# A 61 year old woman with an incidental finding in a thyroid nodule

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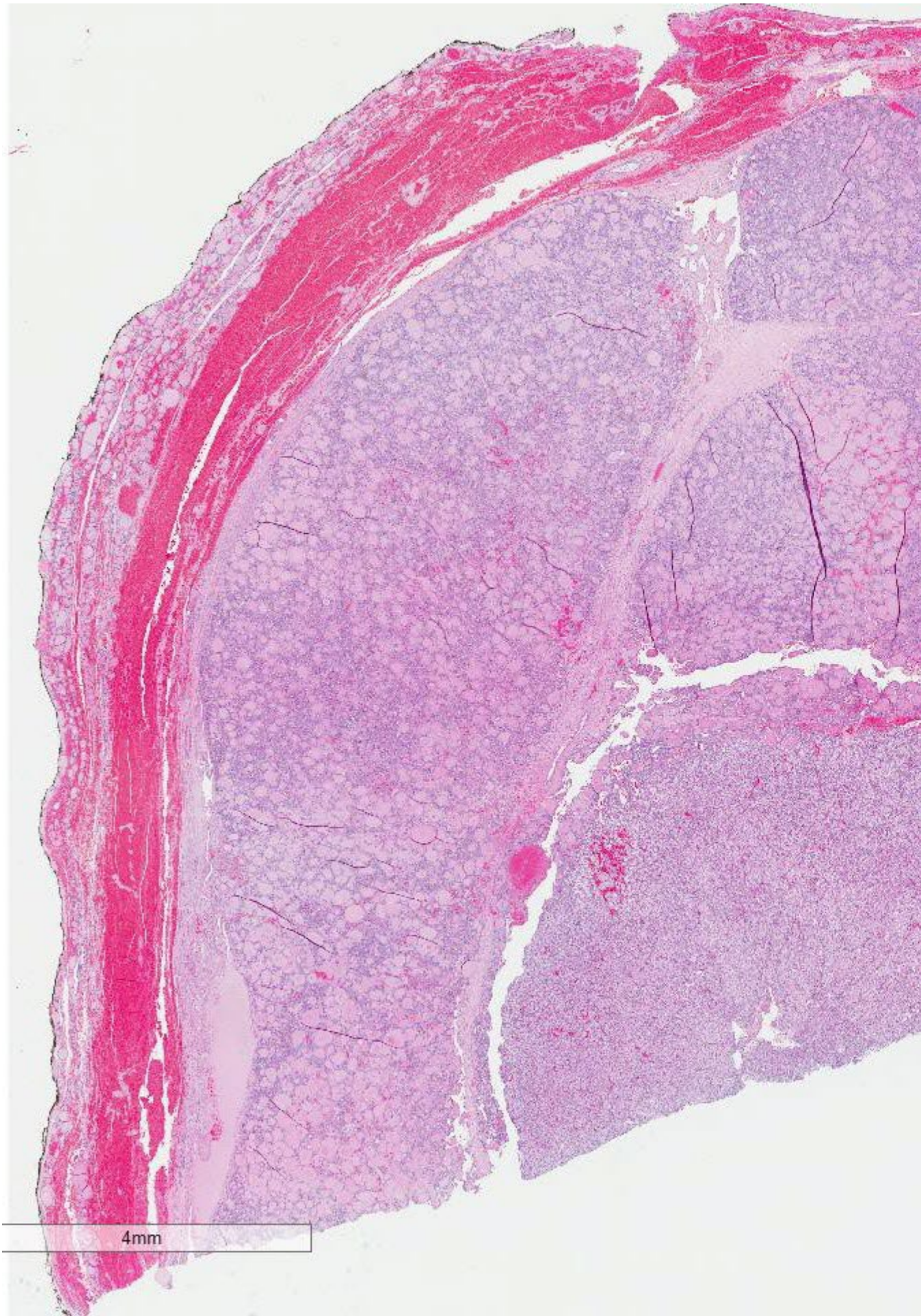
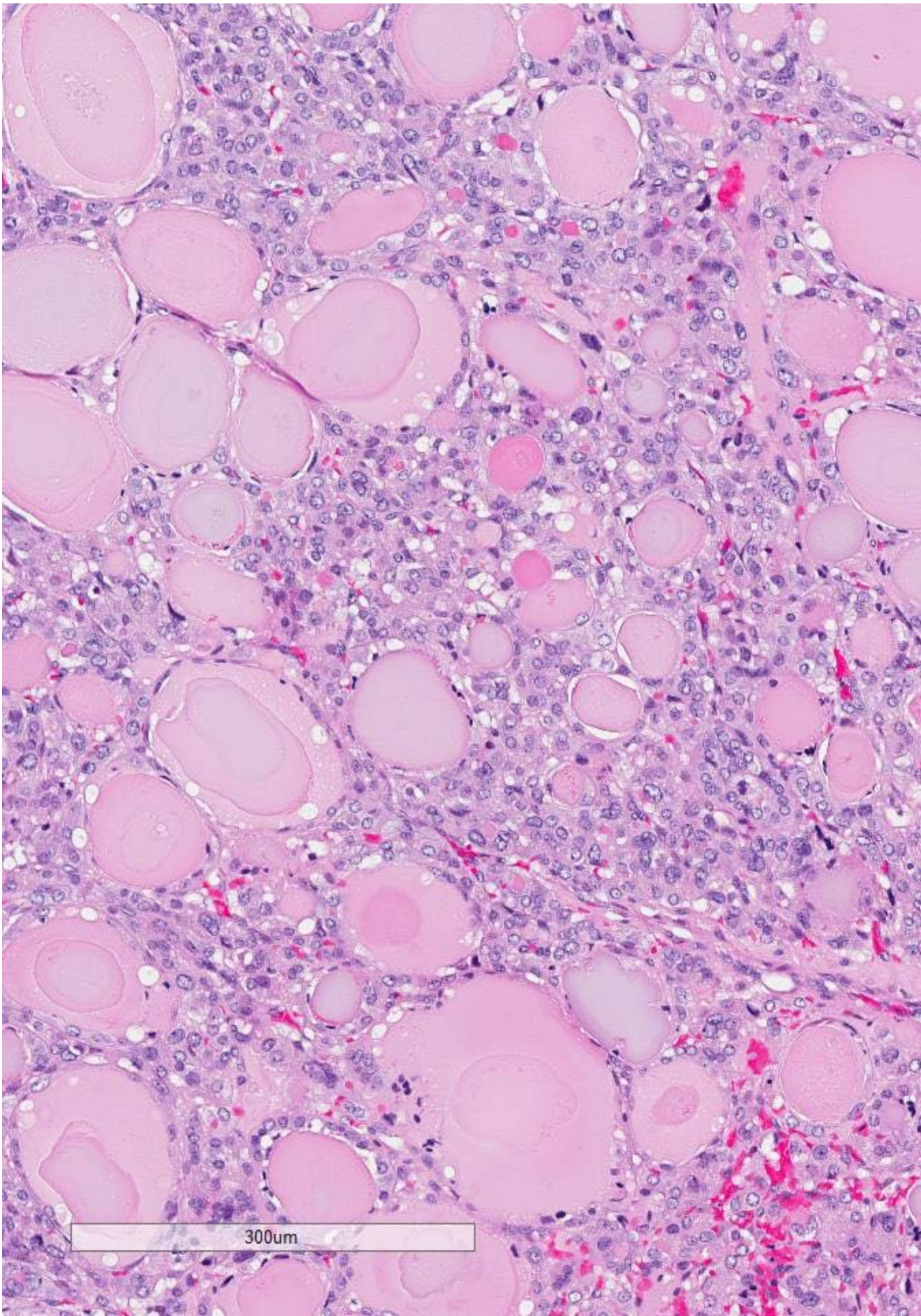
- **Clinical history:** This is a consult case that was sent to Jewish General Hospital (JGH). It is a 61 y/o woman who presented with a 4 cm thyroid nodule in the right lobe with no previous medical history. No other clinical information was provided. No FNA was performed to our knowledge. The patient underwent hemi-thyroidectomy with one lymph node dissection.
- **Histology** (Click image for higher resolution)**:** On low power, there is a well demarcated, partially encapsulated thyroid nodule, mainly with a follicular pattern and a second intranodular component which is mostly well demarcated except a focal area with infiltrative growth into background follicles. This component appears paler and does not demonstrate a follicular pattern.


4mm

On higher power, the main nodule is composed of follicles lined by cells with enlarged ovoid nuclei with chromatin clearing and nuclear grooves characteristic of papillary thyroid carcinoma, follicular variant.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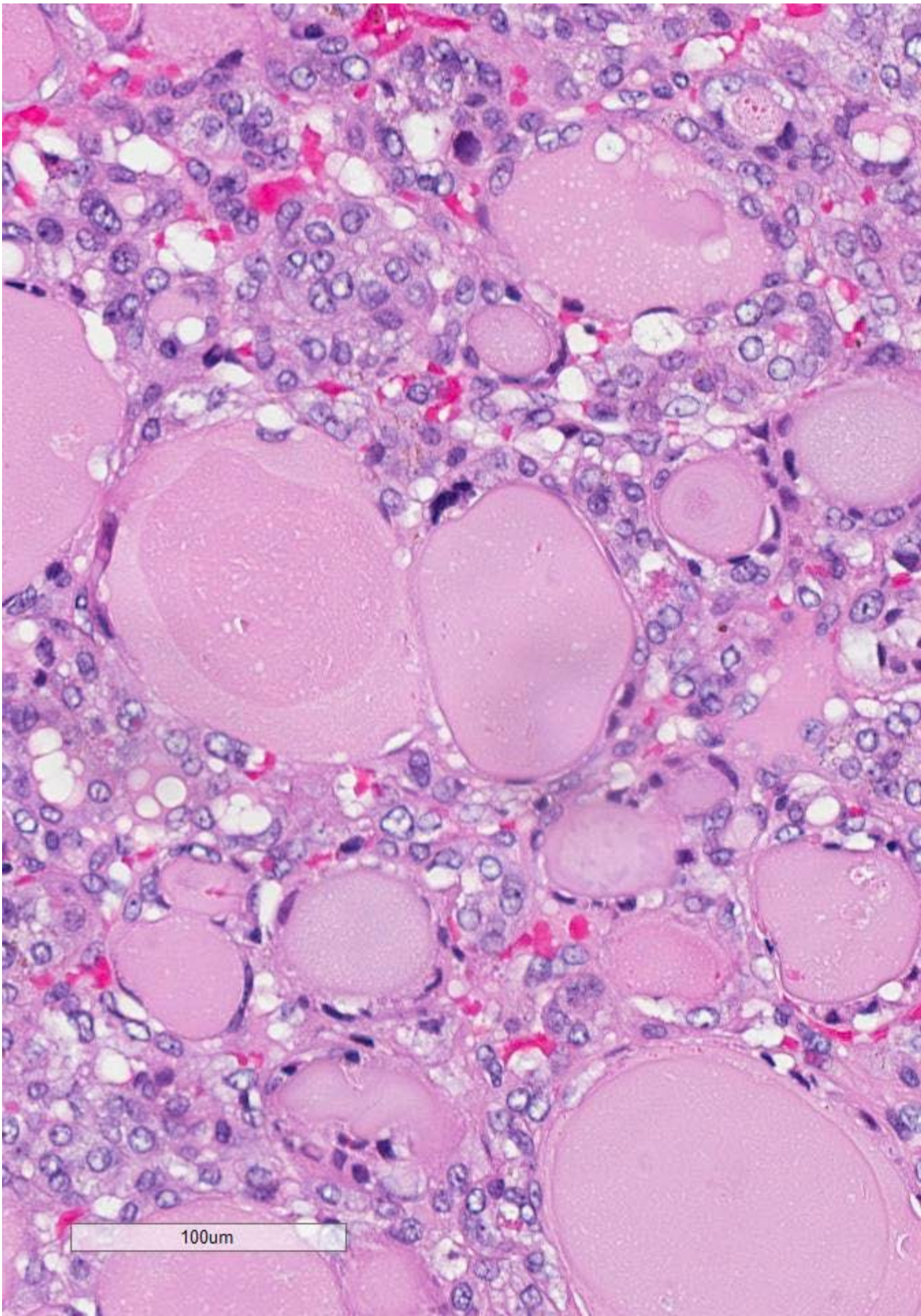
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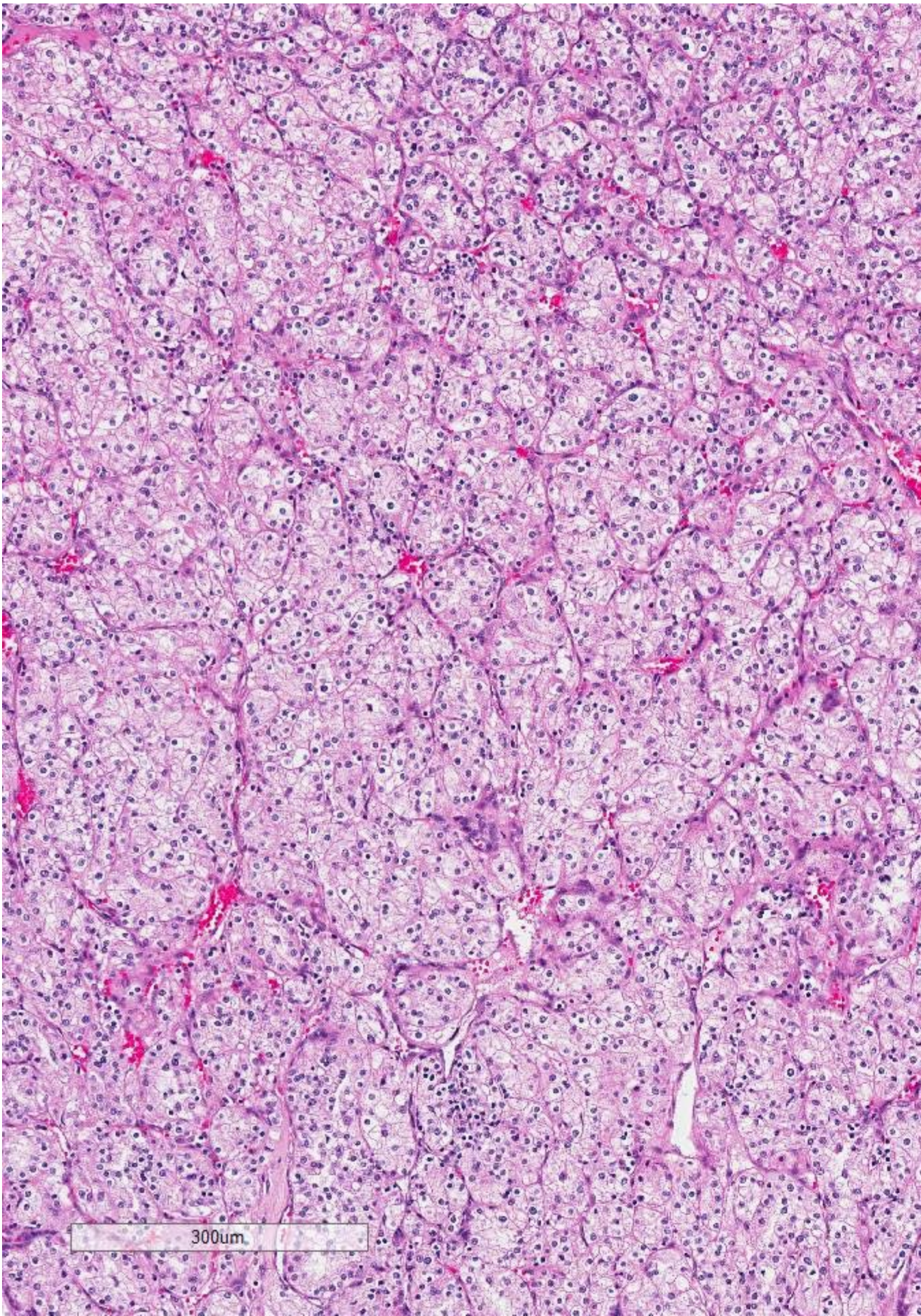
The second pale component contains sheets of cells with distinct borders and a rich capillary network. They have ample clear cell cytoplasm, rounded nuclei, and most of them have inconspicuous nucleoli. Some cells show more eosinophilic cytoplasm with binucleation.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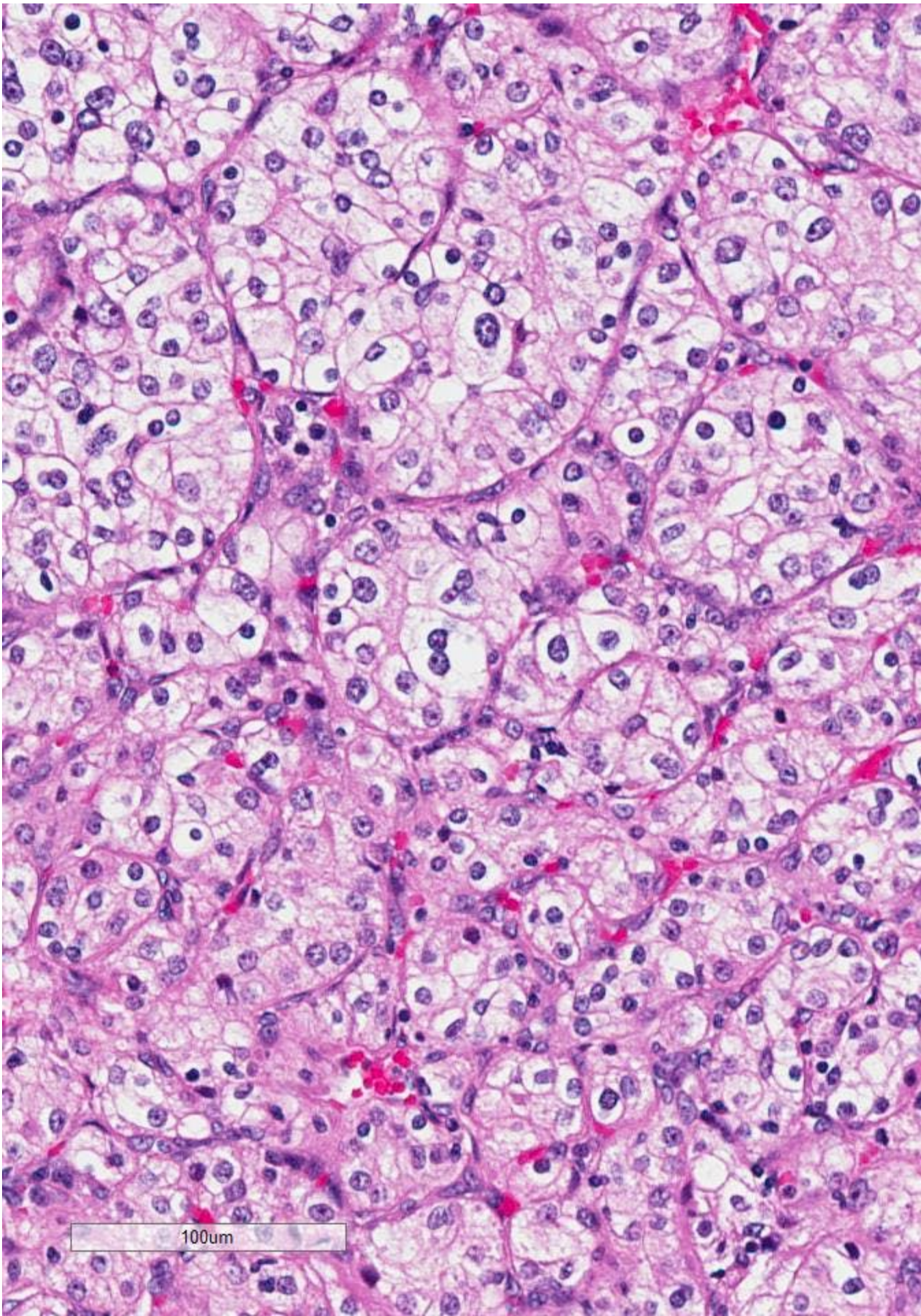
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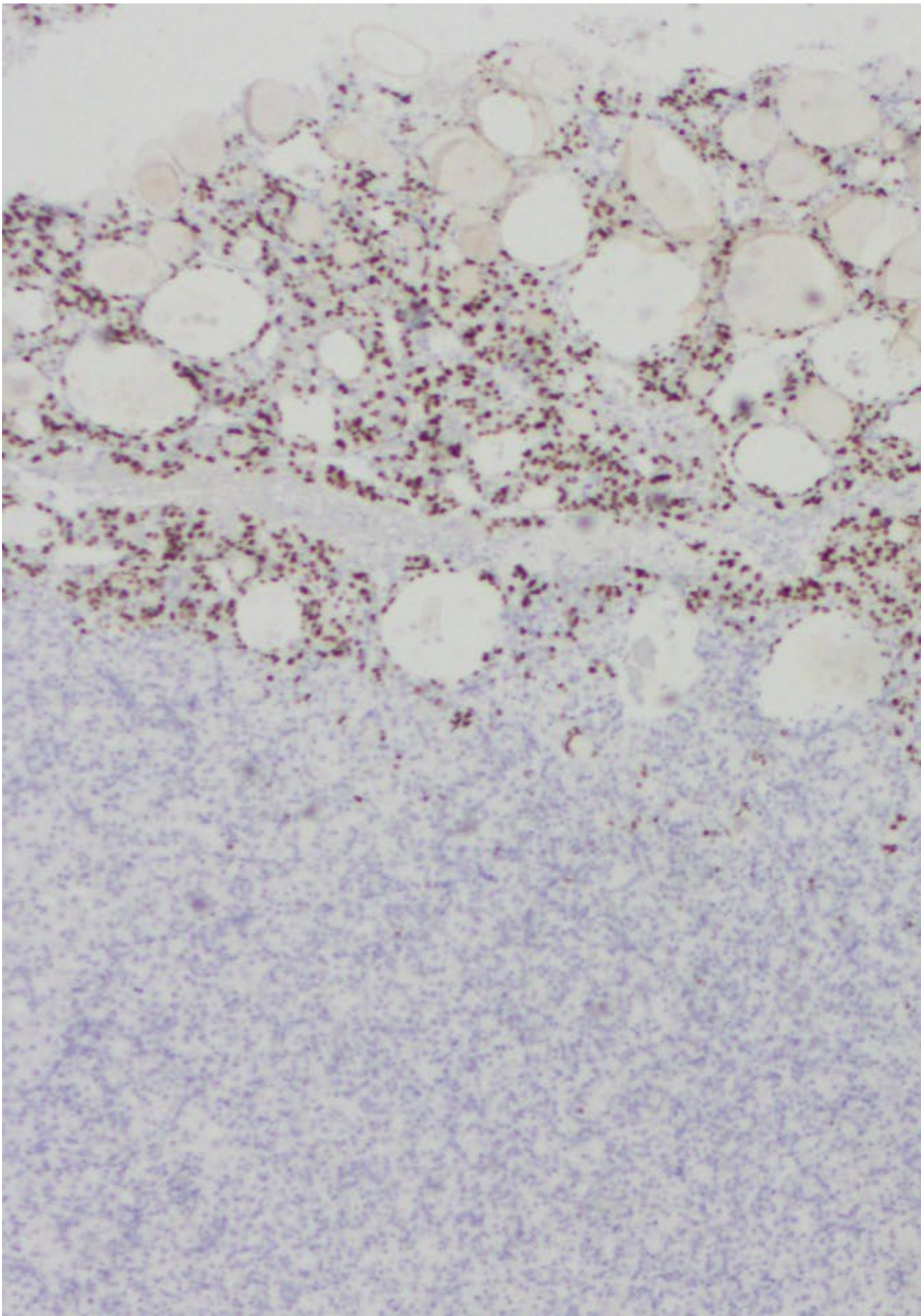
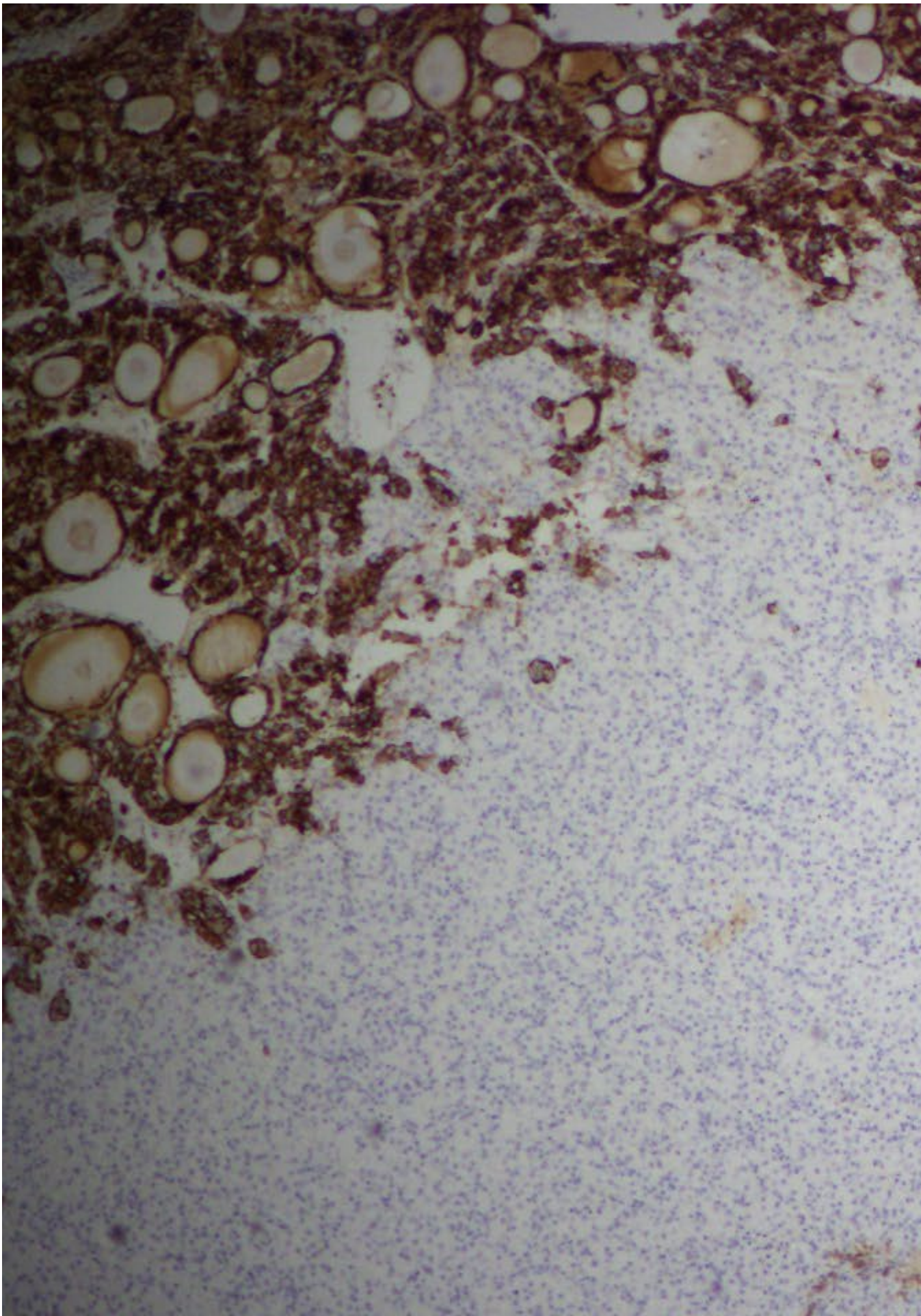
- **Immunohistochemistry:** Initial IHC performed at the hospital of origin showed that the main tumor was positive for TTF-1 and thyroglobulin, while the clear cell component was negative for TTF-1 and thyroglobulin. Both components were negative for calcitonin, CEA, neuroendocrine markers (CD56, synaptophysin and chromogranin), and p63. Ki-67 was 5% in the main tumor and around 10% in the clear cell component.
  The IHC performed at JGH demonstrated that the follicular variant of papillary thyroid carcinoma component was positive for TTF1 and thyroglobulin, while the clear cell component was negative for both markers. CK7 showed the same pattern of staining, while PAX-8 was weakly positive in both components.
  CD10 and RCC were strongly and diffusely positive in clear cell component, while CD117 and DOG-1 were negative.

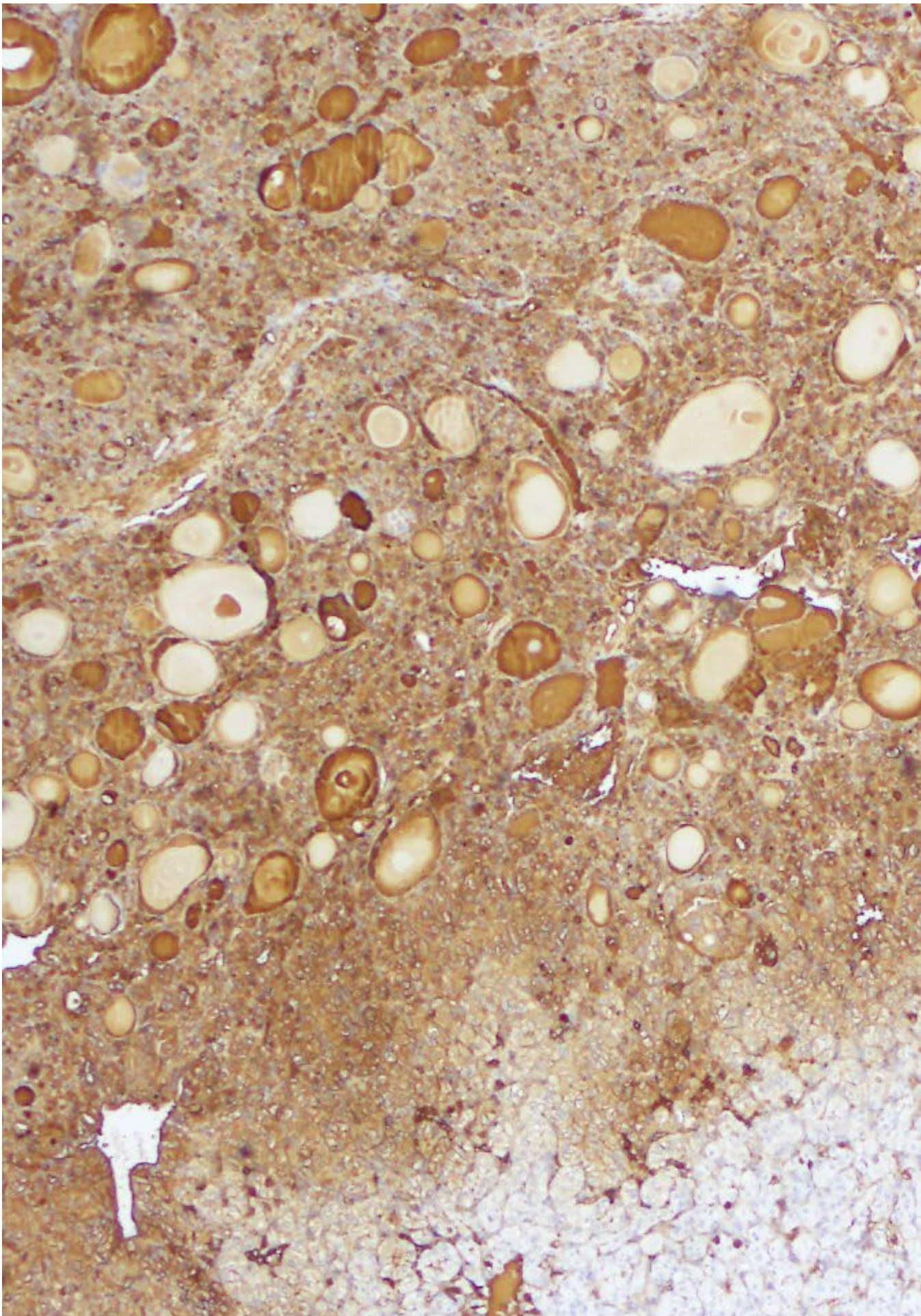
- **TTF-1**



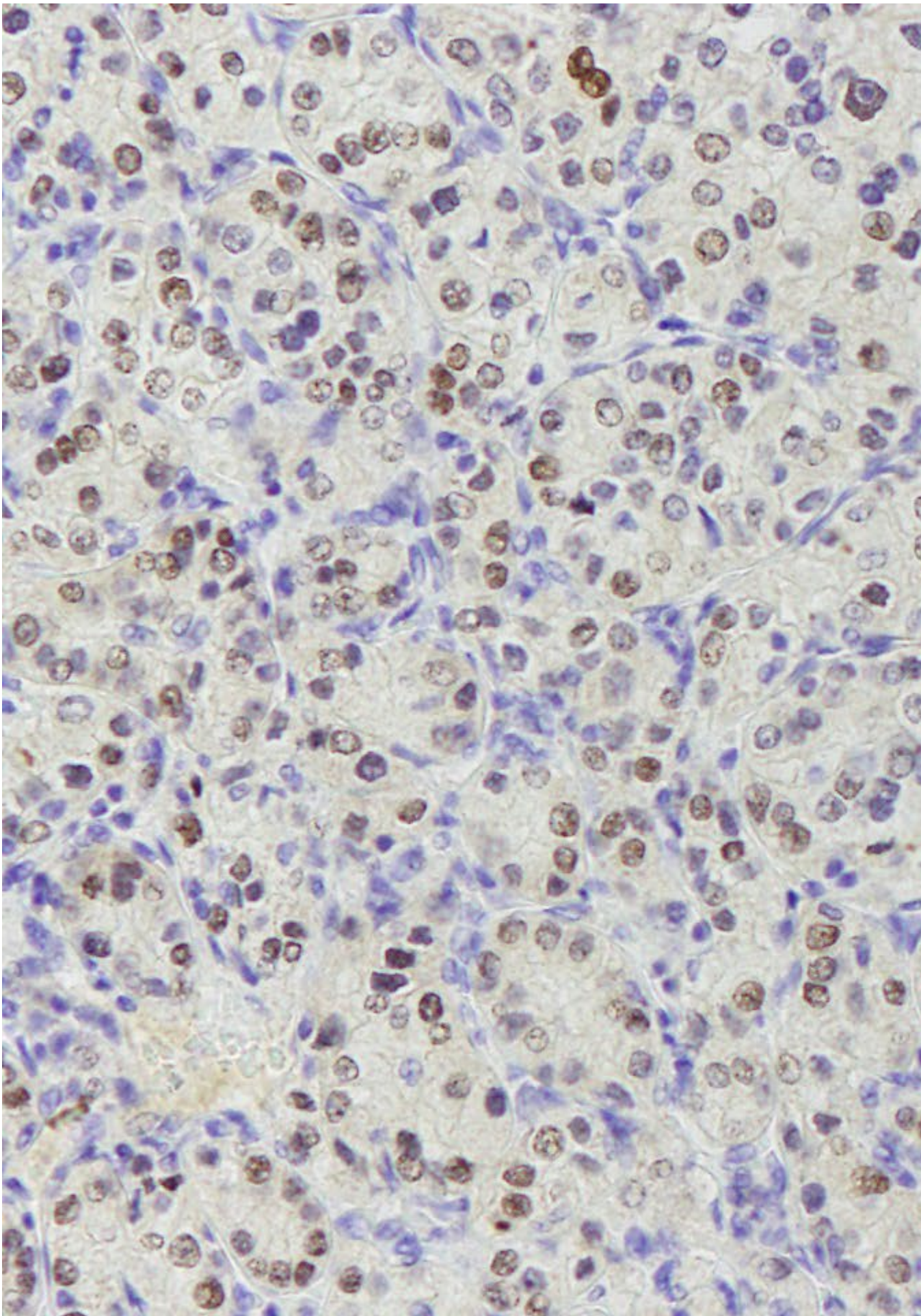
**CK-7**



# Thyroglobulin



**PAX-8**



# Discussion

In general, focal clear-cell change is not uncommon in thyroid nodules. It is a nonspecific finding in benign and malignant thyroid tumors; also seen in Hashimoto thyroiditis and goiter. Cytoplasmic clearing results from accumulation of glycogen, lipid, mucin, and thyroglobulin, or can occur due to dilatation and hypertrophy of mitochondria and Golgi complexes.

**The main differential diagnosis for clear cells in primary thyroid tumors includes:**
1-Papillary thyroid carcinoma, clear cell variant, this is extremely unusual and often is seen in combination with oncocytic cytology of some of the tumor cells
2-Follicular thyroid carcinoma, clear cell variant: clear cell FTC (defined by > 50% clear cells in the tumor) accounts for<1% of thyroid malignancies but is more common than clear cell PTC(https://www.ncbi.nlm.nih.gov/pubmed/28293986). Clear cell cytoplasm predominates, but the coexistence of oncocytic neoplastic cells is not uncommon
3-Medullary thyroid carcinoma, clear cell variant
(https://www.ncbi.nlm.nih.gov/pubmed/4018781)
4-Hirokawa M et al introduced in 2017 a new entity called "chromophobe renal cell carcinoma-like thyroid carcinoma". Two of the patients had associated tuberous sclerosis complex. On histology, the tumors had trabecular pattern with thin vascular stroma, eosinophilic cytoplasm, perinuclear clearing, and a prominent cell border. The nuclei showed wrinkled nuclear membrane and binucleation, which are all features of chromophobe renal cell carcinoma. However, the cases were positive for thyroglobulin, TTF1, CK7 and PAX8, and negative for CD10, calcitonin, and carcinoembryonic antigen, and CD117. The whole panel of IHC confirmed the origin of the tumor from the thyroid instead of kidney
(https://www.jstage.jst.go.jp/article/endocrj/64/9/64_EJ17-0096/_article).
5-Finally, clear-cell changes can also be seen in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma.
IHC Panel of TTF-1, PAX-8, calcitonin and thyroglobulin are helpful for the diagnosis of primary tumors with clear-cell changes. Importantly, thyroglobulin staining has been shown to be variable or largely negative in areas of cytoplasmic clearing, emphasizing the importance of nuclear stains such as TTF-1 and PAX-8 to confirm the thyroidal origin of questionable tumors
(https://www.ncbi.nlm.nih.gov/pubmed/28293986)
The other main differential diagnosis for clear cells in thyroid tumors is **Metastases:** metastases to the thyroid gland range from 1.9% to 24%. It is usually an incidental finding and mostly found in autopsy studies. It is thought to be related to rich blood supply in the thyroid gland; furthermore, abnormal thyroid gland is vulnerable to metastatic growth due to a decrease in oxygen and iodine content alteration.
The most common malignancies that metastasize to the thyroid gland are renal cell carcinoma (48.1%), colorectal cancer (10.4%), lung cancer (8.3%), breast carcinomas (7.8%), melanomas and sarcomas (4.0%).
Renal cell carcinoma can develop late and/or as a solitary metastasis. Metastases are present in about 25% of RCCs at the time of diagnosis or can develop after many years of dormancy (even 20 years later). The usual symptoms include enlarged solitary or multiple neck swellings, painless palpable thyroid nodules, shortness of breath, vocal changes, wheezing and difficulty in swallowing, but most metastases of the thyroid are asymptomatic. They appear as "cold" nodules on radioiodine uptake studies or as "hypoechoic" masses on ultrasound**.** Characteristic

ultrasonographic finding is prominent intra-tumoral vascularity. A multi-institutional study on FNAs of thyroid metastases showed that overall, FNAB is a sensitive and accurate method for diagnosis of metastases to thyroid. One of the major pitfalls for diagnosis of metastatic RCC is to misinterpret it as suspicious for a follicular neoplasm or as suspicious for a Hürthle cell neoplasm due to oncocytic changes of the cells. In these scenarios, IHC and clinico-radiological data are very helpful (https://onlinelibrary.wiley.com/doi/full/10.1002/cncy.21494).

**Differential diagnosis of metastatic RCC:**
In a comprehensive review of useful IHC panels for diagnosis of metastatic clear cell RCC (https://insights.ovid.com/pubmed?pmid=20966644), the most common IHCs used in practice were:

1. PAX-8: PAX-8 has a nuclear staining pattern, and it is an important transcription factor in the development of thyroid, renal and ovarian epithelial tumors. It has high sensitivity (94%) and overall specificity of 88% for metastatic RCC. PAX-8 is usually positive in tumors of Müllerian origin (eg, uterine carcinomas, ovarian surface epithelial neoplasms, and endocervical carcinomas) and thyroid (follicular and parafollicular) origin including anaplastic thyroid carcinoma
2. PAX-2: PAX-2 has a nuclear staining pattern, and it is also a transcription factor with moderate sensitivity (47% to 85%) and high overall specificity (90% to 97%) for metastatic RCC. Nonrenal neoplasms with well-documented PAX-2 immunoreactivity include tumors of Müllerian origin parathyroid tumors, epididymal tumors, and lobular breast carcinoma
3. RCCma (monoclonal ab): Membranous and/or cytoplasmic reactivity is considered positive. Specificities for metastatic RCC range from 48% to 100%, and sensitivities range from 27% to 90%
4. CD10: It has cytoplasmic and/or membranous reactivity. Sensitivities for metastatic CC-RCC ranging from 83% to 100%. In addition, CD10 immunoreactivity is seen in a wide variety of nonrenal neoplasms
5. Carbonic Anhydrase-IX: It is also a sensitive marker for CC-RCC, but the expression is well recognized in a wide variety of other common nonrenal neoplasms.

Other differential diagnoses for metastatic clear cell tumors in thyroid include wide range of clear cell tumors from almost all organs. Some more common ones in a female patient as our patient with useful IHC panel are as follows (https://insights.ovid.com/pubmed?pmid=20966644):

- Breast: Both ductal and lobular carcinomas as well as myoepithelial lesions can have clear cell changes. Use of markers such as Mammaglobin, GCDFP-15, GATA3, p63, S100 can be useful for differential diagnosis. PAX-8 is negative or has rare weak staining in breast lesions.
- Lung: Adenocarcinoma and squamous cell carcinoma are negative for PAX-2 and PAX-8, while they are usually positive for TTF-1 and Napsin-A in adenocarcinoma cases and for p63 and CK5/6 in squamous cell carcinoma.

- Gynecologic tract tumors: Both ovarian and uterine clear cell carcinomas show strong immunoreactivity with PAX-2, and PAX-8; however, CD10 is negative. In vaginal and cervical clear cell adenocarcinomas; similarly, CD10 is negative

- Urinary tract: Use of GATA-3, p63, uroplakin and CK20 can be helpful for urothelial carcinoma with clear cell changes. Clear cell adenocarcinoma of the urinary bladder or urethra both express CD10, PAX-2, and PAX-8. However, diffuse strong staining with CK7 and cancer antigen-125 as seen in these tumors would be uncommon in metastatic CC-RCC.

- Head and neck: Parathyroid tumors are negative for PAX-8 and PAX-2, and they show reactivity with PTH, GATA-3 and chromogranin.

- Pancreaticobiliary Tract, Gastrointestinal Tract, and Liver Tumors show positive tumor specific markers that can be useful in differential diagnosis. Markers such as CK7 and MUC1 for pancreatobiliray tract clear cell adenocarcinomas; Neuroendocrine markers for clear cell well differentiated neuroendocrine tumors, and Nuclear β-catenin for clear cell solid pseudopapillary neoplasm of pancreas has shown to be diagnostic. In gastrointestinal tract, tumors with clear cell variants are mostly negative for PAX-2 and PAX-8. Hepar-1 and glypican-3 are positive in clear cell hepatocellular carcinoma.

**Tumor to Tumor metastases:** It is a very rare phenomenon. Although RCC has been reported to metastasize to the thyroid gland, metastatic RCC to a thyroid neoplasm is very unusual. The definition of cancer metastasizing to tumor (either benign or malignant) has been controversial, and there are some strict criteria for definition such as: (1) the recipient tumor must be a true neoplasm, 2) the donor tumor must be a true metastasis (direct spreading is not acceptable as metastasis)
In a review study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2811566/), metastatic RCC has been seen in a variety of primary thyroid neoplasms including follicular adenoma, Hürthle cell adenoma, PTC and FTC. The common finding in all cases was negative thyroglobulin and TTF-1 and positive RCC markers.

**Final Diagnosis:**
Thyroid: Papillary thyroid carcinoma, follicular variant (pT2 N0a) with intratumoral metastatic clear cell renal cell carcinoma (40%). No Lymph-vascular or perineural invasion and no extrathyroidal extension was identified.
At the time of diagnosis there was no other work-up to confirm any other primary tumor in the patient. The imaging studies done later showed a 7.5 cm mass in the left kidney. The patient had a left nephrectomy and pathology confirmed renal clear cell carcinoma in the left kidney, grade 2, (pT2a Nx). The tumor was involving the left kidney with no peri-renal or hilar involvement. However, there was invasion of the renal vein wall but without associated thrombus.

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