Pathology of the Parathyroid Glands

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Hypoparathyroidism

DiGeorge Syndrome (22q11.2, 10p14-p13)

Familial isolated hypoparathyroidsim (CaR and PTH mutation)

Sporadic idiopathic hypoparathyroidism(CaR activating mutation)

Autoimmune polyglandular syndrome (APS) type I (21q22.3-Autoimmune regulator gene)

Primary Parathyroid Hyperplasia

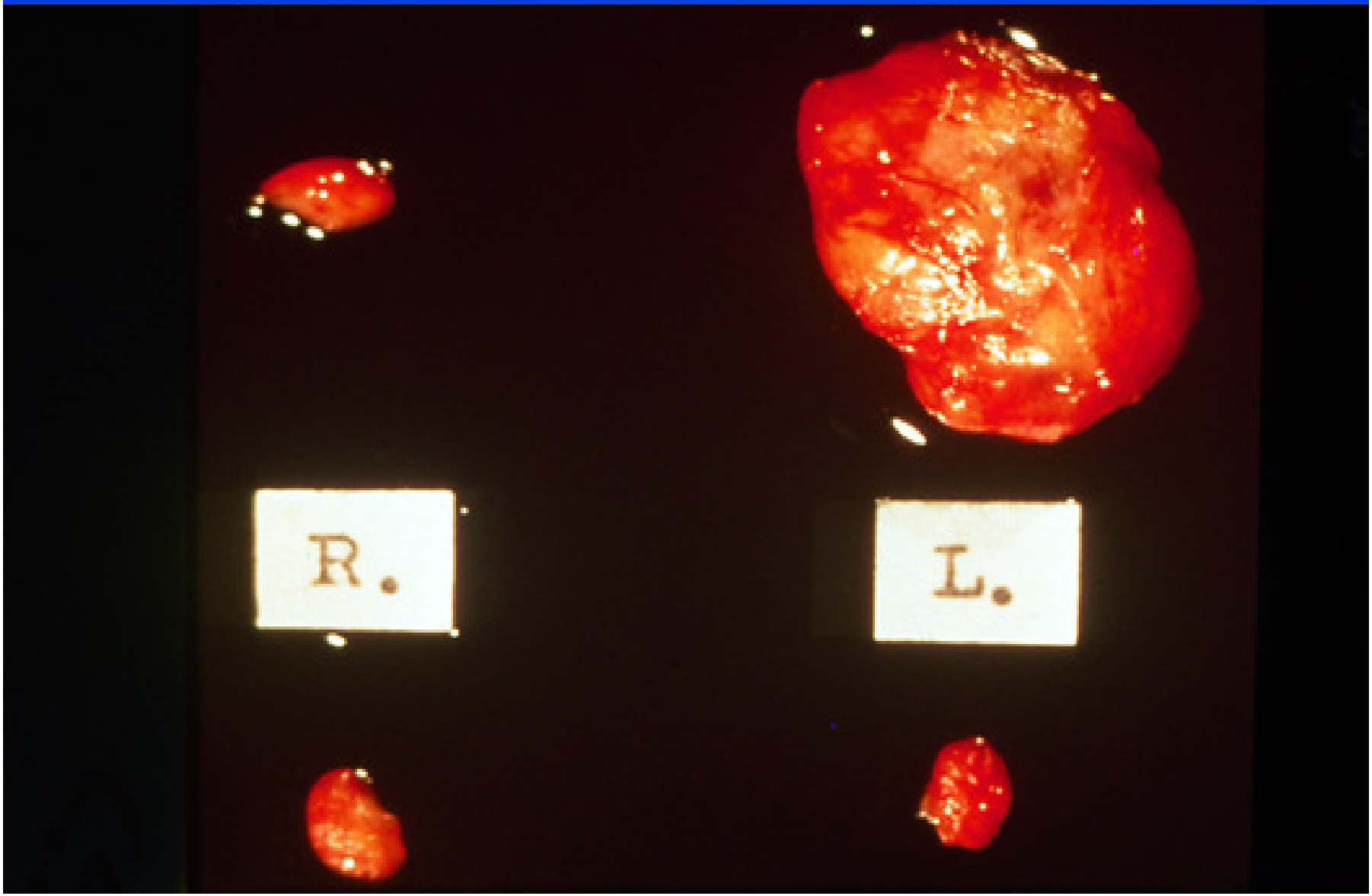
- May involve all four glands or predominantly two or three glands.
- Usually sporadic, but may be familial
- Usually not associated with development of malignancy

Heritable HPT Syndromes

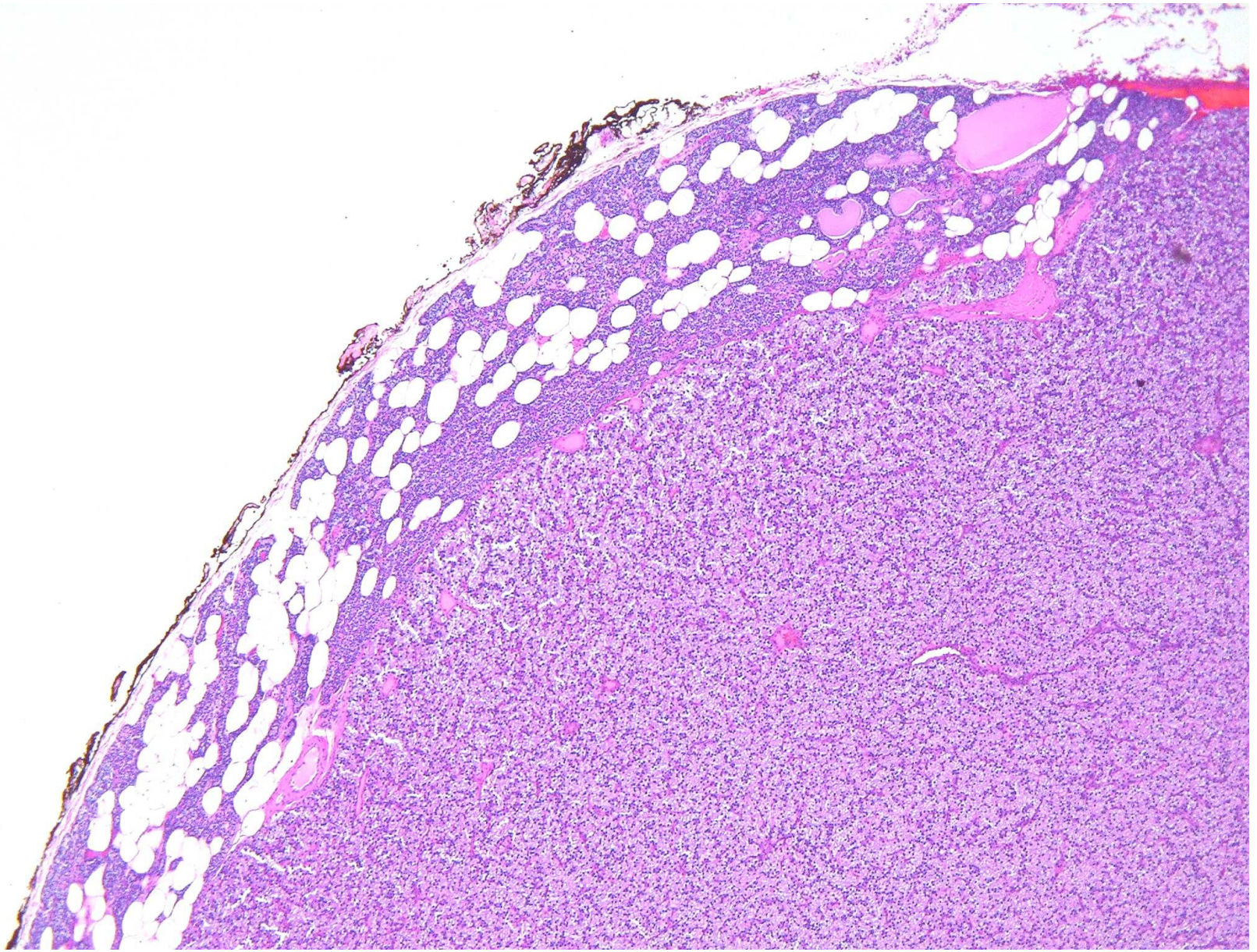
Syndrome	Gene (Locus)	Parathyroid
MEN1	MEN1(11q13)	Hyperplasia (90%)
MEN2A	RET(10q11.2)	Hyperplasia (30%)
FHH	CaSR(3q13-q21)	Mild Hyperplasia
NSHPT	CaSR(3q13-q21)	Severe Hyperplasia
HPT-JT	HRPT2(1q15.q32)	Multiple adenomas and carcinomas

MEN-Multiple endocrine neoplasia; FHH-Familial hypocalciuric hypercalcemia; NSHPT-Neonatal severe hyperparathyroidism; HPT-JT-Hyperparathyroidism jaw-tumor syndrome

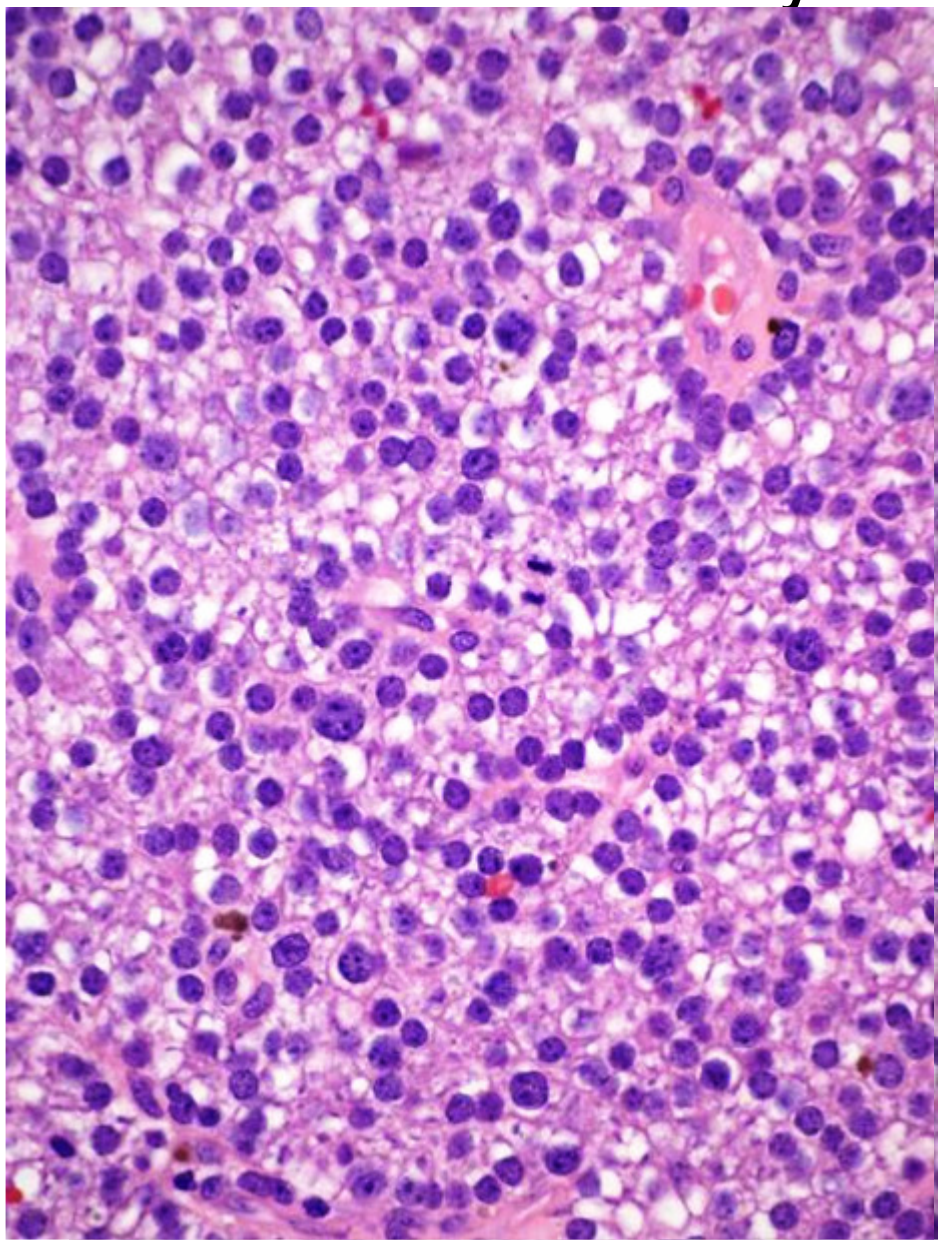
Parathyroid Adenoma and Normal glands



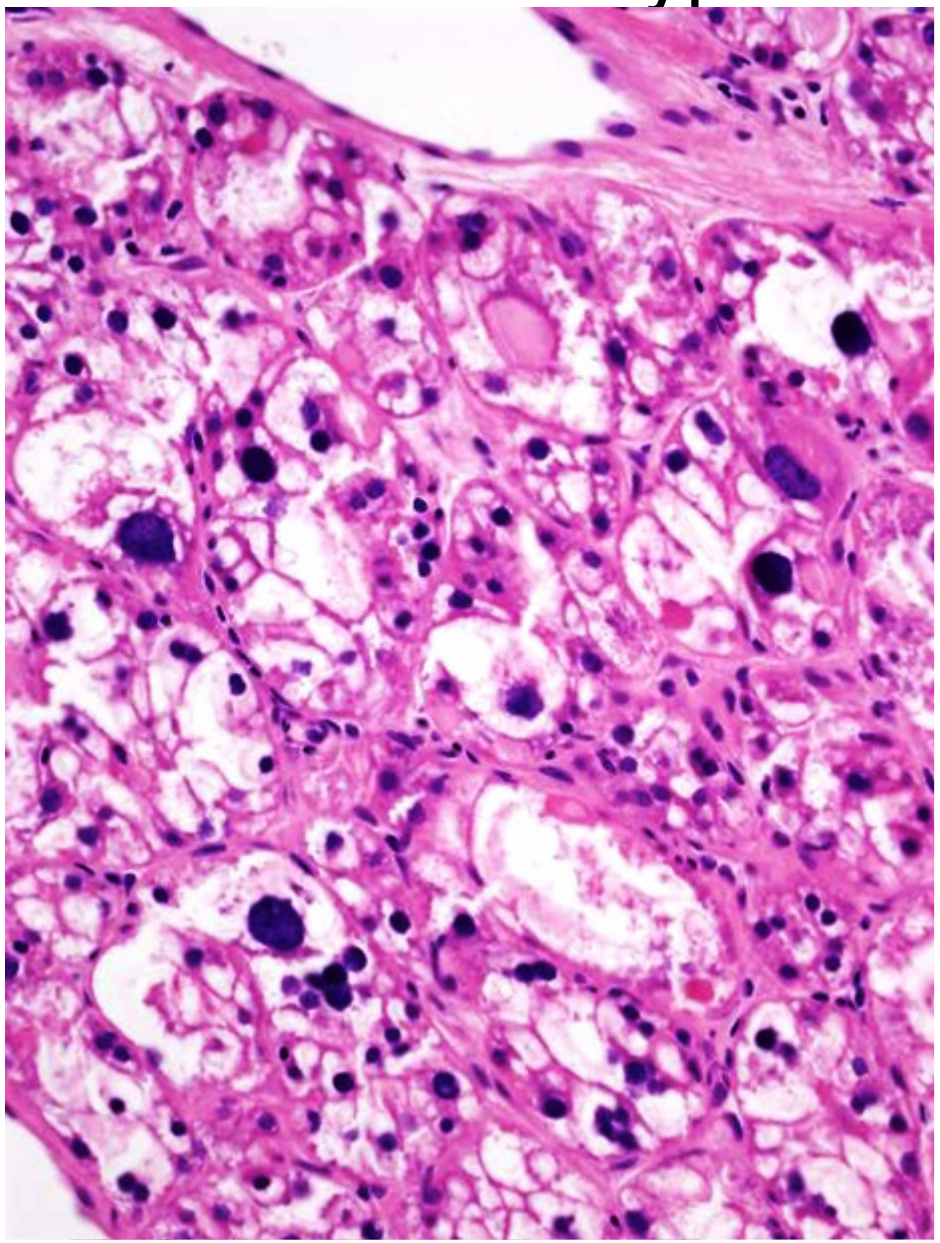
PARATHYROID ADENOMA



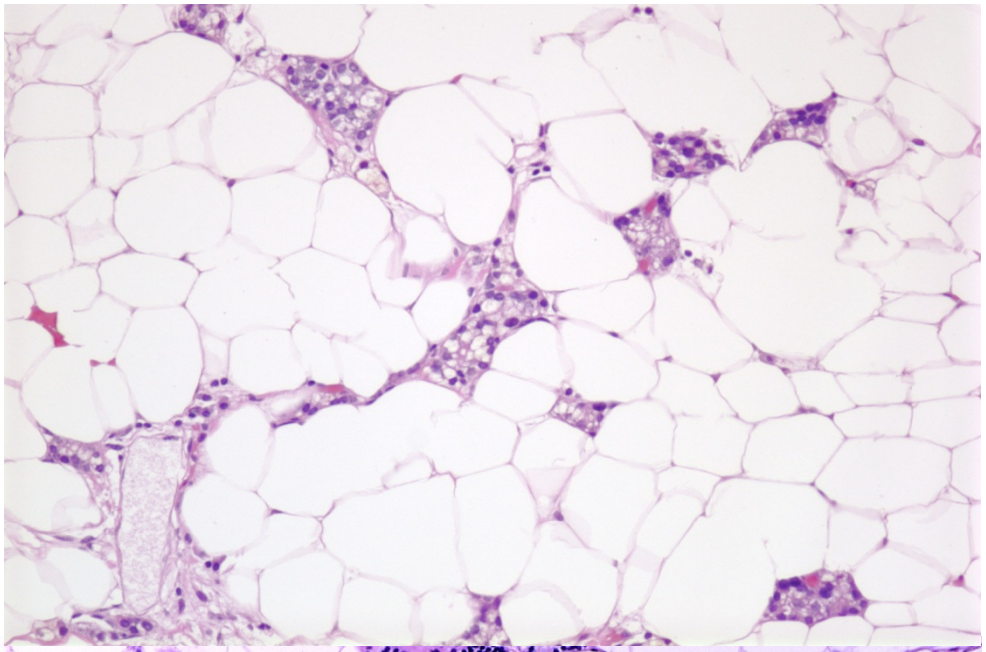
Parathyroid Carcinoma
Cellular Monotony

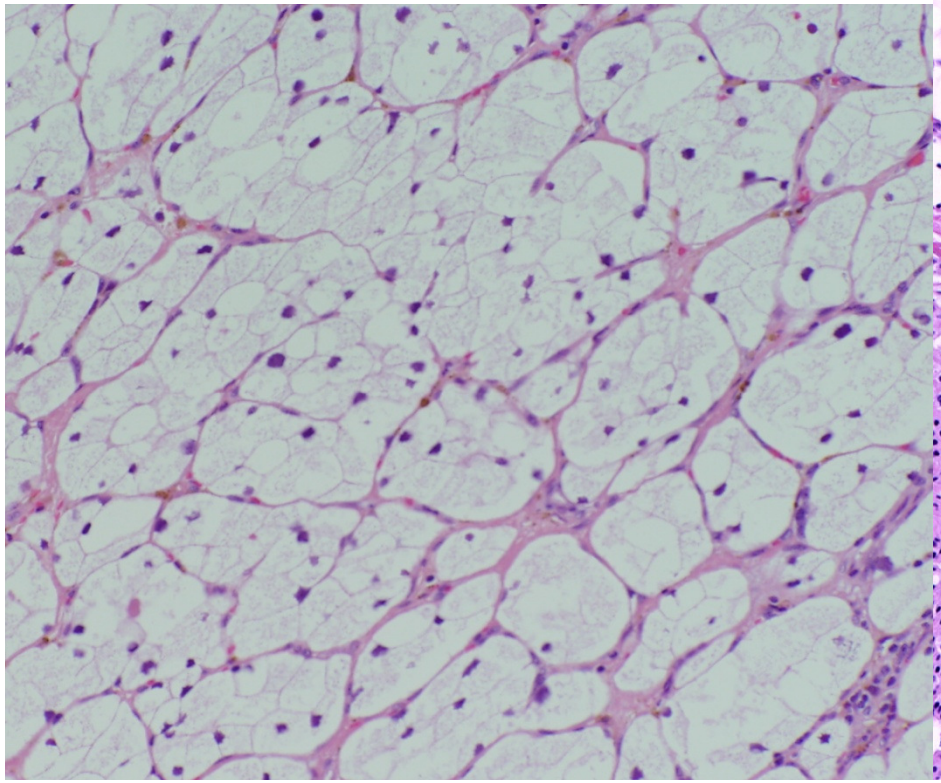


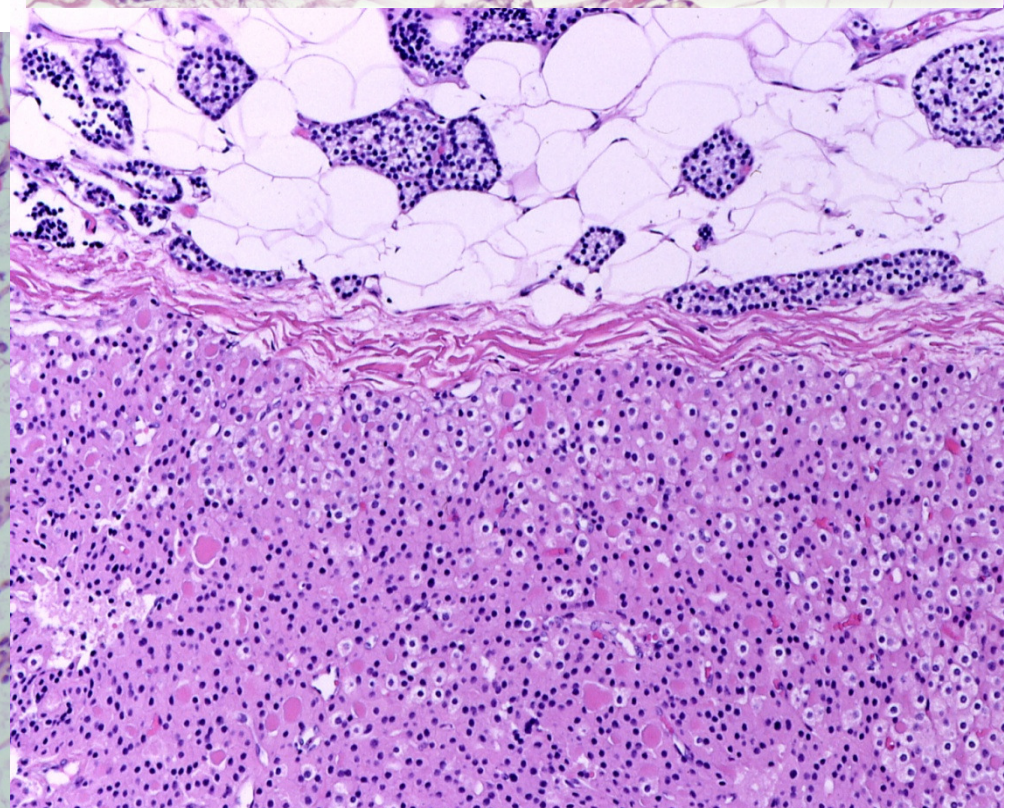
Parathyroid Adenoma
“Endocrine Atypia”



Unusual Parathyroid Adenomas





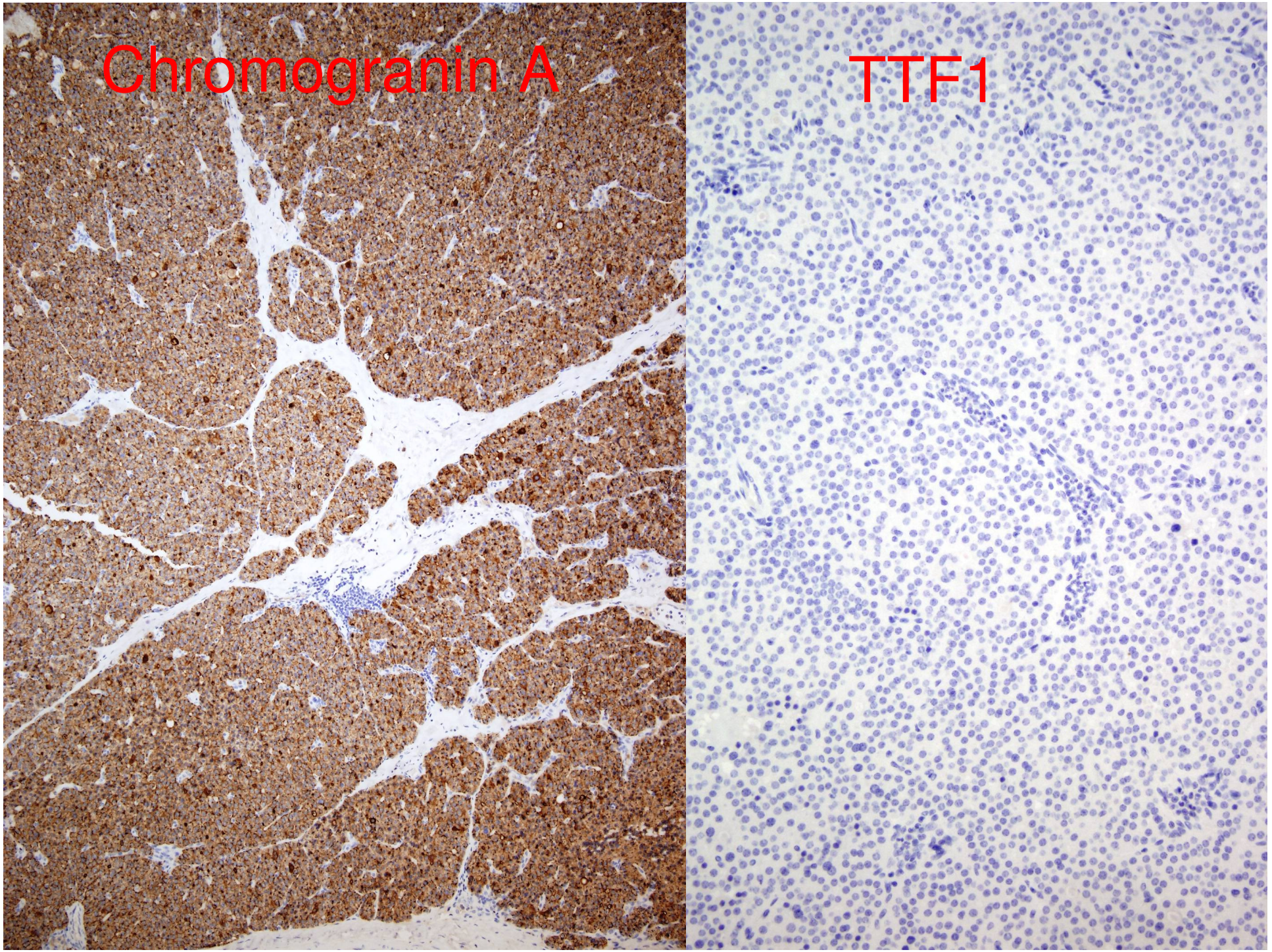


"Double" or "Triple" Parathyroid Adenomas

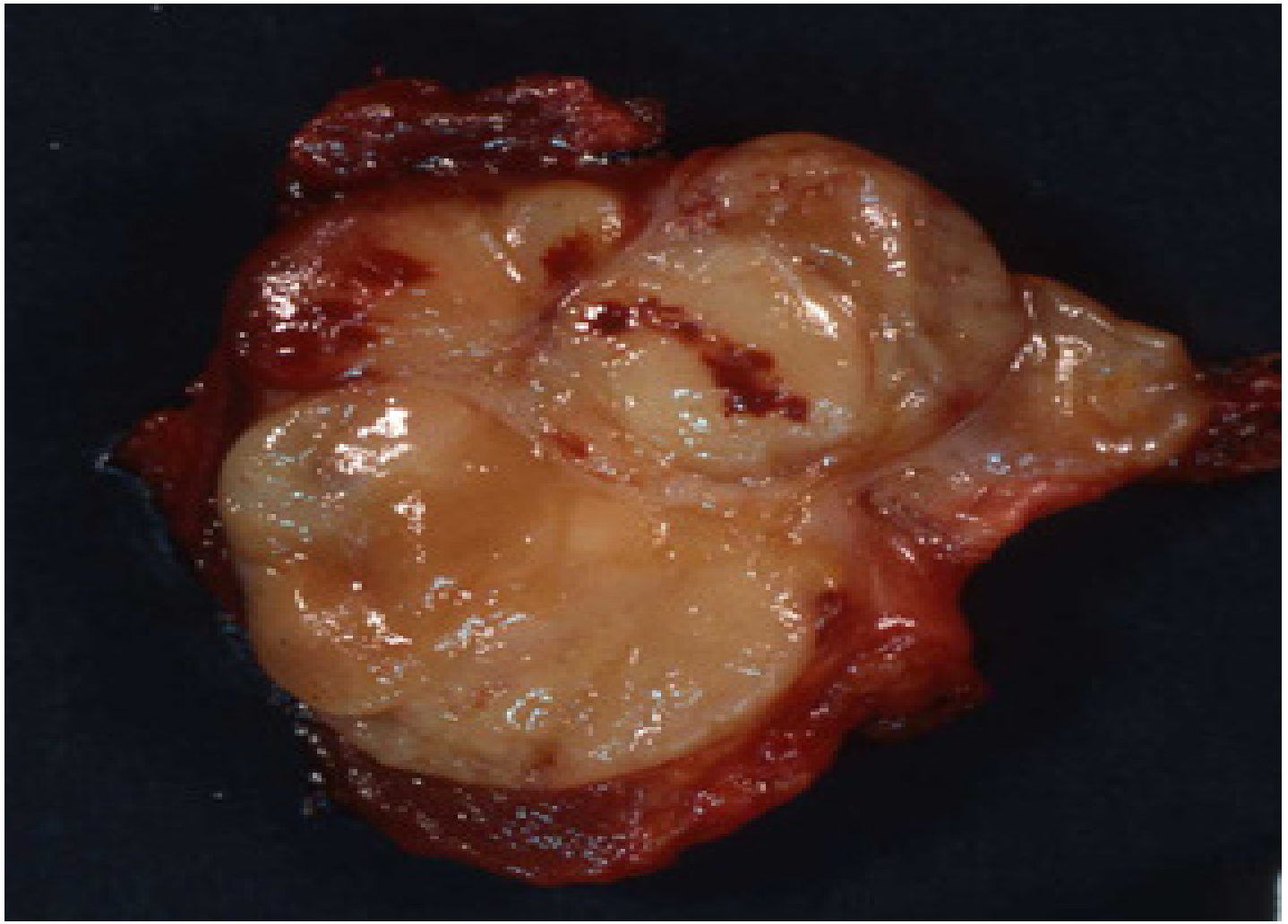
- Rare
- Most are cases of parathyroid hyerplasia, particularly asymmetric hyperplasia.
- Glands involved by hyperplasia may occassionally show rims of normal parathyroid tissue.
- Require resolution of hypercalcemia and hyperparathyroidism and long term follow-up.

Immunophenotype

- Positive
  - Chromogranin
  - Synaptophysin
  - Cam 5.2
  - Parathyroid hormone
- Negative
  - Thyroid transcription factor (TTF)
  - Thyroglobulin


Chromogranin A
TTF1

Parathyroid Carcinoma



Parathyroid Carcinoma vs Adenoma

- Chief cells or mixtures or oxyphilic cells
- Prominent nucleoli
- Pleomorphism not diagnostic of carcinoma as "endocrine atypia" seen in benign lesions
- Atypical parathyroid adenoma
  - Some features of parathyroid carcinoma, but lack unequivocal capsular, vascular, or perineural invasion
  - May adhere to adjacent structures, mitotic activity, fibrosis, trabecular growth, cells within the capsule, but noninvasive

Parathyroid Carcinoma vs Adenoma

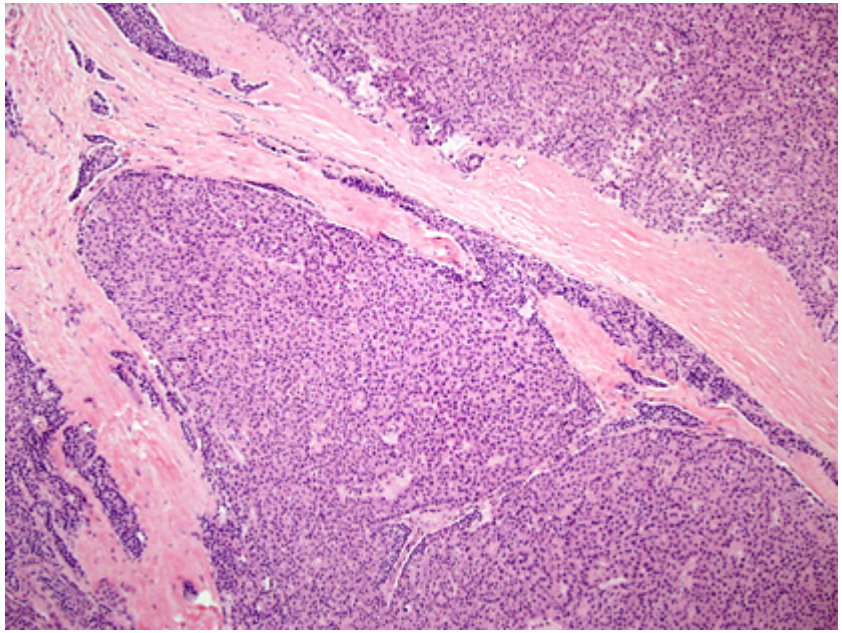
- Vascular invasion, perineural invasion, invade adjacent structures, metastases
- Larger than adenomas, but overlap in size
- Thick fibrous bands, but adenomas can show degenerative changes & cells trapped in capsule
- Mitoses helpful, but can see in adenomas
- Proliferation markers higher in carcinomas
- Patterns (follicular & acinar) often absent
- Monotonous, solid growth, sheets of cells & closely packed nests

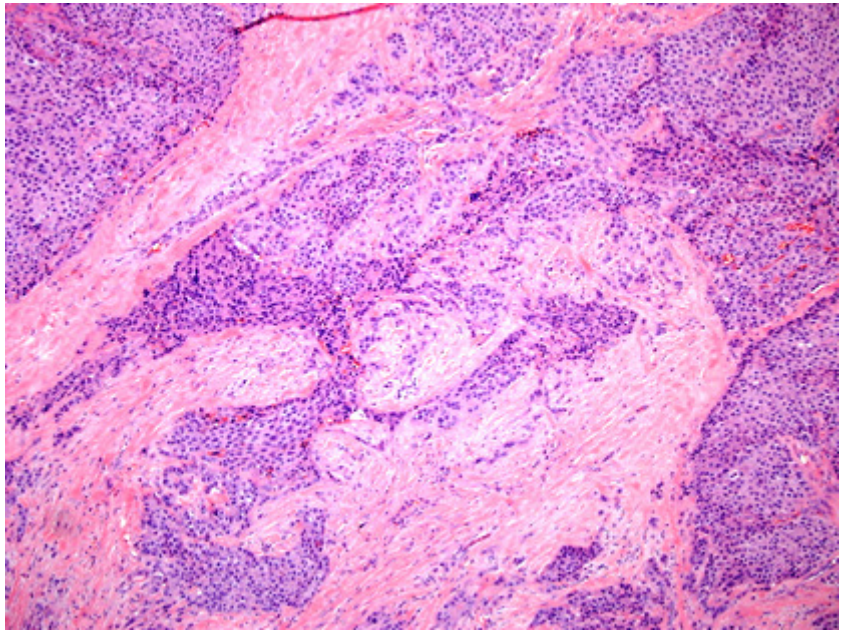
Parathyroid Carcinoma

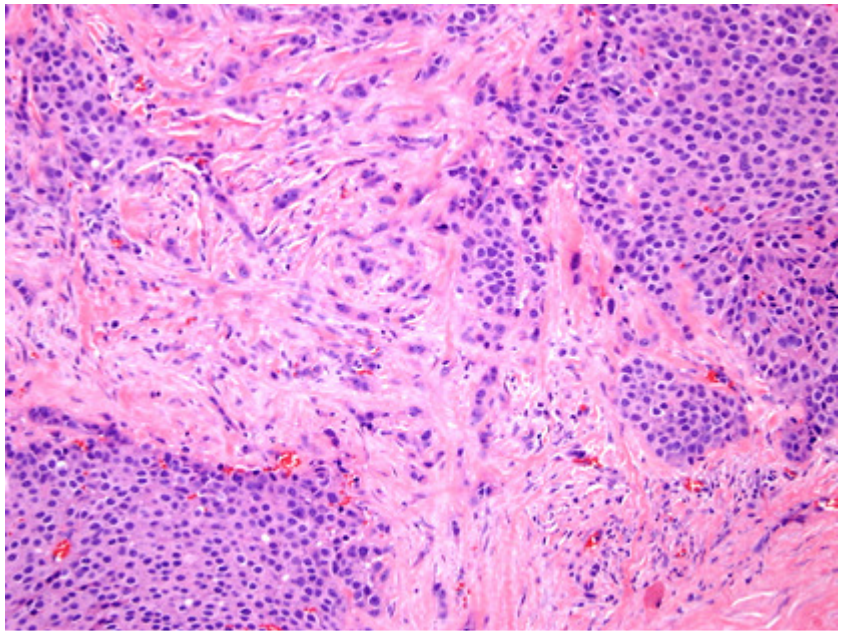
- Thick fibrous bands 90%
- Mitotic Activity 80%
- Capsular invasion 65%
- Vascular invasion 15%

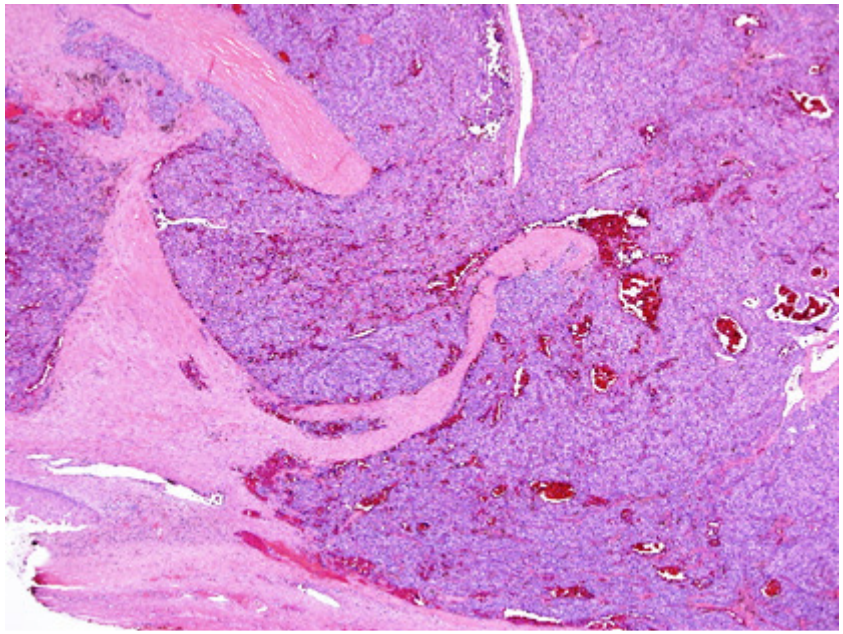
- Schantz and Castleman, Cancer 1973

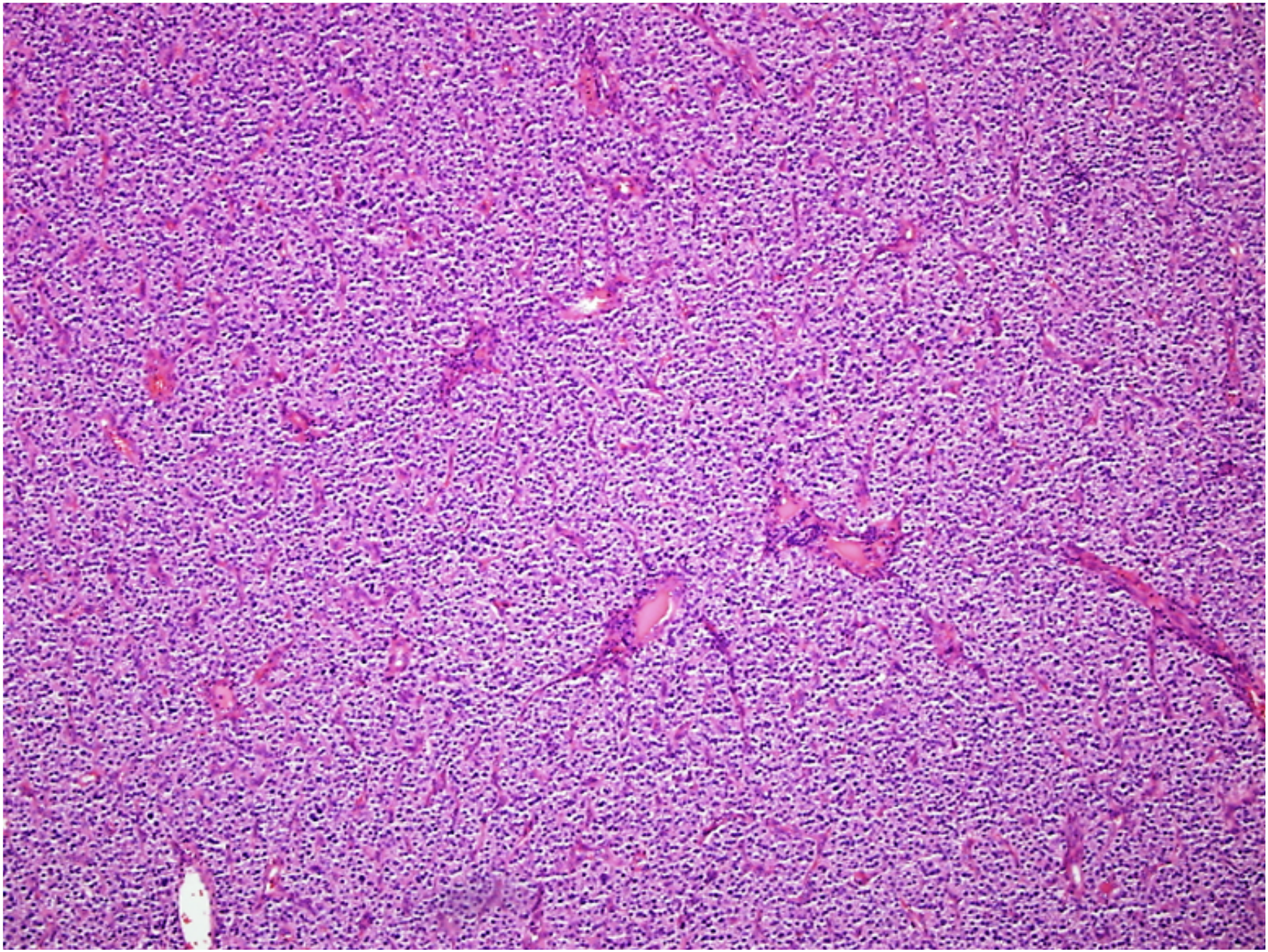
Parathyroid Carcinoma: Infiltrative Growth

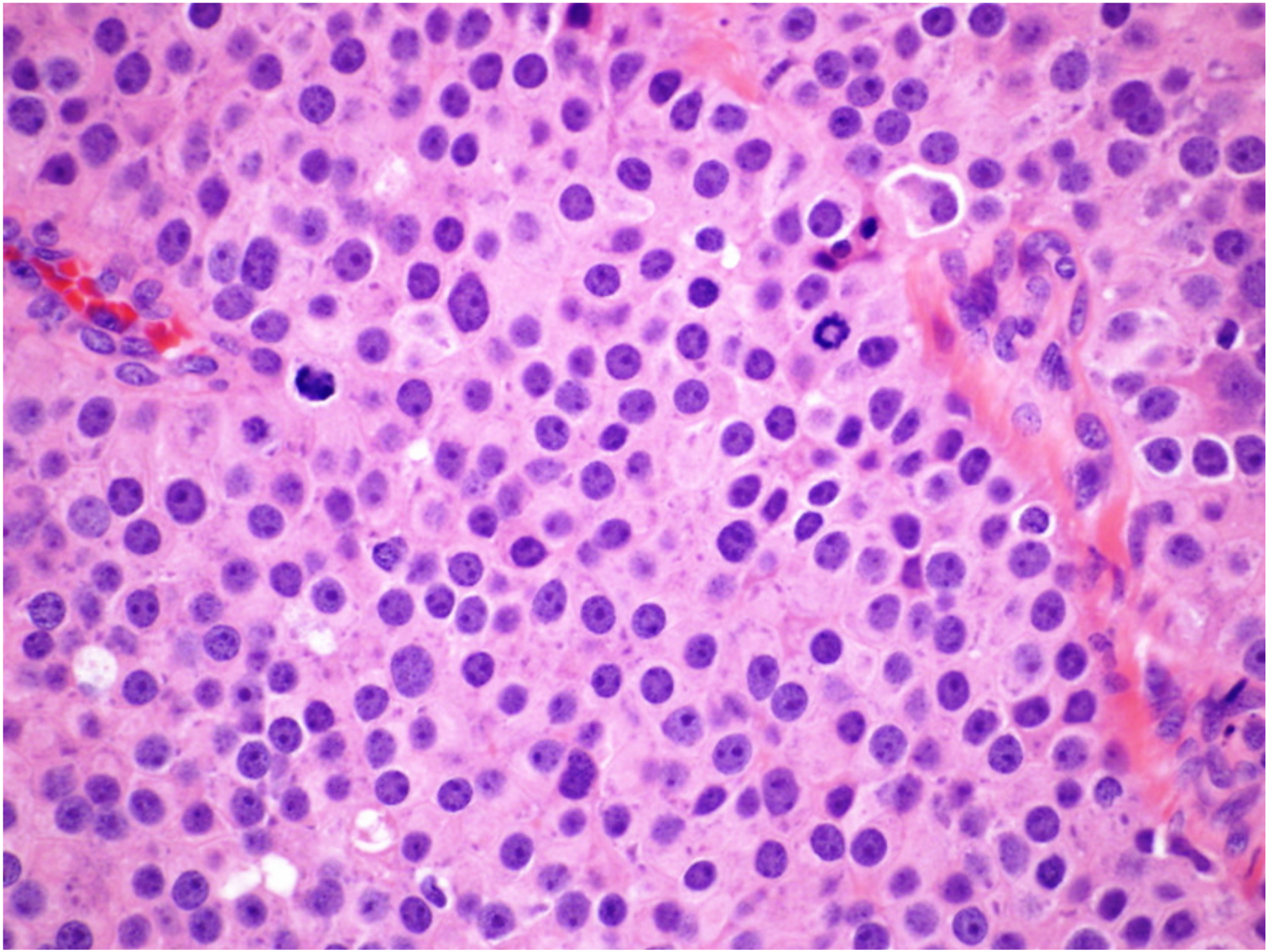


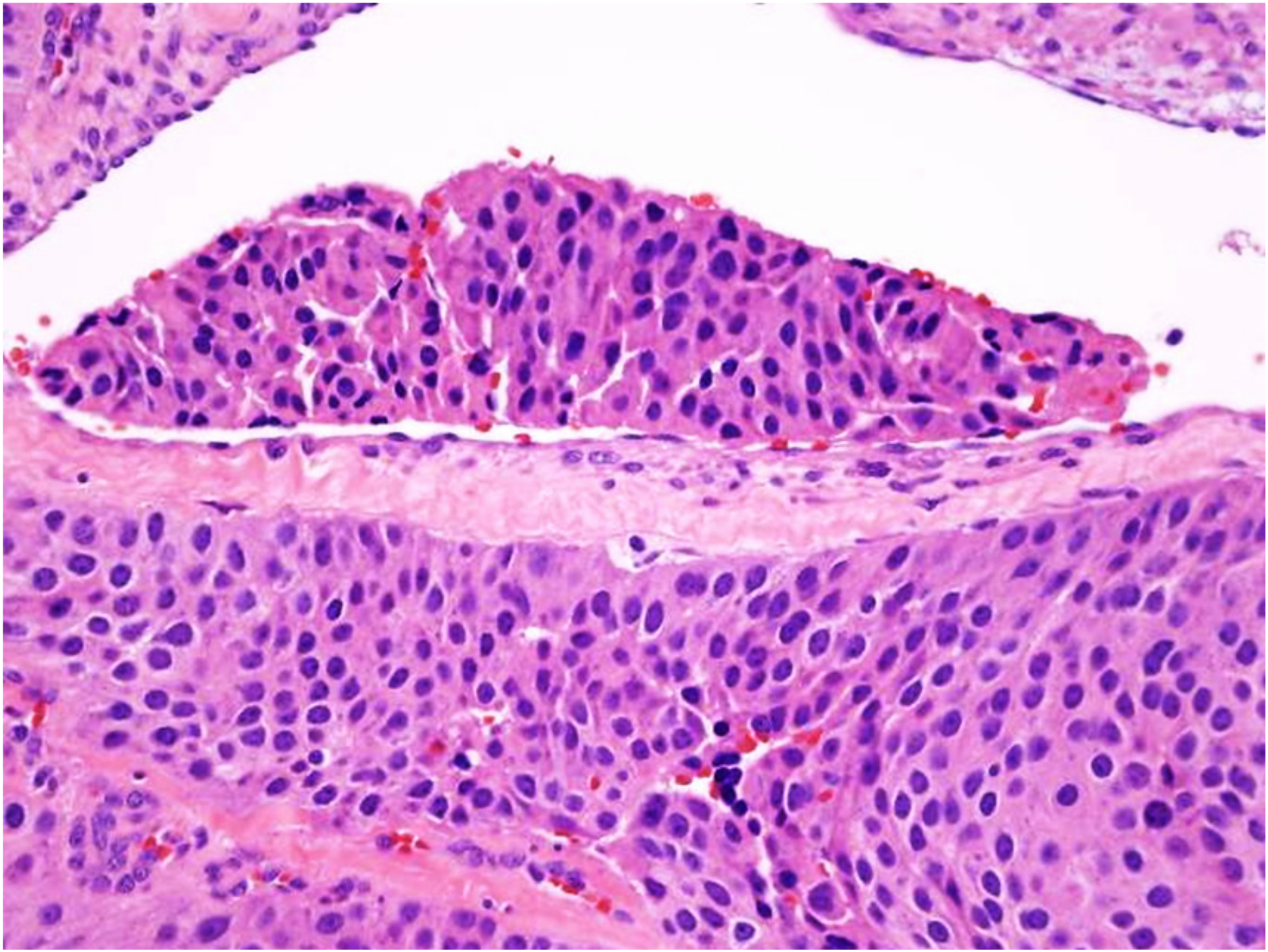






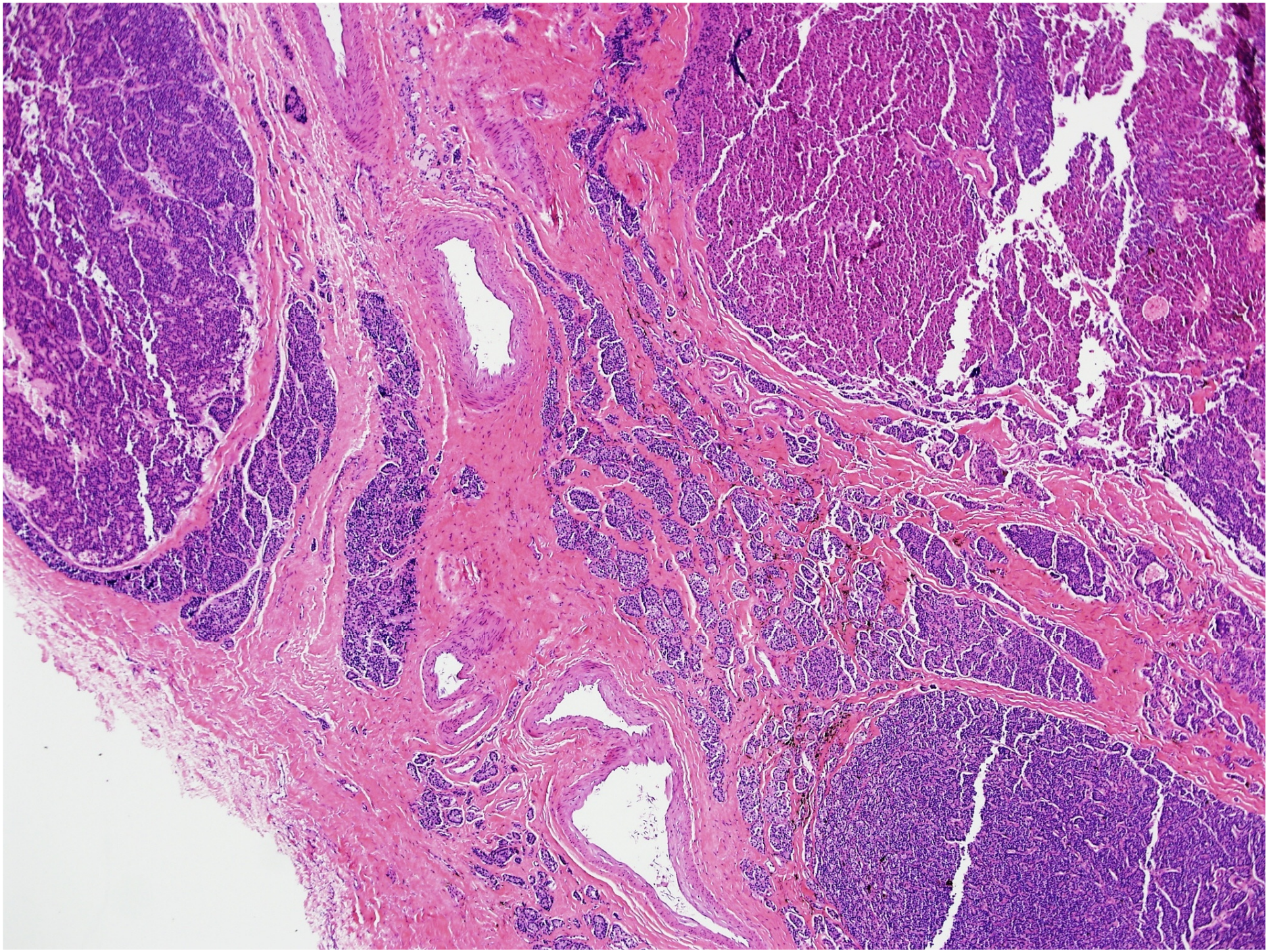




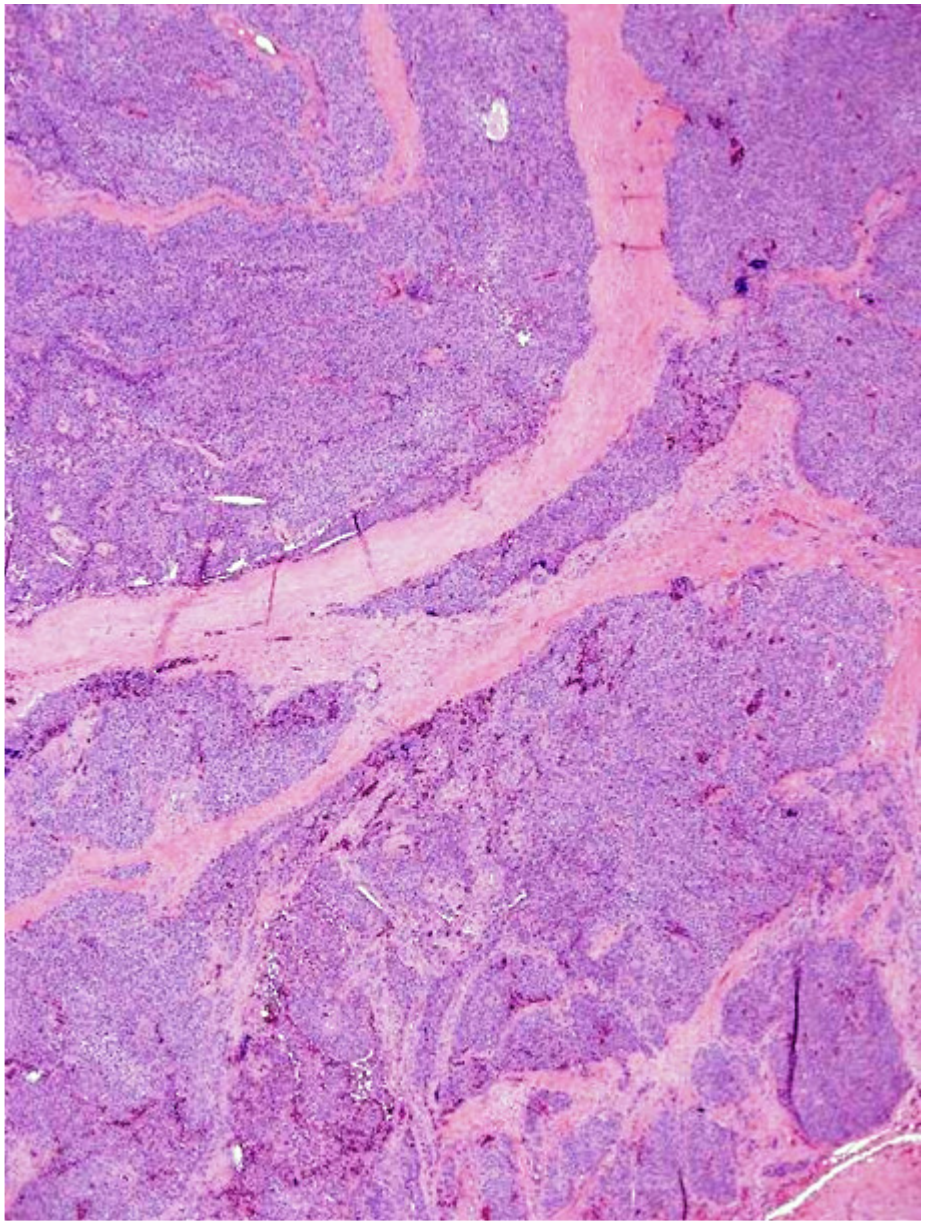


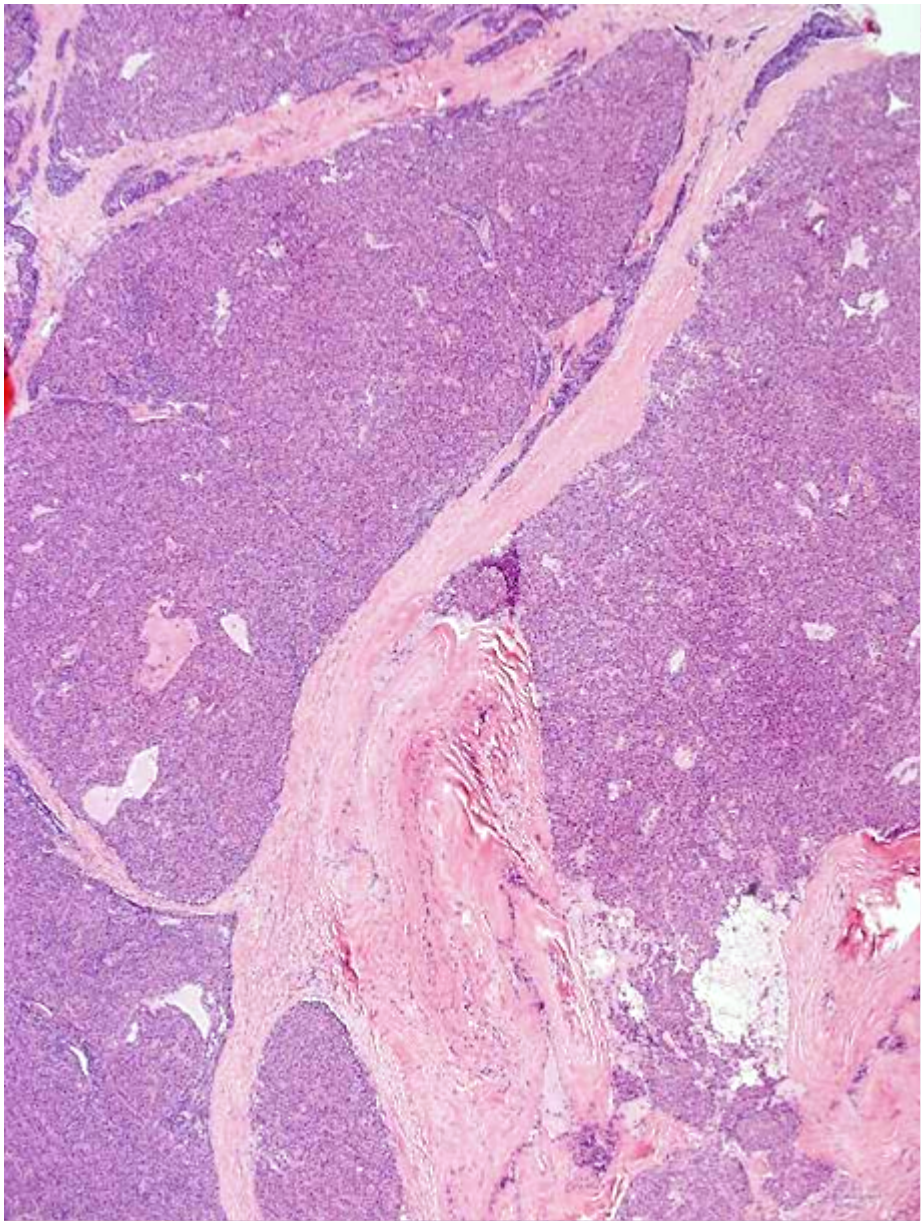
Atypical Parathyroid Adenoma

- Some features of parathyroid carcinoma, but lack unequivocal capsular, vascular, or perineural invasion
- May adhere to adjacent structures, mitotic activity, fibrosis, trabecular growth, cells within the capsule, but noninvasive
- Behavior is generally indolent



Parathyroid Carcinoma & Adenoma: Fibrous Bands



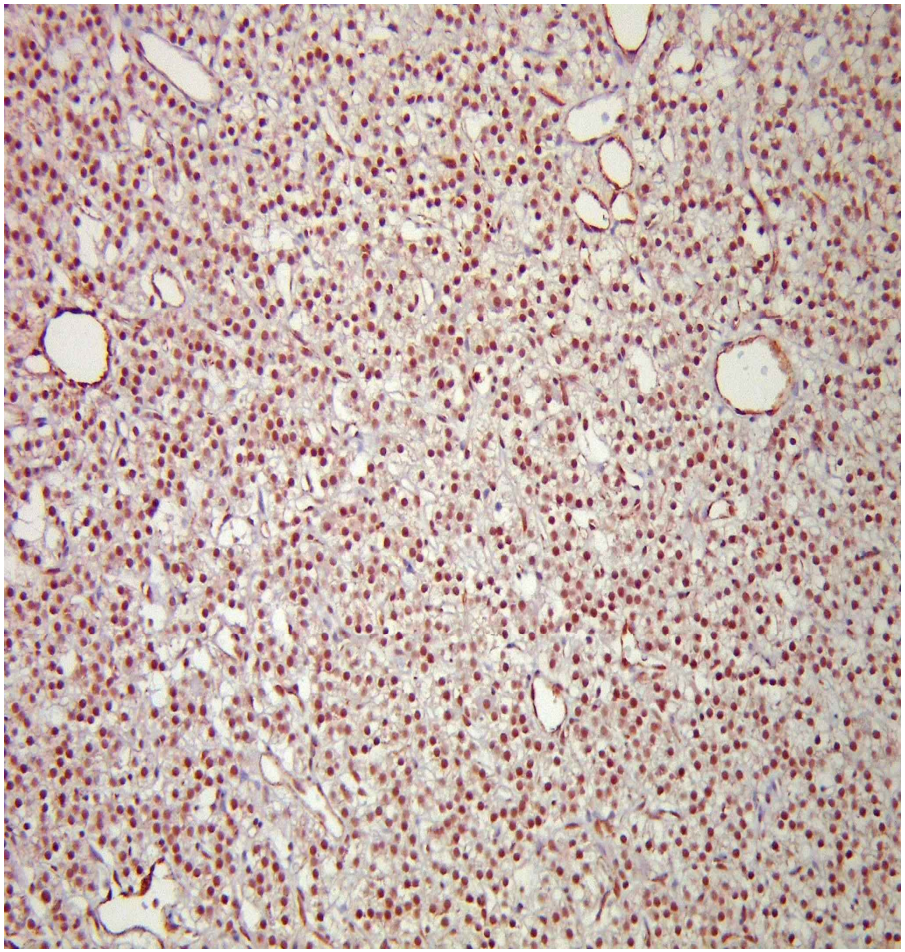


Parafibromin

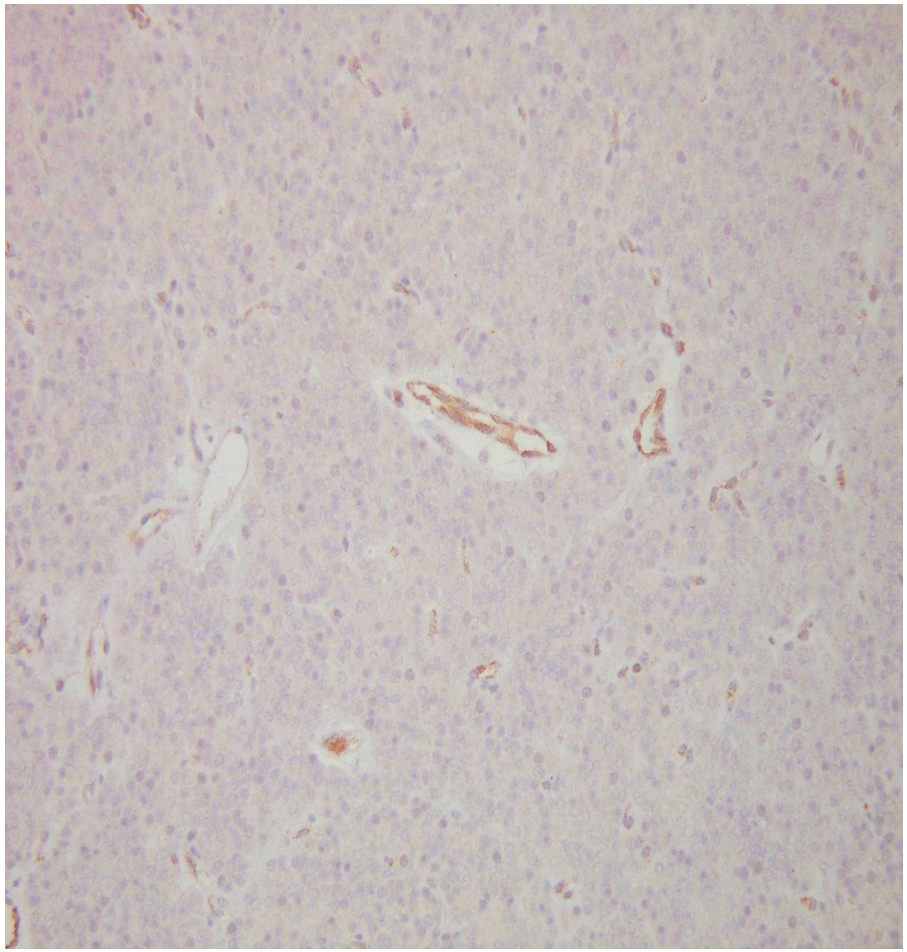
- HRPT2 gene (1q21-q32) mutations associated with familial (HPT-JT & FIHP) & sporadic parathyroid carcinomas, but rare in sporadic adenomas
- HRPT2 gene encodes parafibromin
- Loss of nuclear parafibromin immunoreactivity in parathyroid carcinomas and adenomas (cystic) associated with HPT-JT syndrome
- Loss parafibromin to ddx carcinoma from adenoma?
  - Problems reproducibility & interpretability
  - Tominaga et al. World J Surg 2008
  - Greatest utility would be atypical adenoma versus carcinoma and not much data in this regard

PARAFIBROMIN

Adenoma



Carcinoma

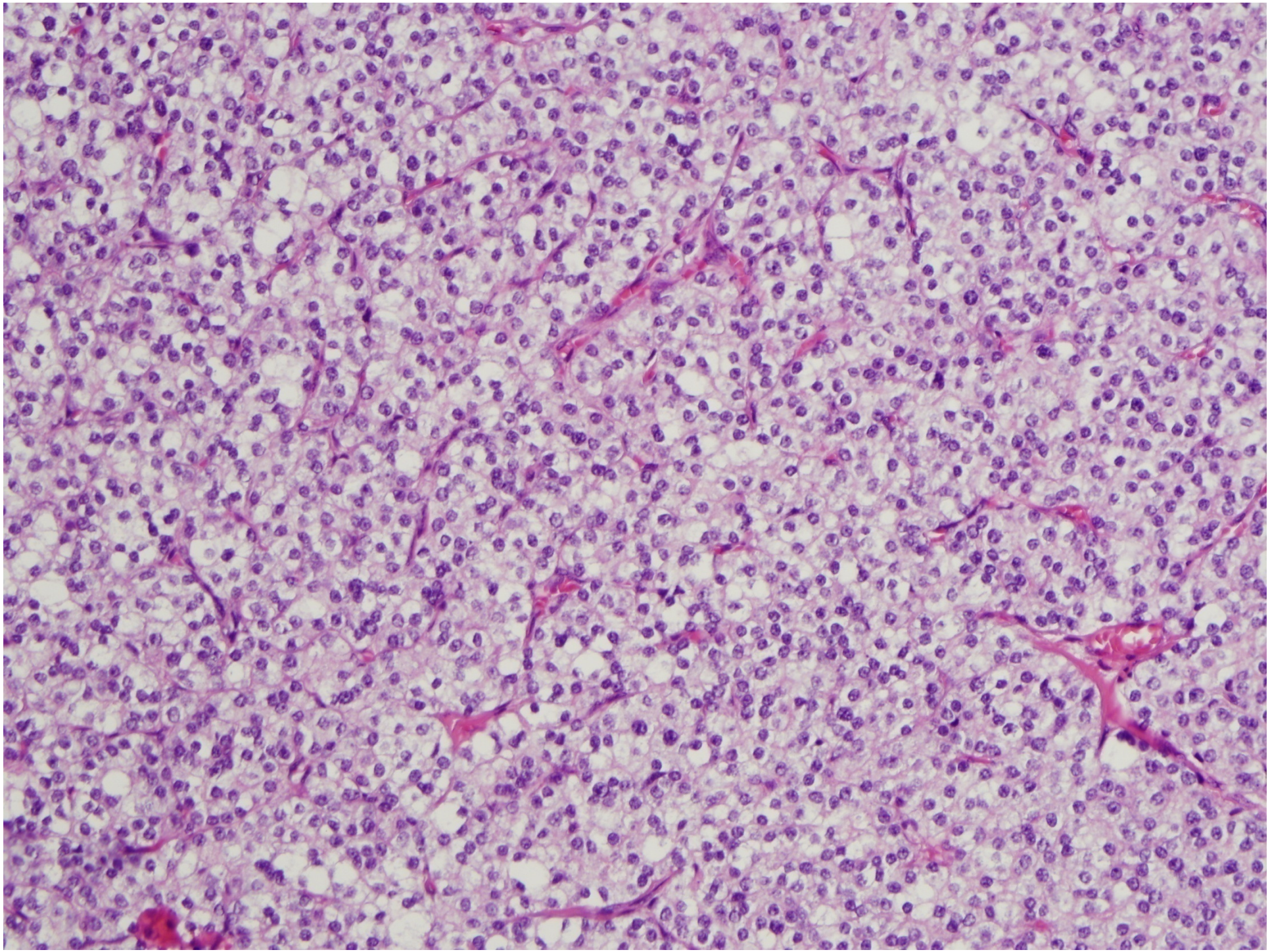


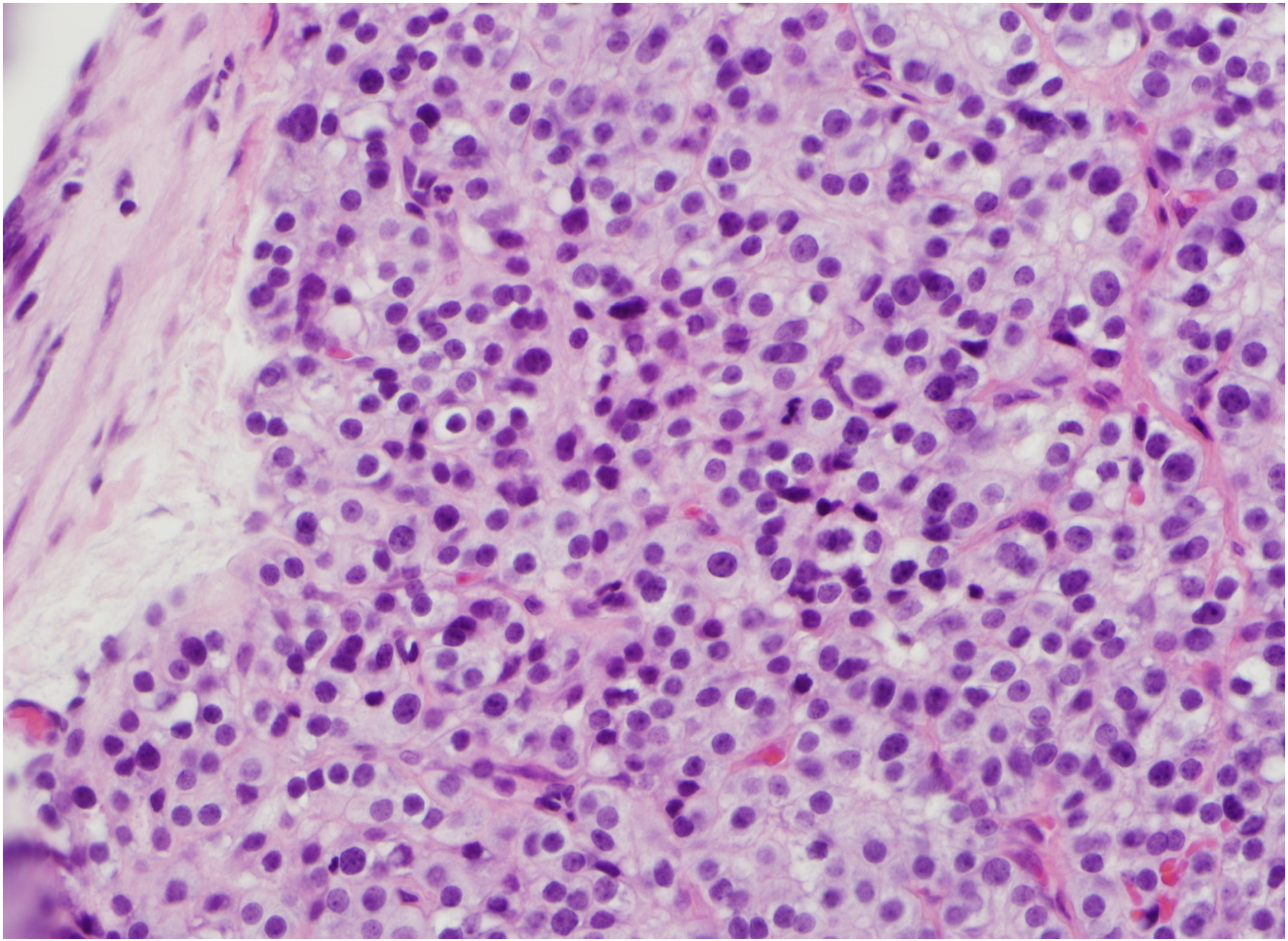
Biomarkers of Malignancy in Parathyroid Tumors

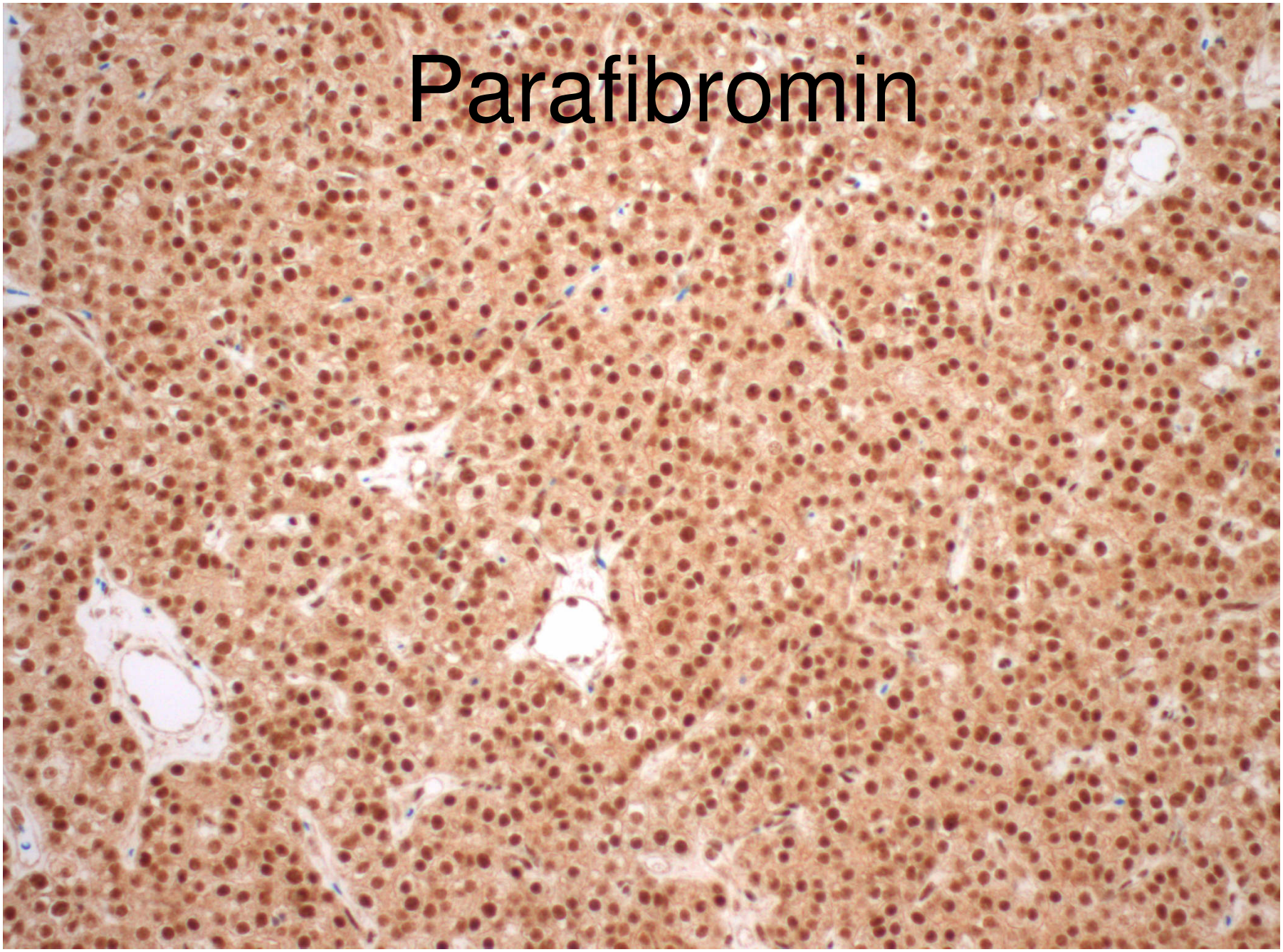
- Parafibromin—Loss or decreased expression
- Galectin-3—Increased expression
- PGP9.5—Increased expression
- Ki-67—Increased expression
- p27—Decreased expression

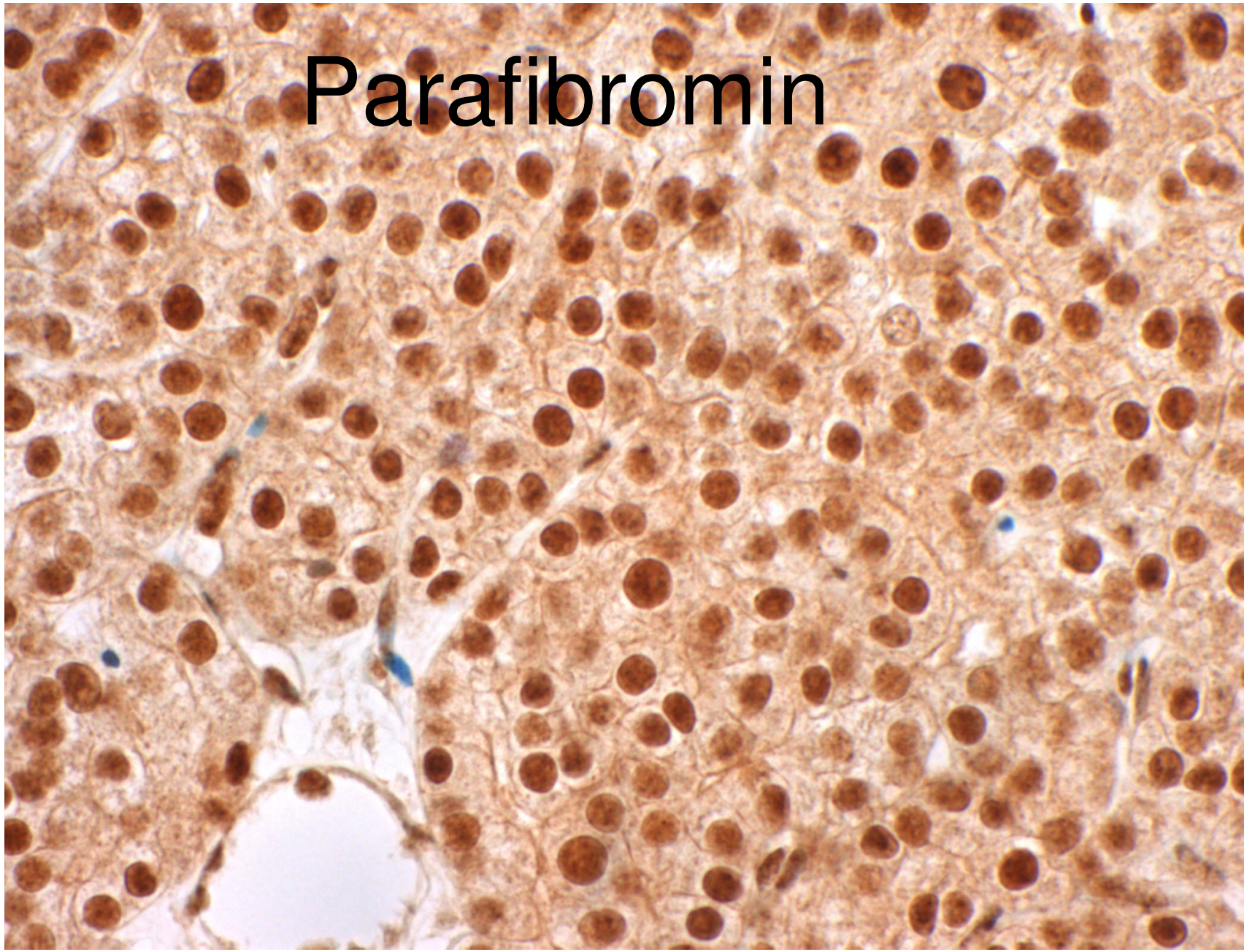
Atypical Parathyroid Adenoma

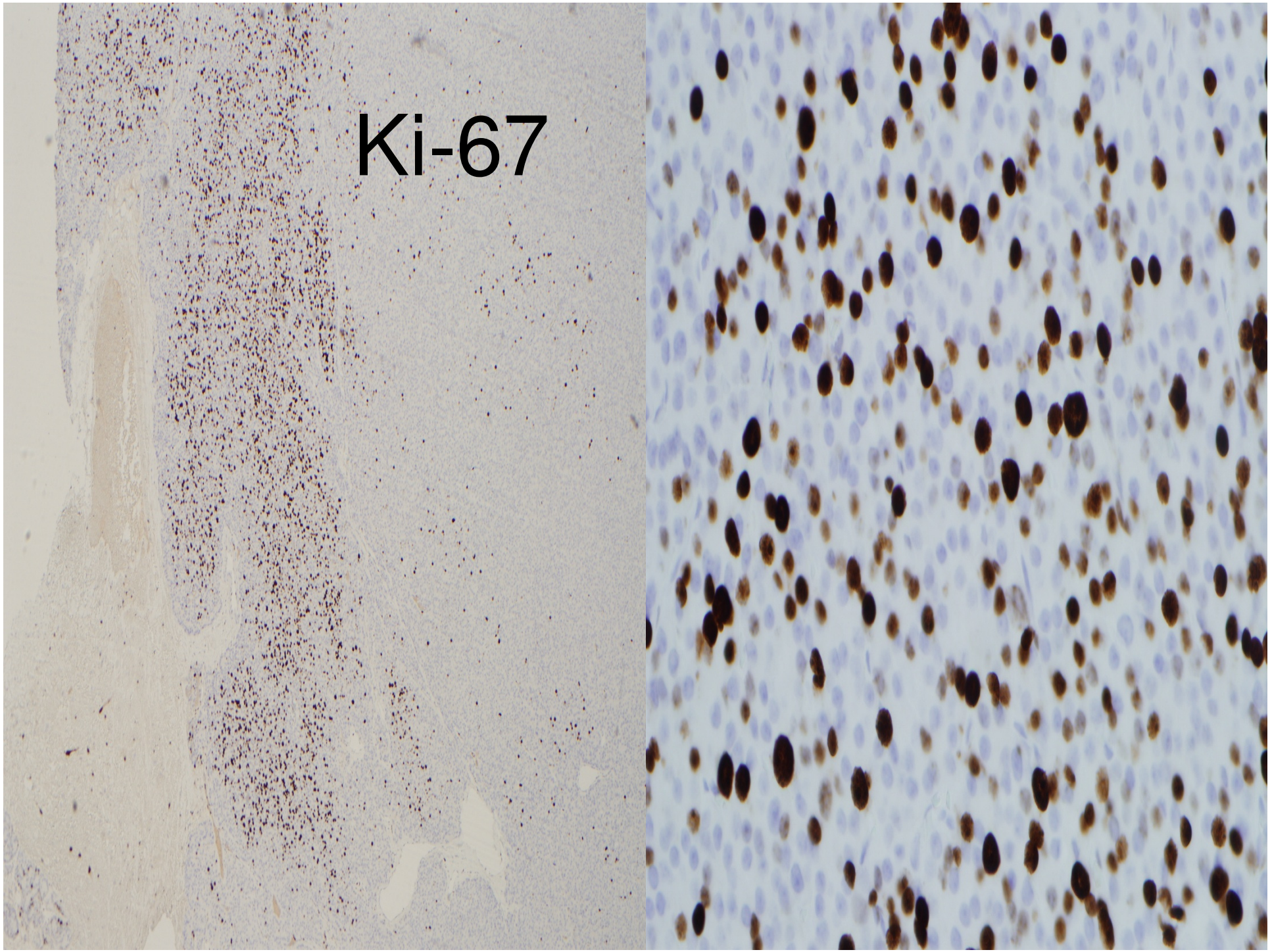
- 52 year old man with marked hypercalcemia
- Partathormone levels 4 times above normal
- At surgery—9.2 gm parathyroid gland excised
- Histological findings summarized on slides:

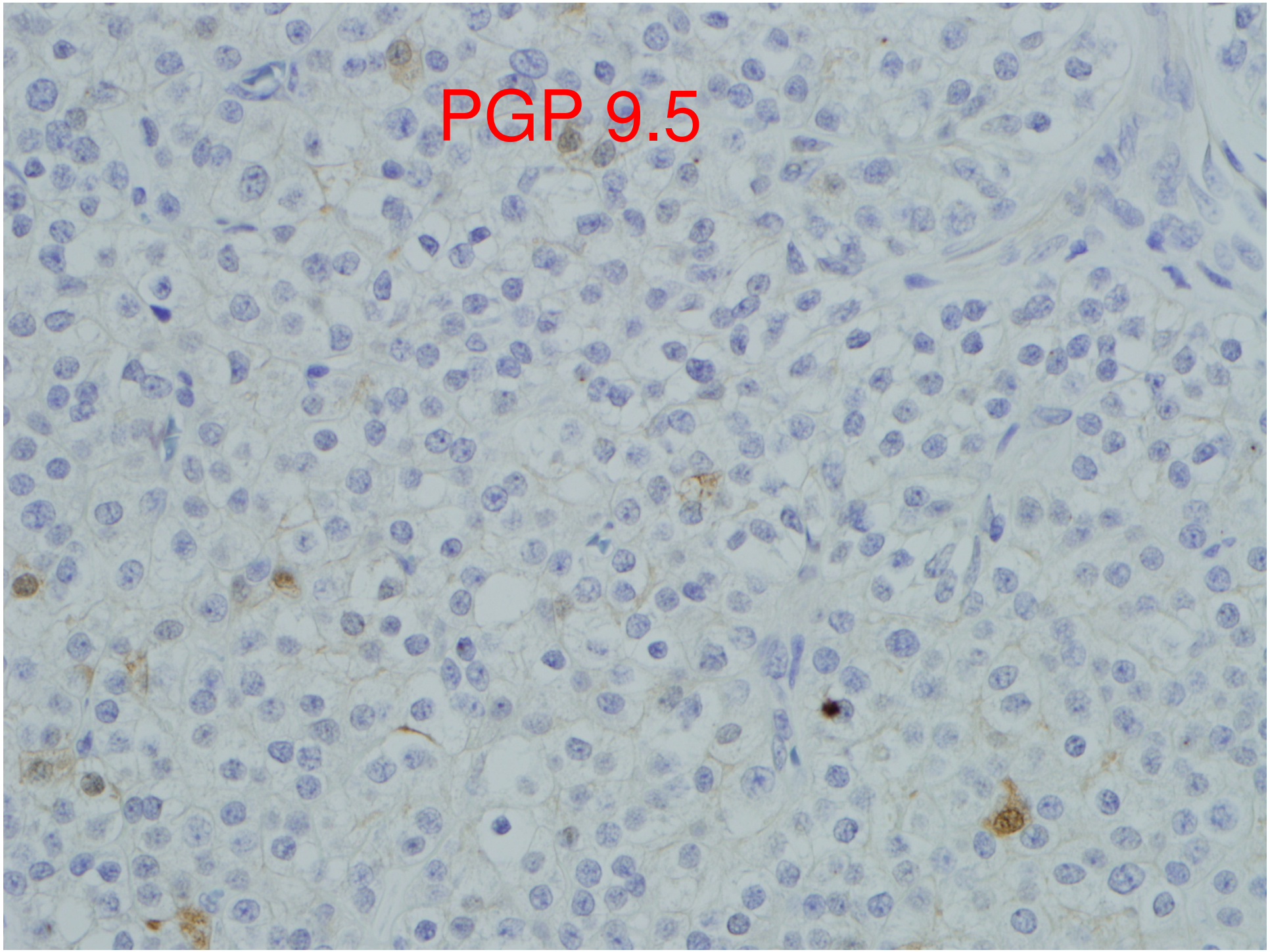





Parafibromin


Parafibromin


Ki-67


PGP 9.5

Diagnosis

- Atypical Parathyroid Adenoma
- Patient is being followed closely

Intraoperative PTH Monitoring

- Traditional parathyroid surgery:
  - bilateral neck exploration and evaluation of all 4 glands
- Unilateral neck exploration:
  - increased as diseased glands are more readily identified through imaging studies
- Intraoperative monitoring of PTH:
  - less risk of missing multiglandular disease
  - useful to confirm diseased gland(s) removed
- (Otolaryngol Clin N Am 37:779-87,2004)

Evolution of Parathyroid Surgery

- Conventional open parathyroidectomy
- Open minimal access parathyroidectomy
- Endoscopic parathyroidectomy

Treatment & Prognosis

- Atypical Parathyroid Adenoma
  - Resection, clinical follow-up, monitor calcium
- Parathyroid Carcinoma
  - En bloc resect parathyroid & ipsilateral lobe thyroid
  - Postoperative adjuvant radiation
  - Recur before metastases (nodes,bone,lung,liver)
  - Time to recur 3 years, can be decades
  - 5 & 10 year survival: 85% & 49%
  - Death - uncontrollable hypercalcemia

Summary

- Parathyroid hyperplasia is usually sporadic, but may be familial
- Parathyoid adenomas are usually treated by minimally invasive surgery
- Parathyroid carcinomas remain difficult diagnostic challenges.
- Atypical parathyroid adenomas should be diagnosed with caution

References

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- Fernandez-Ranvier GG, Khanafshar E, Tacha D, Wong M, Kebebew E, Duh QY, Clark OH. Defining a molecular phenotype for benign and malignant parathyroid tumors. Cancer 115: 334-44, 2009.