MEDULLARY CARCINOMA OF THYROID

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&

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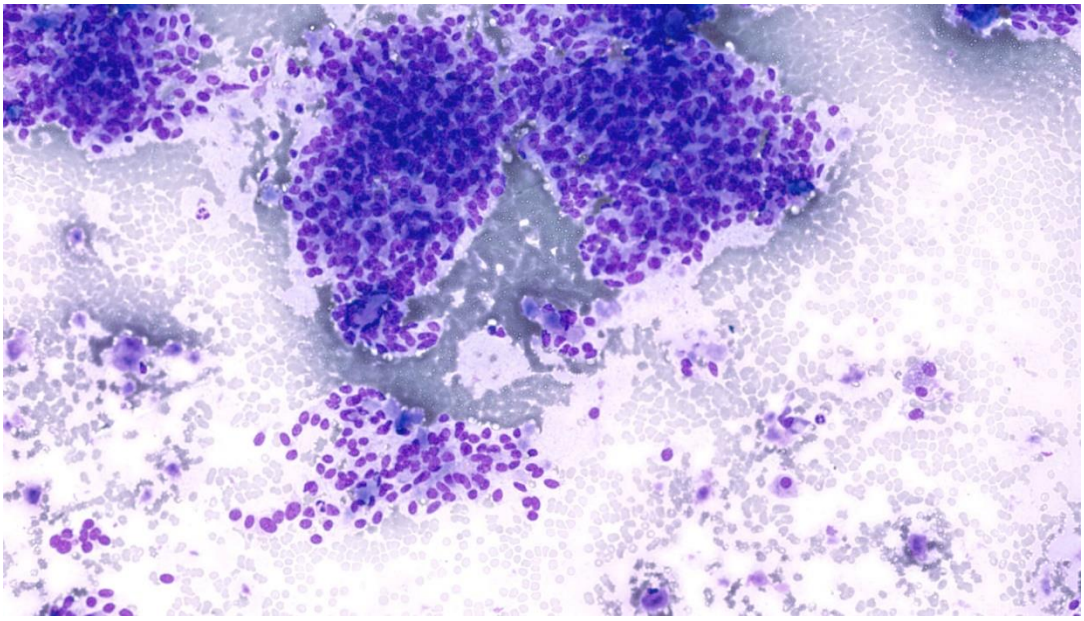
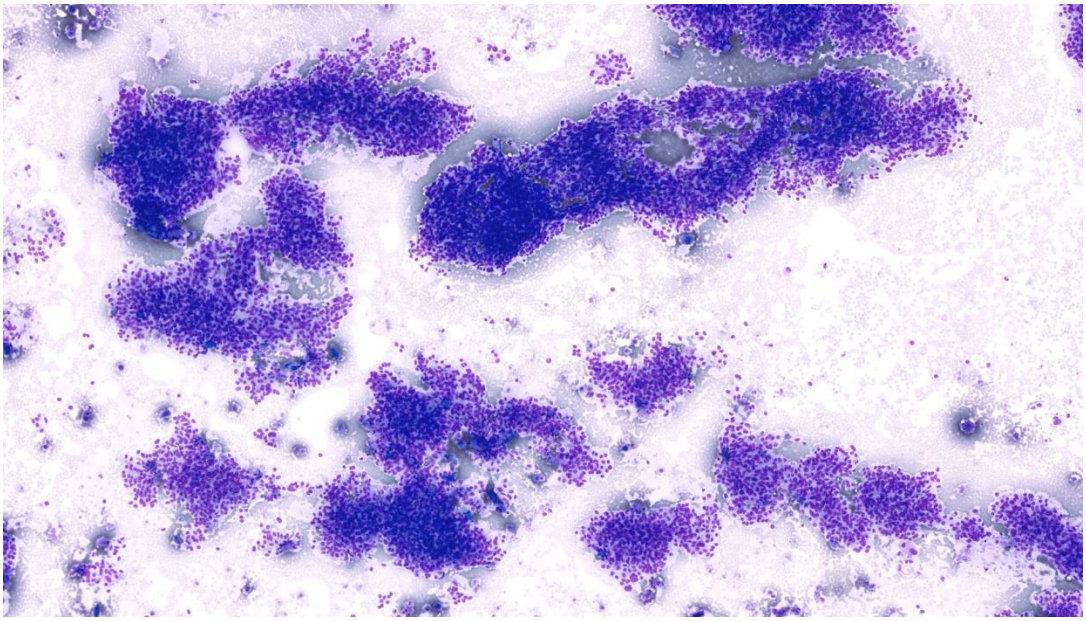
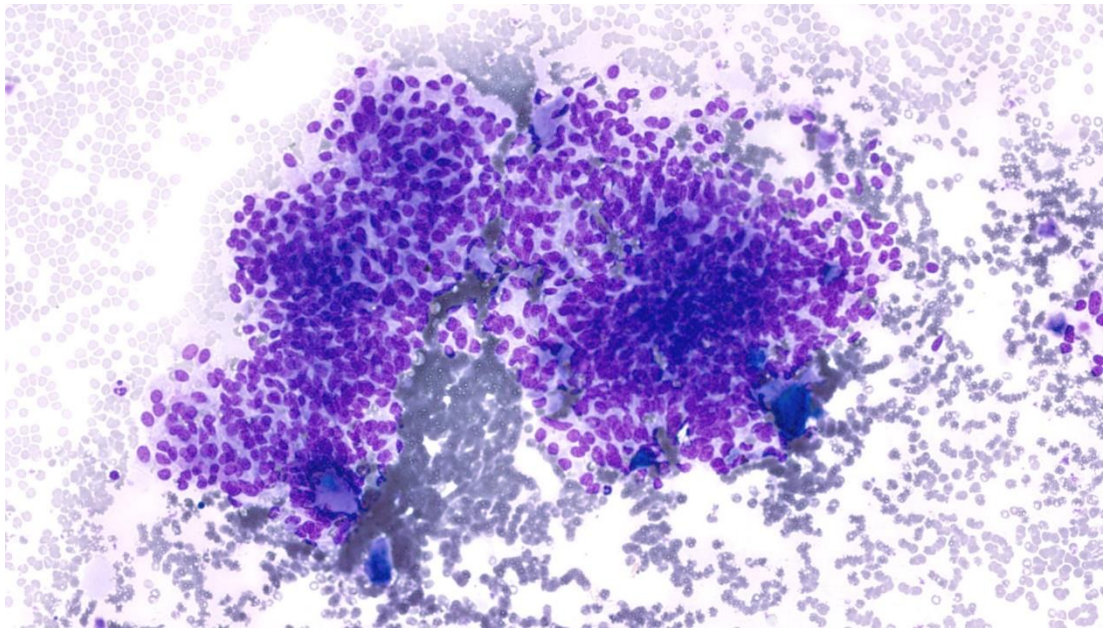
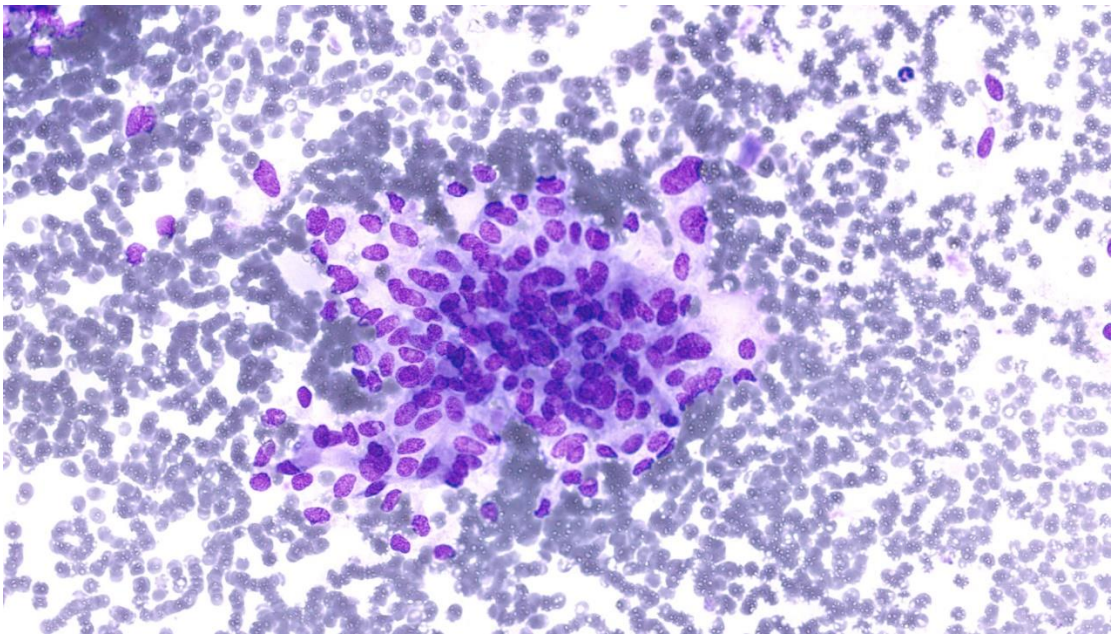
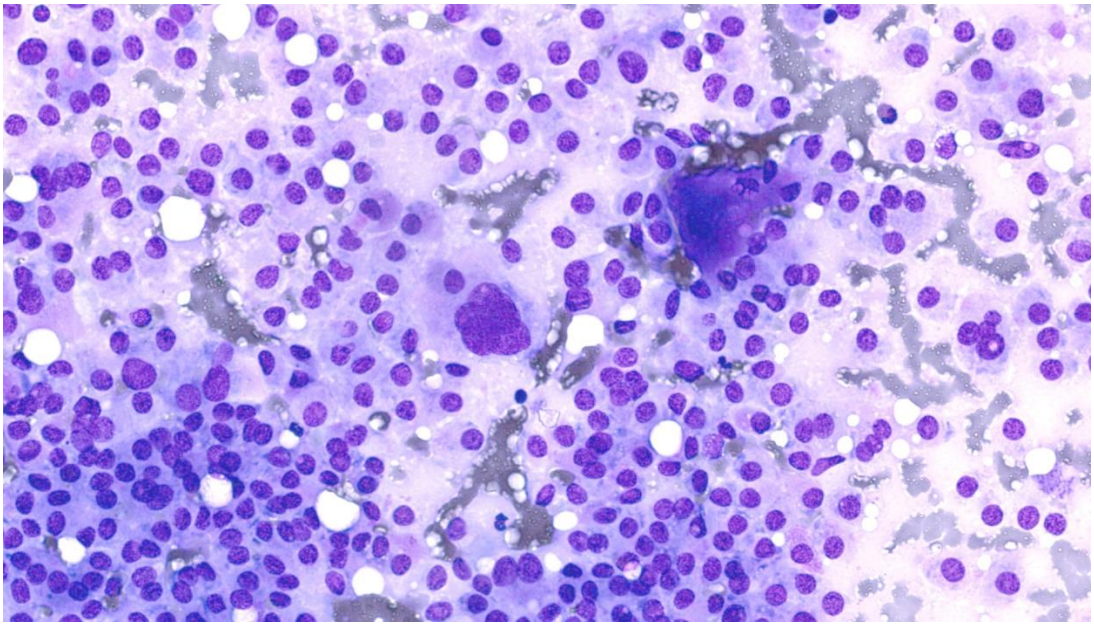
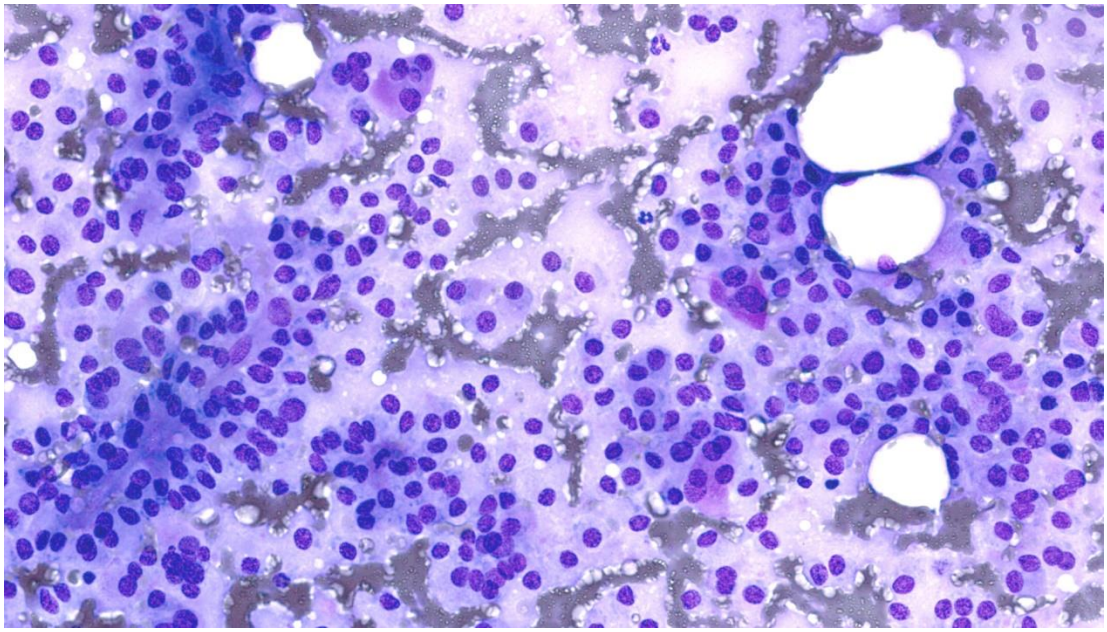


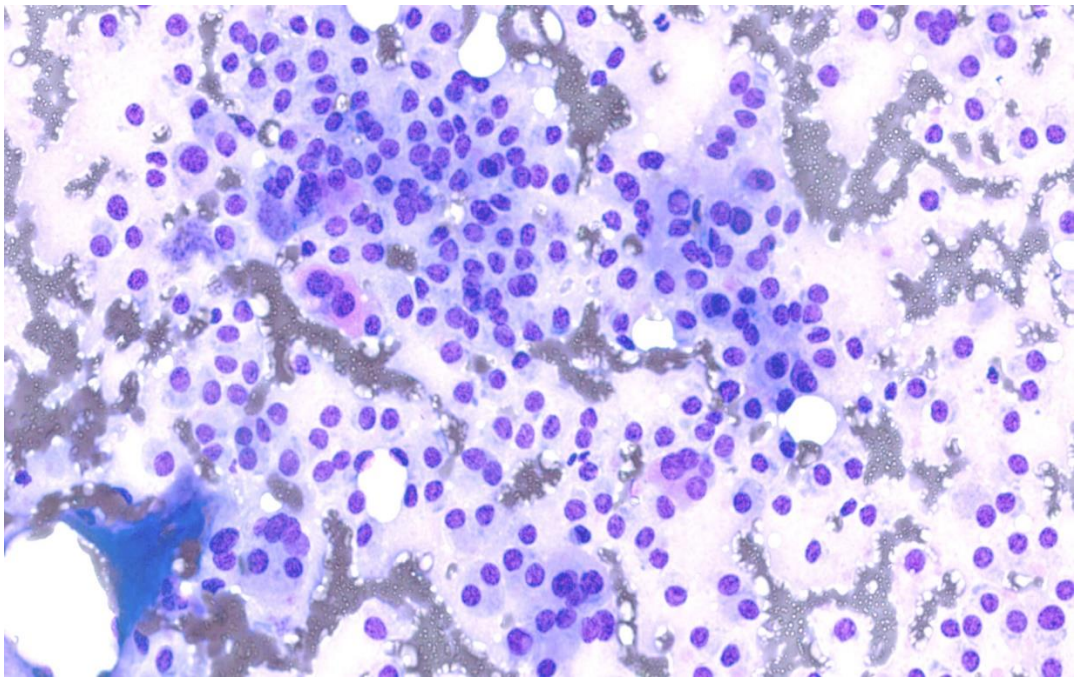


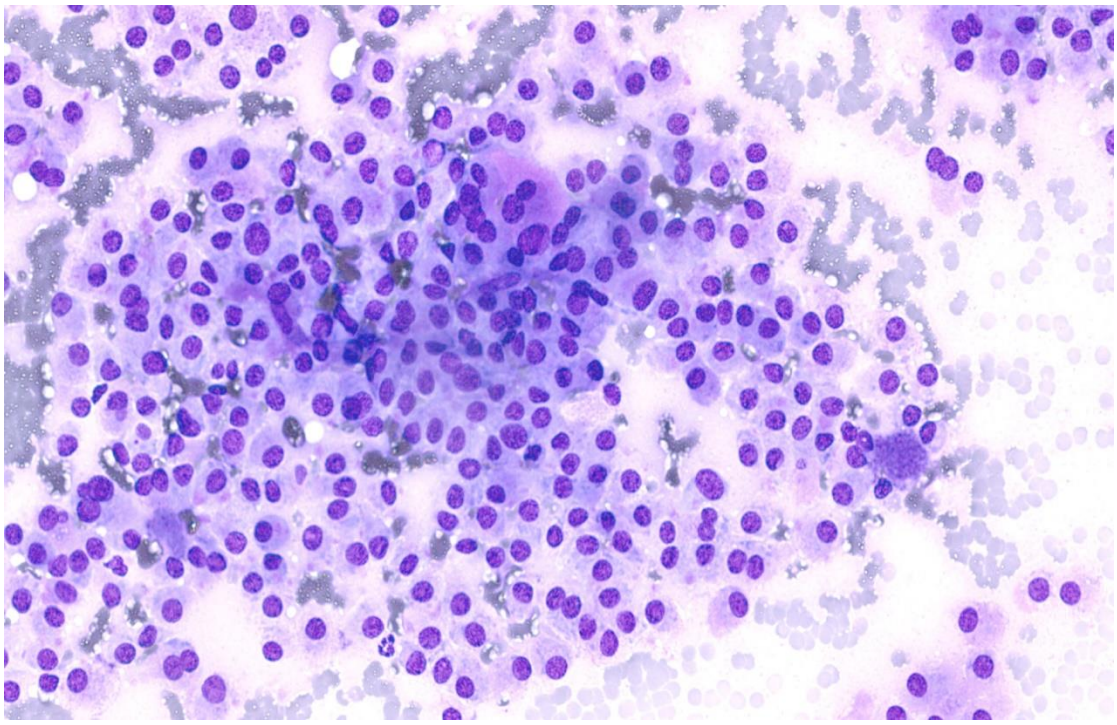


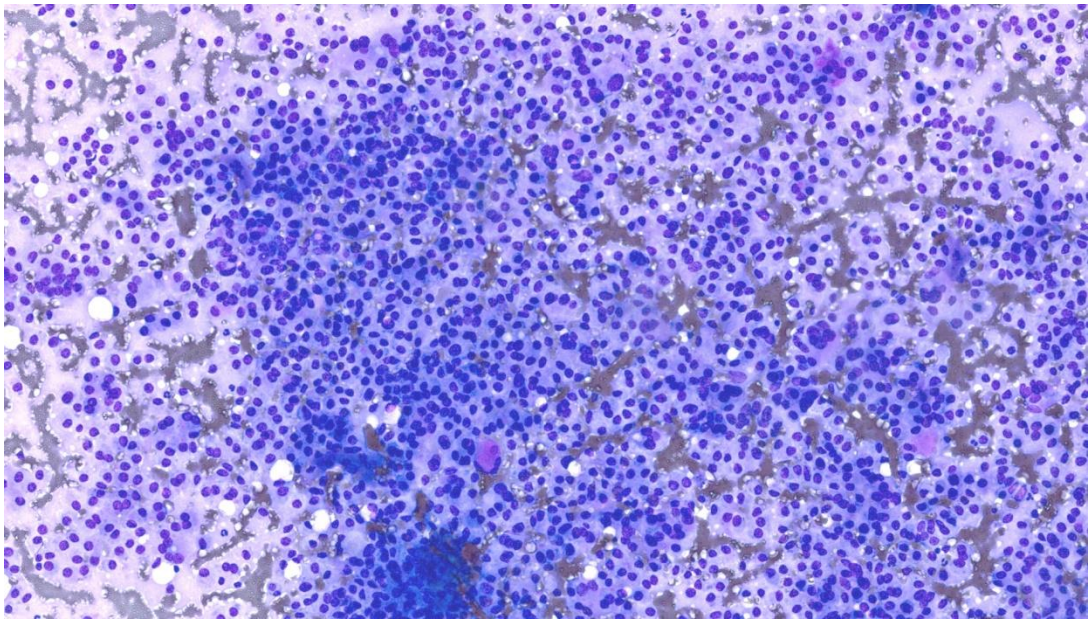


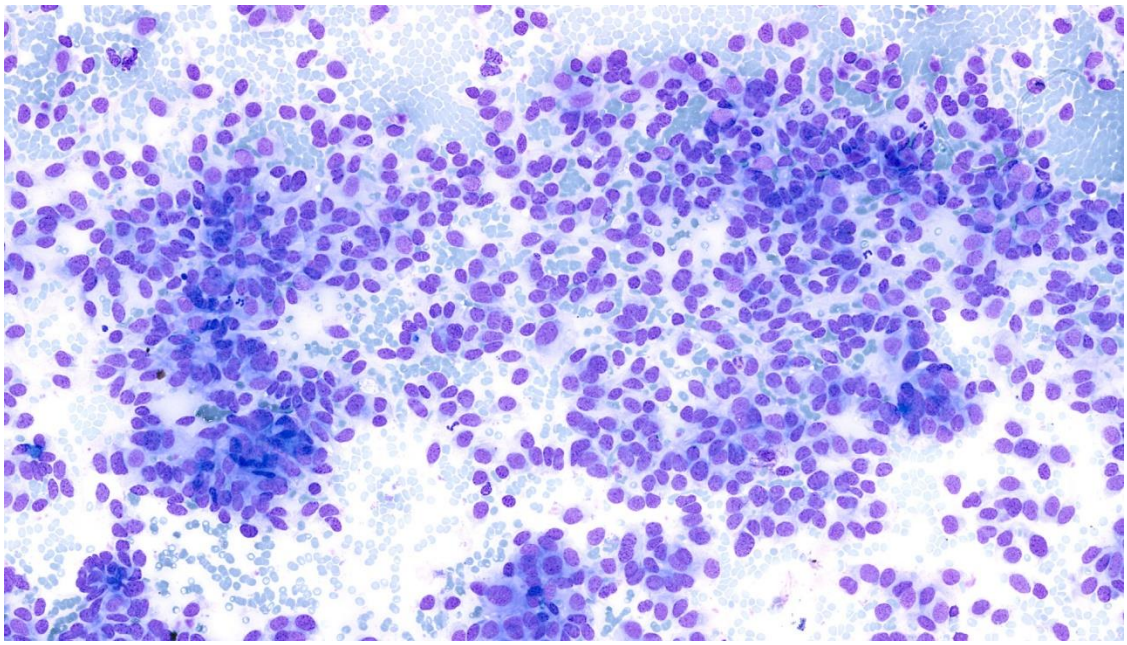


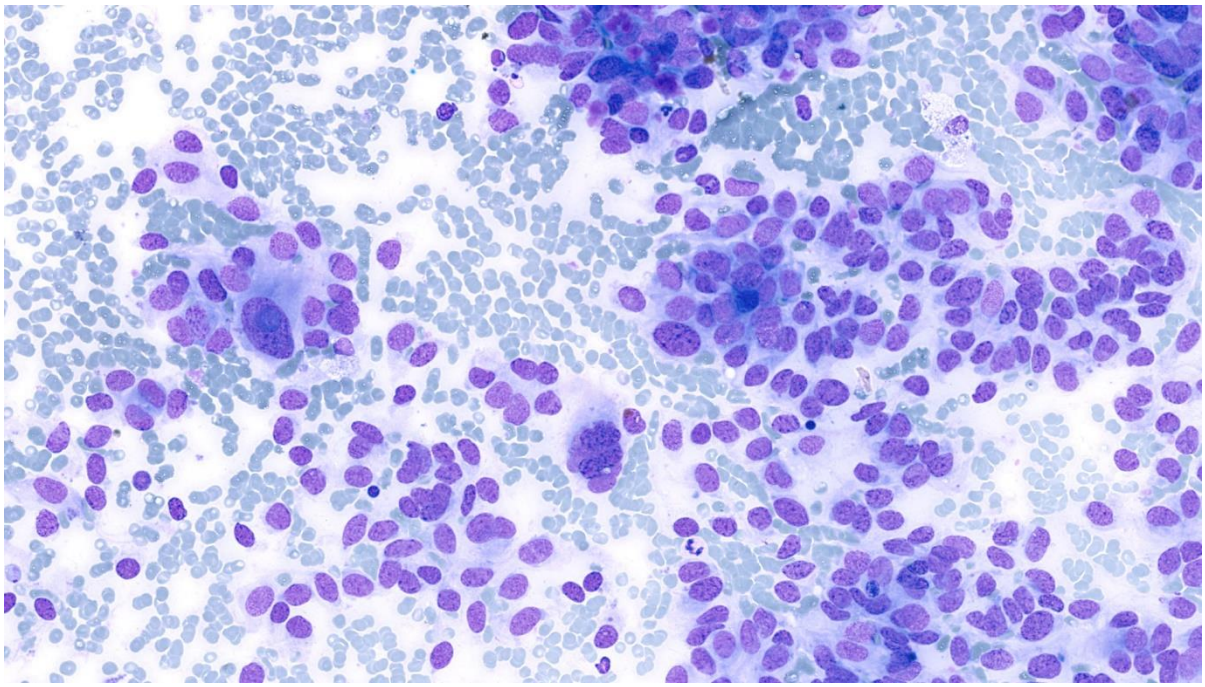


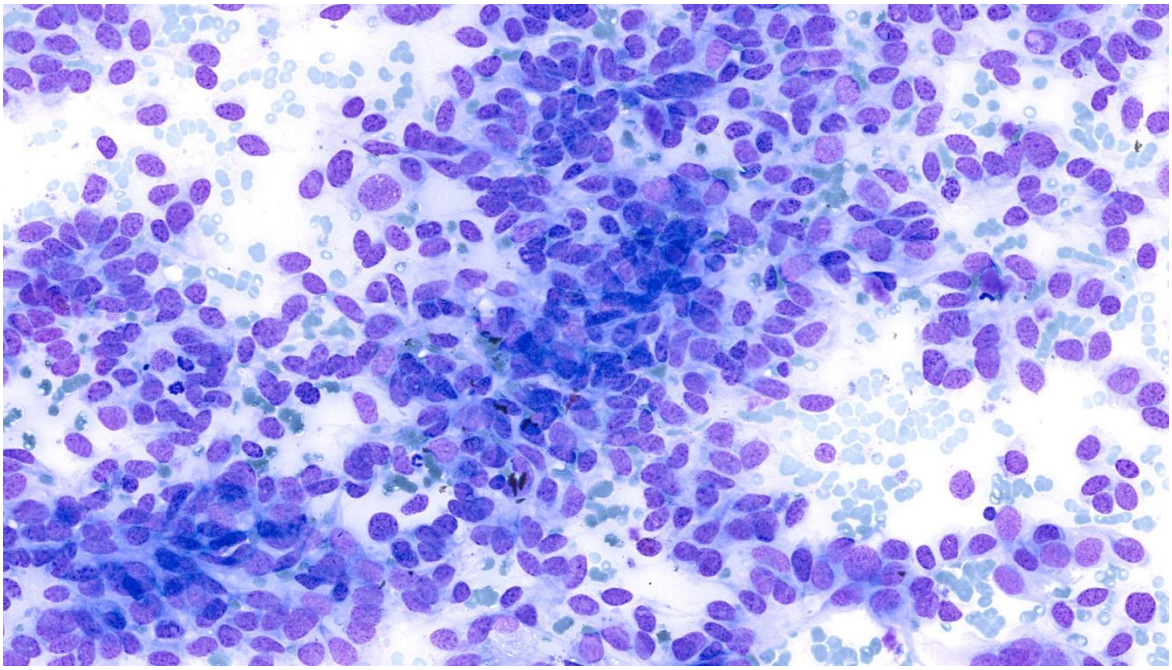












Dr Nalini Gupta

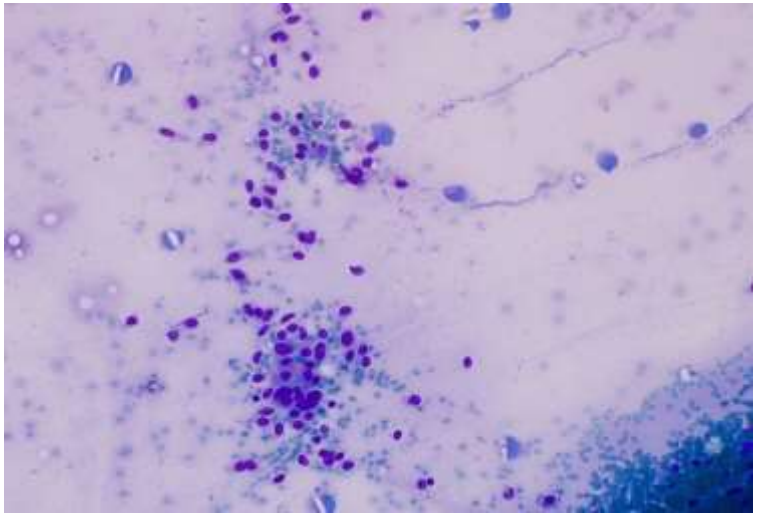
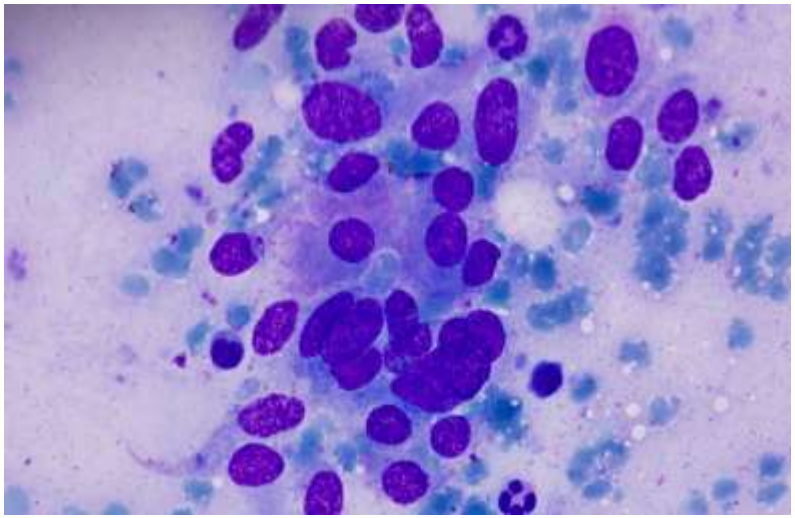
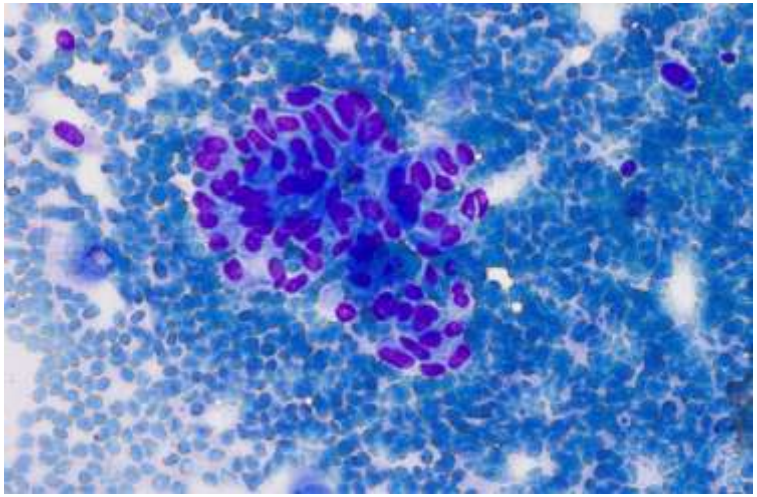
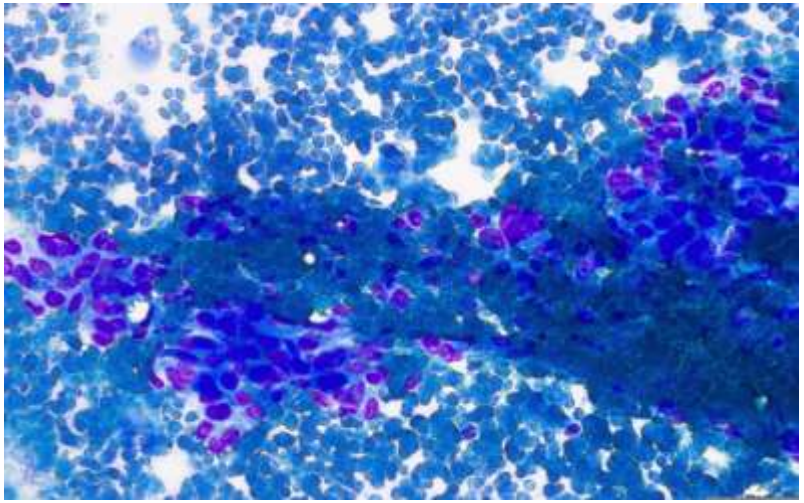
Professor

Department of Cytology and Gynaecologic Pathology

PGIME, Chandigarh

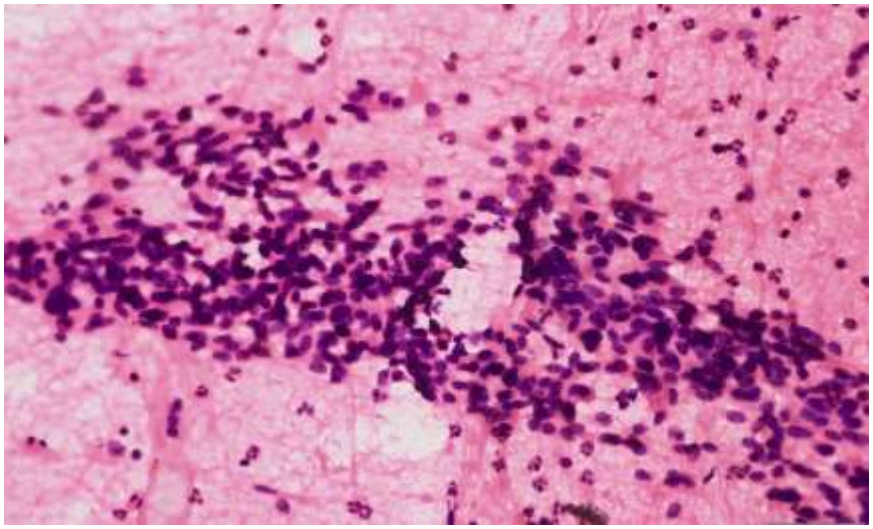
Medullary thyroid carcinoma

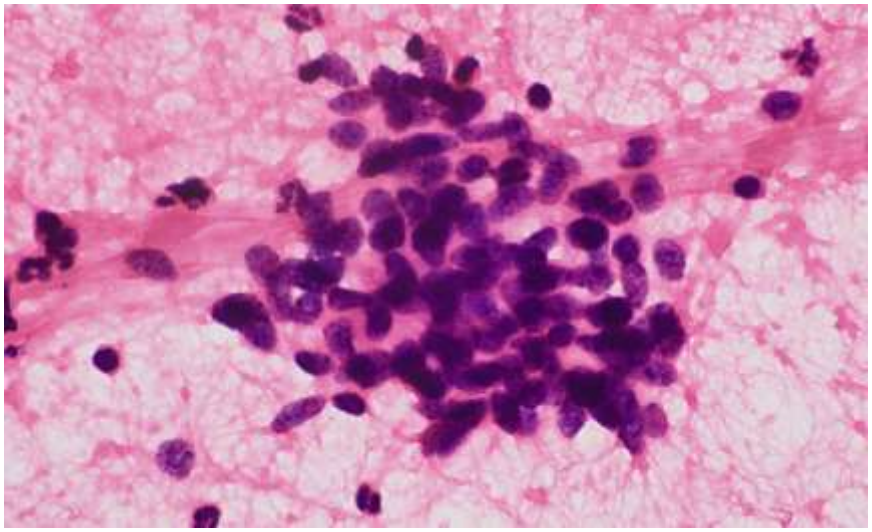
- Total cases of Medullary thyroid carcinoma from Jan 2023 [Primary/ Metastatic]: 30

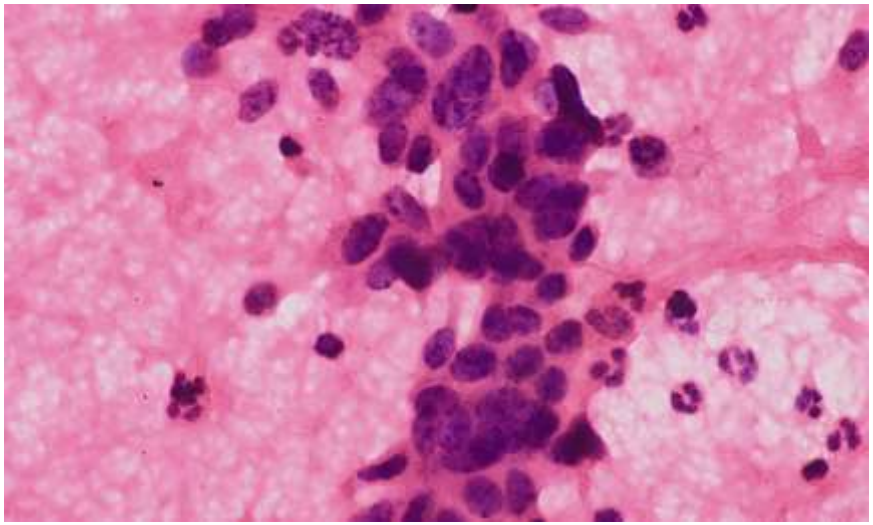





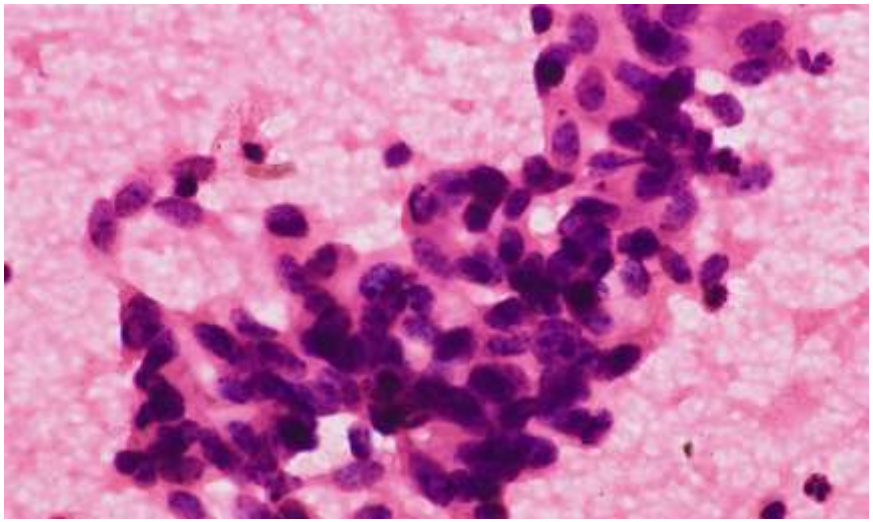
65 F with right thyroid swelling and right cervical lymph node

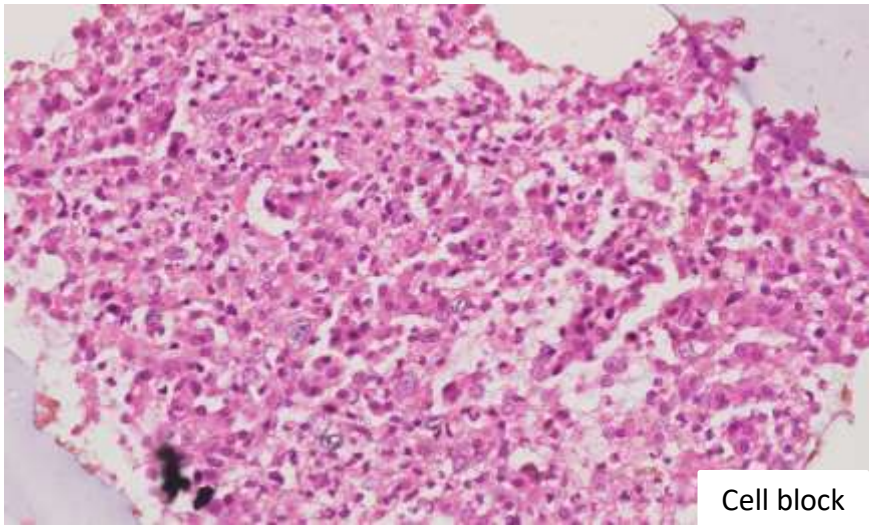
USG guided FNAC was done from both sites



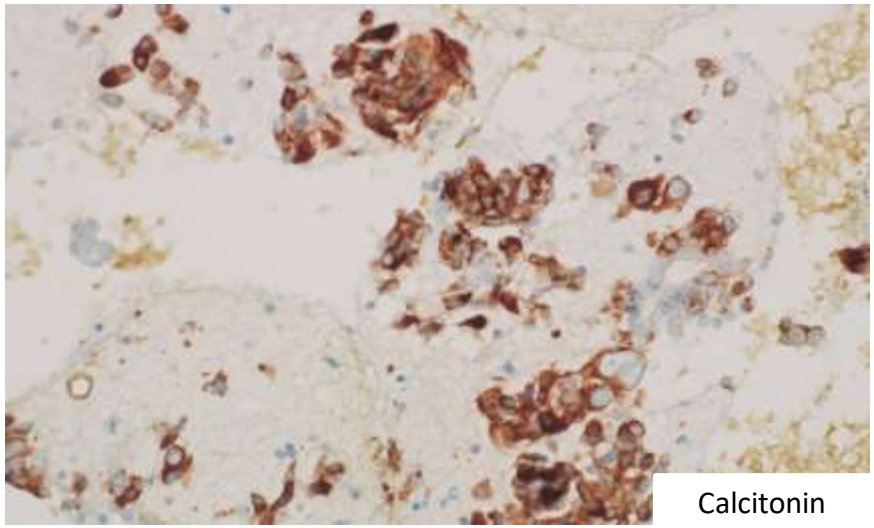




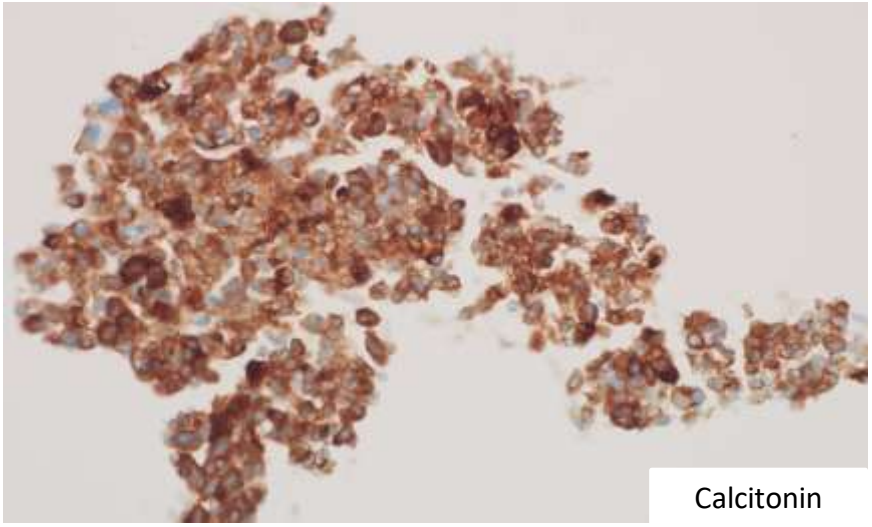




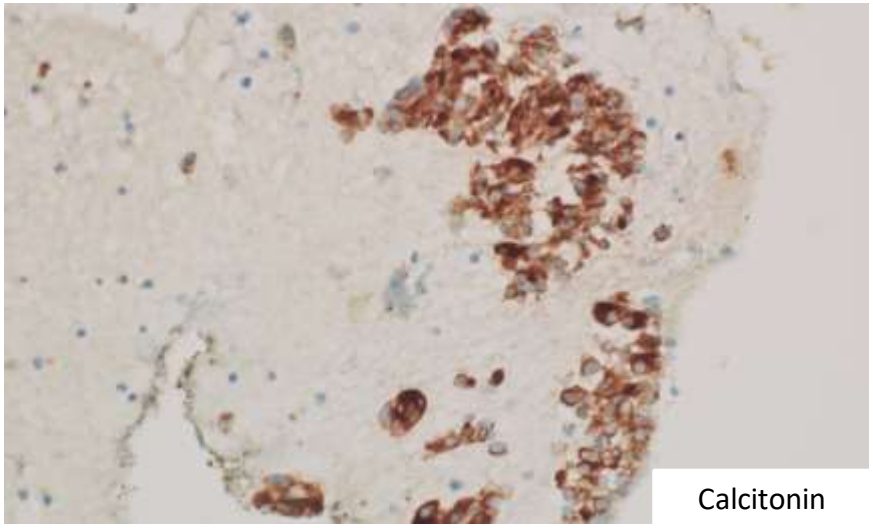
Cell block



Calcitonin



Calcitonin



Calcitonin

Medullary thyroid carcinoma

CLINICOPATHOLOGICAL CORRELATION

MEDULLARY THYROID CARCINOMA

DR SUNIDHI VERNEKAR

ENT

Patient presentation

- 55years old female

- Known case of bronchial asthma on treatment
- Presented in 2016 with H/O neck swelling for one year
  dysphagia
  loose motions and weight loss

- On neck examination 12 x 8 cm swelling in ant aspect of neck suggestive of thyroid swelling was noted.

- Oral cavity, oropharynx, indirect laryngoscopy normal

- Thyroid function test was within normal limits

- Neck ultrasonography was done which showed multiple nodules in right lobe of thyroid gland.
- FNAC was suggestive of ? Medullary thyroid carcinoma

- CT NECK was done to see for the extent of disease which revealed similar findings as the ultrasonography along with laryngotracheal compression.
- Serum Calcitonin levels **180 pg/ml**

Patient underwent total thyroidectomy with right MRND and central compartment neck dissection (level I-VI) in **April 2016.**

- HPE revealed **Medullary thyroid carcinoma with no Lymph nodal mets.**
- Patient had uncomplicated recovery and was started on thyroxine supplementation

- Serum calcitonin post op levels **2.9pg/ml**

Patient was counselled to go for gene testing for RET-oncogene, however patient did not do the testing.

- Following surgery, for two years patient was monitored with serial calcitonin levels which remained within normal limits.

- Later there was an increasing trend noted in serum calcitonin levels associated with episodes of intermittent stridor. Thus radiological imaging was repeated in 2021.

- **CT NECK** showed mass in right tracheoesophageal grove extending into mediastinum causing compression of trachea and another small lesion in the right carotid space.

- Patient underwent repeat surgery for excision of mediastinal lymph node recurrence in **November 2021**.
- HPE suggestive of medullary thyroid carcinoma.

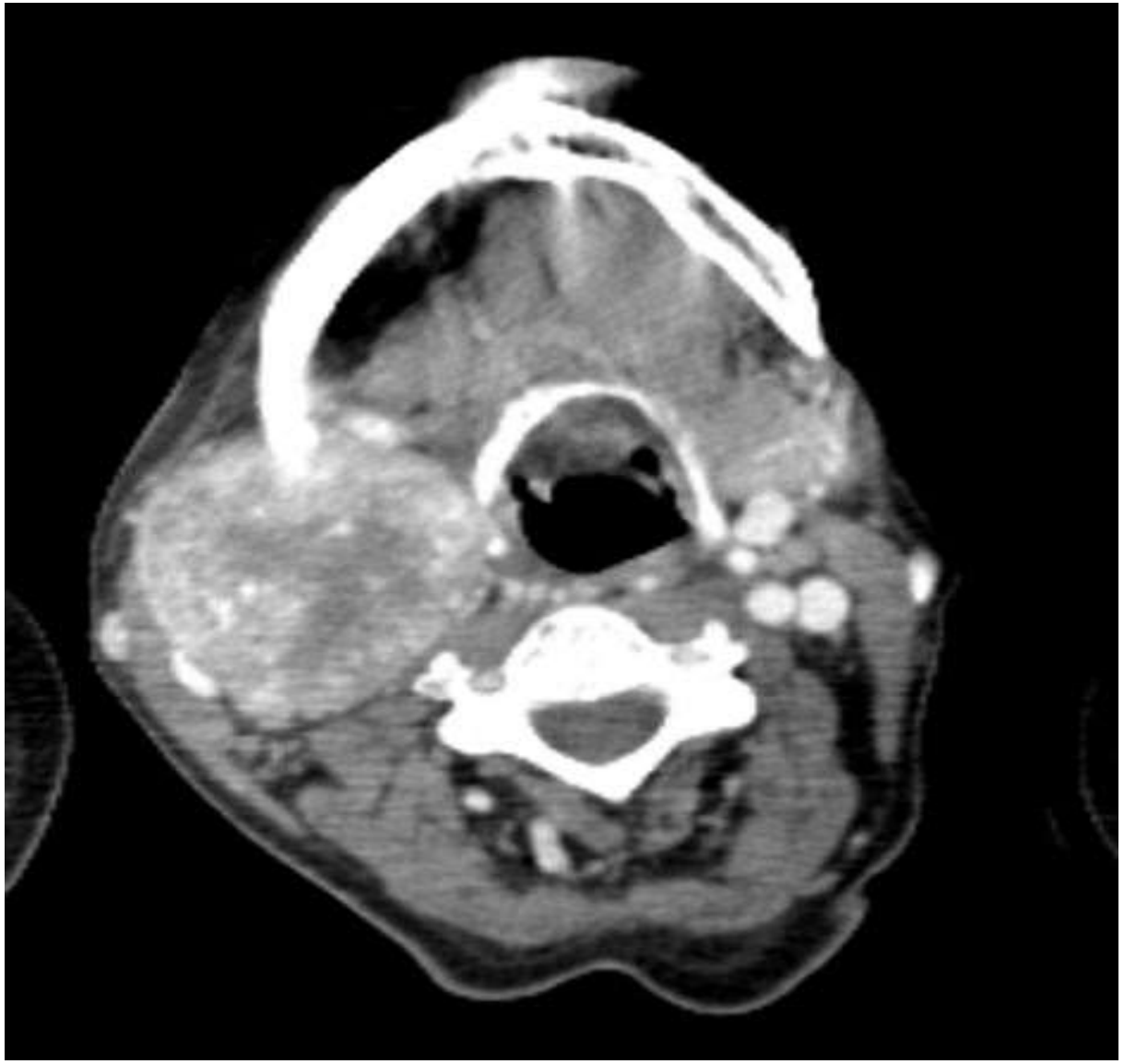
- Patient developed right RLN palsy and hypocalcaemia post surgery hypocalcaemia corrected with oral calcium.

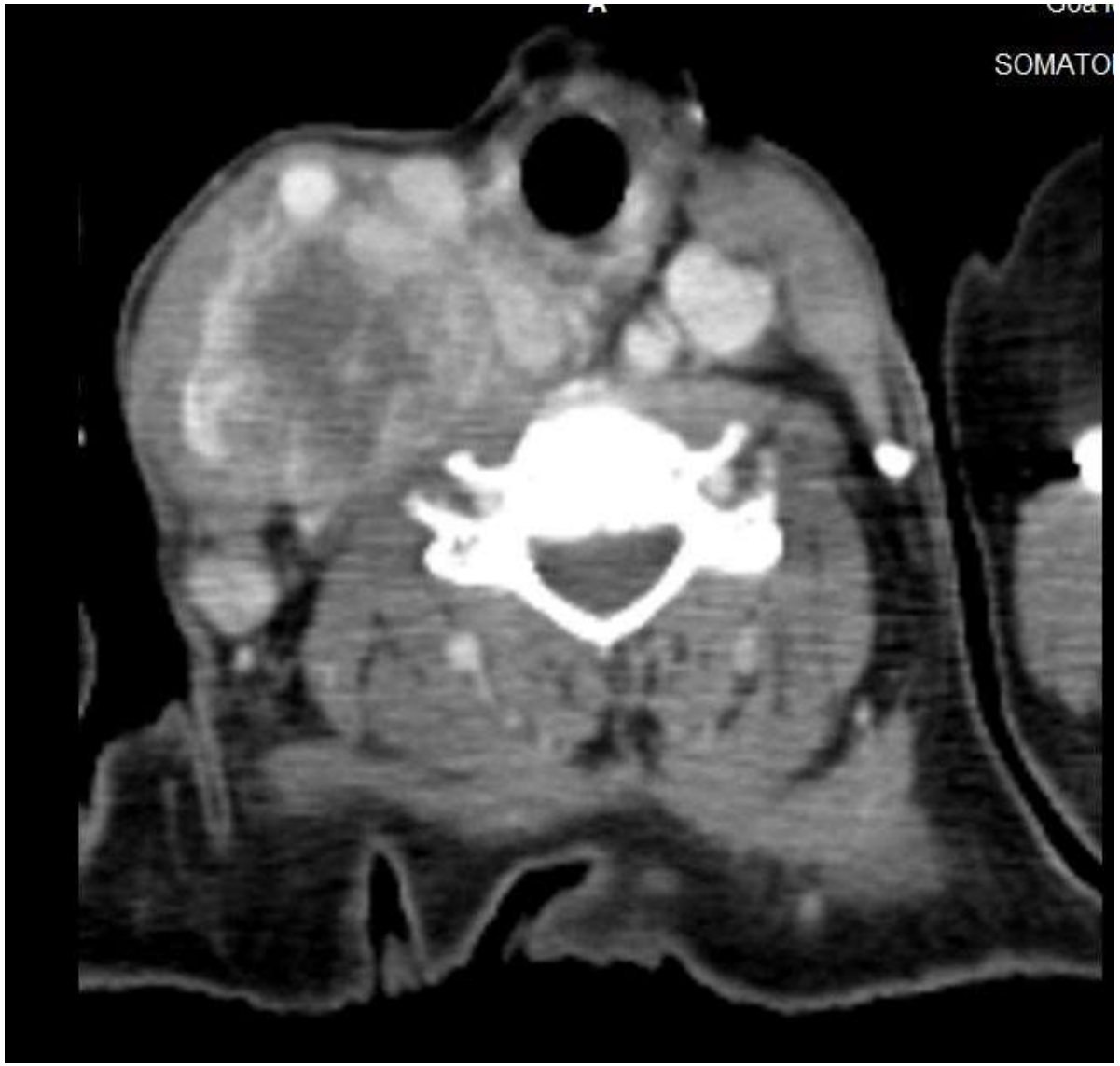
- Following this, patient was referred for External beam Radiotherapy (EBRT) in December 2021.
- Patient discontinued after 6 days of radiotherapy due to pain and generalised weakness.

- Around 6 months post op again rise in serum calcitonin was noticed
- Patient also started having H/O loose motions for few months
- On examination neck swelling was noted in the right level II region displacing the carotids anteriorly.

- Repeat CECT Neck, thorax and abdomen done in July 2022
- Showing recurrent mass in right carotid space and retropharyngeal lymph nodes.
- No evidence of distant mets noted.

- Patient was advised for repeat surgery for excision however she was not willing for surgery.




SOMATO

- Patient was being monitored with serial serum calcitonin levels last levels; **42 pg/ml.**

- Currently patient still has complaints of loose motions due to which she consented for repeat surgery.
- However due to derangement of the thyroid function test currently the surgery is delayed.

- Repeat CECT neck thorax abdomen done in may 2024 showed increase in size of the retropharyngeal lymph node and presence of lymphadenopathy in right paratracheal and paraesophageal region.

Medullary thyroid carcinoma (MTC)

- Rare malignant neuroendocrine tumour, comprising of 2-5%of all thyroid cancers.
- Sporadic form (75%) or hereditary form (25%)
- Hereditary form is autosomal dominant and part of multiple endocrine neoplasia MEN2A, 2B and familial MTC.
- Optimal preoperative workup followed by surgery is the mainstay

MEN 2A	MEN2B
Medullary Thyroid Carcinoma	Medullary Thyroid Carcinoma
Phaeochromocytoma	Phaeochromocytoma
Parathyroid tumours	Ganglioneuromatosis

- Serum markers:
- Serum calcitonin levels : normal values <5 pg/ml for females

  <8.5 pg/ml for males
- > 500pg/ml is highly indicative of distant metastasis.

- Genetic Testing : RET proto-oncogene mutation
- If index patient has RET mutation then genetic counselling and appropriate screening of family members should be considered.
- The individuals who come RET positive can be given an option of prophylactic thyroidectomy.
- Surgery depending on risk levels and codon
- Highest risk , codon 918 surgery within first 6 months of age
- High risk codon 634 surgery around 5 years of age

- Medullary thyroid carcinoma is a tumour arising from parafollicular C-cells which secrete calcitonin and not from the thyroid follicular cells.
- The disease is often bilateral and multifocal especially in inherited diseases, thus total thyroidectomy is a recommended in all preoperatively established MTC's.
- Management of regional nodes is done by appropriate form of neck dissection.

- The clearance needs to be more aggressive as in these Radioactive Iodine (RAI) cannot be given as an adjuvant treatment as RAI works on cancers arising from follicular cells which have the Na-I symporter.

- For recurrent diseases surgery remains the mainstay treatment.
- External Beam Radiotherapy is considered for unresectable and painful bone mets.

Systemic treatment

Vandetanib or cabozatinib (kinase inhibitors) are indicated in symptomatic, progressive and non resectable diseases.

Conventional chemotherapy with Dacarbazine or combination therapy is used in refractory cases.

Newer drugs like specific RET inhibitors like sepercatinib and pralsetinib have promising benefits in RET positive cases.

MEDULLARY CARCINOMA OF THYROID

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Chairman International Affairs Committee of IAC
India's Representative to International Academy of Cytology and EFCS(European Federation of Cytology Societies)

GROSS

- Sporadic: Usually presents as a solitary nodule, not Encapsulated, Greyish tan mass.
- Familial: Bilateral/ Multiple Foci
- Solid, Tan-grey-yellow, May be infiltrative
- Larger tumours have areas of hemorrhage and necrosis most commonly in the upper or middle portion due to higher concentration of Parafollicular C Cells.

Microscopy

- Round, Plasmacytoid, Polygonal or Spindle shaped cells arranged nests, cords or follicles.
- Nuclei are round with finely stippled to coarsely clumped chromatin with indistinct nucleoli.
- Sometimes pseudoinclusions may be present
- Cytoplasm is eosinophillic to amphophillic due to secretory granules present.

Microscopy

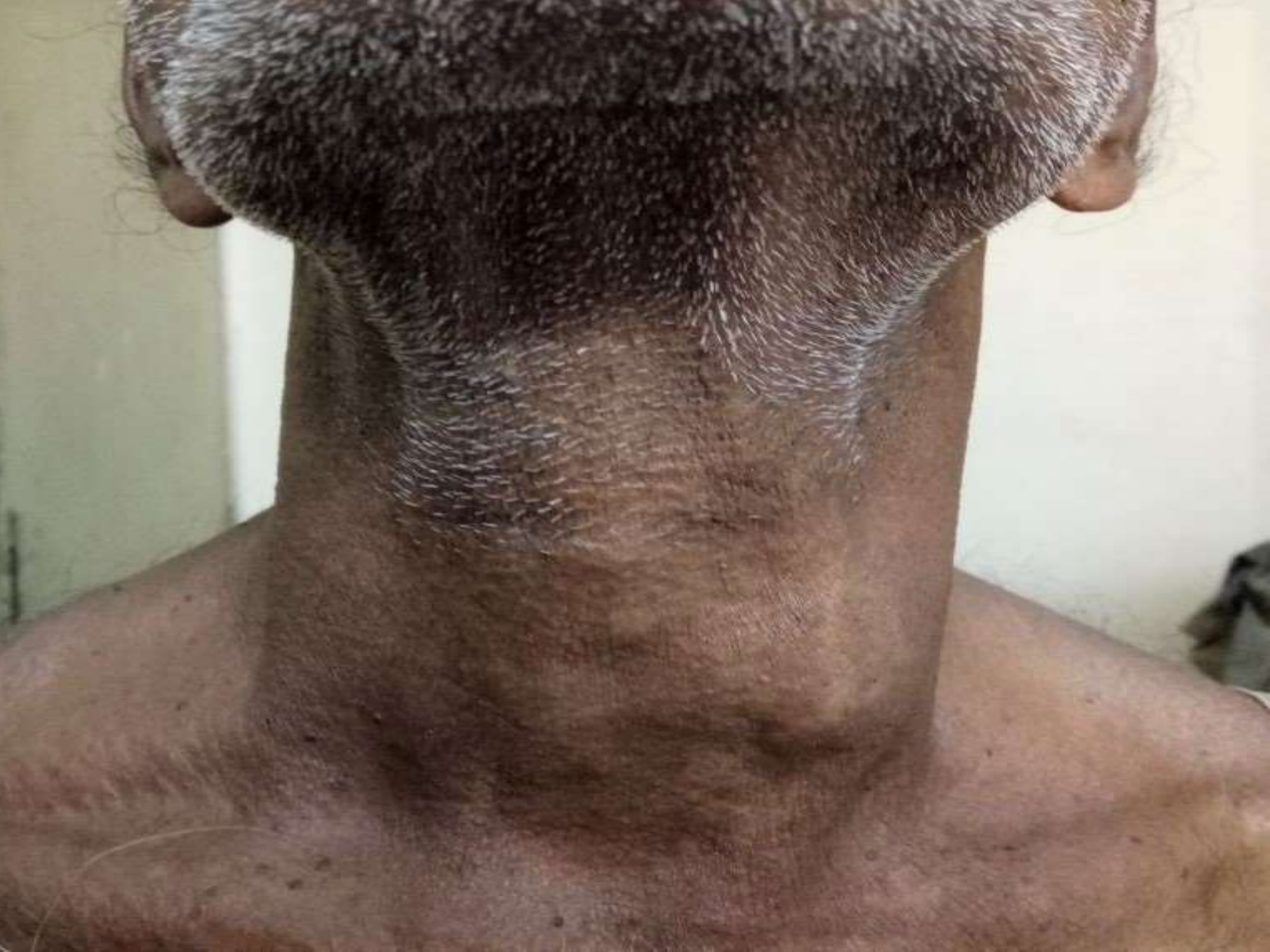
- Amyloid deposits in the stroma is seen due to calcitonin deposition.
- Prominent vascularity with glomeruloid configuration and occasional psammoma bodies may be seen.
- Neutrophilic infiltration, Oncocytic cells, Papillary pattern may be seen occasionally.
- Mucin(42%)
- C cell hyperplasia(Familial variant)

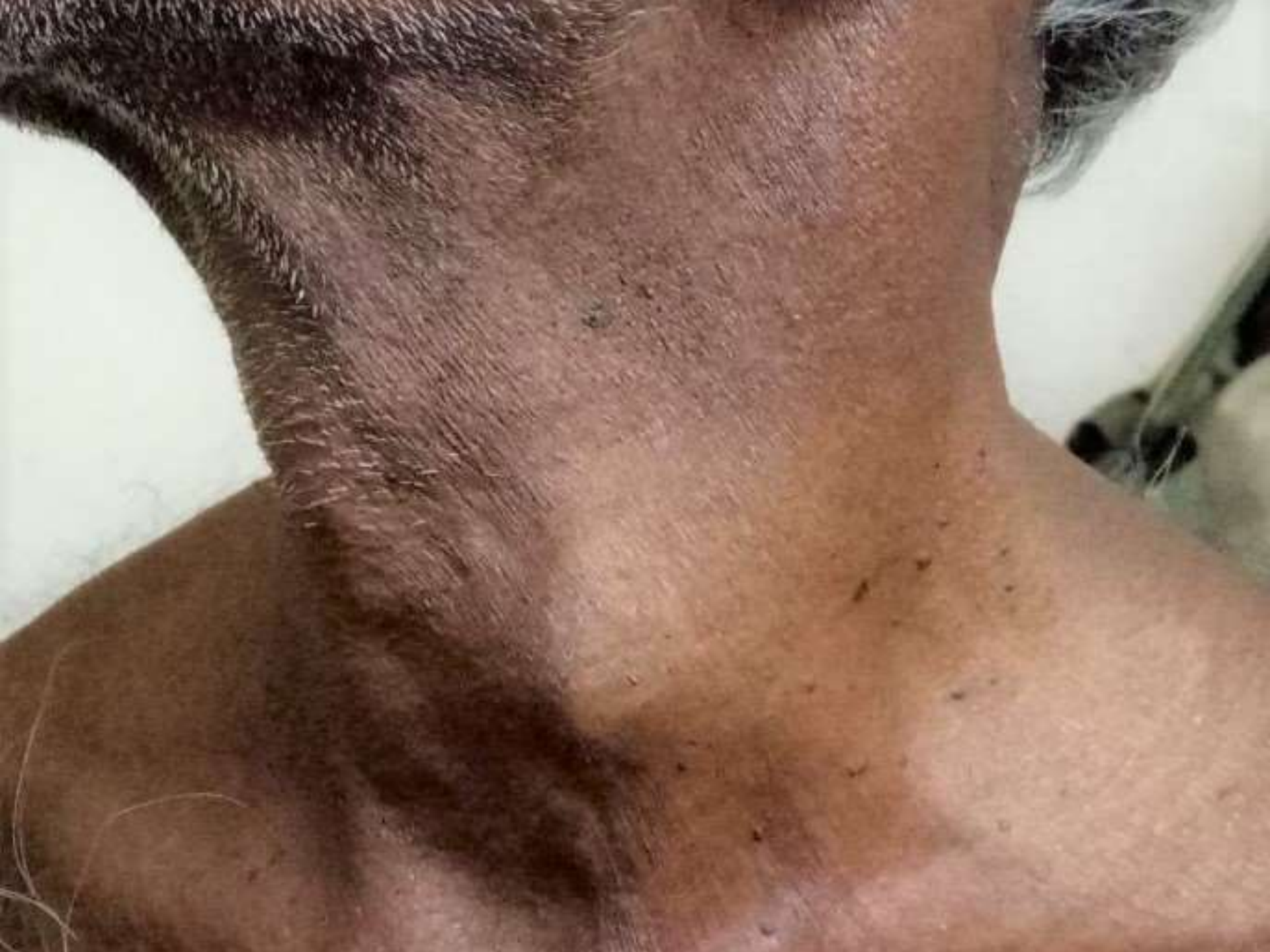
Medullary Carcinoma Thyroid

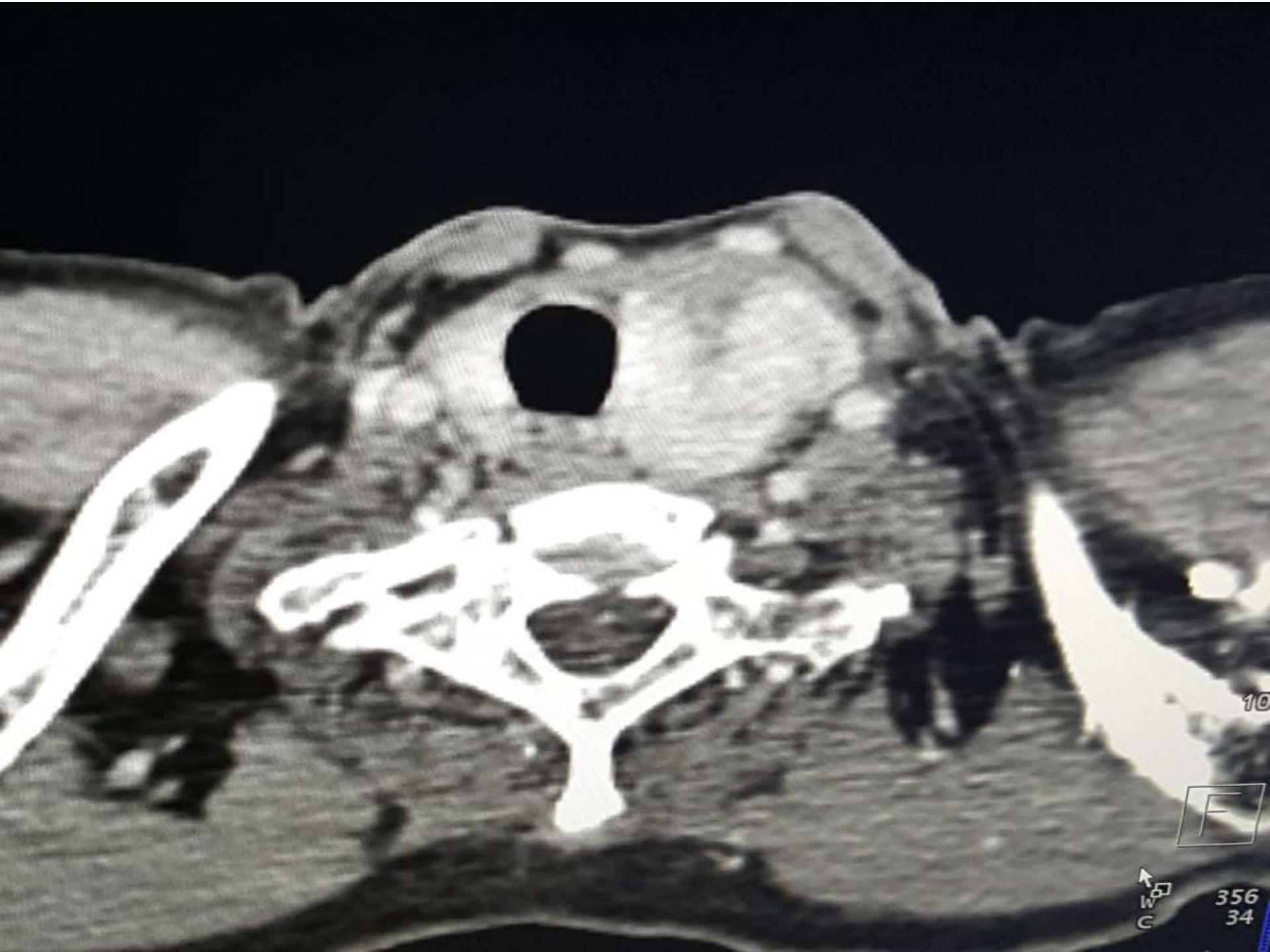
- Glandular/ Follicular/ Tubular
- Oxyphilic
- Giant cells (Anaplastic)
- Clear Cells
- Spindle Cells
- Pigmented- melanin
- Squamous
- Papillae
- Small Cell Carcinoid
- Paraganglioma like: May have melanin
- Microcarcinoma: Presents with Metastatic disease with Systemic symptoms, Amyloid, Desmoplatic Stroma. Poor Prognosis.

1st Case

- 69 yr old male who presented with Solitary Thyroid nodule.



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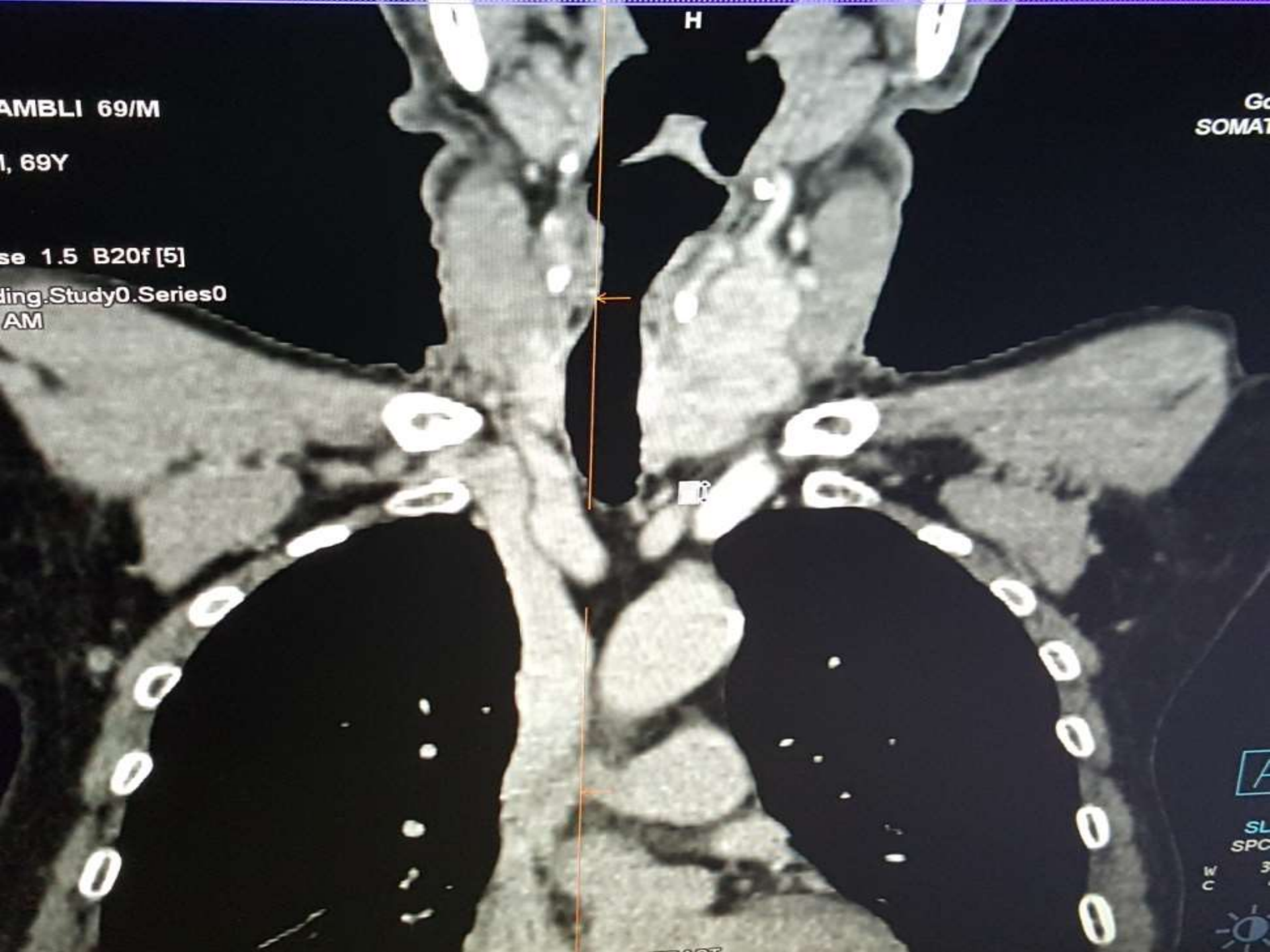
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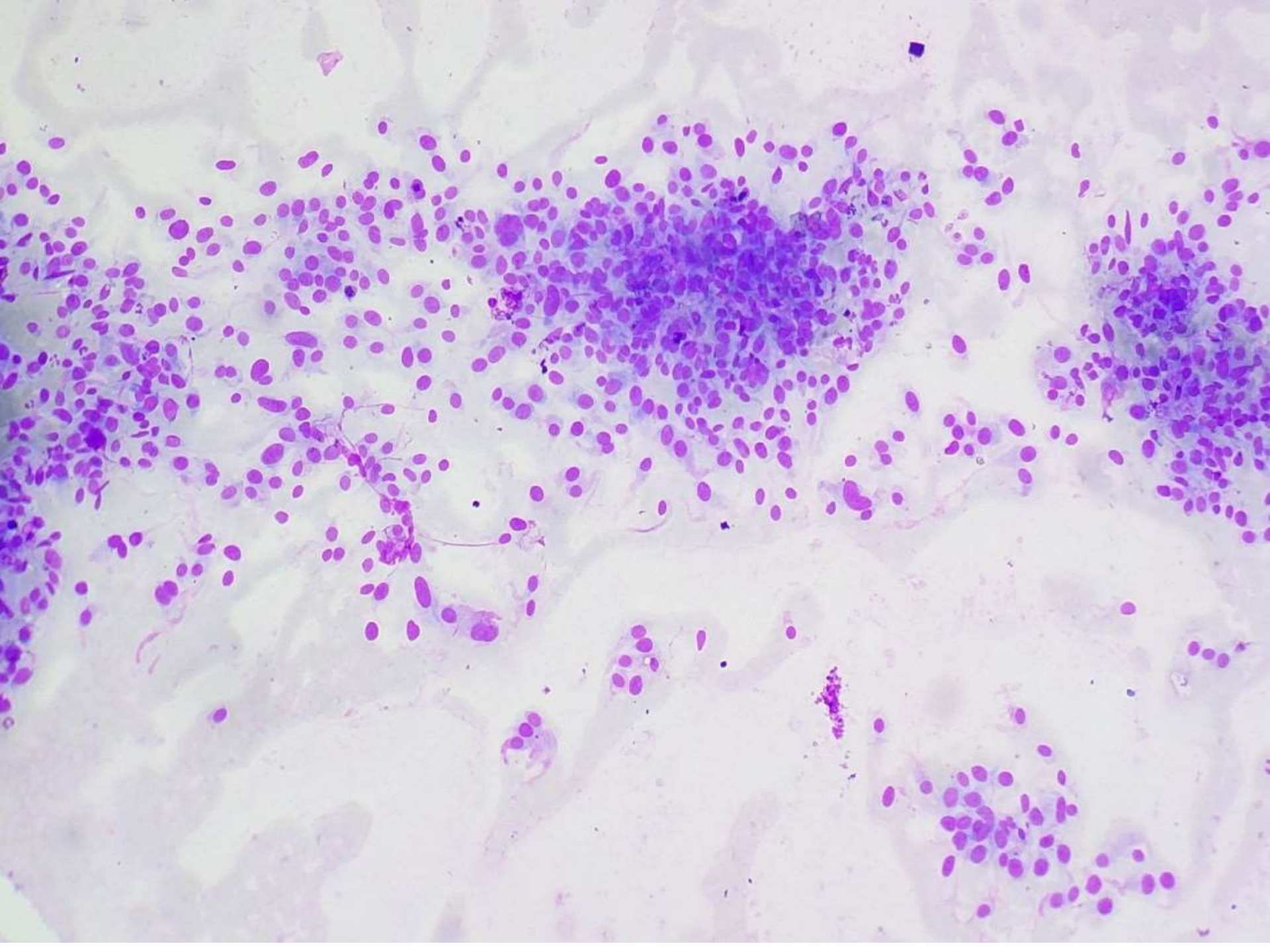
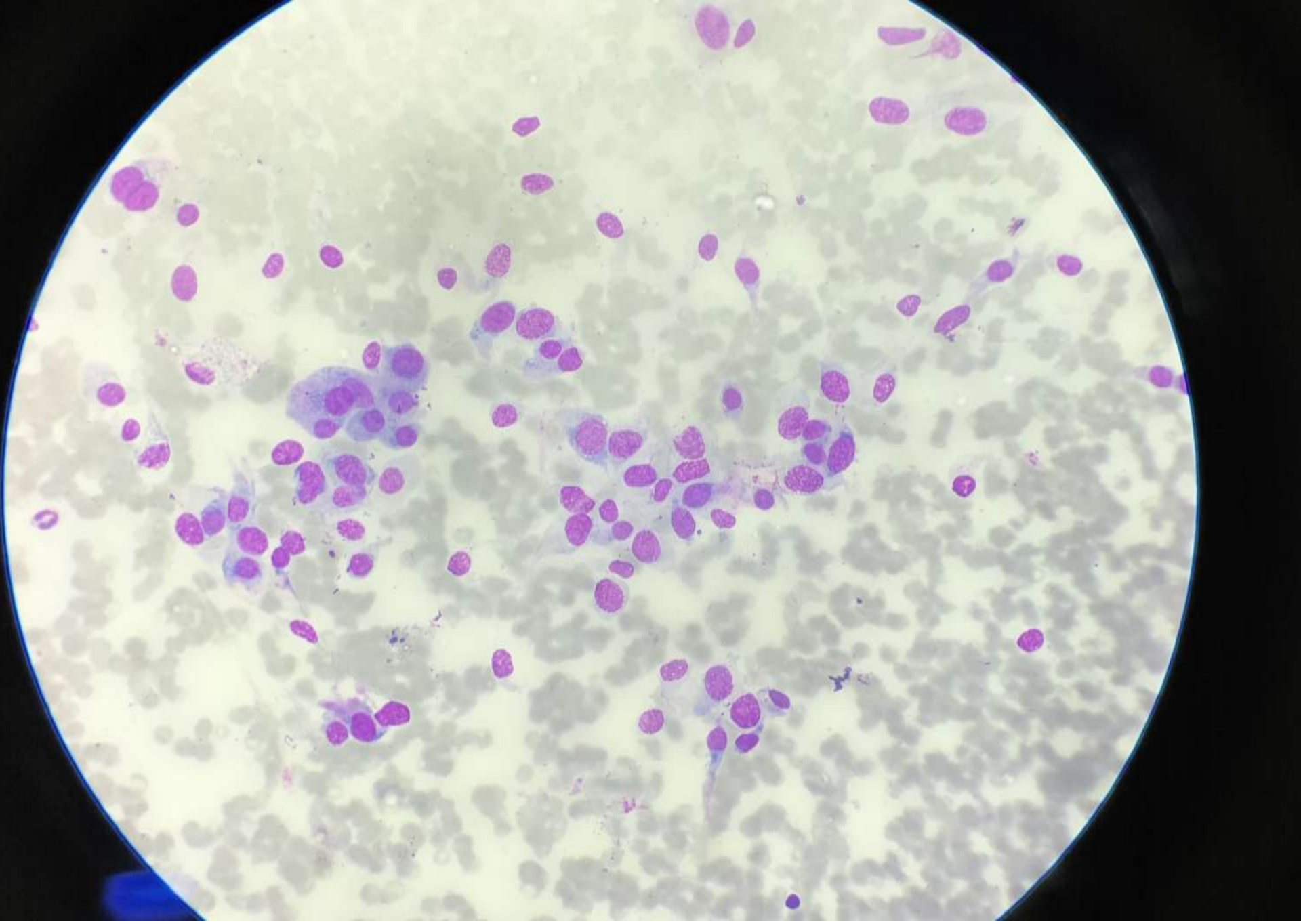
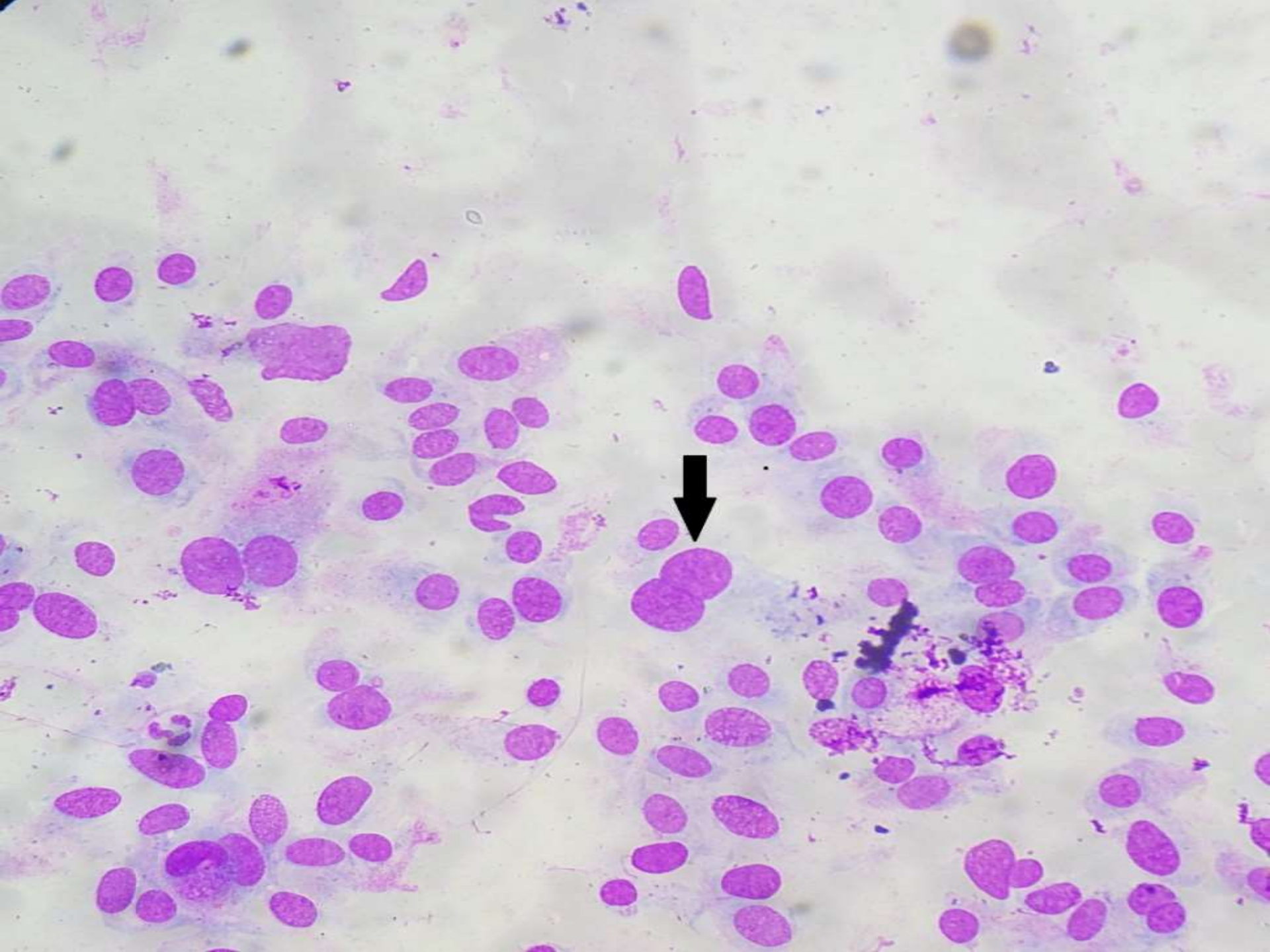
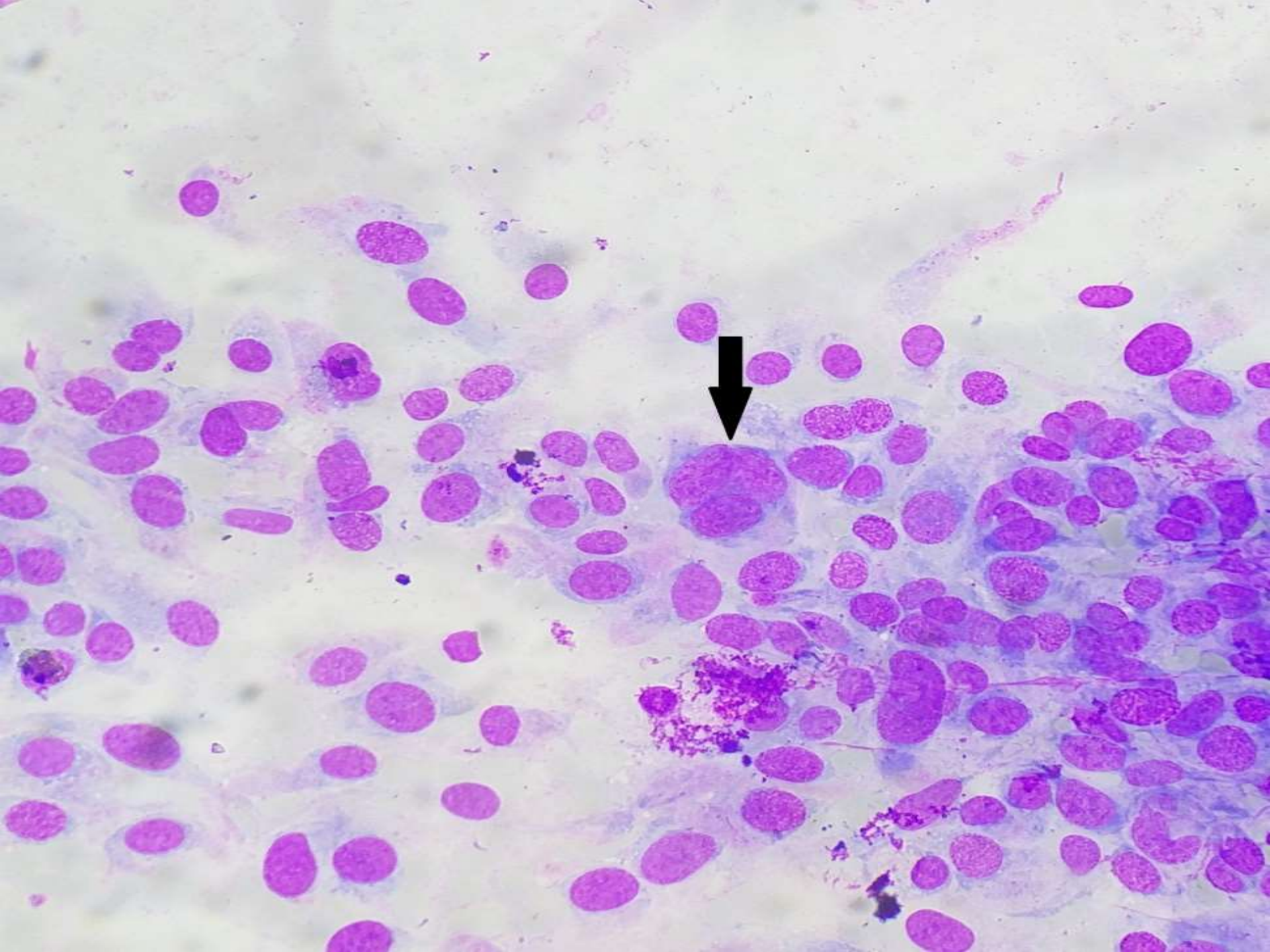
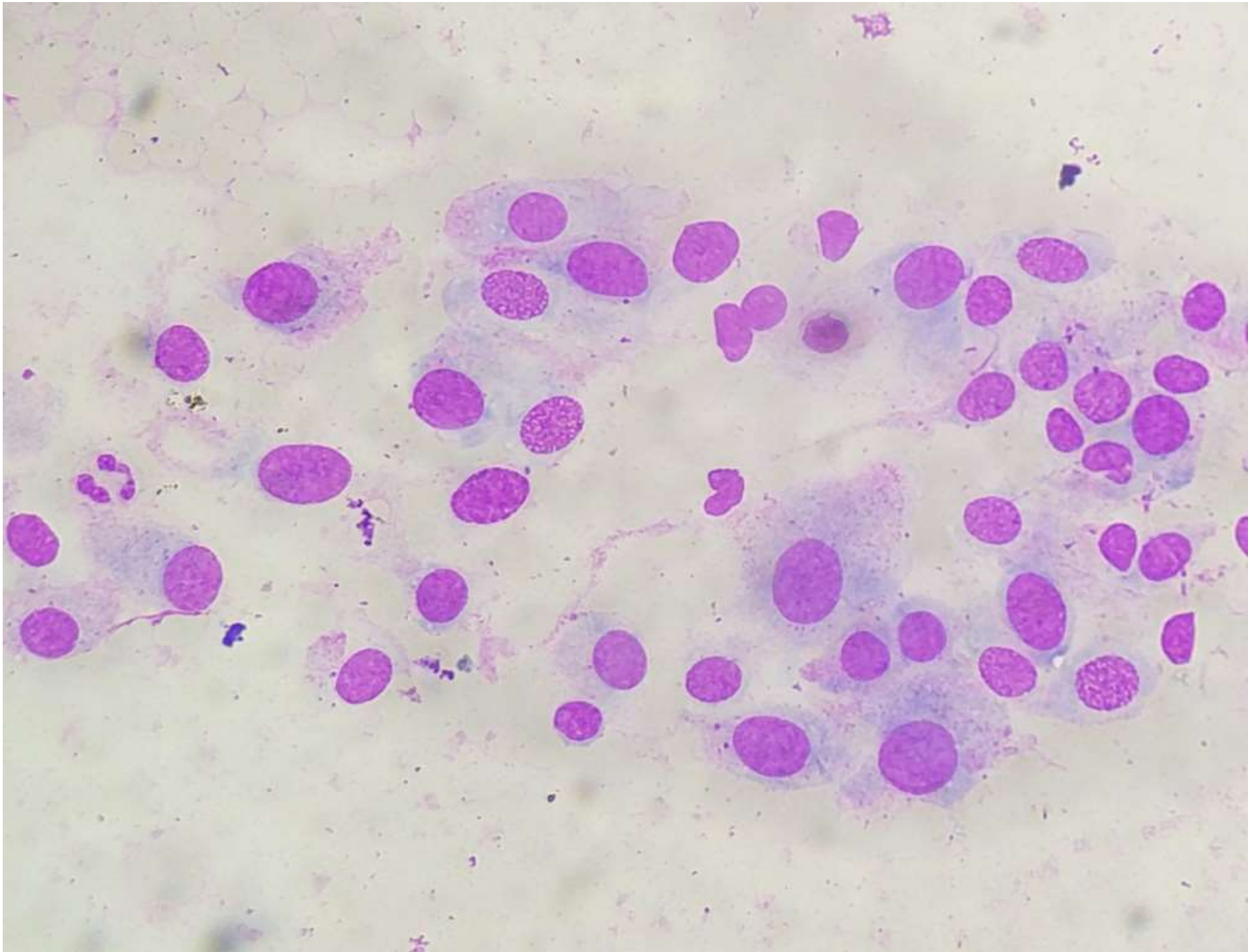
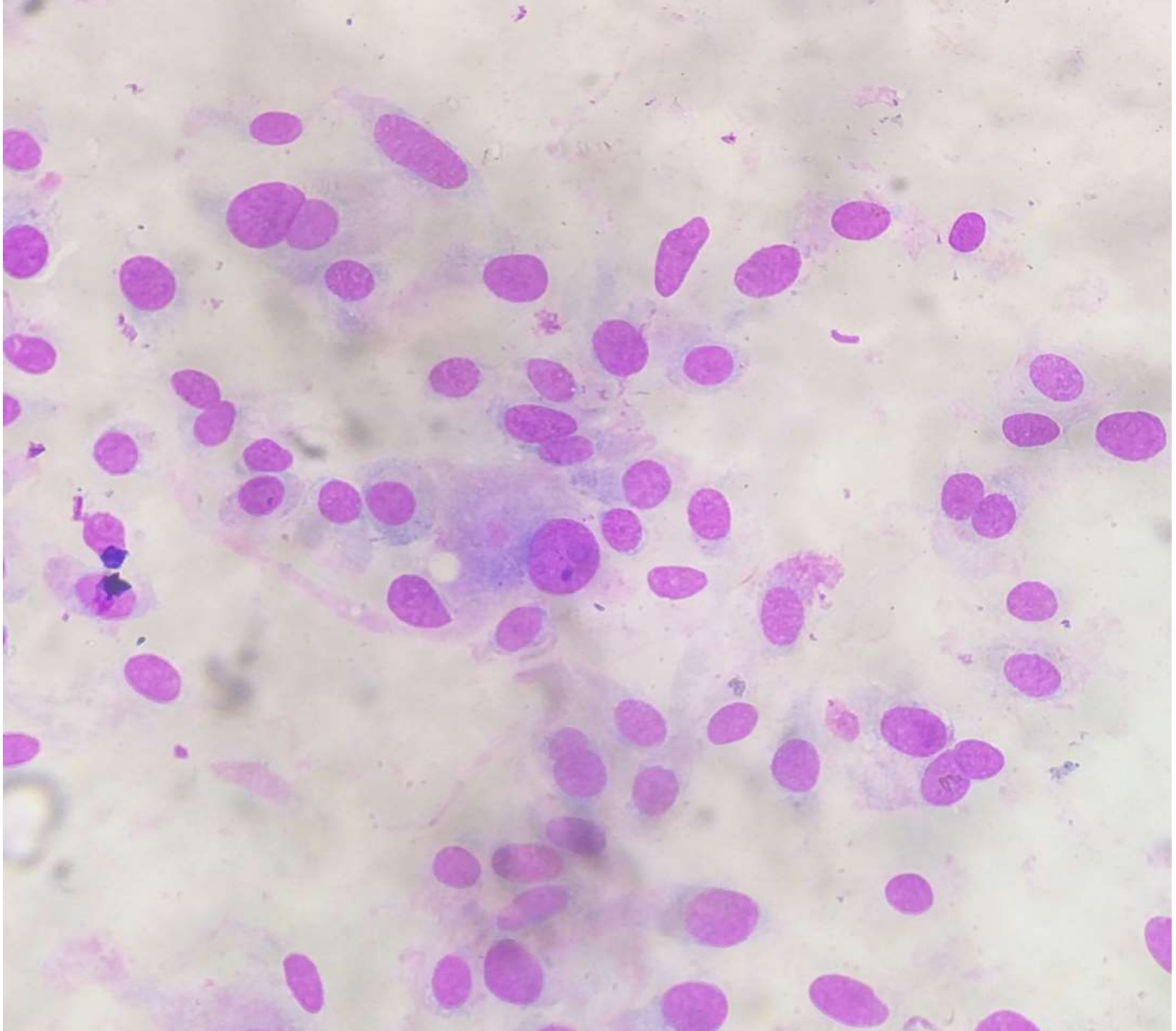


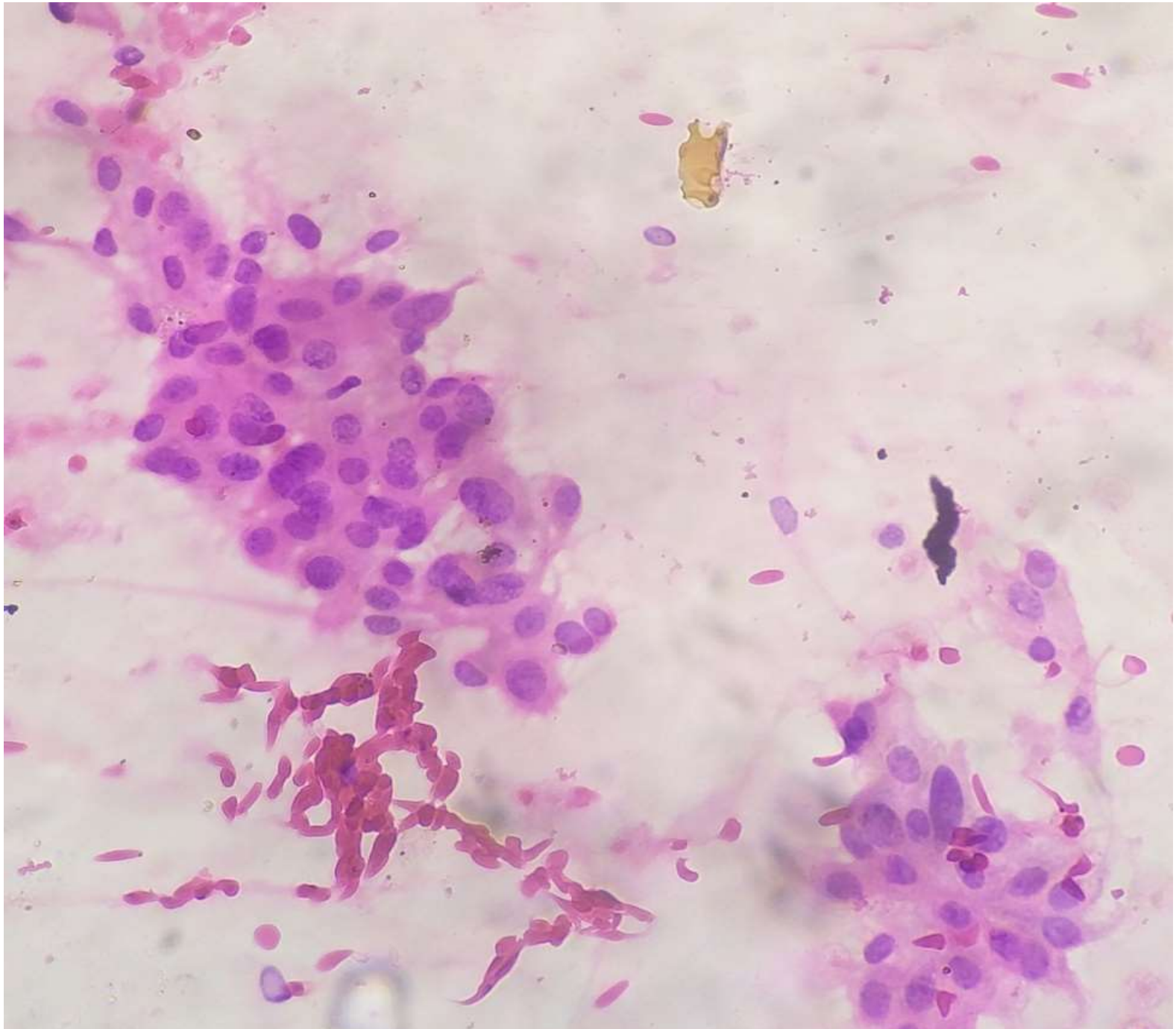


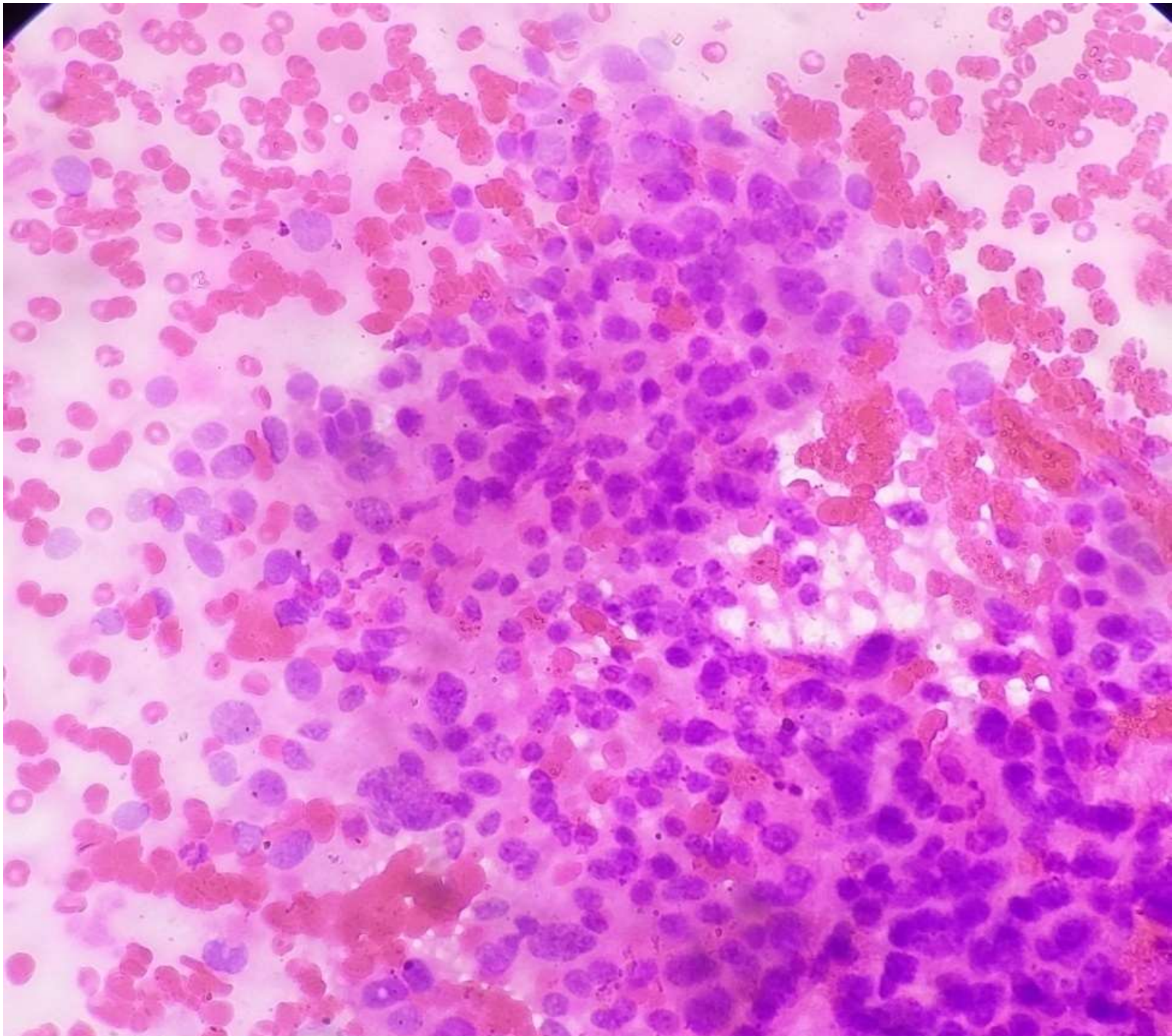


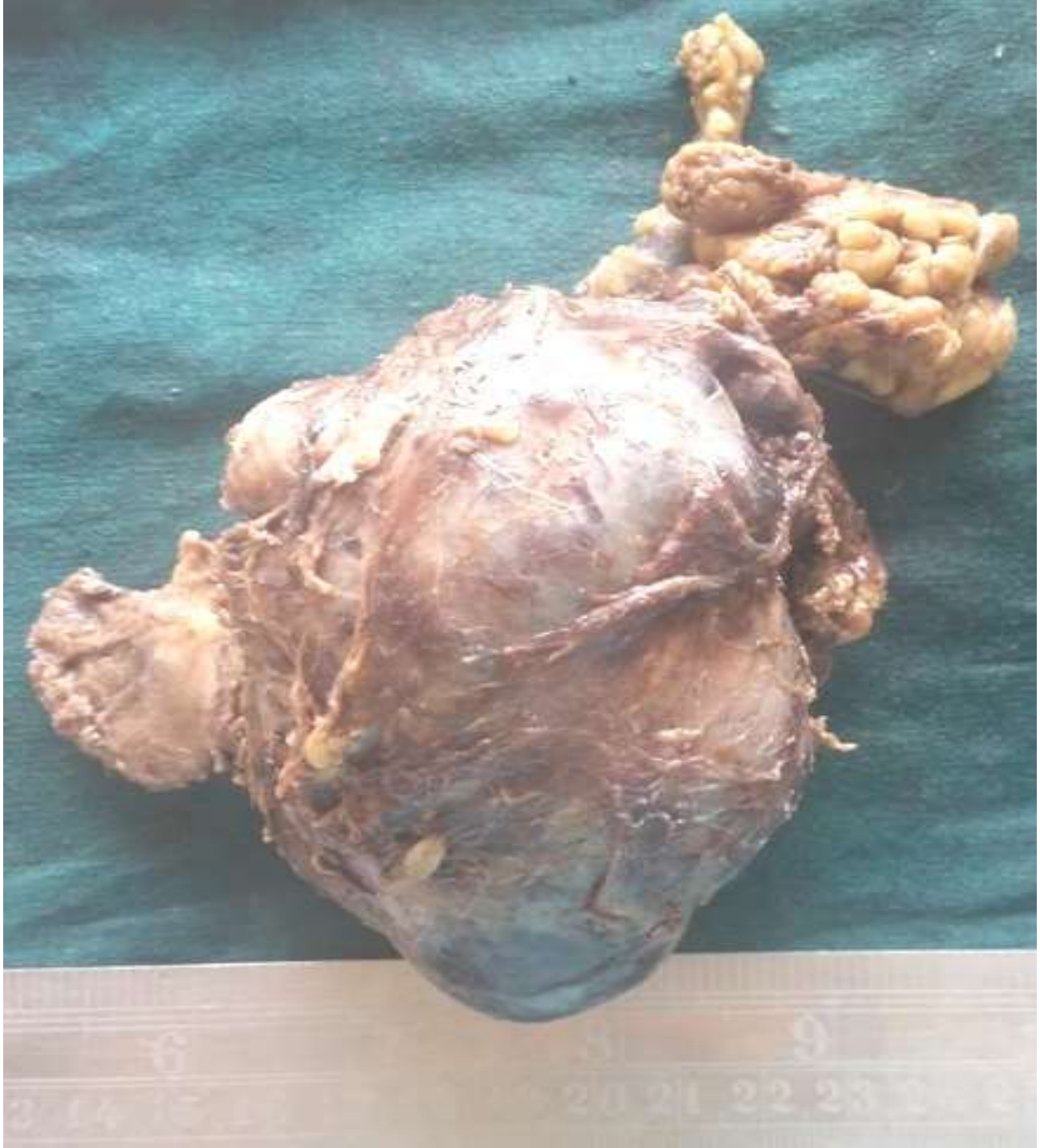


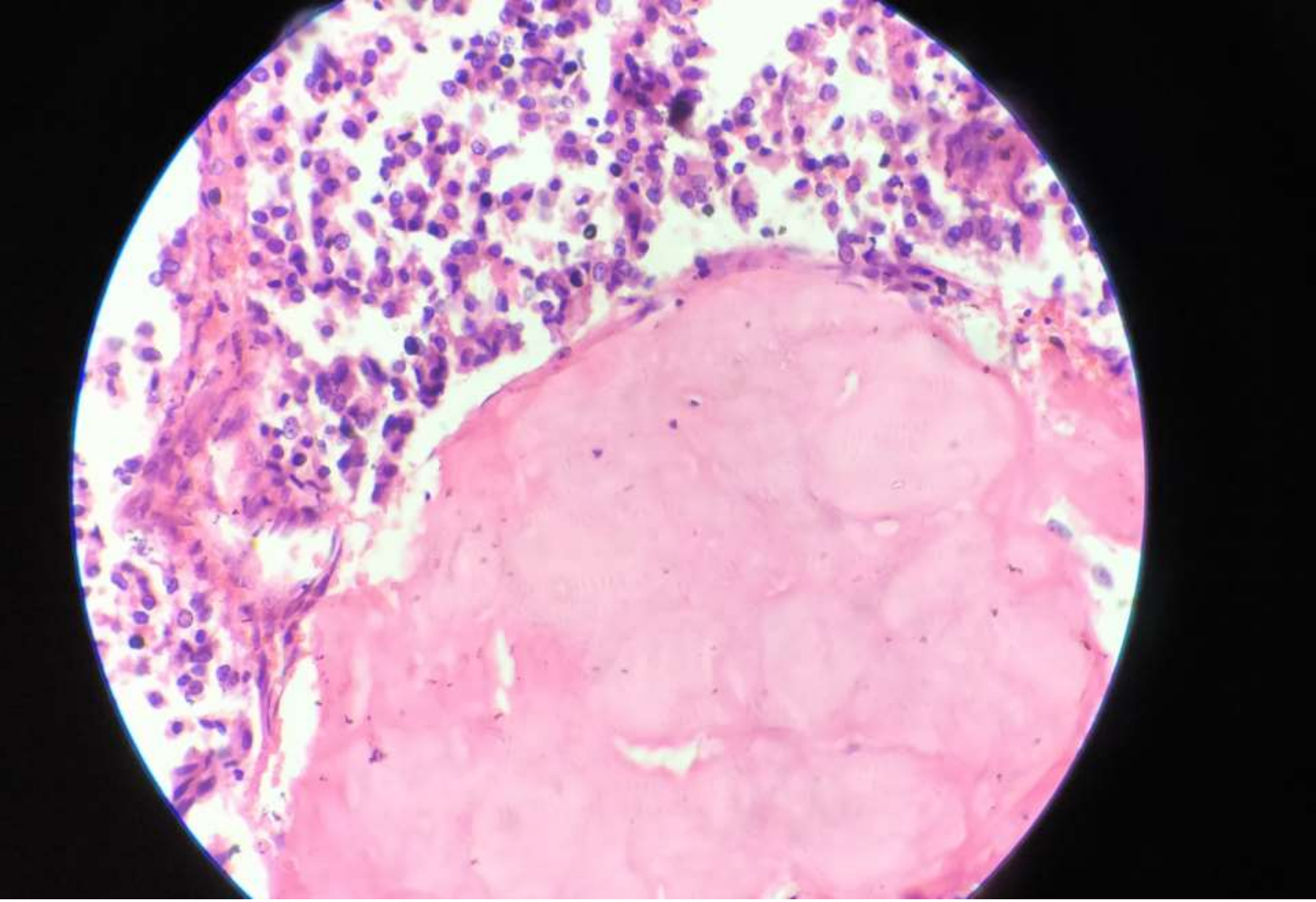


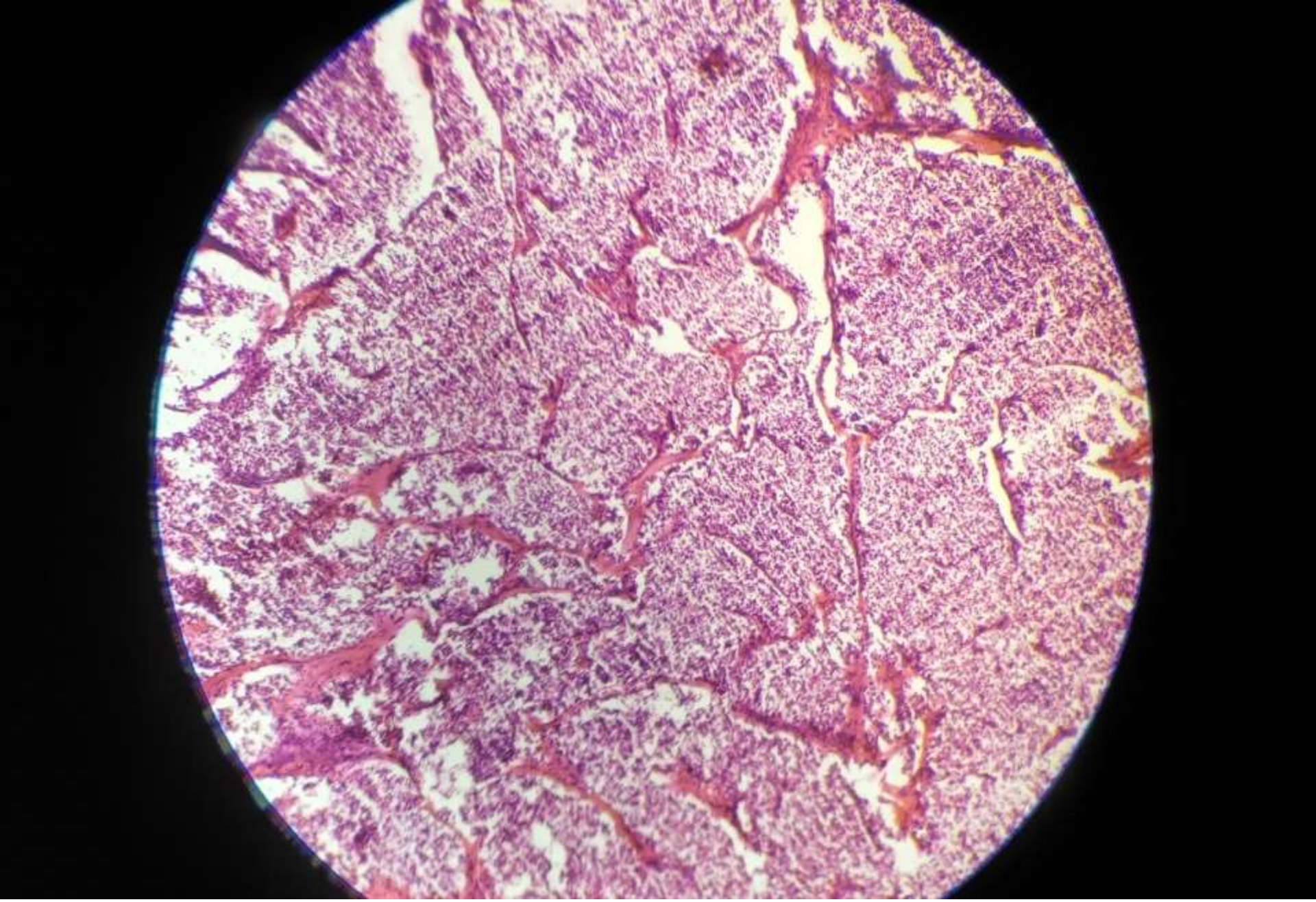


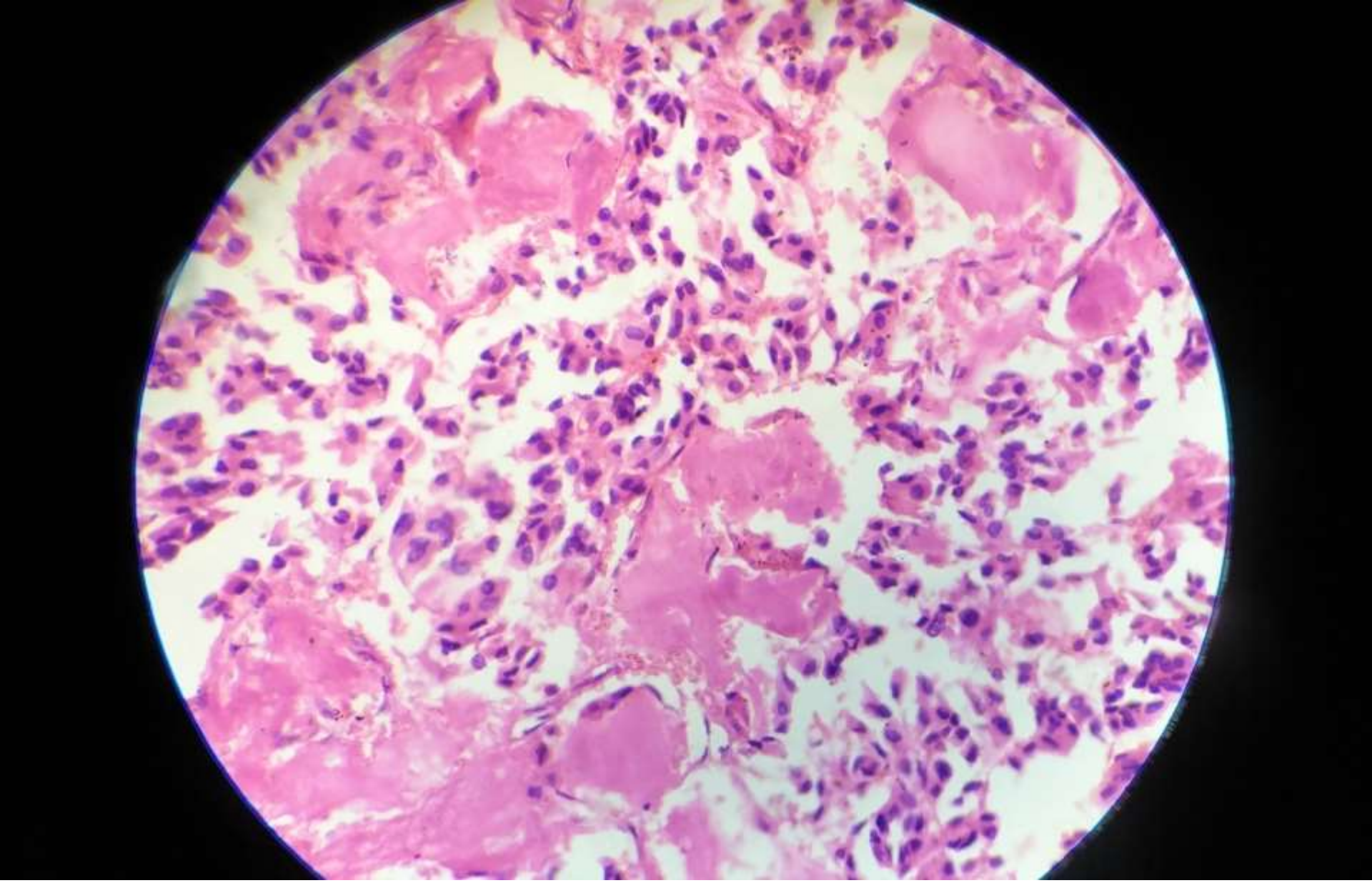


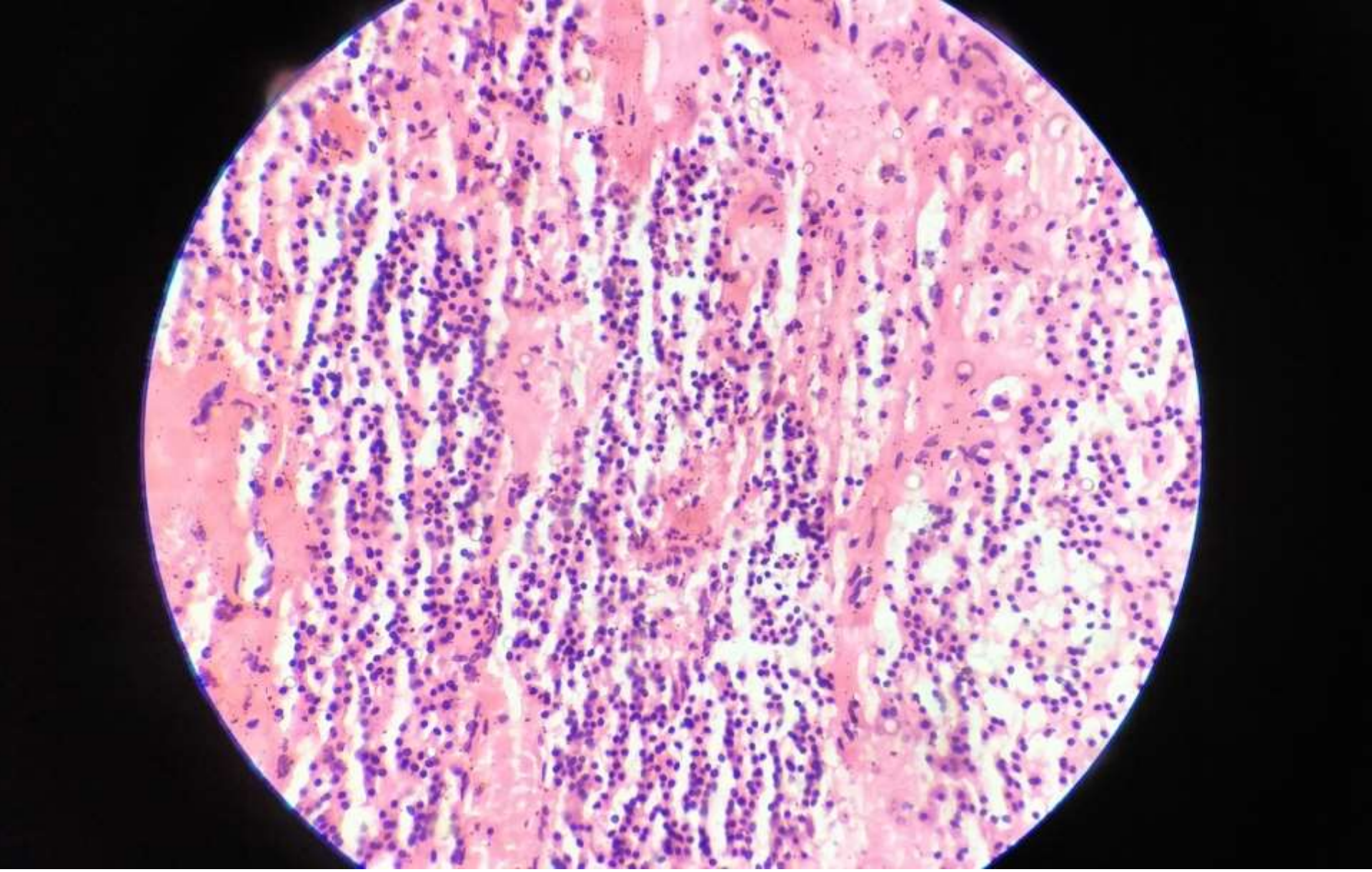


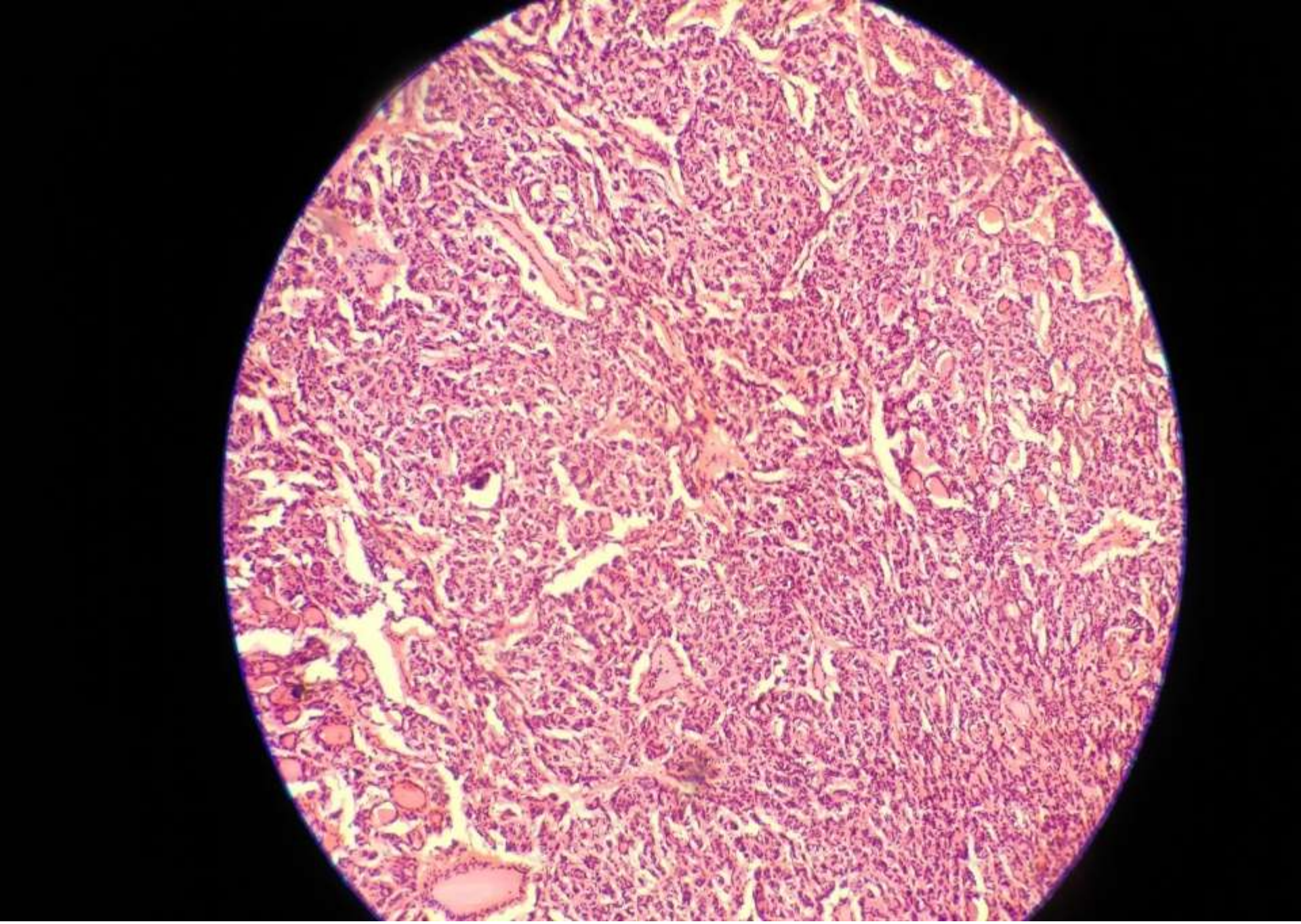


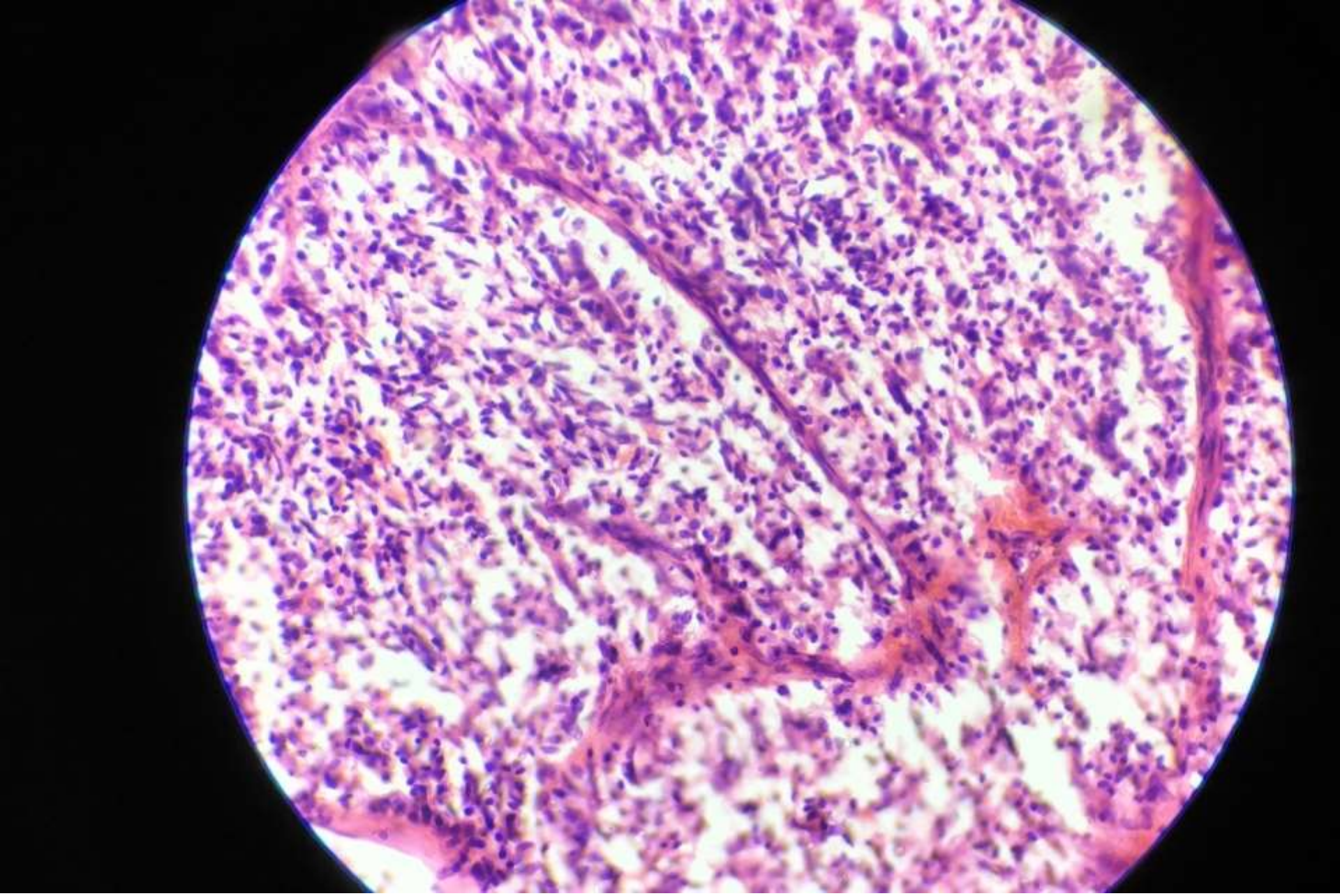


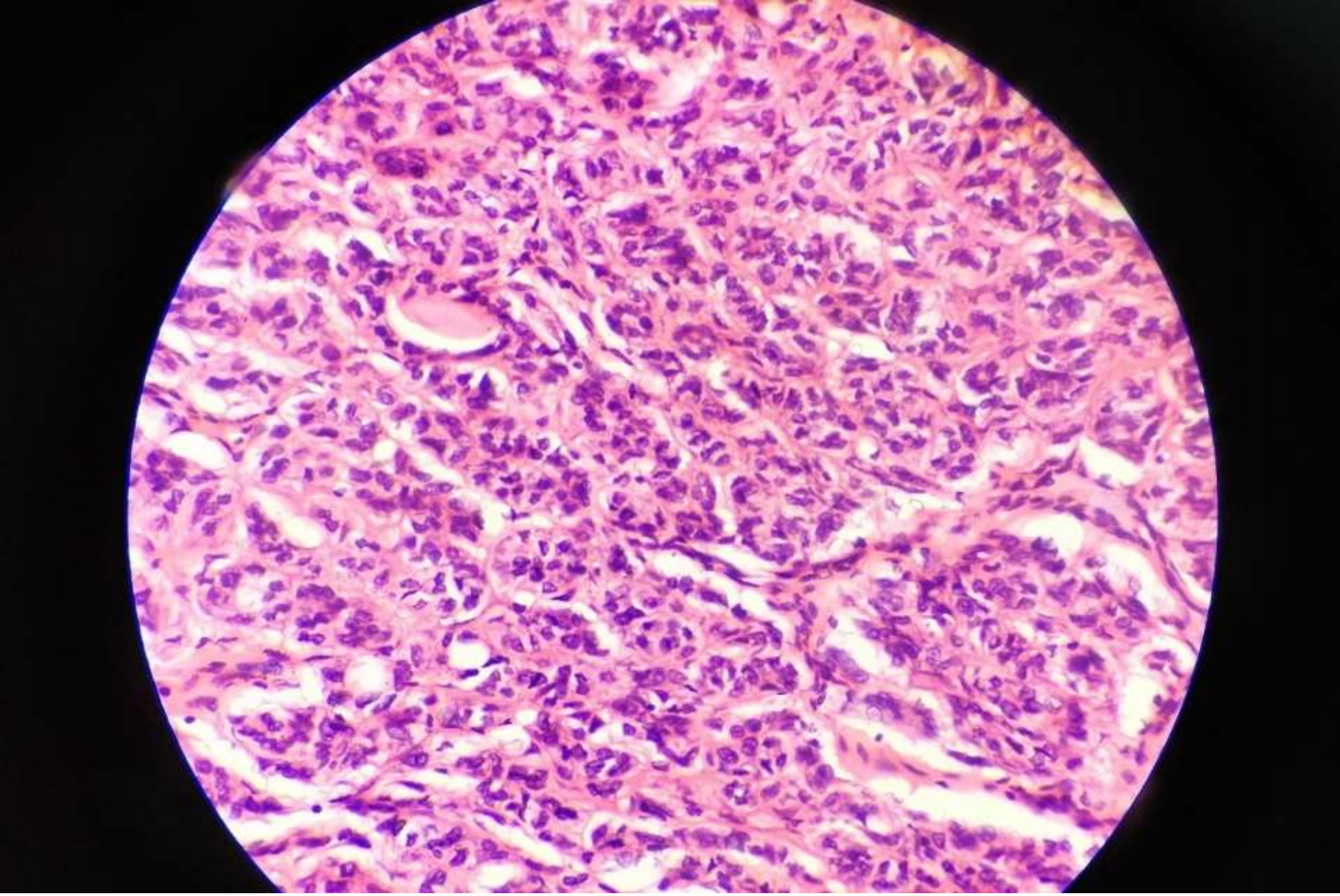


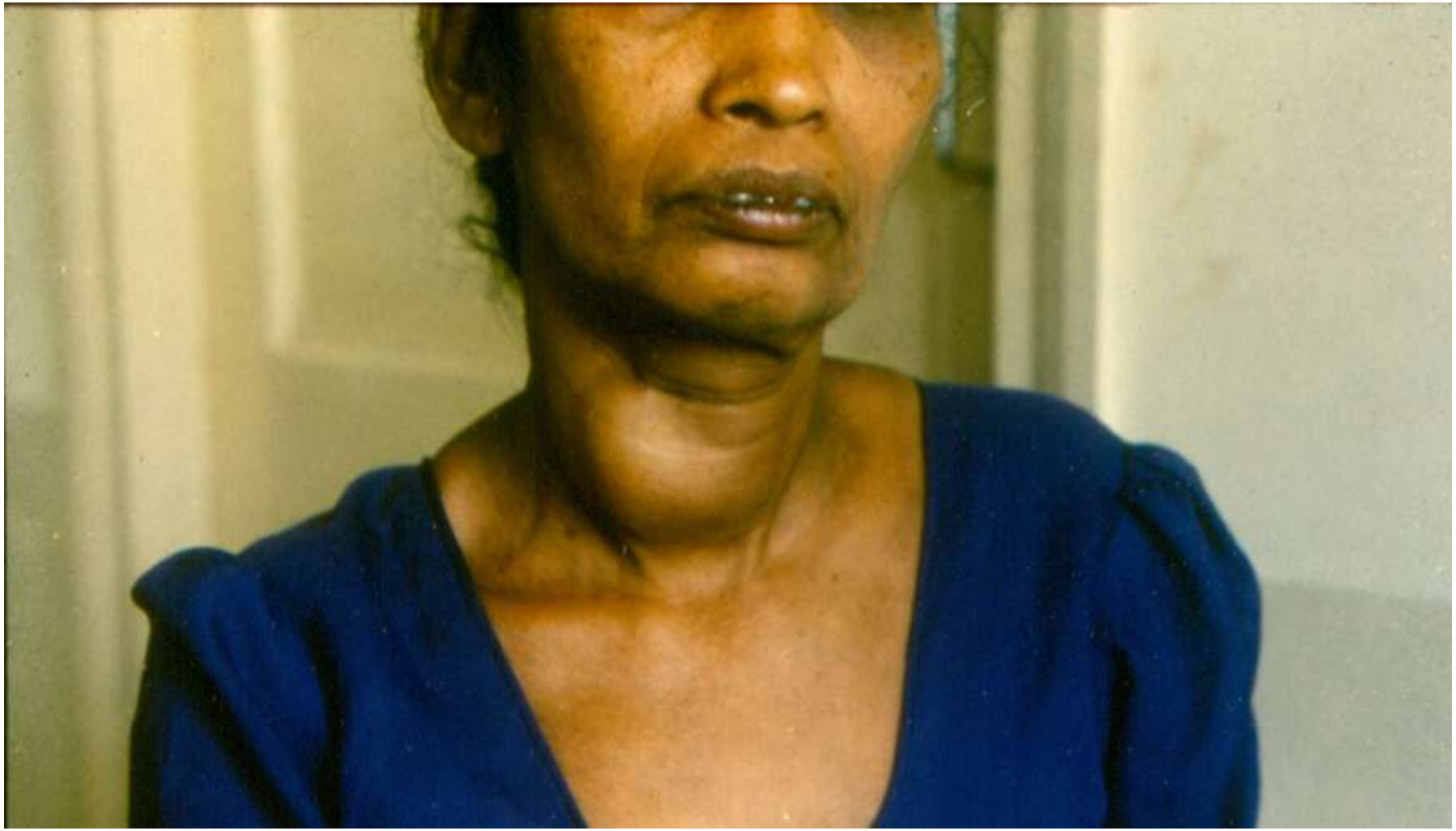


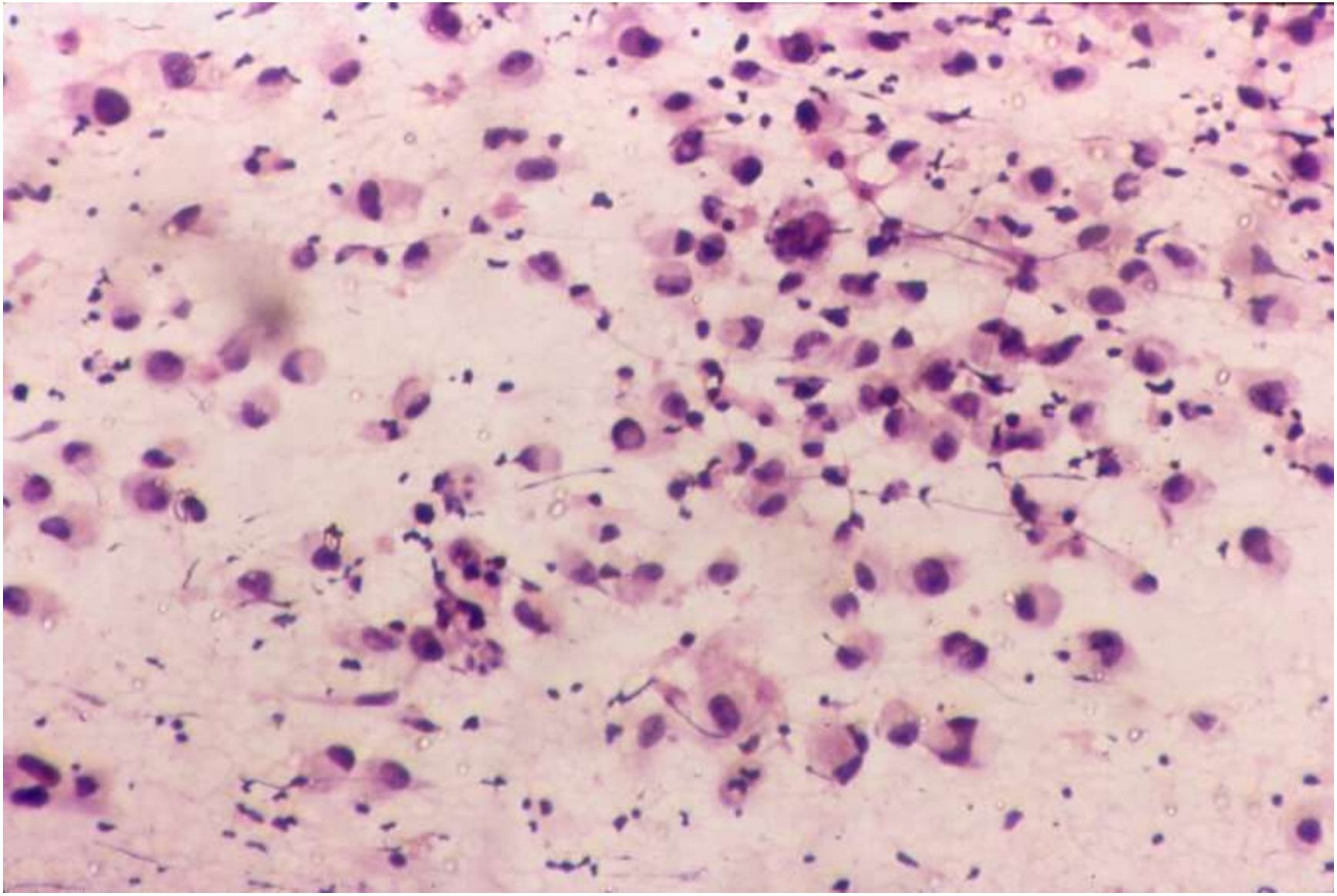


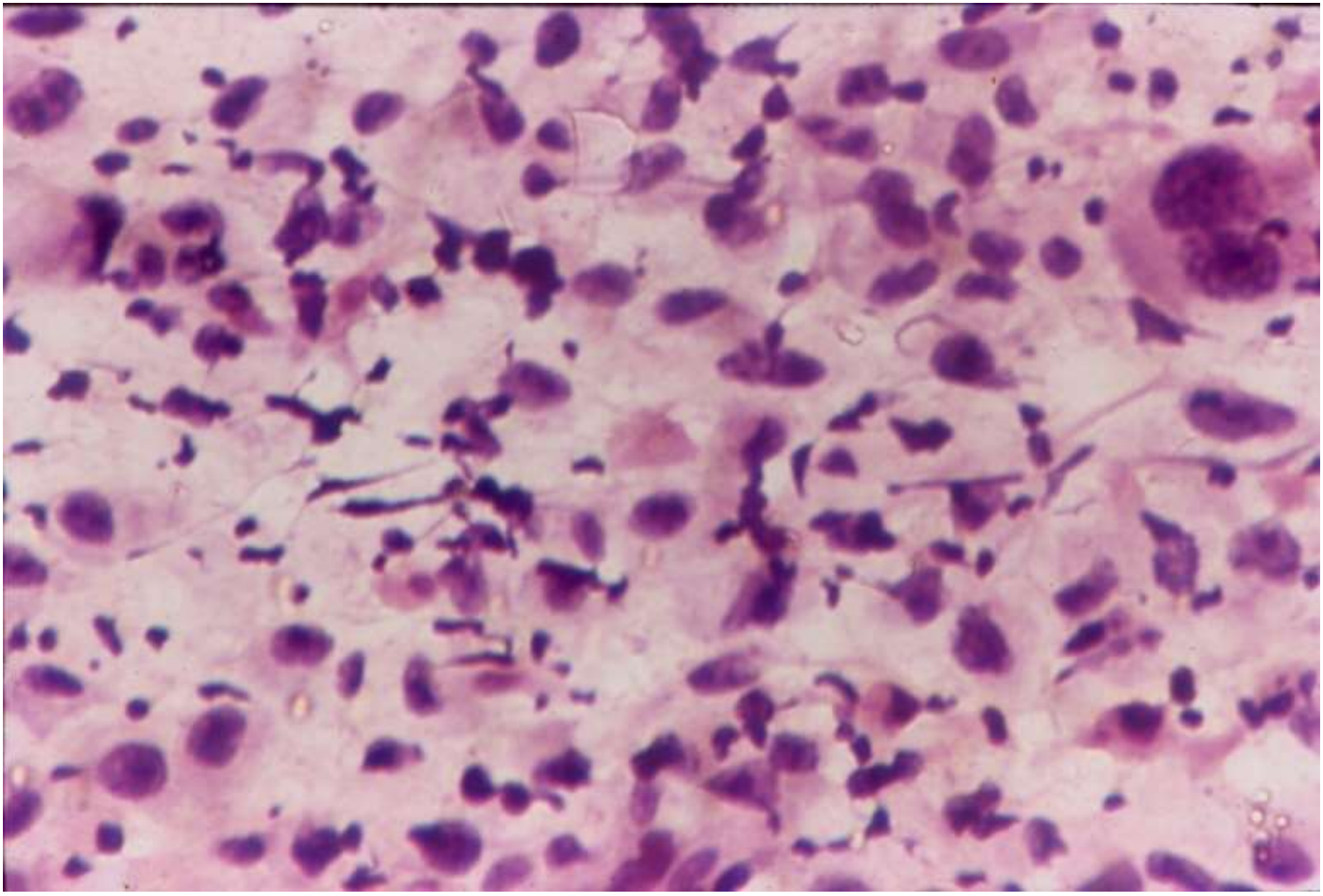


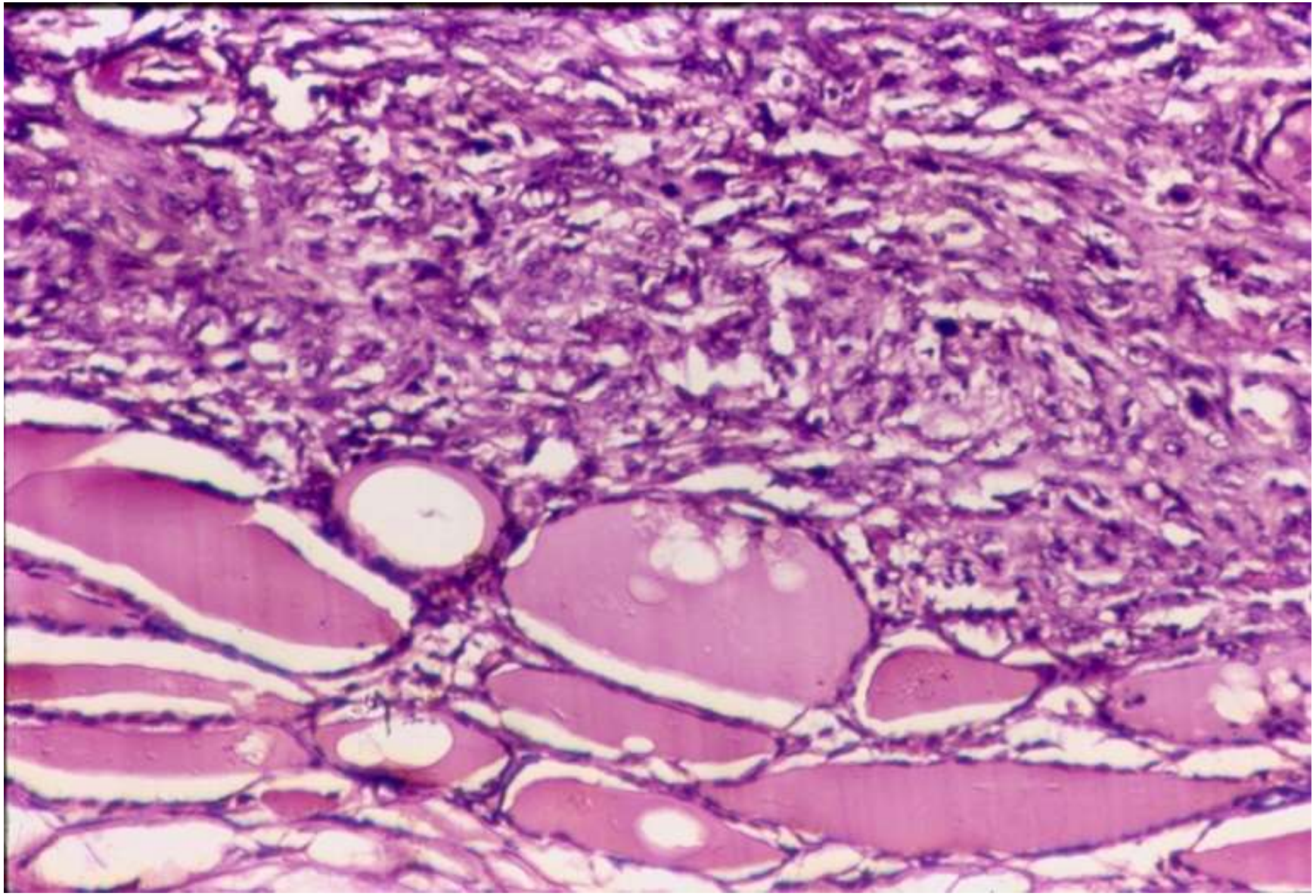


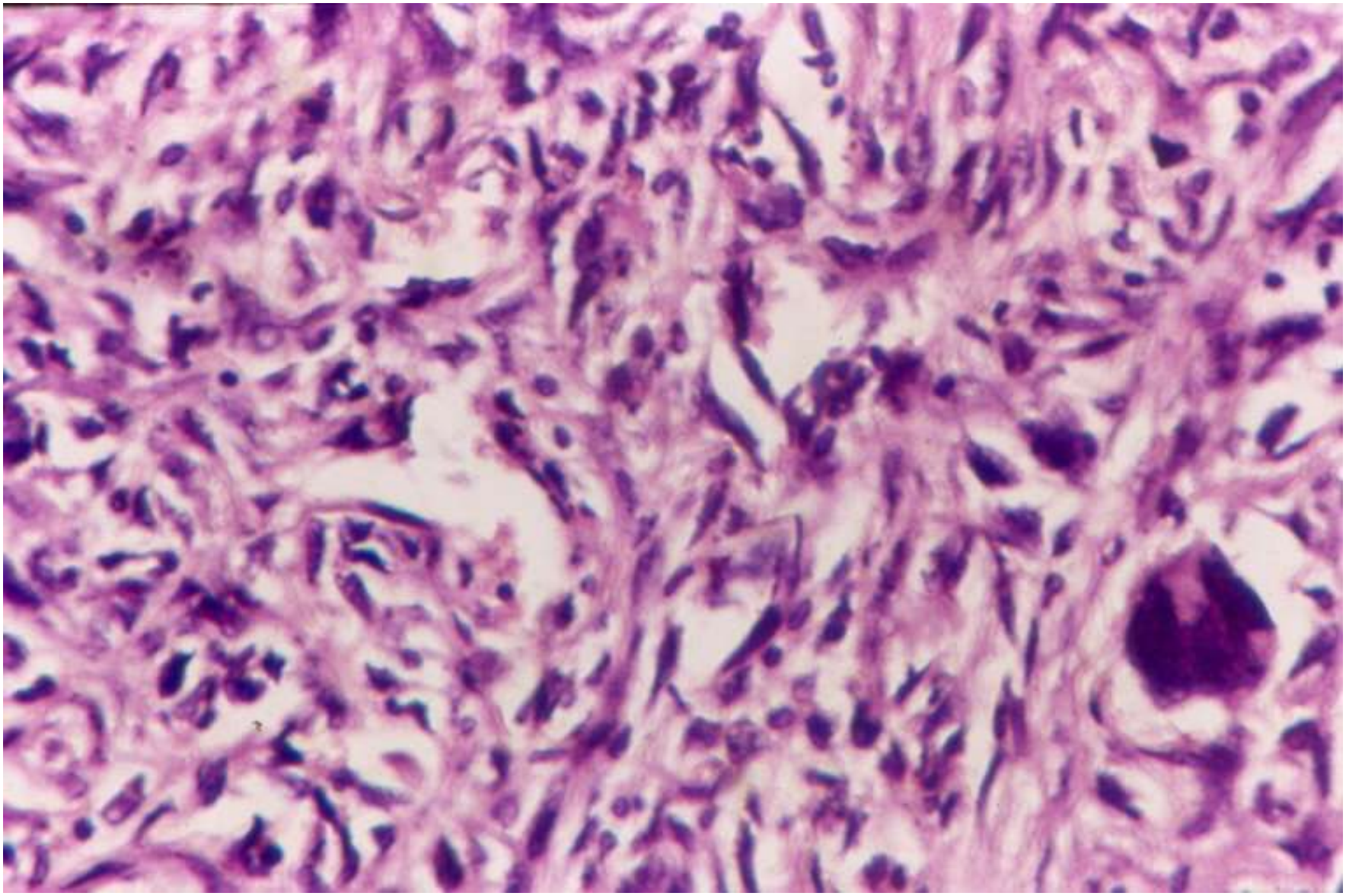


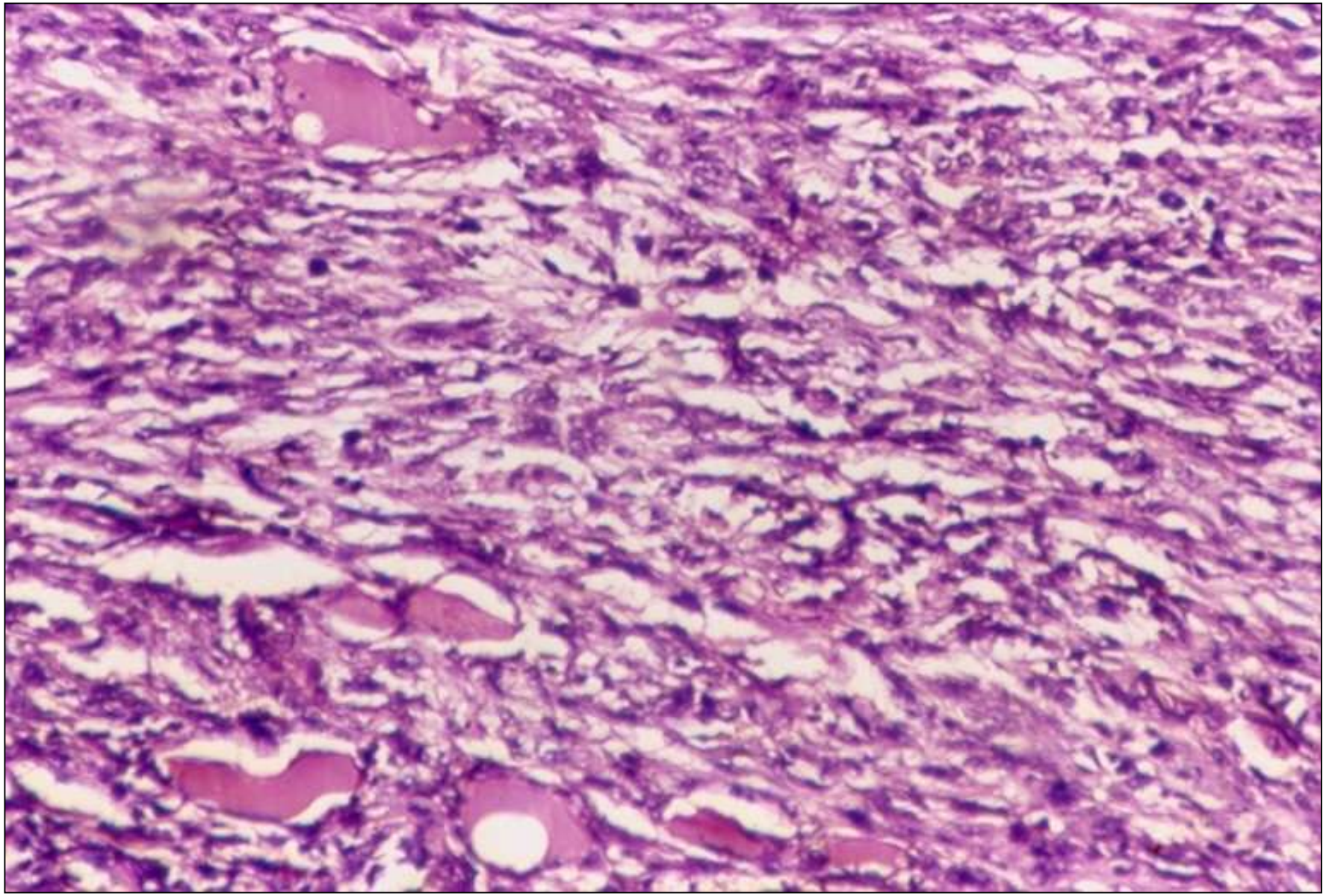


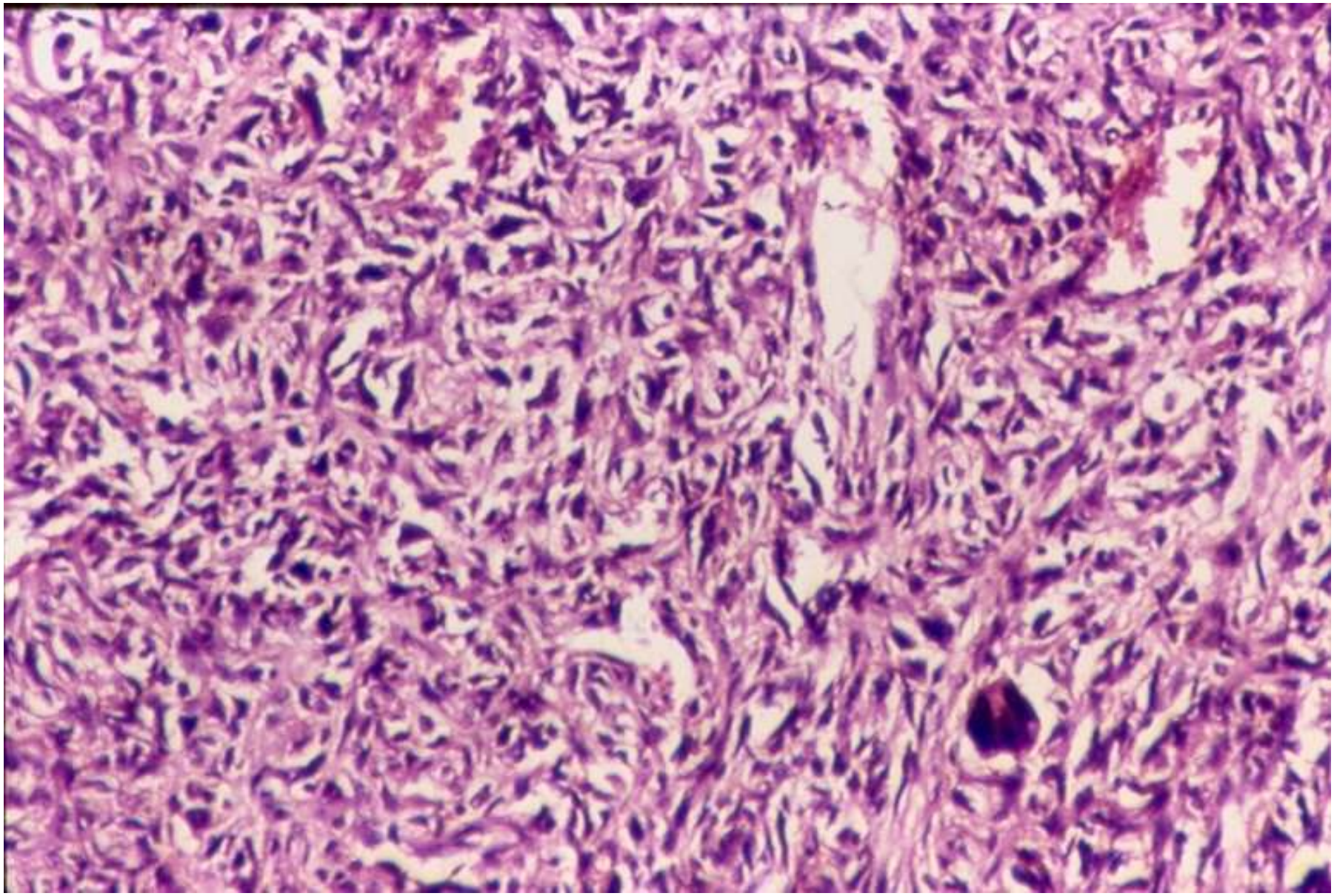


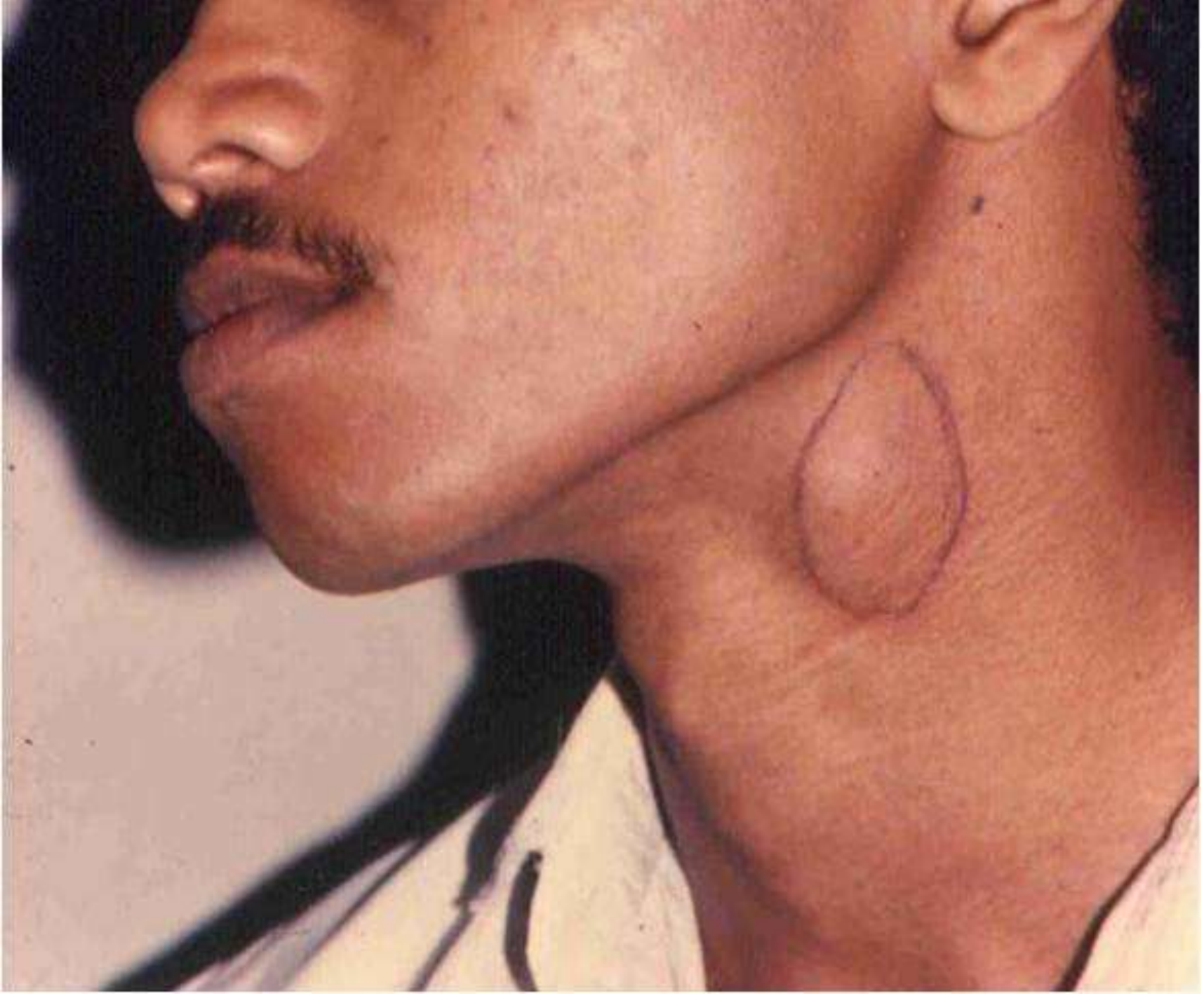


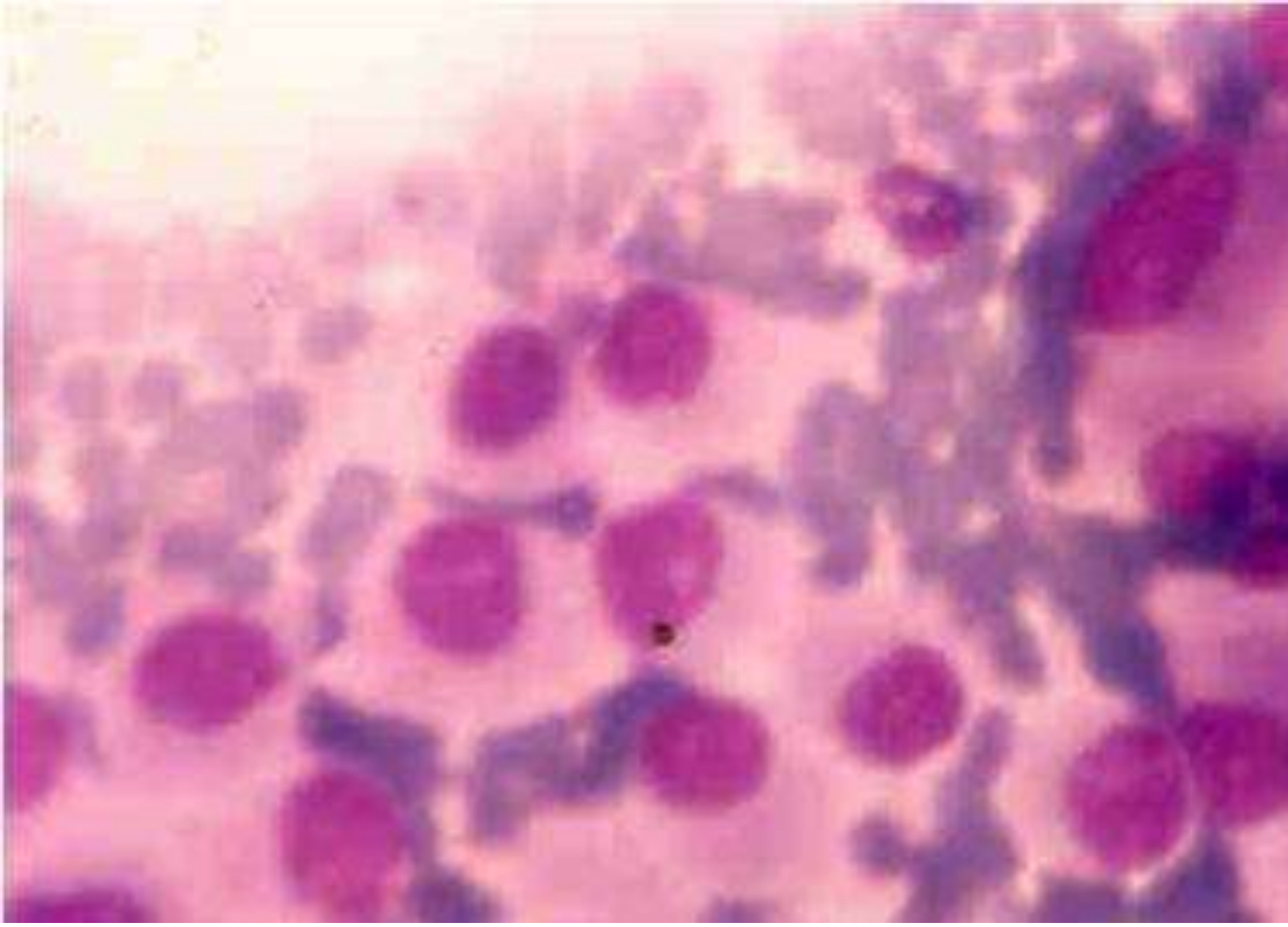


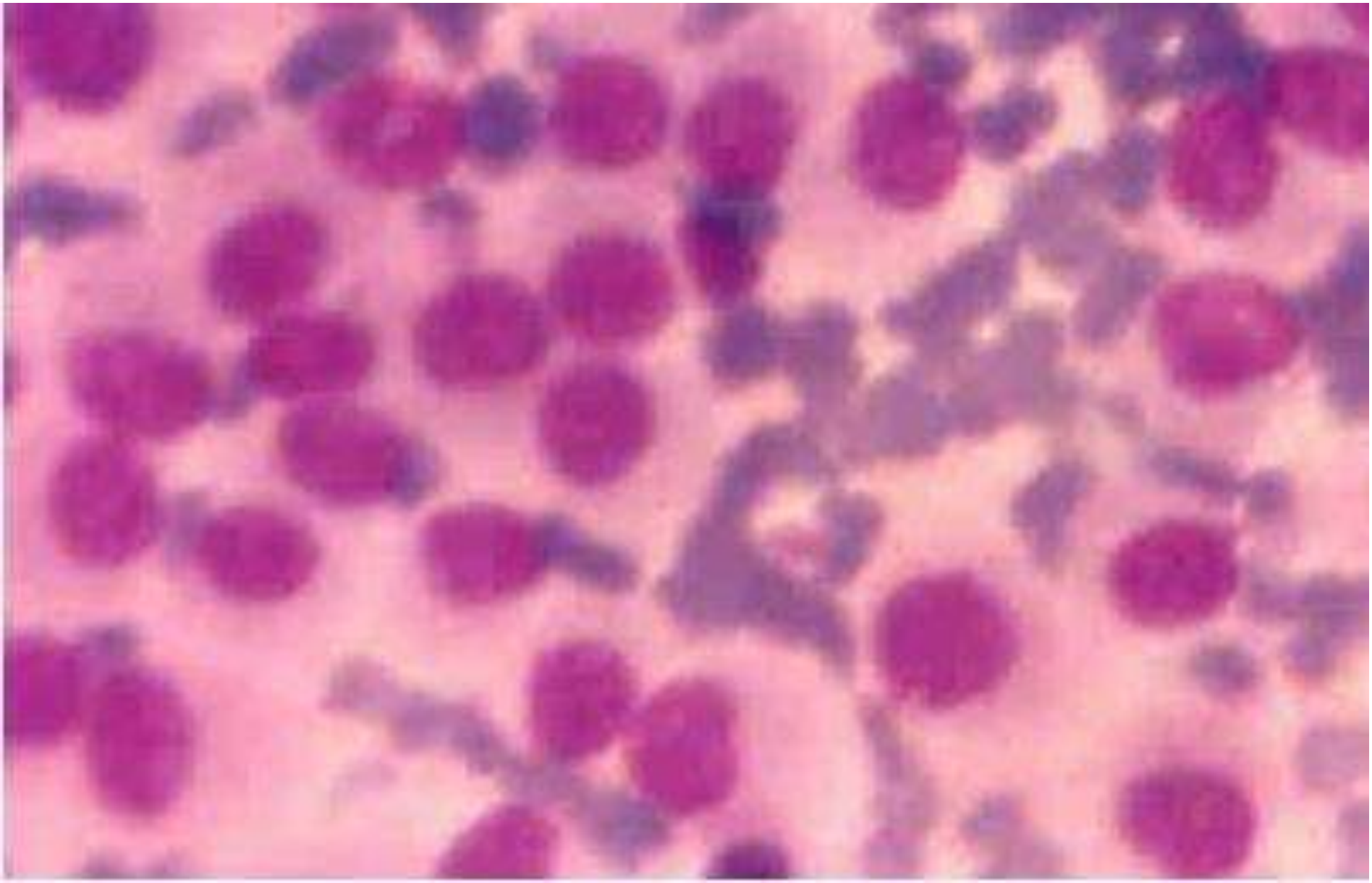


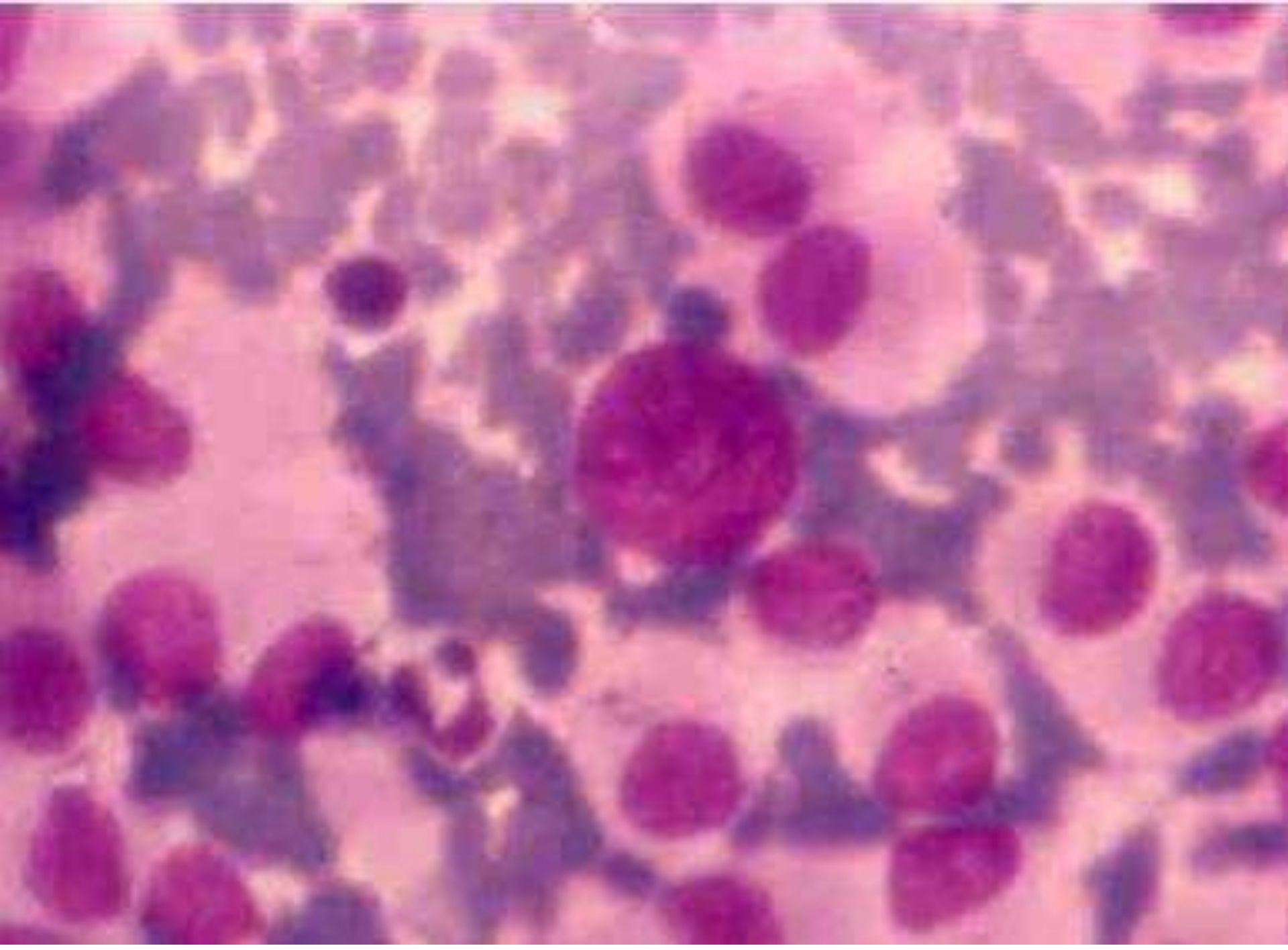


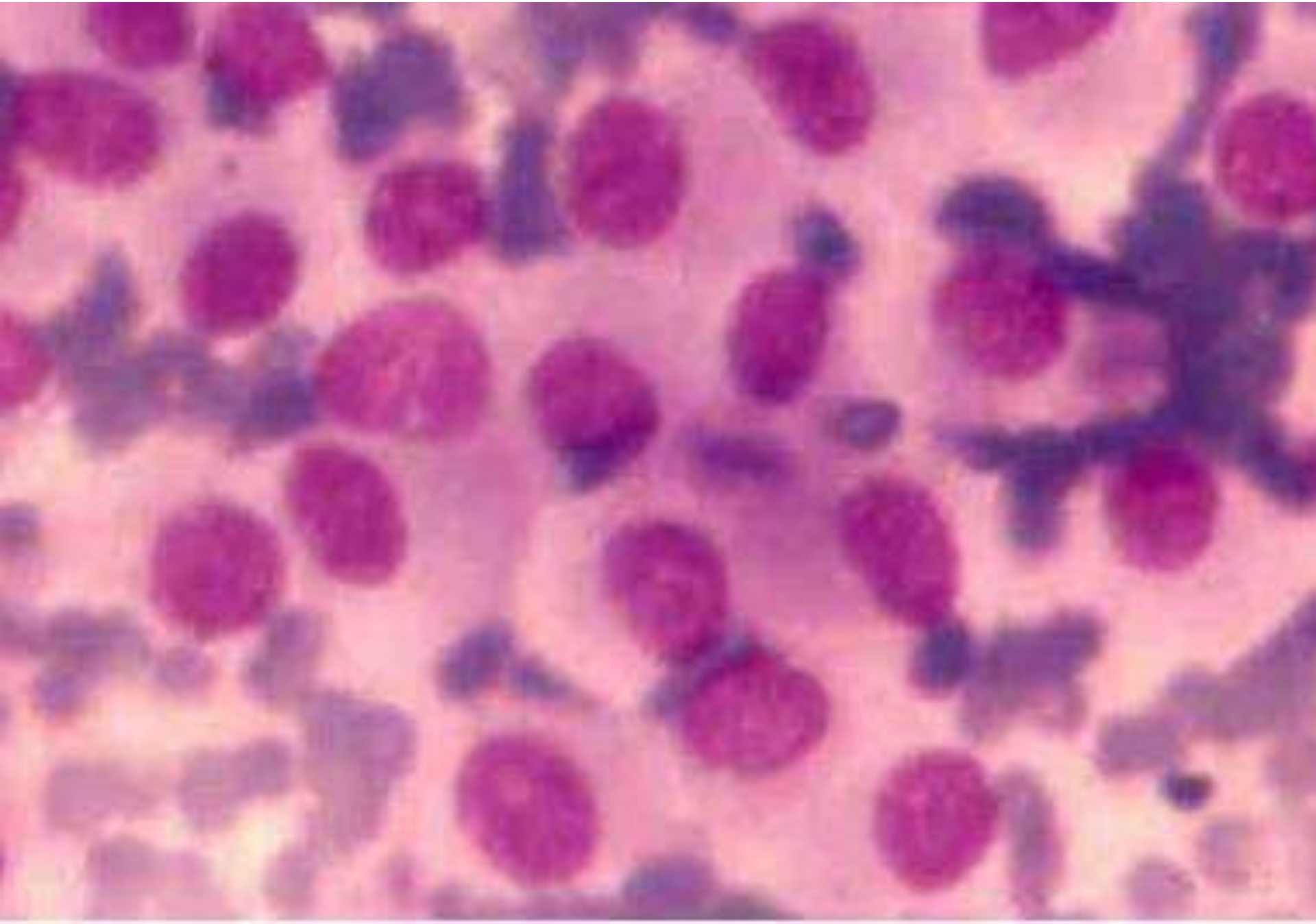












Step 1 – Diffuse
Nodular
MNG
Step 2 – Lab
Step 3 – Pathology
Imaging
Thyroid nuclear Scan
Radiolabelled Isotope
Step 4 - FNAC

- Vascularity
- Plunging goitre
- Mets Squamous Cell Carcinoma
- Tuberculosis
- Lymphoma

Immunohistochemistry

Calcitonin
CEA
Thyroglobulin
PAX8
Chromogranin
Synaptophysis
TTFI
CK
LCA
S1900

MEDULLARY CARCINOMA OF THYROID

DR. SHARVARI PRABHUDESAI

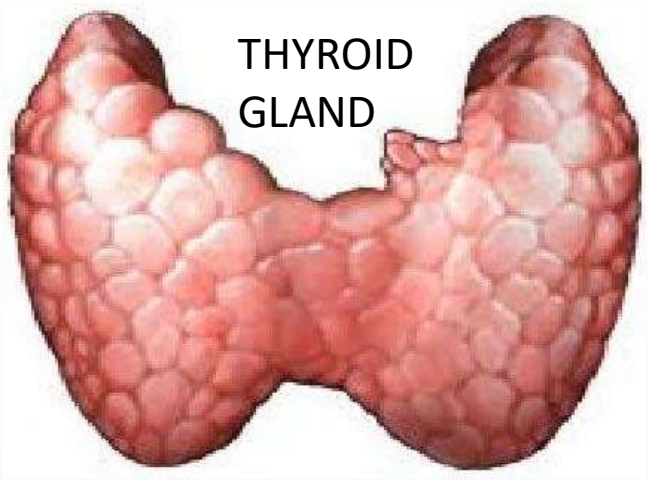
SENIOR RESIDENT

DEPARTMENT OF ENDOCRINOLOGY

OVERVIEW

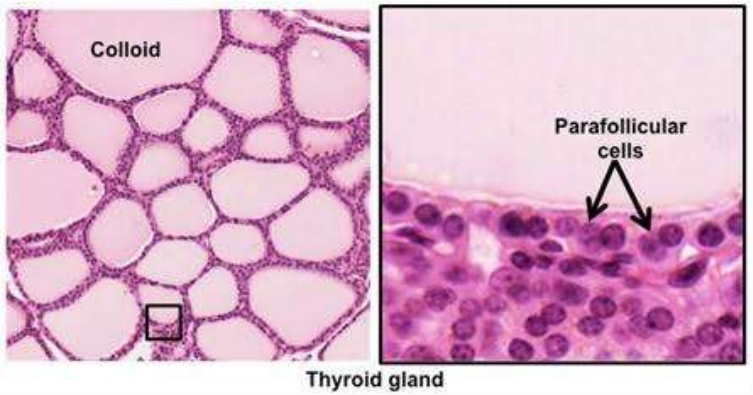
- INTRODUCTION & EPIDEMIOLOGY
- ETIOLOGY
- CLINICAL FEATURES
- DIAGNOSIS
- MANAGEMENT

INTRODUCTION



Follicular cells

Parafollicular C cells



- Well differentiated, neuroendocrine tumor

- 5-10% of thyroid cancers
- 0.4-1.4% of thyroid nodules.

INDIAN DATA

Region Author	North West India (1) Chakraborty, Rai et al 2024	Western India (2) Diwakar, Sarathi et al 2020	South India (3) Finny et al 2007
Duration of study	2012-2022	2008-2020	1982-2002
No of cases	78	97	40
Mean age (years)	43±11	Sporadic 51 years (40±14) Hereditary 46 years (30±15)	41 (9-73)
Sex predominance	Females	Male	Male
Most common C/F	Goitre with lymphadenopathy (80%)	Thyroid nodule (52%)	Goitre (65%) with lymphadenopathy – 30%
Atypical presentations	Ectopic cushings 1 Thyrotoxicosis 2 Hypertensive crisis 1 Prostatic carcinoma 1	-	-
RET positivity	22/47	38/46 in hereditary 11/51 sporadic MEN2A=25 MEN2B8	10
Calcitonin levels pg/ml	1274	922-6706 193-5611	132-5560 *checked in15/40
Primary treatment modality	Surgery (93.6%) Total thyroidectomy with	Surgery (78%)	Total thyroidectomy and neck dissection (65%)

1.Chakraborty AM, Rai A, et al An audit of medullary thyroid carcinoma from a tertiary care hospital in northwest India. Front Endocrinol (Lausanne). 2024 Jan 8

2.Diwaker C, Sarathi V, Hereditary medullary thyroid carcinoma syndromes: experience from western India. Fam Cancer. 2021 Jul;20

3.Finny P, Jacob JJ, et al: a 20-year experience from a centre in South India. ANZ J Surg. 2007 Mar

ETIOLOGY

- Sporadic in 75% cases, inherited in the rest
- MTC is major component of MEN2A and MEN2B and familial MTC.
- Autosomal dominant

MEN 2A (10 cen-10q11.2) Gene : RET 634, missense	**MEN2B** (10 cen-10q11.2) RET 918
MTC (90%)	MTC (>90%)
Phaeochromocytoma (50%)	Phaeochromocytoma (40-50%)
Parathyroid adenoma (20-30%)	Associated abnormalities (40-50%) -mucosal neuromas -marfanoid habitus -medullated corneal nerve fibres -megacolon

FAMILIAL MTC

- Described by Farndon and associates
- Accounts for 15% of HMTCs
- Late age of onset, less aggressive clinical course.
- More than 10 family members with MTC, multiple carriers or affected members over 50 years of age, adequate clinical history to rule out presence of other MEN2 manifestations. *
- Another less rigid definition : at least 4 family members of MTC #
- Variant in spectrum of disease expression in MEN2A.
- Most common FMTC mutation affect extracellular cysteine codons in RET exon 10 or intracellular RET codons other than A883 and M918.

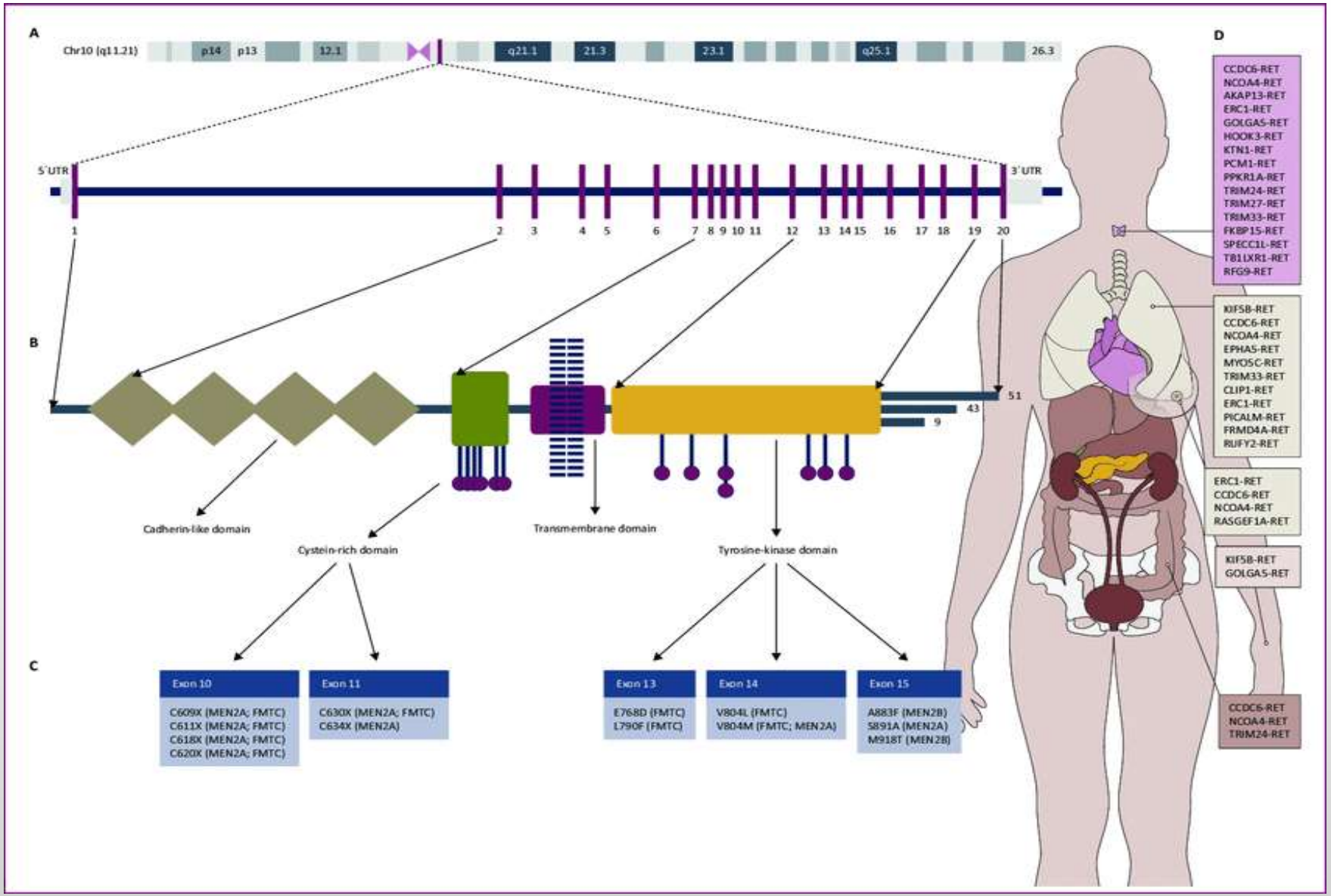
*Brandi ML, Gagel RF, Angeli A, et al.. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab*. 2001

#Eng C, Clayton D, Schuffenecker I, et al.. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. *Jama*. 1996

RET PROTO ONCOGENE

- REarranged during Transfection (RET)
- Discovered in 1985
- Located on chromosome 10q11.2.
- It encodes a single-pass transmembrane receptor of tyrosine kinase family
- Expressed in cells derived from neural crest, branchial arches and urogenital system.
- Germline RET mutations – MEN2A, MEN2B, FMTC
- MEN2A – mutations identified in one of 6 cysteine rich residues (95%) (codon 609,611,618 and 620 in exon 10 and 630 , 634 in exon 11)
- 2 missense mutations –Met918Thr (exon16) in 95% and Ala883Phe (exon 15)- fewer than 4% in MEN2B.
- RET re arrangements found in cancers of thyroid, lung, breast, colorectal, salivary glands.
- RET fusion with partner genes seen in 5-35% of adult PTCs, CCDC6 rearrangement most frequently observed

Takahashi M, Kawai K, Asai N. Roles of the *RET* Proto-oncogene in Cancer and Development. JMA J. 2020 Jul 15;


A
Chr10 (q11.21)
p14
p13
12.1
q21.1
21.3
23.1
q25.1
26.3
5'UTR
3'UTR
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
B
51
43
9
Cadherin-like domain
Cystein-rich domain
Transmembrane domain
Tyrosine-kinase domain
C
Exon 10
C609X (MEN2A; FMTC)
C611X (MEN2A; FMTC)
C618X (MEN2A; FMTC)
C620X (MEN2A; FMTC)
Exon 11
C630X (MEN2A; FMTC)
C634X (MEN2A)
Exon 13
E768D (FMTC)
L790F (FMTC)
Exon 14
V804L (FMTC)
V804M (FMTC; MEN2A)
Exon 15
A883F (MEN2B)
S891A (MEN2A)
M918T (MEN2B)
D
CCDC6-RET
NCOA4-RET
AKAP13-RET
ERC1-RET
GOLGA5-RET
HOOK3-RET
KTN1-RET
PCM1-RET
PPKR1A-RET
TRIM24-RET
TRIM27-RET
TRIM33-RET
FKBP15-RET
SPECC1L-RET
TBL1XR1-RET
RFG9-RET
KIF5B-RET
CCDC6-RET
NCOA4-RET
EPHA5-RET
MYO5C-RET
TRIM33-RET
CLIP1-RET
ERC1-RET
PICALM-RET
FRMD4A-RET
RUFY2-RET
ERC1-RET
CCDC6-RET
NCOA4-RET
RASGEF1A-RET
KIF5B-RET
GOLGA5-RET
CCDC6-RET
NCOA4-RET
TRIM24-RET

RET (cont…)

- *RET* germline mutations → all patients with MEN2A and MEN2B
- somatic *RET* mutations → 50% of sporadic MTCs
- Sporadic MTC *RET* mutation–negative—*HRAS*, *KRAS*, or (rarely) *NRAS*

WHICH TEST TO PERFORM?

Method	Sensitivity	Specificity	Detection of partner	Detection of expression	Screening
IHC	Moderate[a]	Moderate[b]	No	Yes	No
FISH	High	High	No/Yes[c]	No	Rare circumstances
RT-PCR	Moderate/high[d]	High	Yes/No[e]	Yes	Rare circumstances
DNA-seq NGS	Moderate[f]	High/moderate[g]	Yes	No	Yes
RNA-seq NGS	High	High	Yes	Yes[h]	Yes

DNA-seq NGS, DNA sequencing by next-generation sequencing; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; RNA-seq NGS, RNA sequencing by next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction.

CLINICAL FEATURES

Presentation : 4-5th decade

Equal gender distribution

SPORADIC : thyroid nodule → solitary/ inside a MNG.

Rarely in very advanced cases – diarrhea/flushing due to high calcitonin (less common in sporadic)

5-10% of very advanced cases → ectopic ACTH production.

HEREDITARY : Thyroid nodular disease, bilateral and multicentric

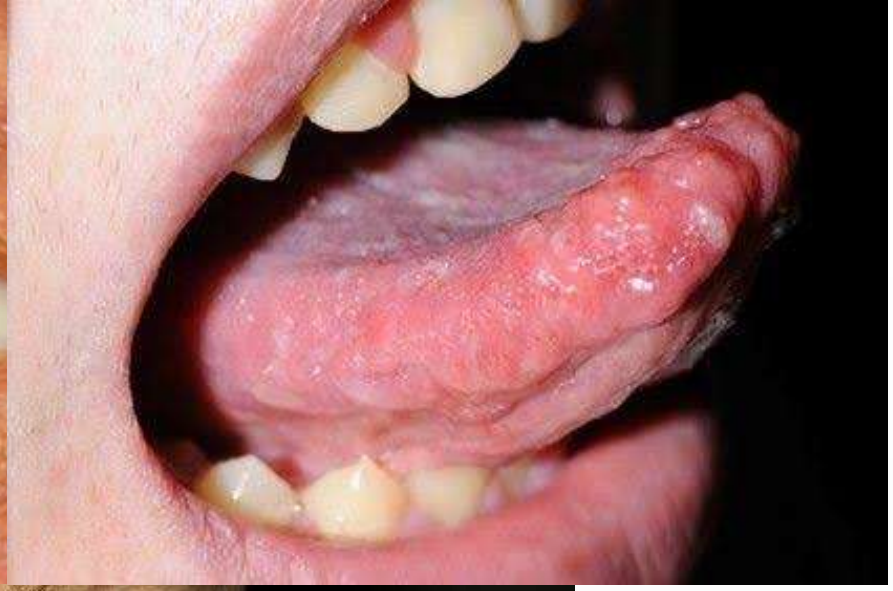
MEN2A, MEN2B and Familial MTC (10-50% of all MEN).

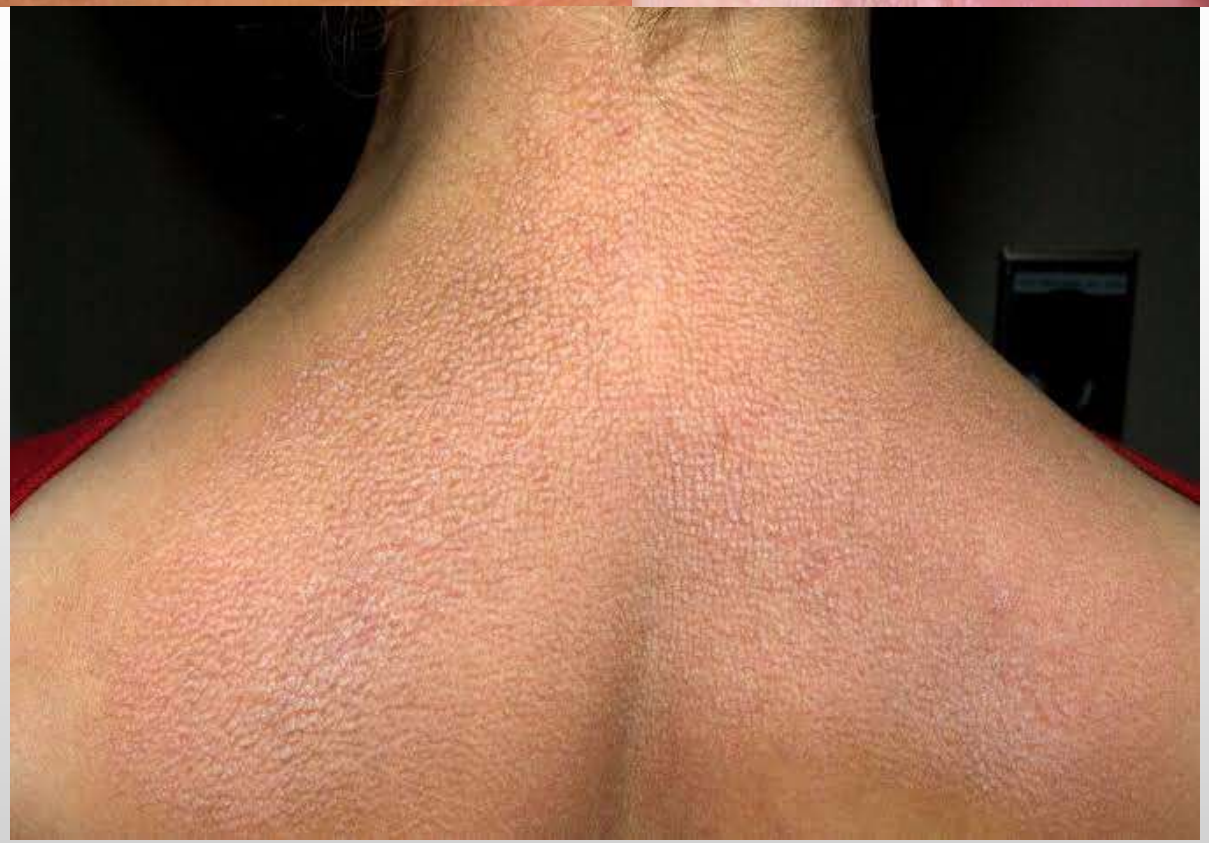
Aggressive course in MEN2B, indolent in FMTC.

MEN2B examination findings : mucosal neuromas, marfanoid habitus, thick lips and eyelids

MEN2A - cutaneous lichen amyloidosis


EyeRounds.org





EVALUATION

- **Thyroid ultrasound** : solid, hypoechoic nodules, sometimes show microcalcifications.
- **FNA** : Typical smear shows – round to oval cells, large polygonal or spindled.

  Cytoplasm scant/abundant, acidophilic granulations

  Multiple nuclei

  Amyloid
- **Role of calcitonin** : ETA recommends measuring serum Ctn *

  ATA guidelines do not recommend for or against use

  AACE,ETA, AME → routine Ctn useful, recommend measurement in high risk groups.

Pre op serum calcitonin < 20-50pg/ml – low chance of occult metastasis.

>500pg/ml → high likelihood of nodal metastasis.

*Wells SA Jr, Asa SL et al; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015 Jun;25

- If pre-op Ctn high (>1000pg/ml) – complete structural imaging to be done.
- In cases of mildly elevated Ctn, may perform calcium stimulated Ctn.
- 2.5mg of calcium element per kg diluted in 50ml of saline→ infuse over 5 mins → collect samples baseline/2/5/15 minutes.

- Carcinoembryonic antigen (CEA) – elevated in diffuse disease with distant metastasis

  Useful in cases of dedifferentiated MTC where Ctn not produced and for monitoring disease progression.

- Pre op evaluation of adrenal and parathyroids
- Development and diagnosis of phaeochromocytoma follows MTC

- 24 hour urinary metanephrines f/b imaging with USG/CT and/or MRI .

  Functional imaging sos.

- Calcium profile with PTH levels.

MEDULLARY THYROID MICROCARCINOMA

- MTCs that measure <= 1cm in size
- In hereditary MTCs, C-cell hyperplasia → microMTC→ invasive microscopic MTC.
- A review of 24 autopsy series published from 21 countries → 0.14% prevalence of occult microMTC. *
- 1988-2007 – 301 microMTC from SEER regions studied.
- microMTCs can behave aggressively!

Kazaure HS, Roman SA, Sosa JA. Medullary thyroid microcarcinoma: a population-level analysis of 310 patients. Cancer. 2012 Feb 1

Characteristic	No. of Patients	Percentage[a]
Demographic characteristics		
Sex		
Women	172	55.5
Men	138	44.5
Age at diagnosis, y		
<45	137	44.1
45-64	113	36.5
≥65	60	19.4
Median (range)	47 (2-86)	
Mean ± SEM	46.5 ± 1.1	
Race		
White	264	85.2
Black	27	8.7
Other	19	6.1
Year of diagnosis		
1988-1997	69	22.3
1998-2002	84	27.1
2003-2007	157	50.6
Follow-up, mo		
Median [interquartile range]	48 [13-96]	
Mean ± SEM	63.3 ± 3.2	
Clinical characteristics		
History of malignancy		
Yes	60	19.4
No	250	80.6
Surgery		
None	6	1.9
Lobectomy	34	11.0
Thyroidectomy	270	87.1
Radiation therapy, n = 309		
None	274	88.6
External beam	15	4.9
Other	20	6.5
No. of lymph nodes removed, n = 309		
None	133	43
≥1	176	57
Median [interquartile range]	6 [2-20]	
Mean ± SEM	14 ± 1.5	
Vital status as of December 31, 2007		
Alive	281	90.6
Dead	29	9.4

Table 3. Tumor Size as an Independent Predictor of Lymph Node Metastases in Patients With Medullary Thyroid Microcarcinoma: Surveillance, Epidemiology, and End Results Program, 1988-2007[a]

Tumor Size, mm	OR (95% CI)	*P*	Probability of LNM, %
2	2.1 (0.5-8.9)	.306	23.1
3	2.8 (0.9-9.2)	.080	22.7
4	2.5 (1.1-5.9)	.042	25.8
5	2.5 (1.2-5.5)	.017	23.1
6	3.3 (1.6-6.8)	.002	28.1
7	2.6 (1.3-5.1)	.007	29.7
8	2.4 (1.2-4.9)	.011	33.1
9	2.1 (1.1-4.5)	.048	32.8
10	3.0 (1.3-6.9)	.012	36.9

Abbreviations: CI, confidence interval; LNM, lymph node metastases; OR, odds ratio

[a]The multivariate logistic regression model was adjusted for age, sex, year of diagnosis, history of malignancy, tumor focality, and tumor extension.

[b]Post-test probability was based on 36.9% pretest probability of LNM in the study.

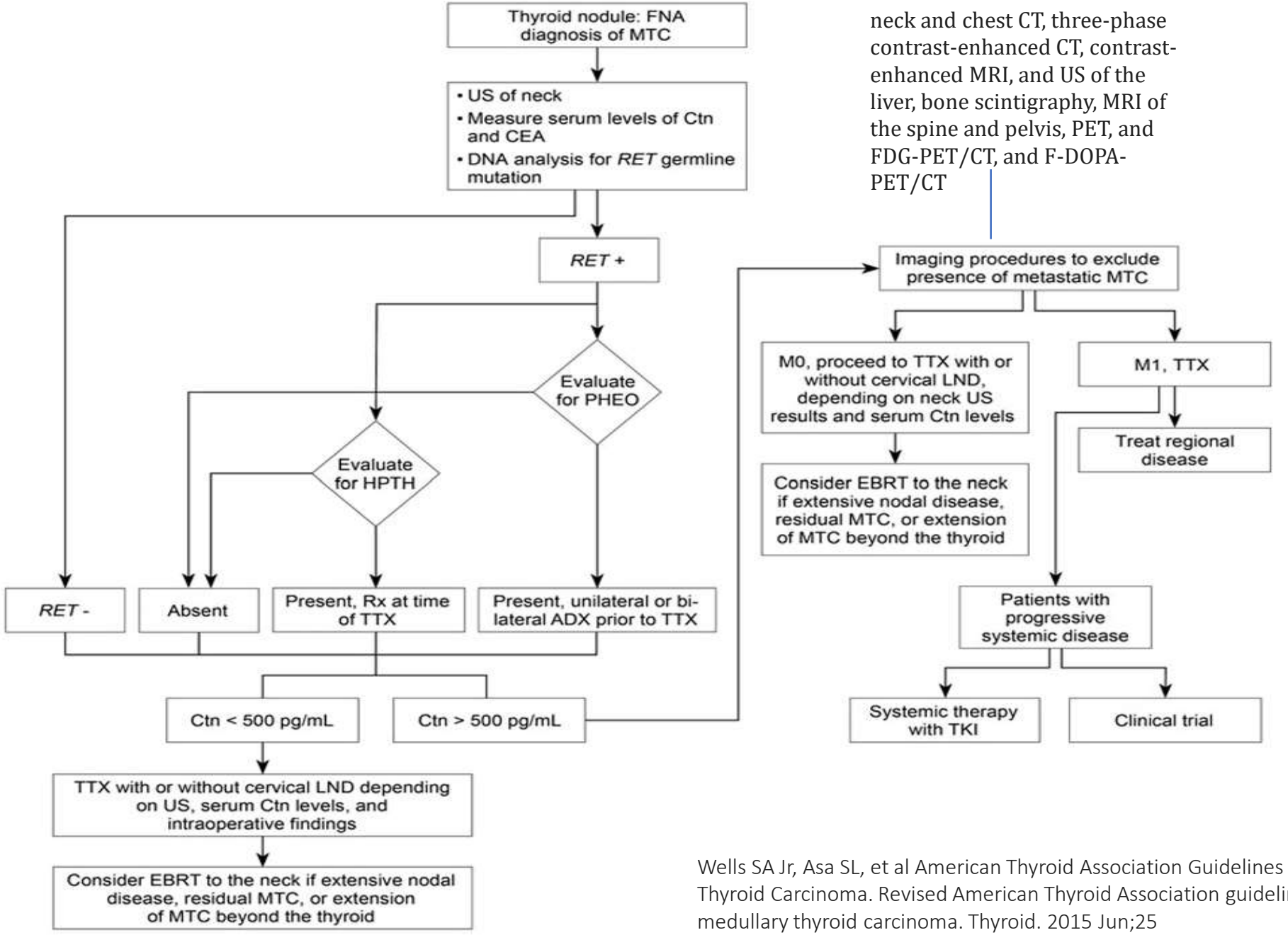
Tumor size was associated independently with risk of lymph node metastases, and further analyses revealed that clinically significant disease is common in small microMTCs.

GENETIC EVALUATION

- All MTC patients should undergo RET genetic screening test (DNA Sanger sequencing or QPCR)
- All first degree relatives of RET mutation proven MTC to be tested.
- ATA risk categories for hereditary MTC :

ATA highest risk (HST)	MEN2B and the *RET* codon *M918T* mutation
High risk (H)	*RET* codon C634 mutations and the *RET* codon A883F mutation
Moderate risk (MOD)	Hereditary MTC and *RET* codon mutations other than M918T, C634, and A883F

Wells SA Jr, Asa SL et al; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015 Jun;25



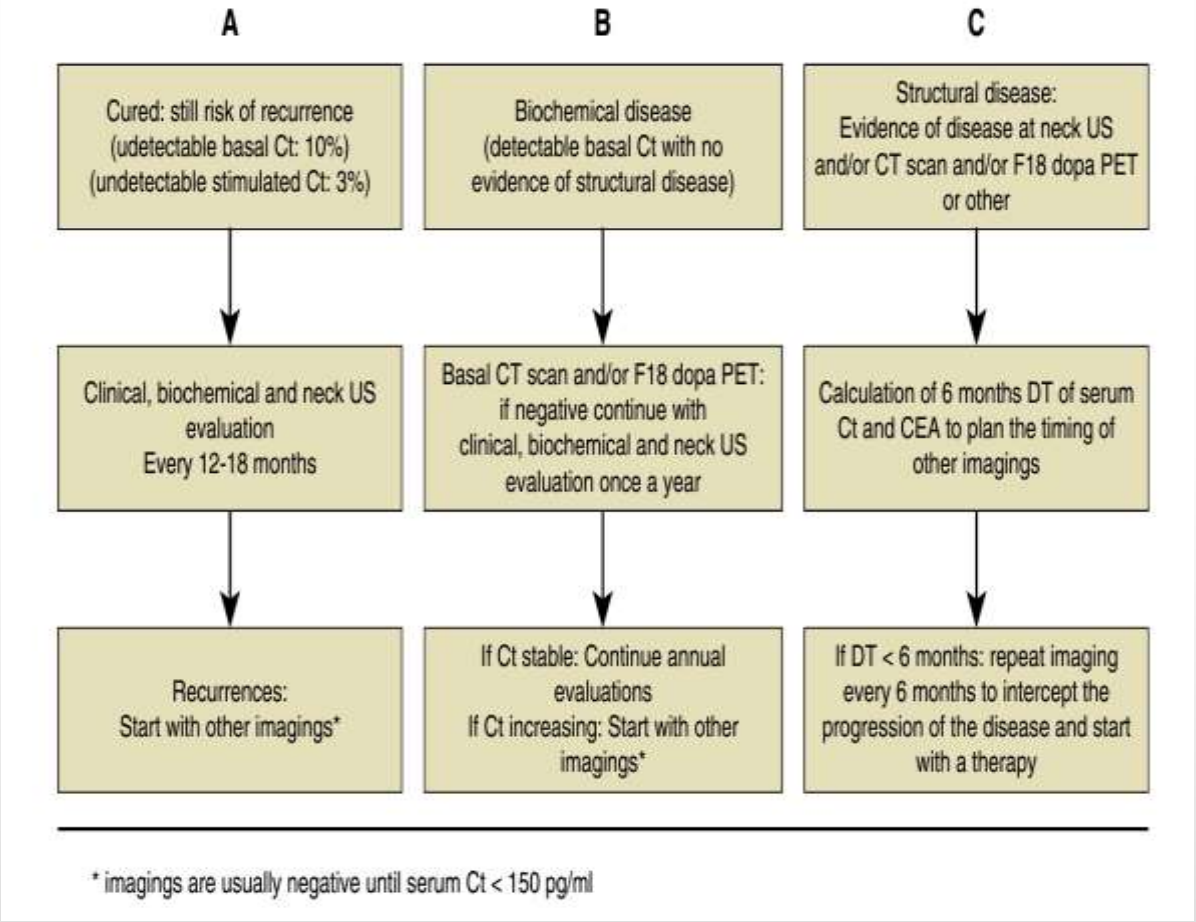
Wells SA Jr, Asa SL, et al American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015 Jun;25

MONITORING OF DISEASE

Post surgical evaluation after 3 months –ft3/ft4/TSH, Ct and CEA, neck USG.

Cured : ct < 10pg/ml, neg neck USG and low normal CEA Values.

Biochemically persistent disease – basal Ct >10pg/ml In absence of structural disease.



Kim M, Kim BH. Current Guidelines for Management of Medullary Thyroid Carcinoma. Endocrinol Metab (Seoul). 2021 Jun;36

MANAGEMENT OF RET germline mutation detected on screening

- Normal exam and US of neck

1. MEN2B (HST) – TTX in 1st year or in the first months of life.

   physical exam, US and Ctn, CEA every 6 months for 1 year then annually.

   screen for phaeochromocytoma at 11 years.

2. MEN2A (H) – TTx at or before 5 years of age. Rest same as above.
3. MEN2A (M) –TTx when Ctn levels elevated, earlier if parents unwilling for long period of monitoring. PHEO screening at 16 years onwards.

- Adults – normal Ctn- annual testing

  If elevated – exclude phaeo, TTx.

TAKE HOME MESSAGE

- MTC is a rare cancer with relatively poor prognosis
- Early diagnosis is key.
- Routine Ctn in all thyroid nodules – still debated.
- All MTC patients in absence of genetic testing should be evaluated to rule out phaeochromocytoma and hyperparathyroidism.
- RET screening recommended to identify carriers and plan mx early.
- Surgery is 1st line.
- Yearly follow up with Ctn, imaging based on category.

SURGICAL MANAGEMENT OF MEDULLARY THYROID CANCER

DR NATHAN GRACIAS FLOR
JUNIOR RESIDENT
DEPARTMENT OF GENERAL SURGERY

Introduction

- Medullary Thyroid Cancer (MTC) is a rare form of thyroid cancer originating from parafollicular C cells.
- Surgical management is the mainstay as MTC is less responsive to radioactive iodine therapy.
- Often associated with genetic mutations, particularly in the RET proto-oncogene.
- Risk Factors: Family history, genetic syndromes (e.g., MEN 2A and 2B).

Diagnosis of Medullary Thyroid Cancer

- Clinical Presentation: Neck swelling(most common), hoarseness, difficulty swallowing.

- Investigations-
- - FNAC
- - Imaging: for local disease and distant spread
- - Biomarkers: Elevated serum calcitonin and carcinoembryonic antigen (CEA) levels.
- - Genetic Testing: Identification of RET mutations, especially in familial cases.

- Indications for imaging to r/o distant mets

1. Neck nodes on USG
2. Calcitonin >500

- CECT neck + thorax + abdomen
- Others- bone scan, FDG PET-CT

TNM

T1	Tumor diameter 2 cm or smaller
T2	Primary tumor diameter >2–4 cm
T3	Primary tumor diameter >4 cm limited to the thyroid or with minimal extrathyroidal extension
$T4_a$	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
$T4_b$	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
TX	Primary tumor size unknown, but without extrathyroidal invasion
N0	No metastatic nodes
$N1_a$	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
$N1_b$	Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal nodes
NX	Nodes not assessed at surgery
M0	No distant metastases
M1	Distant metastases
MX	Distant metastases not assessed

Staging

- I-T1N0
- II-T2N0
- III-upto T3N1a
- IV A- T4a or N1b
- IV B- T4b
- IV C- M1

Surgical Indications

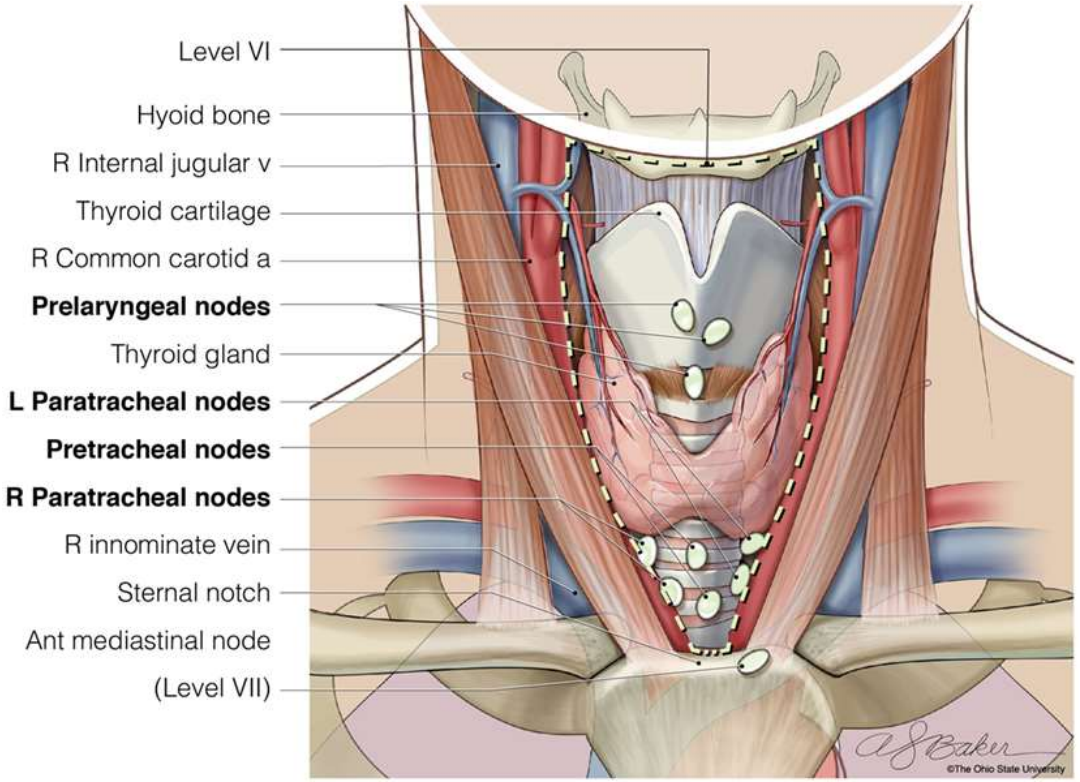
- Surgery is the only curative treatment for MTC.

- Minimum surgery- Total Thyroidectomy

1. Multifocal disease
2. Cells of origin are situated bilaterally
3. Aggressive

Management of the neck

- Based on preop imaging
- Central neck dissection and lateral neck dissection



Complications

1. Parathyroid injury-d/t aggressive nodal dissection

2. Recurrent laryngeal nerve injury

- RLN sacrificed for R0 complete resection

3. Others- hematoma,seroma etc

Adjuvant Radiotherapy

Indications for Radiotherapy:

- Residual disease
- Extrathyroidal extension of the tumor
- Extranodal extension
- Persistent or recurrent disease after initial surgery

Techniques Used:

- External beam radiotherapy (EBRT) is the most commonly used modality.
- Intensity-modulated radiotherapy (IMRT) allows precise targeting of tumor tissues while sparing surrounding healthy tissues.

Outcomes:

- Radiotherapy can improve local control rates.
- It is typically used in conjunction with surgery and not as a primary treatment modality.

- Always r/o pheochromocytoma- treat first
- Always r/o hyperparathyroidism- treat simultaneously

Follow-up

- Regular monitoring of serum calcitonin and CEA levels
- Periodic neck ultrasound and imaging studies.

- Post op calcitonin <10- 10 yr survival of 97%

- If calcitonin >150 or doubled → Imaging(CECT neck + thorax + abdomen)

- Recurrence

- If resectable- Surgery

- Unresectability- Palliative EBRT
  - Extensive ICA involvement
  - Involvement of mediastinal structures

Prognosis

- Prognosis:
- - Depends on the stage at diagnosis and completeness of surgical resection.
- - Early-stage MTC has a good prognosis with appropriate surgical intervention.

Prophylactic thyroidectomy

- Any patient with MEN 2 syndrome → First degree relatives are screened for RET mutation

- High risk(Exon 768/790)- Prophylactic thyroidectomy at 20yrs
- Medium risk(Exon 618,634)- at 5-6 yrs
- Low risk(Exon 918)- at 1yr

Biochemistry investigations of Medullary Carcinoma Thyroid

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Laboratory Evaluation

- Laboratory analysis is an essential part of the evaluation.
- TSH
- T4
- T3
- FT4
- FT3
- Thyroglobulin
- Thyroglobulin antibodies
- Calcitonin
- Thyroid peroxidase antibody (TPO antibody)
- Microsomal antibody

CALCITONIN

Calcitonin is produced and released by parafollicular cells of the thyroid (”the C cells”).

Calcitonin is derived from larger precursors. Precalcitonin (116 amino acids) is cleaved to procalcitonin, which is further cleaved to immature calcitonin (33 amino acids) and then to mature calcitonin, a monomer of a 3.5-kd peptide composed of 32 amino acids, which is the only biologically active form

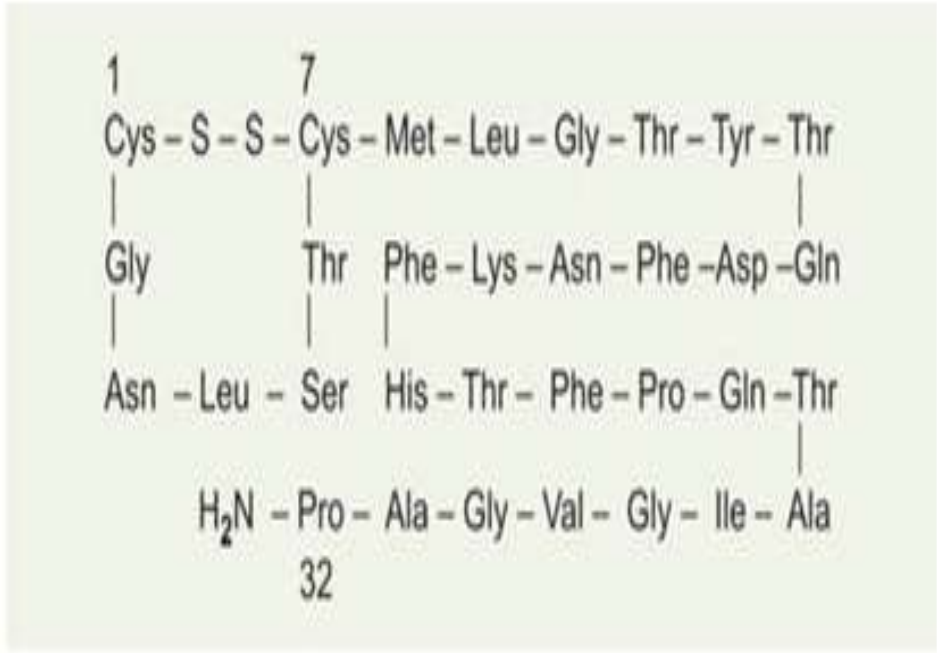


Fig. 33.5: Amino acid sequence of human calcitonin

Procedure for the Calcitonin Test

- **Blood Sample Collection:**
  - The test involves a simple blood draw, usually from a vein in the arm. The procedure is quick, typically taking only a few minutes.

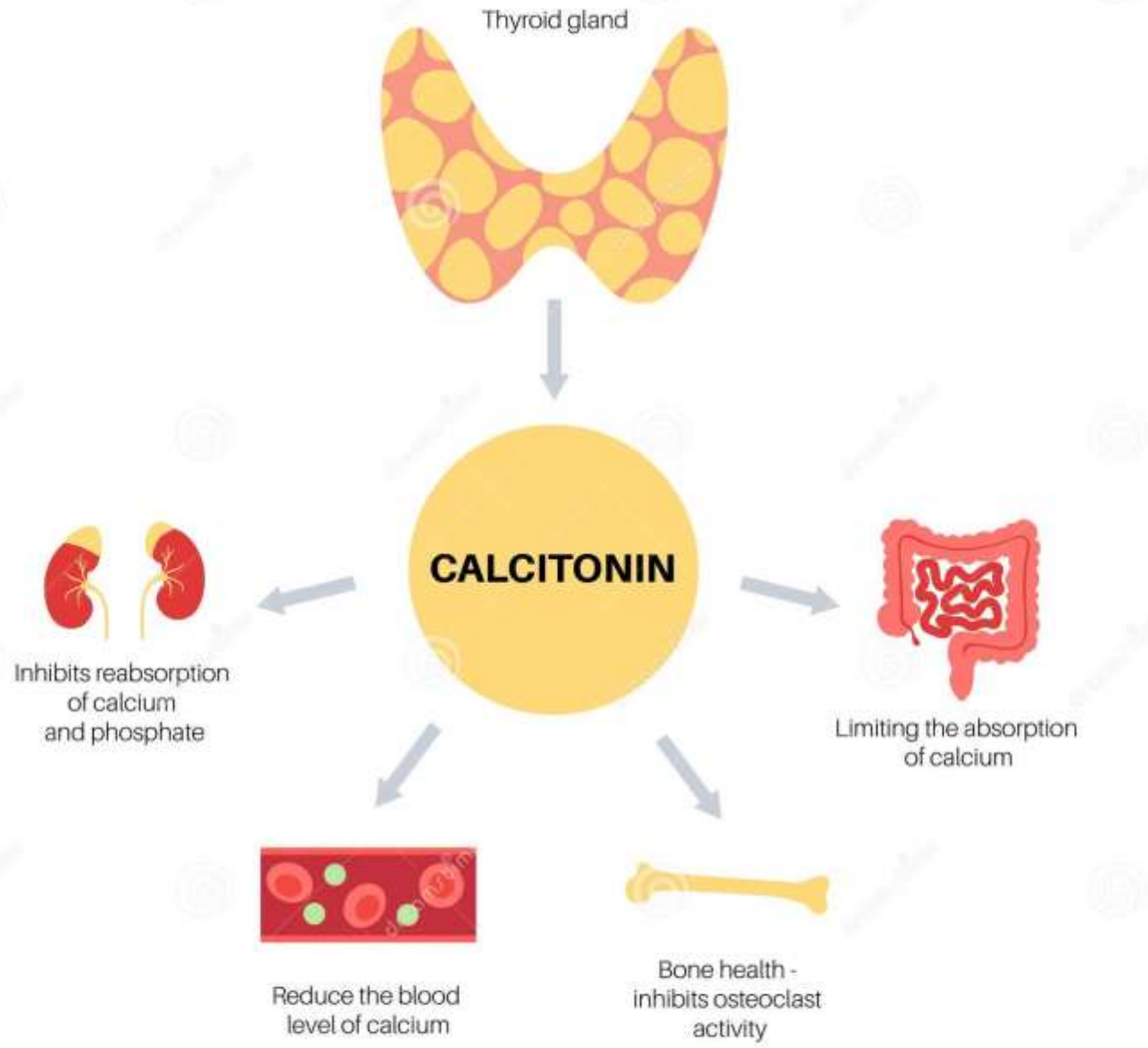
Collect

Serum separator tube or green (sodium or lithium heparin).

Specimen Preparation

Separate serum or plasma from cells ASAP or within 2 hours of collection.
Transfer 2 mL serum or plasma to a Standard Transport Tube. (Min: 1 mL)

- **Laboratory Analysis:**
  - The blood sample is analyzed in a laboratory to measure calcitonin levels using specific immunoassay techniques.
- **Duration:**
  - Results can take a few hours to a couple of days, depending on the laboratory's workload and testing methods.


Thyroid gland
CALCITONIN
Inhibits reabsorption
of calcium
and phosphate
Limiting the absorption
of calcium
Reduce the blood
level of calcium
Bone health -
inhibits osteoclast
activity

Mechanism of Action

1. Role of Cyclic AMP: Calcitonin binds to specific calcitonin receptors on the plasma membrane of bone osteoclasts and renal tubular epithelial cells, activates adenyl cyclase which increases c-AMP level ↑ which mediates the cellular effects of the hormone. This is the principal method by which calcitonin acts.

2. Cellular Shift: It has been suggested that calcitonin may directly affect the relative distribution of bone cells. The hormone both in vitro and in vivo produced a cellular shift, in which the number of osteoclasts decreased.

3. pH Change: Calcitonin regulate pH at cellular level producing more alkaline medium which diminishes resorption.

Purpose of the Calcitonin Test

- **Diagnosis of Medullary Thyroid Cancer (MTC):** The primary purpose of the calcitonin test is to detect high levels of calcitonin, which may indicate MTC, a rare type of thyroid cancer.

- **Monitoring MTC Progression:** The test is also used to track the progression of medullary thyroid cancer and assess treatment effectiveness.

- **Detecting Familial Medullary Thyroid Carcinoma:** The calcitonin test can help identify familial MTC, allowing for early detection in at-risk individuals.

- **Guiding Treatment Decisions:** The test results can guide surgical decisions, especially in patients with a family history of MTC.

You may need a calcitonin test to help check for medullary thyroid cancer or C-cell hyperplasia if:

- You have symptoms of either condition which may include:
- A lump in the front of your neck
- Swollen lymph nodes in your neck (also called "swollen glands")
- Pain in your throat
- Trouble swallowing or breathing

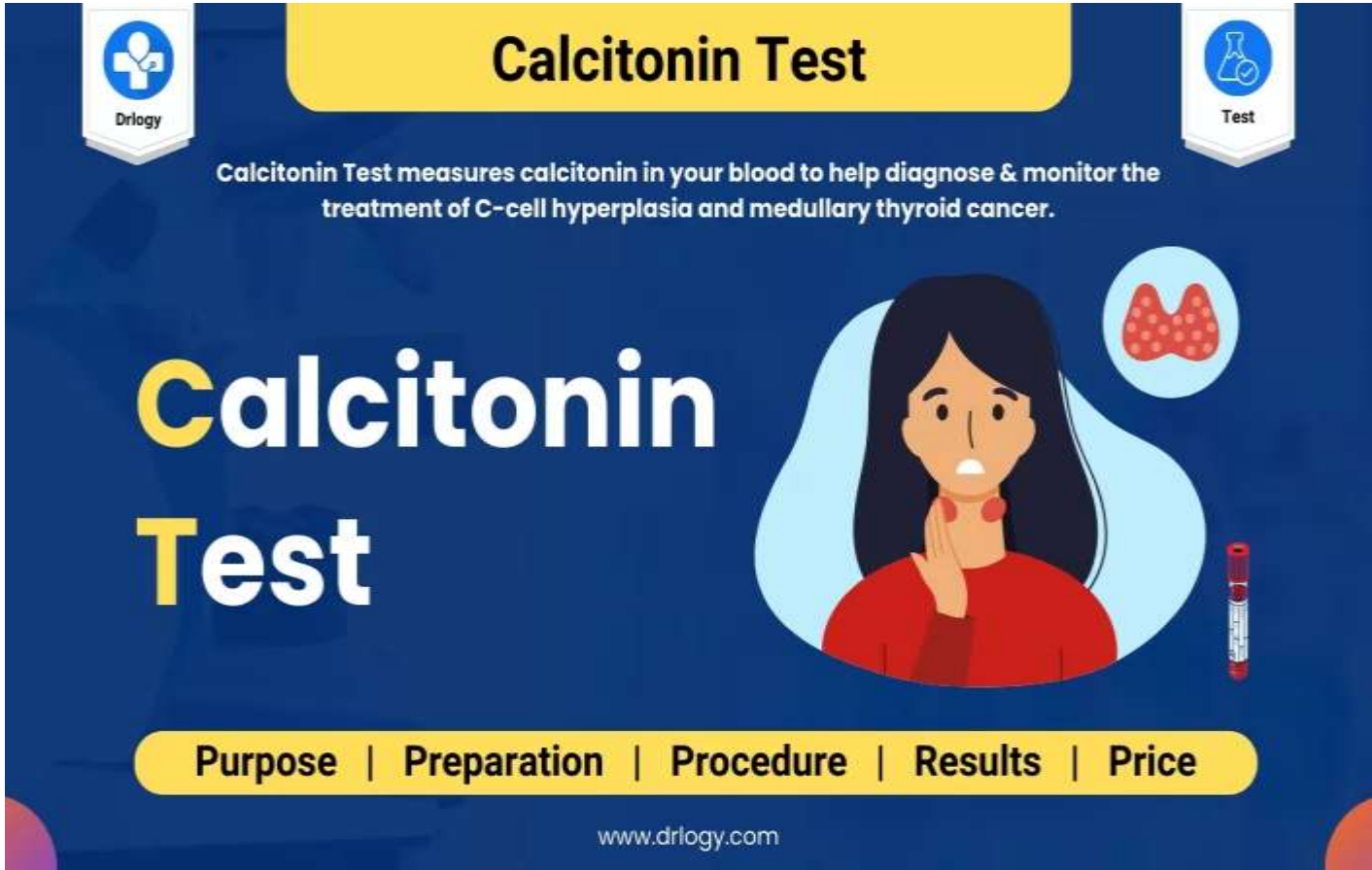


Table 2 - Calcitonin values and risk for medullary thyroid carcinoma*

Value (pg/ml)	Risk for MTC
>100	Extremely high (100%)
≥ 50 and < 100**	Moderate (25%)
≥ 20 and < 50**	Low (8.3%)
<8.5 for men/<5.0 for women	Normal

* Based on Constante et al., 2007. ** It is recommended to systematically investigate non-MTC conditions in patients with calcitonin levels in these ranges.

Increased Levels

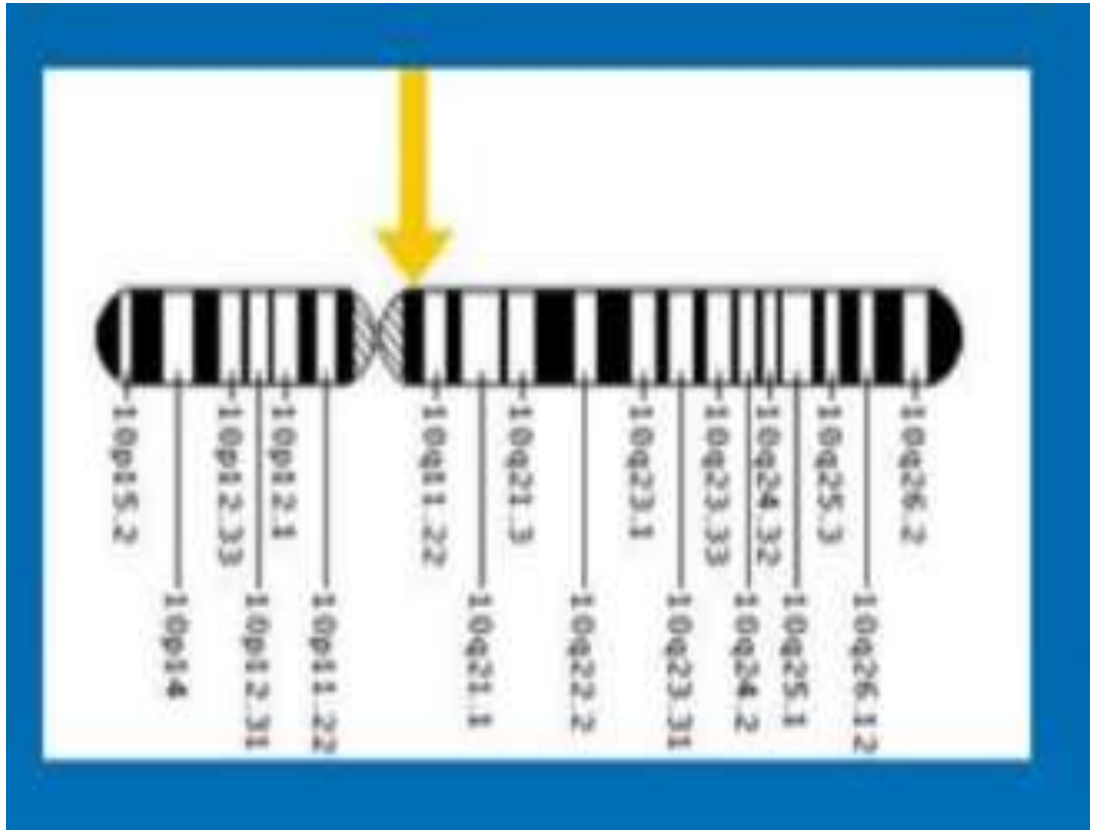
- Medullary carcinoma thyroid
- C-cell hyperplasia
- Non thyroidal cancers like Oat cell carcinoma / Small cell carcinoma, Intestinal / Bronchial / Gastric Carcinoids, Melanoma, Pheochromocytoma, Pancreatic carcinoma & Breast carcinoma
- Hypergastrinemia & other Gastrointestinal disorders
- Acute & Chronic Renal failure
- Hypercalcemia of any etiology stimulating Calcitonin production
- Pulmonary disease
- Pernicious anemia
- Zollinger – Ellison syndrome

Advantage of Calcitonin screening :

- BETTER PROGNOSIS
- early diagnosis and radical surgical treatment reduce MTC-related morbidity and mortality
- Routine screening of Nodular thyroid disease to detect unsuspected sporadic MTC
- For provocative testing in MTC, Calcitonin stimulation test is recommended to increase sensitivity of detection
- To monitor effectiveness of surgery by serial measurement of basal and stimulated calcitonin concentrations

GENETIC TESTING

Cytogenetic Location: 10q11.2
The RET gene is located on the long (q) arm of chromosome 10 at position 11.2.



RET Gene

- Genetic testing for RET germline mutation has shown 100% sensitivity and specificity for identifying those at risk for developing inherited medullary thyroid cancer (multiple endocrine neoplasia (MEN) 2A, MEN 2B, or familial medullary thyroid carcinoma (FMTC)).
- Use of the genetic assay allows earlier and more definitive identification and clinical management of those with a familial risk for medullary thyroid cancer when compared to the existing standard of annual biochemical monitoring.