THE INTERNATIONAL SYSTEM (TIS) FOR SEROUS FLUID CYTOPATHOLOGY

ASHISH CHANDRA, FRCPATH

GUY'S & ST THOMAS', LONDON

WHY STANDARDIZE REPORTING TERMINOLOGY?

- Communication between pathologists, clinicians and patients
- Compare data and share knowledge- risk of malignancy for diagnostic categories, evidence base for recommendations
- Multiple terminology systems exist for the same specimen
- Choice of terminology system? Institutional, national or international?
- Are they all saying the same thing? How different are they? Is the data validated, updated based on emerging evidence?
- All classification and terminologies are fluid …

Ashish Chandra · Barbara Crothers · Daniel Kurtycz
Fernando Schmitt *Editors*

The International System for Serous Fluid Cytopathology

This book is the culmination of an international effort to bring consistency and diagnostic efficiency to effusion cytology for the sake of patient care. The authors recognize special challenges in serous fluid cytopathology, such as reporting the presence of Mullerian epithelium in peritoneal fluids. What is an appropriate serous fluid volume to ensure adequacy? How should mesothelial proliferations be reported and is it appropriate to make an interpretation of malignant mesothelioma? How specific should a report be regarding the origin and subtyping of tumors found in serous fluids? What are the appropriate quality monitors for this specimen type? Special chapters on considerations for peritoneal washings, cytopreparatory techniques, mesothelioma and quality management are included to address these issues. The text contains literature reviews that elucidate existing evidence in support of current practices and recommendations. Expert opinions on where evidence was lacking, the most common practices were adopted by consensus, and where there was no commonality, are employed.

Written by experts in the field, *The International System for Serous Fluid Cytopathology* serves as a collaborative effort between the International Academy of Cytology and the American Society for Cytopathology and calls upon participation of the international cytopathology and oncology communities to contribute to the development of a truly international system for reporting serous fluid cytology.

ISBN 978-3-030-53907-8
9 783030 539078
▶ springer.com

Chandra · Crothers · Kurtycz
Schmitt *Eds.*

The International System for Serous Fluid Cytopathology

The International System for Serous Fluid Cytopathology

Ashish Chandra
Barbara Crothers
Daniel Kurtycz
Fernando Schmitt
Editors

Springer

WE NEED ANSWERS TO PRACTICAL CLINICAL QUESTIONS!

- Evaluating evidence of adequacy (volume & cellularity)
- Defining what is a true negative sample
- The use of atypia and suspicious categories
- Mesothelioma: revisiting the value of cytology in diagnosis
- Peritoneal washings: how to report the presence of epithelial cells

Open Access Article

Cytohistological Correlation in Pleural Effusions Based on the International System for Reporting Serous Fluid Cytopathology

by Daniel Pinto [1,2], Eduardo Cruz [1], Diamantina Branco [1], Cláudia Linares [1], Conceição Carvalho [1], Amélia Silva [1], Martinha Chorão [1] and Fernando Schmitt [3,4,5,*]

[1] Serviço de Anatomia Patológica, Centro Hospitalar de Lisboa Ocidental, EPE, 1349-019 Lisboa, Portugal
[2] NOVA Medical School, 1169-056 Lisboa, Portugal
[3] IPATIMUP-Instituto de Patologia e Imunologia Molecular, Universidade do Porto, 4200-135 Porto, Portugal
[4] Departamento de Patologia, Faculdade de Medicina da Universidade do Porto, 4200-135 Porto, Portugal
[5] RISE@CINTESIS, 4200-450 Porto, Portugal
* Author to whom correspondence should be addressed.

Academic Editor: Ivana Kholová

Diagnostics **2021**, *11*(6), 1126; https://doi.org/10.3390/diagnostics11061126

Cytopathology with Cytohistological Correlation and Risk of Malignancy Assessment

by Alexandros Pergaris [1,2], Dimitra Stefanou [3], Panagiota Keramari [1], Stylianos Sousouris [1], Nikolaos Kavantzas [2], Helen Gogas [3] and Panagiota Mikou [1,*]

[1] Department of Cytopathology, Laiko Hospital, 11527 Athens, Greece
[2] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece
[3] First Department of Medicine, School of Medicine, National and Kapodistrian University of Athens, Laiko General Hospital, 11527 Athens, Greece
* Author to whom correspondence should be addressed.

Academic Editor: Ivana Kholová

Diagnostics **2021**, *11*(12), 2223; https://doi.org/10.3390/diagnostics11122223

Received: 1 November 2021 / Revised: 22 November 2021 / Accepted: 25 November 2021 / Published: 28 November 2021

Cytopathology

ORIGINAL ARTICLE

Categorisation of serous effusions using the International System for Reporting Serous Fluid Cytopathology and assessment of risk of malignancy with diagnostic accuracy

Sana Ahuja, Avneesh Malviya

First published: 15 December 2021 | https://doi.org/10.1111/cyt.13089 | Citations: 2

Cancer Cytopathology

Original Article

Risk of malignancy assessment of the International System for Reporting Serous Fluid Cytopathology: Experience in a community hospital setting and comparison with other studies

Tong Sun MD, PhD, Minhua Wang MD, PhD, He Wang MD, PhD

First published: 22 August 2022 | https://doi.org/10.1002/cncy.22638

Abstract

Background

The International System for Reporting Serous Fluid Cytopathology (ISRSFC) was published recently to provide standard reporting terminology for serous fluid. To date, several ISRSFC reclassification studies have reported a wide range of diagnostic category

THE INTERNATIONAL SYSTEM FOR REPORTING SEROUS FLUID CYTOPATHOLOGY

- Non-diagnostic (ND)
- Negative For Malignancy (NFM)
- Atypia of Undetermined Significance (AUS)
- Suspicious For Malignancy (SFM)
- Malignant, Primary (MAL-P)
- Malignant, Secondary (MAL-S)

FACTORS INVOLVED IN ADEQUACY

Sample volume

- Is there a recommended volume for fluid samples?
- 75ml optimal volume (Rooper et al 2014) for cytological assessment
- 60ml for pericardial fluid (Rooper et al, 2016)
- Smaller volume samples should not be rejected but commented upon
- Aliquot for investigations other than cytology ideally at time of collection

Cellular content

- Do we need to see mesothelial cells?
- Acceptable to find only lymphocytes (TB, chylous effusion) or neutrophils (acute bacterial infections) in benign effusions without mesothelial cells
- Diagnosis of malignancies with a one cell population may be made without mesothelial cells

Cellular preservation

- Can a sample be non-diagnostic in spite of being cellular?
- Loss of quality due to degenerative changes due to delay in reaching the lab, bacterial overgrowth, technical artefacts and contaminants

A Single Tertiary Institution Review of the International System for Serous Fluid Cytopathology and the Impact of Cell Block and Ancillary Studies on its Performance

Kok Hing Lim [1, 2], Syed Salahuddin Ahmed [1, 2], Xin Min Cheng [1, 2], Jacqueline Siok Gek Hwang [1, 2], Jayanthi Karunanithi [1, 2], Sangeeta Mantoo [1, 2], Angela Maria Takano [1, 2], Rehena Sultana [3], Li Yan Khor [1, 2]

Show more

https://doi.org/10.1016/j.jasc.2022.09.001

Highlights

1) We have undertaken one of the largest scale assessments of the International System for Serous Fluid Cytopathology (IS) with over a thousand archival cases reviewed and re-categorised.

2) Being a relatively new system, we believe that our study assists in its validation, as well as contributing to a still-developing consensus on parameters such as expected rates and risk of malignancy for each diagnostic category.

3) We are one of the first groups to compare our archival cell block results with the IS, and demonstrate their predictive value, particularly in the more equivocal atypical and suspicious categories.

Cancer Cytopathology

Original Article

Reassessing the optimal volume for malignancy detection in serous fluid cytology

Daniel Martínez Coconubo MD, Swikrity Upadhyay Baskota MBBS MD, Runjia Li MS, Pooja Srivastava MD, Jackie Cuda BS, SCT ASCP, Samer Khader MD

First published: 25 April 2022 | https://doi.org/10.1002/cncy.22577

We thank the University of Pittsburgh Clinical and Translational Science Institute and Jong H. Jeong, PhD, for providing help with statistical analysis.

Abstract

BACKGROUND

The international system for reporti
submitting at least 50-75 mL of sero
prior studies did not agree on speci
criteria. Our study aims to assess wl
assess the minimum volume necess
fluids.

METHODS

A total of 8530 serous fluid cytology
system. Differences in mean fluid vo

Cancer Cytopathology

Original Article

Risk of malignancy assessment of the International System for Reporting Serous Fluid Cytopathology: Experience in a community hospital setting and comparison with other studies

Tong Sun MD, PhD, Minhua Wang MD, PhD, He Wang MD, PhD

First published: 22 August 2022 | https://doi.org/10.1002/cncy.22638

Abstract

Background

The International System for Reporting Serous Fluid Cytopathology (ISRSFC) was published recently to provide standard reporting terminology for serous fluid. To date, several ISRSFC reclassification studies have reported a wide range of diagnostic category frequency and the associated risk of malignancy (ROM). Herein, the authors applied the ISRSFC to report pleural and peritoneal effusions retrospectively in a community hospital setting.

Methods

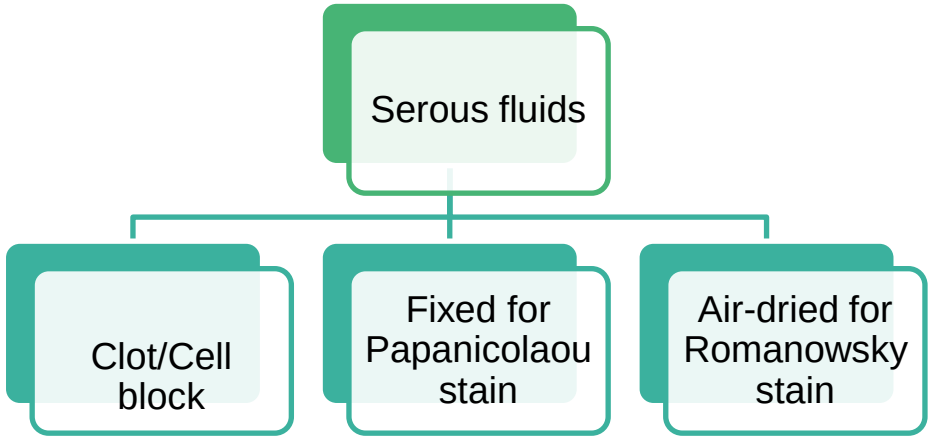
With Internal Review Board approval, 446 peritoneal effusion specimens and 299 pleural fluid specimens from 576 patients in three community hospitals over a 12-month period were reviewed and reclassified according to the ISRSFC.

CASE 1

54 year old male with left sided pleural effusion. Smoker, cough and chest pain for one week.

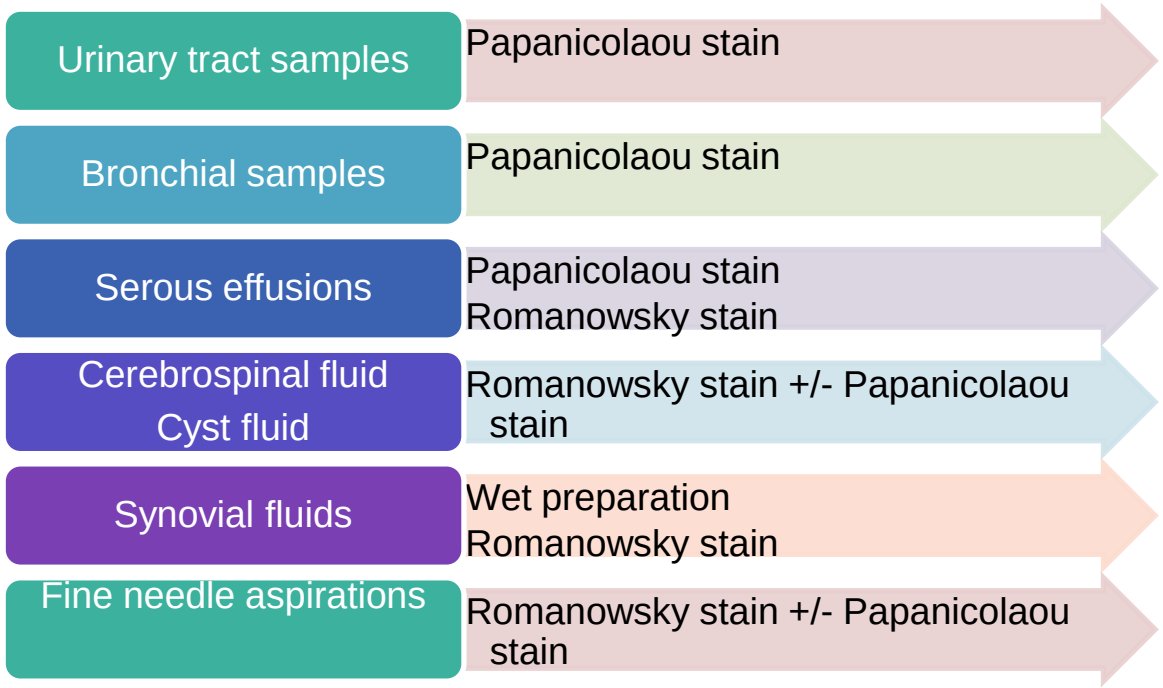
Macro: 2ml of heavily blood-stained fluid received. One ThinPrep and one DQ cytospin prepared.

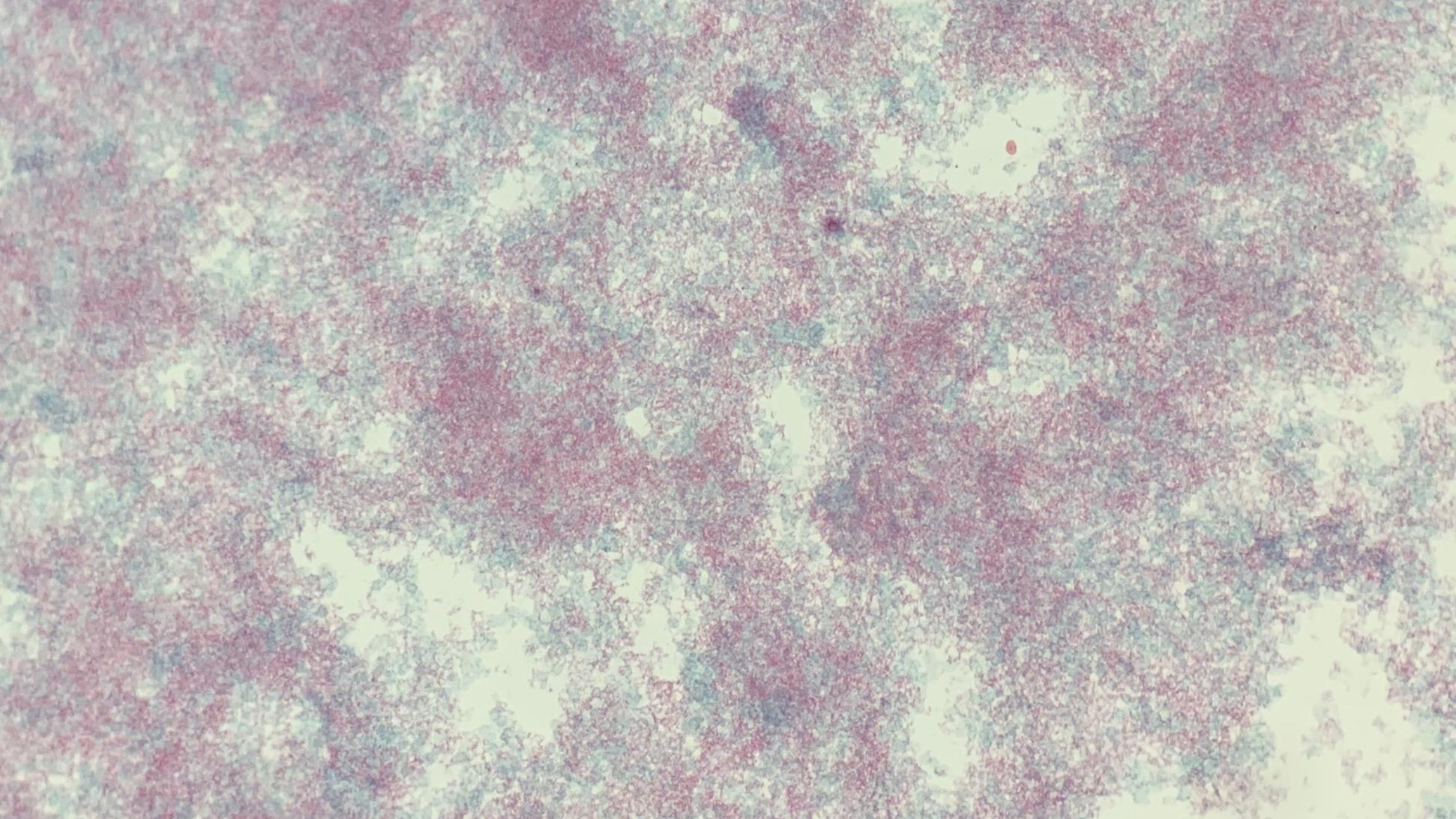
SEROUS FLUIDS

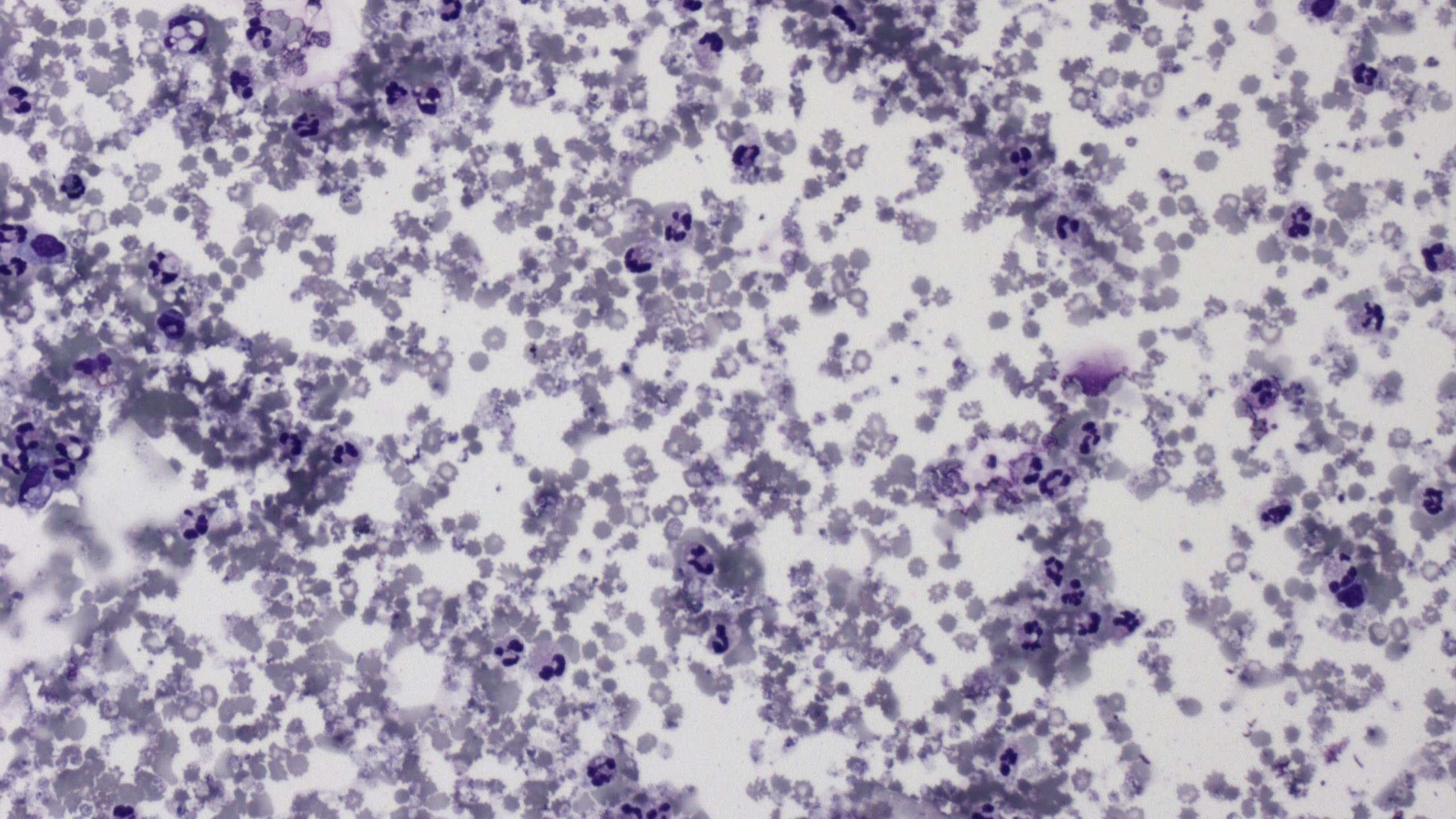


- www.rcpath.org
- Tissue pathways for diagnostic cytopathology

MINIMUM RECOMMENDATIONS FOR SAMPLE PREPARATION AND STAINING





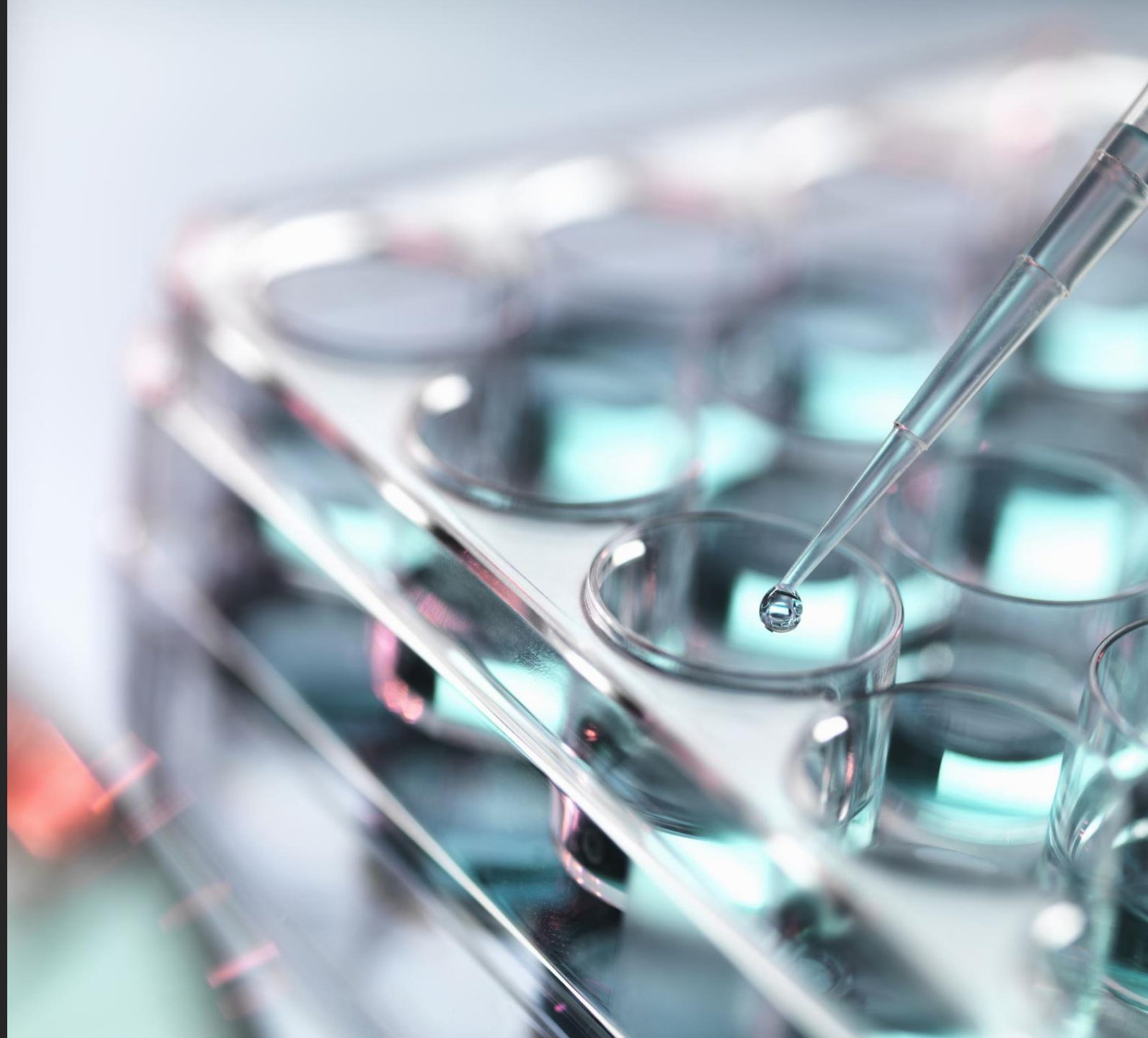


SAMPLE REPORT

1. ADEQUACY STATEMENT

2. DIAGNOSTIC CATEGORY

3. CLINICAL COMMENT



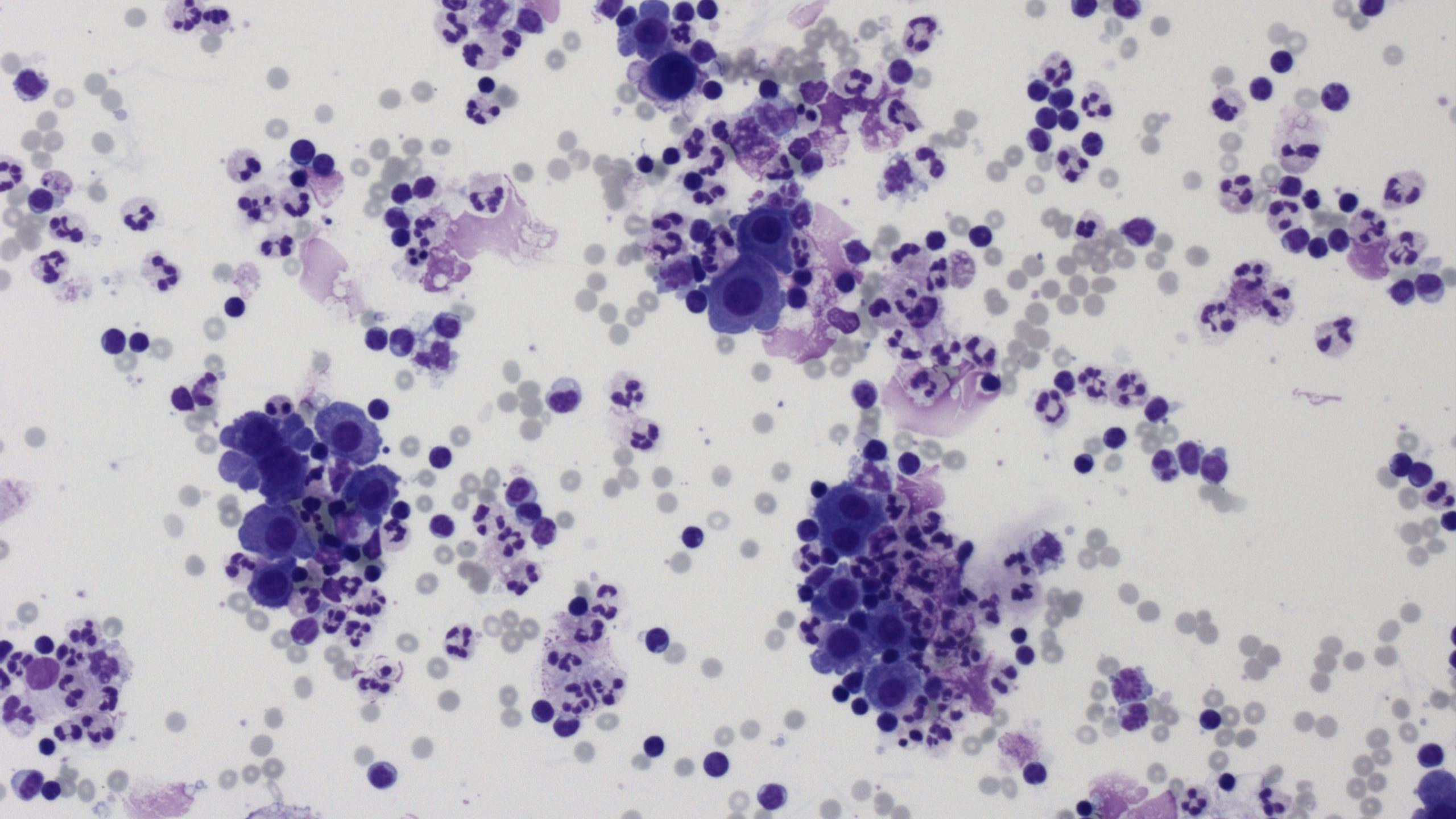
SAMPLE REPORT FOR NON-DIAGNOSTIC CATEGORY

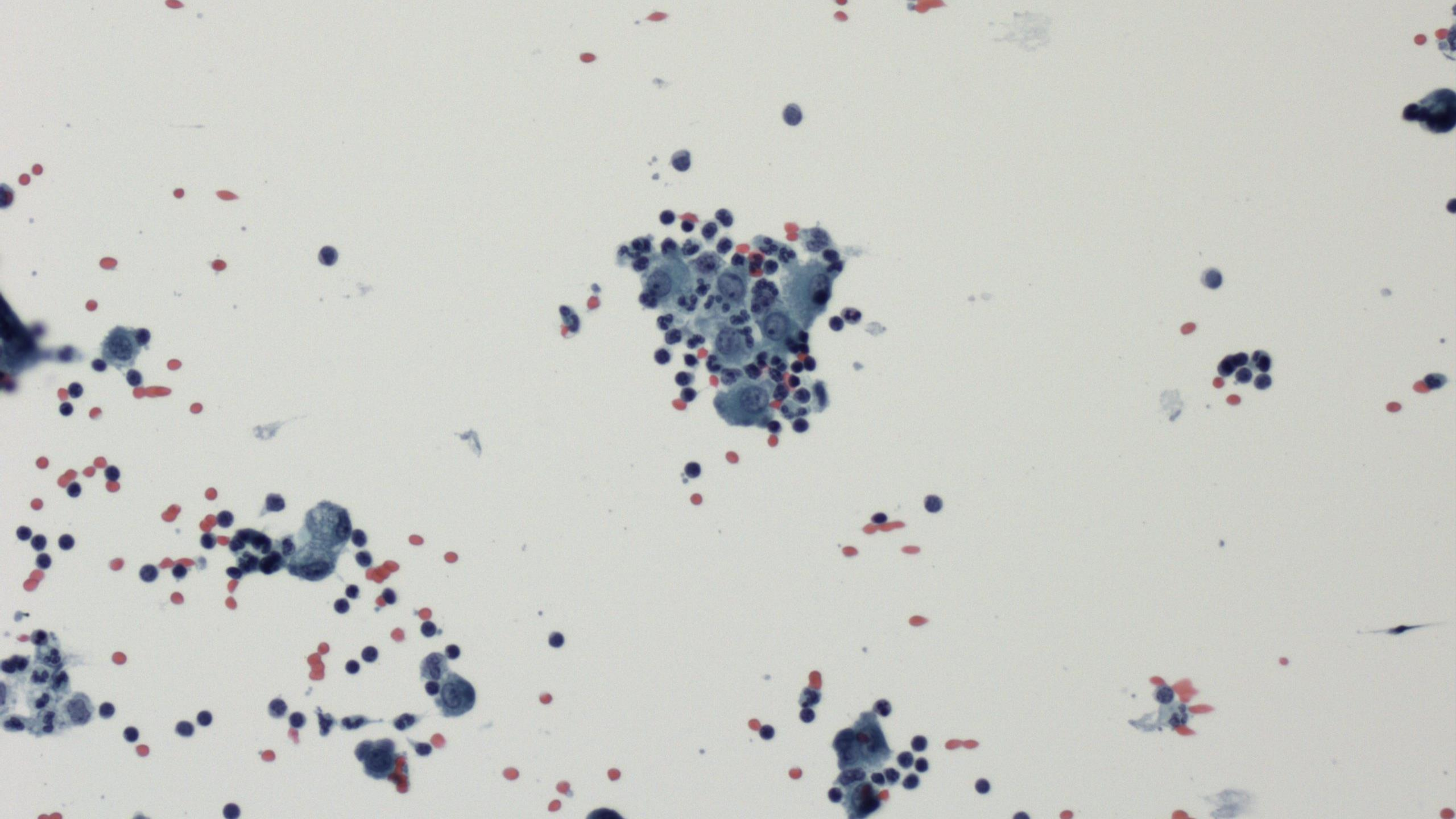
- Evaluation limited by heavy blood-staining, likely non-representative sample.
- NON-DIAGNOSTIC
- Repeat sampling advised (75ml volume if possible).

64 year old male with liver cirrhosis and ascites.

Macro: 60ml of straw coloured fluid. Two cytospins, Pap and Giemsa, prepared

CASE 2





SAMPLE REPORT :

1. ADEQUACY STATEMENT
2. DIAGNOSTIC CATEGORY
3. CLINICAL COMMENT

SAMPLE REPORT FOR NEGATIVE FOR MALIGNANCY CATEGORY

- Satisfactory for evaluation.
- Neutrophils, mesothelial cells and a few lymphocytes are present.
- NEGATIVE FOR MALIGNANCY
- A high proportion of neutrophils is present and may represent spontaneous bacterial peritonitis (SBP). Please correlate with clinical findings.

NEGATIVE FOR MALIGNANCY (NFM)

- Normal (expected) cell populations in variable numbers
- Lymphocytes
- Macrophages
- Mesothelial cells
- Neutrophils
- Eosinophils

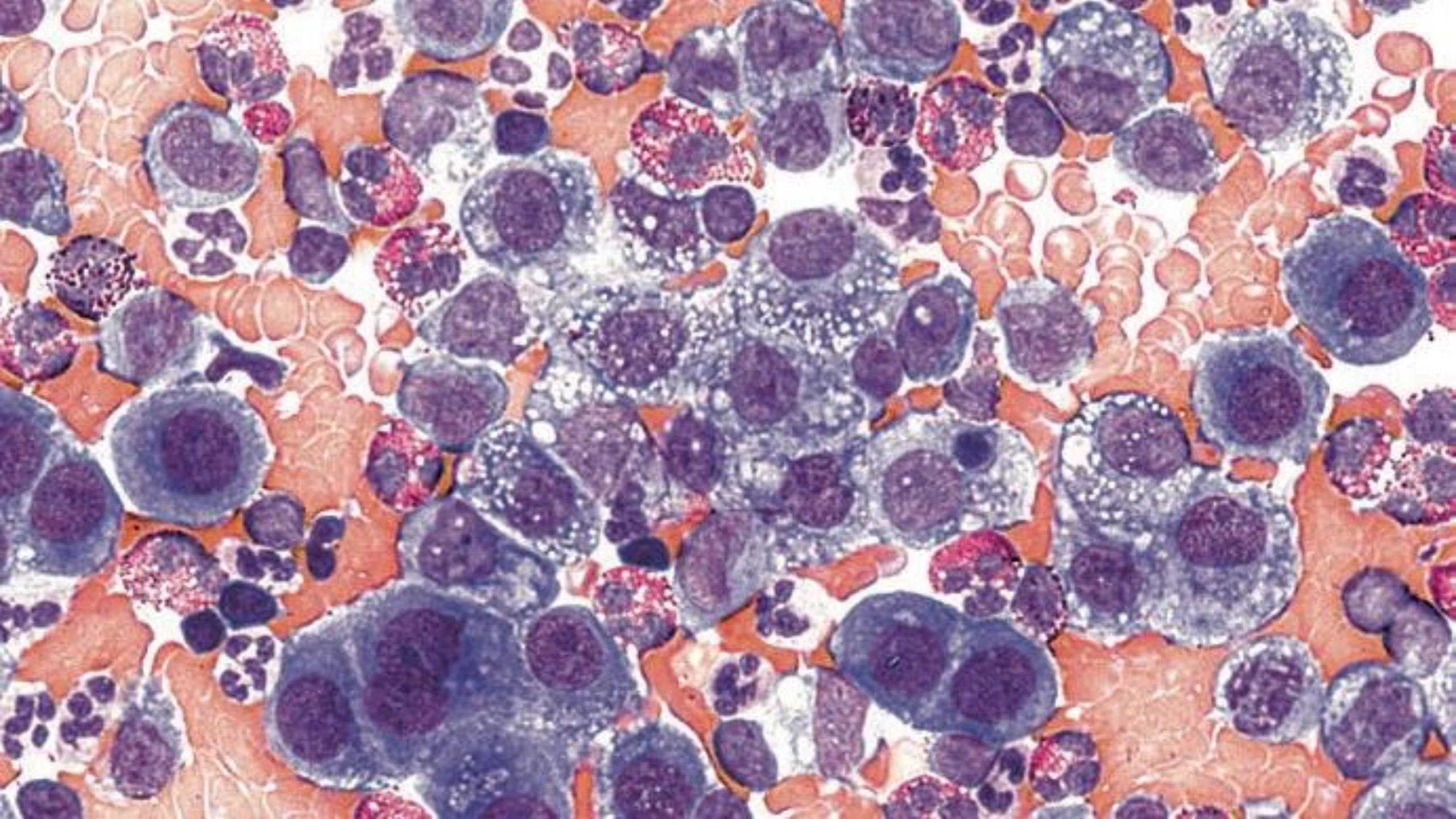
PATTERNS OF REACTIVE EFFUSIONS

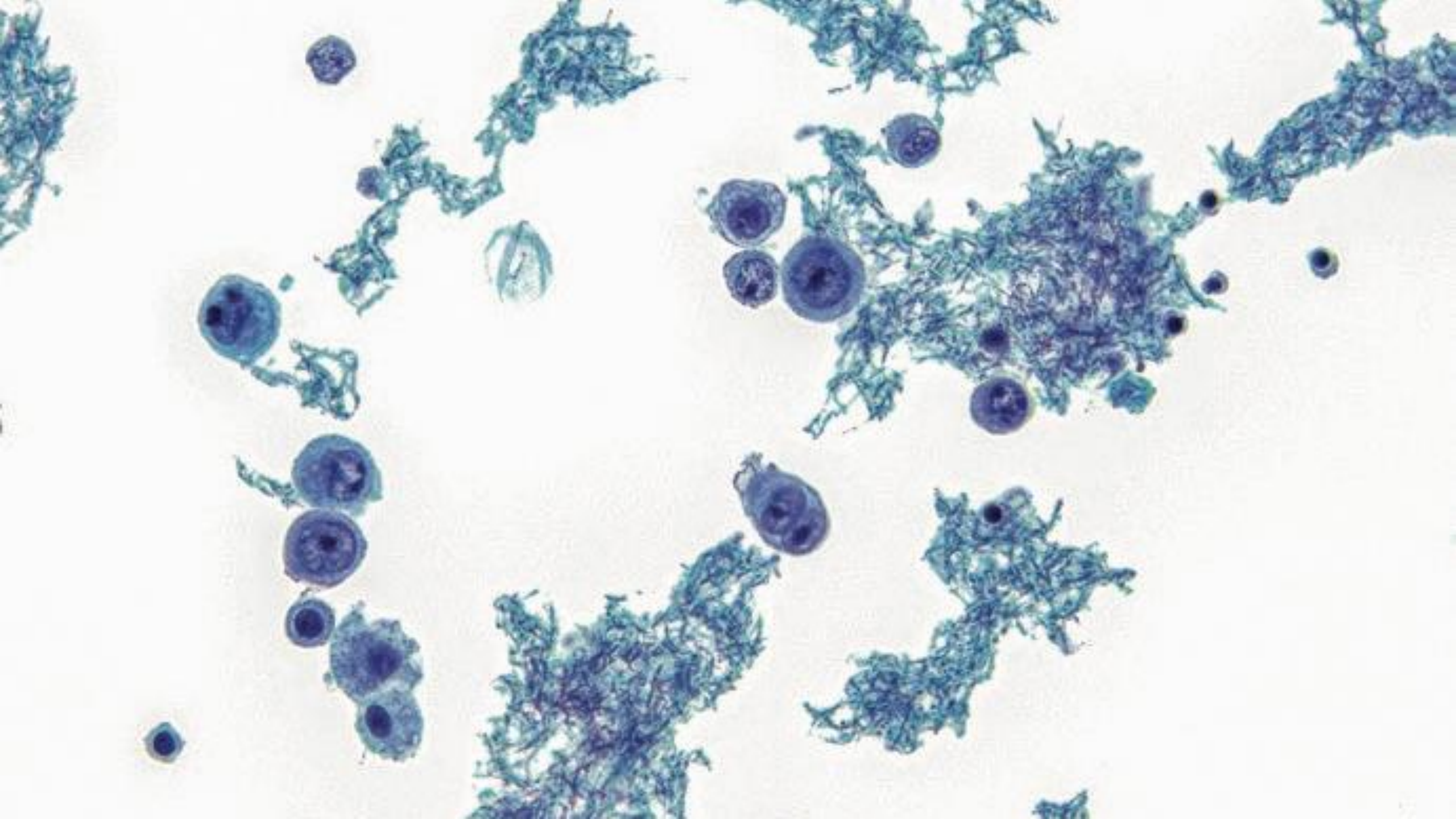
- If specific pattern of reactive effusion present such as eosinophilic or lymphocytic, suggest possible causes in the clinical comment.
- Eosinophilic effusion: Recent pleural fluid aspiration, allergic conditions including hypereosinophilic syndrome etc
- Lymphocytic effusion: Viral infections, TB
- Neutrophilic effusion: Empyema (purulent fluid) usually indicative of bacterial infection, occasionally malignant eg. lung squamous cell carcinoma rupturing into pleural cavity

CASE 3

46 year old female with history of breast carcinoma 6 years ago. Now, cough and small pleural effusion.

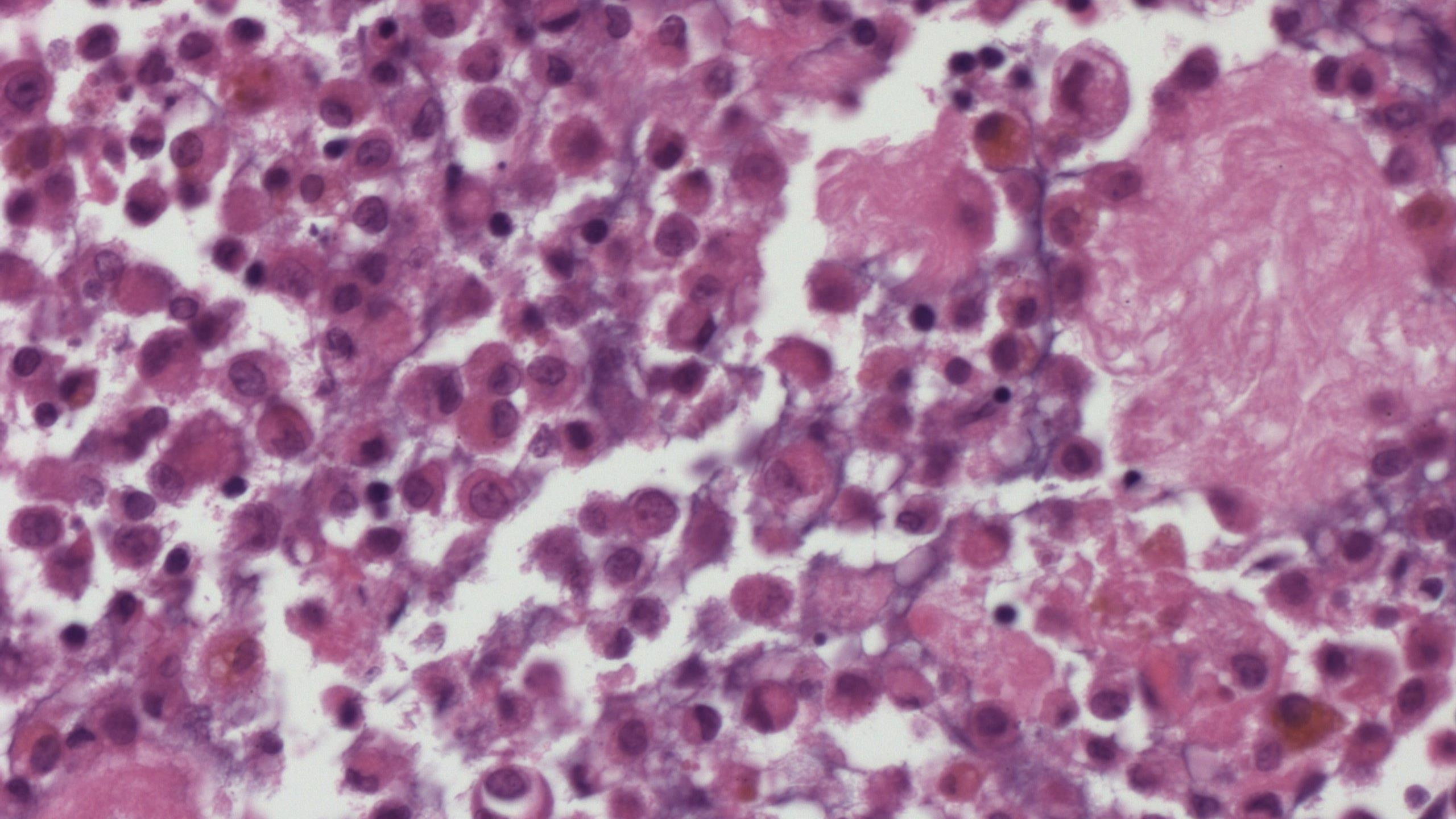
Macro: 20ml straw-coloured fluid.
Cytospins 1 PAP 1 MGG

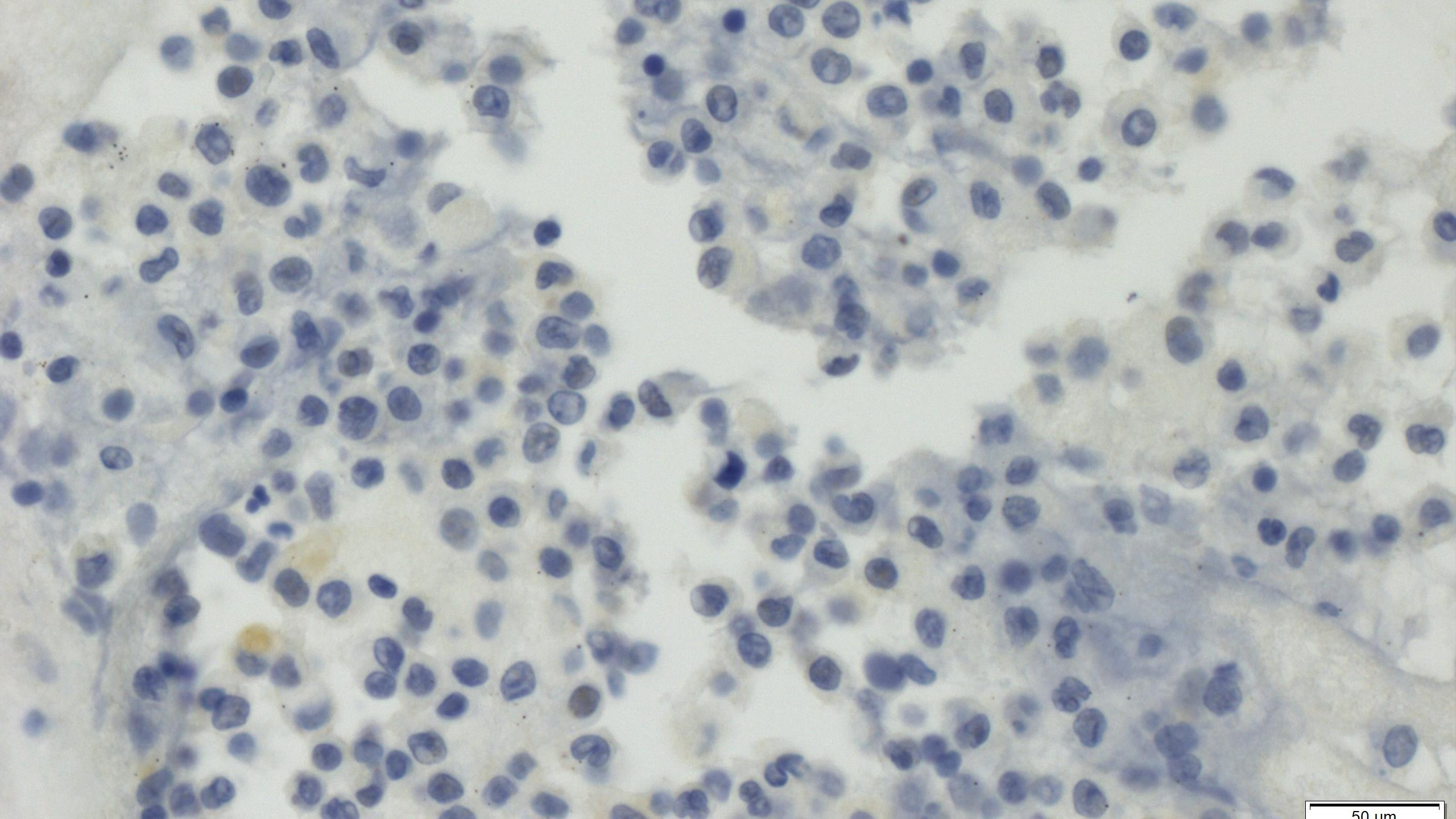




ATYPIA OF UNDETERMINED SIGNIFICANCE (AUS)

- Occasional poorly preserved cells with nuclear enlargement and mild hyperchromasia but no obvious chromatin or nuclear membrane abnormalities
- Likely degenerated macrophages or mesothelial cells
- Cell block made and IHC performed to detect any epithelial cells (BerEP4, GATA3) and mesothelial markers (WT1, calretinin)
- Downgraded to NFM as epithelial markers negative

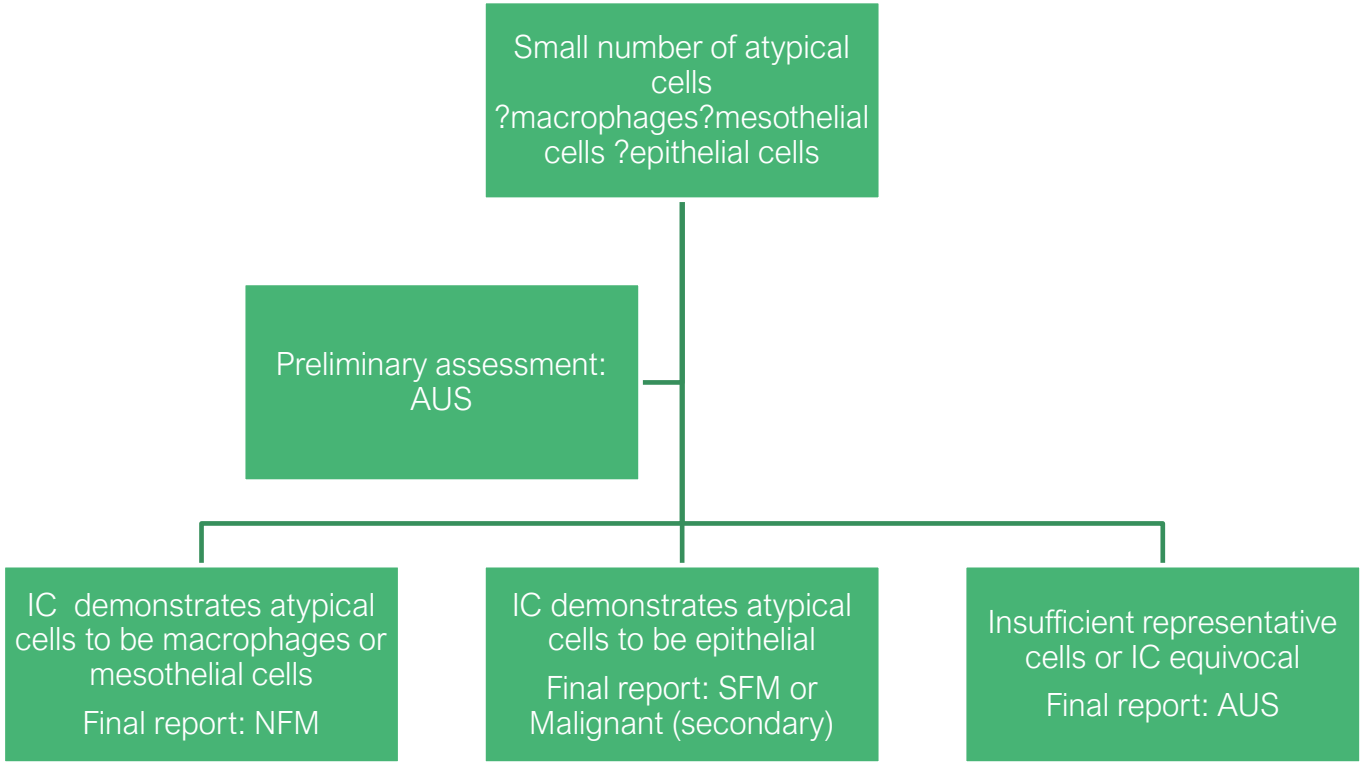



50 µm

ATYPIA OF UNDETERMINED SIGNIFICANCE (AUS)

- Uncommonly used as a diagnostic category in effusions
- Some experienced cytologists don't use it at all
- Can we do without it completely?
- Survey respondents tell us that they use it, albeit variably but should be included in the terminology
- Two-step process – preliminary report (optional) and final report

AUS ALGORITHM



Received: 27 August 2021 | Revised: 5 October 2021 | Accepted: 19 October 2021
DOI: 10.1002/dc.24900

ORIGINAL ARTICLE

WILEY

The international system for serous fluid cytopathology: Interobserver agreement

Lester J. Layfield MD[1] | Zhongbo Yang MD[2] | Maryna Vazmitsel MD[1] | Tao Zhang MD[1] | Magda Esebua MD[1] | Robert Schmidt MD, PhD, MBA[3]

[1]Department of Pathology and Anatomical Sciences, University of Missouri, Columbia, Missouri, USA
[2]Department of Pathology, Rosewell Park Cancer Center, Buffalo, New York, USA
[3]Department of Pathology and Laboratory Medicine, ARUP Laboratories, Salt Lake City, Utah, USA

Abstract

Background: A number of categorization systems had been developed for the reporting of cytology specimens with the aim of providing uniform definitions, criteria, and diagnostic terminology. The intention of these systems is to improve reproducibility of diagnostic categorization with standardized estimates of malignancy risk. Required for

Diagnostic Cytopathology

TIMELY REVIEW

Cytologic diagnosis of "atypical" in serous fluid cytopathology. Approach of the international system for reporting serous fluid cytopathology

Ashish Chandra MD, Fernando Schmitt MD, PhD, FIAC

First published: 09 September 2021 | https://doi.org/10.1002/dc.24864 | Citations: 2

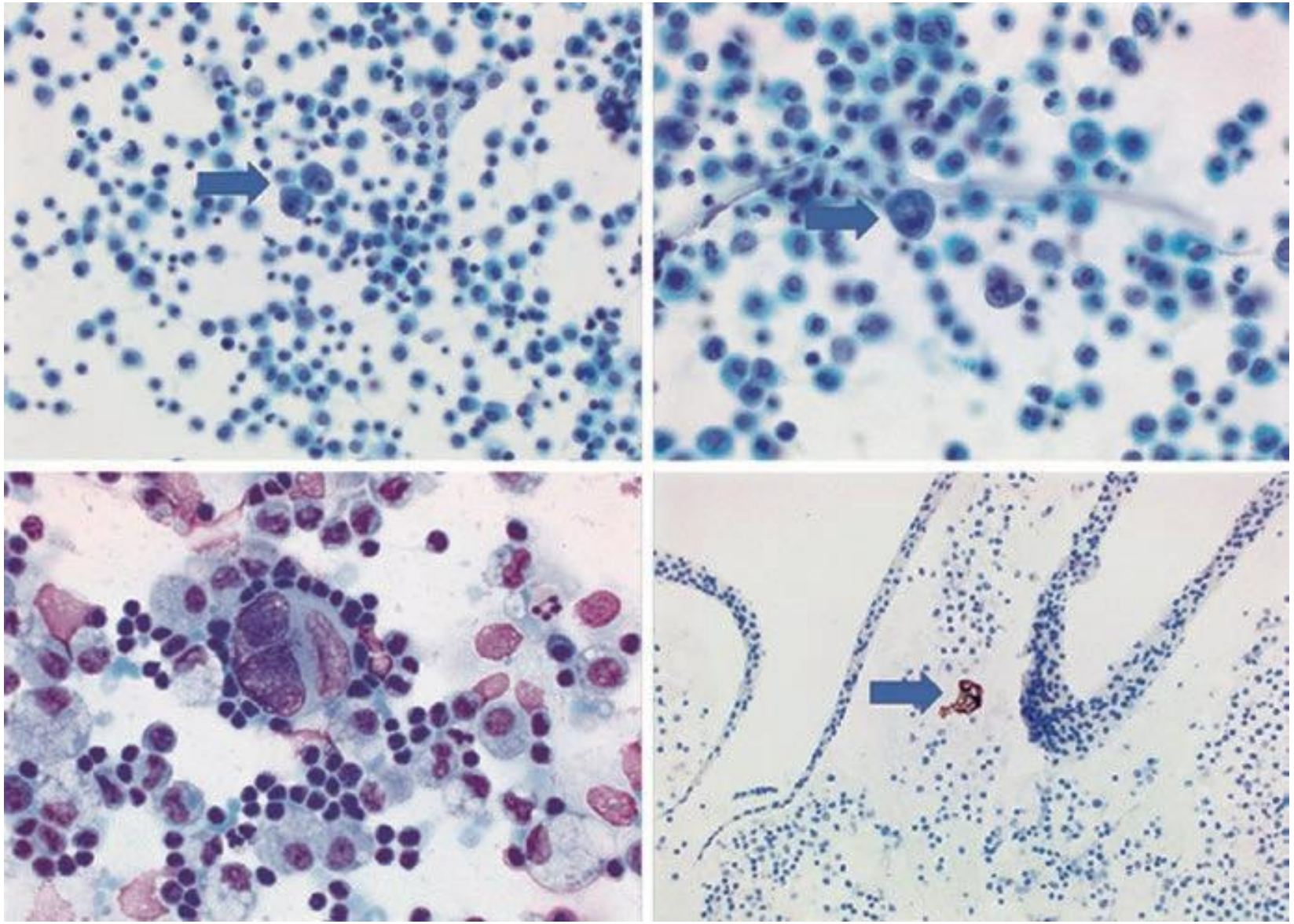
Abstract

Diagnostic uncertainty may occur with almost any entity on cytological evaluation, depending on the quality and quantity of the provided sample. In serous fluid cytopathology, until recently, there had been no defined or agreec criteria for atypia and suspicious categories. Historically, the two descriptive terms appear to have been used almost interchangeably. The international system for serous fluid cytopathology is the first attempt by an expert international authorship to suggest the scenarios in which these terms are

CASE 4

68 year old man with pleural fluid. History of lung carcinoma.

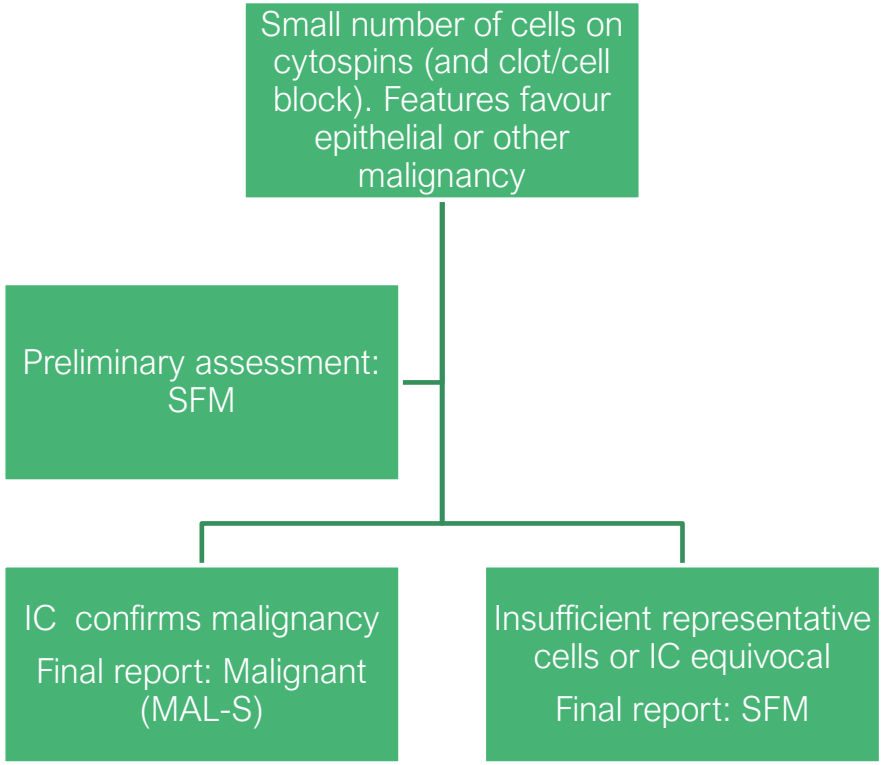
Macro: 30ml of blood-tinged fluid.



SUSPICIOUS SCENARIOS

- Small numbers of cells or groups with nuclear pleomorphism requiring ancillary tests for confirmation of malignancy
- Cells with bland appearances or only mild pleomorphism, maybe numerous (gastric) or small numbers (breast)
- Mucinous material with few or no cells in ascitic fluid (pseudomyxoma)
- Lymphocytic effusions with a monotonous cell population

SFM ALGORITHM



ANCILLARY TESTING OF LUNG ADENOCARCINOMA

- Insufficient cells for PD-L1, ALK, ROS1 (IHC)
- Insufficient cells for mutation analysis (NGS or just EGFR, KRAS)
- Further sample may be needed for targeted chemotherapy
- Restrict use of IHC (TTF1, Napsin A, P40) to a minimum to conserve material for molecular testing

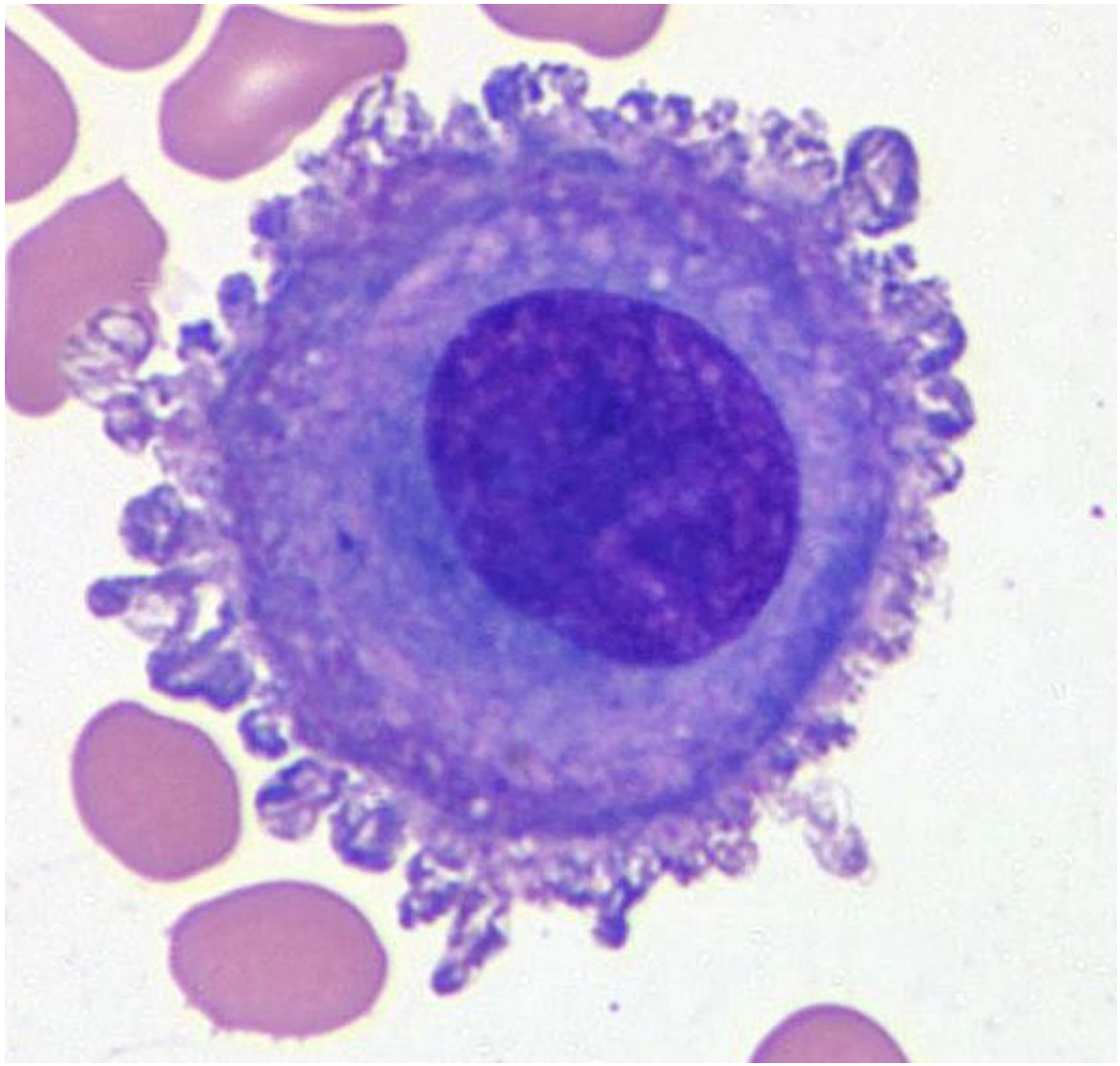
COMPARISON OF AUS AND SFM CATEGORIES: THE INTERNATIONAL SYSTEM FOR REPORTING SEROUS FLUID CYTOPATHOLOGY

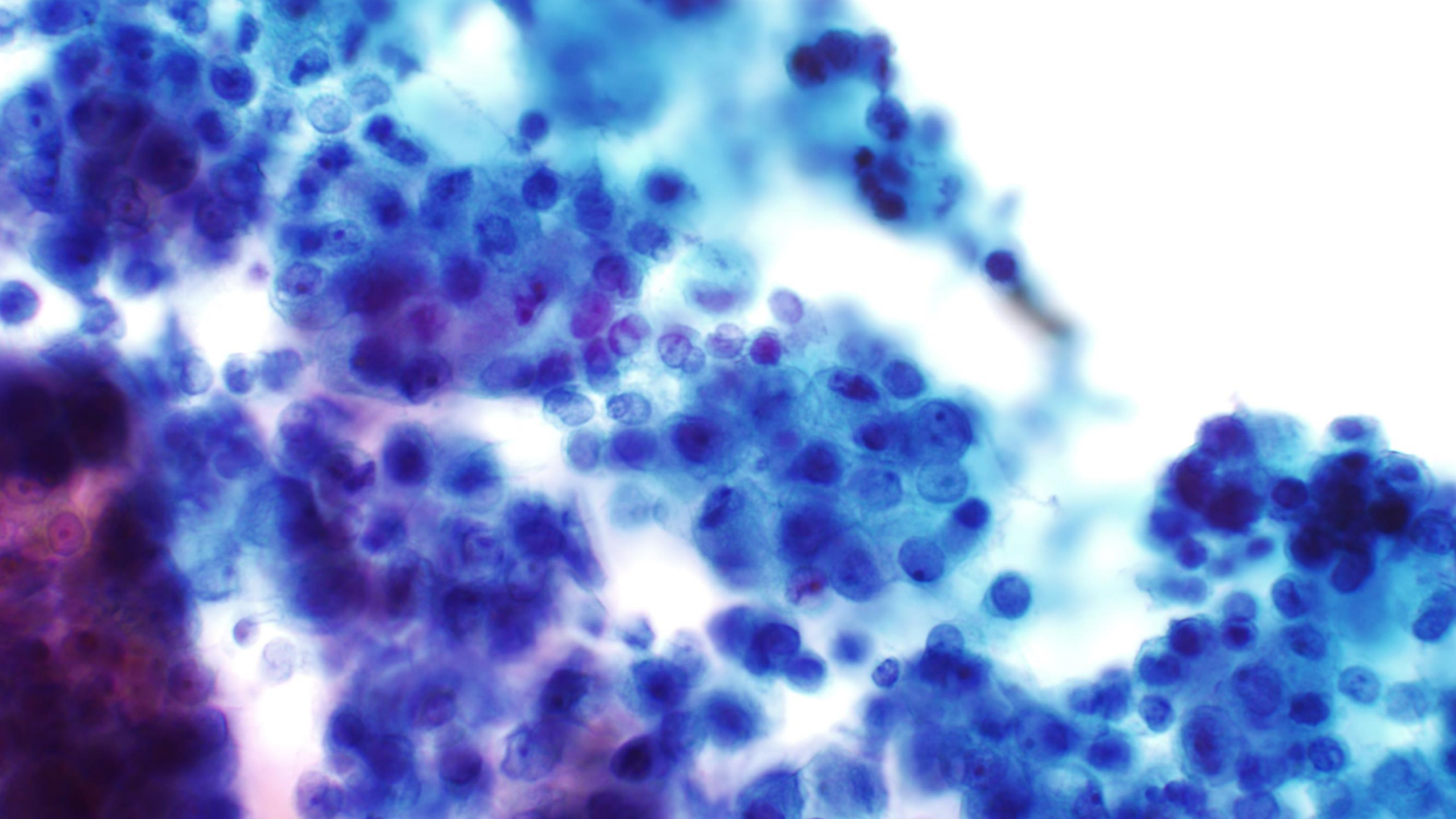
	AUS	SFM
Cytological features	Only mild cytological abnormalities such as nuclear enlargement and hyperchromasia present usually as small numbers of dispersed cells and occasional small groups	Greater degree of cytological abnormalities present usually as small numbers of cells, including architectural features such as occasional 3 dimensional groups
Cell lineage	Benign cell type favoured but epithelial or other malignant cell of origin not excluded	Epithelial or other malignant cell of origin strongly favoured
Immunochemistry	Outcomes may be benign, SFM/malignant or inconclusive	Outcomes usually malignant or inconclusive.
Suggested Risk of Malignancy	~20%	~80%

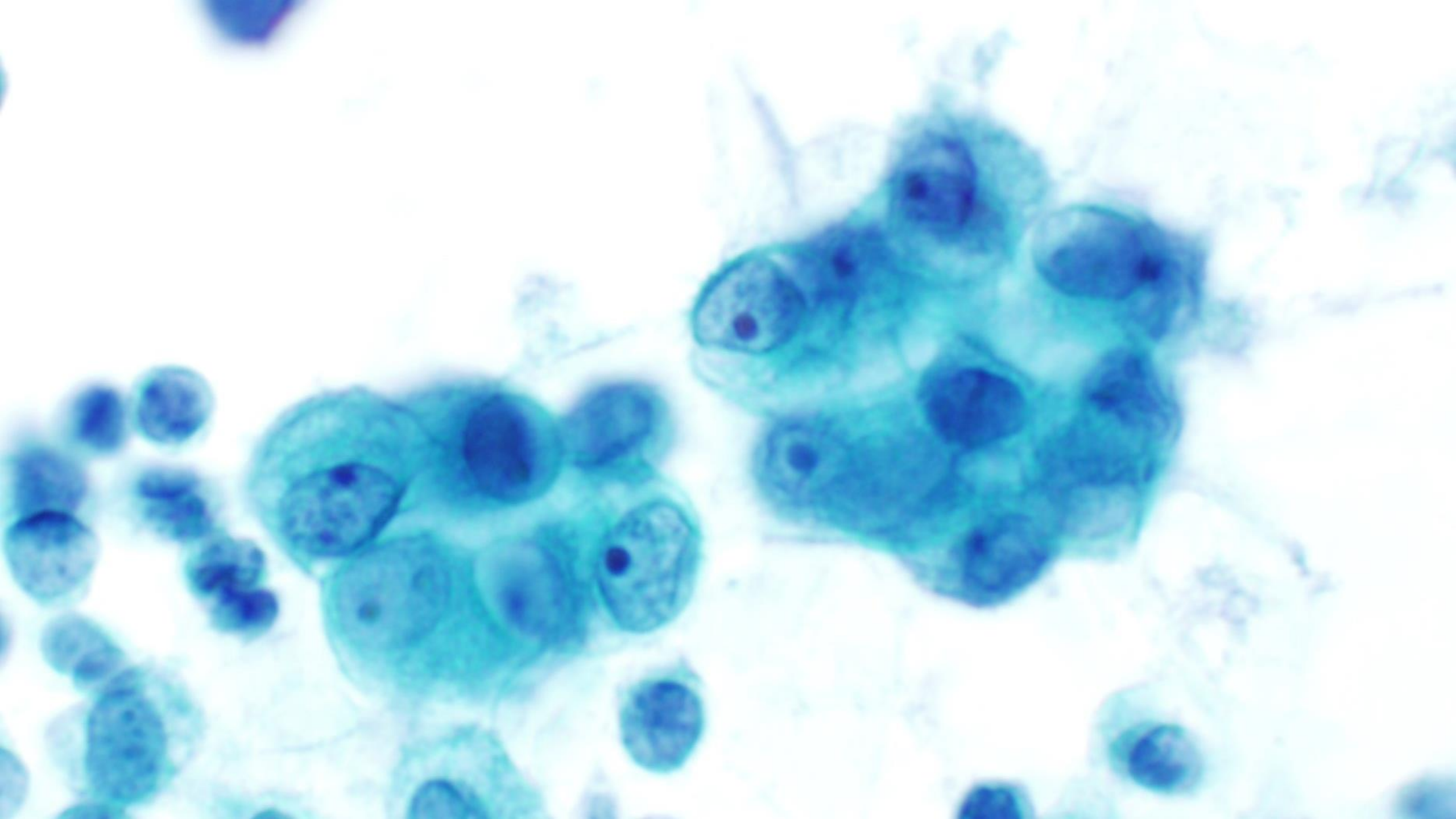
CASE 5

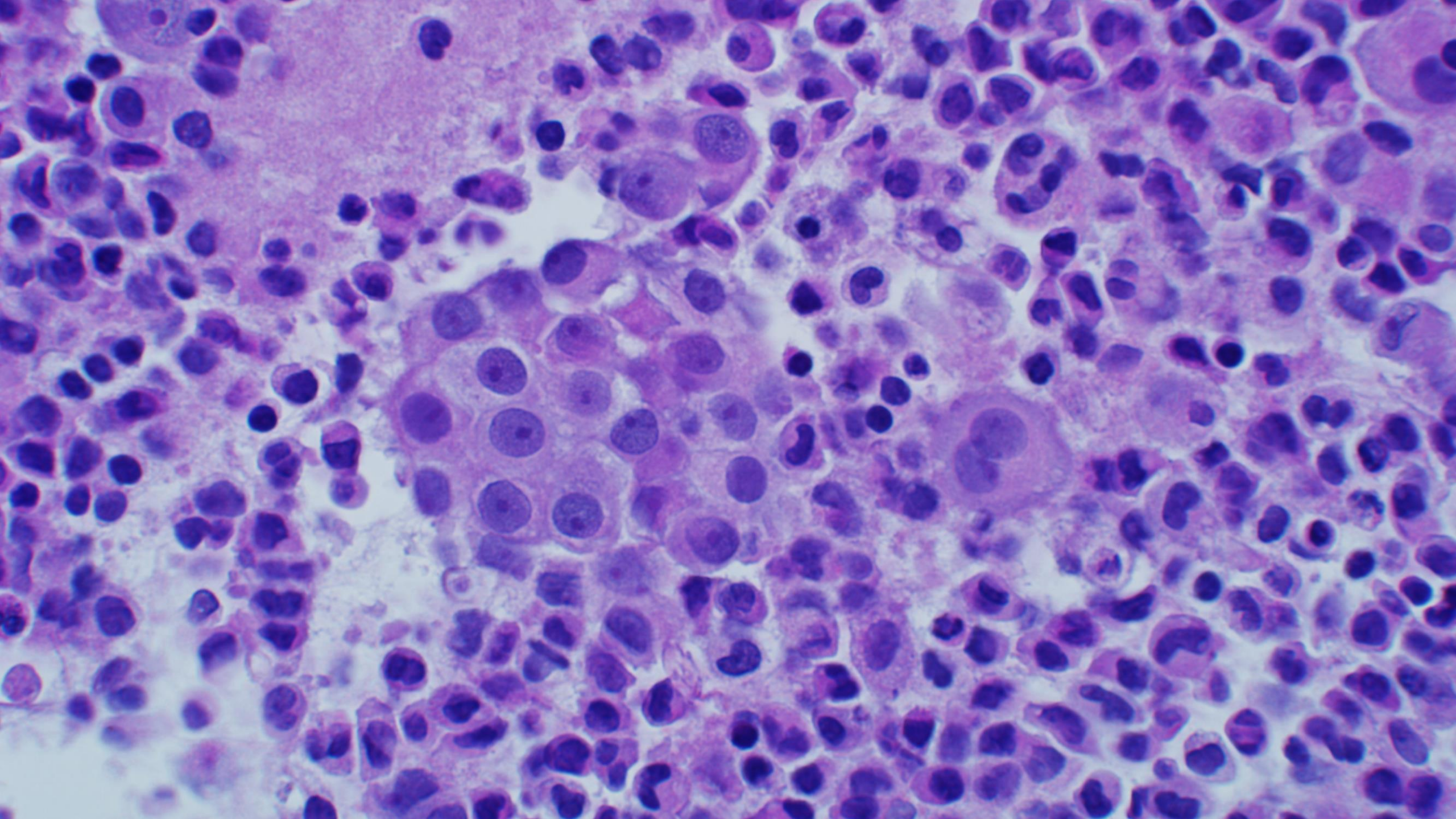
68 year old man.
History of occupational exposure to asbestos.
Unilateral haemorrhagic pleural effusion.

MACRO: 80ml of blood-stained fluid with a clot.
Cytospins 1MGG 1 Pap 1HE









ANCILLARY TESTING OF MESOTHELIAL PROLIFERATIONS

	NFM	MESOTHELIOMA
Desmin (cytoplasmic)	+	-
EMA (membranous)	-	+
BAP1 (nuclear)	+	-
MTA (IHC nuclear / FISH)	IHC - / FISH: No deletion	IHC + / FISH: Deletion detected
P16/CDKN2A (FISH)	No deletion	Deletion detected

Received: 22 July 2022 | Revised: 24 August 2022 | Accepted: 25 August 2022

DOI: 10.1002/dc.25053

TIMELY REVIEW

WILEY

Cytology of malignant pleural mesothelioma: Diagnostic criteria, WHO classification updates, and immunohistochemical staining markers diagnostic value

Nada Shaker MD, MS[1] | **Douglas Wu MD**[1] | **Abdul Majeed Abid MD**[2]

[1]Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

[2]Department of Pathology, UPMC, Pittsburgh, Pennsylvania, USA

Correspondence
Nada Shaker, Department of Pathology, The

Abstract

Malignant pleural mesothelioma (MPM) is a rare but aggressive malignancy with a poor prognosis. Because of this tumor rarity and overlapping histologic features with other malignancy types, the histopathological findings and diagnostic immunohistochemical workup are essential in establishing the final diagnosis of MPMs. We aimed

SAMPLE REPORTS FOR A MESOTHELIAL PROLIFERATION

- Satisfactory for evaluation.
- Small spherical groups and dispersed mesothelial cells with mild nuclear pleomorphism are present suspicious for mesothelioma.
- Immunostains requested for confirmation (on cell block or biopsy).
- If immunostains confirmatory- MALIGNANT (PRIMARY): MESOTHELIOMA. Clinical correlation essential.
- If morphology classic but immunostains not confirmatory: SUSPICIOUS FOR MESOTHELIOMA
- If morphology not classic and immunostains not confirmatory: ATYPICAL MESOTHELIAL PROLIFERATION. Further investigation advised.

MALIGNANT (MAL)

Recognisable abnormal cell population present and adequate for robust diagnosis on which clinical management may be based

Malignant cell type should be specified on morphology alone or supported by immunochemistry

Malignant- Primary: Mesothelioma

Malignant- Secondary:

Metastatic carcinoma – adenocarcinoma, small cell carcinoma, squamous cell carcinoma

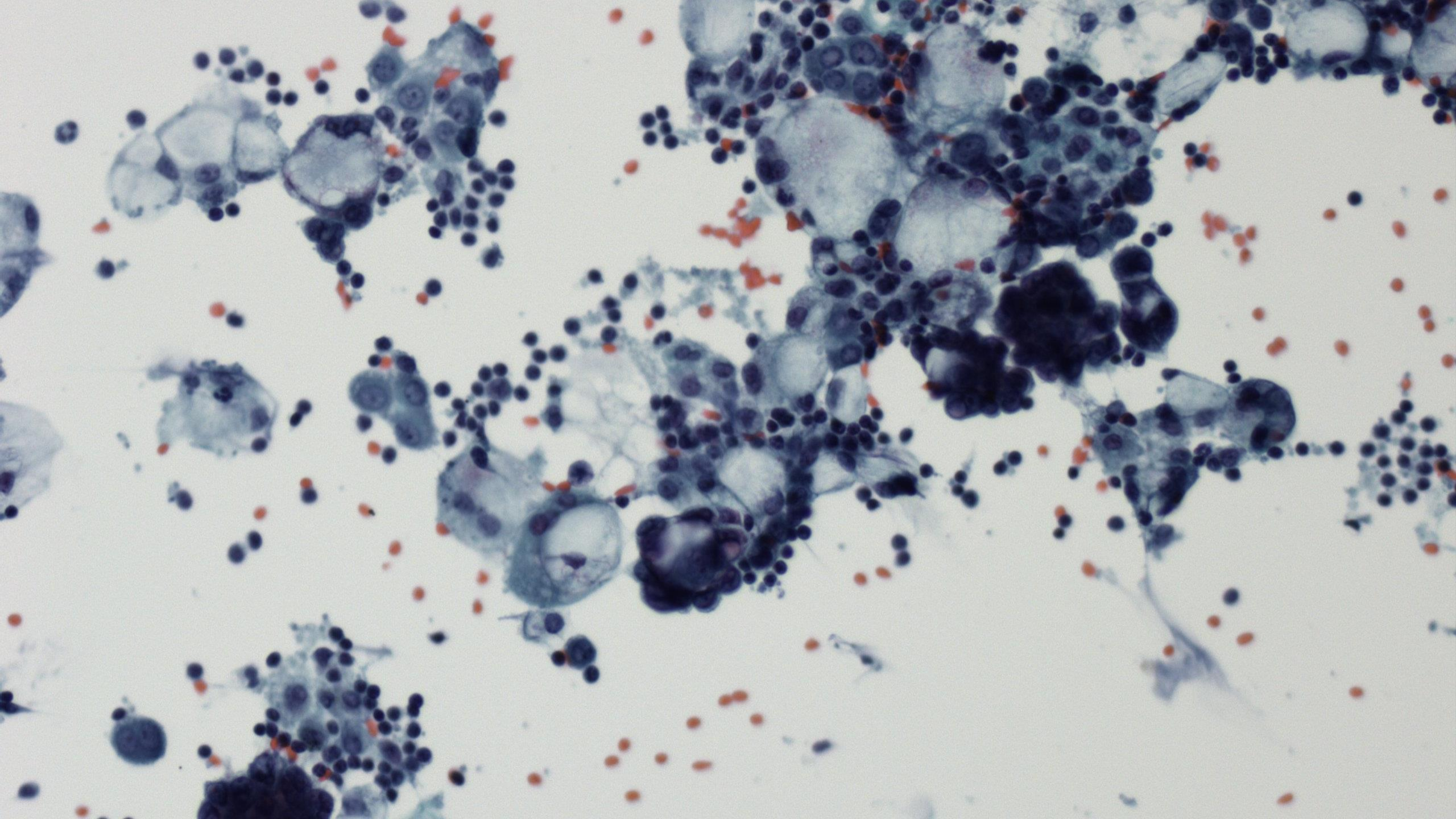
Lymphoma, Melanoma, Other malignancies e.g. sarcoma, leukaemias

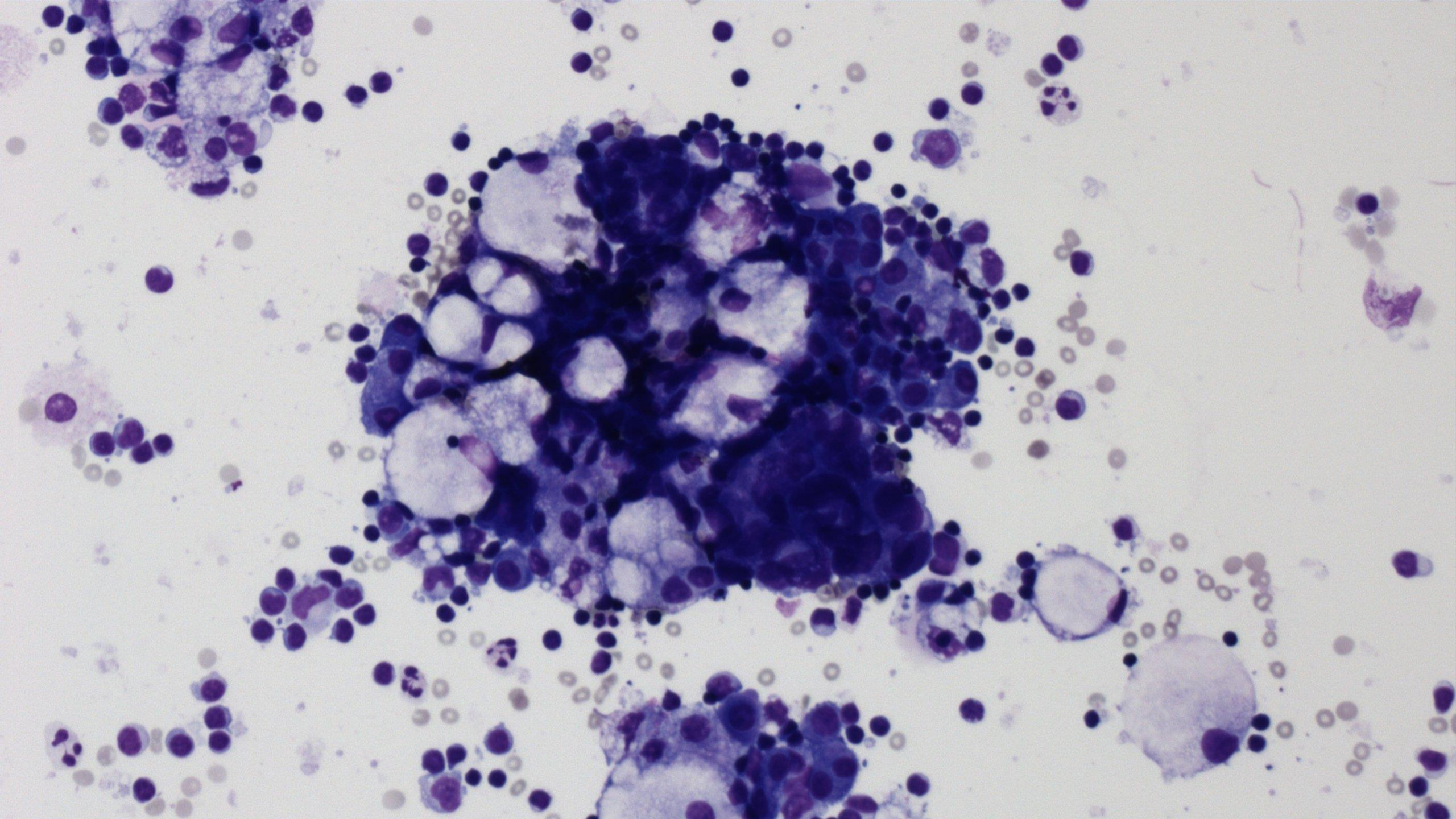
Primary organ site may need to be investigated for adenocarcinomas

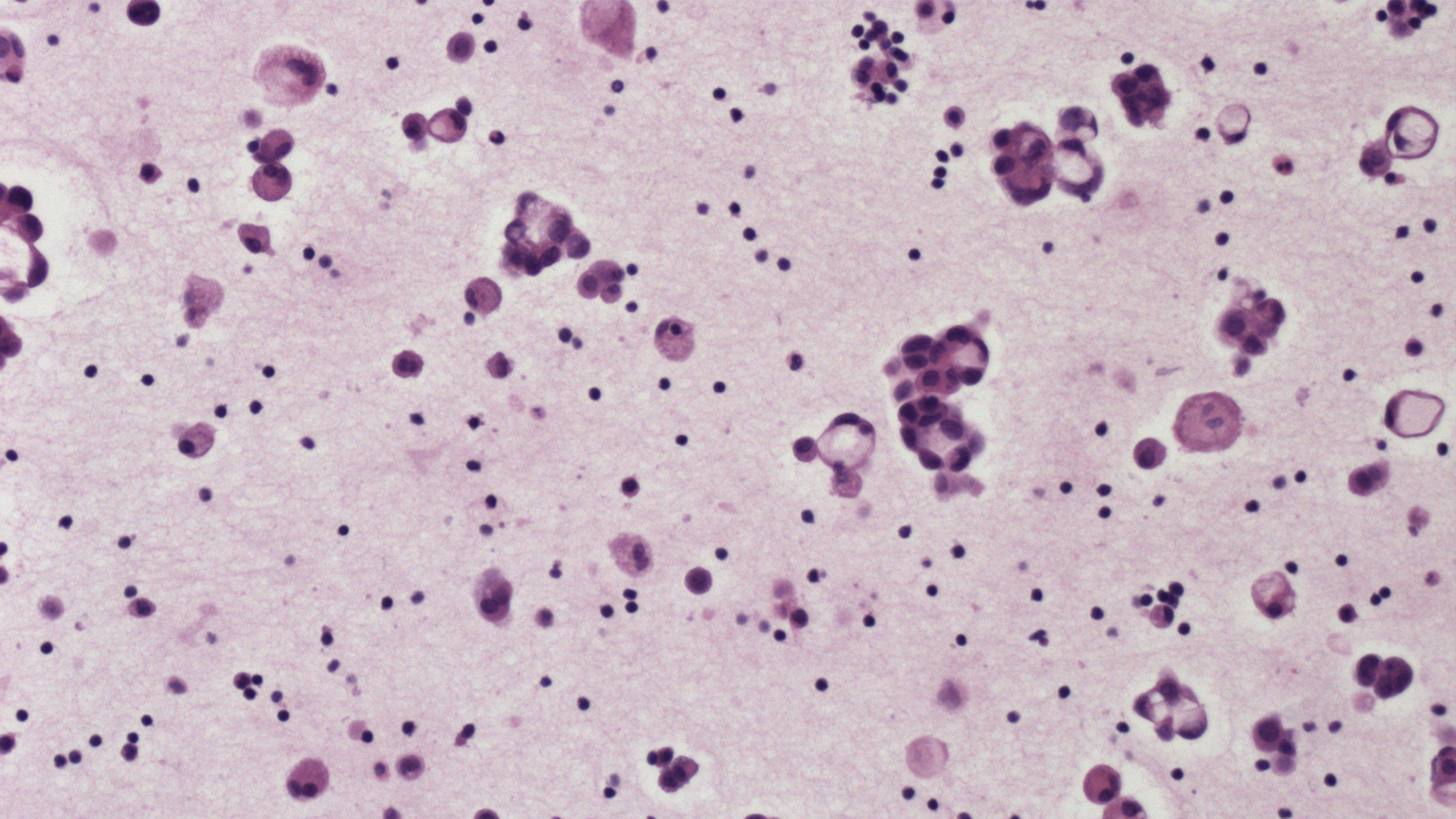
CASE 6

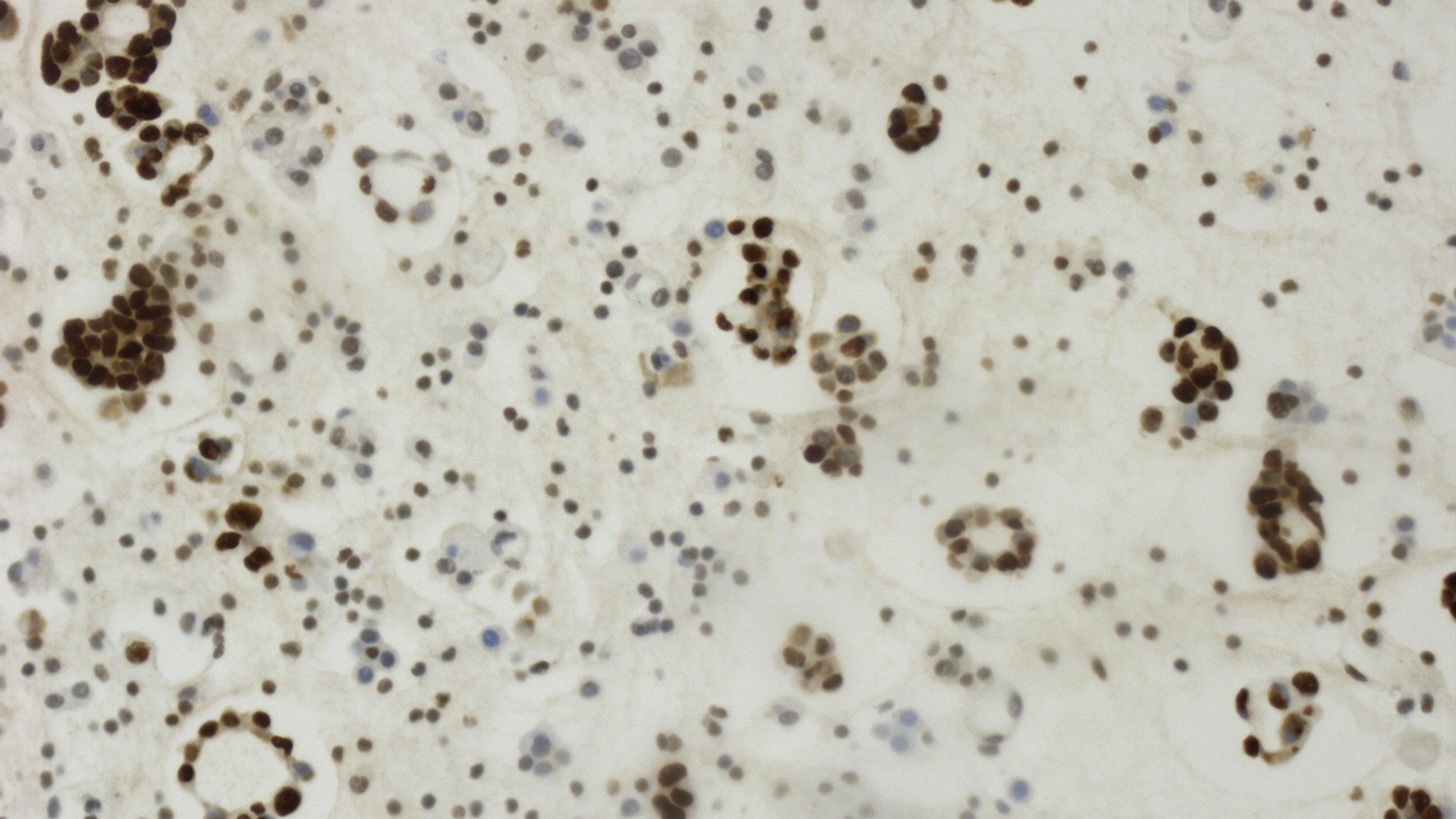
45 year old female. Ascites.

MACRO: 35ml of blood-stained fluid. 1MGG 1 Pap









ASCERTAINING THE PRIMARY

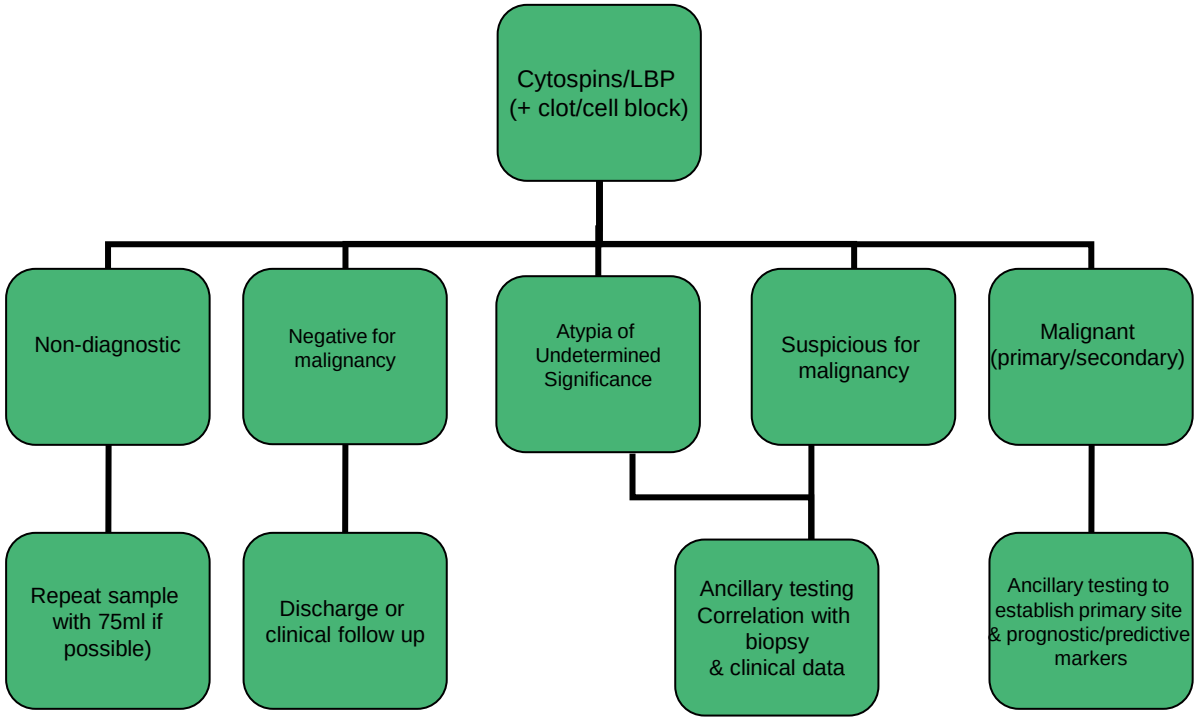
Site specific markers:

- Lung: TTF1, Napsin A, (BAP1+)
- Breast: GATA3, mammaglobin, GCDFP15
- Thyroid: Thyroglobulin, PAX8
- GI: CK20, CDX2
- Ovarian: PAX8, WT1, CA125
- Kidney (CCRCC): PAX8, CAIX, RCC antigen, Vimentin
- Urothelial: GATA3, Uroplakins, p63, p40, 34BE12
- Prostate: PSA, PRAP, PSMA, NKX3.1

SAMPLE REPORT FOR MALIGNANT (SECONDARY)

- Satisfactory for evaluation.
- Spherical groups of tightly cohesive large cells with vacuolated cytoplasm and nuclear pleomorphism are present. Dispersed single cells are also present.
- MALIGNANT (SECONDARY)
- Immunostains requested to ascertain the primary, gynae and GI tracts being the most likely sites.

DIAGNOSTIC CATEGORIES & CLINICAL MANAGEMENT



International System for Reporting Serous Fluid Cytopathology: Implied Risk of Malignancy (ROM)

Diagnostic Category	% ROM (SE)
Non-Diagnostic (ND)	17% (± 8.9%)
Negative for Malignancy (NFM)	21% (± 0.3%)
Atypia of Undetermined Significance (AUS)	66% (± 10.6%)
Suspicious for Malignancy (SFM)	82% (± 4.8%)
Malignant (MAL)	99% (± 0.1%)

REFERENCES

- Farahani S, Baloch Z. Are we ready to develop a tiered scheme for the effusion cytology? A comprehensive review and analysis of the literature. Diagn Cytopathol 2019:1-19
- Valerio E, Nunes W, Cardoso J et al. A two year retrospective study on pleural effusions: A cancer center experience. Cytopathology. July 2019 https://doi.org/10.1111/cyt.12755
- Kaitlin E. Sundling and Edmund S. Cibas, Ancillary studies in pleural, pericardial, and peritoneal effusion cytology. Cancer Cytopathol 2018;126:590-598.
- Pambuccian SE. What is atypia? Use, misuse, and overuse of the term of atypia in diagnostic cytopathology. J Am Soc Cytopathol. 2015;4:44-52.
- Chandra A, Crothers B, Kurtycz D, Schmitt FS. Announcement: the international system for reporting serous fluid cytopathology. Acta Cytol. 2019;24:1-3.
- Rooper LM, Ali SZ and Olson MT. Cancer (CancerCytopathol)2014;122:657-65.VC2014 American Cancer Society.