SPINDLE CELL TUMOURS

Dr. Will. Merchant

Spindle cell

- Muscle
  - Leiomyoma
- Neural
  - Neurofibroma
  - Schwannoma
- Fibrous
  - Fibroma
  - Dermatofibroma
- Fat
  - Spindle cell lipoma
- Epithelial
  - Myoepithelioma
- Other

- LMS
- MPNST
- Fibrosarcoma's, DFSP
- Spindle cell liposarcoma
- Sarcomatoid Ca.
- Synovial sarcoma
- Melanoma

Case 1

- 40 M rapidly growing lump arm

What features to look for in spindle cell tumours for malignancy

Features suggestive of malignancy

- Necrosis
- Nuclear atypia
- Mitoses,[?number]. Atypical forms

- BUT- frequent exceptions
- Accurate diagnostic tumour type most important. ‘If you don’t know what it is, how can you predict how it will behave.’

Cellular Dermatofibroma

- Top tips
  - Variable cellularity
  - Variable cell type
  - Cells wrap around prominent collagen at margin
  - More pink cytoplasm than DFSP
  - Immuno; SMA weak positive. CD34 neg (Beware halo phenomenon]
    - DFSP SMA Neg, CD 34 POS

Storiform pattern

- Interwoven or rush mat pattern of tumour cells.
- Cell arranged in short fascicles which the interweave with each other.
- Commonly seen in spindle tumours of many types.

Case 2

- 75M s/c lump on leg

Case 2

- Lobulated
- Biphasic appearance; myxoid and pleomorphic spindle cell
- Curvilinear vessels
- Nuclear atypia

Myxofibrosarcoma

- Elderly
- Peripheral site
- S/C
- Non-specific immuno [Vimentin focal SMA] or genetics

Case 3

- 20M, rapidly growing lump arm

Case 3

- Micro; Circumscribed unencapsulated tumour. Spindle cells with bland nuclei in a myxoid stroma. Appearance of myofibroblasts. Can become hyalinised.
- Red cell extravasation and patchy lymphocytic infiltrate.
- Immuno; SMA, HHF35 positive
- C.K., CD34 Negative

Nodular fasciitis

- Rule of 3’s
- Third decade, present <3months and 3cm or less in size
- Immuno; myofibroblastic, SMA only
- **Nodular fasciitis: a novel model of transient neoplasia induced by MYH9-USP6 gene fusion.**
- **FISH probe now available**

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LETTER TO THE EDITOR

Detection of *USP6* gene rearrangement in nodular fasciitis: an important diagnostic tool

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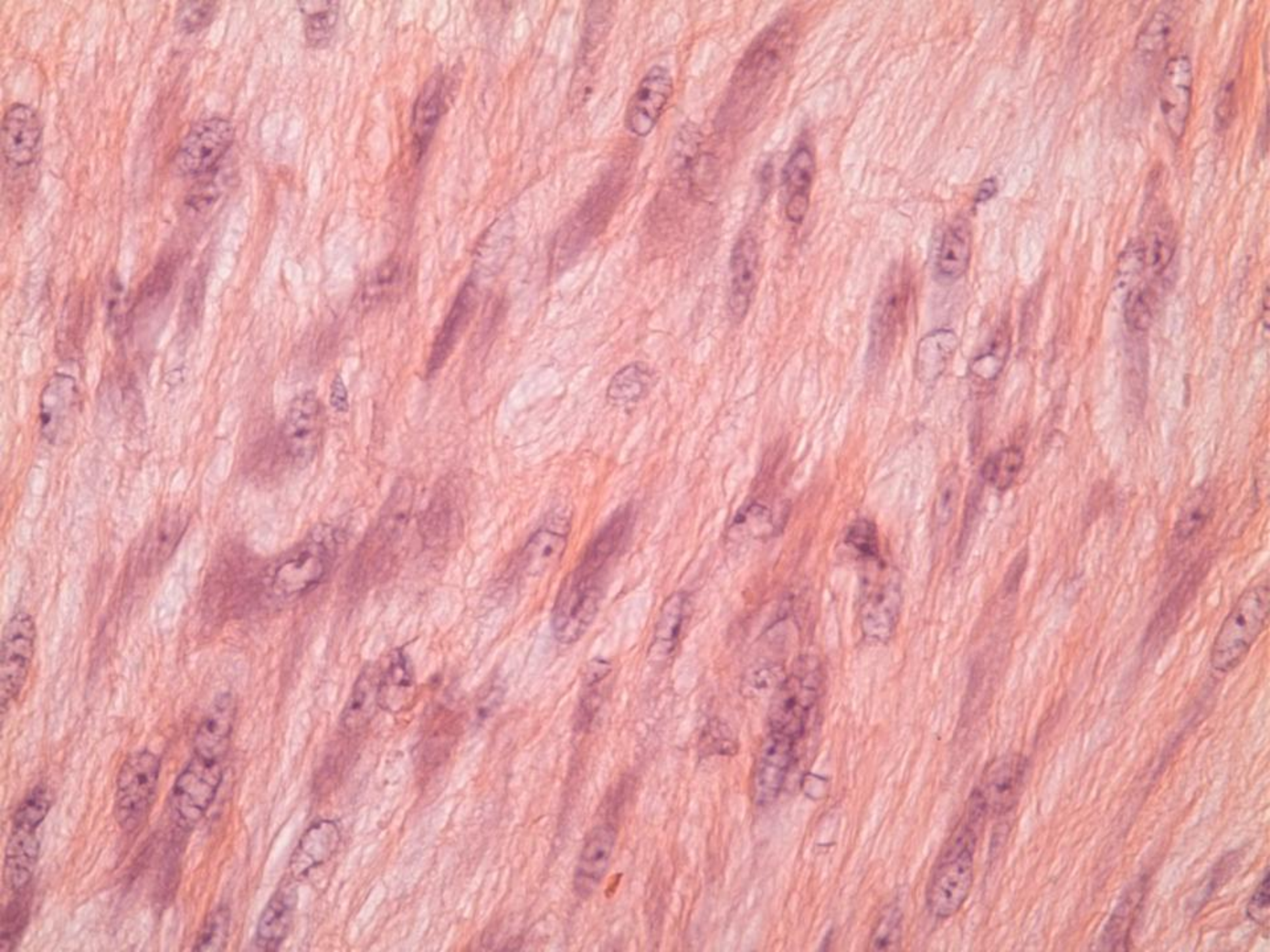
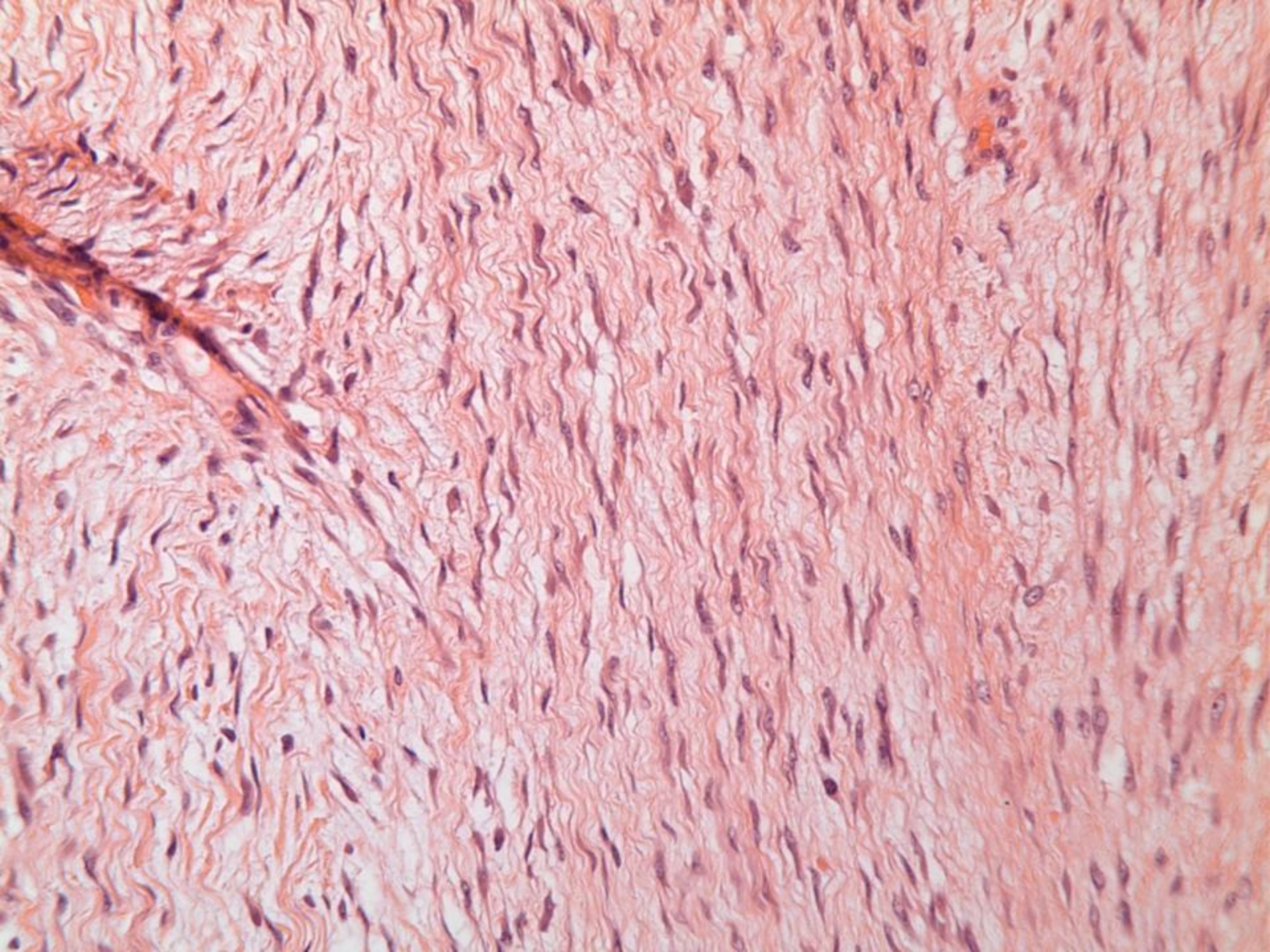
Fibrous

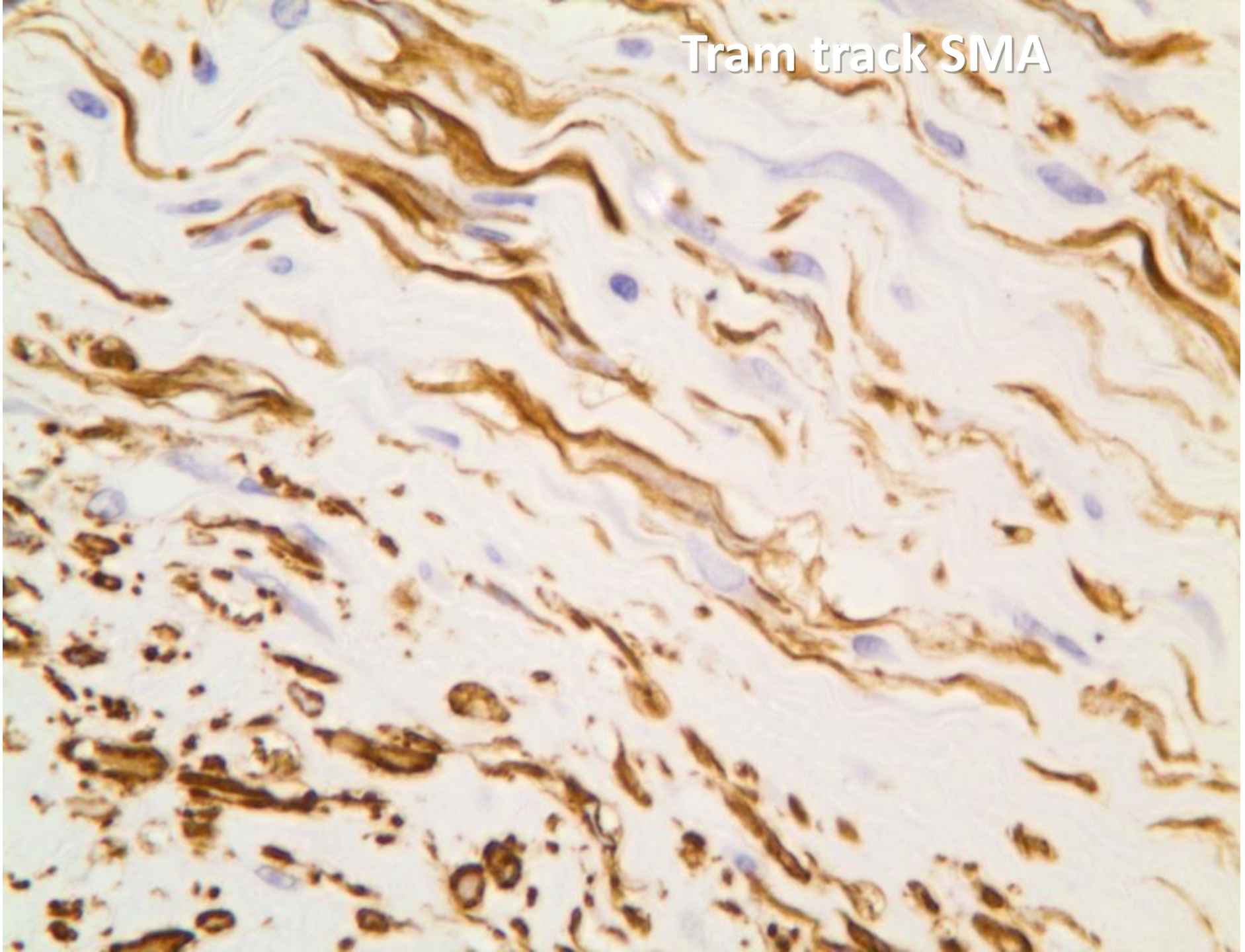
- **Myofibroblast**; Plump spindle cell with pale to purple/basophilic cytoplasm. Elongated nucleus, oval, often eccentric. Not as pink as smooth muscle. Less well defined cytoplasm
- **Fibroblasts**; small cells, often greatly elongated nucleus;wavy.Nucleus, hyperchromatic. Cytoplasm, small amount of poorly defined pale cytoplasm.
- Matrix; Collagen.

Immuno- fibrous

- SMA- tram-track [wispy].
- Desmin – usually neg. Can be positive, esp. at visceral sites.
- H-caldesmon negative.






Tram track SMA

Differential diagnosis

- Fibromatosis, much more organised into long fascicles. Infiltrative growth pattern.
- Malignancy, but Nodular Fasciitis lacks nuclear atypia, necrosis, abnormal mitoses [Can have normal mitoses ++]

Case 4

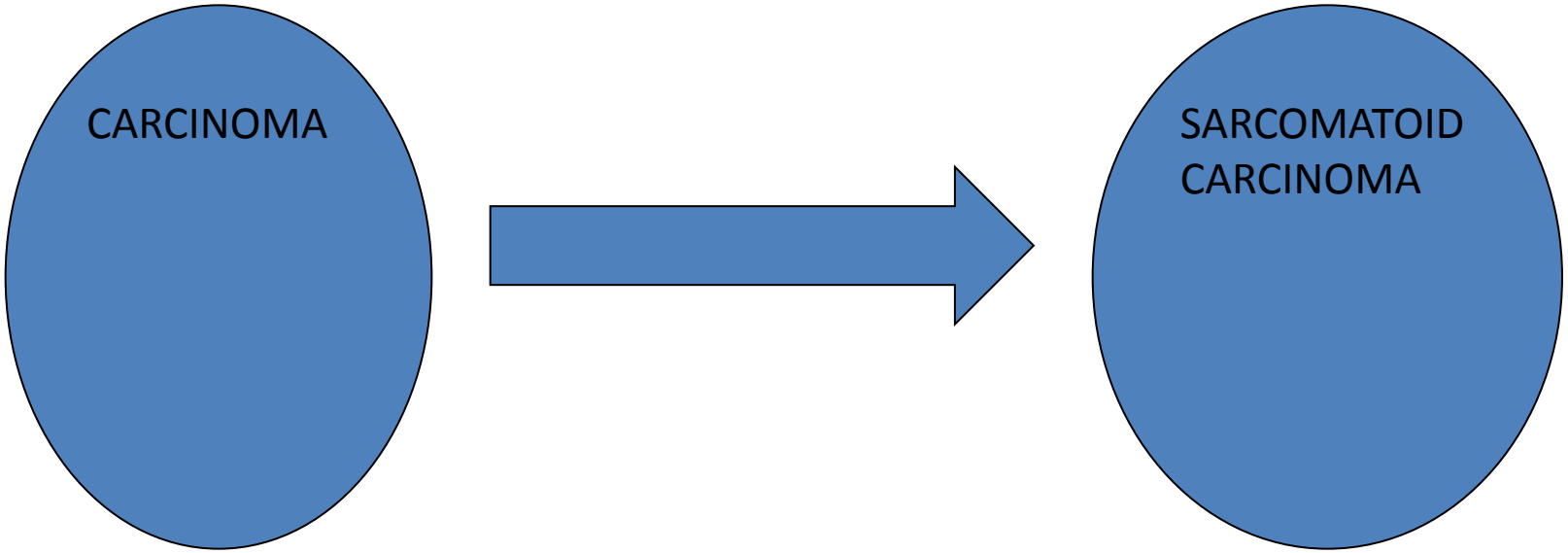
- 70F suspicious mass on x-ray left breast

Case 4
Differential diagnosis

- Fibromatosis
- Phyllodes
- Metaplastic/spindle cell carcinoma

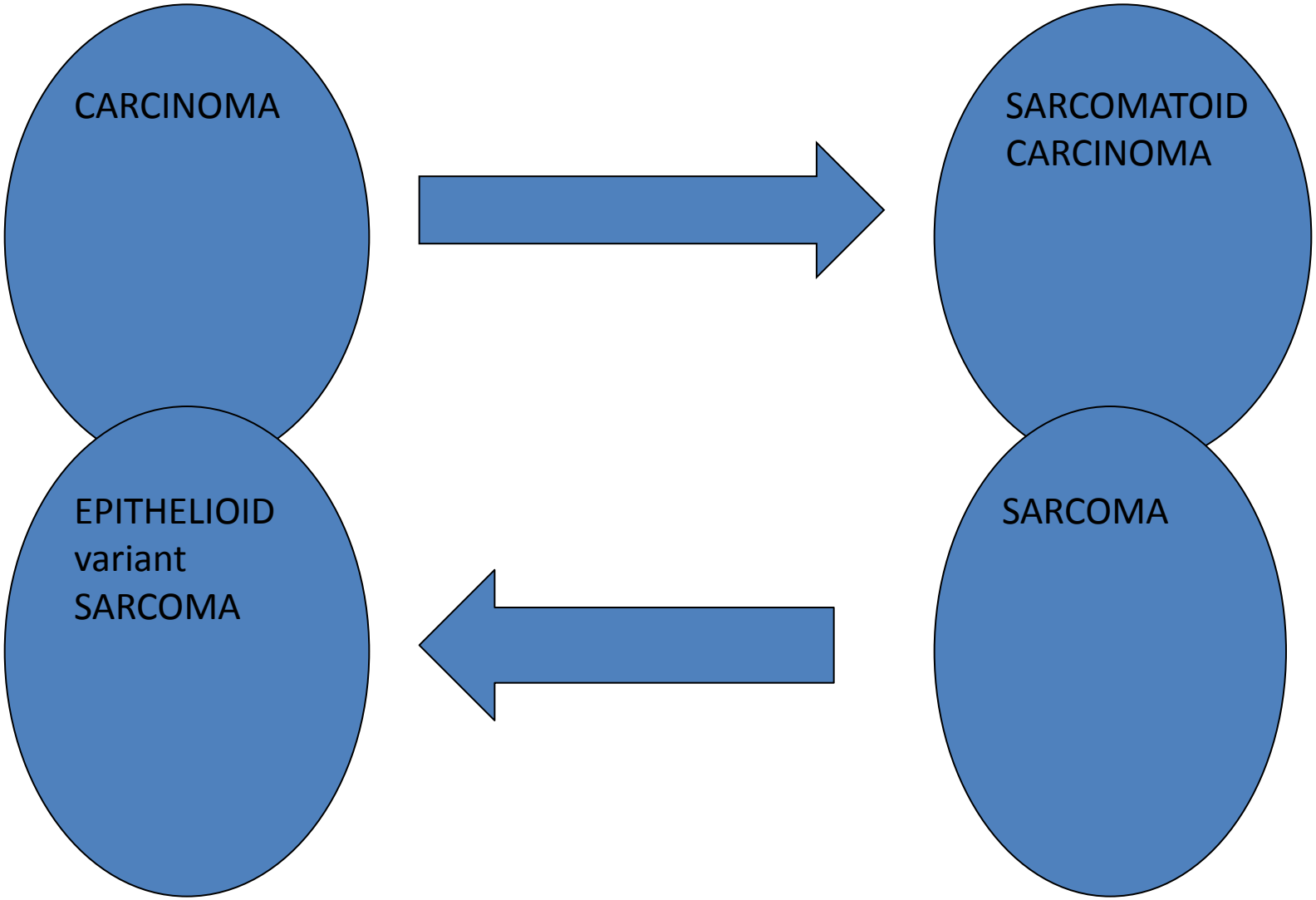
Metaplastic carcinoma

- Cytokeratins; Do LOTS ! ;
  - MNF116, AE1/AE3, [CK5/6, CK14, CK7,34bE12]
- P63, very useful
- S100; occasionally focally positive
- SMA can be positive
- CD34; Neg
- Beta-Catenin, can be focally positive.


CARCINOMA
SARCOMATOID
CARCINOMA

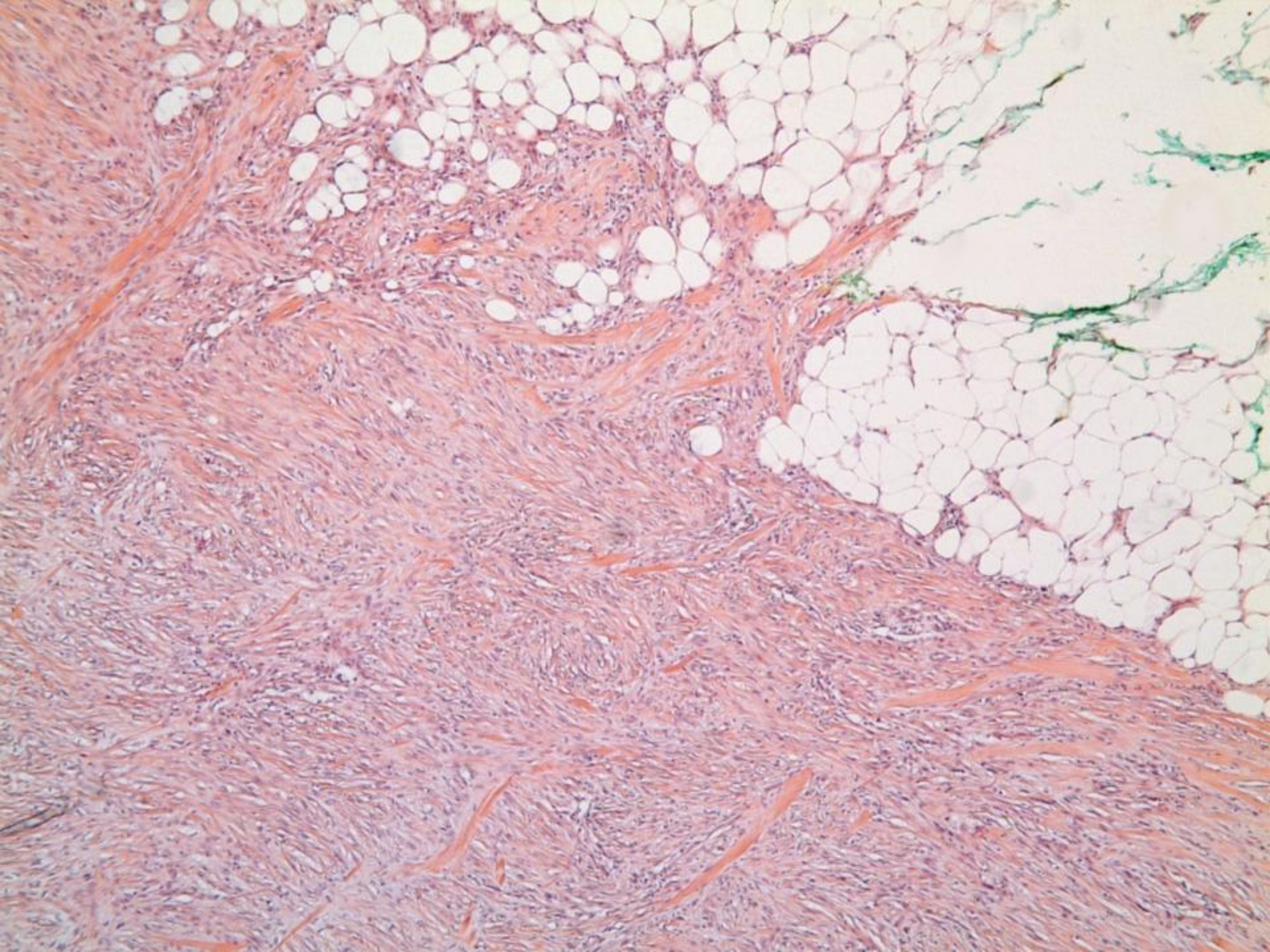
When epithelial tumours go spindly

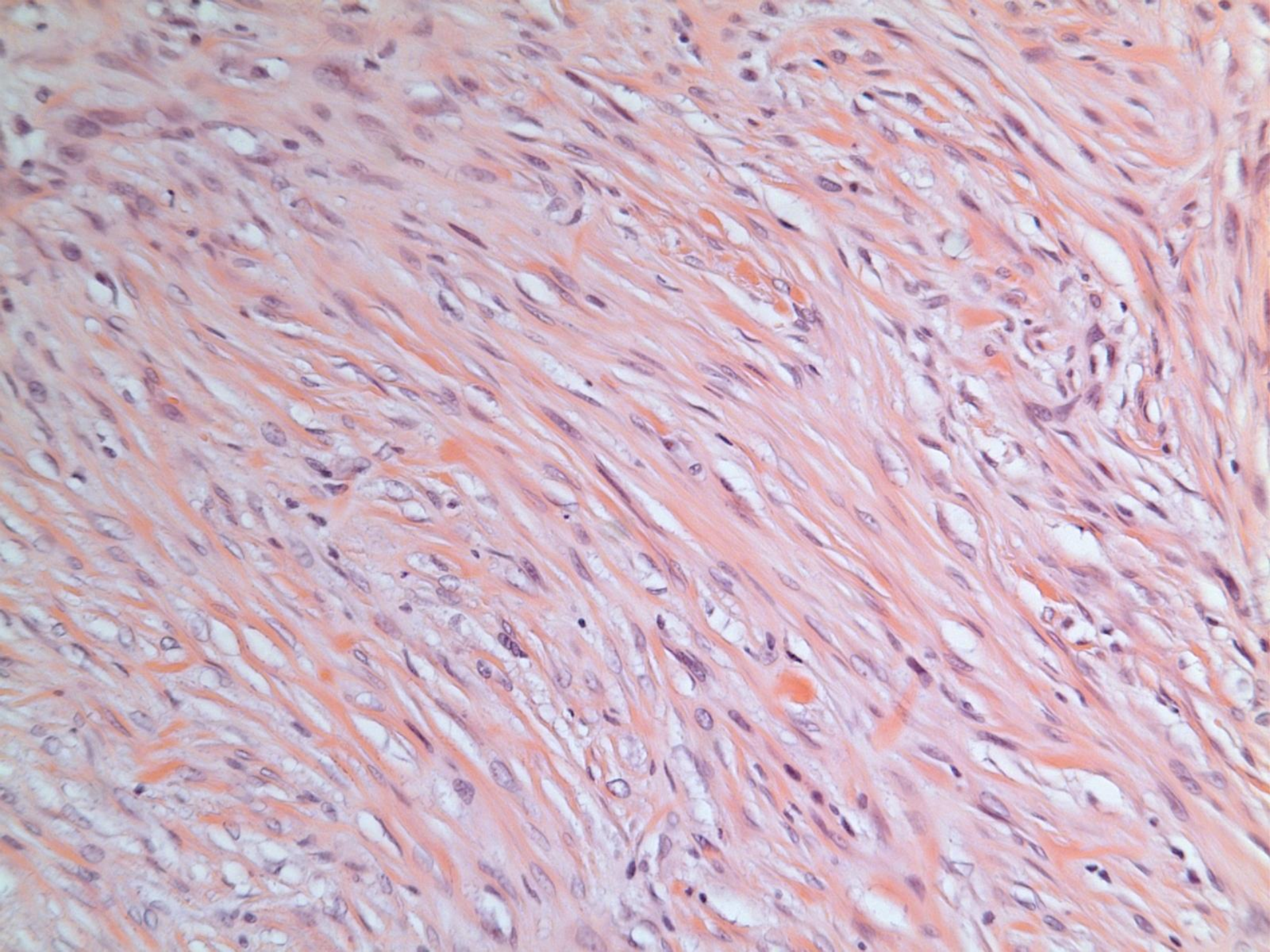
- Acquire SMA, +/- a stroma
- Retain immunological evidence of origin;
  - C.K positive, especially high molecular weight, may be more specific eg 34betaE12 [CK34]
  - P63 positive
- Lack more specific markers of mesenchymal differentiation; CD34, CD31, H-caldesmon.

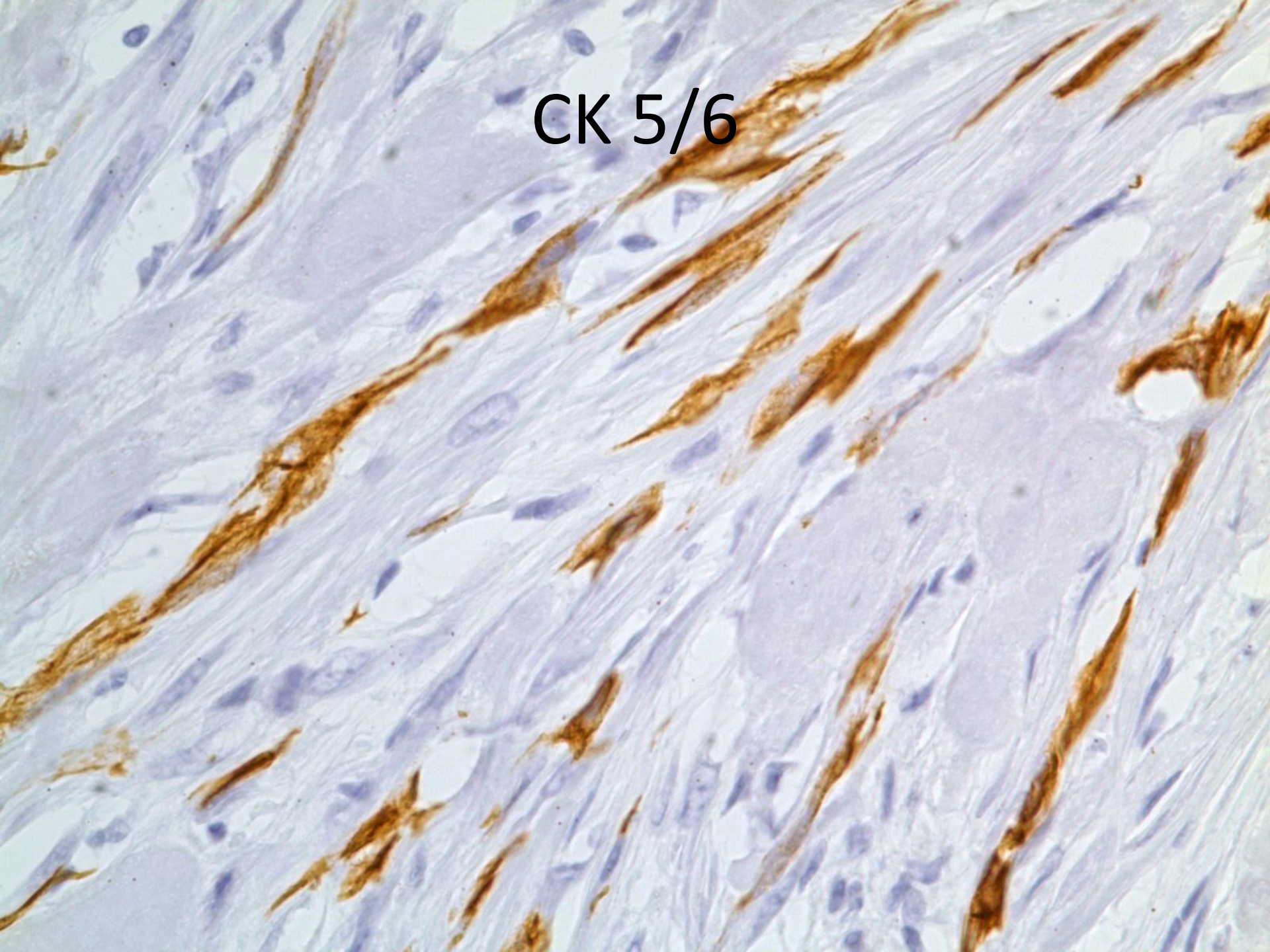

CARCINOMA
SARCOMATOID
CARCINOMA
EPITHELIOID
variant
SARCOMA
SARCOMA

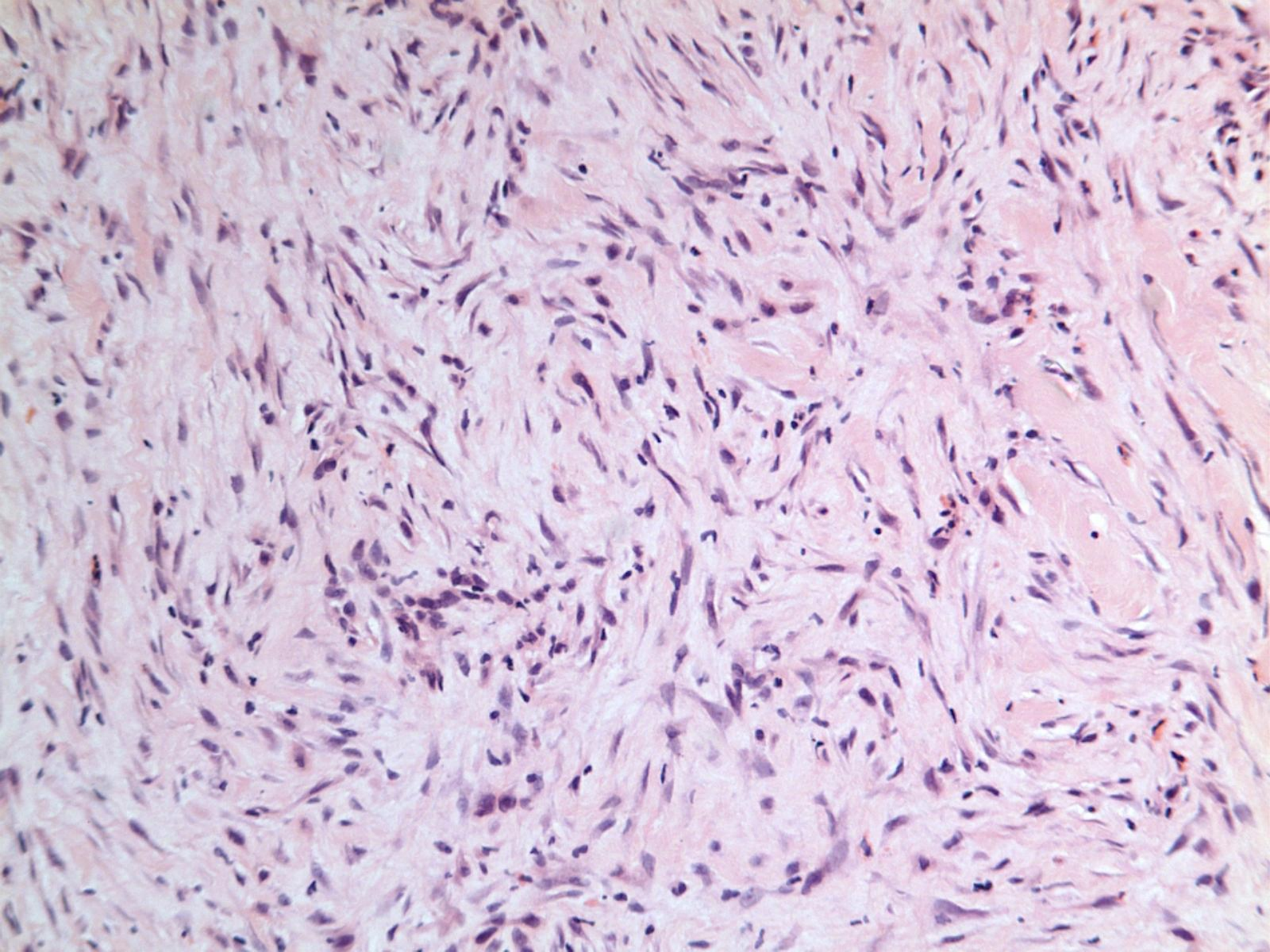
When mesenchymal cells go epithelioid

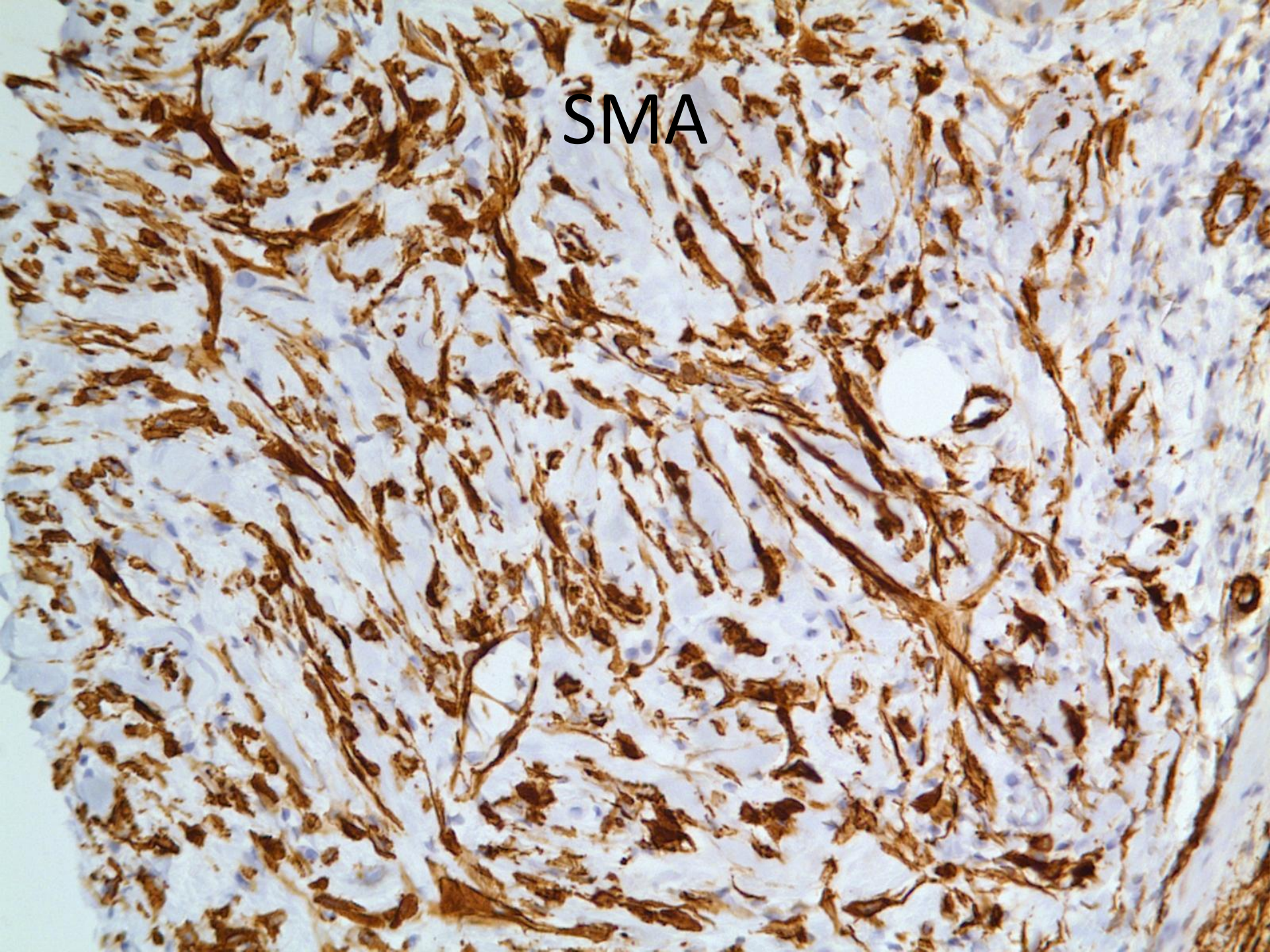
- Cells will acquire Cytokeratin. Usually focal, and rarely high molecular weight.
- Lack more specific marker of epithelial origin, p63, with few exceptions
- Retain more specific markers of origin; CD34, CD31, H-caldesmon.

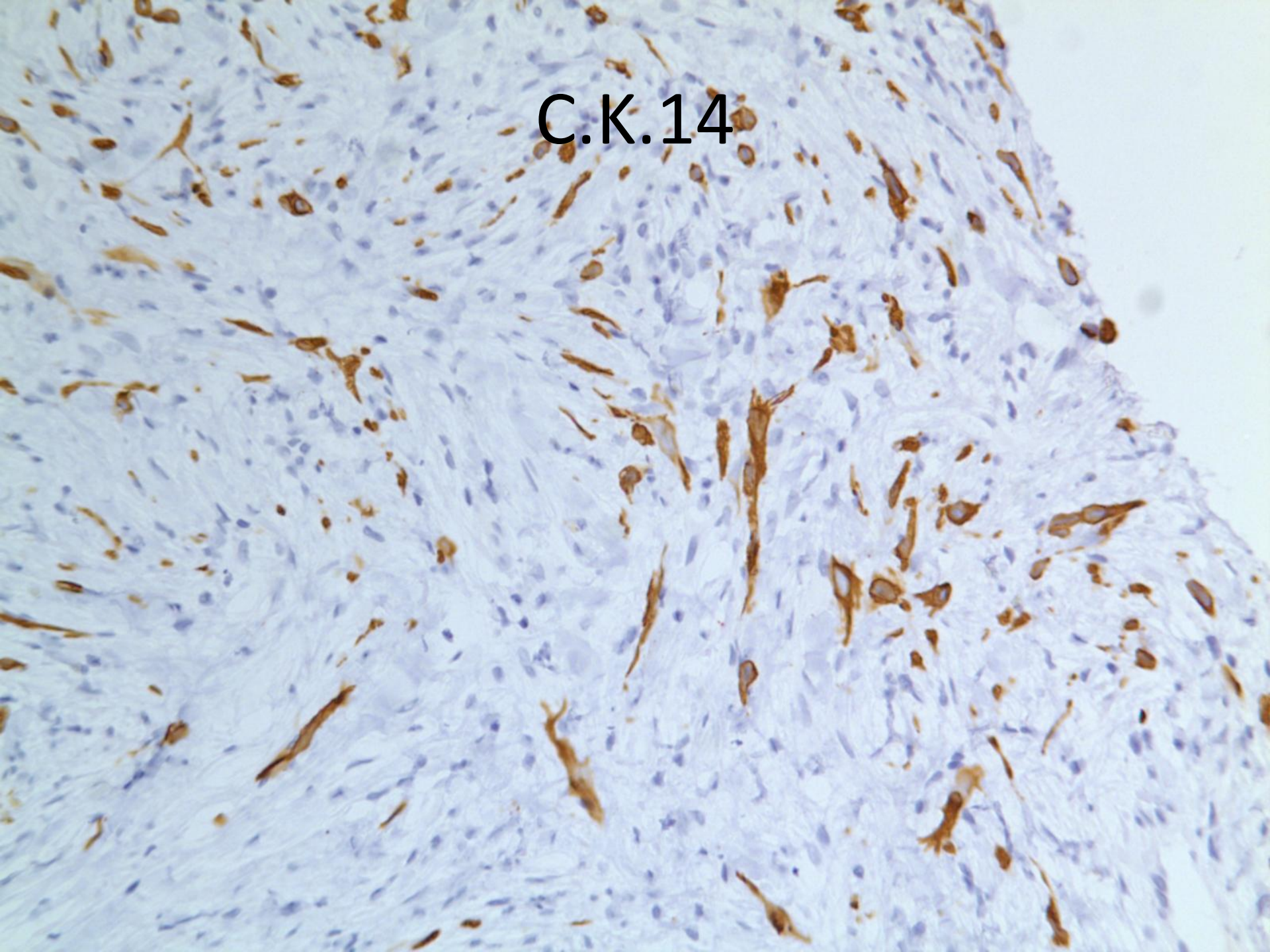


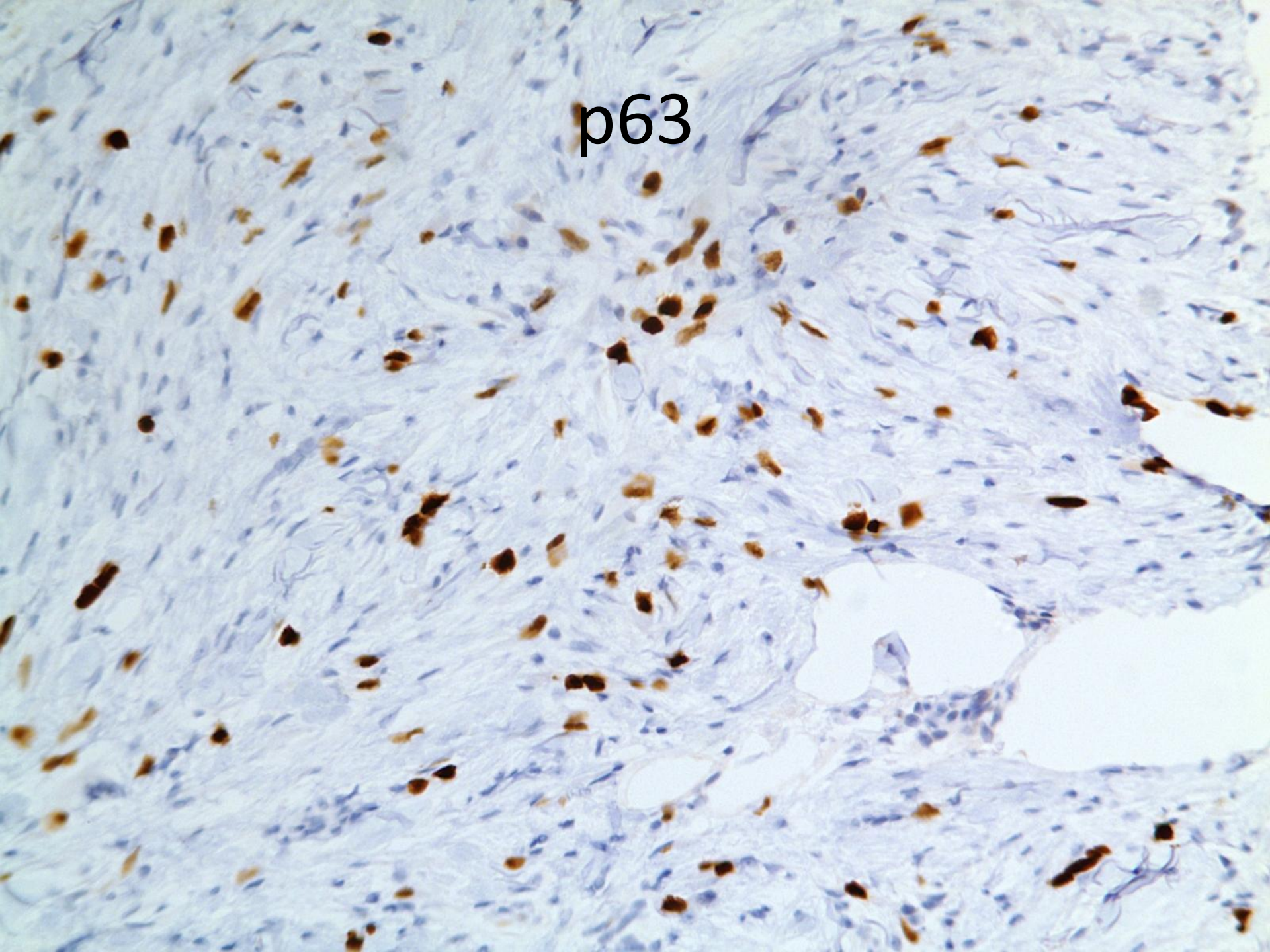



CK 5/6




SMA


C.K.14


p63

P63 in soft tissue tumours

- 650 soft tissue tumours Am.J.Clin.Path.2011:136; 762-6
- Negative; Angiosarcoma's, lipomatous neoplasms, DFSP, SFT,Schwannoma, neurofibroma, LMS.
- Positive mesenchymal tumours; Myoepithelioma/Ca of soft tissues, Neurothekeoma, perineurioma, giant cell tumour of tendon sheath & soft parts.
- Weak focal staining seen in rest eg AFX, RMS

CD34

- Very useful immuno.
- Should be in your panel.
- Has an eclectic range of positive lesions.

CD 34, consistently positive;

- Vascular Tumours, including Kaposi's
- GIST [80%]
- Solitary fibrous tumour [SFT]
- DFSP
- Breast specialist stromal tumours; PASH, F.A., Phyllodes, myofibroblastoma’s.
- Adipocytic tumours, benign and malignant
- Nerve sheath Tumours
- Other; Epithelioid sarcoma, LMS[25%]
- Hemopoietic tumours, AML, ALL.

CD 34 Negative

- Carcinomas of all types [expt Trichilemmomas, rare NUT tumours]
- Melanoma [very rare cases +]
- Fibromatosis
- Nodular Fasciitis

Immunohistochemical Panel

	Main Use	Other points
CK,s Lots	Spindle cell ca.	Occ. Sarcoma, when epithelioid
P63	Spindle cell ca.	Rare in soft tissue
CD 34	Mesenchymal; Phyllodes, DFSP	Very rare in Ca.
Beta-catenin	Fibromatosis, Phyllodes	Rare and weak in Ca
S100	Melanoma Met.	Rare in Ca
SMA	Reactive scars, Nod. Fasciitis	Relatively non-specific

Important points

- Mesenchymal tumours/sarcomas of Breast are rare and most cases where considered turn out to be spindle cell/metaplastic carcinomas or malignant phyllodes.
- Older age group, unlikely to be fibromatosis
- Use broad panel of immunohistochemistry with all those suggested.

Case 5

- Large plaque covering shoulder

Pilar Leiomyoma

- Can be multiple ;linear, grouped, zosteriform
- Can be painful

Smooth Muscle

- Spindle cells with abundant eosinophilic cytoplasm.
- Fascicular pattern, Fascicles at right angles
- Elongated, blunt ended nuclei [cigar shaped].
- Peri-nuclear vacuole – not common. More often GIST.

Case 6

70 Male, deep mass in thigh

What pattern is this?

Case 5

- Giant cell MFH pattern

Giant cell MFH pattern

- Sarcoma's – Leiomyosarcoma, giant cell tumour of soft tissue, osteosarcoma
- Carcinoma's- pancreas , breast

Clues for high grade sarcoma's

- Look for low grade areas at edge.
- Not lots of immuno.

Case 6

- Leiomyosarcoma

Case 7

- 45 Male, deep mass in thigh

Low grade Fibromyxoid sarcoma

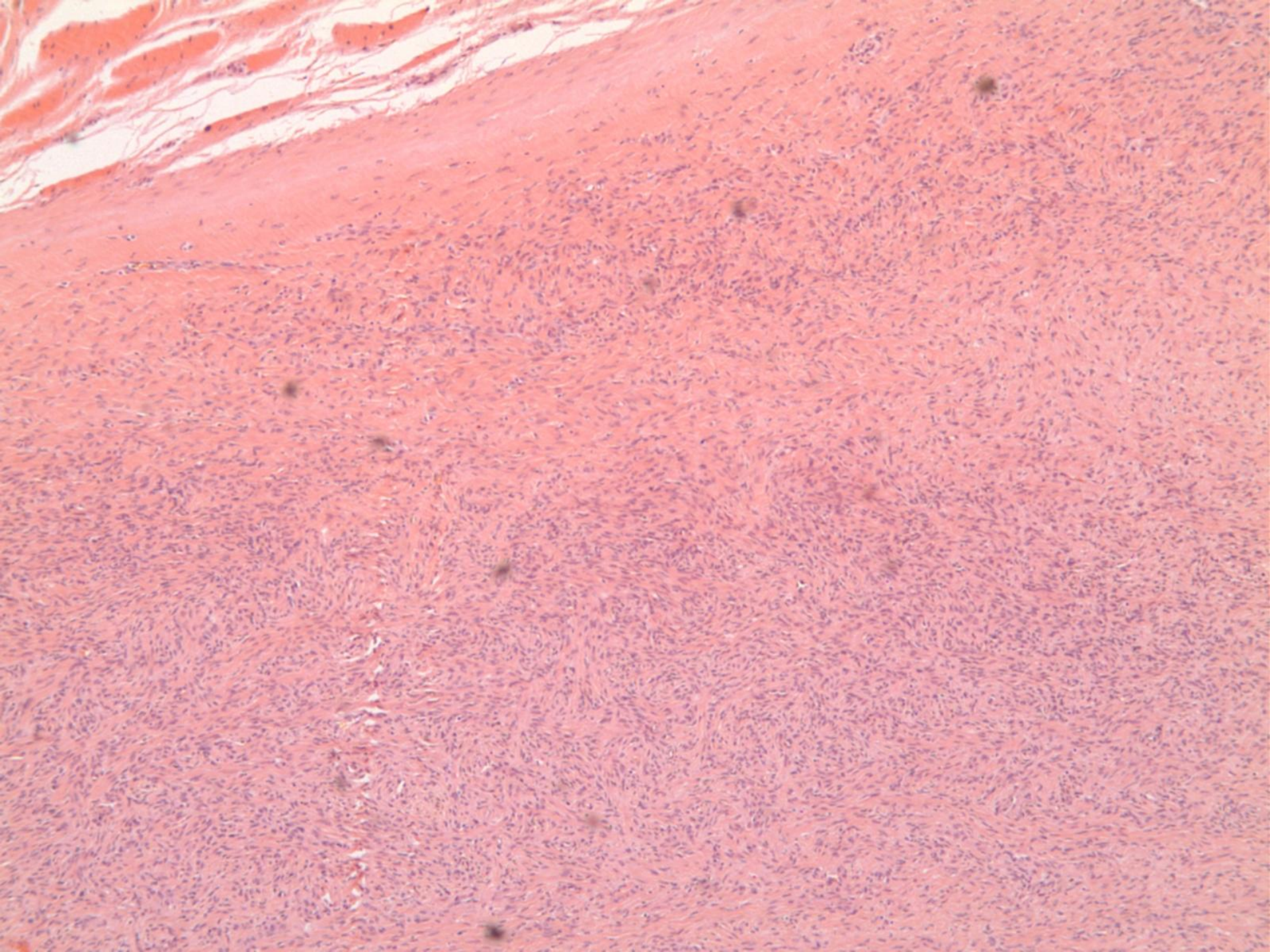
- Hyalinising spindle cell tumour with giant rosettes

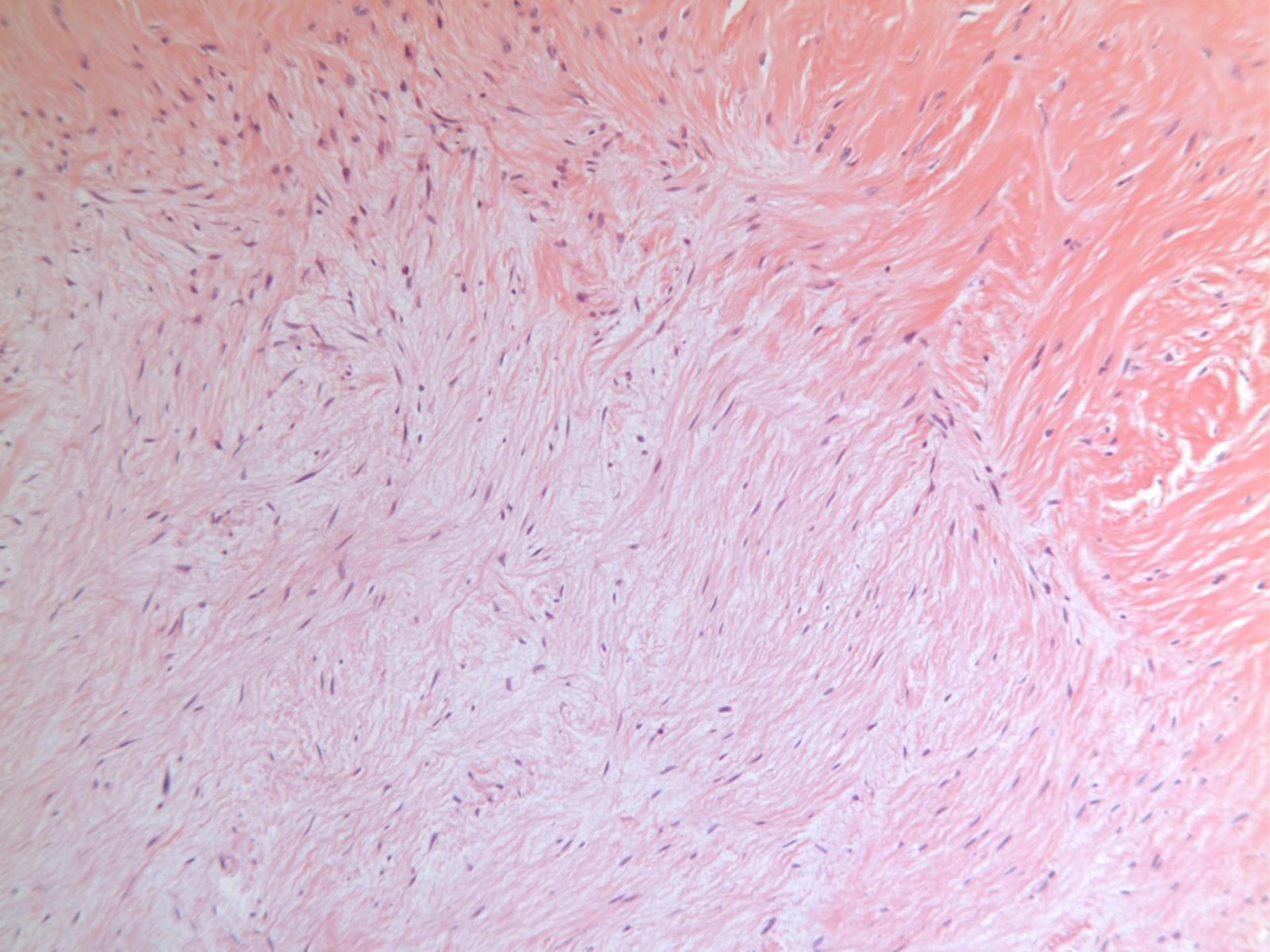
Low grade Fibromyxoid sarcoma

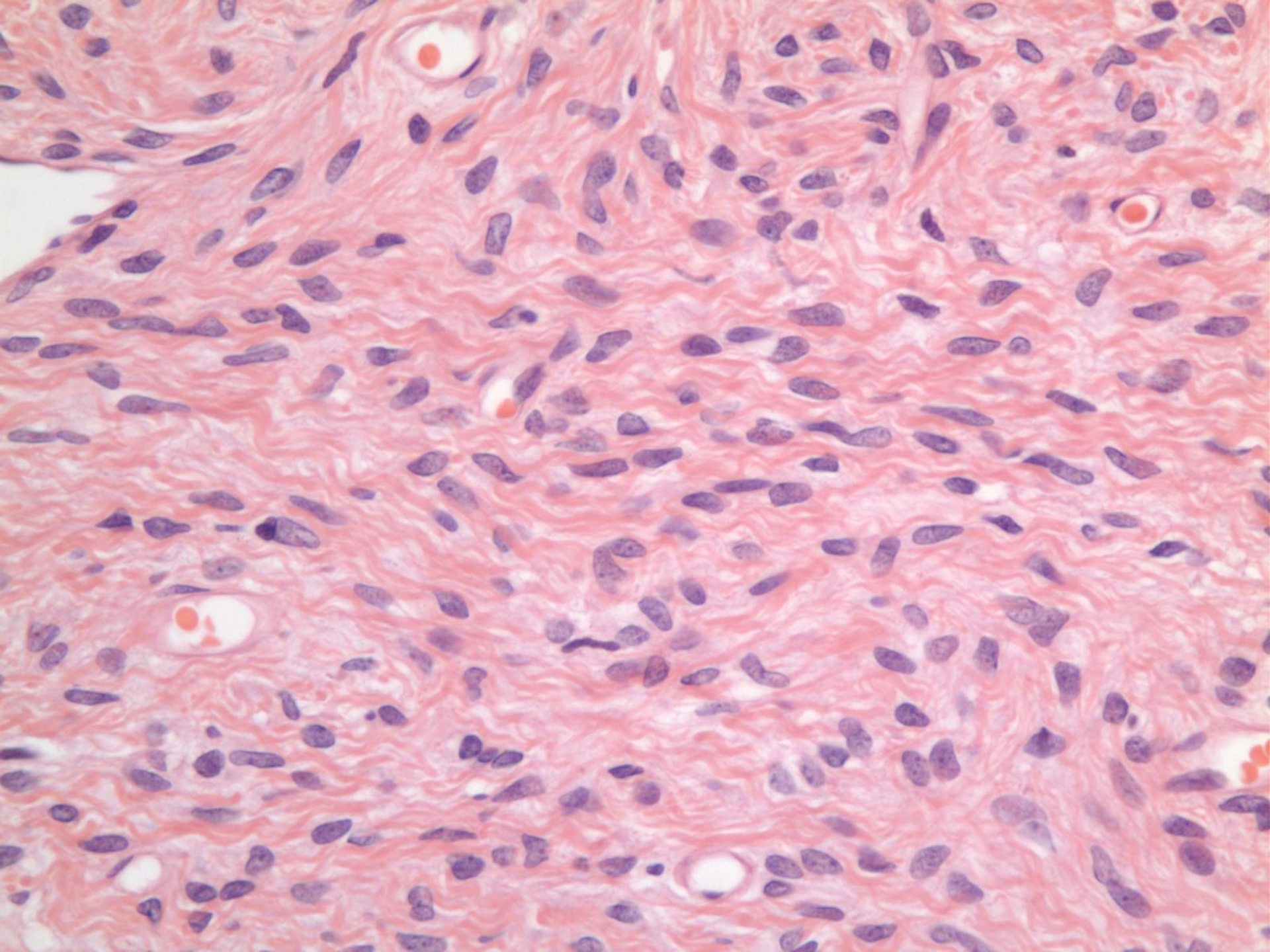
- Young Adults, wide range of sites.
- Often intra muscular but can present as subcutaneous tumour. Circumscribed lobulated tumour.
- Slow growing

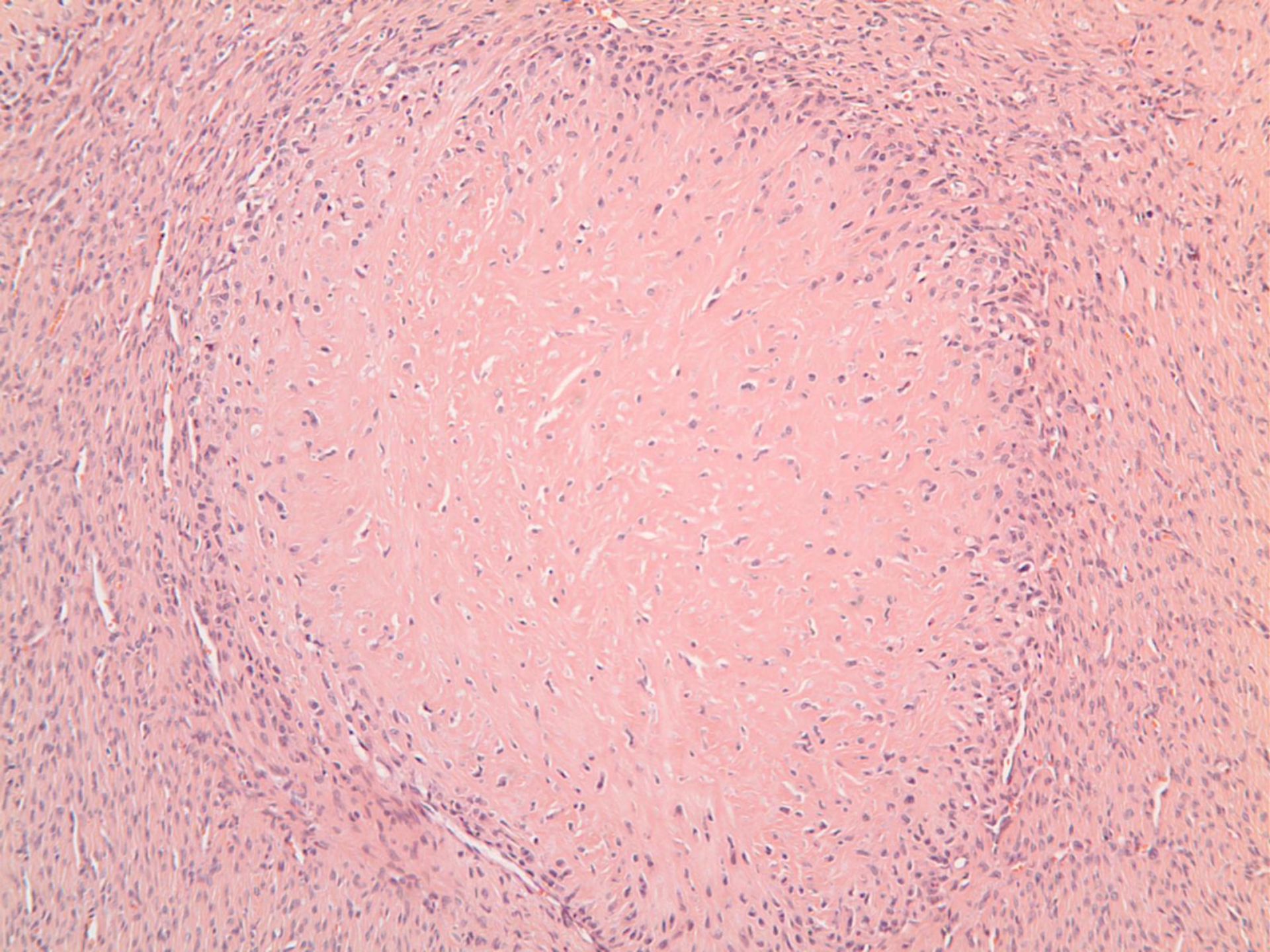
Low grade Fibromyxoid sarcoma

- Micro. Low to moderate cellularity. Very bland appearance
- Cells Spindled, with small hyperchromatic nuclei. Indistinct cytoplasm. Only mild nuclear atypia,
- Alternating myxoid and fibrous stroma.
- Can have branching thick walled capillaries in myxoid zone.
- May have foci higher grade, especially in recurrence.
- Occasionally Giant Rosettes





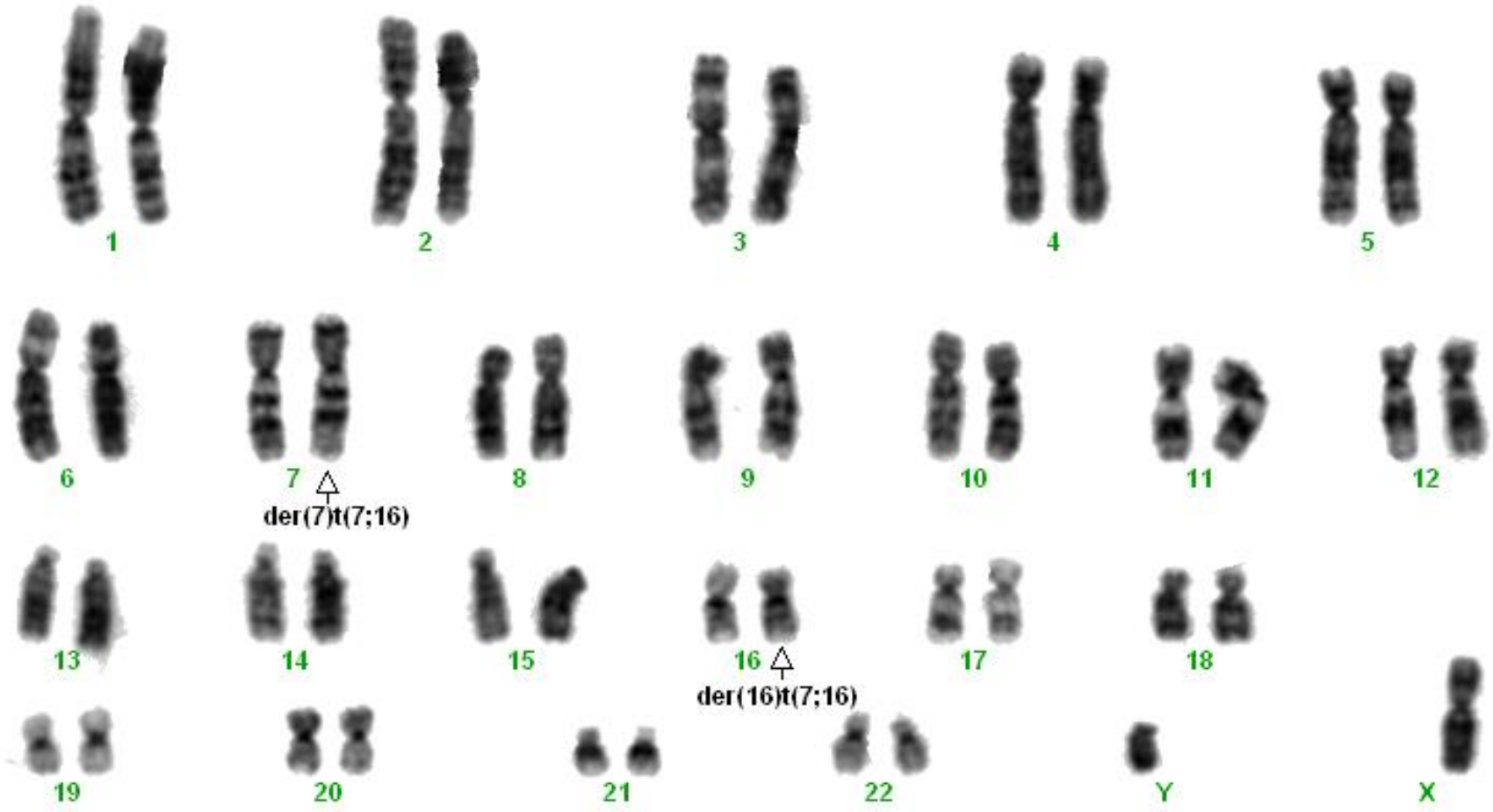




Low grade Fibromyxoid sarcoma

- Immuno. May stain for SMA. Rare cases focal Cytokeratin. Beta catenin and S100 negative.
- EMA- often positive [confuse with perineurioma]
- Recently, MUC 4 immuno shown to be useful.
- Genetics- Translocation Involving FUS gene Chromosome 7 and CREB3l2 on Chromosome 16 in many.
- Can use FISH, PCR better.

N H – t(7;16)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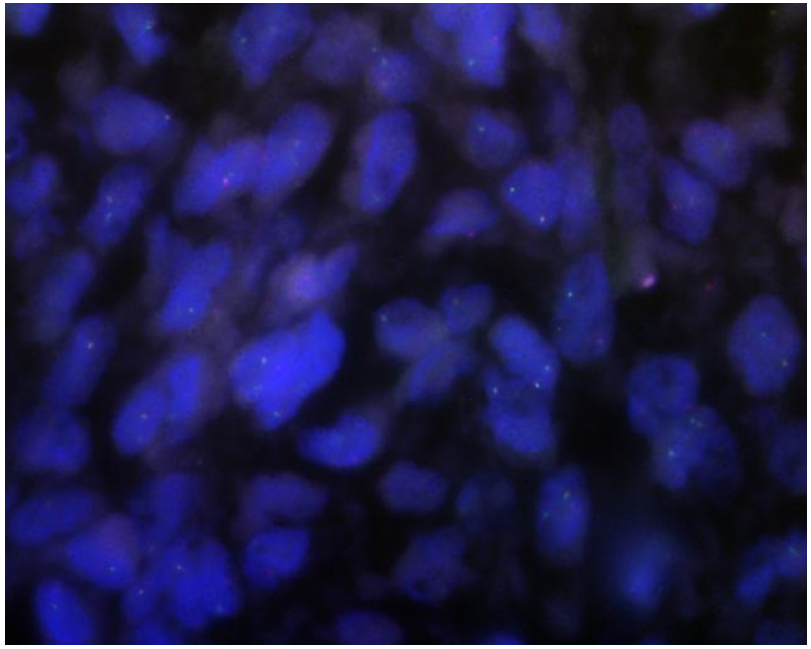
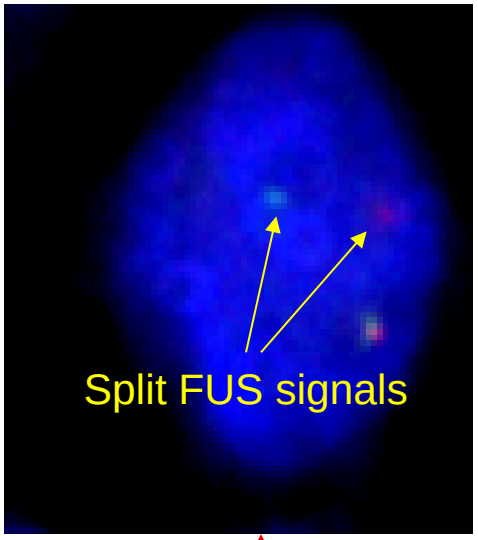
X

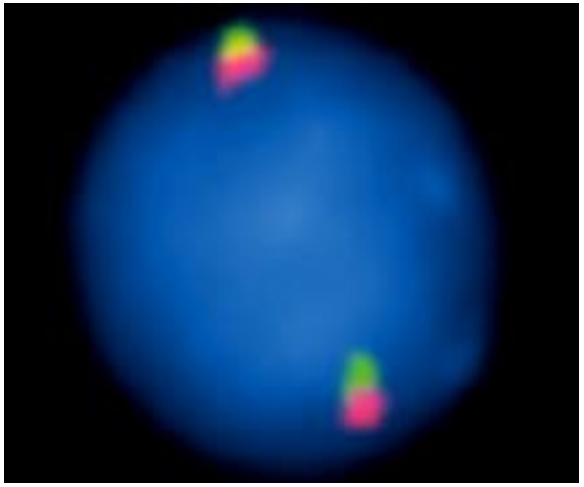
FISH with FUS break-apart probe



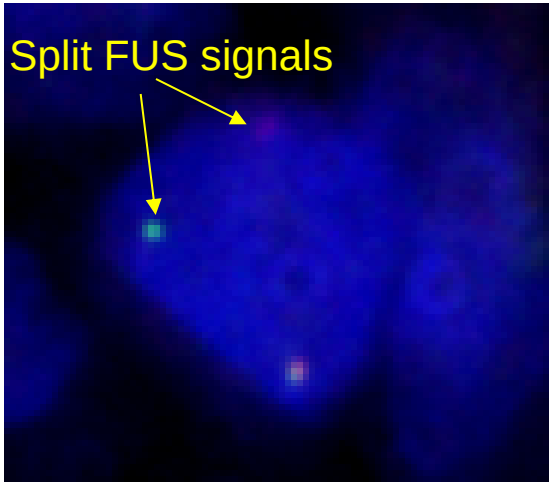
Multiple abnormal cells



FUS rearranged



FUS normal



Fibrosarcoma

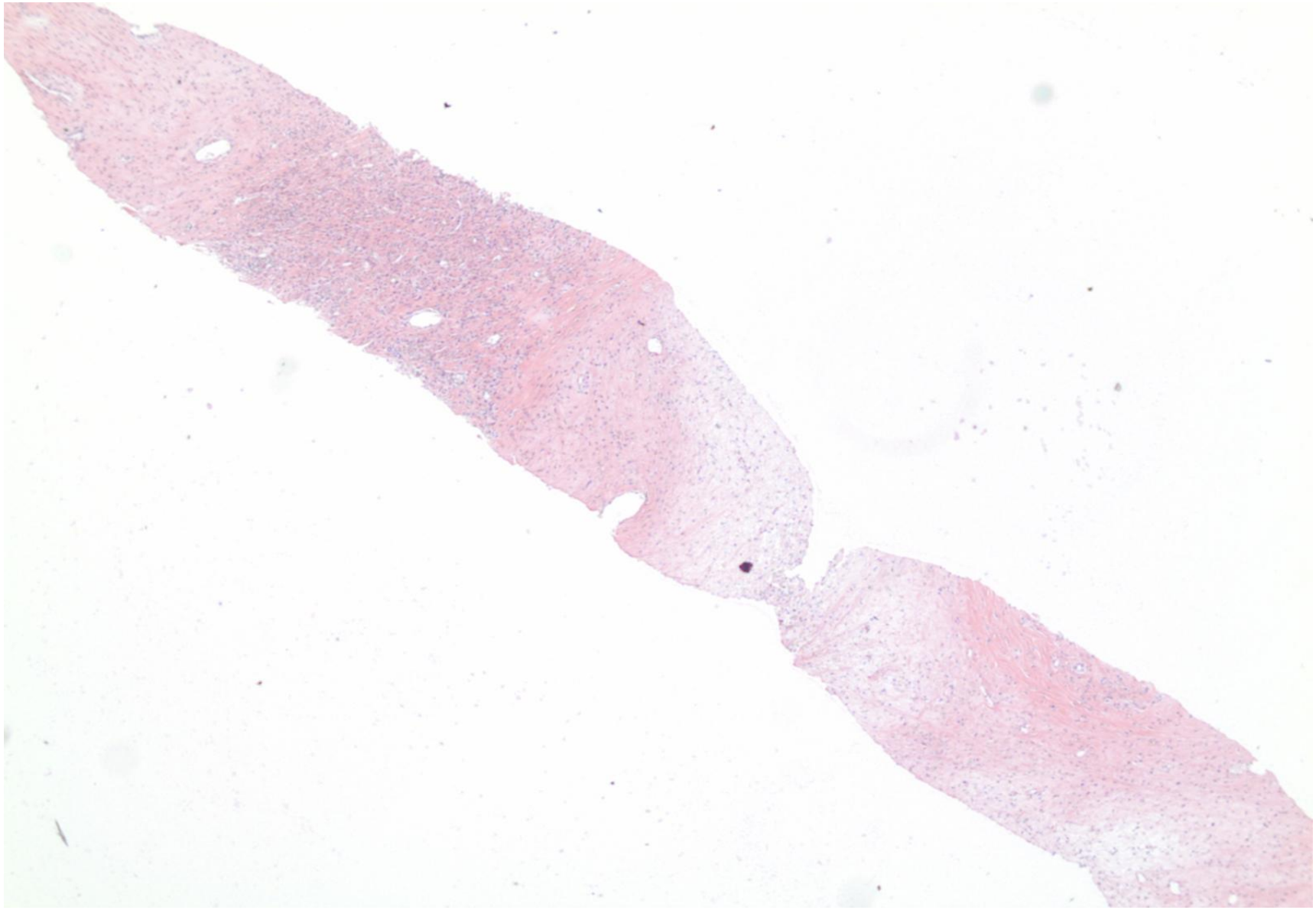
- Can you name any?

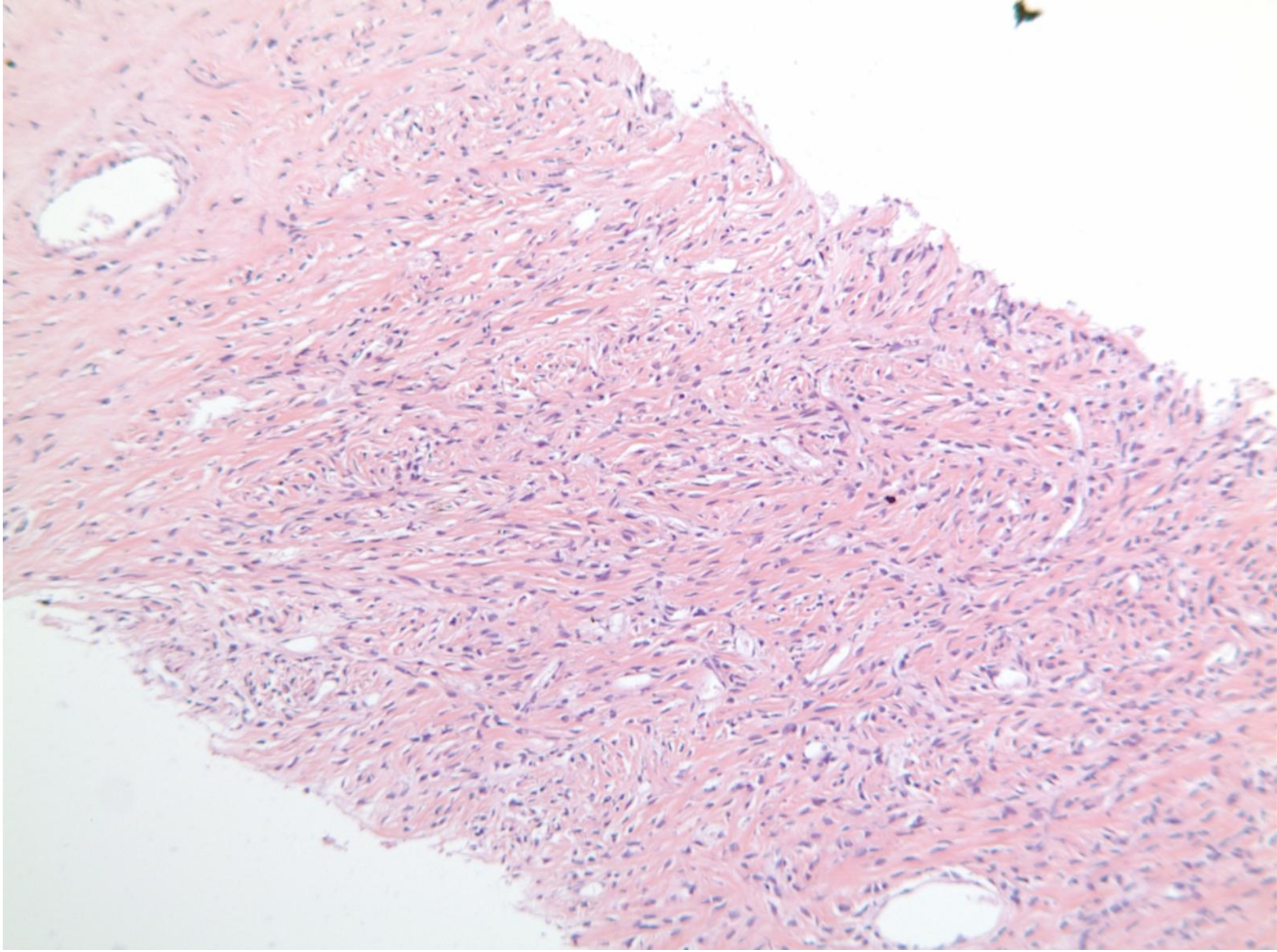
‘Fibro’ ‘sarcoma’ WHO Classification

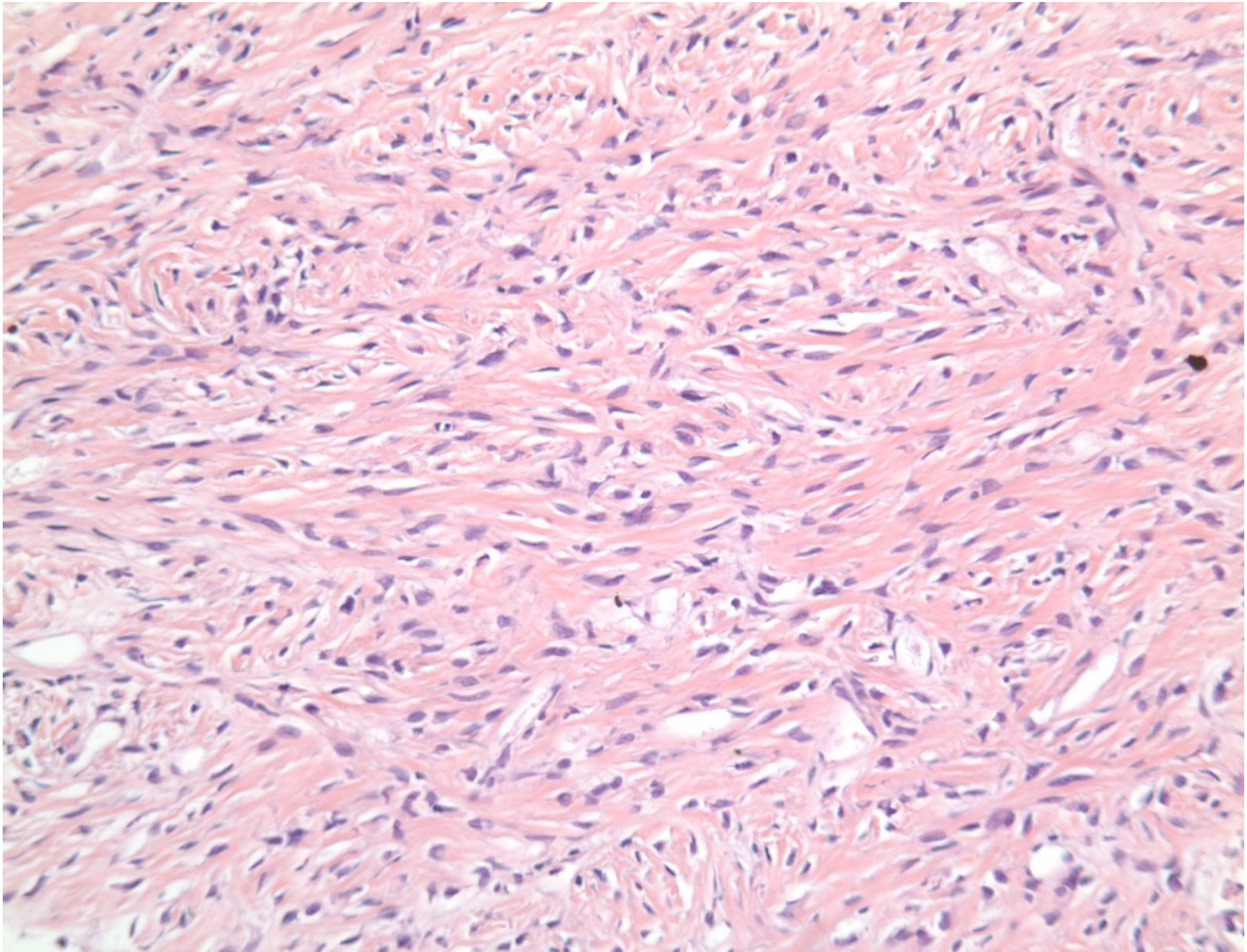
- Myxoinflammatory fibroblastic sarcoma
- Myxofibrosarcoma
- Low grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma
- DFSP
- Infantile fibrosarcoma
- Low grade myofibroblastic sarcoma
- Adult fibrosarcoma [?exists]

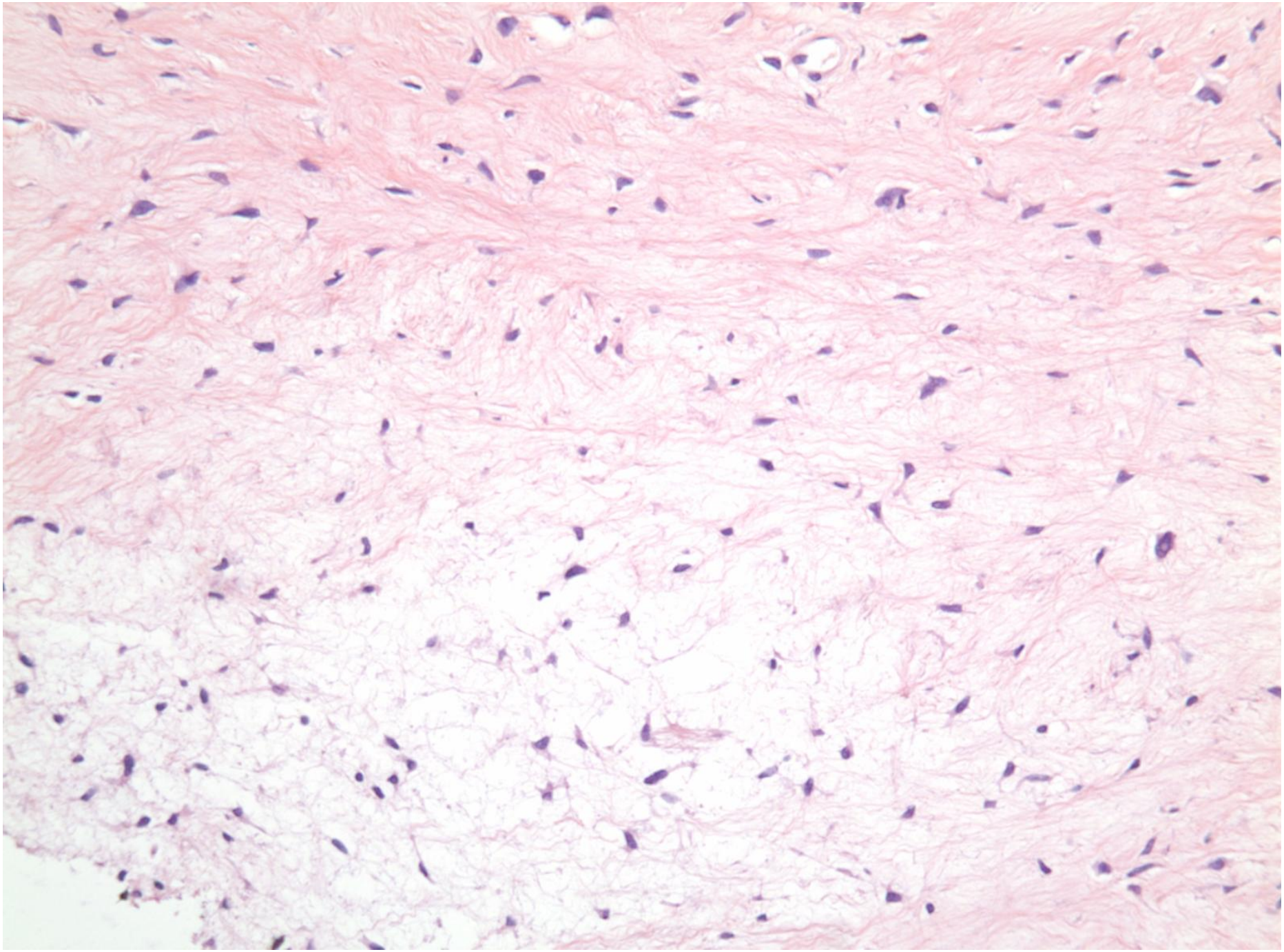
Low grade Fibromyxoid sarcoma

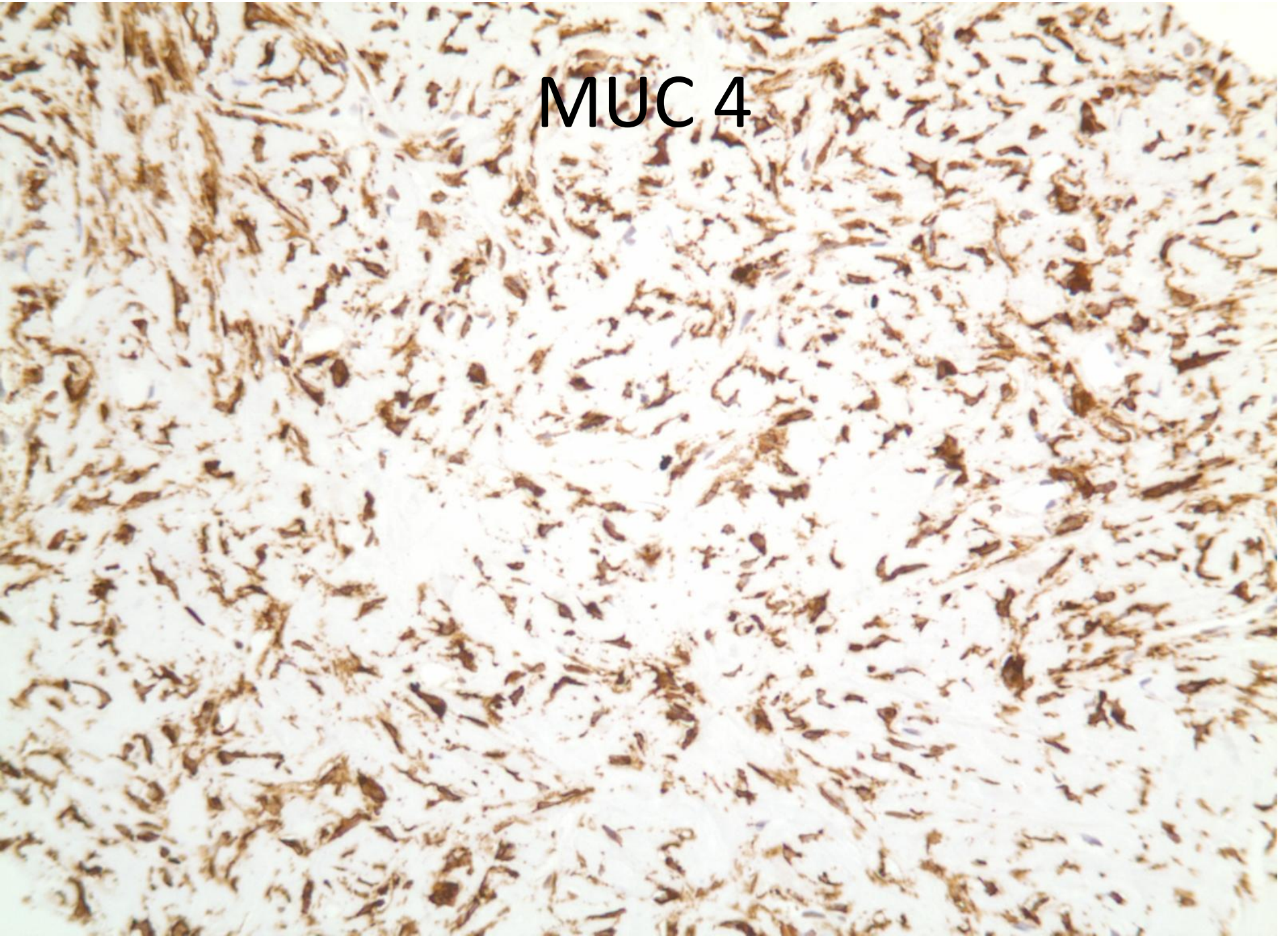
- Prognosis. New reports-
- At 5 years recurrence 10%, Mets 5%
- At > 10years, Recurrence- 64%, mets 45%, death 42%.










MUC 4

Case 8

- 70 Male with ulcerated nodule scalp

Case 8

- Main differential
- How make diagnosis.

High grade cutaneous tumours

- Carcinoma, including metastasis
- Melanoma
- Sarcoma
  - LMS
  - Angiosarcoma
- Lymphoma, anaplastic large cell
- AFX

Atypical Fibroxanthoma AFX
Clinical

- Elderly, sun damaged sites, esp. head & neck
- Raised cutaneous nodule

AFX- cytology

- Tumour cell; high grade atypia with pleomorphic cell, atypical xanthomatous cells and spindle cells in varying proportion

AFX

- Architecture
  - Circumscribed with pushing margin
  - Minimal subcutaneous fat extension
  - No vascular invasion
  - No Tumour necrosis

AFX

- Diagnosis of exclusion; rule out melanoma, carcinoma, sarcoma.
- Exclusion based on architecture and Immunohistochemistry.
- Immuno. Panel; Broad spectrum cytokeratins [several], S100,p63, Desmin.
- NB; can show weak CD31, and p63 positivity.
- CD10 ? Useful, not a lot.

AFX

- Beware if not sun damaged site
- ? Risk if immunosuppressed
- If has any aggressive features –'Pleomorphic dermal sarcoma'

Case 9

- 25 F, ? Haemangioma on leg

Case 9

- What is this?
- What should it really be called.

Case 9

- Kaposi Sarcoma
- Named after Moritz Kaposi, real name Moritz Kohn

Case 10

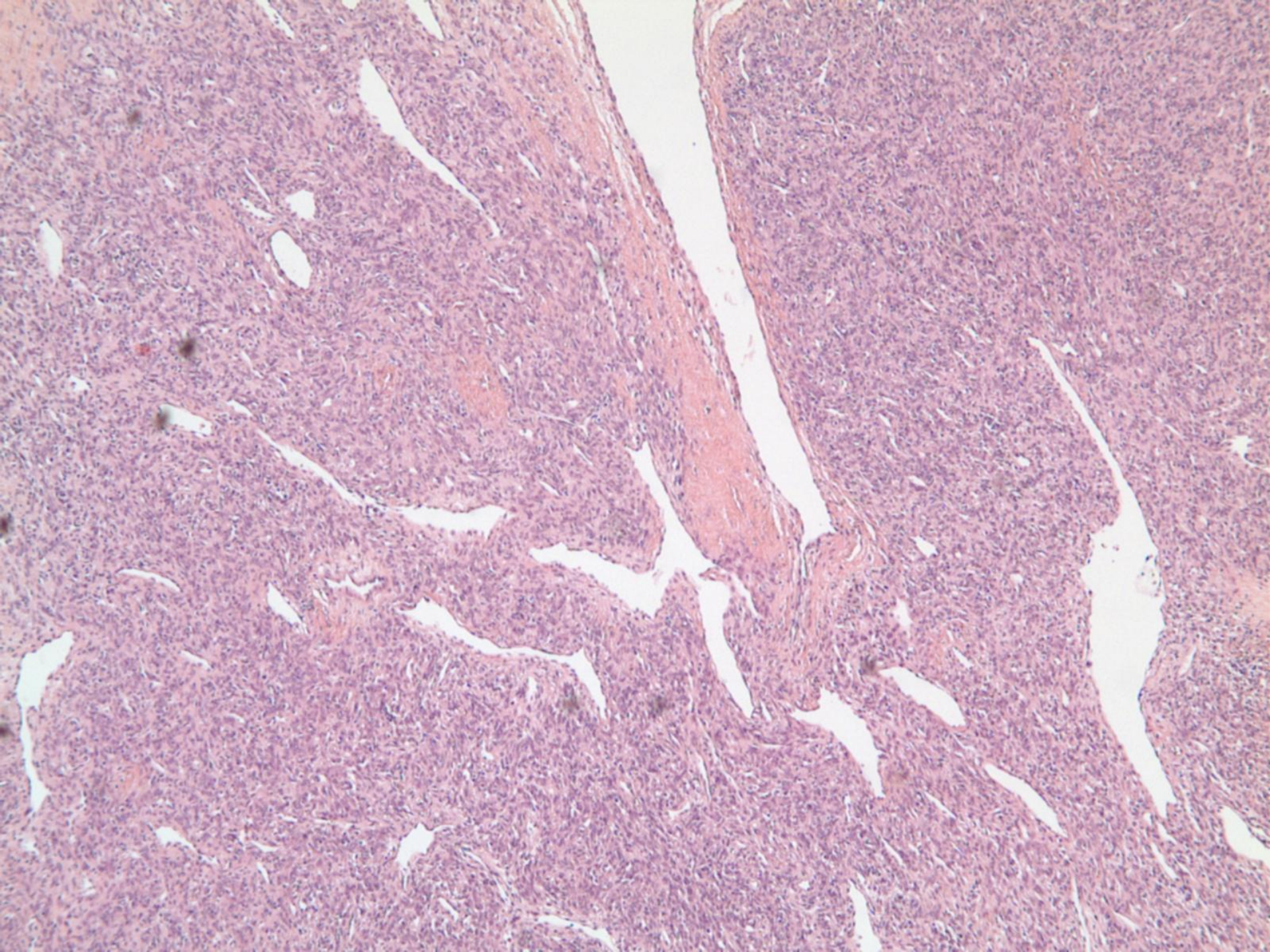
- 30M, ? Haemangioma s/c on arm

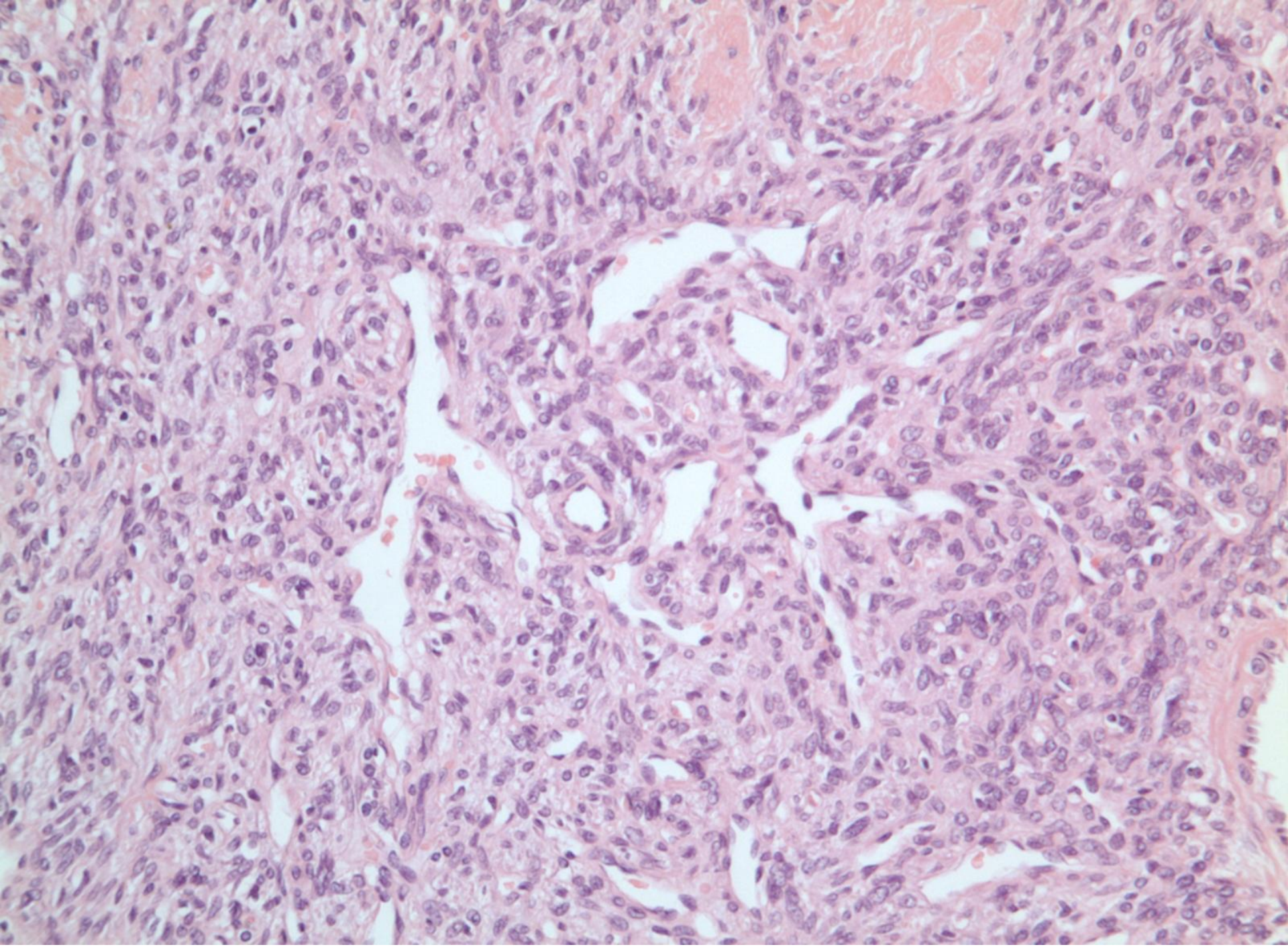
Case 10

- Variable appearance
- In-part- haemangiopericytoma like with small cells
- Foci with bundles of spindle cells with more abundant cytoplasm; odd almost chondroid matrix.

Solitary myofibroma

- Benign
- In young children, can be multifocal ‘infantile myofibromatosis’
- Often secondary changes; hyalinisation, necrosis
- Can see vascular invasion.
- Easy to call malignant





Haemangiopericytoma
HPC

- Once a common soft tissue tumour.
- Now considered a morphological appearance only.

HPC

- Differential diagnosis

Haemangiopericytoma

- Solitary Fibrous Tumour, SFT
- Myopericytoma
- Myofibroma
- Infantile Fibrosarcoma
- Synovial sarcoma
- Round cell liposarcoma
- Endometrial stromal sarcoma

Case 11

- 30 Male lump on ankle

Case 11

- Clear/pale spindle cells.
- Organised pattern

Clear cell sarcoma of tendon and aponeuroses

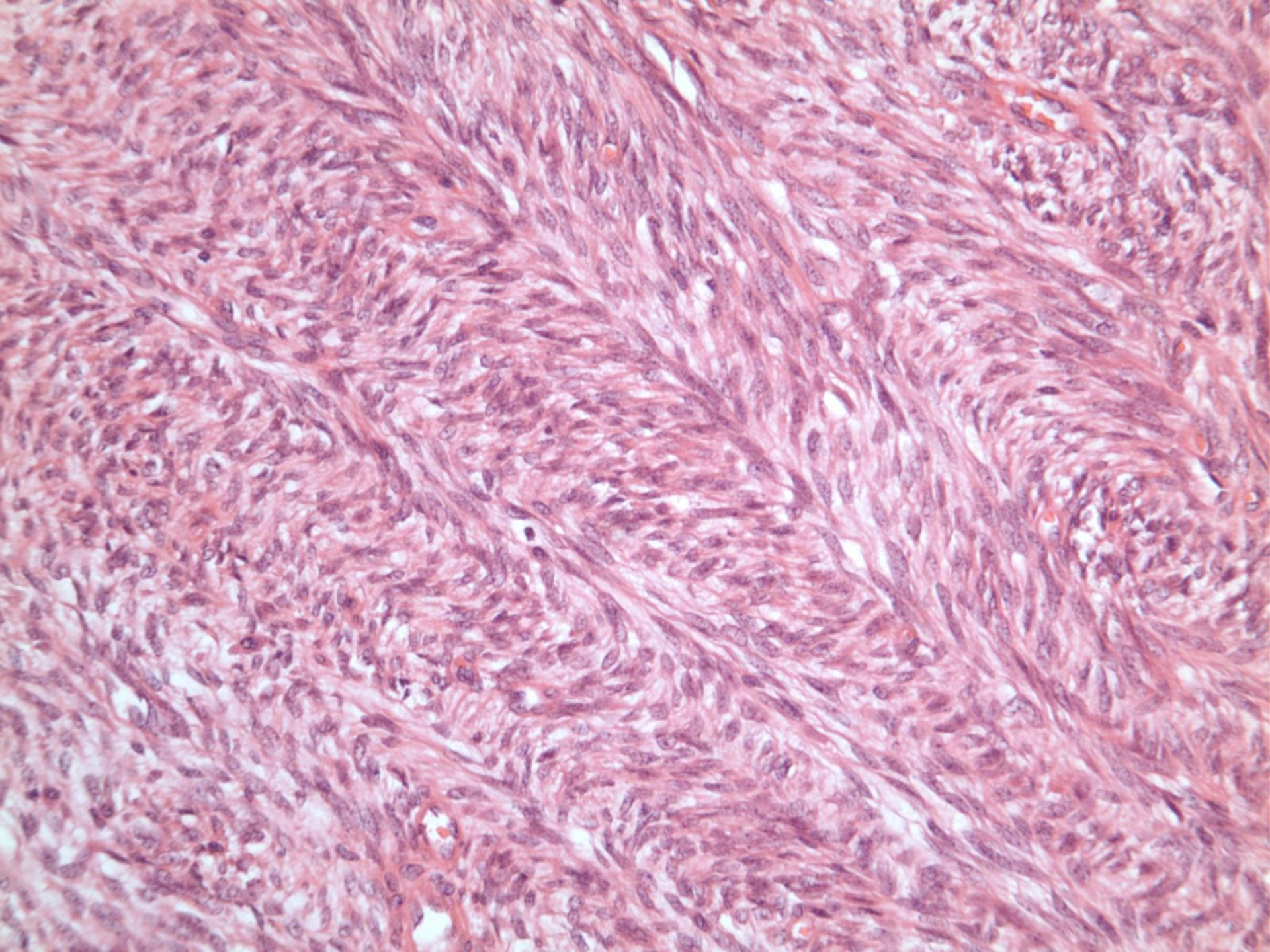
- Usually deep, often peripheral site related to tendons etc in young age.
- Now reported in bowel and skin
- Immuno, same as melanoma
- Has characteristic genetics t11:22
- EWS/ATF1 fusion . Can use FISH for EWRS1

Case 12

- 30 M Lump on chest

Fibrosarcomatous appearance

- Fascicles of spindle cells. Zig-zag pattern; ‘herringbone’
- Cellular ++, with little matrix
- Oval hyperchromatic nuclei, but uniform
- Little pale indistinct cytoplasm.



Fibrosarcomatous appearance

- Differential diagnosis;
  - MPNST
  - Synovial sarcoma
  - Fibrosarcoma
  - Clear cell sarcoma
  - LMS, high grade
  - RMS-spindle cell variant
  - Less likely;
    - melanoma,
    - carcinoma.

Synovial sarcoma

- Immuno; focal C.K., EMA positive. CD56 diffuse.
- Negative CD34 plus others
- FISH/PCR t(X;18) translocation
- Note Calcification. Quite common.
- New immuno- TLE1 – supposably specific

Case 13

- 80 Male Lump on neck

Pleomorphic Lipoma VS Liposarcoma

- Name any useful features?

Pleomorphic Lipoma

- Morphological overlap.
- Diagnosis by; Clinical ;ie age, sex,site
- Immuno; MDM2 lacking
- Cytogenetics or FISH has 13q deletion, no MDM2 amplification. [latter seen in liposarcoma].

Case 14

- 30M, Multiple Lumps and bumps for years. This one increasing in size.

Neural

- Spindle cells with small buckled nuclei.
- Nuclei have tapered end.
- Cytoplasm, pale and poorly defined.
- Variable collagenous to myxoid stroma.
- Schwannoma;
  - Nuclear palisading
  - Thick walled vessels.

Malignant change in Neurofibroma

- What to look for.

Malignant change in Neurofibroma

- Nuclear Atypia
- Cellularity, ie back to back cells
- Mitotic activity- > 1 in 20 hpf.
- Necrosis
- Immuno – s100 becomes patchy or negative in malignancy.
- CD34 ; in benign , has diffuse patterned positivity [Finger print]. Malignant, usually negative.

If only nuclear atypia

- Atypical Neurofibroma - benign

Diagnostic Criteria for NF1

Diagnostic Criteria for NF1

- **Neurofibromatosis 1 is diagnosed in an individual with two or more of the following signs or factors:**
- Six or more café au lait macules: >5mm in greatest diameter in prepubertal individuals; . 15mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal region
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis.
- First-degree relative (parent, sibling, offspring) with neurofibromatosis 1 by the above criteria

Case 15

- 40 M. Testicular swelling

Case 15

- Differential Diagnosis
- How to make diagnosis

Spindle cell variant of well Differentiated liposarcoma

- Can be very spindly, easy to confuse with fibroblast and neural
- Favoured sites- retroperitoneal and paratesticular [as extension of retroperitoneum]
- CD34 and often desmin positive. S100 neg in spindle cells.

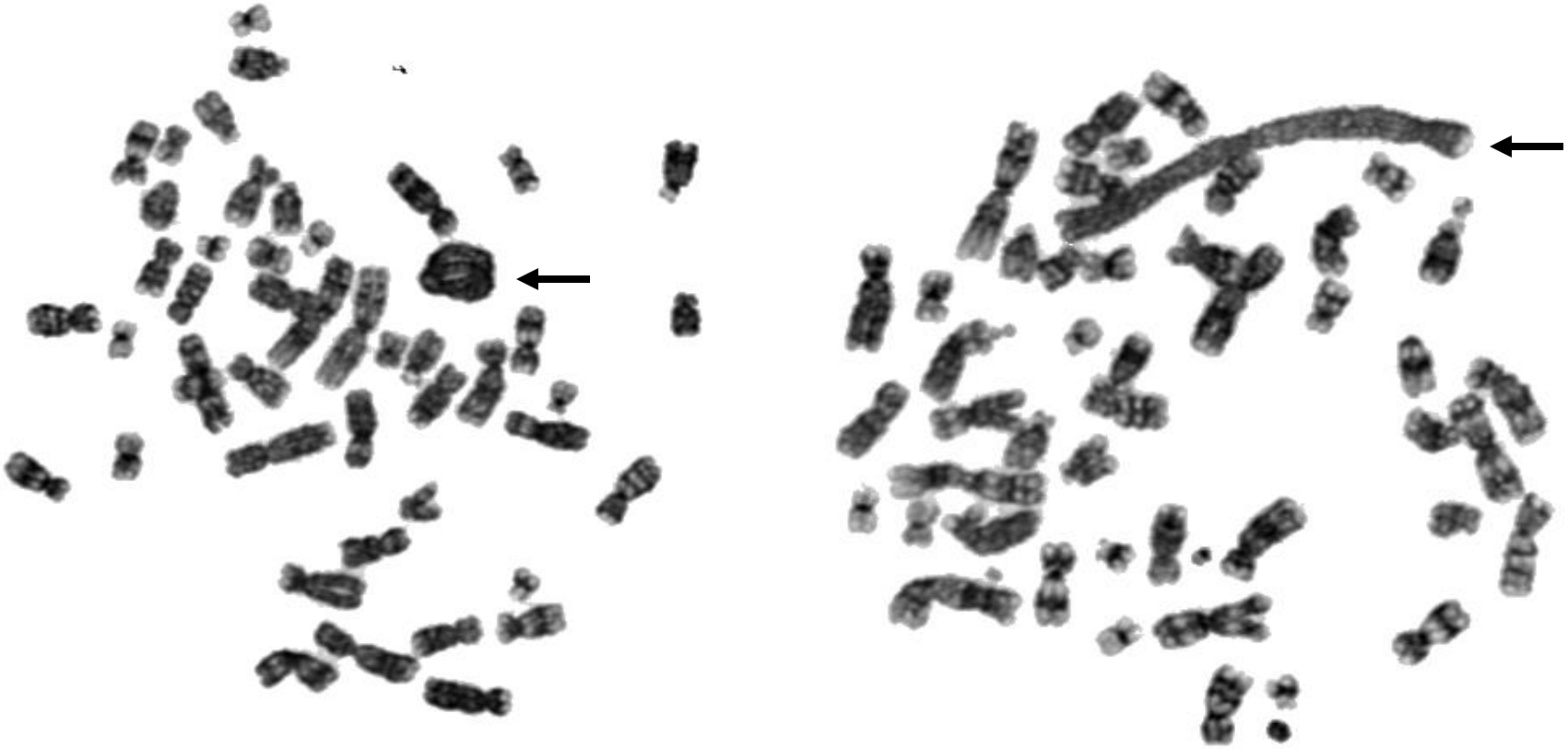
Spindle cell fatty Tumours

- BENIGN
  - Spindle cell lipoma
  - Pleomorphic lipoma
  - Cellular angiofibroma
  - Mammary-type myofibroblastoma
- MALIGNANT
  - Well diff. Liposarcoma
    - Spindle cell
    - Sclerosing
    - Inflammatory

Spindle cell fatty Tumours

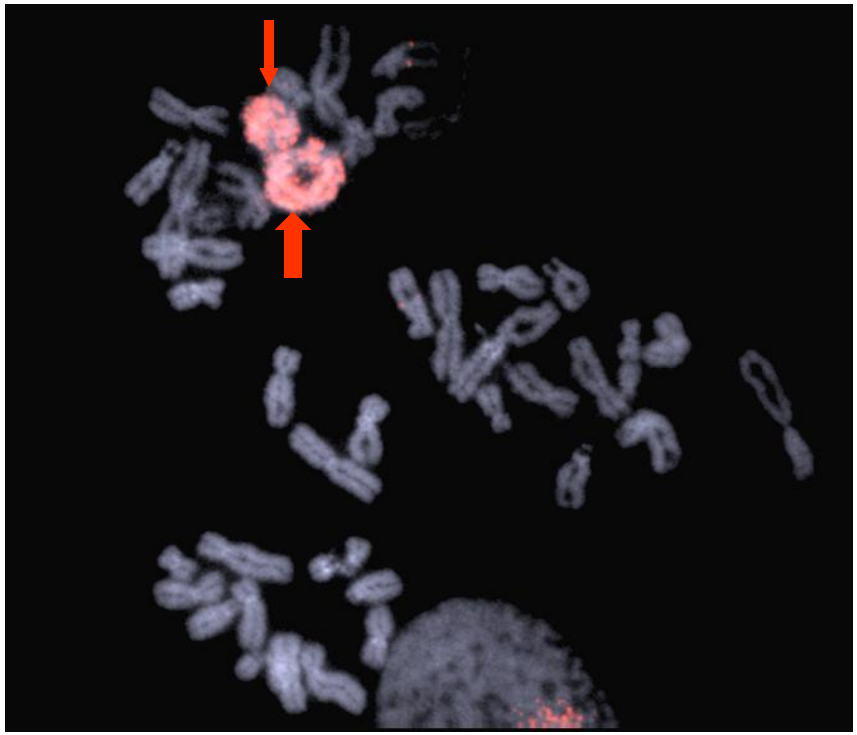
- Can be difficult to separate. Both can be cytologically bland or show nuclear atypia.
- FISH for MDM2 and 13q very helpful

Well-differentiated liposarcoma (WDLPS) with supernumerary rings and giant chromosomes

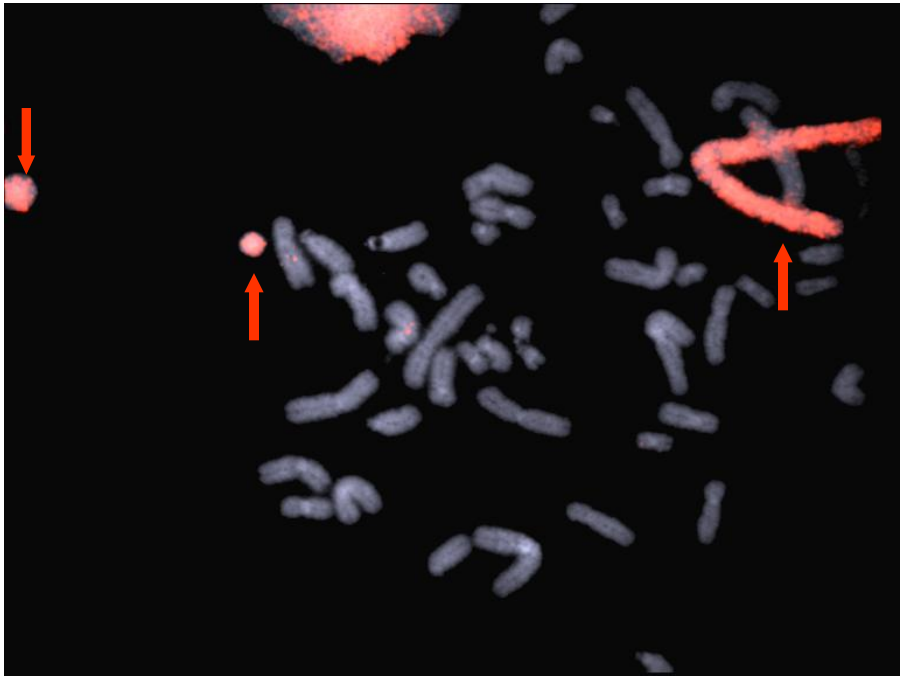


Amplification of 12q13~15:
MDM2, also *CDK4*, *SAS*, *HMGA2*, not *CHOP*

MDM2 amplification in WDLPS



Ring (12)



Giant markers and rings

NB rings seen in lipomas but no *MDM2*

Case 16

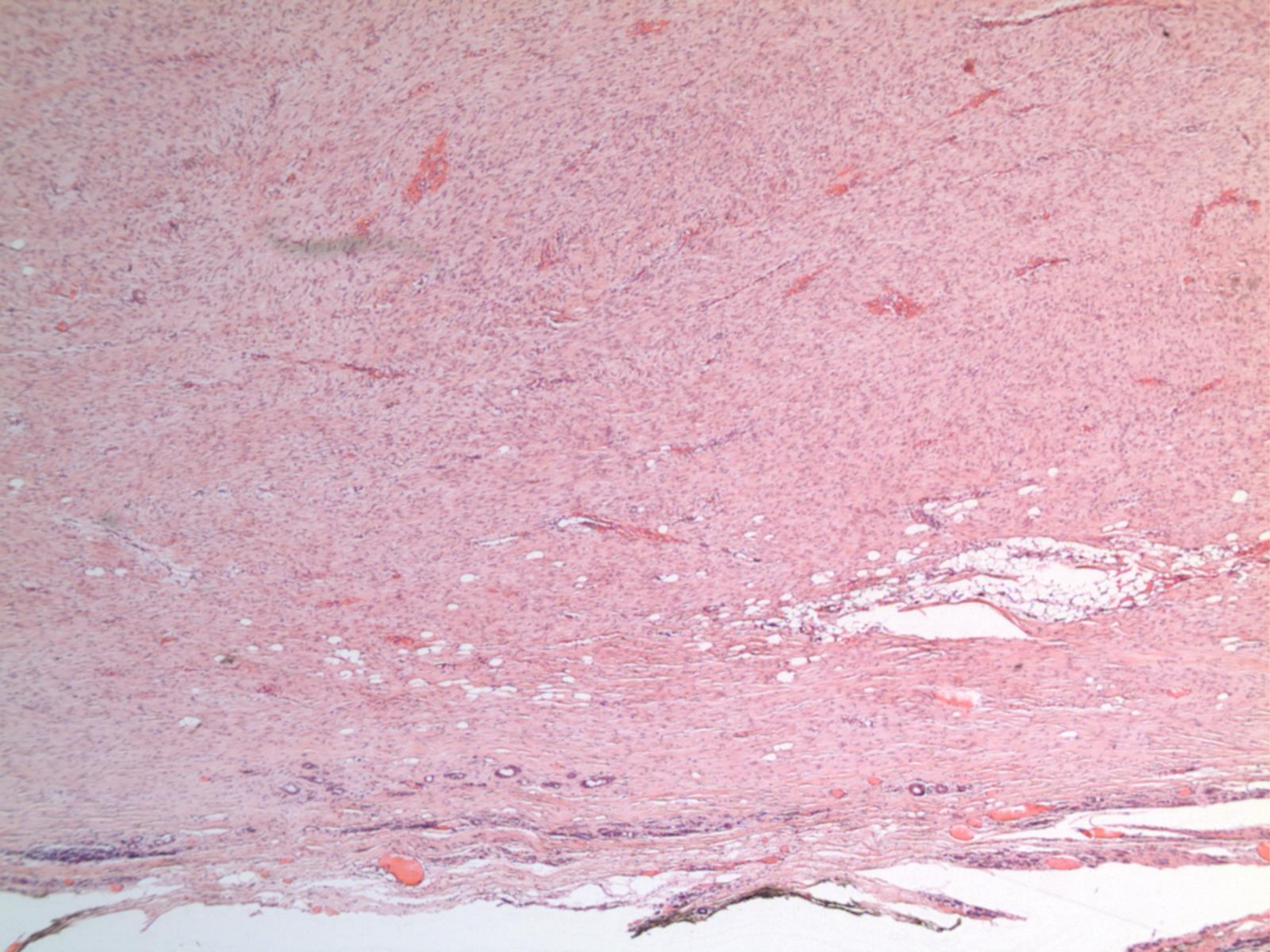
- 70 M, metastatic colorectal carcinoma to liver, resected. Mass noted adjacent to pancreas

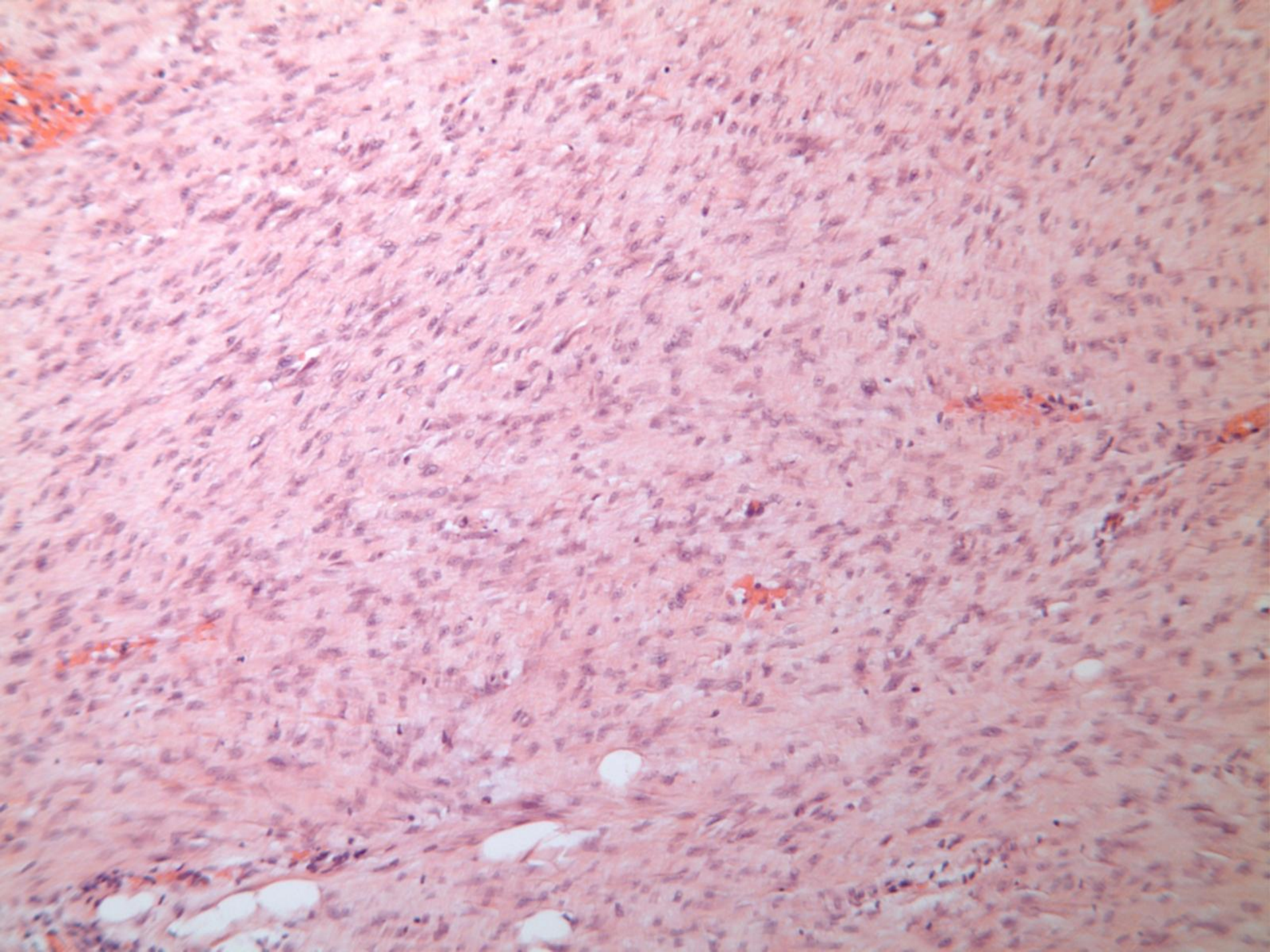
Fibromatosis

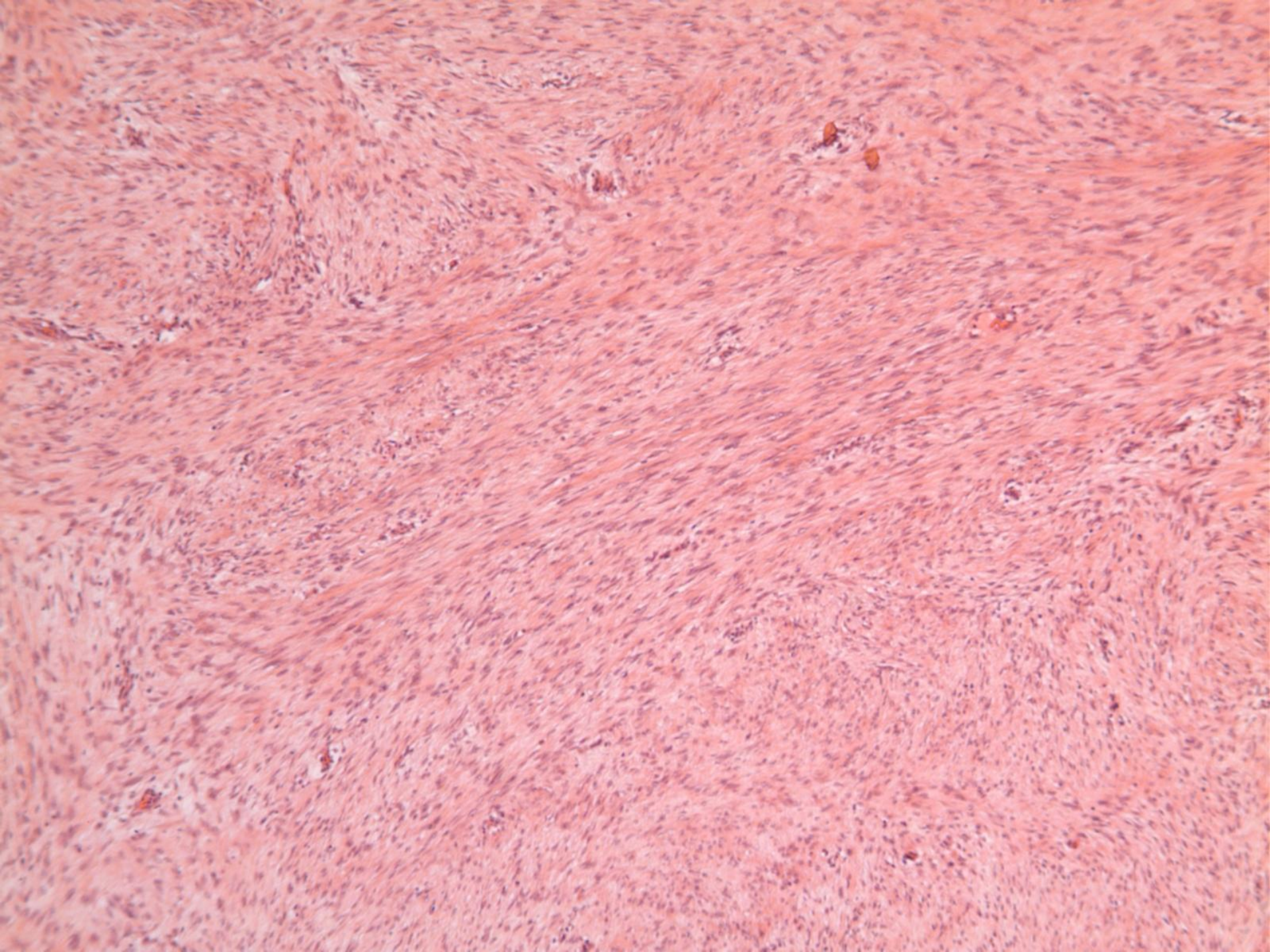
- Characteristic long fascicles of spindle cells. Spindle cells have small elongated nuclei, often wavy.
- Stroma, usually collagenous, can be focally myxoid or keloidal. Infiltrative and entraps structures
- Lymphoid aggregates at periphery common.
- Intra. Abdo. Cases often quite myxoid.

Fibromatosis

- Can be part of FAP/ Gardner's syndrome
- Infiltrative lesion
- Occasionally multi-centric.
- Can follow surgery







Fibromatosis

- Immuno; SMA and HHF35 , may show tram track appearance.
- Beta-catenin, was thought very useful and specific [80%]. Now; can be seen in phyllodes and occ. cell in spindle cell Ca, but focal.
- CD 34 - Negative
- C.K.- Negative
- C-kit /DOG1 Neg

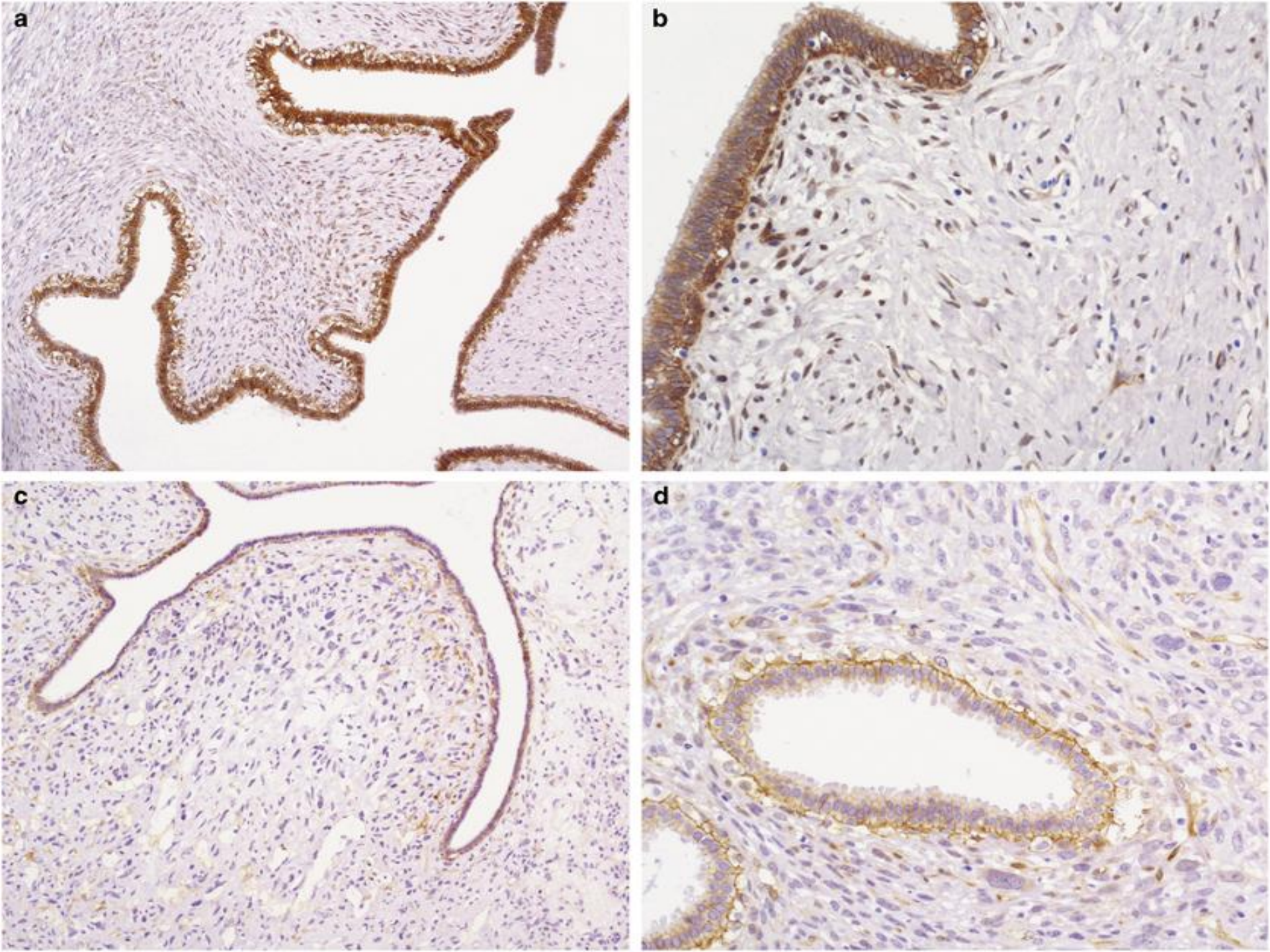
Beta- Catenin

- Involved in wnt-signalling pathway.
- Normal expression is membranous.
- With wnt activation, beta-catenin moves to cytoplasm and nucleus.
- Originally thought to be highly specific for fibromatosis.
- Now noted to be positive in other spindle tumours, but usually weak and focal

Beta-catenin

- 80- 100% Fibromatoses, [diffuse and strong]
- 90% Phyllodes Benign and 57% malignant phyllodes
  - Only cells around epithelial structures
- 23% metaplastic Ca
  - often focal, weak

  - Mod.Path, 23 1438-1448, 2010


a
b
c
d

Fibromatosis, differential

- Scar ; haemosiderin, fat necrosis, macrophages
- Low grade spindle cell carcinoma
- True sarcoma; has nuclear atypia, abnormal mitoses and necrosis. Closest mimic is low grade myofibrosarcoma. Usually occurs in muscle.

Fibromatosis

- Can be locally aggressive
- Recurs in 20%, doesn’t metastasize.

Case 17

- 40M. Tumour on small bowel.
- C-kit positive
- Comment on risk factors

Risk Factor

- You might cock it up.

Remember, Remember Melanoma

- Melanoma can appear very sarcomatous.
- Spindle cell and desmoplastic melanoma very difficult to separate from MPNST.
- Schwann cell and melanocytes share common origin from Neural crest.
- Can present as visceral tumour

Patient re-examined

- Partially regressed melanoma on back.

Case 18

- 25 Male, para-testicular mass

Case 18

- Spindle cell tumour
- Usual differential diagnosis

Spindle cell Rhabdomyosarcoma

- Variant of embryonal RMS
- Often older age group, teens
- Paratesticular by far commonest site, but described elsewhere,especially H+N.
- If thinking smooth muscle or pleomorphic sarcoma NOS, remember are variants of RMS [spindle cell and pleomorphic].
- Can focally express Cytokeratin
- Add myogenin and MyoD1 to immuno panel.

Case 19

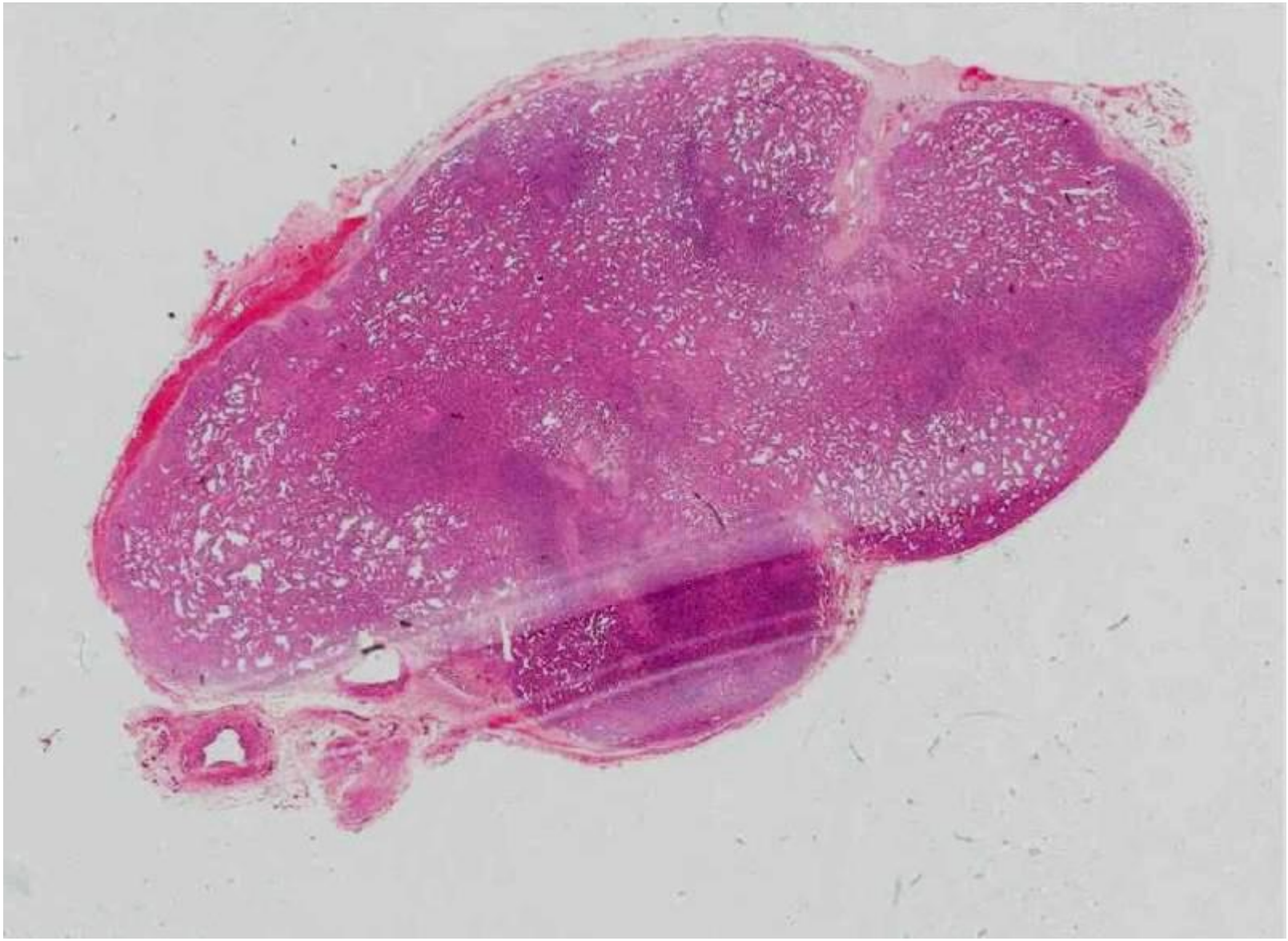
- 30 F, Multiple lumps left leg.

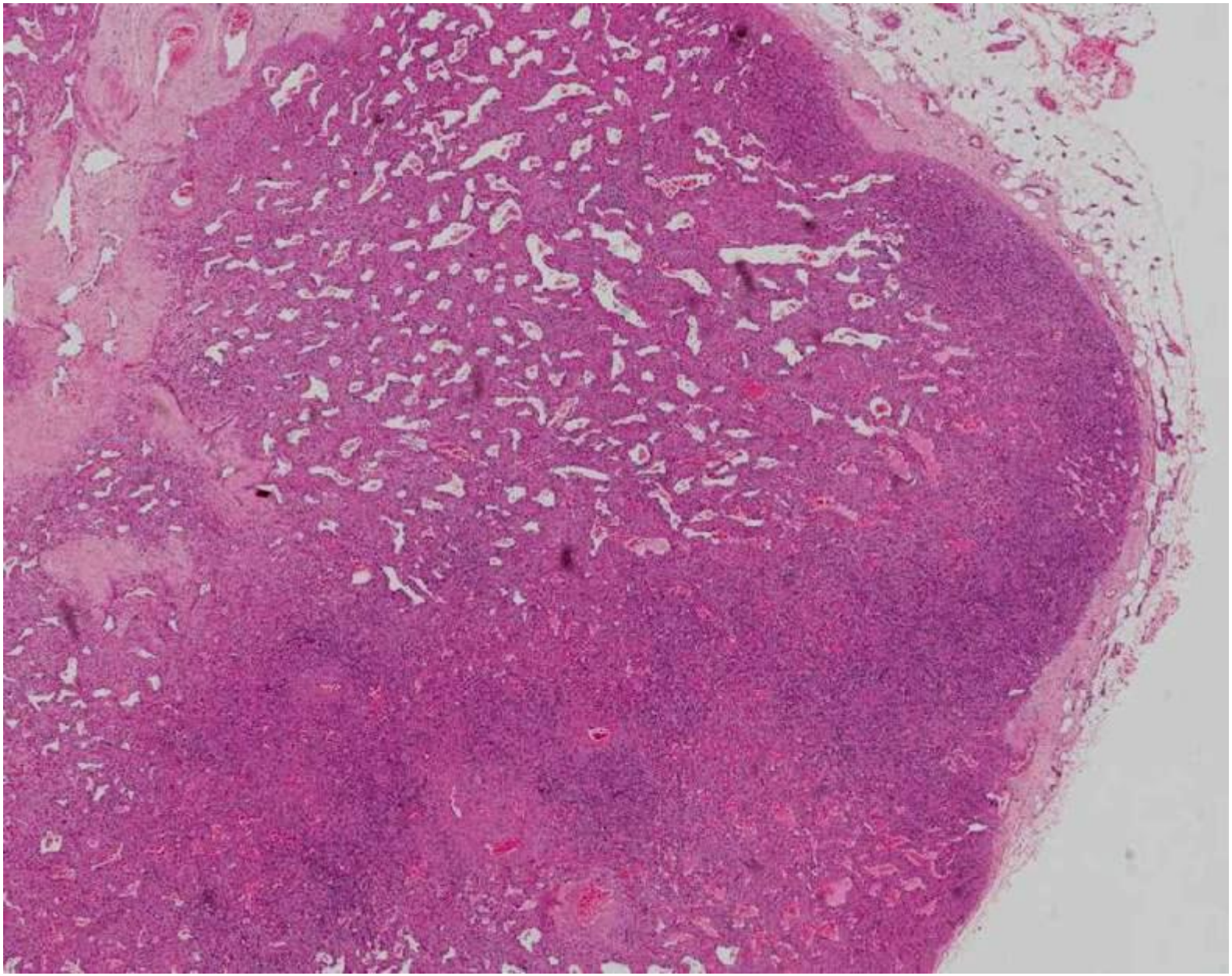
Myopericytoma

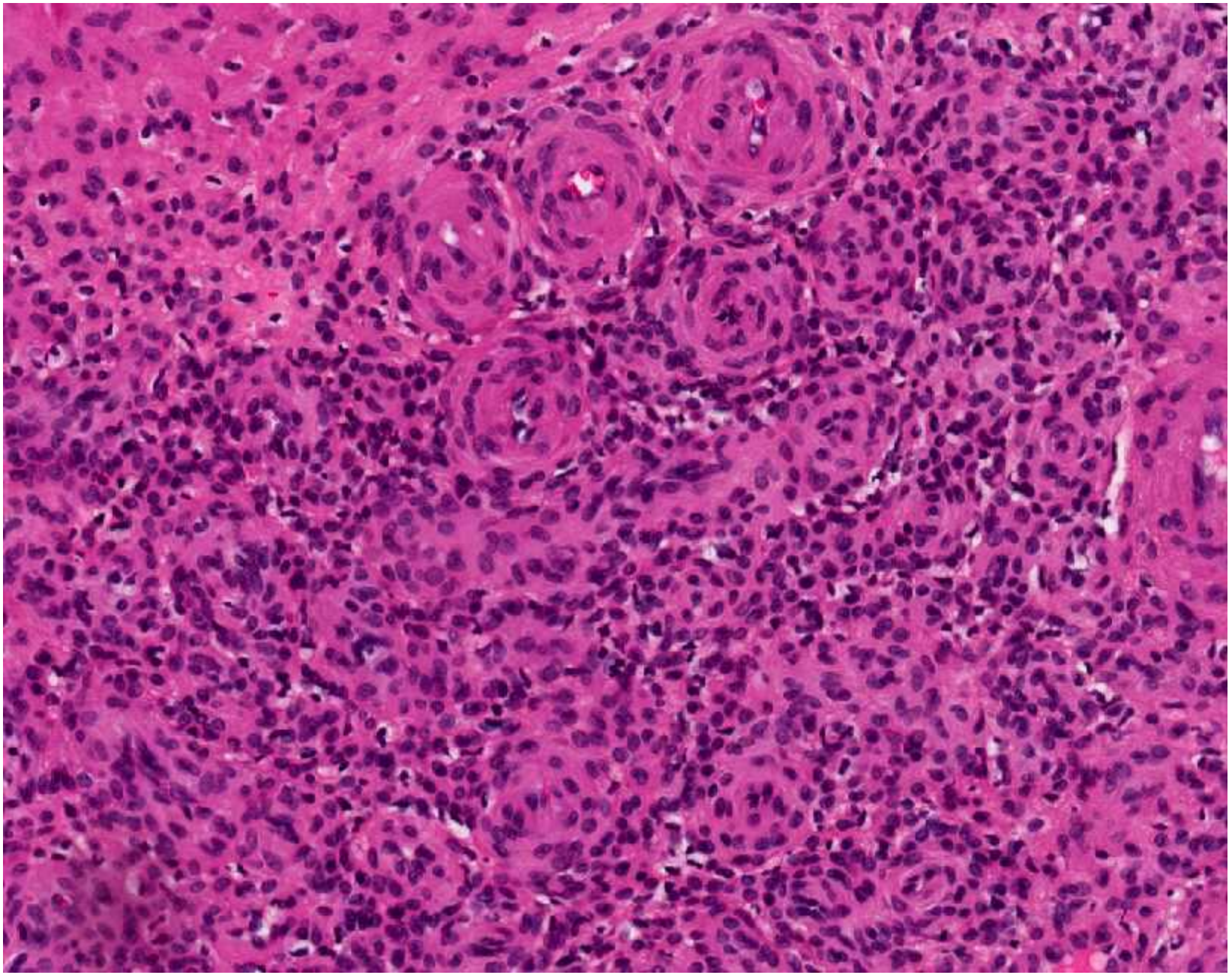
- Tumour showing differentiation towards perivascular myoid cells [Myopericytes].
- Usually subcutaneous, limbs of adults but wide variation.
- Presents as a small nodule =?-painful

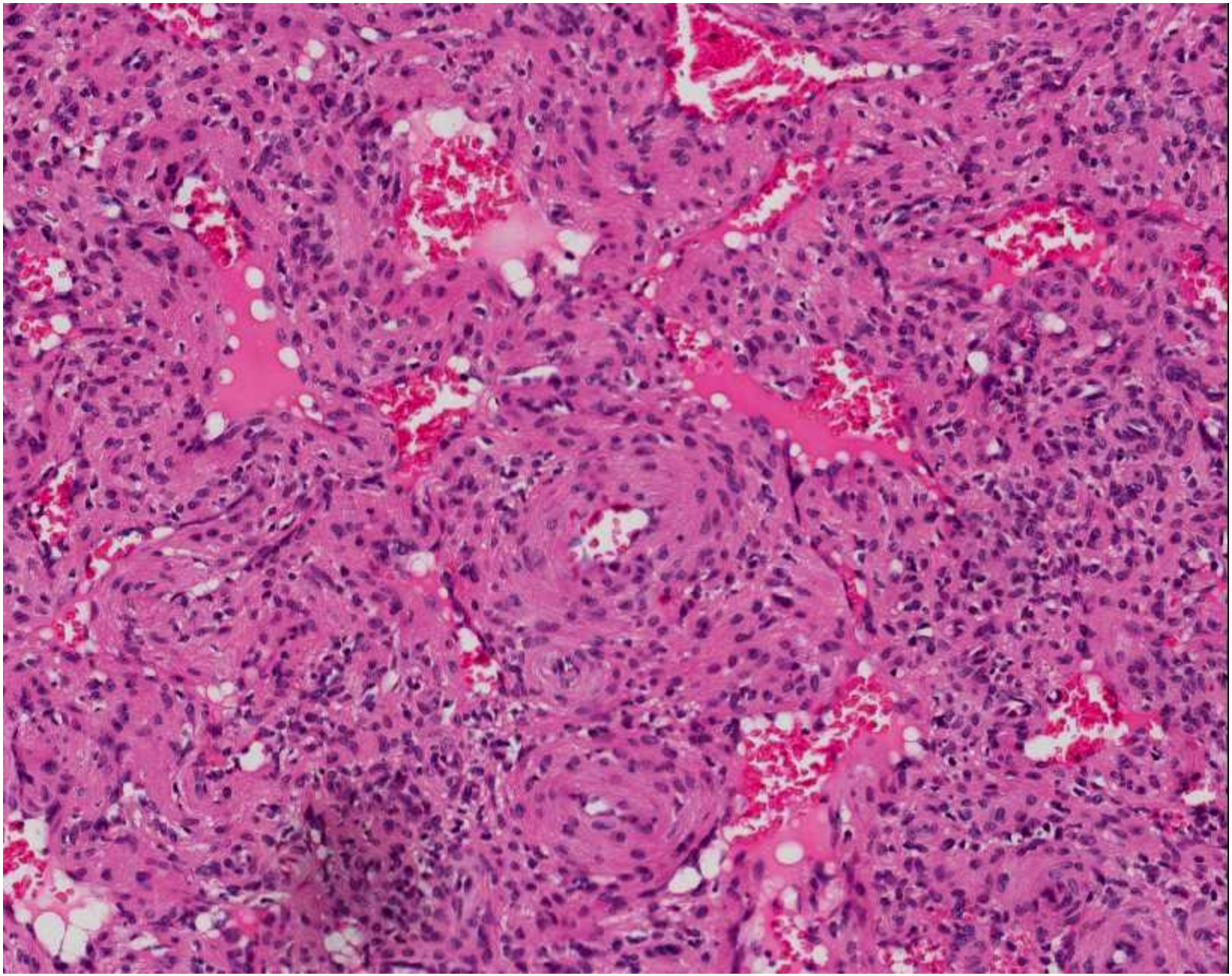
Myopericytoma

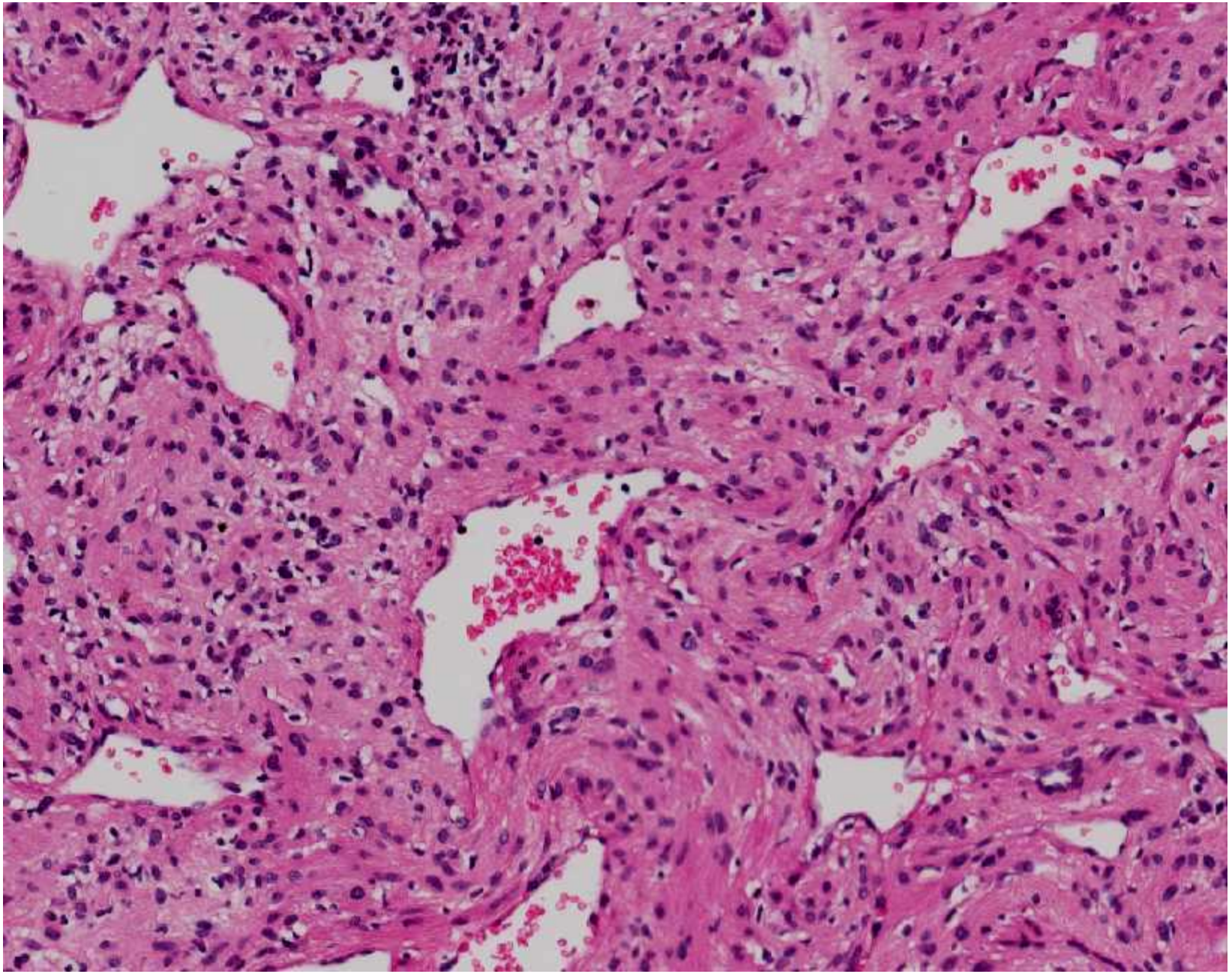
- Well circumscribed tumours
- Prominent vasculature , often gaping , branching pattern [HPC]
- Cells form concentric pattern of growth.
- Spindle to oval myoid appearing cytology
- SMA and H-caldesmon positive, but Desmin rarely positive.











Myopericytoma

- Accounts for many cases which would have been called Haemangiopericytoma [Solitary fibrous tumour accounting for most of the rest]
- Spectrum of tumours; myofibromatosis,myofibroma,glomangiopericytoma and myopericytoma, glomus
  - Granter et al; Am.J.Surg.Path.1998;22:513-525

Myopericytoma

- Most are benign
- Occasional cases are multiple within an anatomical zone.
- Rare malignant cases described, which have prominent cytological atypia.

Case 20

- 60 F. lump in kidney and liver [2002 +2012]

Spindle cell tumour

- Differential diagnosis
- Immuno

Intra. Abdo. tumour
Smooth muscle differentiation

- What should you think of?

Intra. Abdo. tumour
Smooth muscle differentiation

- Leiomyoma/Leiomyosarcoma
- GIST
- PEComa
- Myopericytoma/ angioleiomyoma/glomus
- EBV associated Smooth Muscle tumour

EBV associated SMT

- Immunosuppressed. This case had renal transplant
- Very low grade tumours.
- Often multi-centric, not metastatic.
- Use in-situ hybridisation to identify EBV [EBER]

Case 21

- 50F. Intra-abdominal mass.

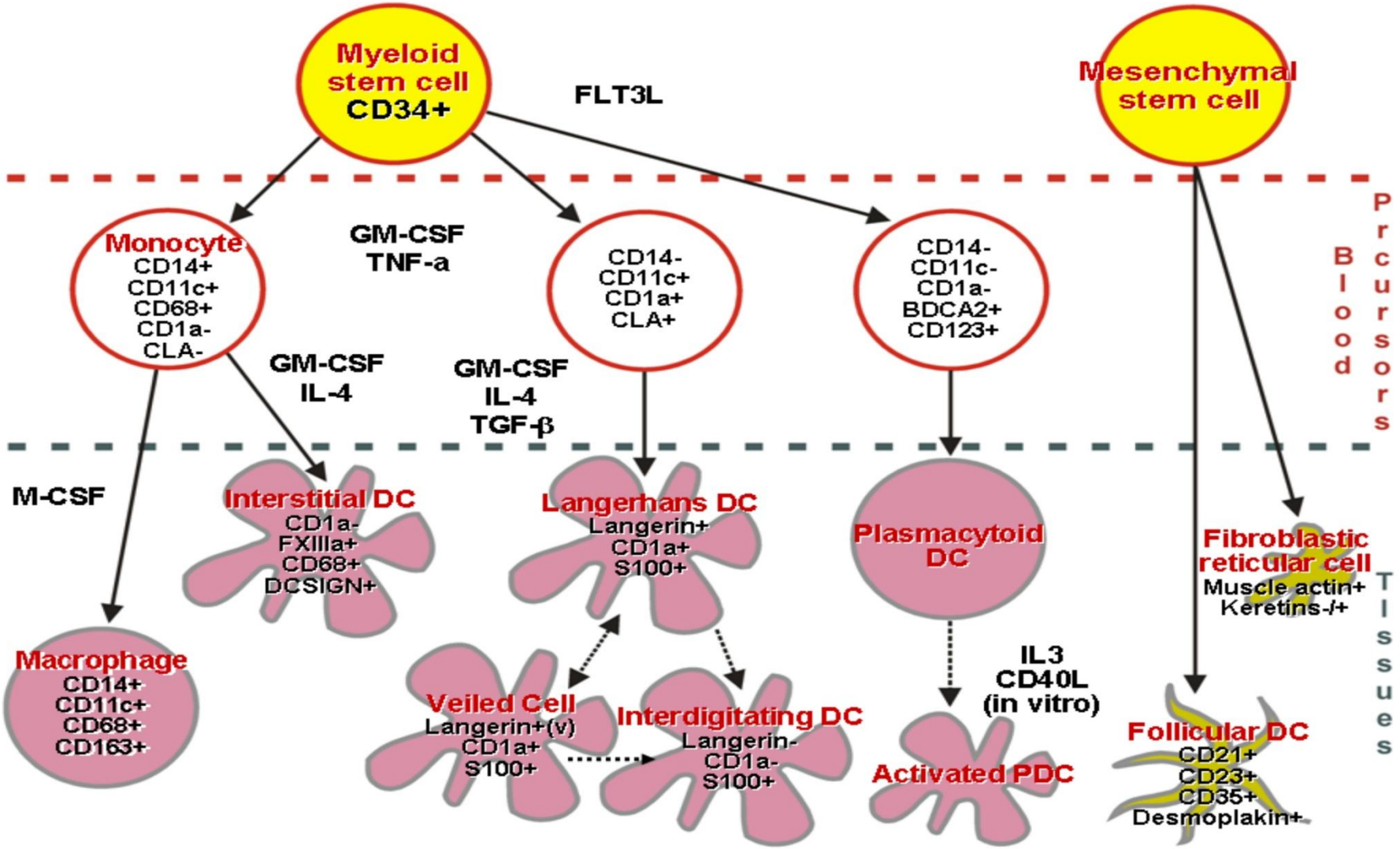
Rare causes of spindle cell tumour

- Soft tissue tumours
- Carcinoma's
- Melanoma's
- Haematopoietic system.
  - Mast cell disease
  - Histiocytic. JXG [spindle cell xanthogranuloma]
  - Follicular dendritic cells.

Follicular dendritic cell sarcoma

- Associated with Castleman's disease
- Can arise in lymph nodes. Intra. Abdo recognised site.
- Spindle cells. Often storiform or whorled pattern
- Sprinkling of lymphocytes.
- EMA, CD21, CD35 positive

Cell of origin for Histiocytic lesions From WHO classification



Take home points

- Never forget Carcinoma and Melanoma
- Very spindly- Fibrous, Neural and **Lipo.**
- Remember basic patterns; HPC, Giant cell MFH, Fibrosarcomatous, storiform.
- Remember to look for low grade areas at margins.

Take home points

- Plump spindle cells- add Rhabdo to list
- CD34 and p63 very helpful immuno.
- FISH, PCR techniques paramount
- Keep open mind, do broad immuno panel including hematopoietic; CD45, CD163, EMA,CD21 at least third line.

THE END

GOOD LUCK !