EoE FRCPath Course

Head, Neck and Endocrine Pathology

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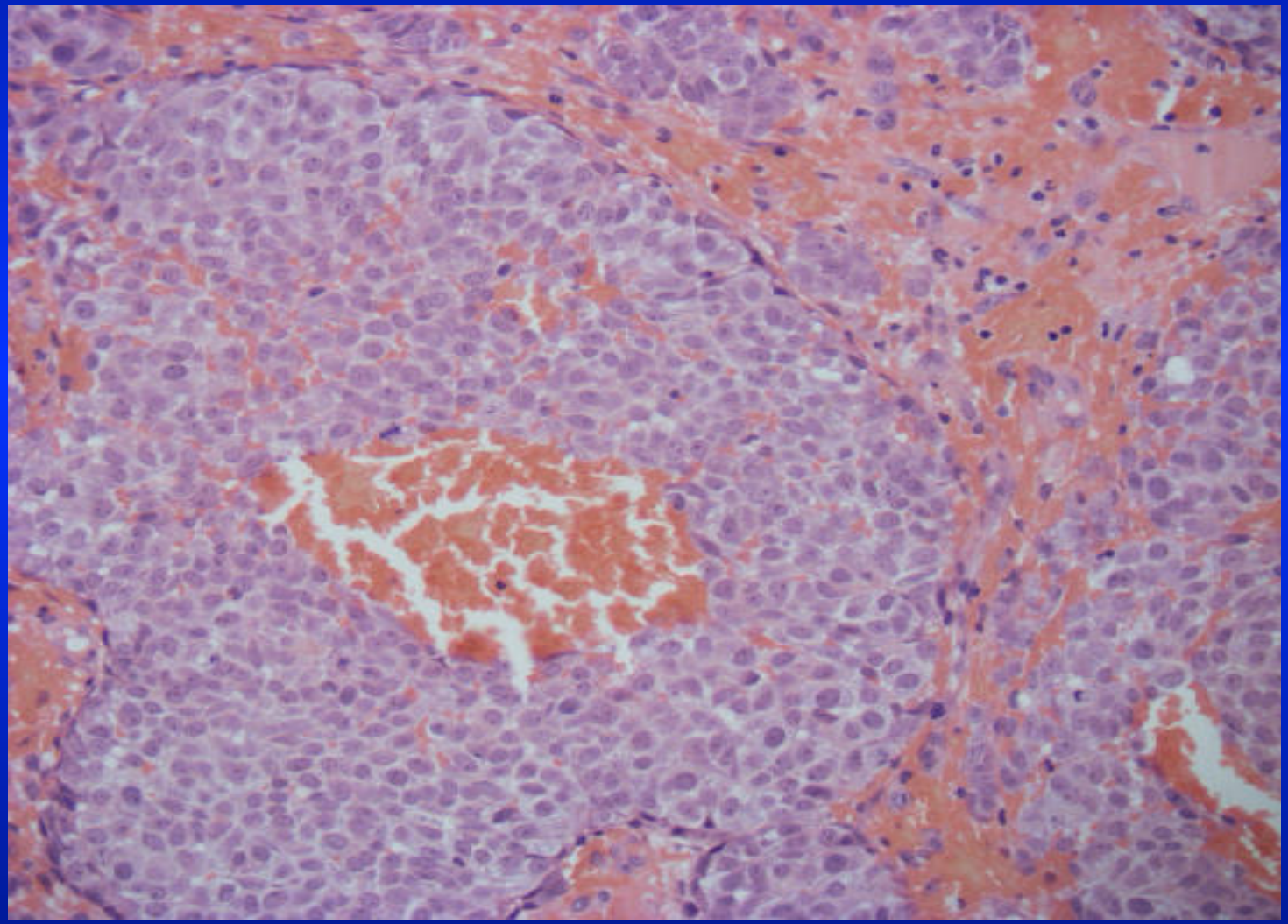
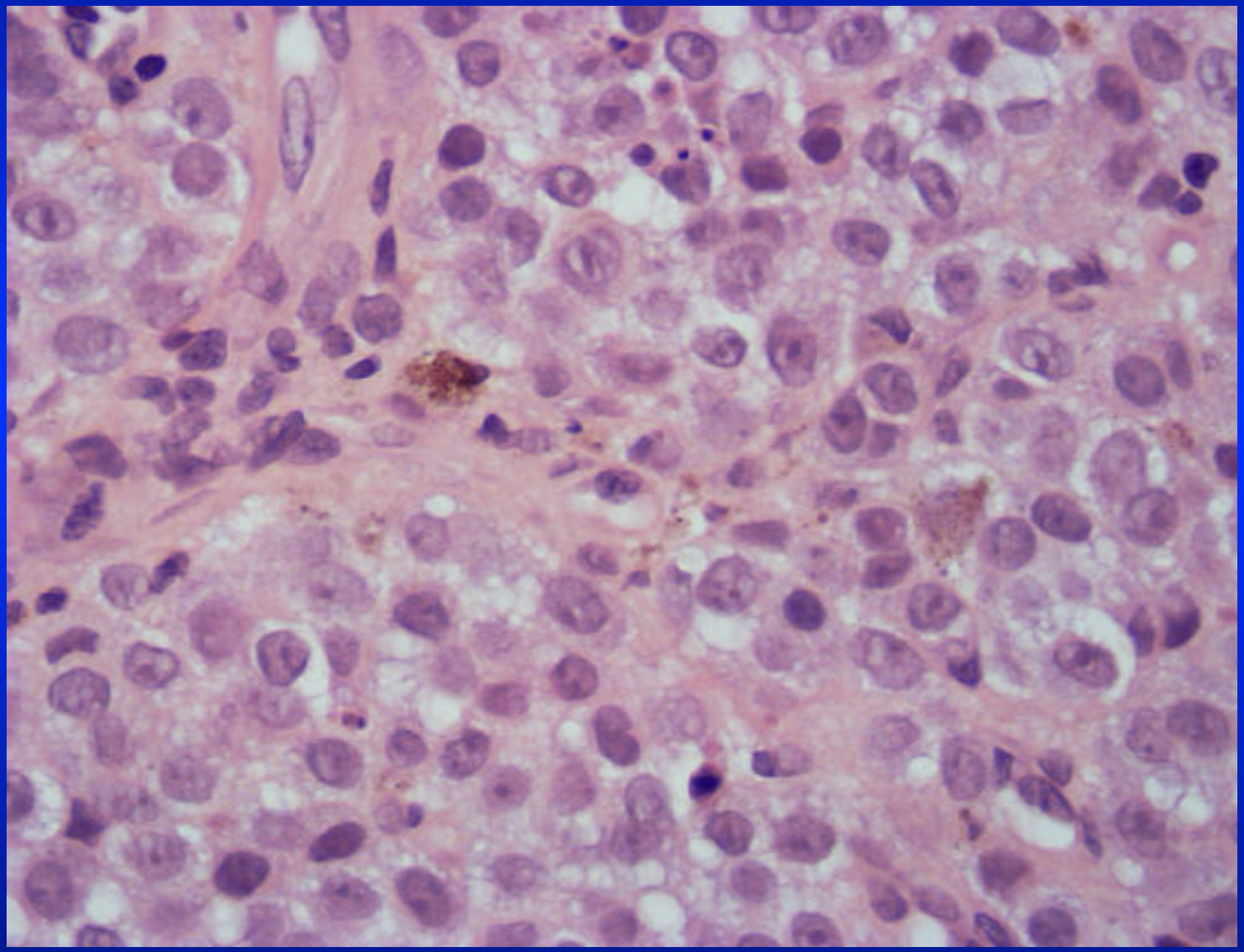
Case 6



Case 6



Case 6

- Ulcerated malignant tumour
- Sheets and nests of cells
- Highly vascular stroma
- Cytoplasmic pigment

Case 6

Differential diagnosis

- Small blue round cell neoplasms
  - Sinonasal undifferentiated carcinoma
  - Lymphoma
  - Rhabdomysarcoma
  - Mucosal malignant melanoma
  - Neuroendocrine carcinoma
- Pleomorphic neoplasms
  - Anaplastic large cell lymphoma
  - Angiosarcoma or other sarcomas

Case 6

Immunohistochemistry

Positive

- Melan A, S100, HMB45

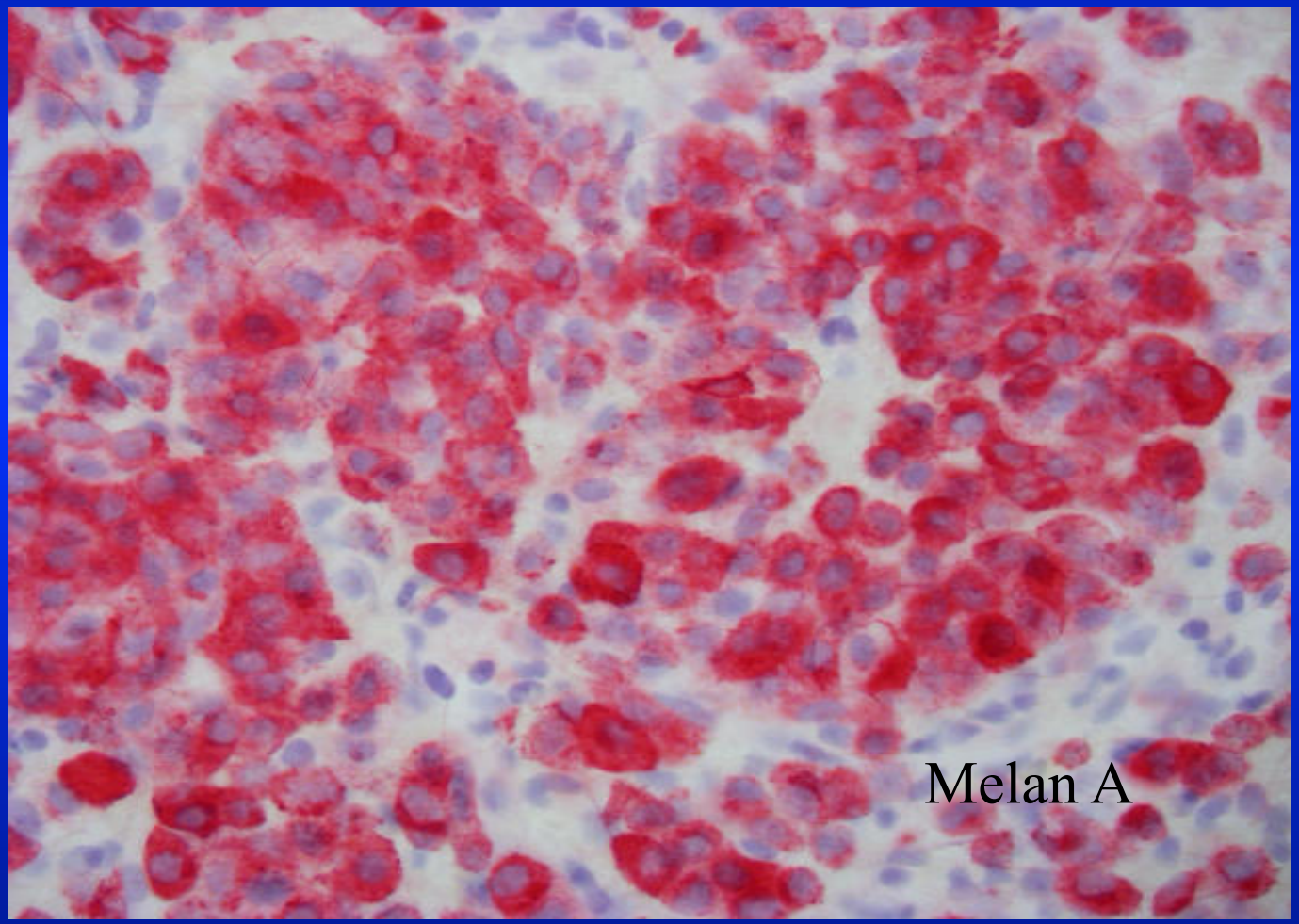
Negative

- Cytokeratin, CD45

Patchy positivity

- NSE

Case 6



Case 6

Diagnosis

- MALIGNANT MELANOMA

Malignant melanoma

- Mucosal malignant melanomas of H&N are rare
- <1% all melanomas
  - 50% are in oral cavity
- <5% all sinonasal tract neoplasms
- M=F
- 5^{th} to 8^{th} decade, peak in 7^{th}
- Usually nasal cavity +/- paranasal sinuses
- Large polypoid bulky tumours
  - 70-80% localised at presentation (stage I)
  - 10-20% regional lymph node mets (stage II)
  - <10% distant mets (stage III)

Malignant melanoma

Micro

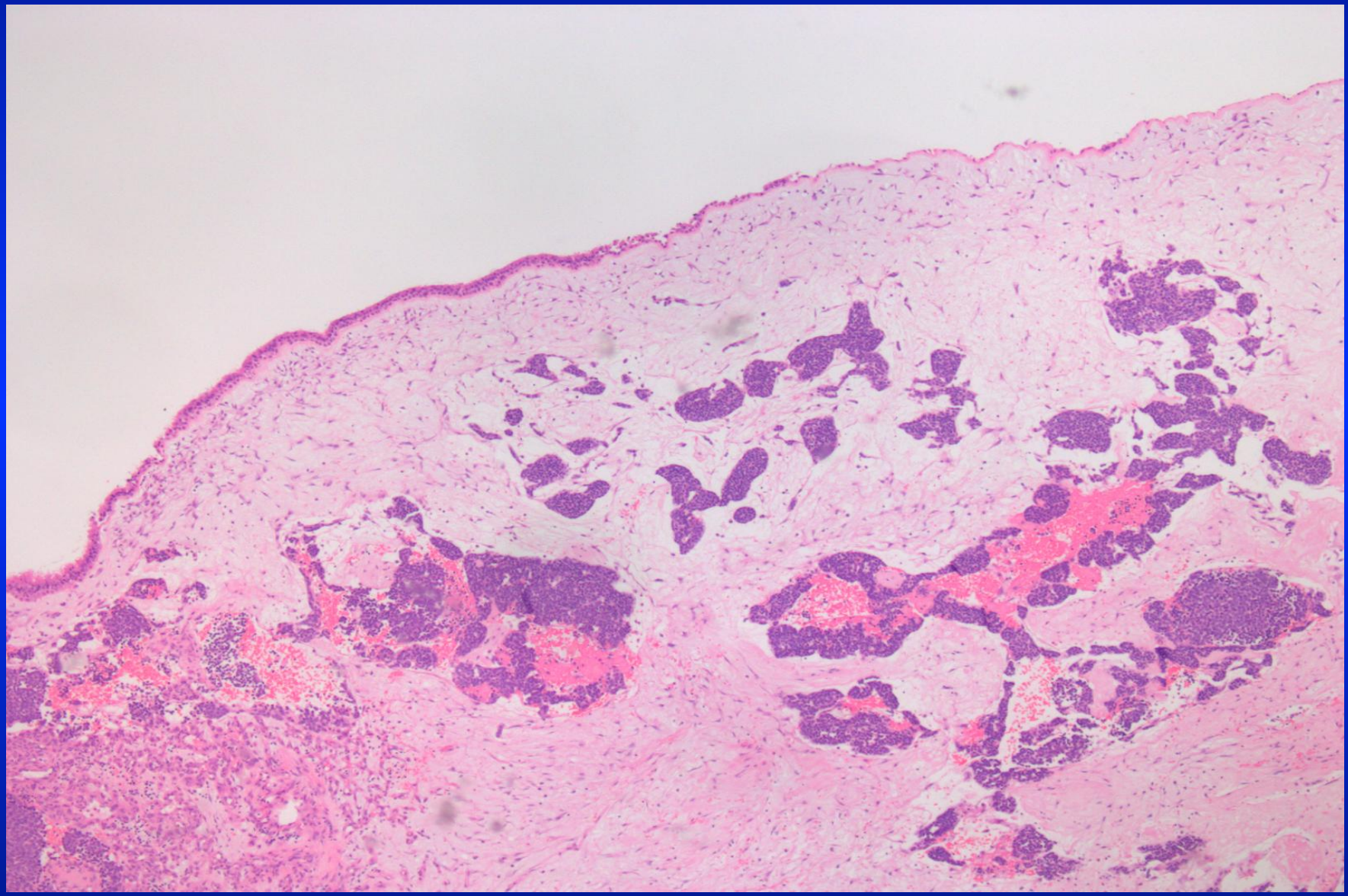
- Medium to large-sized cells
- Epitheloid, spindled, plasmacytoid, rhabdoid
- High N:C ratio, pleomorphic nuclei, prominent nucleoli, i/n inclusions
- Frequent mitoses
- Dense eosinophilic cytoplasm ± melanin
- Intraepithelial melanocytic atypia
  - Favours primary

Malignant melanoma

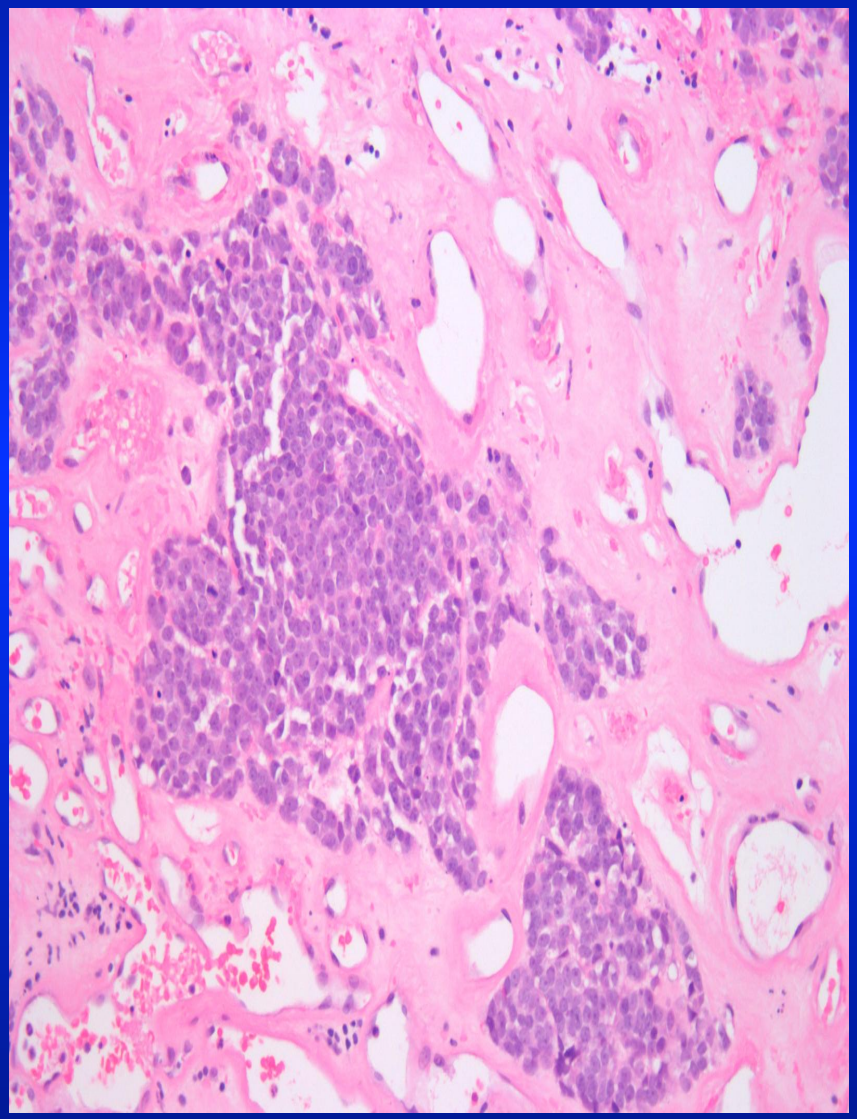
Prognosis and predictive factors

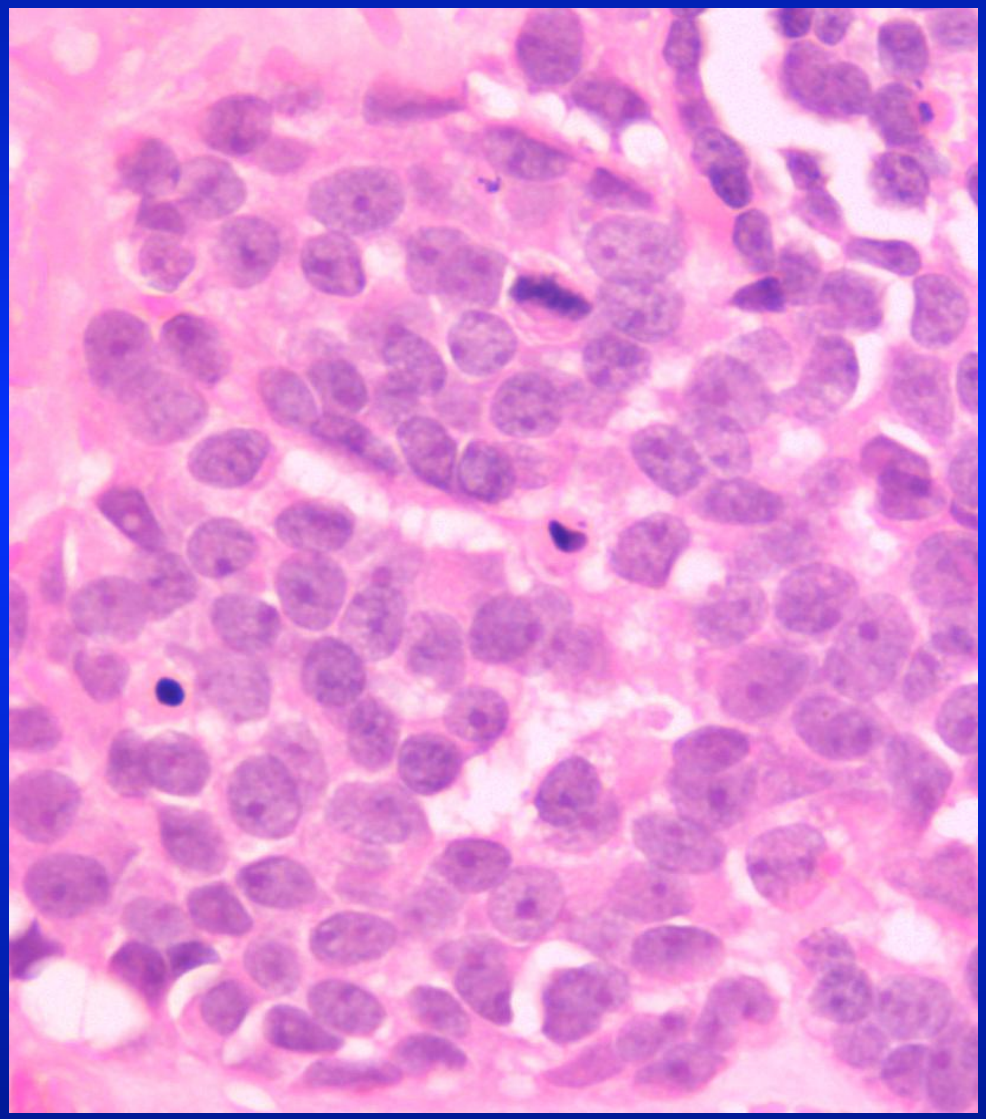
- Surgery is primary treatment modality
- Local recurrence frequent
- Most tumours progress to regional and distant metastasis
- 5 year disease-specific survival 17-47%
- Other poor prognostic factors
  - Large size, paranasal/nasopharyngeal location
  - Vasc invasion into sk.musc and bone, high mitotic count, marked cellular pleomorphism, distant mets

Case 12 PS12.8365



Case 12 PS12.8365





Case 12 PS12.8365

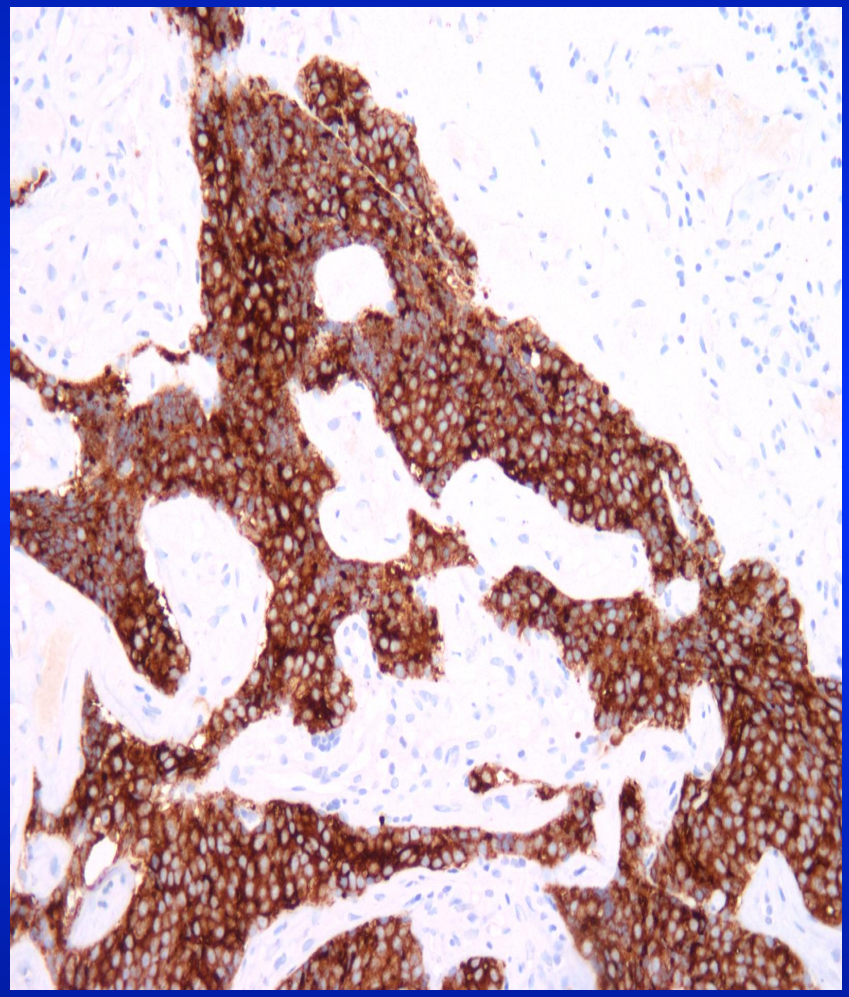
- Lobular, trabecular and sheet-like growth pattern
- Vascular stroma
- Highly cellular
  - Moderately pleomorphic round to oval nuclei
  - Prominent nucleoli
  - Mitotic activity
  - Individual necrotic tumour cells
- Rosettes and fibrillary zones are inconspicuous

Case 12

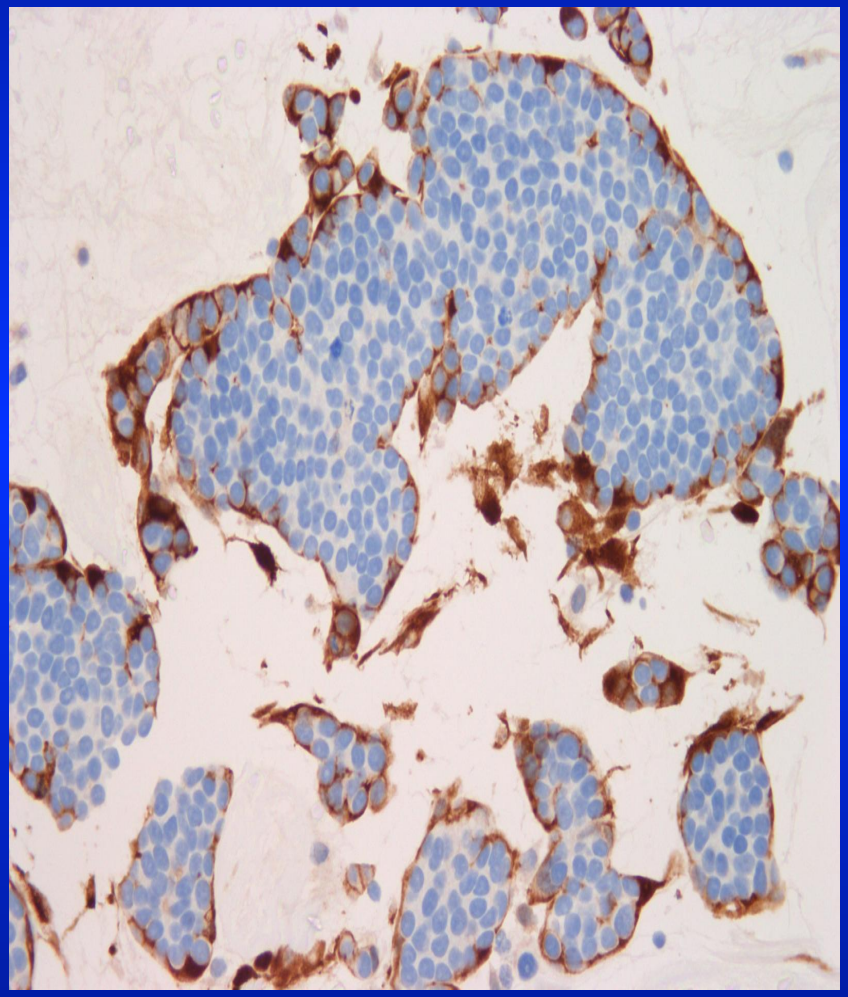
Differential diagnosis

- Small blue round cell neoplasms
  - Sinonasal undifferentiated carcinoma
  - Lymphoma
  - Rhabomysarcoma
  - Mucosal malignant melanoma*
  - Neuroendocrine carcinoma
- Neuroectodermal tumours*
  - PNET/Ewing's sarcoma
  - Olfactory neuroblastoma
  - Melanotic neuroectodermal tumour of infancy

Case 12 PS12.8365



Synaptophysin



S100

Case 12

- Diagnosis
  - OLFACTORY NEUROBLASTOMA

Olfactory neuroblastoma

- Uncommon, 2-3% sinonasal tract tumours
- Age range 2-90 with bimodal distribution
  - Peaks in 2nd and 6th decades
- Typically presents with unilateral nasal obstruction and epistaxis
- Comonest site is cribriform plate region upper nasal cavity
- Polypoid, glistening mucosa-covered vascular mass

Olfactory neuroblastoma

- Submucosal
- Typically lobular or nested pattern
- Richly vascular stroma
- Uniform small round nuclei
- Scanty cytoplasm coarse to fine (“salt and pepper”) chromatin
- Homer-Wright (up to 30%) or Flexner-Wintersteiner (up to 5%) rosettes

Olfactory neuroblastoma

Immunohistochemistry

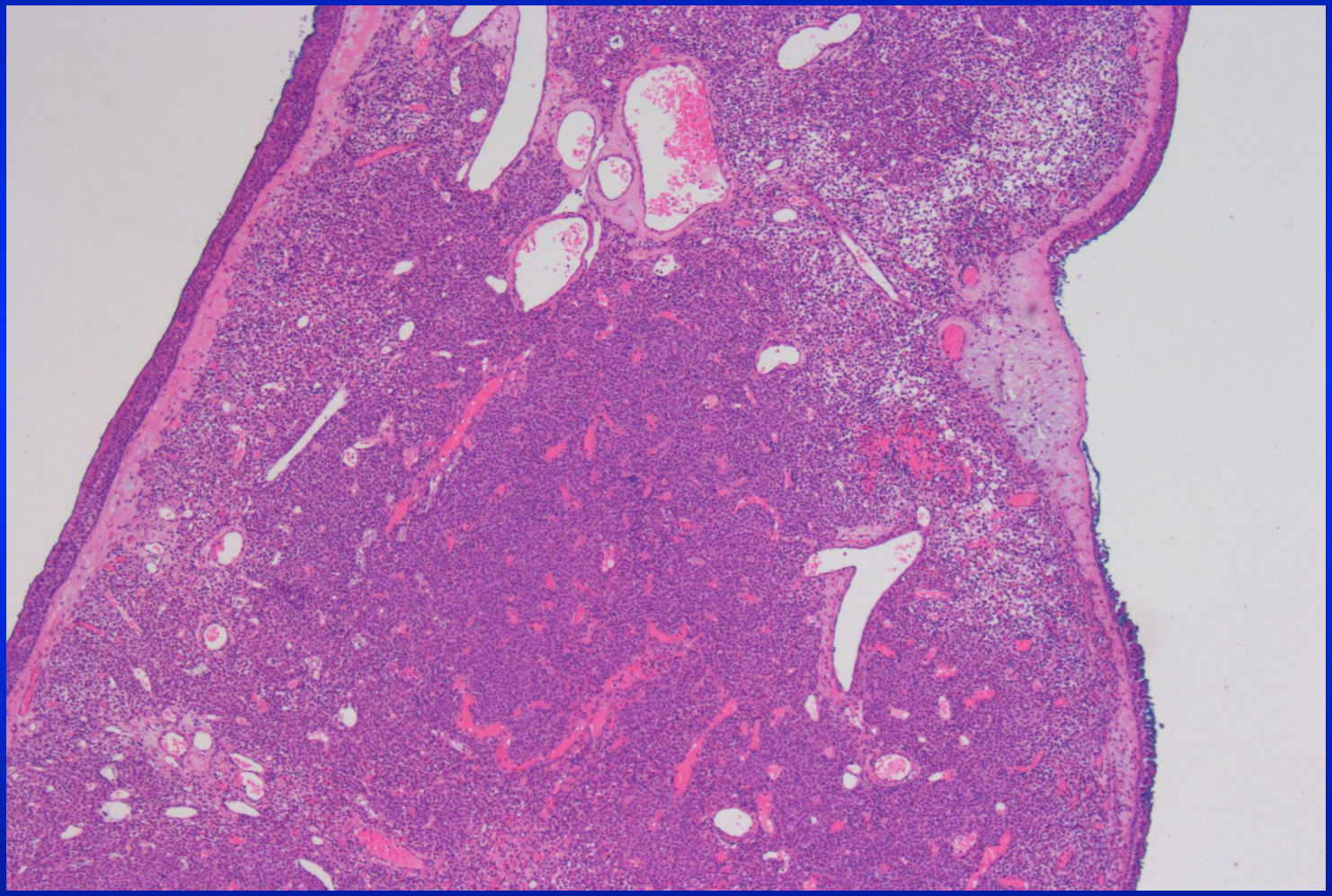
Positive

- NSE
- Synaptophysin
- S100 in sustentacular cells
- Chromogranin, GFAP may be +ve

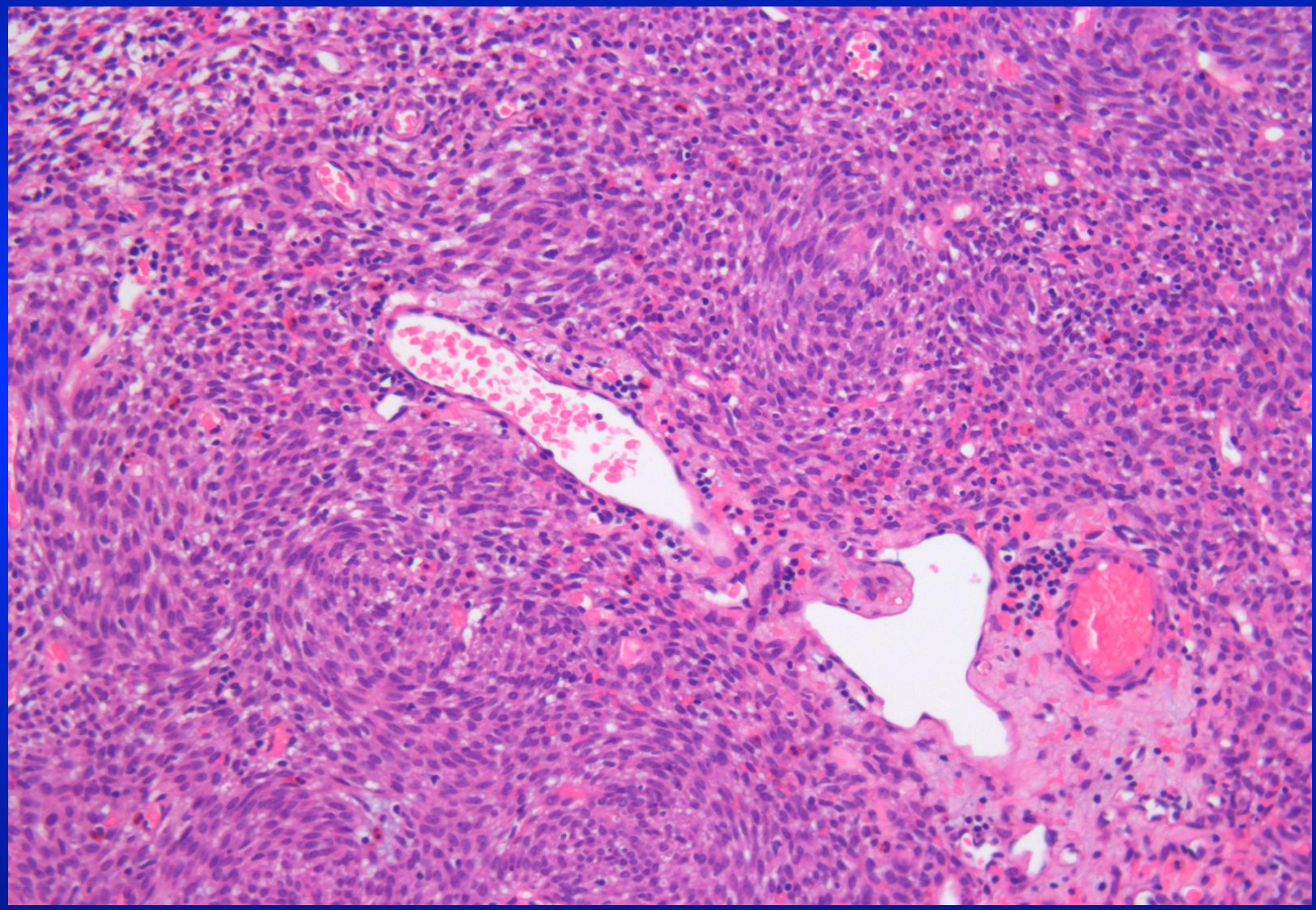
Negative

- Epithelial markers, including EMA and CEA
- LCA, HMB-45 and CD99

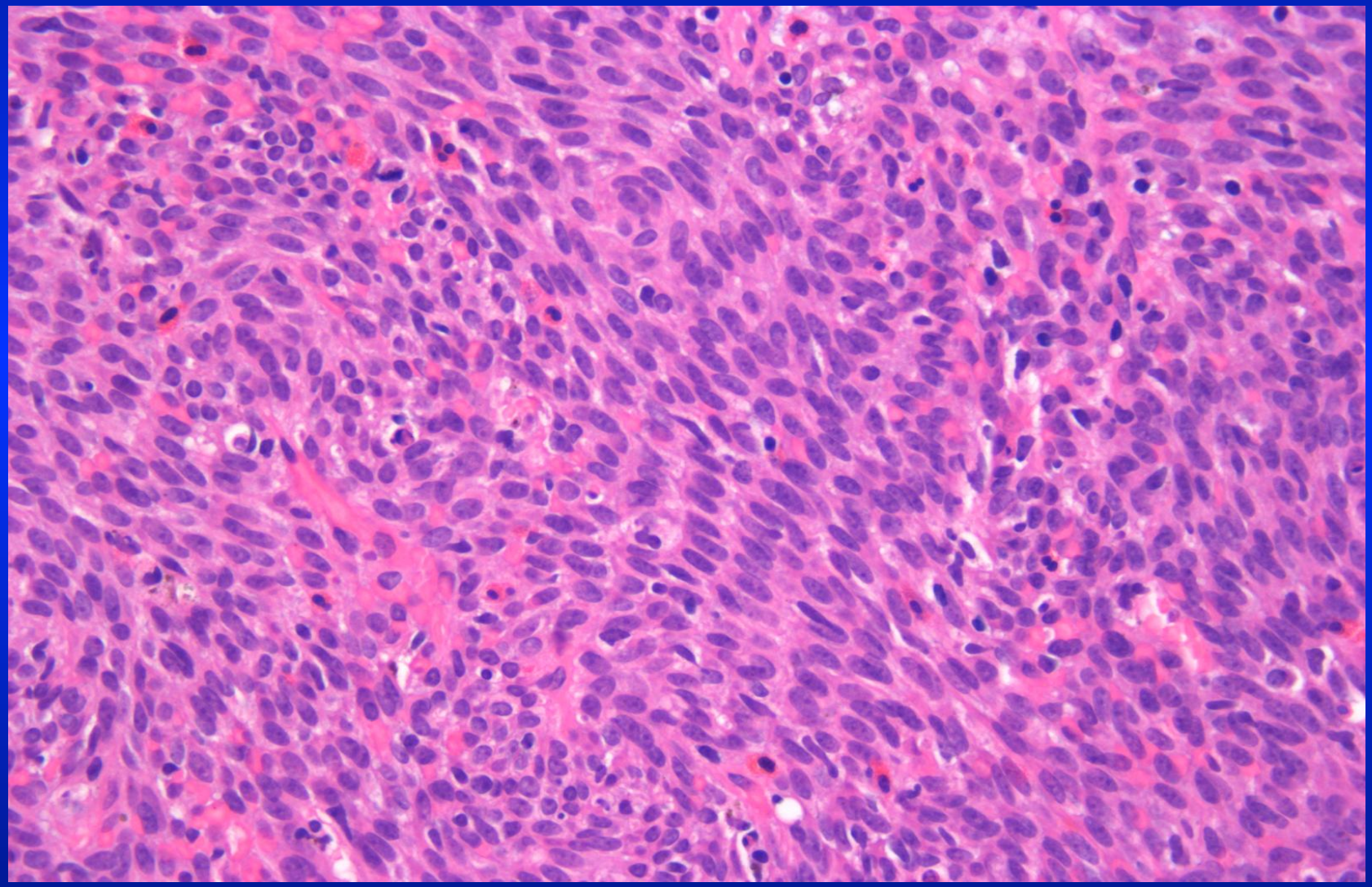
Case 2 PS16.18104



Case 2 PS16.18104



Case 2 PS16.18104



Case 2 PS16.18104

Diagnosis: sinonasal haemangiopericytoma

- Differential diagnosis includes solitary fibrous tumour (SFT), synovial sarcoma, myopericytoma.

Sinonasal haemangiopericytoma (HPC)

- Sinonasal tumour demonstrating perivascular myoid phenotype
- Proposed cell of origin is modified perivascular glomus-like myoid cell
- Occur in nasal cavity/paranasal sinuses
  - <1% of all neoplasms at these sites
  - usually unilateral in nasal cavity
- Slight female preponderance, all ages but most common in adults peak incidence 7th decade

Sinonasal haemangiopericytoma

- Micro
  - Subepithelial, well delineated, unencapsulated and with “Grenz “ zone
  - Closely packed cells arranged in streaming fascicles, whorls or palisades
  - Interspersed with vascular channels
    - Capillary-sized to large gaping vessels that may have staghorn configuration
    - Perivascular hyalinisation
  - Cells are uniform, spindle-shaped with round to oval nuclei, pale eosinophilic cytoplasm
  - Mild nuclear pleomorphism and occasional mitoses
  - No necrosis
  - Extravasated rbcs, mast cells and eosinophils typically present
    - tumour giant cells, fibrosis or myxoid degeneration possible

Sinonasal haemangiopericytoma

Immunohistochemistry

- Positive
  - Factor XIIIA, actin, HHF-35, beta catenin (nuclear)
- Negative
  - CD34 (can be positive but lacks strong diffuse staining), STAT-6, desmin, keratin.

CTNNB1 mutations are consistent aberration in sinonasal HPC

Sinonasal haemangiopericytoma

- Prognosis
  - Indolent behaviour
    - >90% 5 year survival with complete surgical excision
    - 30% recurrence rate
      - Can be many years after initial surgery
  - Aggressive behaviour uncommon, features:
    - Large size, bone invasion, profound nuclear pleomorphism, necrosis, increased mitotic activity (>4/10 high power fields), proliferation index >10%

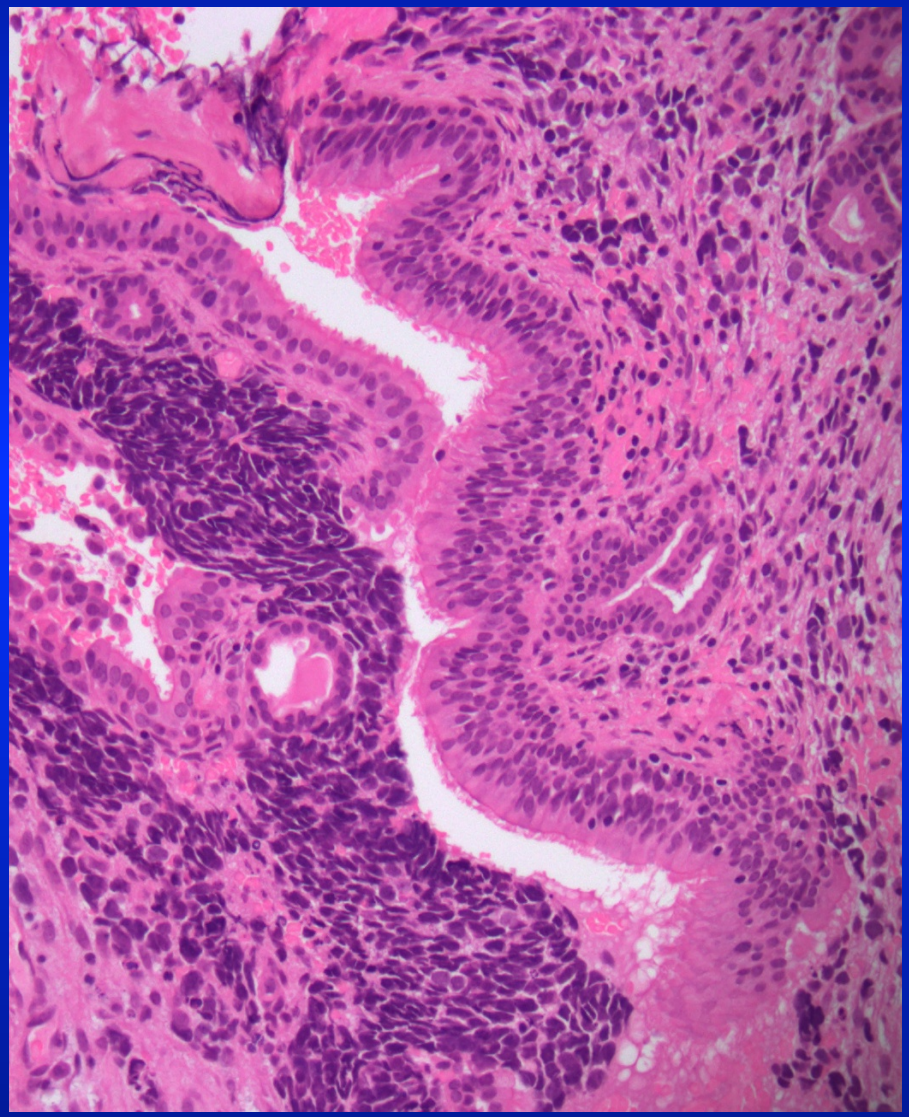
Case 15
TB11.2272 (PQ11.3503)

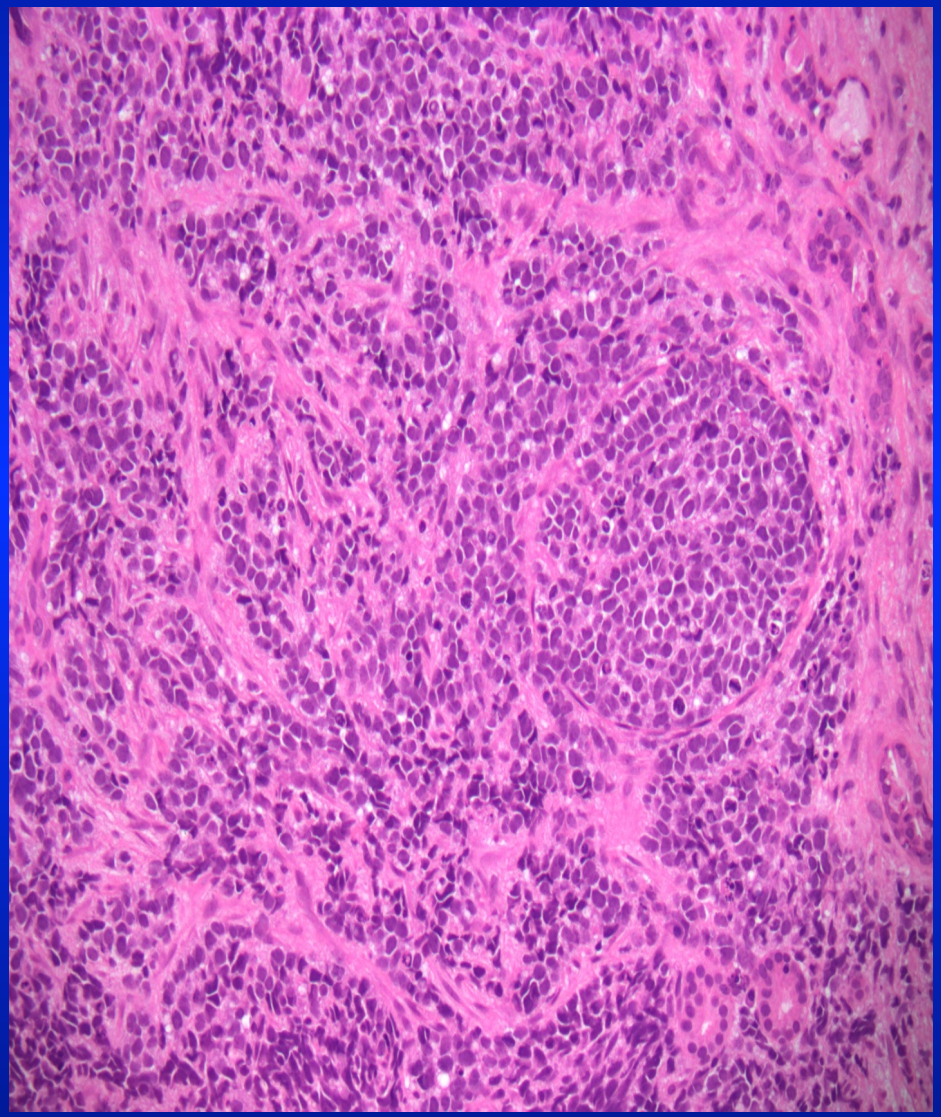
24 year old male with nasal polyp

CT findings

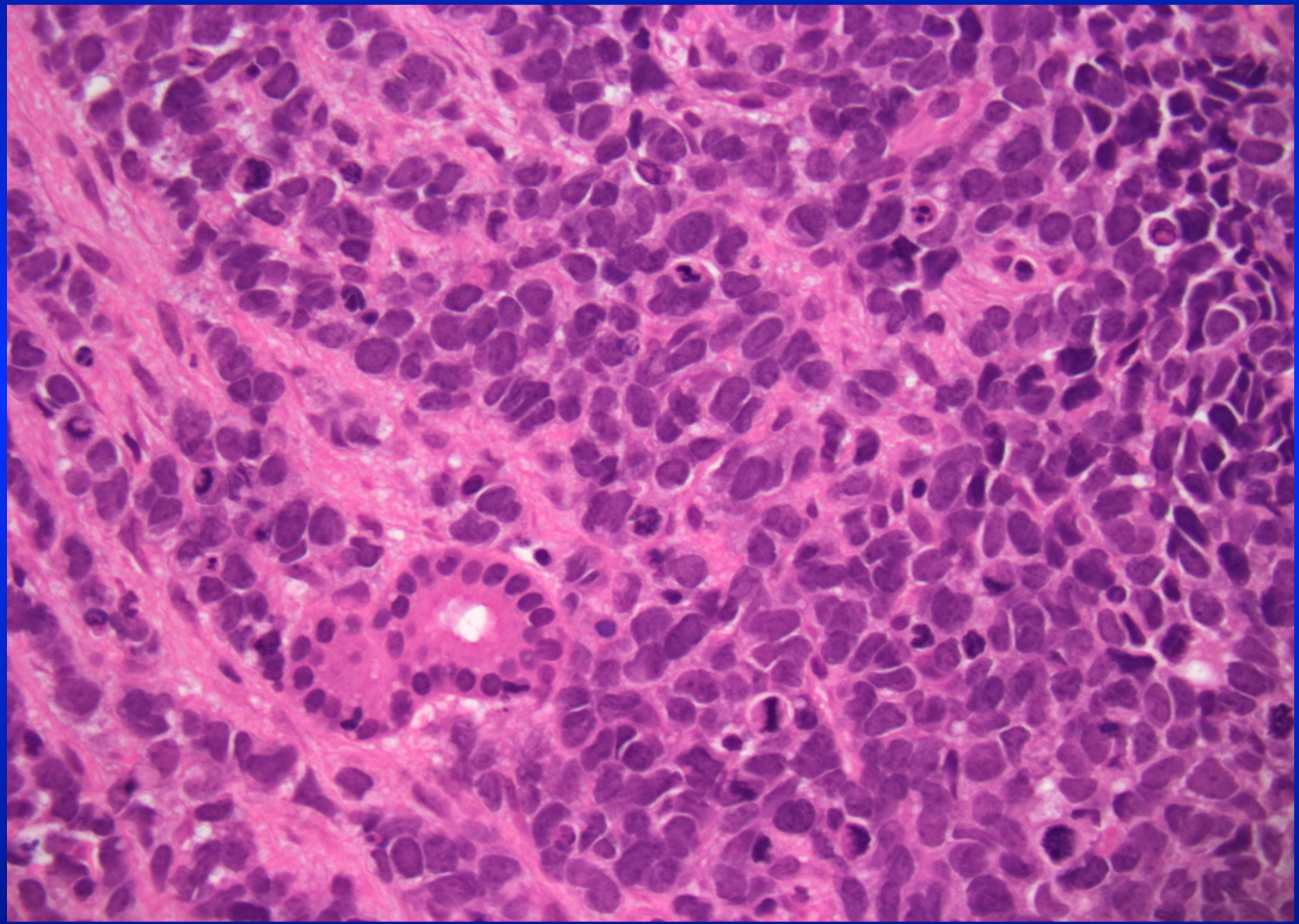
- Tumour left nasal cavity extending into left maxillary cavity and destroying bony structures ? lymphoma

Case 15





Case 15



Case 15

- Respiratory mucosa
  - Infiltrate of malignant cells
  - Nested and trabecular growth patterns
  - Cells have
    - Pleomorphic nuclei with high nuclear to cytoplasmic ratio
    - Nuclear moulding and smearing of nuclear chromatin
    - Mitotic and apoptotic activity
    - Scanty cytoplasm

  "Round blue cell tumour"

Case 15

Differential diagnosis

- Small blue round cell neoplasms
  - Sinonasal undifferentiated carcinoma
  - Lymphoma
  - Rhabomysarcoma
  - Mucosal malignant melanoma*
  - Neuroendocrine carcinoma
- Neuroectodermal tumours*
  - PNET/Ewing's sarcoma
  - Olfactory neuroblastoma
  - Melanotic neuroectodermal tumour of infancy

Case 15

Immunohistochemistry

Positive:

- Skeletal muscle markers (desmin, nuclear myo D1, nuclear myogenin)

Negative:

- Neuroendocrine markers (chromogranin A, synaptophysin, NSE)
- Cytokeratins (MNF116 and AE1/3)
- Lymphoid markers
- S100
- CD99

Case 15

Rhabdomyosarcoma

- Malignant tumour of skeletal muscle phenotype
- 40% occur in head and neck
- 20% in nasal cavity, nasopharynx and nasal sinuses
- Slight male predominance
- Children
  - Commonest sarcoma in childhood
  - Embryonal subtype predominates
- Adults
  - Poor prognosis of <10% 5 year survival
  - Prognosis is determined by patient age, histologic subtyping and tumour clinical group
  - Embryonal subtype has better prognosis than alveolar

Case 15

Rhabdomyosarcoma

Signs and symptoms

- Difficulty breathing, epistaxis, facial swelling, visual disturbance and sinusitis often of short duration
- Large polypoid sinonasal mass which may protrude as gelatinous mass from nostrils

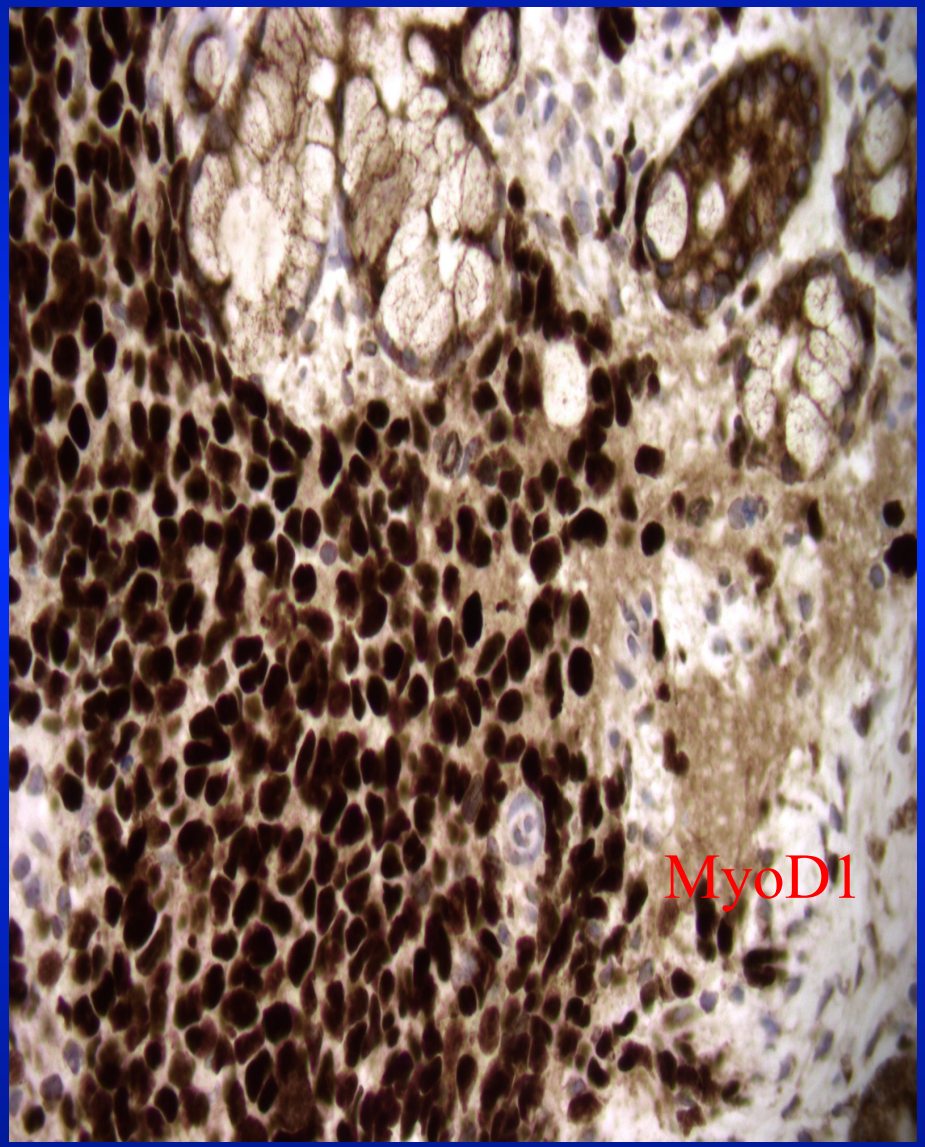
Macro

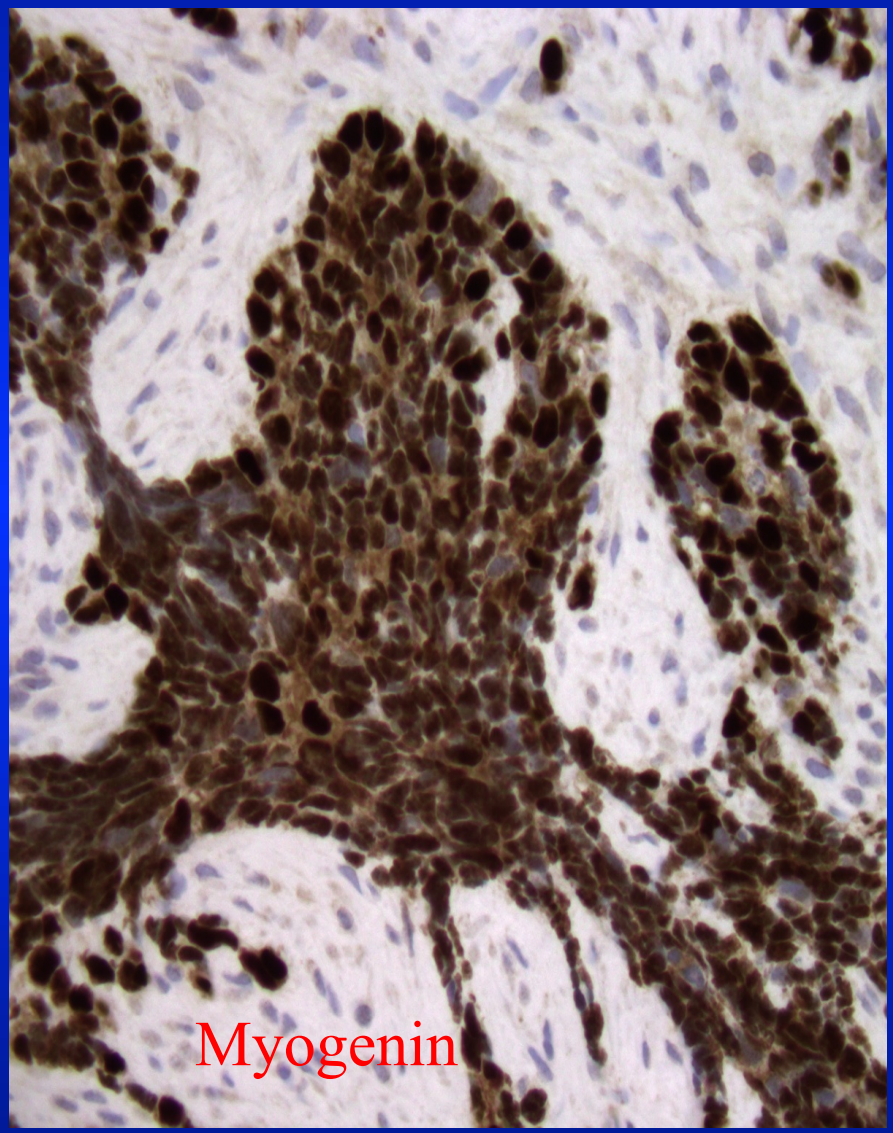
- may resemble sinonasal polyp

Micro

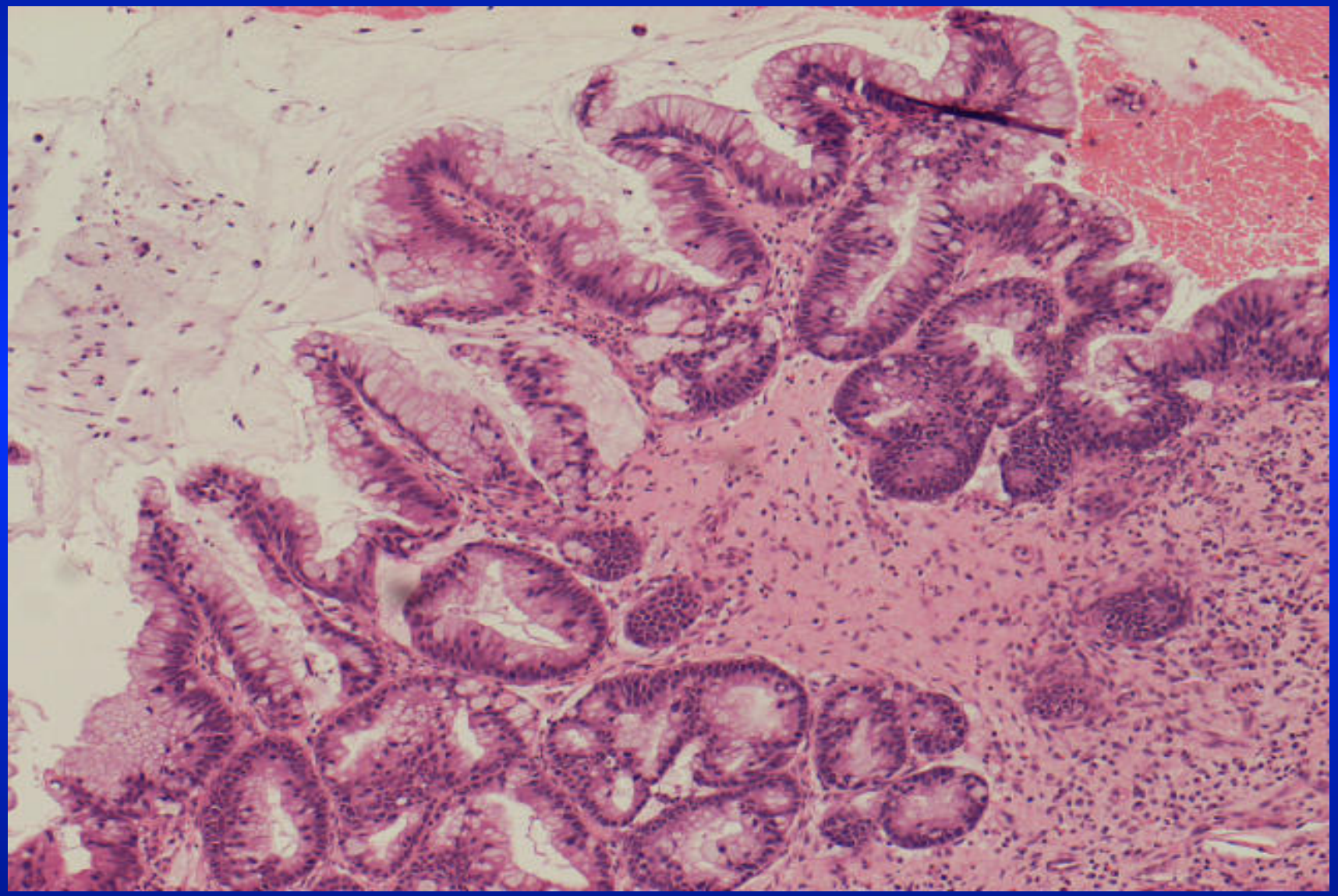
- Two main subtypes; embryonal and alveolar
- This case diagnosed as alveolar subtype
- Immunoreactive for desmin, actin, nuclear myoD1 and nuclear myogenin
- CD99 can be positive in 16% of cases
- Alveolar subtype has consistent translocation t(2:13) or t(1;13)

Case 15

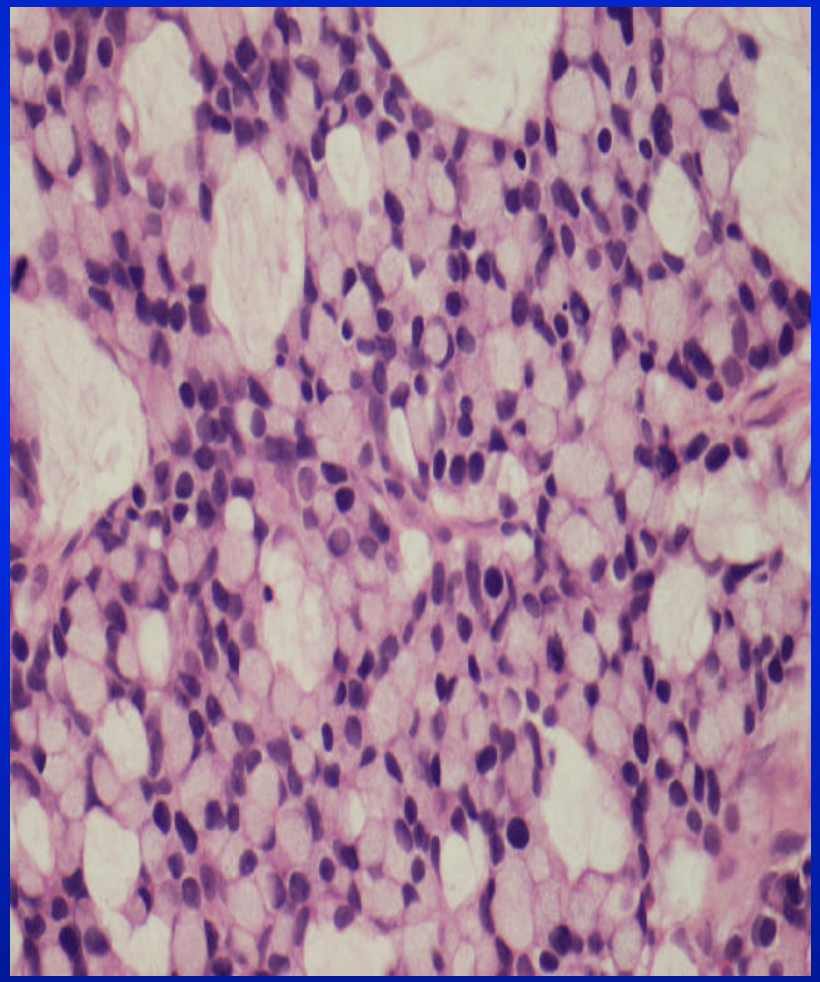


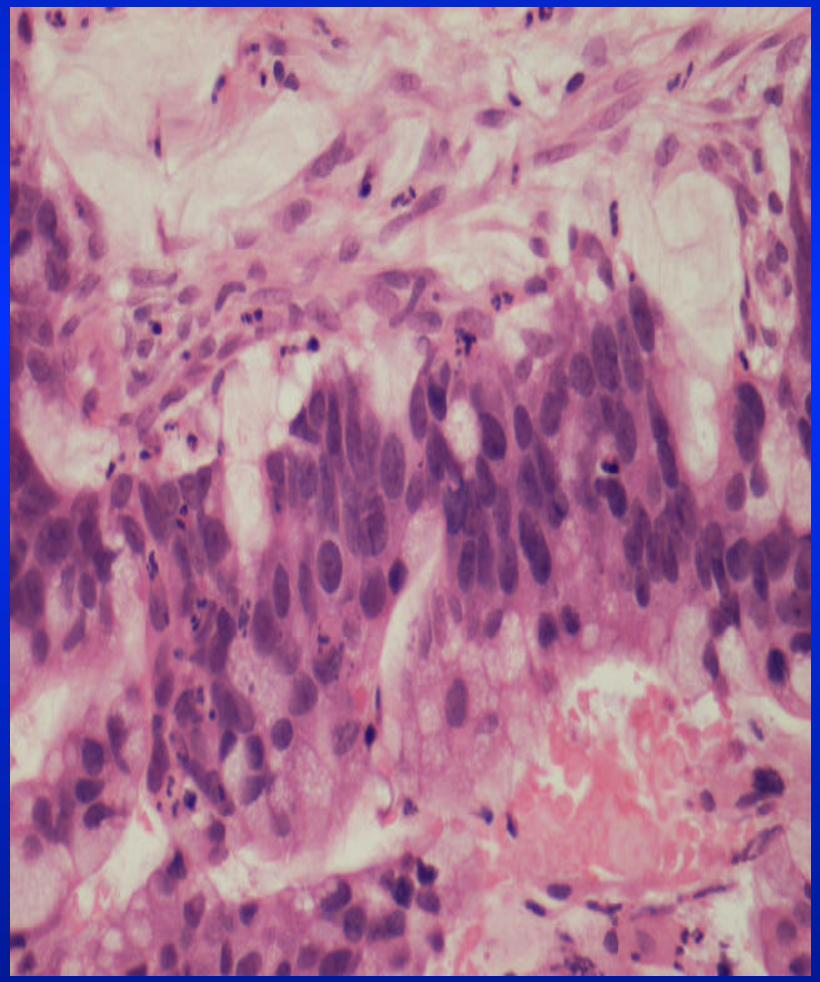


Case 17 PS10.15398



Case 17 PS10.15398





Case 17 PS10.15398

Diagnosis:

Sinonasal intestinal type adenocarcinoma

Adenocarcinoma

- Glandular malignancy of sinonasal tract
- 10-20% sinonasal primary malignant tumours
  - Intestinal
  - Non-intestinal
    - Low or high grade subtypes

Sinonasal ITAC

Clinical

- M>>F
- Wide age range, typically in 5th to 7th decades
- Related to wood or leather dust exposure
  - Larger particles accumulate in nasal mucosa
  - Carcinogens not yet identified
- Non-specific symptoms e.g. unilateral nasal obstruction, rhinorrhoea, epistaxis
- Ethmoid sinus>nasal cavities>maxillary sinus

Sinonasal ITAC

2 classifications proposed:

- 5 or 6 categories
- Barnes
  - Papillary, colonic, solid, mucinous and mixed
- Kleinsasser and Schroeder
  - PTCC types I-III; alveolar goblet, signet ring and transitional types
- Immuno +ve for cytokeratin, EMA, Ber-EP4, CK20, CDX-2

Sinonasal ITAC
Prognosis and predictive factors

Clinical staging unhelpful as most patients have advanced local disease at presentation

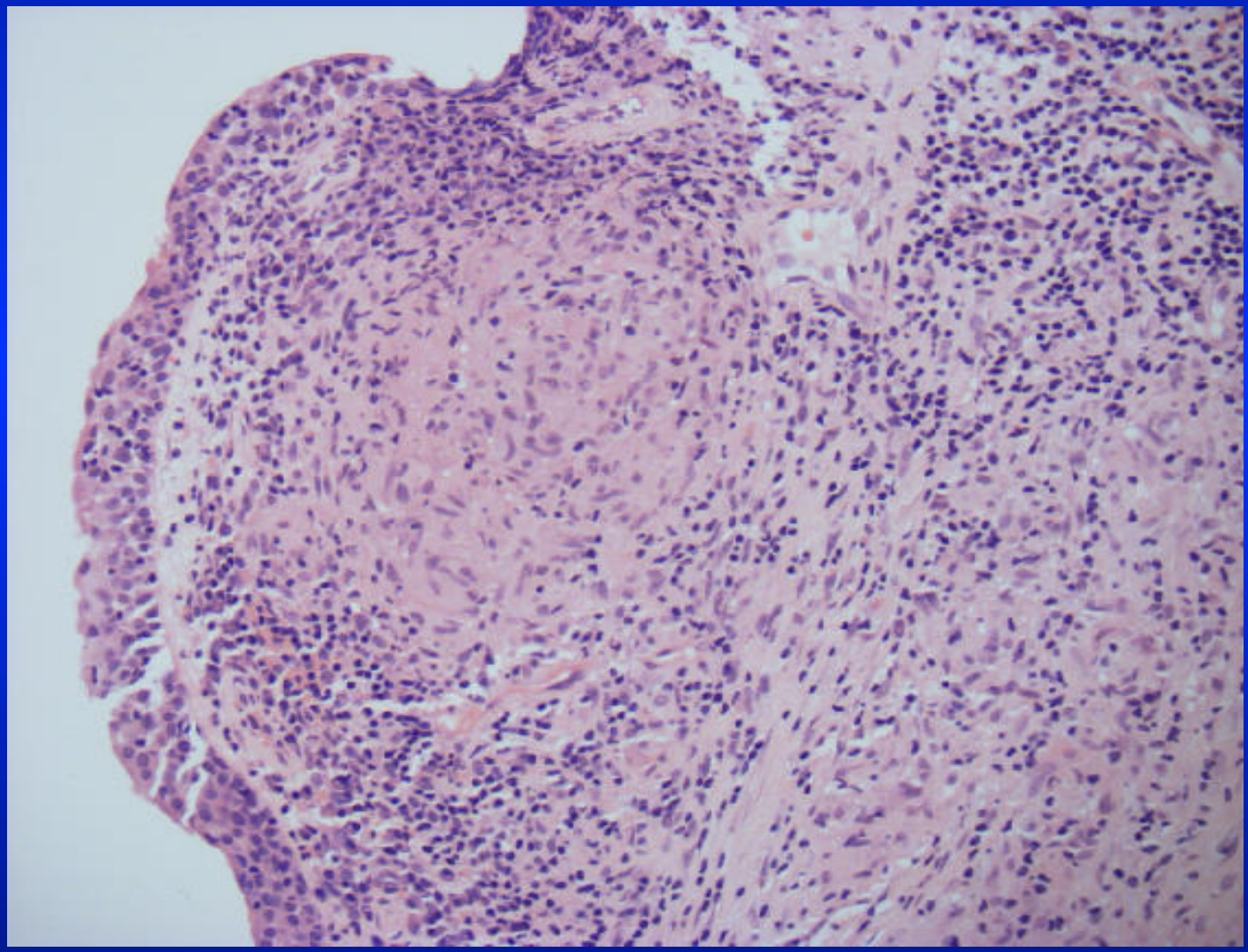
- Locally aggressive, frequent local recurrence (50%)
- Lymph node metastasis and distant spread are rare
- 5 year survival 40%

Adverse features

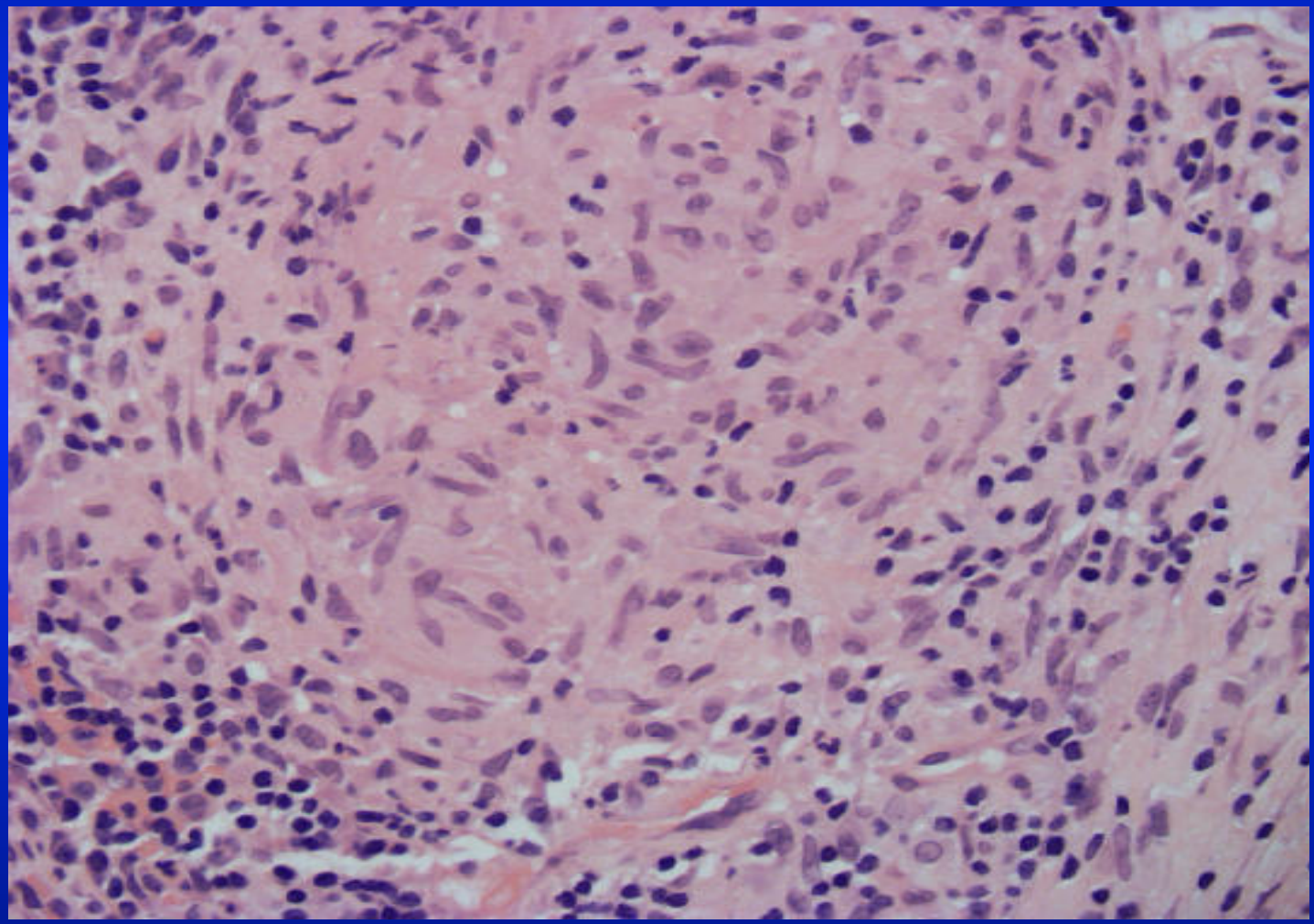
- Solid and mucinous histological subtypes
- H-RAS mutation
- Expression of chromogranin and c-erbB-2

Treatment is by surgical excision +/- RT

Case 7 PS09.31470



Case 7 PS09.31470



Case 7

- Respiratory mucosa
  - Well formed granulomas
  - Inflammatory infiltrate
  - No vasculitis or necrosis

Case 7

Granulomatous inflammation in the nasal mucosa

Differential diagnosis

- Wegener's granulomatosis
  - Vasculitis
    - leukocytoclastic
  - Necrosis
    - Geographic with palisaded histiocytes
  - Granulomatous inflammation
    - Lymphocyte poor
- TB or other microorganism
  - Many cases associated with cervical lymphadenopathy – most represent isolated URT infection rather than secondary spread
- Sarcoid
- Granulomas of foreign body type
  - Can follow local steroid injections
    - Amorphous foreign material

Case 7

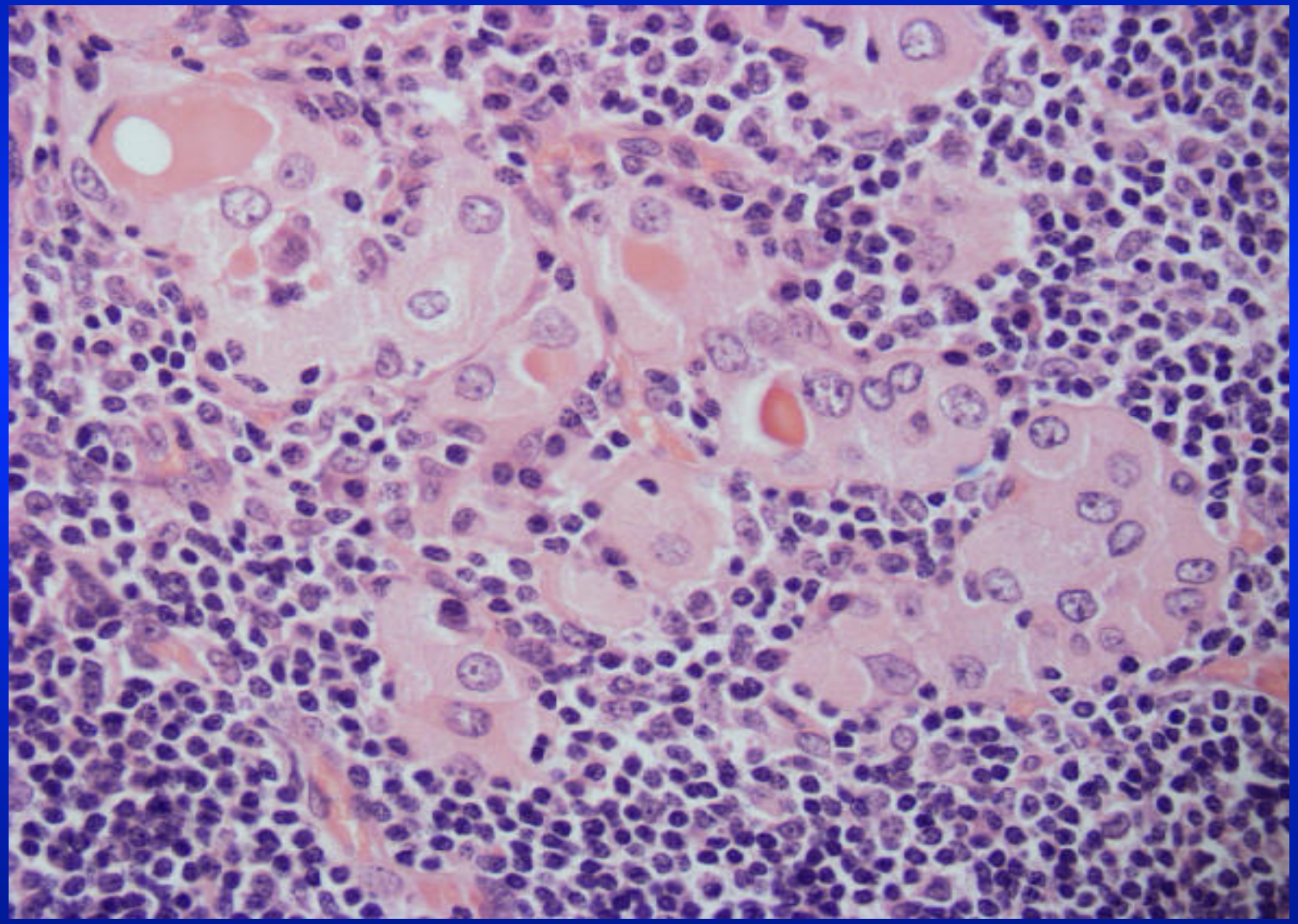
- EVG
- ZN, PASd or Grocott's
- Polarised light

Case 7 PS09.18041

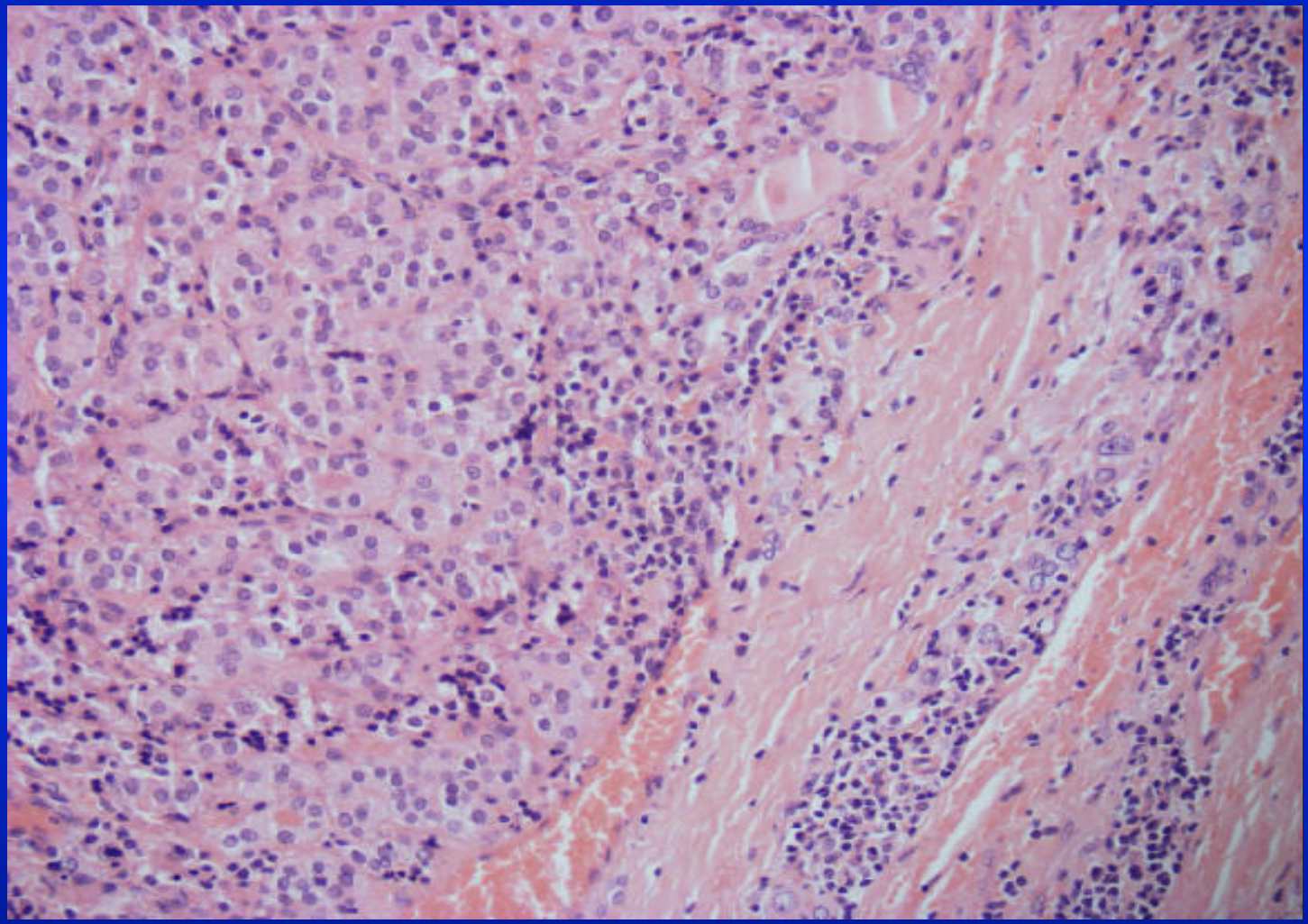
Diagnosis: SARCOIDOSIS

- Granulomas
  - Epitheloid cells
  - Langhan's giant cells
  - Lymphocytes
  - Hyalinisation
  - Necrosis absent/small central fibrinoid focus
  - Intracellular inclusion
    - Schaumann or asteroid bodies

Case 9 PS09.3024



Case 9 PS09.3024



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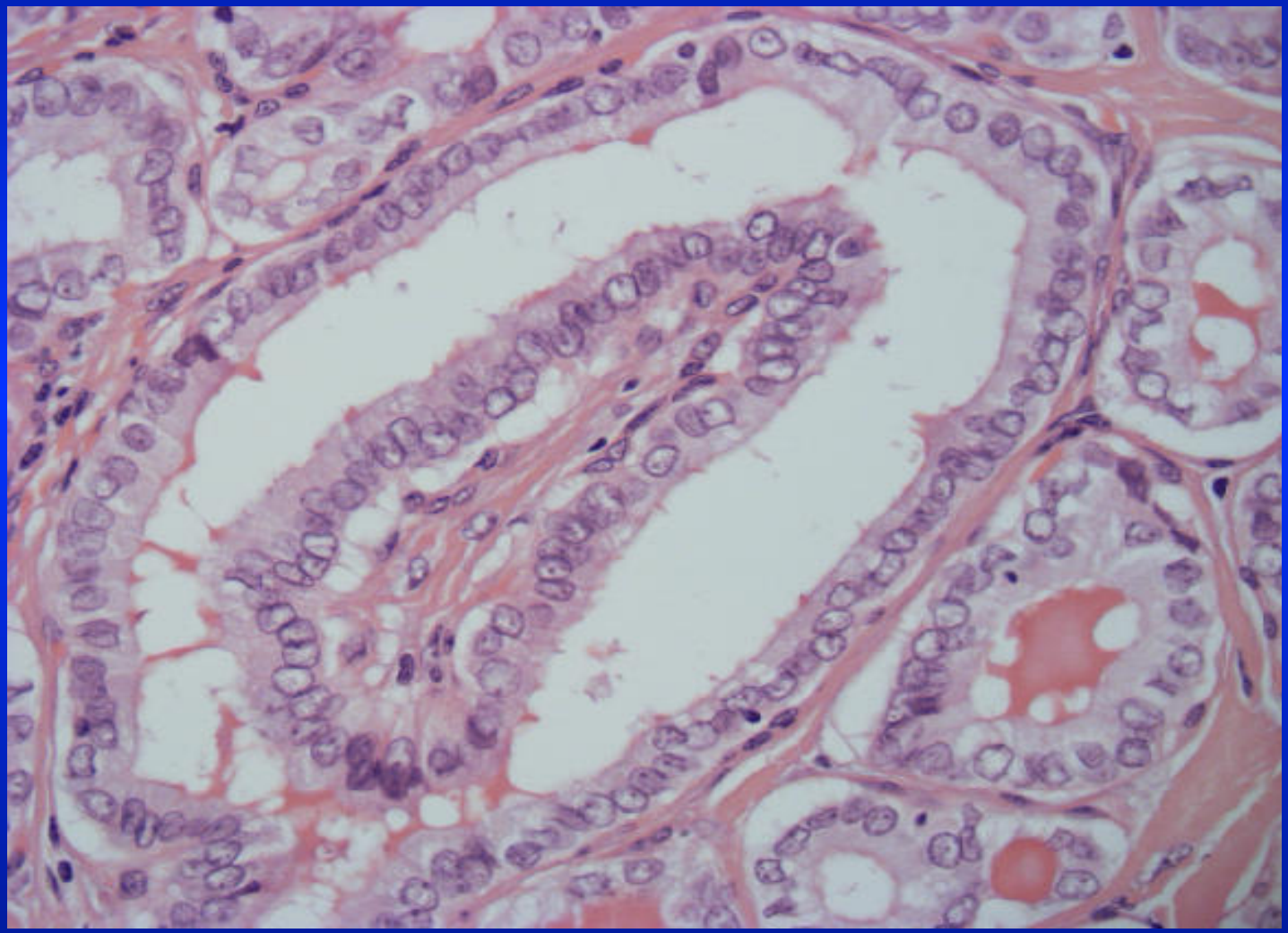


Case 9 PS09.3024

Diagnosis:

- HASHIMOTO'S THYROIDITIS
- ADENOMA/ADENOMATOID NODULE
- MICROPAPILLARY CARCINOMA

Hashimoto's thyroiditis and adenoma/adenomatoid nodule

- Adenomatoid nodules often occur in association with Hashimoto's thyroiditis and can be difficult to distinguish from true adenomas

Follicular Adenoma

- Benign encapsulated tumour
- Architectural pattern different from surrounding thyroid
- Scanty richly vascular stroma
- Secondary changes
  - Degenerative
  - Metaplastic (cartilage)
  - Cyst formation
  - Infarction
- Cowden syndrome, Carney complex

Adenomatoid nodule

- Multiple
- Lack well-defined capsule
- Follicles are morphologically similar to the surrounding thyroid tissue

Hurthle Cell/Oncocytic Adenoma

- Solitary, well-delineated and encapsulated
- Mahogany brown appearance
- Central areas of scarring
- Prone to infarction

Hurthle Cell/Oncocytic Adenoma

- Variety of architectural patterns, usually follicular
- Colloid often dense and may form structures mimicking psammoma bodies
- Cytology
  - Abundant granular eosinophilic cytoplsm
  - Large open nuclei
  - Prominent nucleoli
- Exclusively/predominantly (>75%) oncocytes

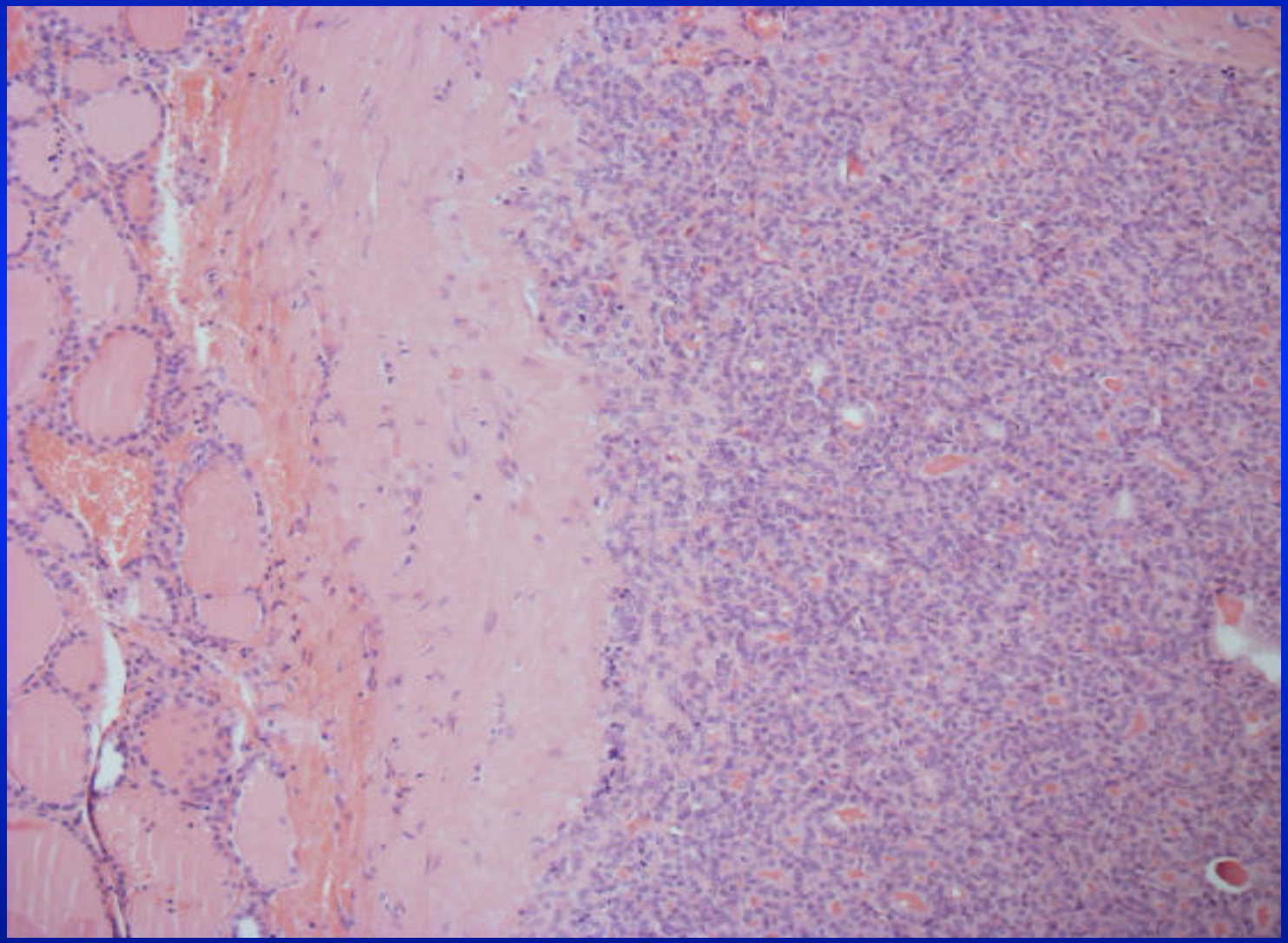
Hashimoto's thyroiditis

- Lymphocytic infiltration of stroma
  - Distributed within and around the lobules
  - Large follicles
  - Prominent germinal centres
- Oxyphilic change in follicular epithelium
  - Small atrophic follicles
  - Nuclear features may resemble papillary carcinoma

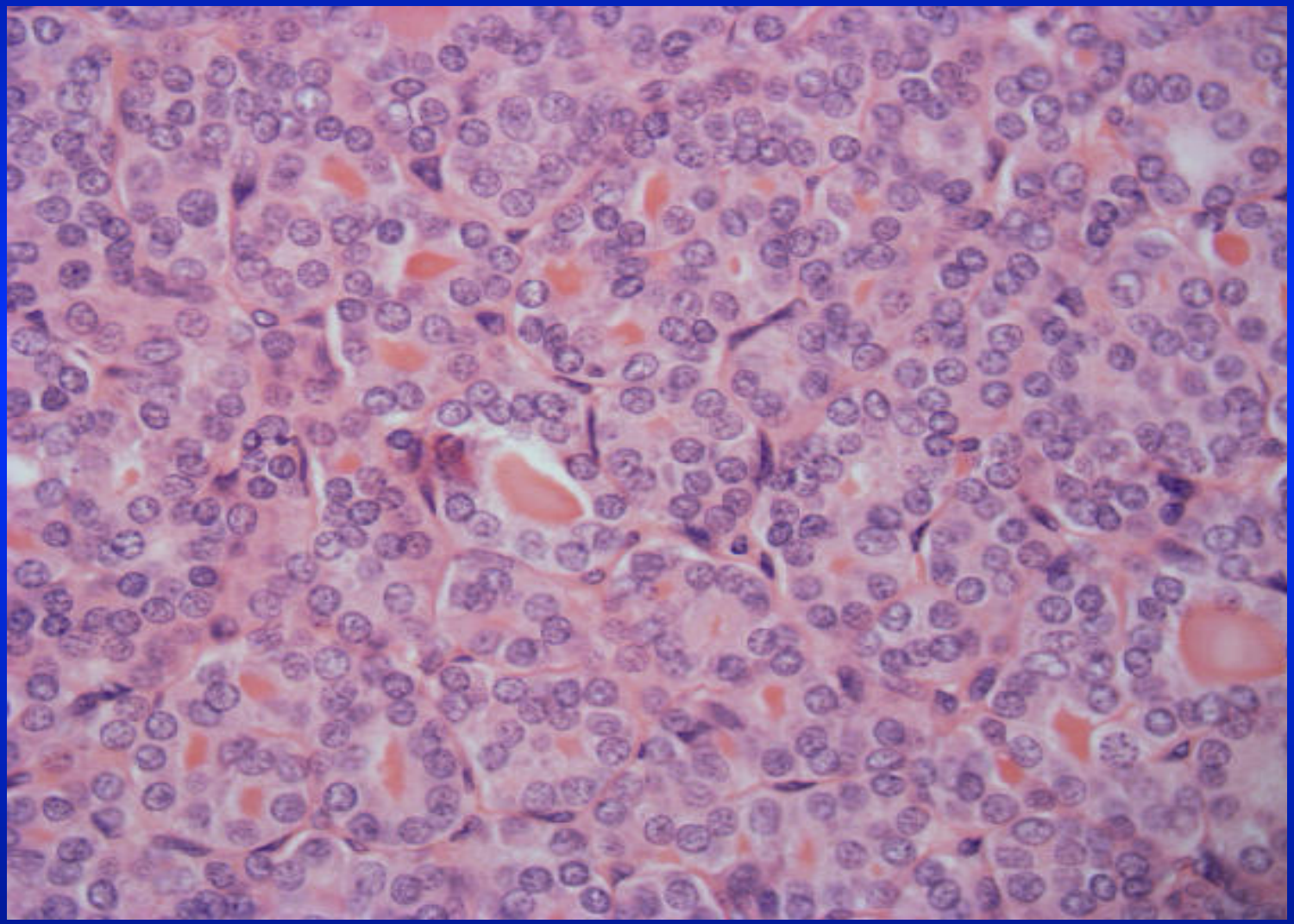
Papillary microcarcinoma

- Extremely common incidental finding in thyroid glands removed for other reasons and in population-based autopsy studies (25% or more)
- Cervical lymph node metastases can occur, distant metastases are extremely rare
- Histological markers of potential aggressiveness
  - Mulitfocal/bilateral
  - > or = to 6mm
  - ETE, especially macroscopic
  - Stromal desmoplasia/infiltrative growth
  - Poorly differentiated component
  - LVI

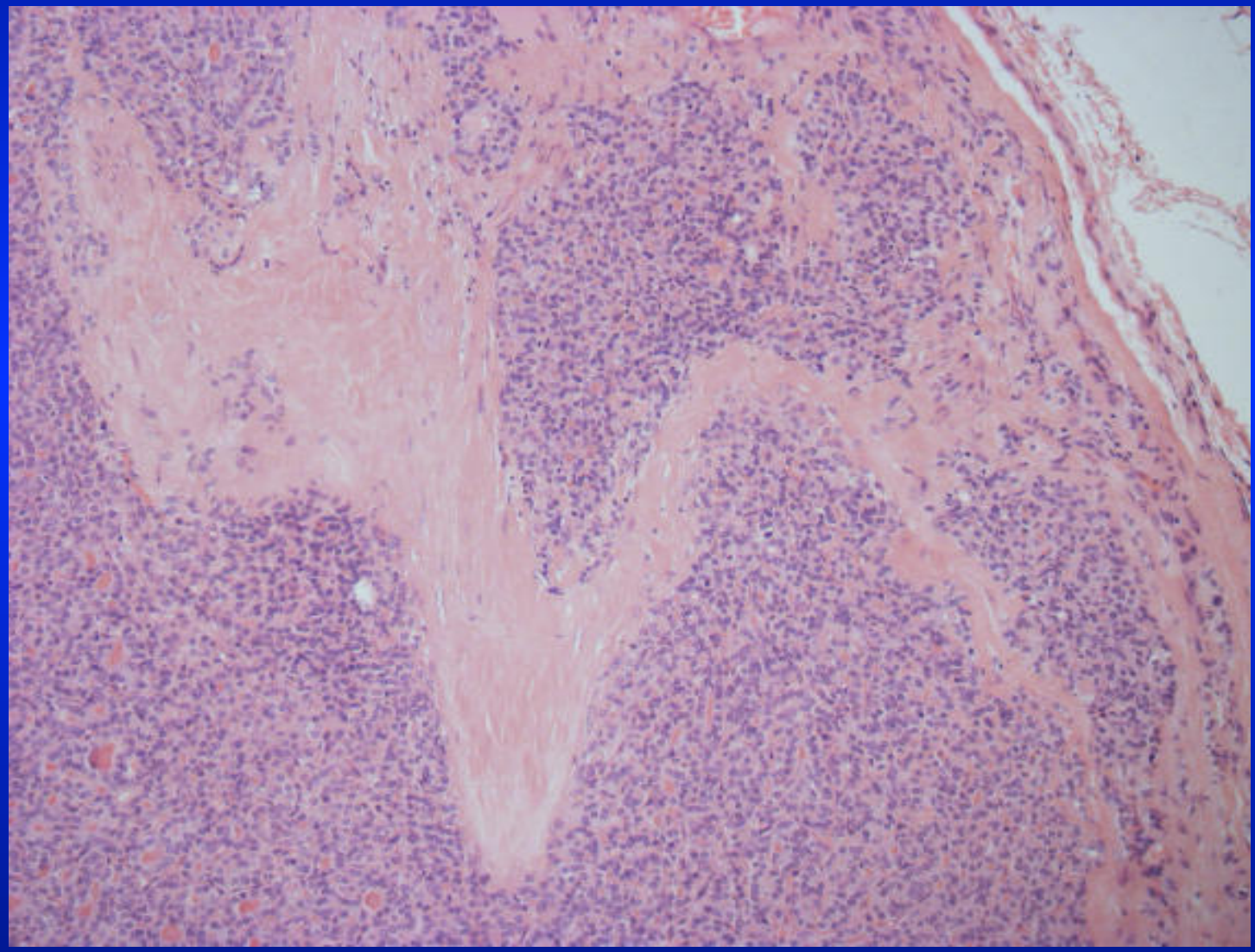
Case 8 PS09.588



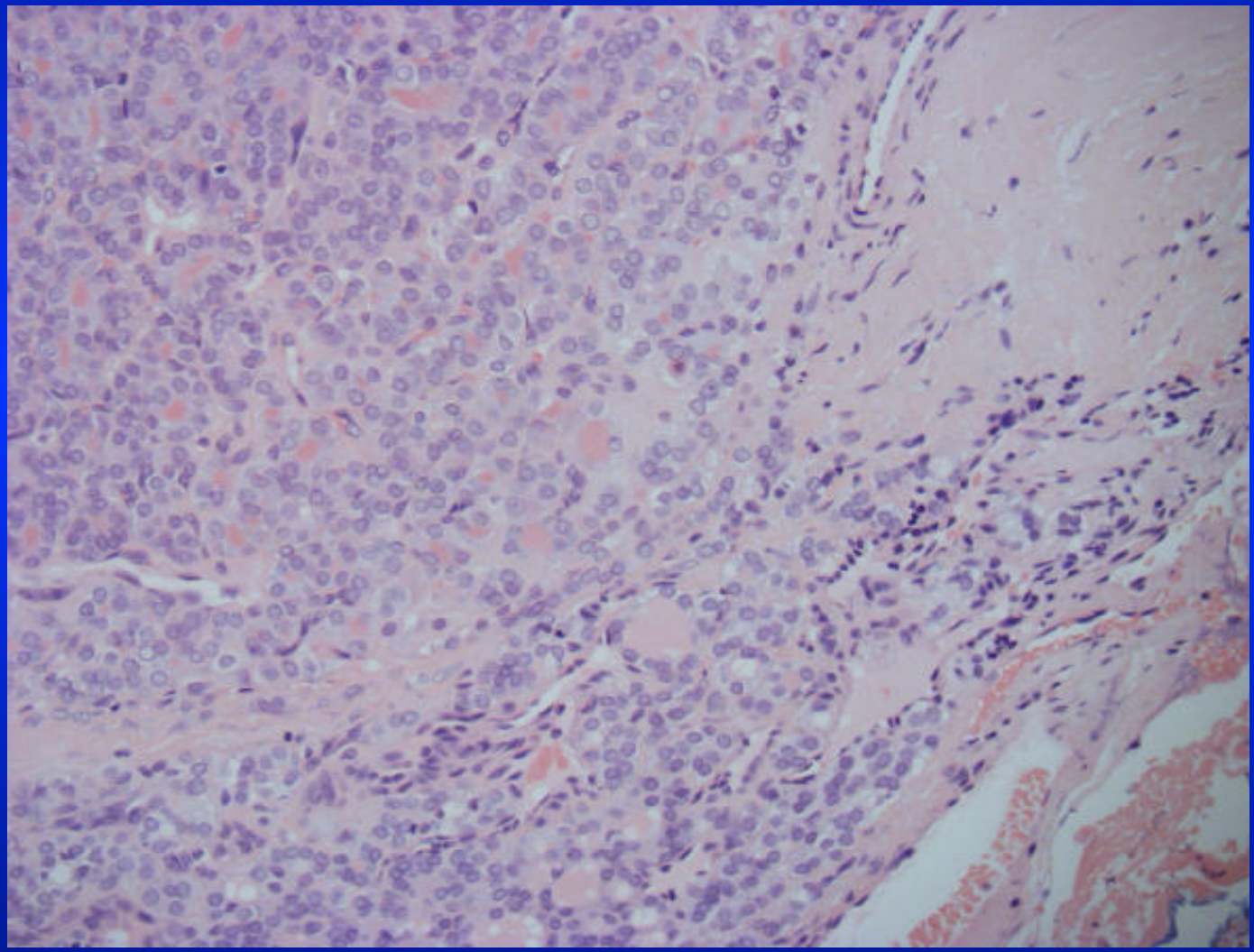
Case 8 PS09.588



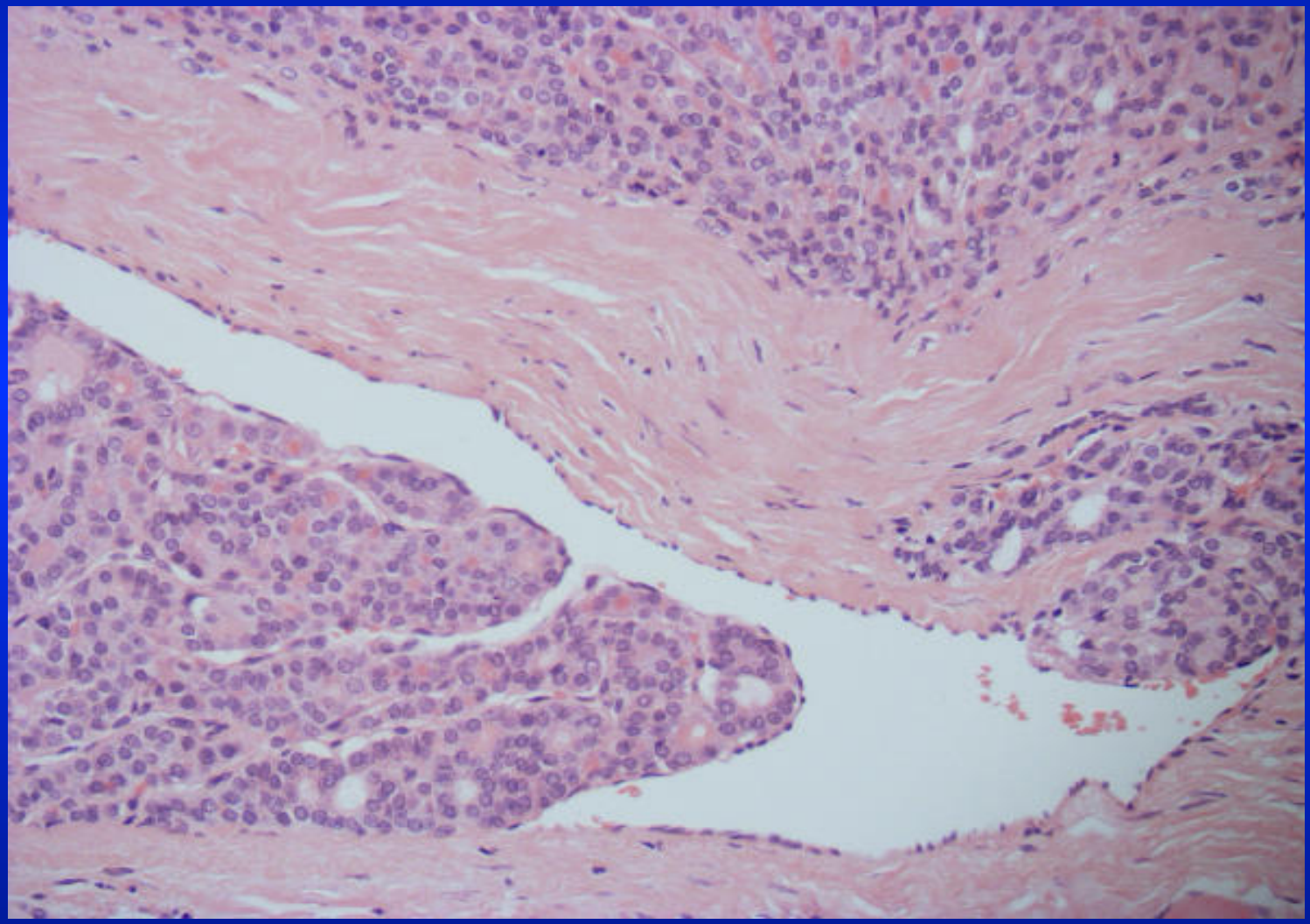
Case 8 PS09.588

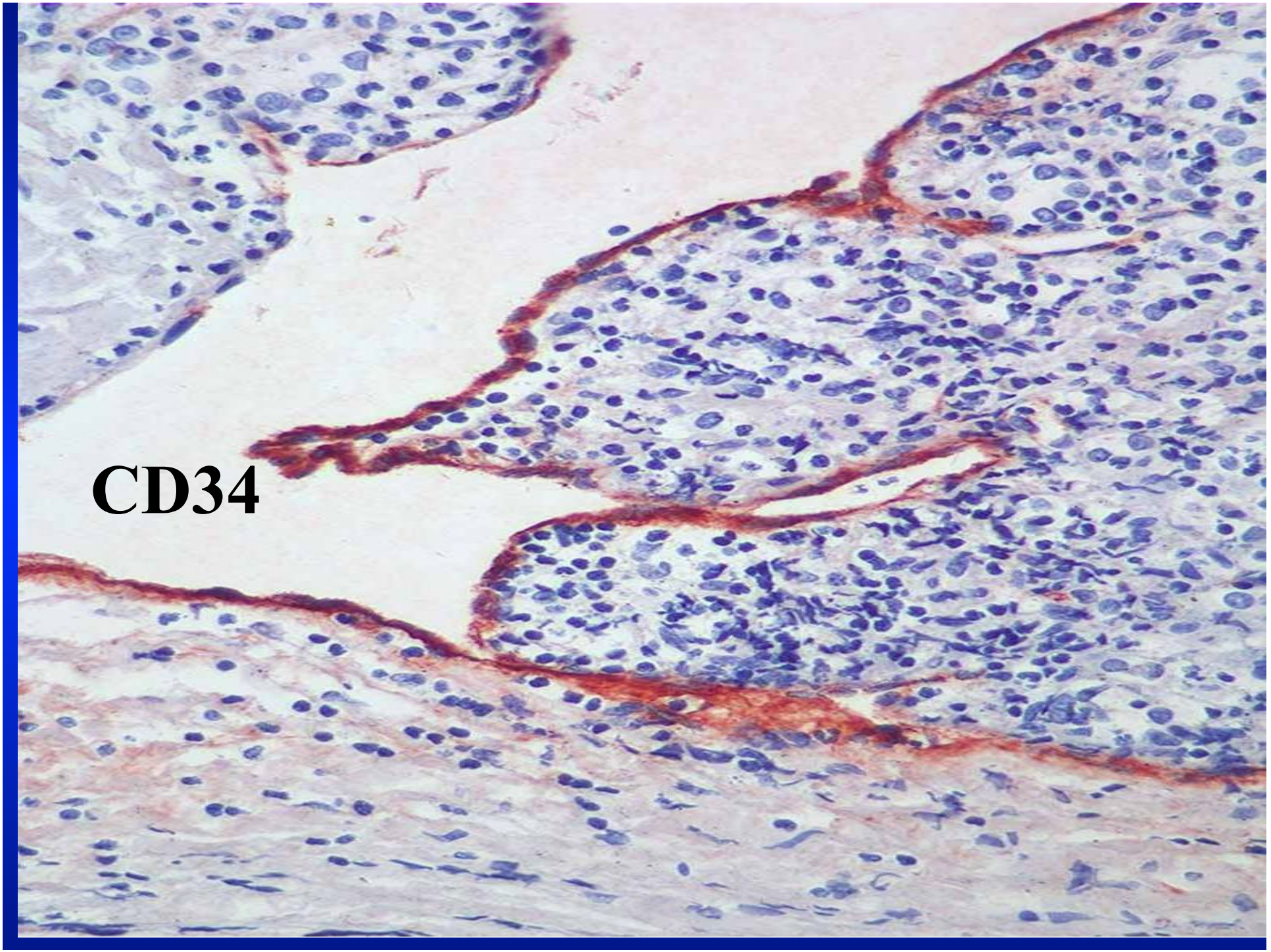


Case 8 PS09.588



Case 8 PS09.588




CD34

Case 8 PS09.588

- Well circumscribed and encapsulated
- Microfollicular growth pattern
- Capsular invasion
  - Full thickness but not into adjacent thyroid
- Vascular invasion
  - Within capsule

Diagnosis:

MINIMALLY INVASIVE THYROID FOLLICULAR CARCINOMA

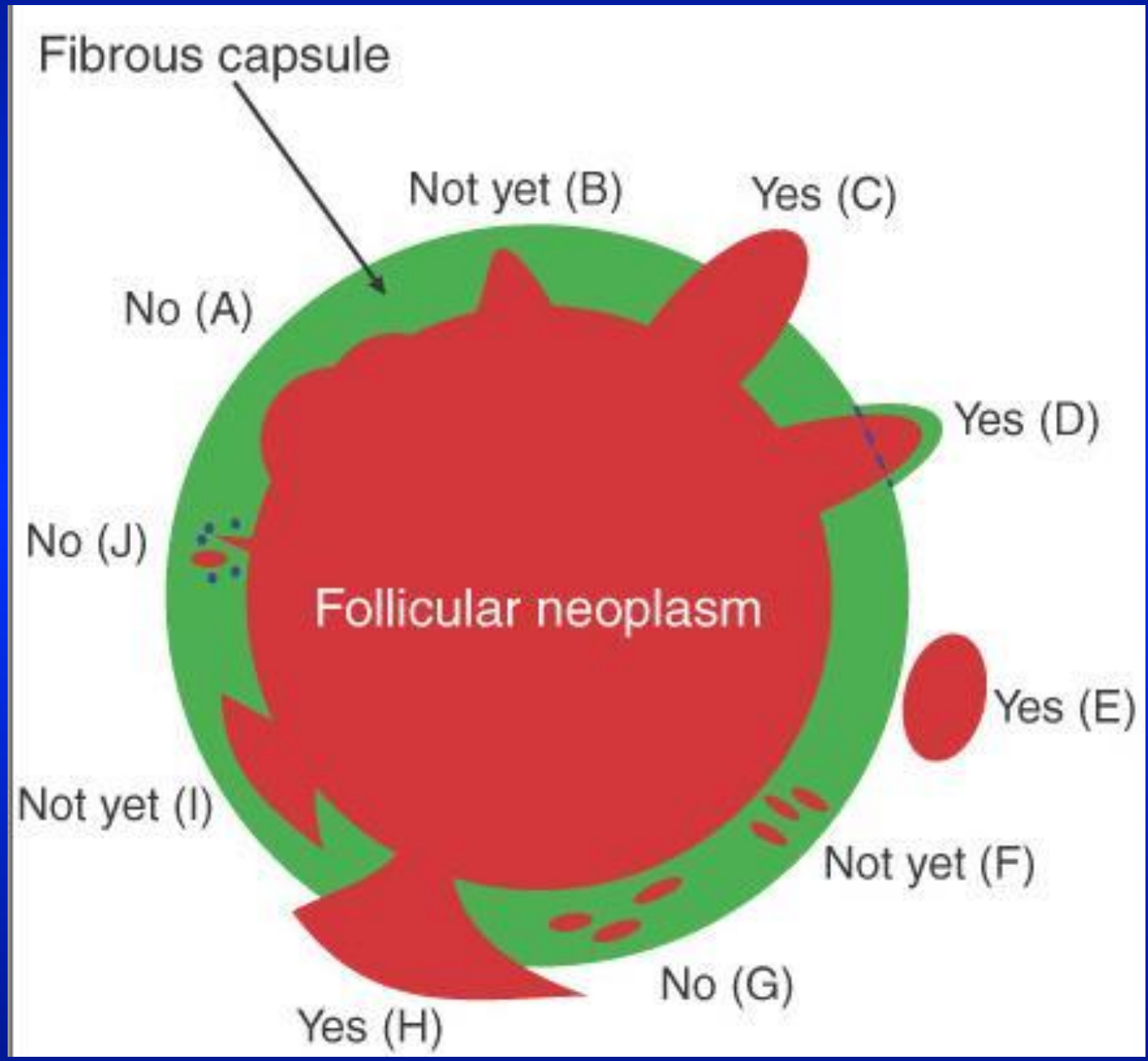
Minimally invasive FTC

- Grossly encapsulated
- Solid and fleshy cut surface
- Capsule tends to be thicker and more irregular than adenoma
- Diagnosis depends on demonstration of capsular and /or vascular invasion

Minimally invasive FTC

- Capsular invasion
  - Capsular interruption must be full thickness
  - Mushroom-like expansion in adjacent area
- Problems
  - Tumour nodule outside main mass
  - Neocapsule
  - Previous FNA
    - Area of rupture usually fissure-like with reparative stromal changes
    - Foci of recent or old haemorrhage

Capsular invasion in follicular neoplasms



Minimally invasive FTC

- Vascular invasion
- Venous calibre vessels
- Within or immediately outside tumour, not within the tumour
- One or more clusters of cells attached to wall
- Endothelial covering (CD31 helpful)

Minimally invasive FTC

- Vascular invasion
- Pitfalls
  - Reactive vascular proliferation in capsule
  - Retraction artefact
  - Artefactually dislodged tumour cells
    - Irregular
    - Not attached to vessel wall
    - Not covered by endothelium

Minimally invasive FTC

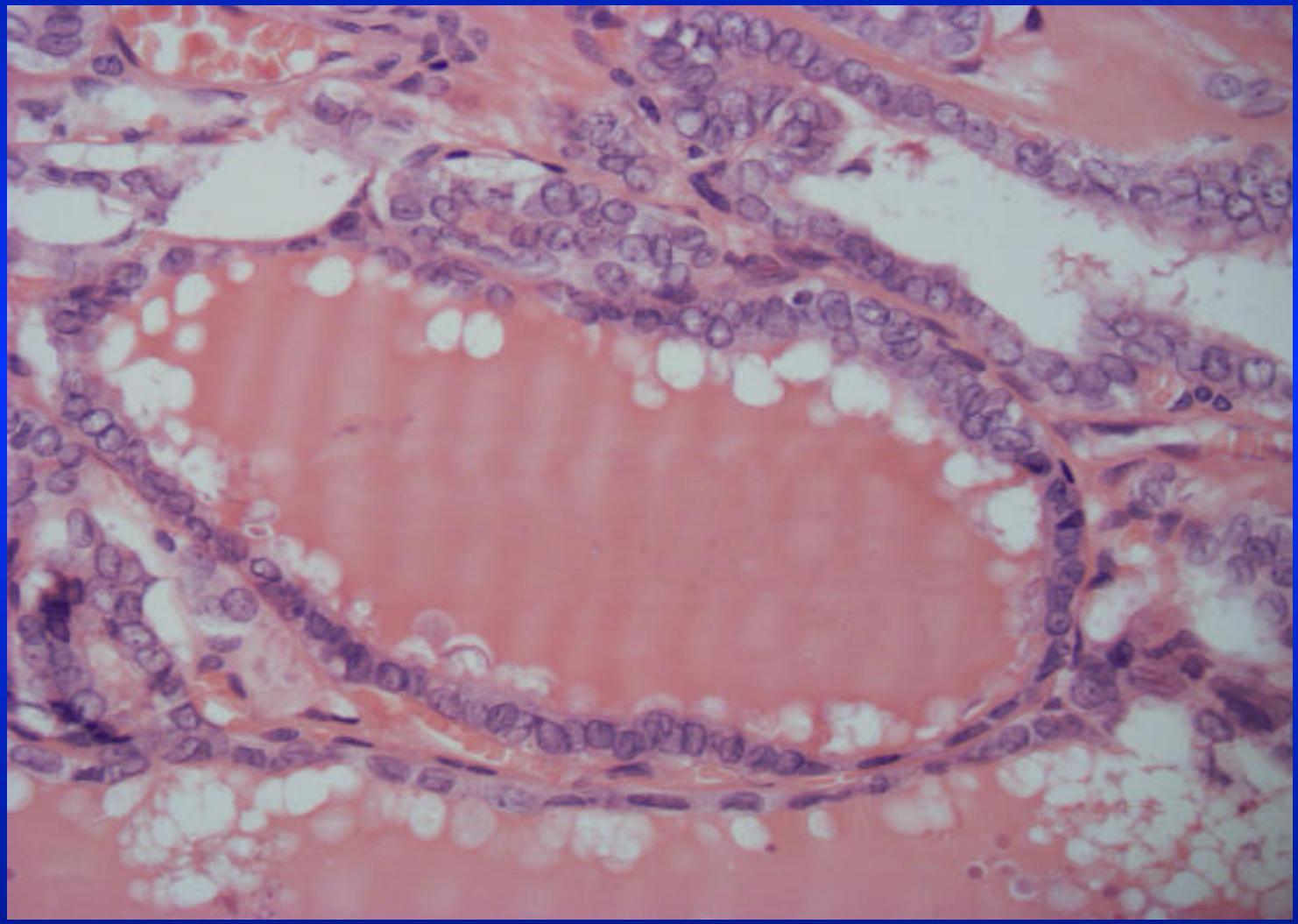
- Differential diagnosis
  - Follicular adenoma
  - Papillary carcinoma, follicular variant

Minimally invasive FTC

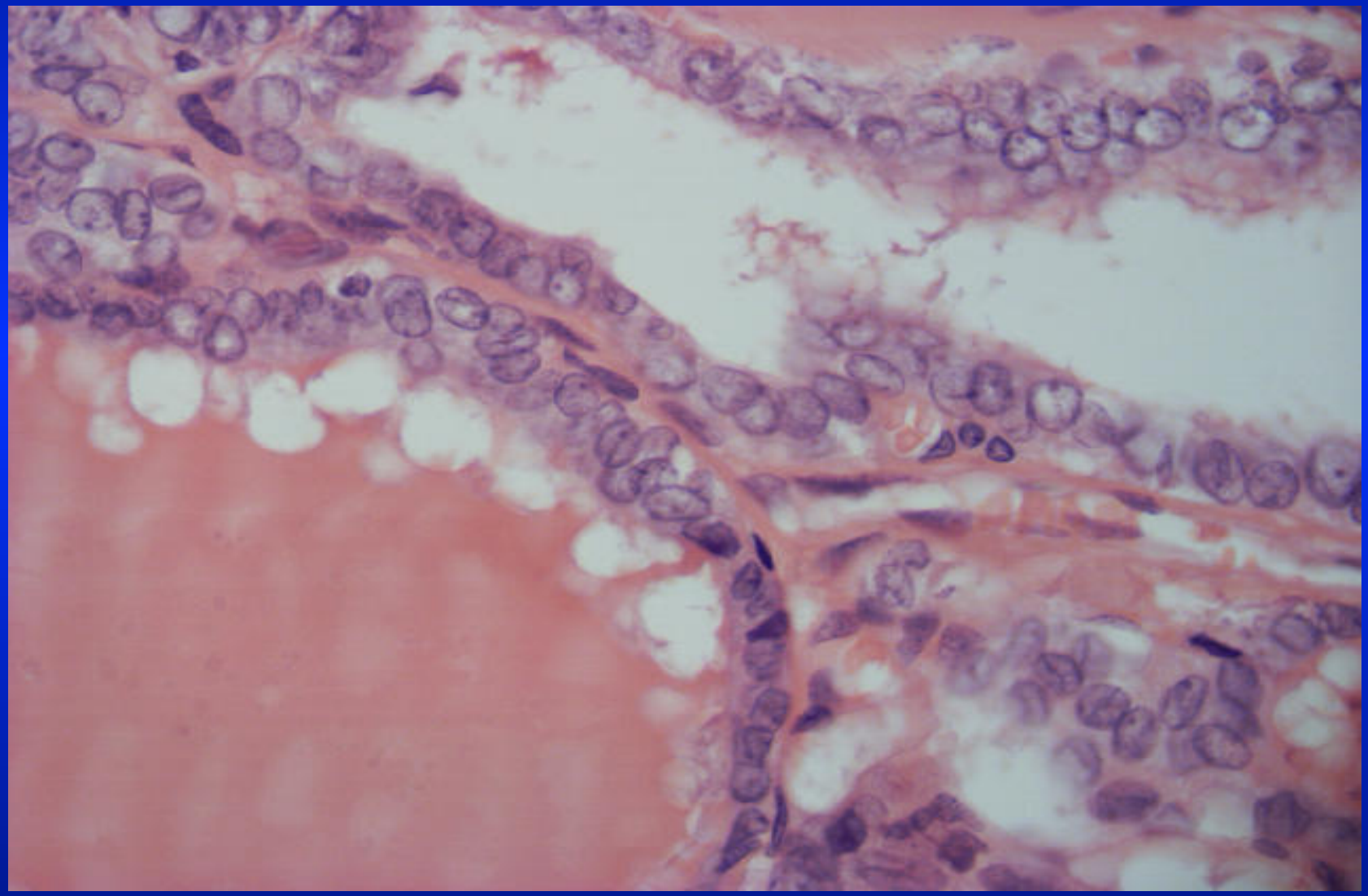
Prognosis

- Capsular invasion only
  - <1% metastasise
- Vascular invasion
  - Approx. 5% metastasise
  - Risk of metastatic disease depends on number of vessels involved (limited <4, extensive >4)
  - Threshold is controversial so RCPath thyroid cancer dataset 2014 no longer specifies number of vessels seen to be involved as core data item

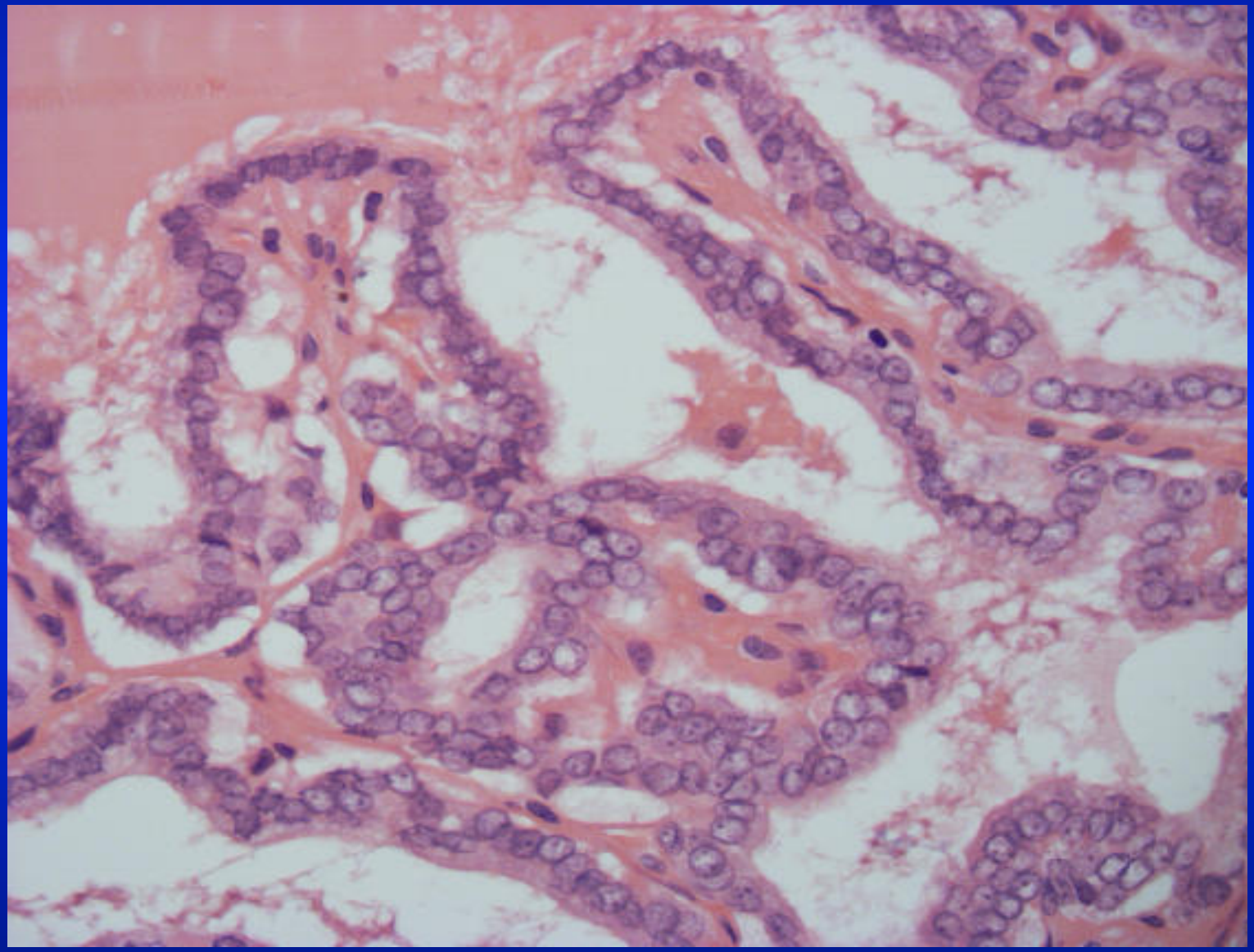
Case 10 PS09.14972



Case 10 PS09.14972



Case 10 PS09.14972



Case 10 PS09.14972

- Encapsulated nodule
- Variably-sized follicles
- Abortive papillae
- Cells lining follicles have optically clear, grooved nuclei
- Thick, scalloped colloid
- Diagnosis: PAPILLARY CARCINOMA, FOLLICULAR VARIANT

Papillary carcinoma Follicular variant

- Papillary carcinoma composed almost entirely of follicles
- Nuclear features are those of classical papillary carcinoma
- Supportive features
  - Invasive growth pattern
  - Fibrous trabeculation
  - Psammoma bodies
  - Thick, strongly eosinophilic colloid with scalloped edges
  - Abortive papillae

Papillary carcinoma Follicular variant

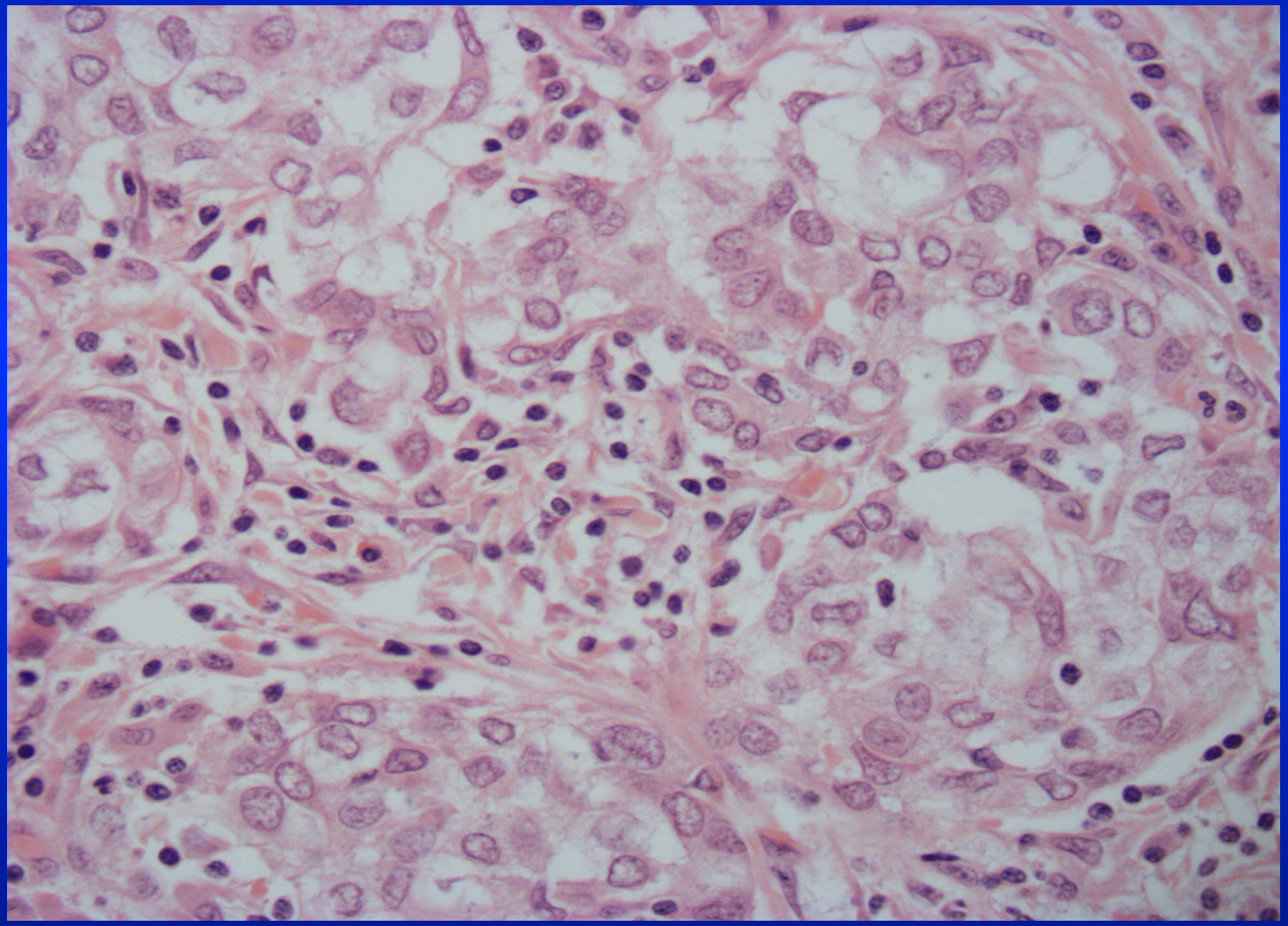
- Subtypes
- Solid
  - Commoner in children
- Macrofollicular
- Diffuse (multinodular)
  - Rare, aggressive clinical course
- Encapsulated
  - Approx one third
  - Nuclear features should be widespread and well-developed
  - Some of the supportive features listed above should be present

Encapsulated neoplasm ?papillary carcinoma

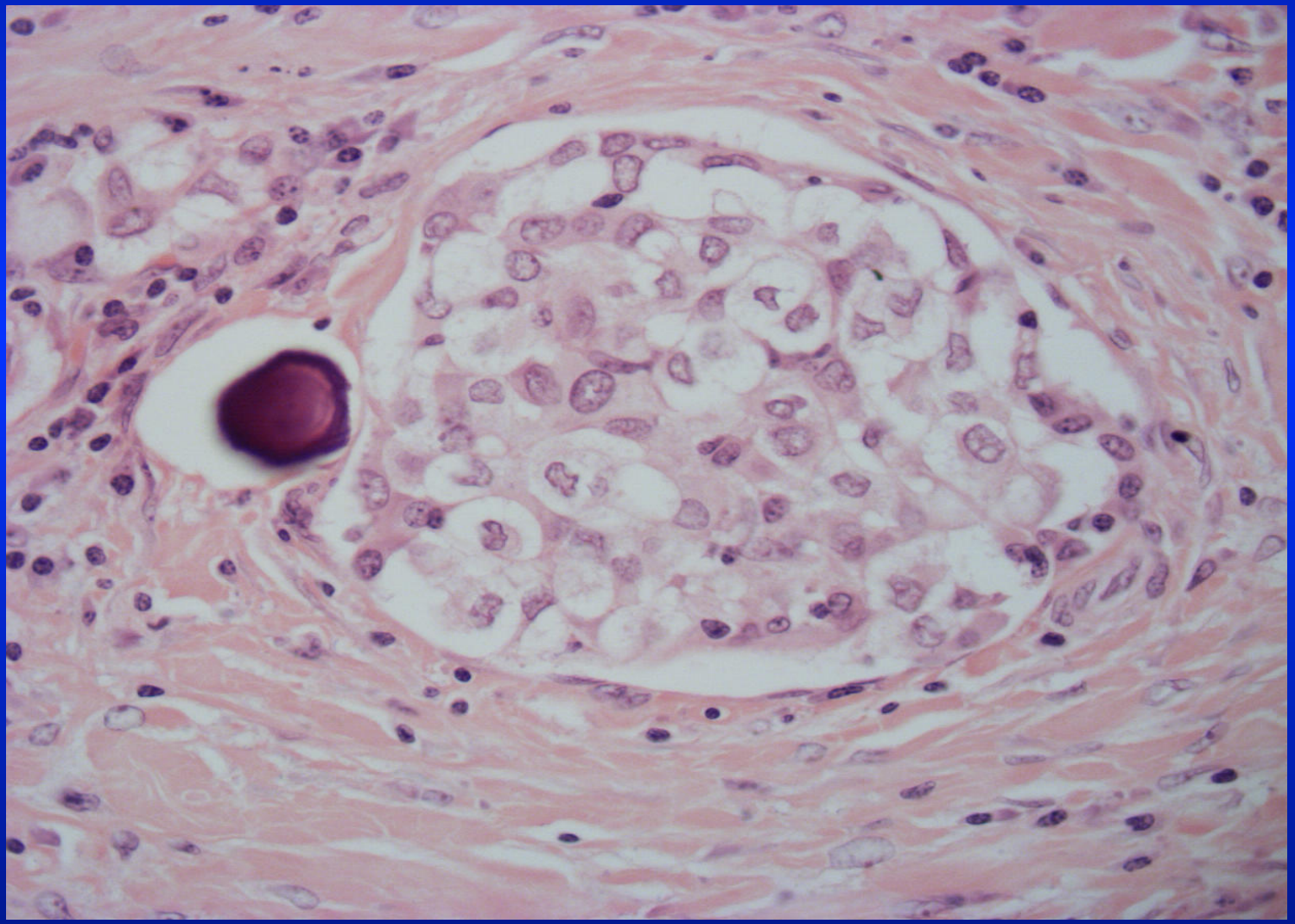
Suggested terminology

- Obvious nuclear changes
  - Papillary carcinoma follicular variant
- Questionable nuclear changes
  - Well differentiated carcinoma NOS*
    - Definite capsular invasion
    - * can favour papillary carcinoma follicular variant or minimally invasive FTC
  - Well differentiated tumour of uncertain malignant potential (WDT-UMP)
    - Capsular invasion questionable or absent
  - Atypical adenoma
    - No invasion

Case 3 PS09.1331



Case 3 PS09.1331

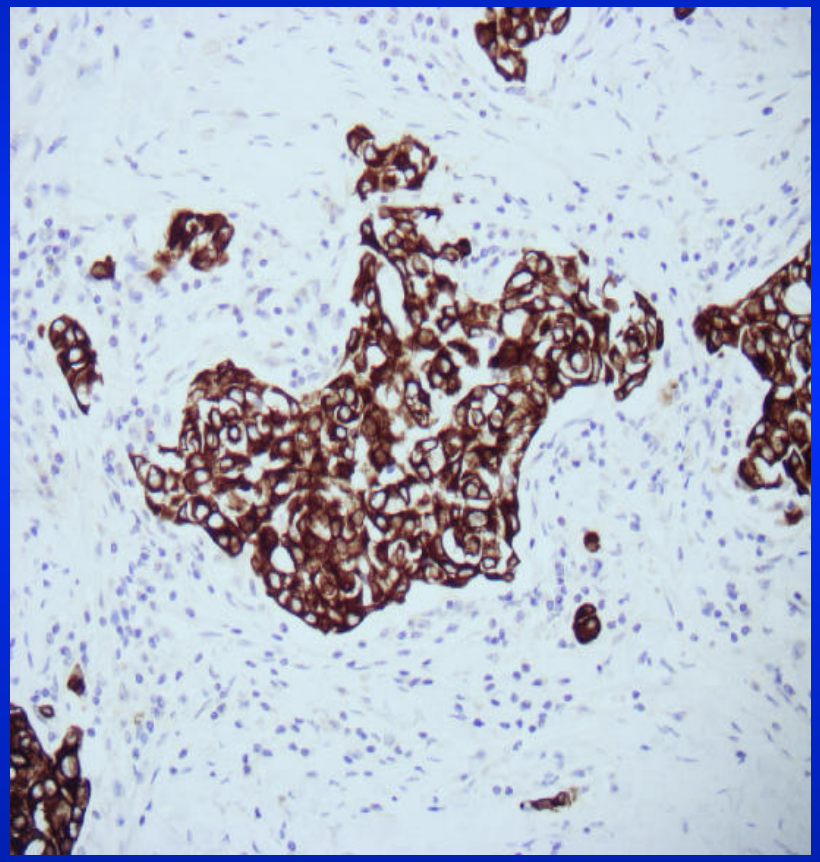


Case 3 PS09.1331

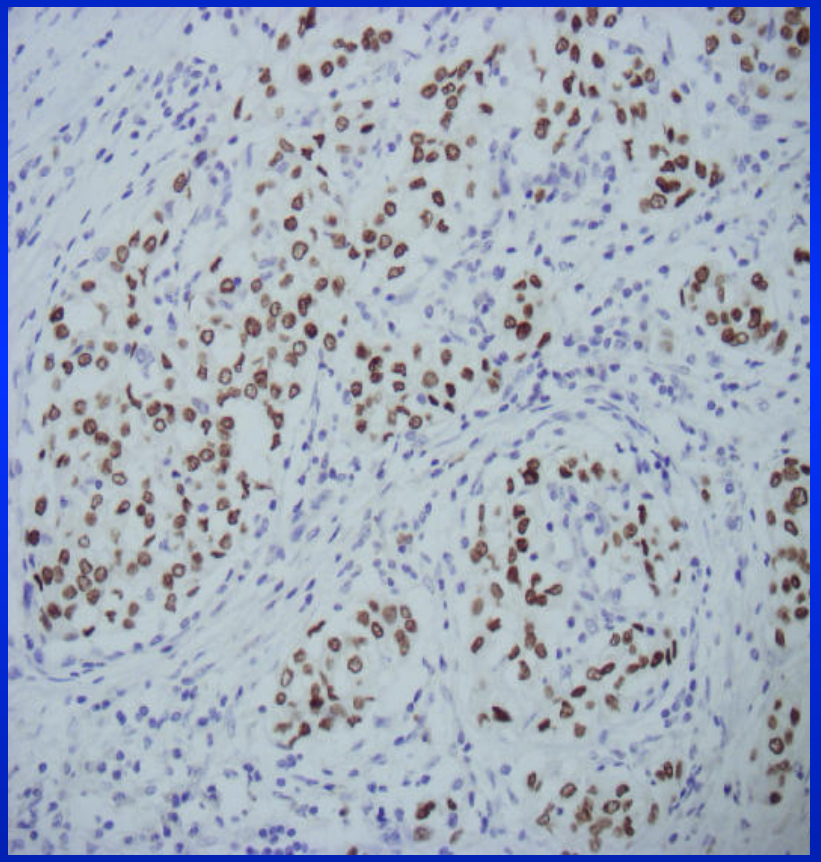
- Unencapsulated infiltrative tumour
- Alveolar growth pattern without papillary areas
- Dense sclerosis
- Psammoma bodies
- Nuclei clear with occasional grooves

Immuno?

Case 3 PS09.1331



CK19



TTF1

Case 3 PS09.1331

- Immuno: CK19, TTF1 positive
- Diagnosis
- PAPILLARY CARCINOMA
  - Diffusely sclerotic subtype

- 4/5 nodes with metastatic spread

Papillary carcinoma diffuse sclerosing variant

- Young patients
- Diffuse involvement one or both lobes
- Histological features
  - Numerous psammoma bodies
  - Extensive squamous metaplasia
  - Dense lymphocytic infiltrate
    - patients often have serological evidence of automimmune disease
  - Stromal fibrosis
- Lung metastases common at presentation (approx. 25% patients)

Case 16 TB13.2637

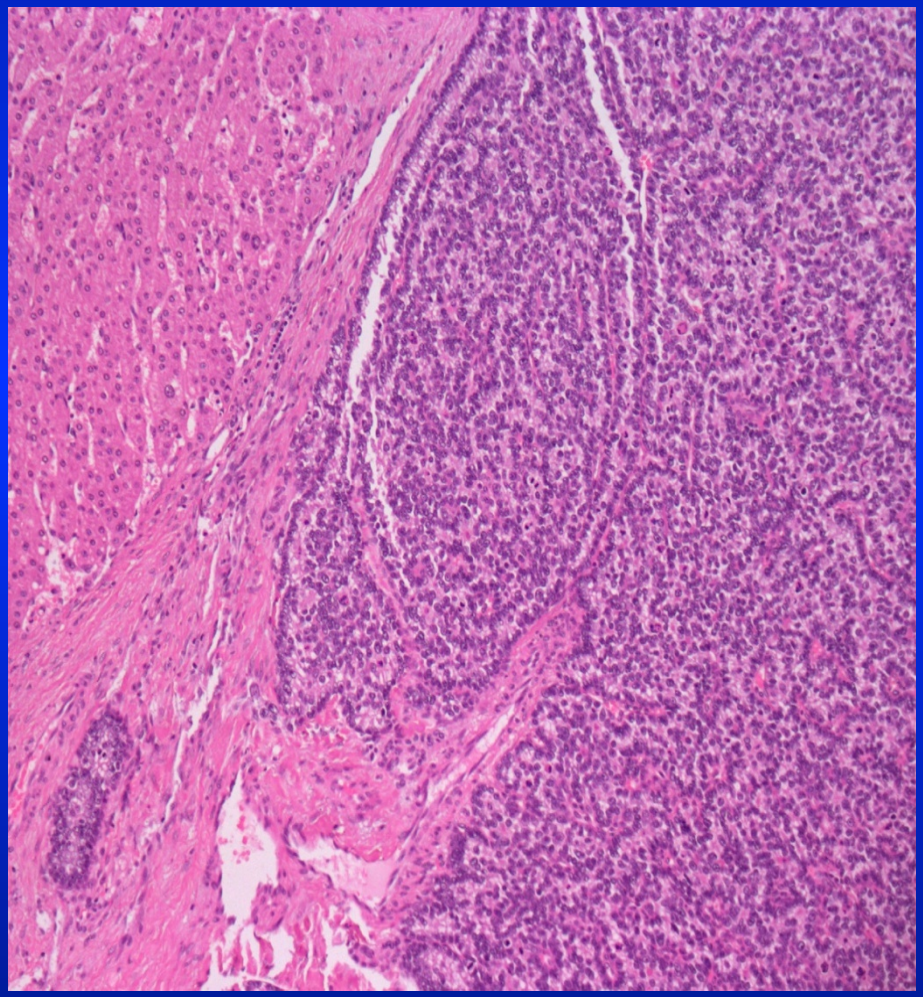
Clinical

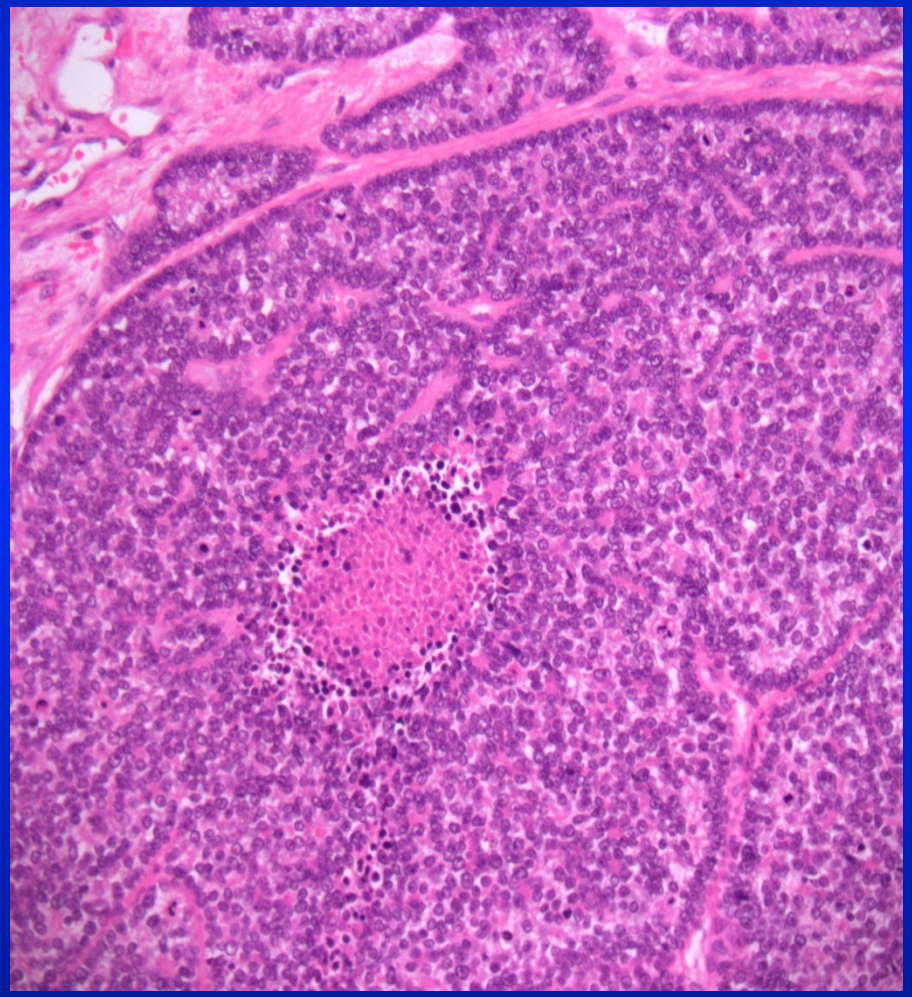
39 year old female, mass in liver

Macro

- Right hepatectomy 2068g
- Fleshy grey tumour mass with haemorrhage and necrosis 150x100x140mm

Case 16



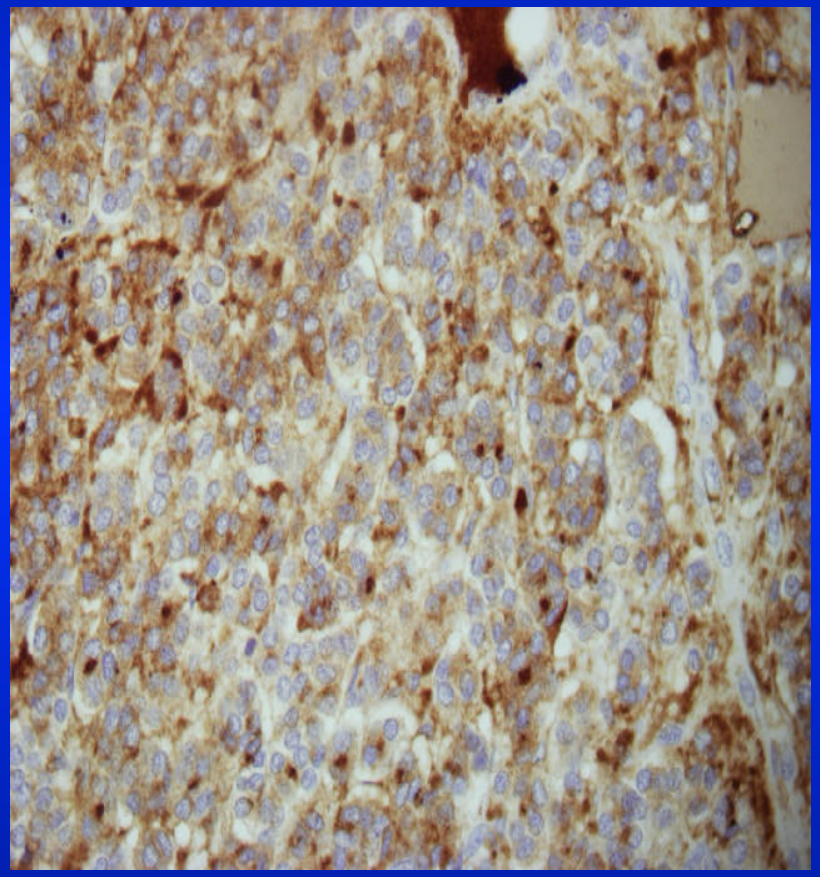


Case 16

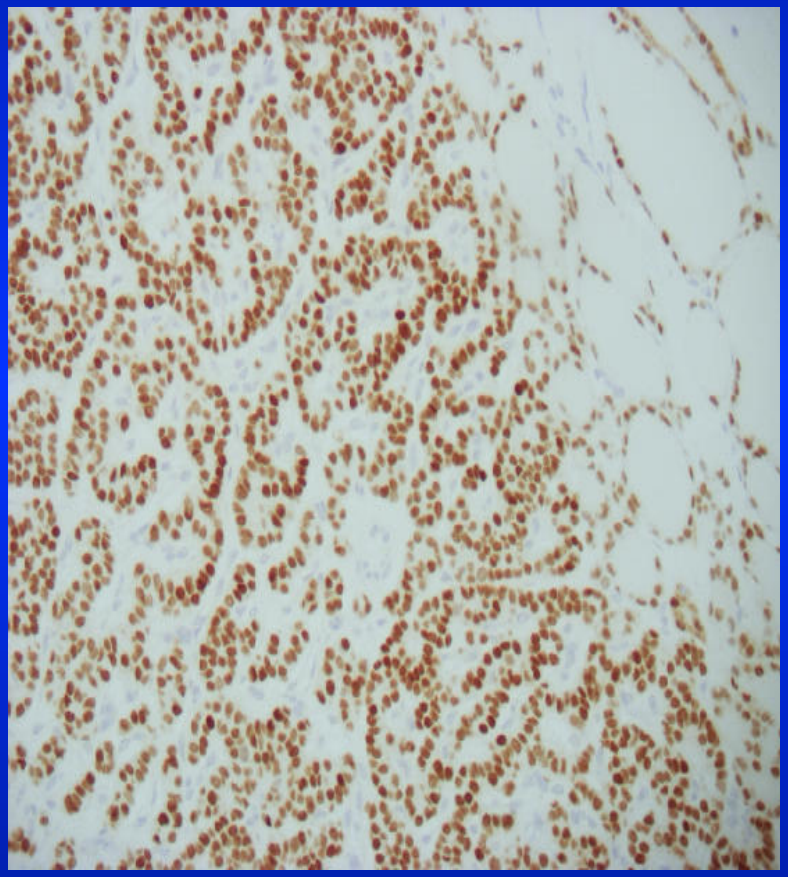
Micro

- Trabecular, insular and follicular growth patterns
- Tumour cells have round to oval nuclei mildly pleomorphic nuclei with stippled chromatin
- Necrosis, multifocal vascular invasion
- Immunohistochemistry
  - Positive: TTF1, pancytokeratin, thyroglobulin (patchy)
  - Negative: Chromogranin, calcitonin , CEA

Case 16

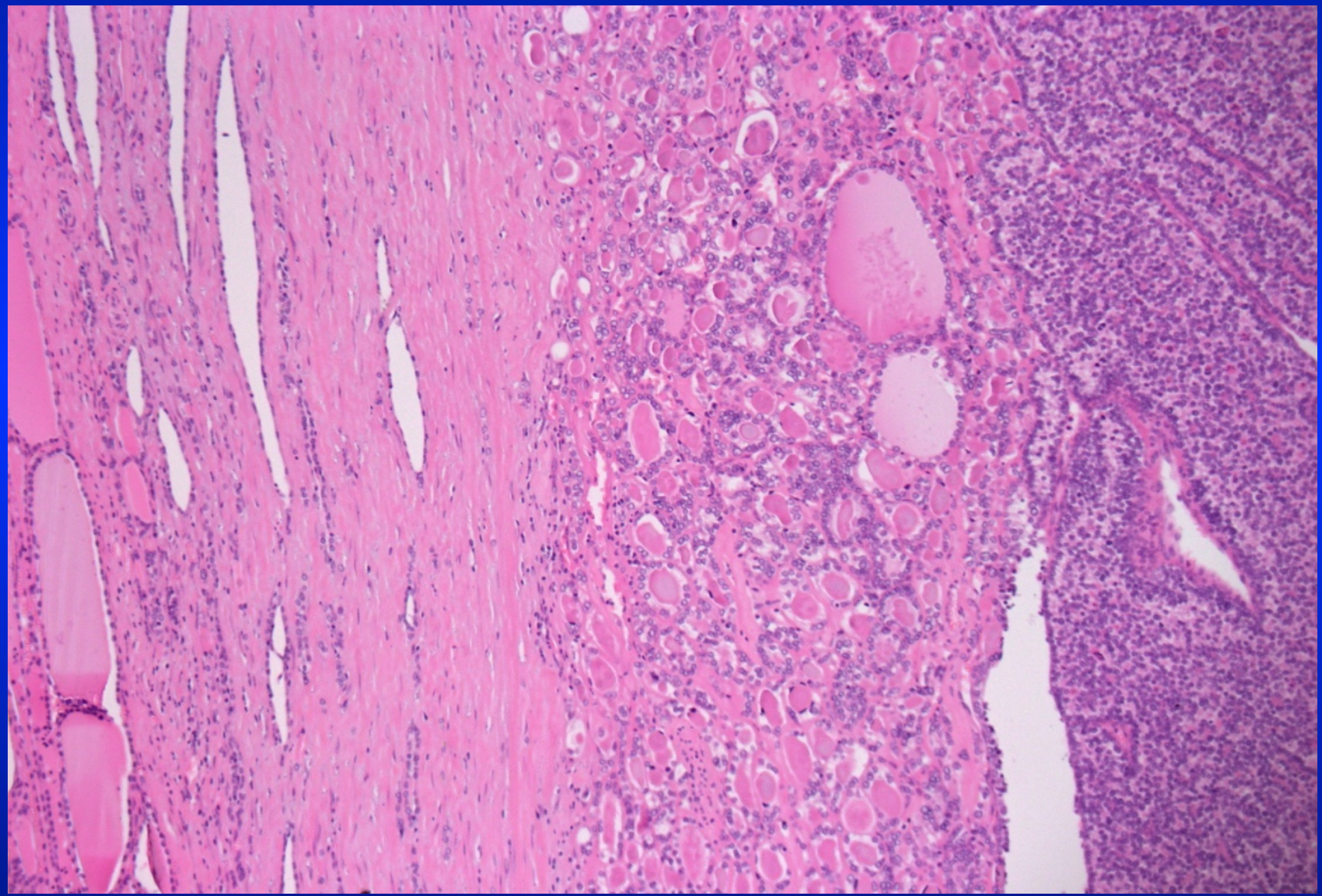


Thyoglobulin

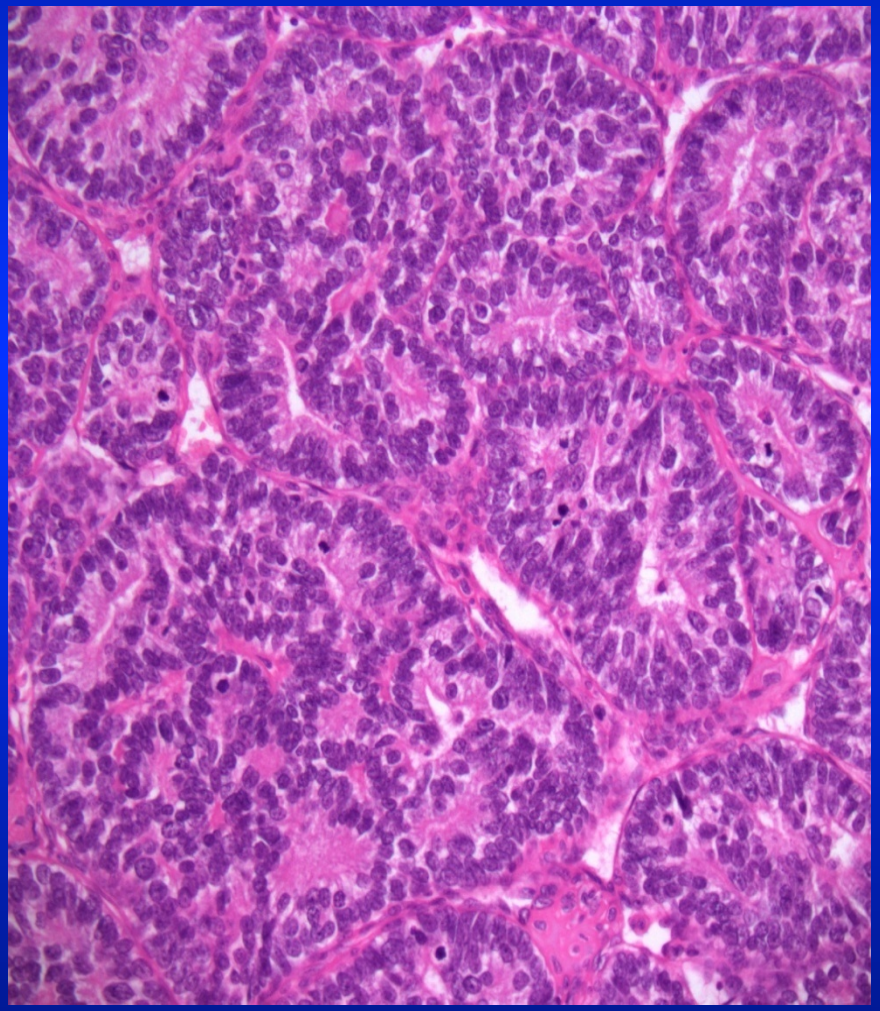


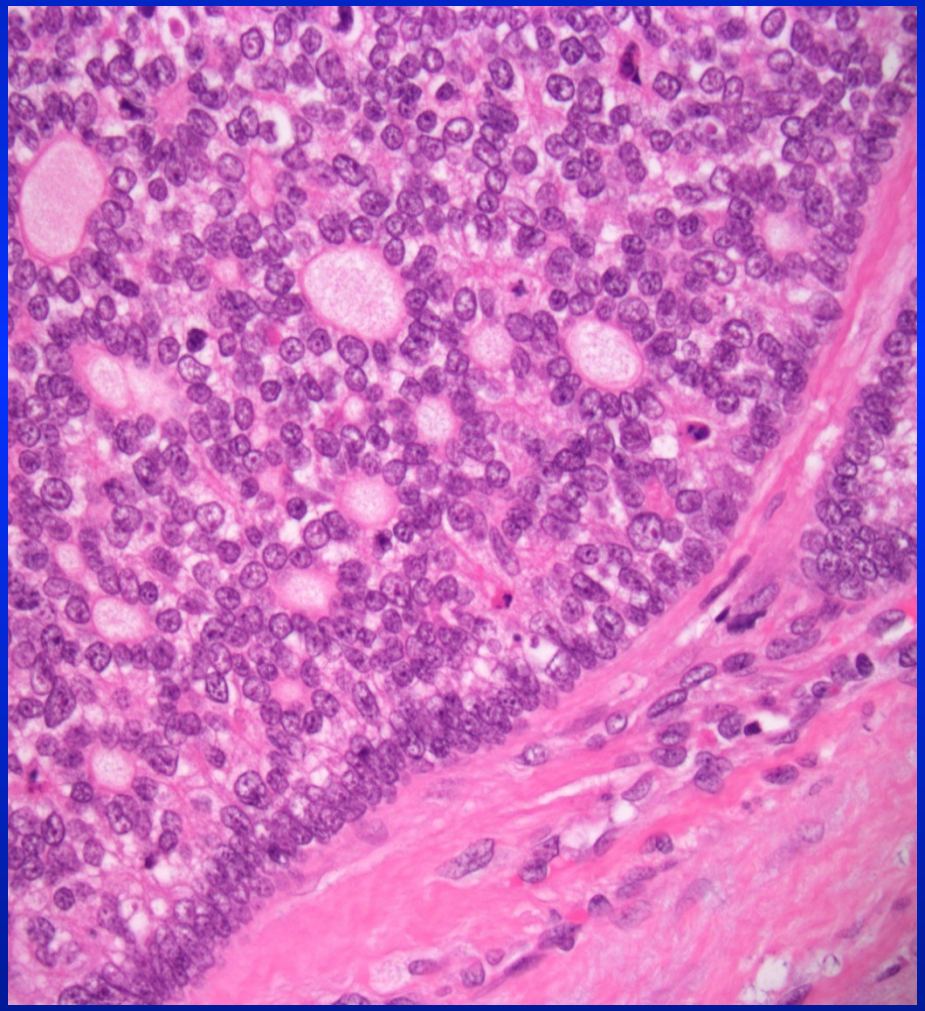
TTF-1

Case 16



Case 16





Case 16

Diagnosis:

Metastatic insular thyroid carcinoma

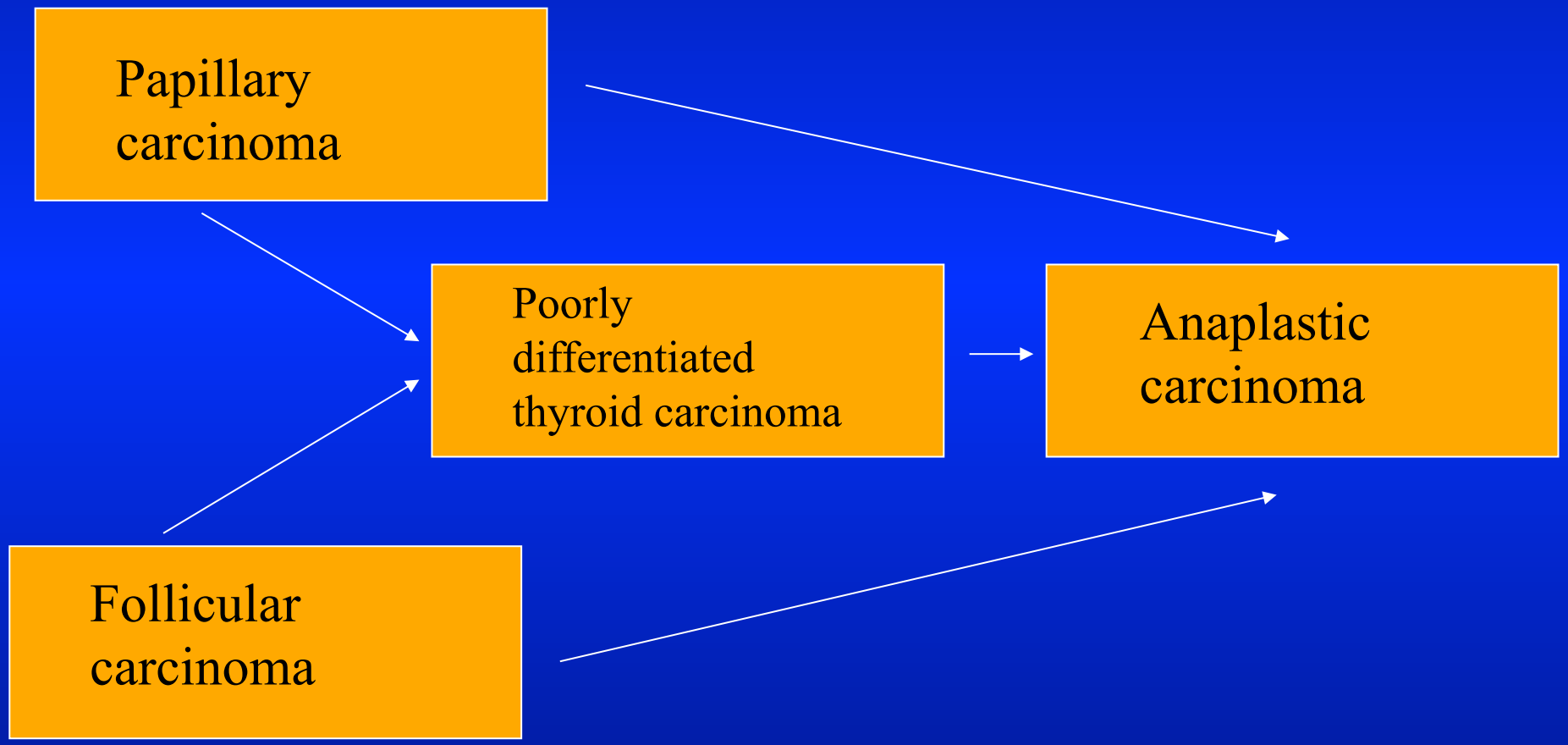
Insular Carcinoma

- Older age group than well-differentiated tumours
- Usually grossly invasive
- Nesting (“insular”) pattern of growth
- Solid to microfollicular arrangement
- Small uniform tumour cells
- Fresh tumour necrosis

Insular Carcinoma

- Immunohistochemical profile
  - TTF-1 and thyroglobulin positive
  - Focal reactivity for neuro-endocrine markers
  - Calcitonin negative
- Express bcl-2 in over 80% cases

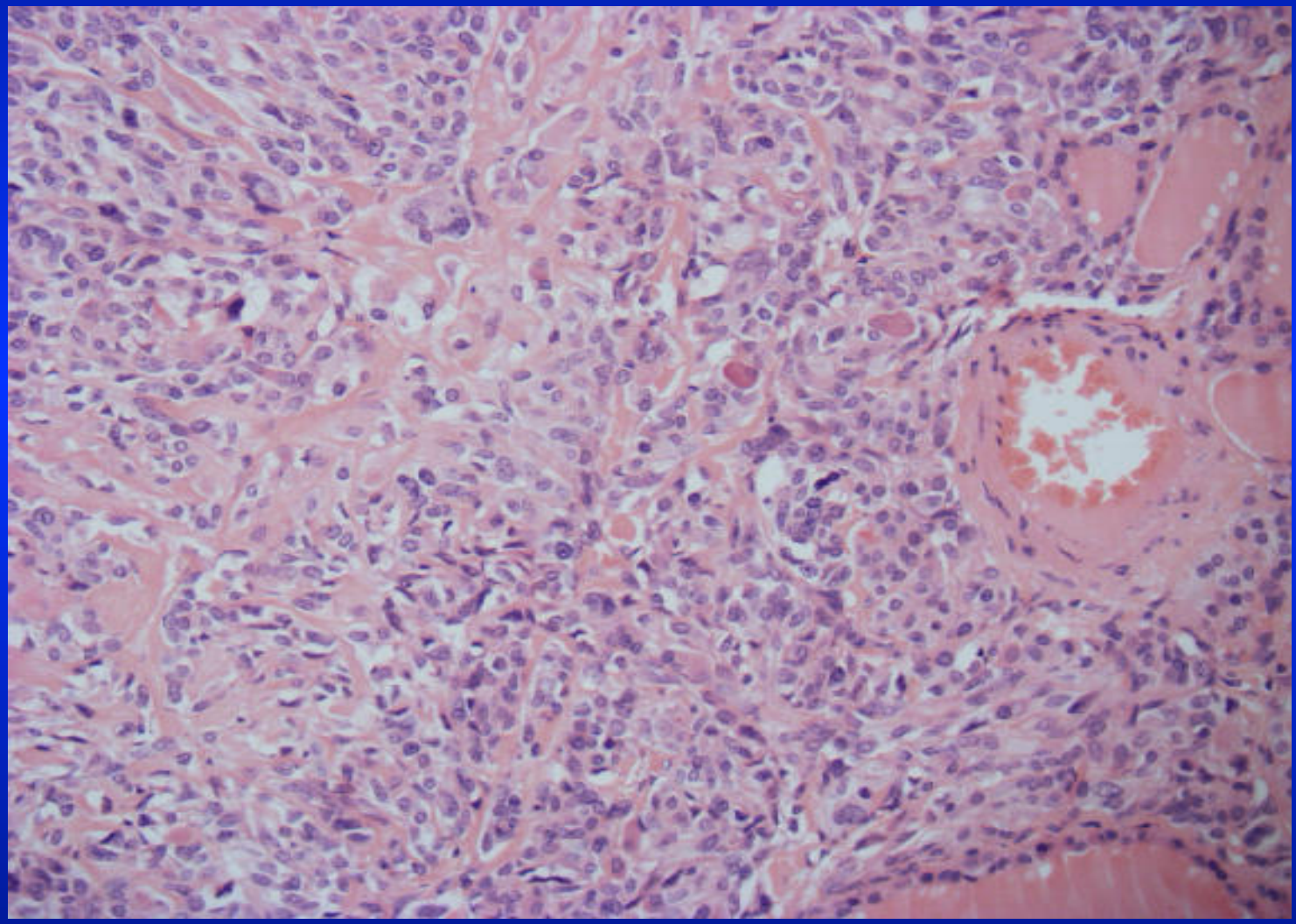
Relationship between thyroid carcinomas



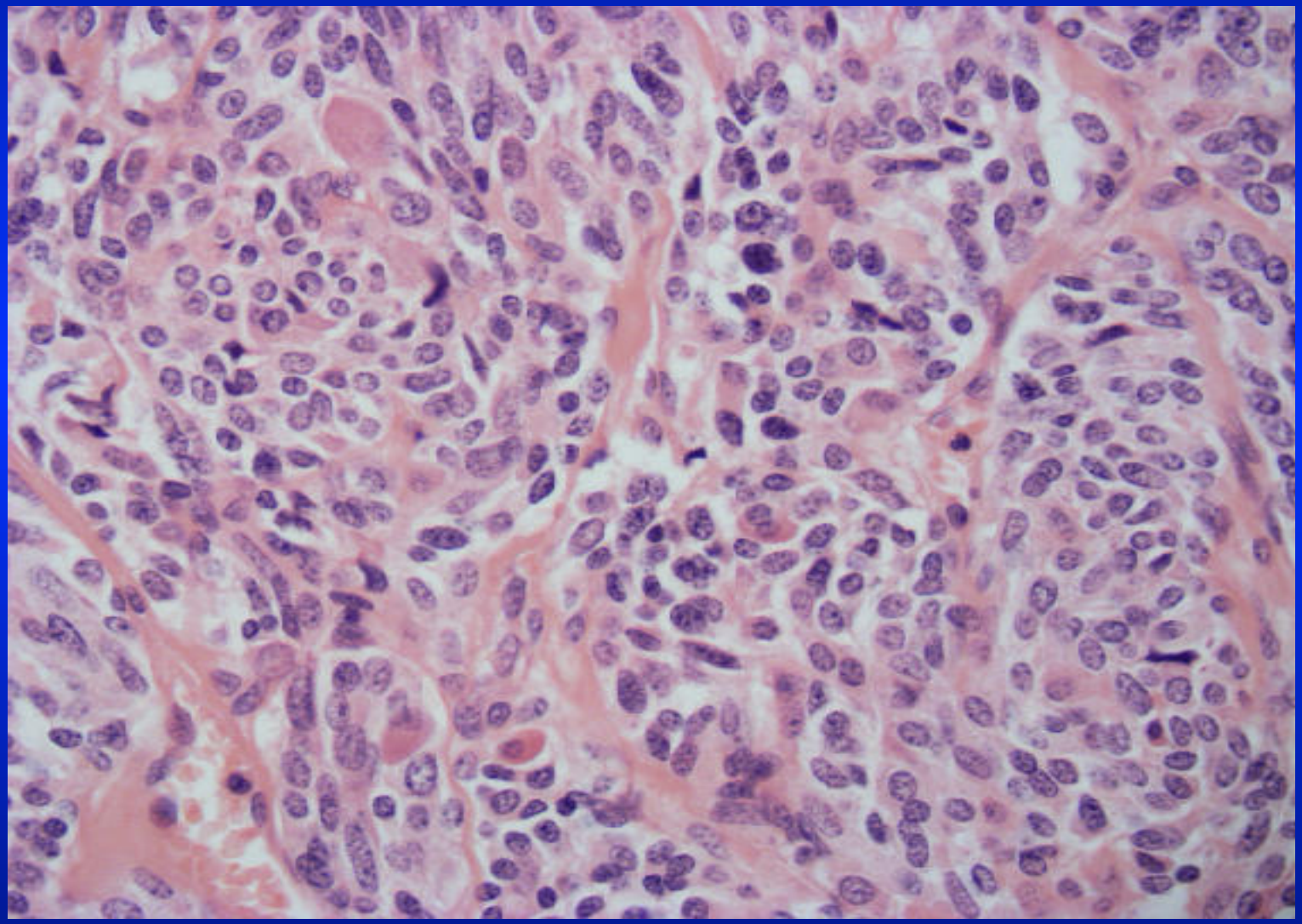
Insular Carcinoma

- Prognosis intermediate between well differentiated follicular carcinoma and anaplastic carcinoma.
- Aggressive behaviour
  - Mean 5 year survival is around 50%.
  - High incidence of nodal and blood-borne metastasis
  - Death is usually due to distant metastasis rather than local invasion.
- The presence of tracheal compression is a worrying symptom.

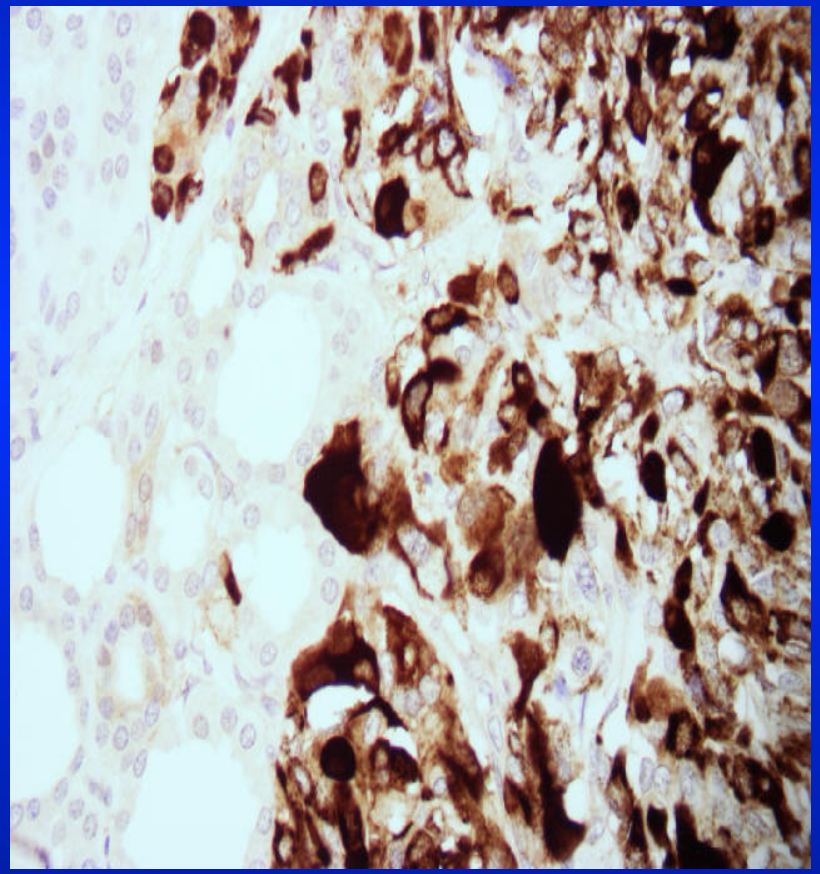
Case 5 PS09.2828



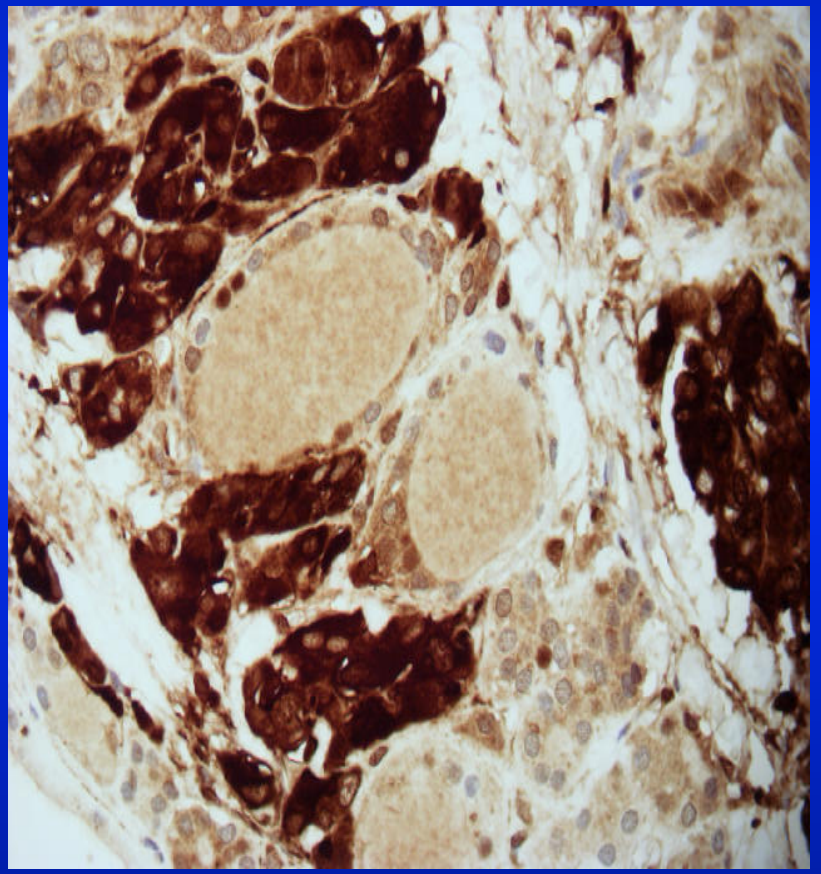
Case 5 PS09.2828



Case 5 PS09.2828



Calcitonin



CEA

Case 5 PS09.2828

Immunohistochemistry

Positive

- Calcitonin, CEA, TTF1, chromogranin

Negative

- thyroglobulin

	MEN-1	MEN-2A	MEN-2B
Pituitary	Adenomas	-	-
Parathyroid	Hyperplasia +++ Adenomas +	Hyperplasia	-
Panc. Islets	Hyperplasia ++ Adenomas ++	-	-
Adrenal	Cortical hyperplasia	Phaeo ++	Phaeo +++
Thyroid	-	C-cell hyperplasia+++ Medullary Ca +++	C-cell hyperplasia+++ Medullary Ca +++
Extra endocrine	-	-	Muocutaneous ganglioneuromas Marfans
Gene locus	MEN 1	RET	RET

Medullary carcinoma

- 5% of thyroid malignancies
- 20 % hereditary (Familial MTC, MEN 2A & 2B)
- Look for C-cell hyperplasia > MEN
- Multiple variants (eg. small cell etc).

C-cell hyperplasia

- Precursor lesion of all familial syndromes
- Central part lateral lobes
- C-cells inter- or intra-follicular location (>6 cells?)
- Diffuse or nodular
  - nodular should be regarded as definite precursor for familial MTC
- CEA positive (greater than normal C-cells)
- Calcitonin positive (greater than medullary carcinoma cells)

Medullary carcinoma

- Composed of C (parafollicular) cells
- Gross
  - Solid, firm, non-encapsulated
  - Grey to yellowish cut surface
  - Most in mid to upper portion of gland
- Micro
  - Solid proliferation of round to oval cells
  - Granular amphophilic cytoplasm
  - Highly vascular stroma, hyalinised collagen , amyloid, coarse calcification (+/- true psammoma bodies)
- Wide variety of cytoarchitectural patterns

Medullary carcinoma

- Immunohistochemistry
- Positive
  - Calcitonin
  - Epithelial markers
  - Thyroid markers
    - TTF-1
  - Panendocrine markers
    - NSE, Chromogranin A, synaptophysin
  - CEA
- Negative: thyroglobulin

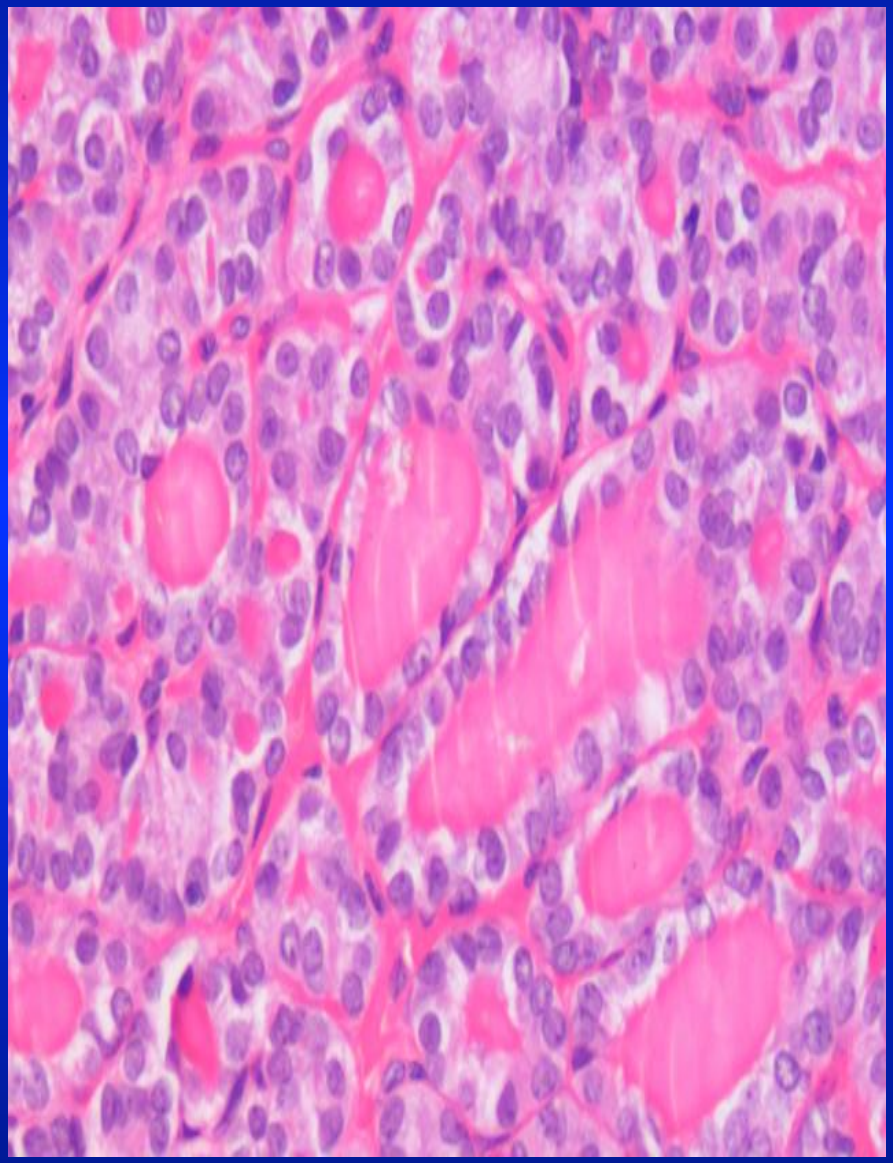
Case 1 PS14.13088

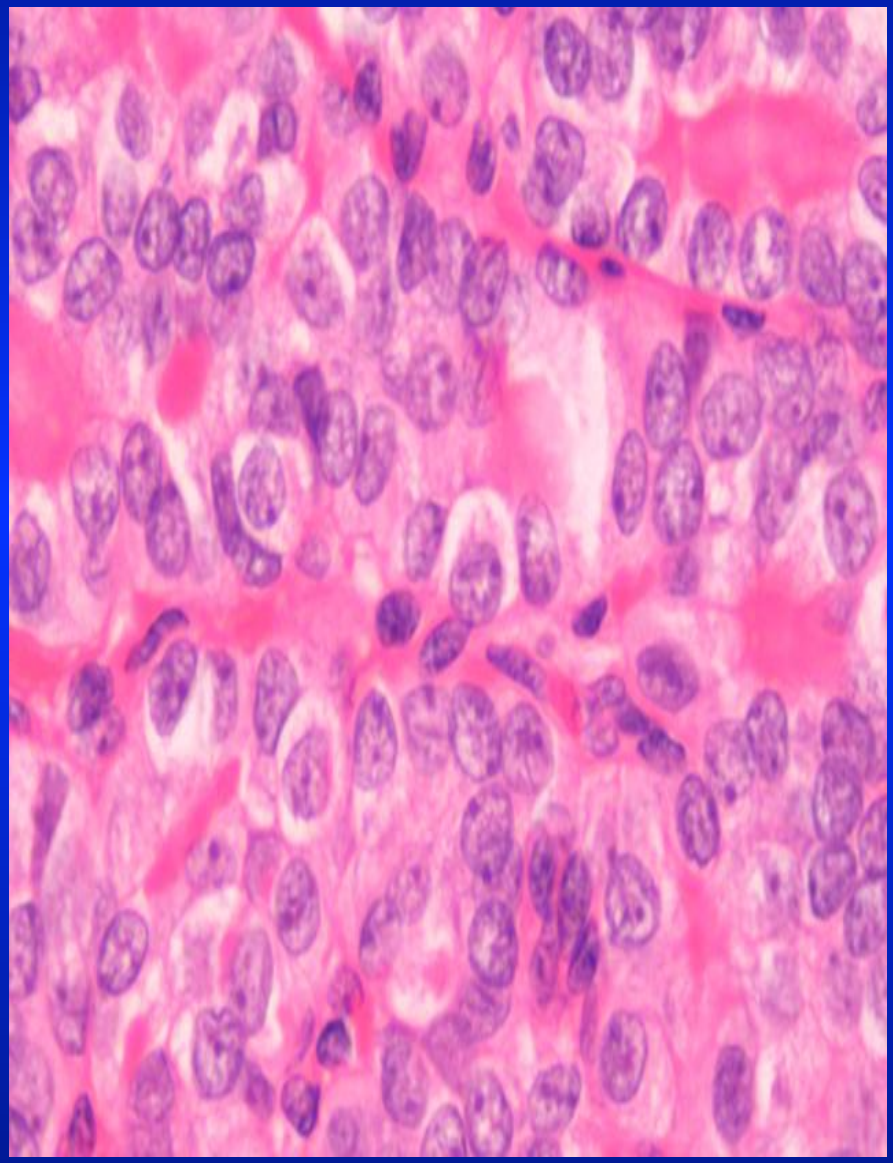
80 year old female high signal thyroid nodule on PET CT. Left thyroid lobectomy

Macro

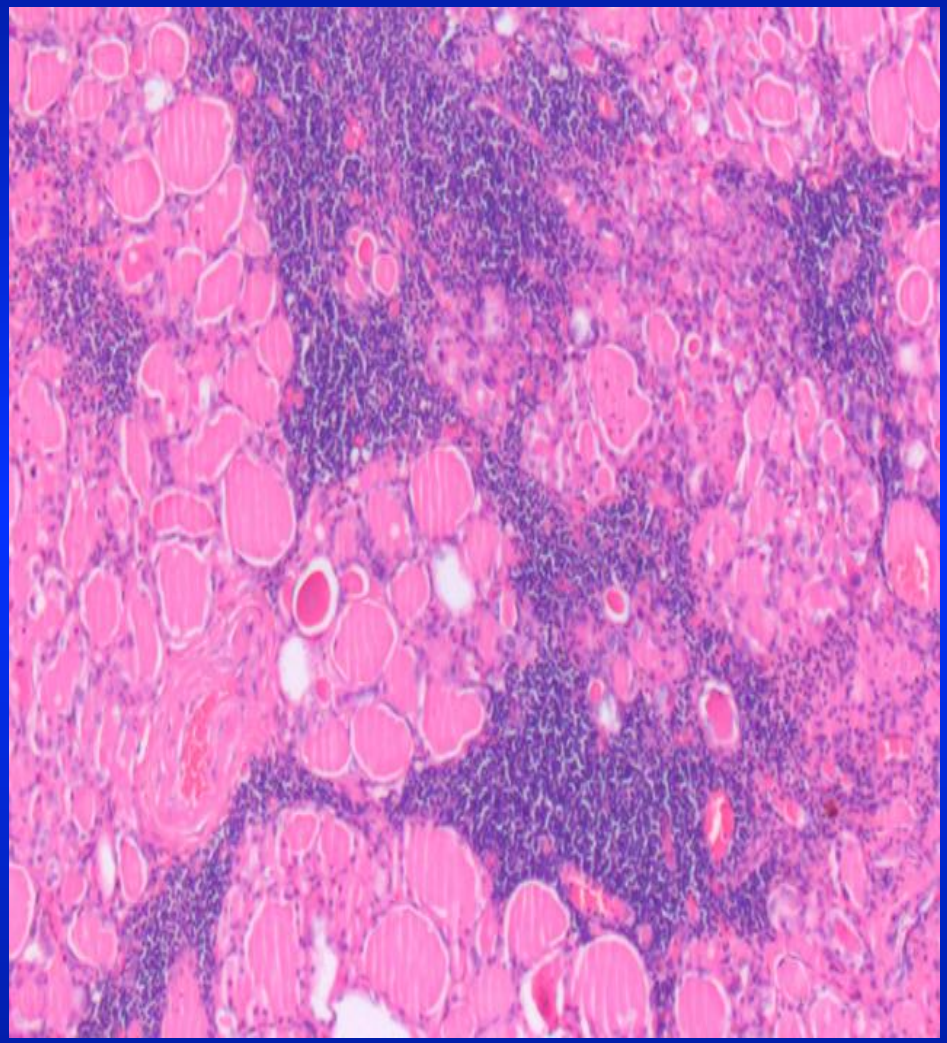
- Left thyroid lobe weighing 5.8g
- Slicing from posterior to inferior showed no focal lesions

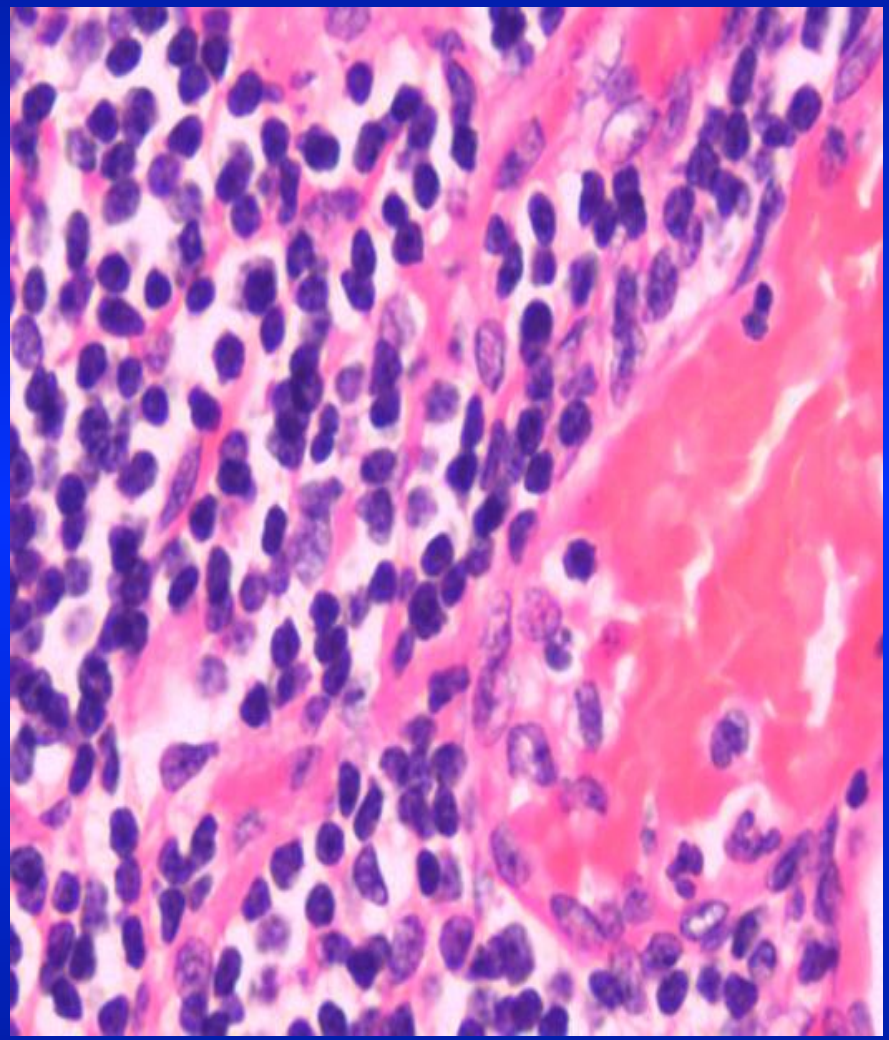
Case 1 PS14.13088





Case 1 PS14.13088





Case 1 PS14.13088

Micro

- multiple variably sized unencapsulated nodules
- small nodule composed of closely-packed follicles with slightly irregular nuclei and pale chromatin
- Hurthle cell change is seen in one nodule (block E)
- Multiple aggregates of small lymphoid cells

Case 1 PS14.13088

Immunohistochemistry

- Lymphoid cells are
  - predominantly B cells which express CD20, CD5 and CD23.
  - negative for cyclin D1.
- Moderate numbers of admixed, reactive CD3 positive T-cells.
- MIB-1 proliferation fraction is <2%.

Case 1 PS14.13088

Diagnosis

- Multinodular goitre
  - Including follicular patterned nodule with features in keeping with NIFTP, formerly known as non-invasive encapsulated follicular variant of papillary thyroid carcinoma
- Small lymphocytic lymphoma (SLL/CLL).

NIFTP

"non-invasive follicular thyroid neoplasm with papillary like nuclear features"

NIFTP has very low risk of adverse outcome.
Lobectomy alone sufficient treatment.

NIFTP

Inclusion criteria

- Major features
  - Encapsulation or clear demarcation
  - Follicular pattern, <1% papillae
  - Solid/trabecular or insular pattern <30% volume
  - No psammoma bodies
  - Nuclear features of papillary thyroid carcinoma
    - With nuclear score of 2 or 3 (see below)
- Minor features
  - Dark colloid, irregularly shaped follicles, multinucleate giant cells within follicles, “sprinkling sign”, follicles clefting from stroma, intratumoural fibrosis

NIFTP

Exclusion criteria

- Any capsular or vascular invasion
- Infiltrative border
- Tumour necrosis
- Papillae >1% volume
- Psammoma bodies
- Mitoses >/= to 3/10 hpf
- Characteristics of other PTC variant
- Oncocytic lesion

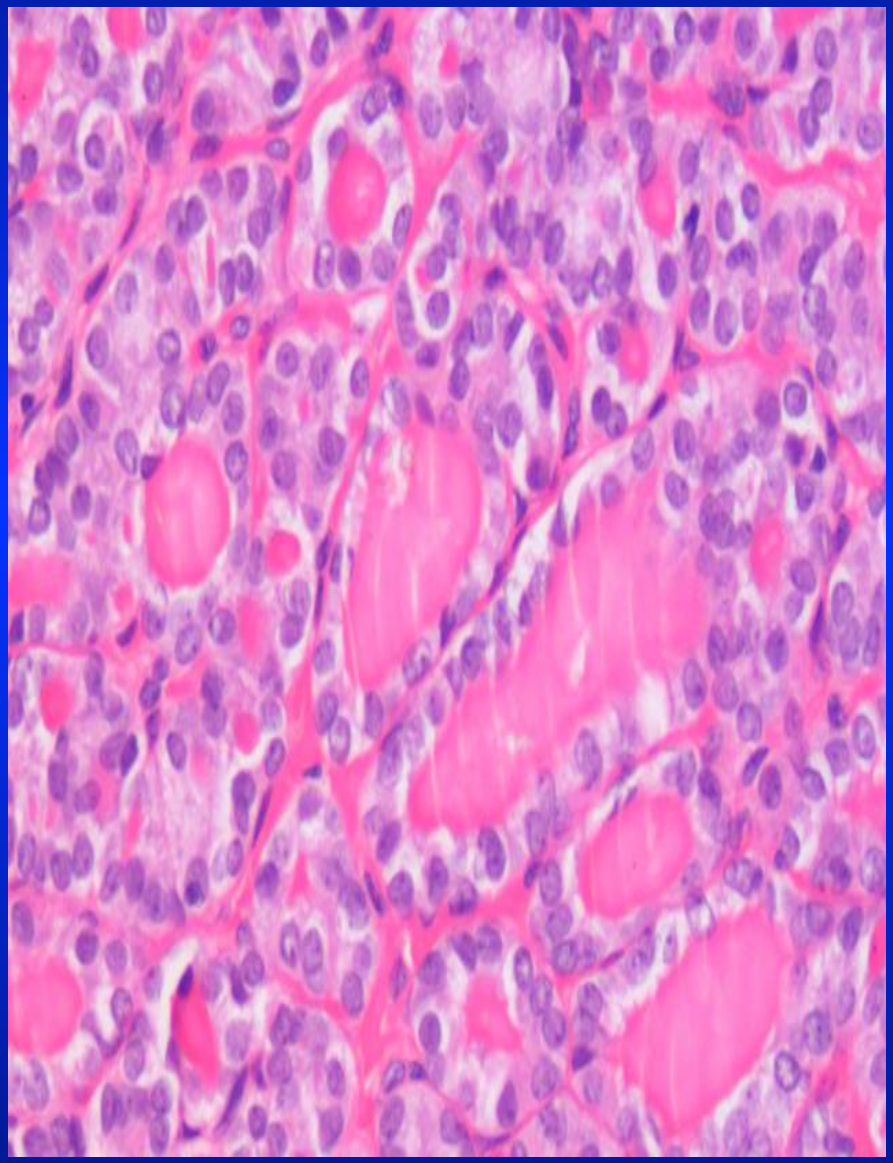
NIFTP

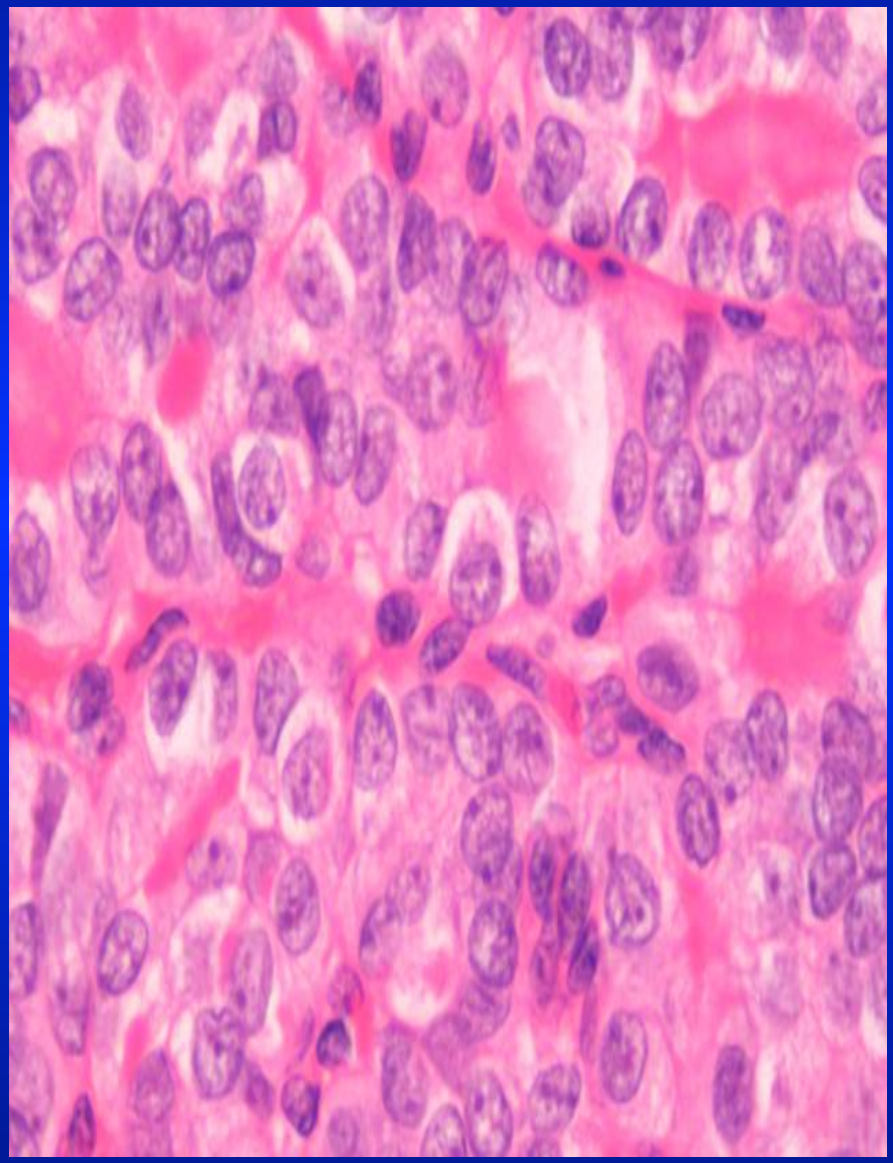
Criteria for scoring the nuclear features of suspected NIFTP lesions:

1. Size and shape
   - Enlargement/elongation/overlapping
2. Membrane irregularities
   - Irregular contours/grooves/pseudoinclusions
3. Chromatin characteristics
   - Clearing/margination/glassy nuclei

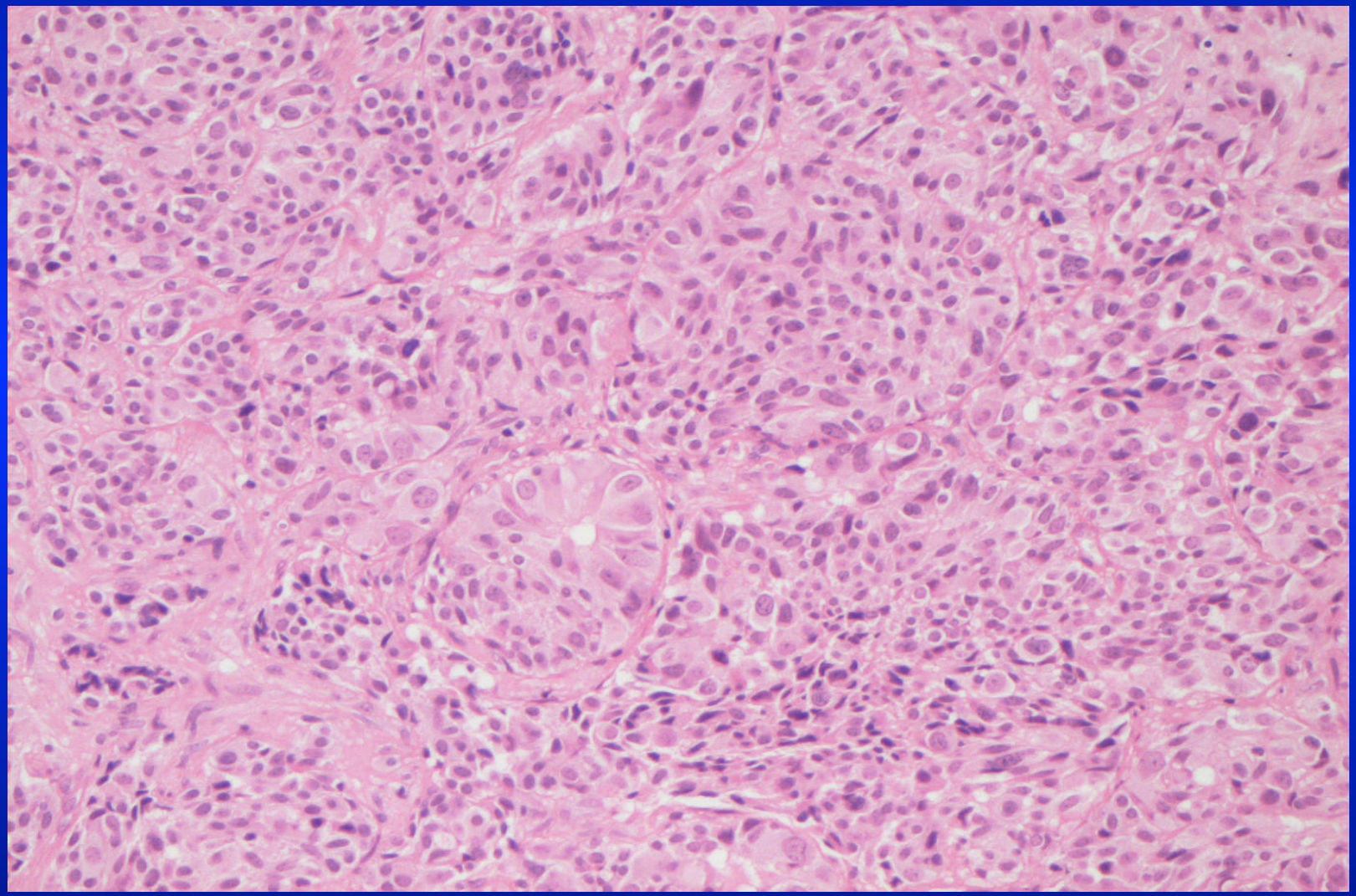
Each of the features is given a score of 1(present/ sufficient) or 0 (absent/insufficiently expressed) to give total score varying between 0 and 3. Score of 2 or 3 is required for diagnosis.

Case 1 PS14.13088

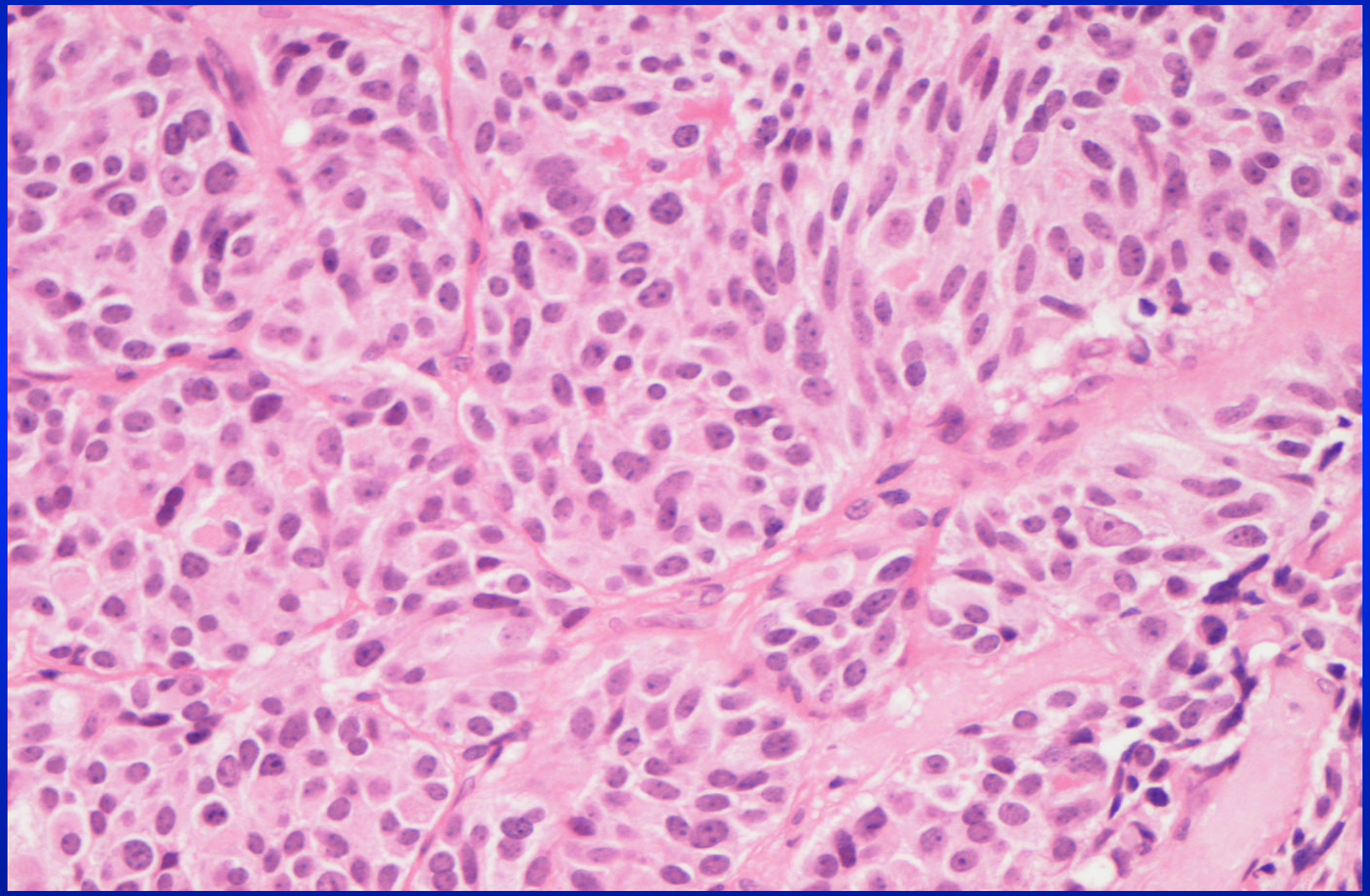




Case 13



Case 13



Case 13 PS09.20490

Immunohistochemistry

Positive

- Pancytokeratin (MNF116), CK7, TTF-1, CEA

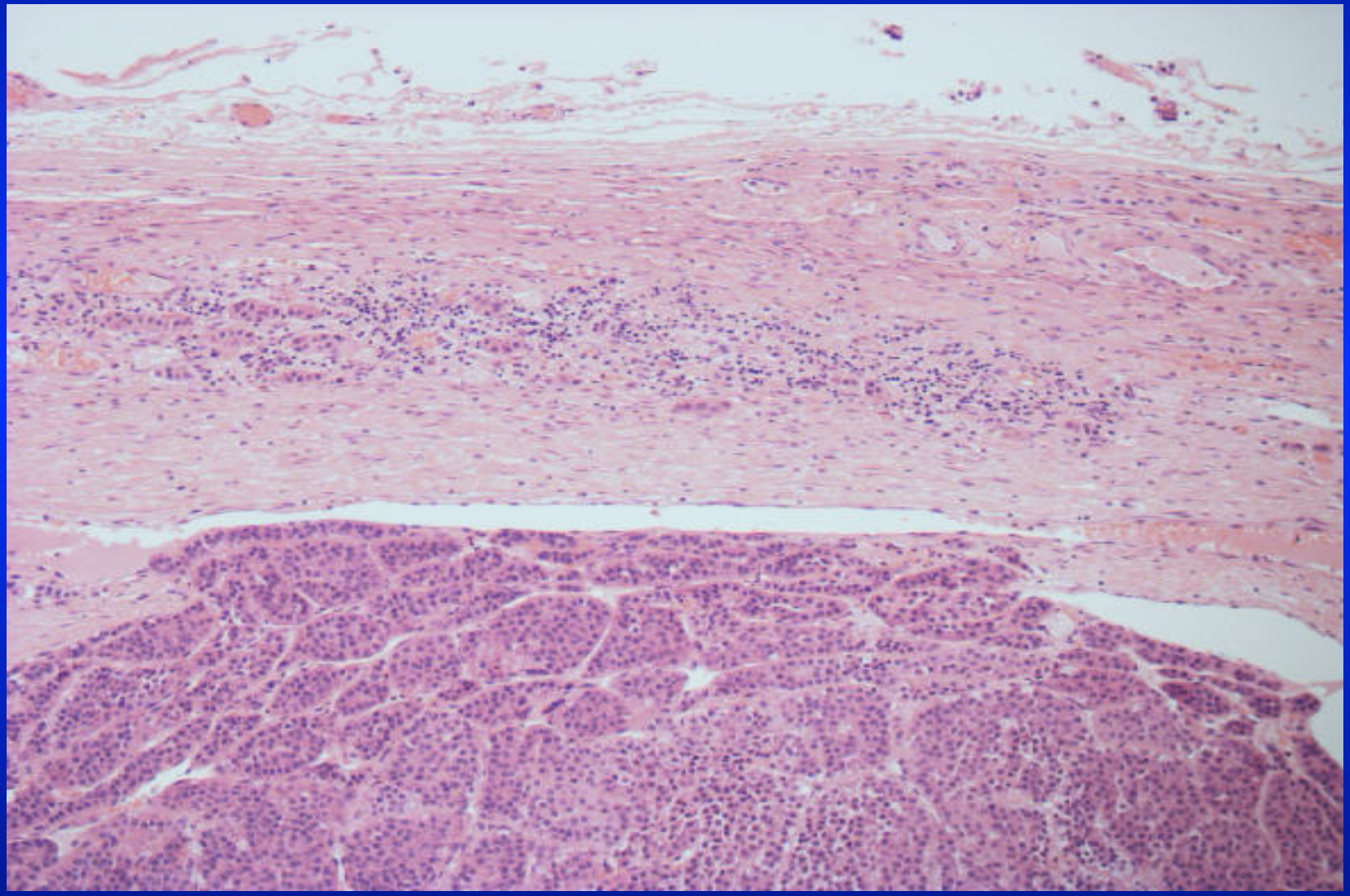
Negative

- CK20 and thyroglobulin

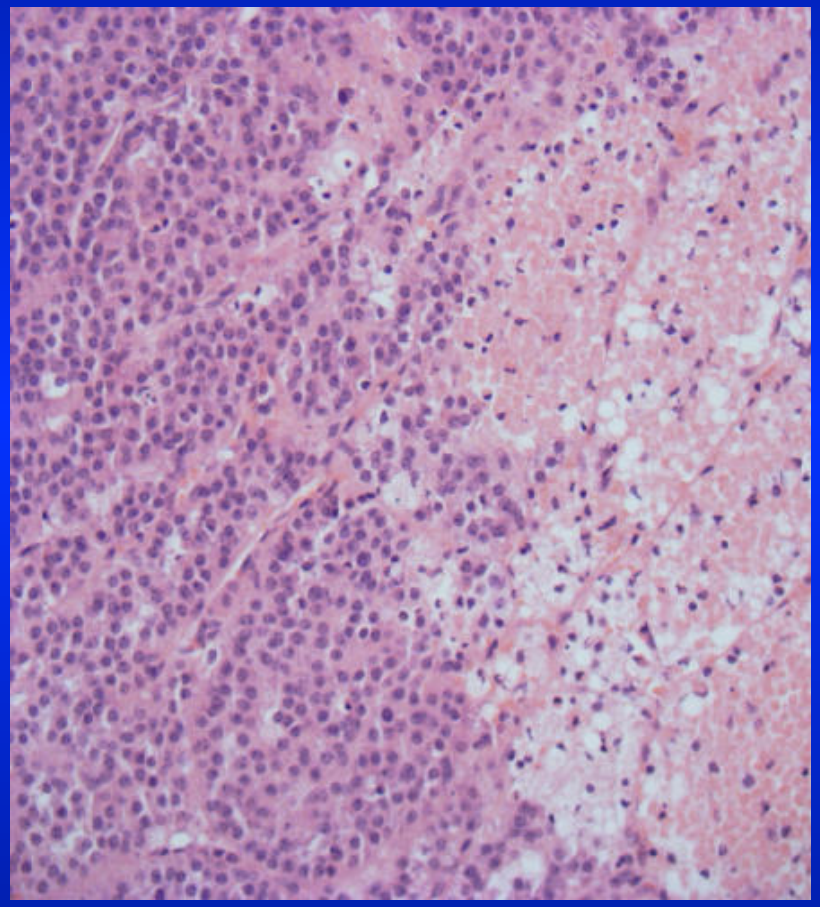
Case 13 PS09.20490

Diagnosis: MEDULLARY CARCINOMA

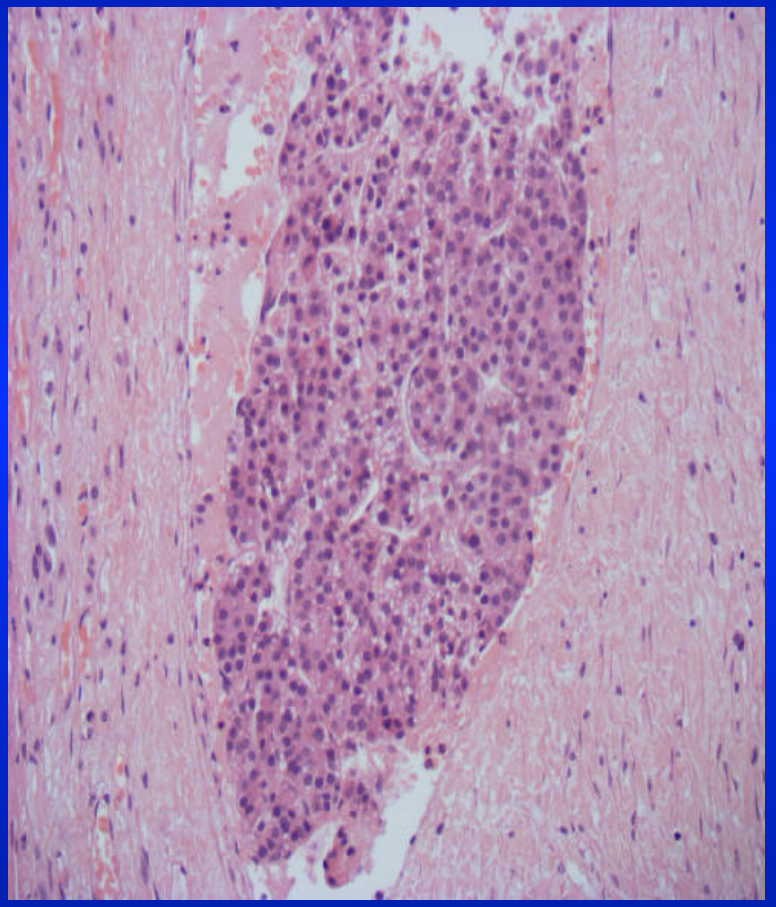
Case 4 PS09.13965



Case 4 PS09.13965

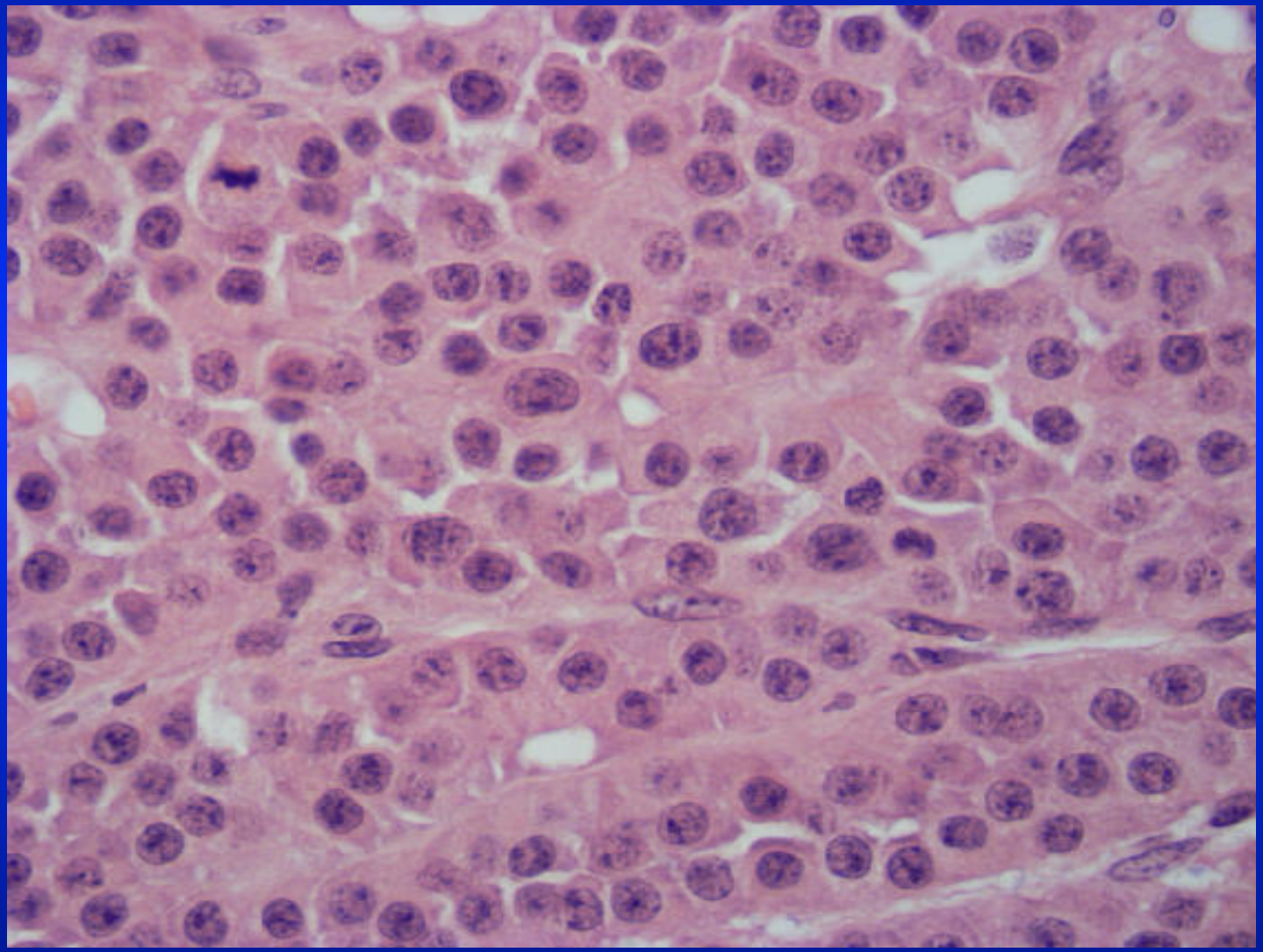


Extensive necrosis



Vascular invasion

Case 4 PS09.13965



Case 4 PS09.13965

- Compressed rim normal adrenal
- Tumour growth pattern
  - Alveolar, trabecular, diffuse
- Confluent tumour necrosis
- Vascular invasion

Case 4 PS09.13965

Tumour cytology

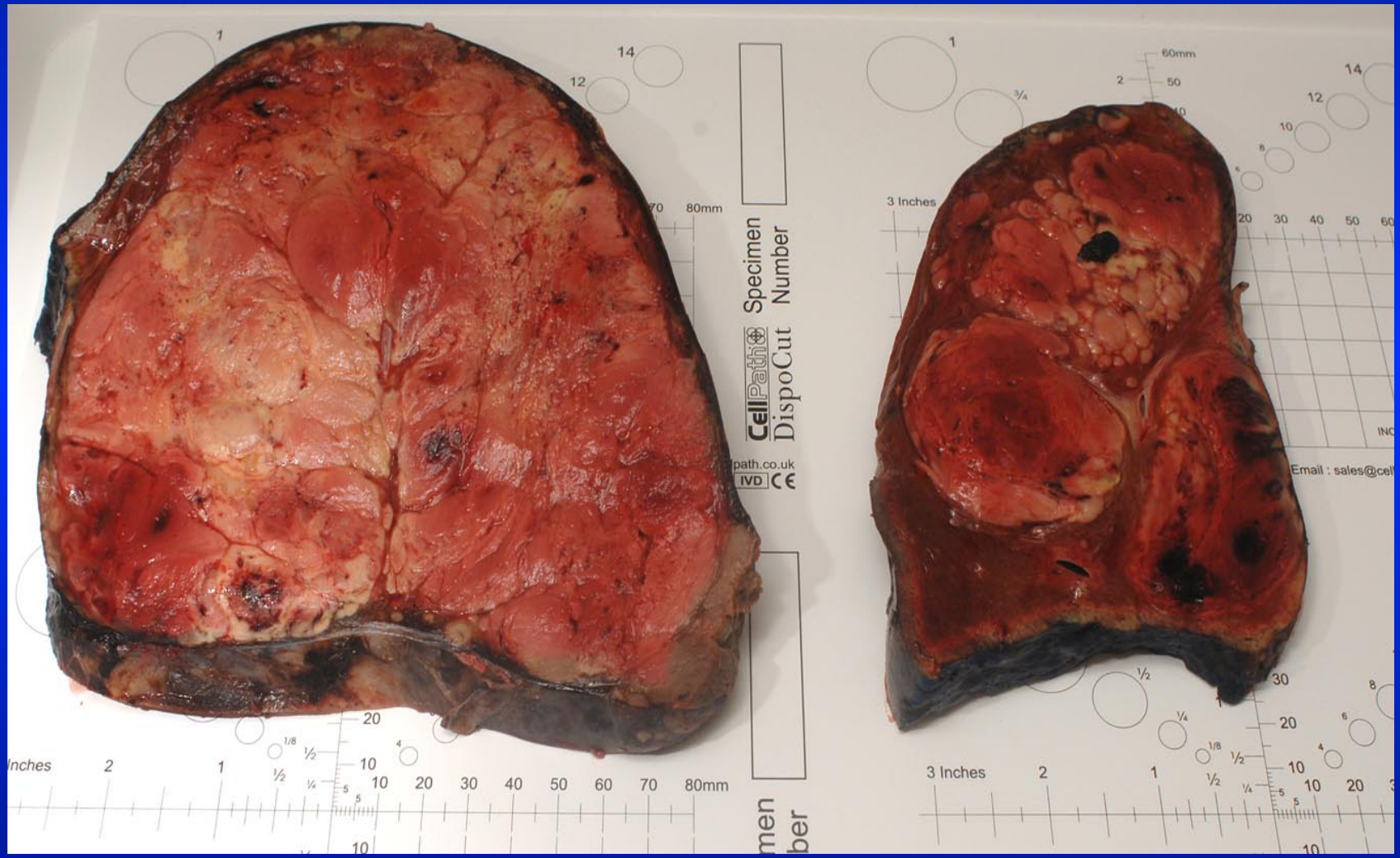
- Mild nuclear pleomorphism, finely granular chromatin
- High mitotic activity

Differential diagnosis:

ACC, phaeochromocytoma, HCC

Case 4 PS09.13965

Case 4 PS09.13965



Case 4 PS09.13965

Immunohistochemistry

Positive

- Pancytokeratin, synaptophysin, Melan A
- Chromogranin A and inhibin (focally)

Negative

- S-100, hepatocyte marker, calretinin

Diagnosis: ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma

- Gross description
- Weight
- Dimensions
- Adrenal capsule intact or breached
- Excision complete/incomplete

Adrenocortical carcinoma

NO absolute criteria for diagnosis of malignancy

EXCEPT

- Extensive invasion of local structures and metastasis

Weiss Malignancy Criteria

- Well established (Am J Surg Path 1984; 8; 163-9)
- More recently modified to improve inter-observer reproducibility (Aubert et al., 2002; 26; 1612-19)

Malignancy criteria in cortical adenoma

	Weiss system	Modified Weiss system
Clear cells comprising ≤ 25% of the tumour	✓	✓ x 2
Diffuse architecture > one third of the tumour	✓	–
Confluent necrosis	✓	✓
High nuclear grade (Fuhrman grade 3 or 4)	✓	–
Mitotic rate >5/50 HPF	✓	✓ x 2
Atypical mitoses	✓	✓
Venous invasion	✓	–
Sinusoidal invasion	✓	–
Capsular invasion	✓	✓
A score of three or more indicates aggressive/malignant behaviour		

Adrenal cortical carcinoma

Histology contd.

Also comment on

- Extra-adrenal invasion (NOT other organs)
- Invasion other organs

Prognostic factors:

Age and stage most important

Other: mitotic activity, venous invasion, >50g, >6.5cm, MIB-1 >4%, p53 +ve

Case 11 PQ14.3080

- 59 year old male with left neck swelling for 3-4 months

Case 11 PQ14.3080

Micro

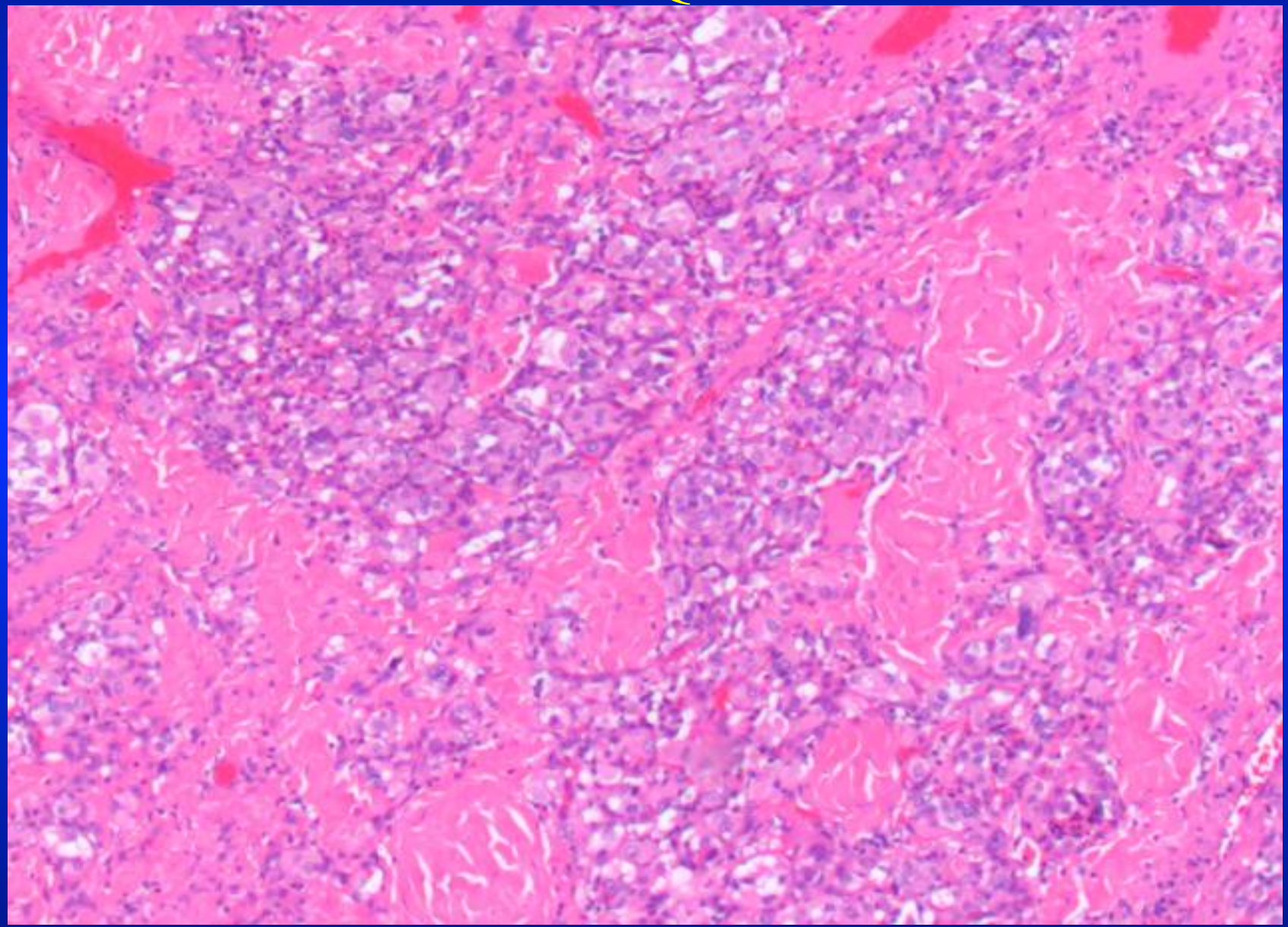
- Well circumscribed tumour
  - composed of nests of polygonal cells
    - Abundant granular cytoplasm
    - Anisonucleosis and nuclear pleomorphism
    - Occasional mitoses
  - intervening highly vascular fibrous septae
  - no necrosis or vascular invasion

Case 11 PQ14.3080

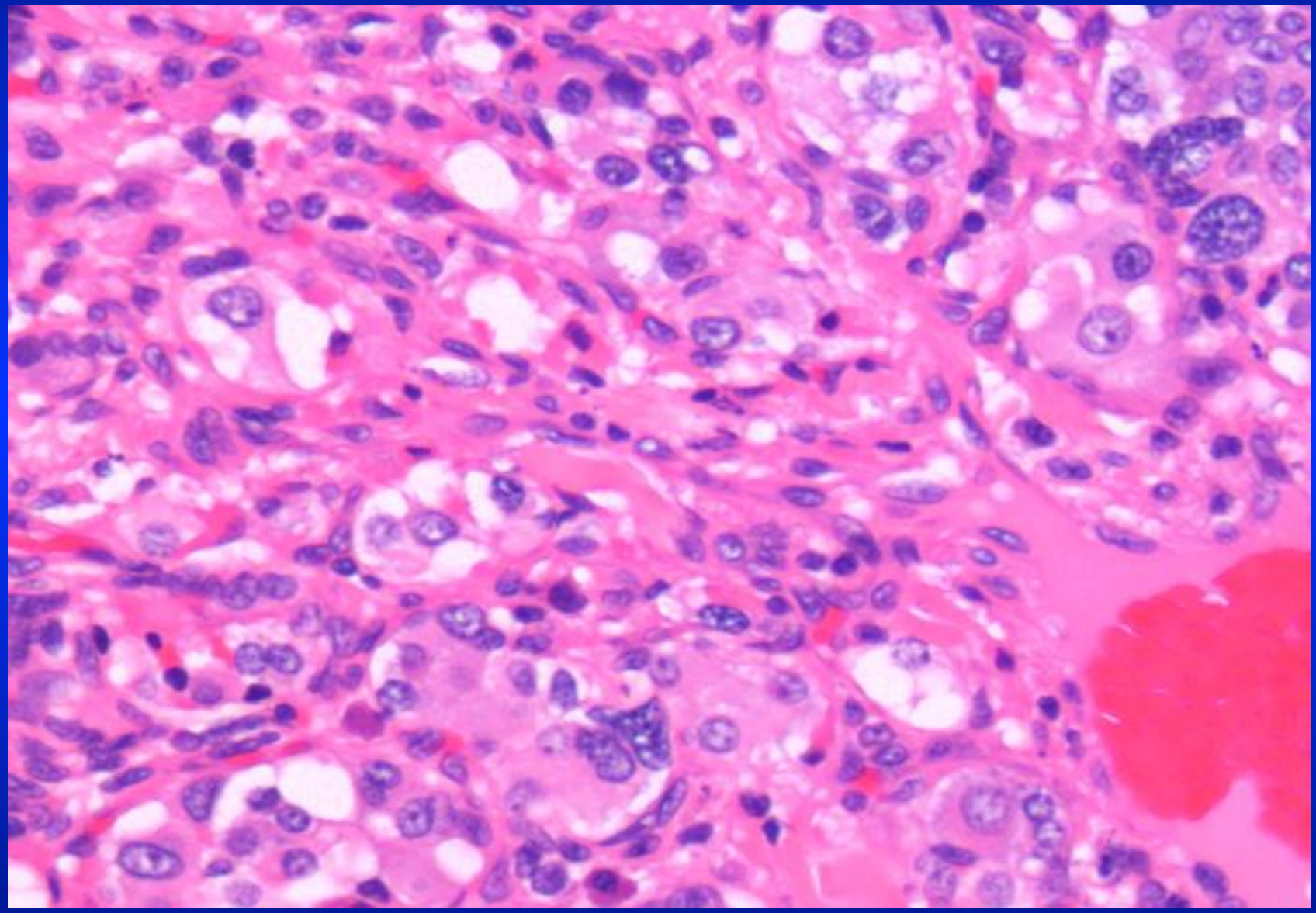
Micro (contd.)

- Nodular proliferation within tumour
- Moderately pleomorphic cells with bean-shaped grooved nuclei and small nucleoli
- Eosinophils, eosinophil microabscesses and necrosis

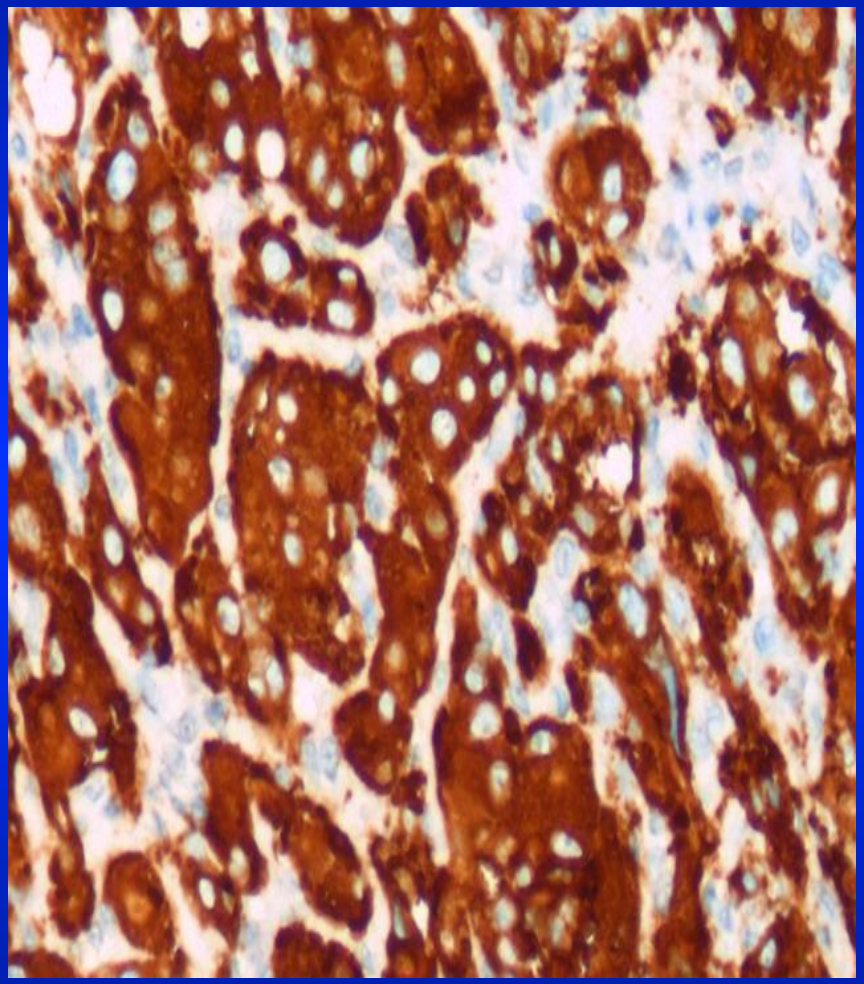
Case 11 PQ14.3080



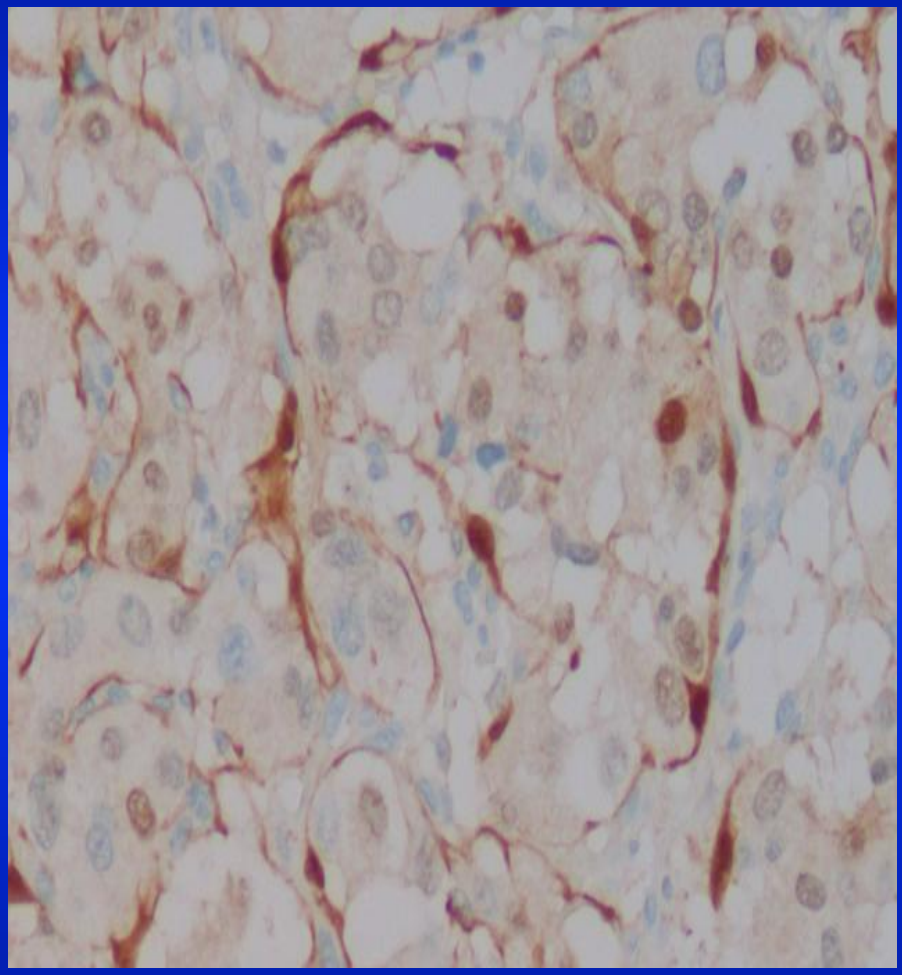
Case 11 PQ14.3080



Case 11 PQ14.3080

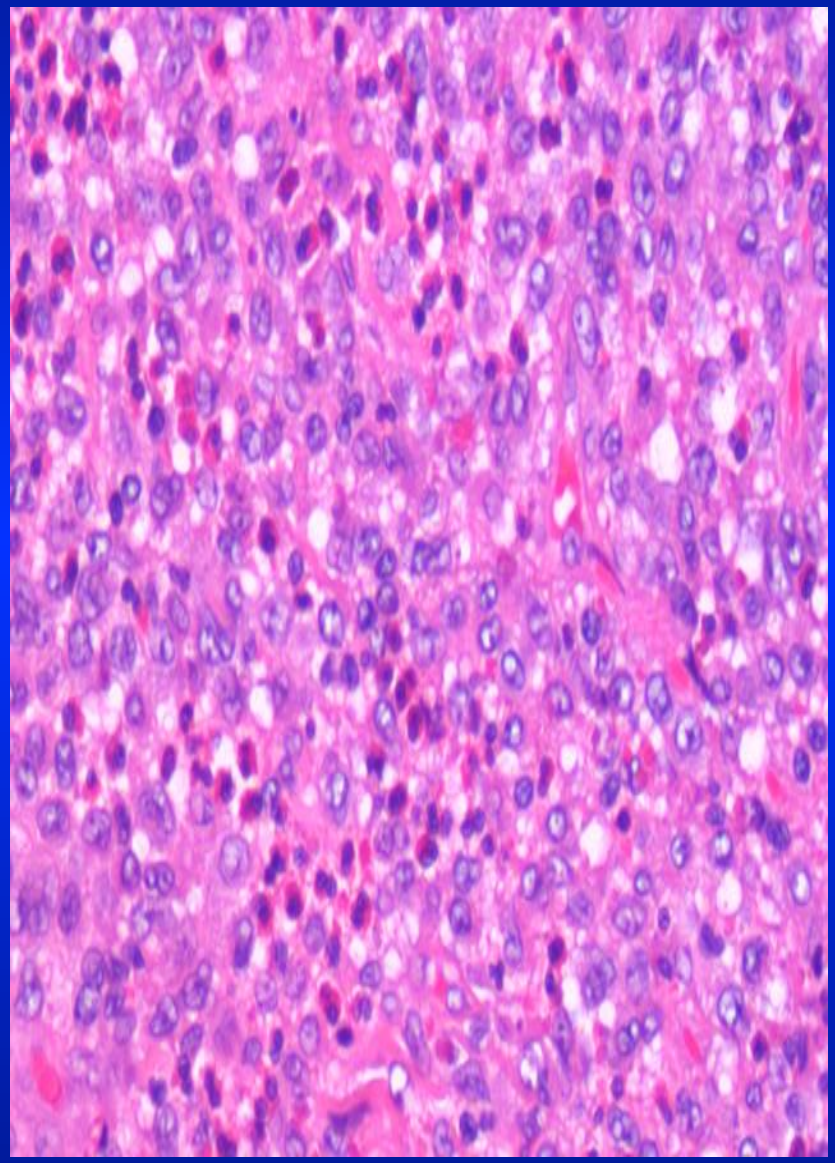


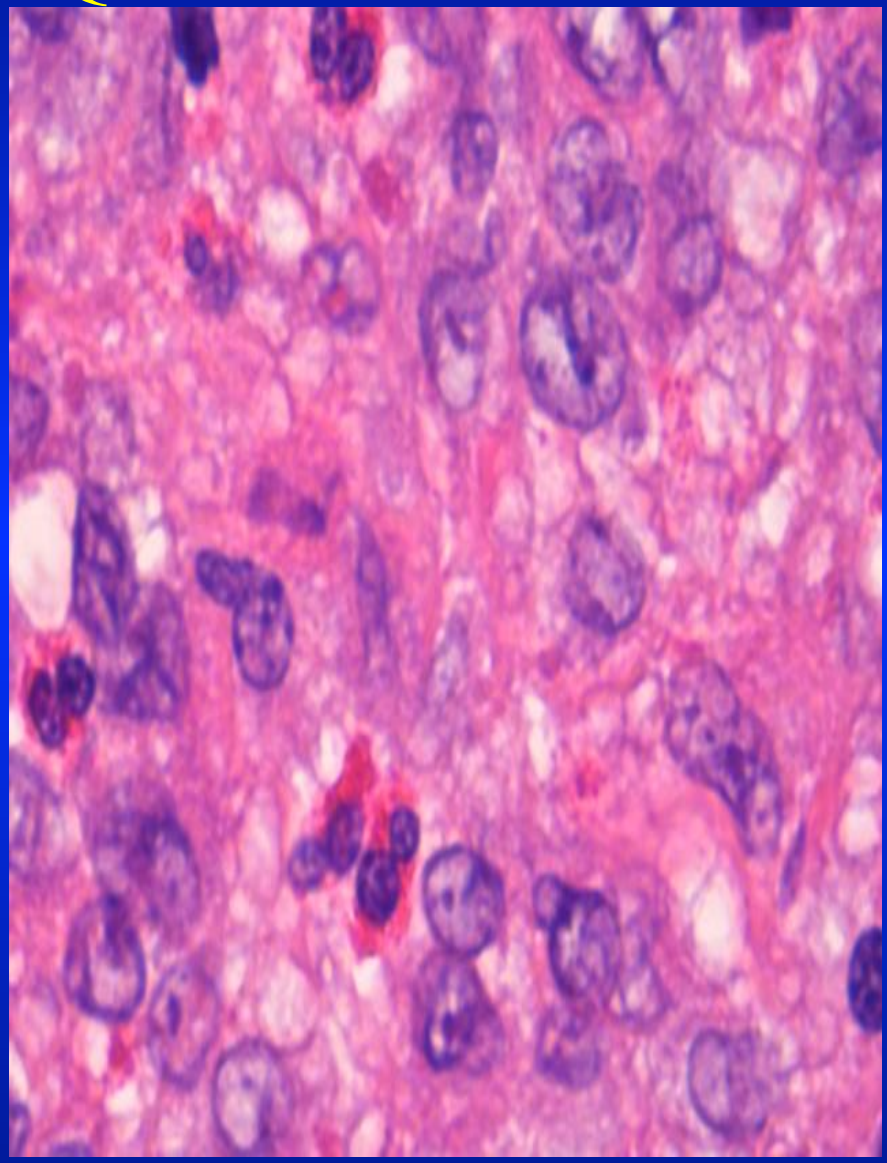
Synaptophysin



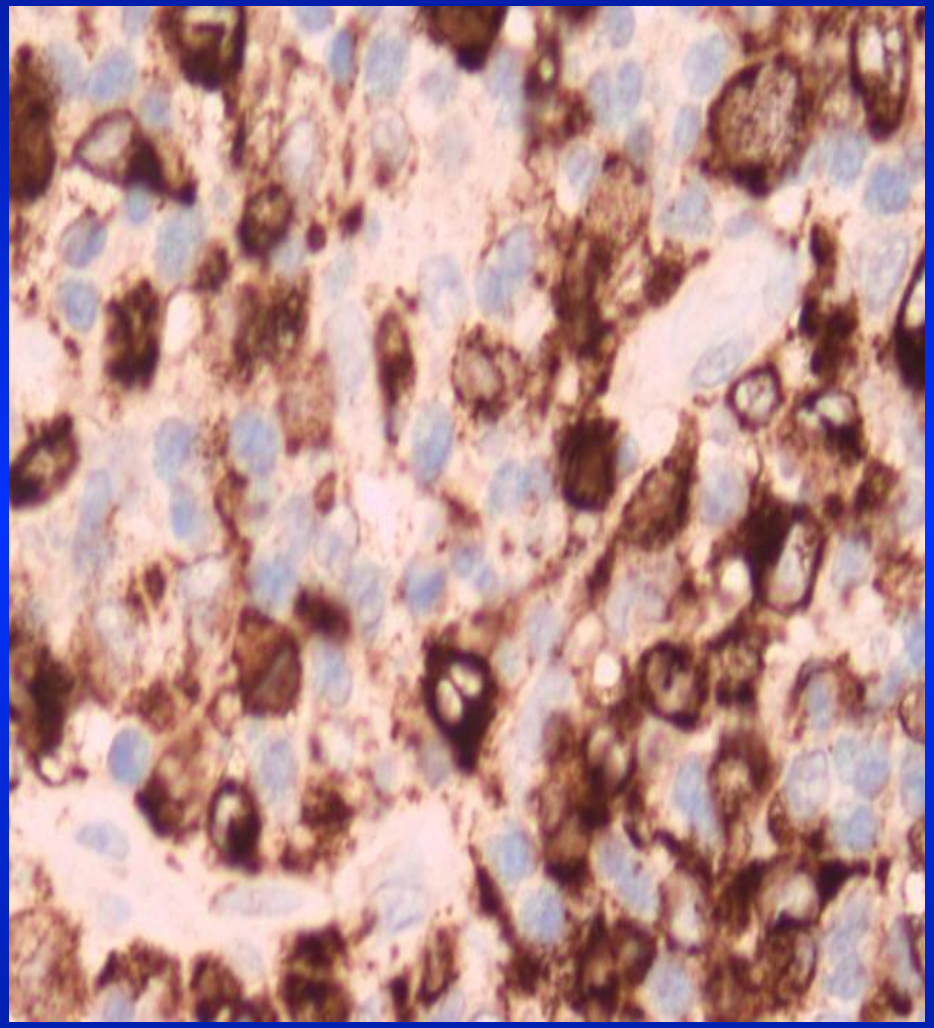
S100

Case 11 PQ14.3080

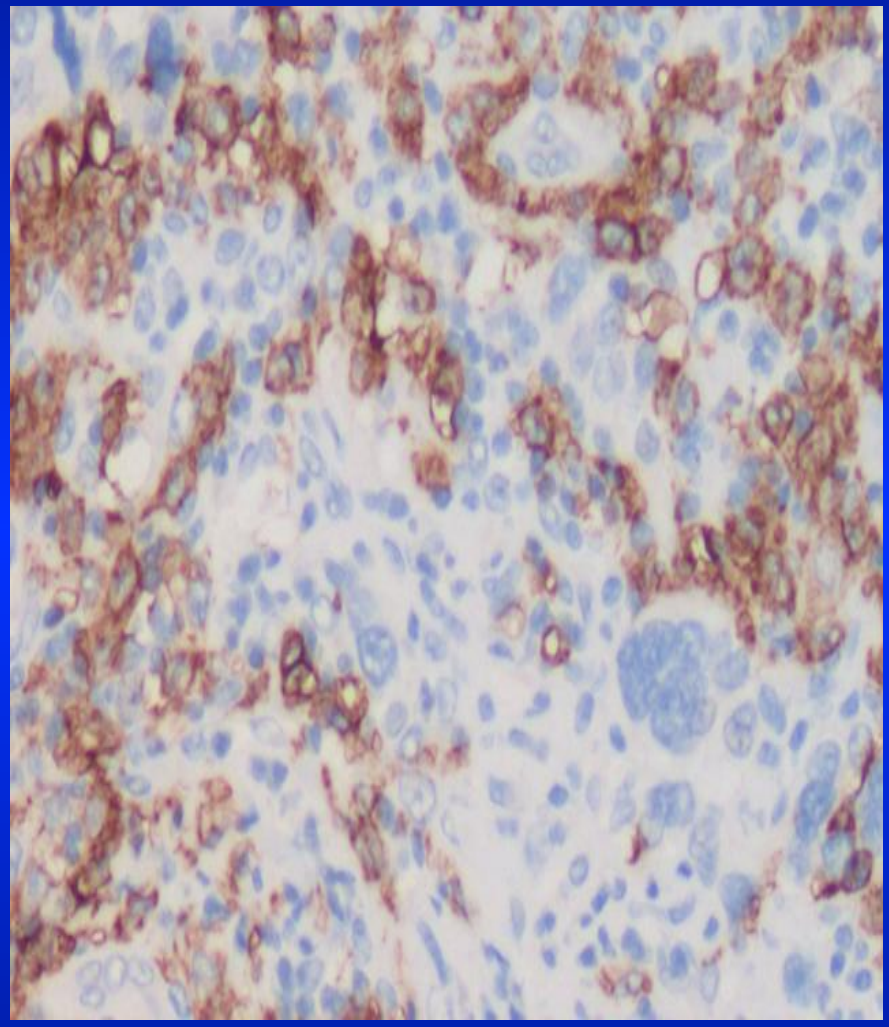




Case 11 PQ14.3080



Langerin



CD1a

Case 11 PQ14.3080

Immunohistochemistry

- Positive in tumour:
  - Neuroendocrine markers; chromogranin A, synaptophysin, CD56, S100 (sustentacular cells)
- Positive in cellular nodule
  - CD1a , S100 and Langerin (B and T cell markers negative)
- Diagnosis:
  - Carotid body paraganglioma containing a focus of Langerhans cell histiocytosis

Case 11 PQ14.3080

Carotid body paragangliomas

- Commonest group of extraadrenal paragangliomas
- Bifurcation of common carotid artery
- 10 fold more common in people living at high altitude (benign)
- Incidence of malignancy is approximately 10%
  - Mets to regional lymph nodes, lungs and skeletal system

Case 11 PQ14.3080

Carotid body paragangliomas

- Benign versus malignant
  - No reliable morphological criteria
  - High mitotic activity
  - Decreased immunohistochemical reactivity for neuropeptides
  - Few S100 positive sustentacular cells

This case did not have any features suggesting an aggressive biological course

Familial Paraganglioma Syndromes

Phaeochromocytomas and paragangliomas are associated with inherited syndromes e.g.

- MEN II
- Von Hippel-Lindau (VHL) disease
- Neurofibromatosis (NF) type 1
- Familial paraganglioma-phaeochromocytoma syndromes
  - mutations in the SDH gene

Paraganglioma-phaeochromocytoma Syndromes Genotypic-phenotypic correlations

SDH mutations	Family history (%)	Age (years) of presentation	No of tumours	Sites
SDHB	31	30	Single	Abdo, pelvis, retroperitoneum, adrenal
SDHD	61	30	Multiple/single	Head and neck
SDHC	63	38	Single	Head and neck

Malignant phaeochromocytoma

- WHO defines as ‘metastasis to site where paraganglial tissue is not normally found’
  - ?local invasion
- ≈10% of all cases
- Metastasise to bone, liver, lung, kidney
- No single diagnostic or clinical feature predicts malignancy

Current RCPath Guidelines (2012)

- No absolute criteria for malignancy
- Suspicious features:
  - Coarse nodularity
  - Confluent necrosis
  - Absence of hyaline globules
  - >3 mitoses/20 HPF
  - Atypical mitotic figures
  - Absence of sustentacular cells (S100+)
  - MIB1 index > 2.5%
- PASS not recommended at present

PASS score

The American Journal of Surgical Pathology 26(5): 551–566, 2002

Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) to Separate Benign From Malignant Neoplasms

A Clinicopathologic and Immunophenotypic Study of 100 Cases

Lester D. R. Thompson, M.D.

PASS

- 50 histologically benign tumours
- 50 histologically malignant
  - 33 of which clinically malignant
- Histological features related to malignancy identified
- These features weighted by specificity for clinical malignancy, and developed into scoring scheme
- Immunohistochemistry not incorporated

PASS criteria

Feature	Score
Large nests of cells or diffuse growth >10% of tumor volume	2
Necrosis (confluent or central in large cell nests)	2
High cellularity	2
Cellular monotony	2
Presence of spindle-shaped tumor cells (even focal)	2
Mitotic figures (>3 per 10 high power fields)	2
Extension of tumor into adjacent fat	2
Vascular invasion	1
Capsular invasion	1
Profound nuclear pleomorphism	1
Nuclear hyperchromasia	1
Total possible score	**20**

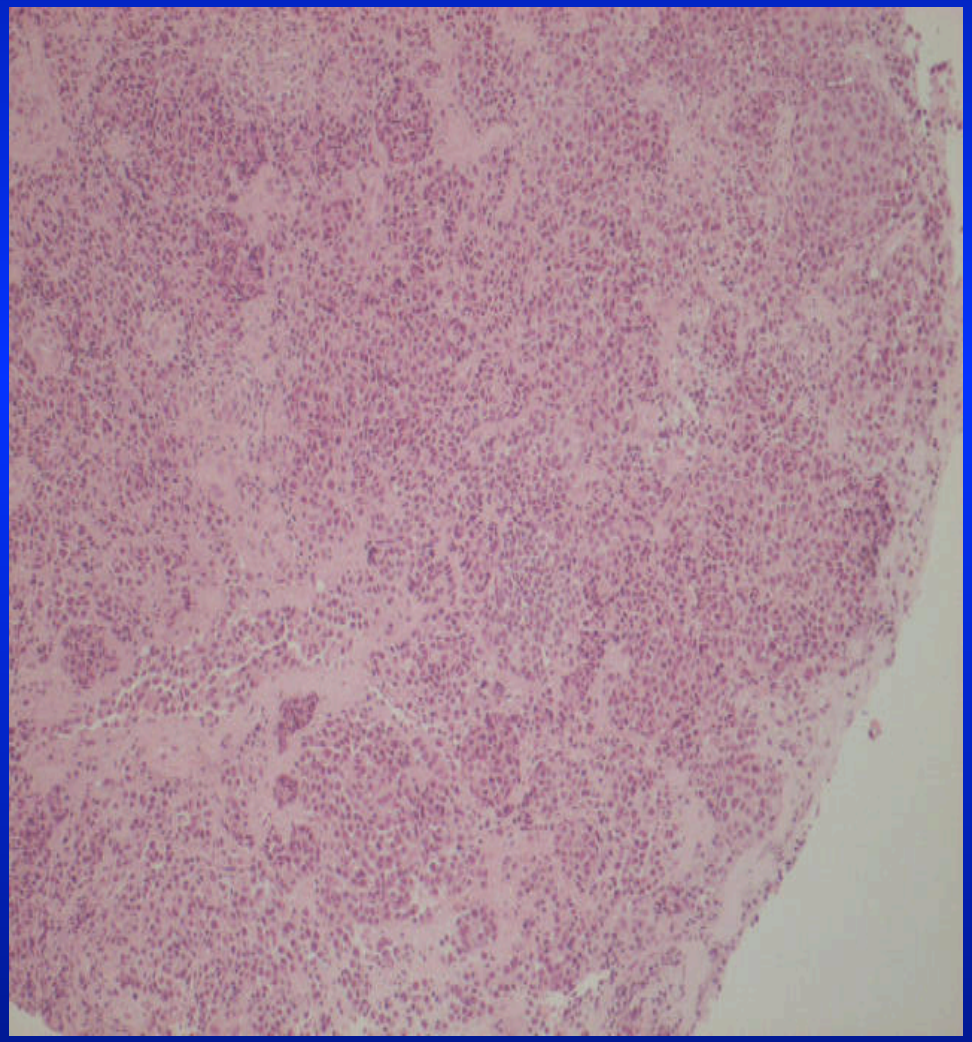
PASS criteria

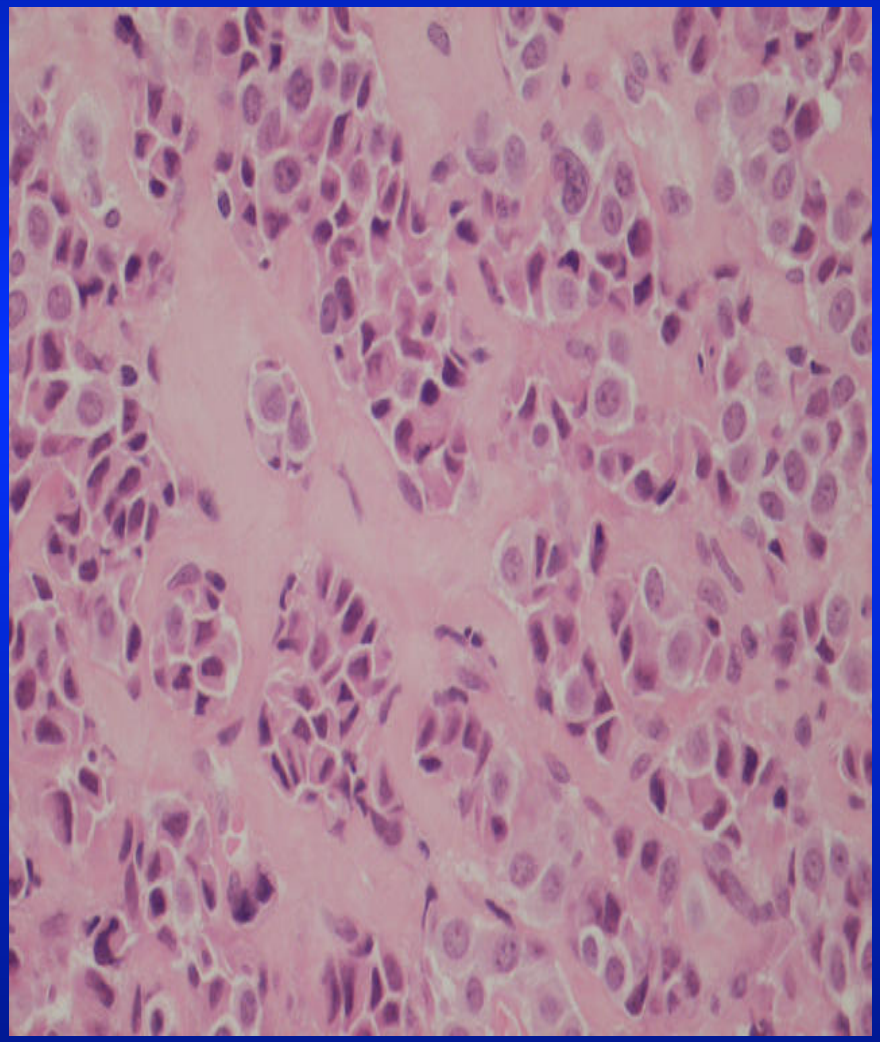
- 50 tumours had a PASS ≥ 4, including all 33 malignant cases
- 50 had PASS < 4, none of which were malignant (mfu 14.1 years)
- Very high PASS score did not predict metastasis

Problems with PASS

- Many criteria very subjective
  - **Inter-user** variability (Wu et al, Am J Surg Path 2009, 33, 599-608)
- Still little published supporting data

Case 14 PQ10.48





Case 14 PQ10.48

Fragments of squamous epithelium showing a subepithelial neoplastic proliferation

- Variably packed nests and clusters of epithelioid cells set in partly hyalinised vascular stroma
- Cells have moderate amount of amphophilic cytoplasm and round to oval nuclei
- Mitoses inconspicuous
- No in situ change in epithelium

Focally the tumour has an infiltrative growth pattern

Case 14 PQ10.48

Immunohistochemistry

Positive

- Pancytokeratin AE1/AE3, CK7, neuroendocrine markers (Crg A, synaptophysin), TTF-1, calcitonin

Negative

- CK5/6, CK14, S100, HMB45, thyroglobulin, CK20, CEA

Case 14 PQ10.48

Diagnosis:

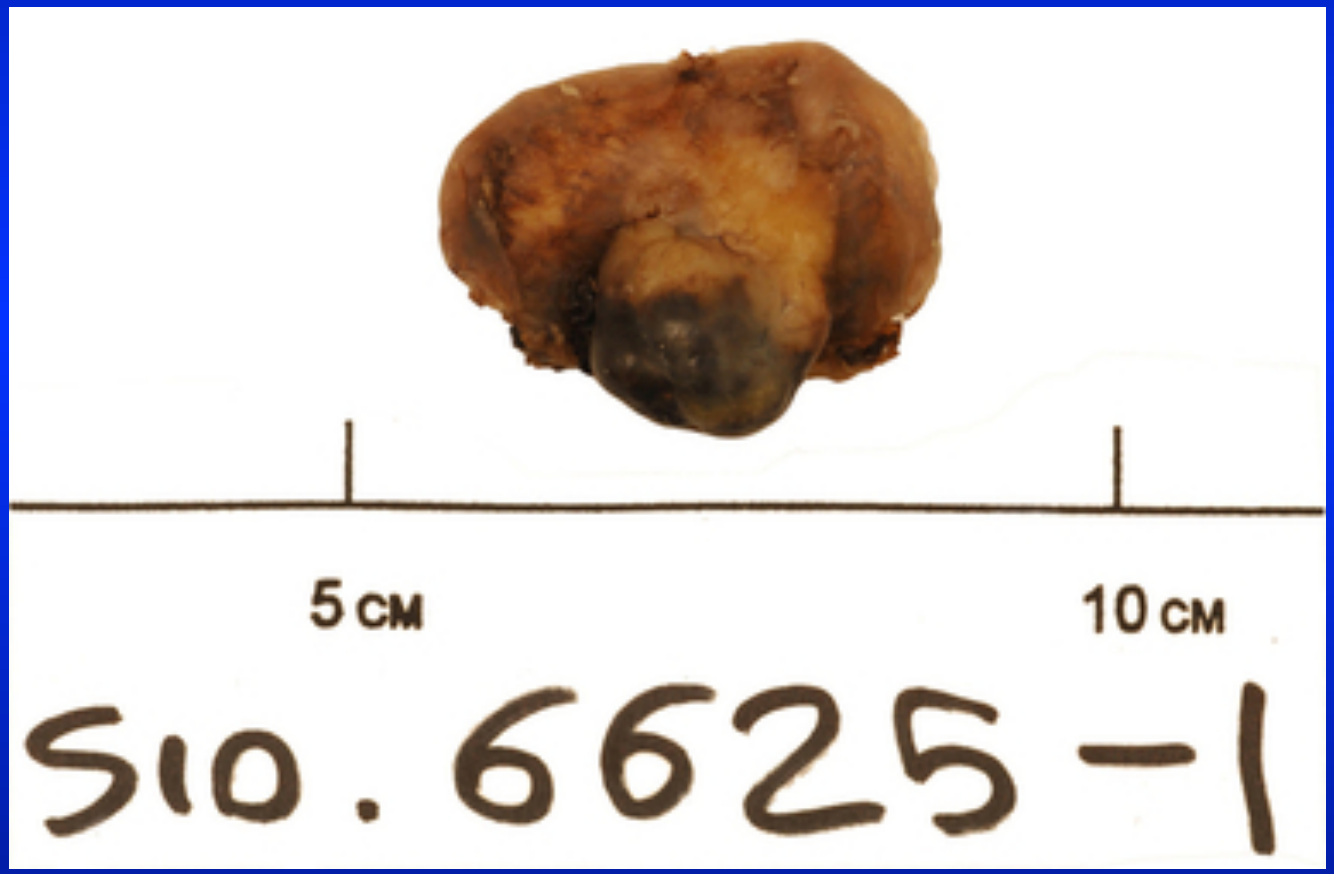
WELL DIFFERENTIATED
NEUROENDOCRINE CARCINOMA

Case 14 PQ10.48

Diagnosis: well differentiated neuroendocrine carcinoma

- Least common neuroendocrine neoplasm of larynx
- M:F = 3:1, age range 45-80
- Most are in supraglottic larynx
- IHC positive for cytokeratin, EMA, CEA and neurooendocrine markers, variable positivity for other peptides including calcitonin

PS10.6625



Neuroendocrine Tumours

- Heterogeneous group of tumours
- Vary from benign to highly malignant
- Uncommon

Neuroendocrine Tumours

Terminology

- Typical carcinoid
  - Well differentiated (Grade I) neuroendocrine carcinoma
- Atypical carcinoid
  - Moderately differentiated (Grade II) neuroendocrine carcinoma
- Small cell carcinoma neuroendocrine type
  - Small cell neuroendocrine carcinoma, poorly differentiated (Grade III) neuroendocrine carcinoma
- Combined small cell carcinoma NE type with non-small cell carcinoma
- Paraganglioma

Neuroendocrine tumours

- Atypical carcinoid 54%
- Small cell carcinoma, neuroendocrine type 34%
- Paraganglioma 9%
- Typical carcinoid 3%

Case 14 PQ10.48

- Differential diagnosis
  - Atypical carcinoid, paraganglioma, malignant melanoma, medullary carcinoma

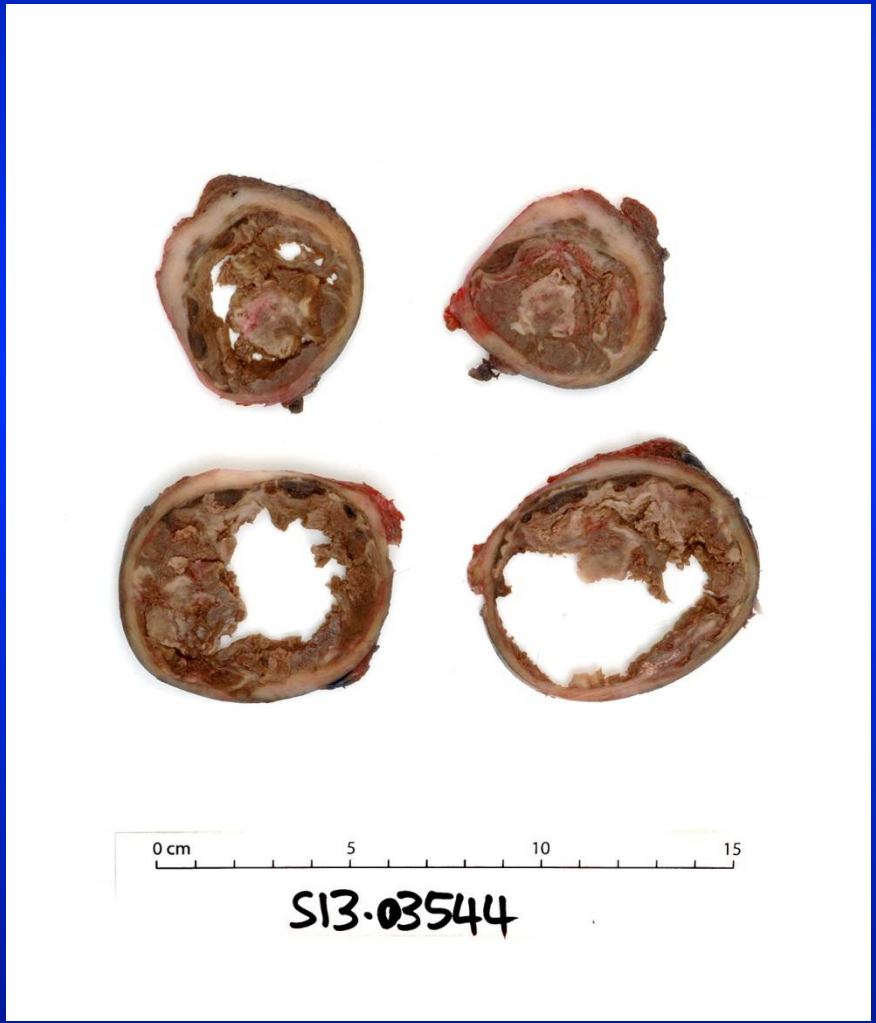
- Surgery is treatment of choice
- Approx 33% patient experience distant mets (liver, bones)

Case 18
TB13.925 (PS13.3544)

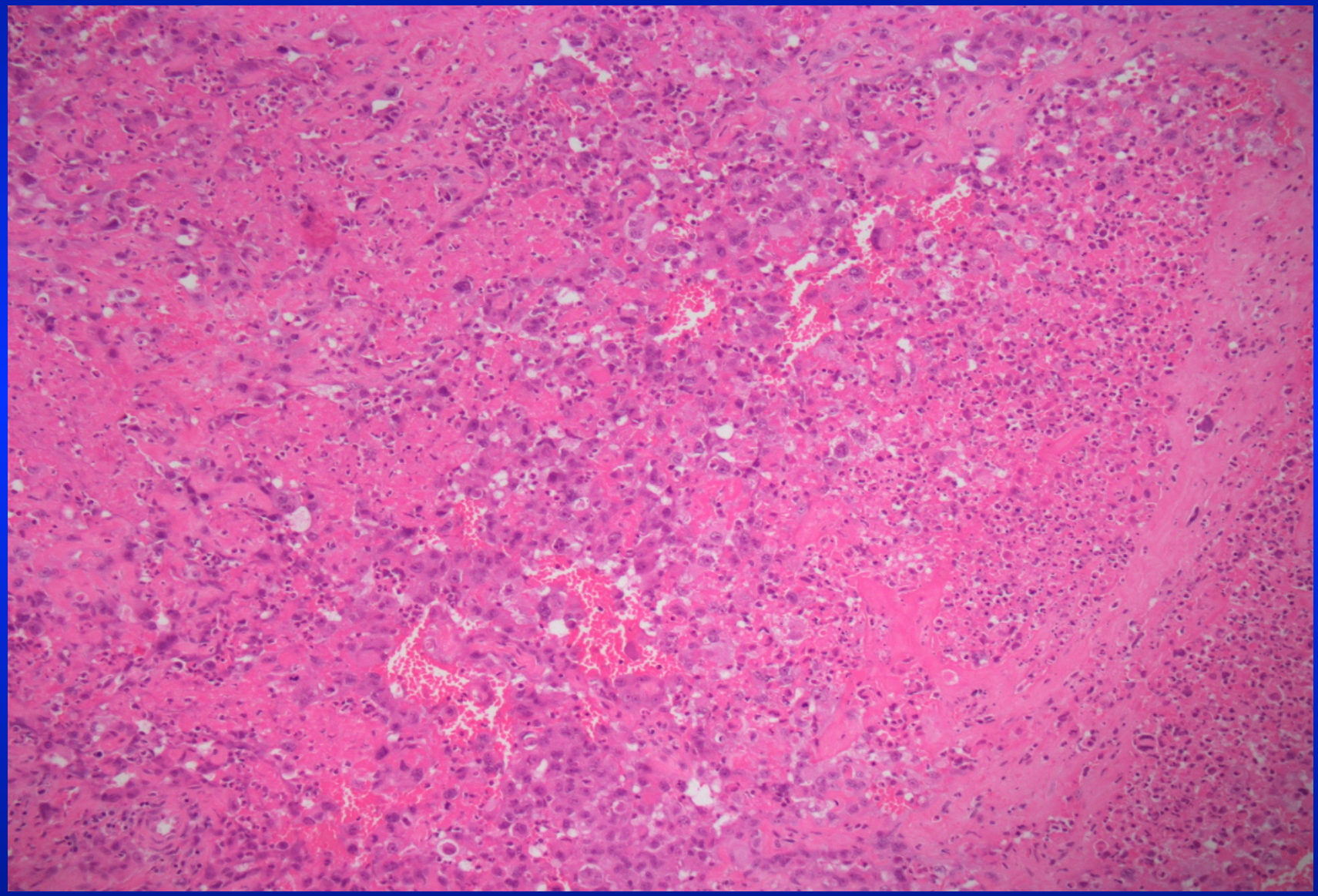
73 year old male presented with enlarged right thyroid lobe

Case 18

Right thyroid lobe
- Wt. 198.7g
- Circumscribed and appeared encapsulated
- Variegated cut surface with cystic and solid areas



Case 18



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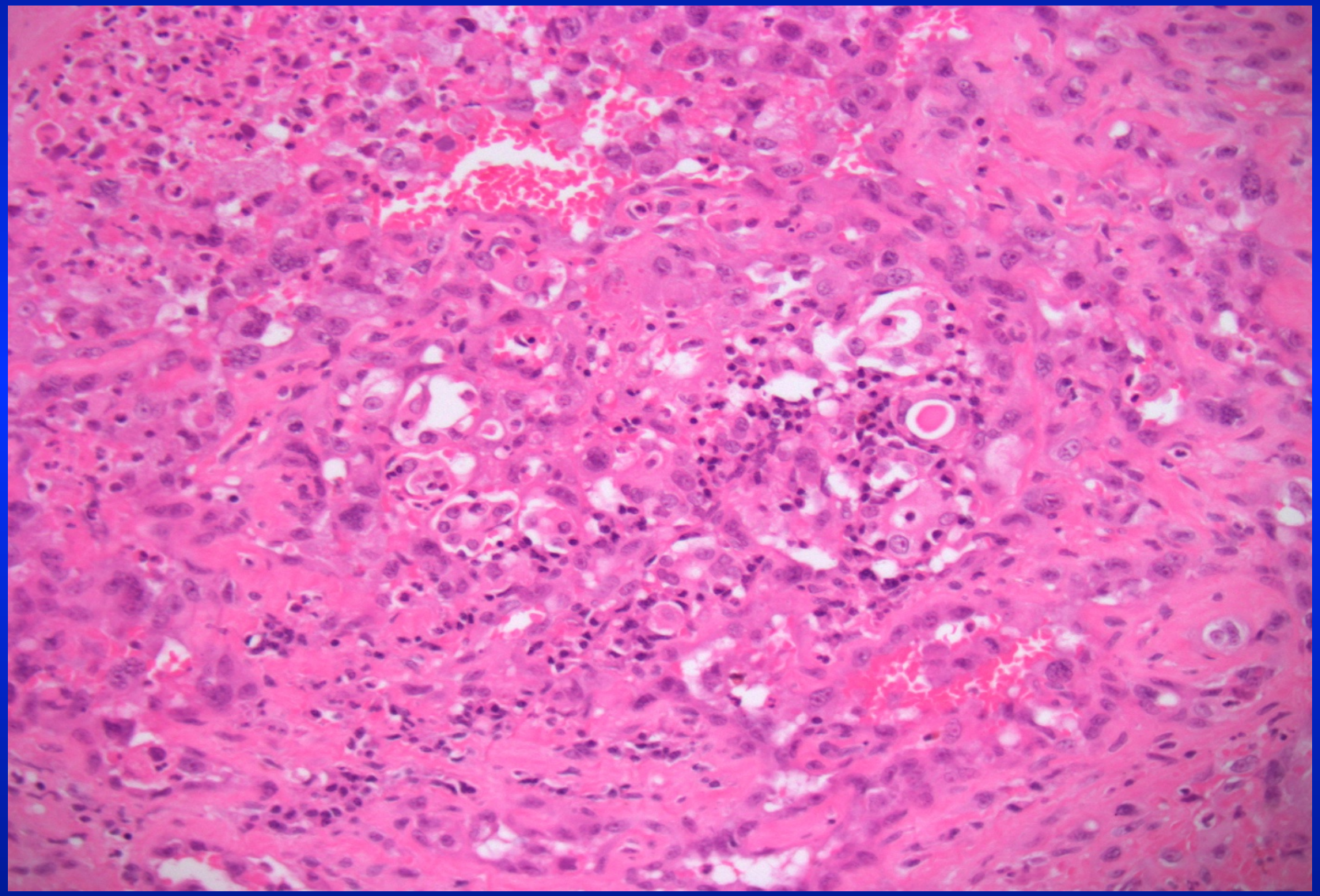

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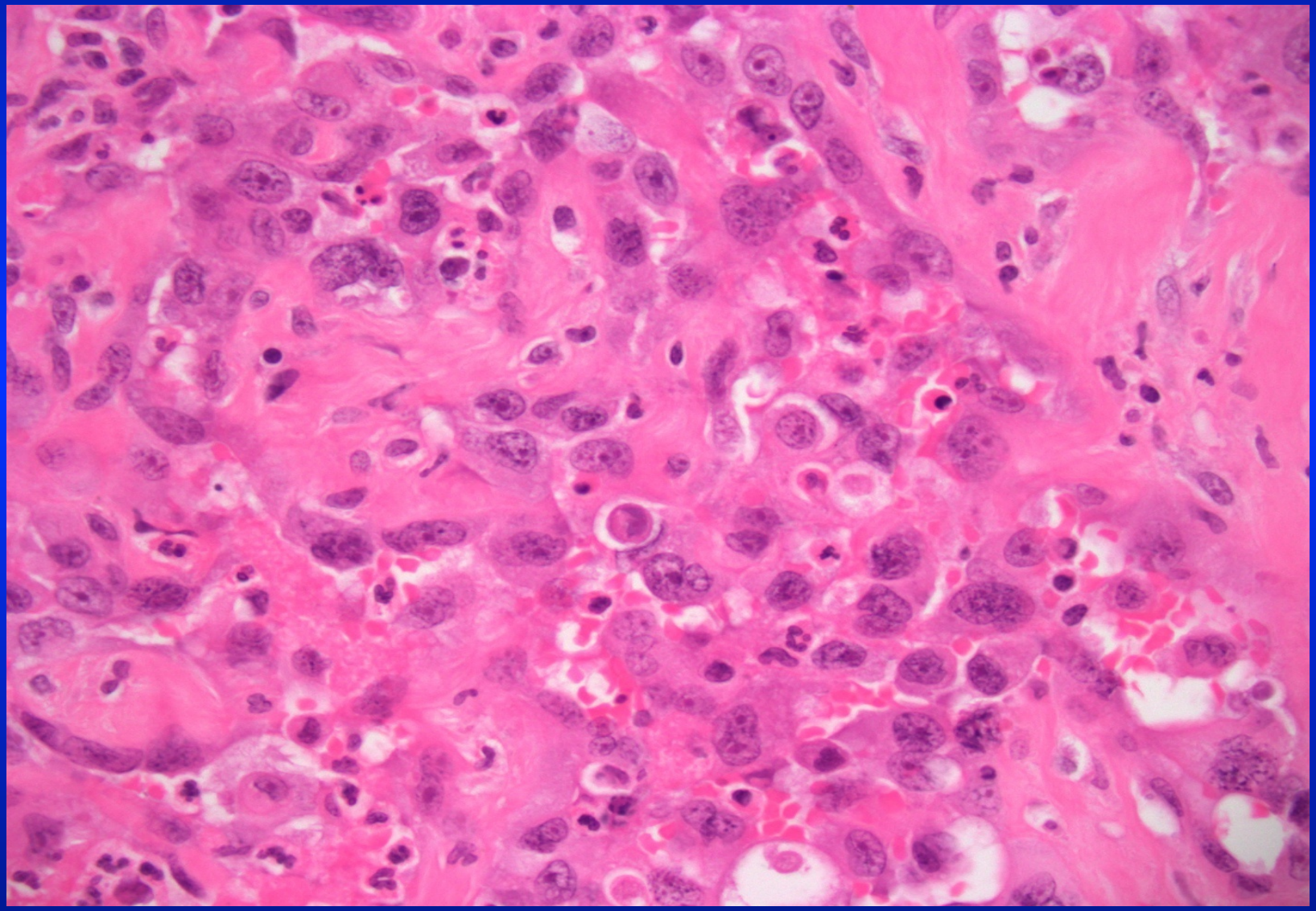


Case 18

Microscopic features

Extensively necrotic malignant neoplasm

Epitheloid cells

- intracytoplasmic neolumina containing erythrocytes
- lining anastomosing blood-filled spaces
- solid sheets
- Numerous mitoses including atypical forms

Case 18

Immunohistochemistry

- Positive: CD31, CD34, vimentin, pancytokeratin
- Negative: thyroglobulin, TTF-1

Diagnosis:

THYROID ANGIOSARCOMA

Case 18

THYROID ANGIOSARCOMA

Originally reported in Alpine countries

Not exclusive to mountainous areas

Typically present as “cold” nodule in patients with mean age in 7th decade most often in longstanding multinodular goitre

F:M 4.5:1

Most patients die in <6 months but tumours entirely within the thyroid have longer survival

Case 19 TB13.3082/PS12.13991

Male 58 right thyroid lobectomy for follicular lesion

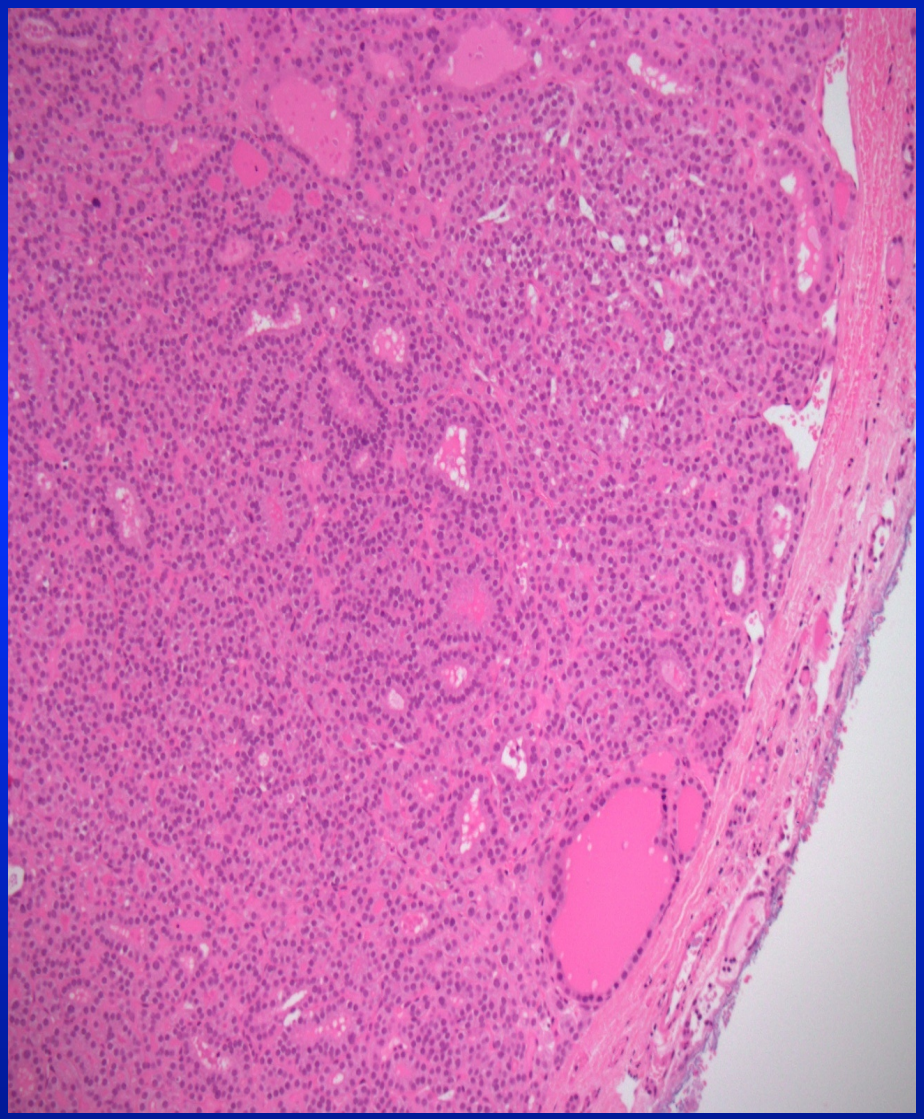
Macro

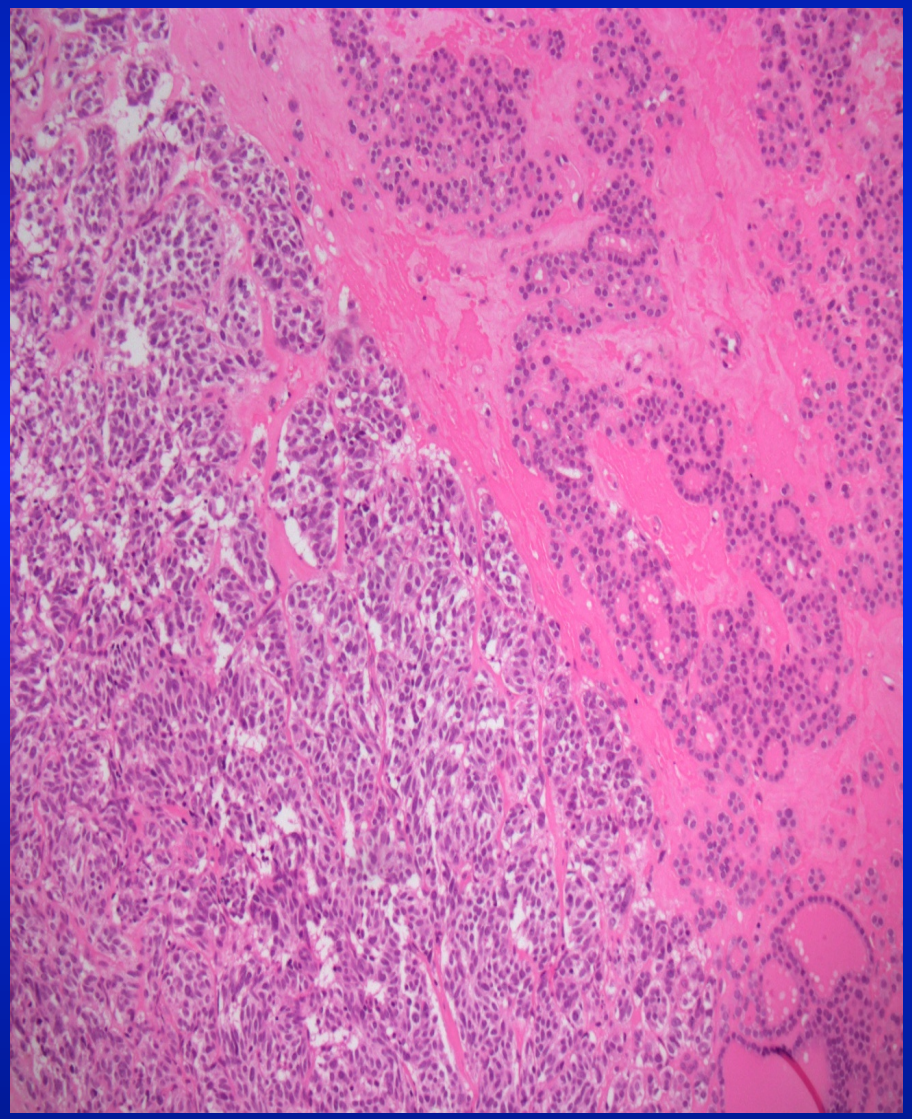
- Wt. 64.4g
- Fleshy haemorrhagic apparently unencapsulated nodule measuring 52 x 55 mm and occupying most of right lobe

Micro

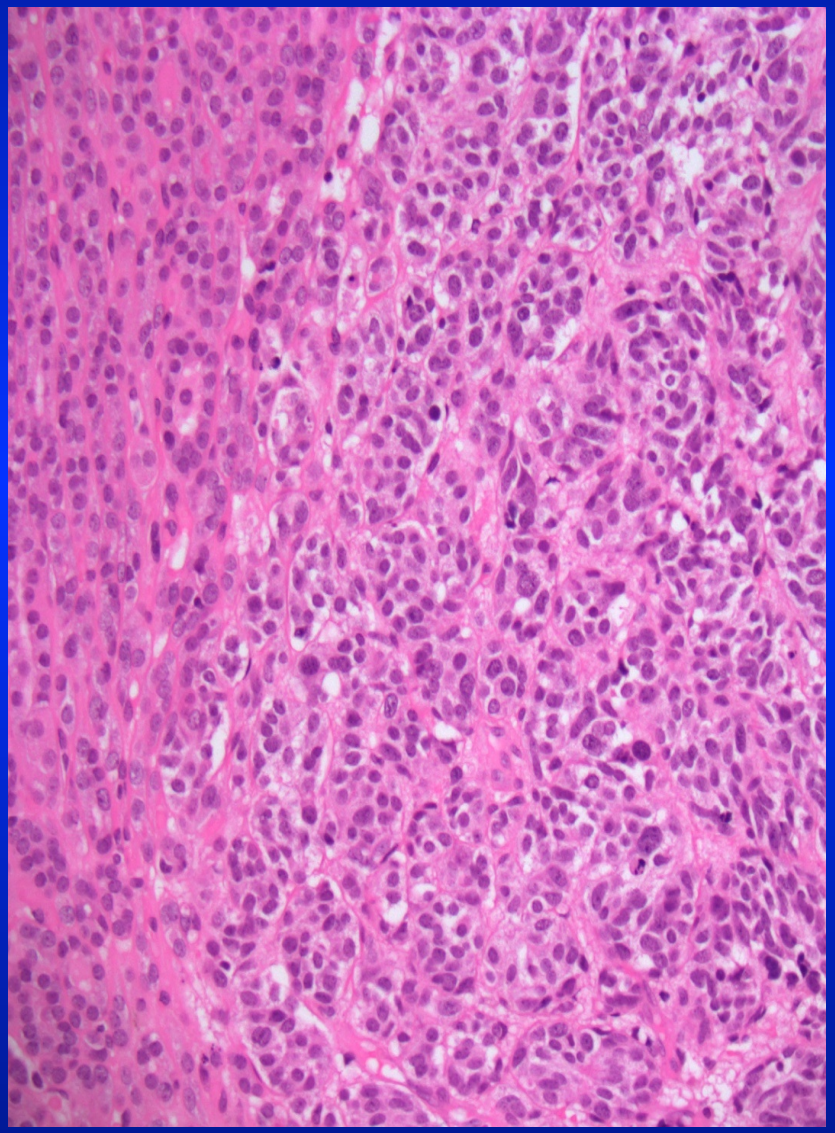
- Cellular follicular lesion with lobulated outline and containing nodules composed of nests of neuroendocrine cells

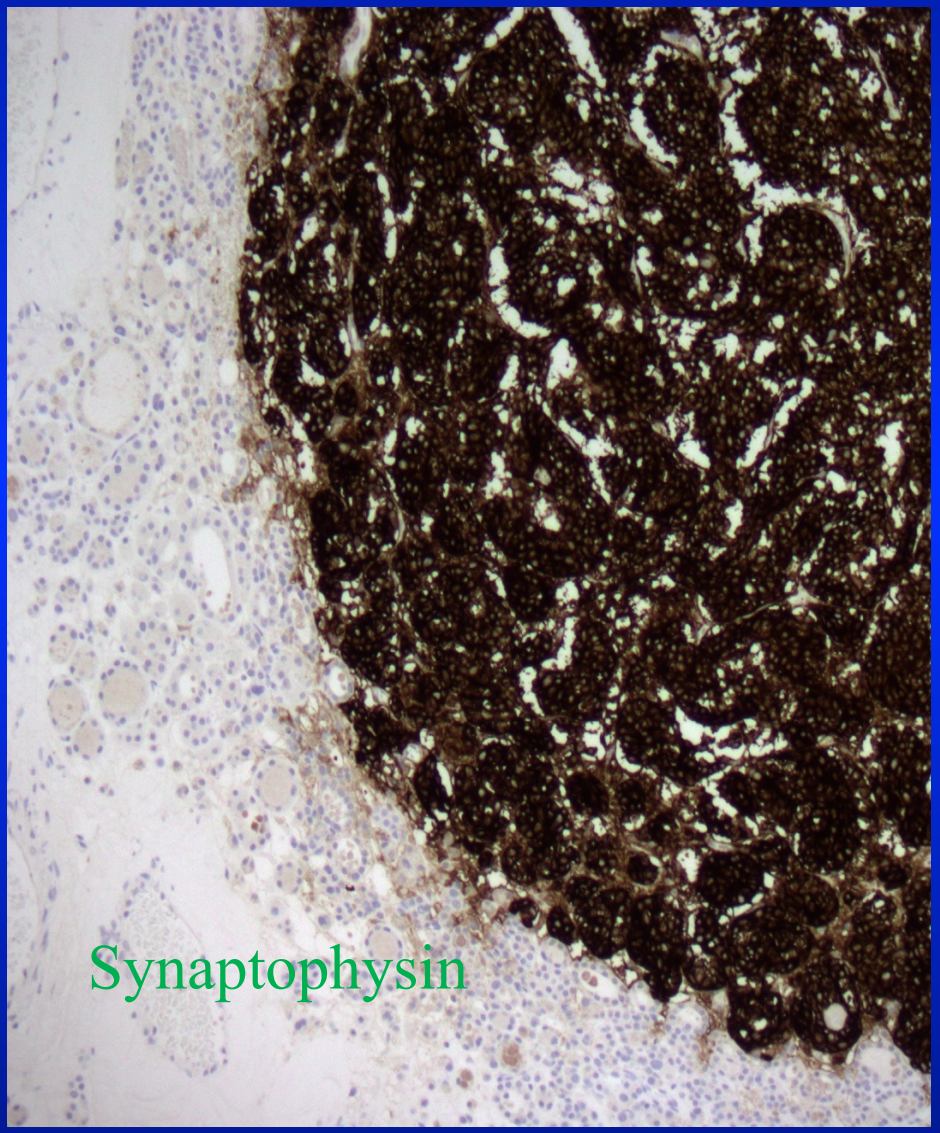
Case 19





Case 19





Case 19

Immunohistochemistry

Positive: neuroendocrine markers (synaptophysin, CrgA), TTF-1 (weak)

Negative: calcitonin, CEA, S100, thyroglobulin, CDX2, glucagon, somatostatin, insulin and gastrin

Proliferation index higher in neuroendocrine cell groups than in surrounding thyroid

Case 19

Diagnosis:

FOLLICULAR ADENOMA with

?foci of neuroendocrine differentiation or ? metastatic deposits of neuroendocrine carcinoma

PETCT scan showed possible primary in right lung

Has vertebral bony metastases and mediastinal lymph node involvement

Treated with radiotherapy and somatostatin

Case 20

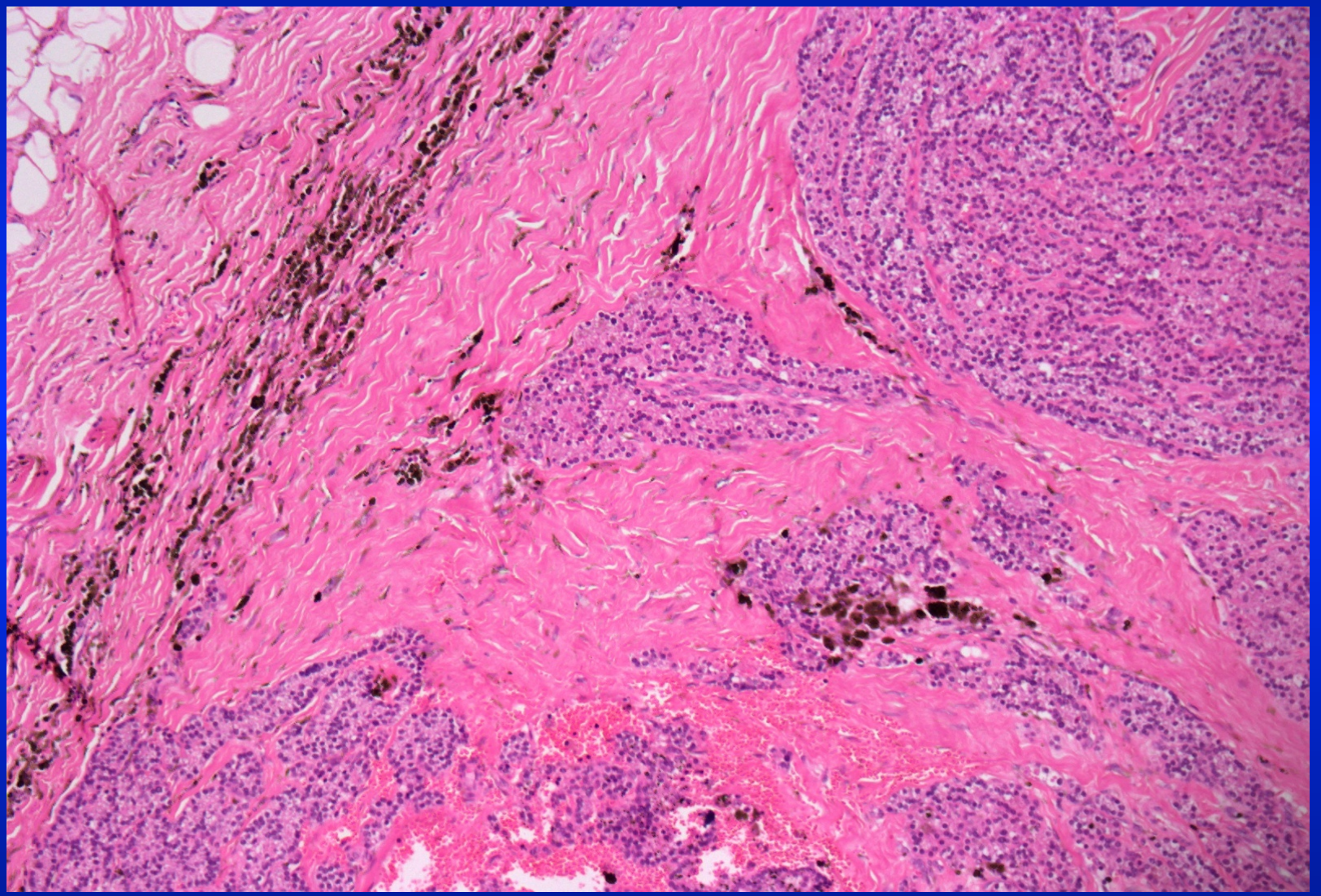
60 year old female with hyperparthyroidism. Nodular mass left parathyroid adherent to left lobe of thyroid

Serum corrected calcium 2.79 (normal range 2.1-2.5mmol/L)

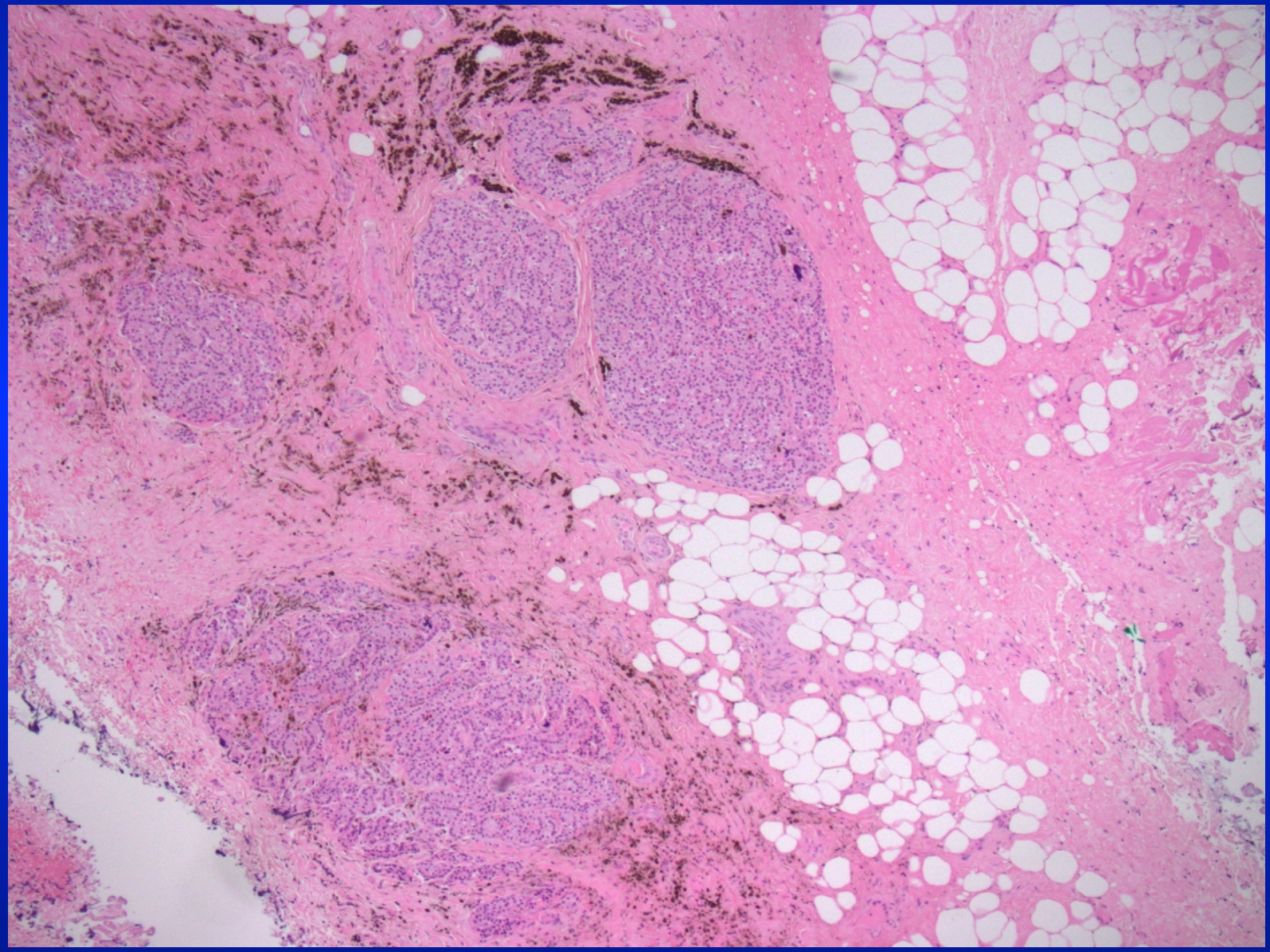
Macro:

Left hemithyroid with well circumscribed unencapsulated nodule at one edge. Showed cystic degeneration and variegated cut surface on sectioning

Case 20



Case 20



Case 20

Differential diagnosis parathyroid adenoma with degenerative changes vs parathyroid carcinoma

Adenoma favoured

- Fibrosis and haemosiderin interpreted as degenerative
- No direct infiltration into thyroid
- Low proliferation index (<2.5%)
- Immuno: positive for cyclin D1, PTH and parafibromin; negative for TTF-1, PGP 9.5

Parathyroid carcinoma

	Parathyroid adenoma	Parathyroid carcinoma
Incidence	85% primary hyperparathyroidism	1% primary hyperparathyroidism
Sex	F.M 3:1	F=M
Age	Mean 56-62	Decade younger
Renal involvement (stone)	4-30%	Common (48-56%)
Bone involvement	14-20%	Common (63-91%)
Palpable neck mass	Rare	More common
Hypercalcaemia	Present	More severe (3.5-4.0mmol/l)
Weight	Usually <1g	Larger tumour average 12g

Parathyroid carcinoma

Most patients present with symptoms/signs of hypercalcaemia

- Polyuria and polydipsia
- Weakness
- Renal colic
- Bone pain and fracture
- Recurrent pancreatitis

Most cases are sporadic but rarely may occur in setting of MEN or hyperparathyroidism-jaw syndrome

Parathyroid neoplasia - histological criteria for diagnosis of malignancy

Absolute criteria of malignancy	Features associated with malignancy
Invasion into surrounding tissues	Capsular invasion
Histologically documented regional or distant metastases	Vascular invasion
	Mitoses (>5/10 hpf)
	Broad intratumoural fibrous bands
	Coagulative tumour necrosis
	Diffuse sheet-like monotonous small cells with high N:C ratio
	Diffuse cellular atypia
	Macronucleoli in many cells

Parathyroid carcinoma

Immunohistochemistry

- PTH
- MIB1 proliferation index
  - Overlap between adenoma and carcinoma
  - Mean 2.03 to 3.28% adenoma vs 6.05-8.4% carcinoma
- Cyclin D1
  - Overexpression reported to occur commonly in carcinoma (91%)

Immuno	Normal/Adenoma	Carcinoma
PGP9.5	+ve	-ve
Parafibromin	-ve	+ve
APC	+ve	-ve

Glomagiopericytoma/ sinonasal-type haemonagiopericytoma

- Macro
  - Generally up to 8 cm, mean 3cm
  - Appearance variable
    - Red to greyish pink
    - Soft oedematous friable
    - often haemorrhagic