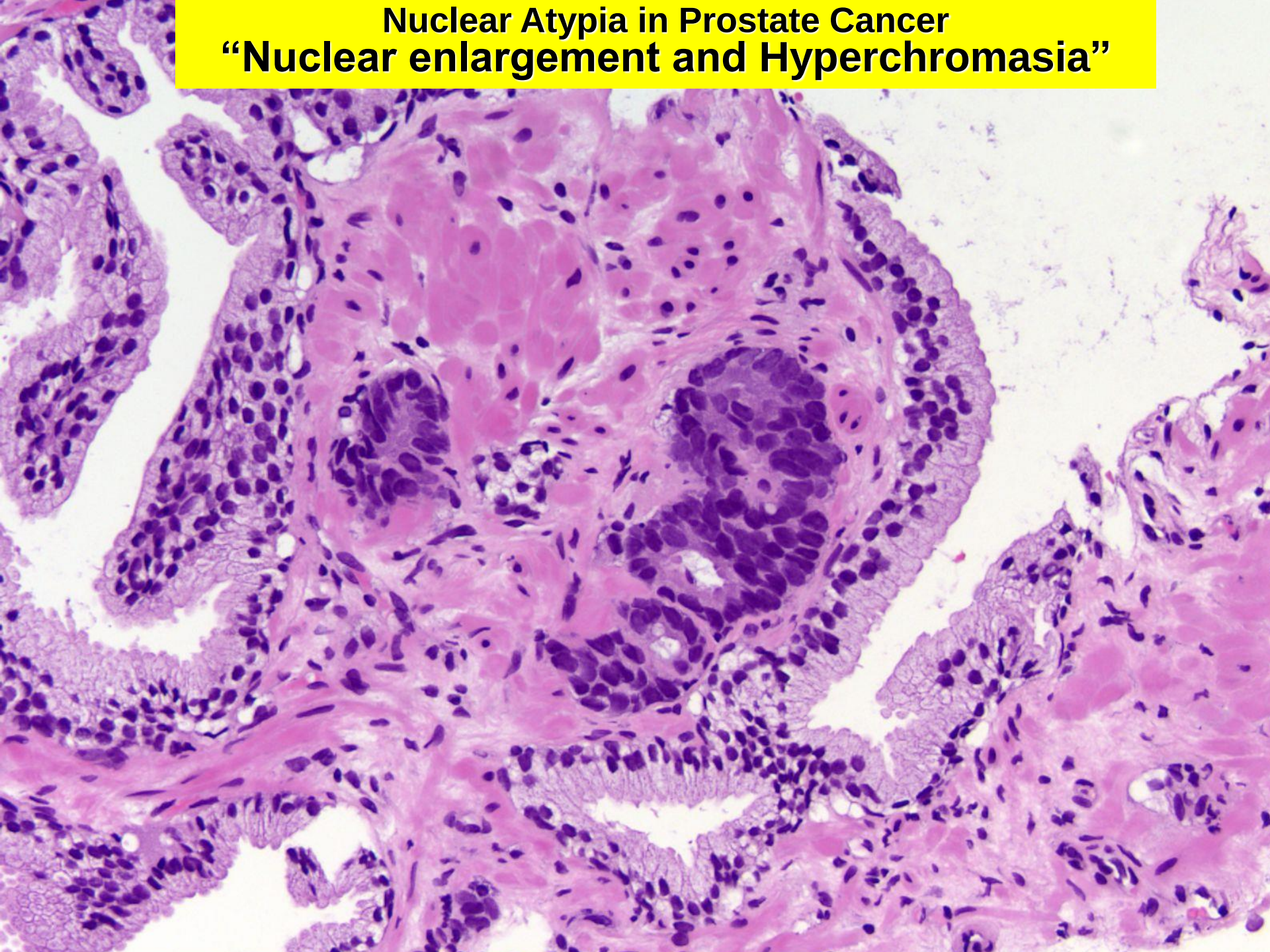
Prostate adenocarcinoma, Gleason score 3+3=6



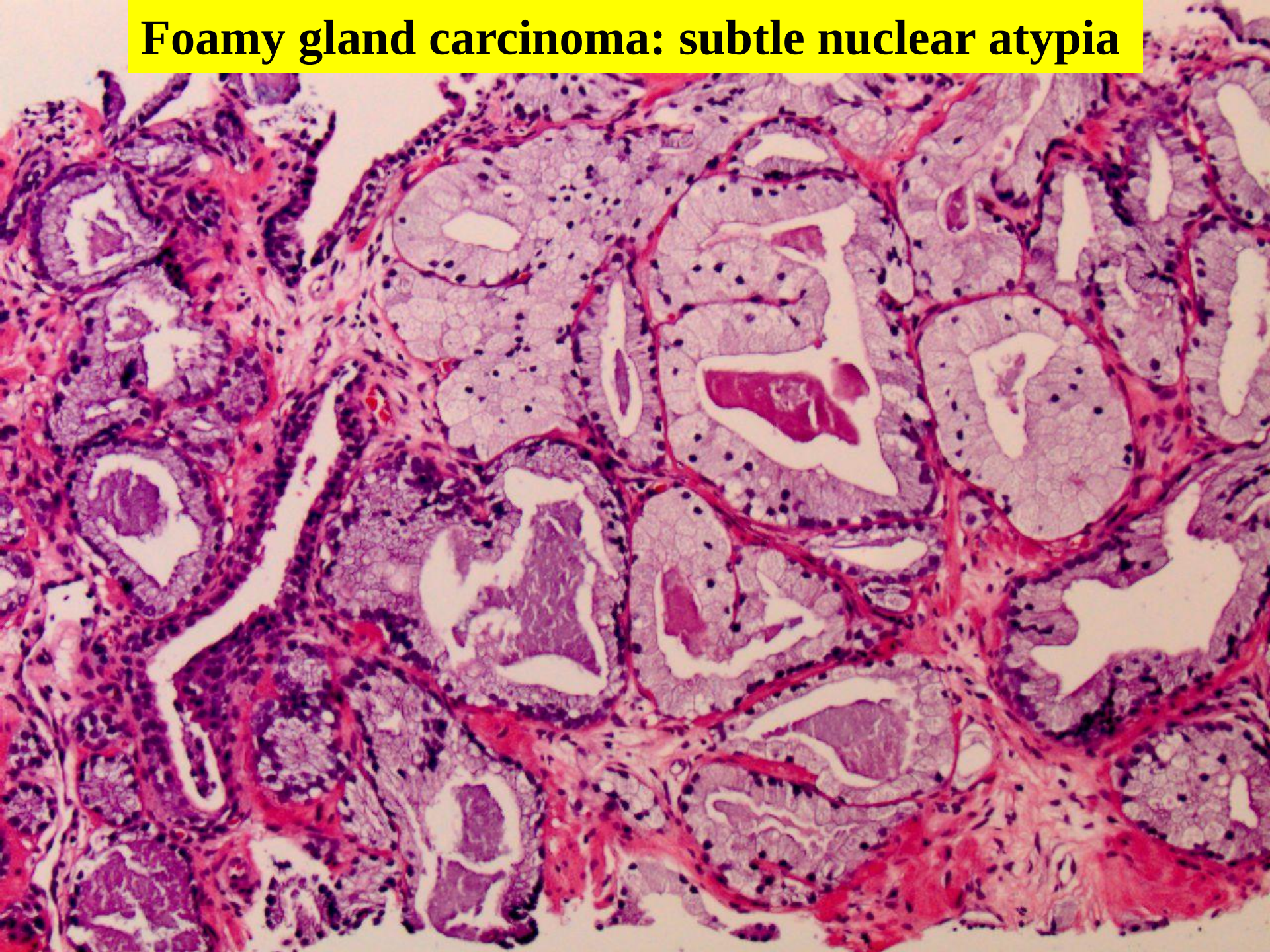
Case 1

Nuclear Atypia in Prostate Cancer

“Nuclear enlargement and Hyperchromasia”



Foamy gland carcinoma: subtle nuclear atypia



Histological Criteria for Diagnosis of Limited PCa in Prostate Biopsy

Major

Architectural

Infiltrative pattern (small glands or confluent/irregular cribriform glands)

Loss of basal cells

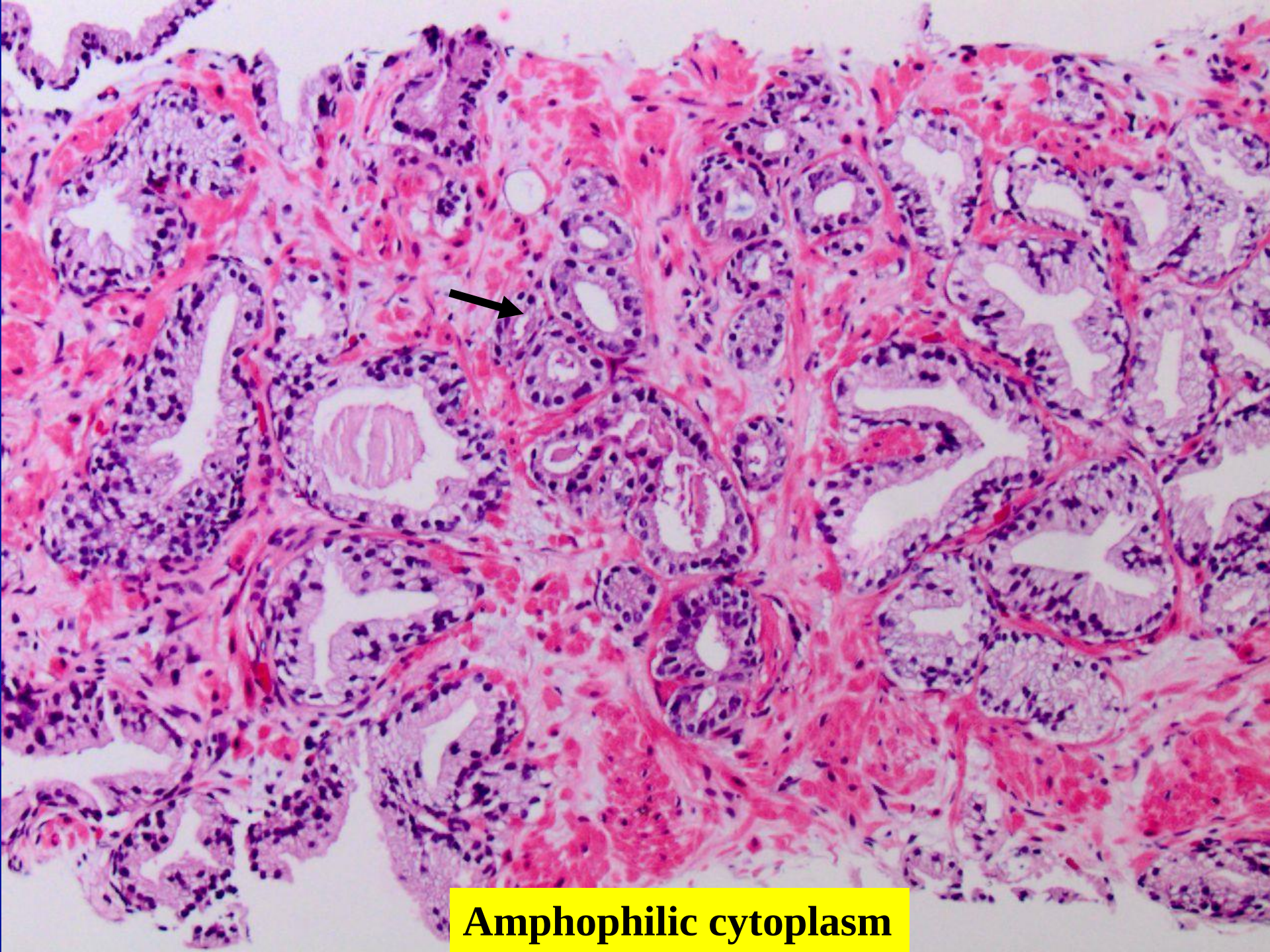
Nuclear atypia:

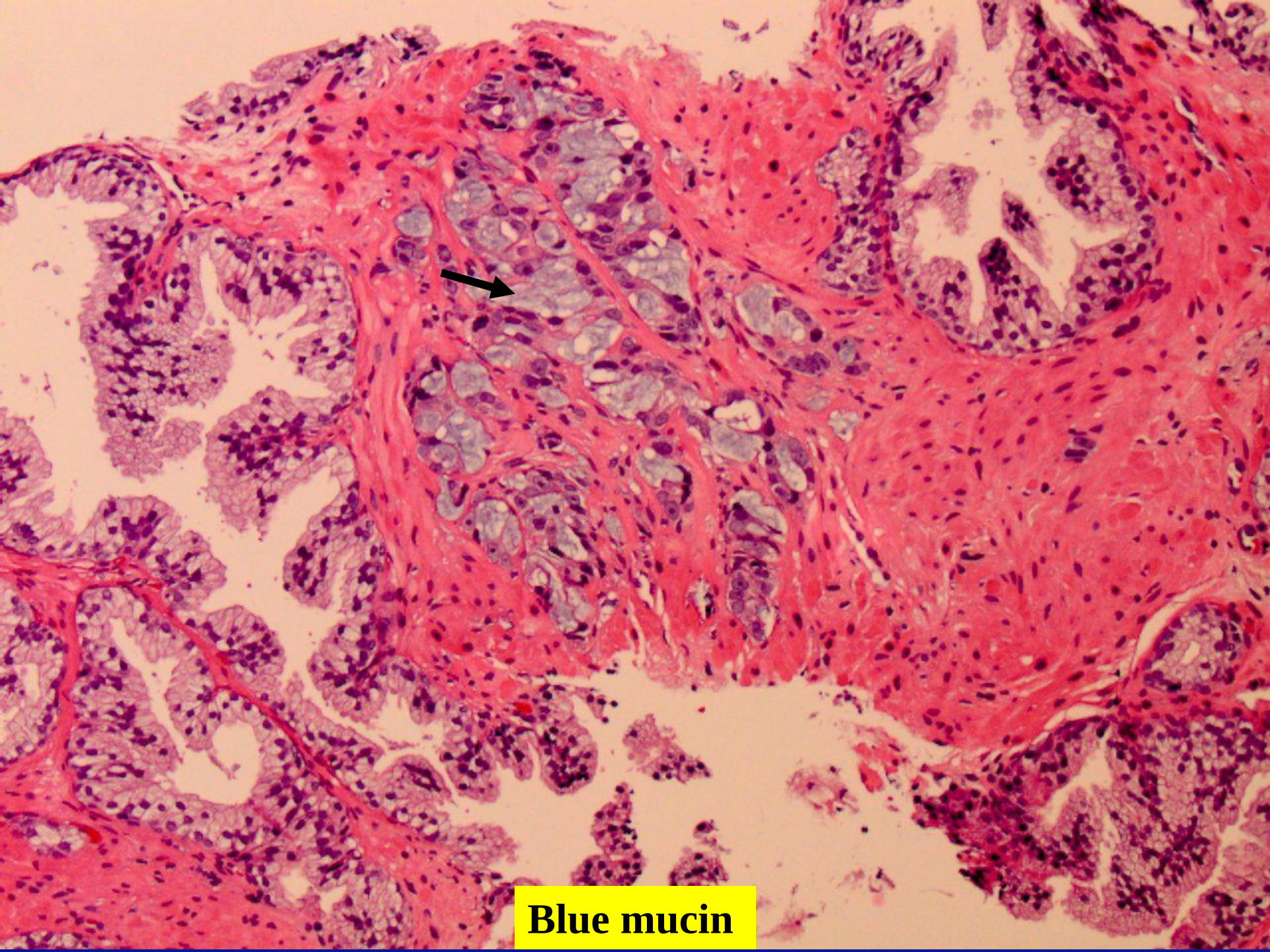
- Nuclear enlargement
- Prominent nucleoli
- Hyperchromasia

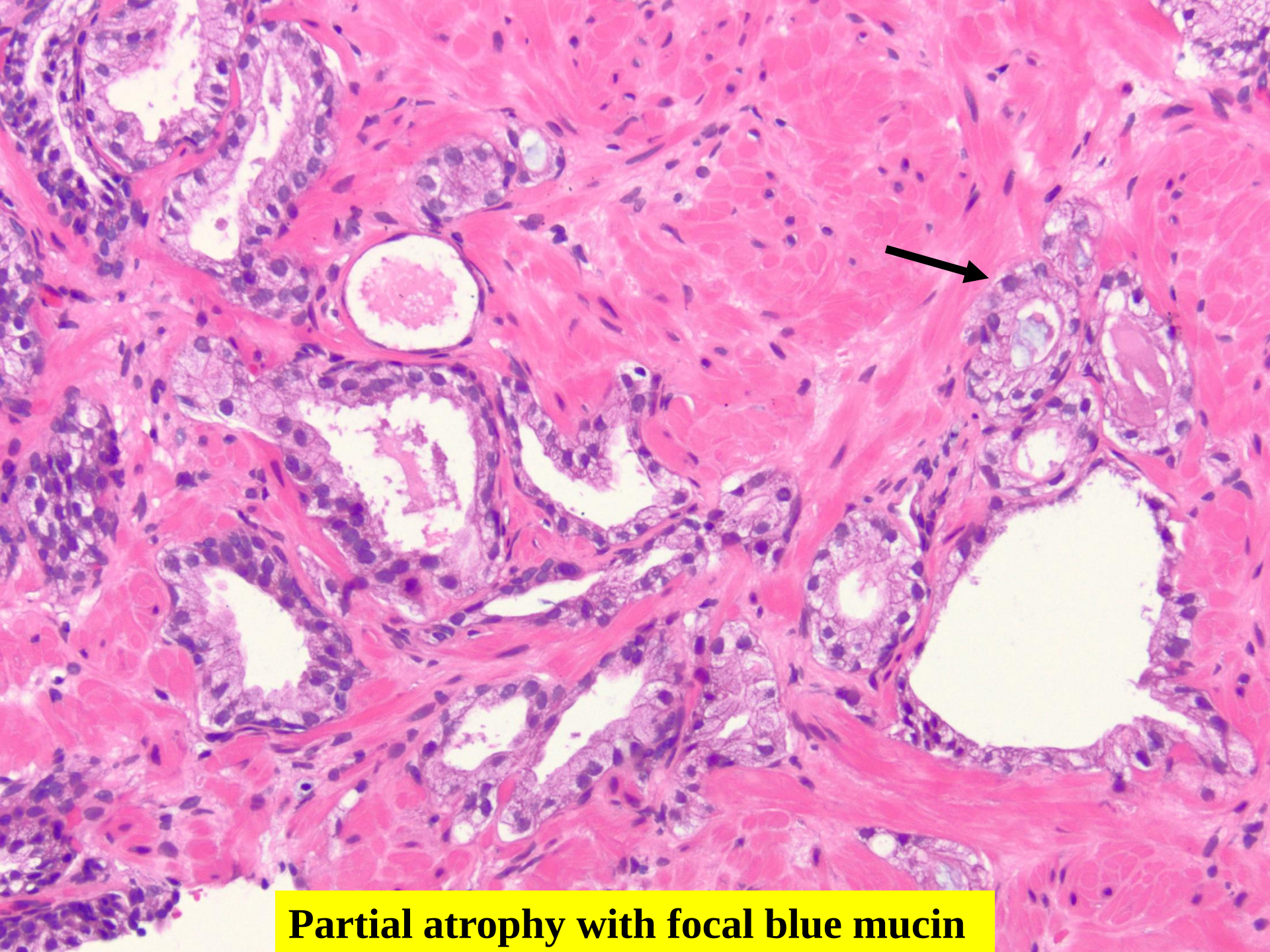
Minor

- Intraluminal blue mucin
- Pink amorphous secretions
- Mitotic figures
- Crystalloids
- Adjacent HGPIN
- Amphophilic cytoplasm

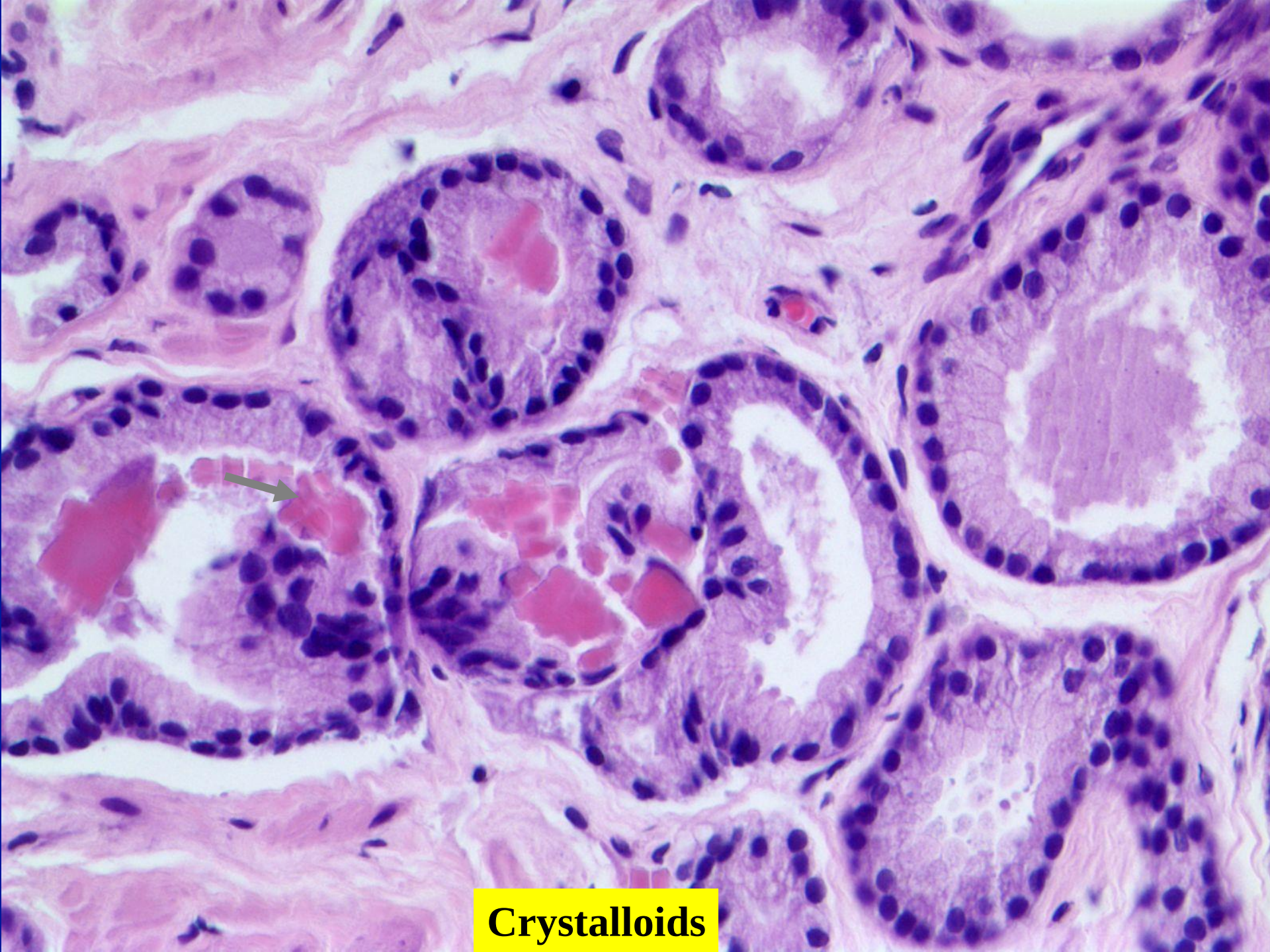
Algaba 1996

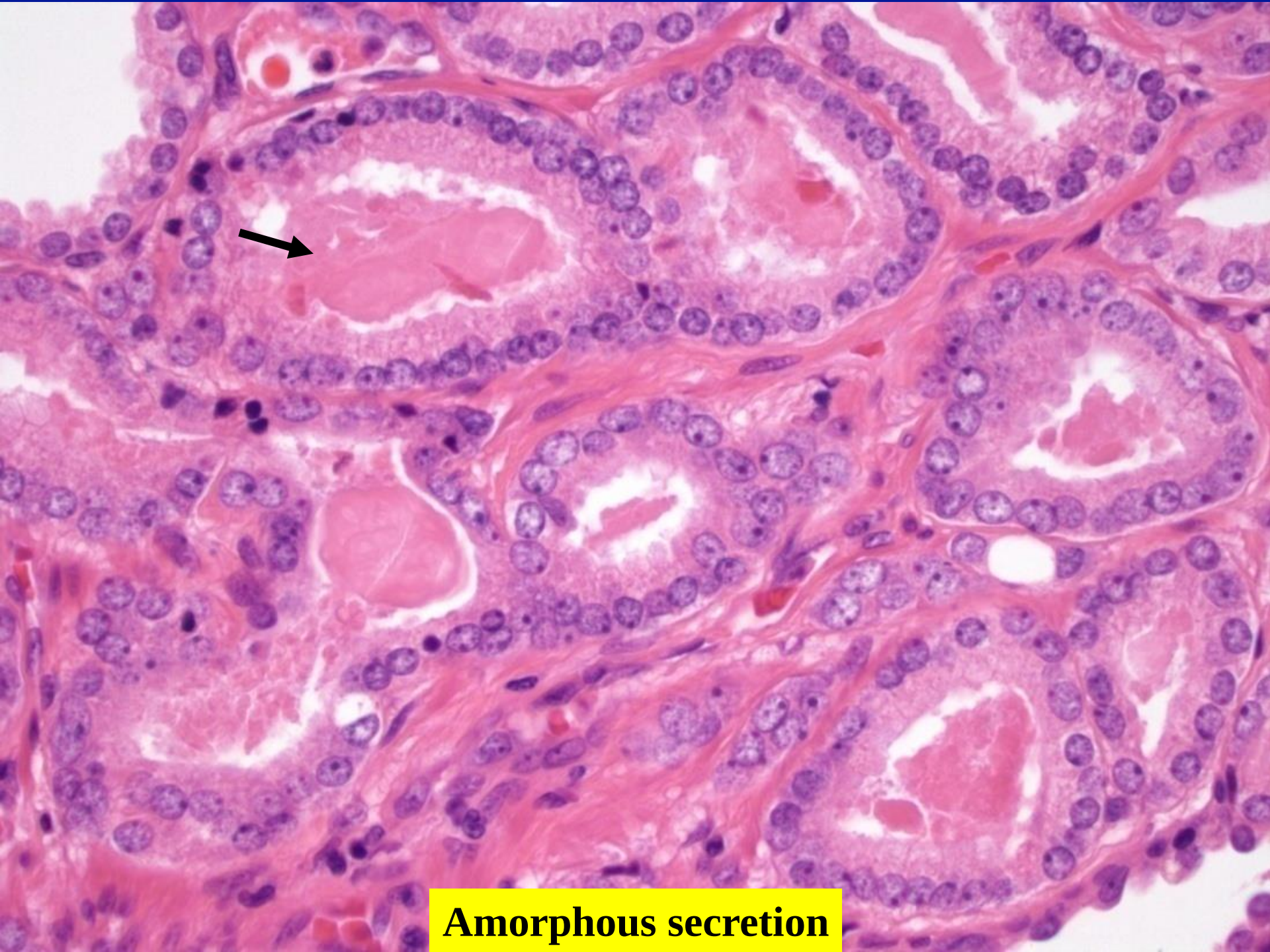

Amphophilic cytoplasm


Blue mucin



Partial atrophy with focal blue mucin


Crystalloids


Amorphous secretion


Stromal retraction

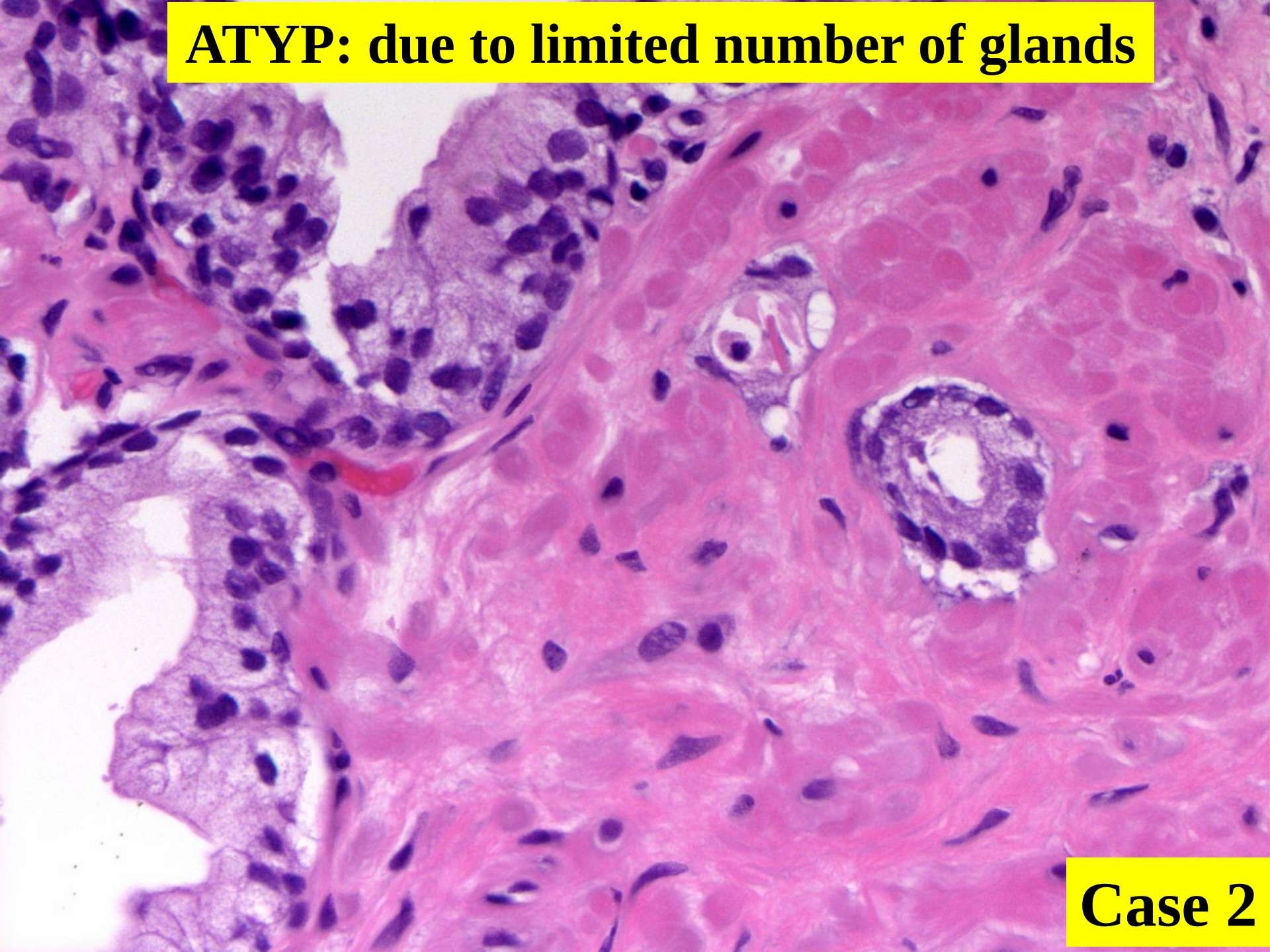
Diagnosis of Limited PCa in Prostate Biopsy

Quantitative Threshold

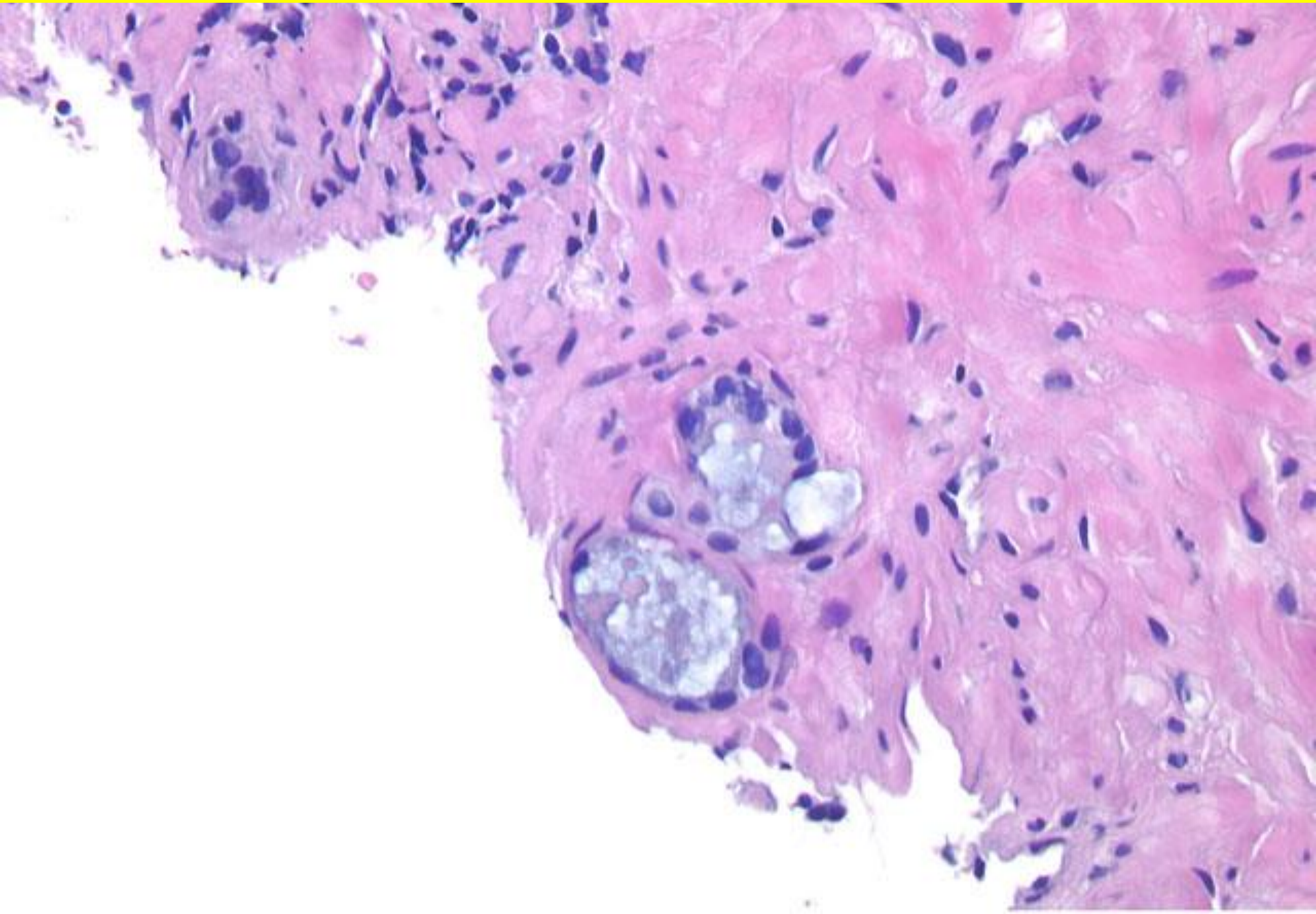
# of atypical glands required to make a definitive PCa diagnosis depends on architectural/cytological atypia

Most urological pathologists require $\geq$ 3 glands to make a confident PCa diagnosis (Algaba, 1996)

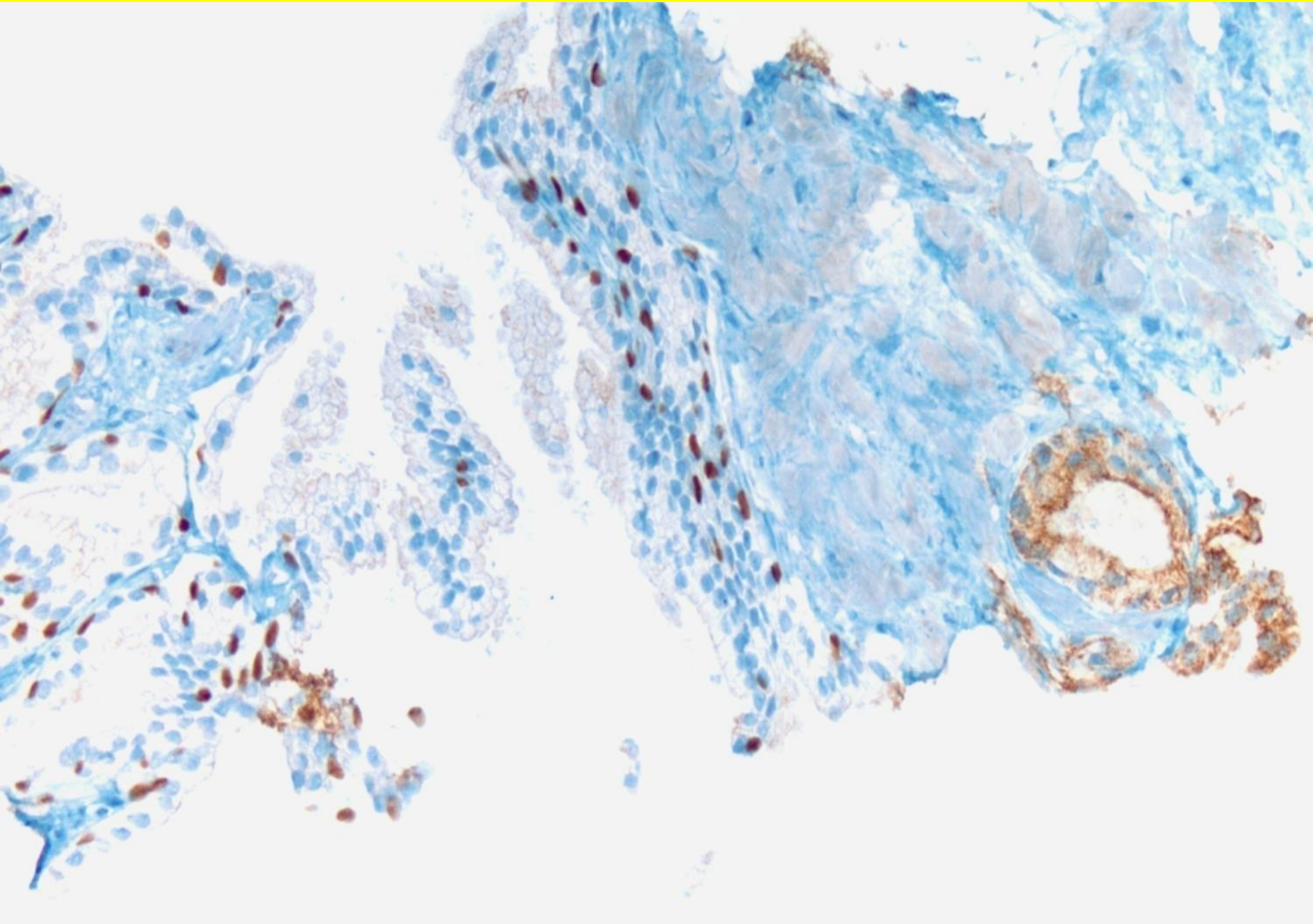
You need large number of glands to make a diagnosis of PCa when presenting with subtle histological variations that mimic benign lesions


ATYP: due to limited number of glands
Case 2

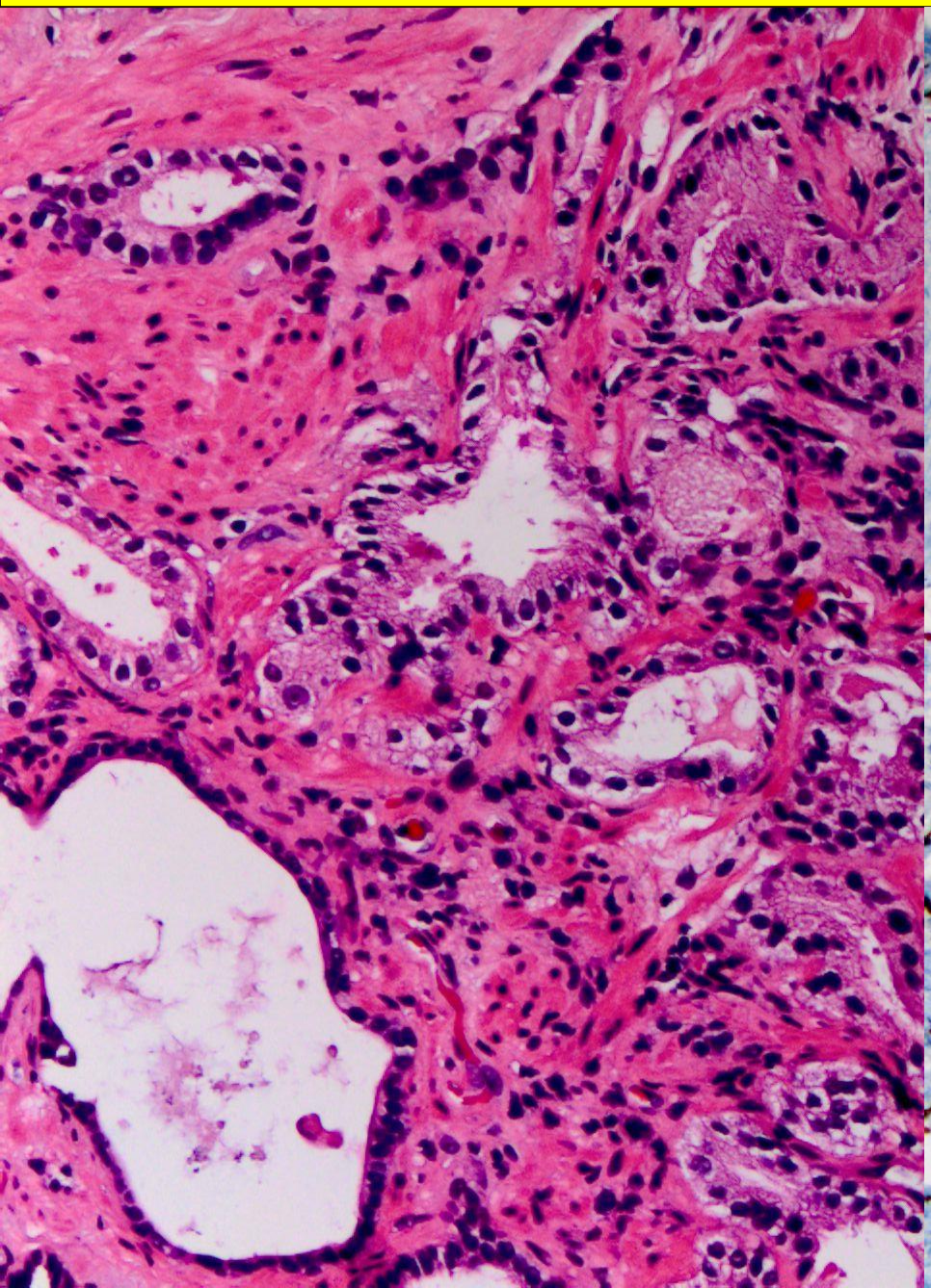
ATYP: due to limited atypical histological features

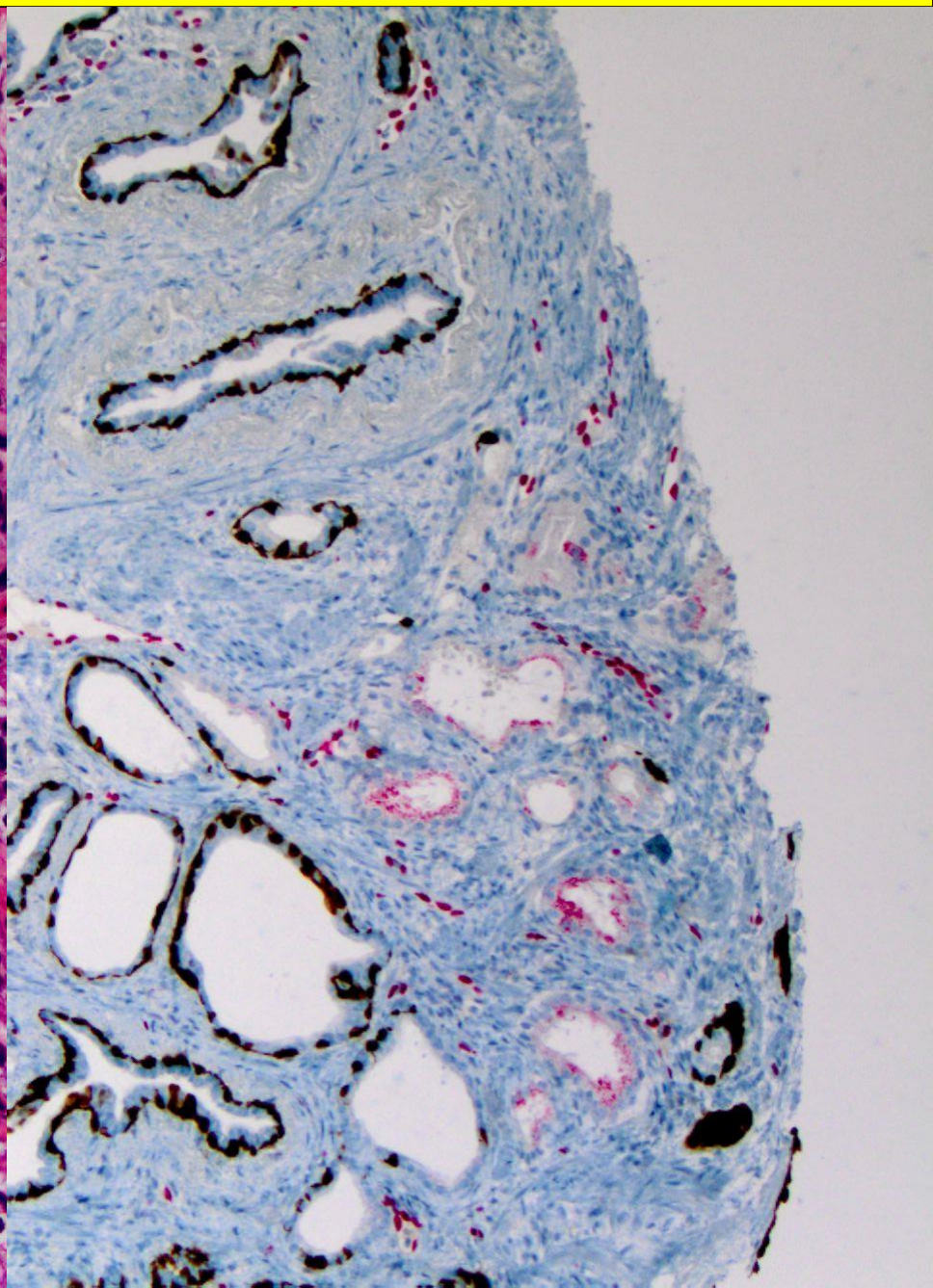


ATYP: Atypical glands at the edge of the biopsy core

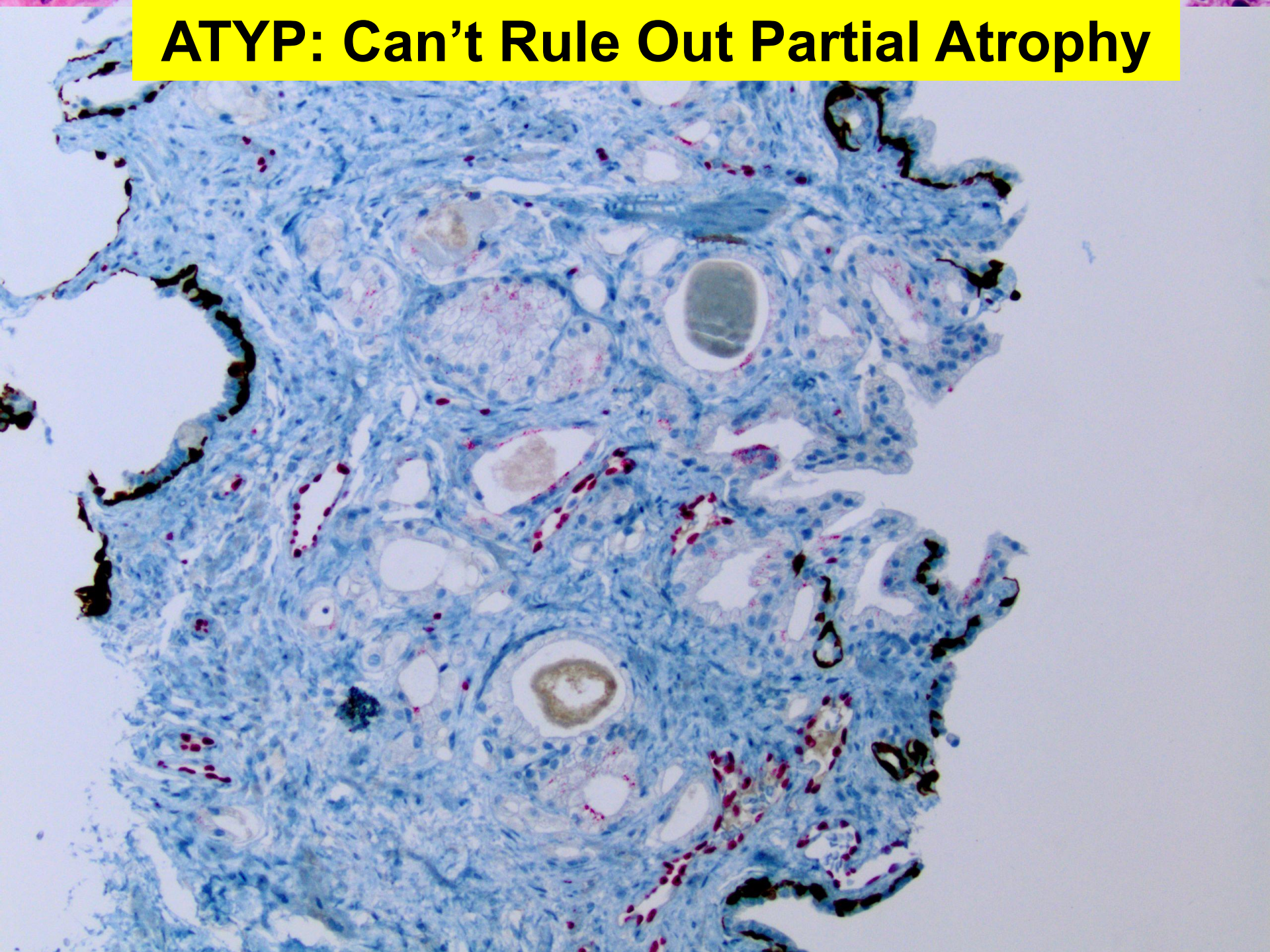


Case 3: ATYP, cannot rule out adenosis

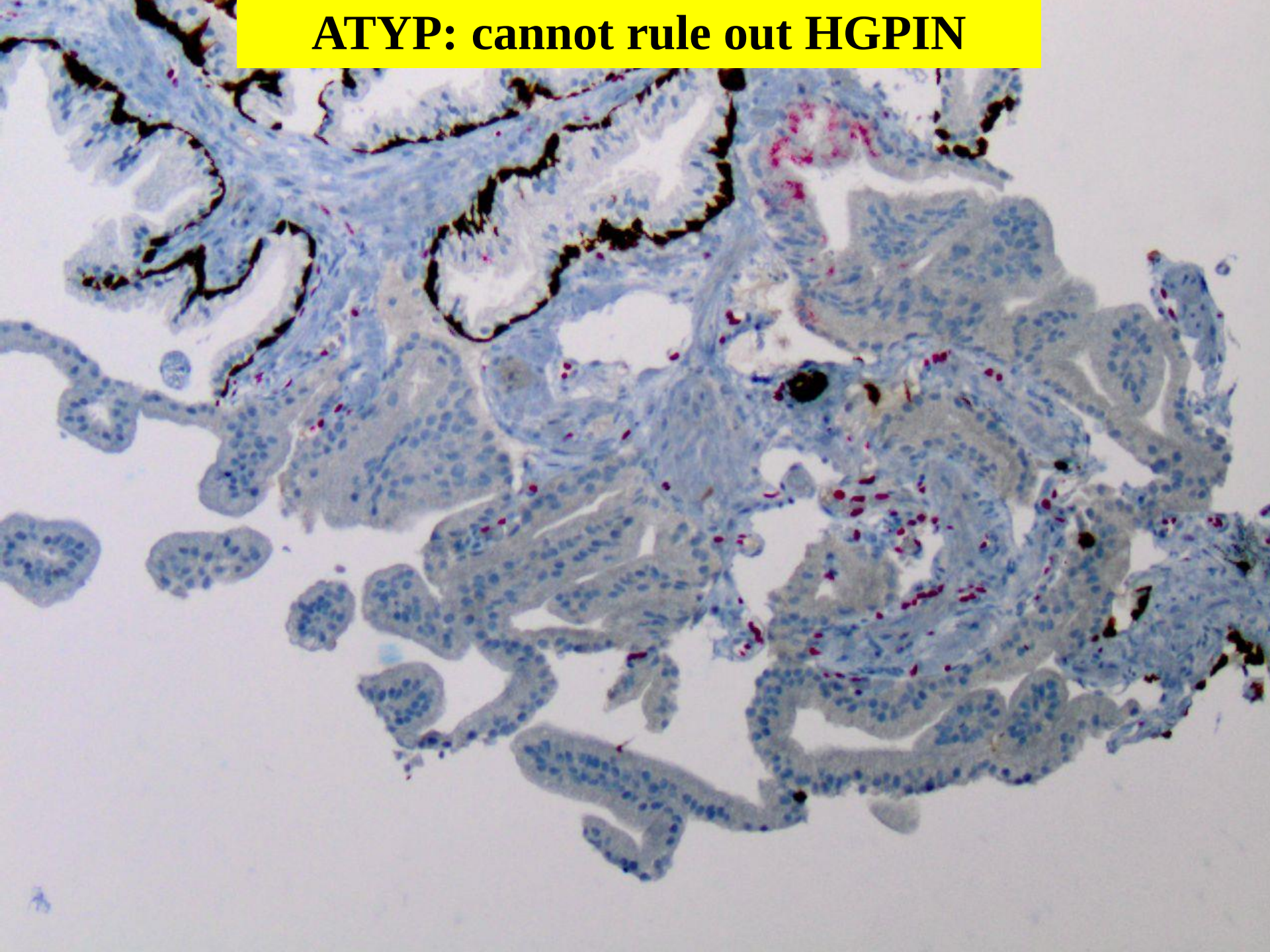




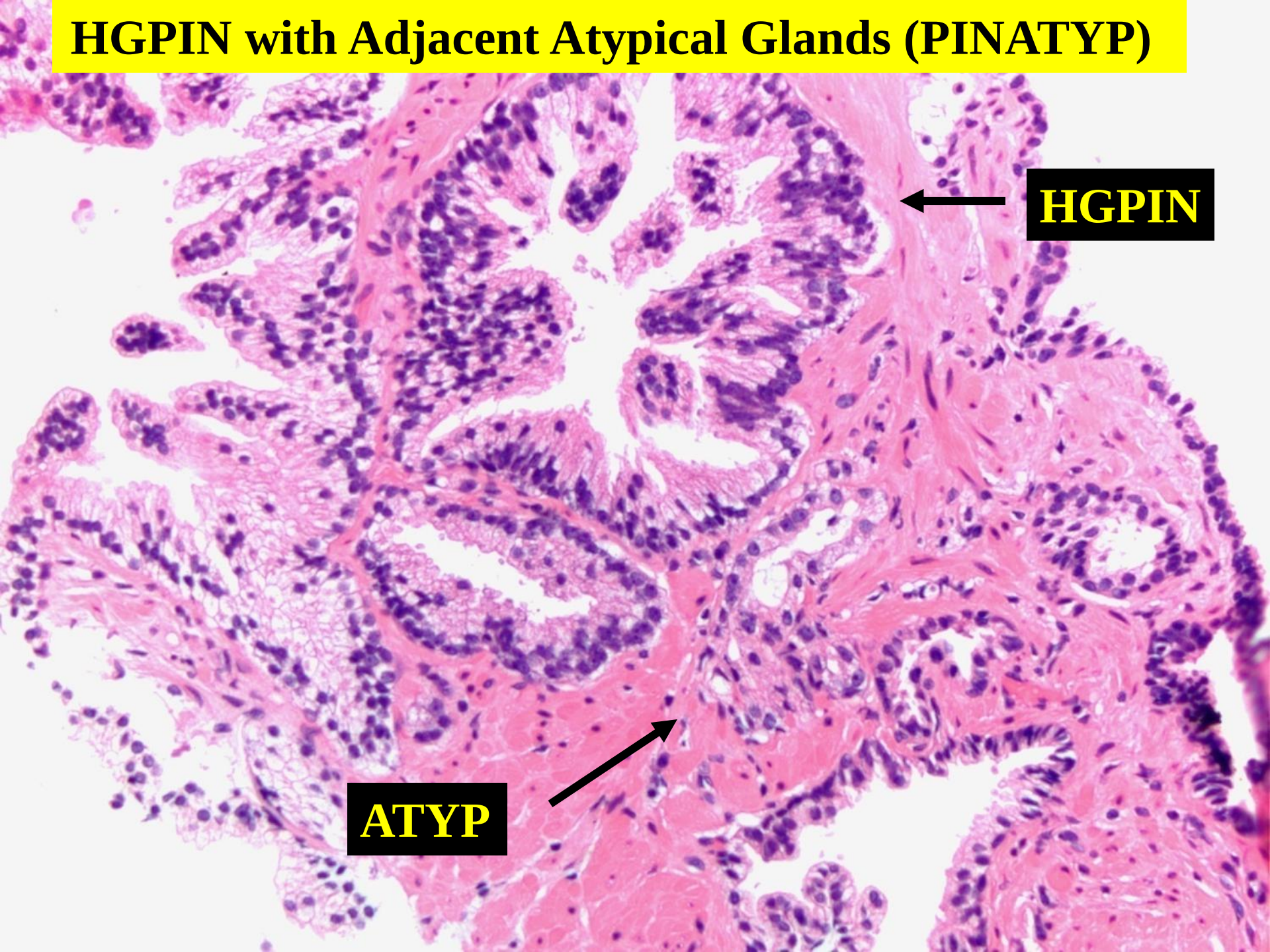
ATYP: Can’t Rule Out Partial Atrophy



ATYP: cannot rule out HGPIN



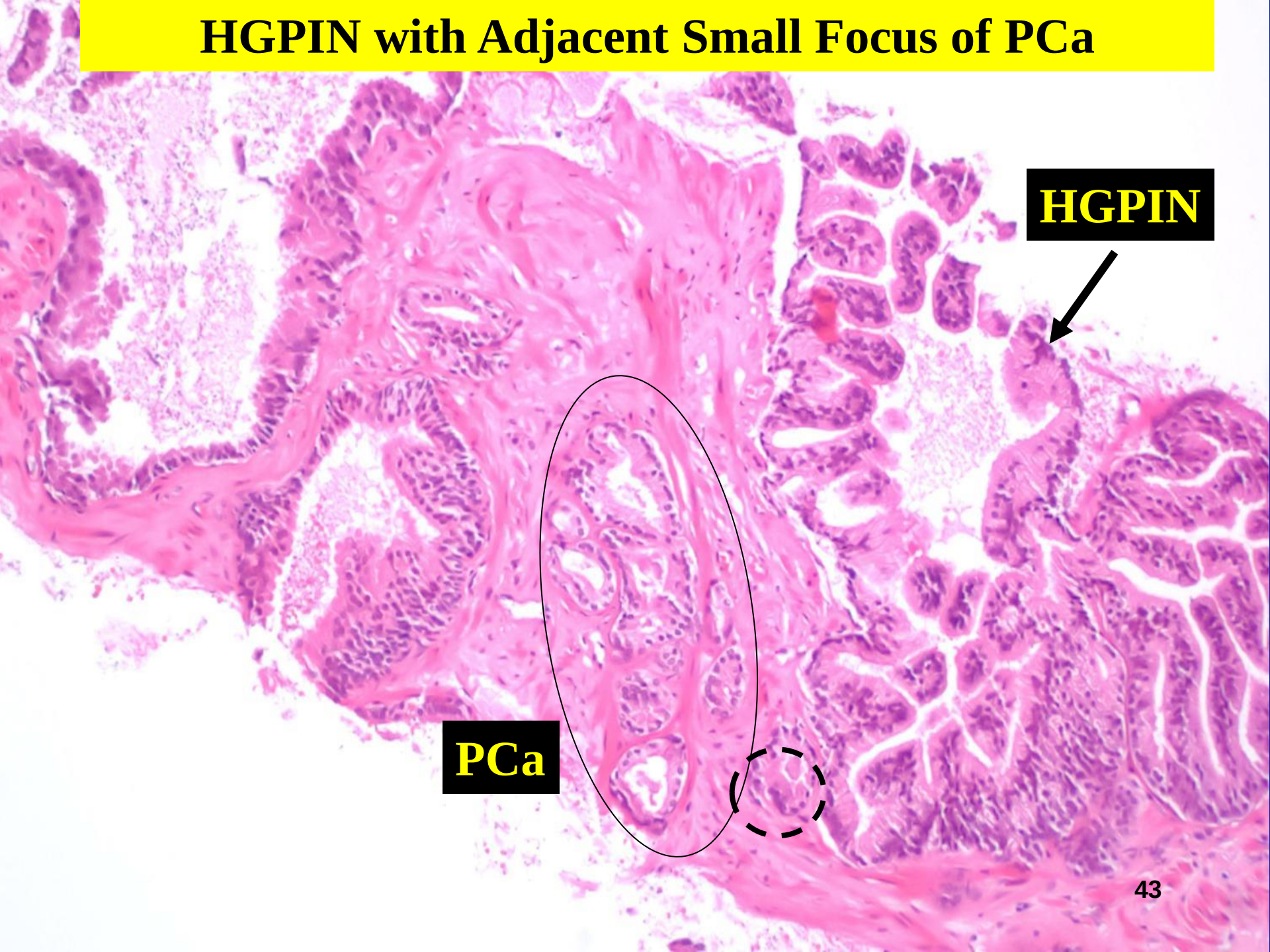
HGPIN with Adjacent Atypical Glands (PINATYP)



Distinction between PINATYP and HGPIN with adjacent small focus of PCa

	HGPIN with adjacent small focus of atypical glands (PINATYP)	HGPIN with adjacent small focus of cancer
Number of atypical glands	A few	> a few
Distance of atypical glands to HGPIN	Close	Away
Similarity between HGPIN and adjacent small glands	Similar	Dissimilar
Discordant IHC staining	No	Yes

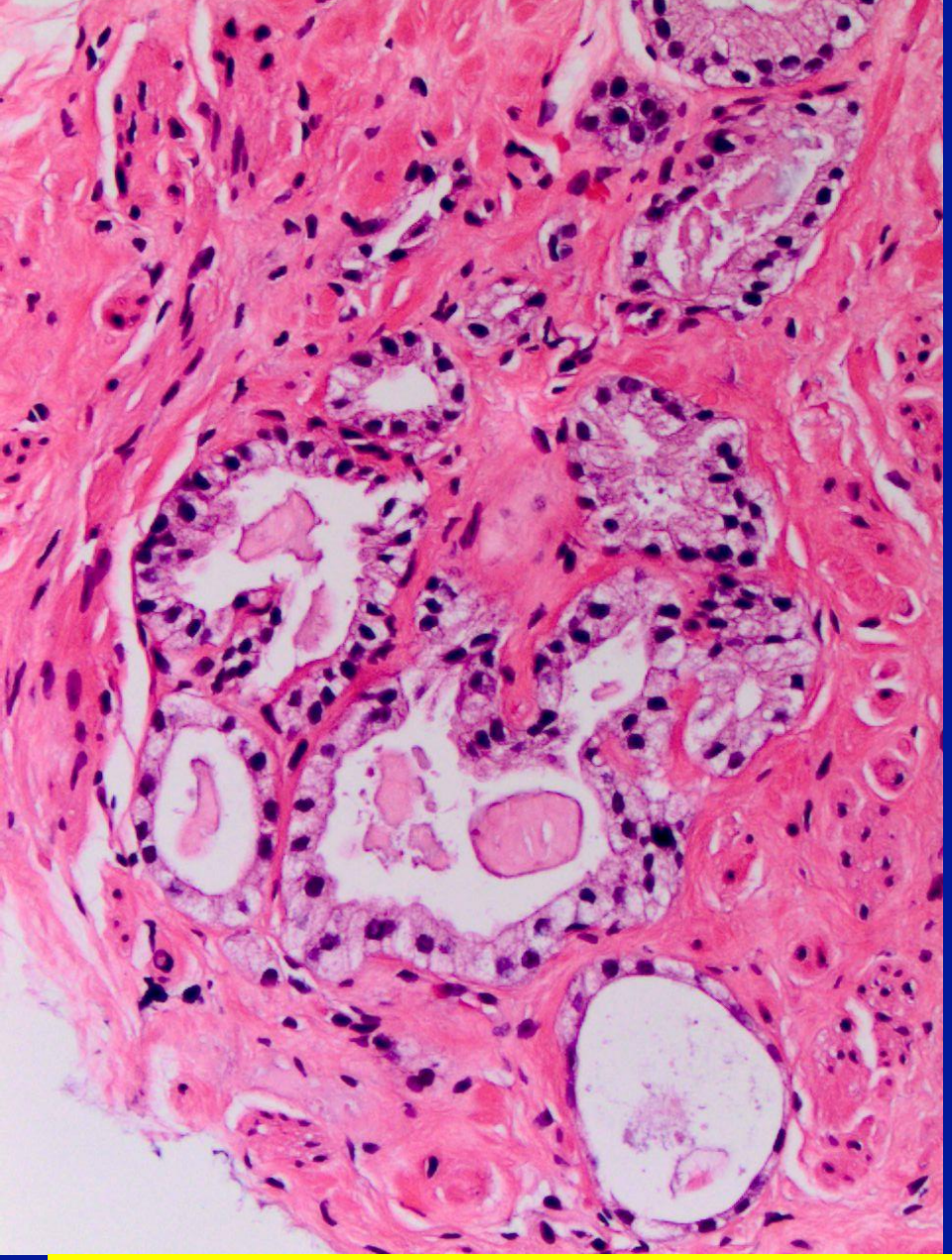
HGPIN with Adjacent Small Focus of PCa

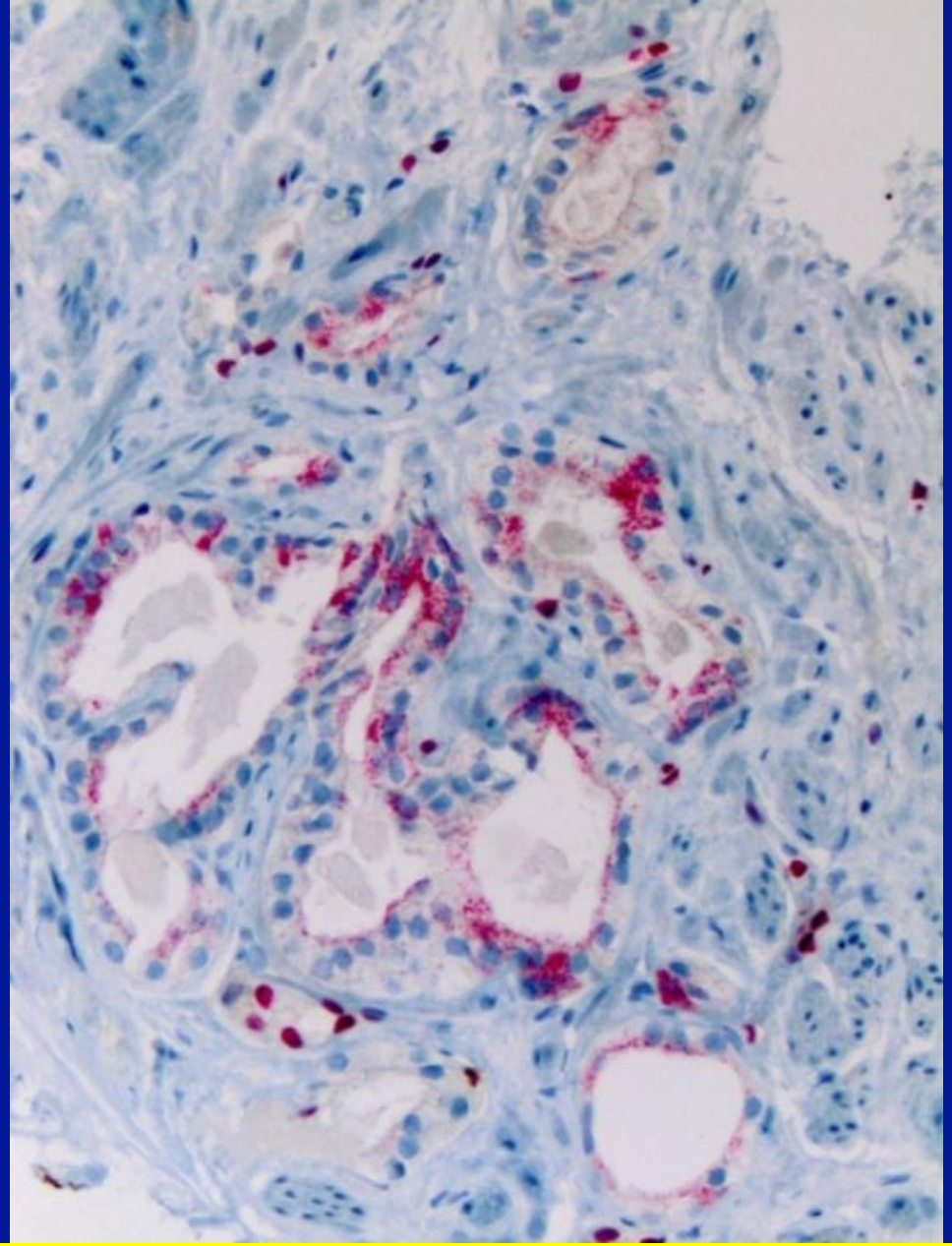


Histological features that argues against cancer diagnosis

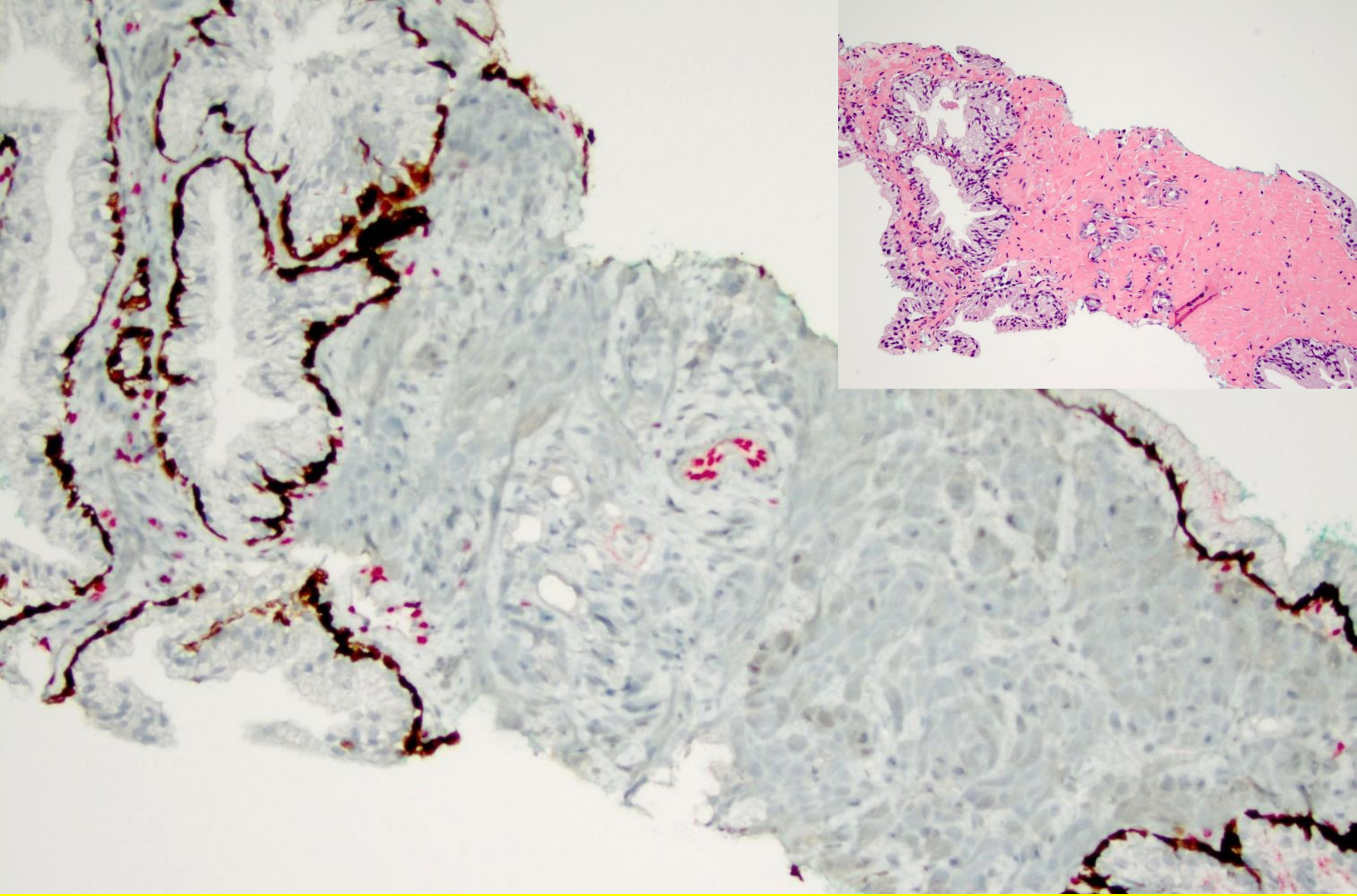
Small and large glands intermingle without cytoplasmic and cytological difference
Large glands with branching and papillary infolding
Nuclear atypia in the background of inflammation
Random nuclear atypia
Pale-clear atrophic cytoplasm
Corpora amylacea
A few atypical glands in proximity to large HGPIN glands

Marker	Sensitivity	Specificity	Pitfalls
Basal cell markers HMWCK, CK5/6, p63	High p63+HMWCK >p63>HMWCK	Low	- Partial atrophy, adenosis, and HGPIN commonly demonstrate patchy positivity/may entirely lack basal cells - P63 positive prostate cancer
AMACR	High (~80%)	Low	Majority of HGPINs and Nephrogenic adenomas and significant proportion of partial atrophy, adenosis and benign glands express AMACR

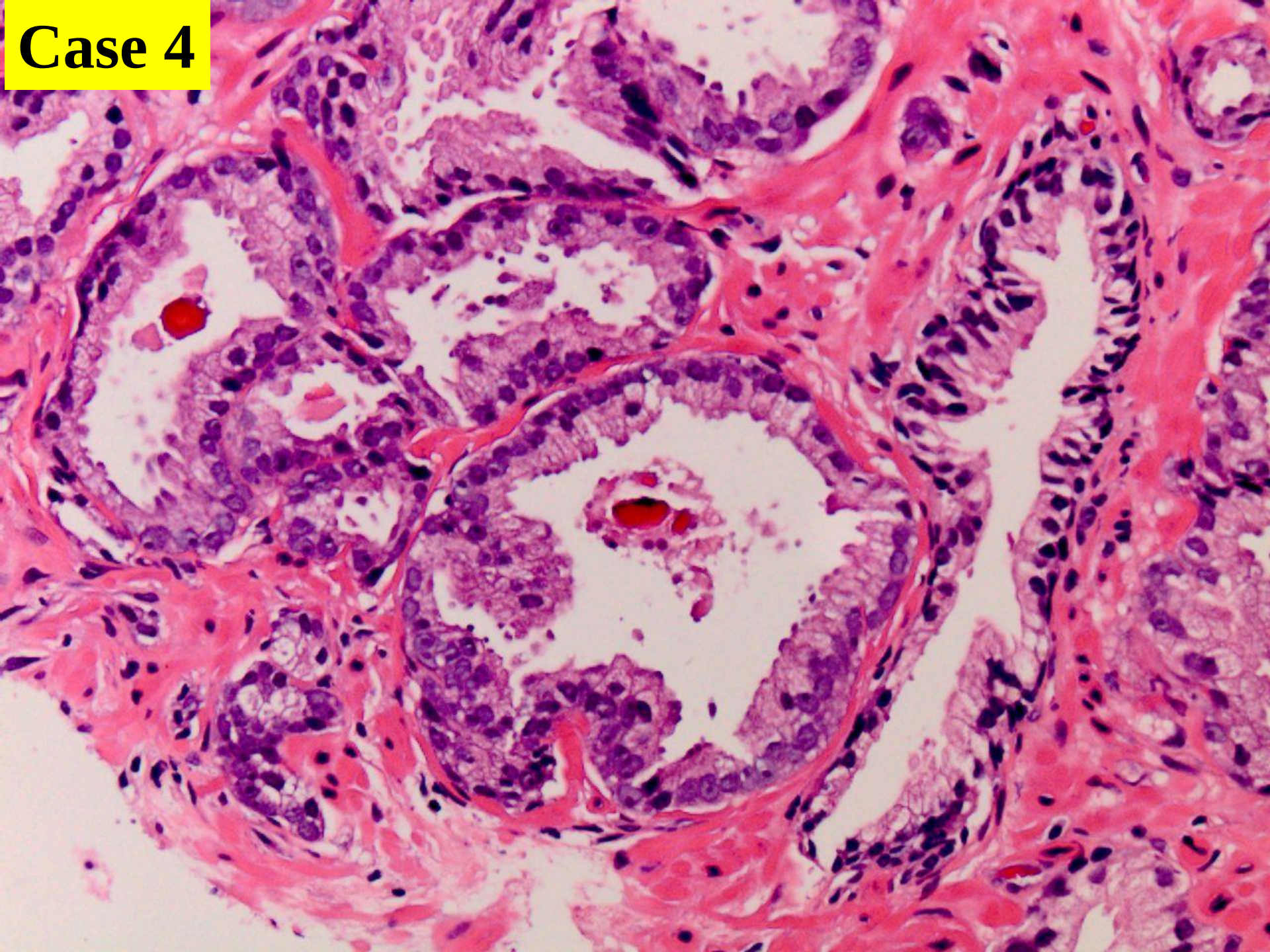


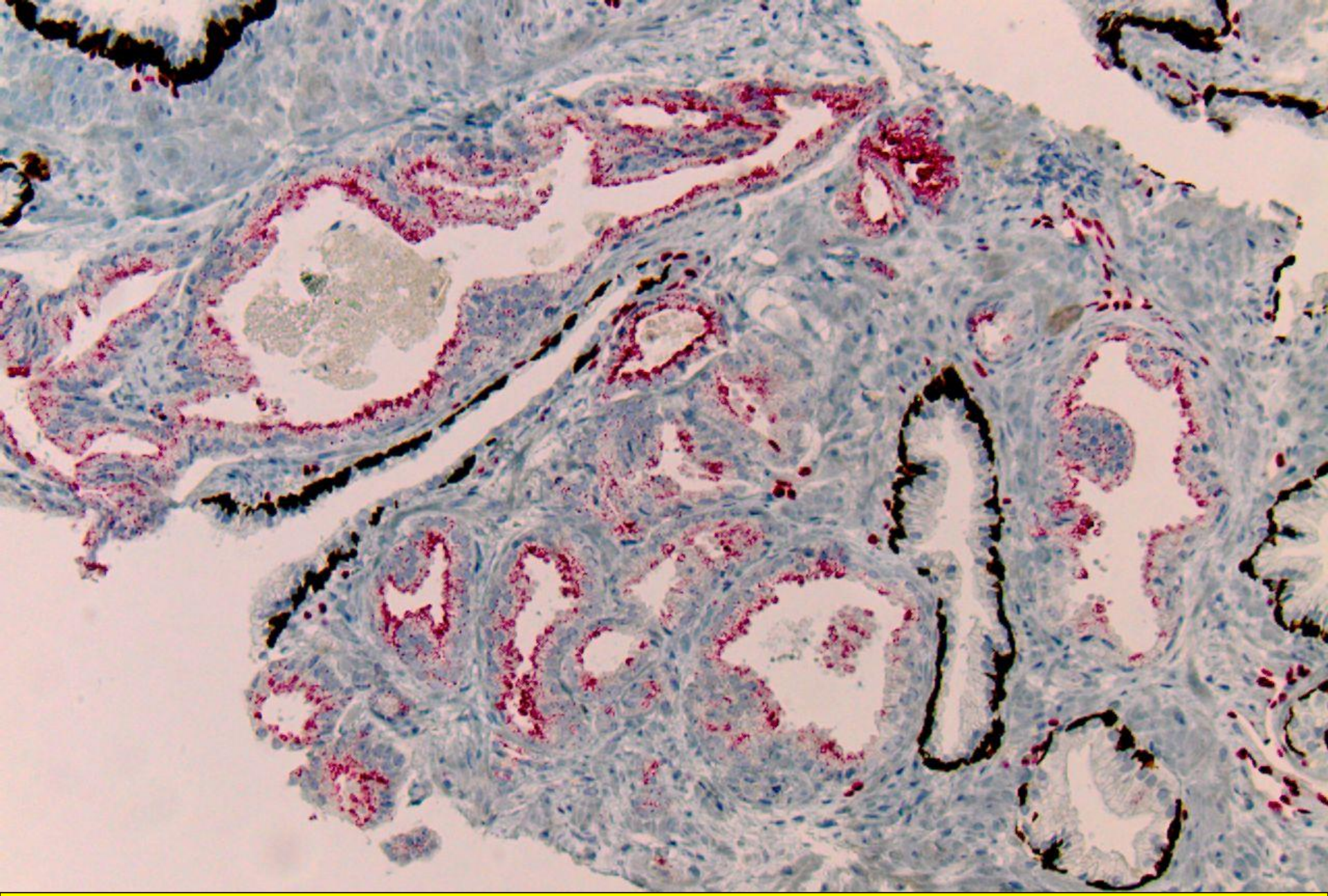


Small proportion of Partial atrophy lesions may demonstrate immunophenotype typical of a cancer!

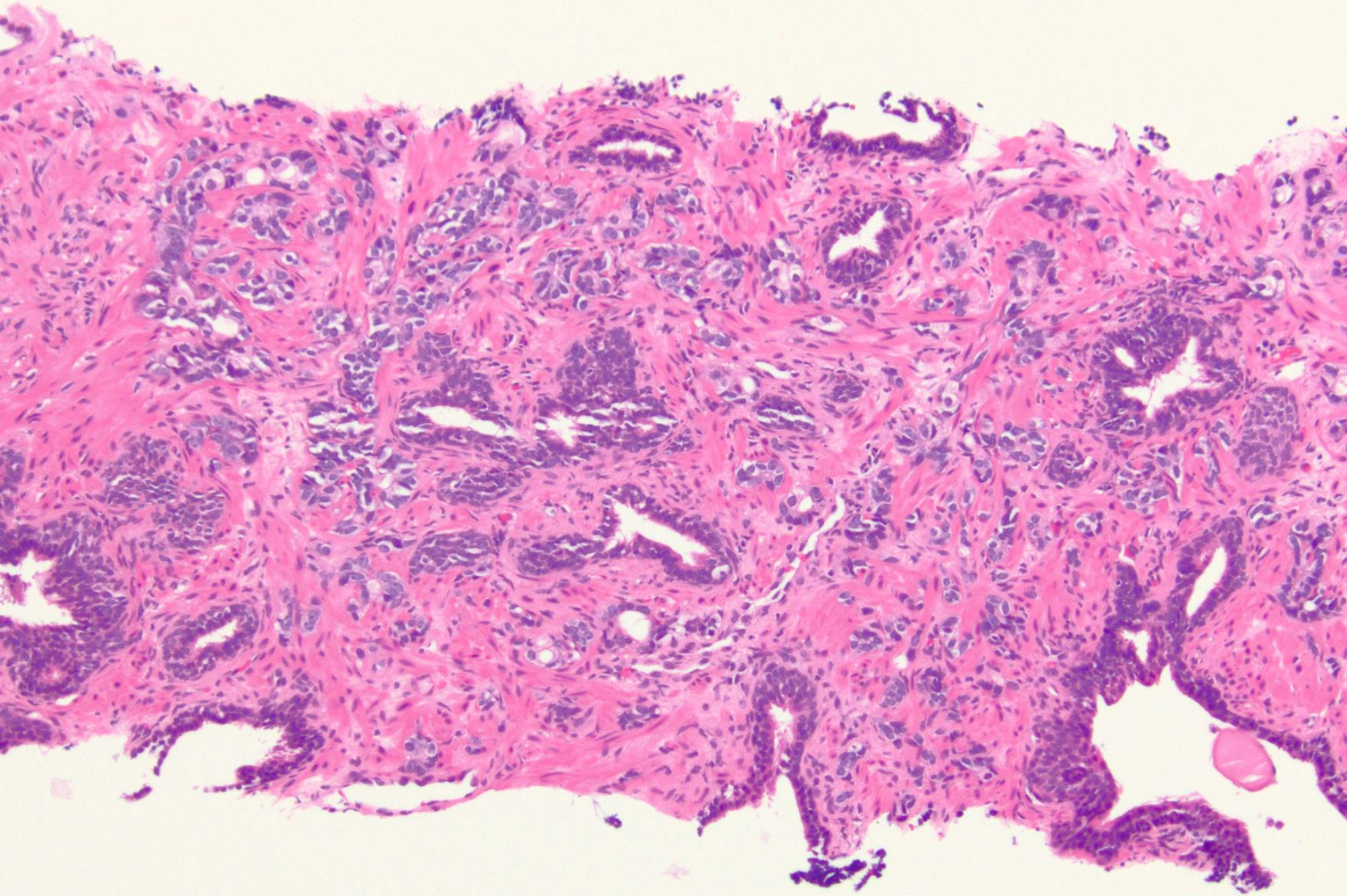


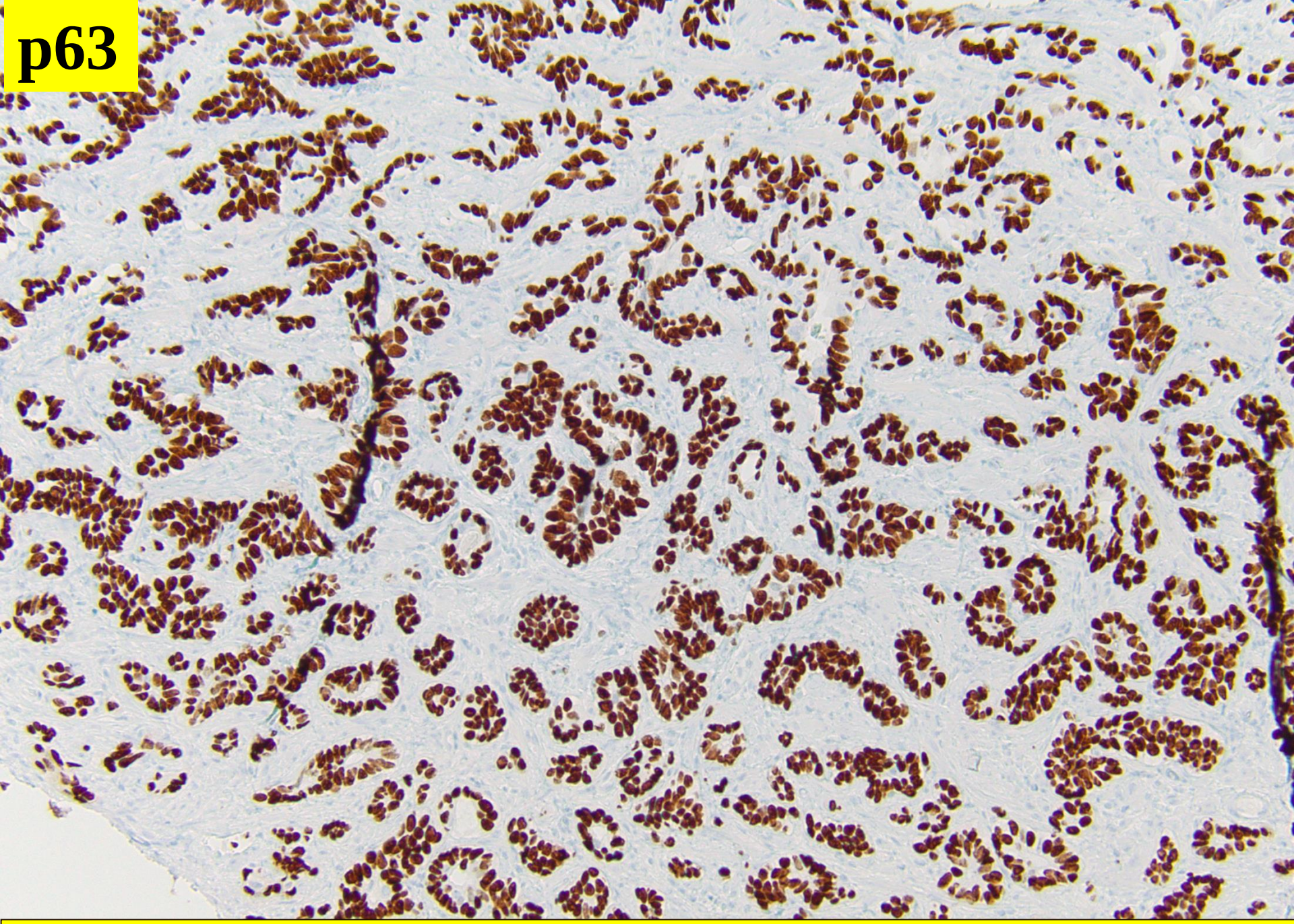
Basal cell markers: Strong internal control is critical to ensure adequate reaction


Case 4



Case 4: Prostate adenocarcinoma with pseudohyperplastic features, Gleason score 3+3=6





P63 positive prostate adenocarcinoma, Gleason score 3+4=7, GG2

Marker	Sensitivity	Specificity	Pitfalls
Basal cell markers HMWCK, CK5/6, p63	High p63+HMWCK >p63>HMWCK	Low	Partial atrophy, adenosis, and HGPIN commonly demonstrate patchy positivity/may entirely lack basal cells P63 positive prostate cancer
AMACR	High (~80%)	Low	Majority of HGPINs and Nephrogenic adenomas and significant proportion of partial atrophy, adenosis and benign glands express AMACR
ERG	Low (40-50%)	High	Positive in 18% of HGPINs associated with PCA

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Original contribution

The diagnostic use of ERG in resolving an "atypical glands suspicious for cancer" diagnosis in prostate biopsies beyond that provided by basal cell and α-methylacyl-CoA-racemase markers☆

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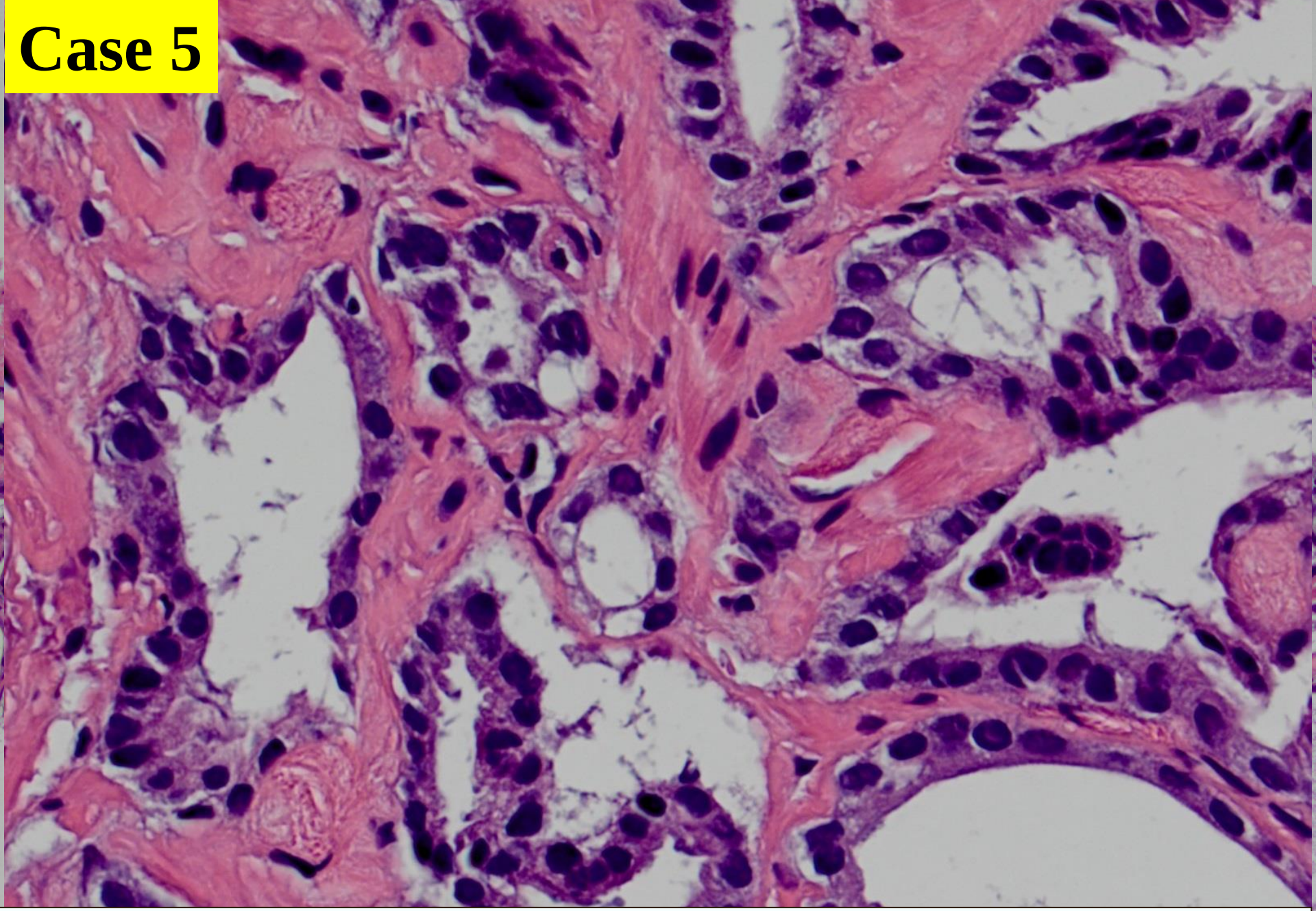
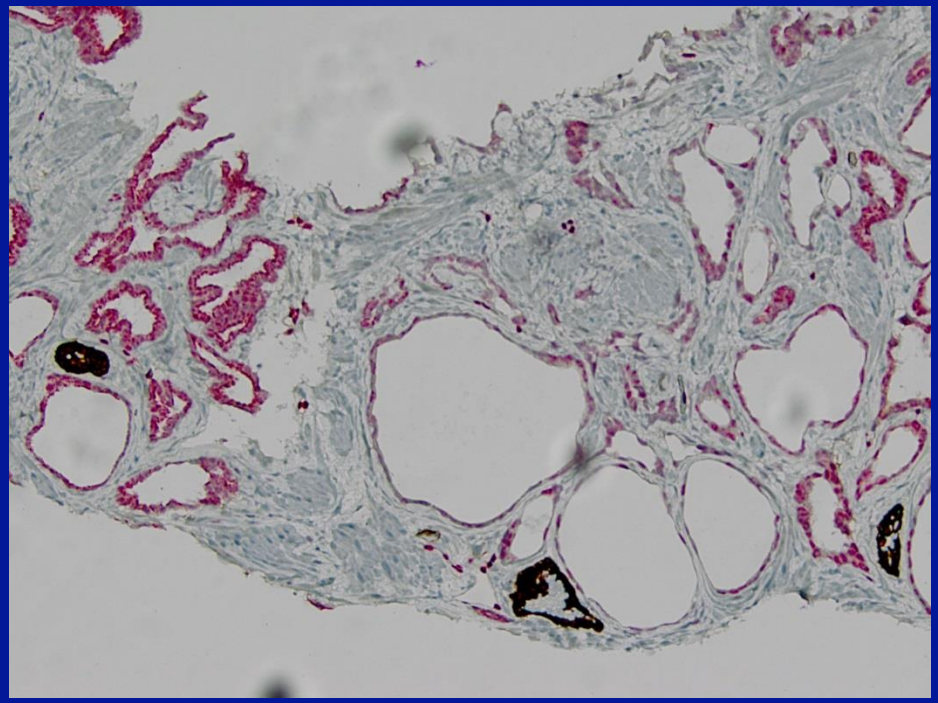
[b]*Department of Pathology, New York University, New York, NY 10016, USA*

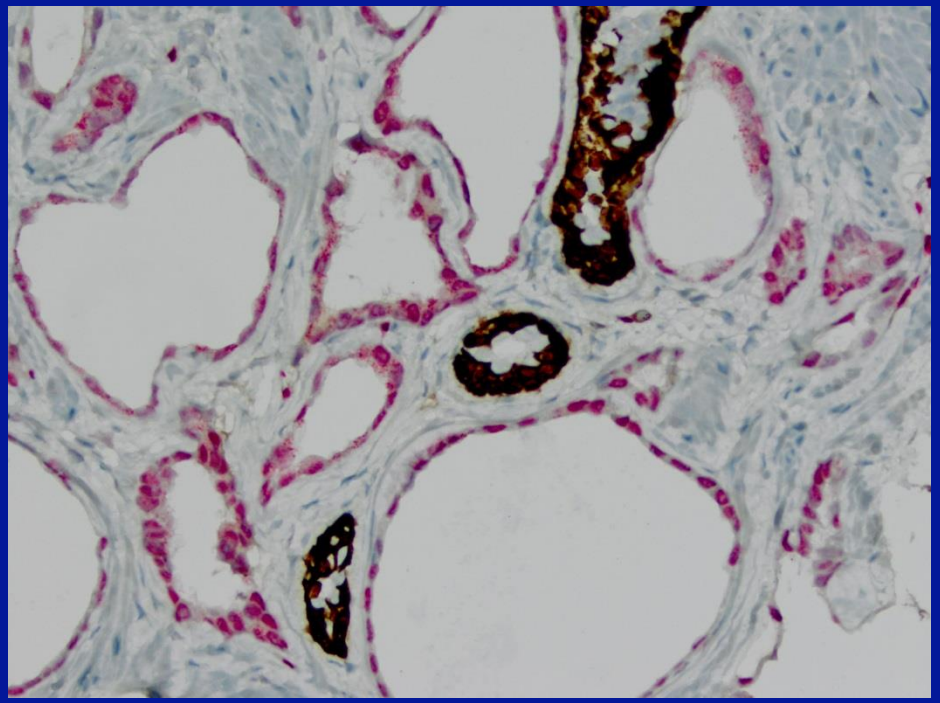
- ERG positive small ATYP glands where the diagnosis of HGPIN or PINATYP is excluded is diagnostic of cancer
- Convert small proportion of ATYP cases to definitive cancer where either qualitative or quantitative features are inadequate



61 year old male, elevated PSA 8 ng/ml

Case 5

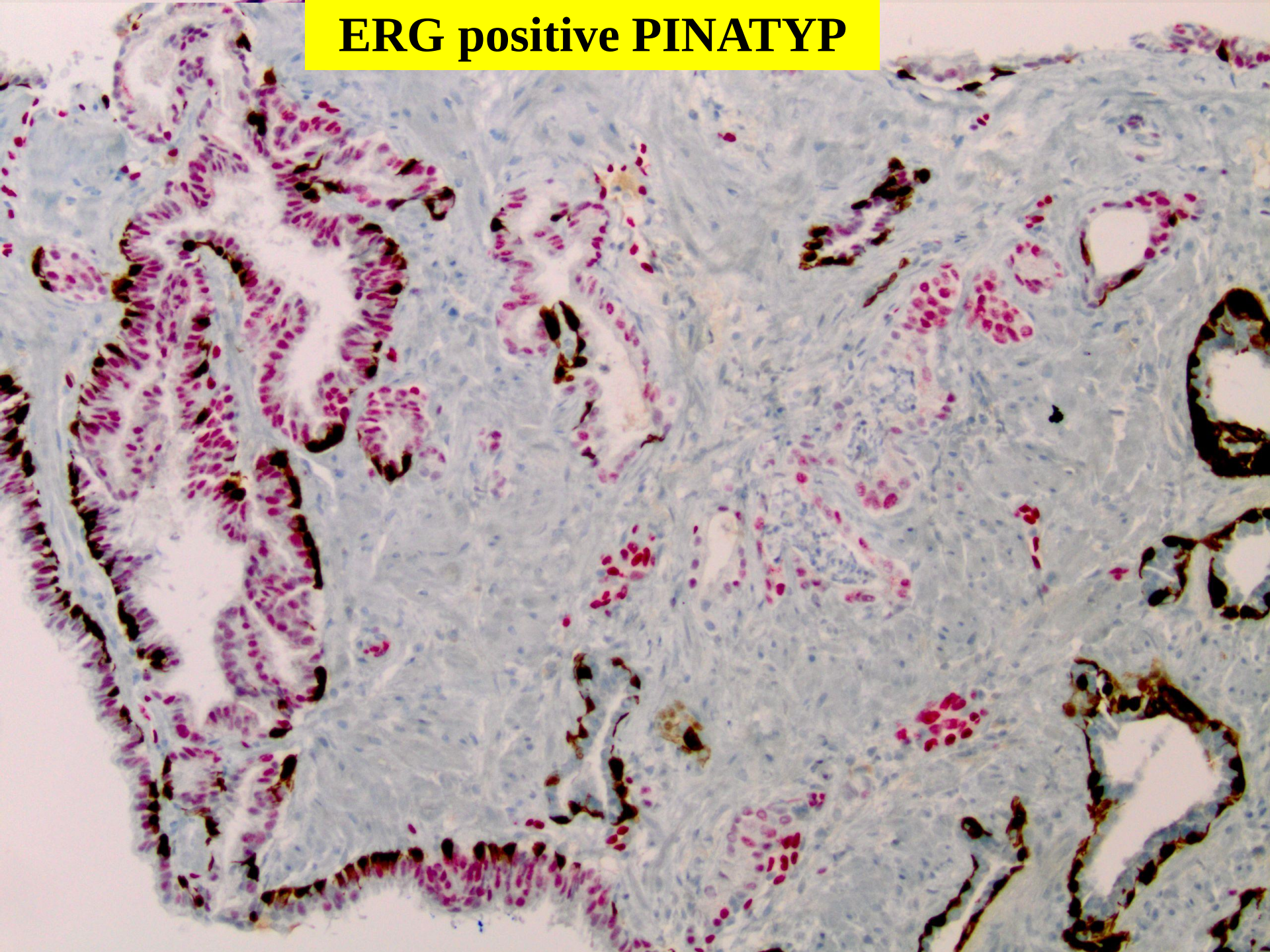




PIN4-ERG

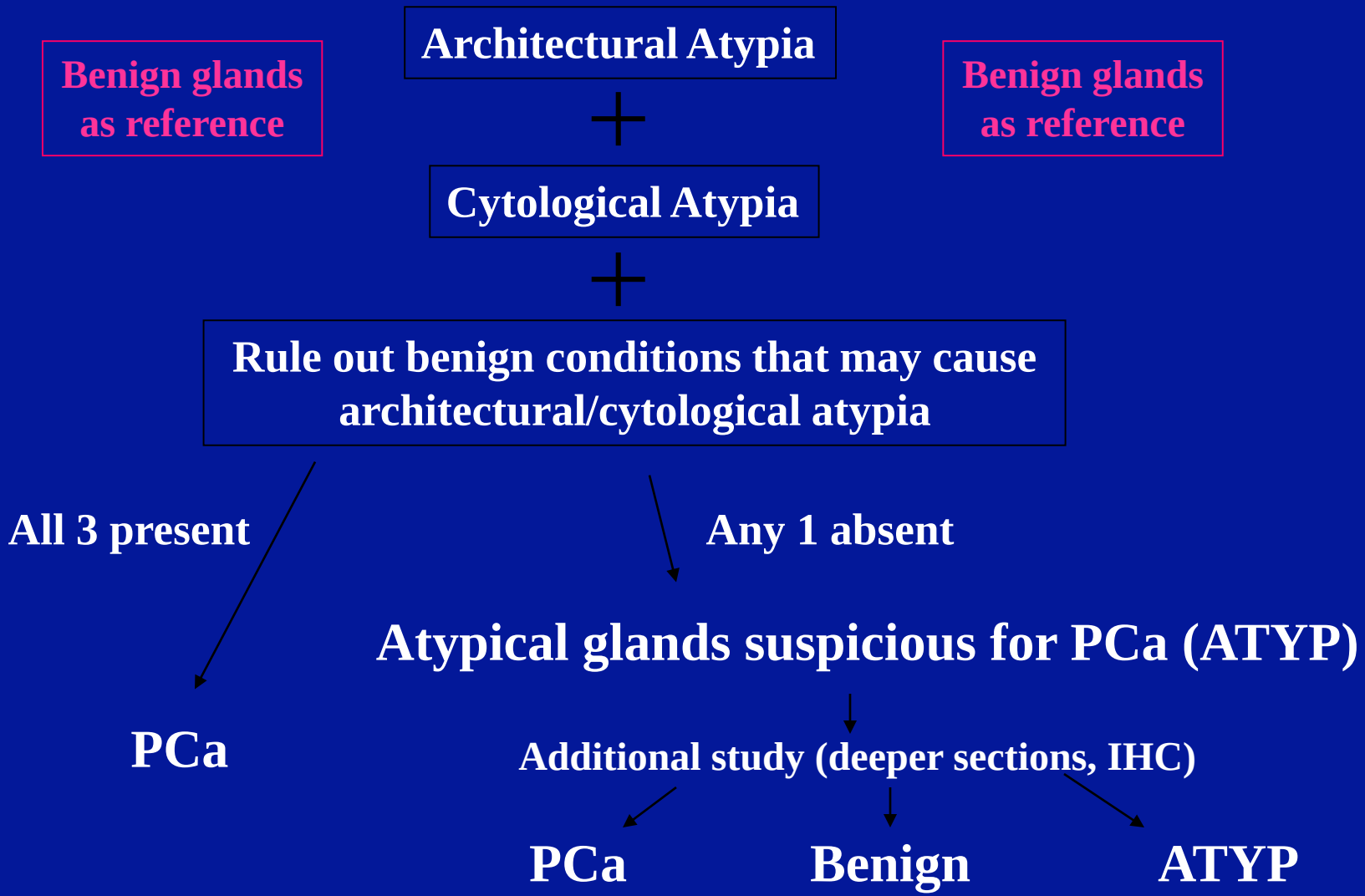
Case 5: Prostate adenocarcinoma with atrophic features, Gleason score 3+3=6

ERG positive PINATYP



Diagnosis of Limited PCa in Prostate Biopsy

A 3-step Approach



Practical Pearls

- Use a methodical approach to evaluate prostate biopsies; use constellation of architectural and cytological features to make a cancer diagnosis
- Use benign glands as a reference
- Hesitate to make cancer diagnosis when histological features that argues against cancer diagnosis are present
- Use IHC to support morphological impression; know its limitations; make sure appropriate controls are present

Practical Pearls

- Diagnosis of histological variations of prostate cancer that mimic benign lesions in prostate biopsy require stringent quantitative and qualitative criteria and/or the presence of conventional acinar adenocarcinoma

Thank you!