

Thyroid FNA cytology

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

Third Edition (2023)

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- Fine needle aspiration (FNA) is the **most accurate and cost-effective** method for evaluating thyroid nodules

- The goal of preoperative FNA and cytologic analysis is to inform conservative management of thyroid nodules unlikely to cause harm, while conversely leading to surgical management aimed at effectively treating thyroid cancer.

- Lower rates of both **non-diagnostic and false-negative cytology** from FNA procedures performed using ultrasound guidance compared to palpation
  - for nodules with a **higher** likelihood of either a nondiagnostic cytology (those with greater than 25–50% cystic component) [3] or **sampling error** (those that are difficult to palpate or posteriorly located nodules), **US-guided FNA is preferred**

I. Nondiagnostic
Cyst fluid only
Virtually acellular specimen
Other (obscuring blood, clotting artifact, drying artifact, etc.)
II. Benign
Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other
III. Atypia of Undetermined Significance
Specify if AUS-nuclear atypia or AUS-other
IV. Follicular Neoplasm
Specify if oncocytic (Hürthle cell) type
V. Suspicious for Malignancy
Suspicious for papillary thyroid carcinoma
Suspicious for medullary thyroid carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
Other
VI. Malignant
Papillary thyroid carcinoma
High-grade follicular cell-derived non-anaplastic thyroid carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic malignancy
Non-Hodgkin lymphoma
Other

Diagnostic categories

Format of the Report

- For clarity of communication, each thyroid FNA report should begin with a **general diagnostic category**
- Additional descriptive comments are **optional** and left to the discretion of the **cytopathologist**.
- **Notes and recommendations** can be useful, **especially** with relation to the NIFTP terminology

- Each category has an **implied cancer risk**, which ranges from 1% to 2% overall for the “Benign” category to virtually 100% for the “Malignant” category

Risk of malignancy (ROM)

with expected ranges based on **follow-up of surgically resected nodules** with recommended clinical management

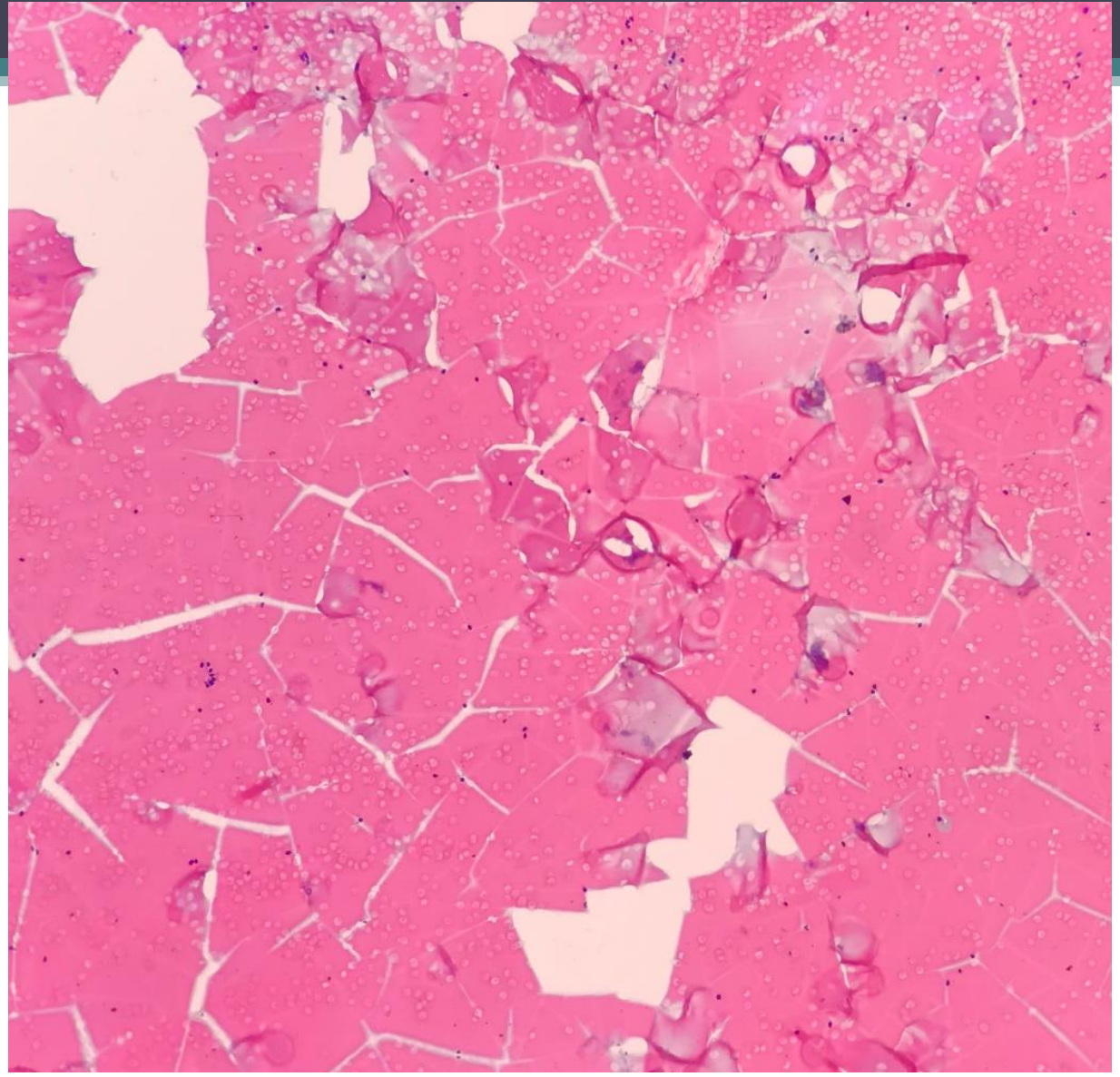
Diagnostic category	ROM[a] Mean% (range)	Usual management[b]
Nondiagnostic	13 (5–20)[c]	Repeat FNA[d] with ultrasound guidance
Benign	4 (2–7)[e]	Clinical and sonographic follow-up
Atypia of Undetermined Significance[f]	22 (13–30)	Repeat FNA[d], molecular testing, diagnostic lobectomy, or surveillance
Follicular Neoplasm[g]	30 (23–34)	Molecular testing[h], diagnostic lobectomy
Suspicious for Malignancy	74 (67–83)	Molecular testing[h], lobectomy or near-total thyroidectomy[i]
Malignant	97 (97–100)	Lobectomy or near-total thyroidectomy[i]

Criteria for Adequacy

- **Adequate**: contains a minimum of **six groups** of **well-visualized** (i.e., well stained, well preserved, undistorted, and unobstructed) follicular cells, with **at least ten cells per group**

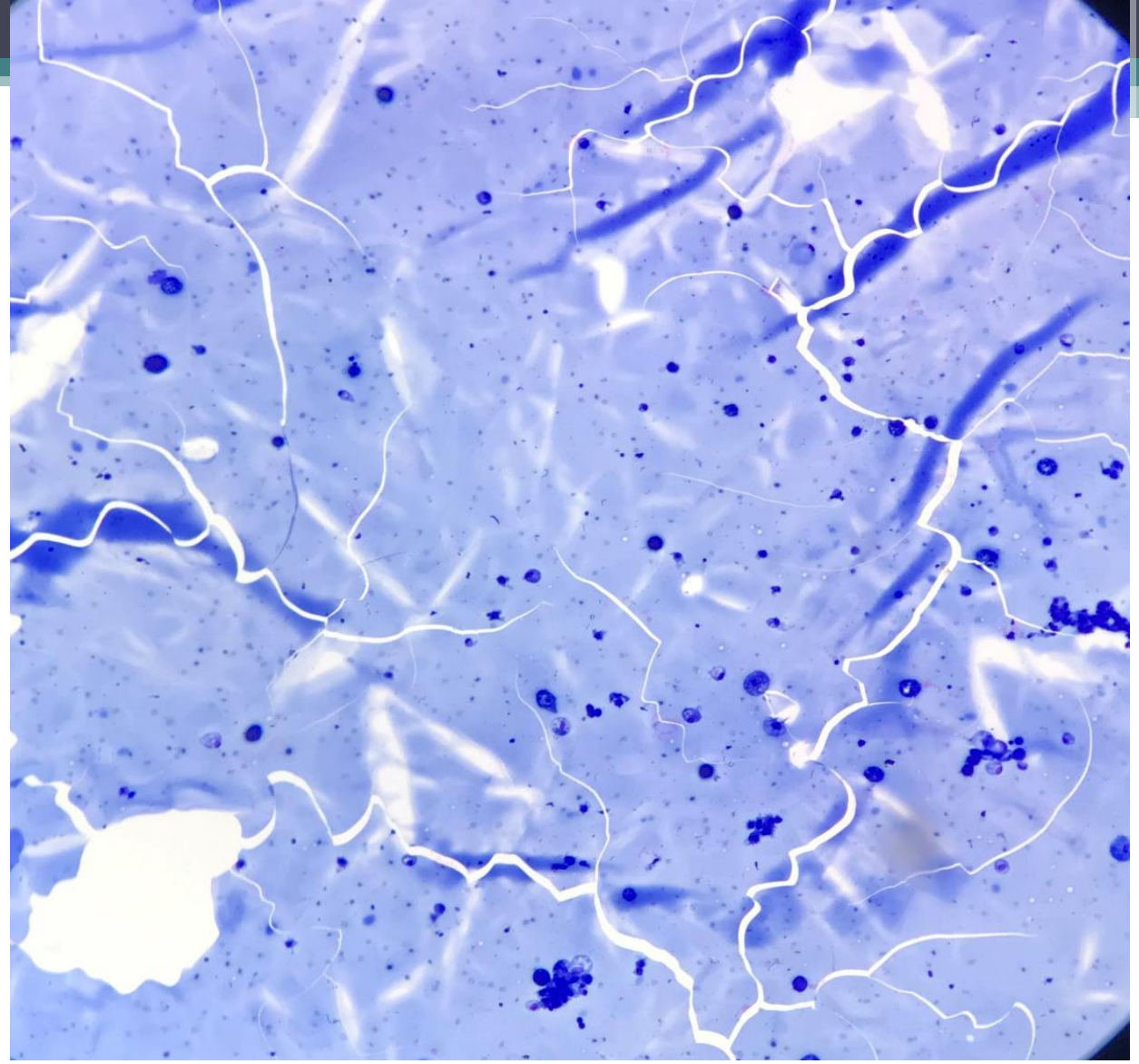
  Either on **one slide** or distributed among **several** for adequacy determination.

- **Exceptions** (minimum number of follicular cells is **not required**):
  1. ***Aspirates with cytologic atypia*** → mandatory to report **any** significant atypia
     - must be reported in the **appropriate TBSRTC diagnostic category** (i.e., TBSRTC categories III–VI: AUS, Suspicious or Malignant).
  2. ***Solid nodules with inflammation*** → lymphocytic (Hashimoto) thyroiditis, thyroid abscess, or granulomatous thyroiditis may contain **only** numerous inflammatory cells
     - interpreted as **benign** (TBSRTC category II)
  3. ***Colloid nodules*** (abundant, easily identifiable colloid)
     - considered **Benign** (TBSRTC category II)



Papanicolaou (pap)

Alcohol fixation



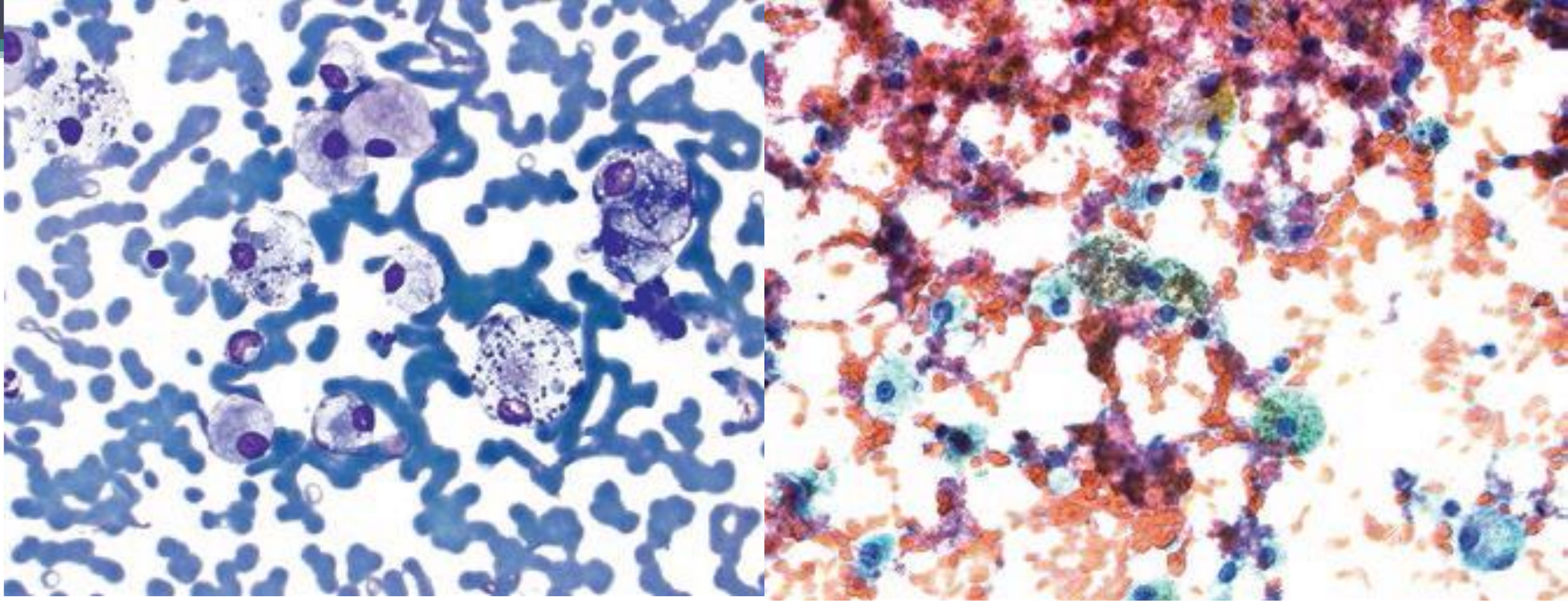
Giemsa, Wright-Giemsa

Air-drying smears

Benign. The presence of **abundant colloid**

Non-diagnostic

- Cyst fluid (with or without histiocytes), and fewer than six groups of ten benign follicular cells >>>
  - the possibility of a cystic papillary thyroid carcinoma cannot be excluded if a sample consists entirely of fluid and histiocytes
  - **In the proper clinical setting** (e.g., ultrasound evidence of a simple, unilocular cyst), some specimens may be **considered clinically adequate**, even though they are reported as ND



Nondiagnostic. Cyst fluid only.

Thyroid lesions with cystic degeneration, common in hyperplastic nodules, may yield only histiocytes, with or without hemosiderin. Histiocytes have abundant, finely vacuolated cytoplasm, uniform oval nuclei, and may contain cytoplasmic cell degeneration products

(**left**: smear, Diff-Quik stain; **right**: smear, Papanicolaou stain)

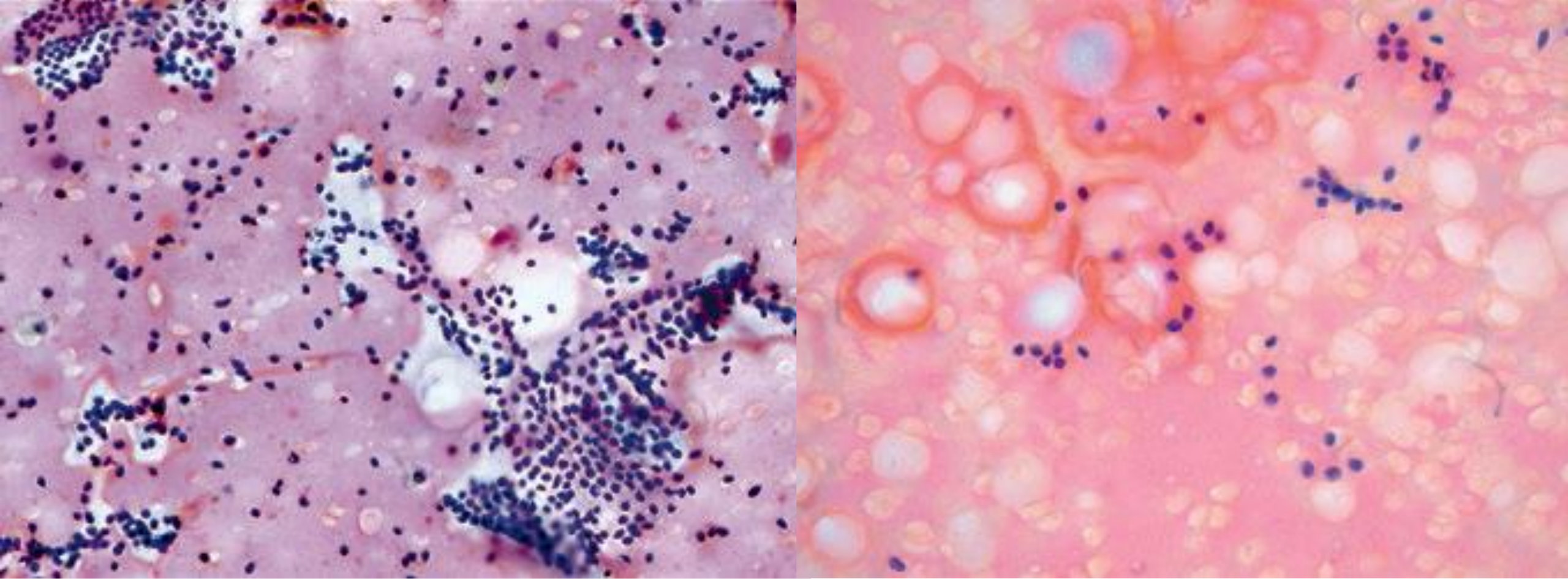
- **Nodular goiter (NG)**
  - **Most commonly sampled lesion by FNA**
  - **Clinical terminology** that refers to an enlarged thyroid gland with single or multiple nodules, benign or malignant.
  - **Not recommended** as a terminology for **pathologic diagnosis**, since a variety of lesions including **hyperplasia, thyroiditis, and neoplasm** can produce clinically enlarged nodular thyroid gland.

- The term **"Follicular Nodular Disease" (FND)** has been recommended by the **2022 WHO** classification of thyroid neoplasms **(and 2025)** to refer to the **spectrum of changes previously designated as** colloid nodule, hyperplastic nodule, adenomatous nodule, or **benign follicular nodule**

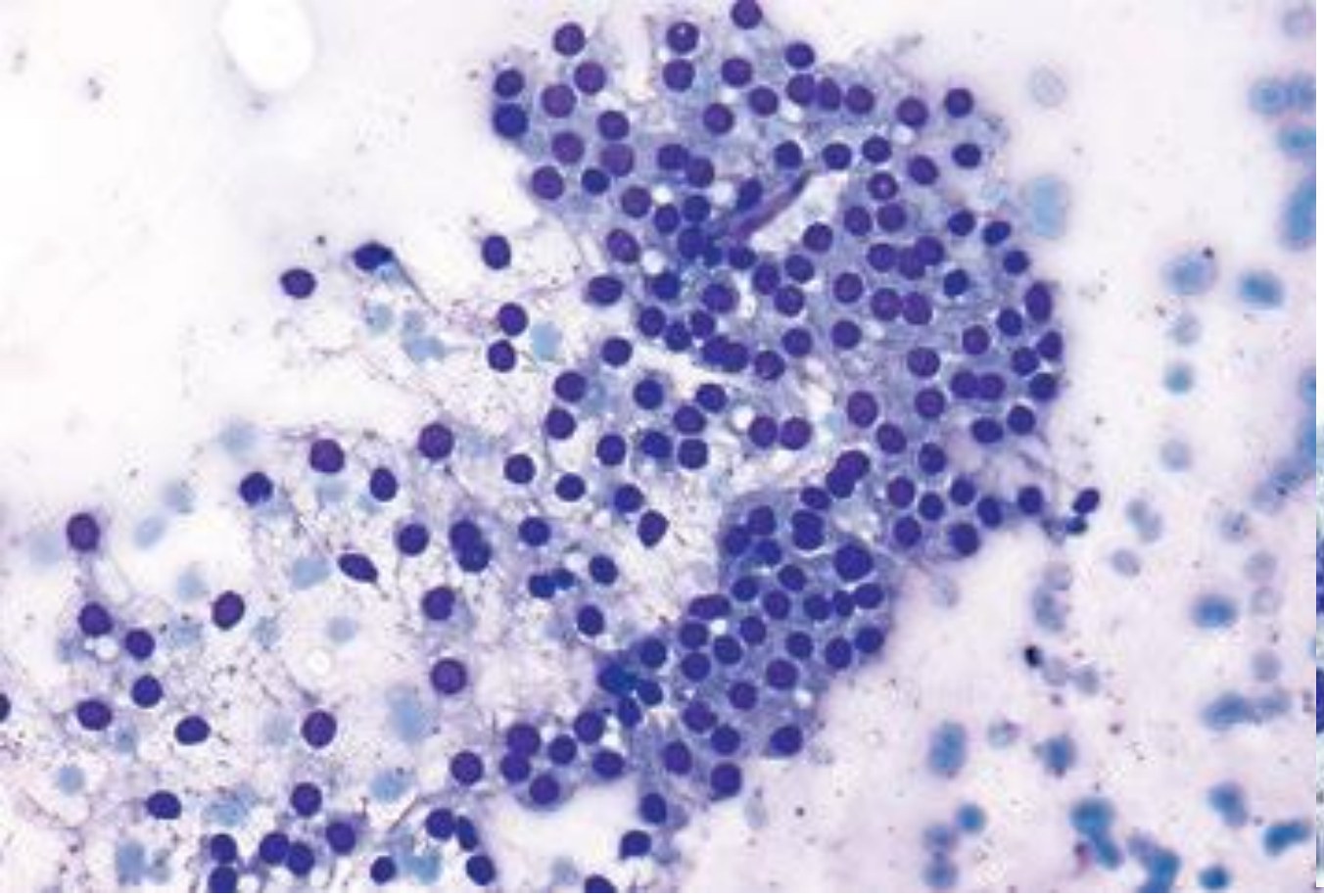
- The terminology of FND avoids designating these lesions as **hyperplastic or neoplastic** in nature

- **FND** encompasses a group of **benign lesions** with **similar cytologic features** that are classified histologically as:
  - Nodular hyperplasia
  - Hyperplastic (adenomatoid) nodules
  - Colloid nodules
  - Nodules in Graves' disease
  - Uncommon subset of *follicular adenomas* composed predominantly of macrofollicular or normofollicular architecture.

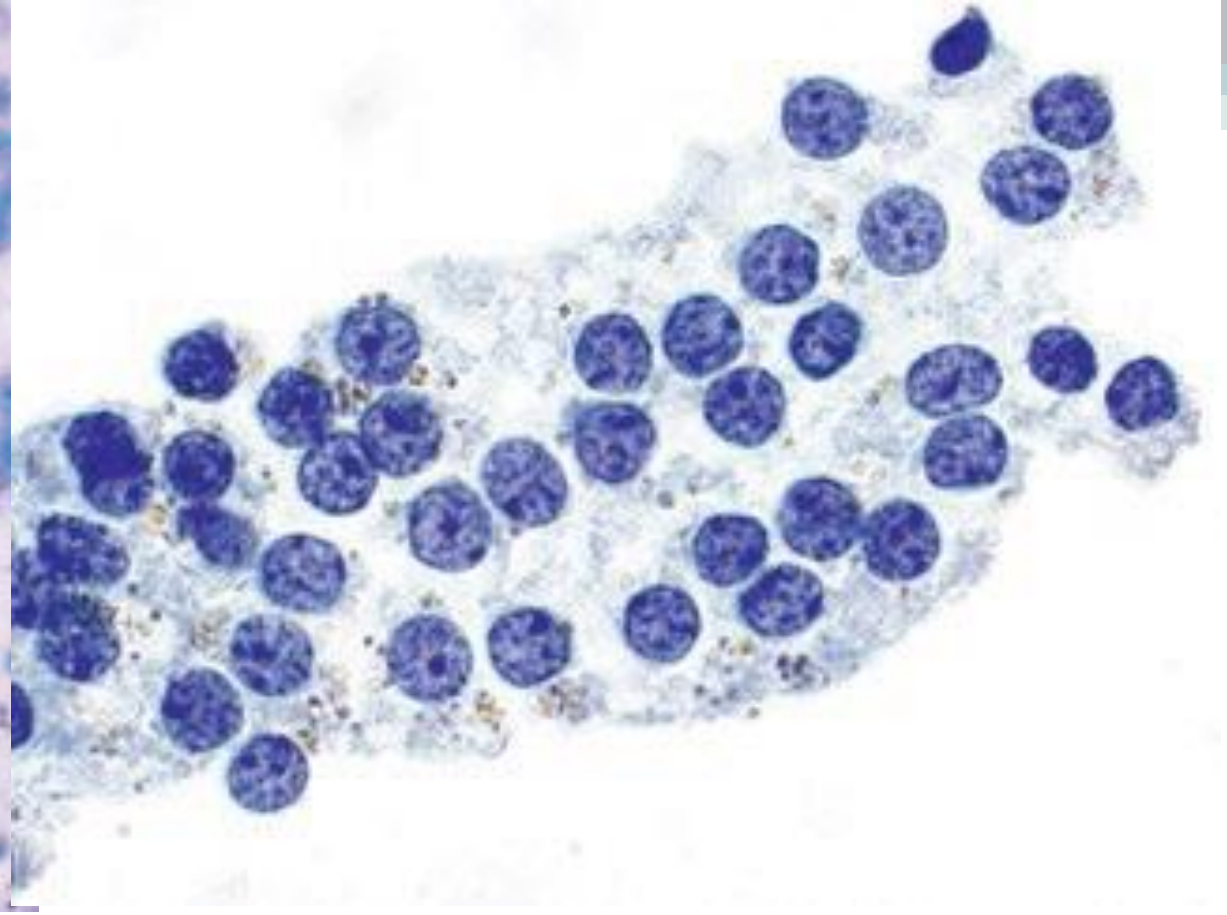
✓The **distinction** among these different histologic entities **may not be possible by FNA**, but this is of **little importance** because they are **all benign**, and can be managed in a similar, **conservative** manner.



Follicular nodular disease.
(**left**) Monolayered sheets of follicular cells are the predominant finding. Stripped follicular cell nuclei are present in the background. When watery colloid is admixed with blood (note the pale-staining red blood cells), it can be difficult to recognize (smear, Papanicolaou stain).
(**right**) Colloid is easier to recognize when it forms characteristic folds and lacunae (smear, Papanicolaou stain)

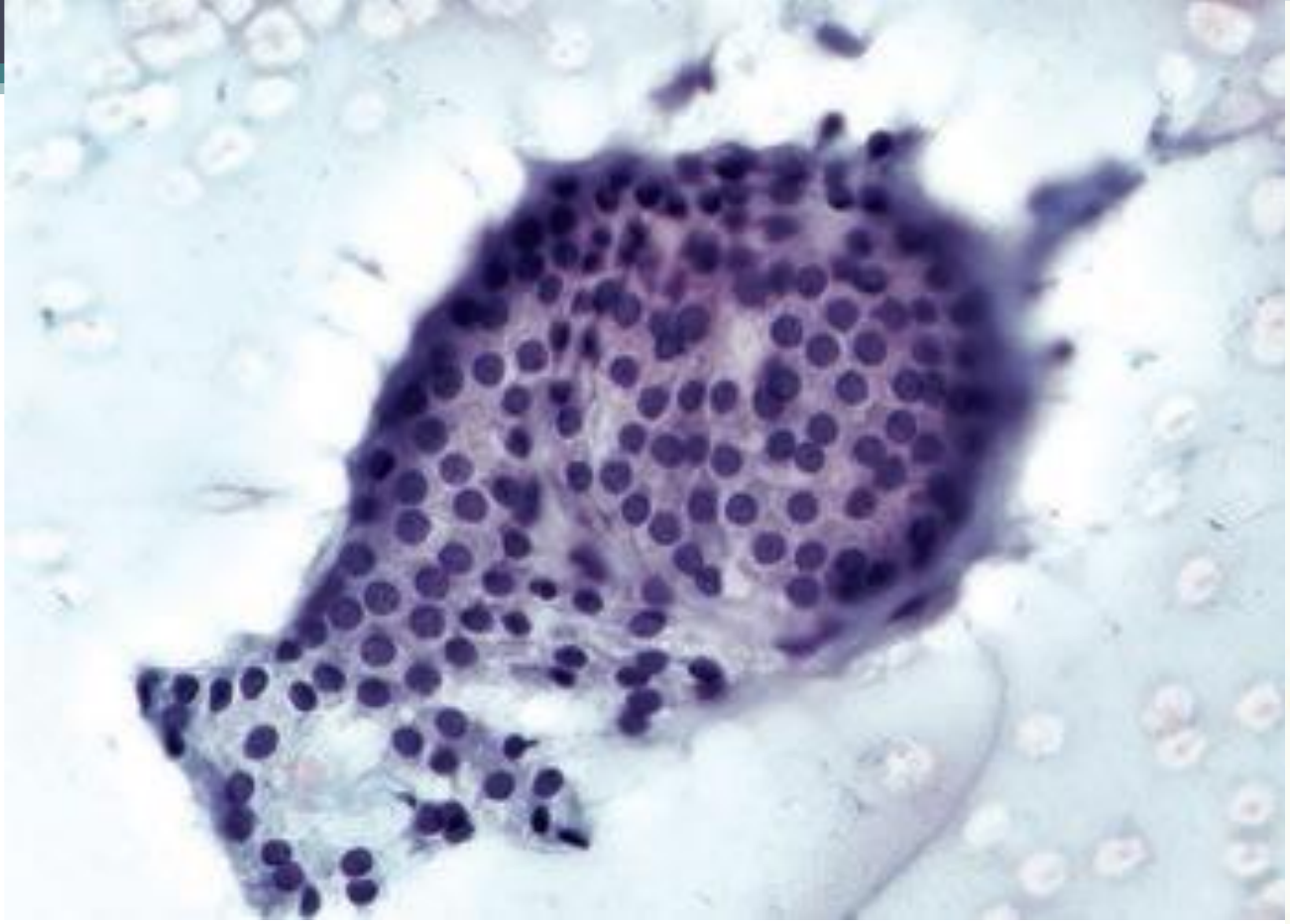


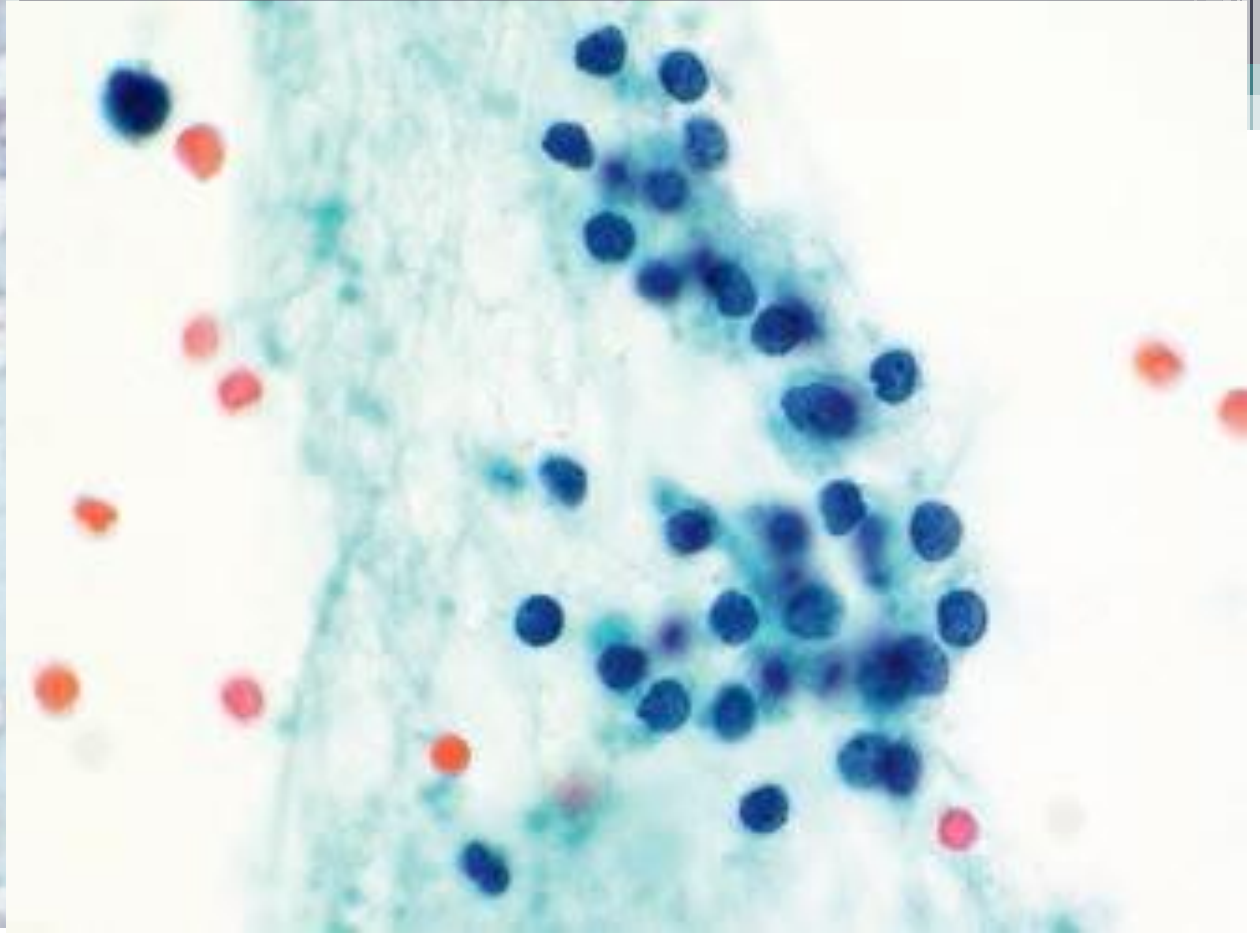
Benign follicular cells have delicate cytoplasm and ill-defined borders. The nuclei are uniformly spaced and approximately the size of red blood cells. Watery colloid is present in the background (smear, Diff-Quik stain).



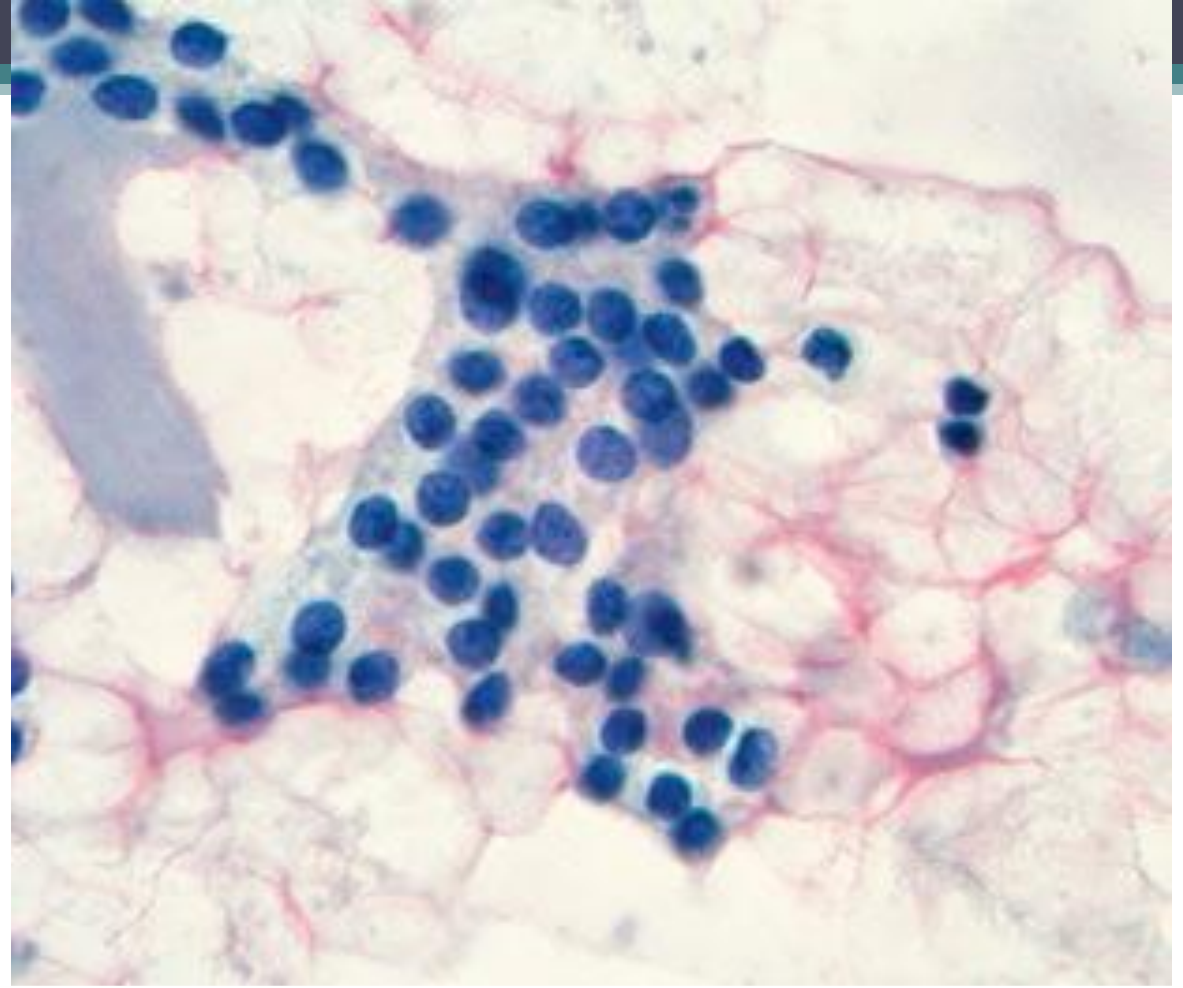
Follicular cells may contain golden-brown cytoplasmic hemosiderin pigment (ThinPrep, Papanicolaou stain)

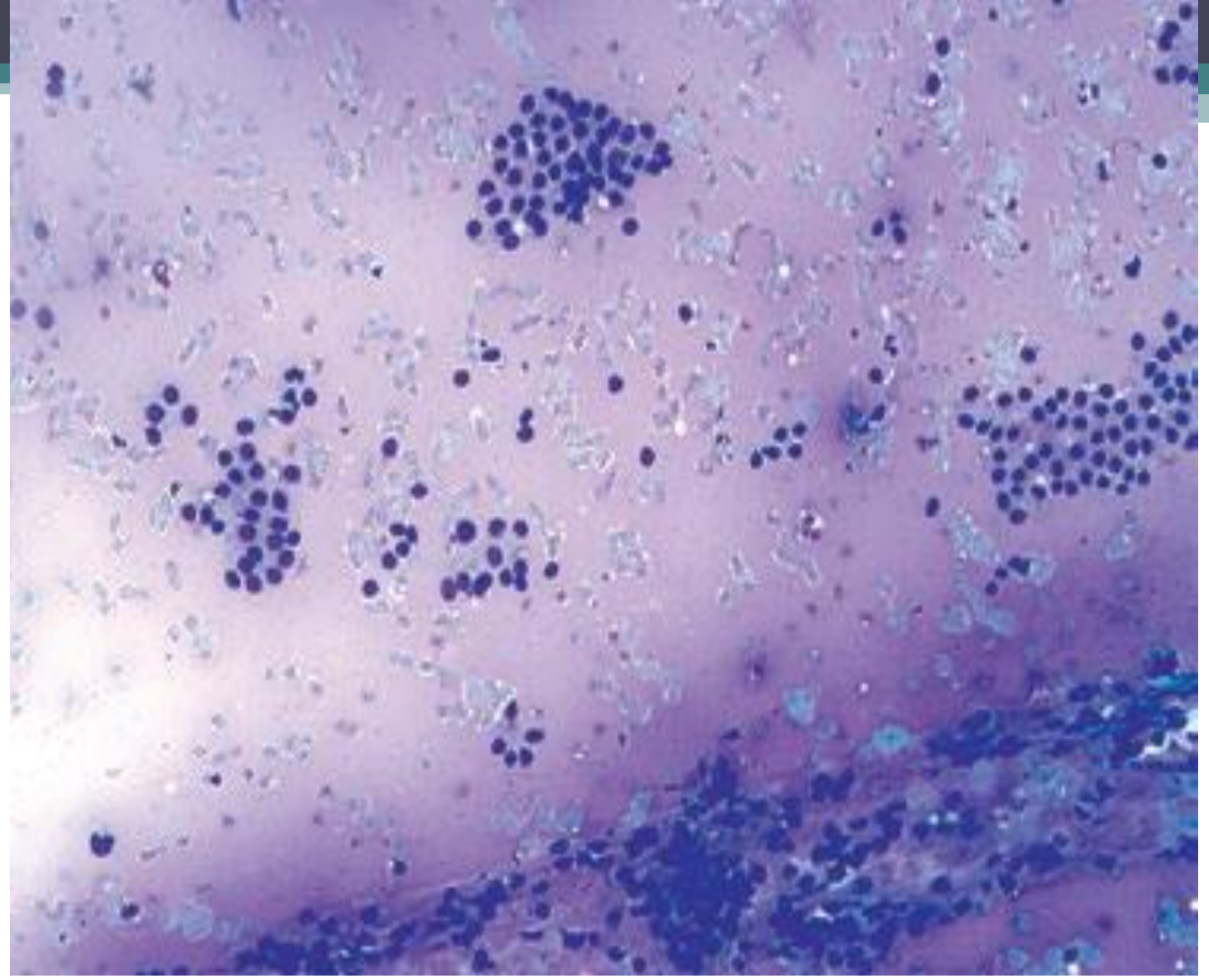
Follicular nodular disease



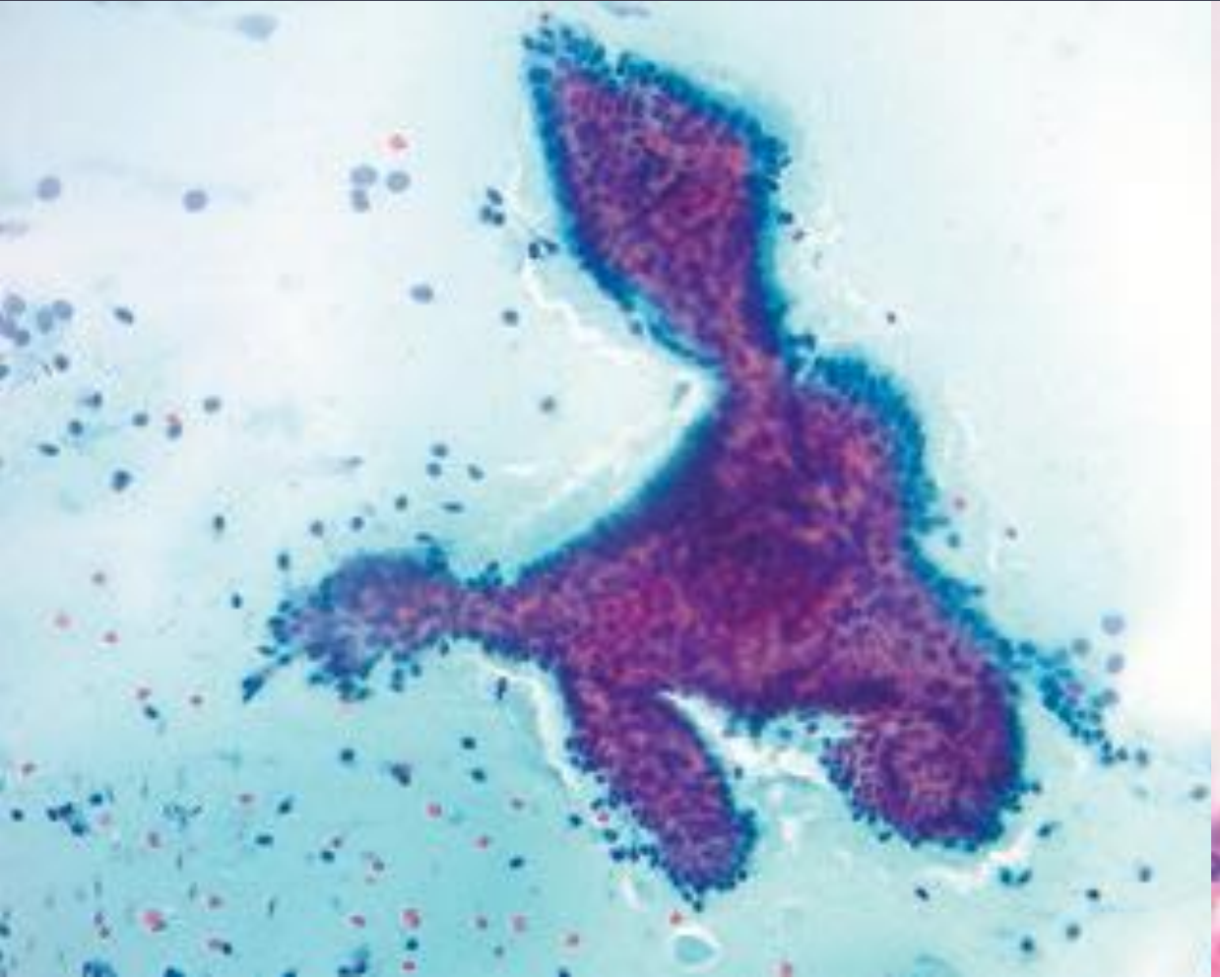


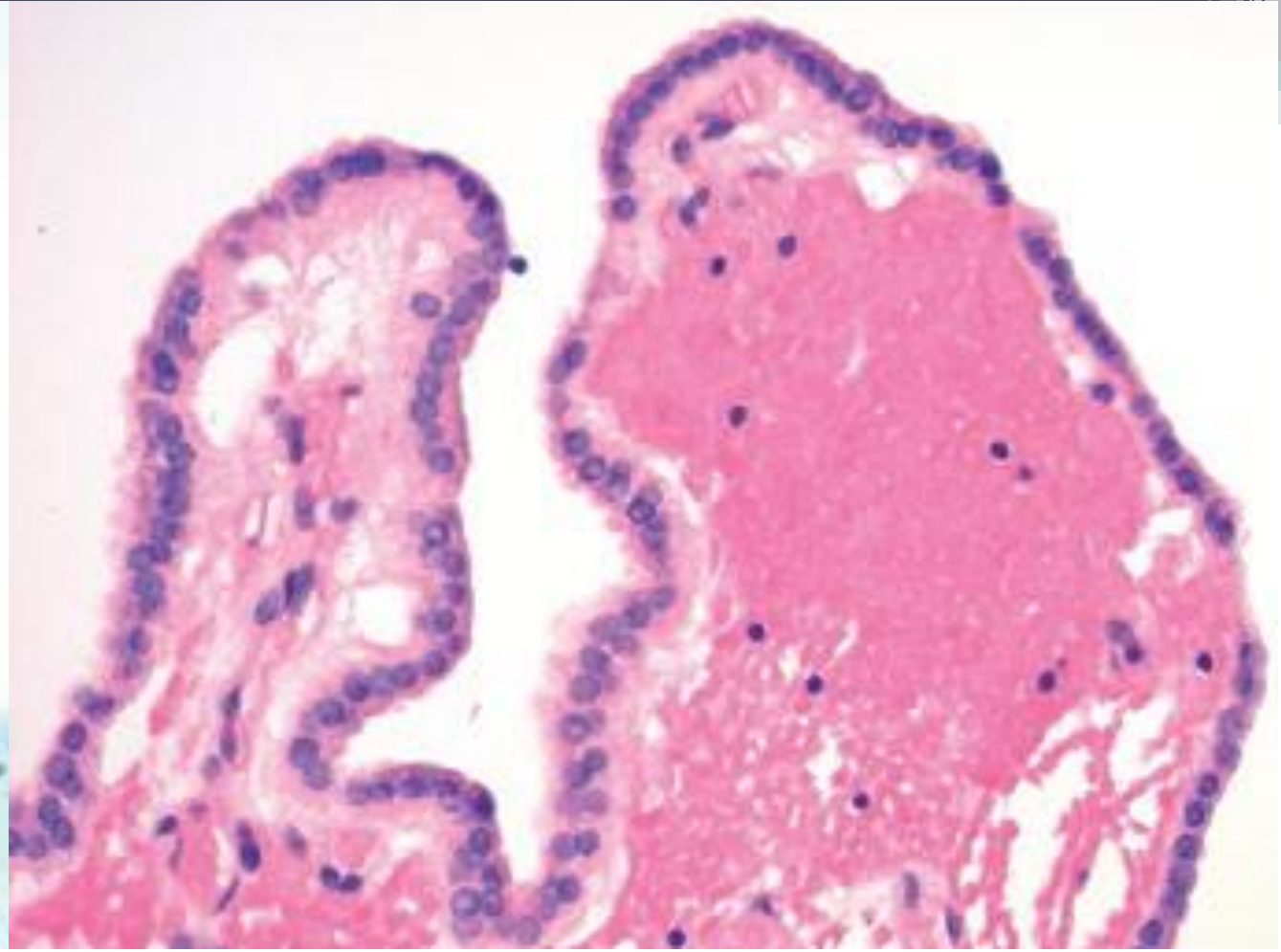
Follicular nodular disease.
Benign follicular cells have round to oval, monomorphic nuclei with finely granular chromatin and inconspicuous or absent nucleoli



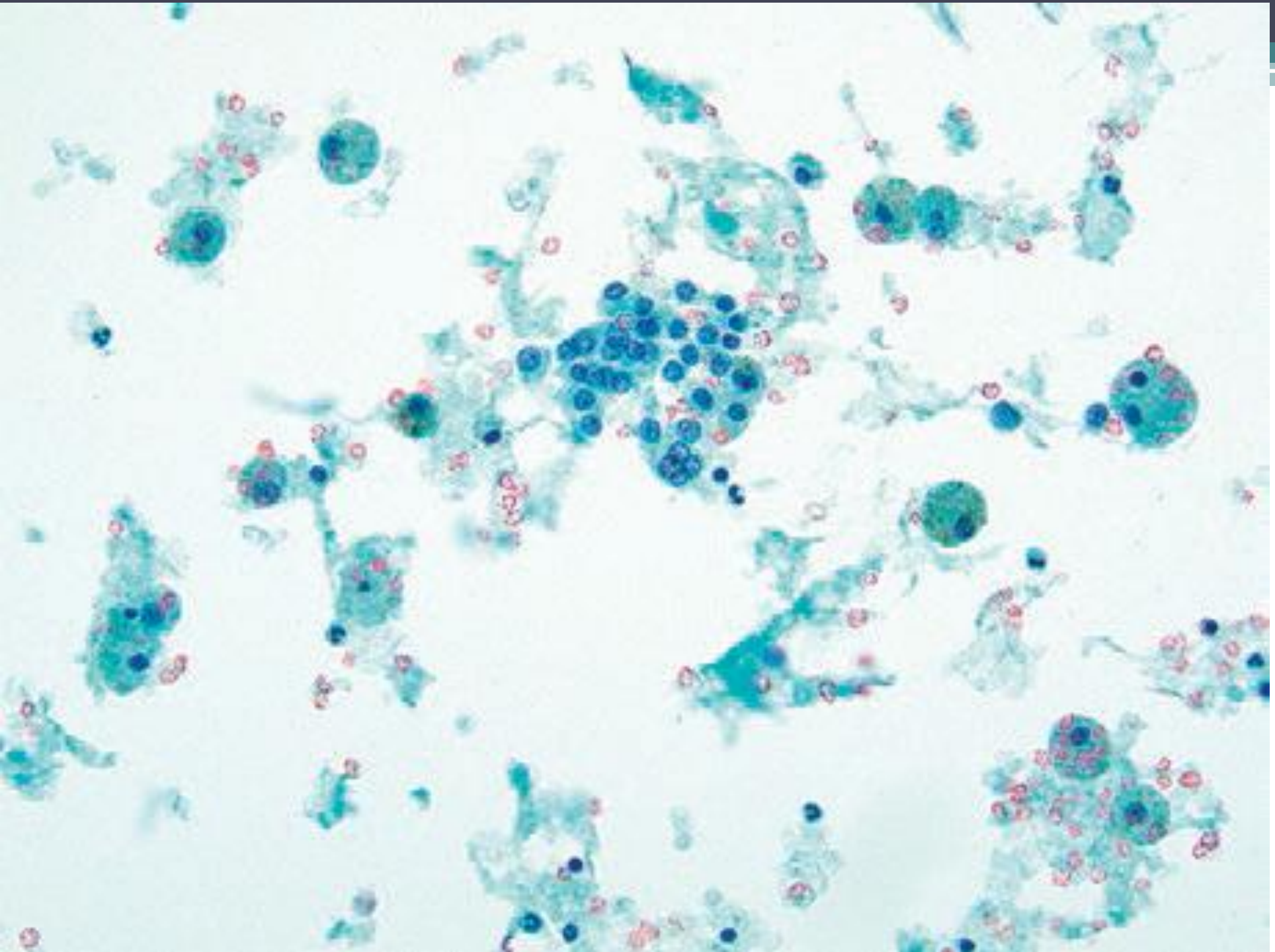


Follicular nodular disease.
(**left**) Nuclear overlapping, crowding, and slight anisonucleosis may be observed in some clusters, but there is no significant nuclear enlargement or atypia (smear, Papanicolaou stain).
(**right**) Small-sized follicles without significant nuclear overlapping or atypia of follicular cells (middle and left side of photo) represent small fragments of macrofollicles, not neoplastic microfollicles; they are lined by cells of same size and shape as those of benign flat sheets present in upper and right side of photo. Watery colloid is seen in the background (smear, Diff-Quik stain)

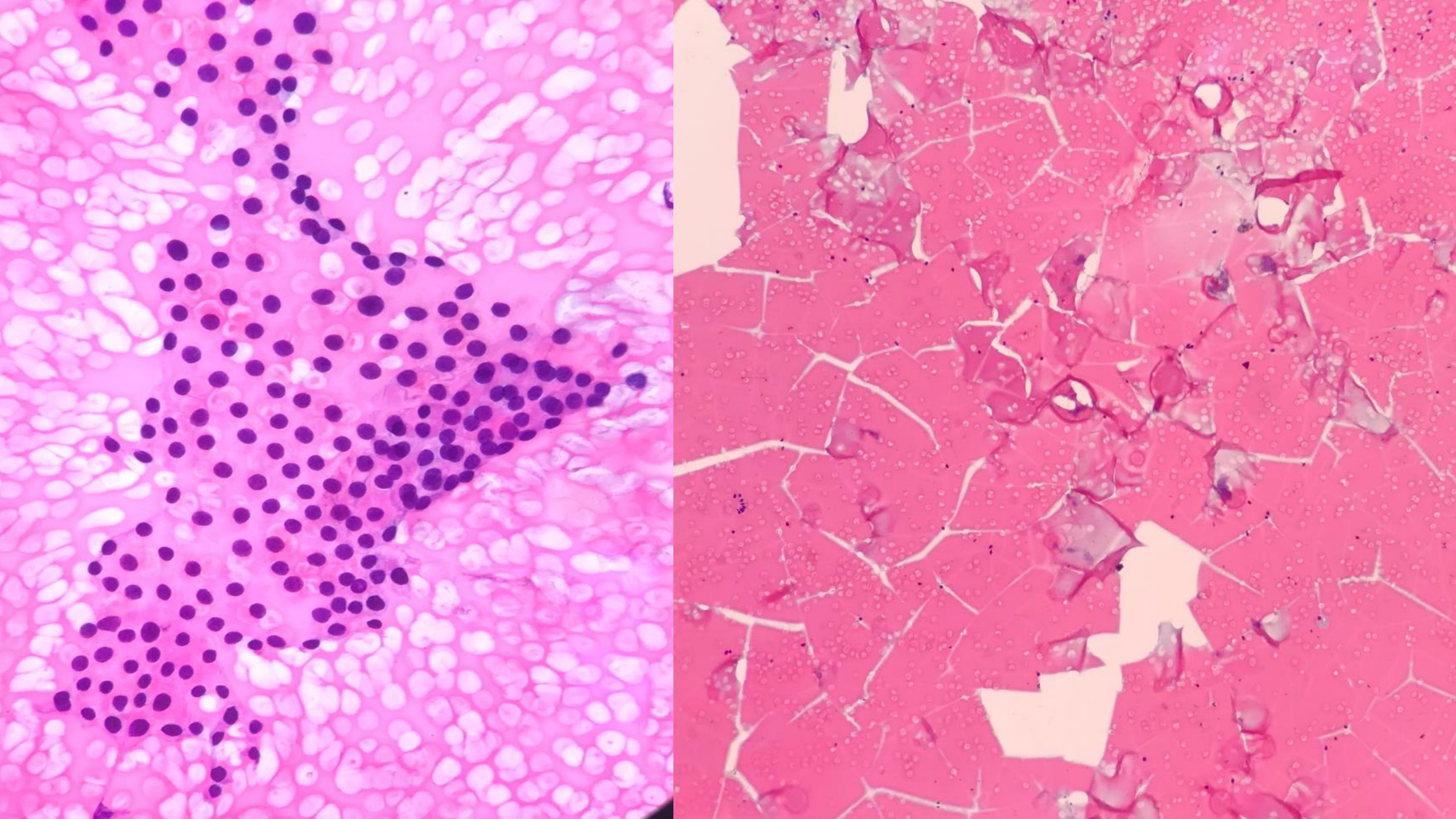


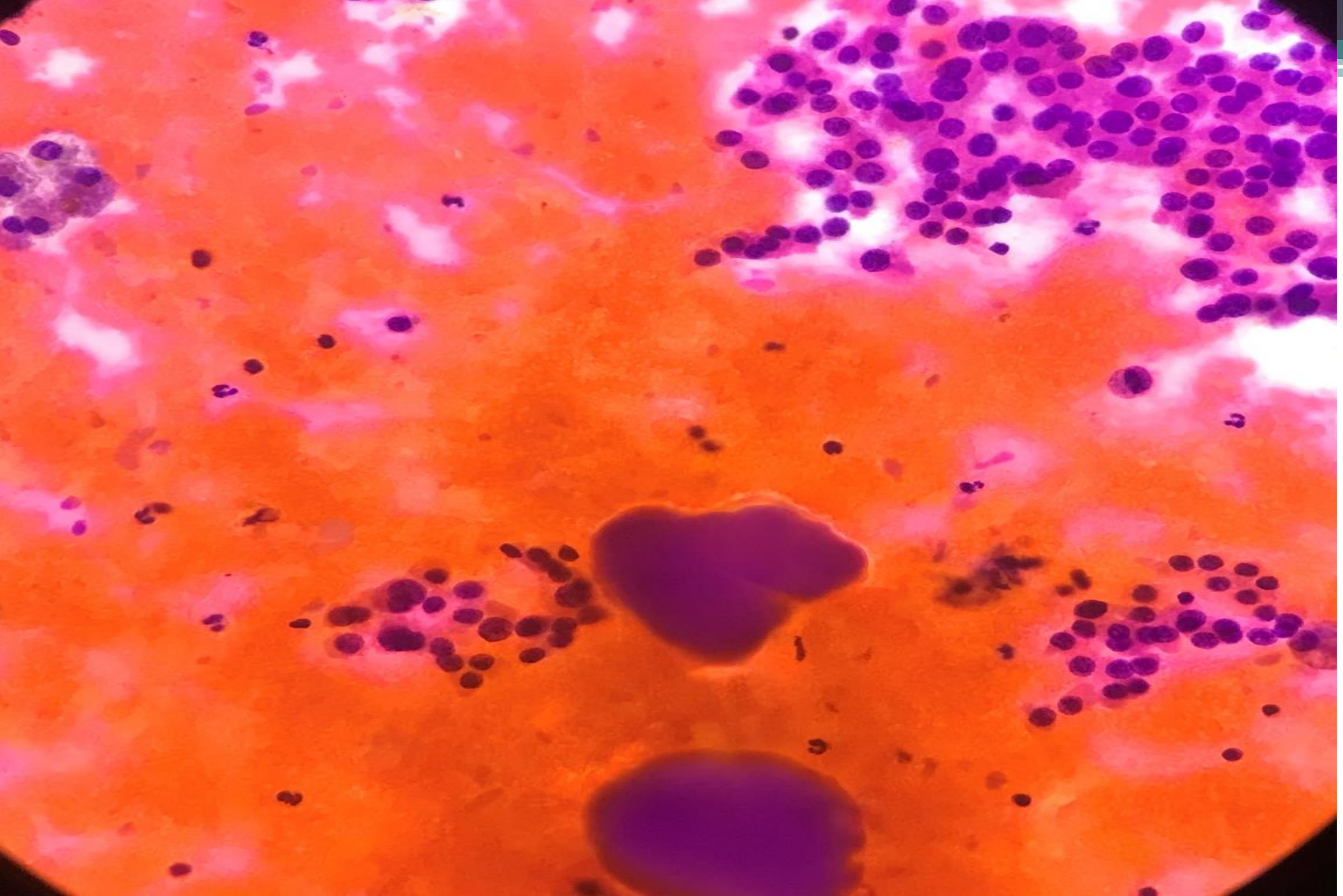


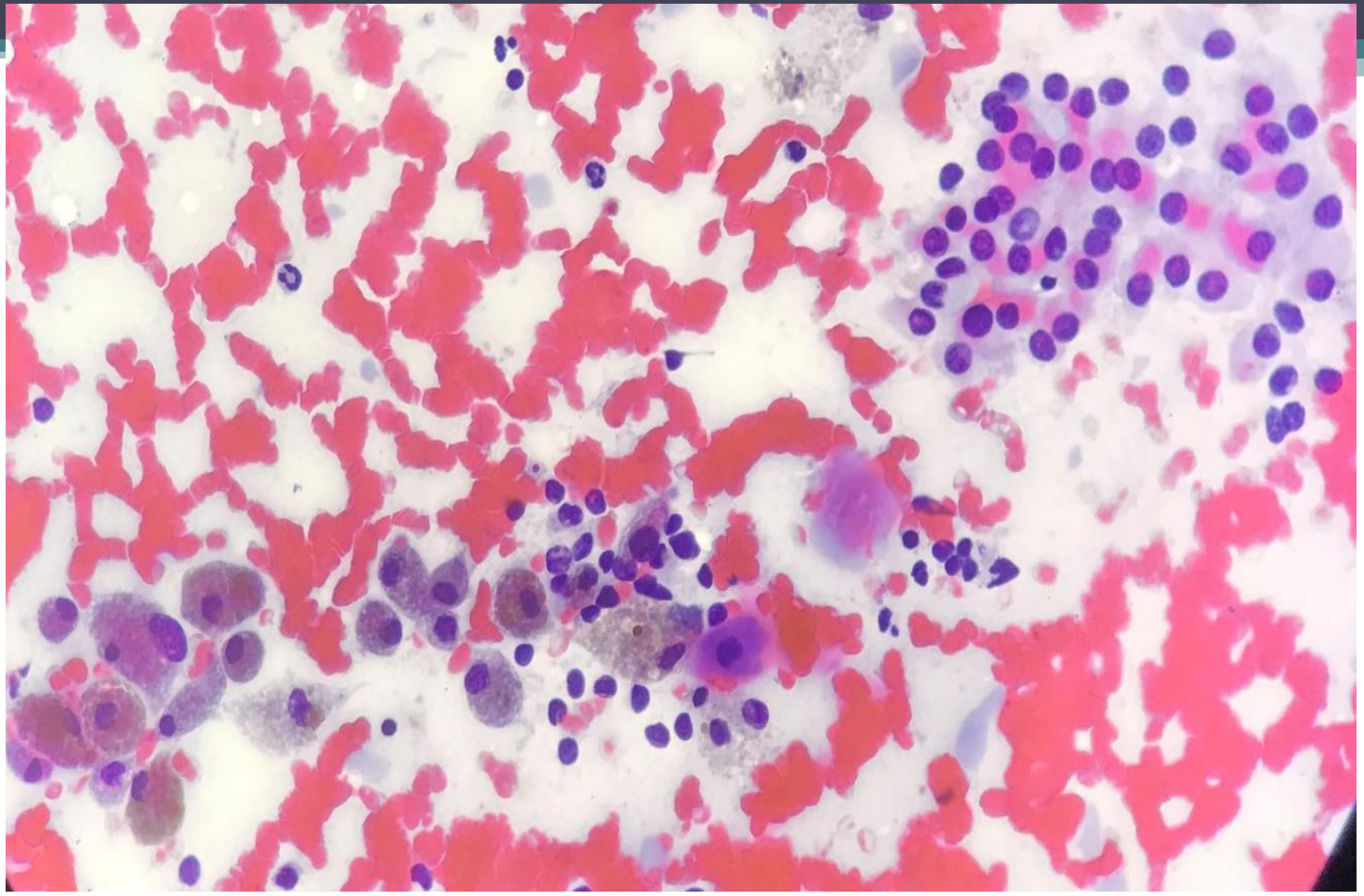
Follicular nodular disease.
Papillary hyperplasia may be seen in association with a hyperplastic nodule or follicular adenoma.
(**left**) The follicular cells usually remain arranged in flat sheets; true papillae with fibrovascular cores are rarely apparent. Nuclear features of papillary thyroid carcinoma are absent (smear, Papanicolaou stain).
(**right**) Follow-up histology revealed papillary hyperplasia associated with follicular nodular disease (H&E stain)

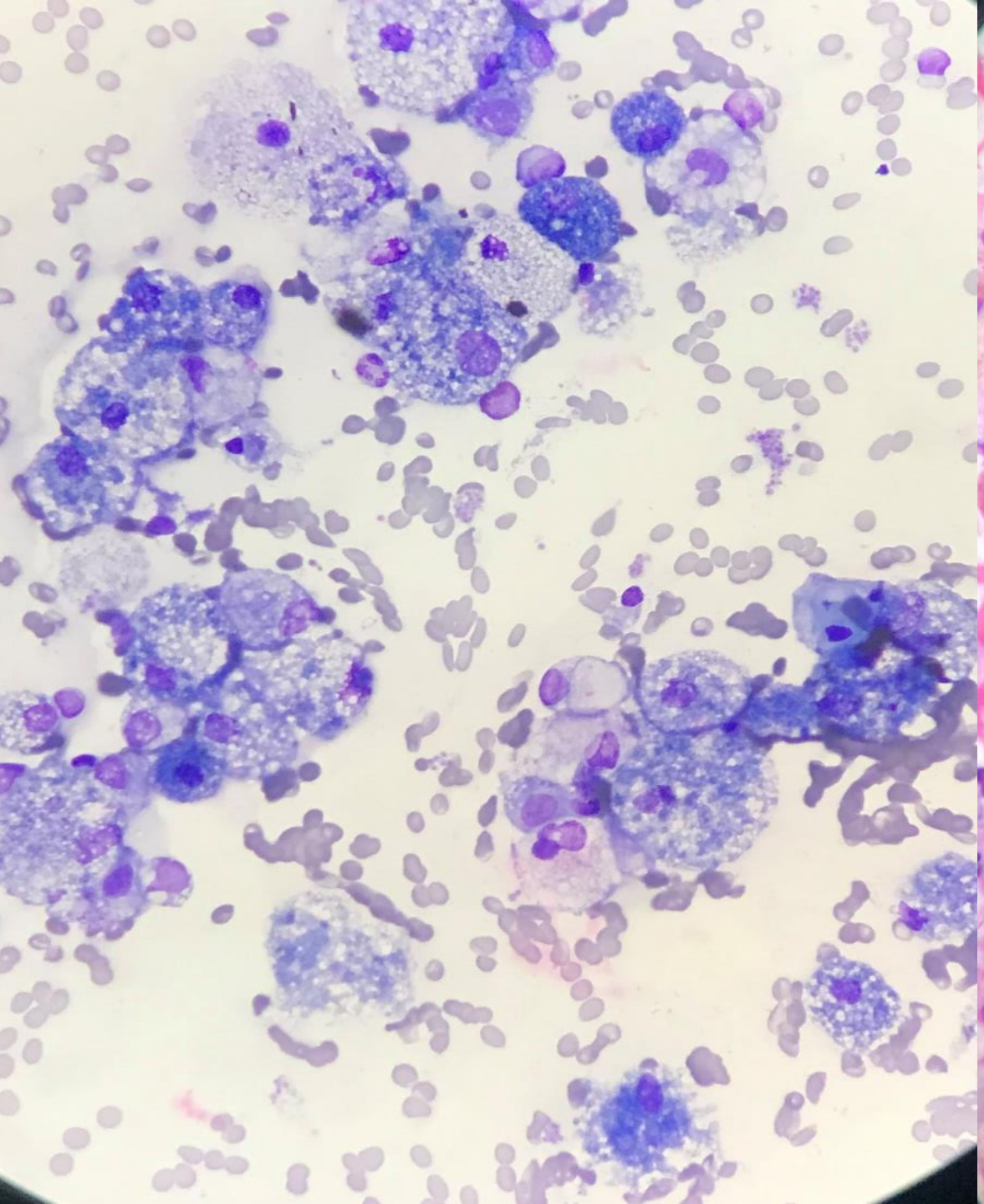
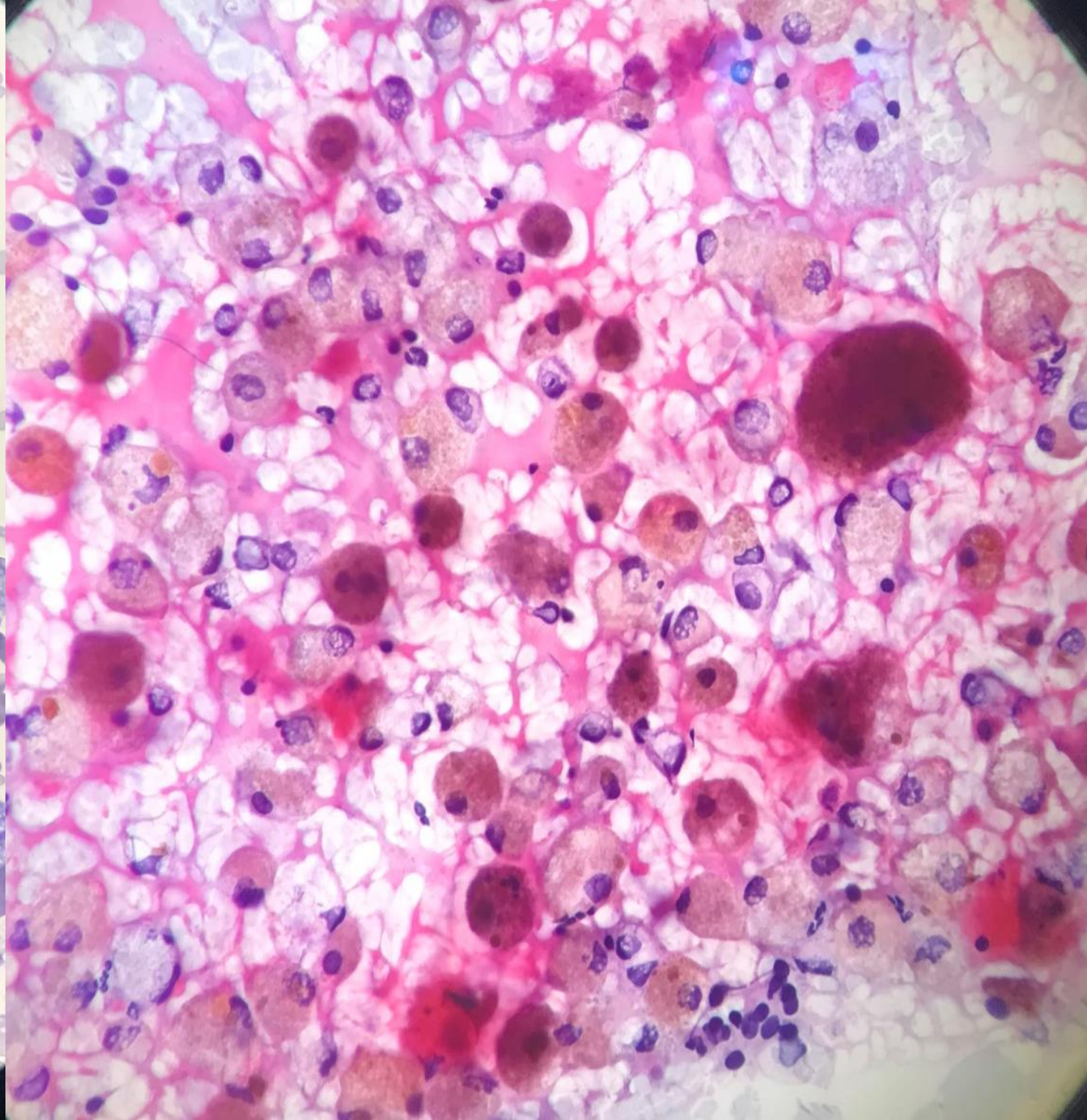


Benign thyroid cyst.
Prominent cystic degeneration often occurs in follicular nodular disease. Abundant macrophages and few benign thyroid follicular cells are present

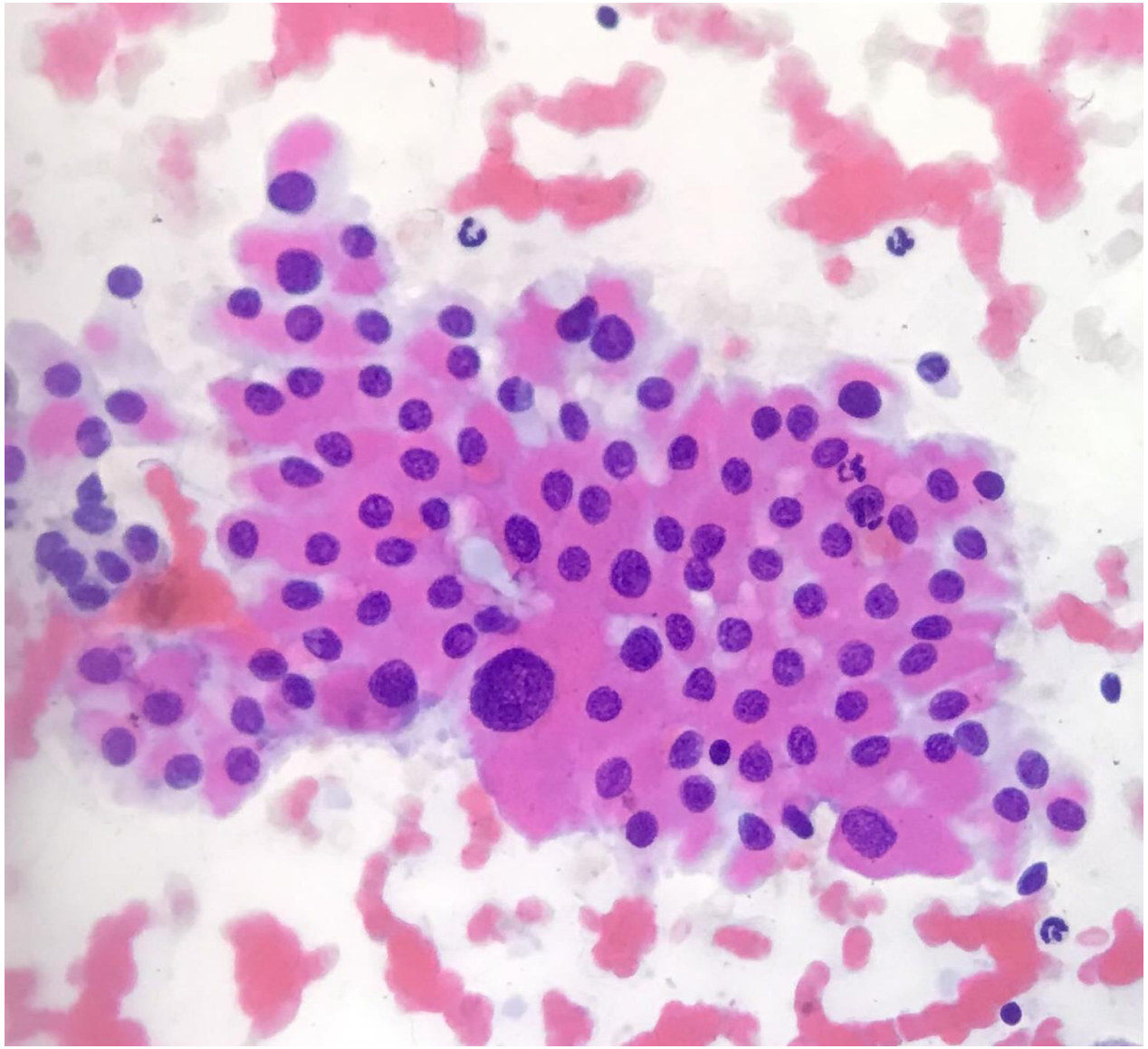


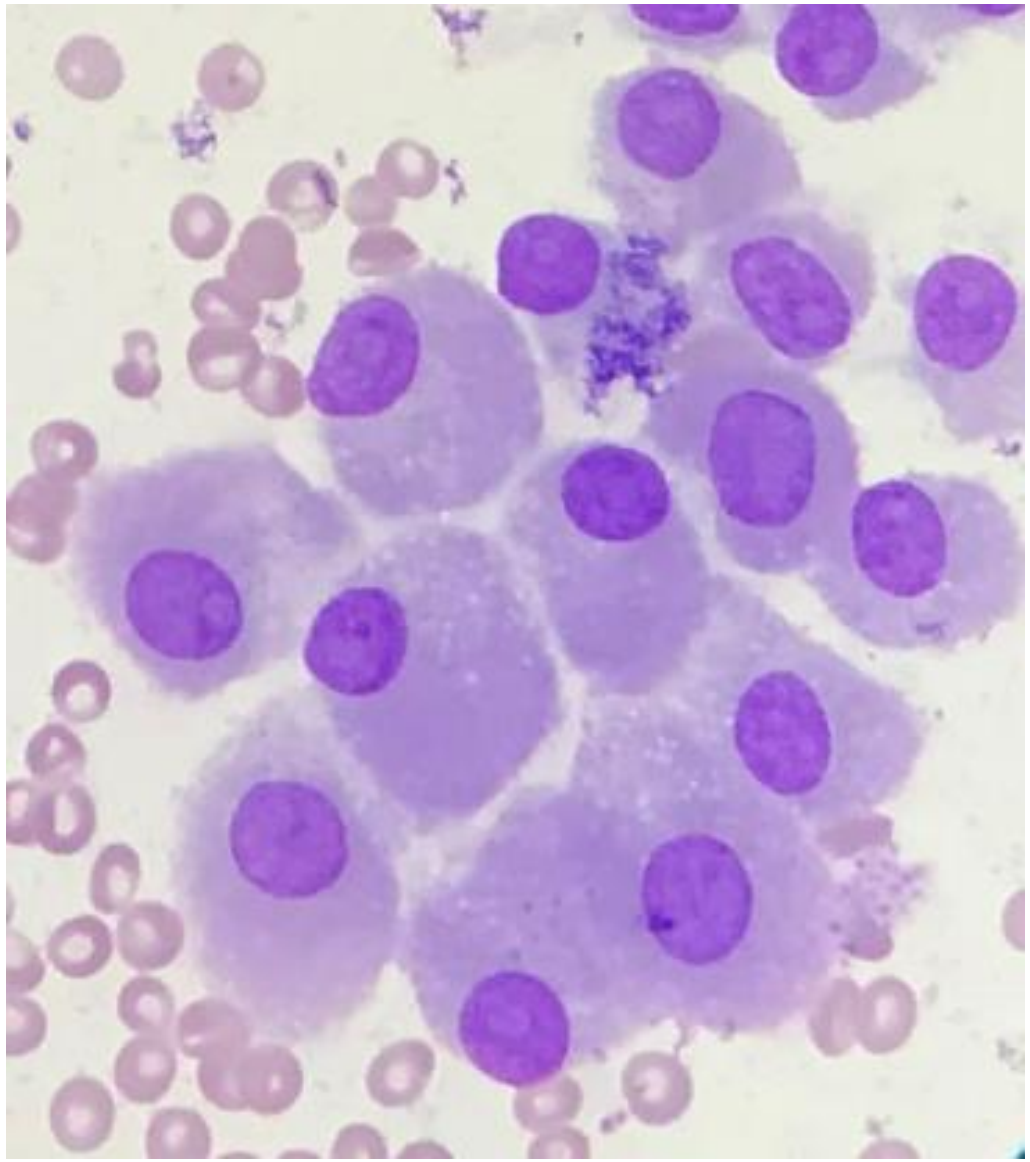


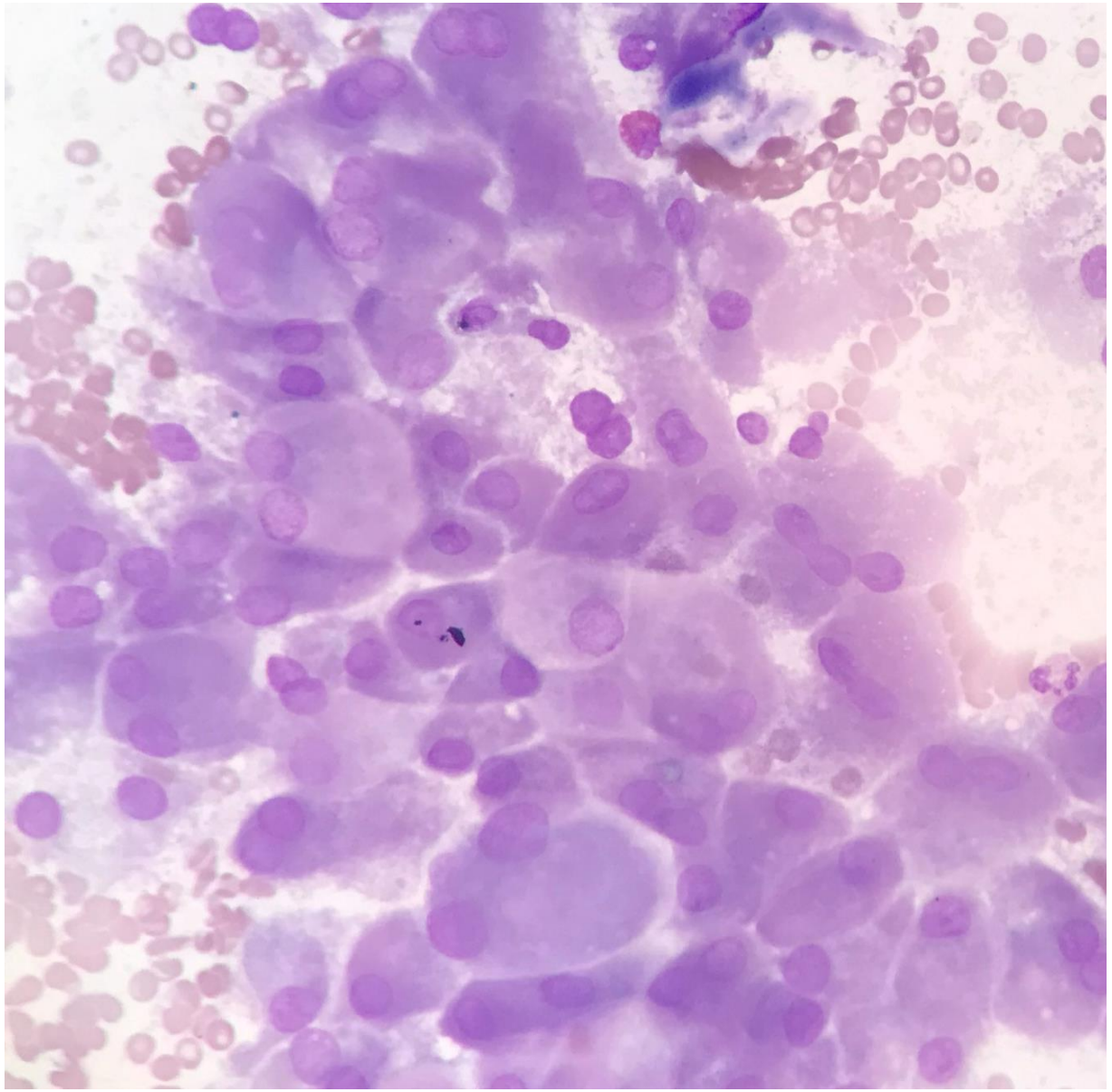


Oncocytes (Previously termed Hürthle cells)

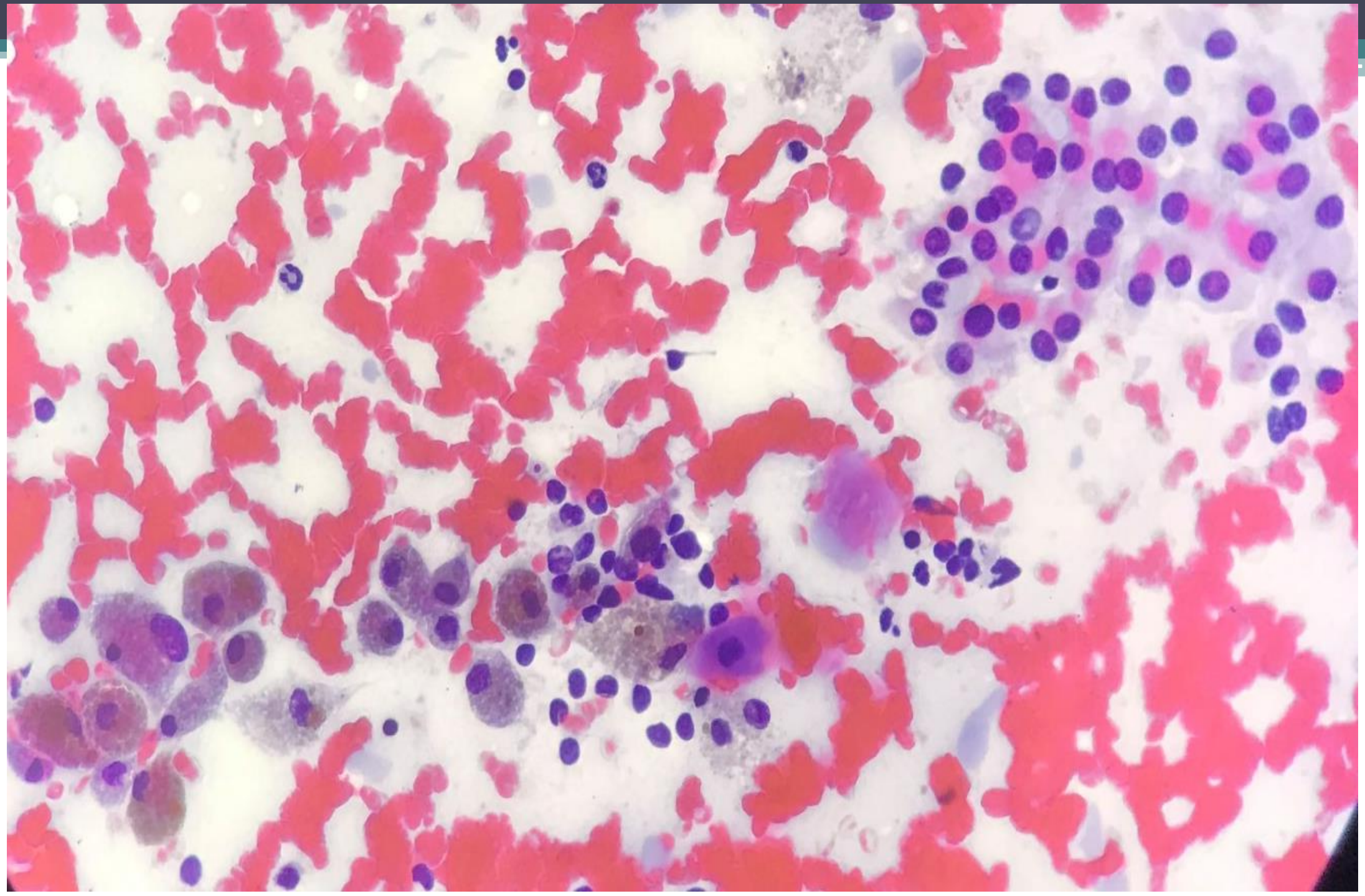


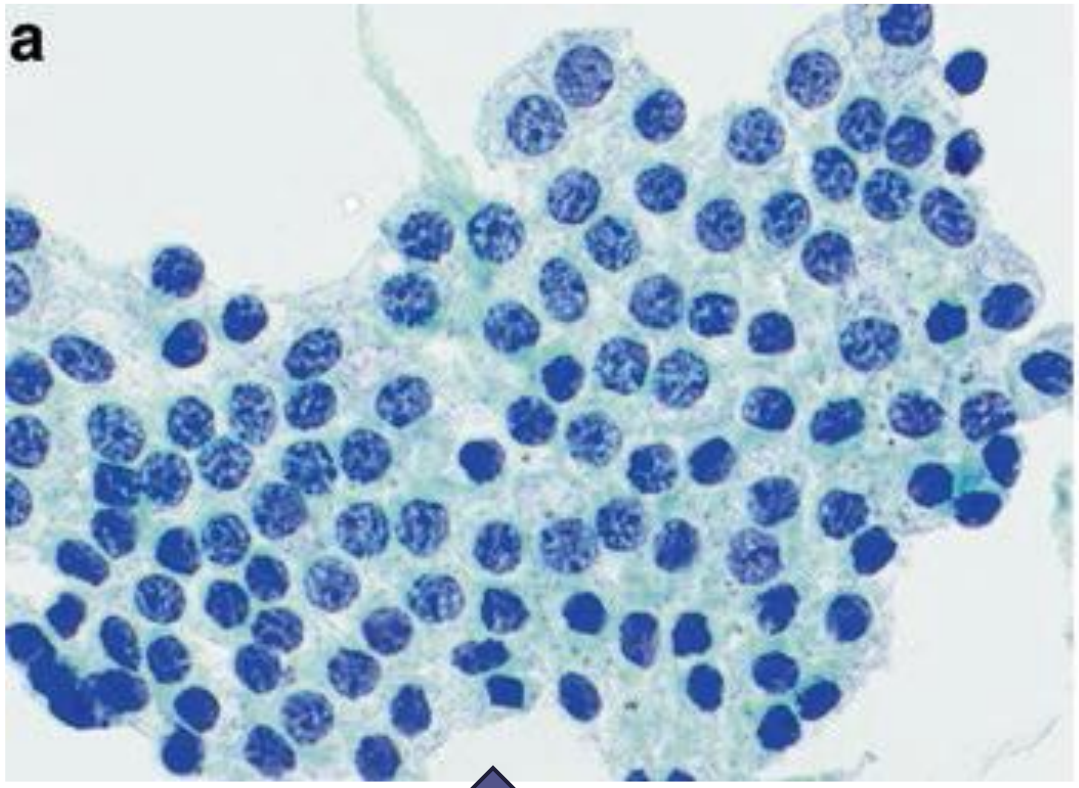


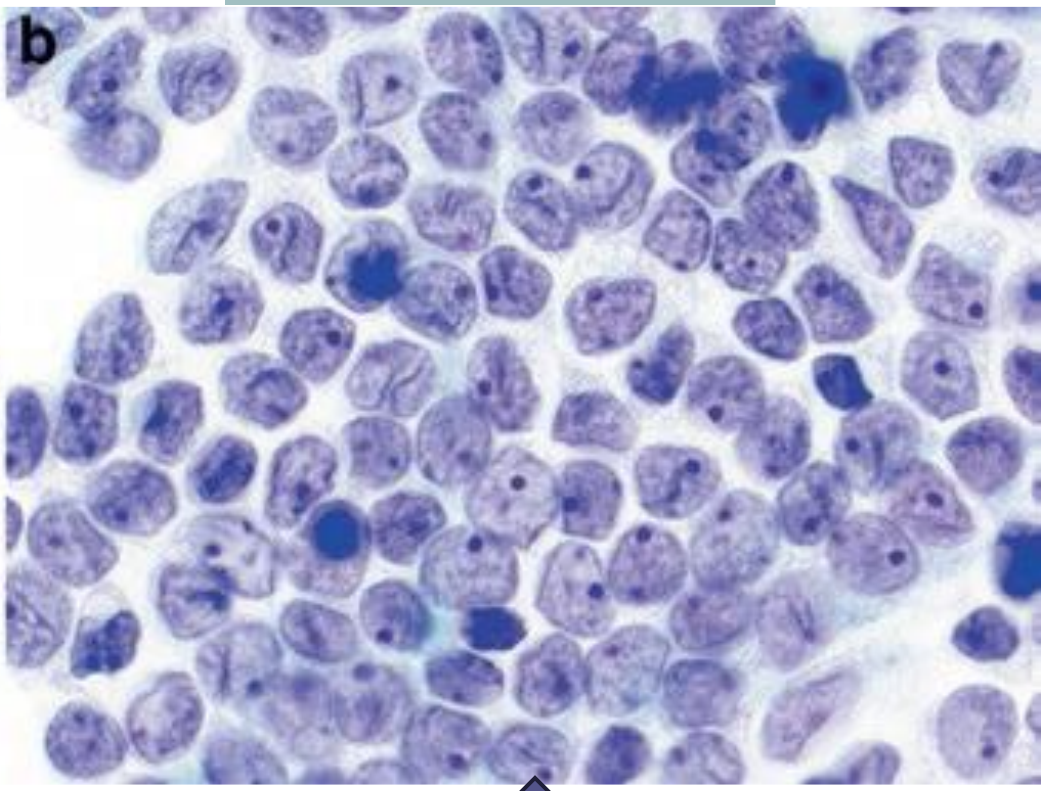


Follicular nodular disease (FND).

Oncocytes (Hürthle cells)

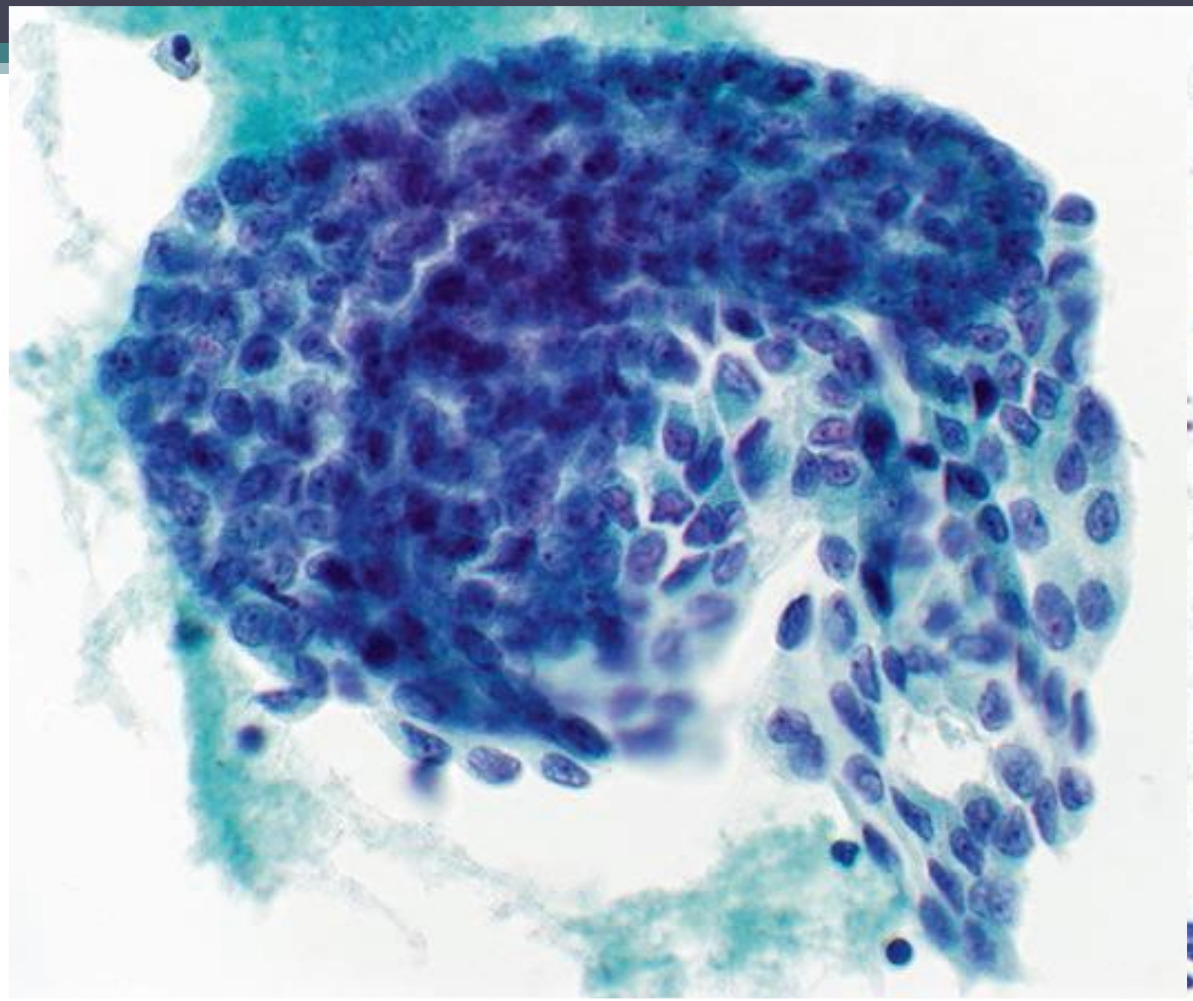




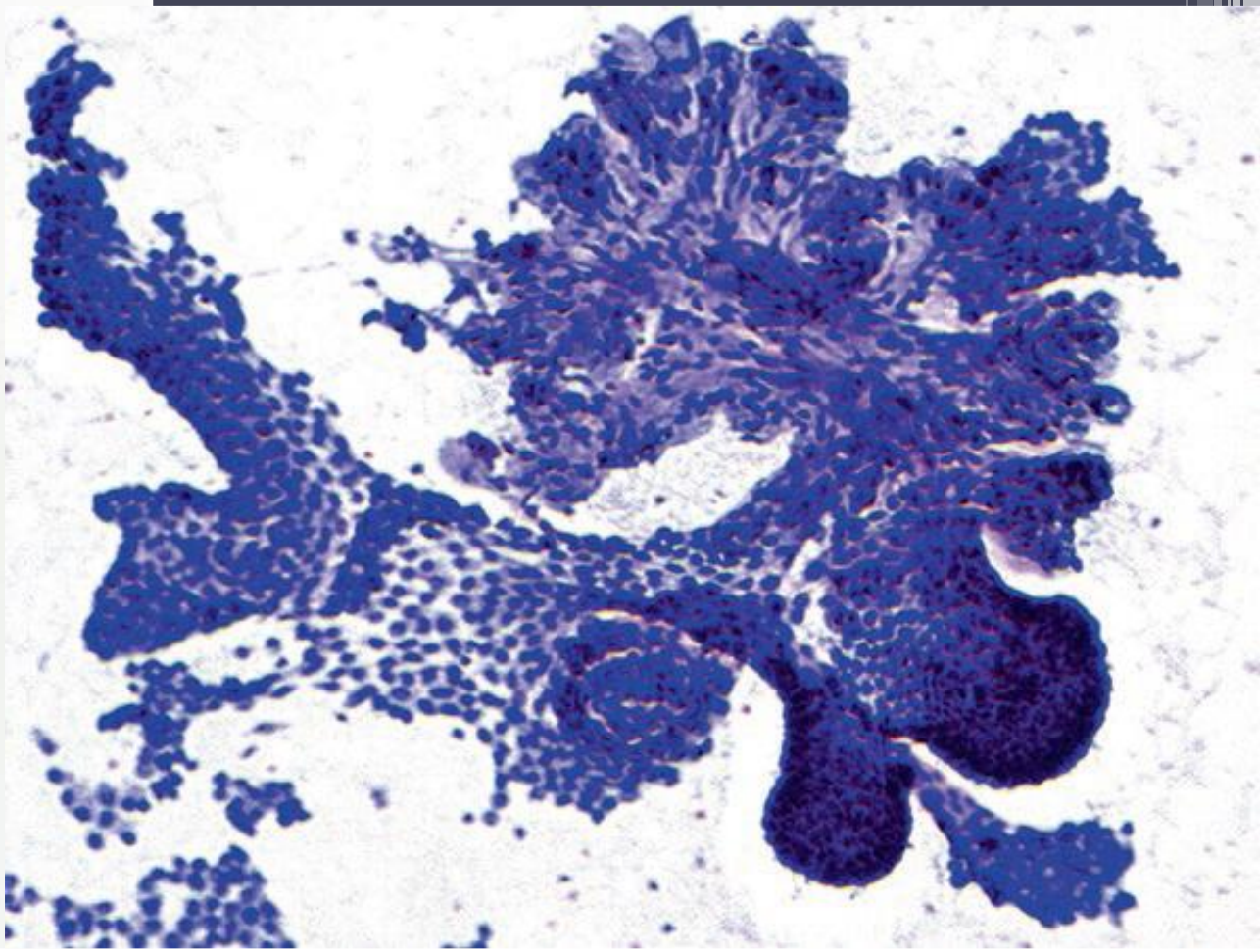


Comparison of **benign** follicular cells with the cells of **papillary** thyroid carcinoma:

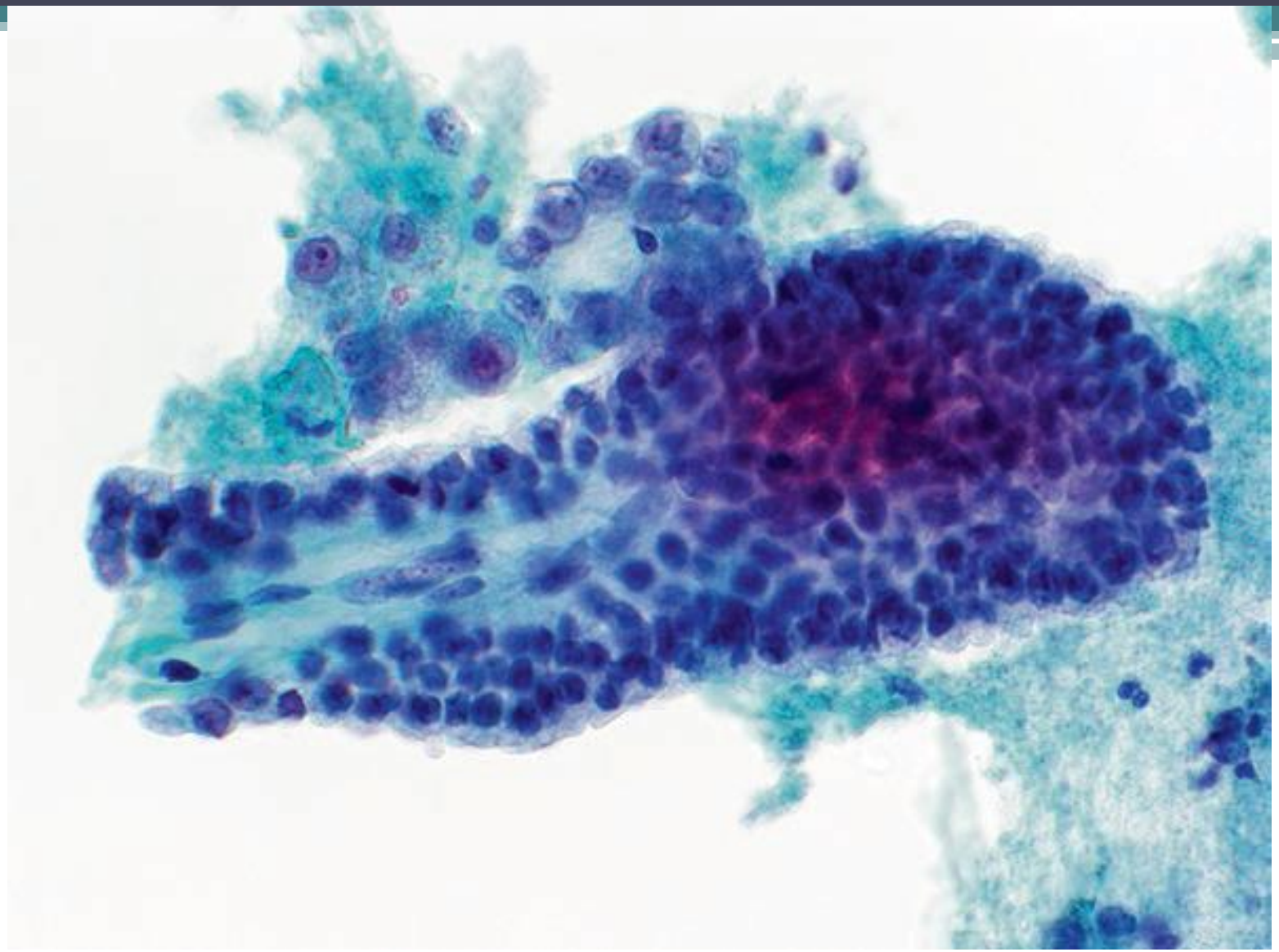
- **Nucelli**: larger, paler, more crowded, and more irregular



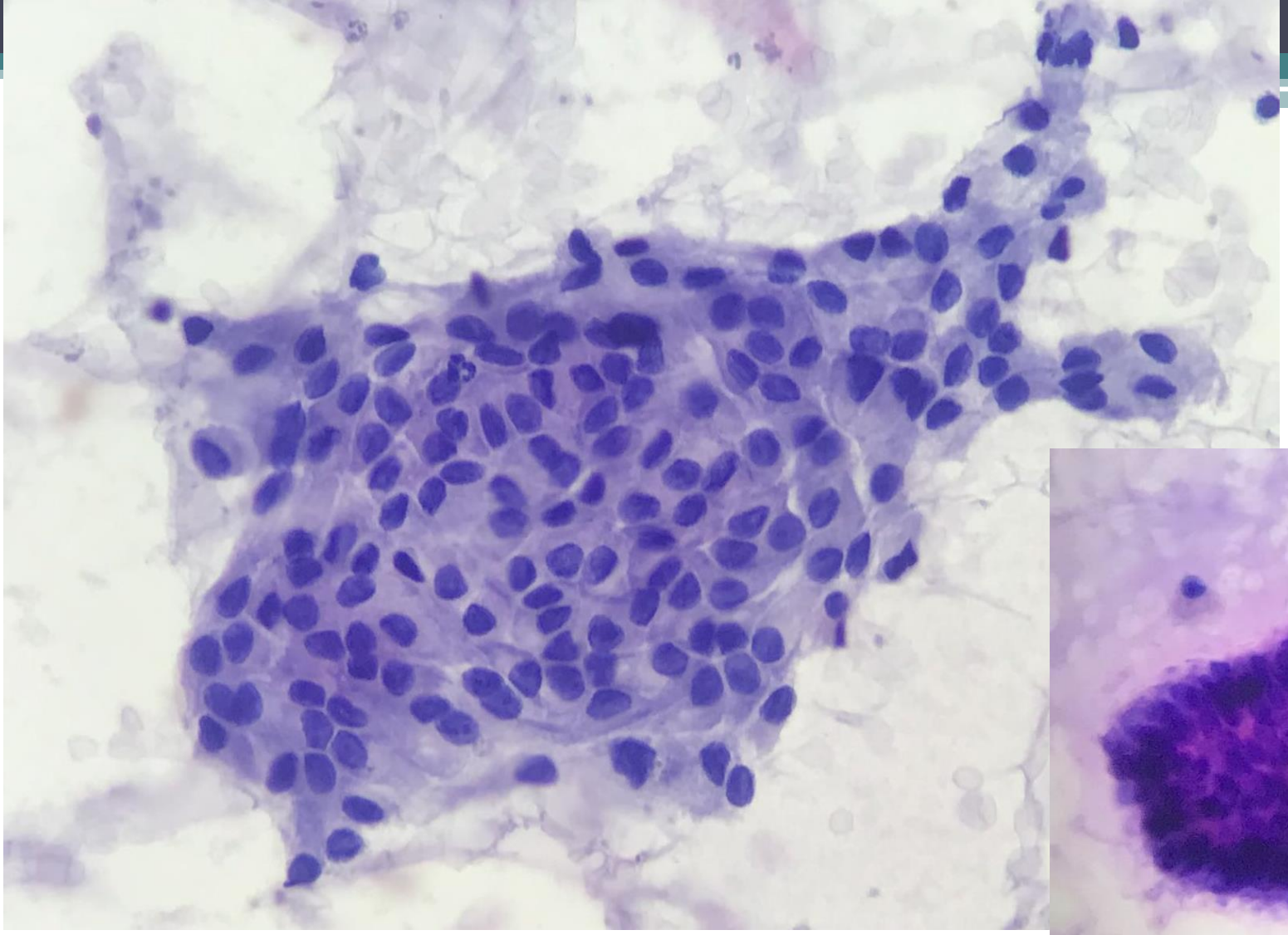
Cellular swirls are highly characteristic of the conventional (classic) papillary thyroid carcinoma

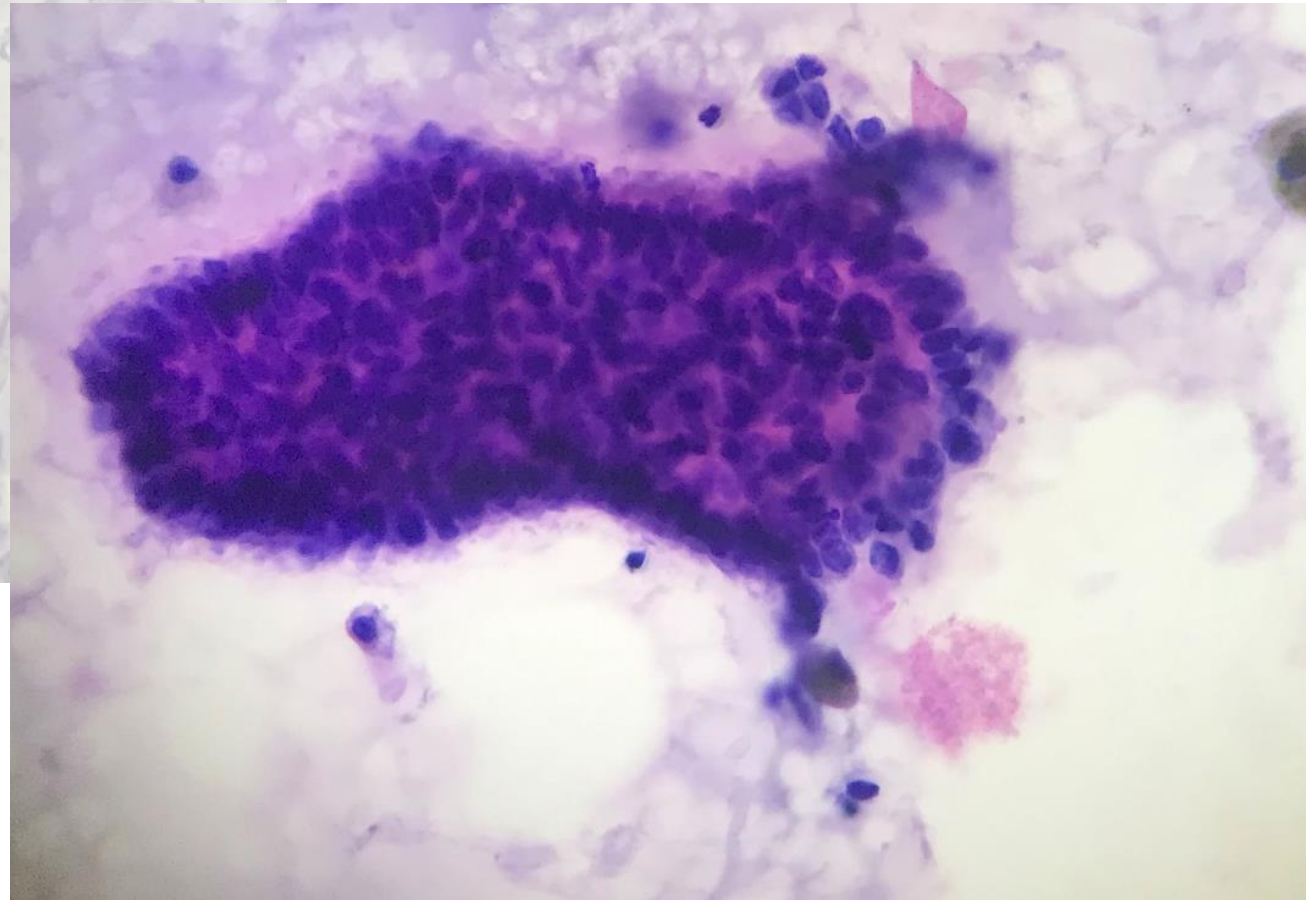


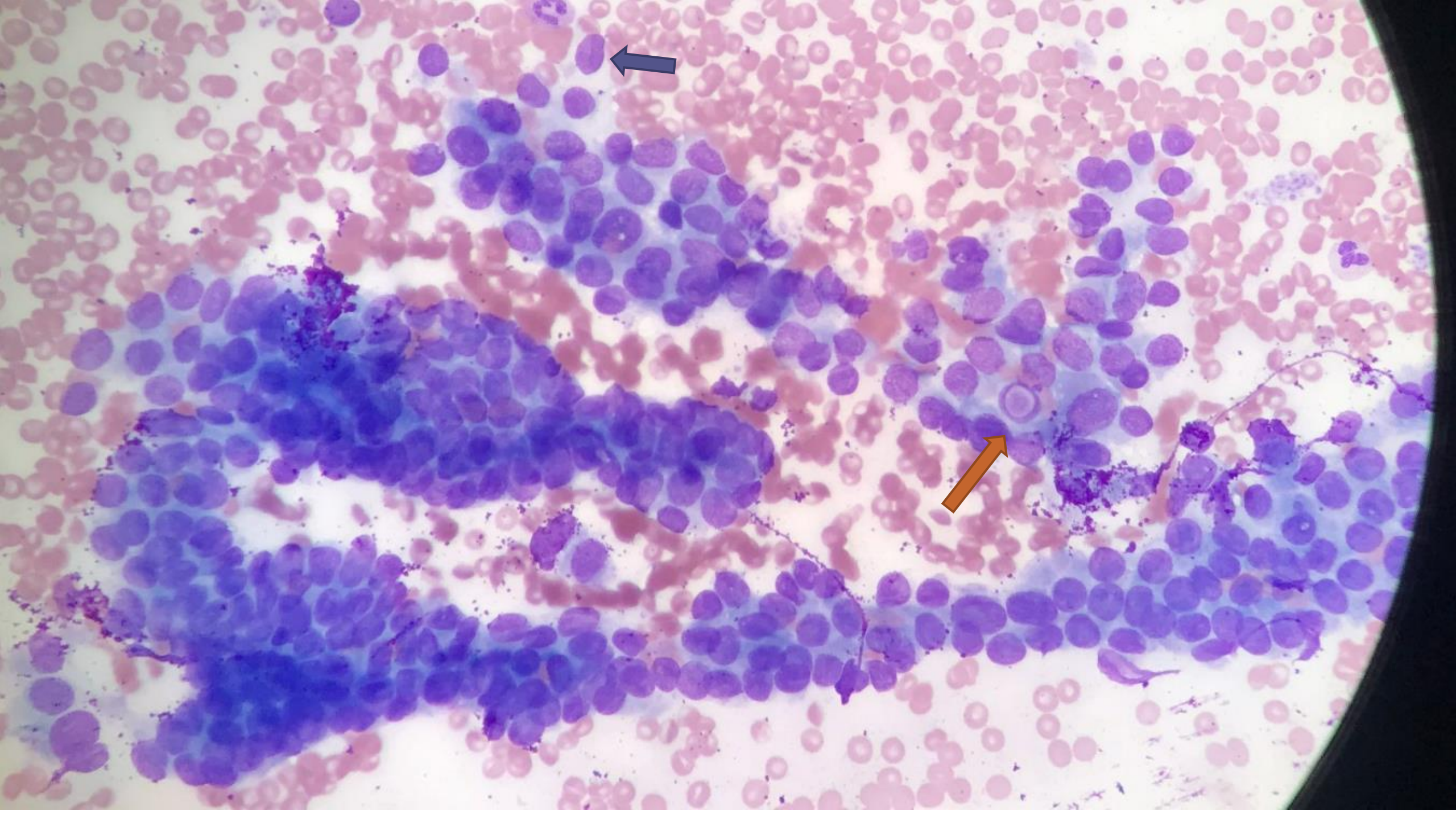
mixture of **flat sheets** and rounded**, papillary-like** fragments without fibrovascular cores

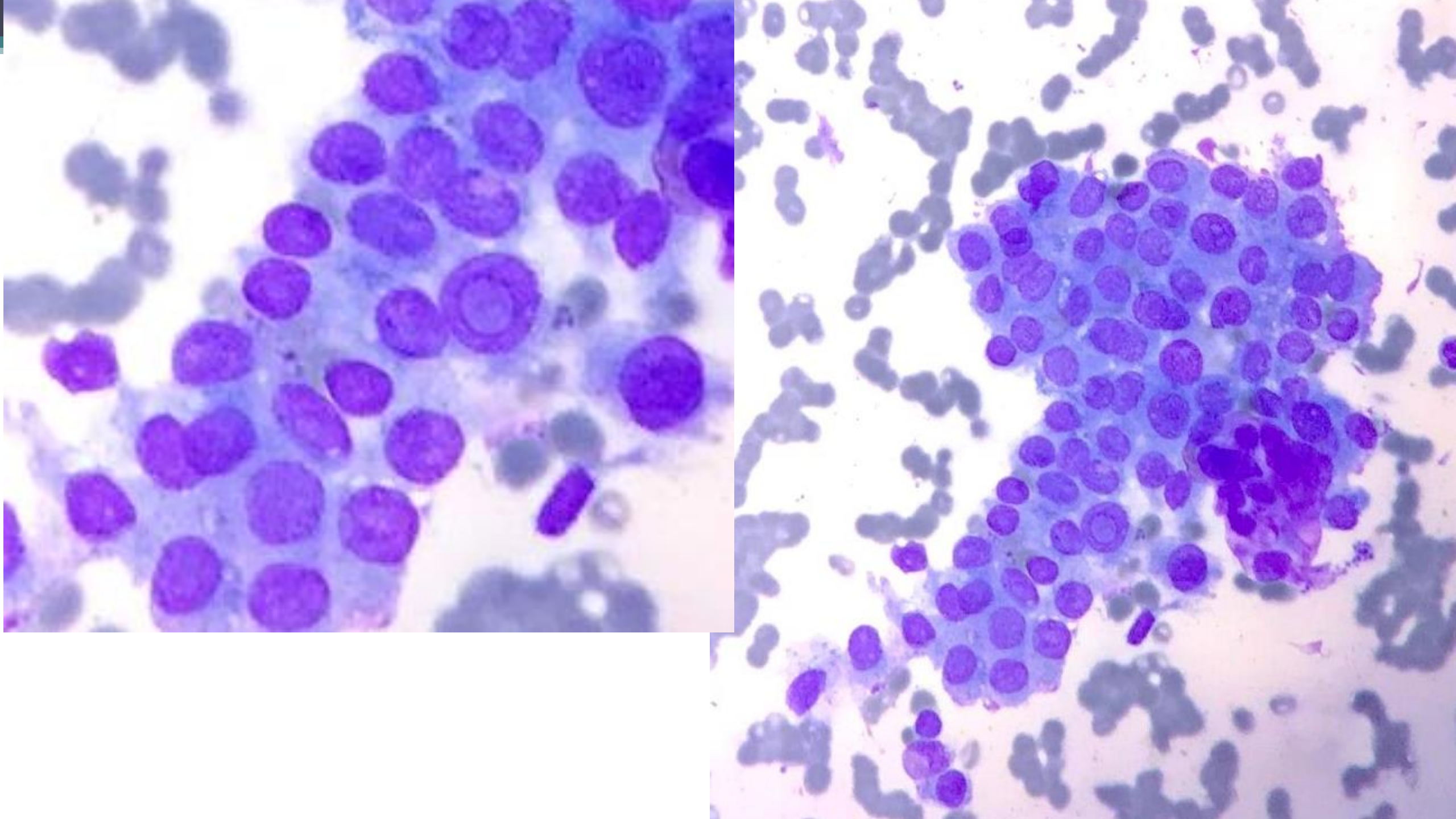


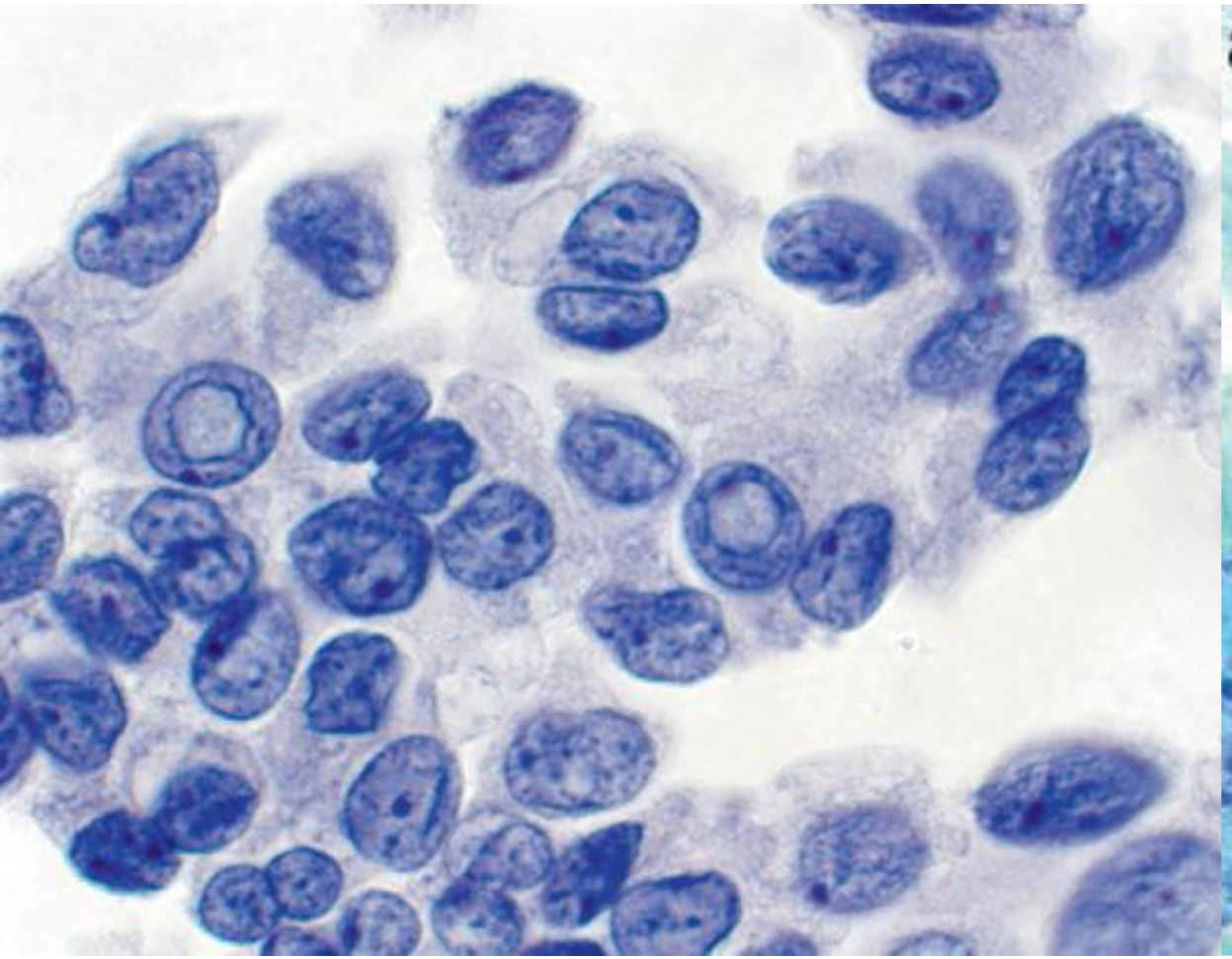
The neoplastic cells surround a **fibrovascular core**

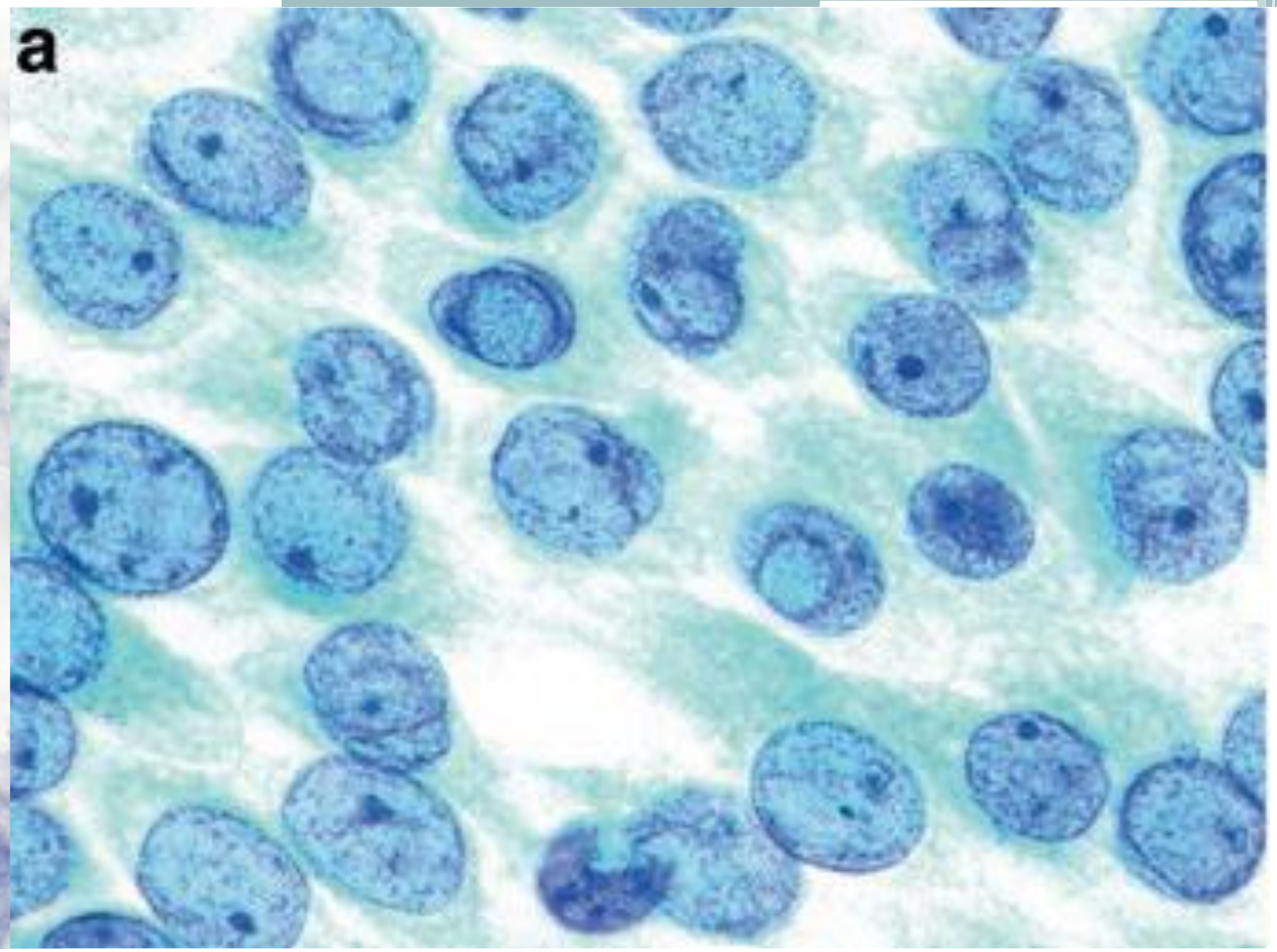











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Atypia of Undetermined Significance (AUS)

2018 edition: Atypia of Undetermined Significance (AUS) /**Follicular Lesion of Undetermined Significance (FLUS)**

Rate: 1% to over 20% of thyroid FNAs

diagnostic categories III

I. Nondiagnostic
Cyst fluid only
Virtually acellular specimen
Other (obscuring blood, clotting artifact, drying artifact, etc.)
II. Benign
Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other
III. Atypia of Undetermined Significance
Specify if AUS-nuclear atypia or AUS-other
IV. Follicular Neoplasm
Specify if oncocytic (Hürthle cell) type
V. Suspicious for Malignancy
Suspicious for papillary thyroid carcinoma
Suspicious for medullary thyroid carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
Other
VI. Malignant
Papillary thyroid carcinoma
High-grade follicular cell-derived non-anaplastic thyroid carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic malignancy
Non-Hodgkin lymphoma
Other

Three different patterns>>>called **"indeterminate" aspirate:** each with **distinct cytologic features** and **follow-up risk of malignancy (ROM)**

- **"Suspicious for malignancy" (SFM) : have a higher ROM :75%**
- **"Follicular Neoplasm" (FN) or "Oncocytic Follicular Neoplasm" (OFN): 30%**
- **Atypia of undetermined significance (AUS): overall lower ROM: 20%**
  - This category is reserved for cases with a **lesser degree** of atypia, nuclear and/or other in nature, which is **insufficient** to qualify for either the FN/OFN or SFM categories.

Risk of malignancy (ROM) ??

- Challenging
- Only a minority of AUS cases undergo excision
- Estimating the ROM based on histologic follow-up alone, overestimates the ROM due to selection bias
- AUS nodules are usually resected only if there are worrisome clinical or sonographic features, an abnormal repeat aspiration result, and/or an abnormal molecular testing result

- **Clearly lower than** that of the SFM category
- But **overlaps** with the risks associated with the **FN or OFN** categories

- **ROM is higher (~20–30%)** than initially predicted when TBSRTC was introduced in 2007 (~5–15%)

ROM

Differs according to the **nature** of the atypia **:**

- **Nuclear atypia** (previously referred to as cytologic atypia in the second edition of Bethesda) approximately **twofold higher ROM compared** with other types of atypia, including those with only architectural atypia

- **Oncocyte predominant AUS** has a lower ROM than other AUS patterns

NIFTP is also estimated to **reduce** the ROM of an AUS diagnosis by **6–20%**

Definition

This diagnostic category **reserved** for specimens that :

- Contain one or more of a heterogeneous group of findings that **raise concern for neoplasm/malignancy**
- But are **insufficient** to be classified as a follicular neoplasm, suspicious for malignancy, or malignant
- The findings are **more marked** than can be ascribed confidently to benign changes

Most frequently, AUS is due to **atypia in follicular cells** (typically nuclear and/or architectural in nature) or a predominance of **oncocytic** cells

Rate: **1% to over 20%** of thyroid FNAs are AUS

AUS **subclassification (2023)**

- To reflecting **clinical risk and subsequent management**
- **Enhanced communication** with other pathologists and clinical providers
- Now subclassified into one of two broad subcategories in this update:
  - AUS with **nuclear atypia** : raises a low level of concern for **papillary carcinoma** or NIFTP **("AUS with nuclear atypia")**
  - **Other (non-nuclear) features** result in an AUS interpretation **("AUS—Other").**
    - Such as **architectural or oncocytic**

Important for AUS

- **Adequacy of the specimen: qualitative , quantitative**
- **Specify if it is scant or otherwise compromised by limiting factors**
- If there is atypia in a **scant or suboptimal aspirate**, including this **information in the report further guides management**
  - **Repeat aspirate** : initial aspirate is scanty cellular or poorly preserved/ degenerated
  - **Molecular testing or core needle or surgery** : for follow-up of a cellular, well-preserved aspirate with diffuse mild nuclear atypia.

AUS subclassification / criteria

AUS with Nuclear Atypia

~~Cytologic atypia~~

- Focal Nuclear Atypia
- Extensive But Mild Nuclear Atypia
- Atypical Cyst Lining Cells
- Histiocytoid" Cells
- Nuclear and Architectural Atypia

AUS-Other

~~Hürthle cell aspirates~~

- Architectural Atypia
- Oncocytic/Oncocyte Atypia
- Atypia, Not Otherwise Specified (NOS)
- Atypical Lymphoid Cells, Rule Out Lymphoma

AUS with Nuclear Atypia

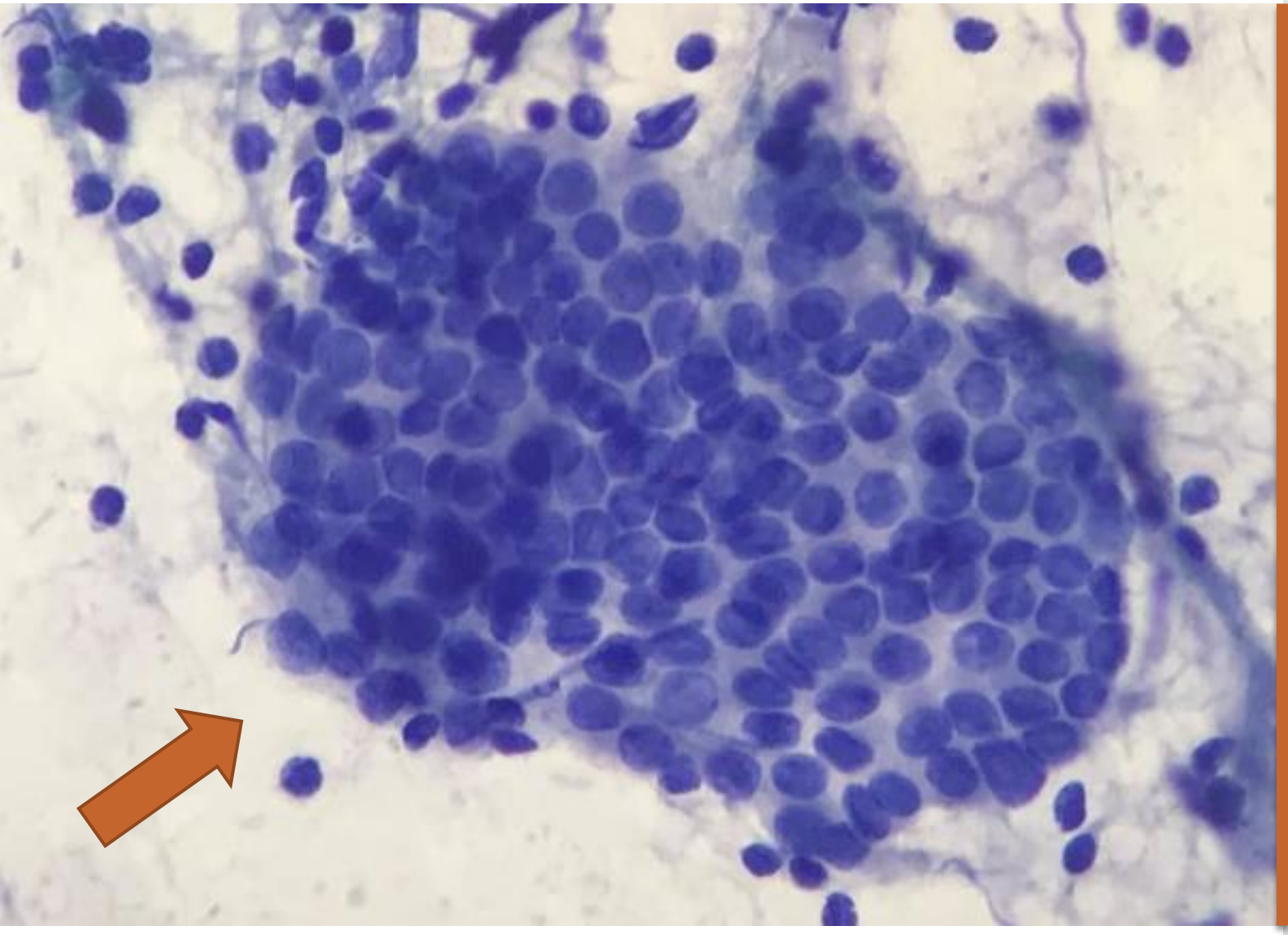
AUS Nuclear → ***Focal nuclear atypia***

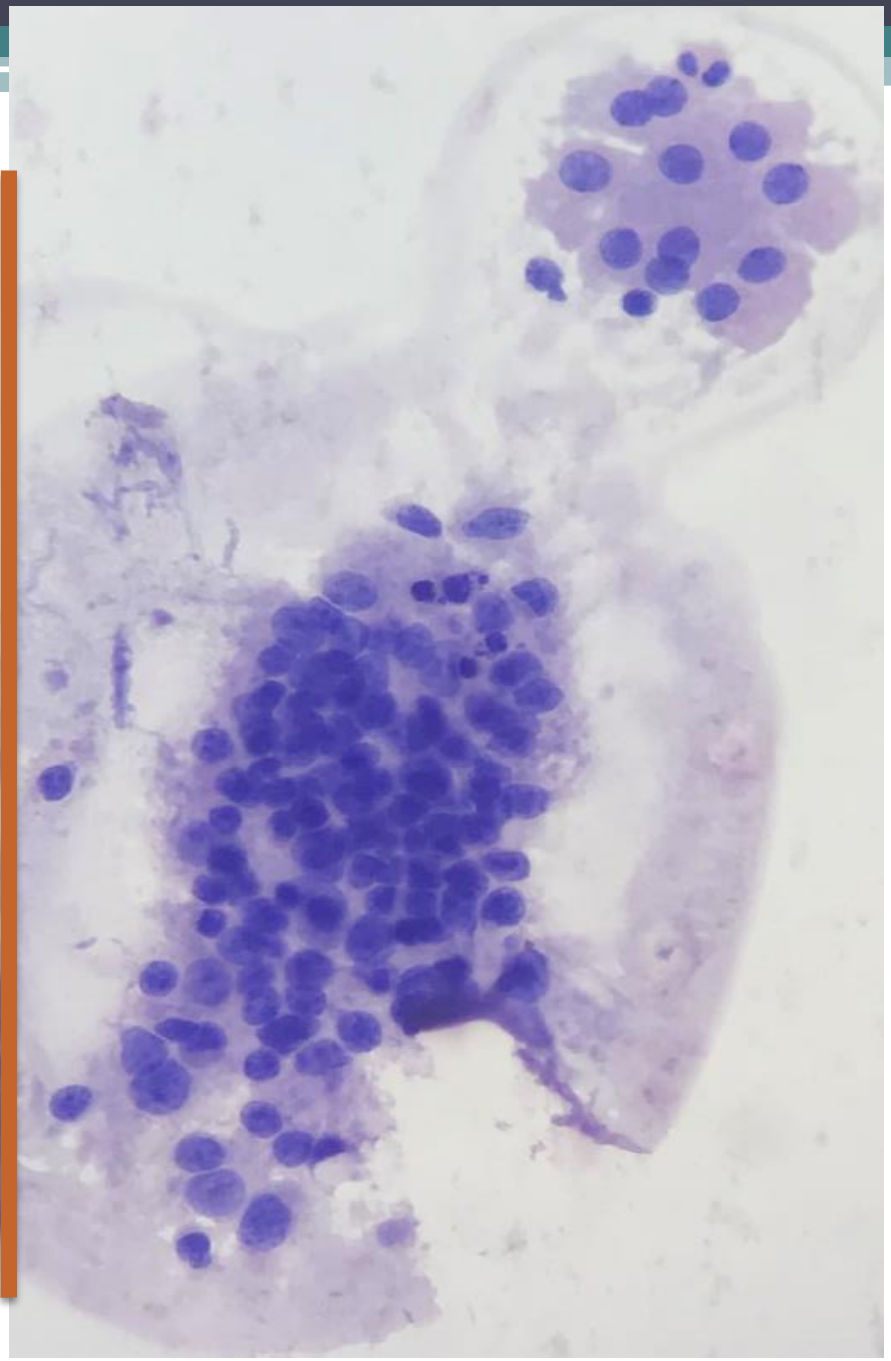
1. **Most** of the aspirate appears **benign**, **but**

   rare cells have **nuclear** enlargement, pale chromatin, and irregular nuclear contours ,<u>especially</u> common in patients with lymphocytic (Hashimoto) thyroiditis

   - **Nuclear pseudoinclusions are typically <u>absent</u>**
     - ×**Rare** pseudoinclusions by **themselves** may prompt an AUS diagnosis,
     - ×**but** if they are **accompanied** by other compelling features of papillary carcinoma, the case should be considered **suspicious for malignancy**.

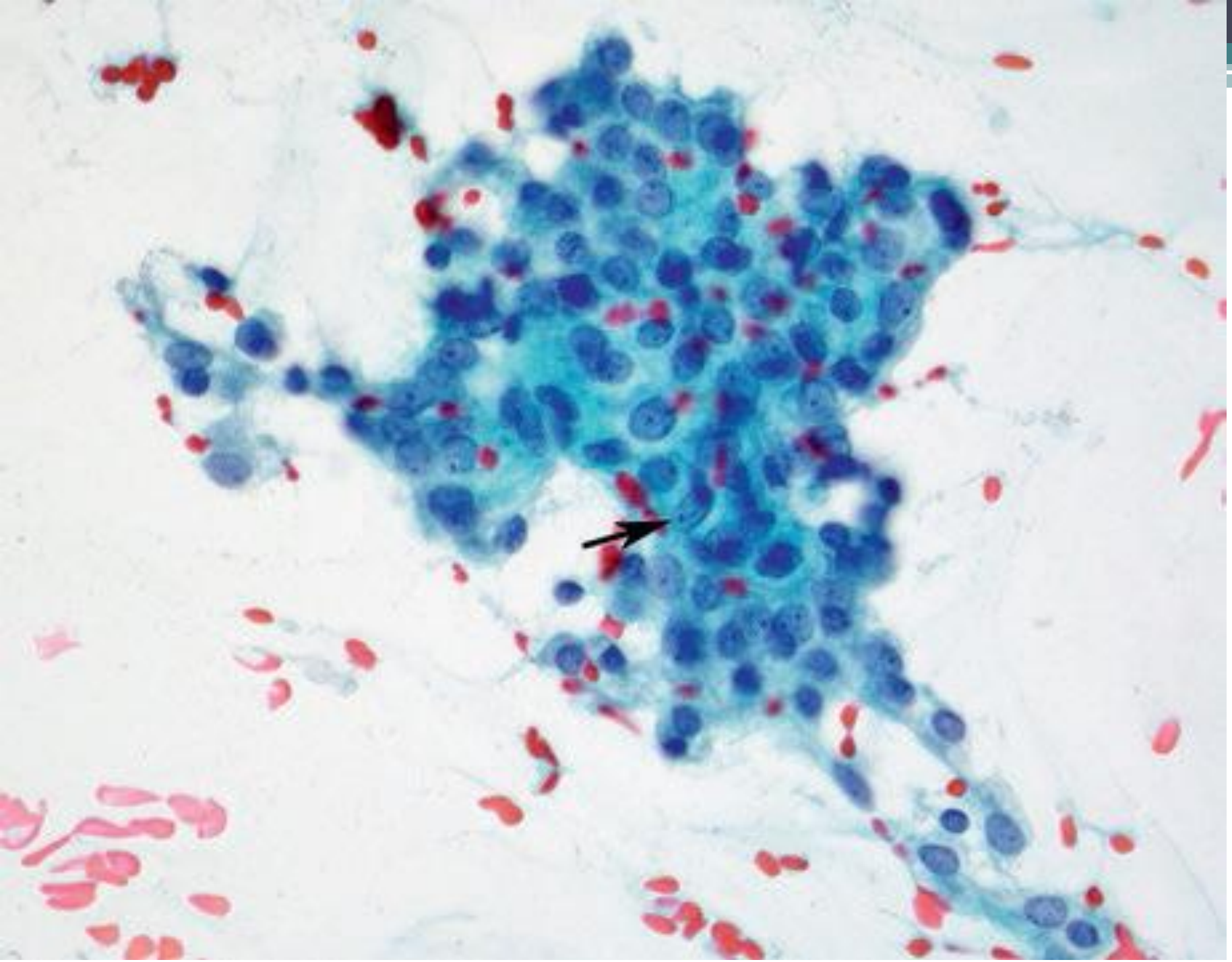
2. Alternatively, a sample may be paucicellular and contain cells as described above





AUS Nuclear → ***Extensive but mild nuclear atypia***

- **Many,** if not most, cells have **mildly** enlarged nuclei with **slightly** pale chromatin and only **limited** nuclear contour irregularity.
- Nuclear pseudoinclusions are typically **absent**



AUS with nuclear atypia.
Follicular cells show mild enlargement, small distinct nucleoli, and pale chromatin. Nuclear contours are uniform with only a rare nuclear groove (arrow).
Molecular testing identified an *HRAS* mutation.
Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was diagnosed at lobectomy (smear, Papanicolaou stain)

AUS Nuclear →

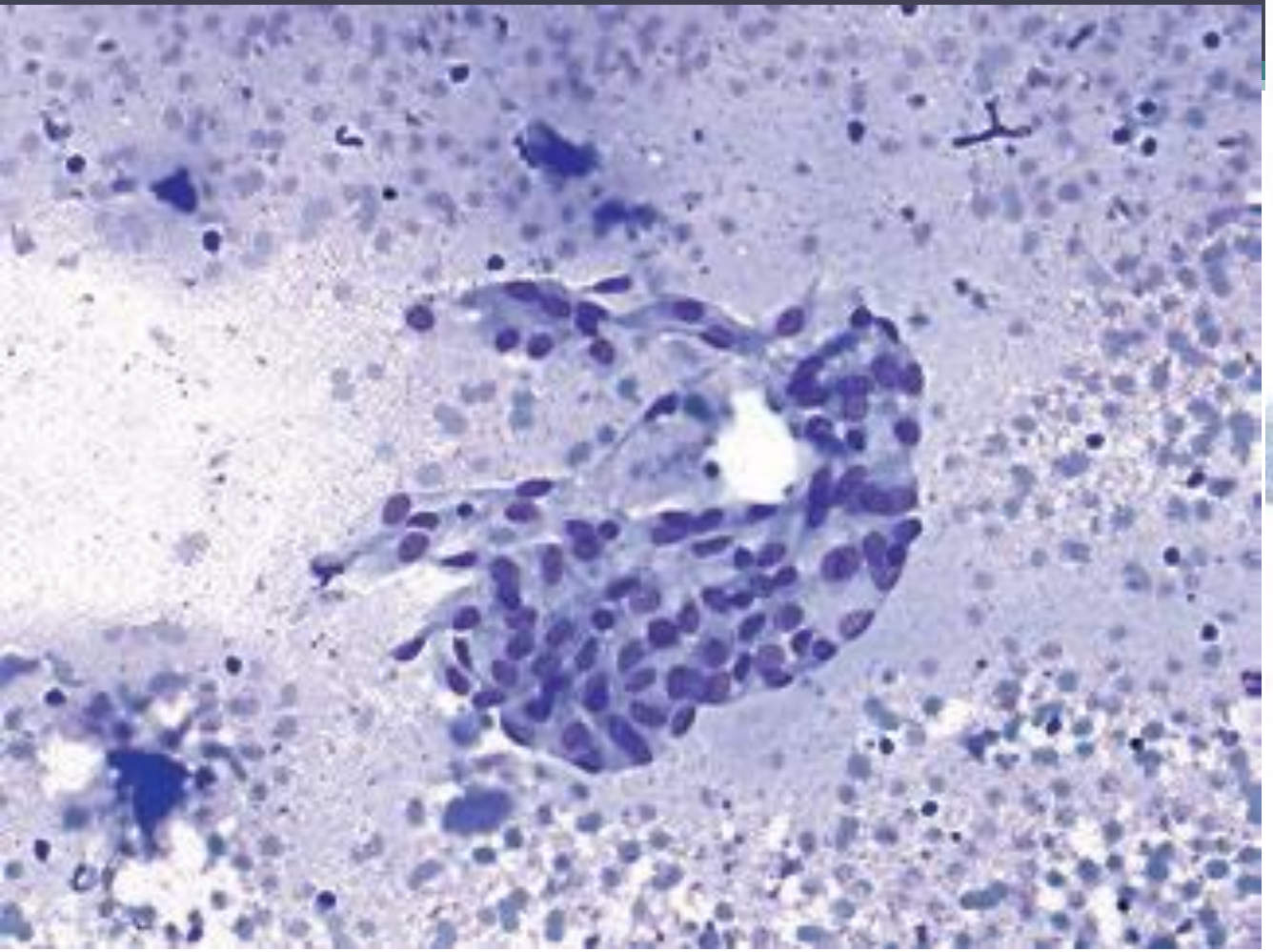
Atypical cyst-lining cells

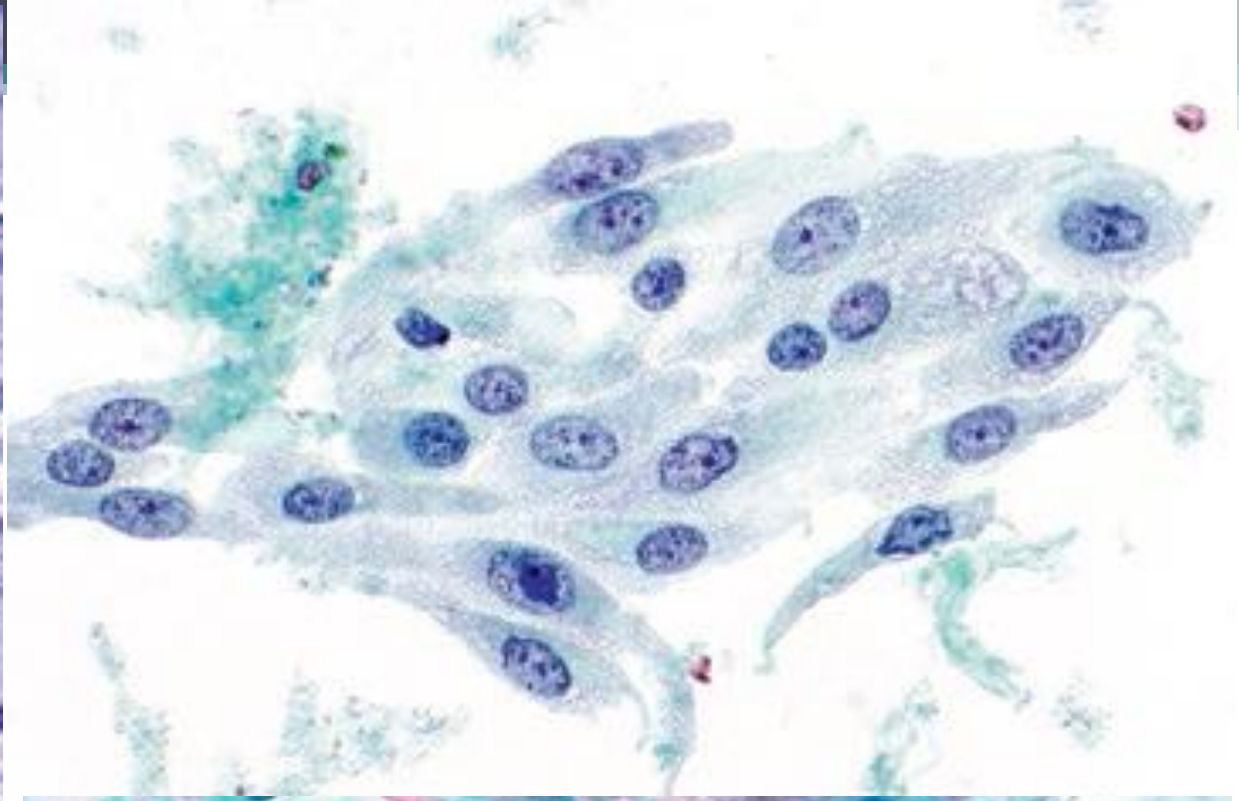
Cyst lining cells:

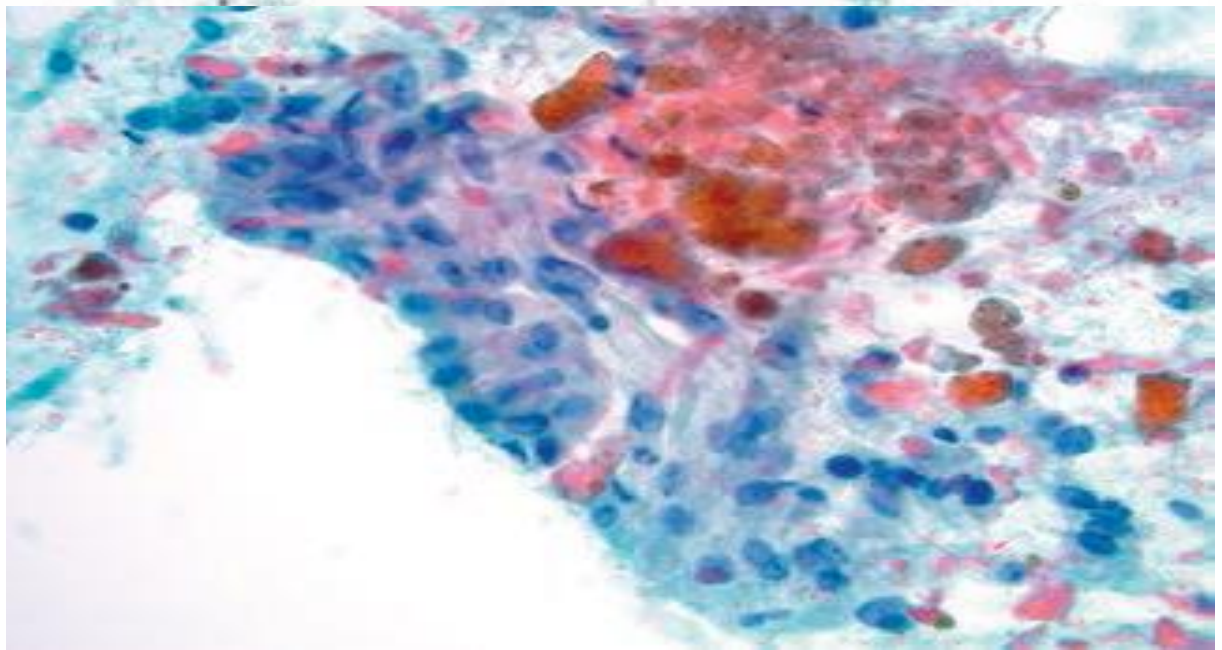
- Associated with **cystic degeneration** of thyroid nodules: Are virtually **always** associated with hemosiderin-laden **macrophages**

- **Reactive** follicular and/or mesenchymal cells
- Cytomorphology has been **well described** and diagnosed as **benign**

- Very characteristic features : typically elongated, with pale chromatin, occasional intranuclear grooves, and relatively large nucleoli
- Spindle-shaped morphology of the cell and nucleus is helpful in distinguishing these cells from papillary carcinoma



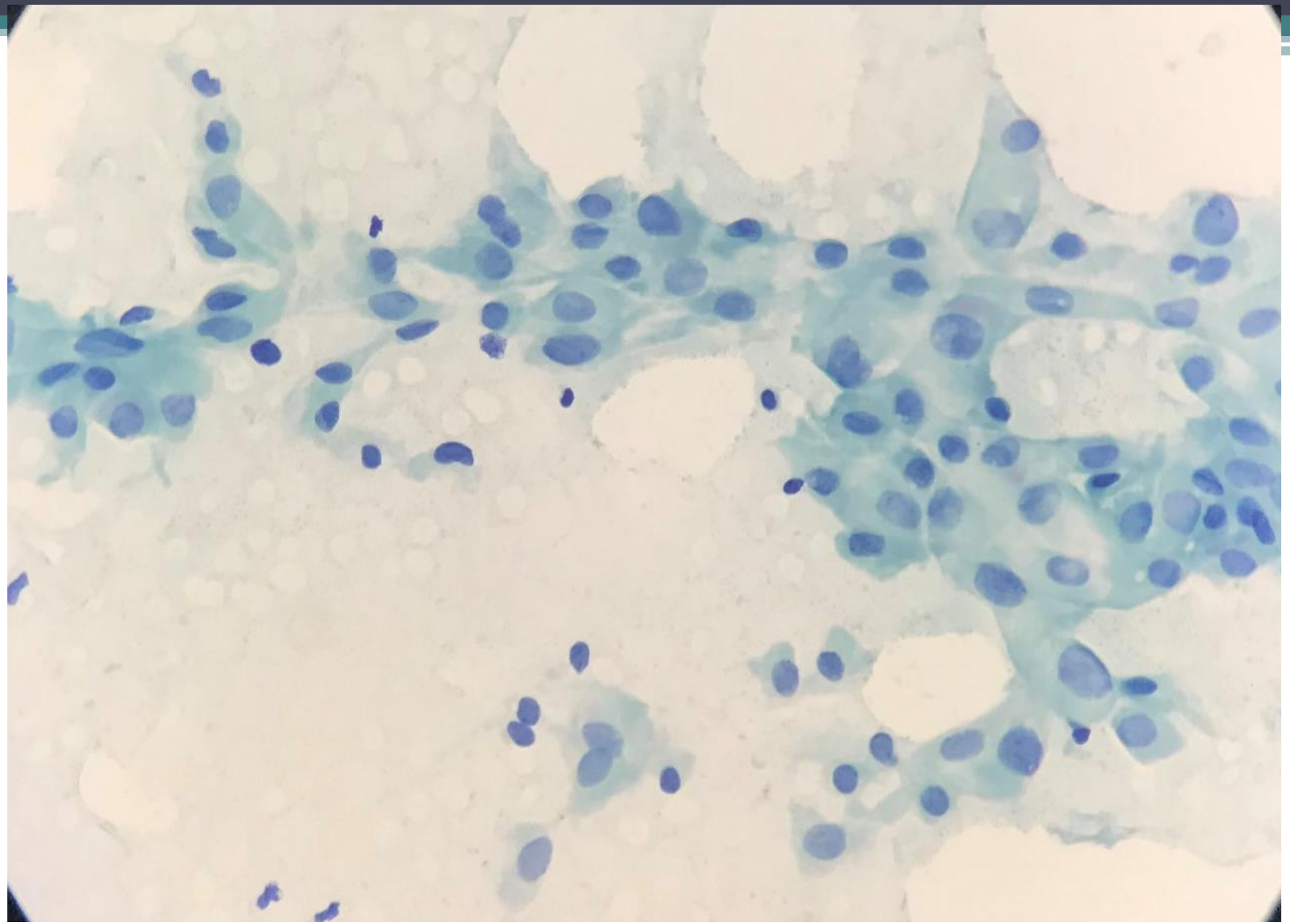




Follicular nodular disease:

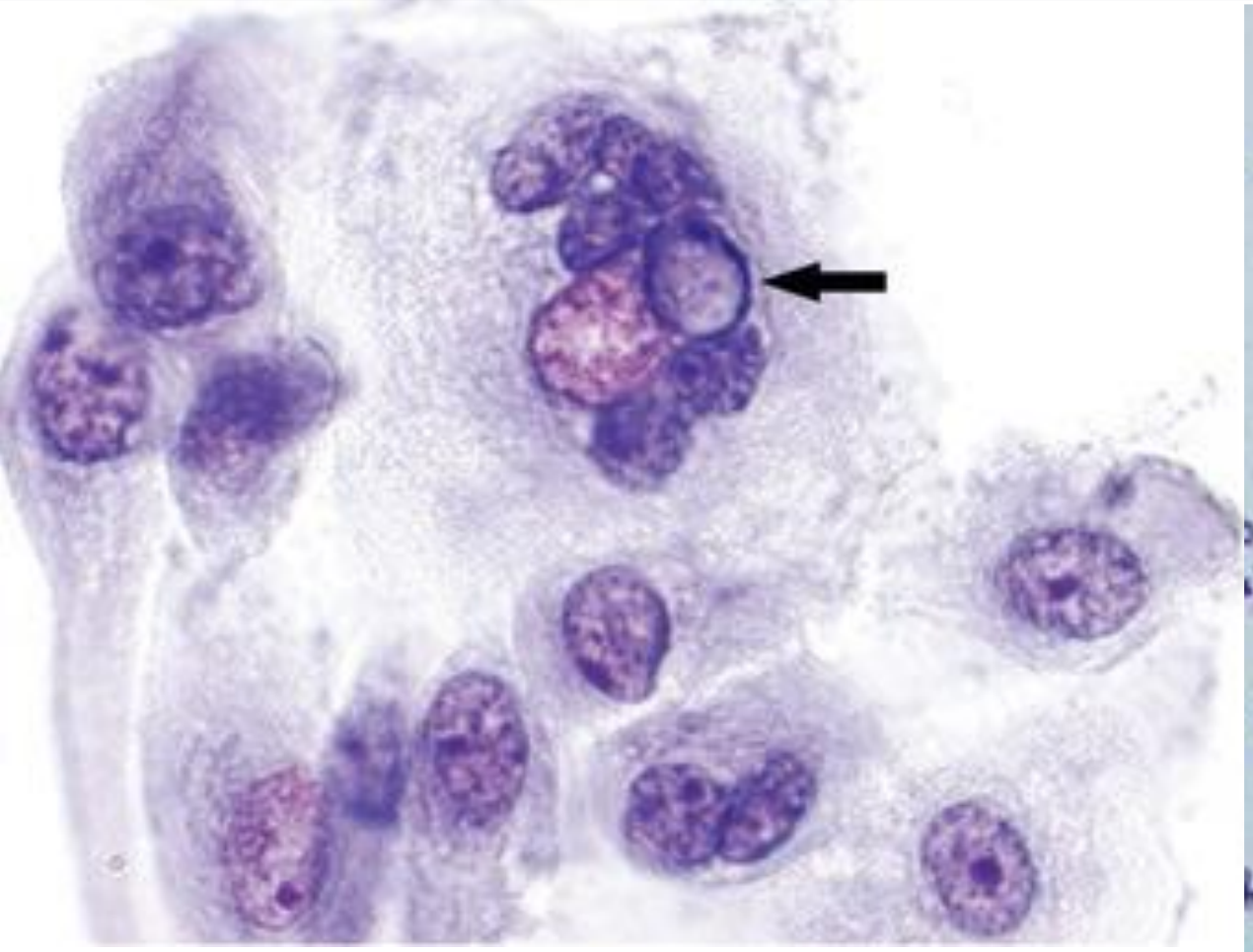
cyst lining cells.

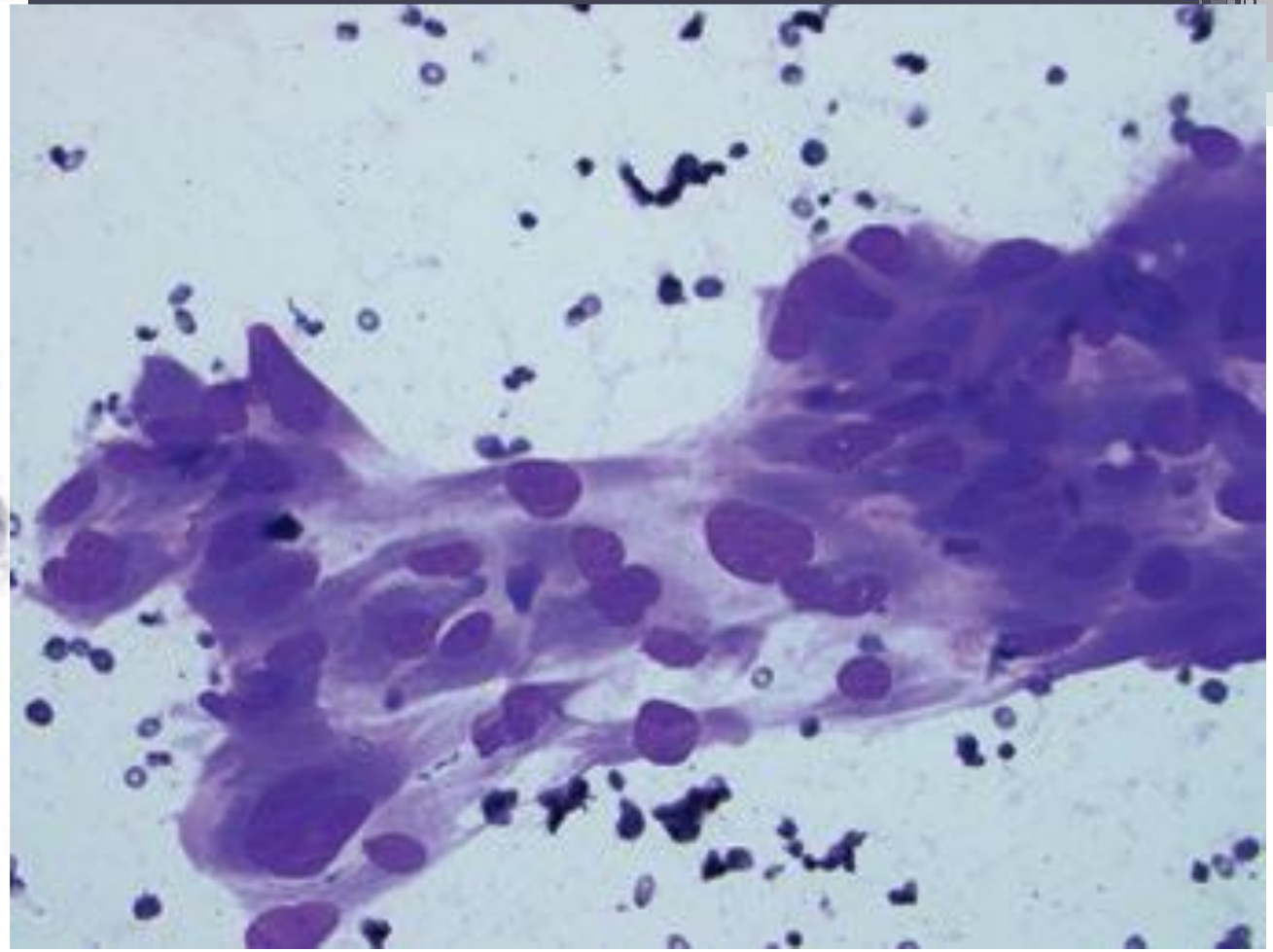
Reparative changes



Atypical cyst-lining cells

- In **rare** cases, there is **more atypia than usual** >>> diagnose these as **AUS**.
  - **Due to the presence** of more cohesive cells, nuclear grooves, prominent nucleoli, less elongated nuclei and cytoplasm, pulled out cytoplasm and/or rare intranuclear pseudoinclusions
  - in an **otherwise predominantly benign-appearing sample**

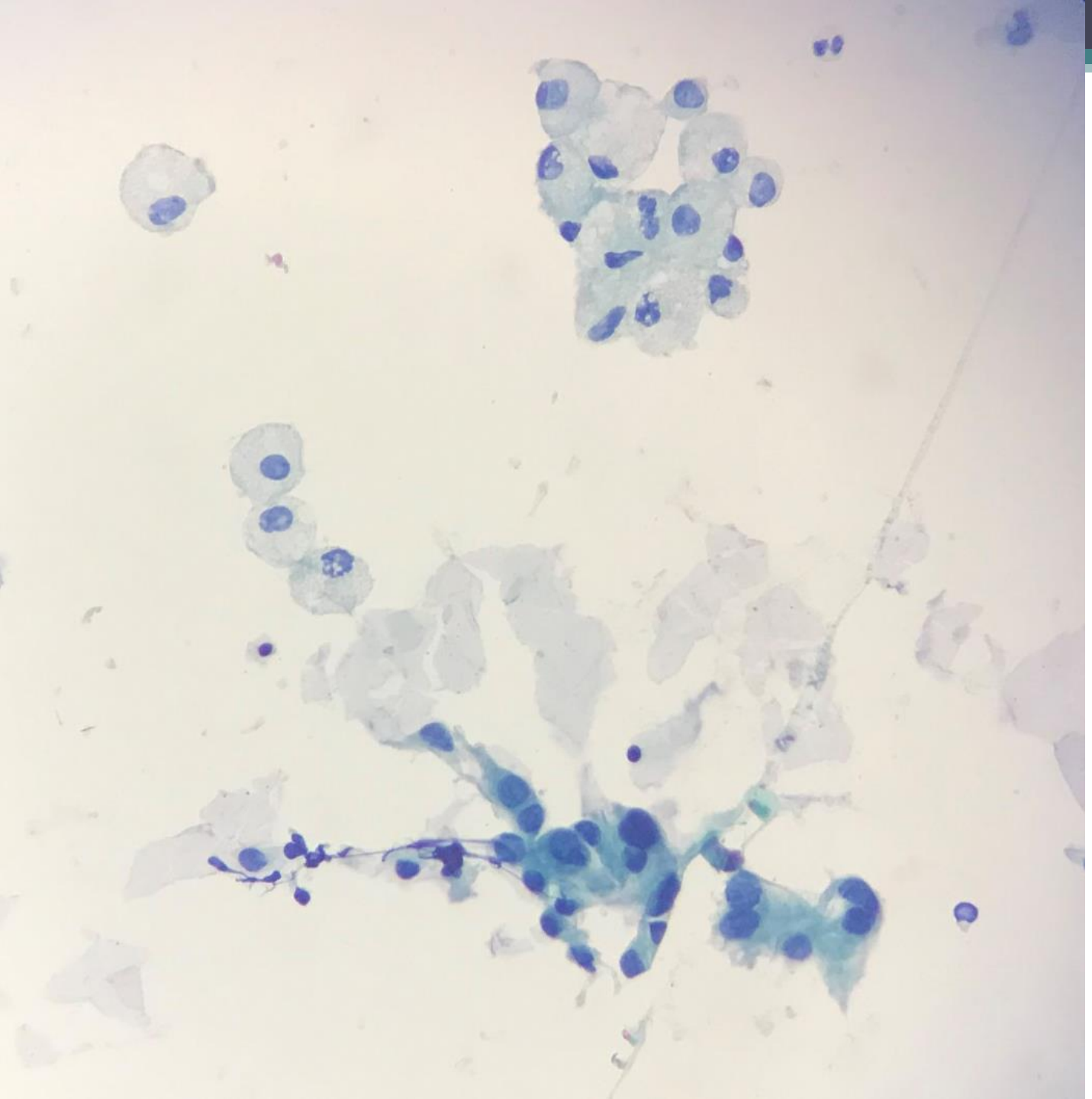


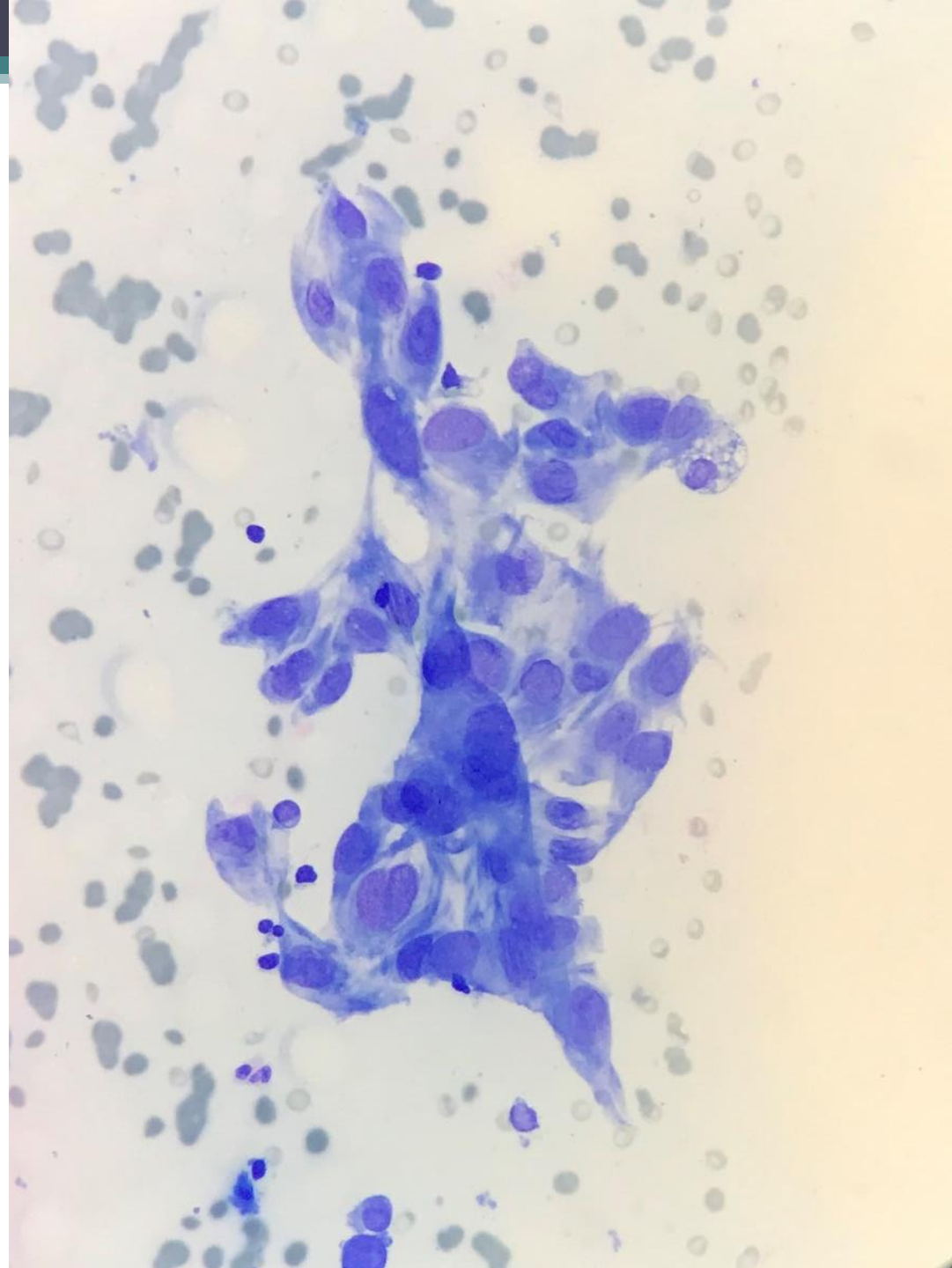


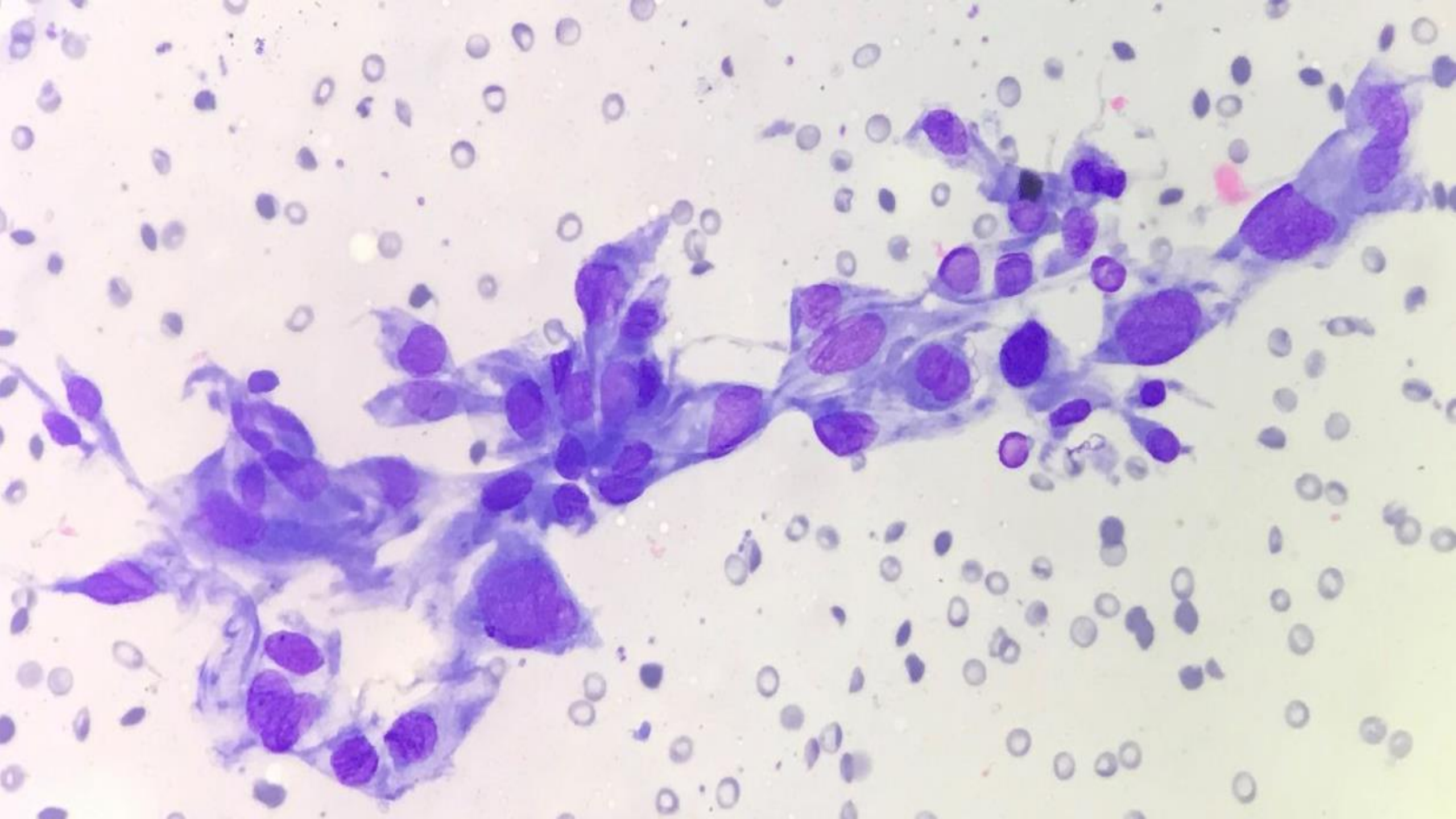
AUS with nuclear atypia.

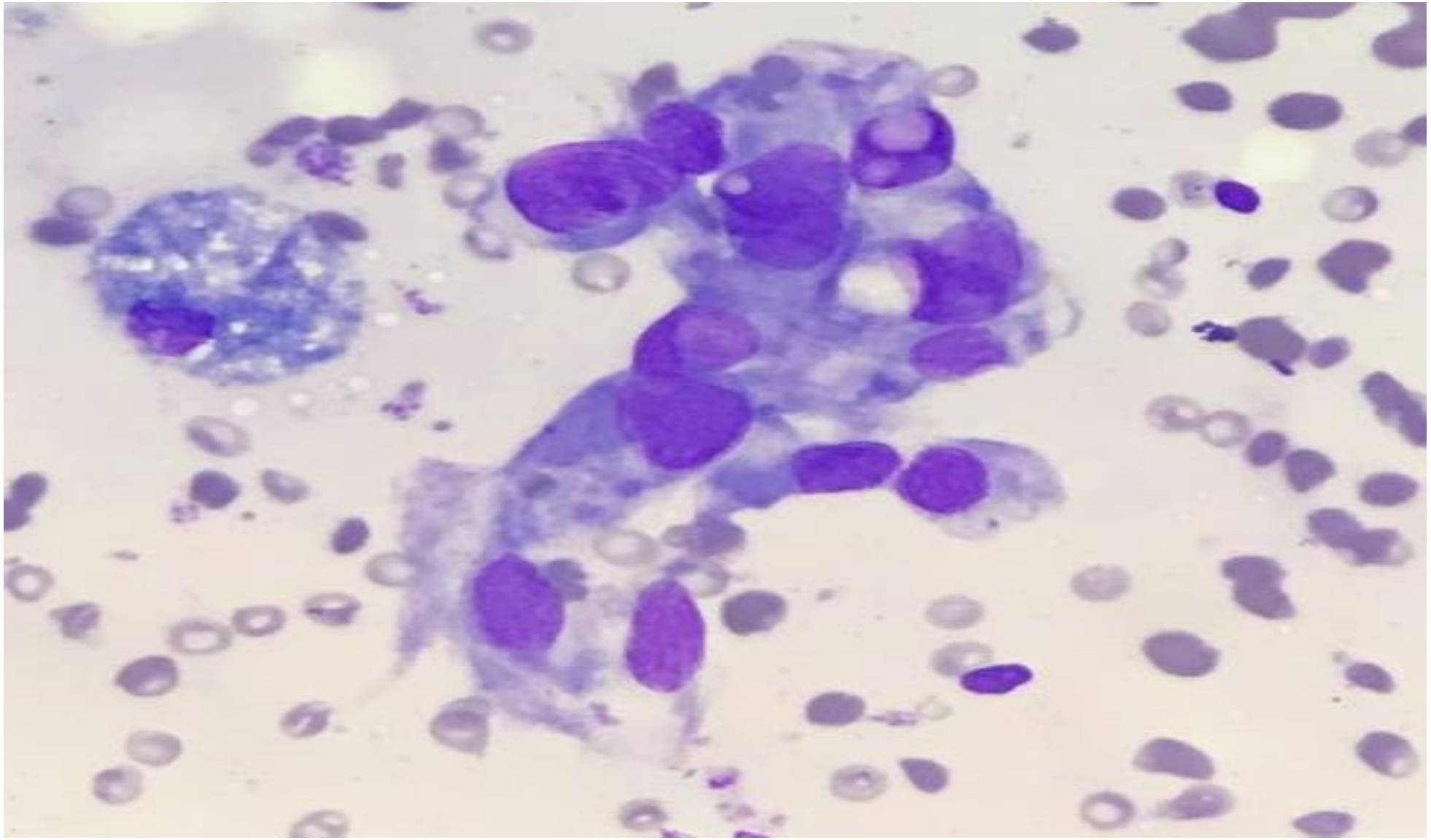
(**left**) In this sparsely cellular specimen, some cells have abundant cytoplasm, enlarged nuclei, and prominent nucleoli. One cell has an apparent intranuclear pseudoinclusion (arrow). Such changes may represent atypical but benign cyst lining cells. However, a papillary carcinoma cannot be entirely excluded (ThinPrep, Papanicolaou stain).

(**right**) Reparative-like changes of cyst lining cells can mimic some cytologic features of papillary carcinoma (smear, Romanowsky stain)









AUS Nuclear → ***"Histiocytoid" cells***

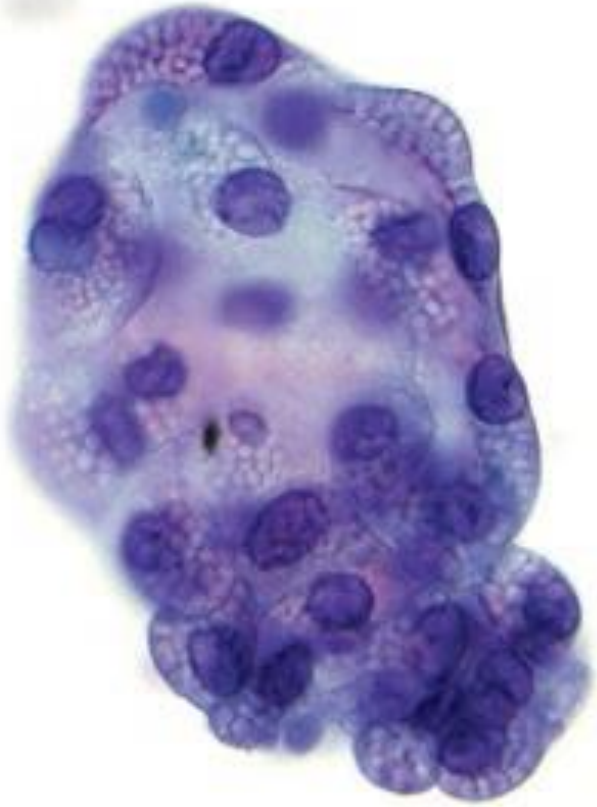
- **Characteristic of cystic papillary carcinoma**, which can be difficult to diagnose

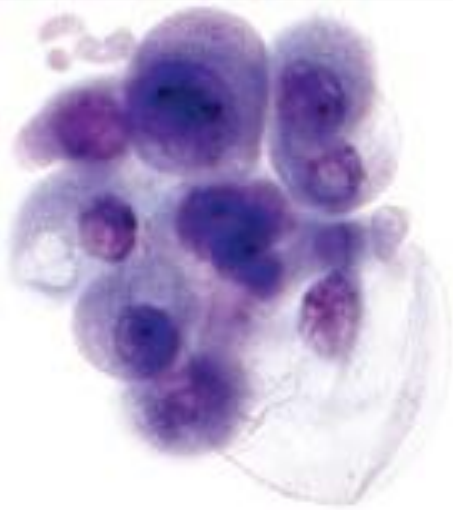
- Aspirates containing histiocytoid cells often have **numerous histiocytes** but **few benign follicular cells**.

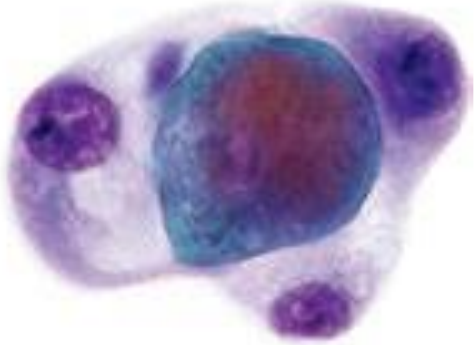
Atypical "histiocytoid" cells

- **Larger** than histiocytes
- typically isolated but sometimes in **microfollicular** arrangements or **clusters**

- **Compared with histiocytes**:
  - **Larger rounder** nuclei
  - **Higher** N/C ratio
  - **"Harder" (glassier)** cytoplasm, without the hemosiderin or microvacuolization of histiocytes
  - although larger, discrete **"septate" vacuoles** are present.







Cystic papillary carcinoma :cells often show **degenerative vacuoles**; these cells have been termed "**histiocytoid**."
A useful feature for recognizing them and distinguishing them from histiocytes is the **sharply defined edges of the vacuoles**, as opposed to the "fluffy"vacuoles of histiocytes

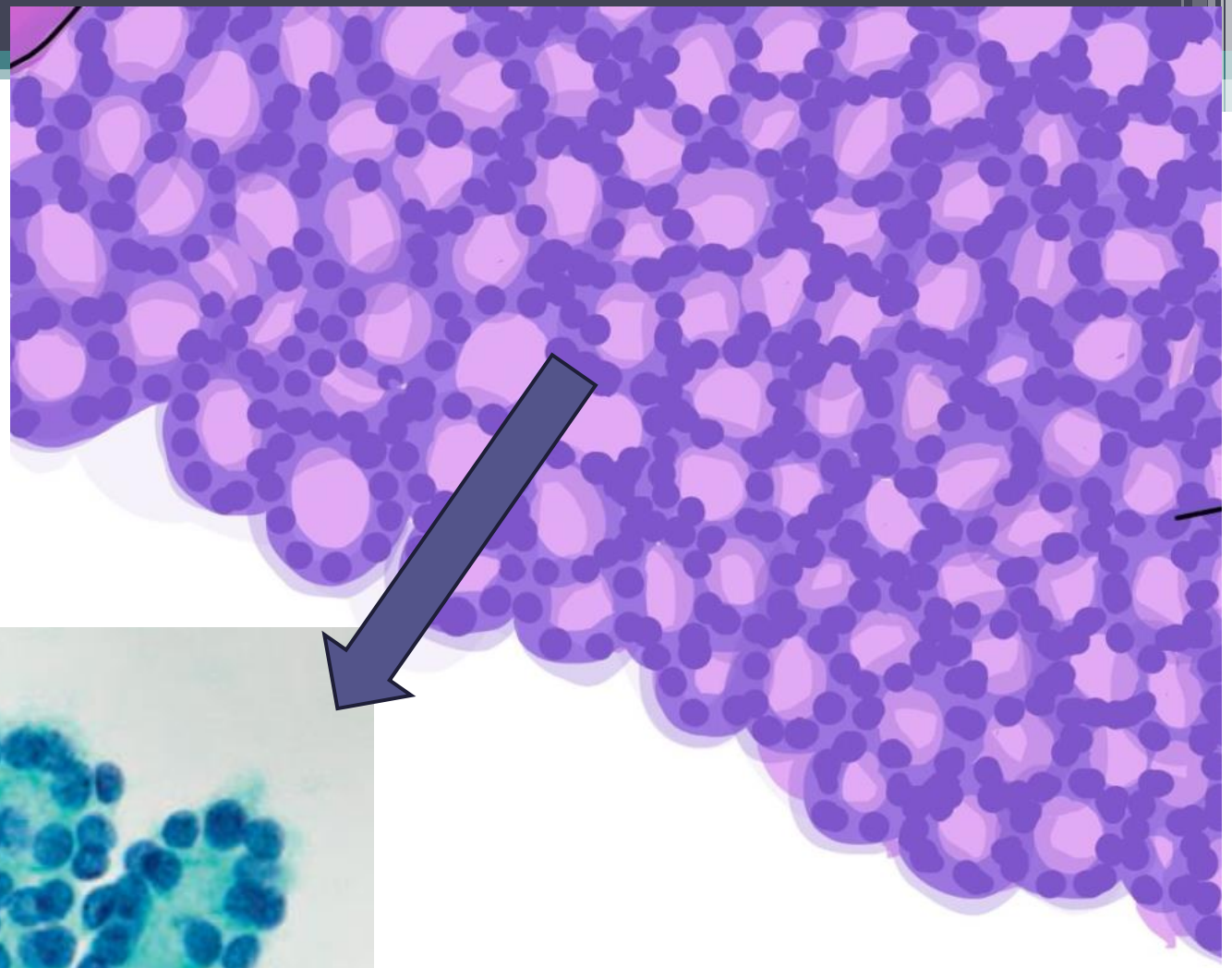
In this example, a **loose cluster** and a **microfollicular** group exhibit both "**hard**" cytoplasm and **large** cytoplasmic vacuoles

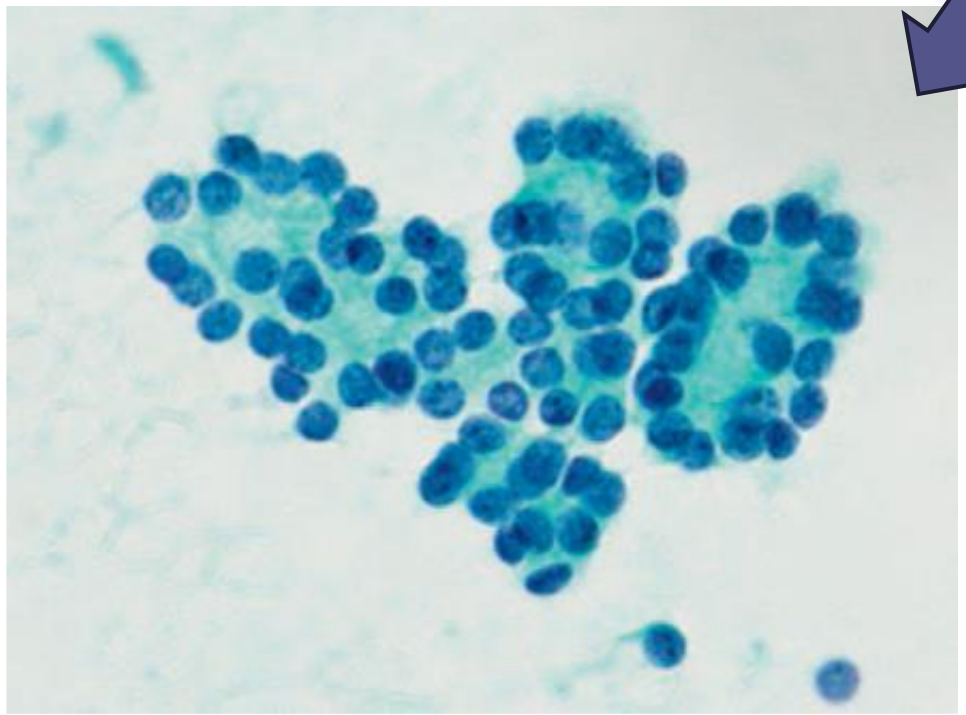
AUS with **nuclear atypia**.

AUS: Other (non-nuclear)

AUS: Other (non-nuclear) →

Architectural Atypia

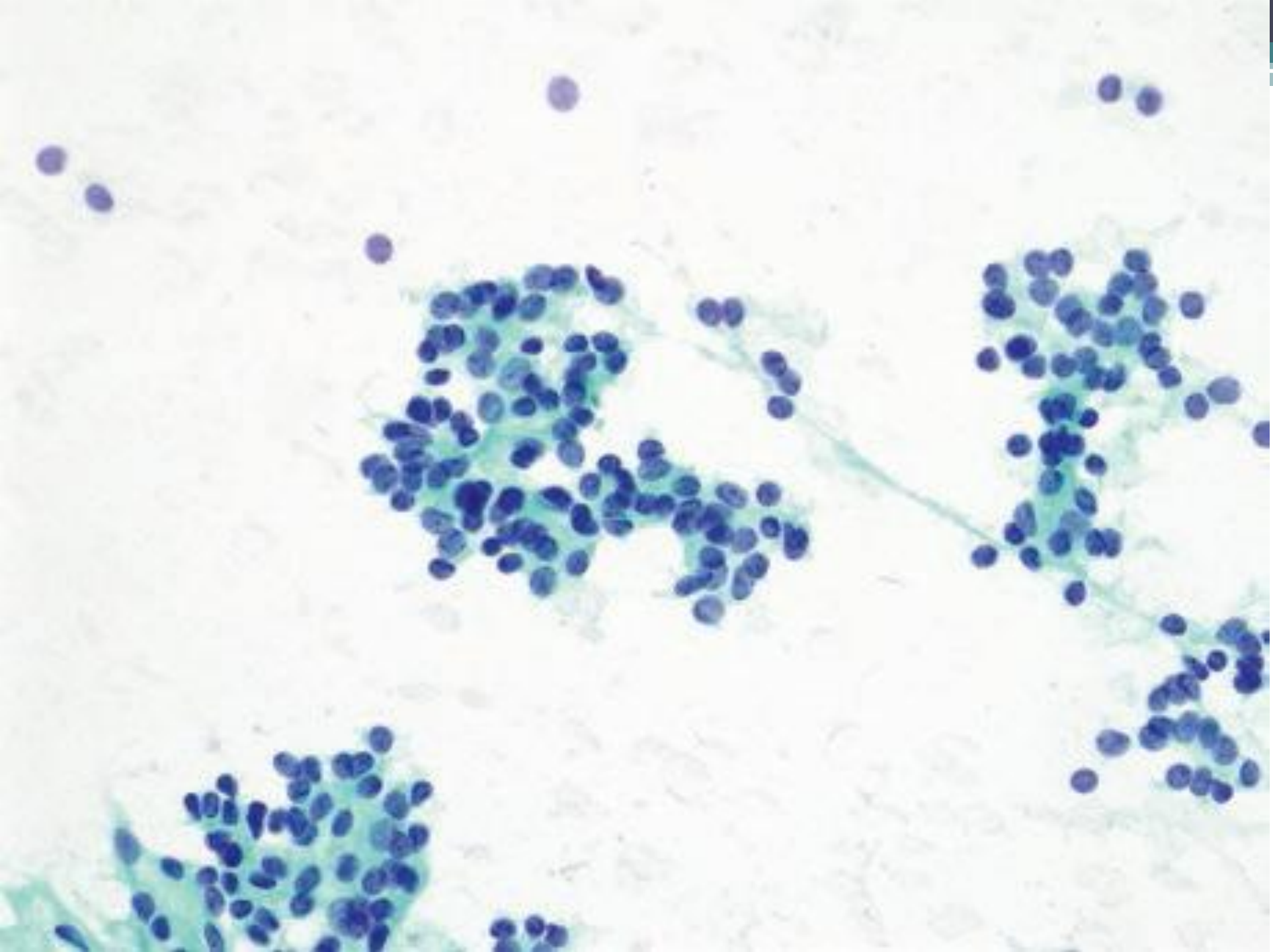




AUS: nuclear → **Nuclear and Architectural Atypia**

- **Grouped with aspirates exhibiting <u>only nuclear atypia</u>**
- Since the ROM is **similar to nuclear category** regardless of the presence or absence of coexisting architectural atypia.

- **Mild** cytologic atypia as outlined above may **coexist with architectural alterations**, such as an increased presence of **microfollicles or crowded three-dimensional groups.**

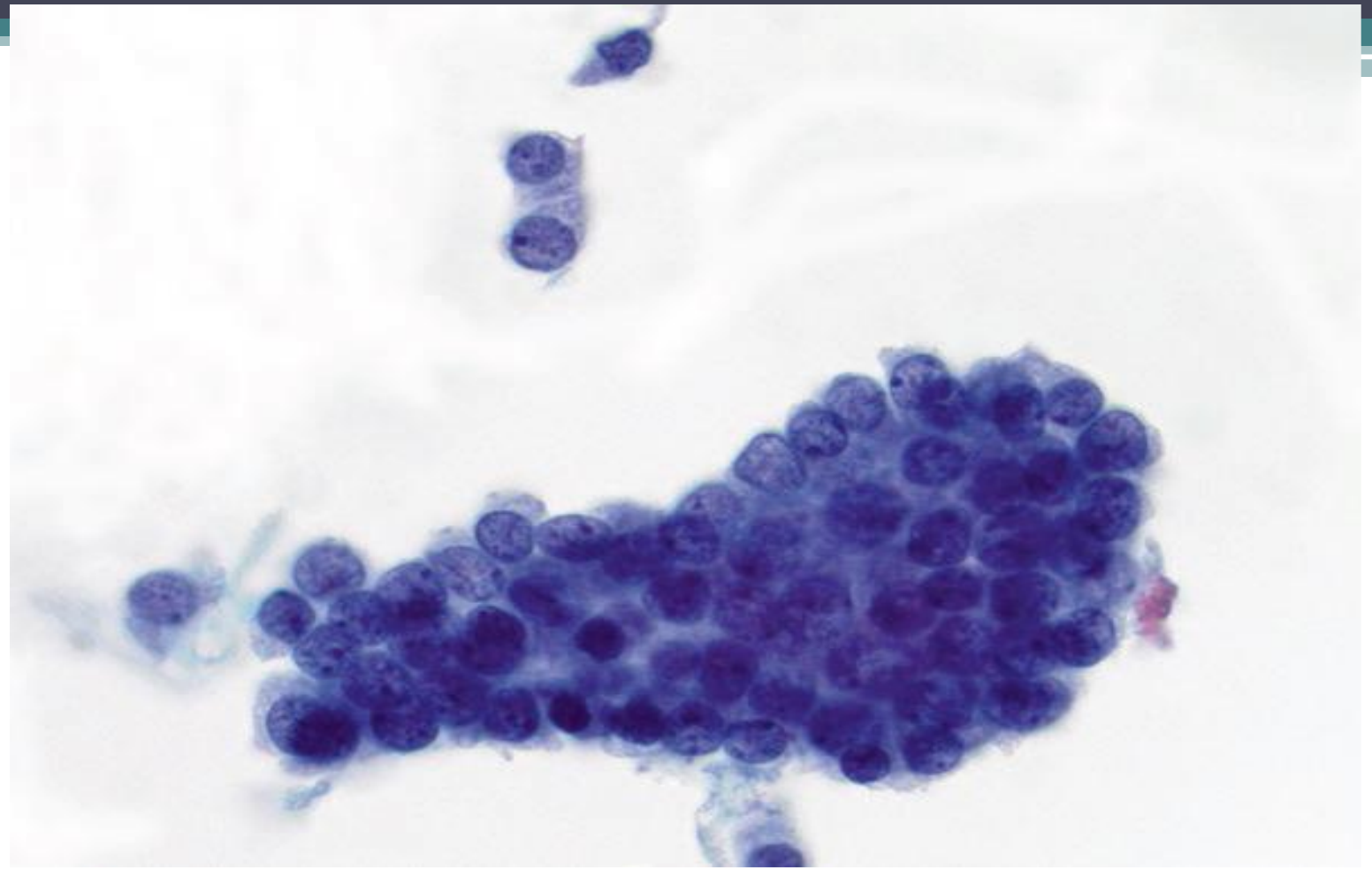


AUS with nuclear and architectural atypia.

Nuclear atypia is evident, with nuclear enlargement, crowding, and chromatin pallor, and infrequent nuclear grooves.

Architectural atypia is manifested by a crowded three-dimensional configuration of follicular cells.

The excised nodule was diagnosed as minimally invasive encapsulated follicular variant of papillary thyroid carcinoma

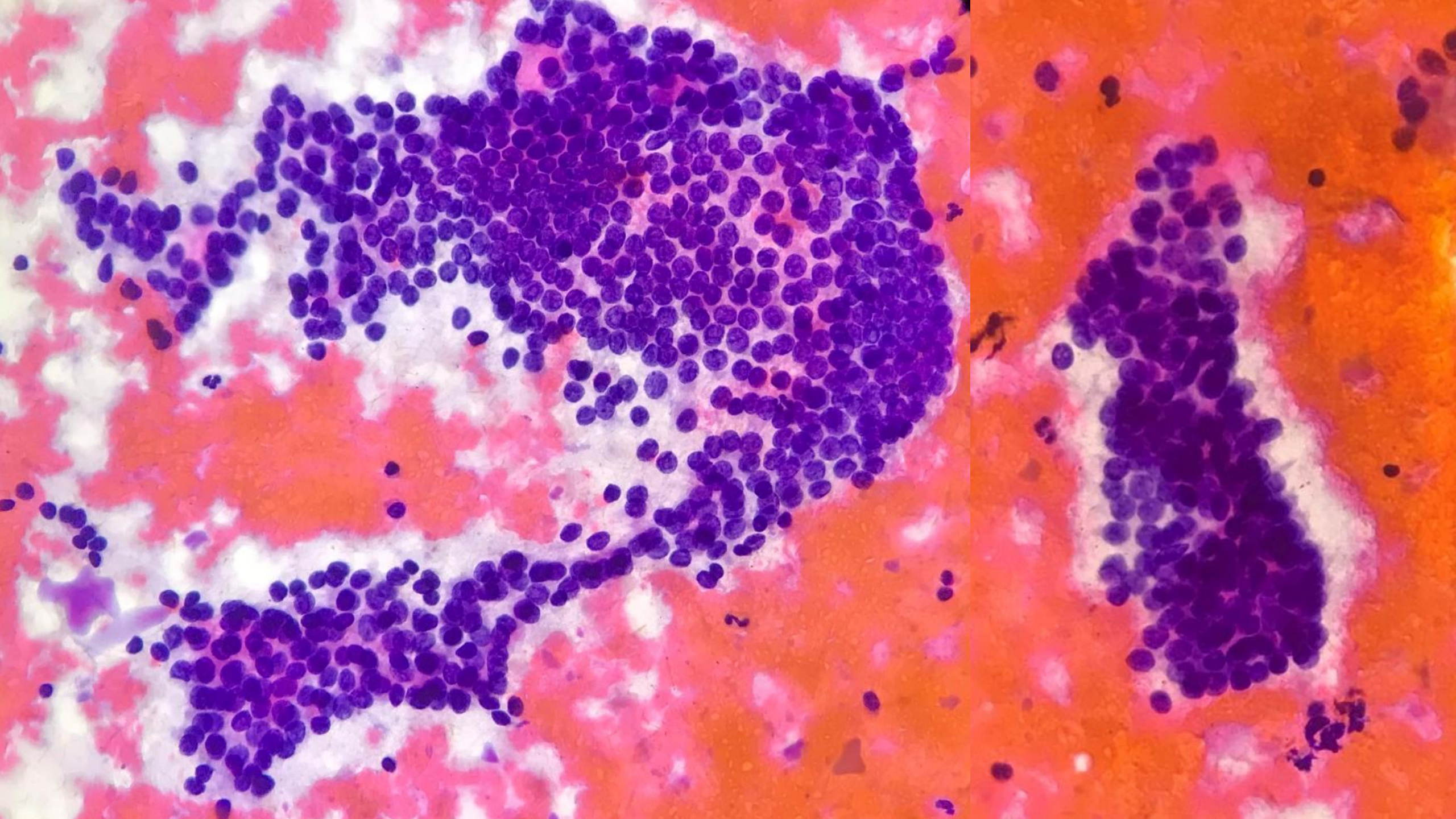


AUS with **architectural and nuclear atypia**.

Architectural atypia is manifested by a **crowded three-dimensional configuration** of follicular cells.

Nuclear atypia is also evident, with nuclear enlargement, slight chromatin pallor, and a rare nuclear groove.

The excised nodule was diagnosed as NIFTP



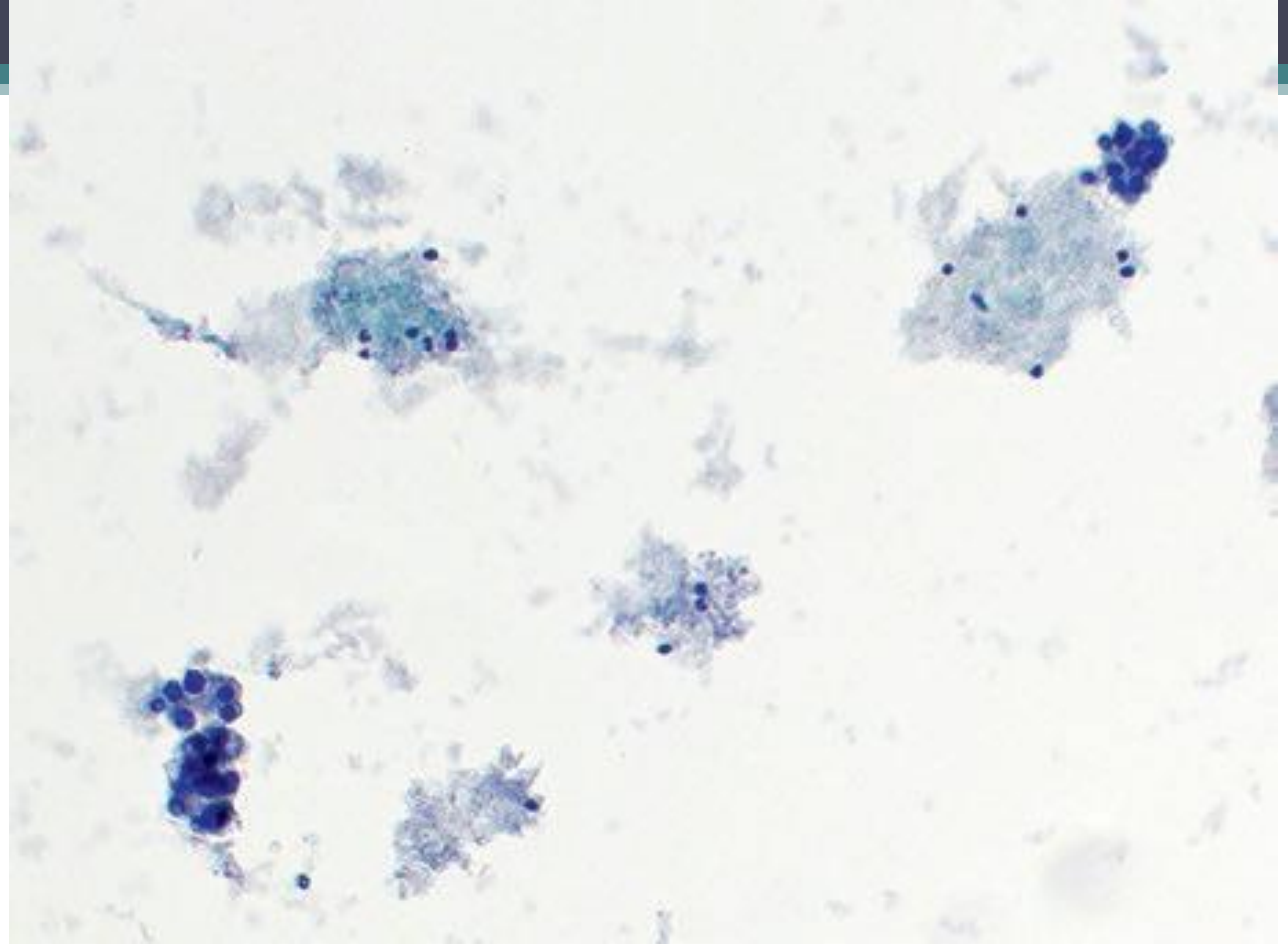
AUS: Other (non-nuclear) →

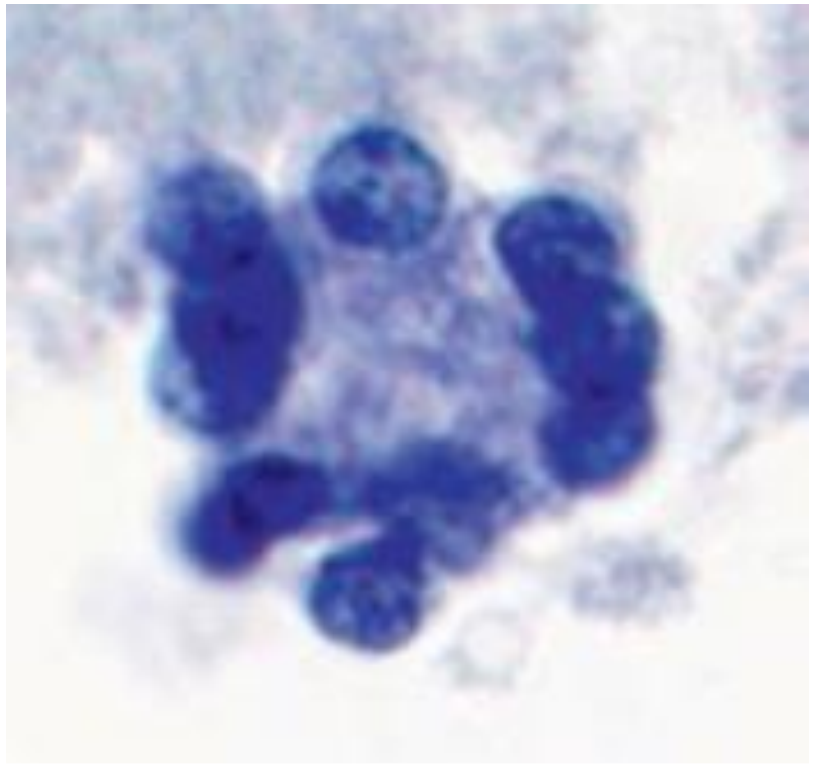
Architectural atypia

1.

- A **scantly** cellular specimen + **scant colloid**
- with **rare** clusters of follicular cells almost **entirely in microfollicles or crowded three-dimensional groups**

  - Although this pattern is **low risk**
  - **AUS** is warranted **due to** concern regarding **limited sampling** of a lesion that would merit an **FN diagnosis** if the specimen were more **cellular**.

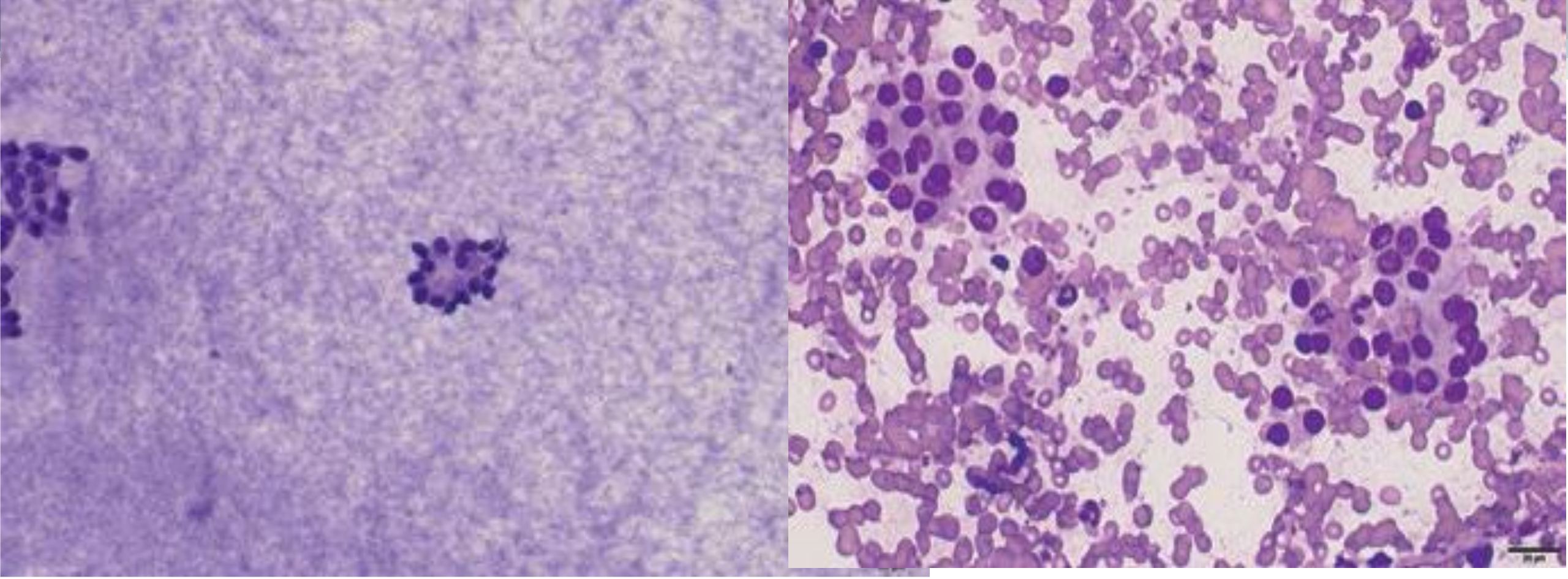




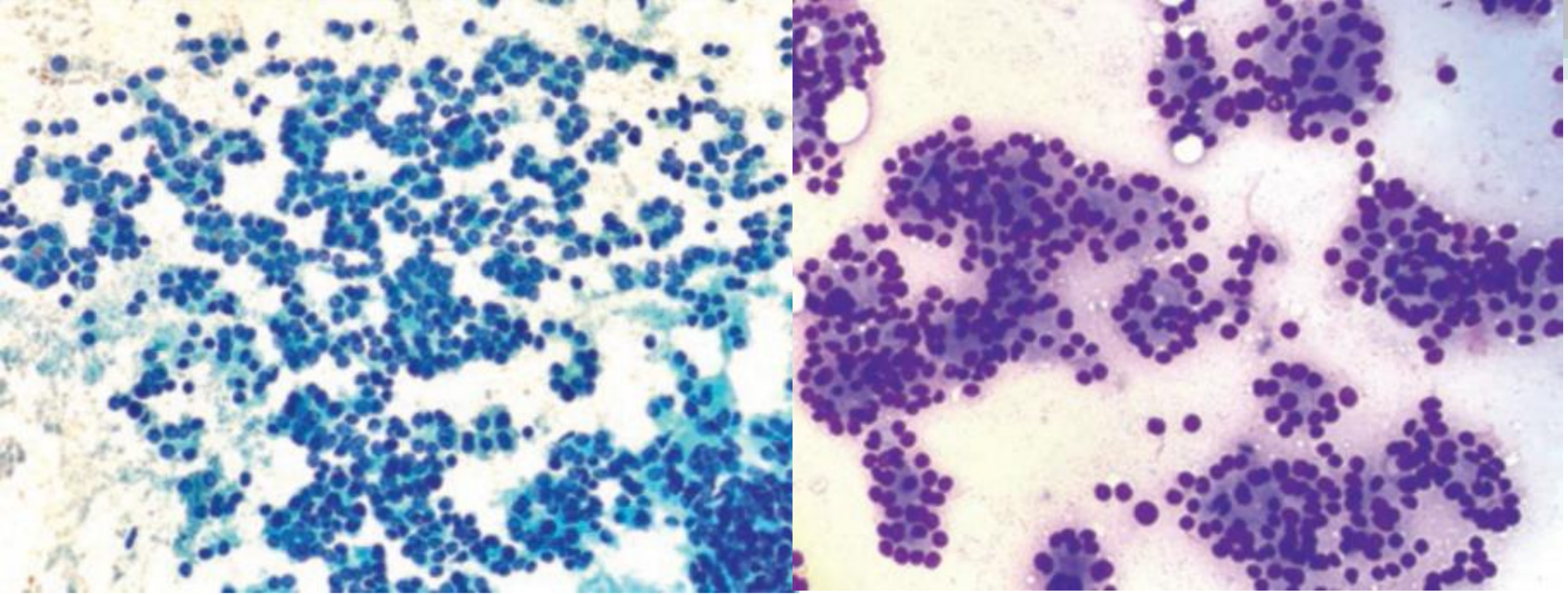
AUS with **architectural atypia**

Left: Scanning magnification reveals a **sparsely** cellular specimen with a **predominance of microfollicles**.

Right: High magnification of a microfollicle



AUS with architectural atypia



Follicular neoplasm.

Highly cellular aspirate composed of uniform follicular cells arranged in **microfollicles** (smears, **left**: Papanicolaou stain, **right**: Diff-Quik stain).

AUS: Other (non-nuclear) →

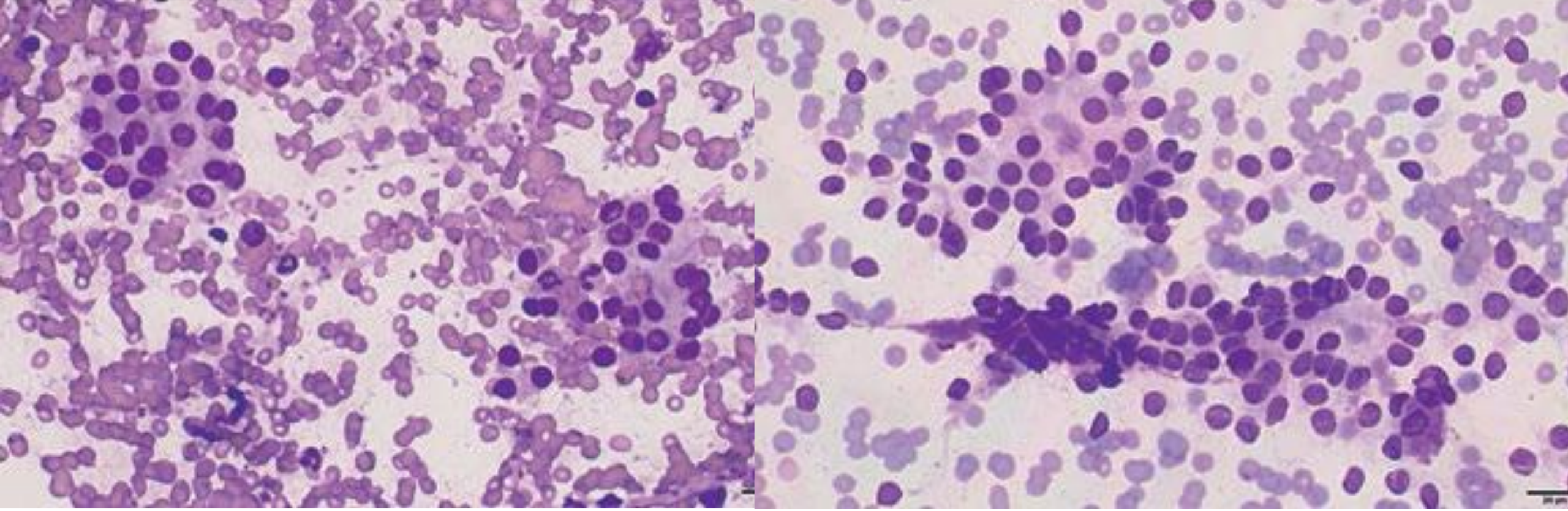
Architectural atypia

2.

- A **moderately to markedly cellular** specimen exhibits architectural atypia as described above in **most follicular cells (50–70% of follicular cells)**

  but **without** a marked predominance (at least **70%** of follicular cells) that would **warrant a FN diagnosis.**

- This pattern **should not be confused** with an overall **mixed**, but predominantly macrofollicular, aspirate, which should be called benign.



AUS with architectural atypia.
examples of *DICER1* mutated nodules in pediatric patients show variable cellularity and architectural atypia

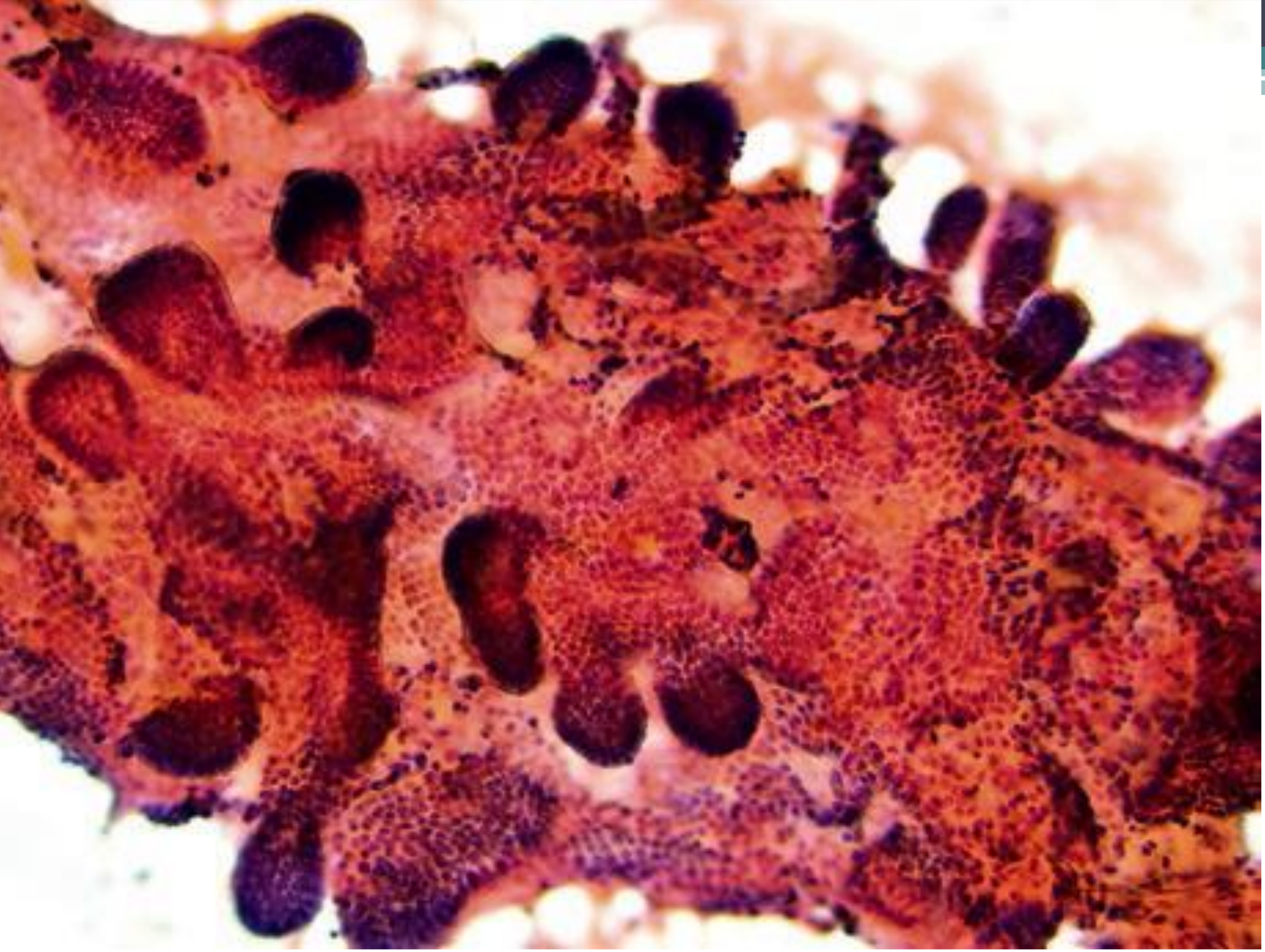
Papillae ???

- In the absence of any nuclear features of papillary carcinoma >>> indicative of papillary hyperplasia, benign papillary proliferations (**Graves**' disease and other **hyperplastic thyroid nodules**) should be interpreted as **benign**

- Papillary architecture + **focal or mild** nuclear atypia >>>> **AUS**

✓ It is critical to **carefully examine the cells, especially their nuclear features**

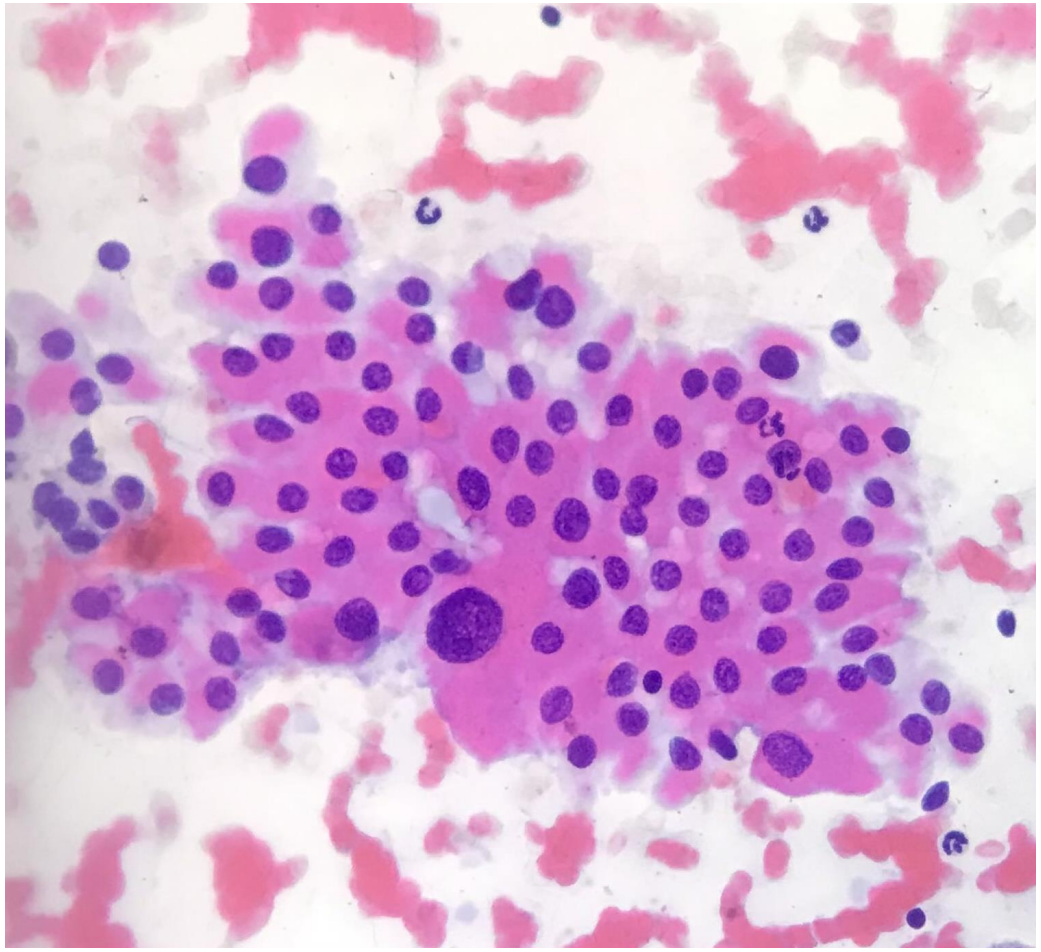
✓ a diagnosis of papillary carcinoma should not be rendered on architecture alone

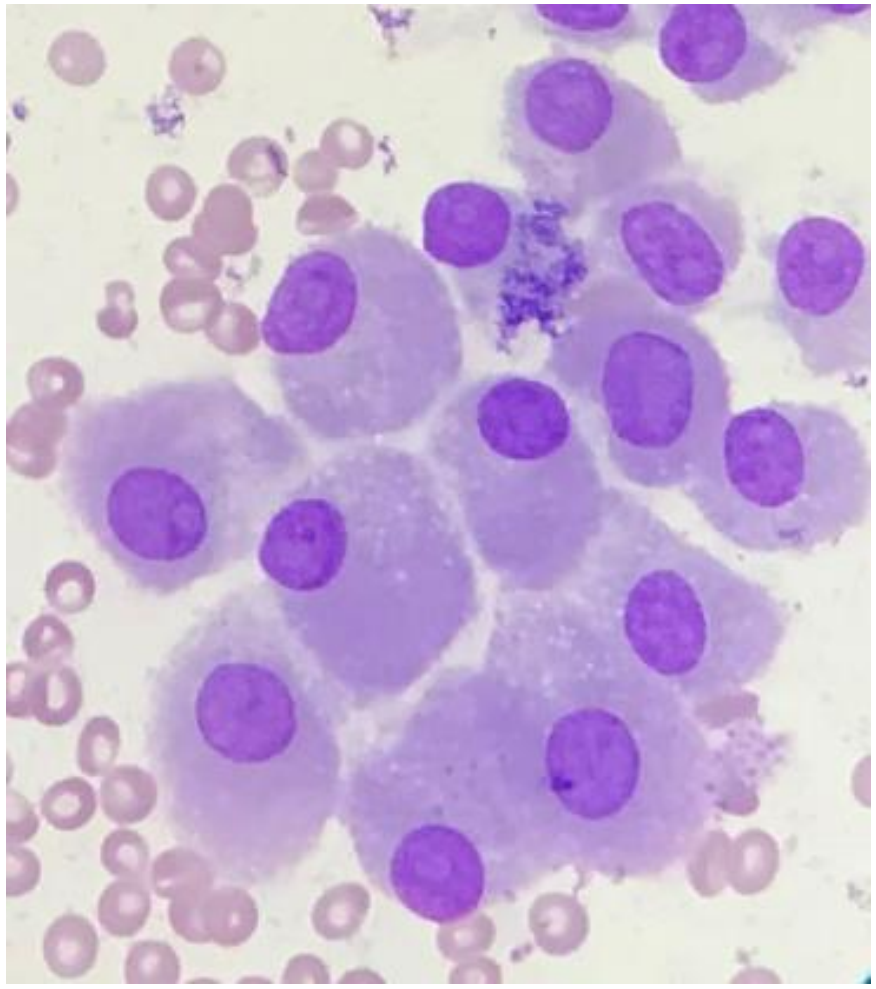


Benign (papillary hyperplasia).

It is critical to **carefully examine the cells, especially their nuclear features**;
a diagnosis of papillary carcinoma should not be rendered on architecture alone.

AUS: Other (non-nuclear) → **AUS Oncocytic /Oncocyte Atypia**





Metaplastic / hyperplastic changes:

- Lymphocytic (Hashimoto) thyroiditis
- Multinodular goiter (MNG)/FND

Mixture of elements:

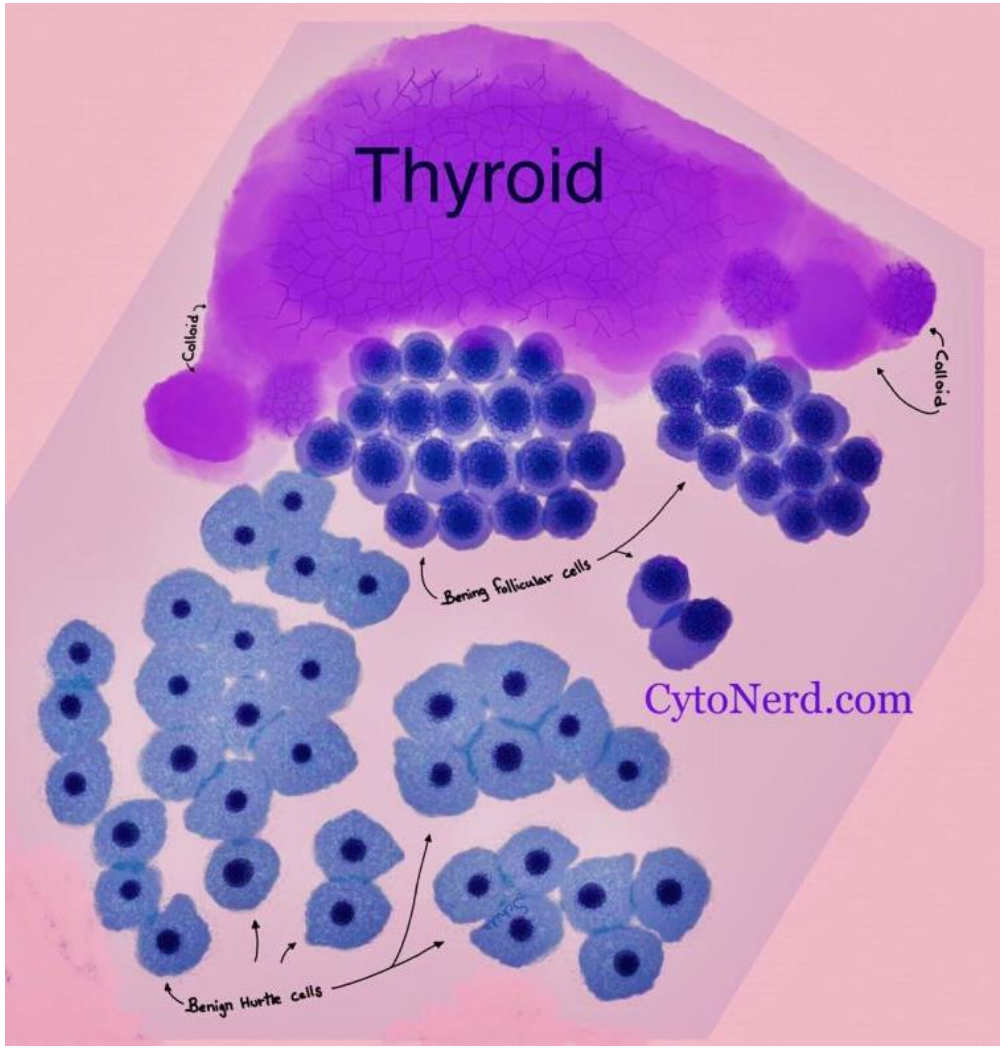
✓ **Oncocytes** are present as a **uniform flat sheet**

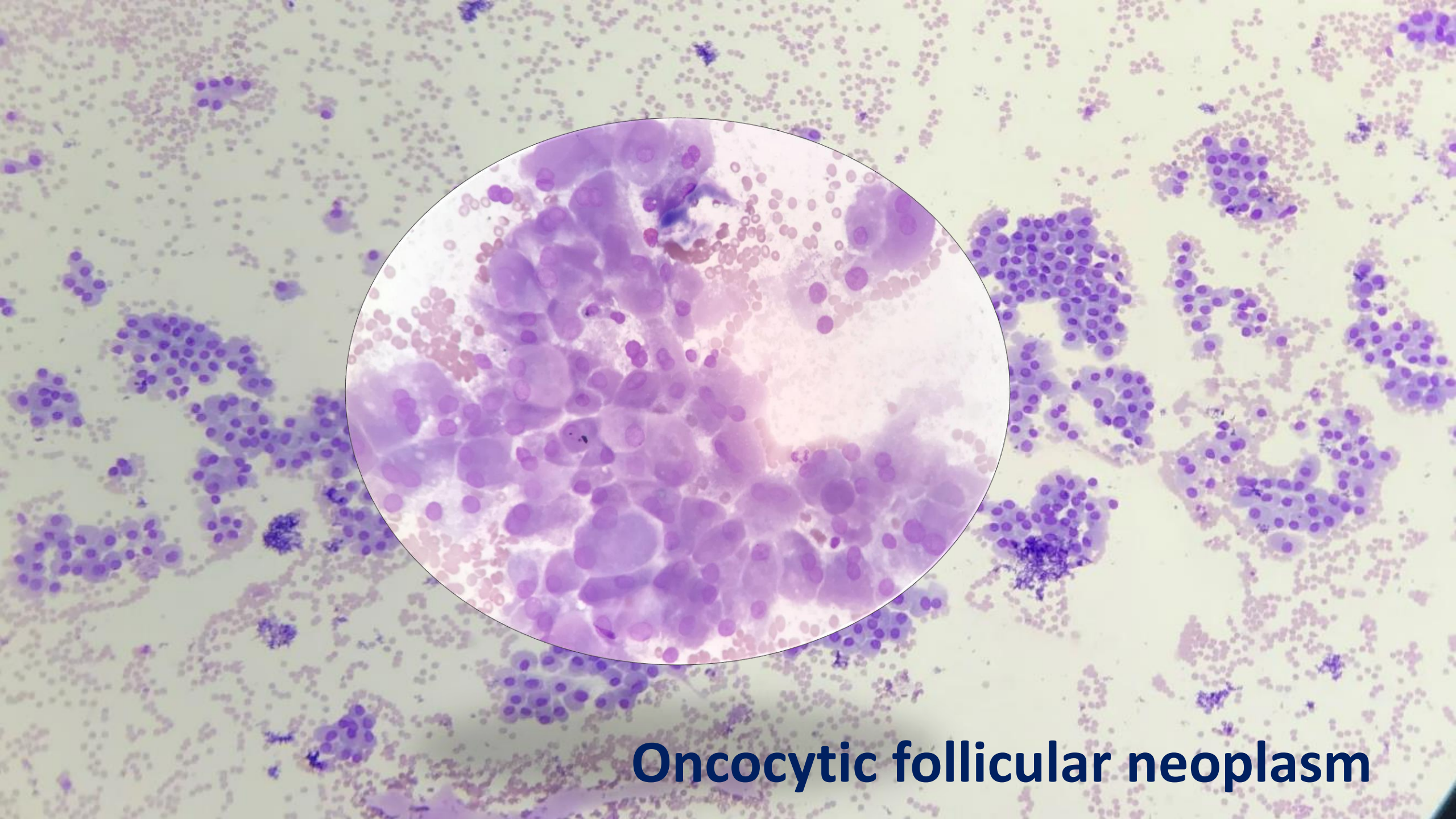
+ Benign **non-oncocytic** follicular cell

+ **Abundant colloid**

+ **Lymphocytic inflammation**

✓ **Interpret as benign**





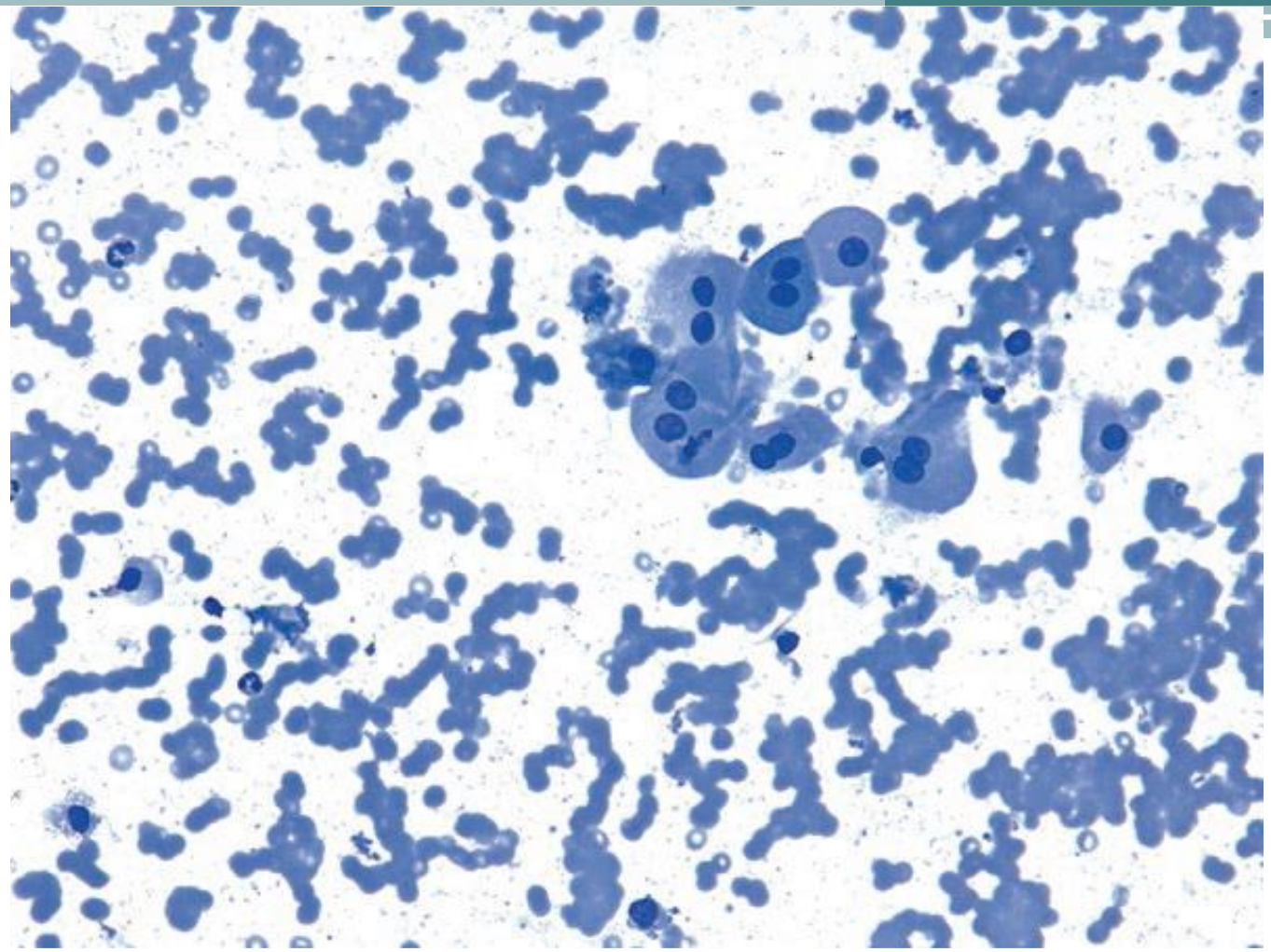
Oncocytic follicular neoplasm

AUS : Oncocytic /Oncocyte Atypia

1.

Sparsely cellular aspirate comprised **exclusively** (or almost exclusively) of oncocytic cells with **minimal colloid**

- Although this pattern is **very low risk**, AUS is warranted due to concern for **limited sampling** of a lesion that would merit an **OFN diagnosis** if the specimen were **highly cellular.**
- **Correlation** with clinical/laboratory findings and radiologic risk stratification can be useful in determining the best diagnostic category.



AUS, oncocytic cell type.
Sparsely cellular with abundant blood and predominantly oncocytic cells

AUS : Oncocytic /Oncocyte Atypia

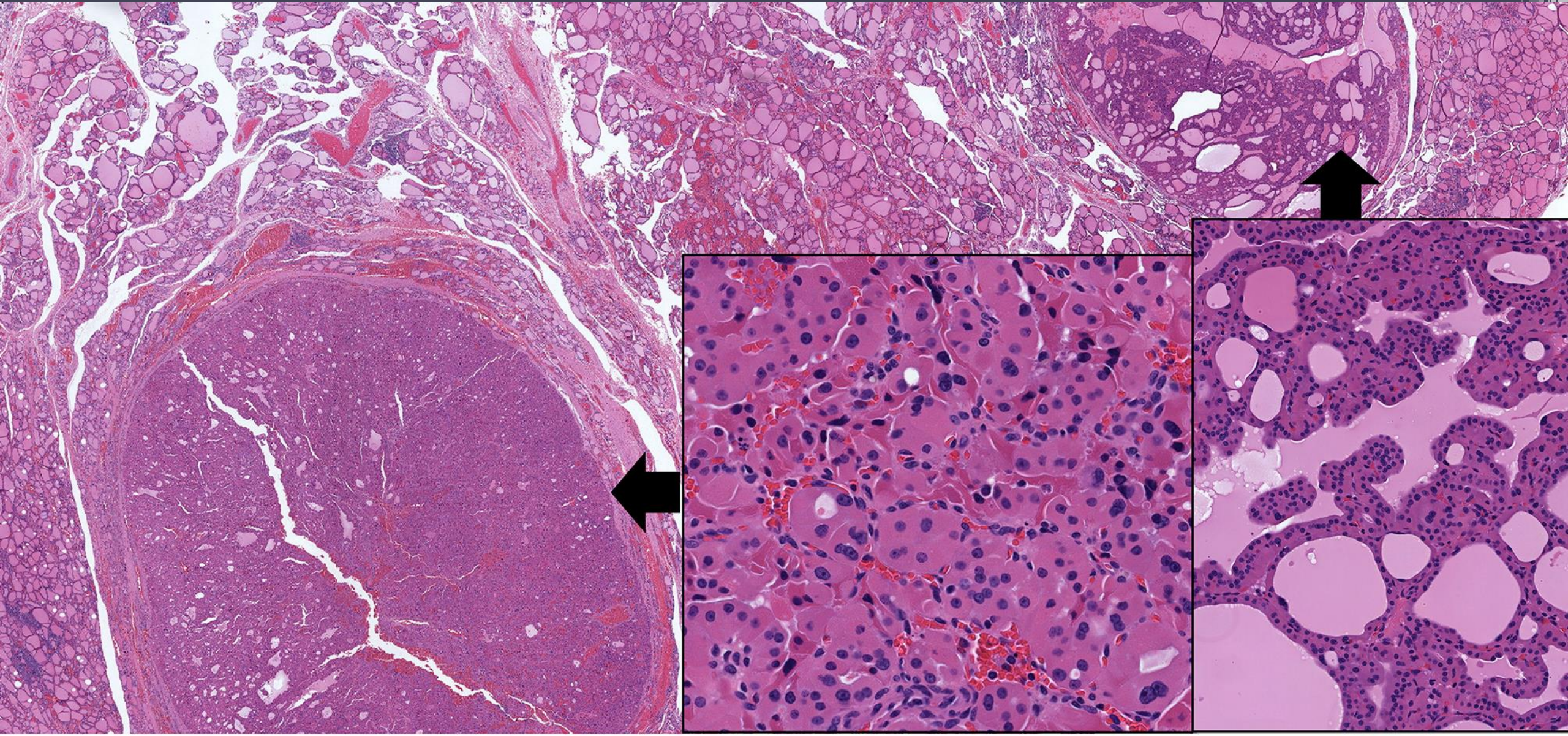
2.

Moderately or markedly cellular sample composed **exclusively (or almost exclusively) of oncocytic cells without lymphocyte, without colloid**

+ BUT **clinical / imaging** setting suggests a **benign oncocytic cell nodule**

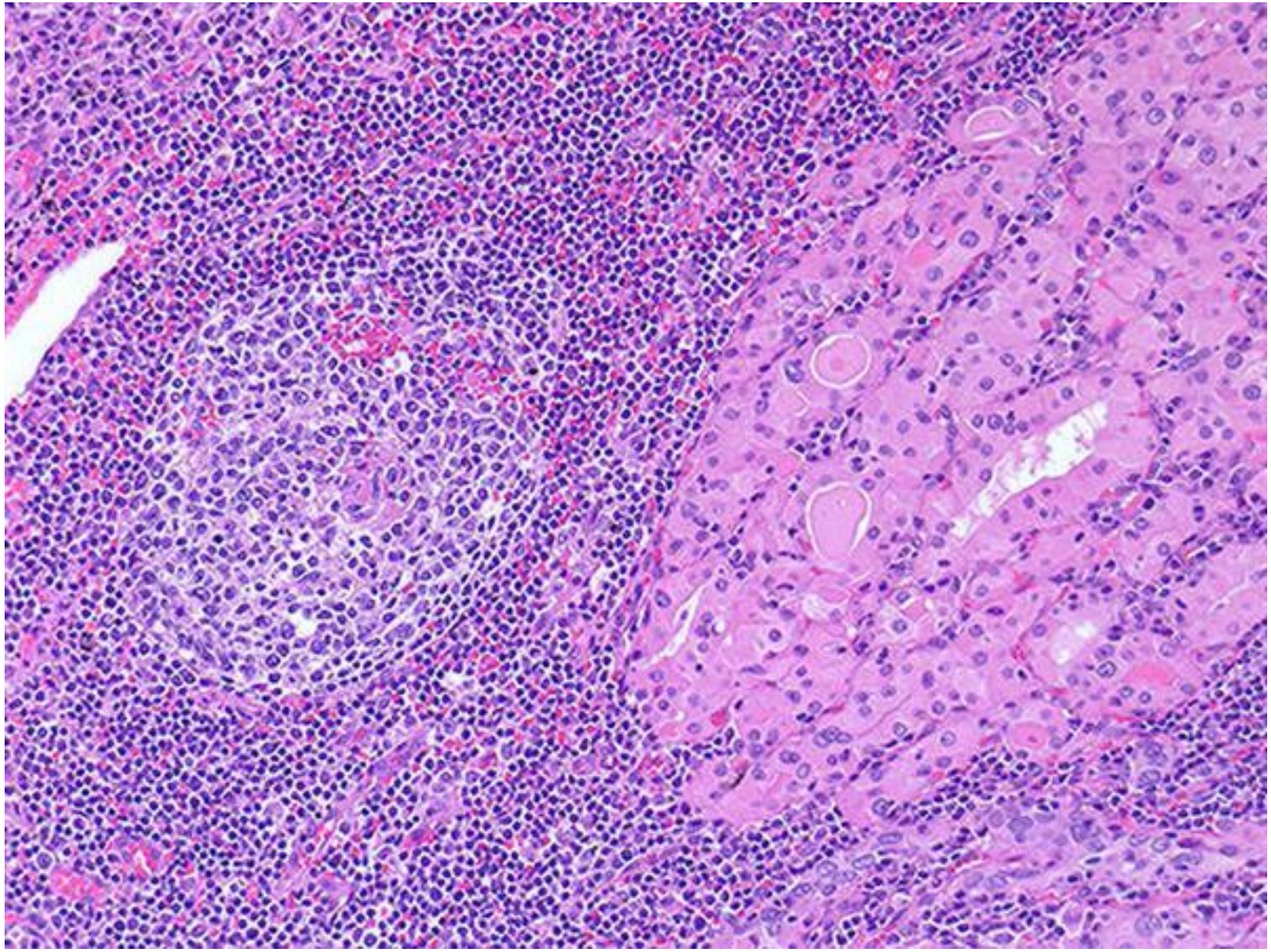
✓**Lymphocytic (Hashimoto) thyroiditis**
✓**Multinodular goiter (MNG)**

➢**AUS+NOTE**
➢**Avoid unnecessary lobectomy**



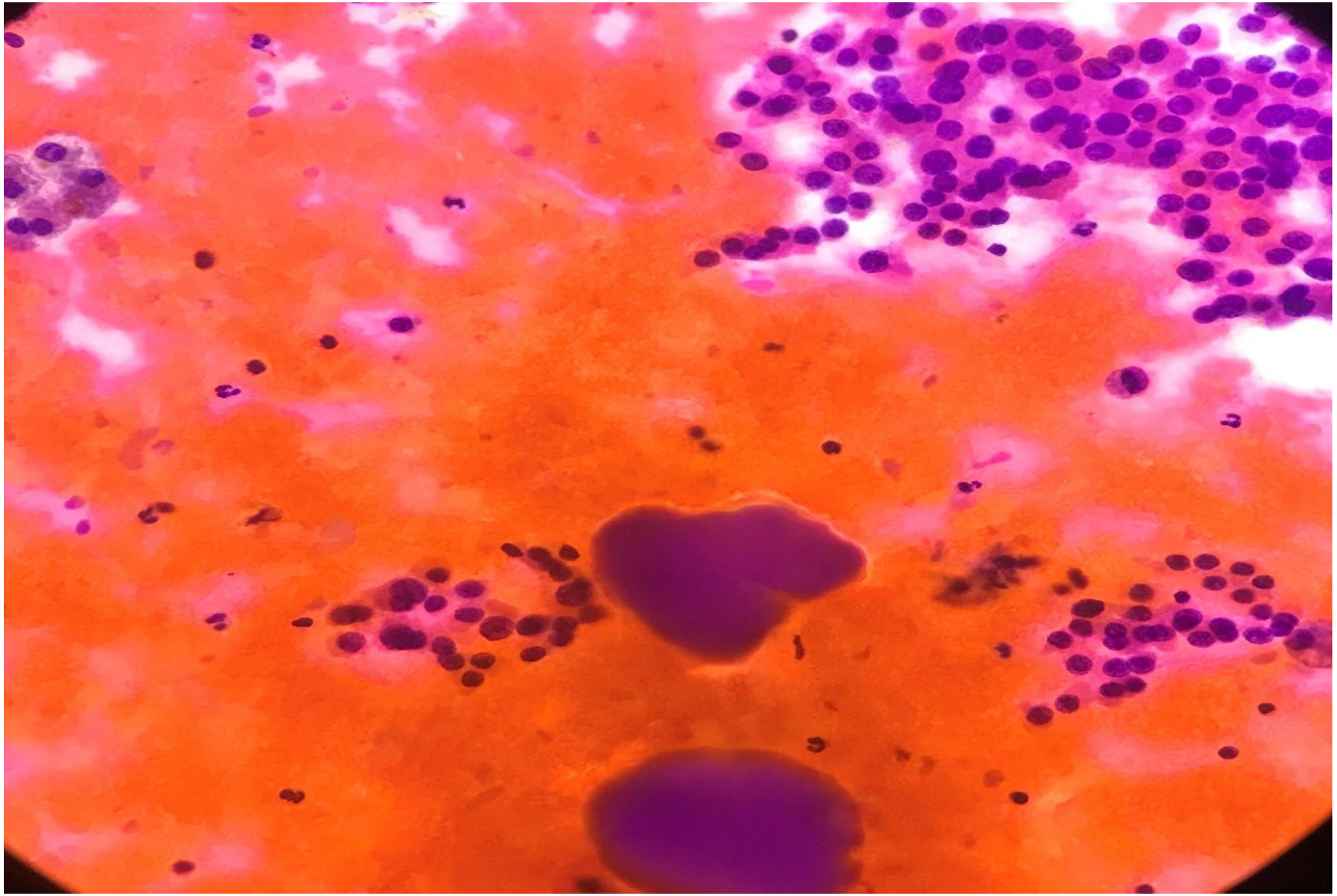
Multinodular goiter (MNG)

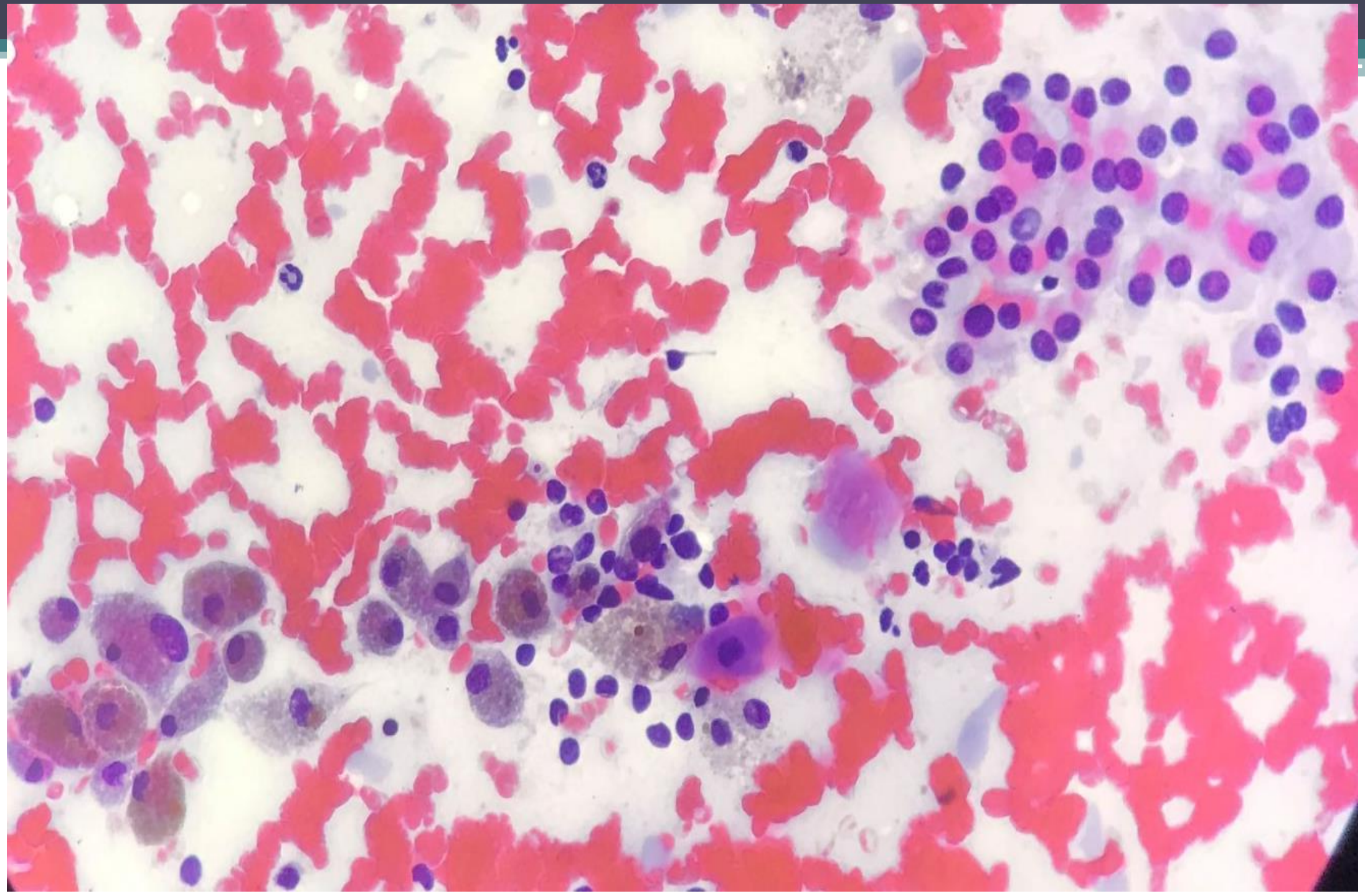
Lymphocytic (Hashimoto) thyroiditis



A) Benign diagnosis

- The oncocytic cells are all in **cohesive flat sheets without nuclear atypia**
- **Abundant colloid**
- In the absence of high-risk clinical or radiologic findings



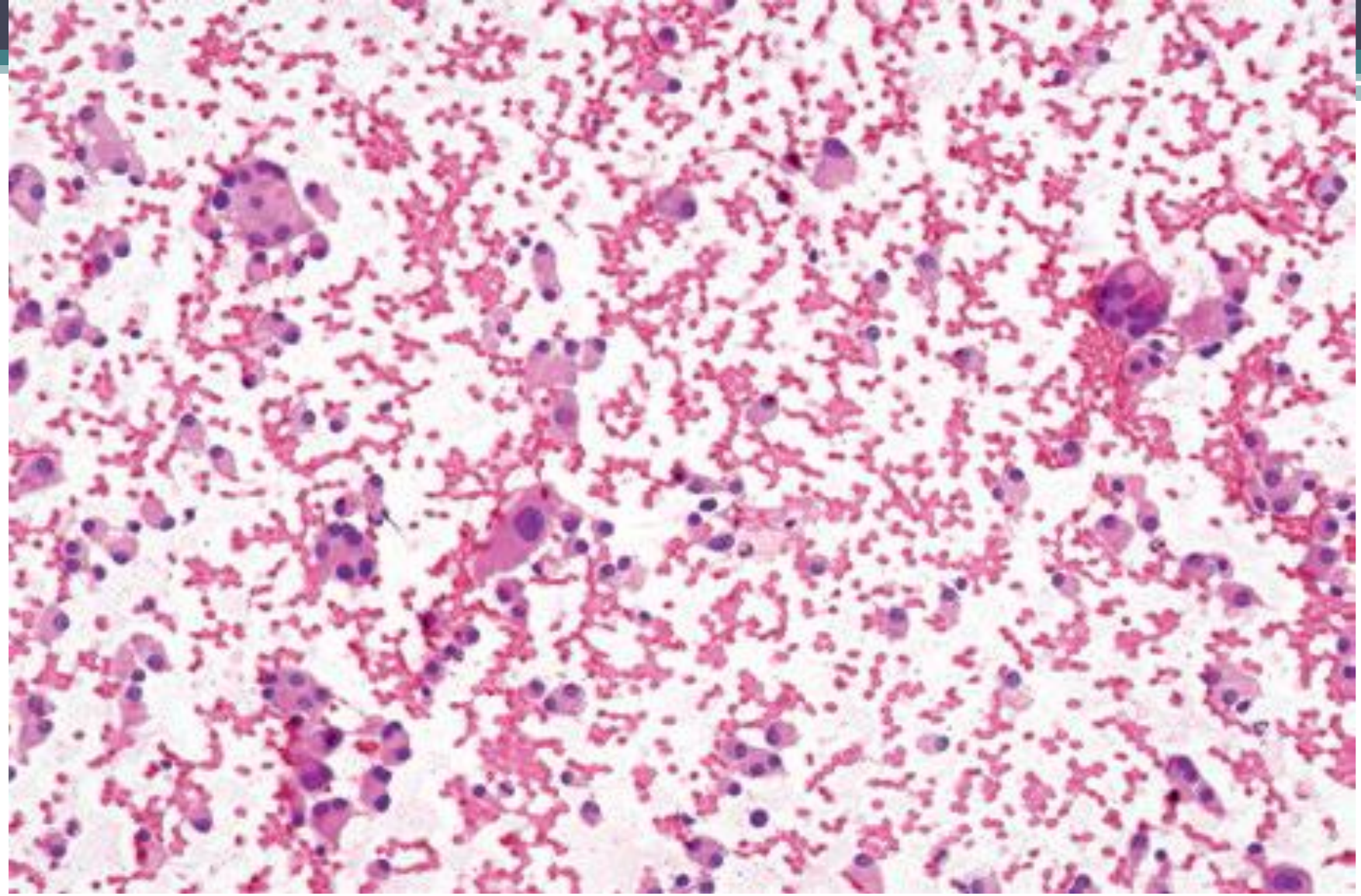


B) AUS , oncocytic

- **Clinical evidence of lymphocytic (Hashimoto) thyroiditis**
- **But lymphocytes are absent .**
- **A repeat aspirate or additional clinical evaluation** may resolve the diagnostic uncertainty.

C) AUS , oncocytic

- Only abundant oncoctyes
- **Imaging: Multiple nodules**
- **MNG with multiple hyperplastic oncocytic cell nodules and lymphocytic (Hashimoto) thyroiditis with oncocytic metaplasia are more probable** than concurrent oncocytic type follicular neoplasms



AUS, oncocytic cell type (patient with history of Hashimoto thyroiditis).
This patient had a subcentimeter nodule with modestly cellular smears showing exclusively oncocytic follicular cells without polymorphous lymphocytes in a bloody background

Notes

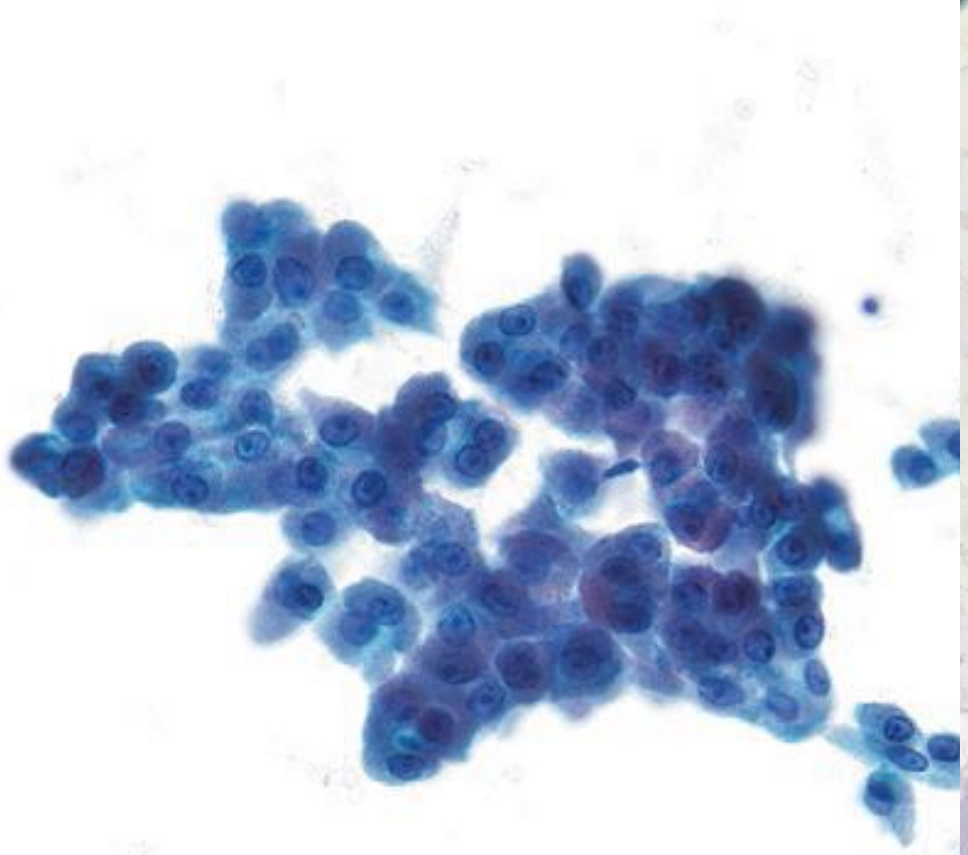
Rick of malignancy in Hashimoto's

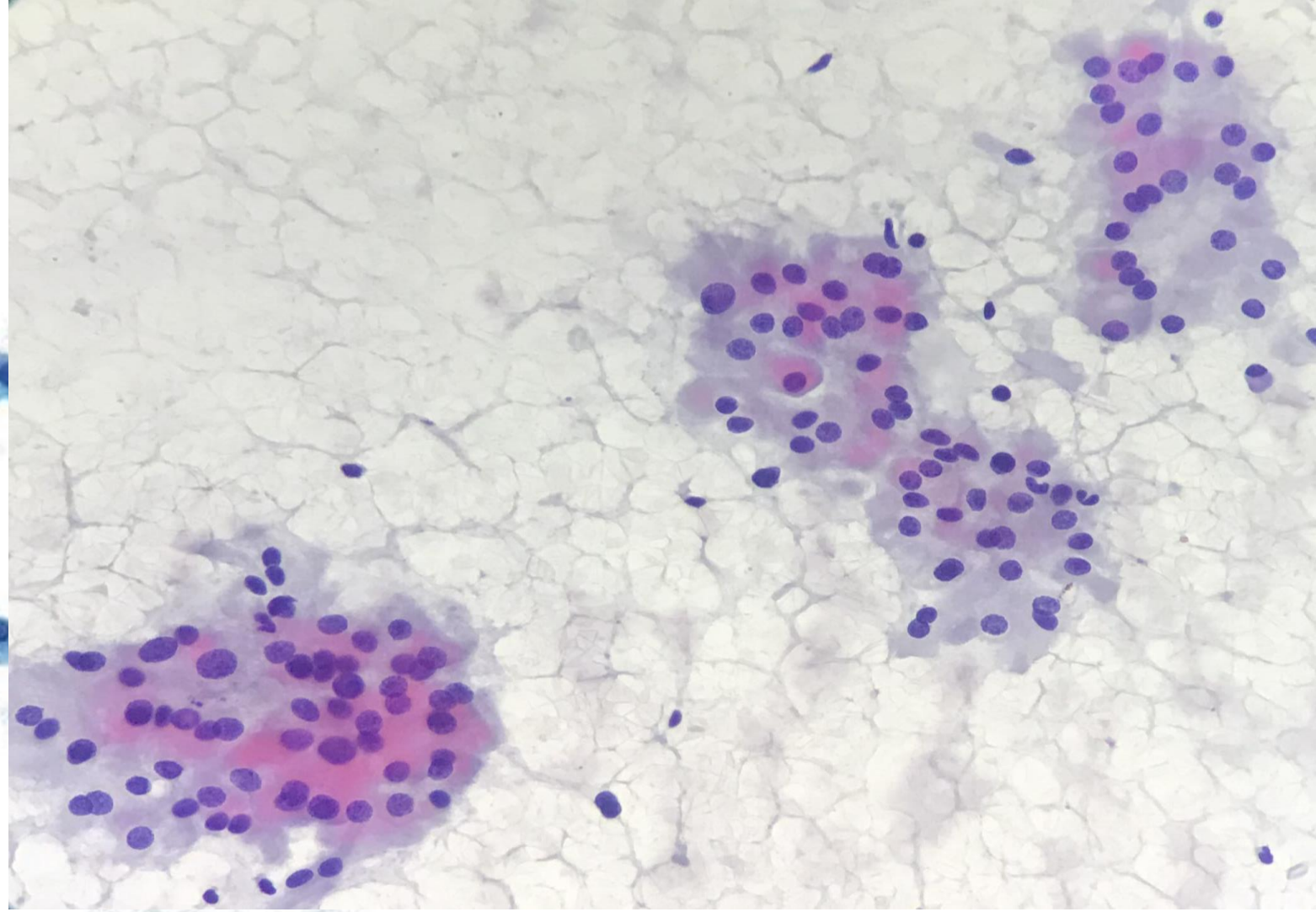
- The **great majority of malignancies** that develop in patients with known Hashimoto thyroiditis are **papillary carcinomas**

- **Oncocytic (Hürthle cell) carcinoma** in this setting is **rare**.

  - In this setting, the clinical decision **to follow a patient** **rather than perform a lobectomy** will often be based on clinical and sonographic correlation

  - it is **not clear** whether a **repeat aspiration** is likely to add any helpful information





AUS, Hürthle cell type (patient with **multinodular goiter**).
This patient had two nodules, both showing **almost exclusively oncocytic** follicular cells

AUS: Other (non-nuclear) → **Atypia, Not Otherwise Specified (NOS)**

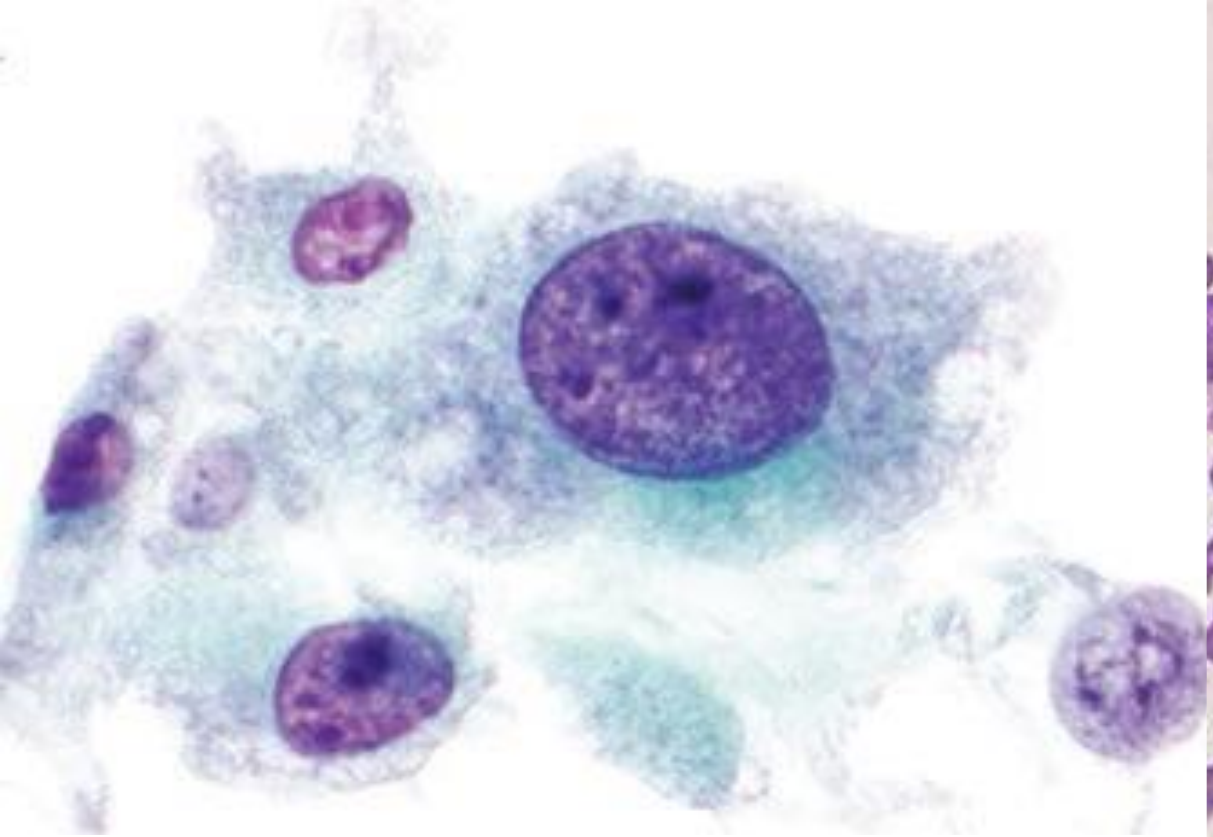
1.

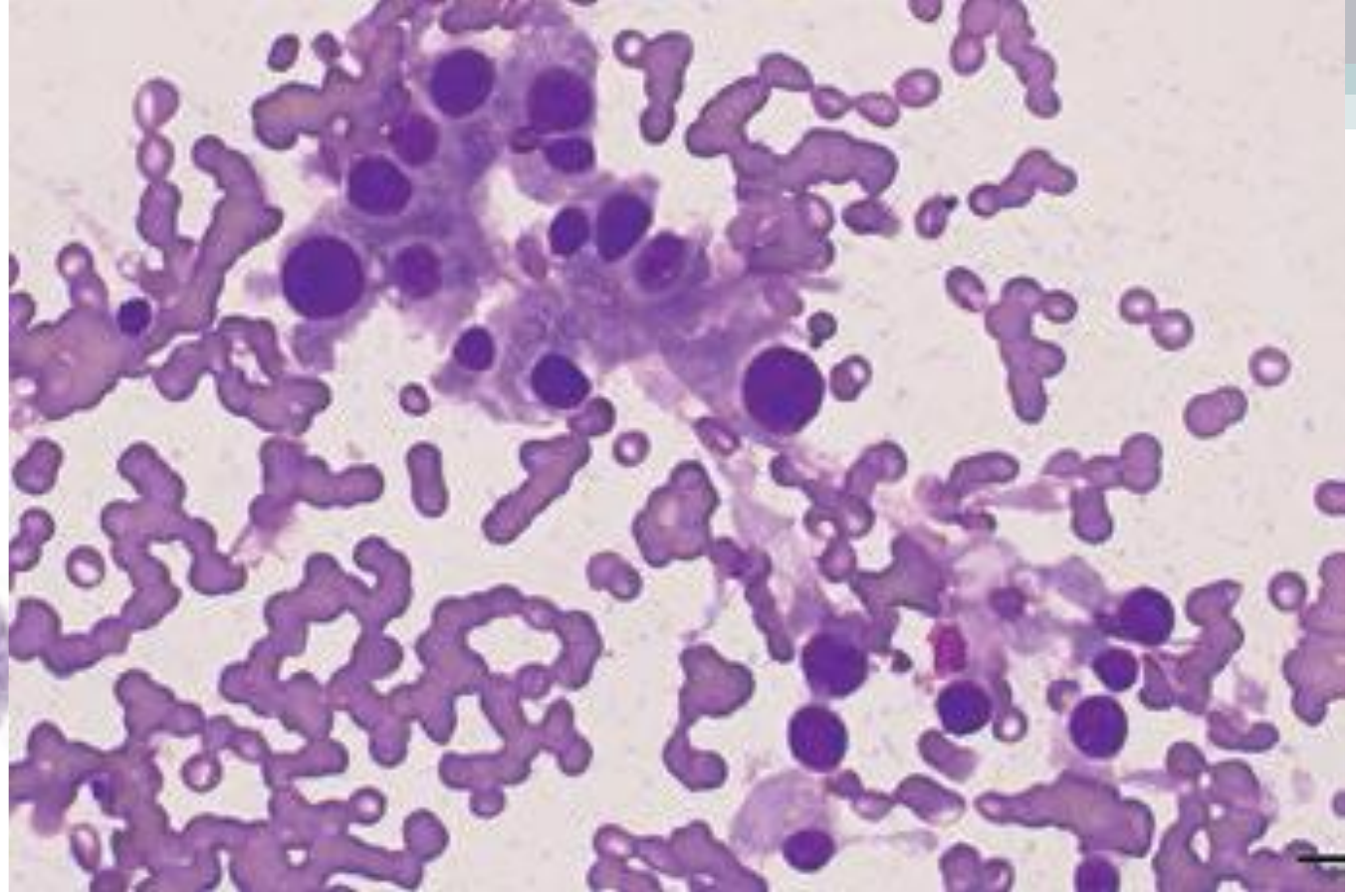
A **minor population** of follicular cells shows nuclear enlargement, pleomorphism, giant nuclei, hyperchromatic, and prominent nucleoli

- This pattern of nuclear atypia **does not raise** concern for **papillary** carcinoma

History of radioactive iodine, methimazole, carbimazole, or other pharmaceutical agents >>> diagnosed as **benign, in **appropriate** available clinical **history**

but **AUS >>> when the findings are particularly **pronounced** or **uncertain** clinical history.

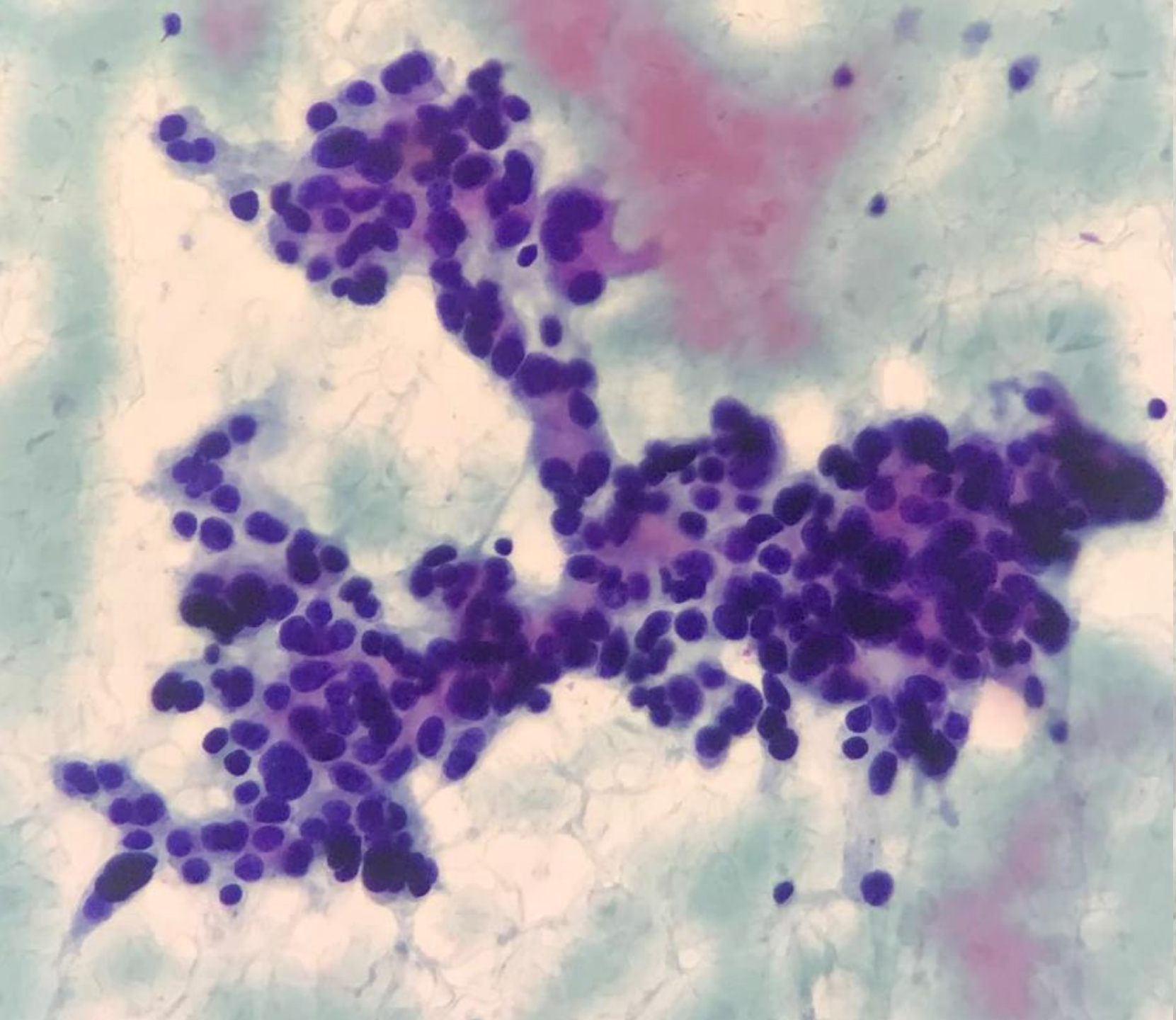
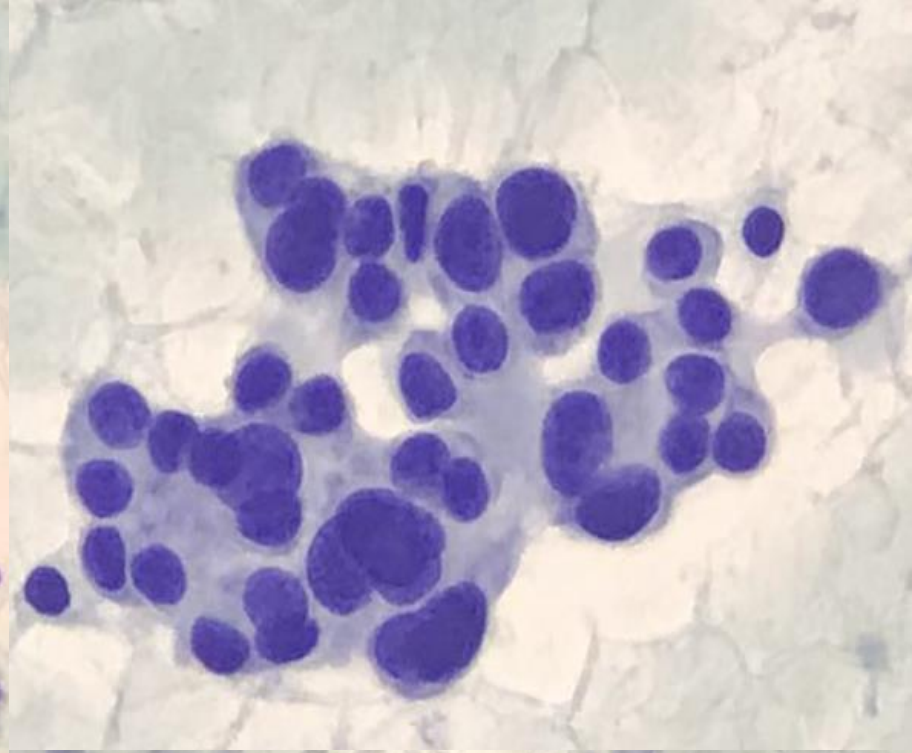
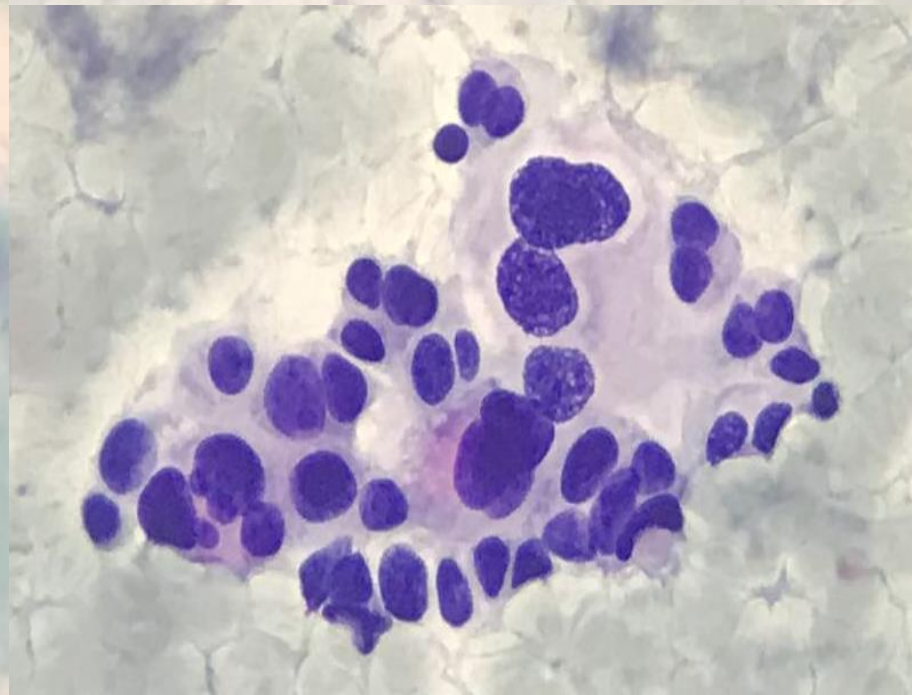


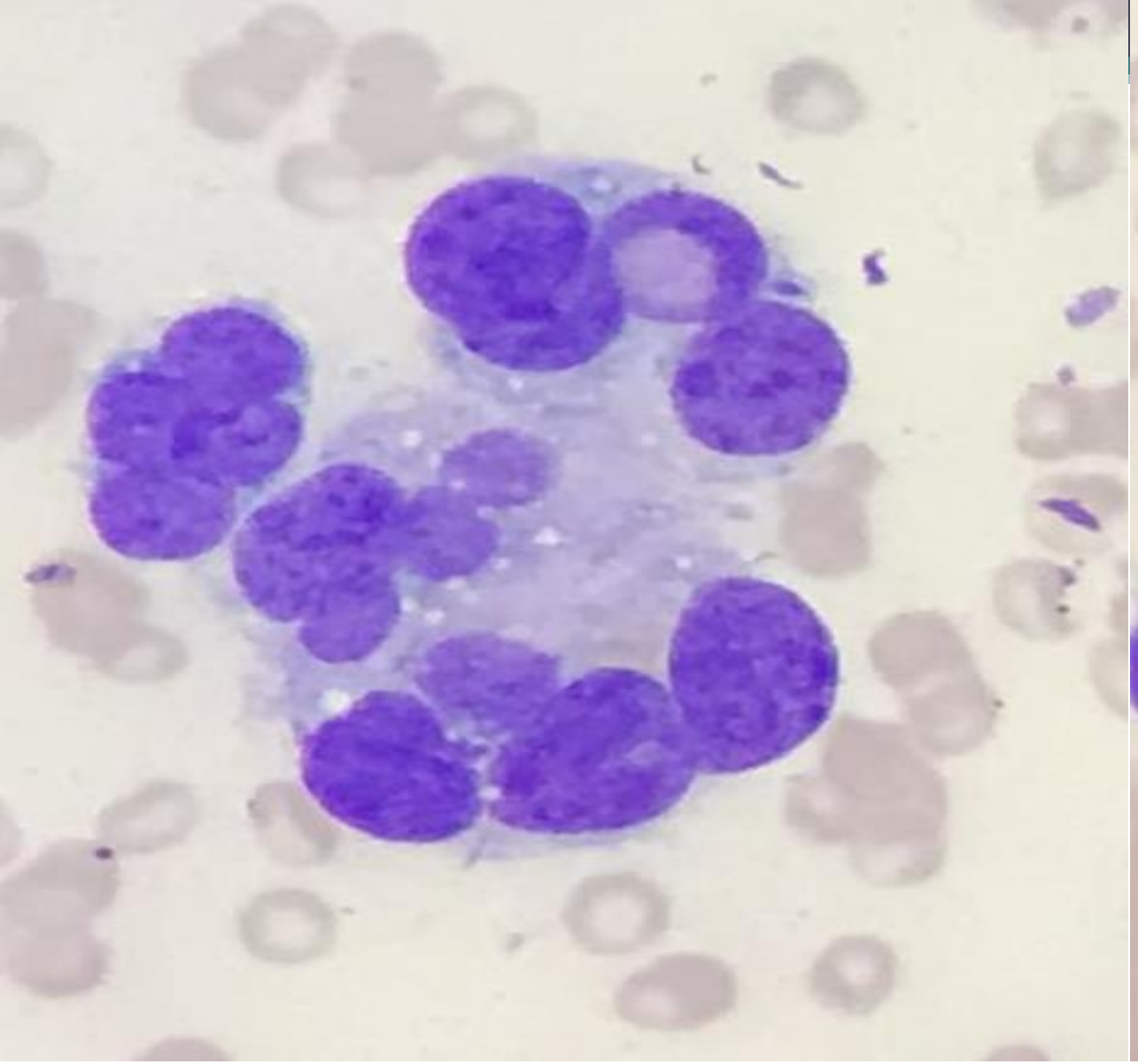


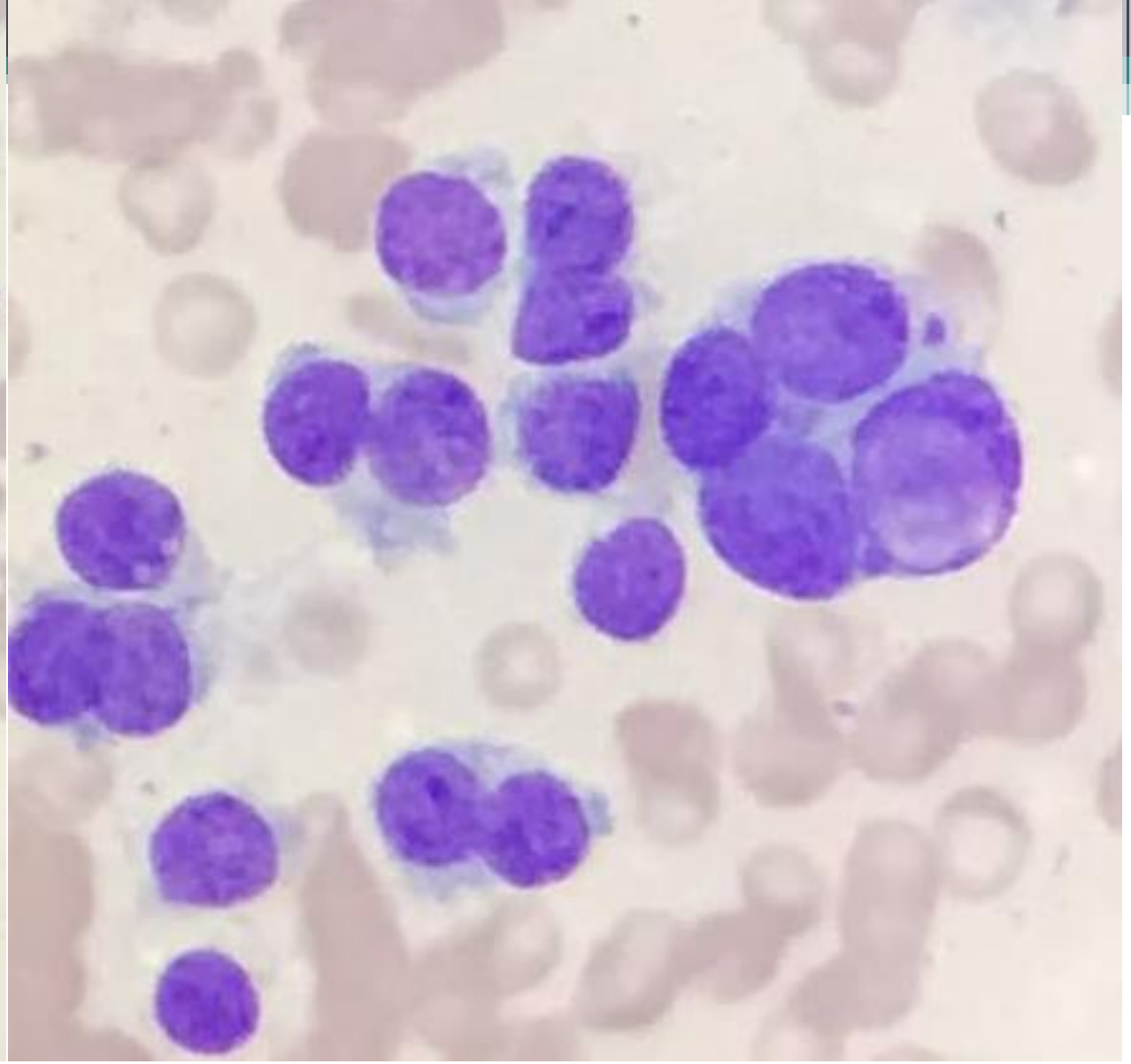
follicular cells, in a patient with **Graves' disease** treated with **methimazole** (Tapazole), show **marked** nuclear enlargement and **anisonucleosis**

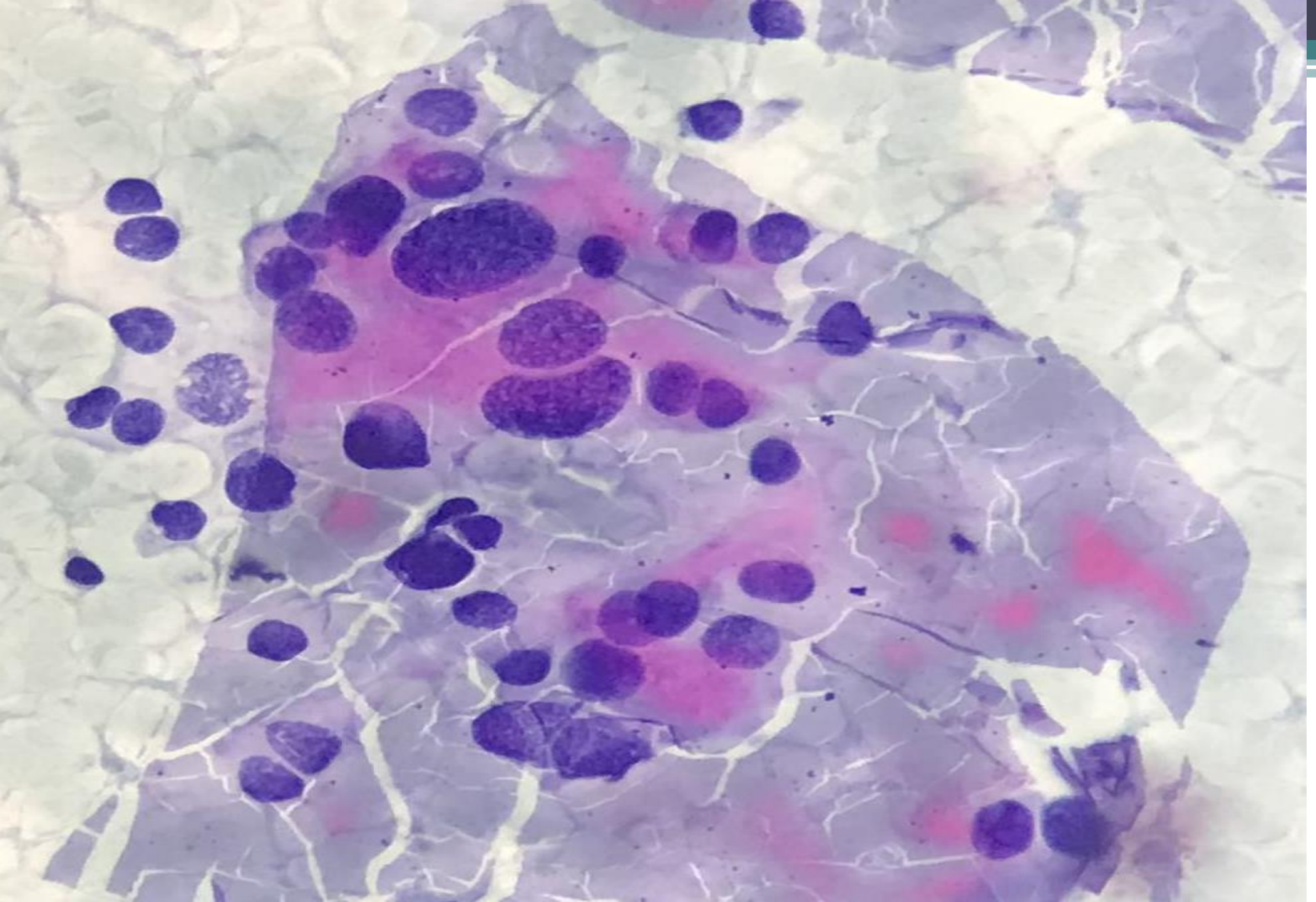
These atypical follicular cells were obtained from a patient with a **history of ionizing radiation to neck**

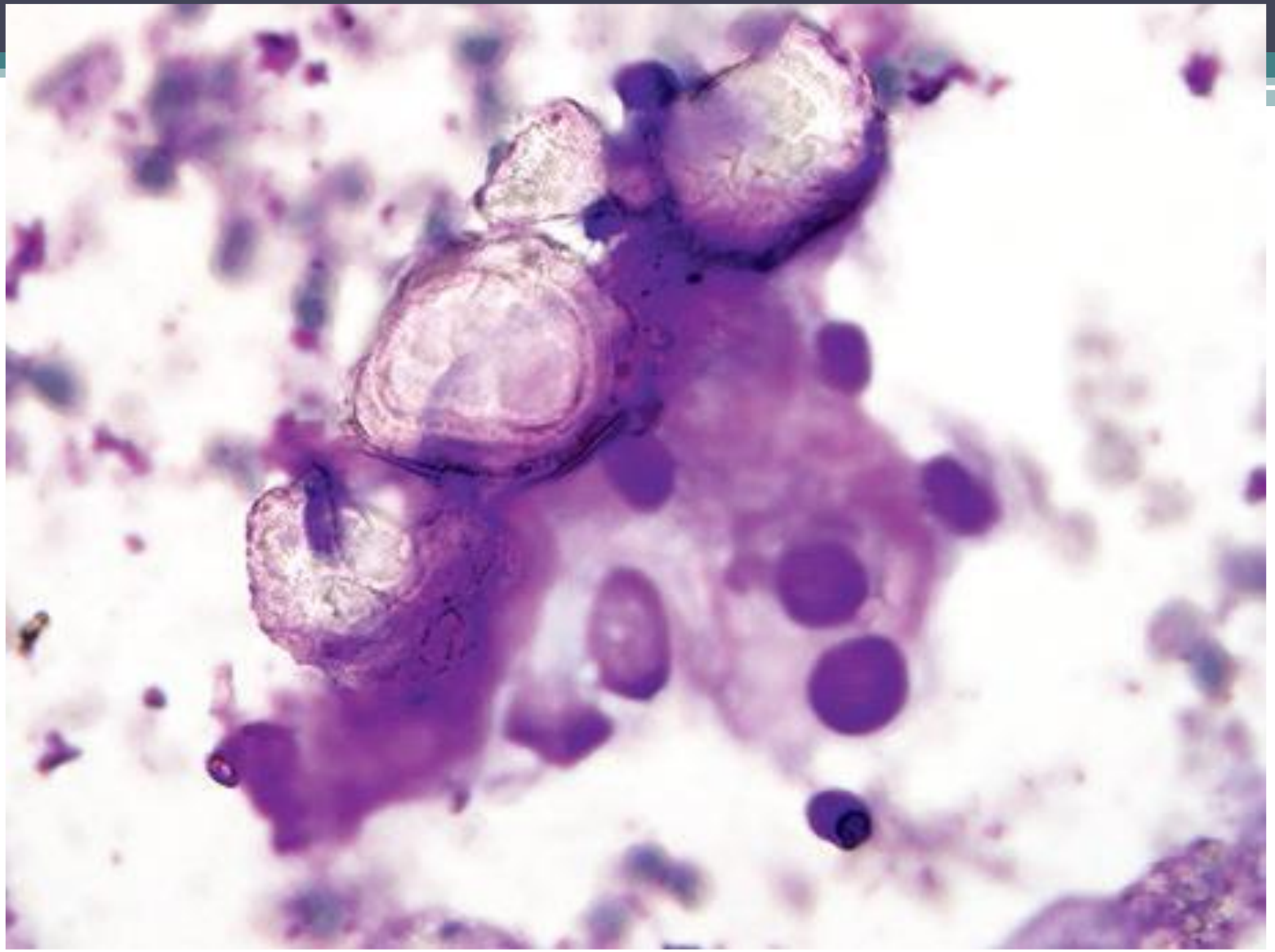
AUS, NOS









AUS, NOS
Psammoma bodies

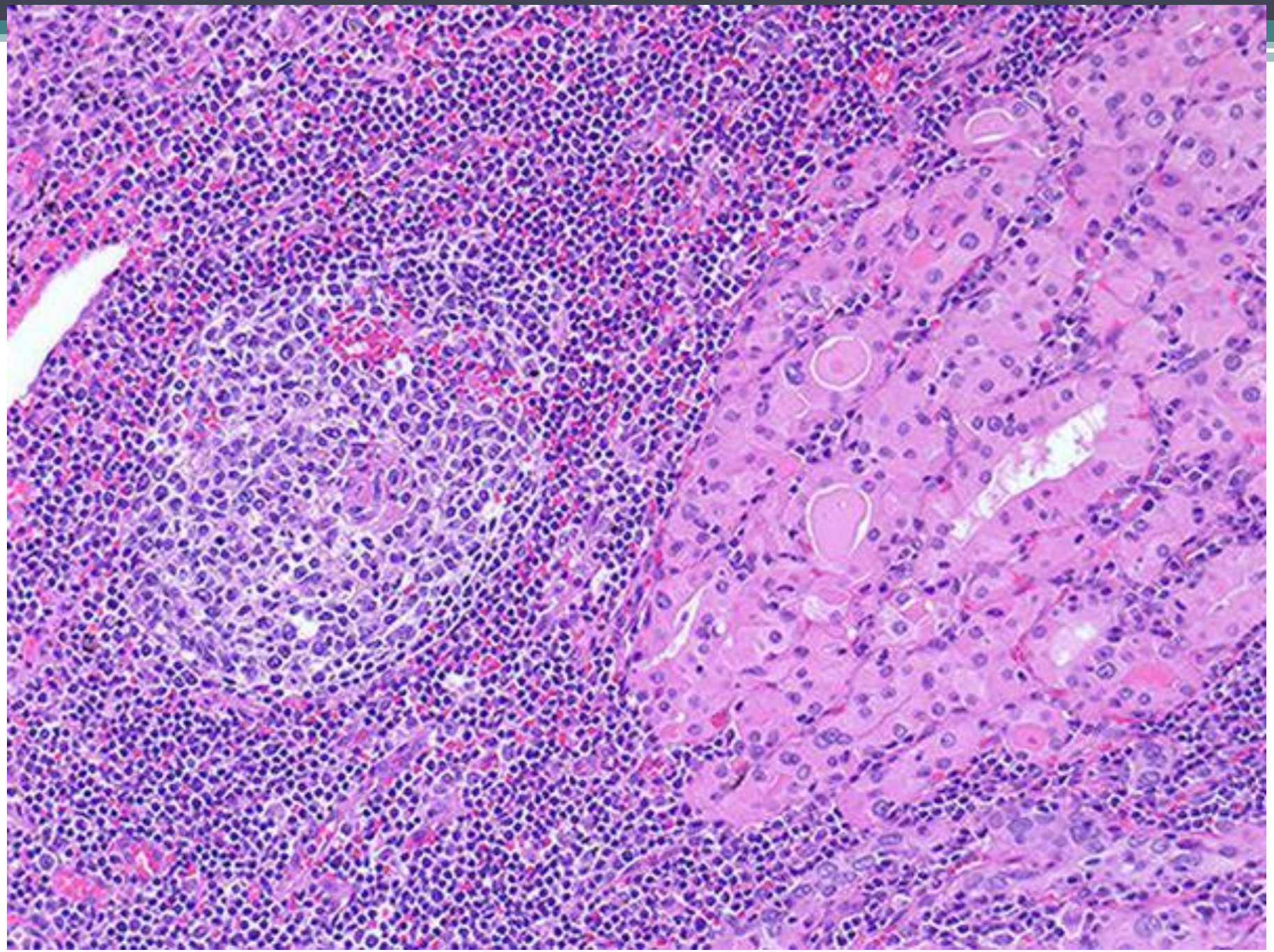
They form at the tip of a papilla due to circumferential avascular necrosis, resulting in the **concentric lamellations** of the classic psammoma body.

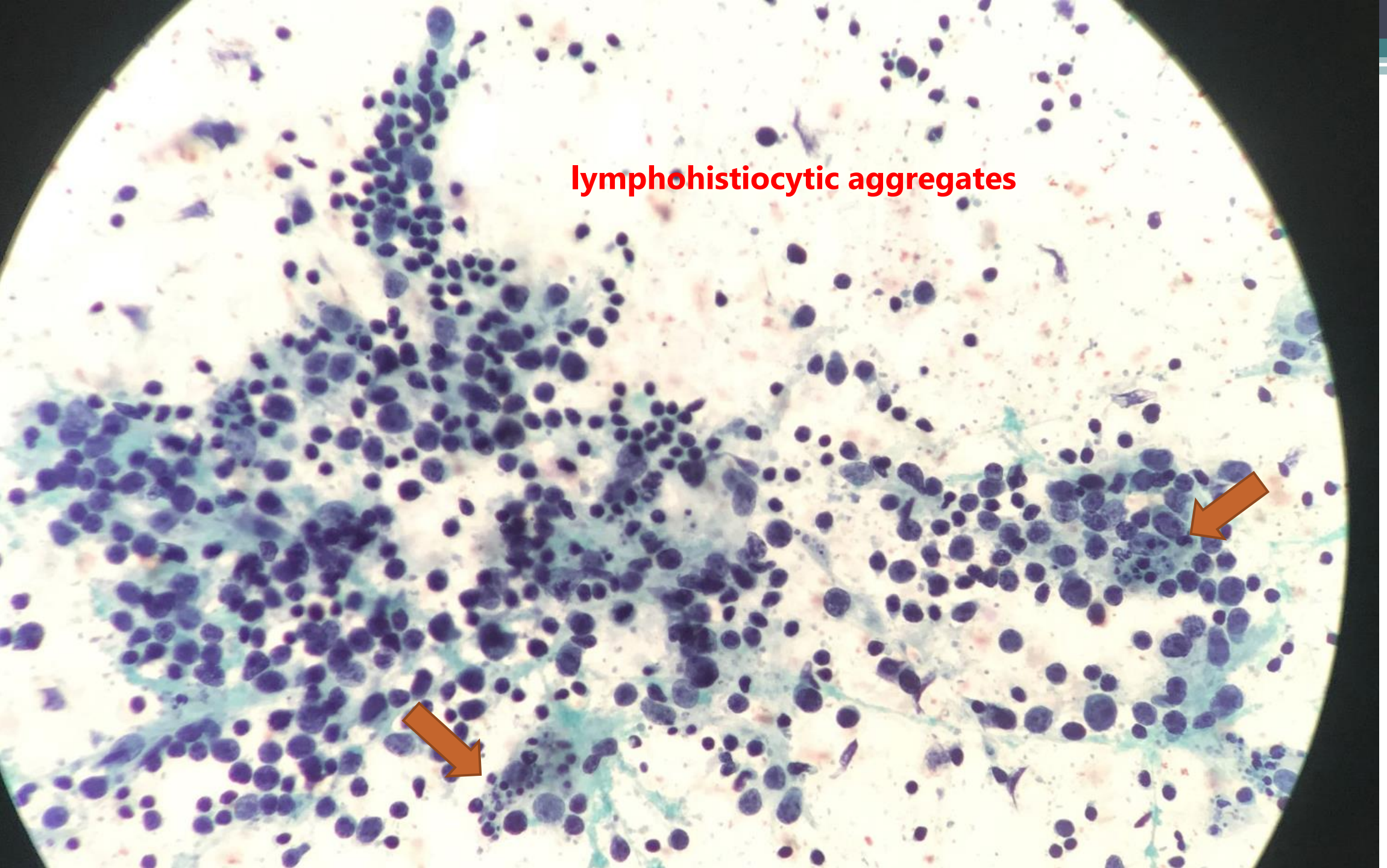
Atypical Lymphoid Cells, Rule Out Lymphoma

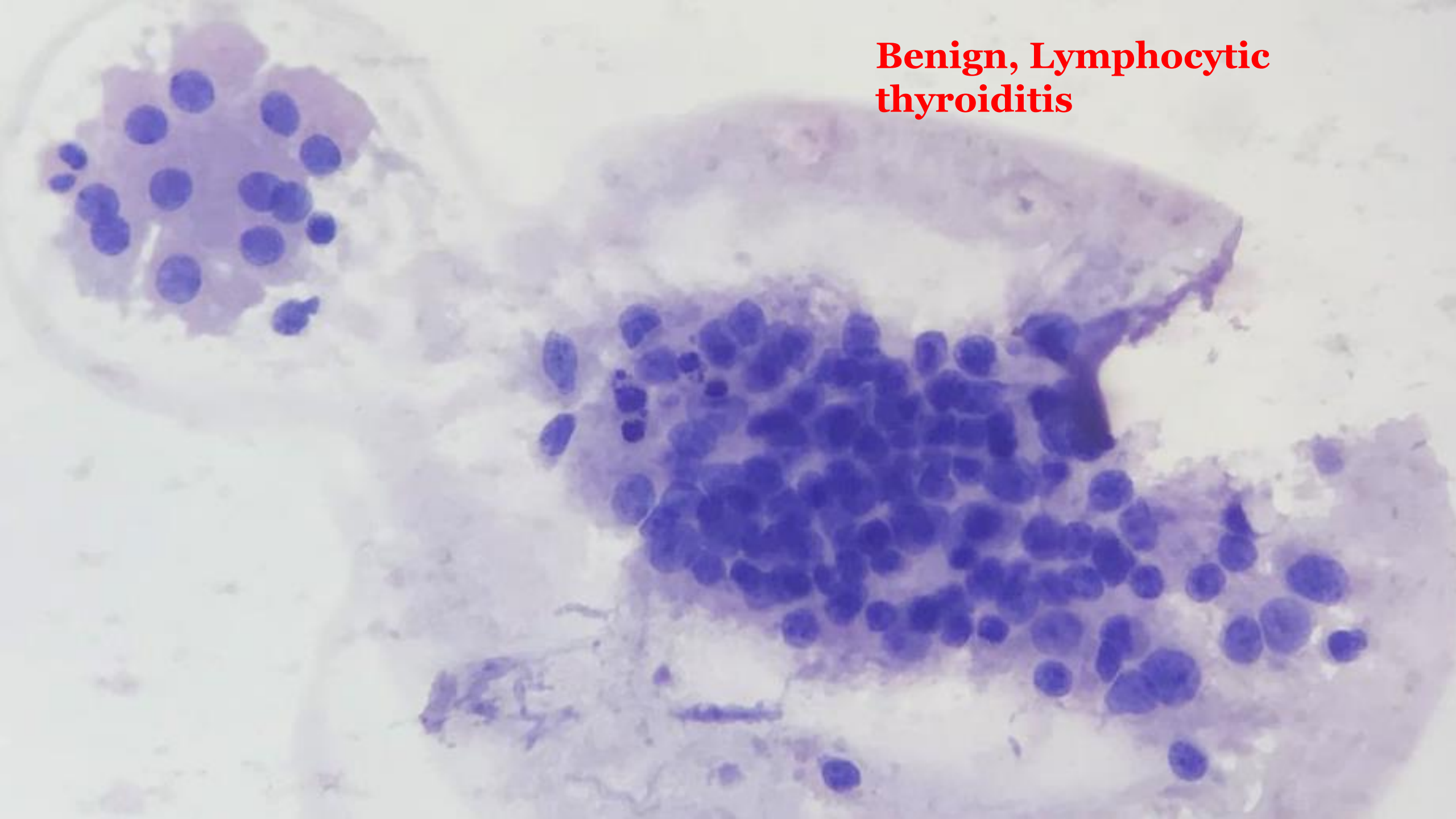
- An **atypical or monomorphous** lymphoid infiltrate
- But the degree of atypia is **insufficient** for the general category "suspicious for malignancy or malignant."

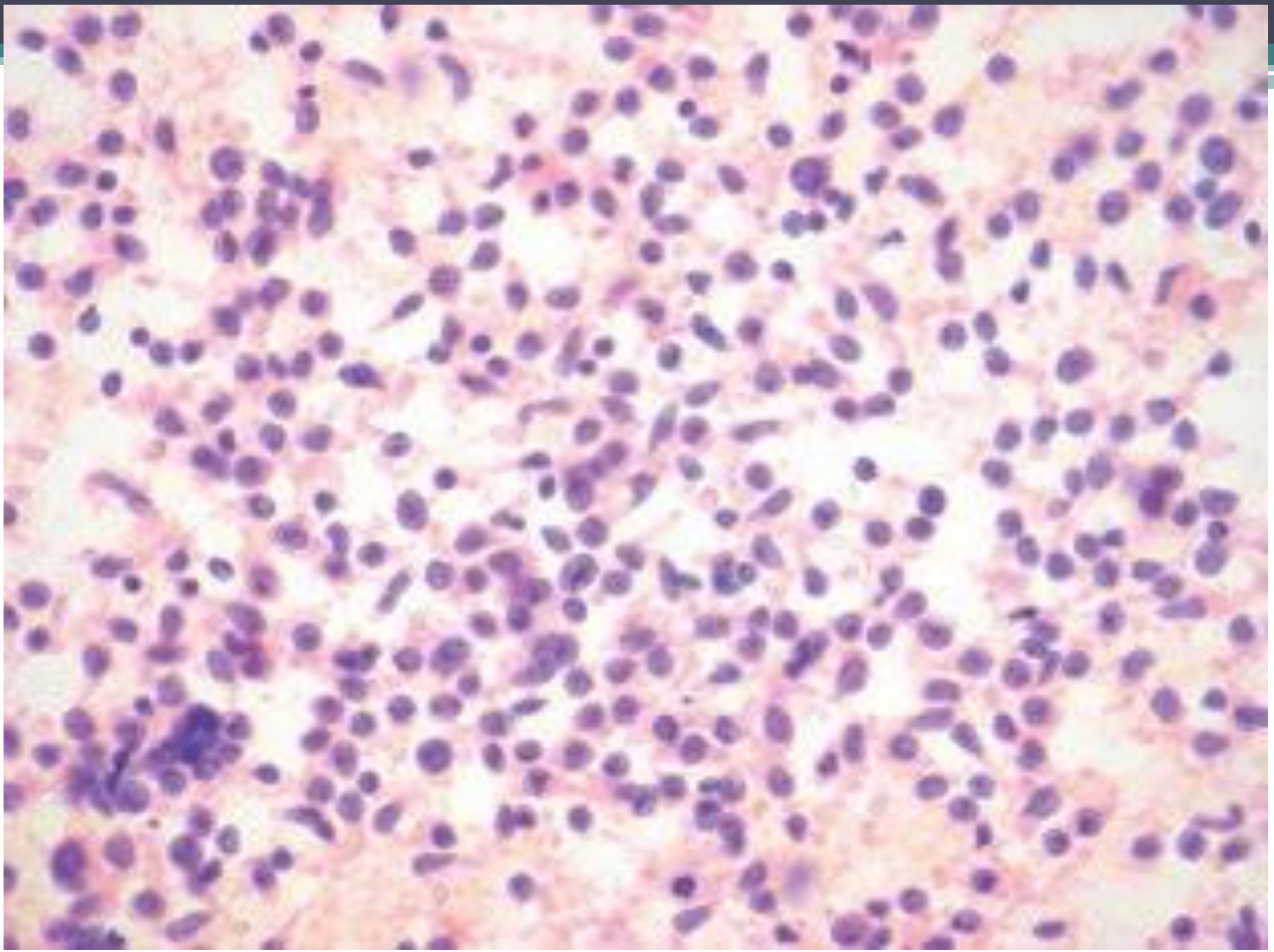
- **Especially** in the setting of l**ong-standing Hashimoto** thyroiditis and/or a **large or rapidly growing** nodule.

- If **clonality studies** are not available >>> **AUS** diagnosis+ **recommendation** for a **repeat** aspirate for **flow cytometry**, is appropriate.




lymphohistiocytic aggregates


Benign, Lymphocytic thyroiditis



AUS with atypical lymphoid cells.

Smear of a diffuse lesion suspected to be Hashimoto thyroiditis clinically shows extensive infiltration by **monotonous small lymphocytes** with slight variation in nuclear size and contour showing oval and occasionally kidney-shaped nuclei. Small distinct nucleoli can be observed in many cells; however, mitoses and necrosis are not seen

Explanatory Notes

Compromising factors

- like sparse cellularity, air-drying artifact, obscuring blood, and excessive clotting artifact ,By **themselves >>> do not warrant** an AUS diagnosis

- **if** adequacy criteria are **not satisfied** and there is **no atypia**>>> should be **called non diagnostic**

a diagnosis can be made on many compromised specimens:

- **if** there are **sufficient well-preserved, well-visualized** follicular cells , >>>can still be diagnosed as **benign**,
- **if** there is **discernible atypia >>>** can **be diagnosed as abnormal (e.g., AUS)**

Specimen preparation artifacts may potentially raise concern for AUS

- **Inadvertent air-drying of alcohol-fixed smears** may result in follicular cells with enlarged nuclei , have pale but slightly smudgy chromatin and irregular nuclear outlines

- **Excessive blood clotting** can impair the presentation of follicular cells, often the false impression of architectural crowding due to the entrapment of cells in the clot or the false impression of nuclear grooves due to fibrin strands

Specimen preparation artifacts may potentially raise concern for AUS

If

- ✓ Artifacts are **focal, clearly recognizable**
- ✓ Associated with **benign material elsewhere**

→ **should be diagnosed as benign**

× **Only rare** cases where there is **uncertainty** about cytologic changes : artifactual in origin **or** truly atypical? → should result in an **AUS diagnosis + Comment .**

Diagnosis: AUS

Comment: The mentioned atypical cells could be related to degeneration/ or be artifactual. Clinical / imaging correlation and repeated thyroid FNA are advised

AUS overdiagnosis !!

- Presence of **some oncocytic cells** or **cyst lining cells**, with their **customary mild nuclear** alterations (e.g., nuclear grooves, finely granular or pale chromatin), does not warrant an AUS designation if there is **ample evidence of benign follicular cells and abundant colloid.**

- **Only hypercellulary without nuclear atypia**

- **Isolated follicular cells** with minimal alterations (isolated nuclear enlargement, pale chromatin, or nuclear grooves) or **occasional micro-follicles (in benign aspirate)** also do not merit the AUS category

AUS overdiagnosis !!

Distinction between AUS and **suspicious** for malignancy:

- **Problematic** in aspirates with **focal** features of papillary carcinoma
- **AUS**: rare cells (typically **less than 20** in number) with enlarged, often overlapping nuclei, pale chromatin, irregular nuclear outlines, and nuclear grooves
- findings are even more **highly associated with papillary carcinoma (SFM):** When nuclear changes accompanied by **diffuse severe nuclear atypia, rare well-defined, intranuclear pseudoinclusions, distinctive nuclear groove and/or psammomatous calcifications**

Limiting AUS interpretations

- A **provisional** goal of limiting AUS interpretations to **approximately 7%** of all thyroid FNAB interpretations was proposed in the **first edition of TBSRTC atlas**

- Since many laboratories struggled to achieve this figure**, an upper limit of 10% was adopted** as a more achievable target in the **second edition** and remains a reasonable figure

- **Additionally, it has also been proposed that the AUS: Malignant ratio may be a useful laboratory quality measure that should not exceed 3.0**

AUS Management

2015 **American Thyroid Association** guidelines :

- **Conservative** management
- Either **repeat FNA** or **molecular testing** (PCR, NGS)

Repeat FNA usually results in a **more definitive** cytologic interpretation

In **contrast to the adult** management guidelines, the 2015 American Thyroid Association pediatric guidelines recommended **more aggressive** management for an initial AUS in **children** to include diagnostic surgery

The decision regarding **surgery** (typically lobectomy) **vs. continued observation** is based on findings of :

- ✓Cytologic features (can not exclude PTC)
- ✓Molecular
- ✓Clinical
- ✓radiologic
- ✓clinical risk factors
- ✓patient preference

Core needle biopsy (CNB)

Role of thyroid core needle biopsy:

- Recurrent **AUS** and **unsatisfactory** Bethesda groups
- Medullary thyroid carcinoma
- Suspicious cytology report
- Anaplastic/undifferentiated carcinoma
- Lymphoma
- Metastasis
- Parathyroid

Large tissue samples: permit a wide range of **histochemical and IHC analyses**

Sample Reports

Example 1
Specimen adequacy is limited by scant epithelial cellularity.
ATYPIA OF UNDETERMINED SIGNIFICANCE.
AUS-Other.
Sparsely cellular aspirate comprised of follicular cells with architectural atypia. Colloid is absent.
Note: A repeat aspirate may be helpful in order to further characterize the lesion.

Example 2
ATYPIA OF UNDETERMINED SIGNIFICANCE.
AUS-Nuclear.
Both mild nuclear and architectural atypia are present.

Example 3
ATYPIA OF UNDETERMINED SIGNIFICANCE.
AUS-Nuclear.
Follicular cells, predominantly benign-appearing, with focal nuclear atypia.
Note: Molecular testing or a repeat aspiration may be helpful in clarifying these findings.

Example 4

(FNAB of a patient with multiple, bilateral nodules; multinodular goiter)

ATYPIA OF UNDETERMINED SIGNIFICANCE.

AUS-Other.

The specimen is **moderately cellular and consists almost exclusively of oncocytic cells**. Colloid is scant, and there is no apparent increase in lymphoid cells.

Note: **In a patient with multiple nodules, the findings likely represent oncocytic cell hyperplasia** in **the setting of multinodular goiter**; however an oncocytic follicular neoplasm cannot be entirely excluded. Molecular testing may be beneficial.

Example 5

(FNAB of a nodule in a patient with a history of Hashimoto thyroiditis)

ATYPIA OF UNDETERMINED SIGNIFICANCE.

AUS-Other.

The sample consists **exclusively of oncocytic cells with focal endocrine atypia.**

Note: **In a patient with Hashimoto thyroiditis, these findings more likely represent oncocytic cell metaplasia/hyperplasia**; however an oncocytic follicular neoplasm cannot be entirely excluded. Molecular testing may be helpful in further clarifying the findings.

Example 6

(FNAB of a nodule in a patient with Graves' disease treated with ^{131}I)

ATYPIA OF UNDETERMINED SIGNIFICANCE.

AUS-Other.

Follicular cells with likely **treatment-related atypia.**

Note: **In the context of treatment of hyperthyroidism with radioiodine, these findings likely represent reactive, treatment-related changes. Suggest clinical/radiologic correlation and follow-up as warranted**.

Example 7

(FNA of a nodule in a patient with a long-standing history of Hashimoto thyroiditis)

ATYPIA OF UNDETERMINED SIGNIFICANCE.

AUS-Other.

Numerous **relatively monomorphic lymphoid cells.**

Note: **The findings are atypical and raise the possibility of a lymphoproliferative process** arising in the background of the patient's long-standing chronic lymphocytic thyroiditis. **Immunophenotyping studies** could not be performed since only smears were made from the aspirate. Repeat FNA with aspirate collected for flow cytometry would be helpful in reaching a more definite diagnosis.

Note

1. Hypercellular benign smears without nuclear atypia

- **Note :** Due to hypercellularity of the mentioned nodule, clinical/ imaging correlation and follow up thyroid FNA are advised.

2. Sonography: TIRADS 5/highly suspicious nodule with benign cytomorphology

- **Note :** Sonography report of the mentioned nodule was in favor of TIRADS V. Clinical/ imaging correlation and repeated thyroid FNA are mandatory.

3. Degenerated smear + focal nuclear atypia: AUS

- **Note:** The mentioned atypical cells could be related to degeneration/ or be artifactual. Clinical / imaging correlation and repeated thyroid FNA are advised

4. AUS: Nuclear atypia, highly concern about PTC but, no satisfied for suspicious

- **Note:** The possibility of malignancy (PTC?) cannot be excluded. Clinical/ imaging correlation and repeated thyroid FNA/ core needle biopsy are mandatory. Frozen section study is advised before any thyroid radical surgery.

Note

AUS, Oncocytic

- **Note:** Presence of hurthle cells in the mentioned nodule could be attributed to hurthle cell changes in the context of nodular goiter / chronic lymphocytic thyroiditis. Clinical/ imaging correlation and follow up thyroid FNA are mandatory.

Oncocytic (Hurtle cell) neoplasm

- **Note**: Presence of hurthle cells in the mentioned nodule could be attributed to hurthle cell changes in the context of nodular goiter / chronic lymphocytic thyroiditis or less probably a hurthle cell neoplasm. Clinical/ imaging correlation and follow up thyroid FNA are mandatory.

- **Note:** Presence of hurthle cells in the mentioned nodule could be attributed to hurthle cell changes in the context of nodular goiter / chronic lymphocytic thyroiditis or a hurthle cell neoplasm. Clinical/ imaging correlation is mandatory.

❖ Evaluation of serum calcitonin level and CEA are advised to exclude any remote possibility of C-cell origin in the mentioned nodule.

AUS, Architectural (micro-follicle)

- **Note :** Based on cytological features, follicular nodular disease (hyperplastic nodular goiter) and follicular neoplasm are the main differential diagnoses. Clinical/ imaging correlation and follow up thyroid FNA are advised.

Pituitary adenoma

WHO classification 2021:

Pituitary Neuroendocrine Tumor (Pit NET)

~~Pituitary adenoma~~
>>>Pituitary Neuroendocrine Tumor (PitNET)

Neuroendocrine:

- Cells of the **anterior** pituitary are considered **Neuroendocrine cells**
- **Hormone-producing**
- Expressing neuroendocrine features and **markers (IHC: chromogranin – synaptophysin)**
- **Biologically related to other neuroendocrine tumors** : Pancreas -Gastrointestinal tract – Lung

~~"Adenoma" Considered Inadequate~~: >>>>>Tumor

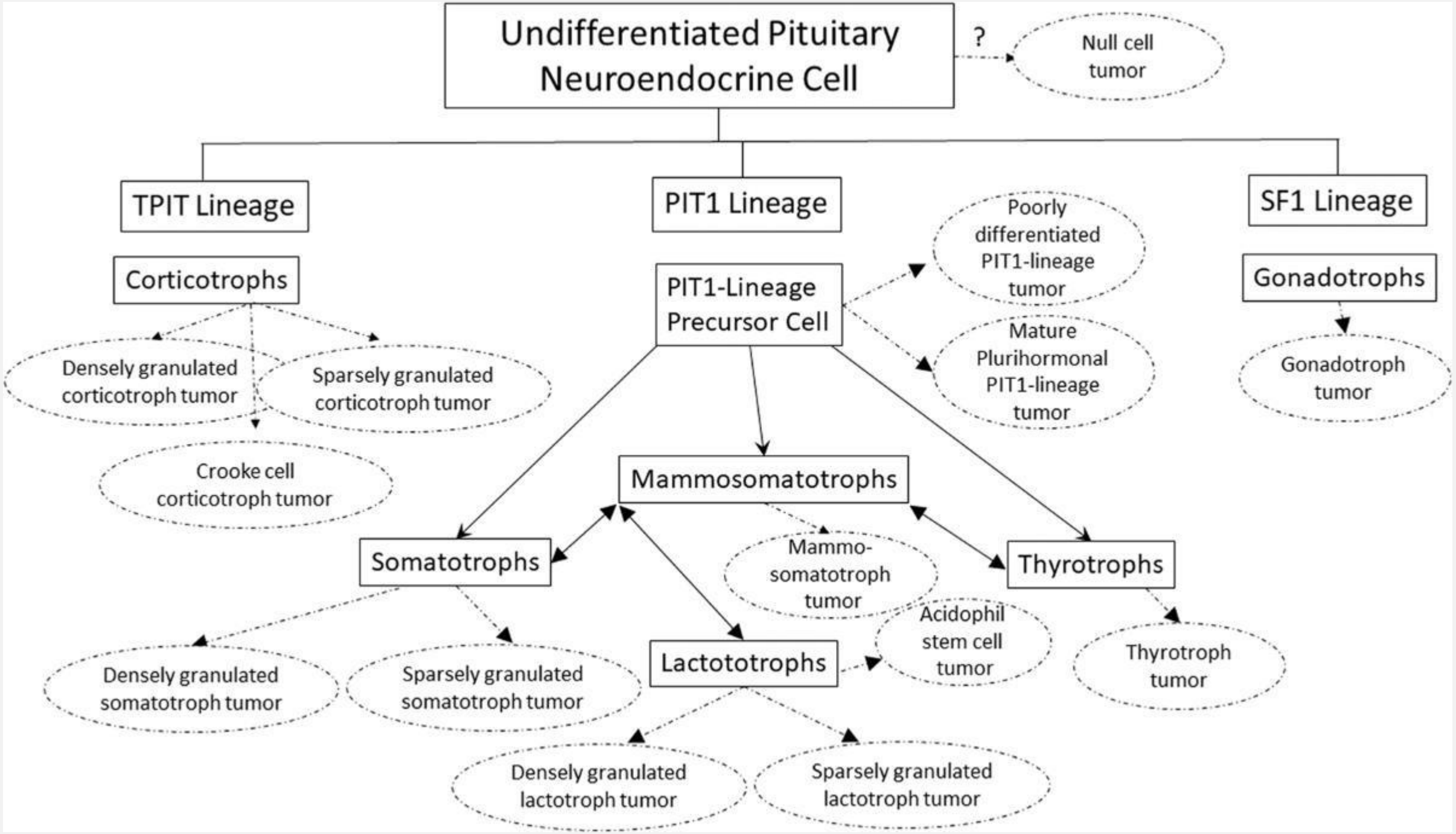
- The word **adenoma traditionally** implies: A benign glandular neoplasm / non-aggressive tumor

- However, it became clear that **some pituitary tumors** can show:
  - Invasive growth: Local destruction - cavernous sinus invasion
  - Frequent recurrence
  - Resistance to therapy
  - Rare metastatic potential

Importance of IHC in pituitary adenomas

Modern IHC-based classification:

1. Identify the exact cell lineage
2. Determine the true hormone-producing tumor type
3. Detect silent adenomas
4. **Predict biologic behavior and recurrence risk**
5. **Guide targeted therapy**


Undifferentiated Pituitary Neuroendocrine Cell
?
Null cell tumor
TPIT Lineage
PIT1 Lineage
SF1 Lineage
Corticotrophs
Densely granulated corticotroph tumor
Sparsely granulated corticotroph tumor
Crooke cell corticotroph tumor
PIT1-Lineage Precursor Cell
Poorly differentiated PIT1-lineage tumor
Mature Plurihormonal PIT1-lineage tumor
Gonadotrophs
Gonadotroph tumor
Mammosomatotrophs
Somatotrophs
Mammo-somatotroph tumor
Thyrotrophs
Densely granulated somatotroph tumor
Sparsely granulated somatotroph tumor
Lactototrophs
Acidophil stem cell tumor
Thyrotroph tumor
Densely granulated lactotroph tumor
Sparsely granulated lactotroph tumor

Markers and interpretation:

Paraffin block NO: P05-294- Block NO 5

1- **Chromogranin**: Positive in nearly all tumor cells
2- **Synaptophysin**: Positive in nearly all tumor cells
3- **Pit-1**: Positive in nearly all tumor cells
4- **Growth hormone (GH)**: Positive in nearly all tumor cells
5- **Prolactin**: Positive in some tumor cells
6- **SF1**: Negative in tumor cells
7- **GATA3**: Negative in tumor cells
8- **TSH**: Negative in tumor cells
9- **ACTH**: Negative in tumor cells
10- **FSH**: Negative in tumor cells
11- **LH**: Non-specific reaction
12- **CAM5.2**: Positive in nearly all tumor cells with mixed fibrous body pattern (50%) and diffuse cytoplasmic patterns
13- **Ki67 index**: Up to 1% of tumor cells

Final interpretation: Sellar/ Suprasellar mass, Trans-sphenoidal Resection:

- **Compatible with Pituitary Neuroendocrine Tumor (Pit NET) / Pituitary adenoma with immunophenotyping features favoring Mammosomatotroph adenoma**

Markers and interpretation:

Paraffin block NO: P05-337- Block NO 3

1- **Chromogranin**: Positive in nearly all tumor cells
2- **Synaptophysin**: Positive in nearly all tumor cells
3- **ACTH**: Positive in nearly all tumor cells with diffuse strong cytoplasmic reaction
4- **SF1**: Negative in tumor cells
5- **Pit-1**: Negative in tumor cells
6- **GATA3**: Negative in tumor cells
7- **Growth hormone (GH)**: Negative in tumor cells
8- **Prolactin**: Negative in tumor cells
9- **TSH**: Negative in tumor cells
10- **FSH**: Negative in tumor cells
11- **LH**: Negative in tumor cells
12- **CAM5.2**: Positive in most of tumor cells with intense diffuse cytoplasmic pattern
13- **Ki67 index**: Positive in about 1-2% of tumor cells.

Final interpretation: Sellar/ Suprasellar mass, Trans-sphenoidal Resection:

- **Compatible with Pituitary Neuroendocrine Tumor (Pit NET) / Pituitary adenoma, with immunophenotyping features favoring densely granulated Corticotroph adenoma**

Markers and interpretation:

Paraffin block NO: P05-154- Block NO 2

1- **Chromogranin**: Positive in nearly all tumor cells
2- **Synaptophysin**: Positive in nearly all tumor cells
3- **Pit-1**: Positive in nearly all tumor cells
4- **SF1**: Negative in tumor cells
5- **GATA3**: Negative in tumor cells
6- **Growth hormone (GH)**: Positive in some tumor cells
7- **Prolactin**: Negative in tumor cells
8- **TSH**: Negative in tumor cells
9- **ACTH**: Negative in tumor cells
10- **FSH**: Negative in tumor cells
11- **LH**: Negative in tumor cells
12- **CAM5.2**: Positive in nearly all tumor cells with evidence of fibrous body pattern
13- **Ki67 index**: Up to 2% of tumor cells

Final interpretation:

Sellar/ Suprasellar mass, Trans-sphenoidal Resection:

- **Compatible with Pituitary Neuroendocrine Tumor (Pit NET) / Pituitary adenoma with immunophenotyping features favoring sparsely granulated somatotroph adenoma**

Diagnosis: **Brain, Sellar/ Suprasellar mass, Trans-sphenoidal Resection:**

- **Compatible with Pituitary Neuroendocrine Tumor (Pit NET) / Pituitary adenoma with immunophenotyping features favoring Gonadotroph adenoma**

- **Ki67 index: 6-7 %**

- **Fragments of non-neoplastic anterior pituitary gland are also present.**

- **Please see the note**

Note:

- Based on the recent WHO classification of CNS tumors and published literature, pituitary adenomas with increased proliferation (Ki67 index ≥3%) may be related to poor prognosis and a higher risk of tumor recurrence. So, clinical/imaging correlation and patient close follow up are advised.
- Please see IHC report NO: I05-122 from our path lab.

- Follicular cell-derived neoplasms
  - Benign tumors
    - Thyroid follicular nodular disease
    - Follicular thyroid adenoma
    - Follicular thyroid adenoma with papillary architecture
    - Oncocytic adenoma of the thyroid
  - Low risk neoplasms
    - Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
    - Thyroid tumors of uncertain malignant potential
      - Follicular tumor of uncertain malignant potential
      - Well-differentiated tumor of uncertain malignant potential
    - Hyalinizing trabecular tumor
  - Malignant neoplasms
    - Follicular thyroid carcinoma
    - Invasive encapsulated follicular variant papillary thyroid carcinoma
    - Papillary thyroid carcinoma
    - Oncocytic carcinoma of the thyroid
    - Follicular-derived carcinomas, high-grade
      - Poorly differentiated thyroid carcinoma
      - Differentiated high-grade thyroid carcinoma
    - Anaplastic follicular cell-derived thyroid carcinoma

WHO Classification of Endocrine and Neuroendocrine Tumors



Thanks For your attention