Small Round Cell Pattern in Liquid-based Cytology: Cytopathology Case Presentation

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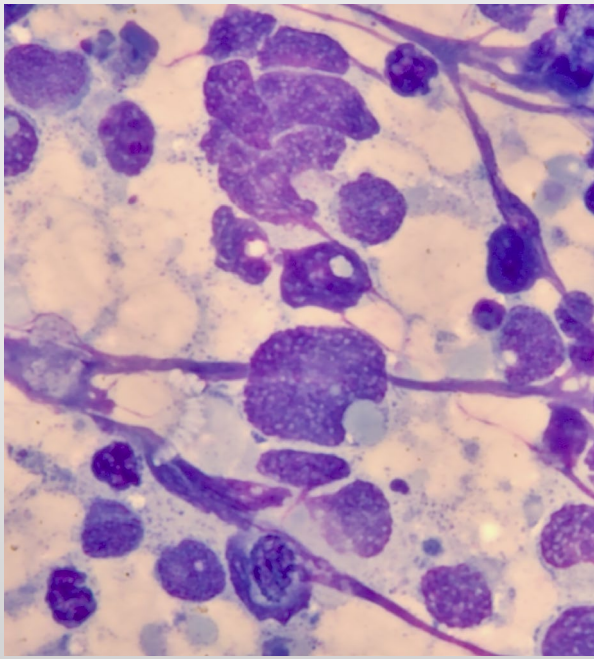
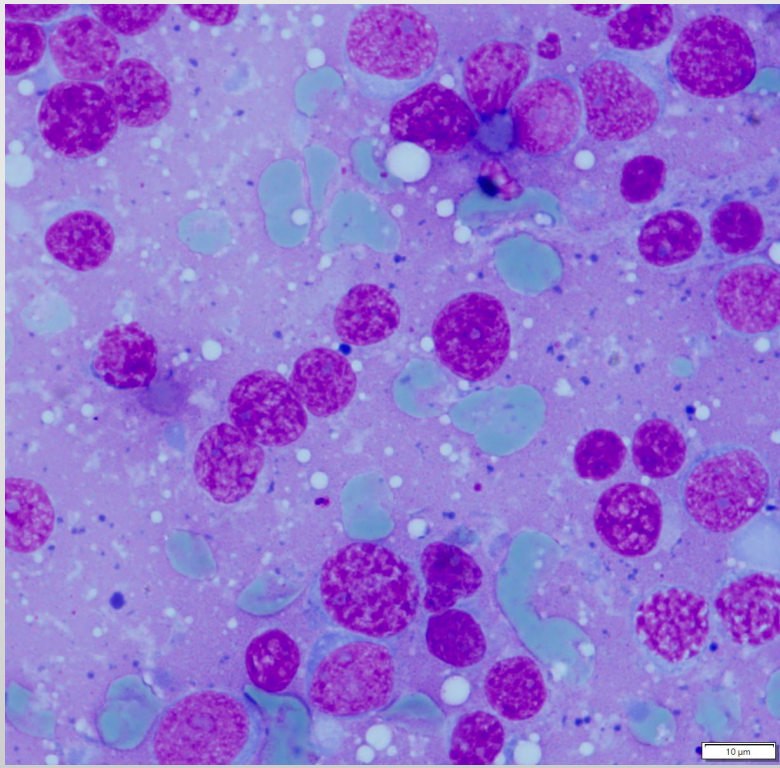
Introduction

- Small round cell tumors (SRCT) or small blue round cell tumors (SBRCTs) represent a diverse group of highly aggressive malignancies characterized by small, round, and poorly differentiated cells.
- These tumors can arise in various tissues and organs, including the lungs, and they often pose significant diagnostic challenges due to their overlapping cytomorphologic features.
- Accurate and timely diagnosis of SRCTs is critical for initiating appropriate treatment, making cytologic methods an essential component of the diagnostic process.

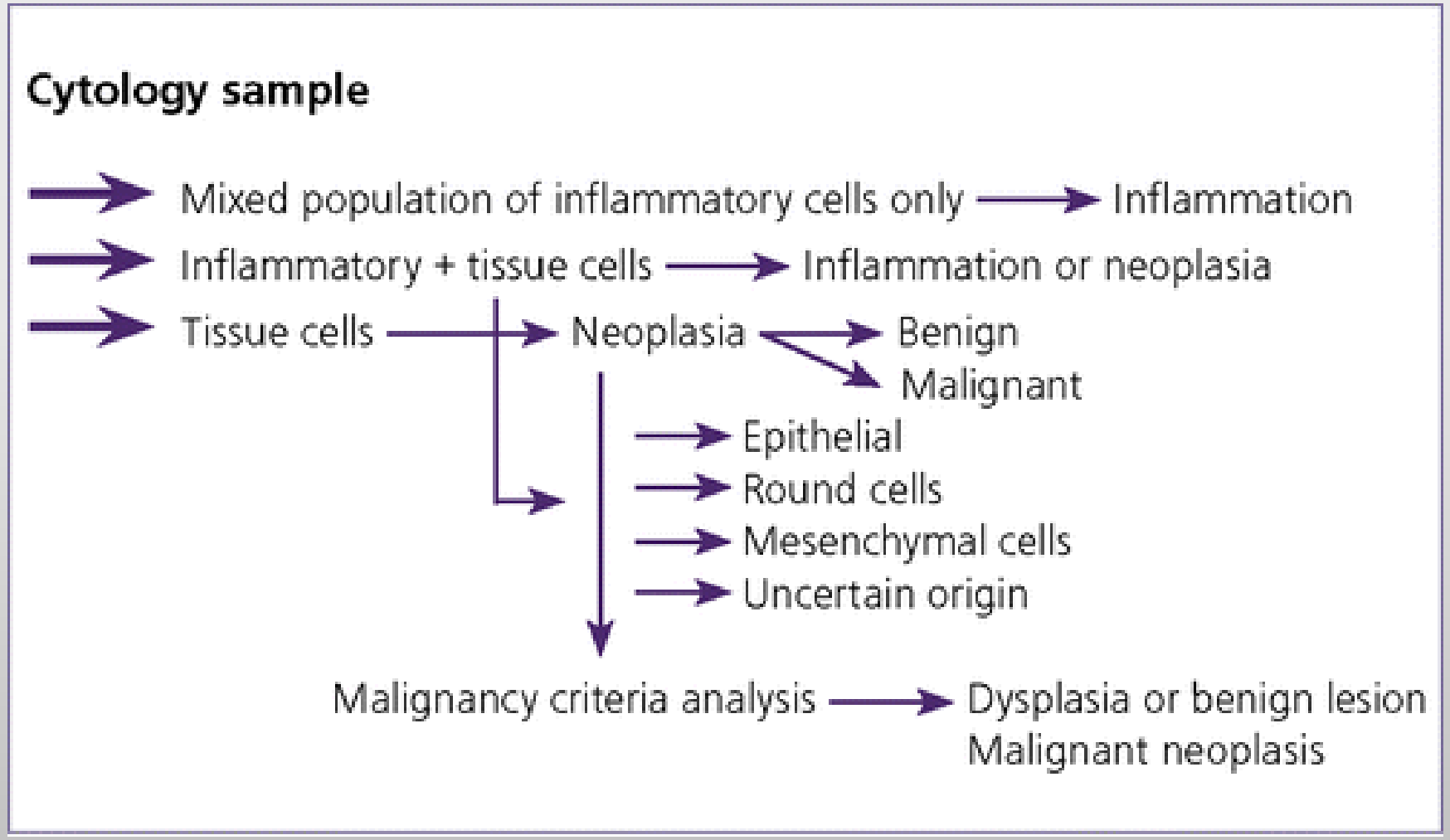


Small vs large

- Small cell carcinoma (SCC): less than 3 times the diameter of a normal resting lymphocyte (about 12-18 micrometers)
- Large cell carcinoma (LCC): more than 3 times the diameter of a lymphocyte
- Small cell lymphoma: about the size of a normal resting lymphocyte (around 6-12 micrometers in diameter)
- Large cell lymphoma: more than twice that of a small lymphocyte (which measures about 6–12 micrometers)

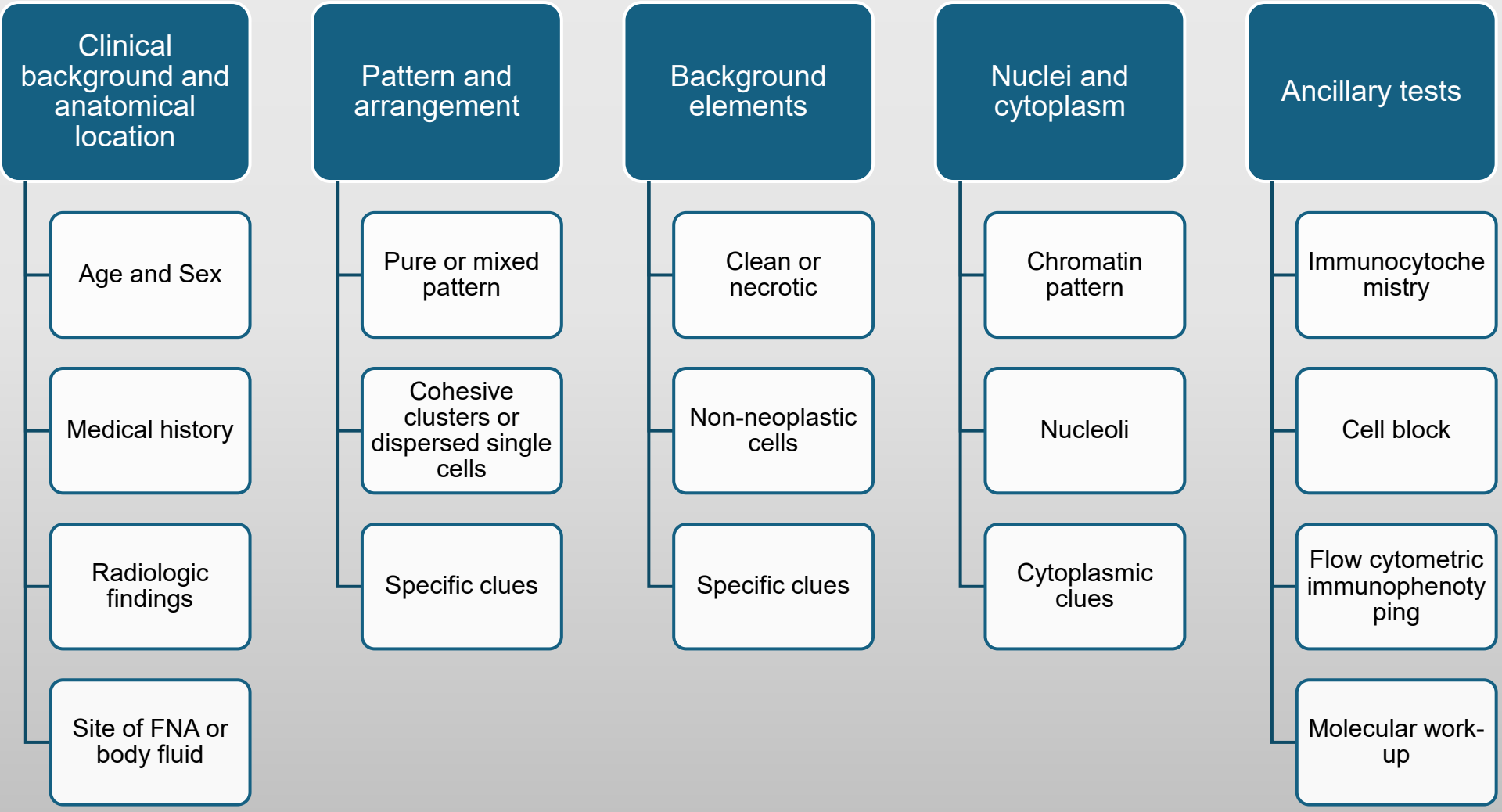


Stepwise Approach to Diagnosis of cytology sample



Understanding cytology as a useful tool for the general practitioner
Antonio Giuliano and Aimee Nudds
Companion Animal 2013 18:7, 308-313

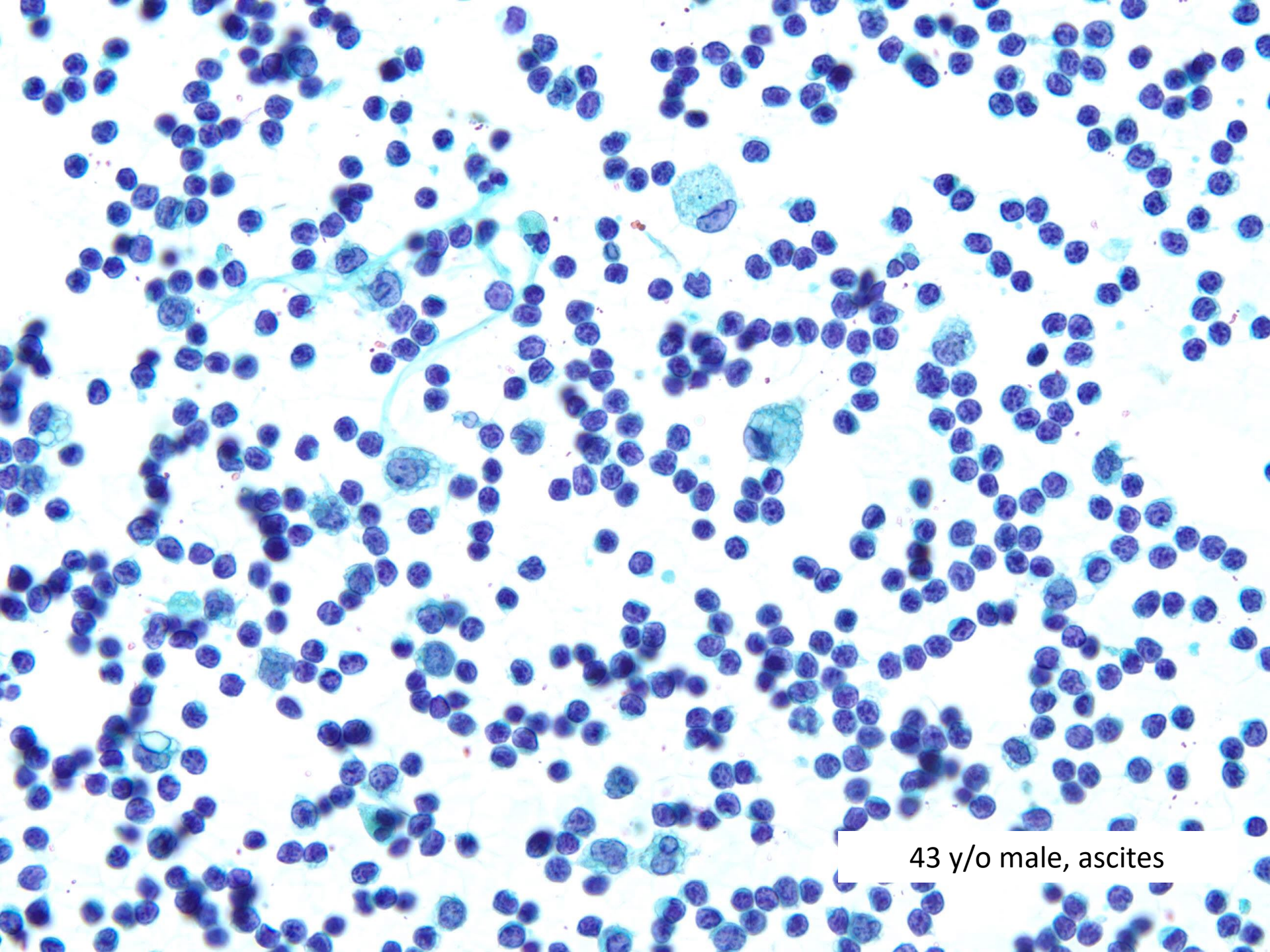
Stepwise Approach to Diagnosis of Small cell pattern cytology

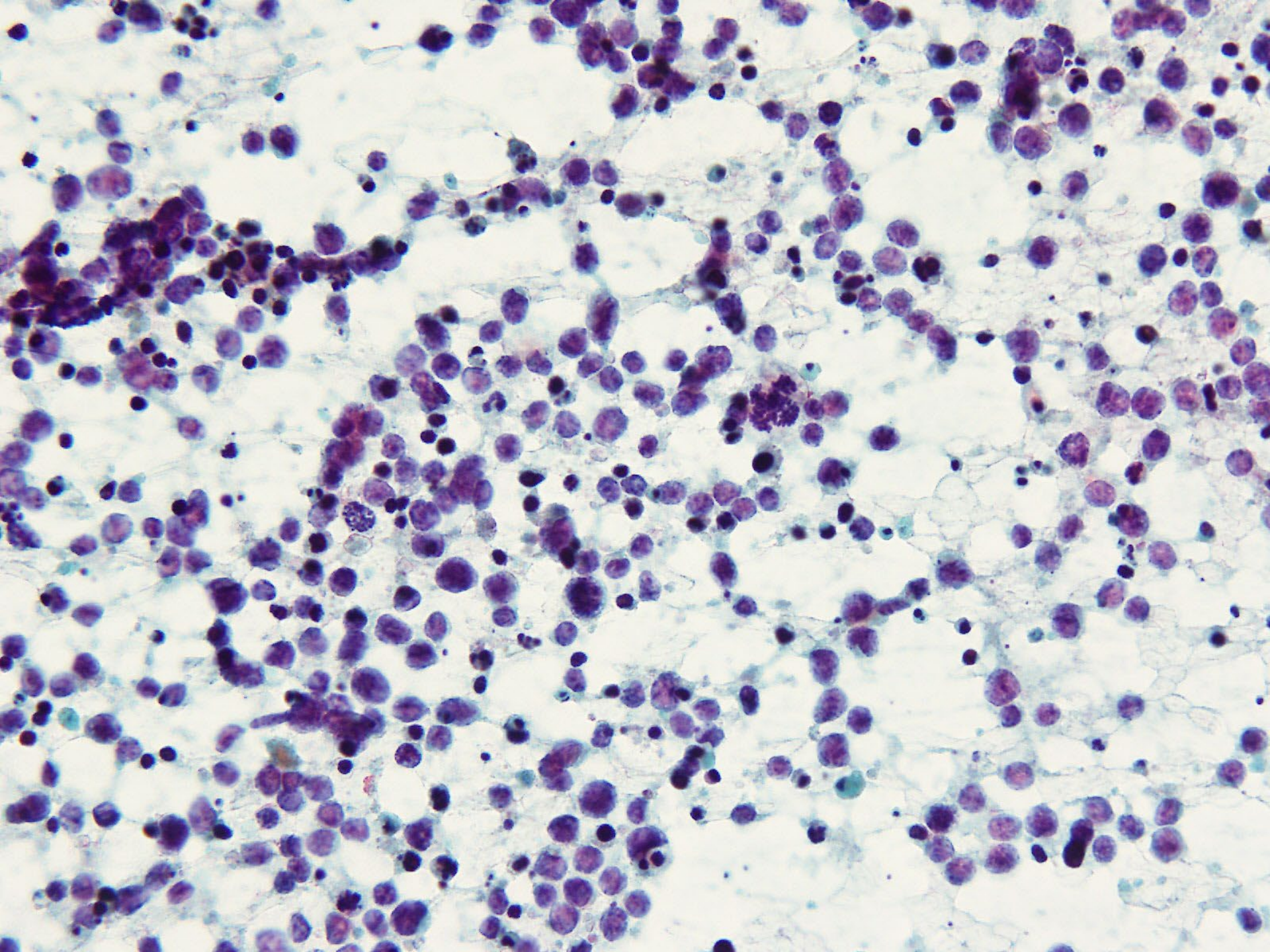


Cytomorphological Features of SRCTs

The following features are typically assessed：

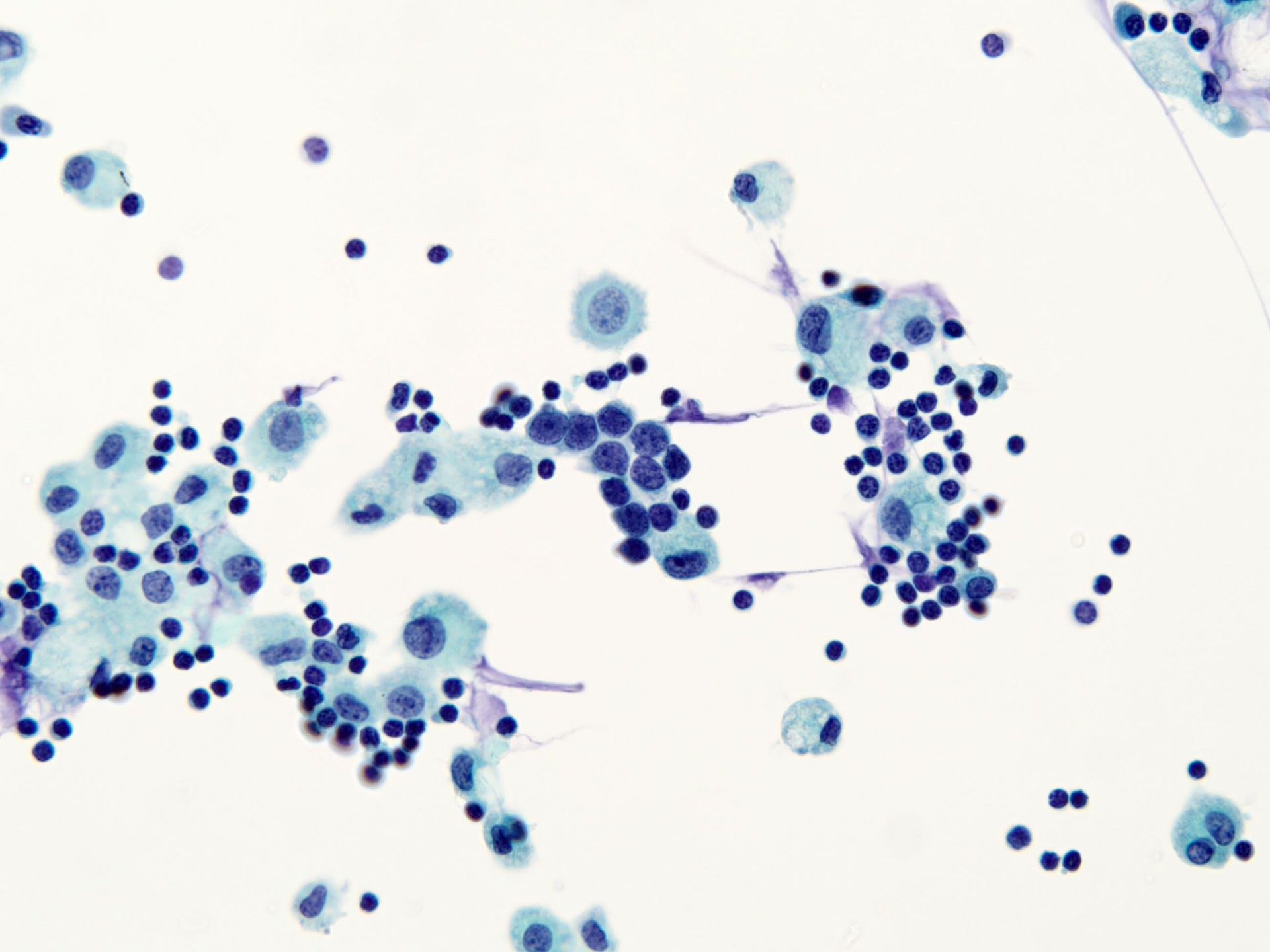
- Low-power field: Pure or mixed pattern
  - ✓Cellular Arrangement
  - ✓Background Elements
- High-power field
  - ✓Nuclear Features
  - ✓Cytoplasmic Characteristics

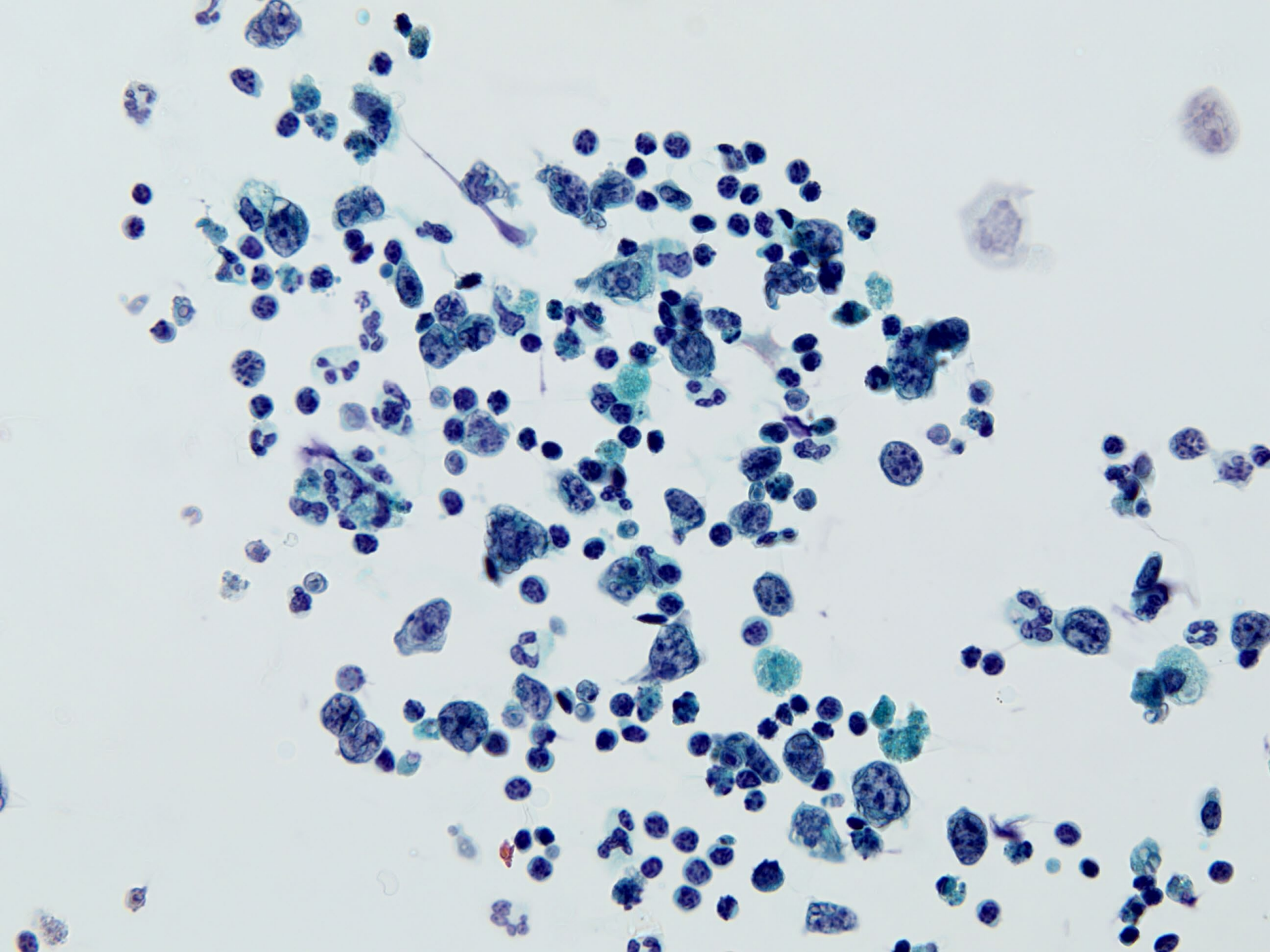

43 y/o male, ascites



Cellular Arrangement:

- Clusters and single cells: SRCTs commonly present as loosely cohesive clusters or as isolated single cells
- Cohesive groups or clustering of tumor cells: Epithelial malignancies
- Dispersed pattern: Suggest a diagnosis of hematolymphoid lesions when coupled with other features like lymphoglandular bodies.

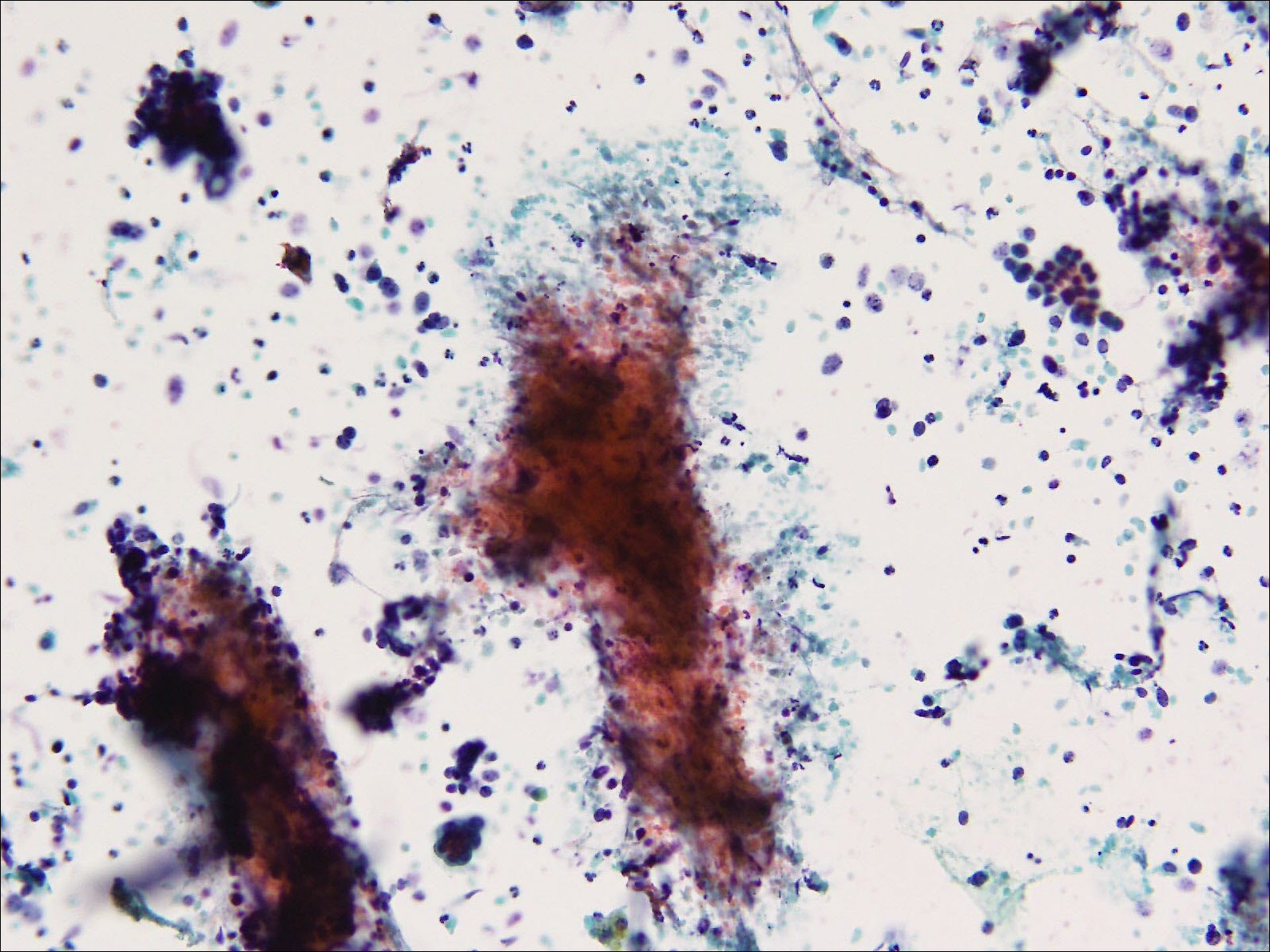


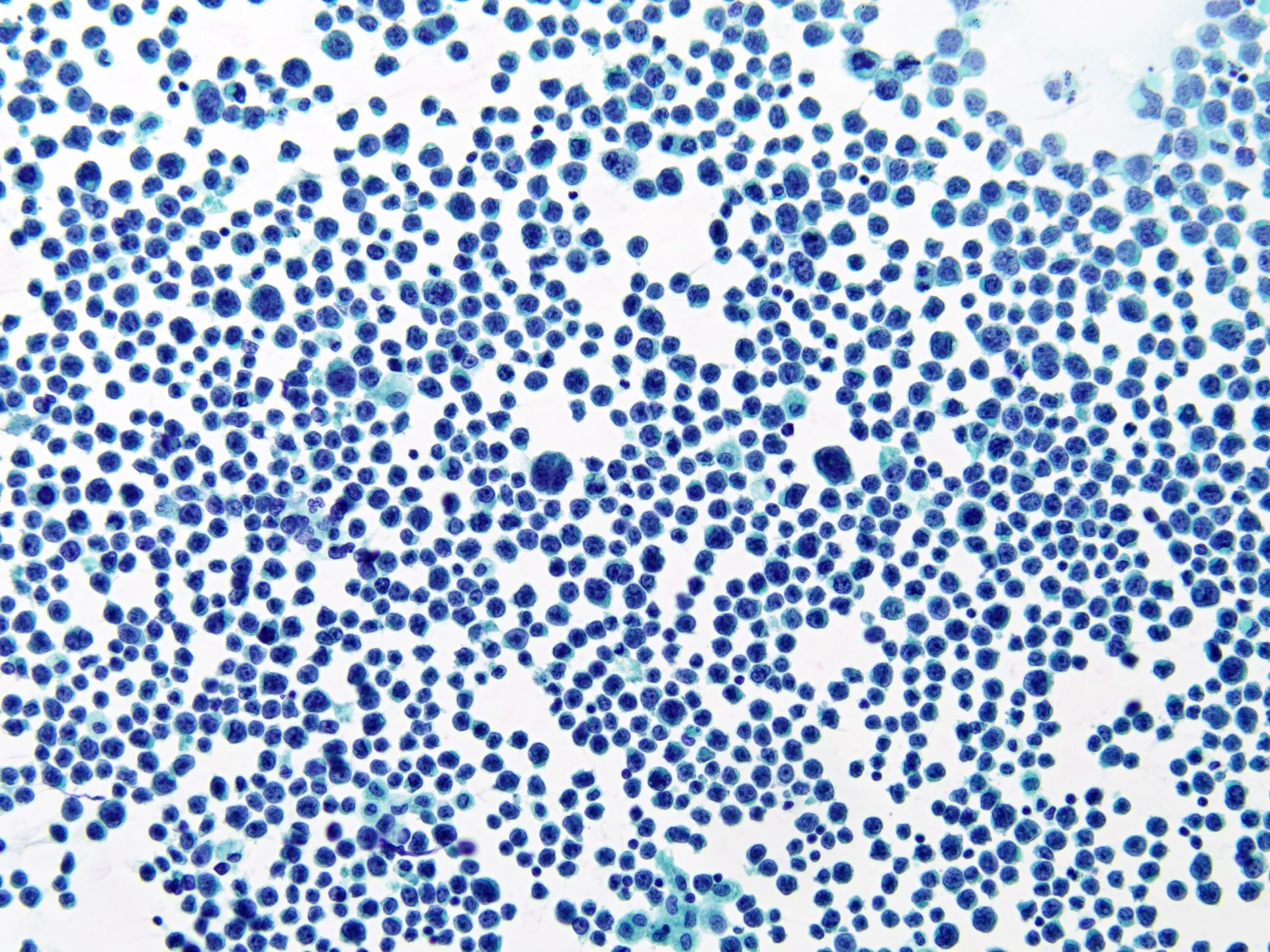


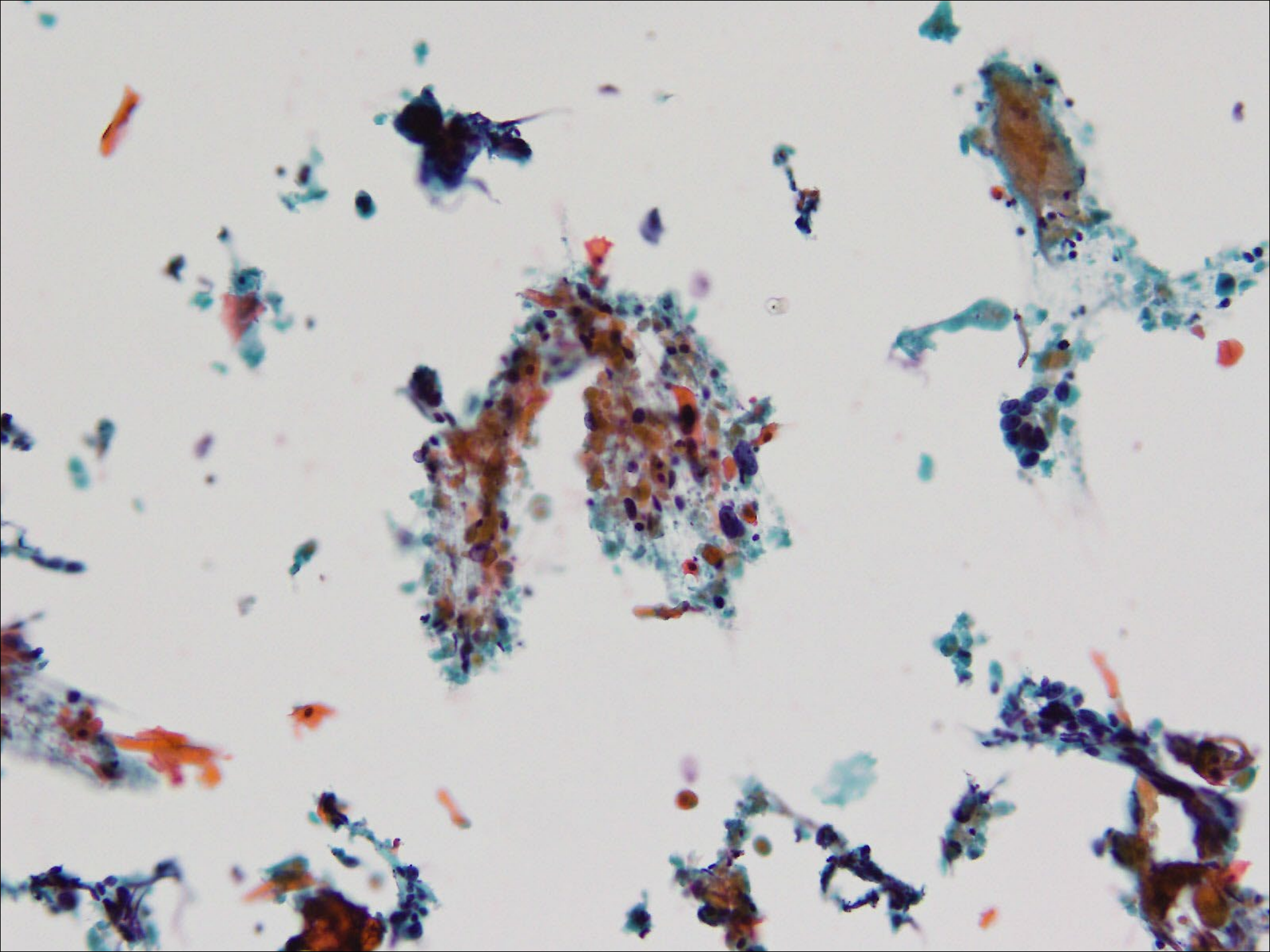
Background Elements:

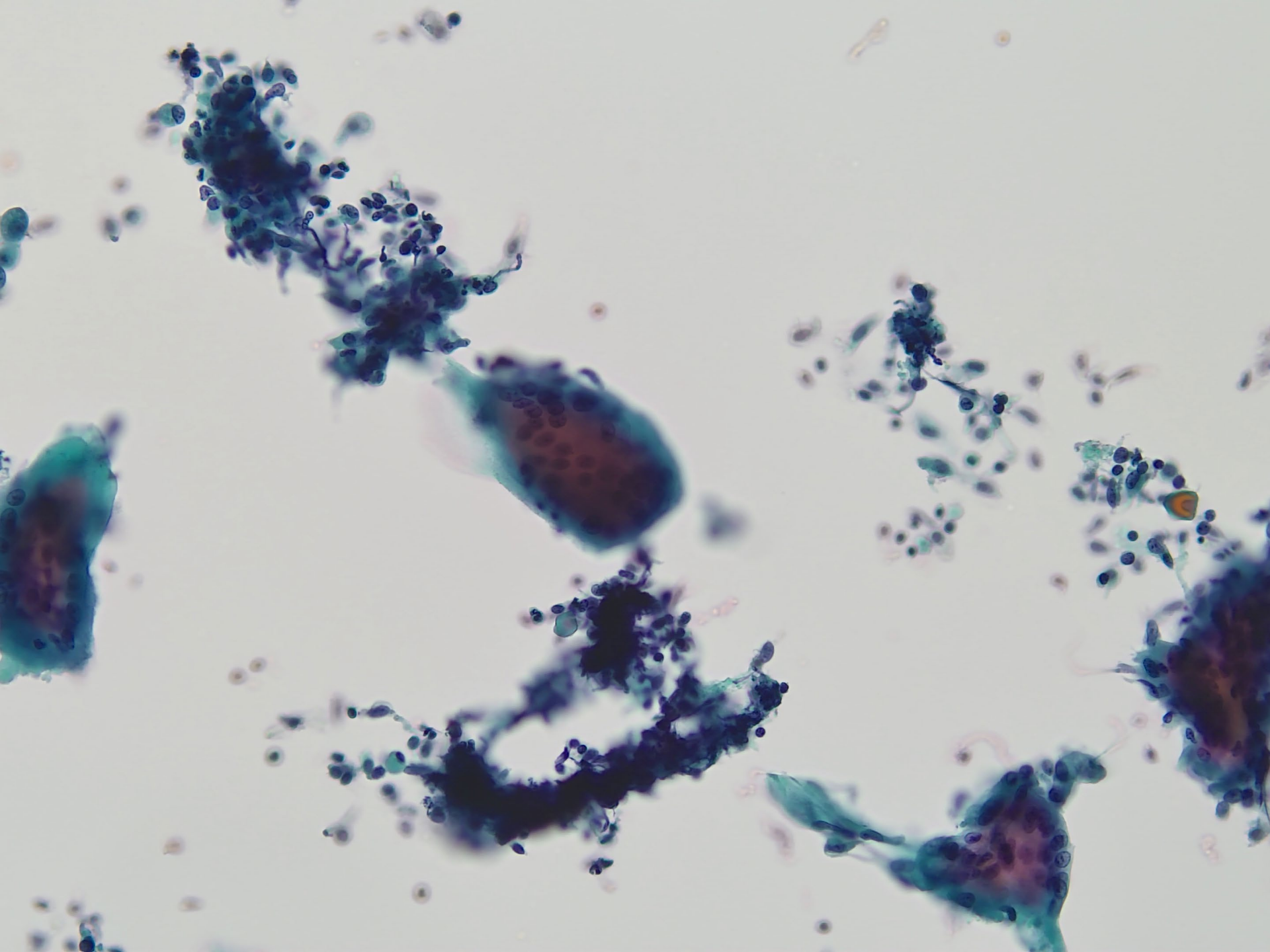
Clean vs. Necrotic Background:

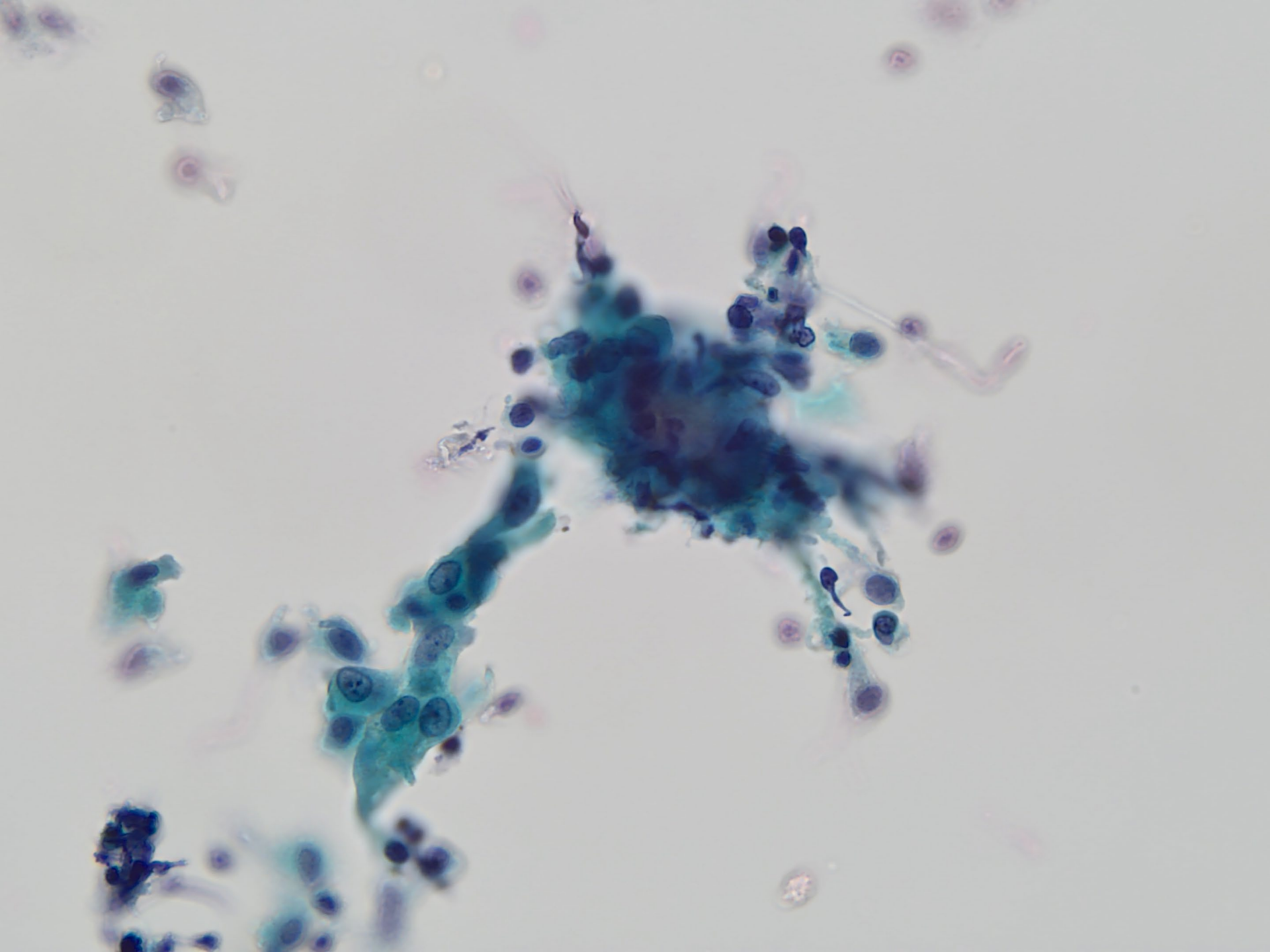
- A necrotic background with karyorrhectic debris is often associated with carcinoma.
- A clean background with occasional lymphoglandular bodies is more typical of lymphoid malignancy.
- Nucleated and/or anucleated squames
- Inflammatory cells; reactive lymphoid background
- Multinucleated giant cells; granulomas





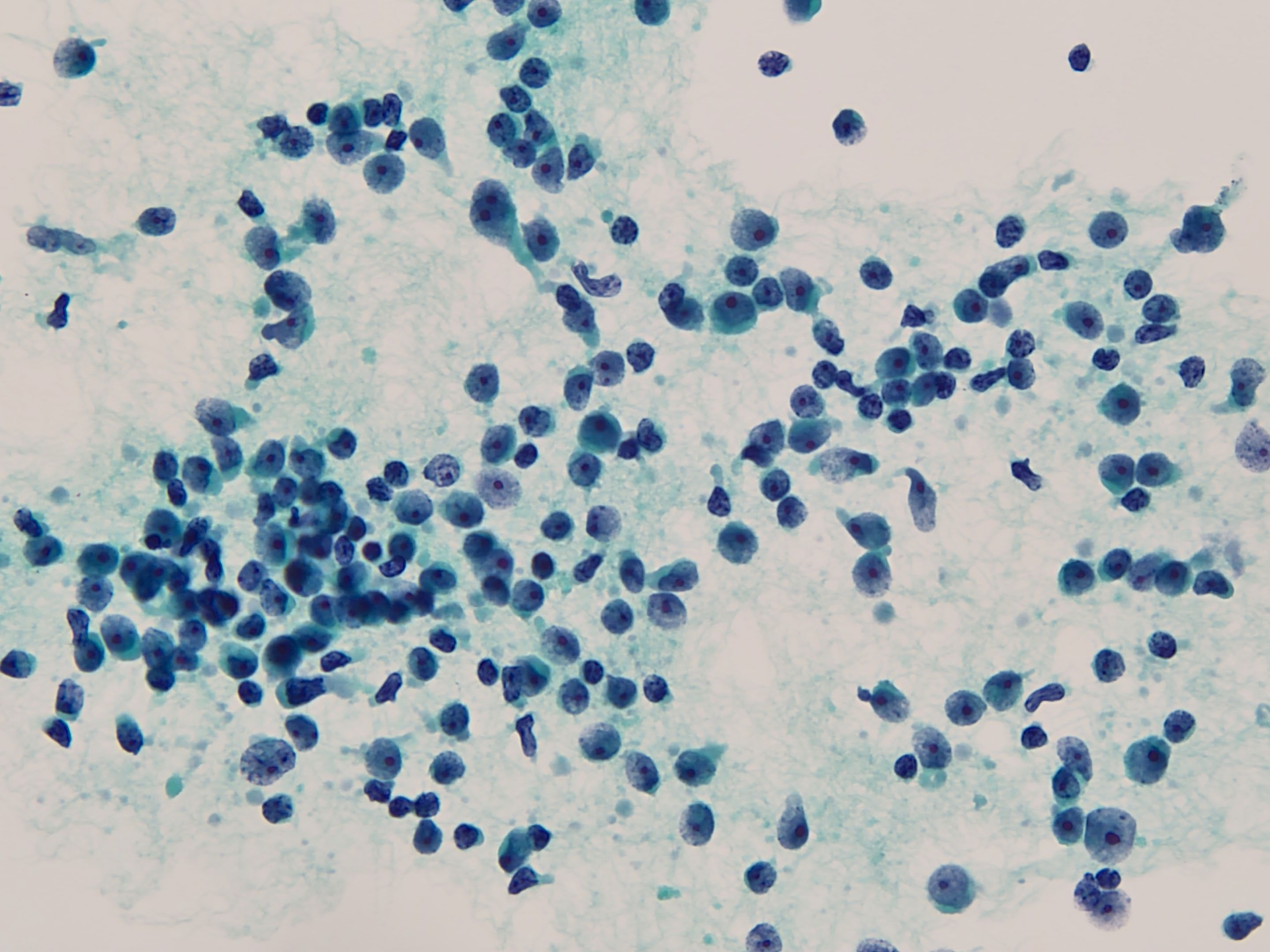






Nuclear Features:

- **Nuclear Size and Shape:** The nuclei are generally round to oval, with a high nuclear-to-cytoplasmic ratio; often hyperchromatic with dense, dark-staining chromatin, which may appear coarse or fine depending on the tumor type.
- **Nucleoli:** Prominent nucleoli are observed in poorly-differentiated carcinoma, lymphoma, and sarcoma, while small cell carcinoma often has inconspicuous or absent nucleoli.
- **Mitotic Figures:** High mitotic activity is a feature of many SRCTs, reflecting their aggressive nature. The presence of abnormal mitotic figures can also aid in distinguishing between SRCT and mimickers.



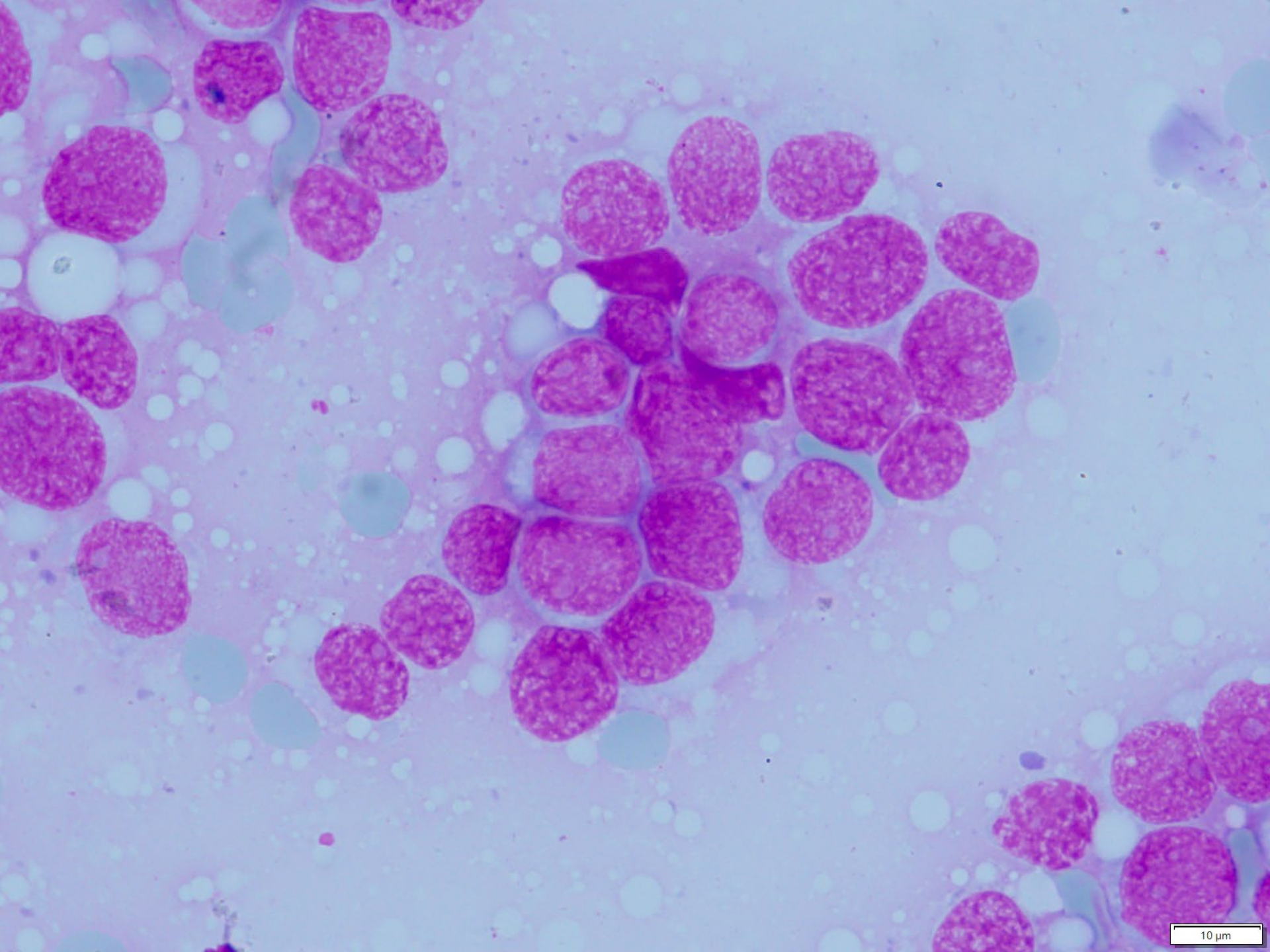
Cytoplasmic Characteristics:

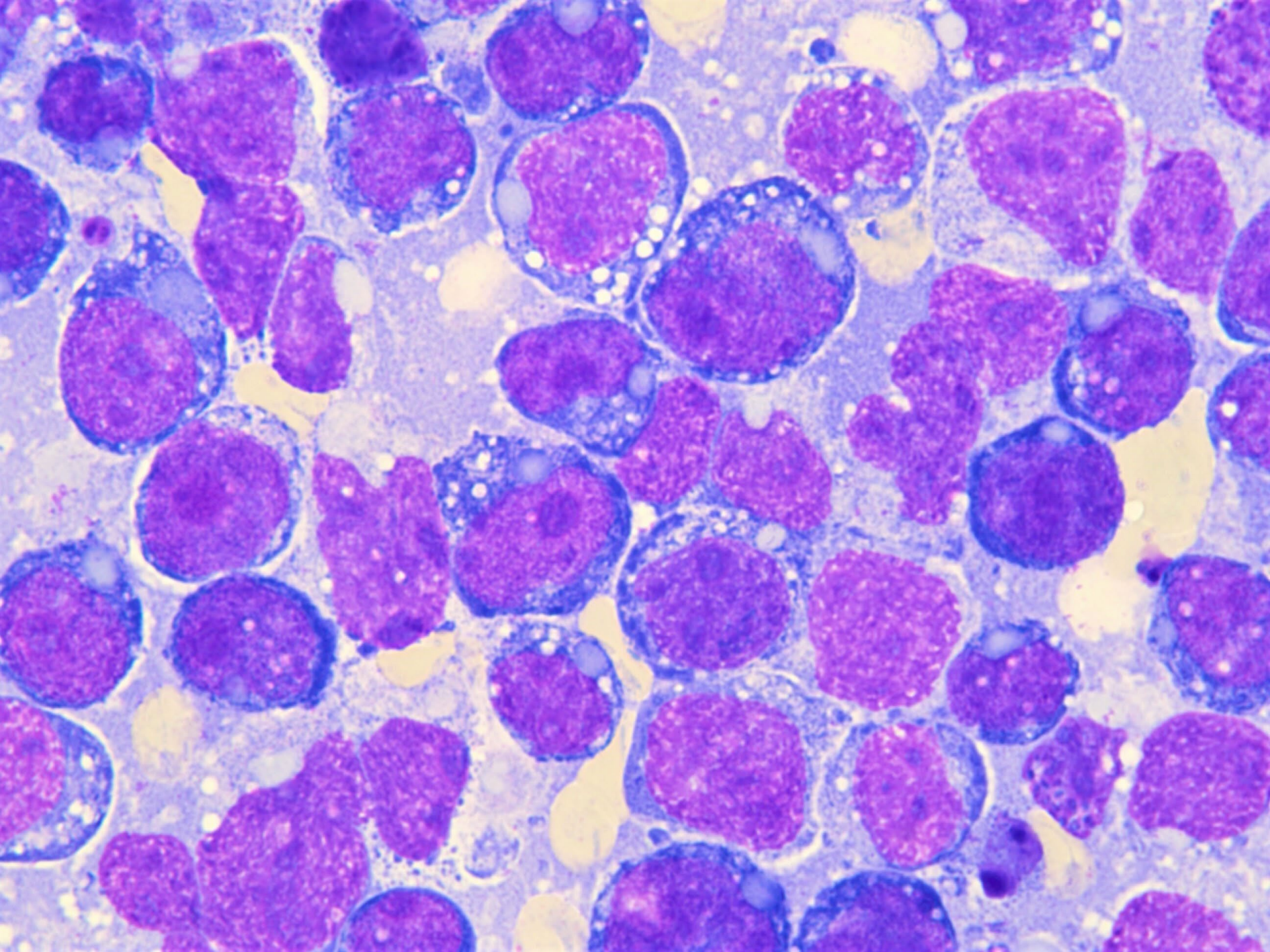
- **Scant Cytoplasm:**

  The cytoplasm is generally scant in SRCTs, appearing as a thin rim around the nucleus. In some cases, such as lymphoma, the cytoplasm may contain fine vacuoles.

- **Cytoplasmic Granularity:**

  Cytoplasmic granularity may be observed, correlating with neuroendocrine differentiation.


10 µm

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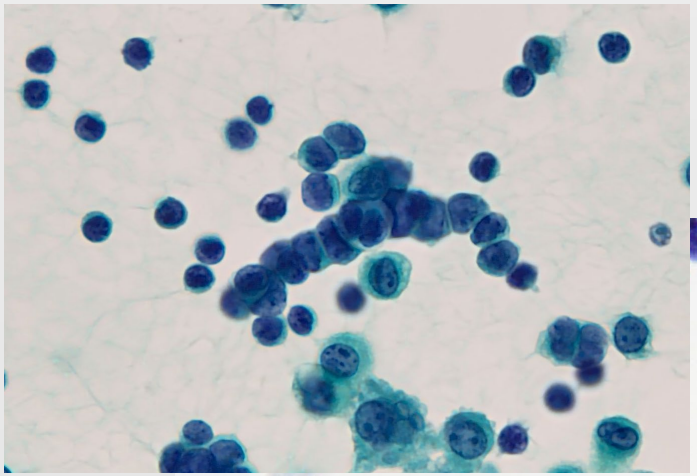
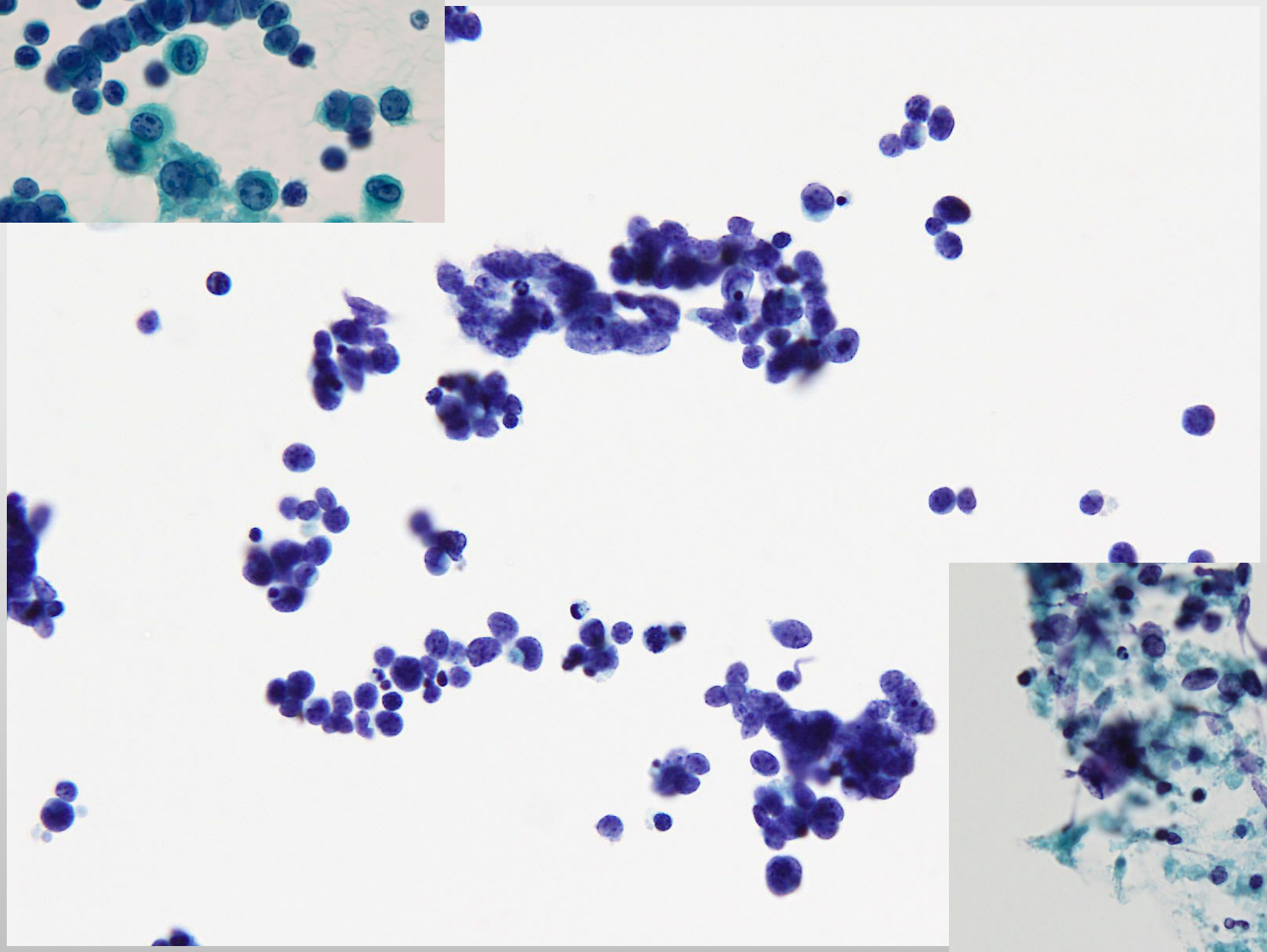
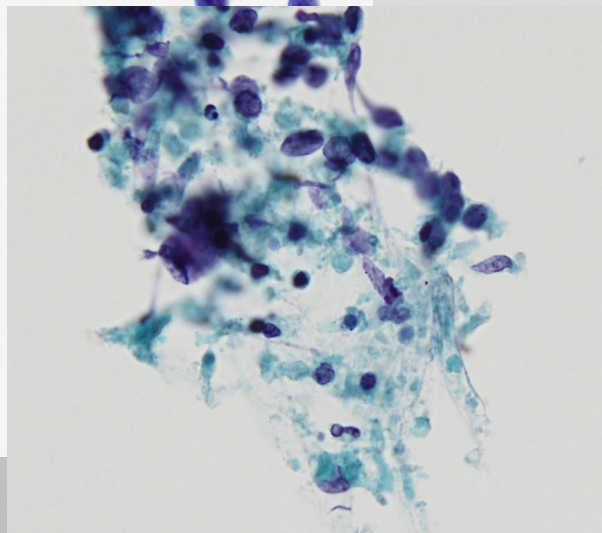
Case 1.

- ✓60-year-old female patient
- ✓Right neck lymphadenopathy
- ✓FNA of right neck lymph node

001 (128)Z22-01472_LN_FNA

Small Cell Carcinoma (SCC):

- **Cellular Arrangement:** SCC typically presents as loosely cohesive clusters of cells, often accompanied by a dispersed single-cell population. The clusters may exhibit nuclear molding or crush artifact.
- **Nuclear Features:** Small, round to oval, and hyperchromatic, with a finely granular chromatin pattern; "salt and pepper," with inconspicuous or absent nucleoli.
- **Cytoplasmic Characteristics:** Cytoplasm is scant and may be basophilic.
- **Background Elements:** Necrotic debris, apoptotic bodies and mitotic figures are frequently observed, reflecting the high proliferative activity of these tumors.

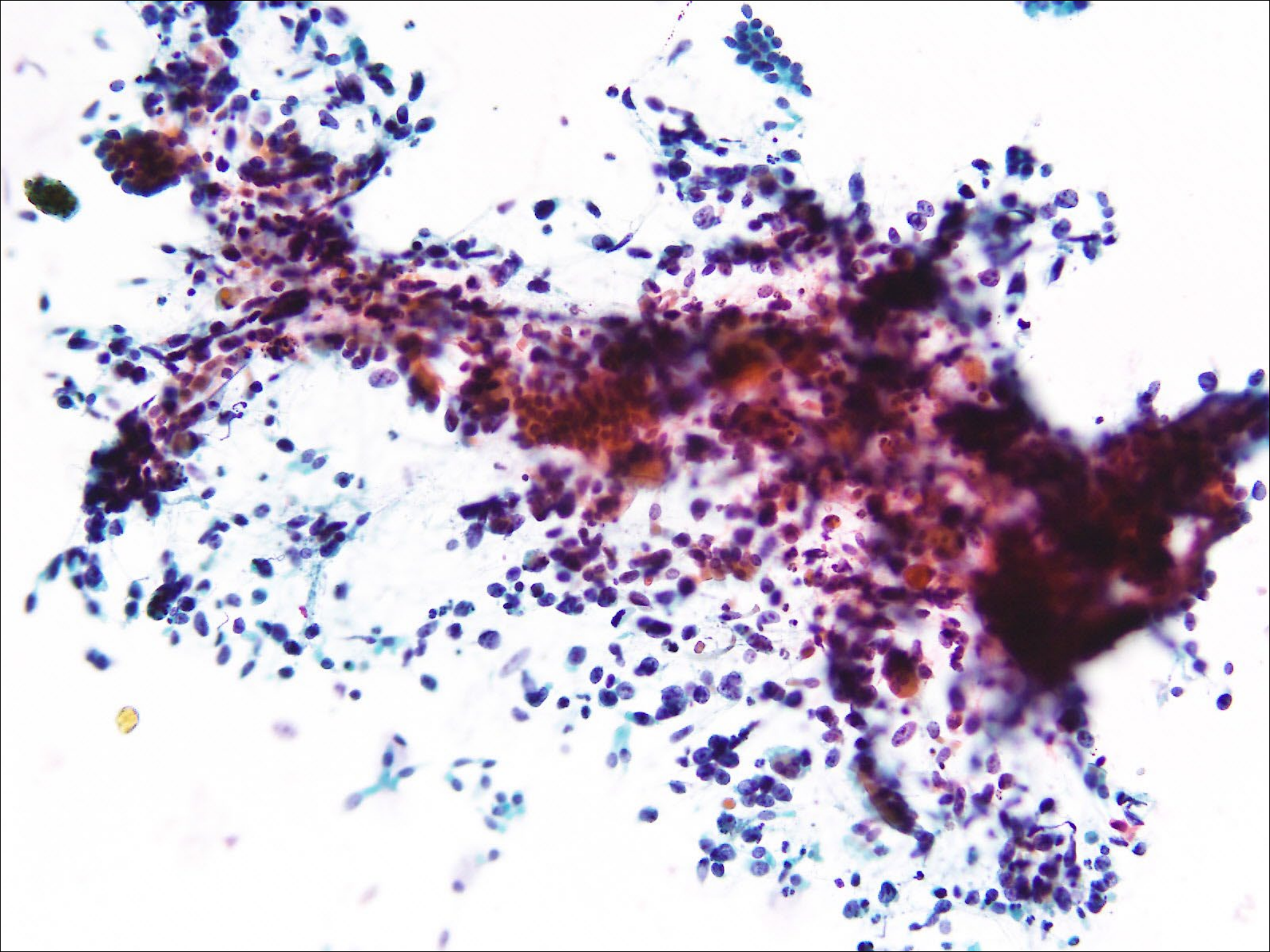
Case 2.

- ✓55-year-old male patient
- ✓Right neck lymphadenopathy
- ✓FNA of right neck lymph node

002 (123)Z23-03689_LN_FNA

Basaloid Squamous Cell Carcinoma (BSCC):

- **Cellular Arrangement:** In cellular clusters or as single cell; palisading arrangement of nuclei
- **Nuclear Features:** Larger nuclei compared to those in small cell carcinoma, with coarse chromatin and prominent nucleoli. Nuclear pleomorphism is often more pronounced in BSCC.
- **Cytoplasmic Characteristics:** Moderate amount of cytoplasm, which is more abundant than that of small cell carcinoma. The cytoplasm may be eosinophilic and occasionally shows keratinization, which is a distinguishing feature from SCC.
- **Background Elements:** Can be necrotic, and keratin debris is often present, which helps distinguish it from other SRCTs.



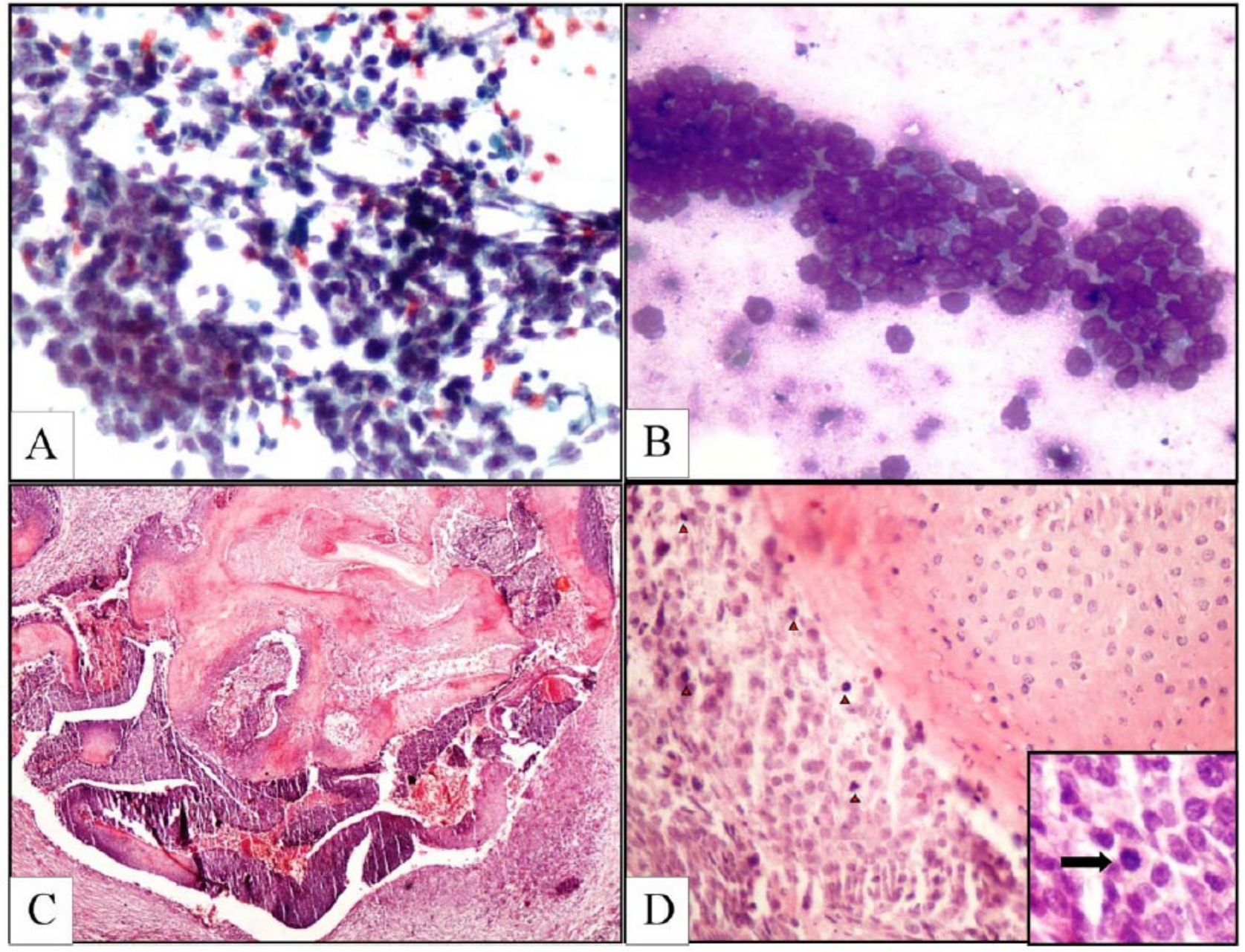
Case 3.

- ✓27-year-old female patient
- ✓Left neck mass
- ✓FNA of left neck subcutaneous nodule

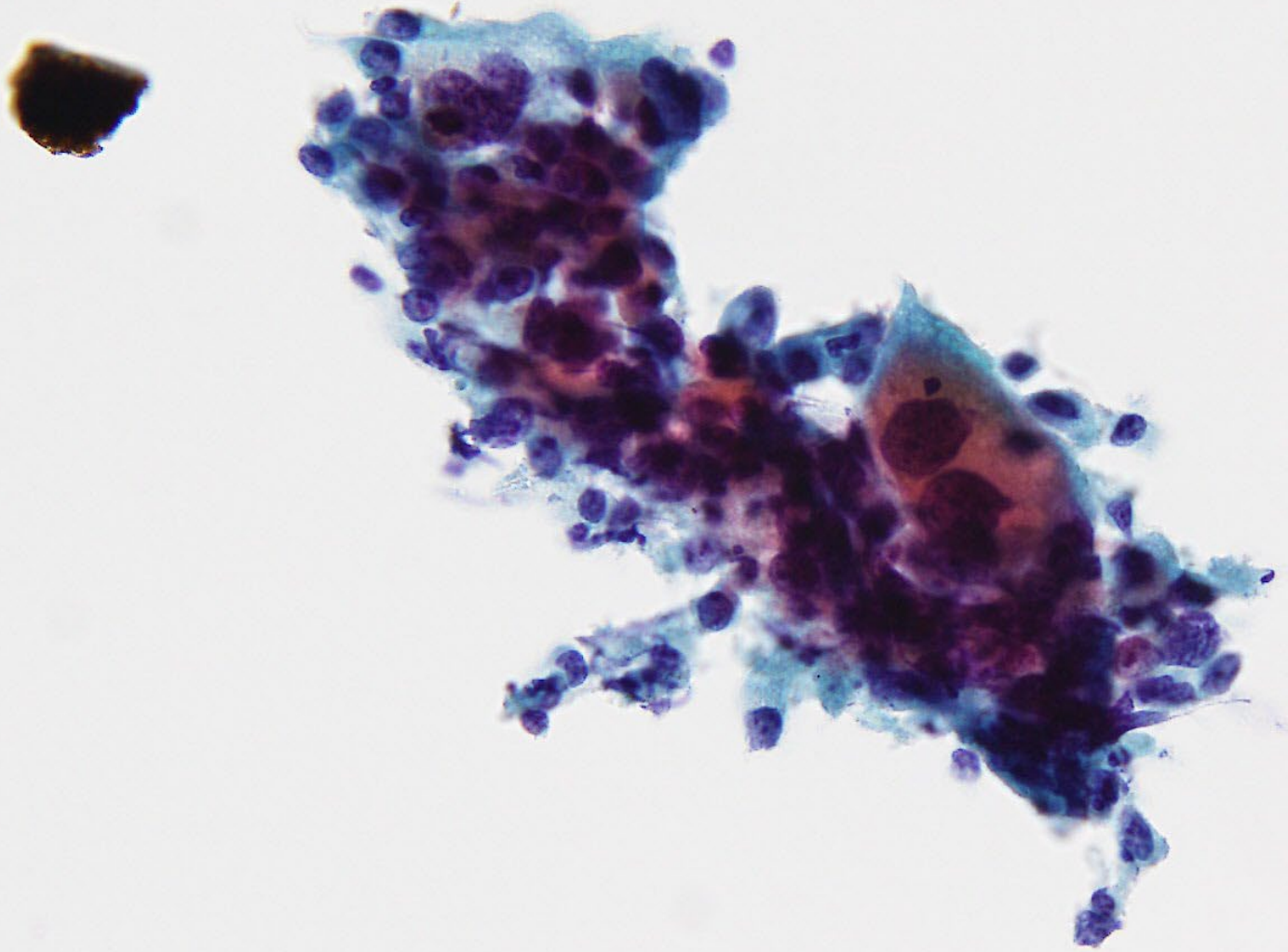
003 (127)Z22-02891_LN_FNA

Pilomatrixoma:

- **Cellular Arrangement:** Tumor cells dispersed singly or cohesive to loose monolayer clusters with irregular edges.
- **Nuclear Features:** Uniform and small basaloid cells with round to oval nuclei, open, finely granular chromatin and prominent nucleoli.
- **Cytoplasmic Characteristics:** Cytoplasm of the basaloid cells is scant, delicate, and ill-defined
- **Background Elements:** Basaloid cells admixed with nucleated and anucleated squames/clusters of yellowish ghost cells; foreign body-type giant cells; calcium deposits; a background of amorphous debris and chronic inflammatory cells.



Gupta M, Bansal R, Tiwari G, Sharma S. Aggressive pilomatrixoma: a diagnostic dilemma on fine-needle aspiration cytology with review of literature. Diagn Cytopathol. 2014 Oct;42(10):906-11.



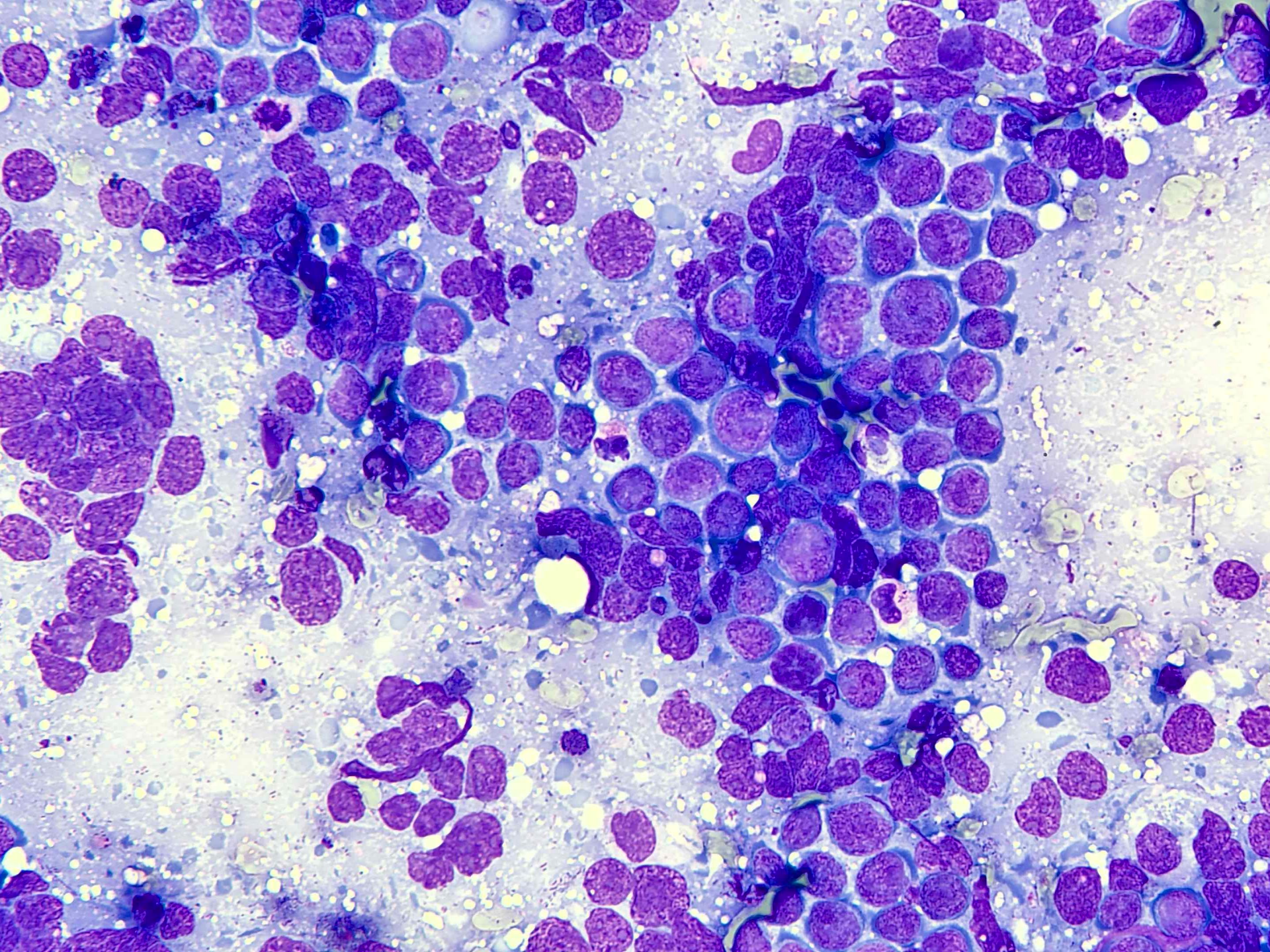
Case 4.

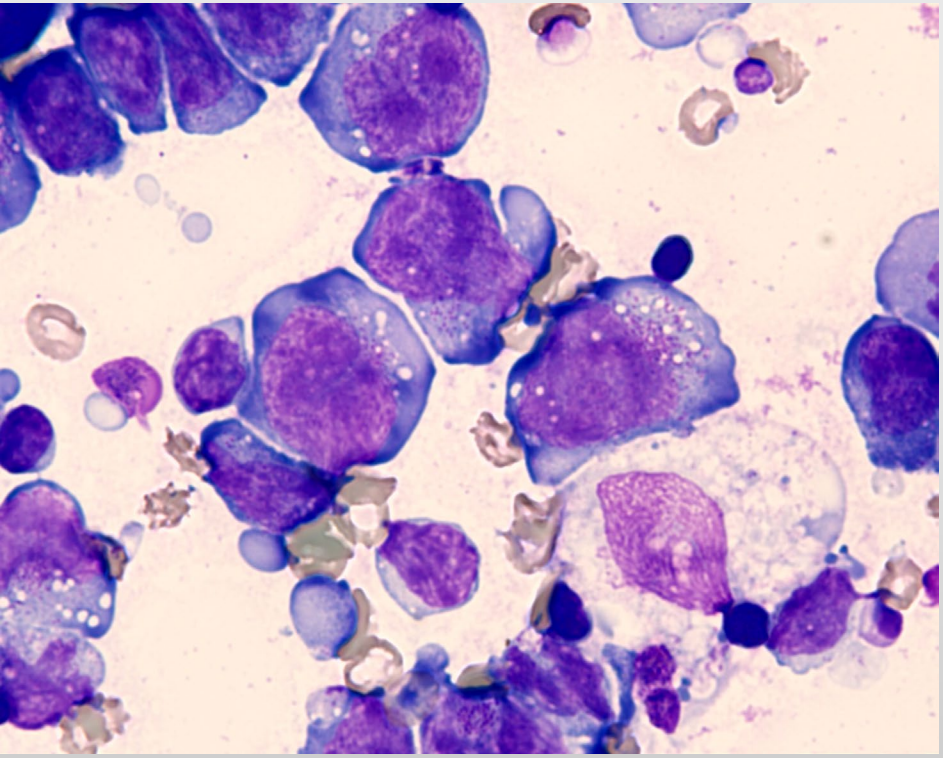
- ✓77-year-old male patient
- ✓Left neck lymphadenopathy
- ✓FNA of left neck lymph node

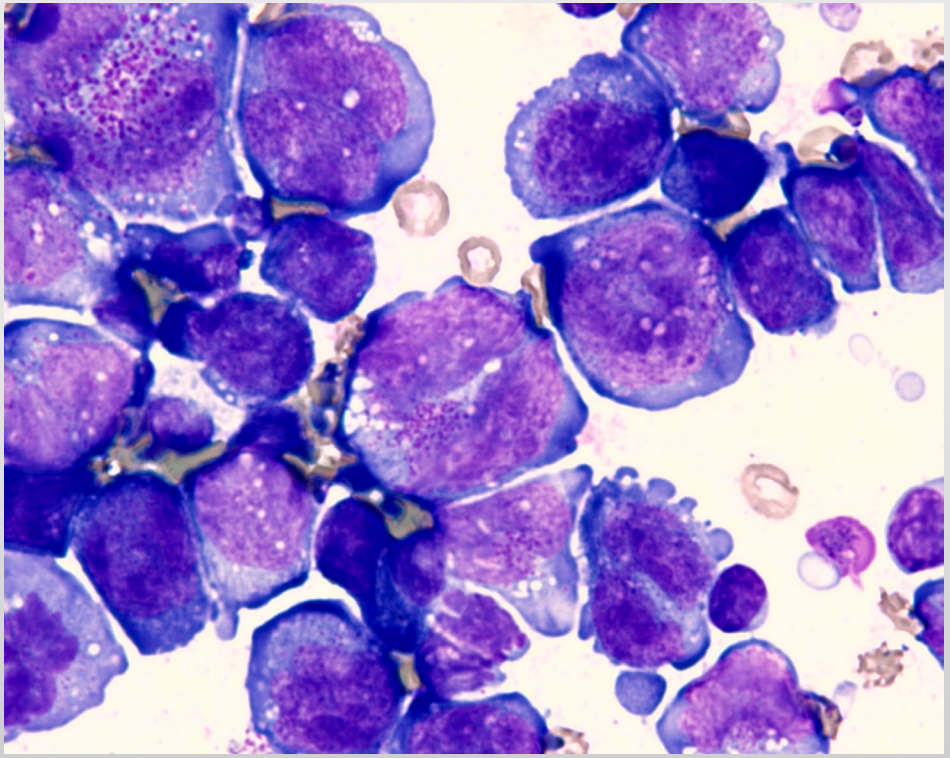
004 (108)Z20-00503_Lymph node

Lymphoma

- **Cellular Arrangement:** Lymphoma cells are typically dispersed as single cells rather than forming clusters; usually monotonous.
- **Nuclear Features:** Round to slightly irregular nuclei with clumped chromatin and one or more prominent nucleoli. In some subtypes, such as Burkitt lymphoma, the nuclei may show a "starry sky" pattern due to numerous interspersed macrophages.
- **Cytoplasmic Characteristics:** Scant cytoplasm; usually appears as a thin rim around the nucleus; fine cytoplasmic vacuoles / cytoplasmic projections in specific types
- **Background Elements:** Typically clean, though lymphoglandular bodies and occasional apoptotic bodies may be observed. Necrosis is less common.







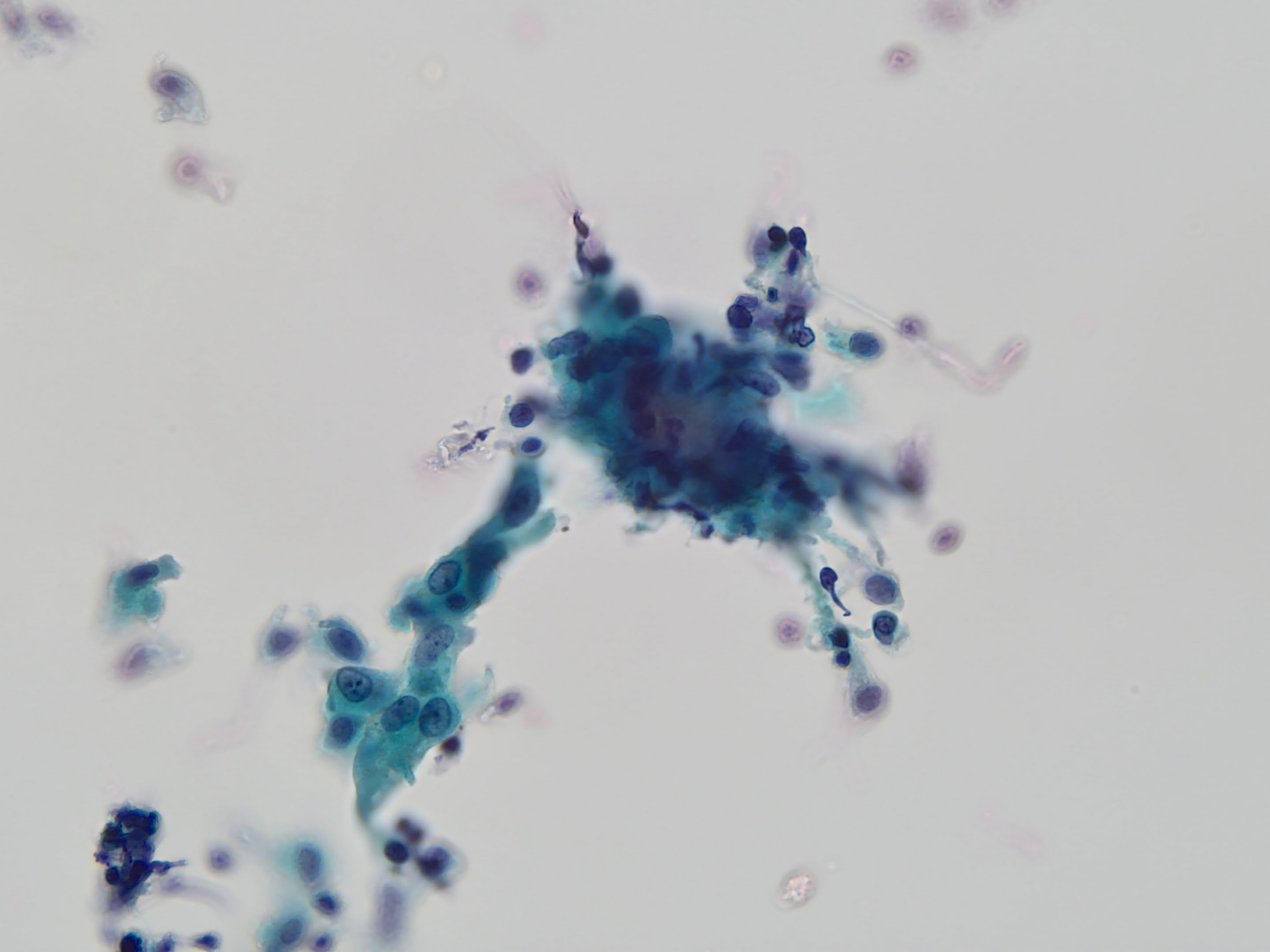
Case 5.

- ✓27-year-old male patient
- ✓Left neck lymphadenopathy
- ✓FNA of left neck lymph node

005 (106)Z23-00191_Lymph node

Metastatic Nasopharyngeal Carcinoma (NPC):

- **Cellular Arrangement:** Cohesive clusters or syncytial groups of cells; lymphoplasma cells intermingling with tumor cells
- **Nuclear Features:** Pleomorphism, fine chromatin, and prominent nucleoli; sometimes bizarre, lobulated nuclei with macronucleoli
- **Cytoplasmic Characteristics:** Cytoplasm is typically pale, fragile, and indistinct
- **Background Elements:** A reactive lymphoid background with plasma cells; tingible body macrophages; necrotic debris



Liquid-Based Cytology (LBC)

- SurePath LPT method appeared to have a significantly higher diagnostic sensitivity for lung cancer (71.6%) compared to the CPS method (57.8%). The combination of both methods further increased the sensitivity to 76.5%.
- The diagnostic value of LBC on residual pulmonary CNB: A higher sensitivity (96.4%) of combined LBC/CNB in distinguishing malignancies from benign lesions
- LBC with FNA specimens from cervical lymphadenopathy is a useful and reliable method for the diagnosis of malignant diseases, especially of metastatic carcinomas, due to its increased sensitivity compared with CS cytology.

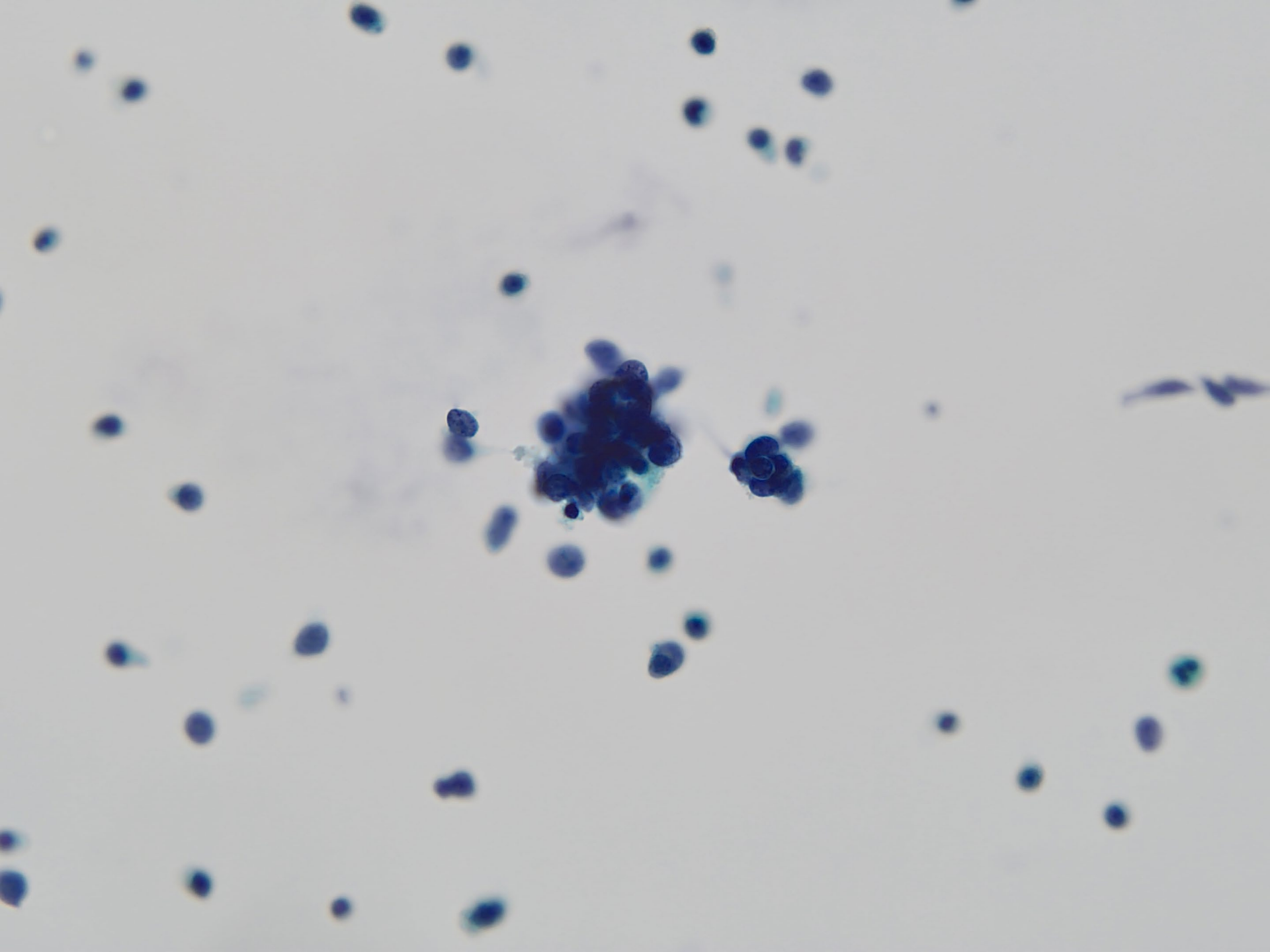
Fan, Y.-B., et al. (2010). "Clinical application of the SurePath liquid-based Pap test in cytological screening of bronchial brushing for the diagnosis of lung cancer." Cytotechnology, 62(1), 53-59.

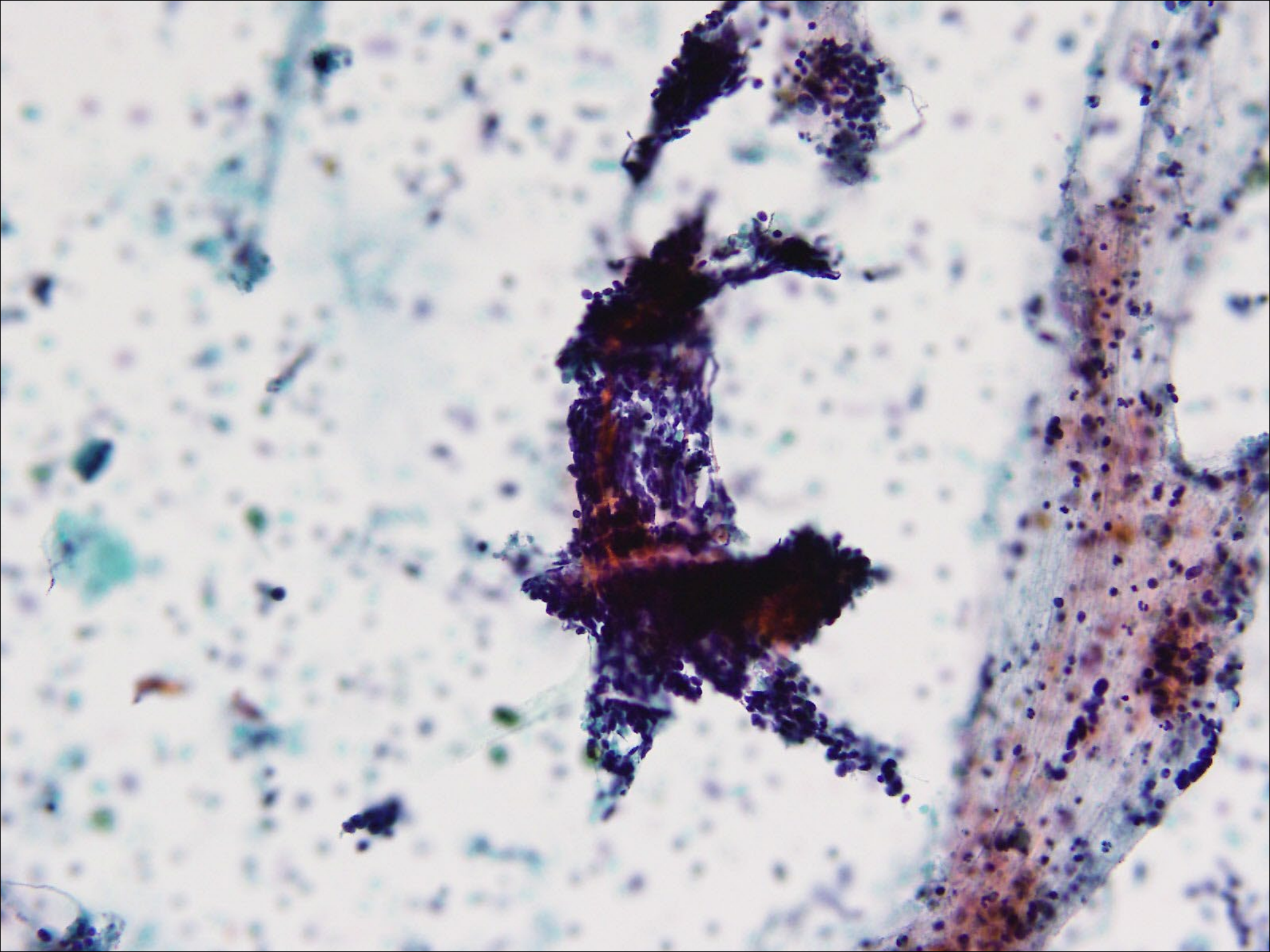
Lan Z, Zhang X, Ma X, Hu Y, Zhang J, Yang F. Utility of liquid-based cytology on residual needle rinses collected from core needle biopsy for lung nodule diagnosis. Cancer Med. 2021 Jun;10(12):3919-3927.

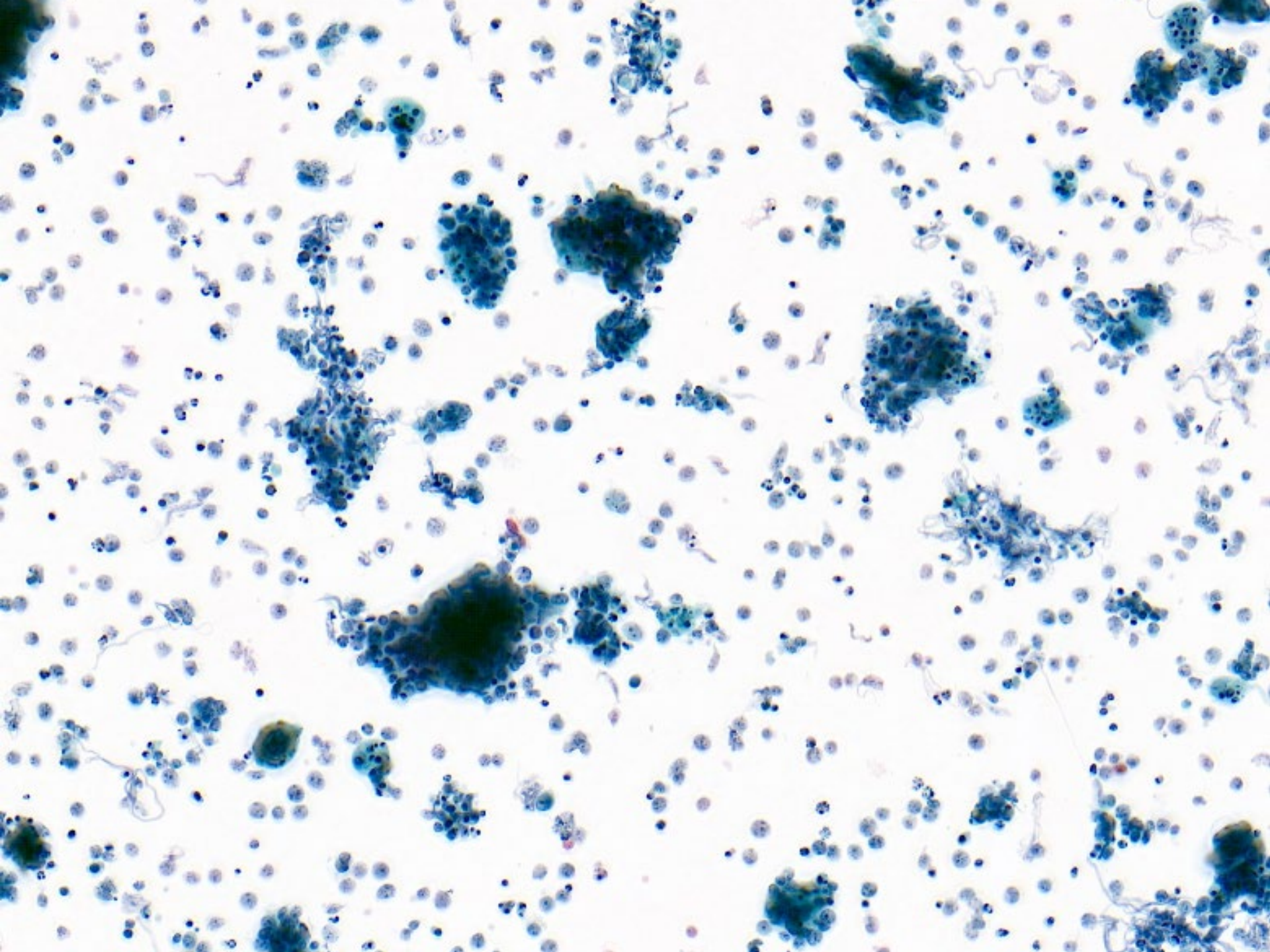
Bandoh N, Goto T, Akahane T, Ohnuki N, Yamaguchi T, Kamada H, Harabuchi Y, Tanaka S, Nishihara H. Diagnostic value of liquid-based cytology with fine needle aspiration specimens for cervical lymphadenopathy. Diagn Cytopathol. 2016 Mar;44(3):169-76.

Pitfalls in Liquid-Based Cytology

- Informative background: LBC remove background material such as tumor diathesis and necrosis.
- SurePath LBC produces prominent 3D configurations for epithelial clusters that occasionally cause difficulty in recognizing nuclear characteristics.
- Lymphoid cells tend to be clumped together and appear smaller in LBC; lymphoid cell aggregates might be erroneously considered as epithelial cells.
- Granulomas seen on LBC are ill-formed architecturally as compared to those seen in CS.

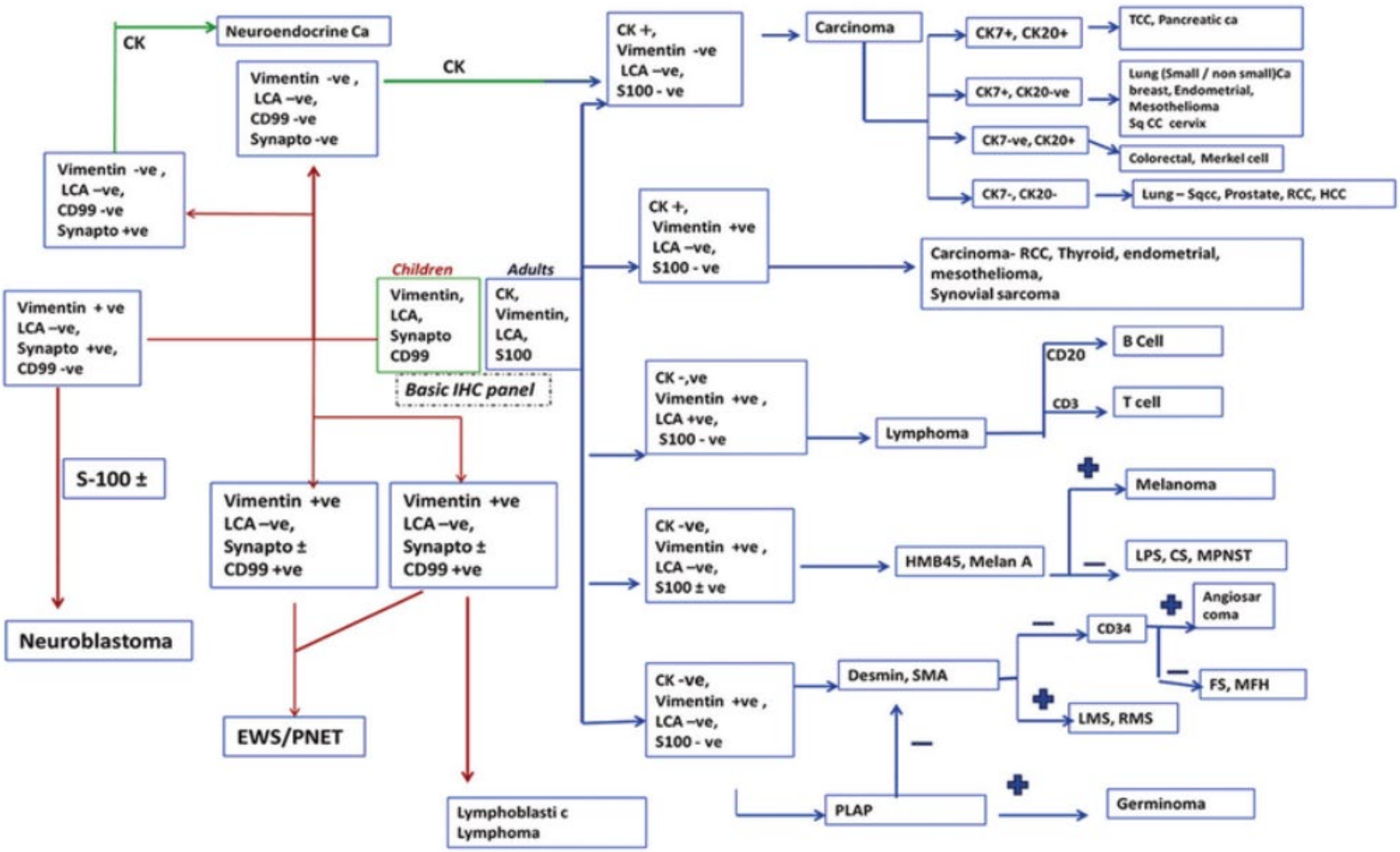






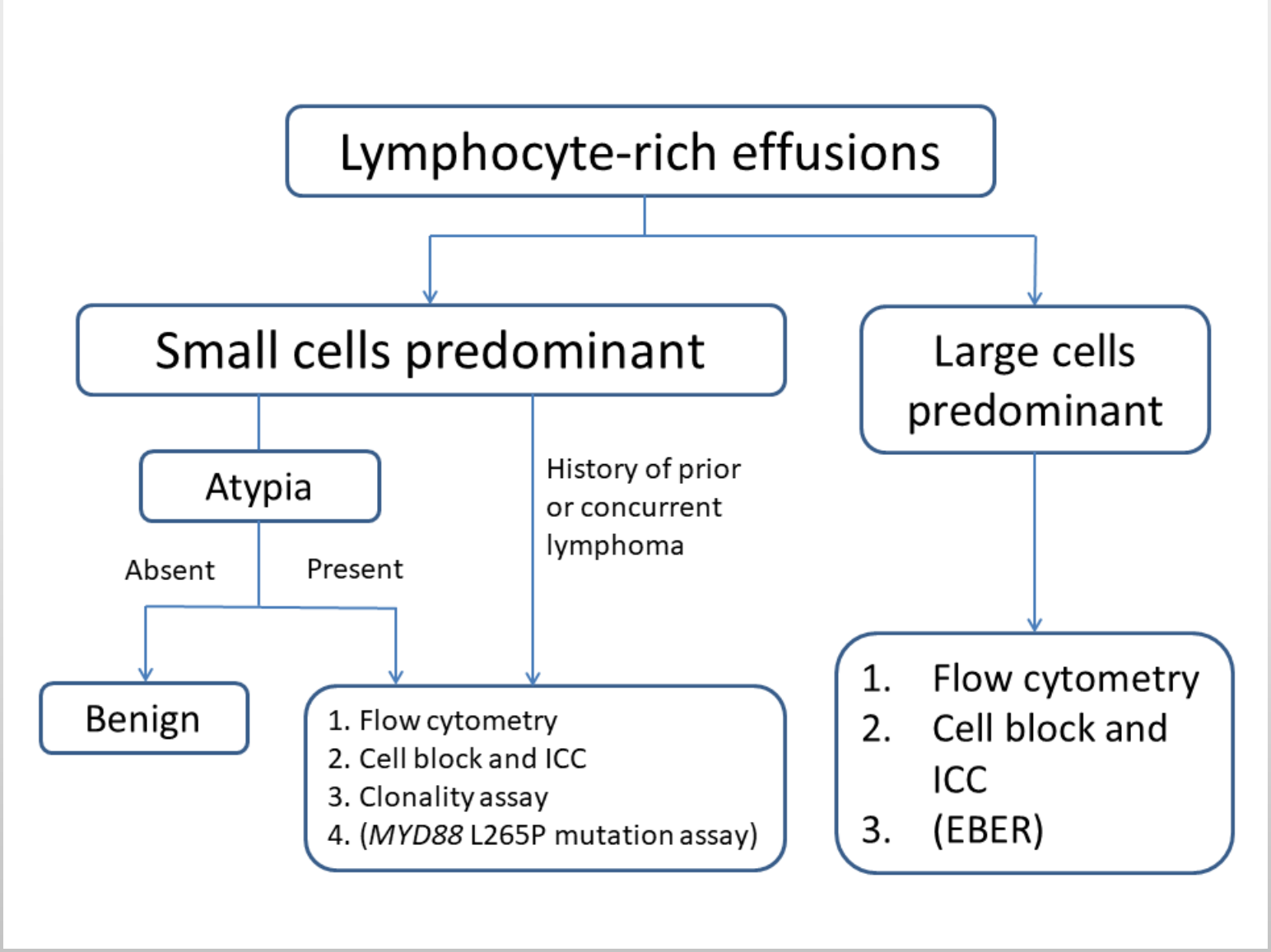
Immunocytochemistry and Molecular Techniques

- Immunocytochemistry and molecular techniques are essential for confirming the diagnosis of SRCTs, especially when cytomorphological features overlap.
  - ✓ **Small Cell Carcinoma:** positive staining for neuroendocrine markers such as synaptophysin, chromogranin, and CD56, along with TTF-1
  - ✓ **Basaloid Squamous Cell Carcinoma:** positive staining for epithelial markers such as p63 and cytokeratin (CK5/6)
  - ✓ **Lymphoma:** Immunophenotyping is critical, with B-cell lymphomas typically expressing CD20, CD19, and CD79a, while T-cell lymphomas express CD3, CD5, and CD7. Molecular techniques such as gene rearrangement studies can confirm clonality and aid in distinguishing lymphoma from other SRCTs



Bn, Nandeesh & Rao, Shilpa & Sadashiva, Nishanth & Mahadevan, Anita & Chickabasaviah, Yasha & Santosh, Vani. (2020). Clinicopathological Study of Extra-Axial Small Round Cell Tumors of the Cranium. Neurology India. 68. 1175-1182.

Algorithmic approach for diagnosis of effusion lymphomas



Liu CY, Chuang SS. A Simple and Practical Guide for Triaging Lymphocyte-rich Effusions for Ancillary Studies. Adv Anat Pathol. 2021;28(2):94-104.

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