Common Diagnostic Pitfalls in Follicular Pattern and Papillary Lesions of the Thyroid

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OBJECTIVES

- Discuss the most frequently encountered diagnostic pitfalls in thyroid cytopathology
- Enumerate the helpful diagnostic clues in the differential diagnoses of thyroid conditions

Introduction

- FNA is the most important diagnostic tool in the evaluation of thyroid nodules
- Main goal is to triage patients having nodules with high-risk of malignancy for surgery
- Thyroid FNA can be challenging, with many potential diagnostic pitfalls
- Aim of presentation is to increase awareness of potential diagnostic pitfalls and offer ways to avoid them

Potential pitfalls

- Cystic lesions of the thyroid
- Lymphocyte-rich lesions of the thyroid
- Follicular neoplasm with atypia
- Papillary thyroid carcinoma
- Poorly differentiated carcinoma
- Anaplastic carcinoma
- Parathyroid tissue sampling
- Ectopic thyroid tissue

Nondiagnostic Thyroid FNA

- Specimen deemed satisfactory for evaluation if it has at least 6 groups of benign, well-visualized follicular cells, with each group consisting at least 10 follicular cells
- Tissue fragments with multiple follicles can be split up and counted as separate and distinct groups
- Exception to adequacy requirement:
  - Abundance of colloid
  - Abundance of lymphocytes
  - Presence of atypia

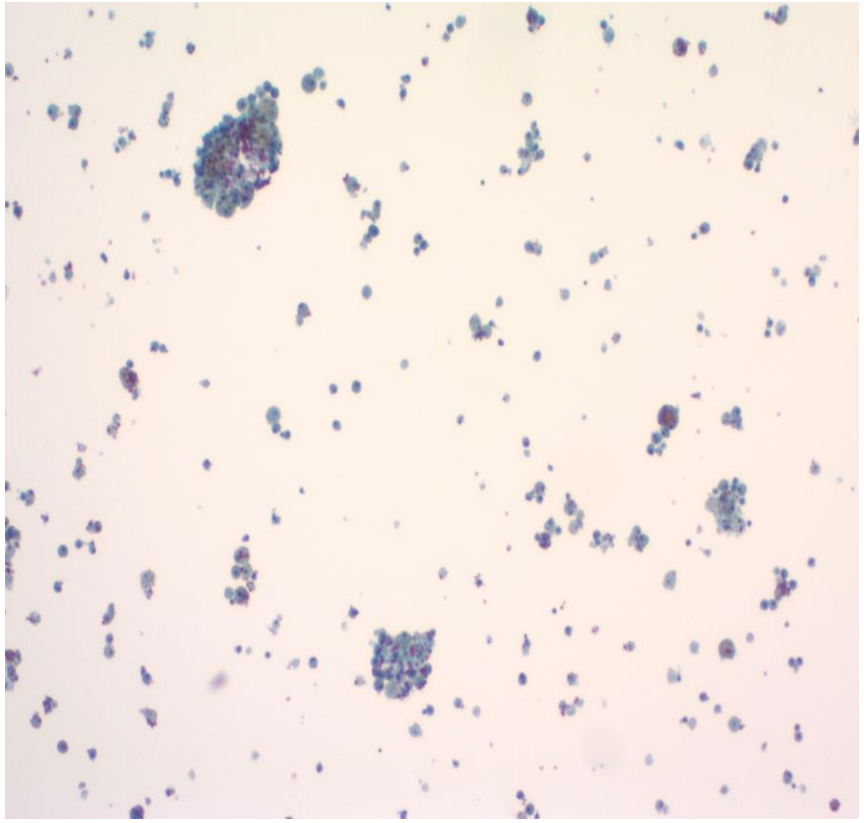
Cystic lesions of the thyroid

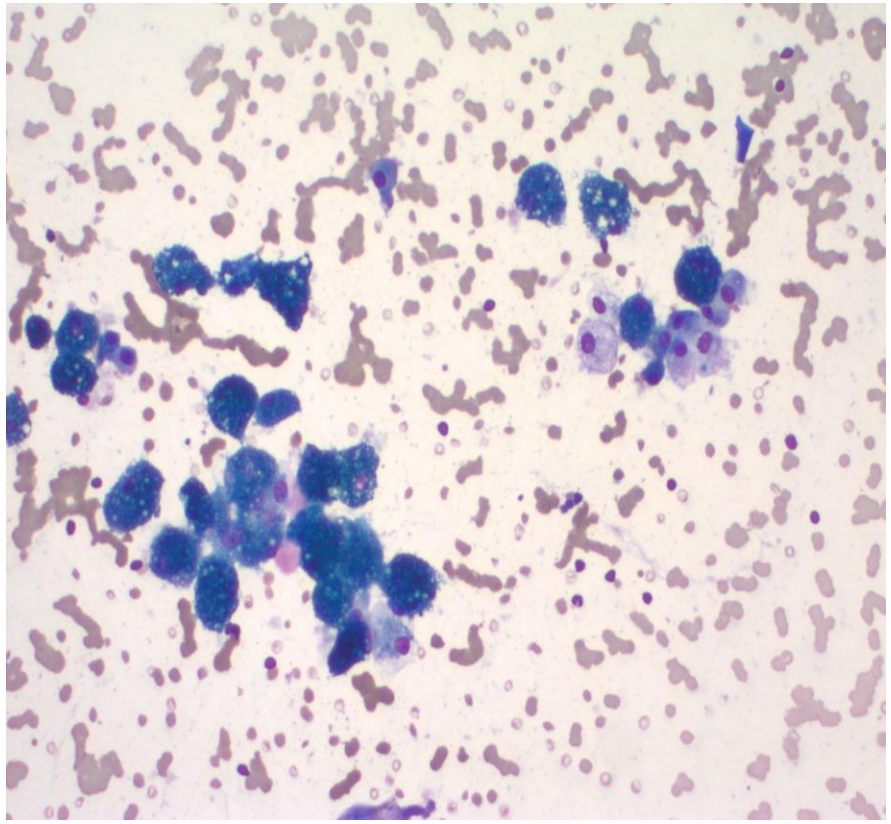
- Fluid cyst only
- Cystic degeneration in hyperplastic nodule
- Cystic papillary thyroid carcinoma

Cystic lesions of the thyroid

- Fluid cyst only
  - Abundant macrophages
  - Few to no follicular cells
  - Cysts collapse after drainage

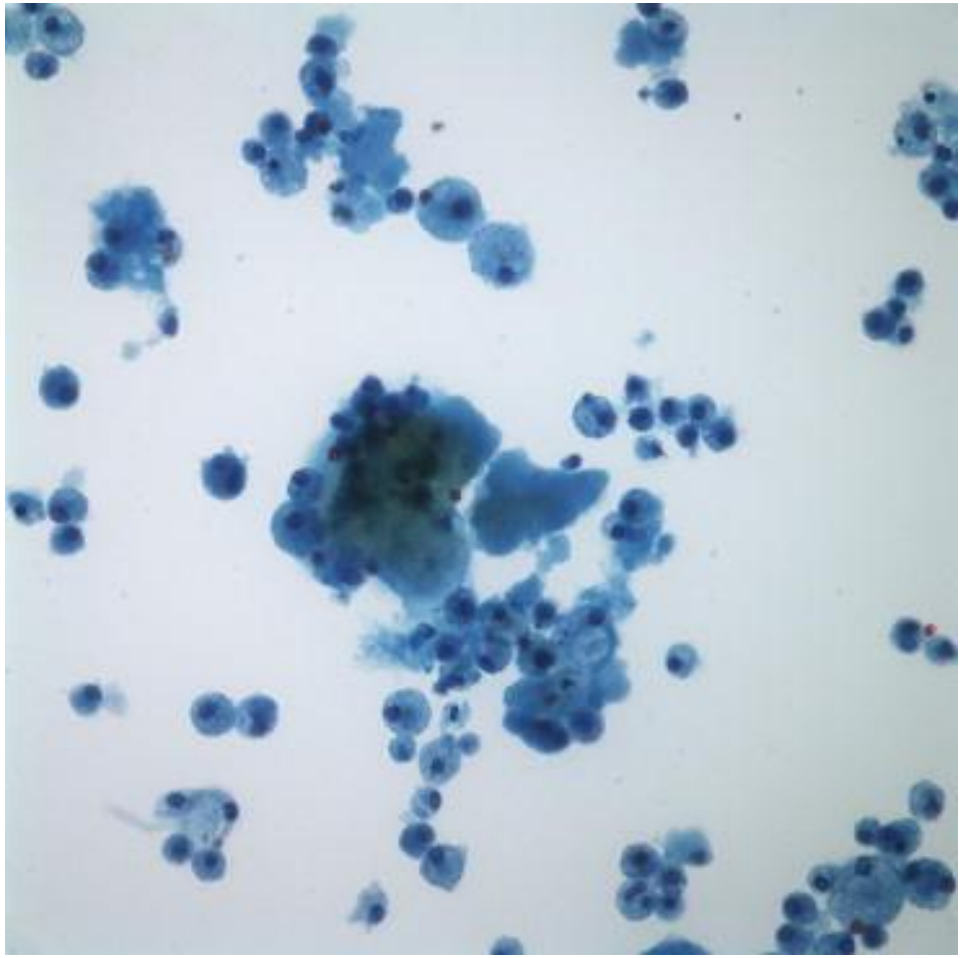
Fluid cyst only

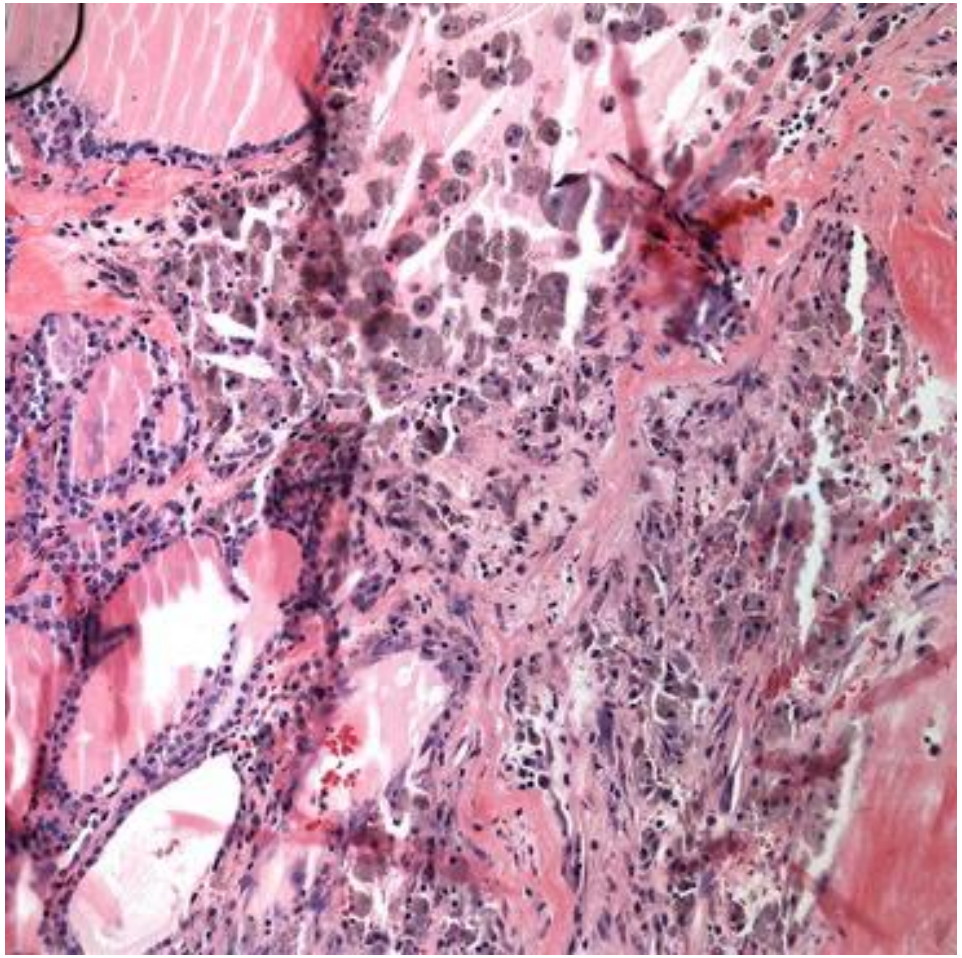




Cystic lesions of the thyroid

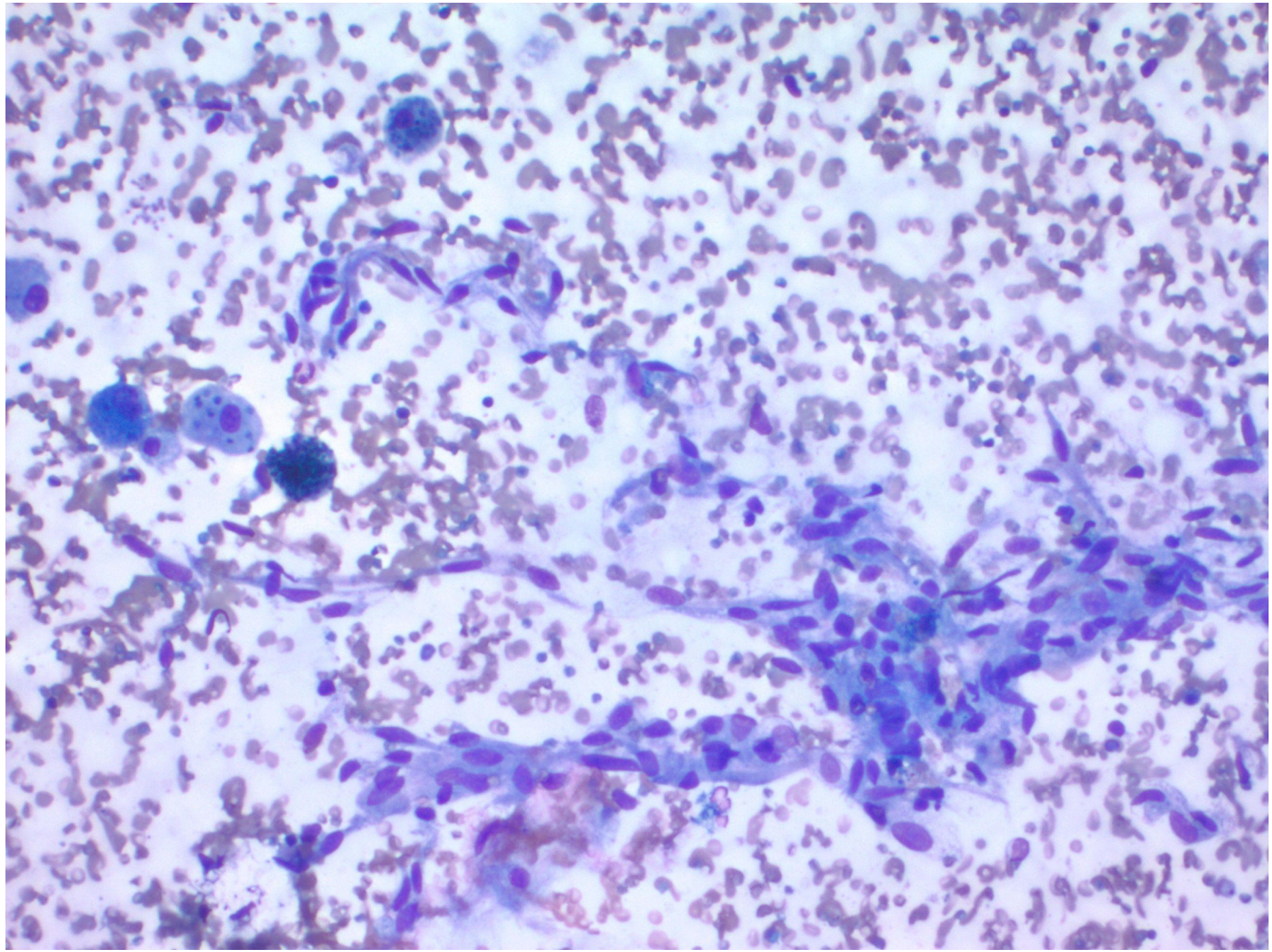
- Cystic degeneration in hyperplastic nodule
  - Numerous macrophages in a variety of hyperplastic nodules undergoing cystic degeneration
  - Low cellularity
  - Cysts collapse after drainage

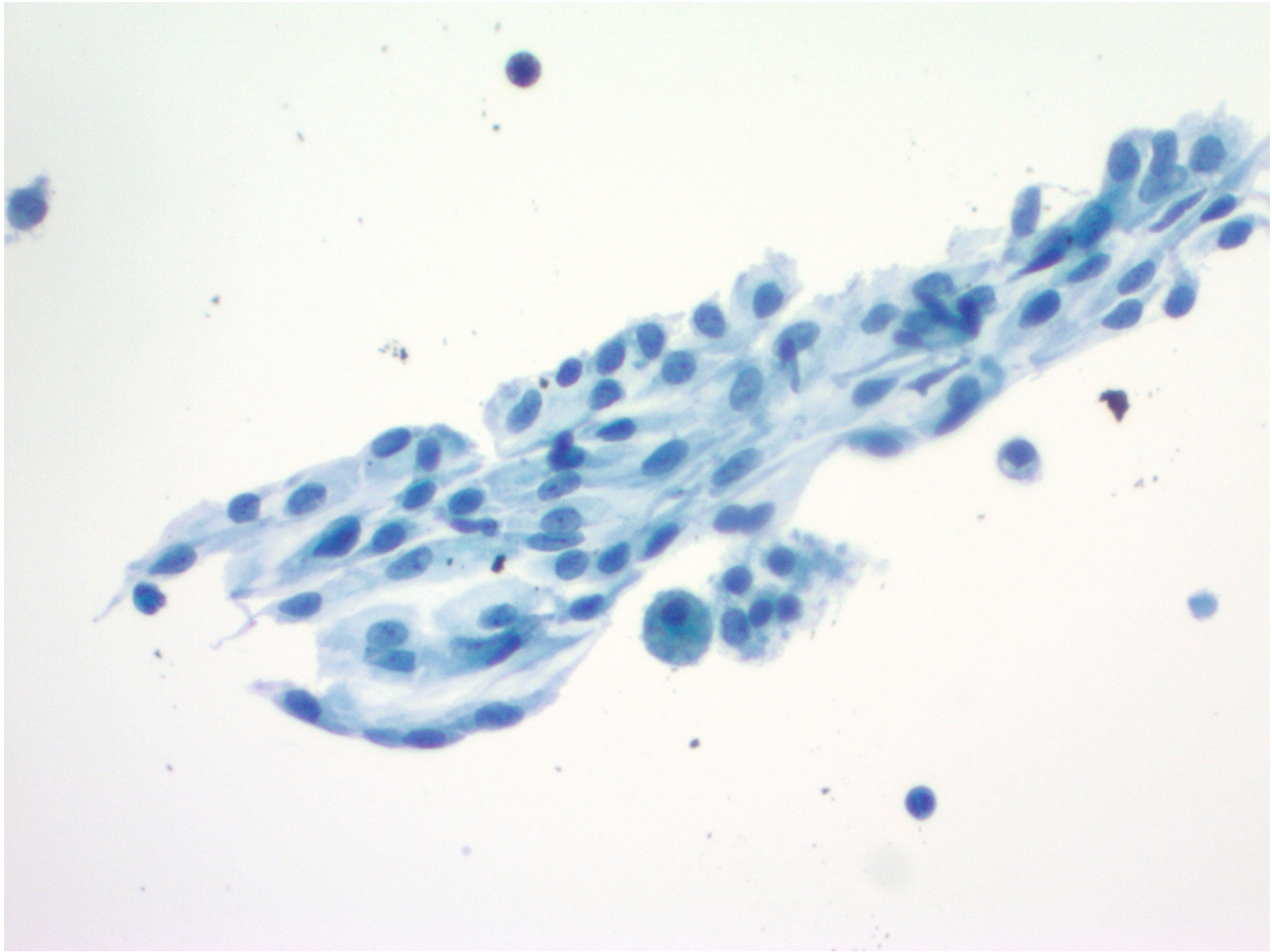




Cystic lesions of the thyroid

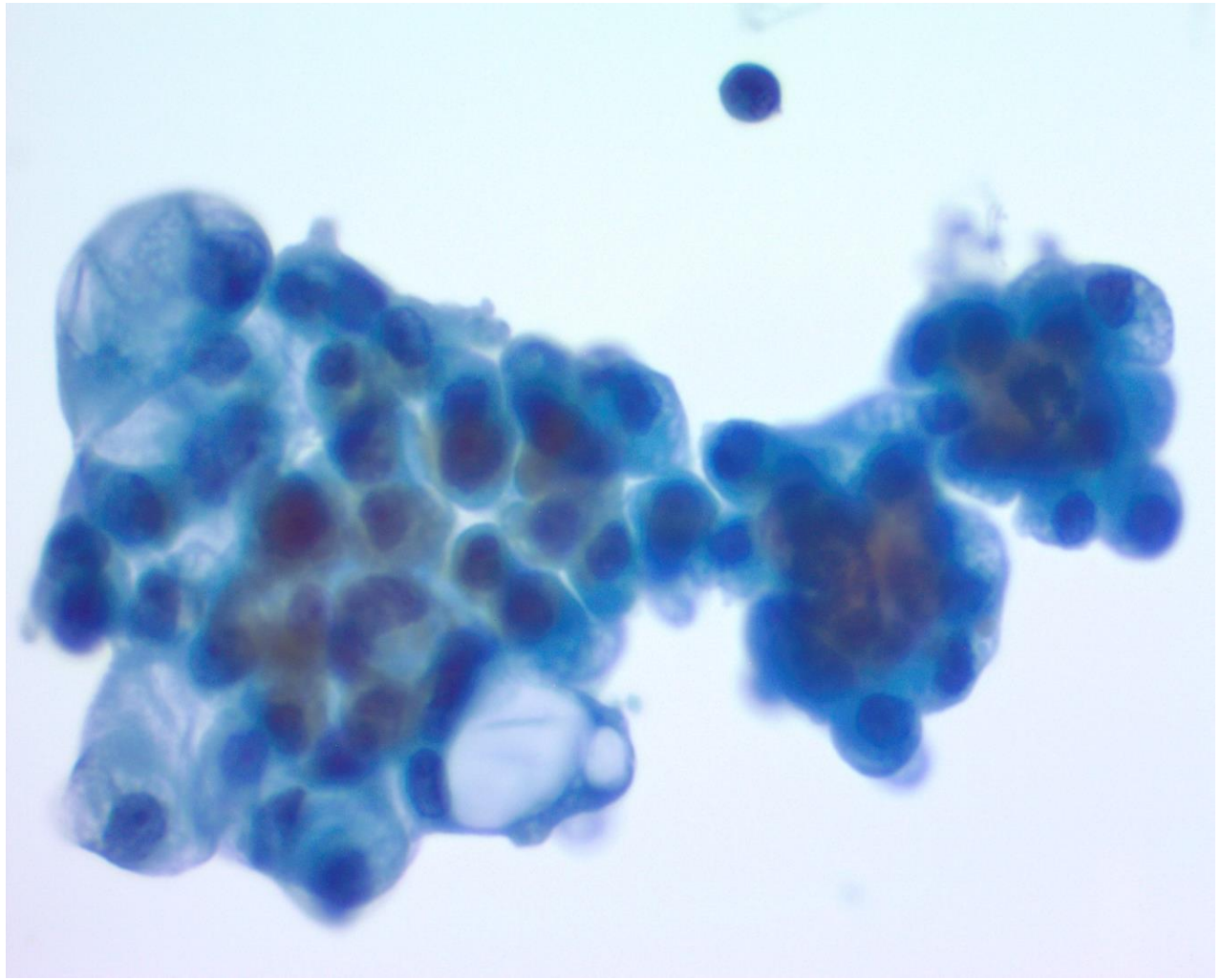
- Cystic degeneration in hyperplastic nodule
  - Cyst lining cells show reactive changes – pulled-out appearance that mimics reparative epithelium
  - May be diagnosed as AUS
  - Dystrophic calcifications can mimic psammoma bodies





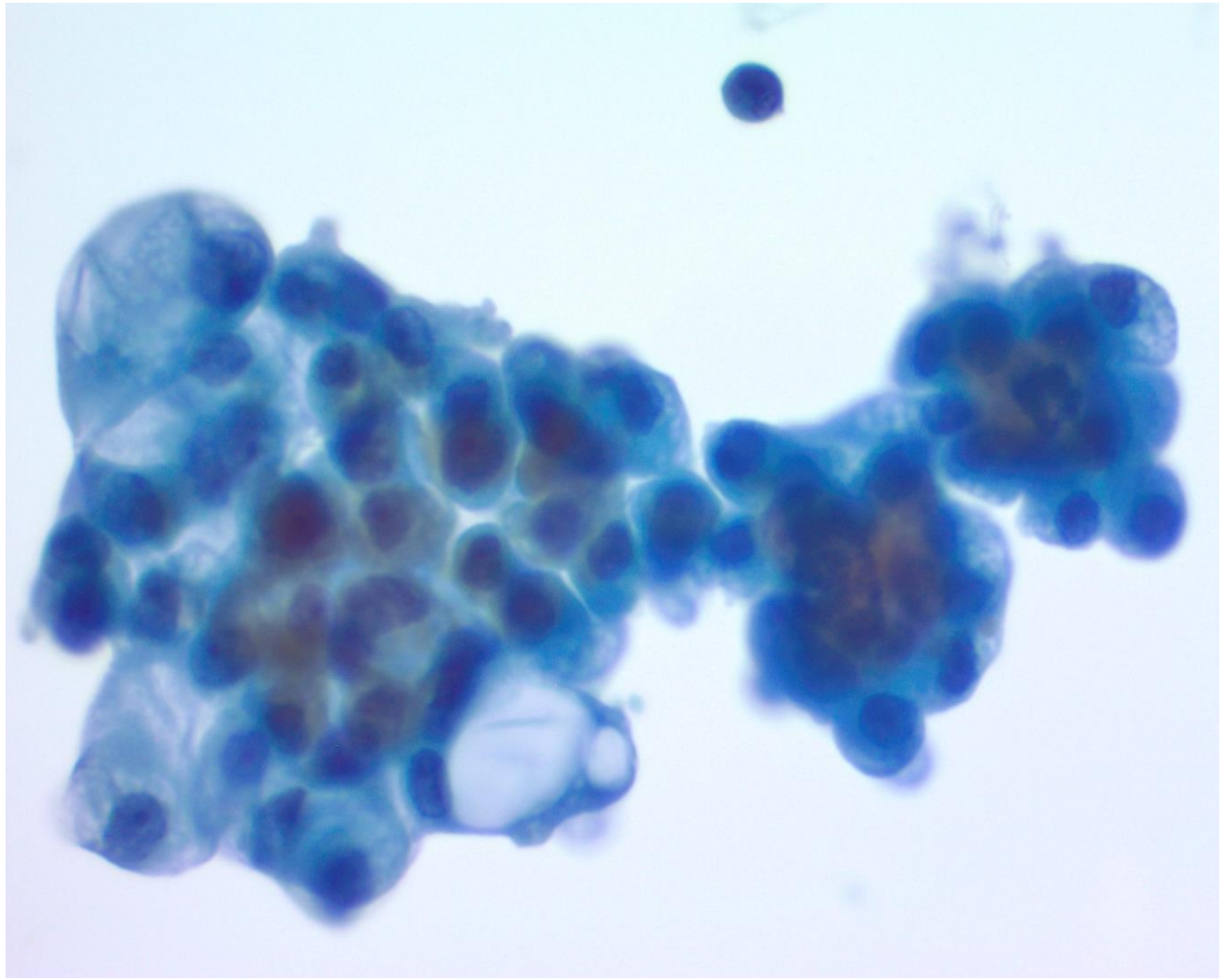
Cystic papillary carcinoma

- Recurrence of cyst with hemorrhagic or chocolate-colored contents raises possibility of malignancy
- Tumor can be partially or totally cystic, unilocular or multilocular
- Tissue fragments exhibit scalloped borders



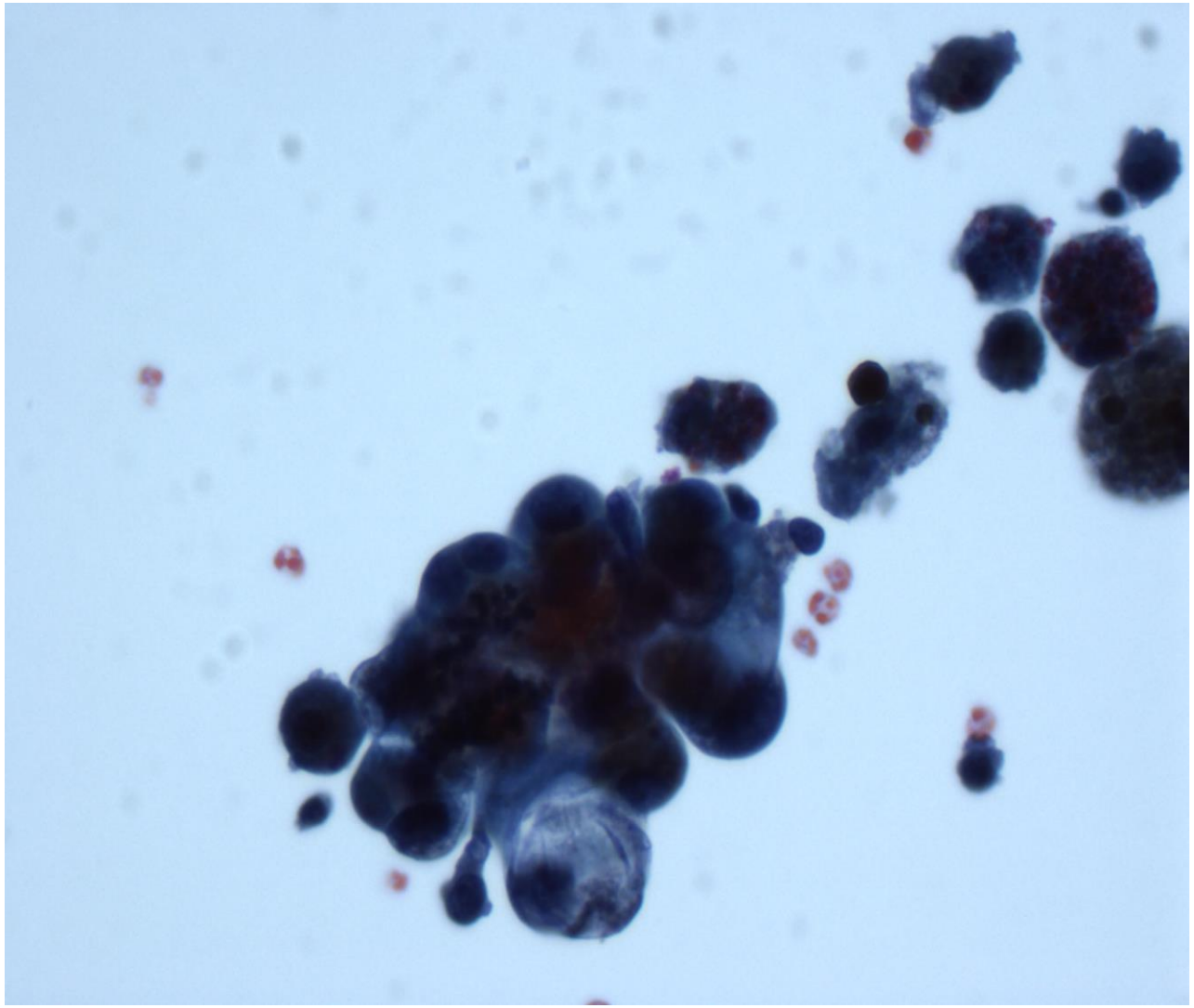
Cystic papillary carcinoma

- Cells arranged in cartwheel pattern with nuclei at the outside perimeter
- Cytologic features commonly seen:
  - 3-dimensional fragments
  - Anisonucleosis
  - Nuclear crowding
  - Nuclear enlargement
  - Intranuclear inclusions and cytoplasmic vacuoles



Cystic papillary carcinoma

- Fine, powdery chromatin may not be present as the chromatin stains intensely due to degeneration
- Combination of macrophages, hemosiderin, and cellular debris in the background may obscure distinction from cystic goiter
- Atypical histiocytoid cells of cystic PTC may be difficult to distinguish from histiocytes

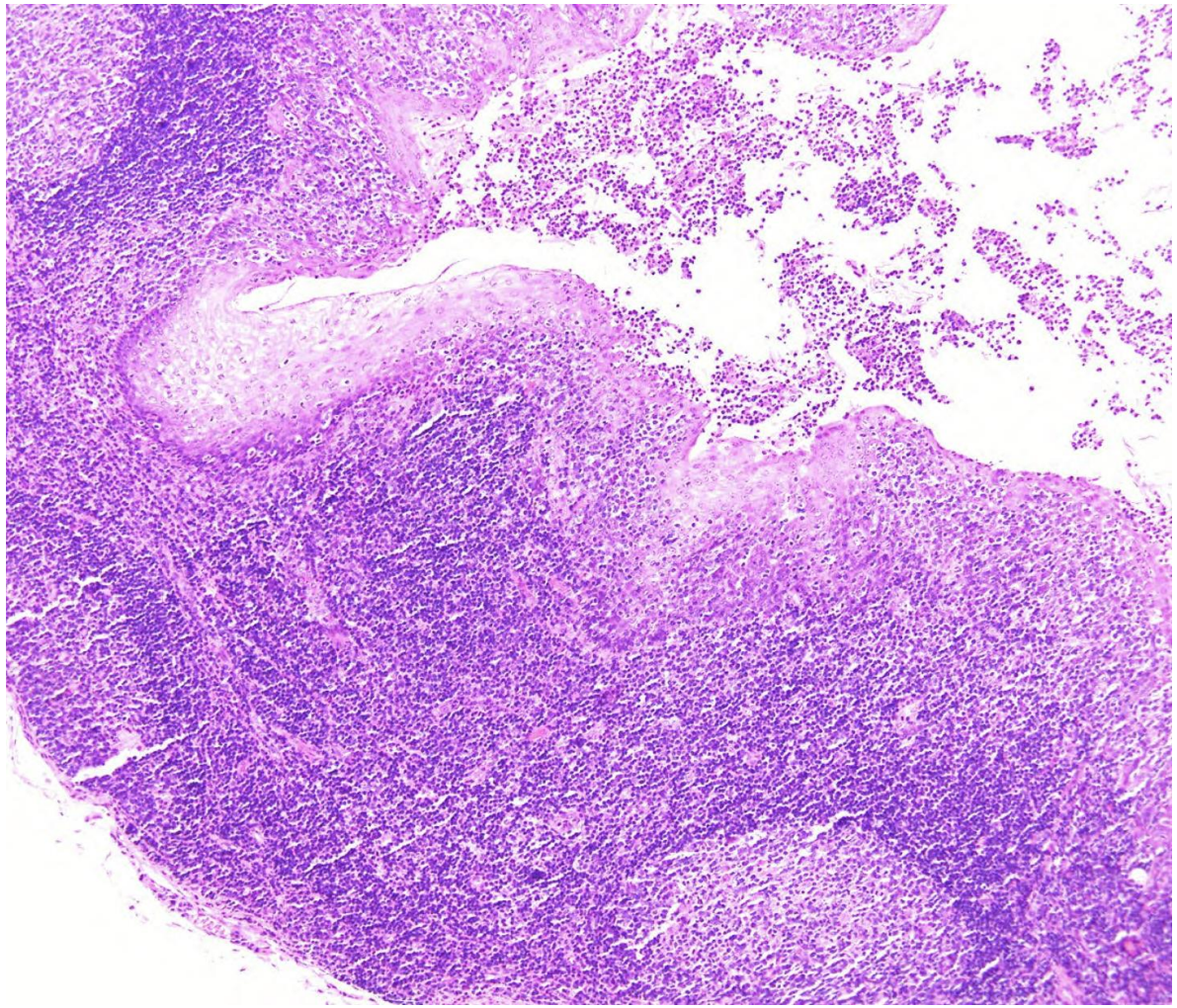


Cystic lesions of the thyroid

- Presence of squamous cells
  - Associated with a variety of different entities
    - Benign lympho-epithelial cysts, epidermoid cysts, thyroglossal duct remnants, squamous metaplasia in Hashimoto thyroiditis, malignancy
  - Most commonly, abundant anucleated and bland squamous cells plus background lymphocytes compatible with benign lesions

Cystic lesions of the thyroid

- Lymphoepithelial cysts
  - Bear close resemblance to counterparts in the salivary gland
  - Cysts lined predominantly by squamous epithelium and focally by columnar epithelium
  - Epithelium bordered by fibrous capsule and surrounded by lymphoid tissue, often with follicles and germinal centers



Lymphocyte-rich lesions of the thyroid

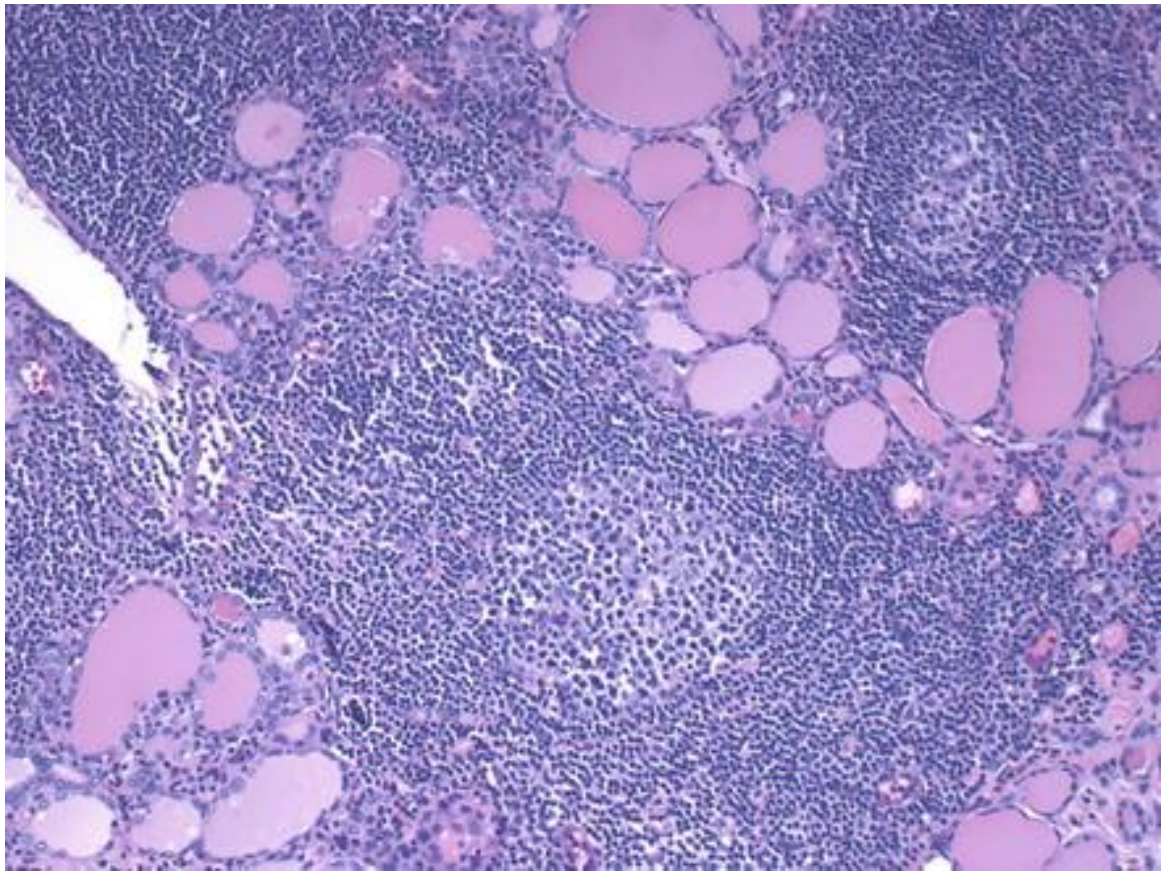
- Hashimoto thyroiditis
- Granulomatous thyroiditis
- Lymphoid neoplasms

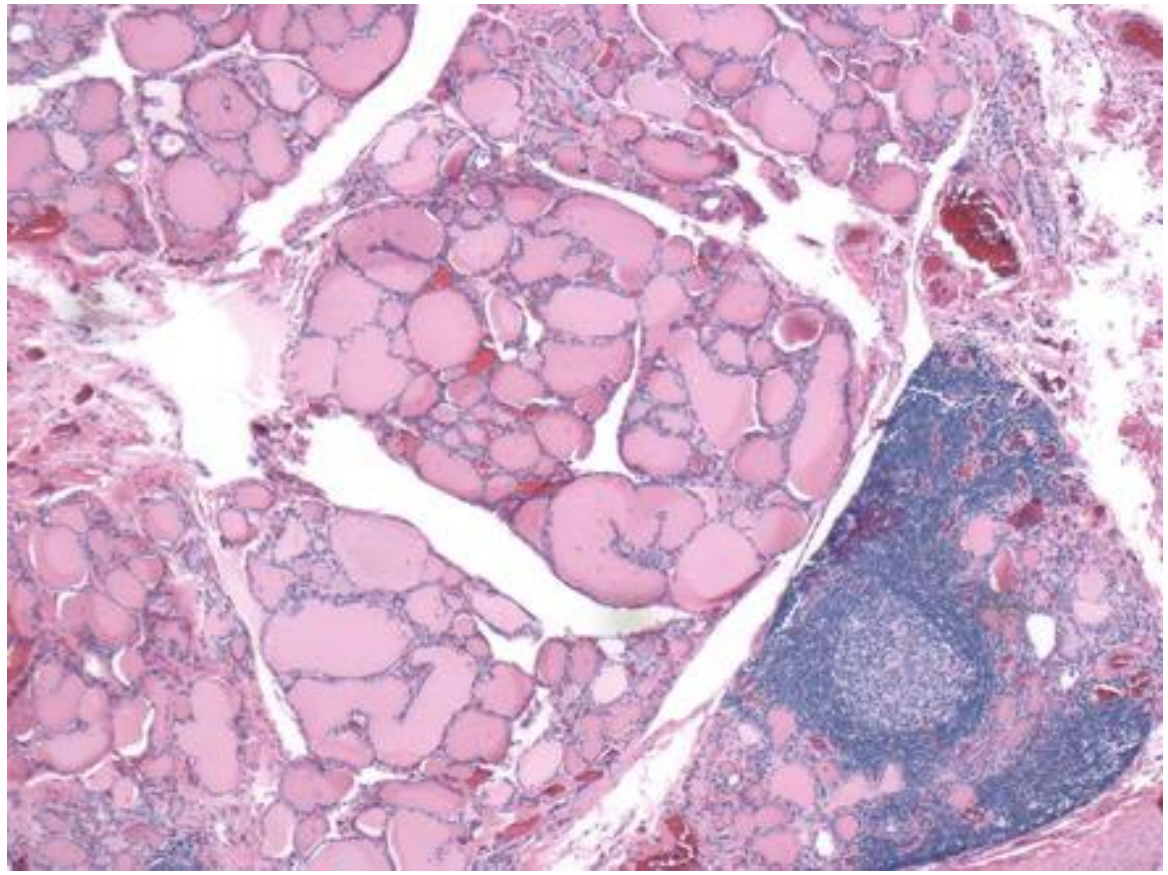
Lymphocyte-rich lesions of the thyroid

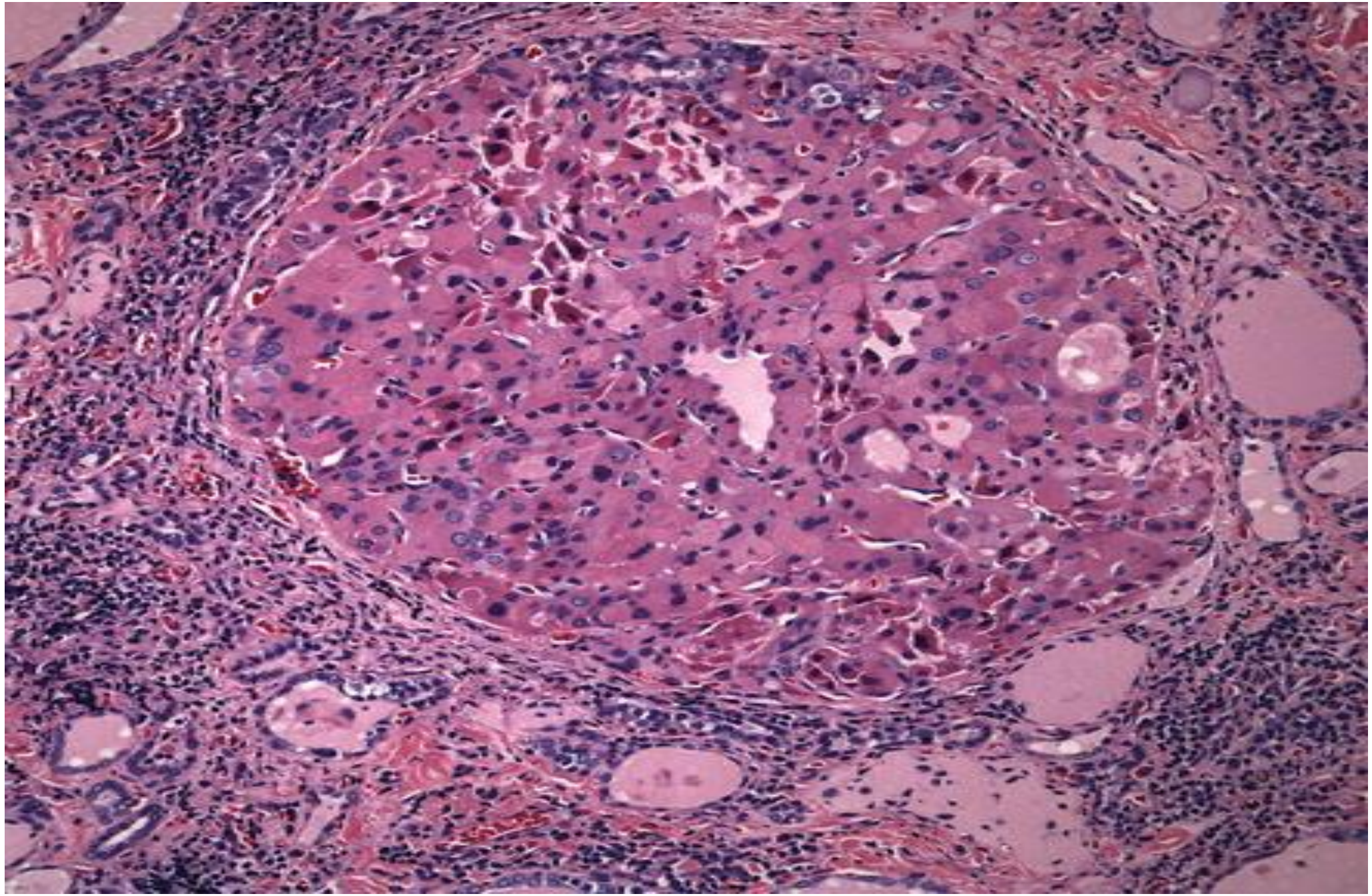
- Hashimoto thyroiditis
  - Very cellular with numerous lymphoid cells
  - Intense infiltration of the gland by polymorphous population of lymphocytes and plasma cells
  - Occasional clusters of Hurthle cells
  - Normal follicular cells infrequent or absent altogether

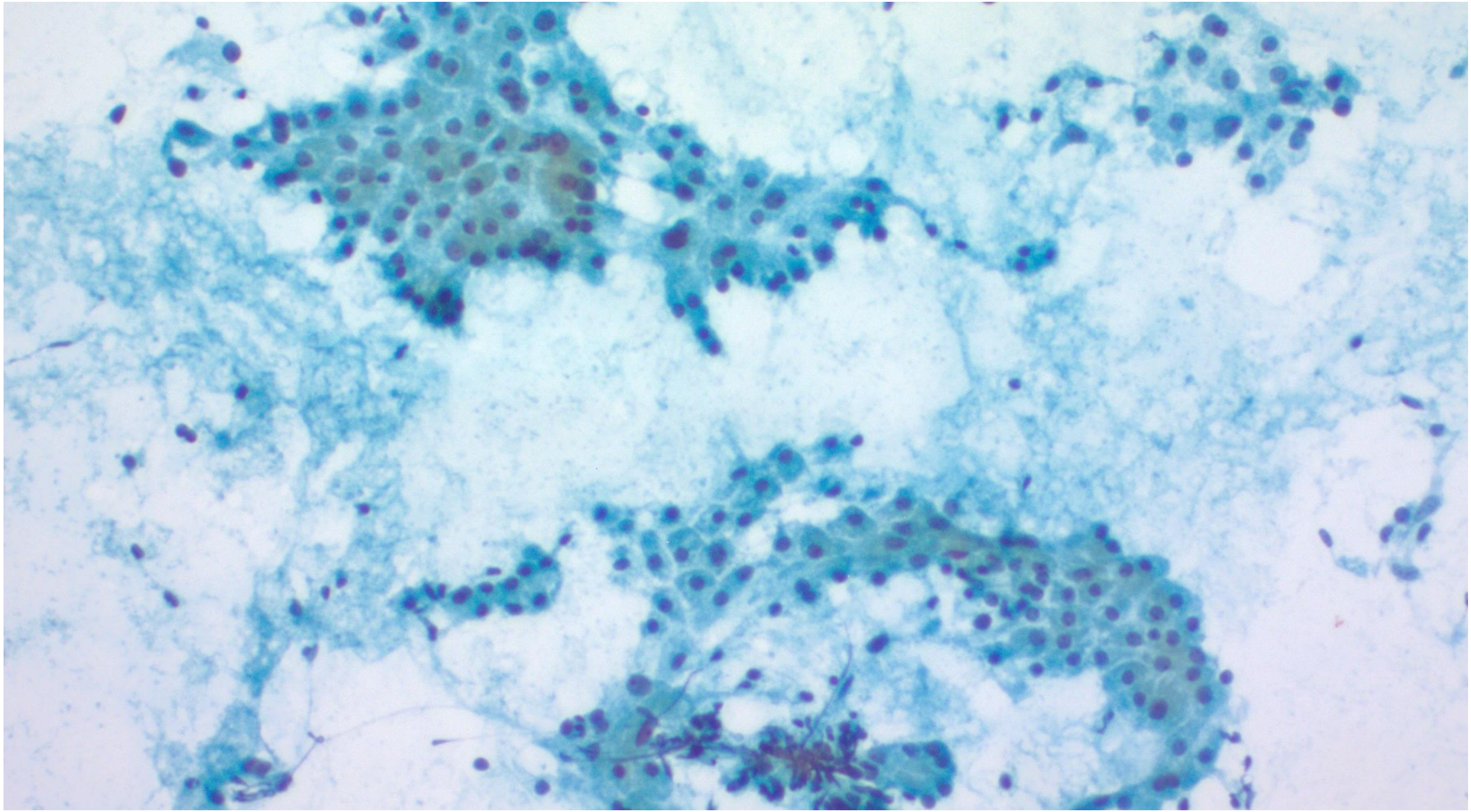
Lymphocyte-rich lesions of the thyroid

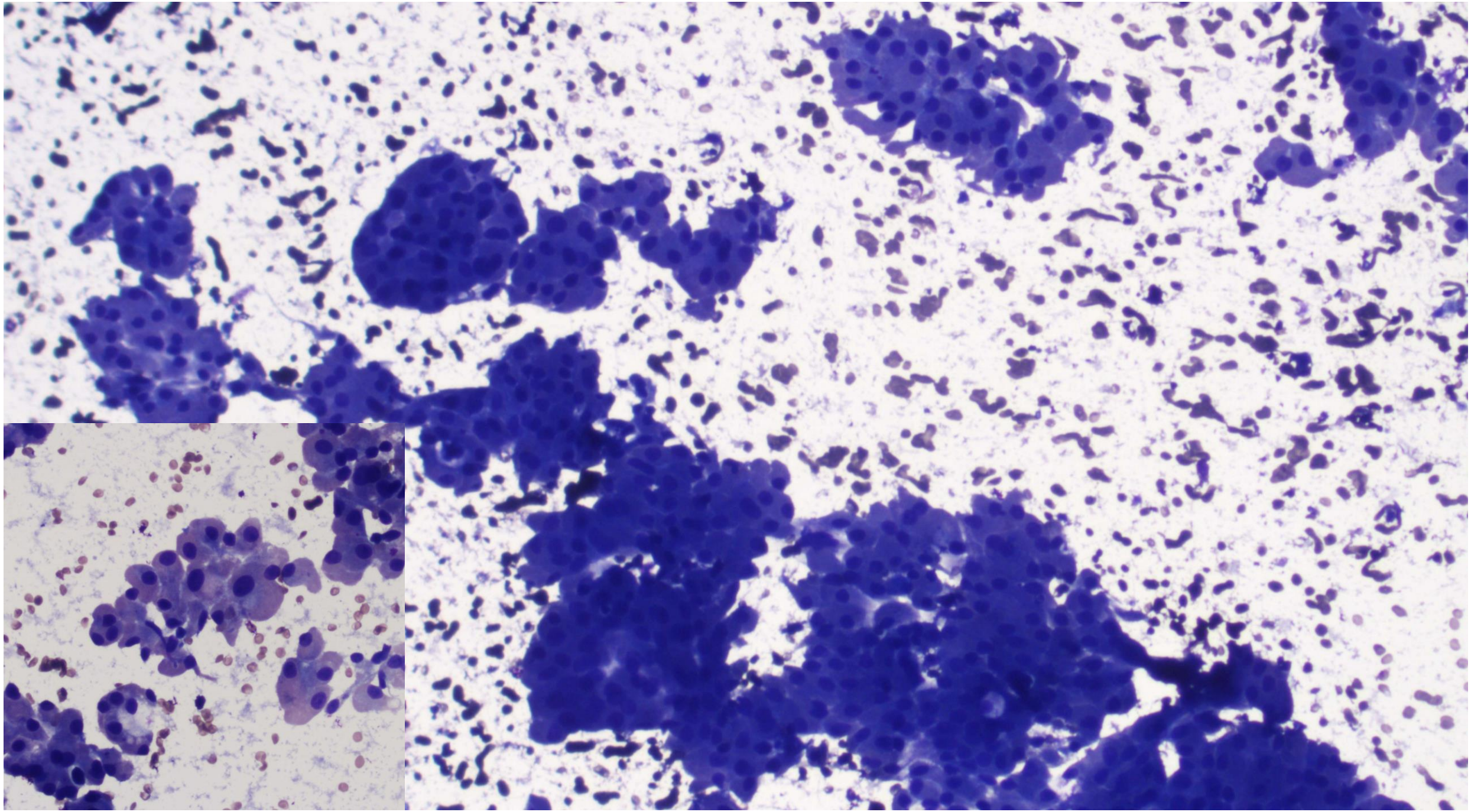
- Hashimoto thyroiditis
  - Proportion of Hurthle cells varies widely from case to case
  - Abundant Hurthle cells may form nonneoplastic Hurthle cell nodules, with little to no lymphoid infiltrate, mimicking Hurthle cell neoplasm
  - Hurthle cell neoplasm cells usually have more prominent nucleoli but no prominent lymphoid infiltrate

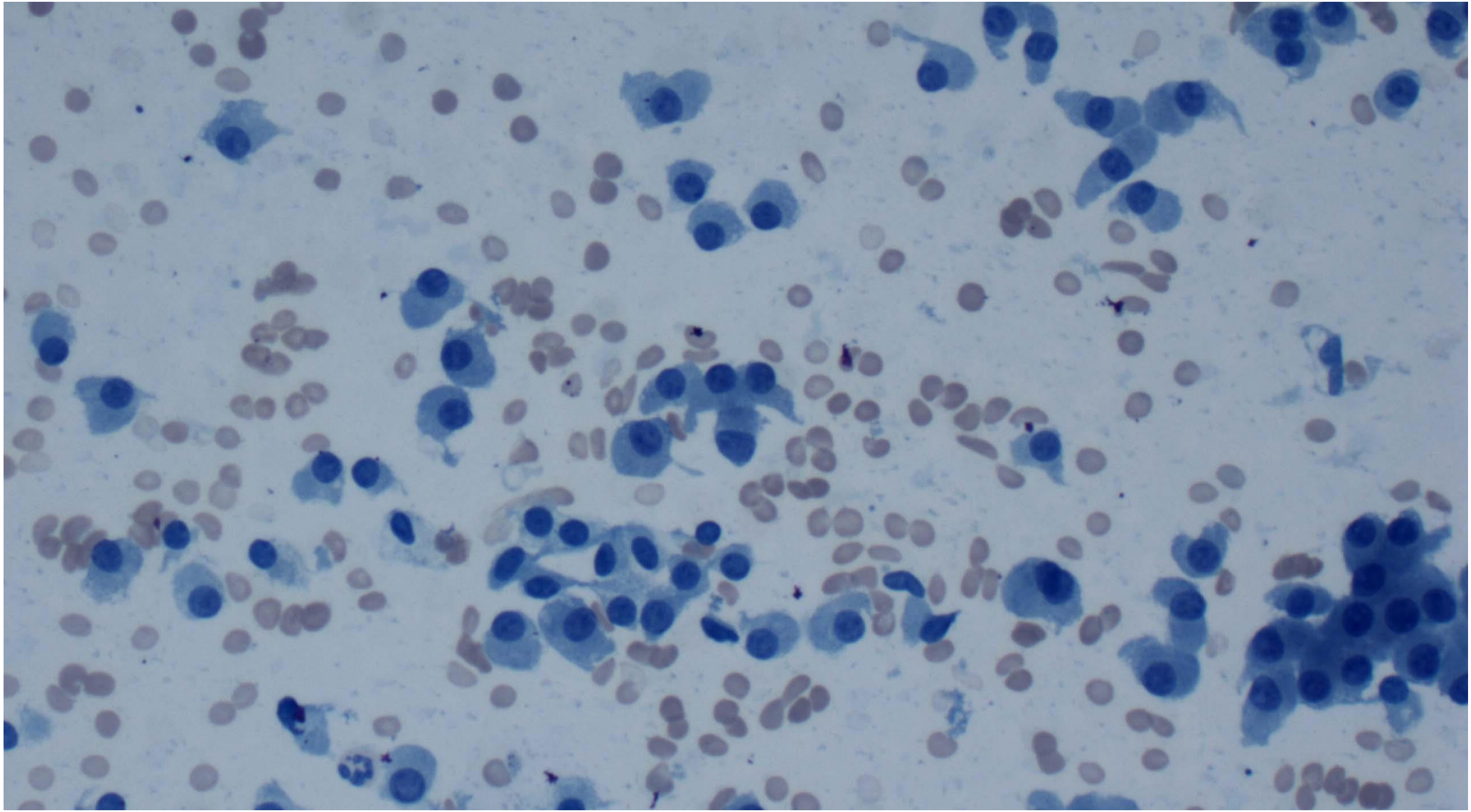






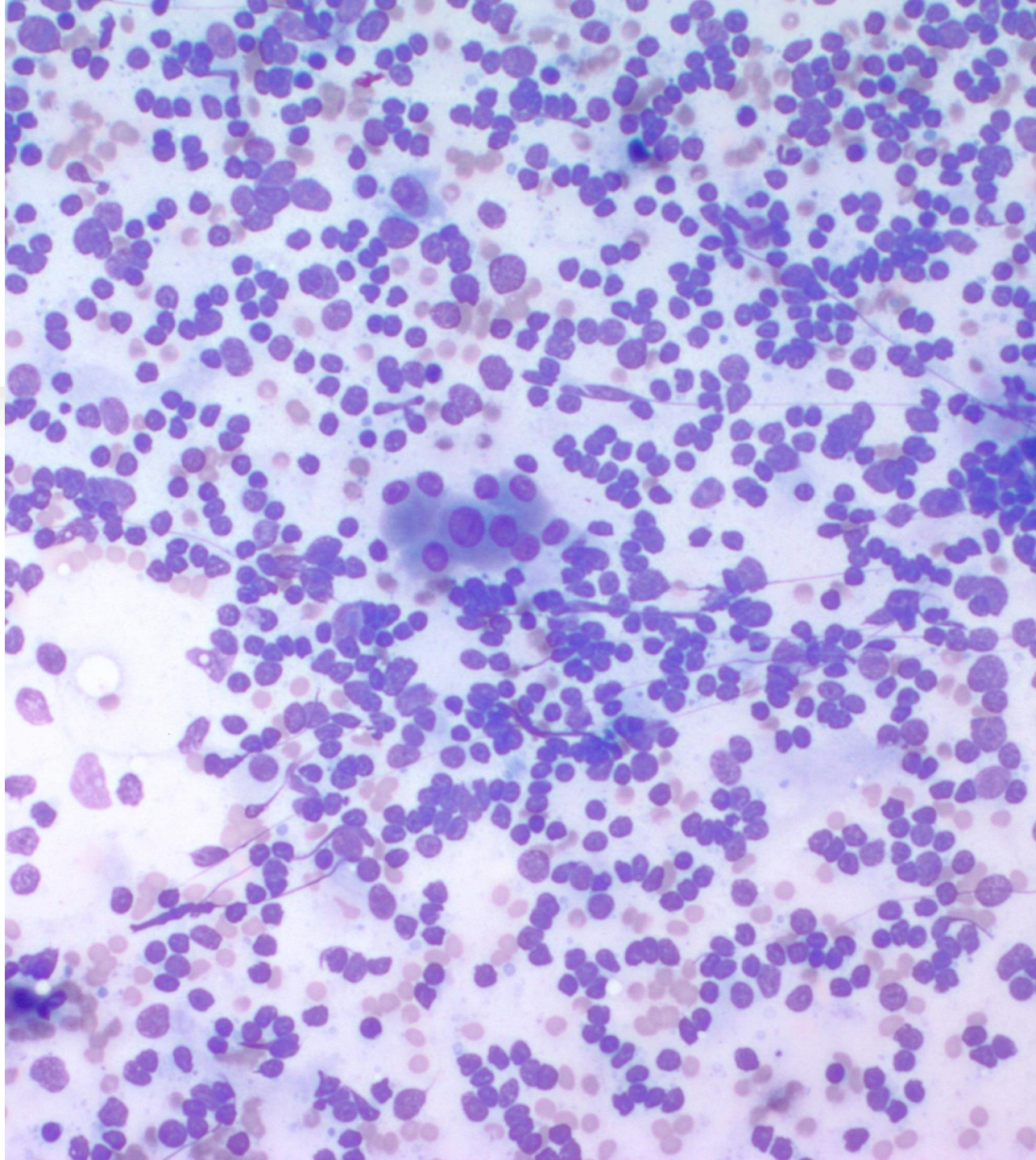






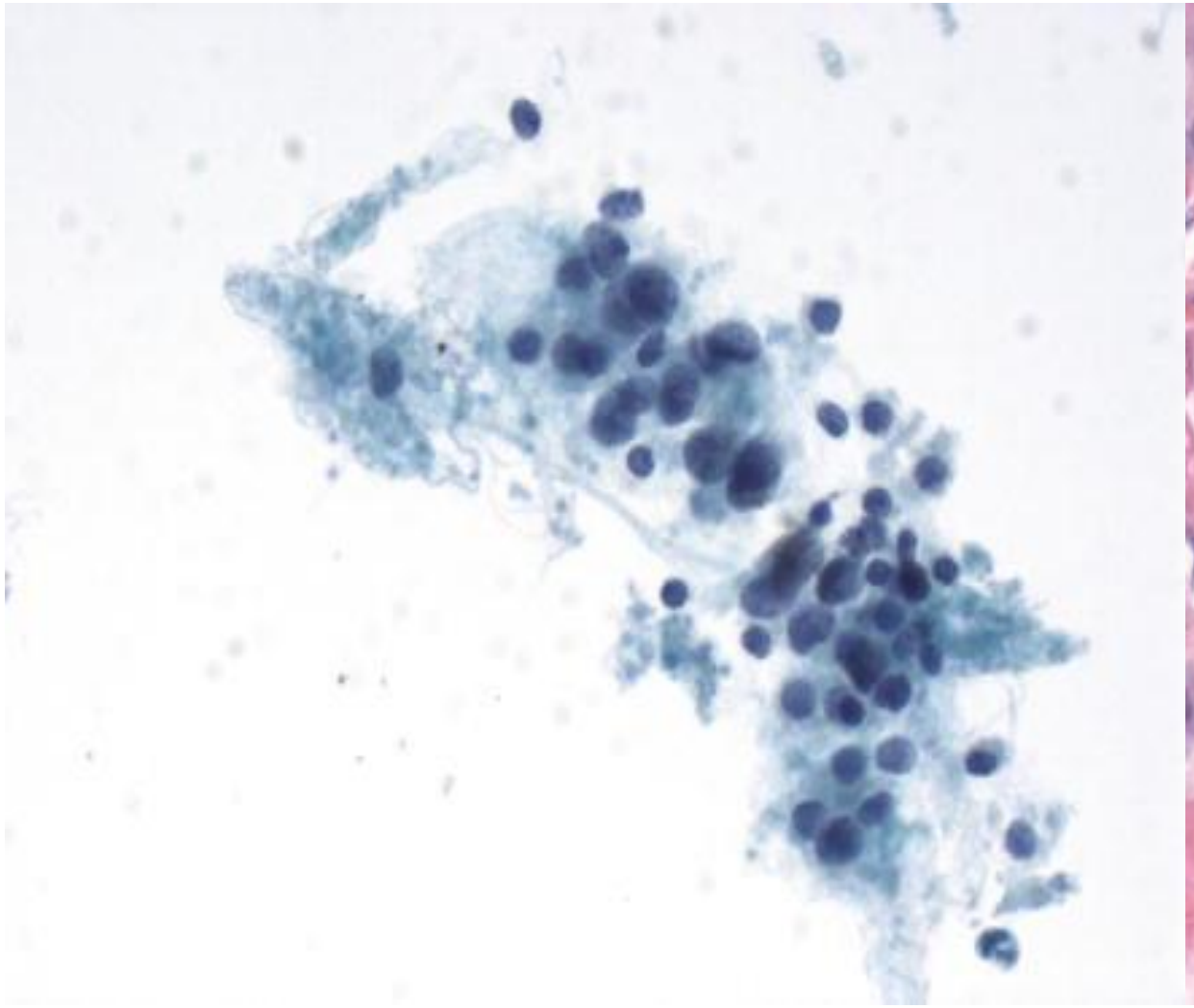
Hashimoto thyroiditis

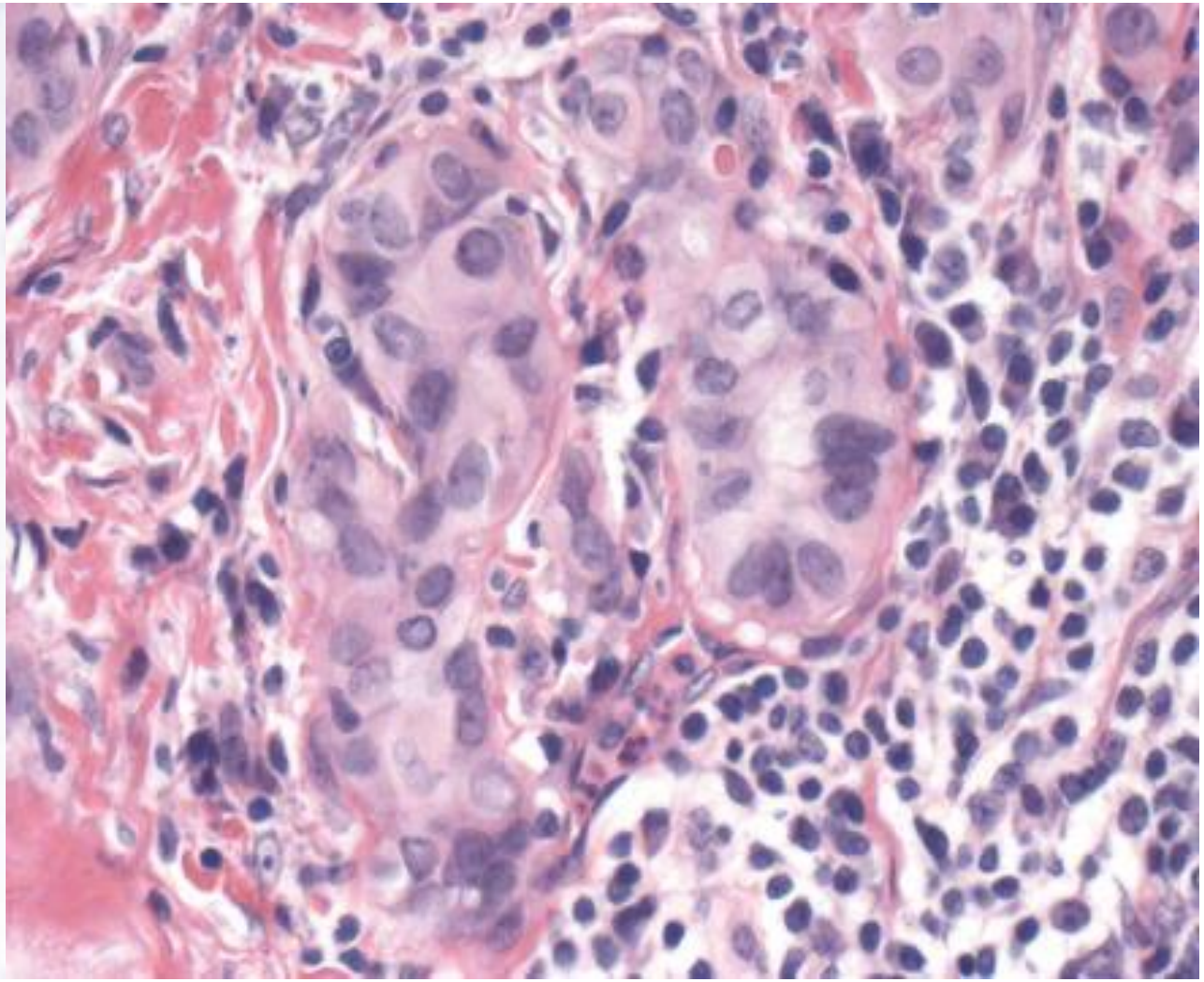
- In florid cases with atrophy of follicular cells, lymphocytes predominate
- Follicles with germinal centers mimic intrathyroidal lymph node
- Can also lead to a misdiagnosis of malignant lymphoma
- Flow cytometry important

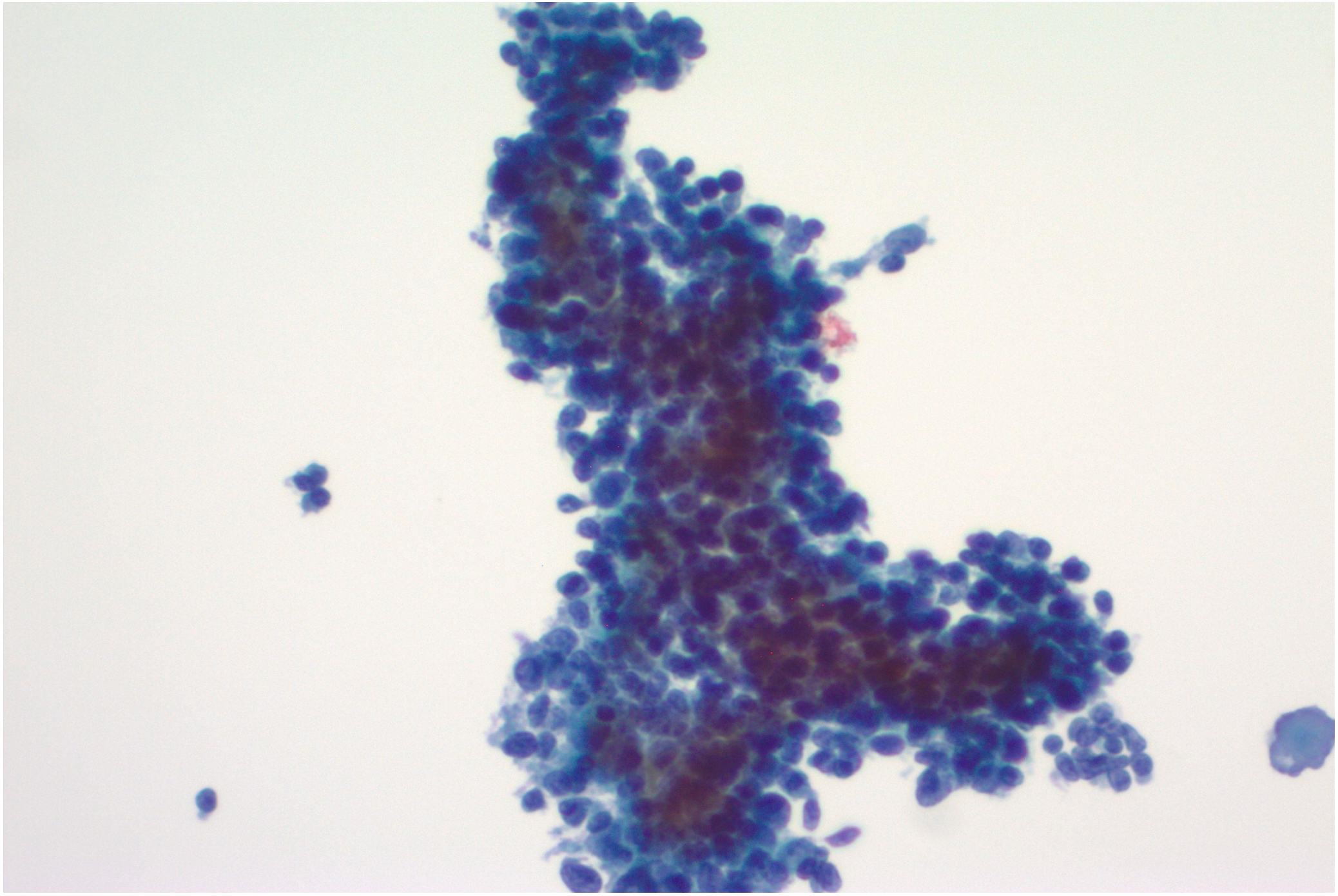


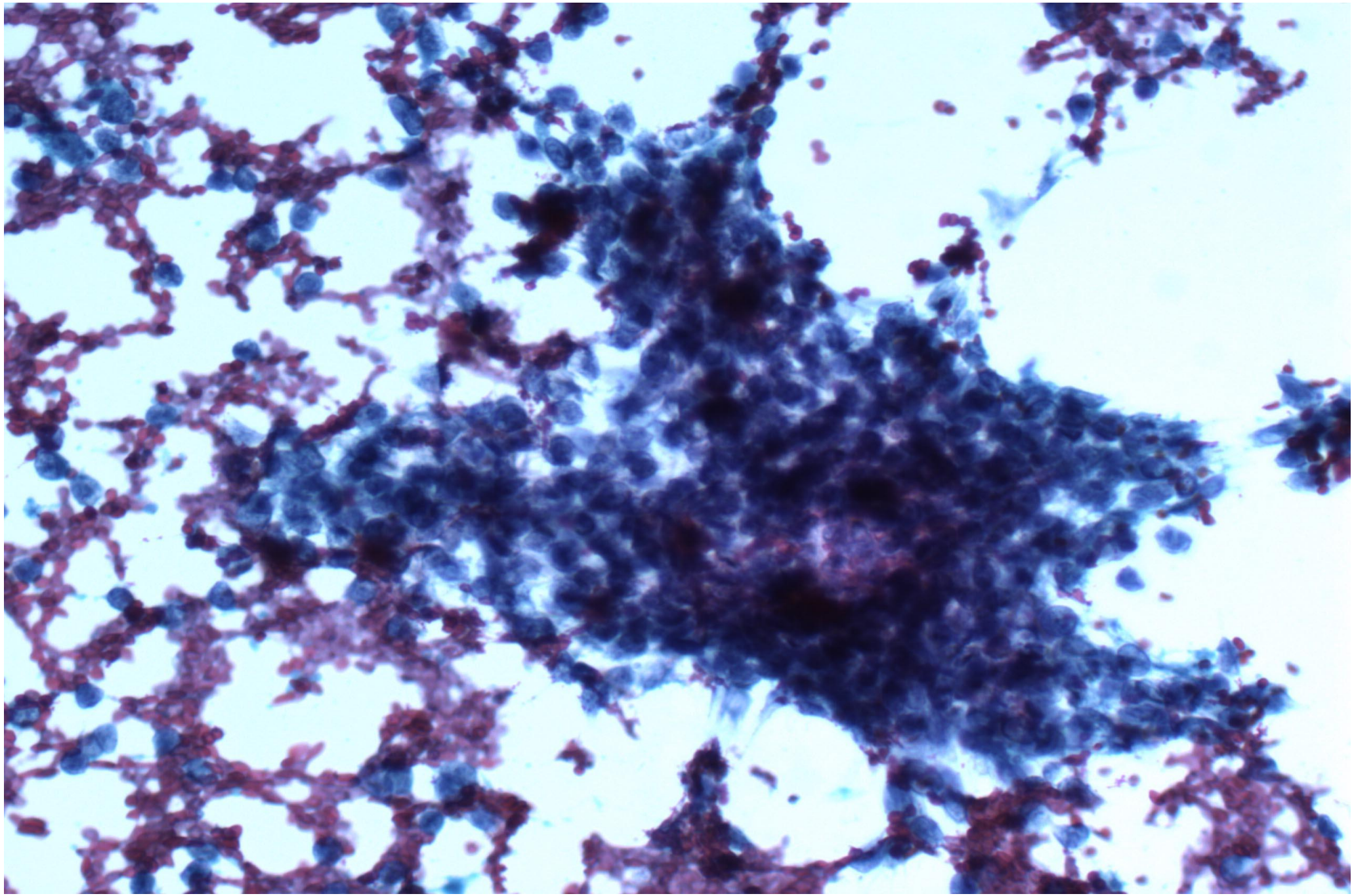
Lymphocyte-rich lesions of the thyroid

- Hashimoto thyroiditis
  - May be confused with subacute thyroiditis when occasional multinucleated giant cells present
  - Syncytial tissue fragments of follicular epithelium with papillary-like architecture can be confused with PTC
  - Hurthle cells can exhibit nuclear enlargement, grooves and chromatin clearing, suggesting PTC



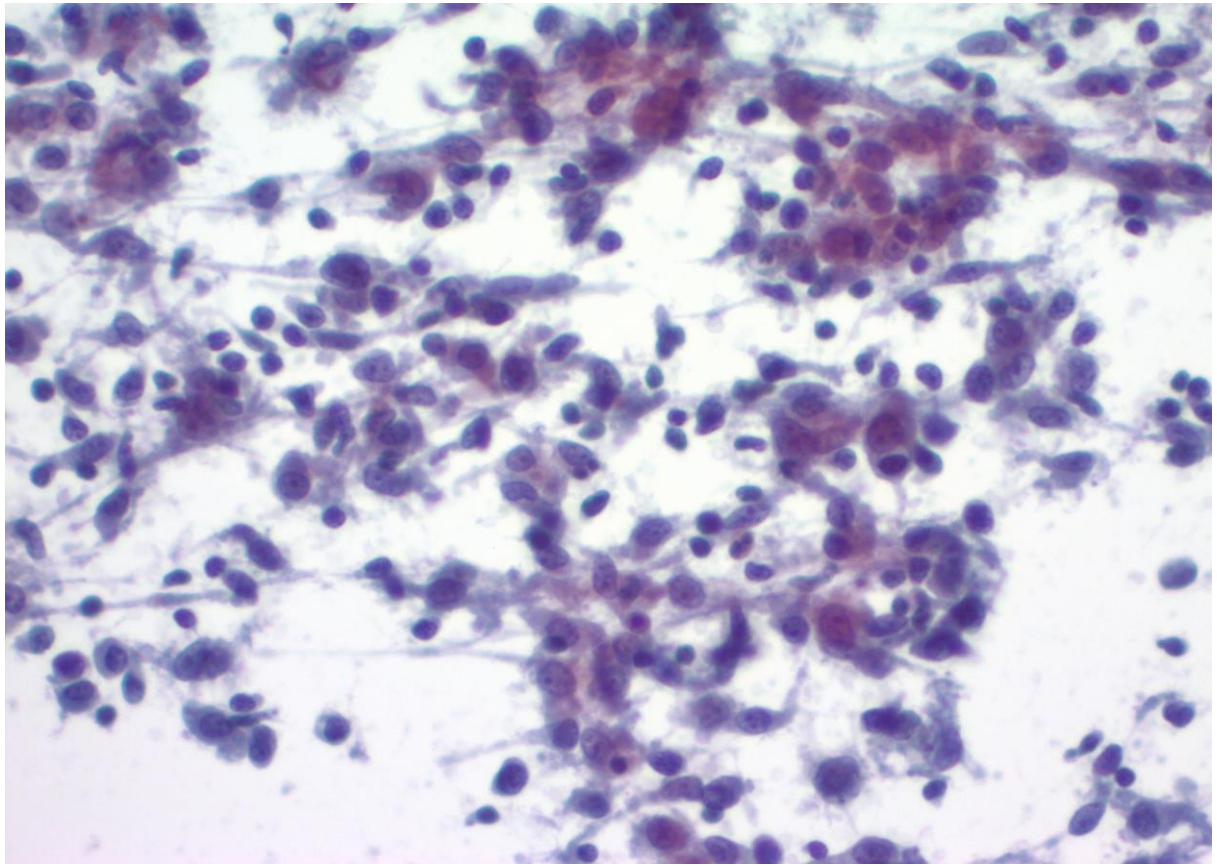


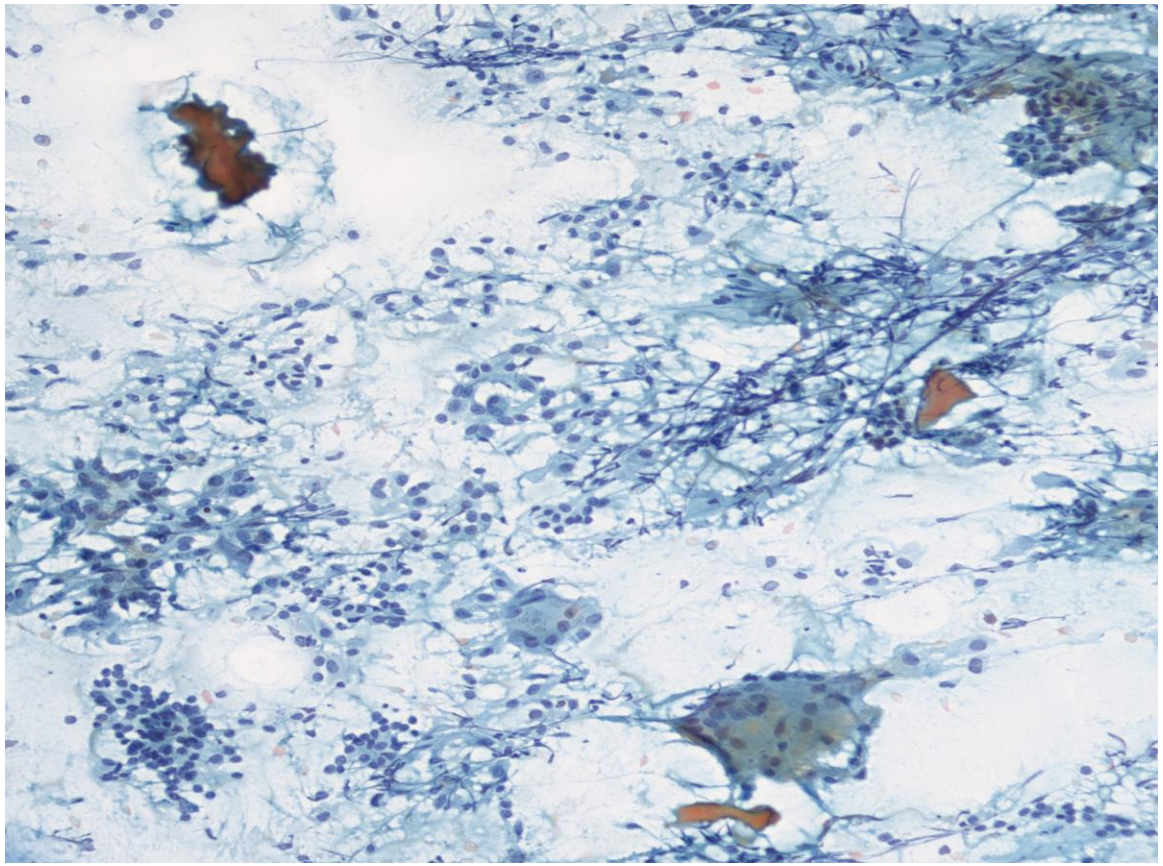




Lymphocyte-rich lesions of the thyroid

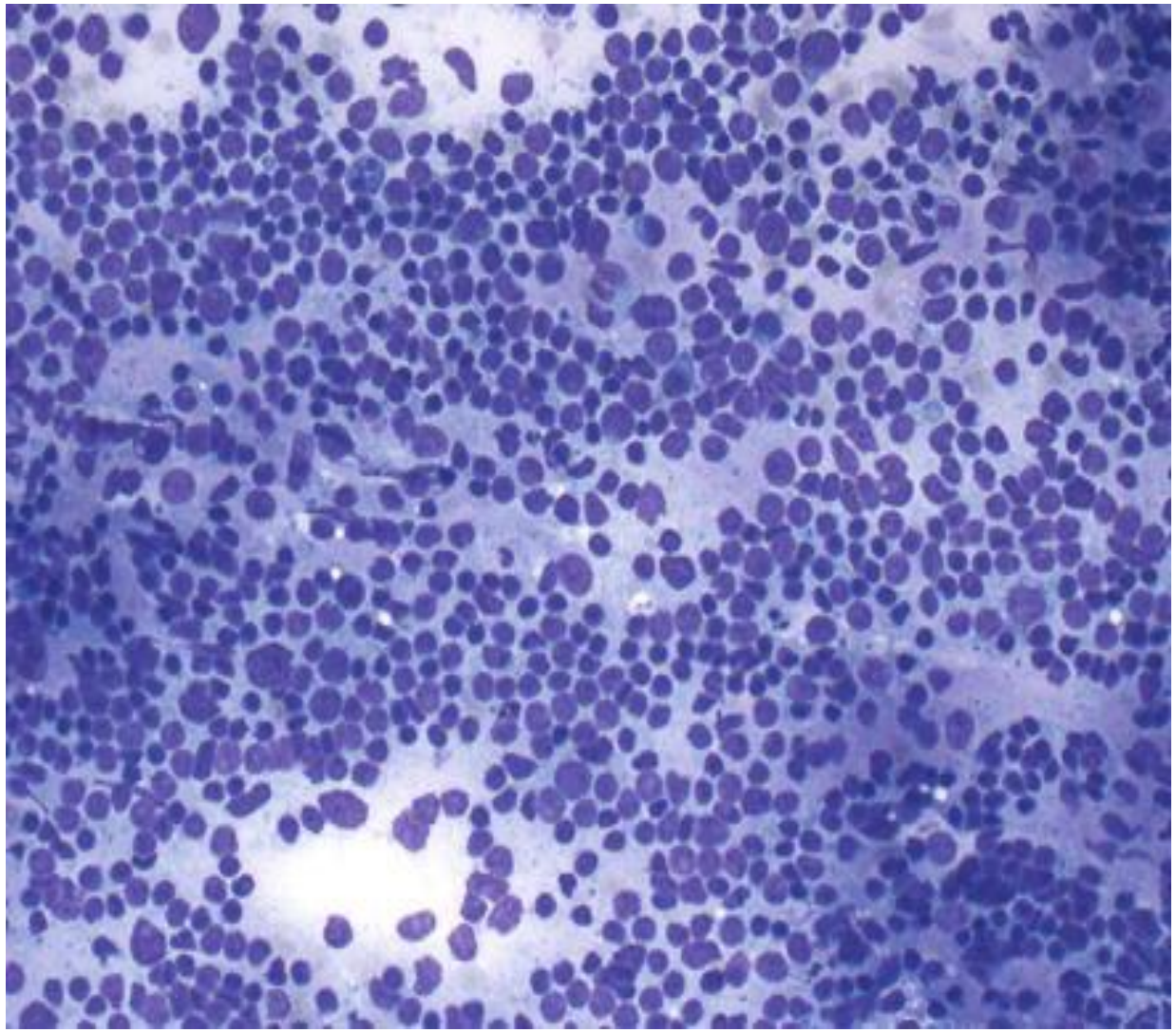
- Granulomatous thyroiditis
  - Variable cytologic features, depending on disease stage
  - Initial stage has features of acute thyroiditis
  - Later stages show hypocellularity with giant cells, epithelioid cells, lymphocytes, macrophages and scant degenerated follicular cells
  - May have only giant cells and can be confused with granulomatous conditions such as sarcoidosis
  - Predominant inflammatory cells can be confused with final stages of Hashimoto thyroiditis

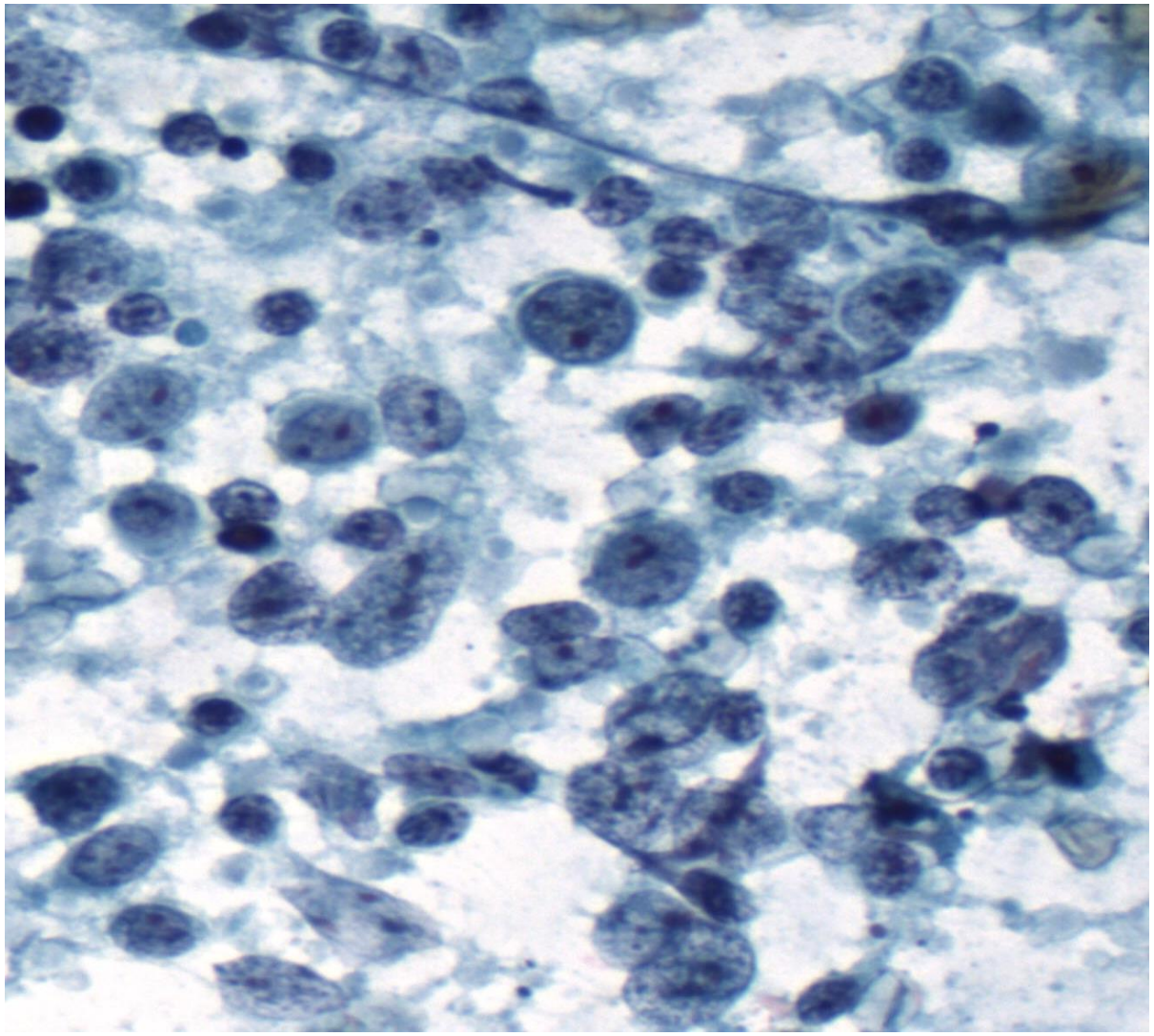




Lymphocyte-rich lesions of the thyroid

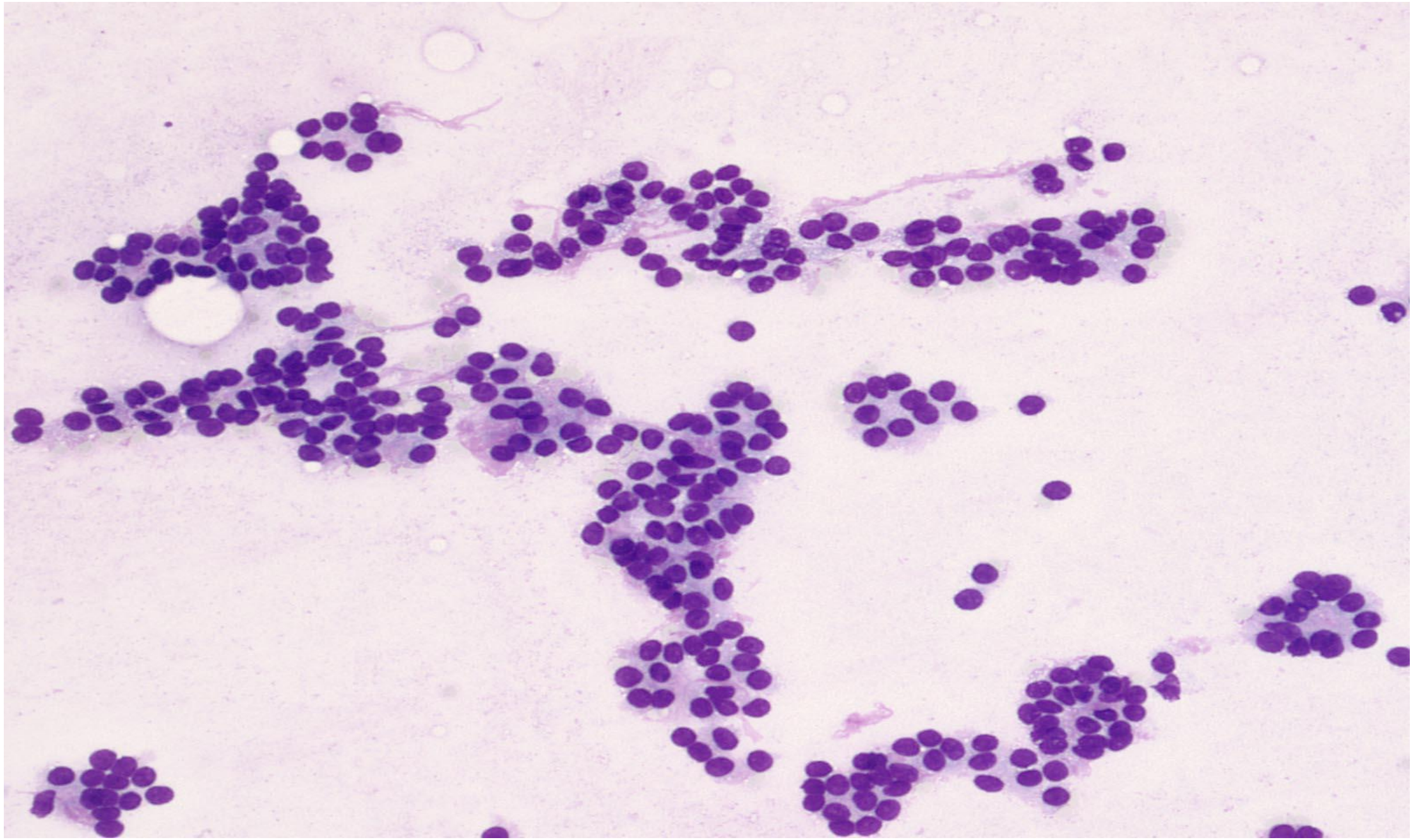
- Lymphomas
  - Almost always arise in a background of Hashimoto thyroiditis and of B-cell lineage
  - Primary lymphomas mainly of 2 types:
    - Diffuse large B-cell lymphoma
    - Extra-nodal marginal zone B-cell lymphoma
  - Cytologic diagnosis challenging for low grade lymphomas arising in the background of Hashimoto thyroiditis

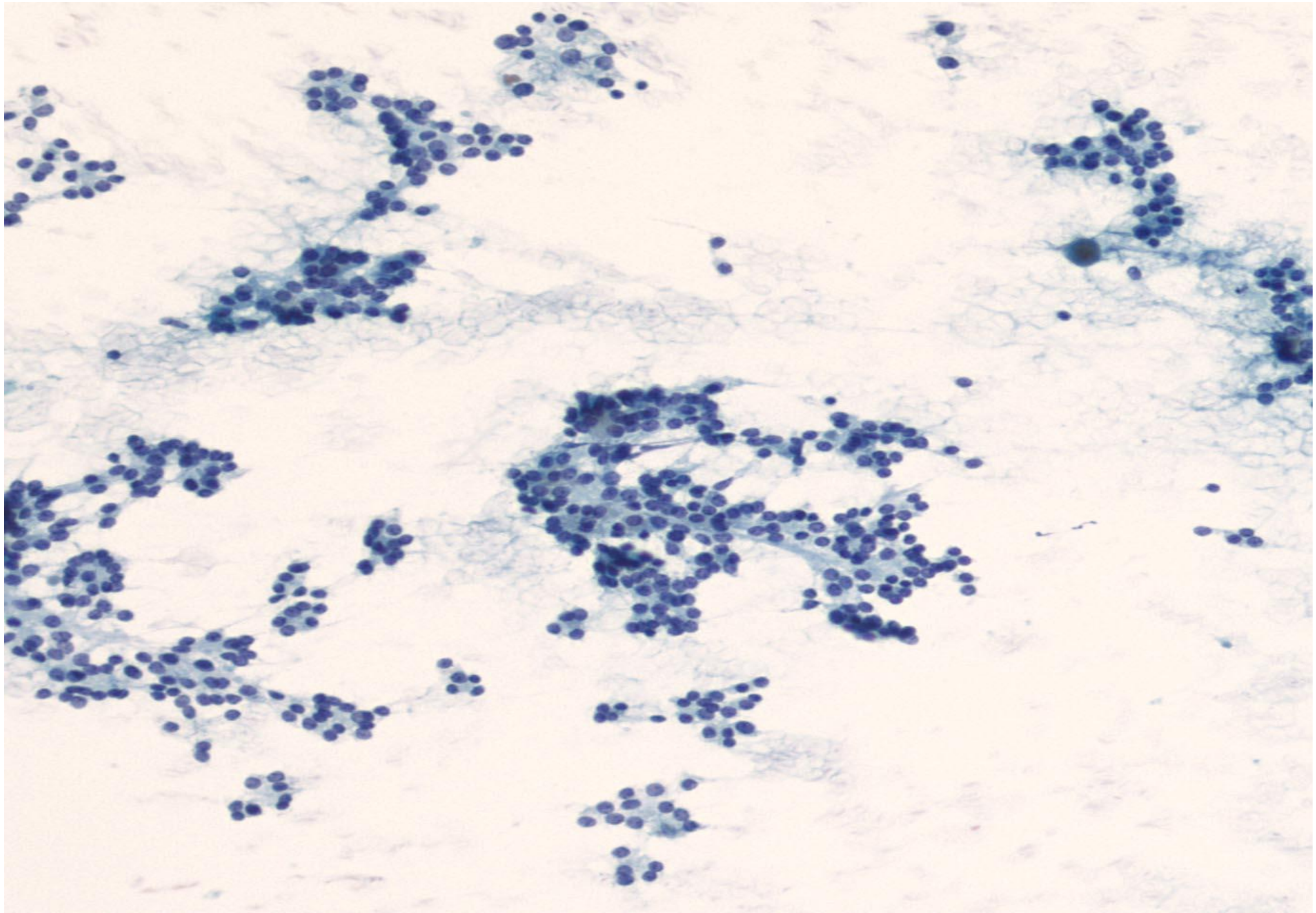


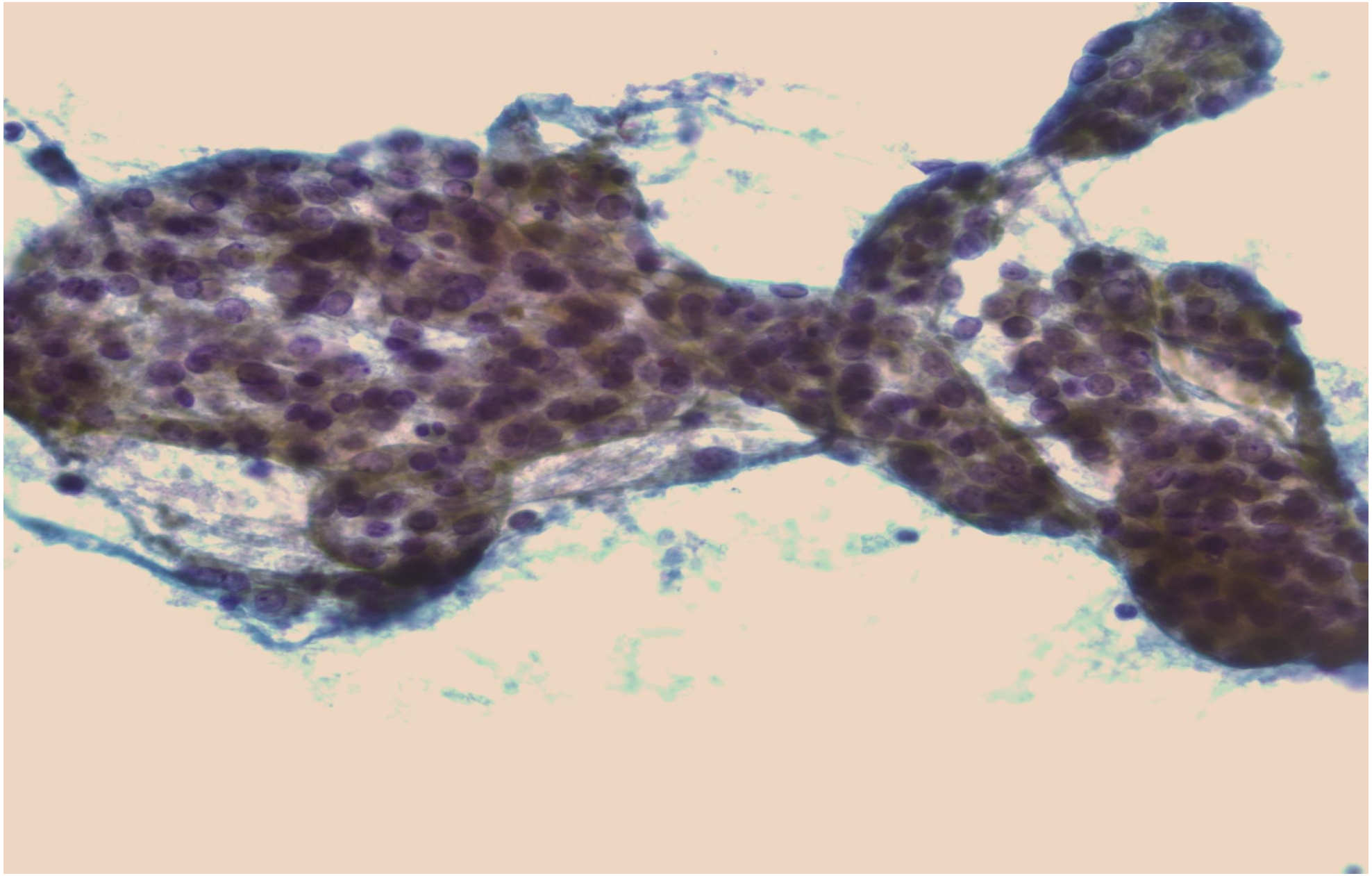


Follicular neoplasm with atypia

- Follicular variant of PTC
  - Infiltrative FVPTC
  - Encapsulated FVPTC
  - Noninvasive encapsulated FVPTC
    - Indolent biologic behavior, similar to follicular adenomas
    - Now known as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)







Follicular neoplasm with atypia

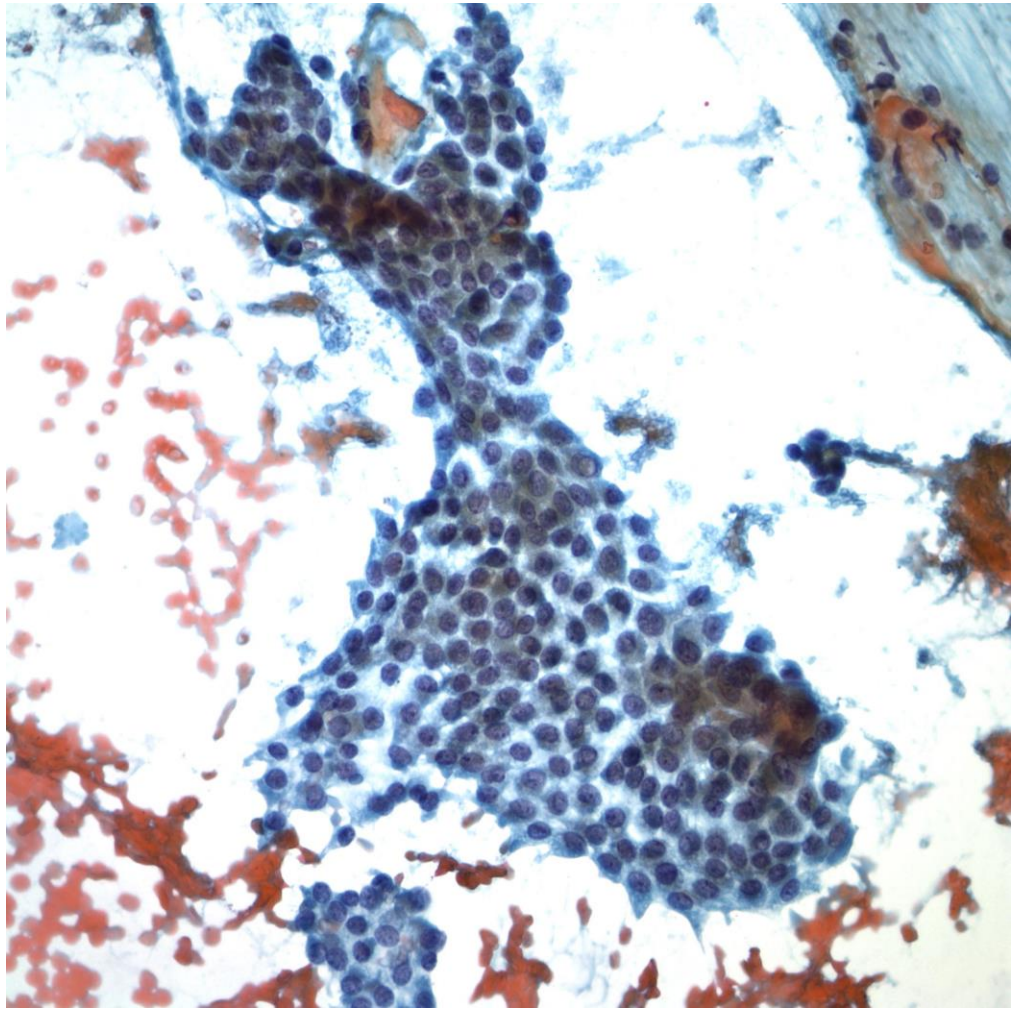
- Distinction among the 3 subtypes not possible by FNA
- To avoid diagnostic pitfall of interpreting NIFTP as PTC by FNA, follicular patterned lesions lacking papillary structures should not be diagnosed as malignant

Papillary thyroid carcinoma

- PTC has true papillary architecture but a number of variants have no papillary architecture
- Some of the variants have tendency towards more aggressive clinical behavior, hence recognition is important
- Smears typically show papillary structures, sheets, loosely cohesive groups, or syncytial fragments
- Variable cellularity

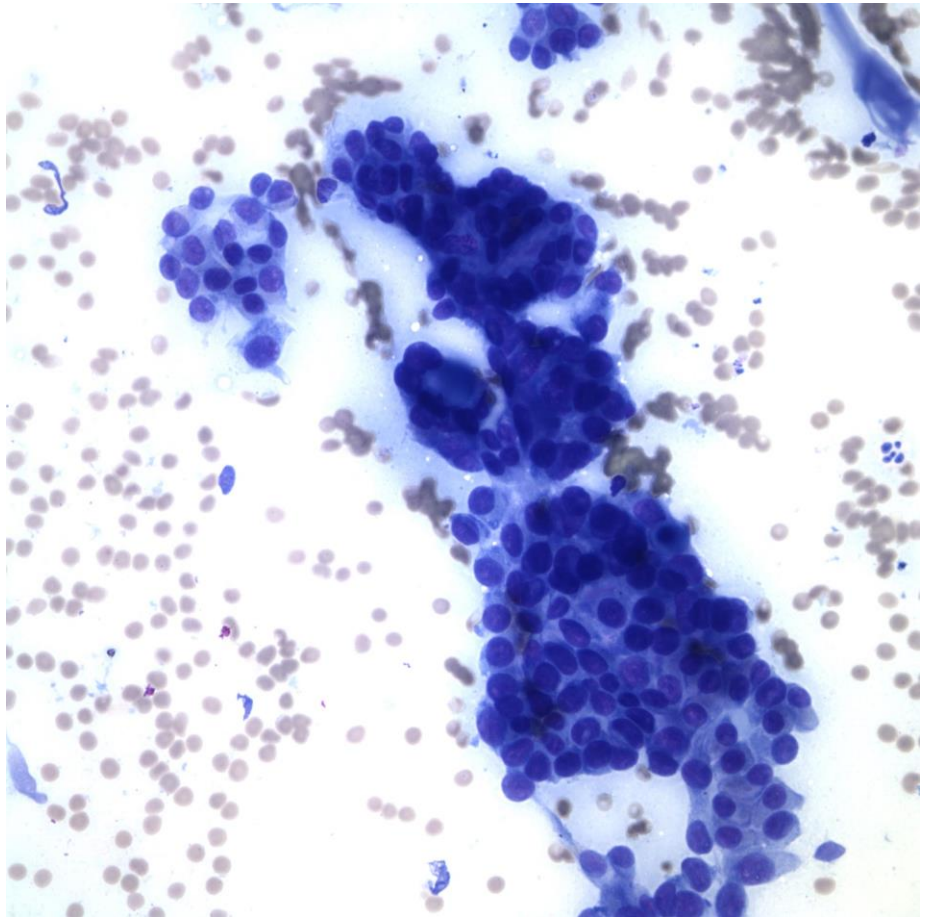
Papillary thyroid carcinoma

- Nuclear crowding/overlapping
- Hallmark feature: presence of nuclear features – enlargement, elongation, grooves, membrane irregularity, powdery chromatin, nuclear inclusions, nucleoli



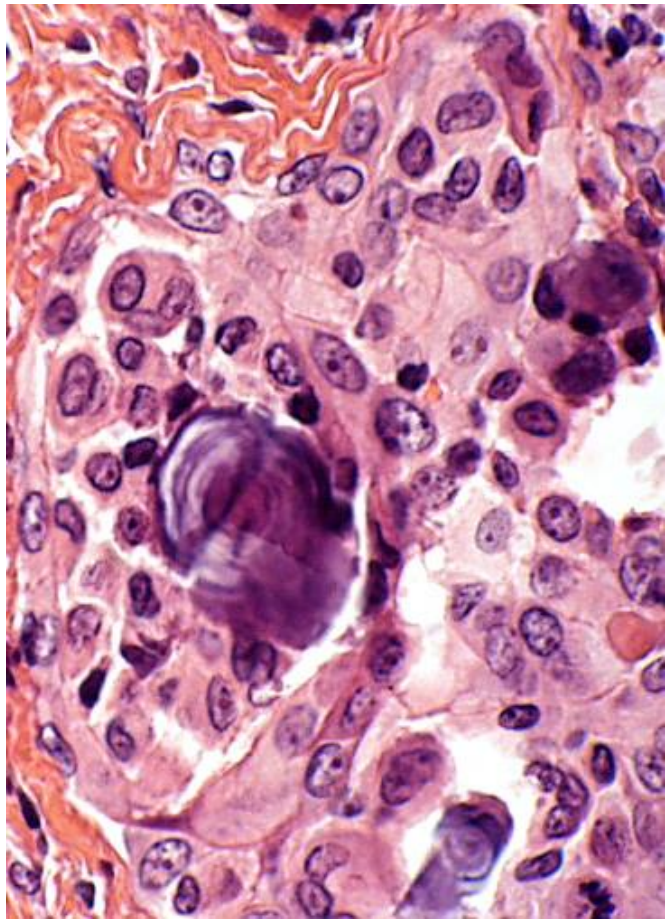
Papillary thyroid carcinoma

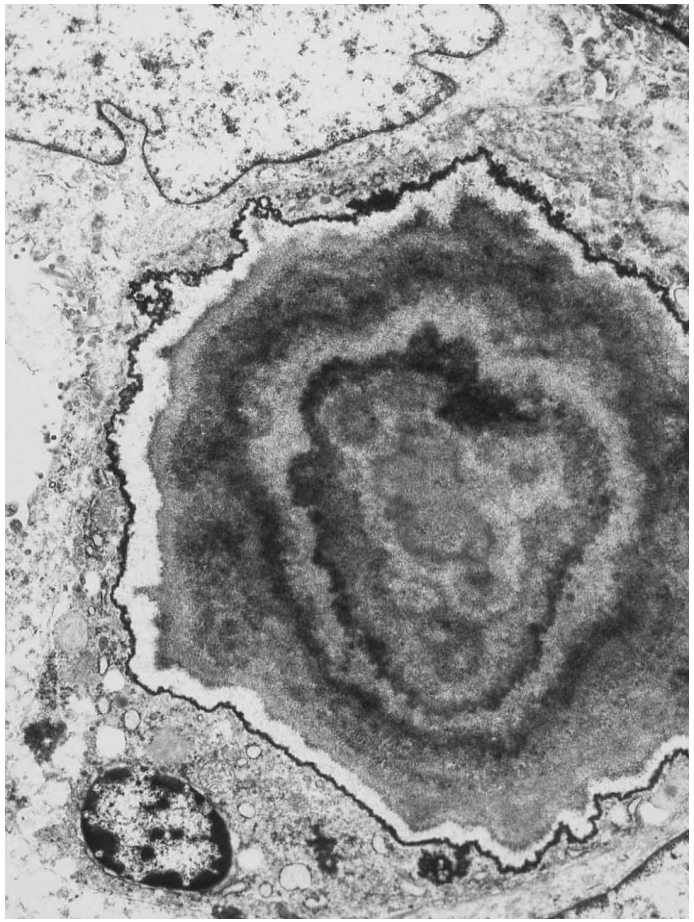
- Variable cytoplasm – from scant in classic PTC to abundant, squamoid, vacuolated or Hurthle-like in other variants
- Concentric laminated calcifications
- Multinucleated foreign body-type giant cells



Papillary thyroid carcinoma

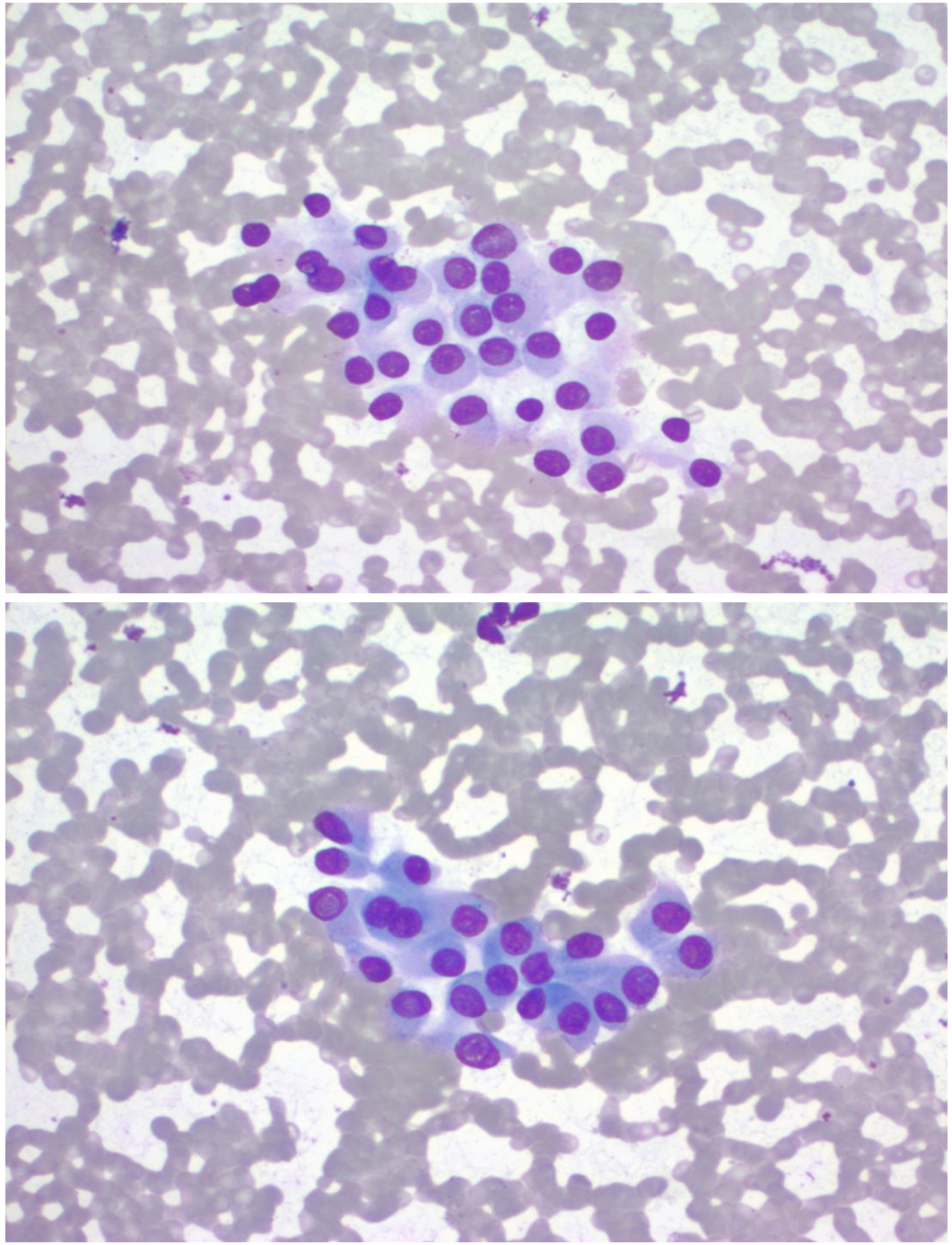
- Psammoma bodies must be distinguished from nonspecific, dystrophic calcifications





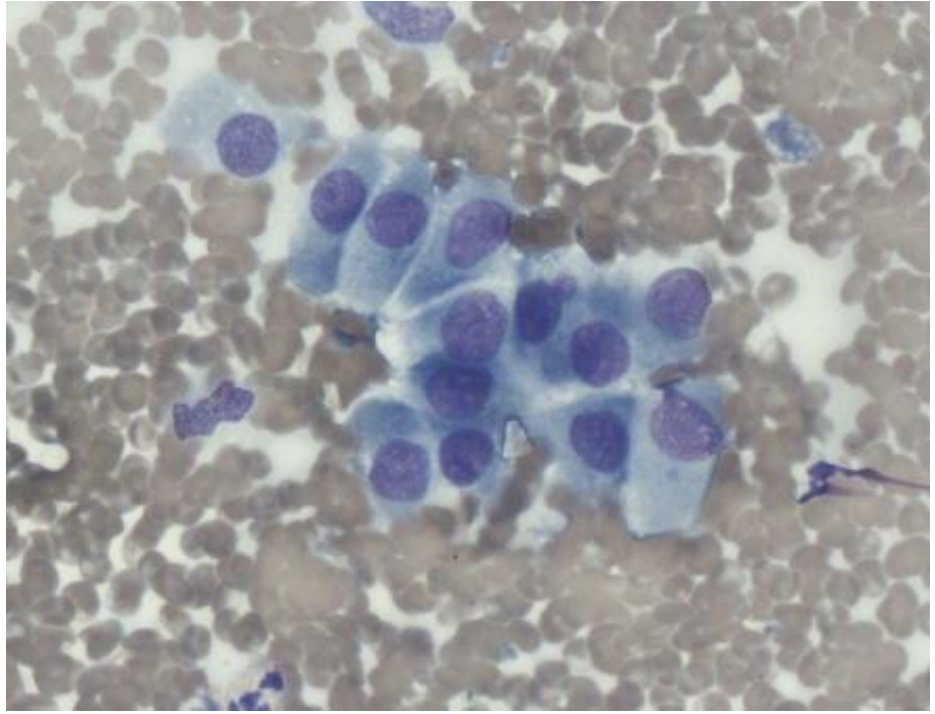
Papillary thyroid carcinoma

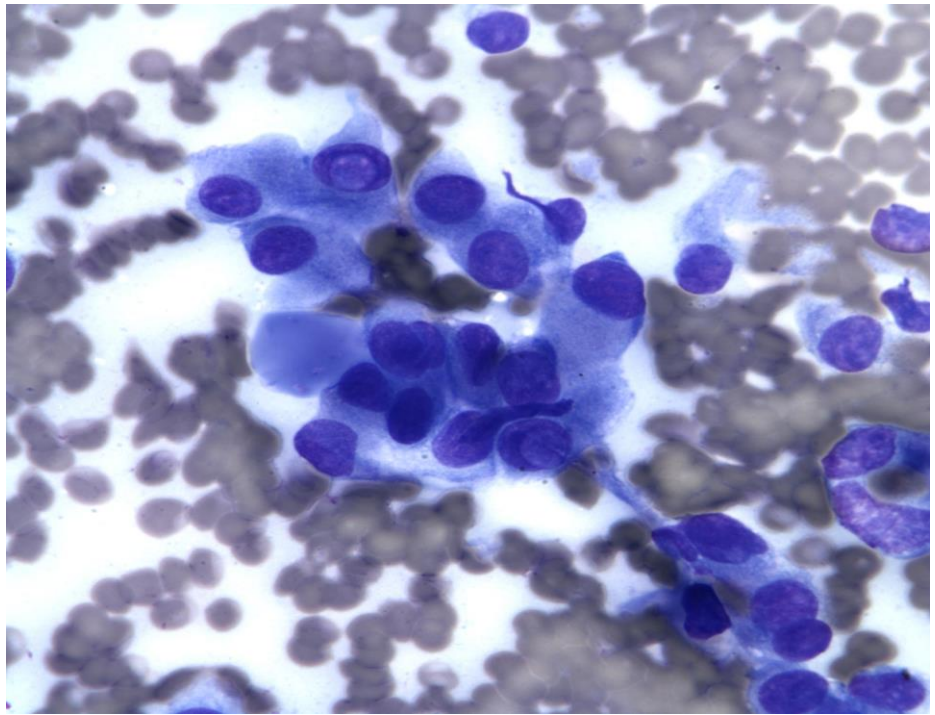
- Presence of conventional nuclear features helps to distinguish oncocytic variant of PTC from Hurthle cell neoplasm



Tall cell variant

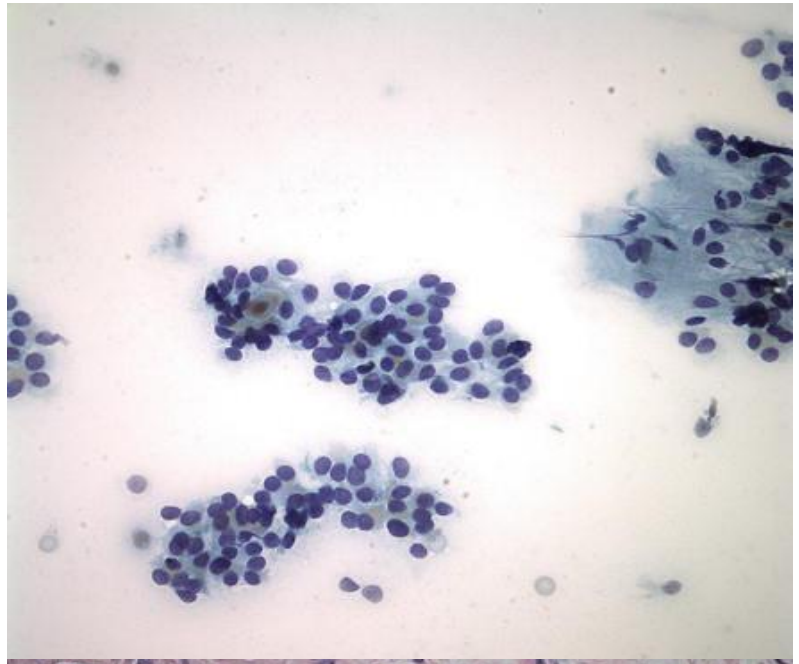
- Tall cell variant seen as large polygonal cells with abundant, eosinophilic cytoplasm, thereby resembling Hurthle cells

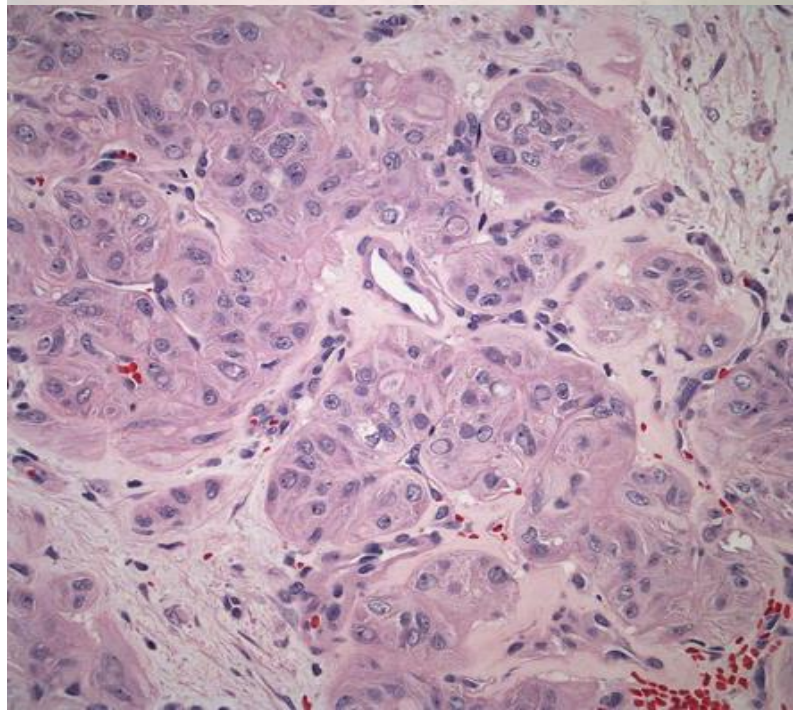




Papillary thyroid carcinoma

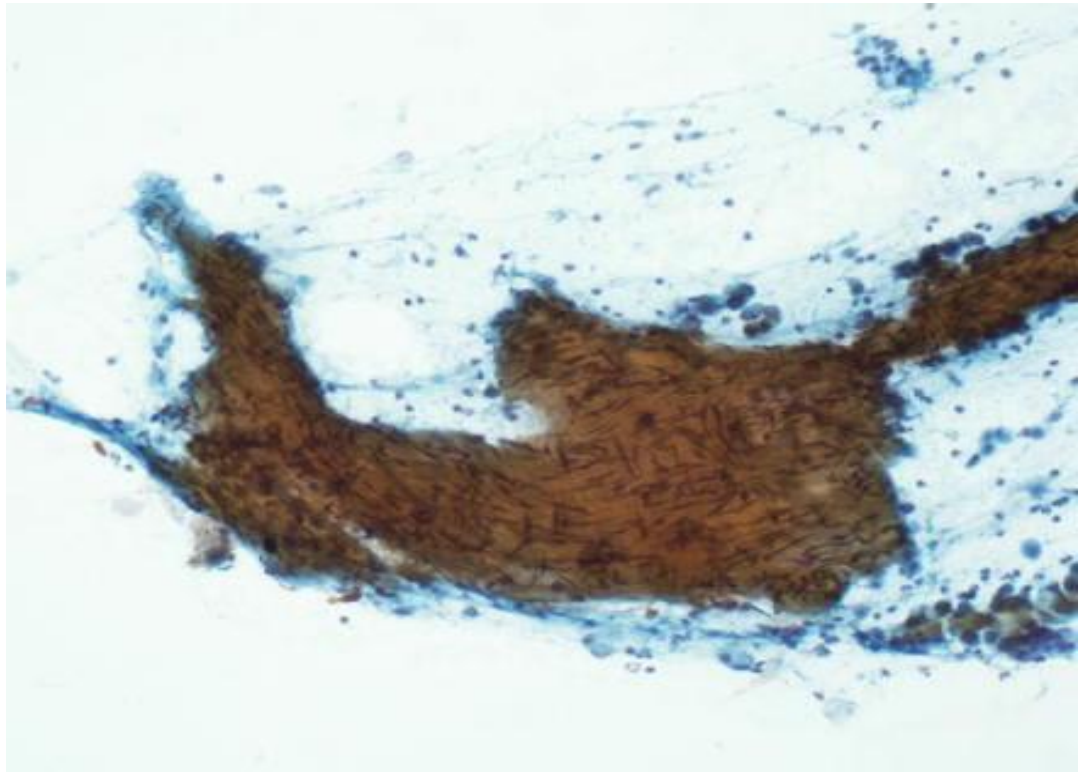
- Intranuclear pseudoinclusions are found in several other benign and malignant entities, most notably hyalinizing trabecular tumor
  - HTT – trabecular growth, stromal hyalinization, absence of papillae, elongated cells, acellular hyaline material, cytoplasmic positivity for MIB-1, lack of $BRAF^{V600E}$ mutation
- Longitudinal nuclear grooves can also be seen in oncocytic neoplasms and NIFTP
- Occasional cases can have abundant colloid, so can be misrepresented as benign thyroid nodule

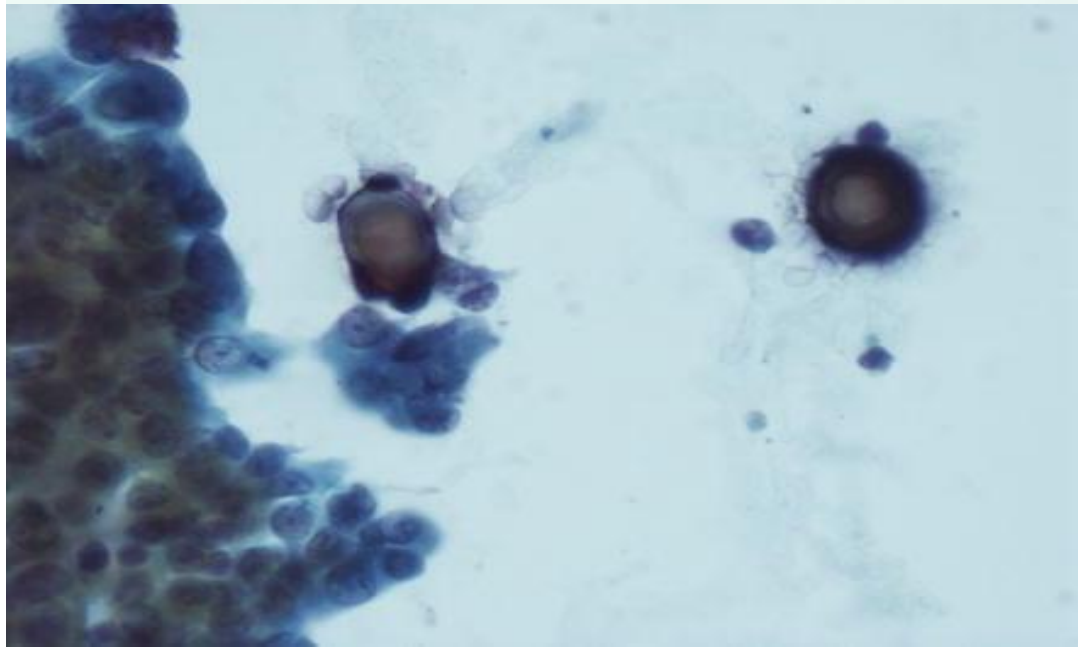




Diffuse sclerosing variant

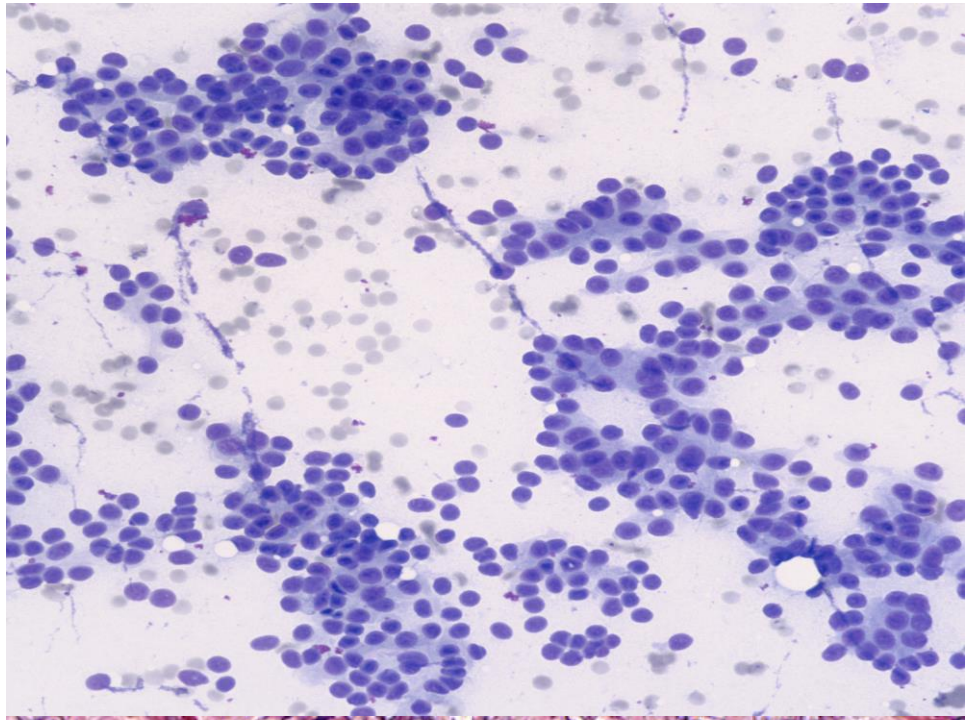
- Presence of marked lymphocytic infiltrate in diffuse sclerosing variant can obscure the neoplastic follicular cells, mimicking thyroiditis

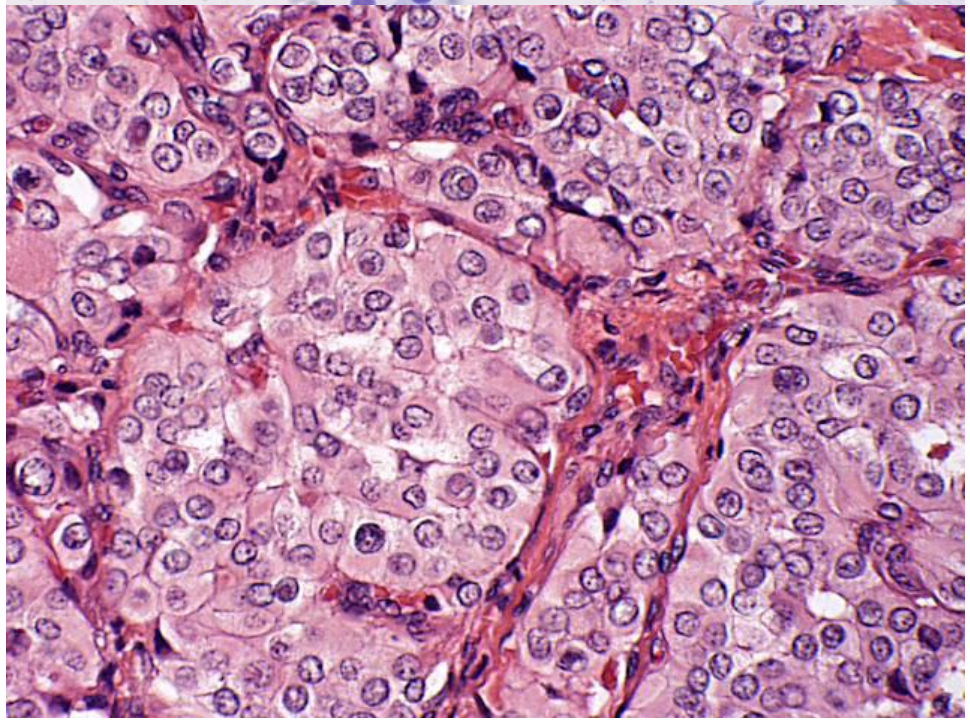




Solid variant

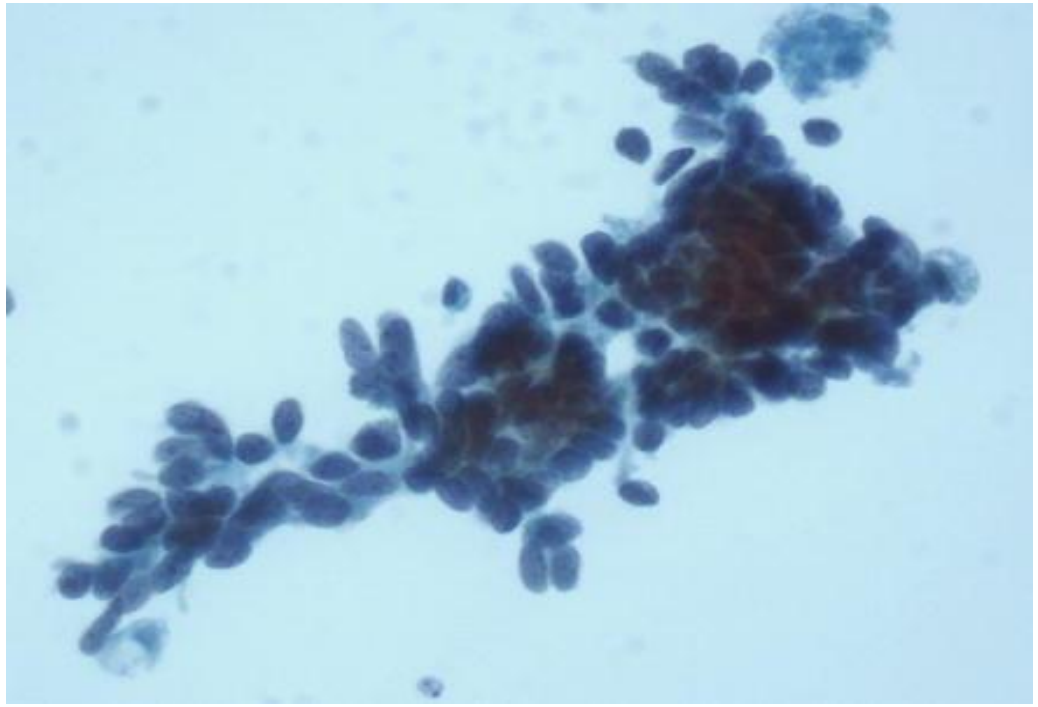
- Papillary structures not present in solid variant, may lead to misdiagnosis as poorly differentiated carcinoma
- The finding of nuclear features of PTC and the absence of tumor necrosis favor the diagnosis

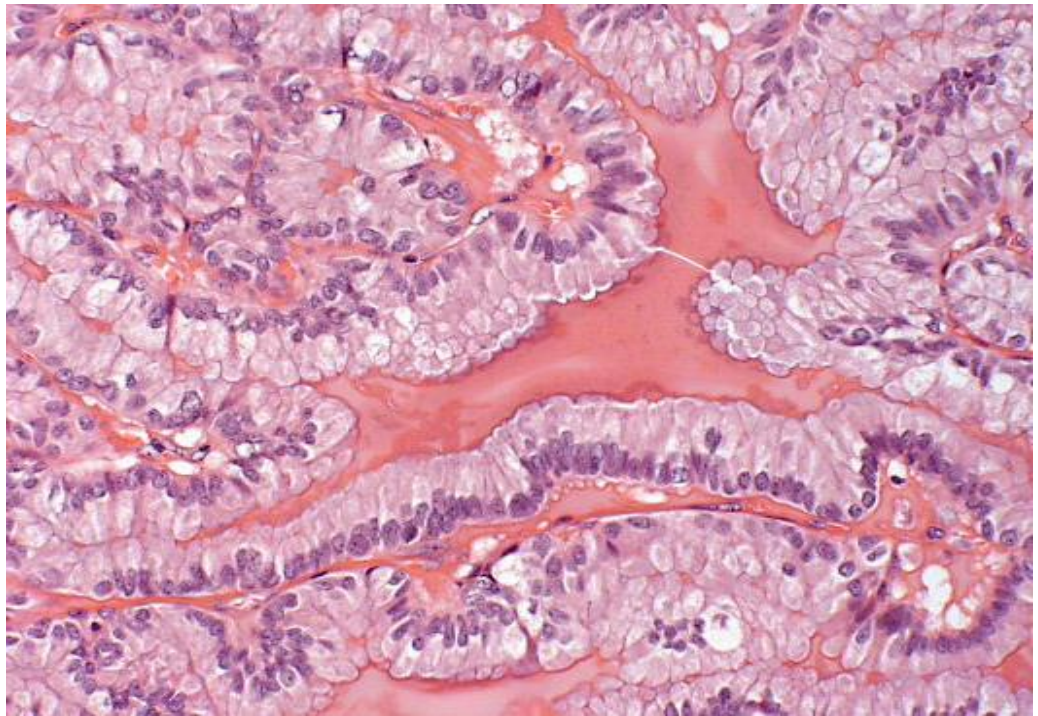




Columnar variant

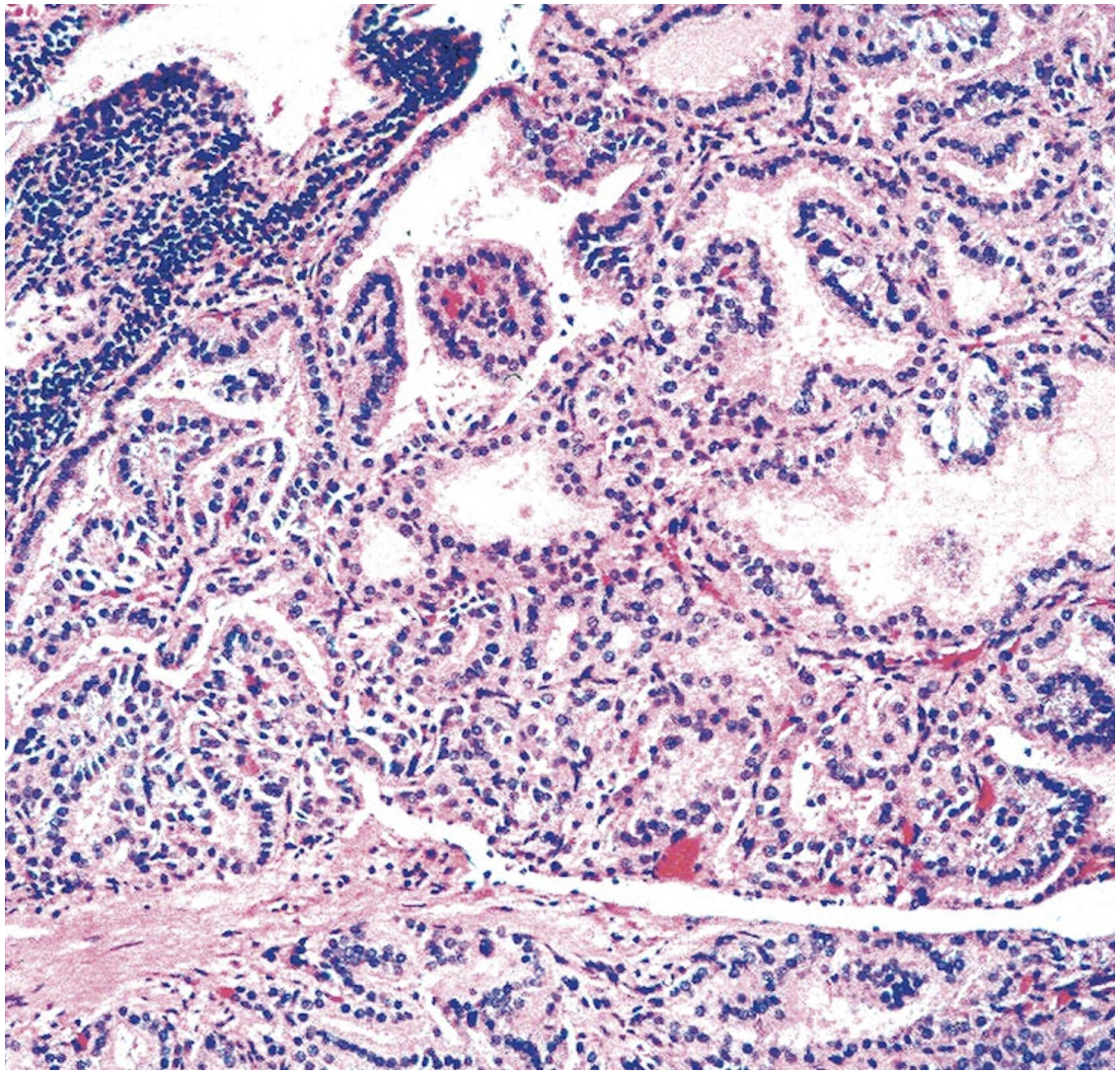
- Nuclei in columnar variant do not demonstrate the typical nuclear features, hence may be confused with metastatic adenocarcinoma





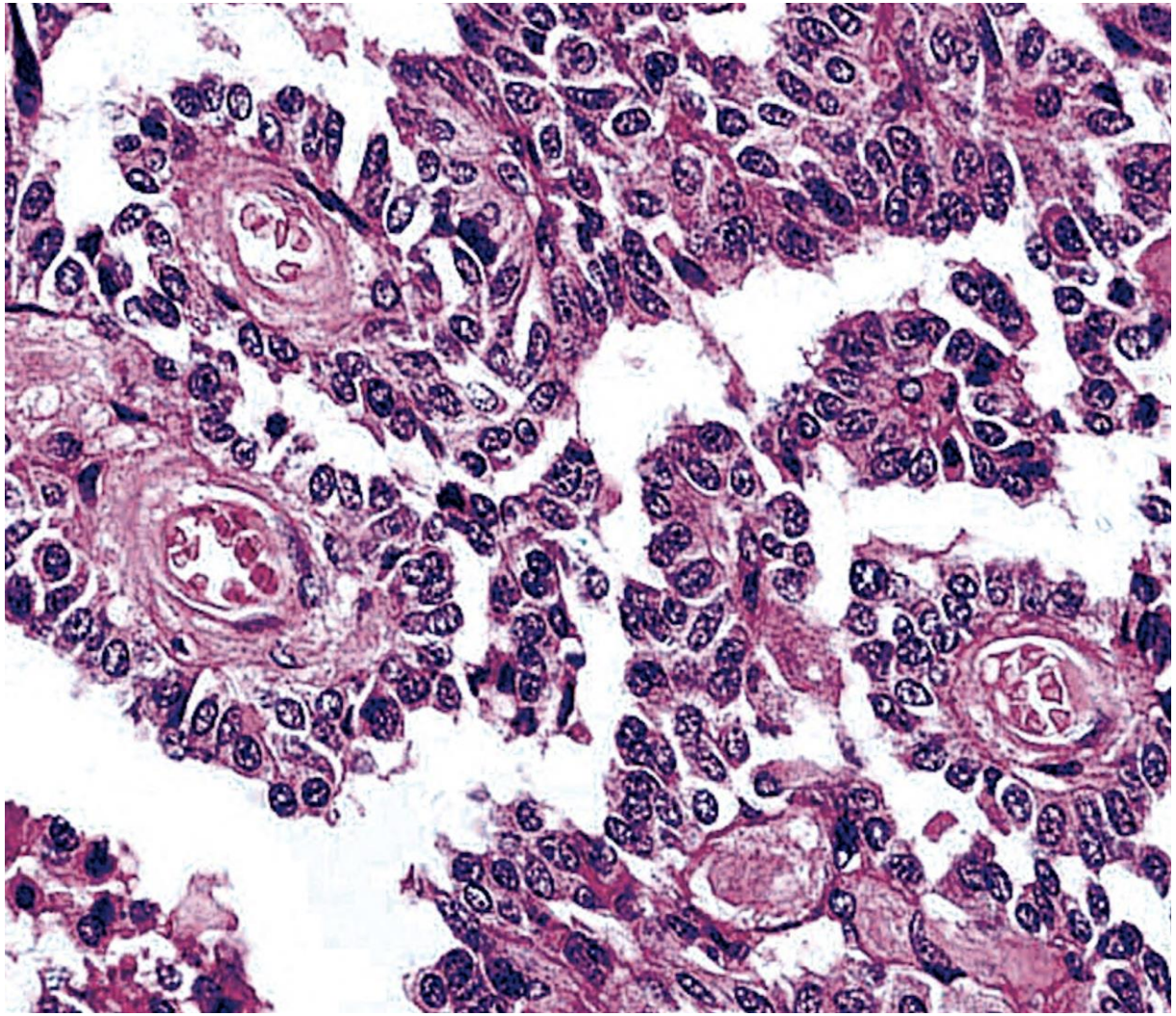
Papillary foci of Grave's disease

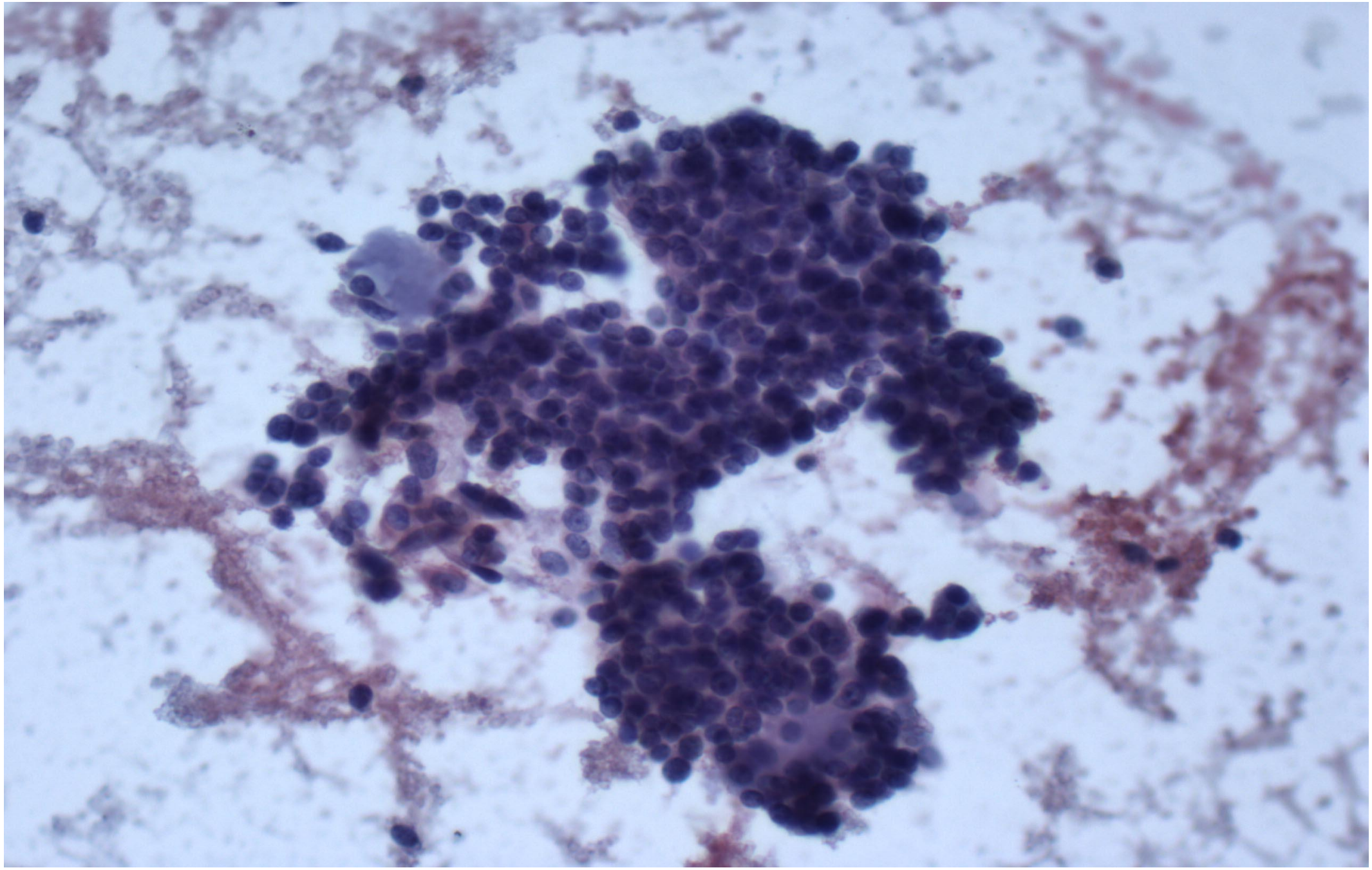
- May have abundant papillary infoldings
- Cytoplasm may be tall or columnar
- Nuclei are small and round and lack nuclear clearing



Medullary thyroid carcinoma, pseudopapillary variant

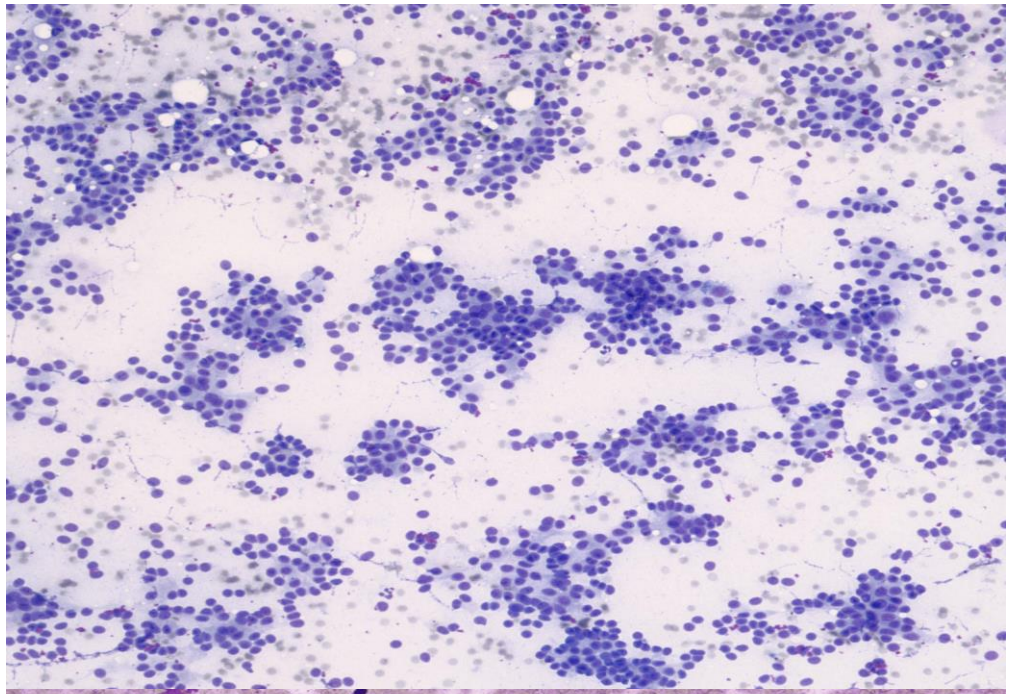
- May occasionally contain true papillary architecture
- Tumor cells show nuclear features of neuroendocrine tumors with salt and pepper nuclei
- Positive for calcitonin and neuroendocrine markers

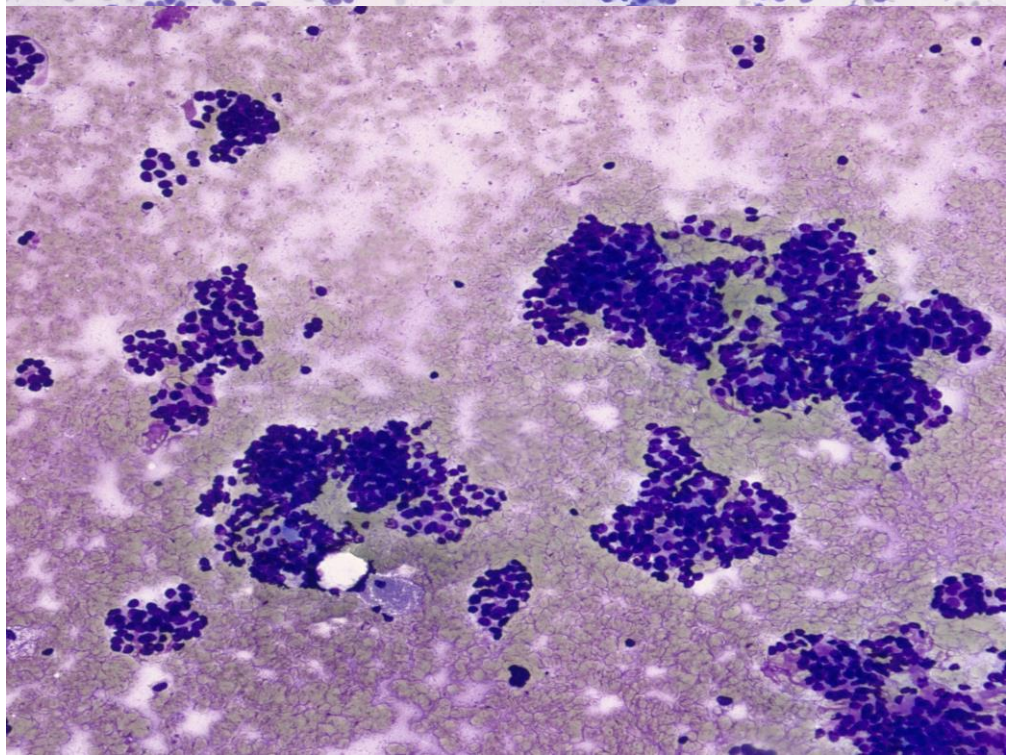




Poorly differentiated thyroid carcinoma

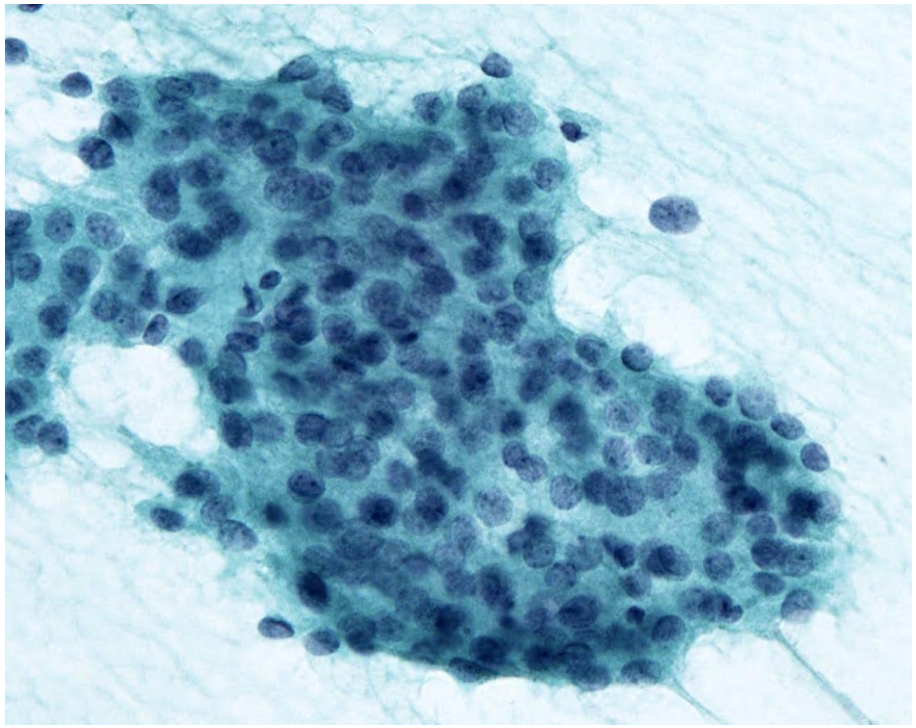
- Intermediate between well-differentiated and anaplastic thyroid carcinoma
- May arise de novo or associated with a well-differentiated thyroid carcinoma
- Highly cellular aspirate with scant colloid
- Tumor cells in loosely cohesive clusters or isolated single cells
- Microfollicular structures with or without intraluminal colloid

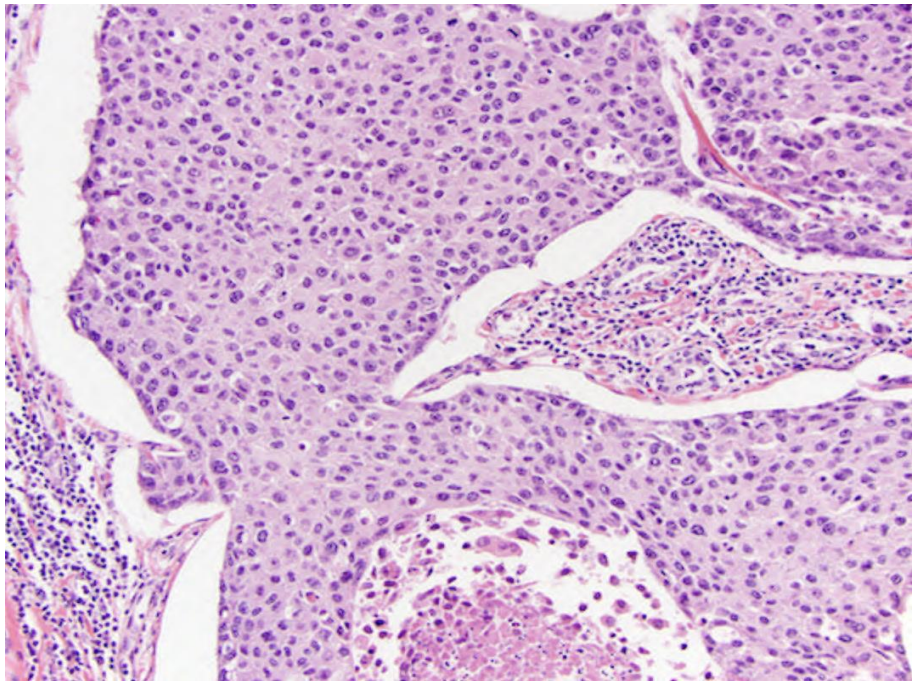




Poorly differentiated thyroid carcinoma

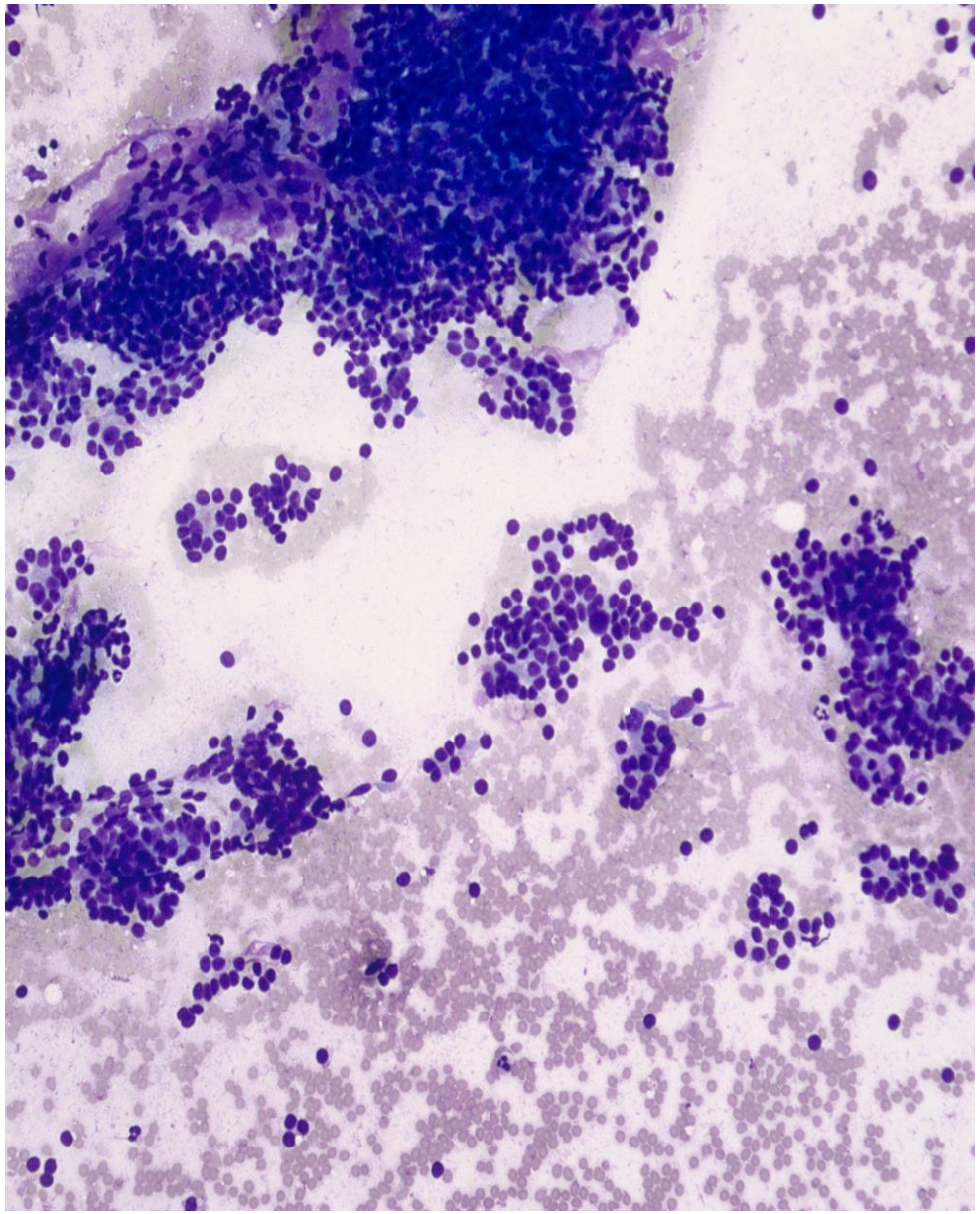
- Small to medium sized cells with scant cytoplasm, round nuclei, granular chromatin, indistinct nucleoli
- Necrosis, apoptosis and mitotic activity often present
- Cytomorphologic features overlap with those of follicular neoplasms
- Typical nuclear features of PTC not seen





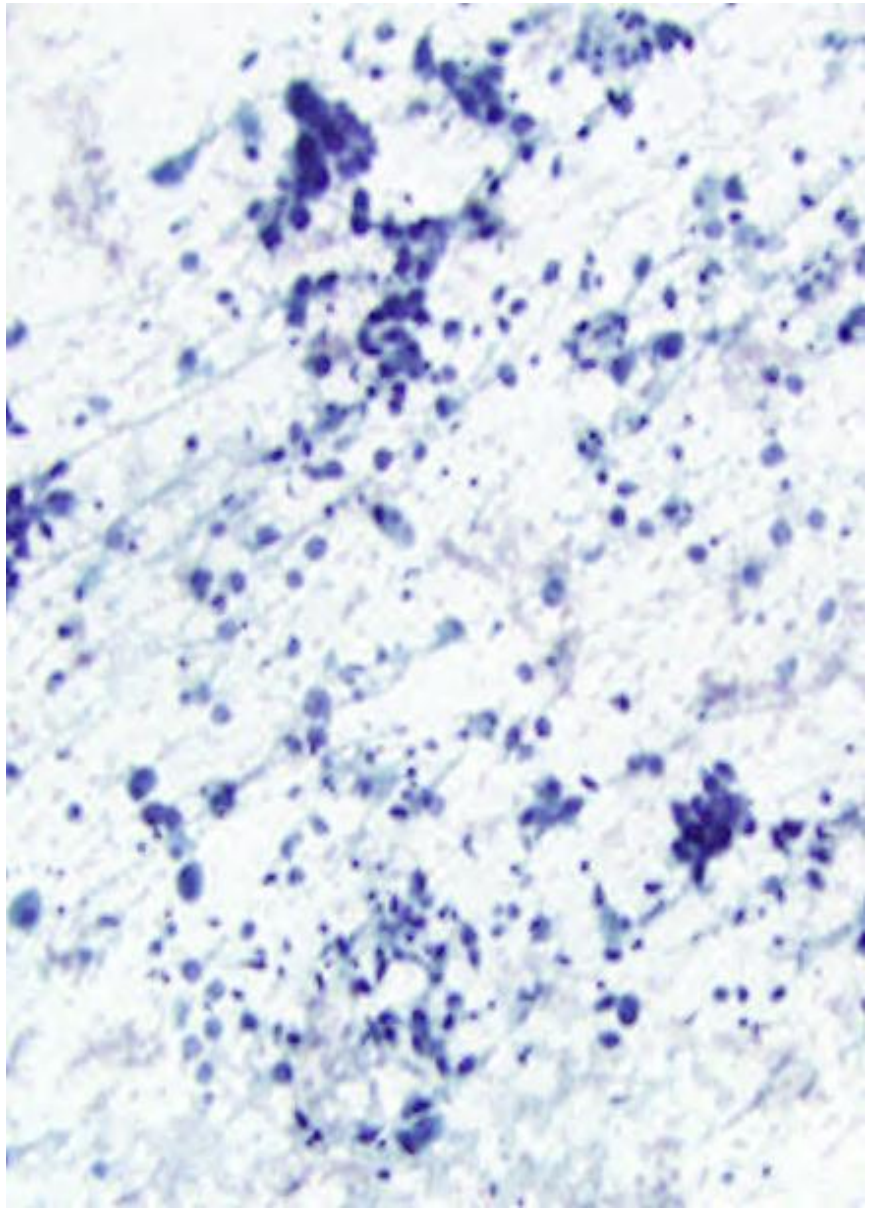
Poorly differentiated thyroid carcinoma

- May be misclassified as FVPTC when nuclear grooves and overlapping of cells are present
- Can mimic follicular neoplasm when microfollicles predominate
- Cases with conspicuous single cell pattern can mimic medullary carcinoma
  - Chromatin pattern, necrosis and mitosis helpful
  - Immunohistochemistry may be needed: calcitonin and PAX-8



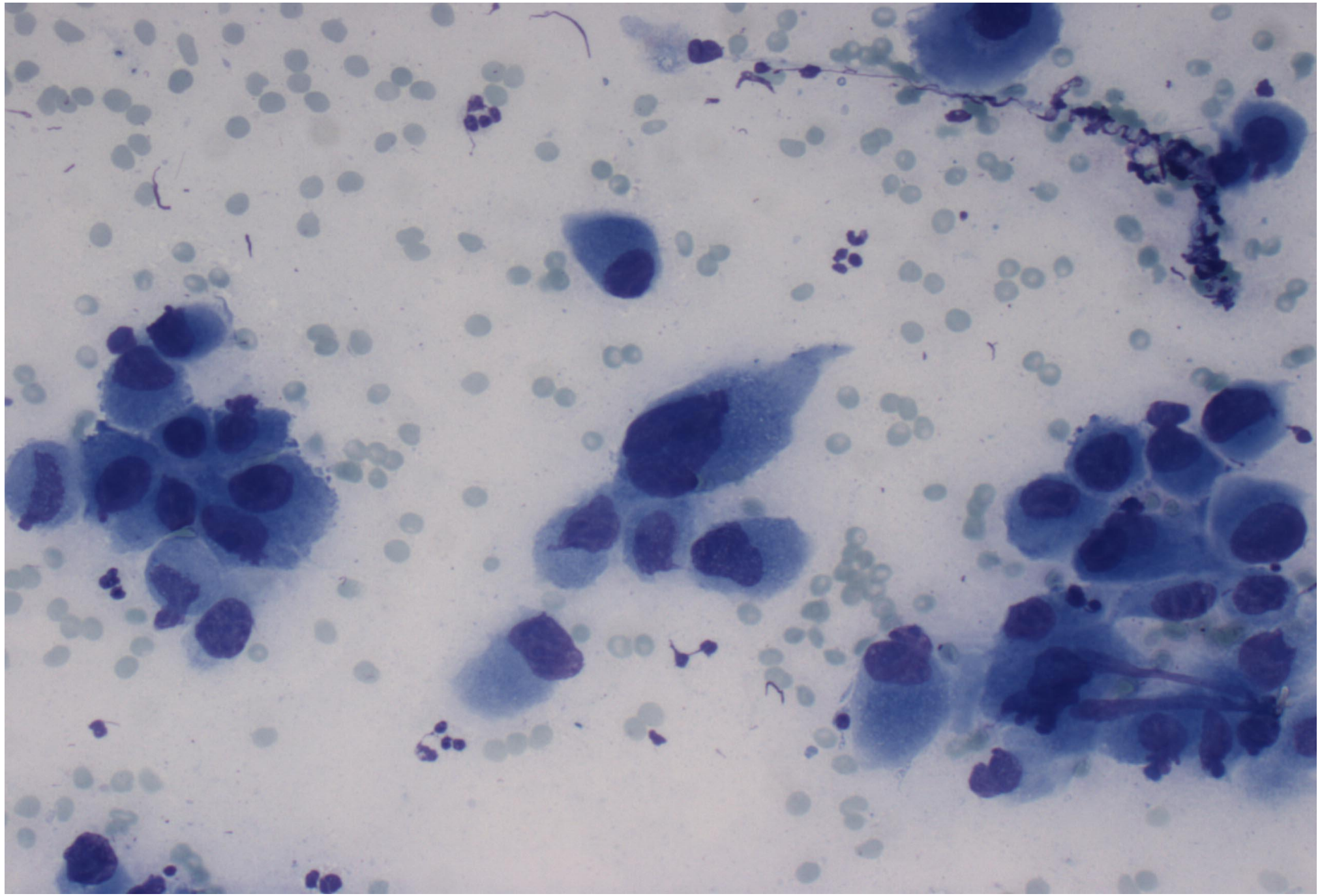
Poorly differentiated thyroid carcinoma

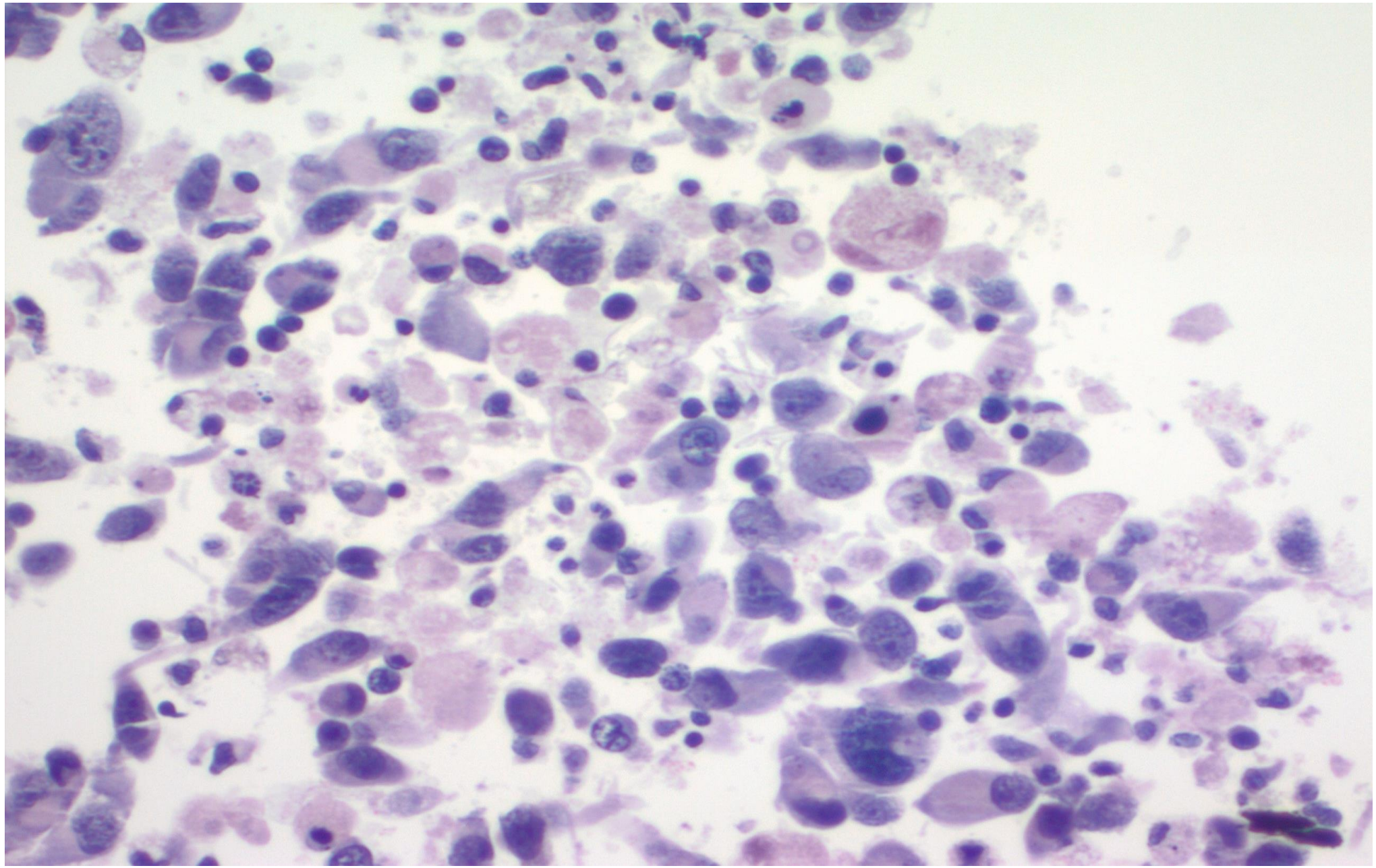
- Predominant single cells and loosely-cohesive small cell pattern can mimic low-grade lymphoproliferative process
  - Presence of lymphoglandular bodies helpful
  - Flow cytometry is key
  - Immunohistochemistry essential: CD45, PAX-8



Anaplastic carcinoma

- History very important – rapidly enlarging mass
- Usually very cellular specimen
- Noncohesive, large cells with marked nuclear pleomorphism
- Cells may be epithelioid or spindle shaped
- Multinucleated giant cells usually present
- Extensive necrosis common, mitoses are numerous
- May be associated with differentiated thyroid cancer



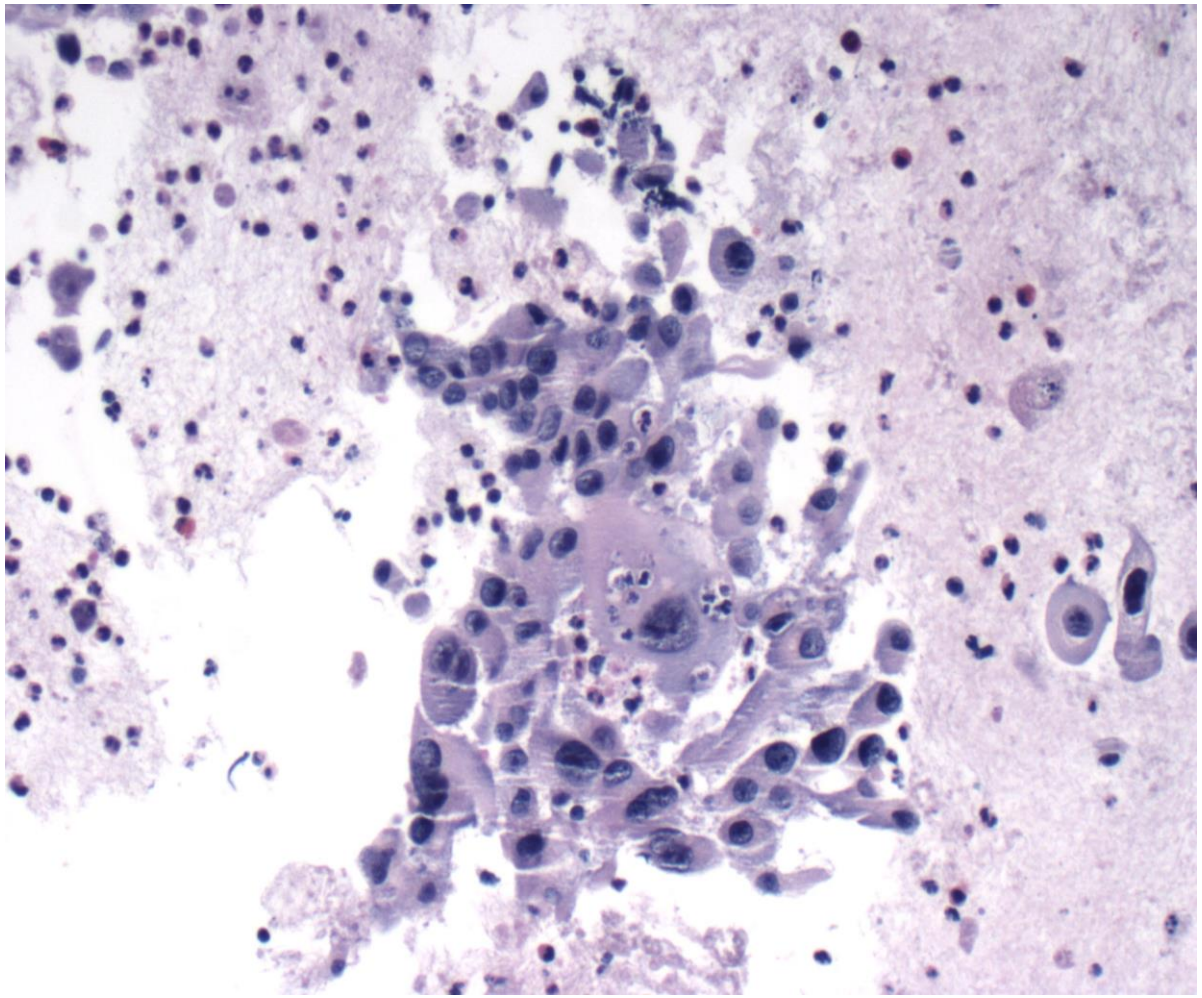


Anaplastic carcinoma

- Extensive collagen deposition can mimic Riedel's thyroiditis
- Radioactive iodine-induced changes in benign follicular cells after treatment for Graves' disease
- When laryngeal or thyroid cartilage is inadvertently sampled, megakaryocytes can mimic anaplastic carcinoma cells

Anaplastic carcinoma

- Can mimic poorly differentiated squamous cell carcinoma, malignant lymphoma, sarcoma, melanoma
- IHC essential in the work-up

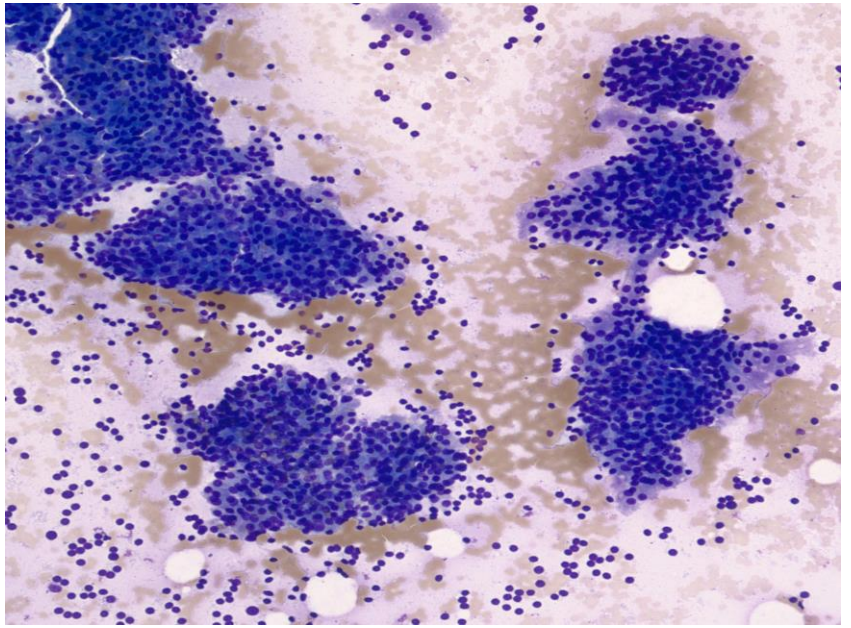


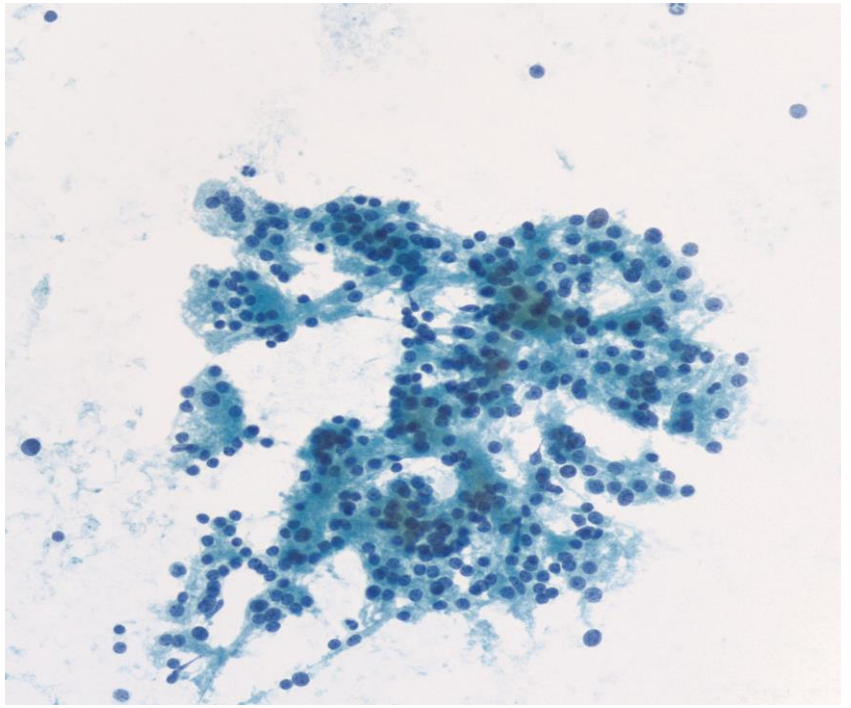
Parathyroid tissue sampling

- Thyroid tissue has overlapping cytomorphologic features with parathyroid
- High cellularity
- Cells arranged as cohesive sheets, ribbon-like cords or occasional microacini
- Isolated cells and naked nuclei can be present
- Round nuclei with stippled chromatin pattern
- Cytoplasm scant to moderate

Parathyroid tissue sampling

- Colloid-like material can be produced by hyperplastic parathyroid gland, can be confused with true colloid
- When the cells present as small, tight, 3-dimensional clusters in the absence of colloid, may be misdiagnosed as follicular neoplasm
- Parathyroid adenoma can show tissue fragments with papillary-like architecture, can mimic PTC





Parathyroid tissue sampling

- Oncocytic parathyroid adenoma may have follicular structures, and may lead to misdiagnosis as Hurthle cell neoplasm
- When there is a suspicion of parathyroid tissue
  - Obtain additional material: for PTH and/or thyroglobulin IHC
  - Ask for sample to be sent for parathyroid assay
  - Prepare additional ThinPrep for PTH IHC

Ectopic thyroid tissue

- Thyroid tissue unconnected to the thyroid gland
- Diagnostic dilemma
  - Ectopic thyroid tissue
  - Metastatic thyroid malignancy
  - Benign thyroid inclusion in a lymph node

Ectopic thyroid tissue

- Different cytomorphologic features:
  - Normal appearing follicular cells
  - Follicular cells and polymorphous population of lymphocytes
  - Cytologic features of malignancy
- Presence of unequivocal nuclear features of PTC and psammoma bodies diagnostic of metastasis

Ectopic thyroid tissue

- Presence of thyroid tissue in lateral neck nodes almost always represents nodal metastasis
- Presence of cytologically benign-appearing follicular cells does not necessarily imply a benign process
- Presence of cytologic atypia in follicular cells in a lymphoid background does not always indicate metastatic thyroid carcinoma

Conclusions

- Because of potential pitfalls, when evaluating thyroid FNAs , careful attention should be paid to cytologic and clinical features
- Judicious use of IHC and other ancillary studies can help to reduce errors and lead to more accurate FNA interpretations and improved patient care

THANK YOU!

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