Updates on the Current Classification of Fatty Tumors of Soft Tissue

When is Molecular Testing Cost-effective and Appropriate?

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Atypical Lipomatous Tumor/Well-differentiated Liposarcoma

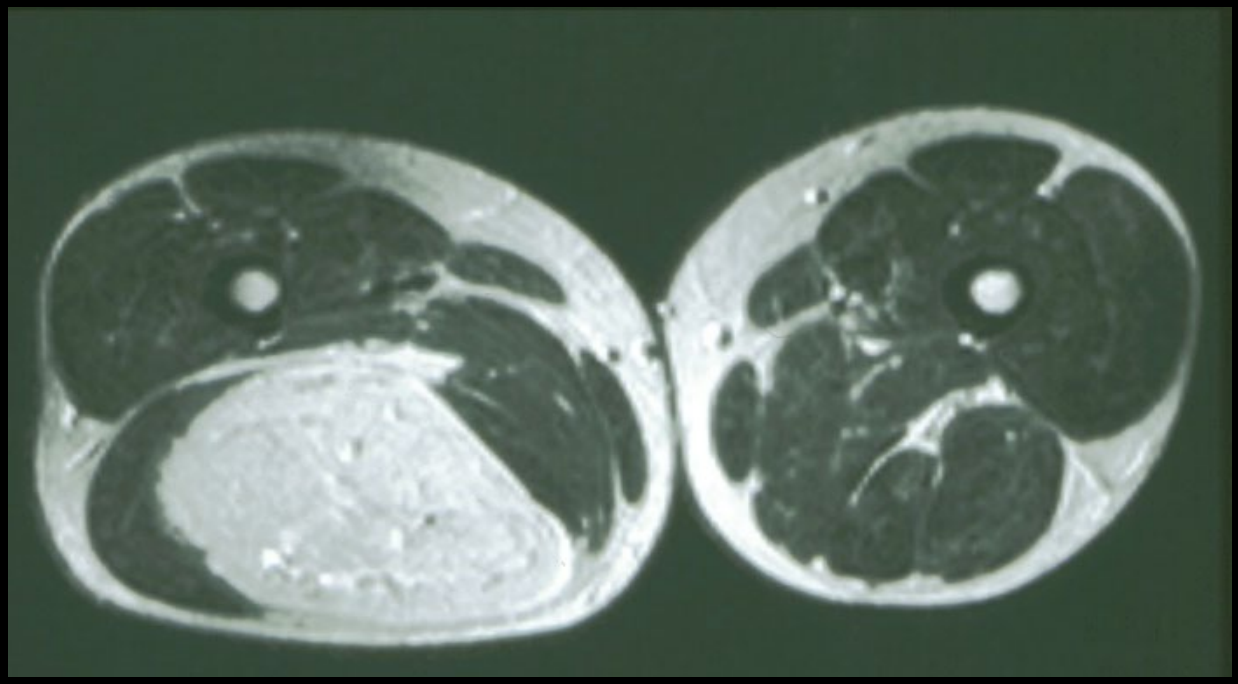
The term “well-differentiated liposarcoma” is synonymous with the designation “atypical lipoma” referring to a lesion that may locally recur but, in the absence of de-differentiation, will not metastasize.

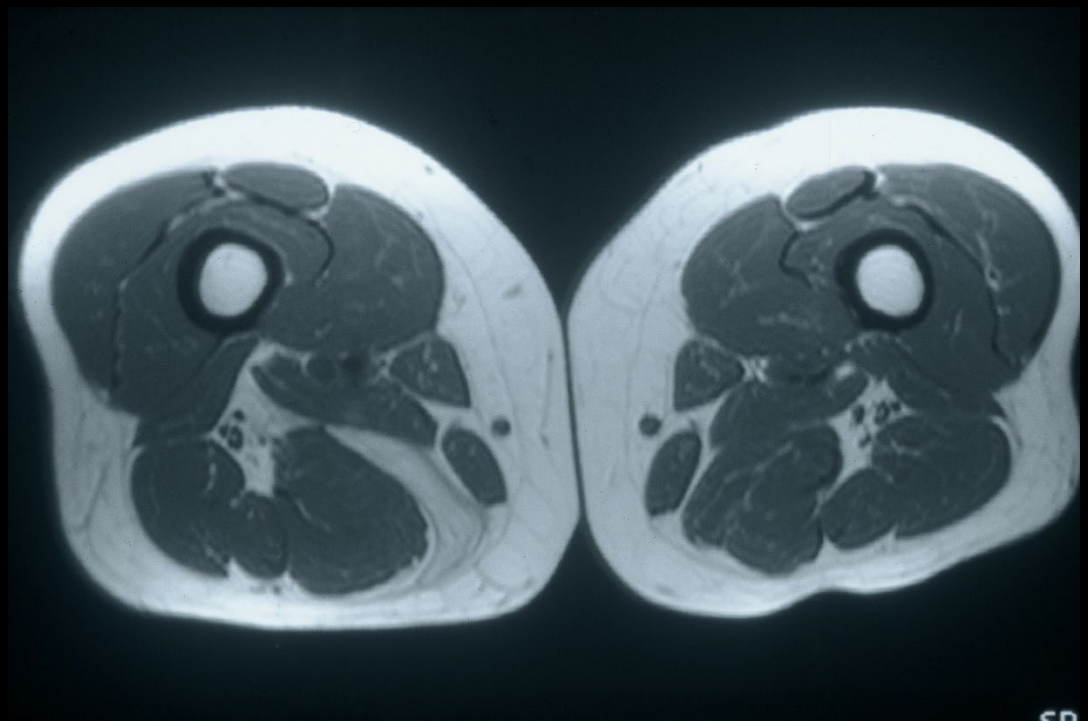
ALT/WDS

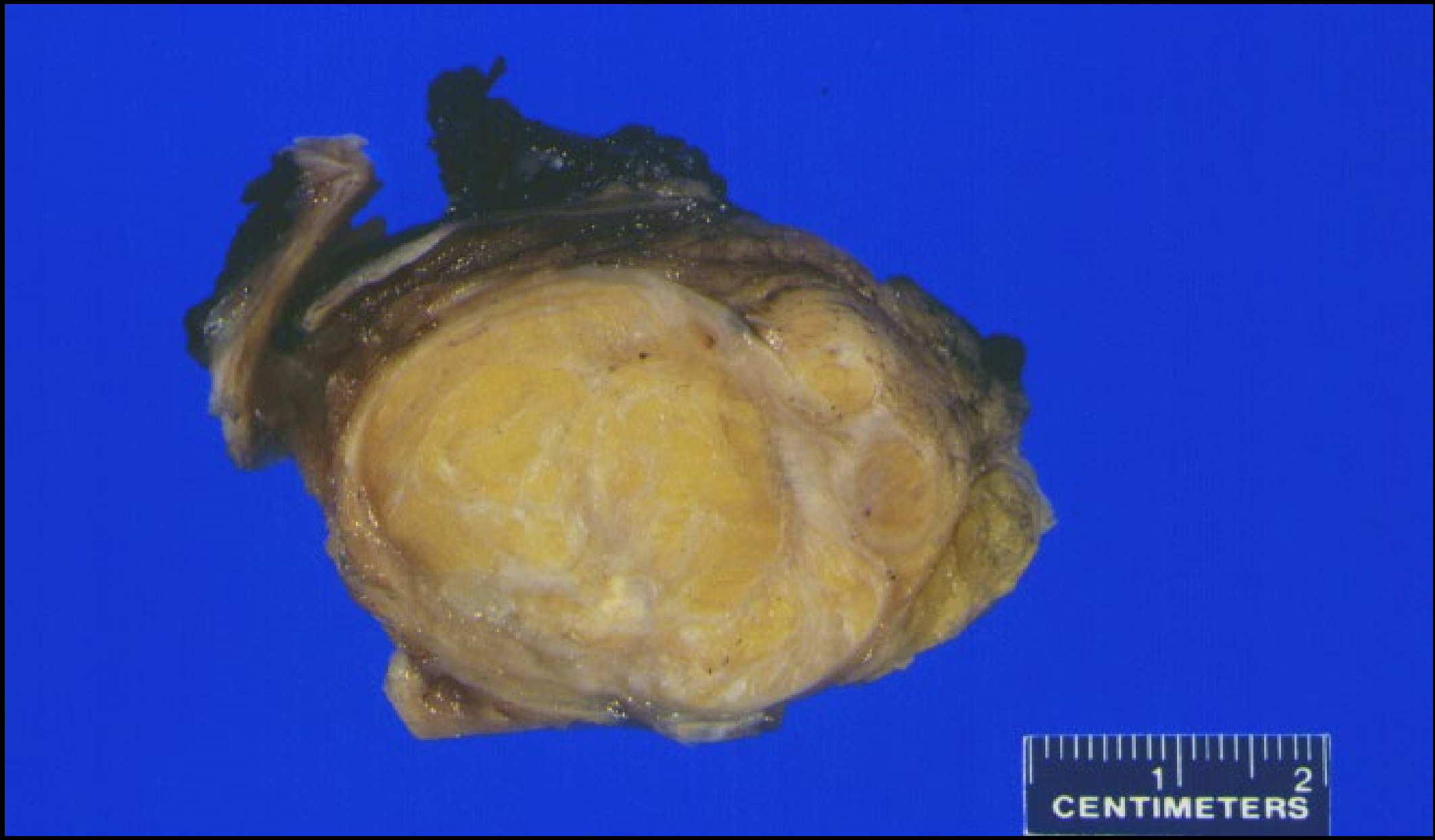
- Older adults
- Deep soft tissues, especially extremities and retroperitoneum
- Cytogenetic abnormalities, most commonly ring or giant marker chromosomes
- Potential for local recurrence and de-differentiation with mets

Imaging just isn't that good at identifying ALT vs. Lipoma.

MRI may suggest it if there are different areas of signal intensity.



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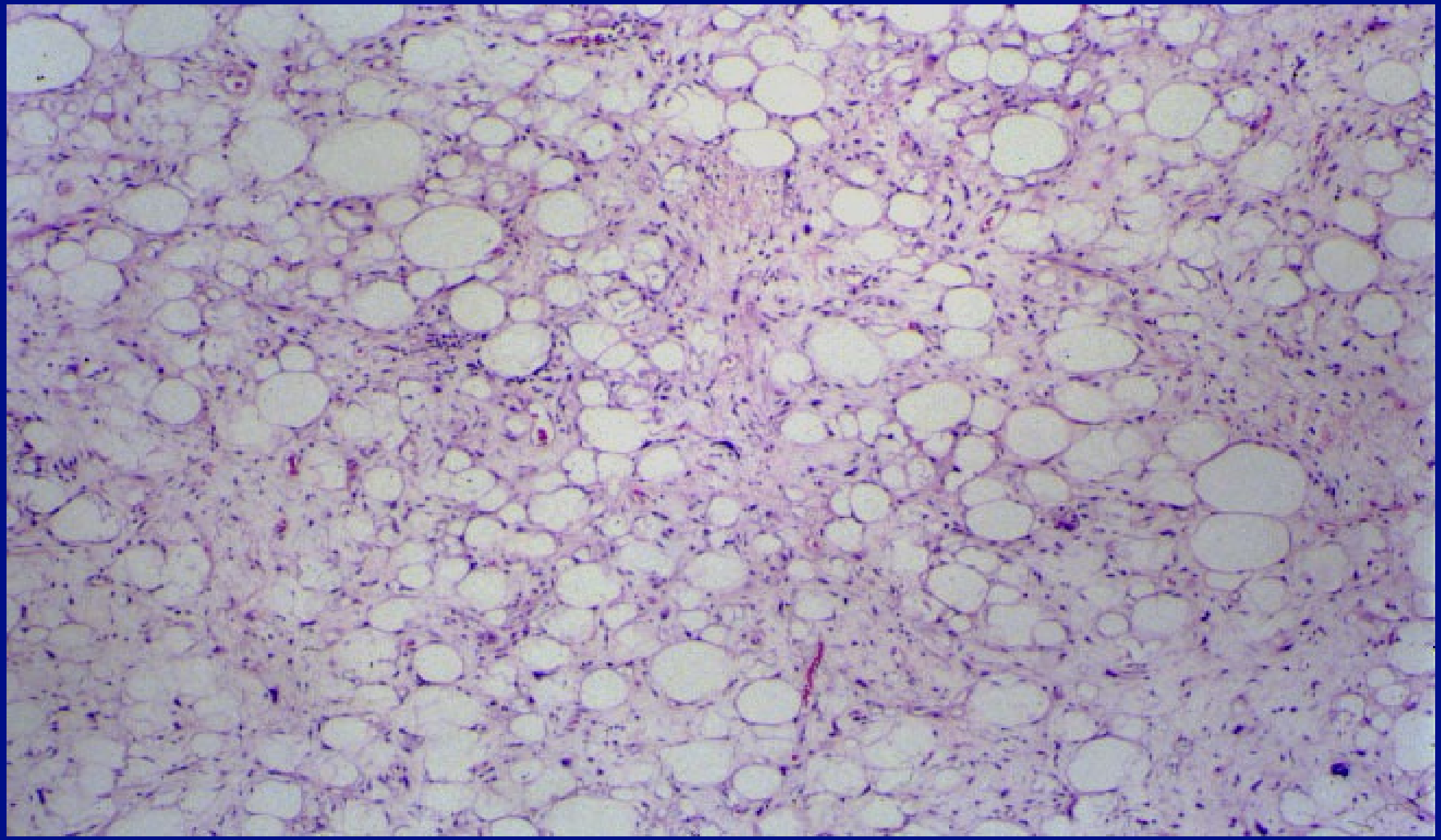
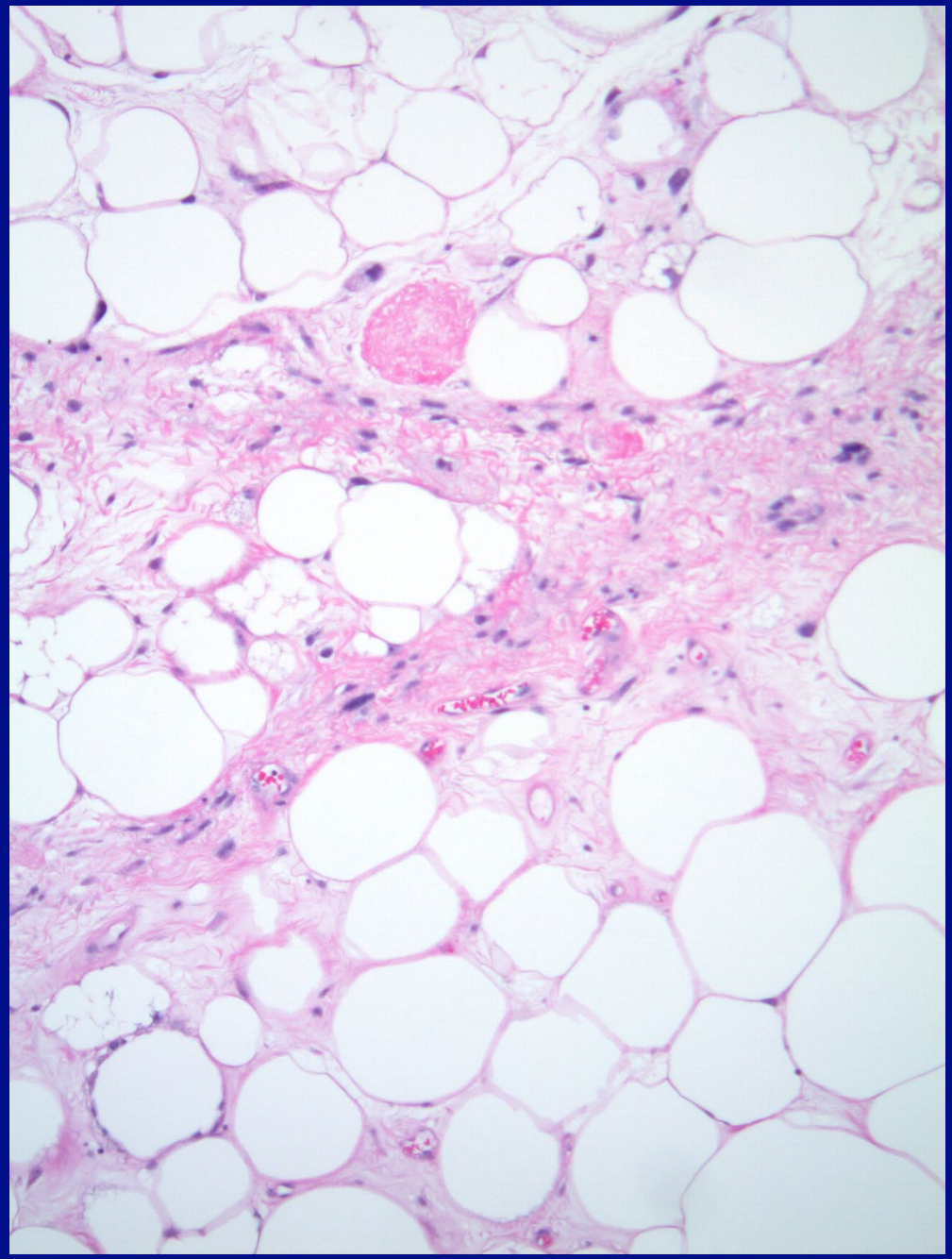
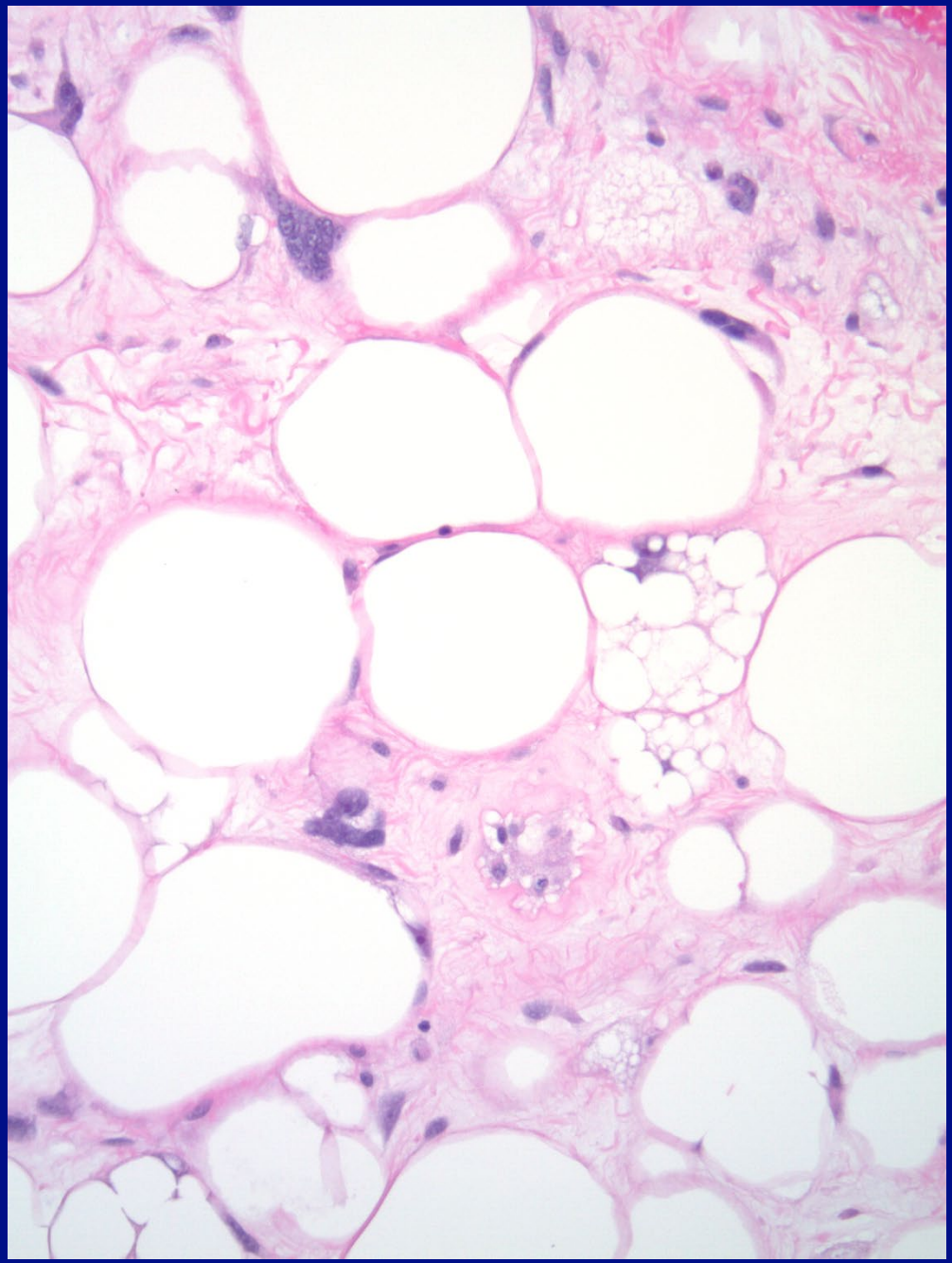


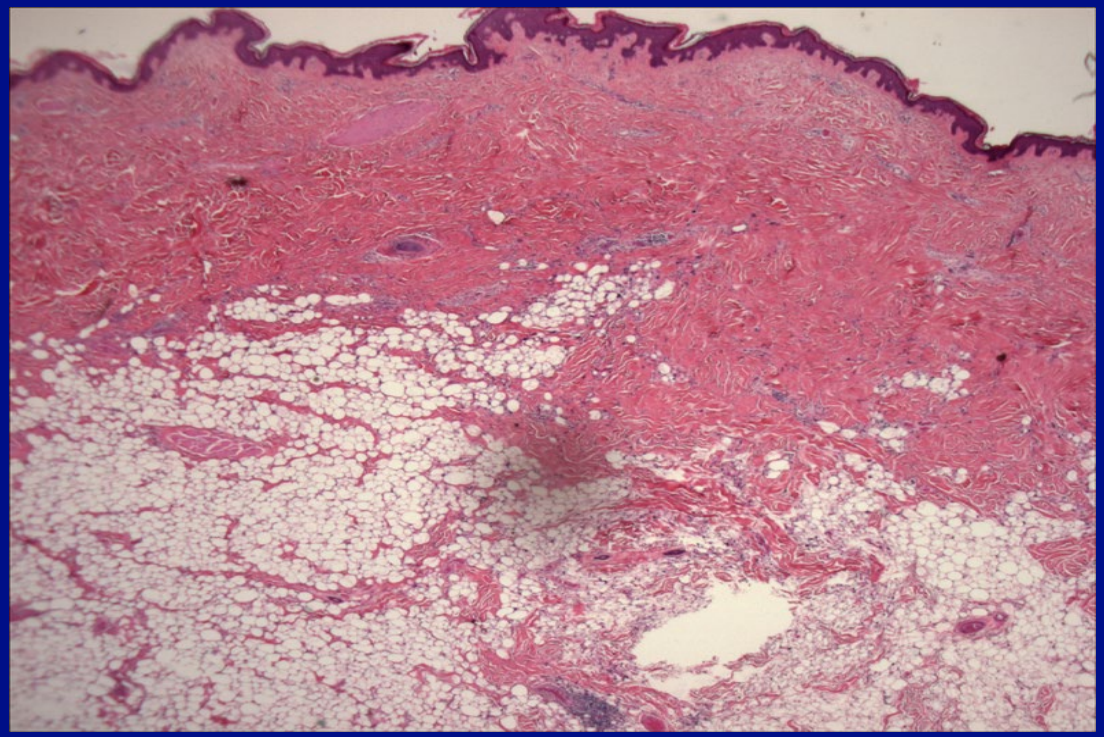
Classic Atypical Lipomatous Tumor/Well Differentiated "Lipoma-Like Liposarcoma

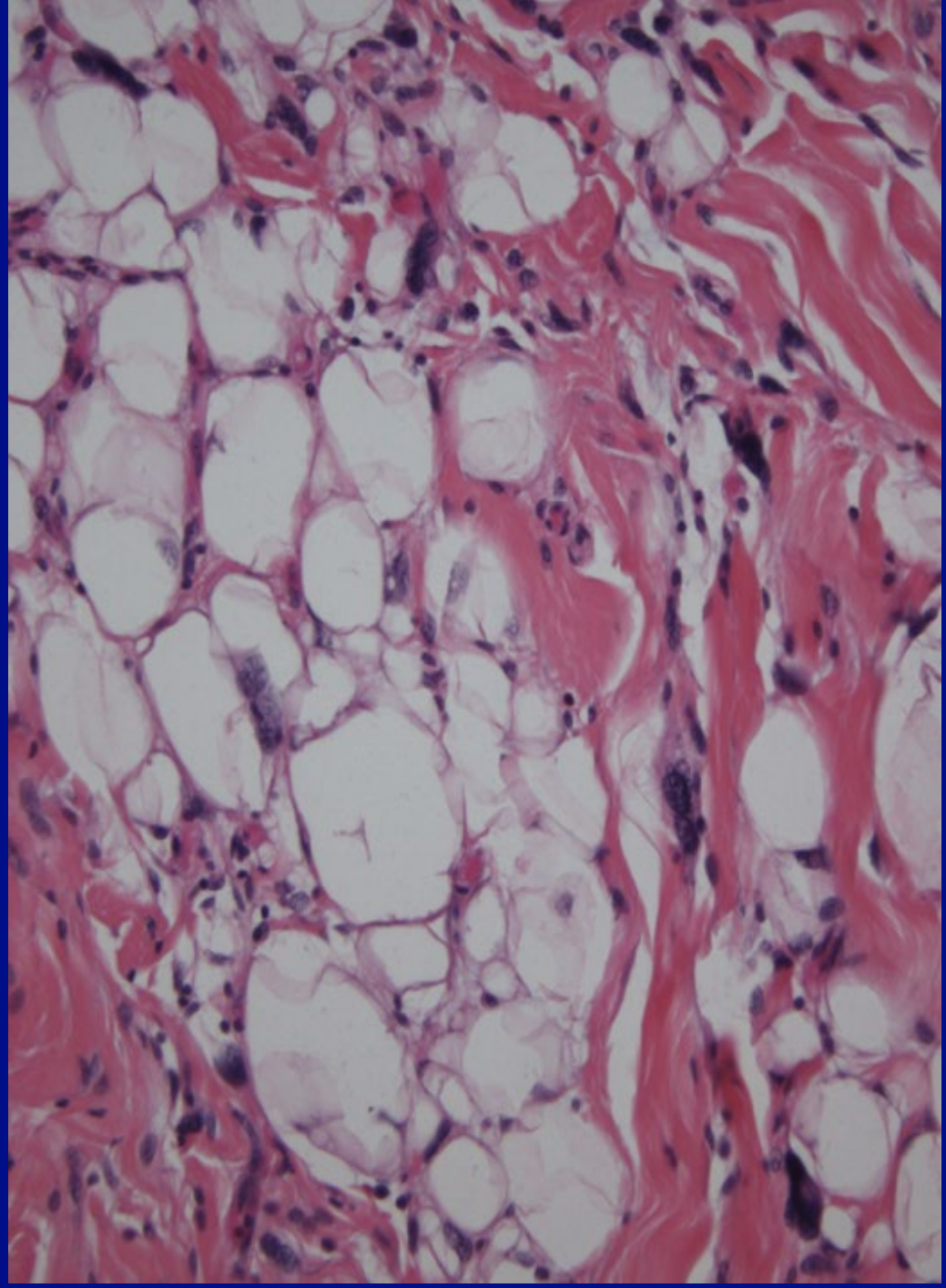




Well differentiated liposarcoma of the subcutis

Dedifferentiation has been documented but is very rare!



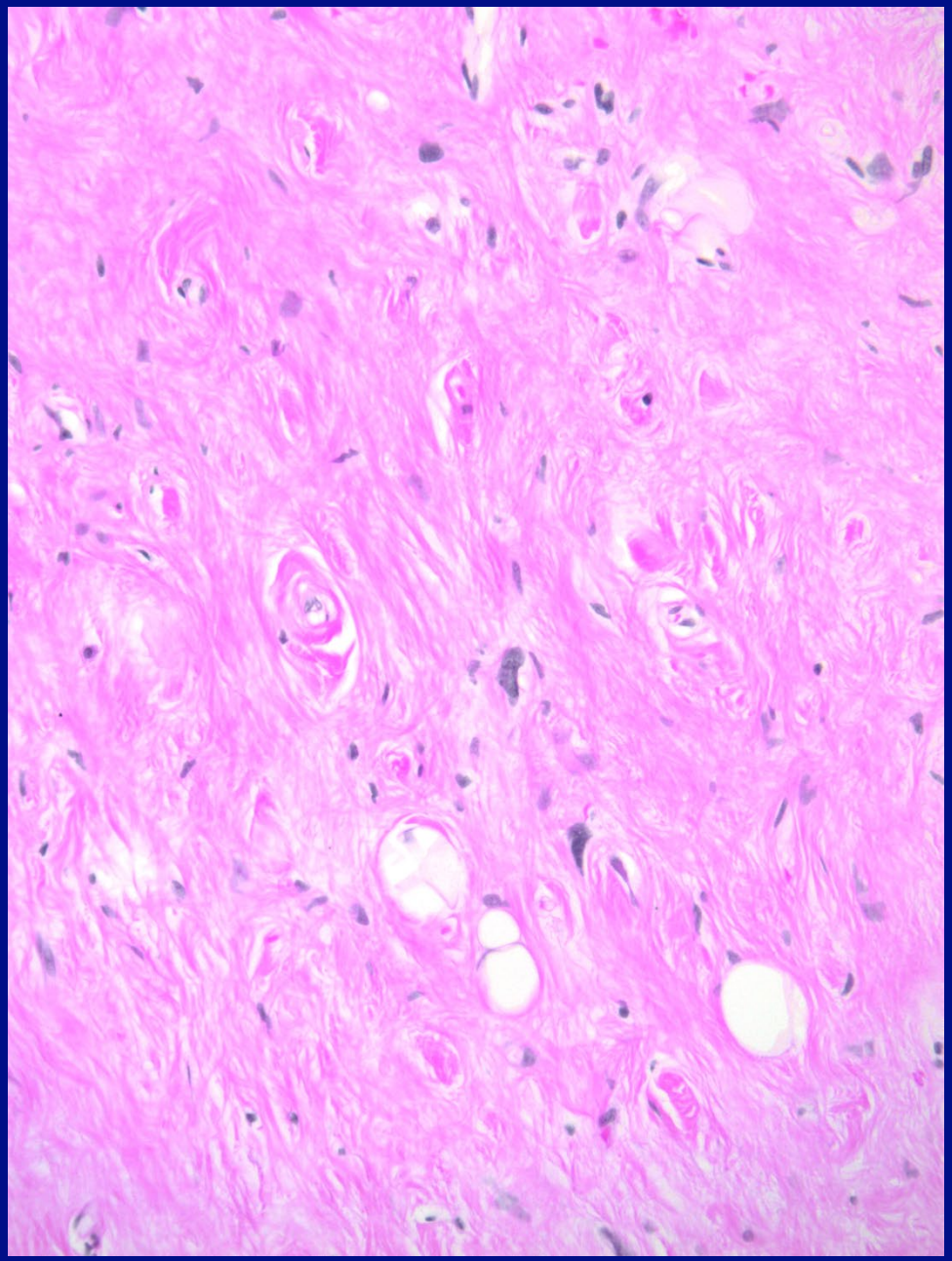


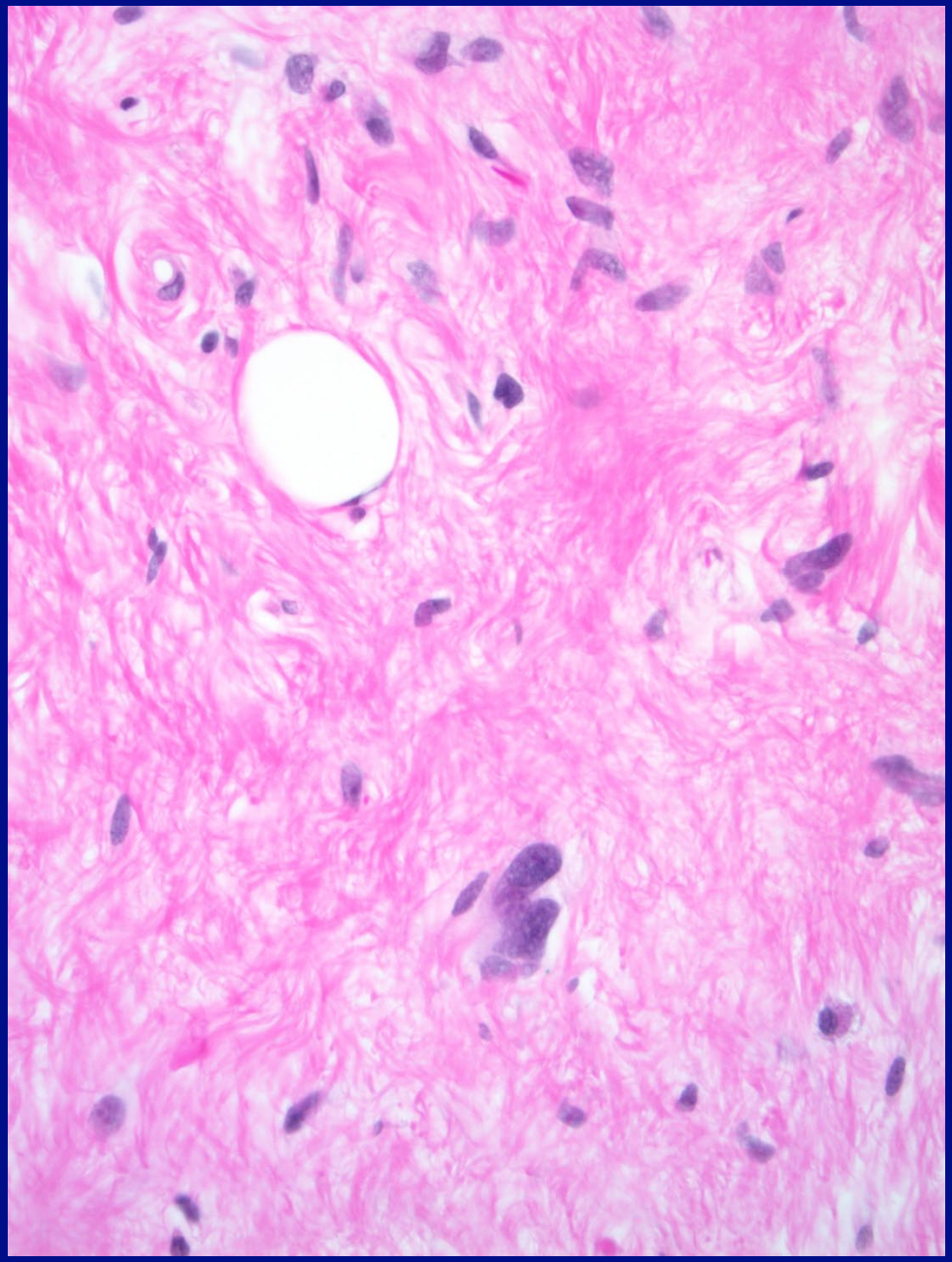
Classic Subtypes of Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma

- Lipoma-like
- Sclerosing
- Inflammatory

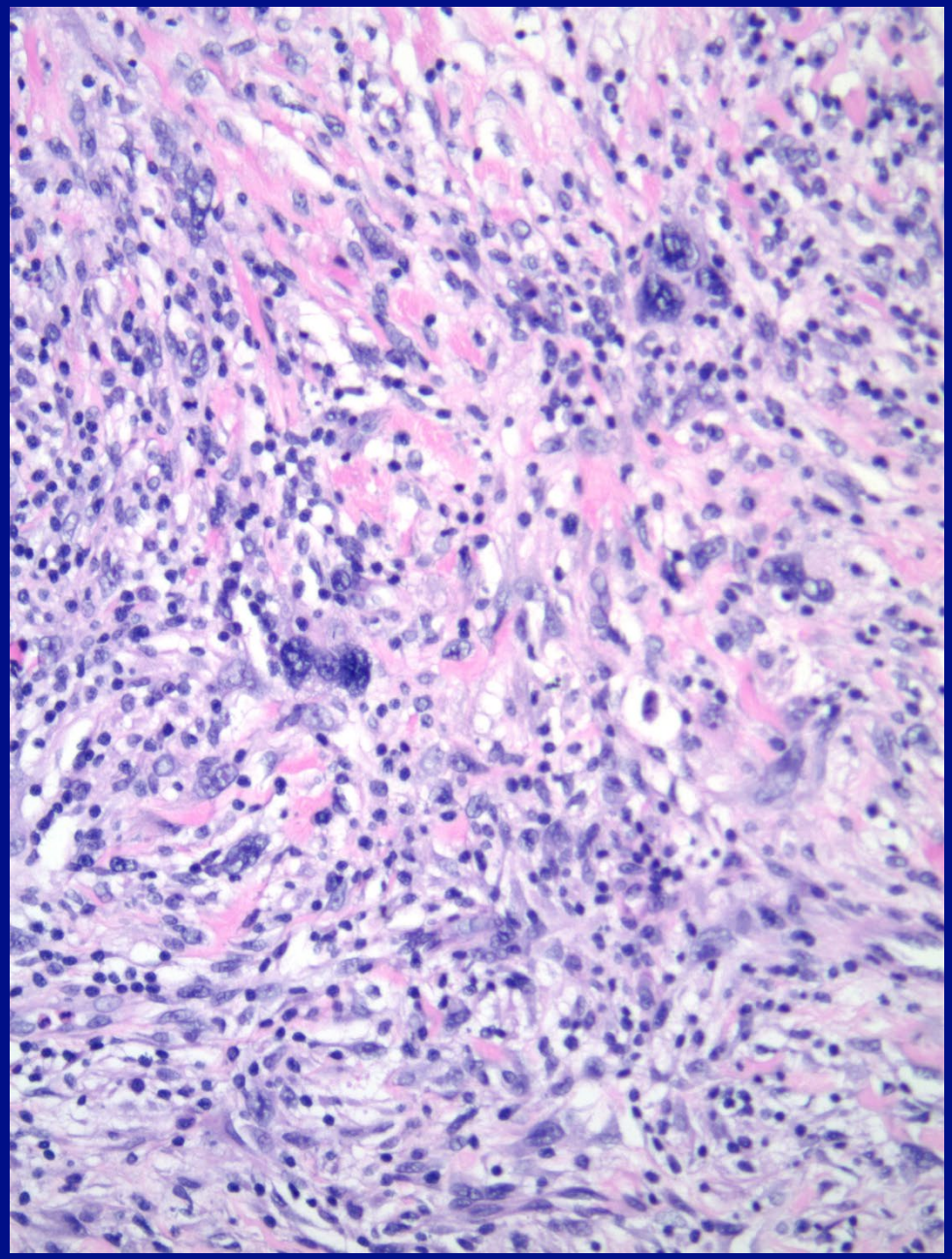
No prognostic relevance…only need to recognize as ALT

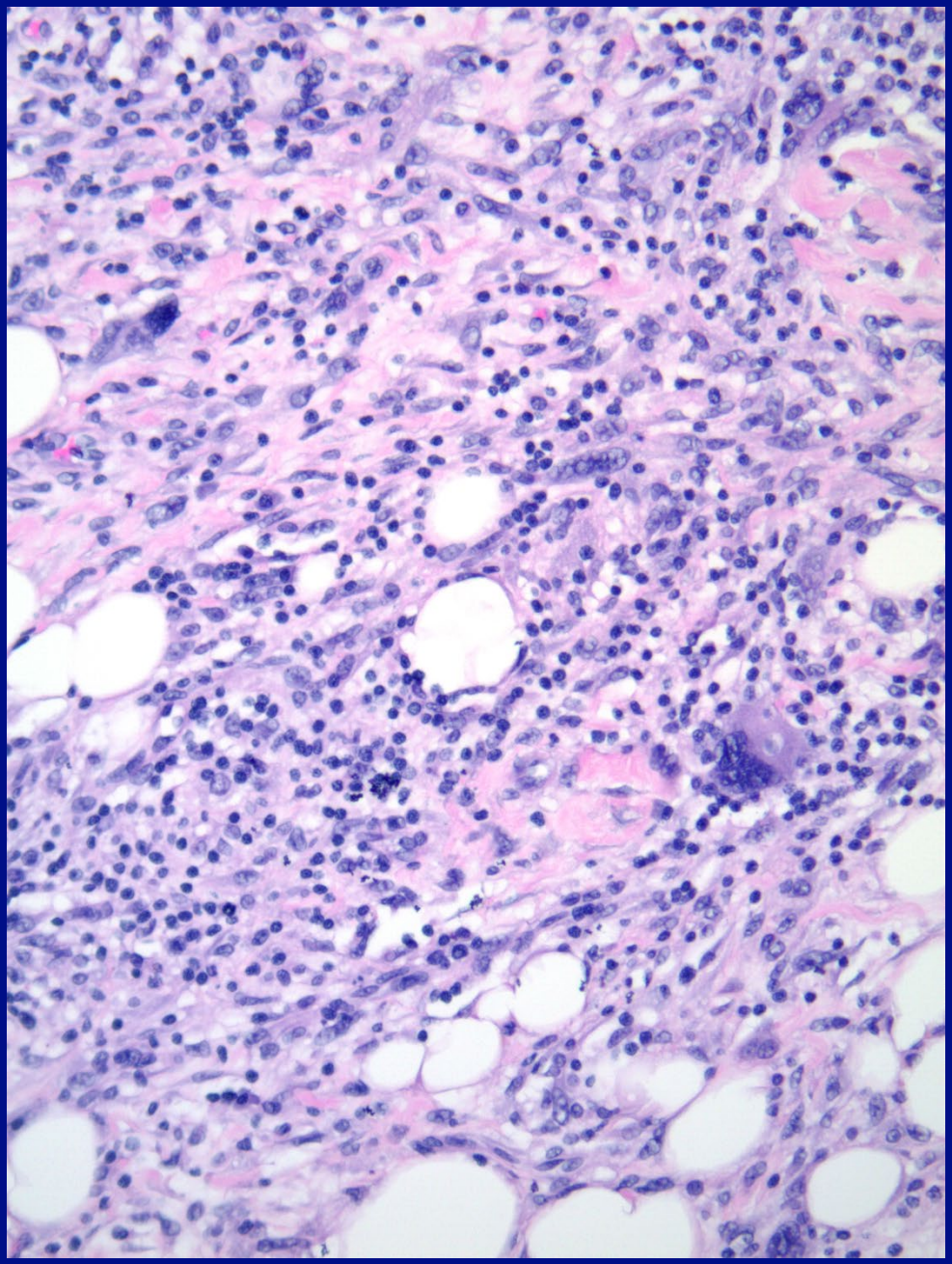
Well Differentiated “Sclerosing” Liposarcoma





Well Differentiated “Inflammatory” Liposarcoma

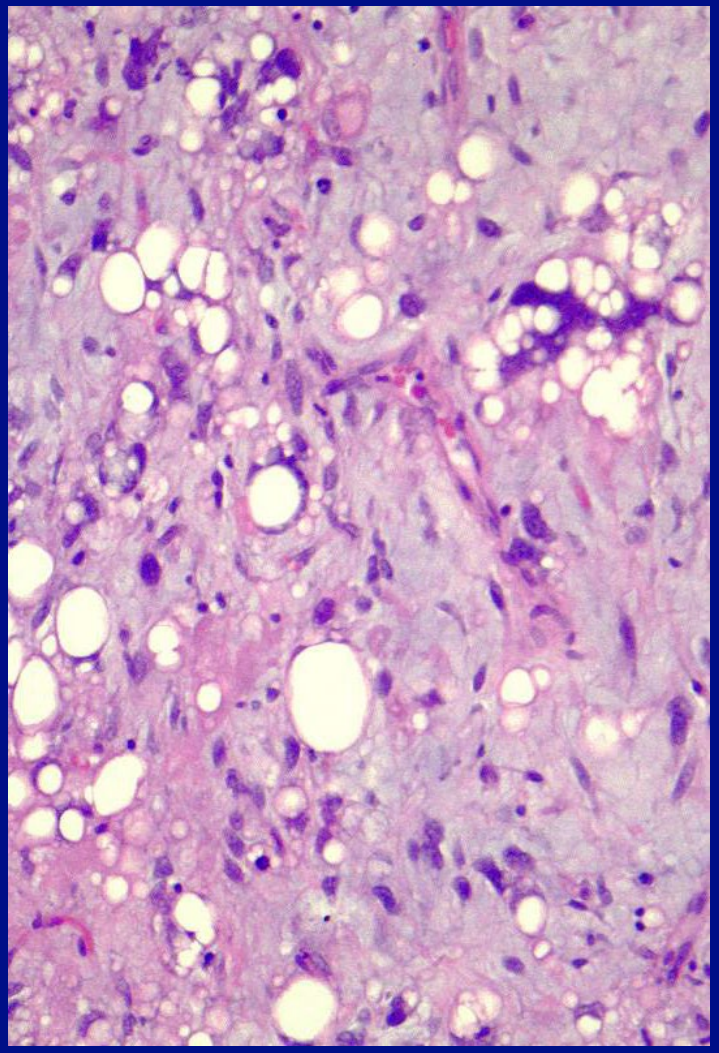


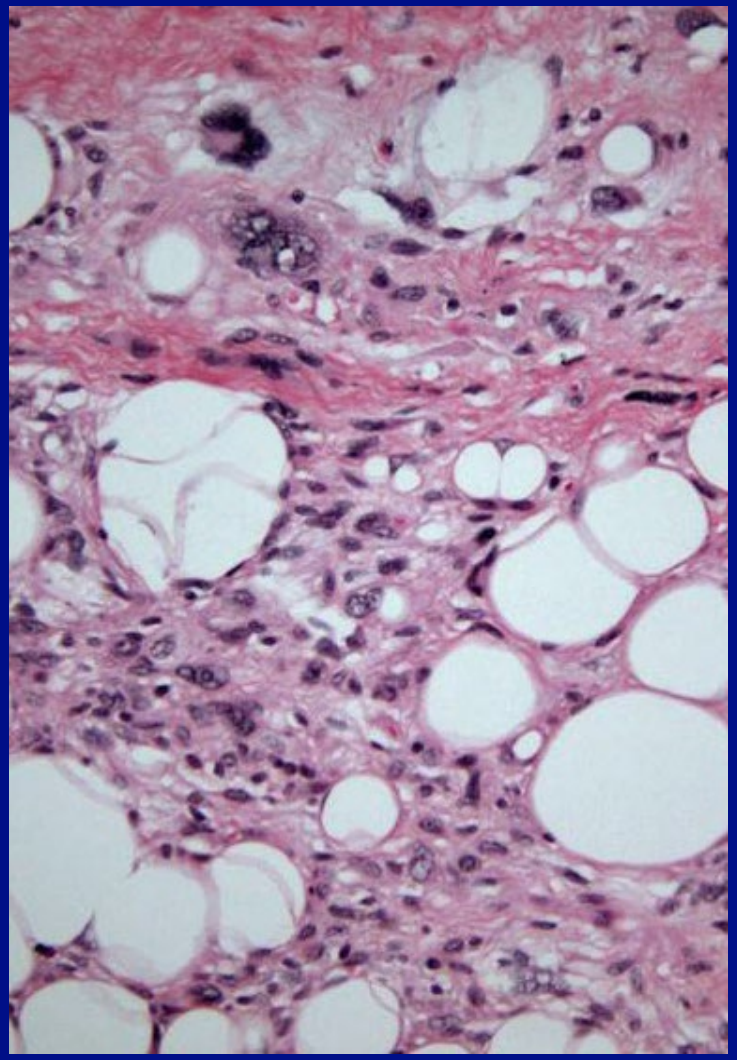


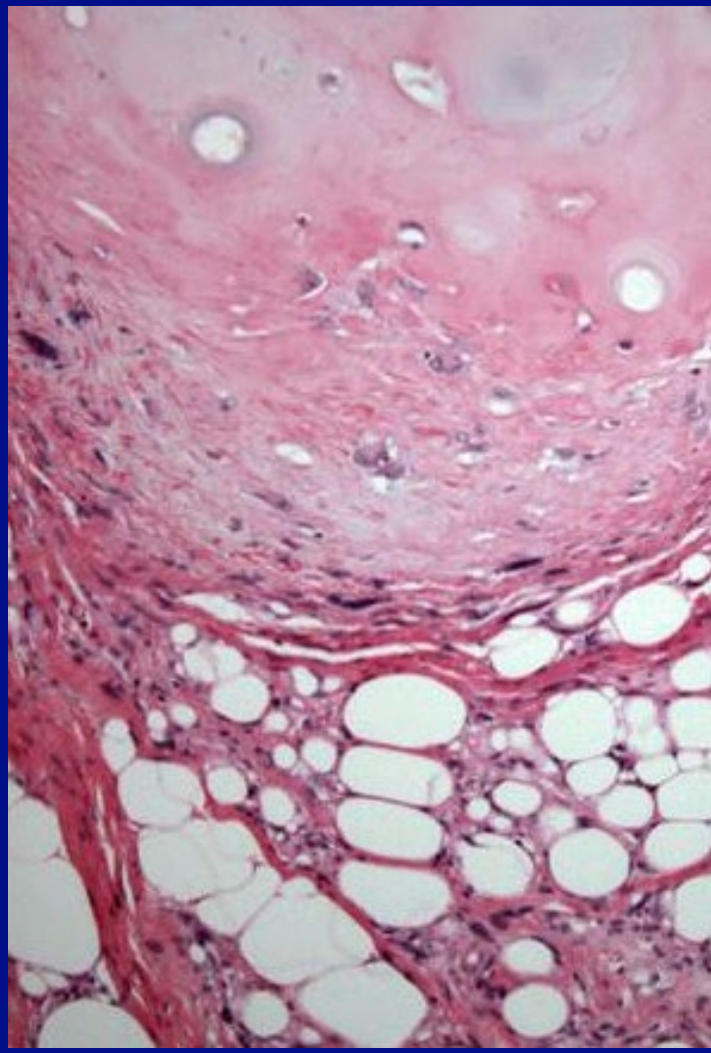
The Spectrum of Atypical Lipomatous Tumor

Myoid/myxofibrosarcoma-like, Cellular, Osseous/Cartilaginous Metaplasia, etc.

Evans HL. Atypical Lipomatous Tumor, its Variants, and its Combined Forms. A Study of 61 cases, with a minimum follow-up of 10 years. *Am J Surg Pathol* 2007;31:1-14.







Karyotypes in Lipomatous Tumors

ALT/WDL: Giant marker chromosomes (open arrow) and supernumerary ring chromosomes (black arrows), containing amplified DNA 12q13-15.

Lipoma: 12q, 6p, and 13q aberrations

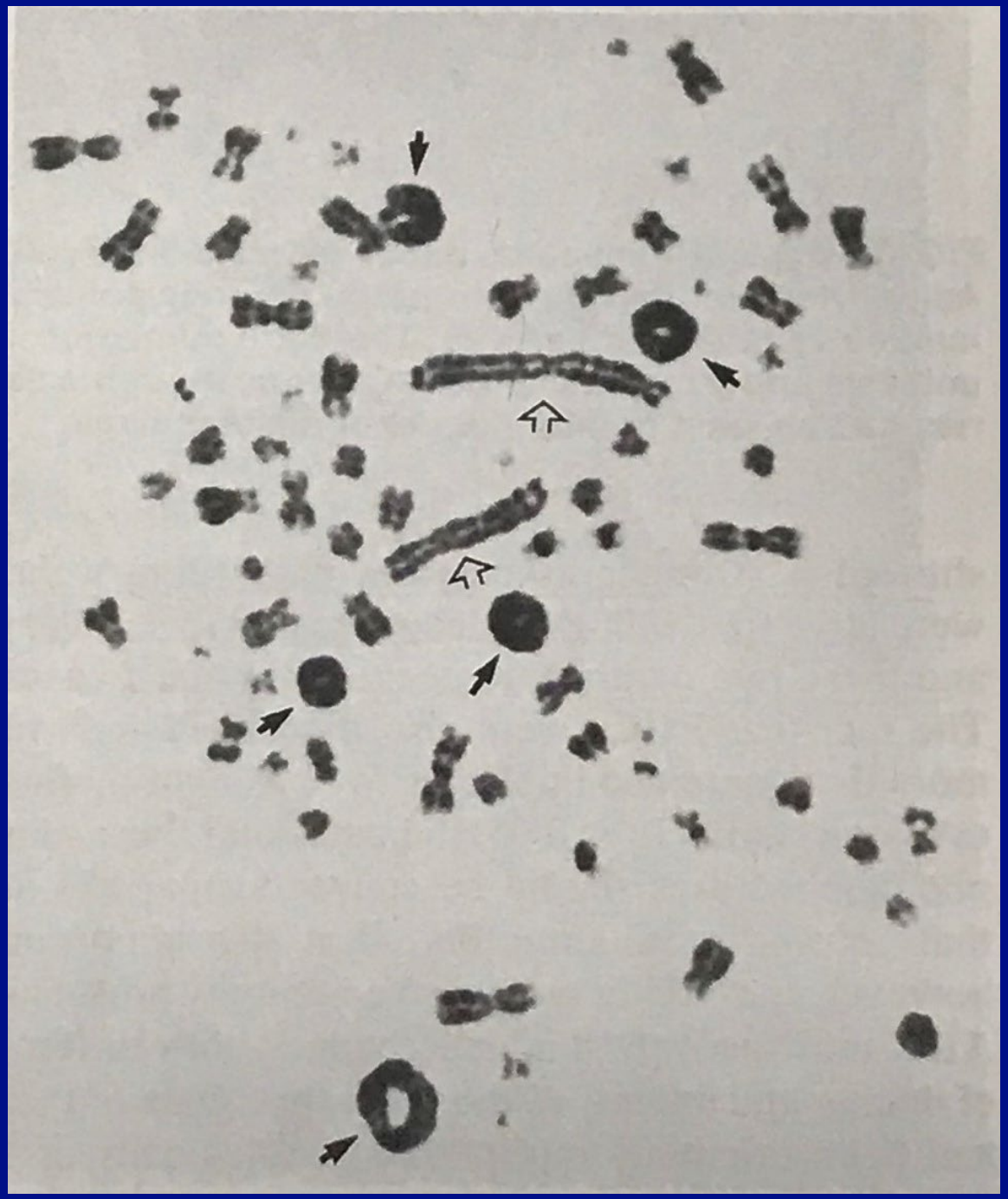
Spindle cell/pleomorphic lipoma: 16q aberrations

Lipoblastoma: 8q aberrations

Hibernoma: 11q aberrations

Rosai J, et al. Combined morphologic and karyotypic study of 59 atypical lipomatous tumors: Evaluation of their relationship and differential diagnosis with other adipose tissue tumors (a report of the CHAMP group). *Am J Surg Pathol* 1996;20:1182-9. Supernumeray ring or giant marker chromosomes in 63% cases.

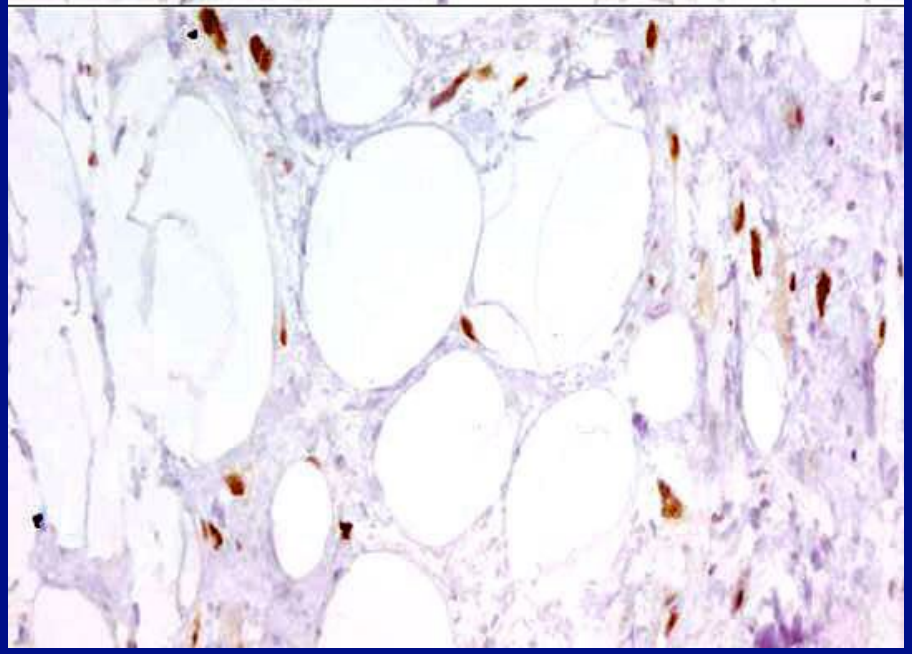
Fletcher CD, et al. Correlation between clinicopathologic features and karyotype in lipomatous tumors. A report of 178 cases from the Chromosomes and Morphology (CHAMP) Collaborative Study Group. *Am J Pathol* 1996;148:623-30.

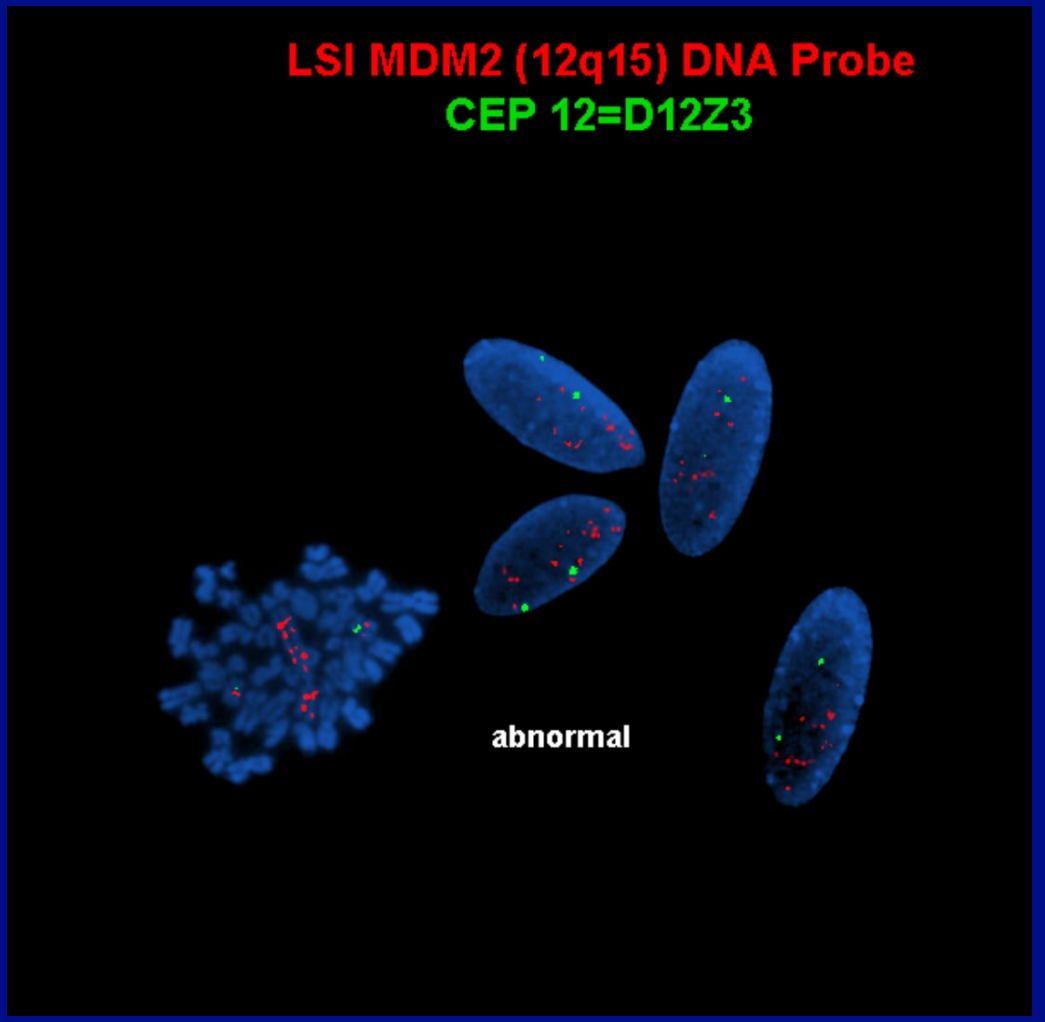


ALT/WDS *MDM2* via IHC and FISH

1) IHC not as sensitive as FISH

2) IHC is best done on more cellular tumors



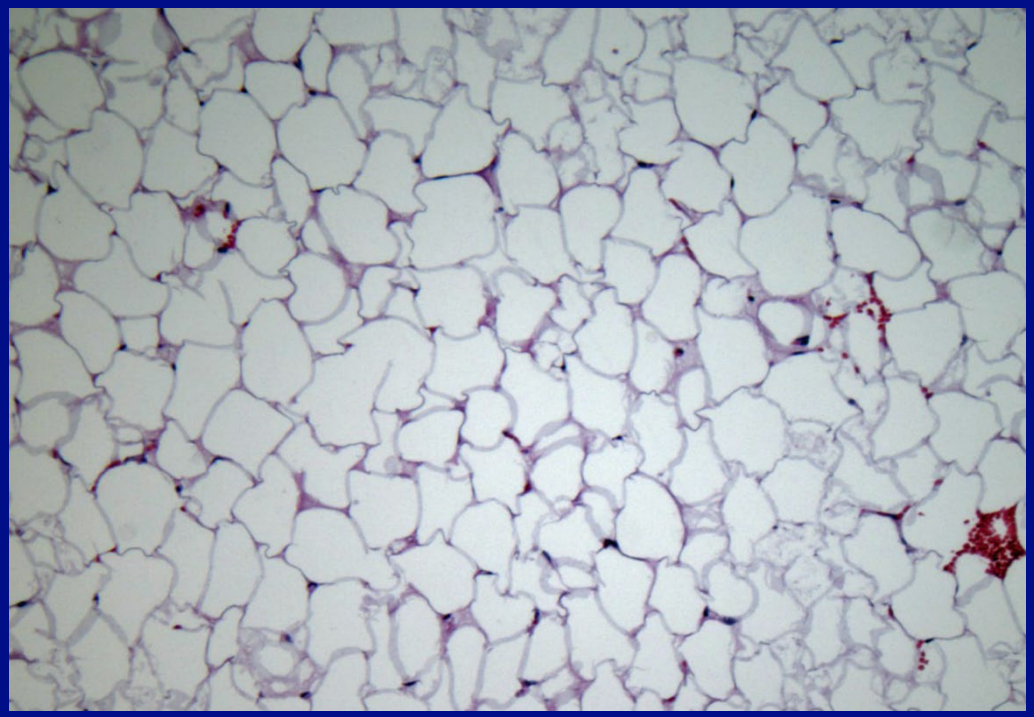


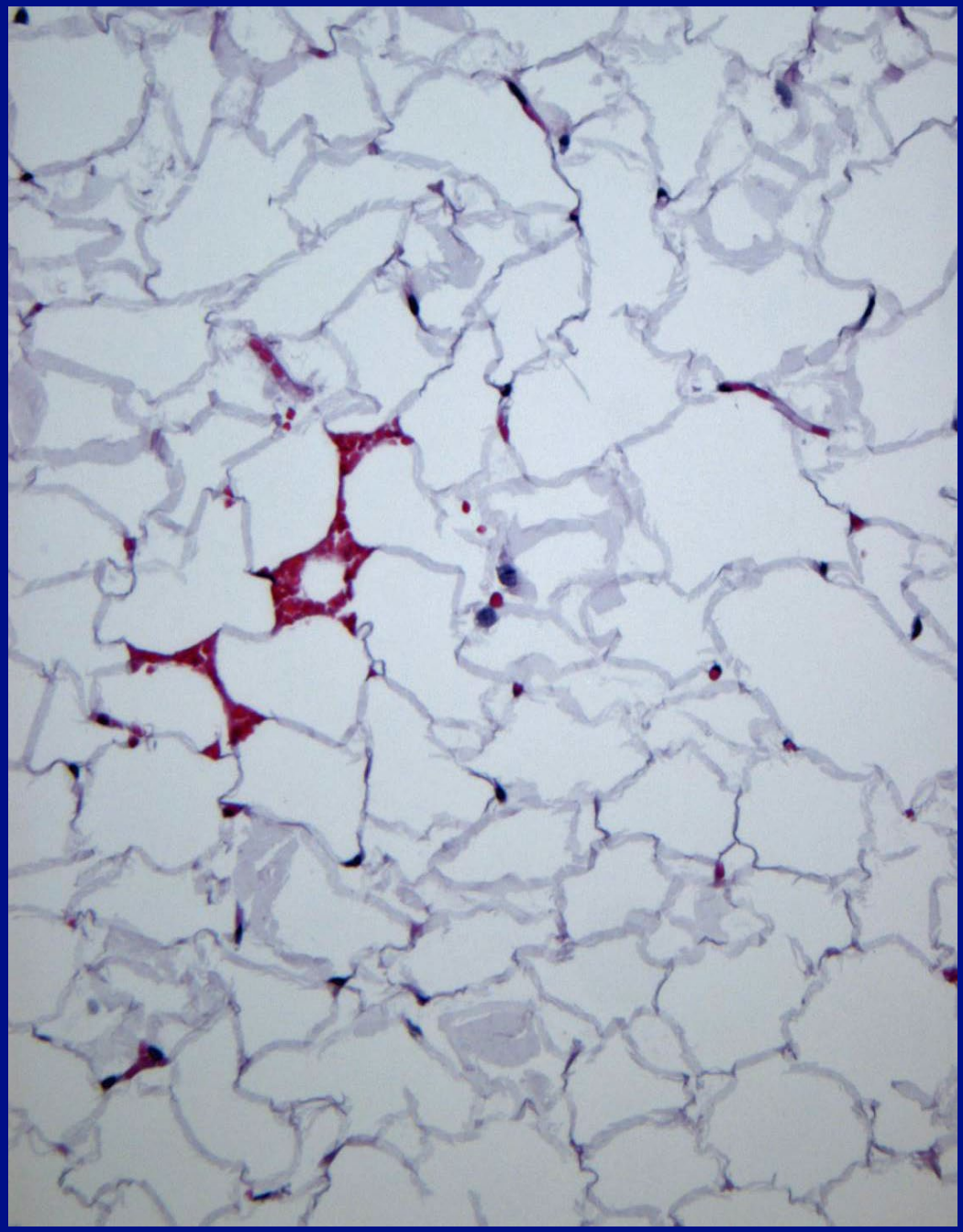
FISH Figures courtesy of Dr. John Reith and Dr. Julia Bridge

Old thinking: All mature fatty tumors of the retroperitoneum should be considered well differentiated liposarcomas!

Ida CM, et al. Primary retroperitoneal lipoma: a soft tissue heresy? Am J Surg Pathol 2008; 32:951-4.
HMGA2 rearrangement, neg MDM2 and CDK4 FISH, t(3;12)

Macareno RS, et al. Retroperitoneal lipomatous tumors without cytologic atypia: are they lipomas? Am J Surg Pathol 2009;33:1470-6.
19 tumors, no atypia. Rearrangements of 12q15 in 4 of 7 cases, No ring or giant marker chromosomes, neg FISH MDM2/CDK4, pos HMGA2 in 8 of 19 cases. F/U 10 cases, median 6 mo. No recurrences or mets





Potential Pitfalls

- Extensive fat necrosis. ?Dysplastic lipoma.
- Plemorphic spindle cell lipomas, especially in unusual locations.
- Lipoblastomas in adults.
- Massive localized lymphedema of the morbidly obese.
- Small biopsy specimens.

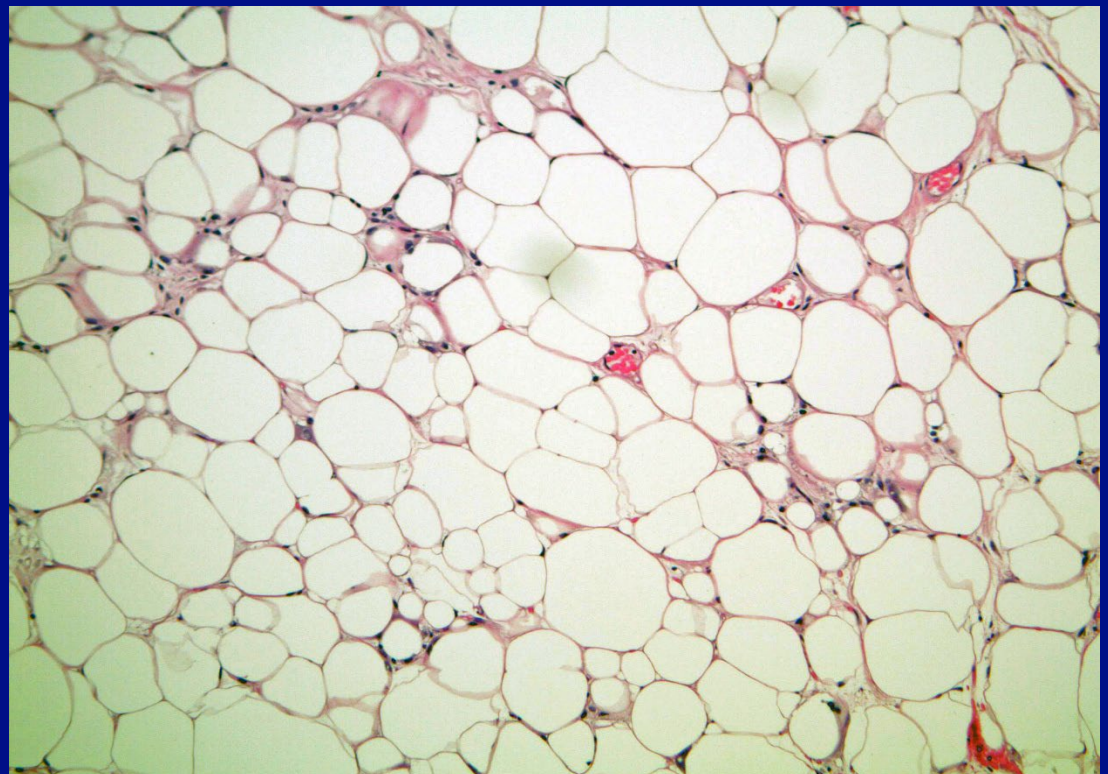
When do you need molecular studies!

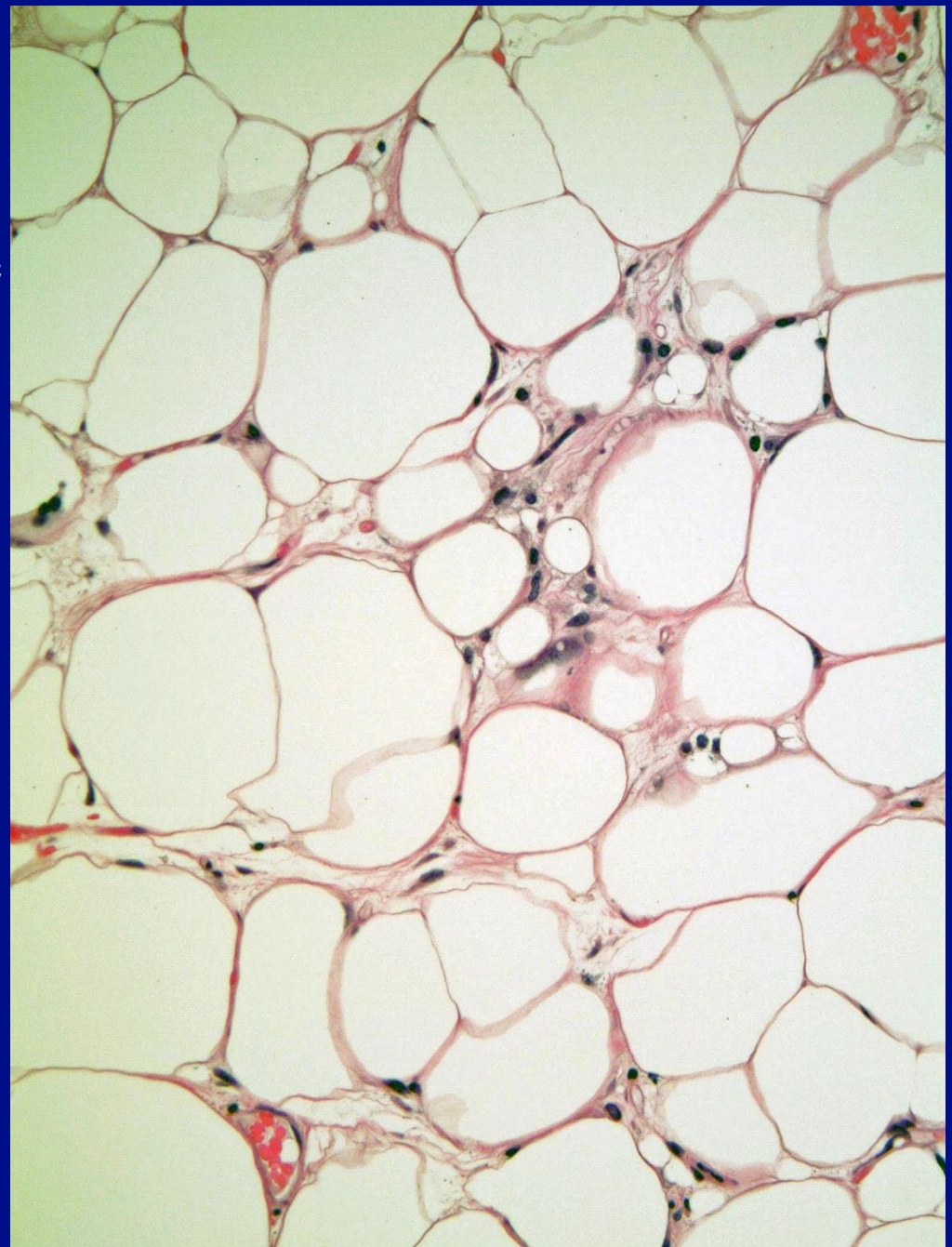
FAT NECROSIS

Can be microscopic or macroscopic. Causes variation in adipocyte size and shape and increased non-lipogenic tissue, worrisome at low power for atypical lipomatous tumor.

If accompanied by mild atypia, think about “Dysplastic Lipoma”, p53 overexpression RB1 gene abnormalities, neg MDM2, M>F, subcutis of shoulders, upper back, and neck. 2/47 locally recurred.

Michal M, et al. Am J Surg Pathol 2018;42:1530-40.

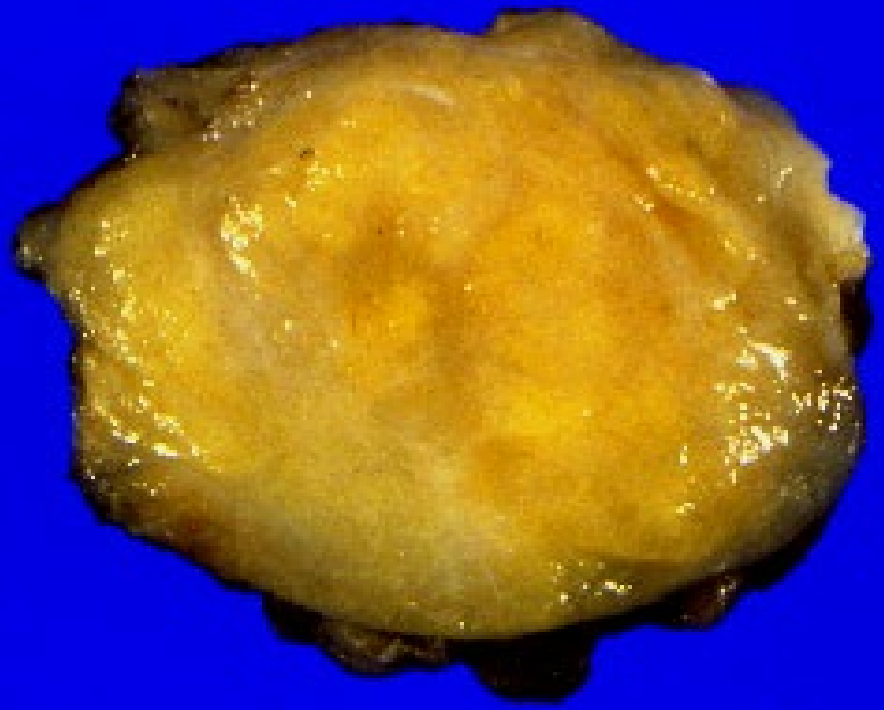




Spindle Cell and Pleomorphic Lipoma

- Elderly, males>>females
- Head, neck, upper back & shoulders, subcutis (20% unusual locations, especially in females)
- Spindled cells and pleomorphic floret cells +CD34 with RB1 nuclear loss
- Chromosomal abnormalities, most commonly loss of 16q and 13q
- Consistent nonallelic deletion of RB1, 13q14.
- Relationship with cellular angiofibroma and mammary-type myofibroblastoma?

Chen BJ, et al. Loss of retinoblastoma protein expression in spindle cel/pleomorphic lipomas and cytogenetically related tumors: an immunohistochemical study with diagnostic implications. Am J Surg Pathol 2012;36:1119-1128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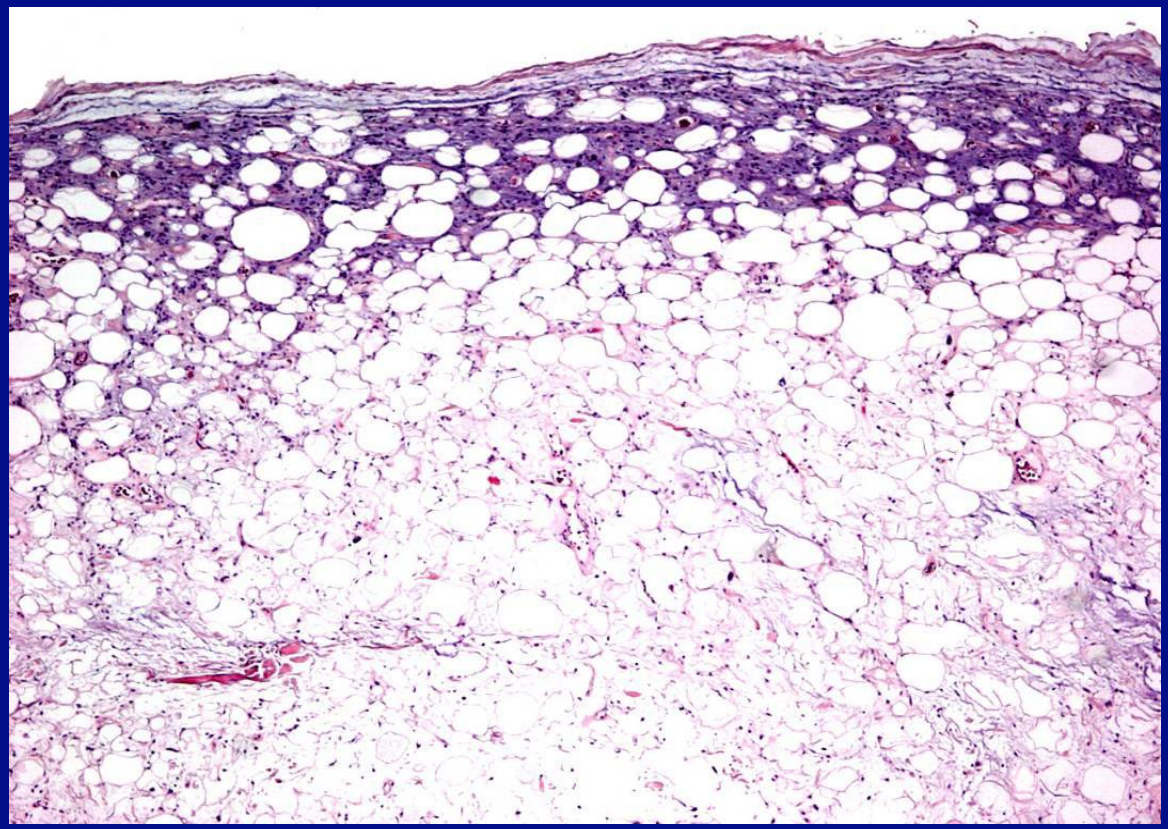
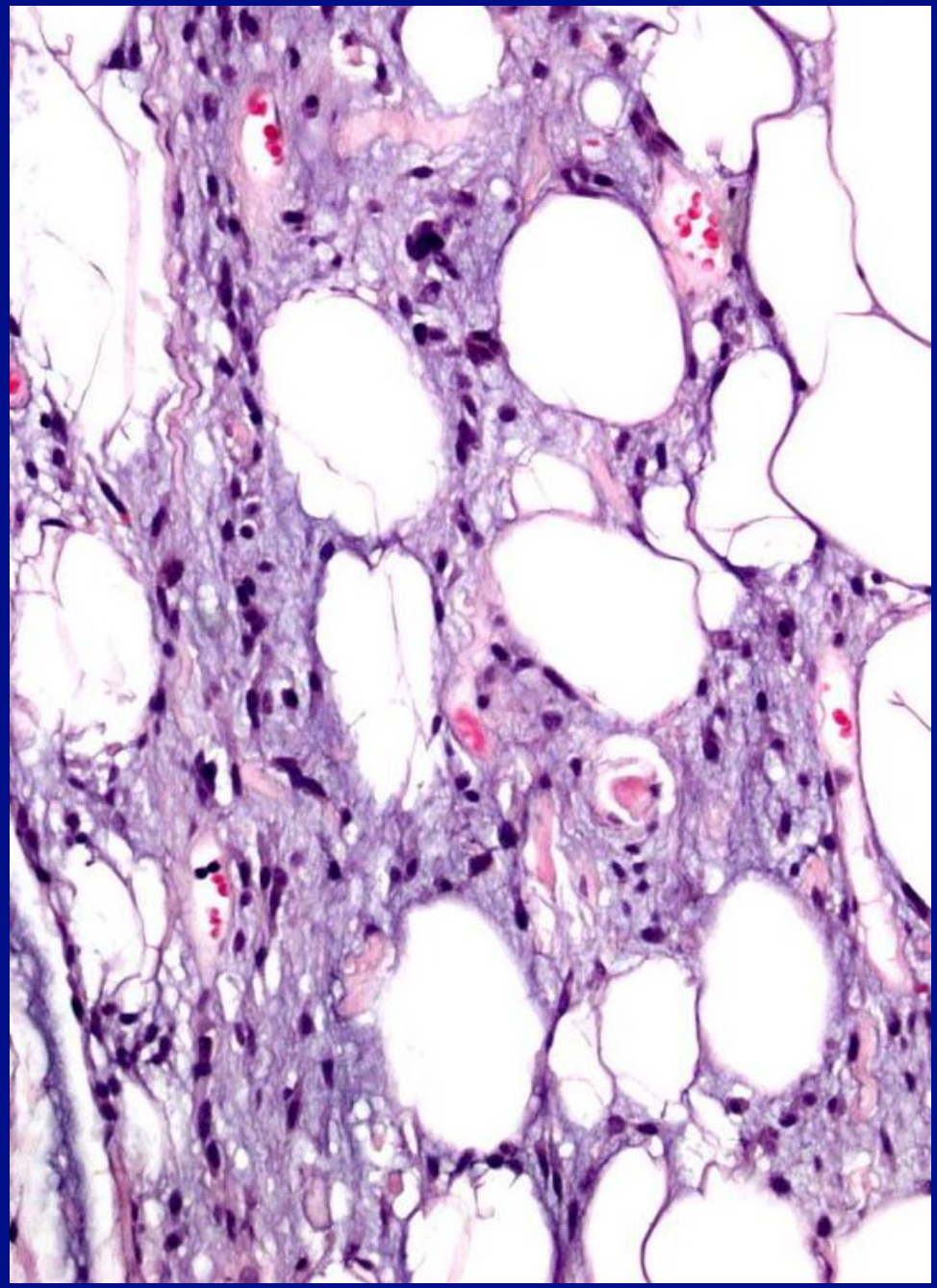
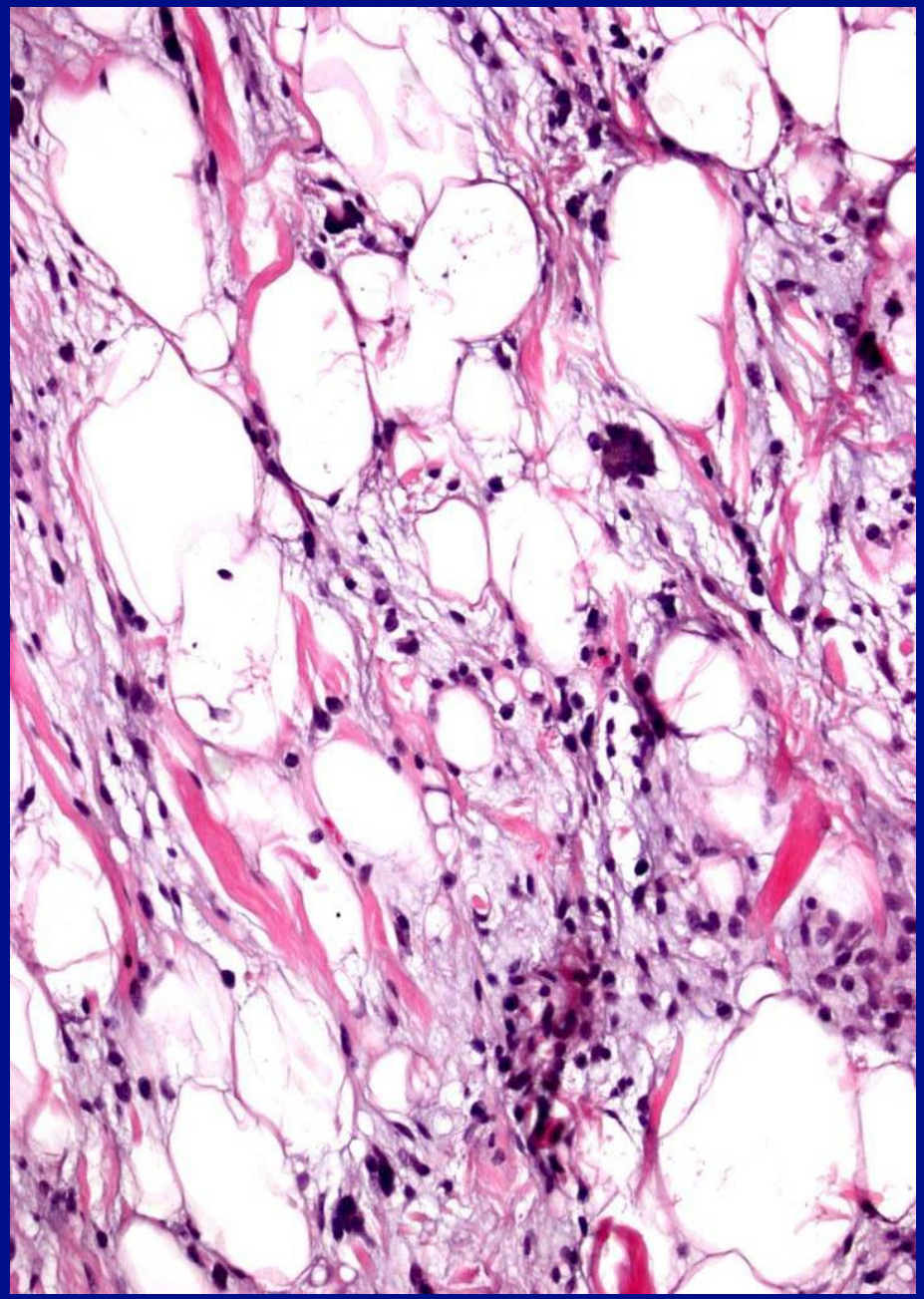
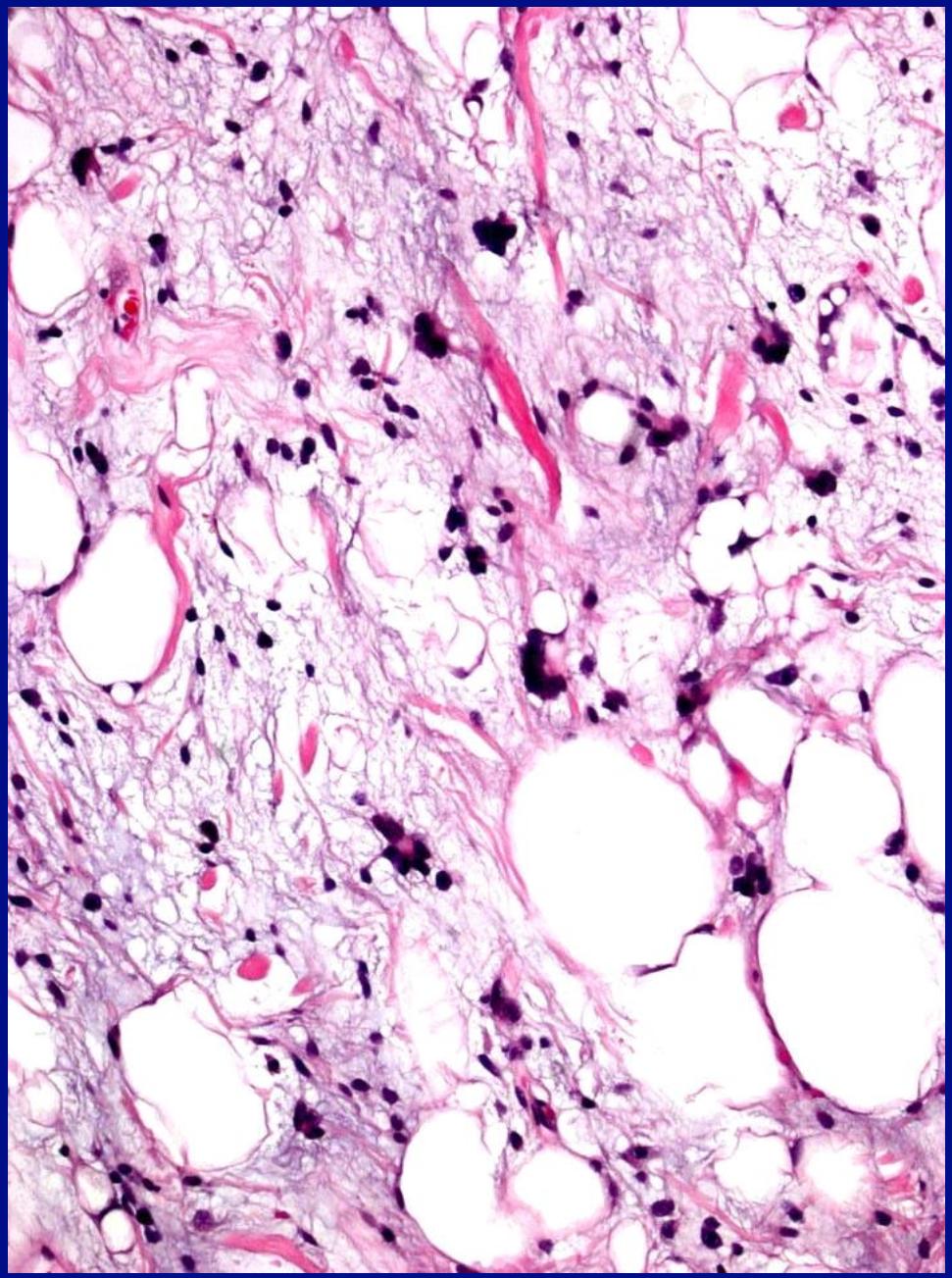
Classic Spindle Cell Lipoma



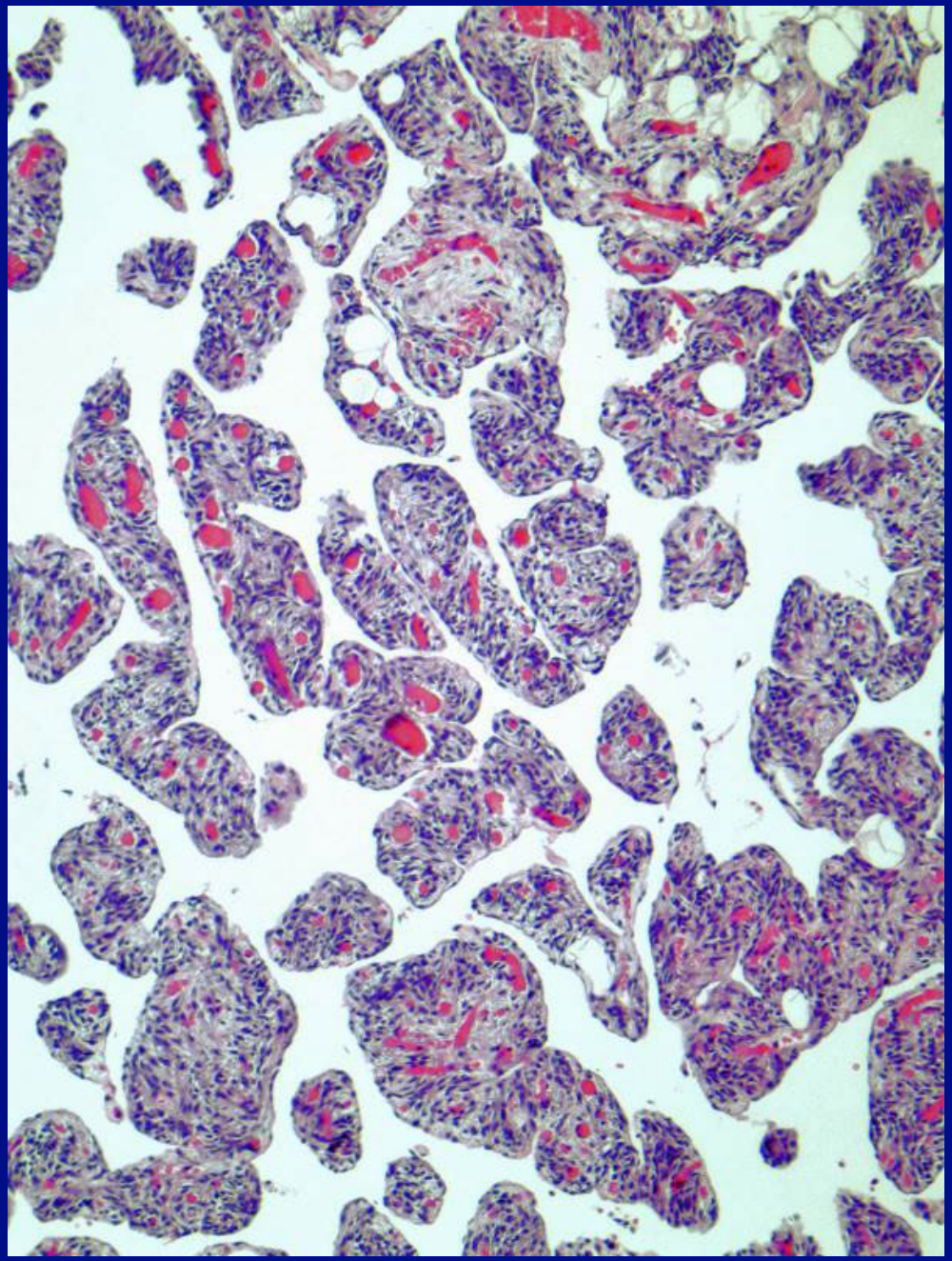


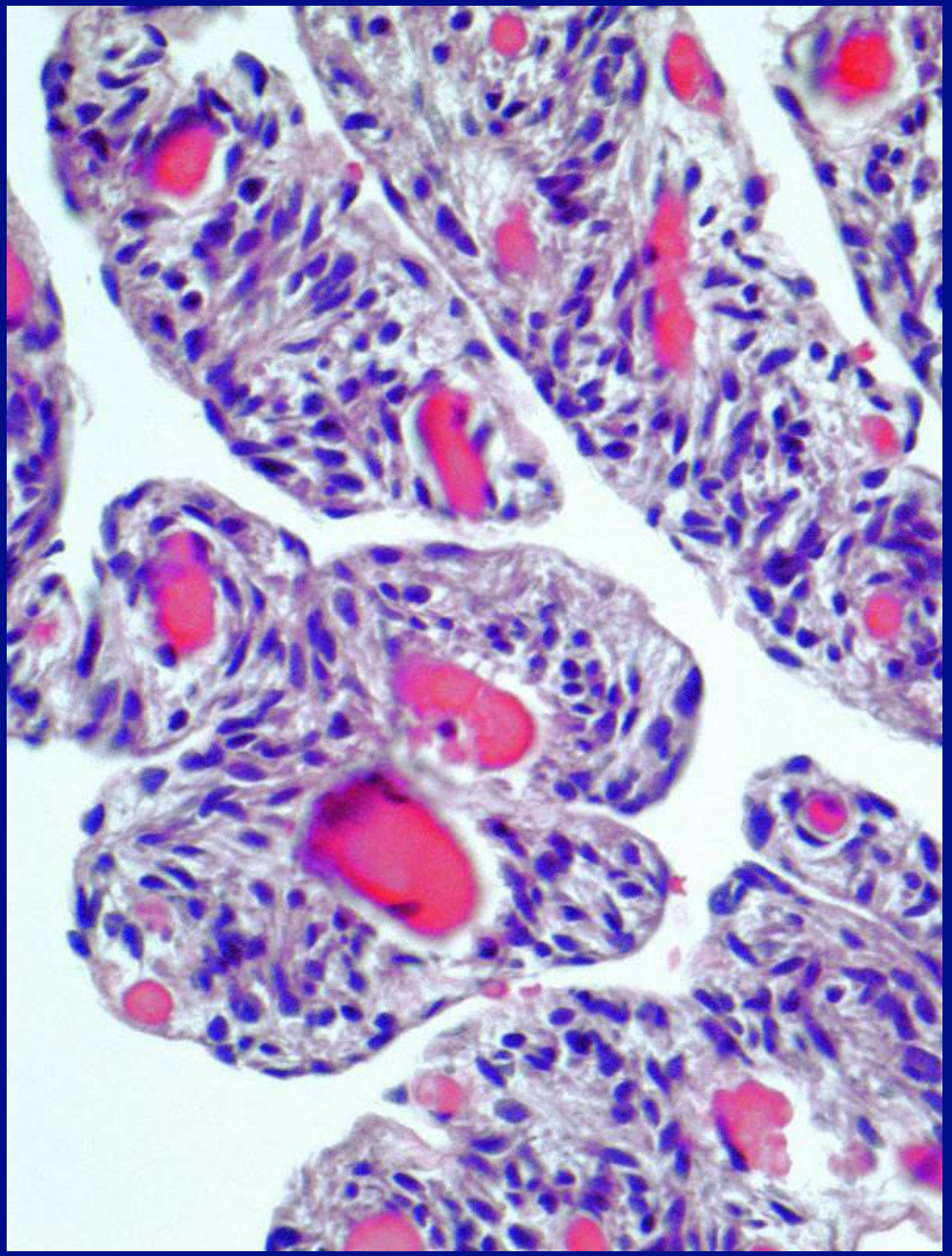
Spindle Cell/Plemorphic Lipoma



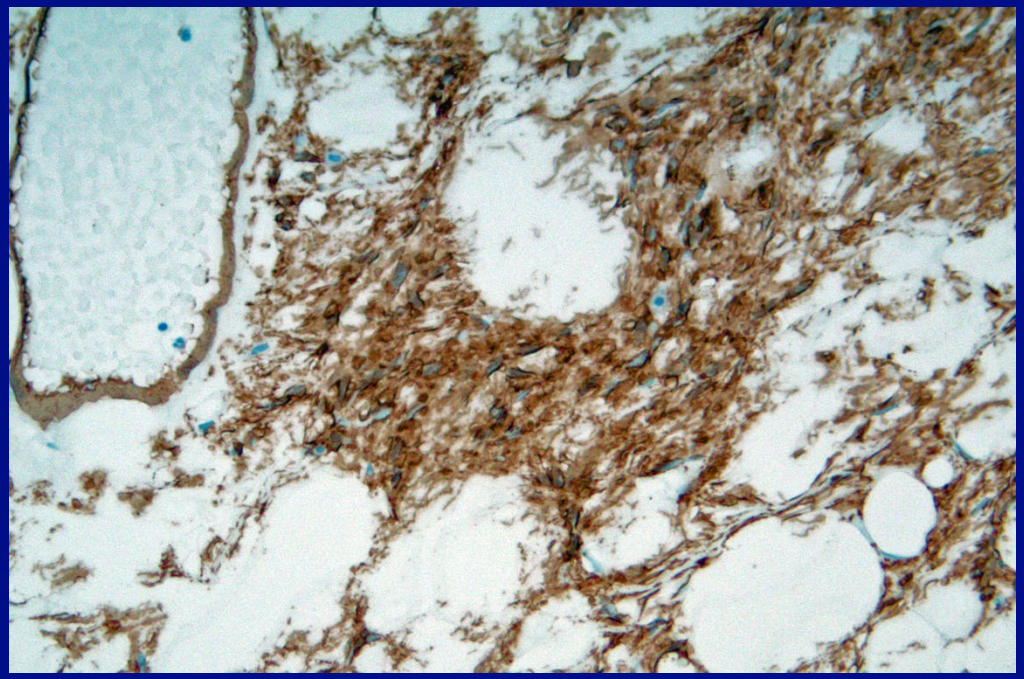


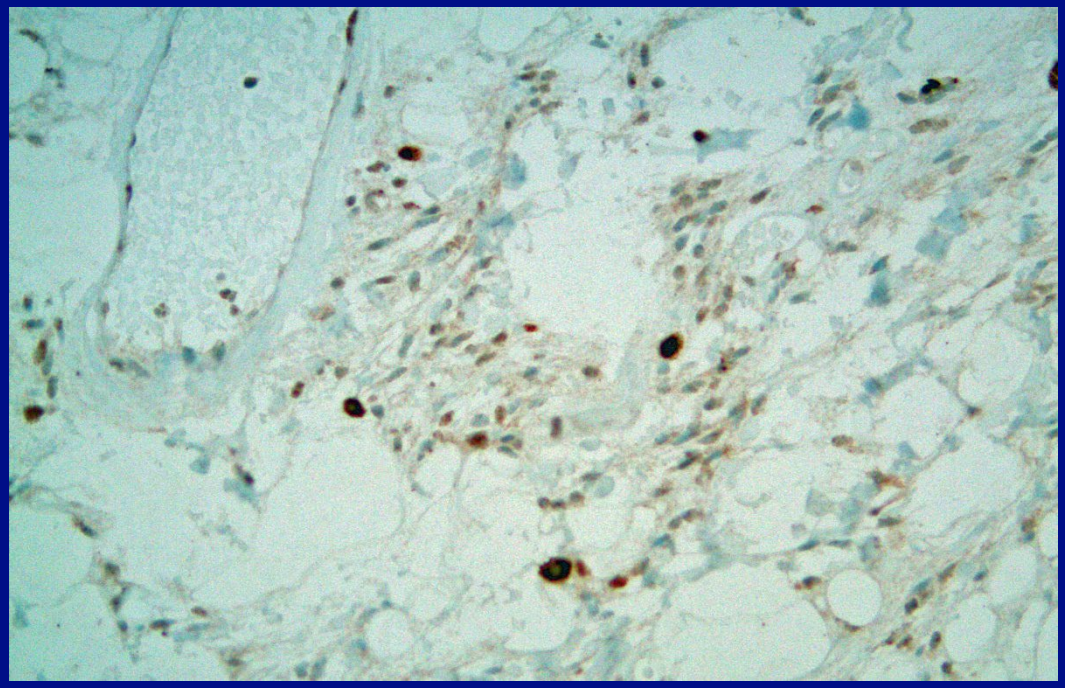
Spindle Cell/Plemorphic Lipoma, Pseudoangiomatous Variant

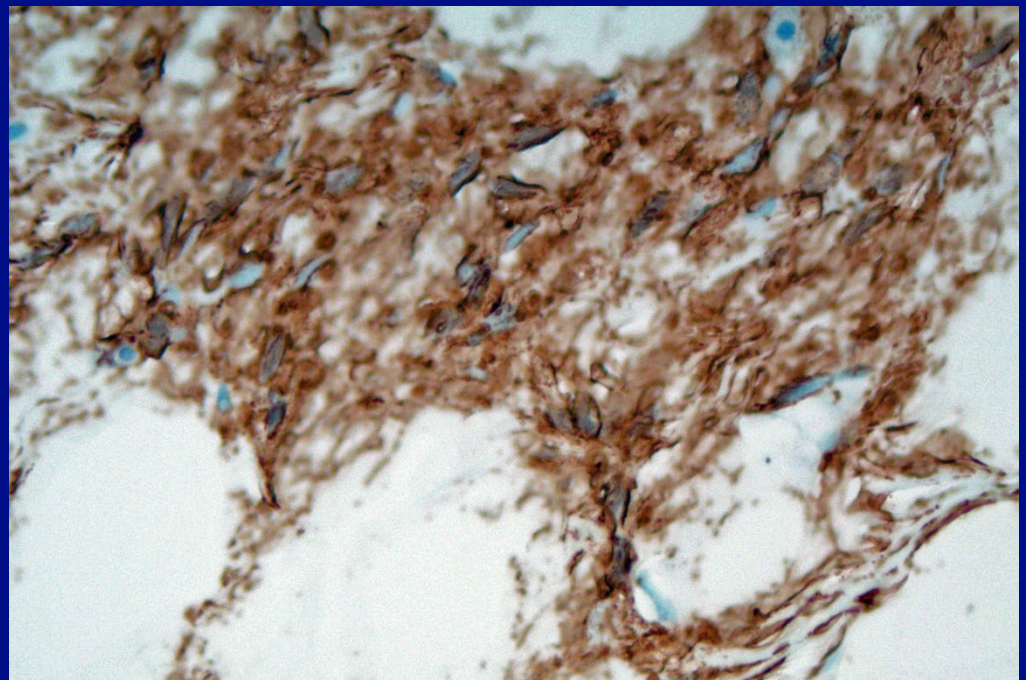


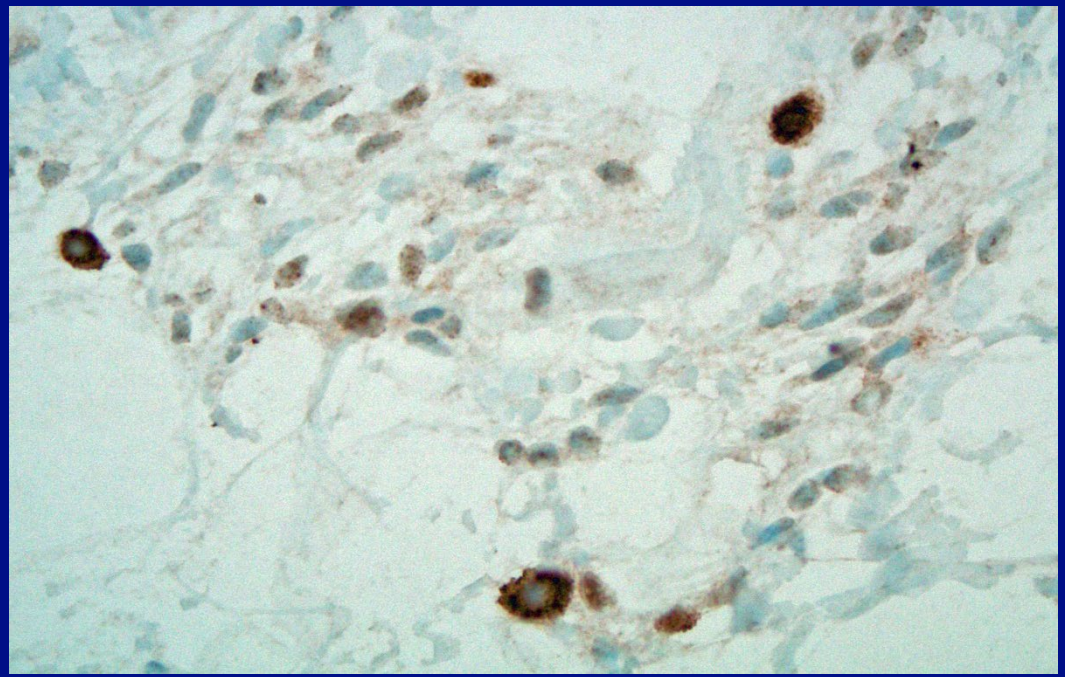


CD34 **Spindle Cell/Plemorphic Lipoma** MDM2







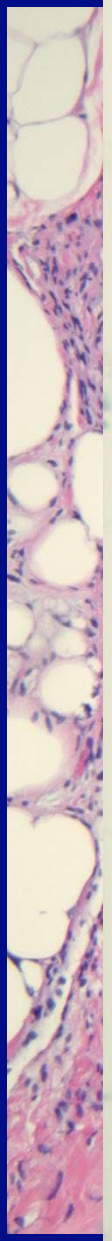


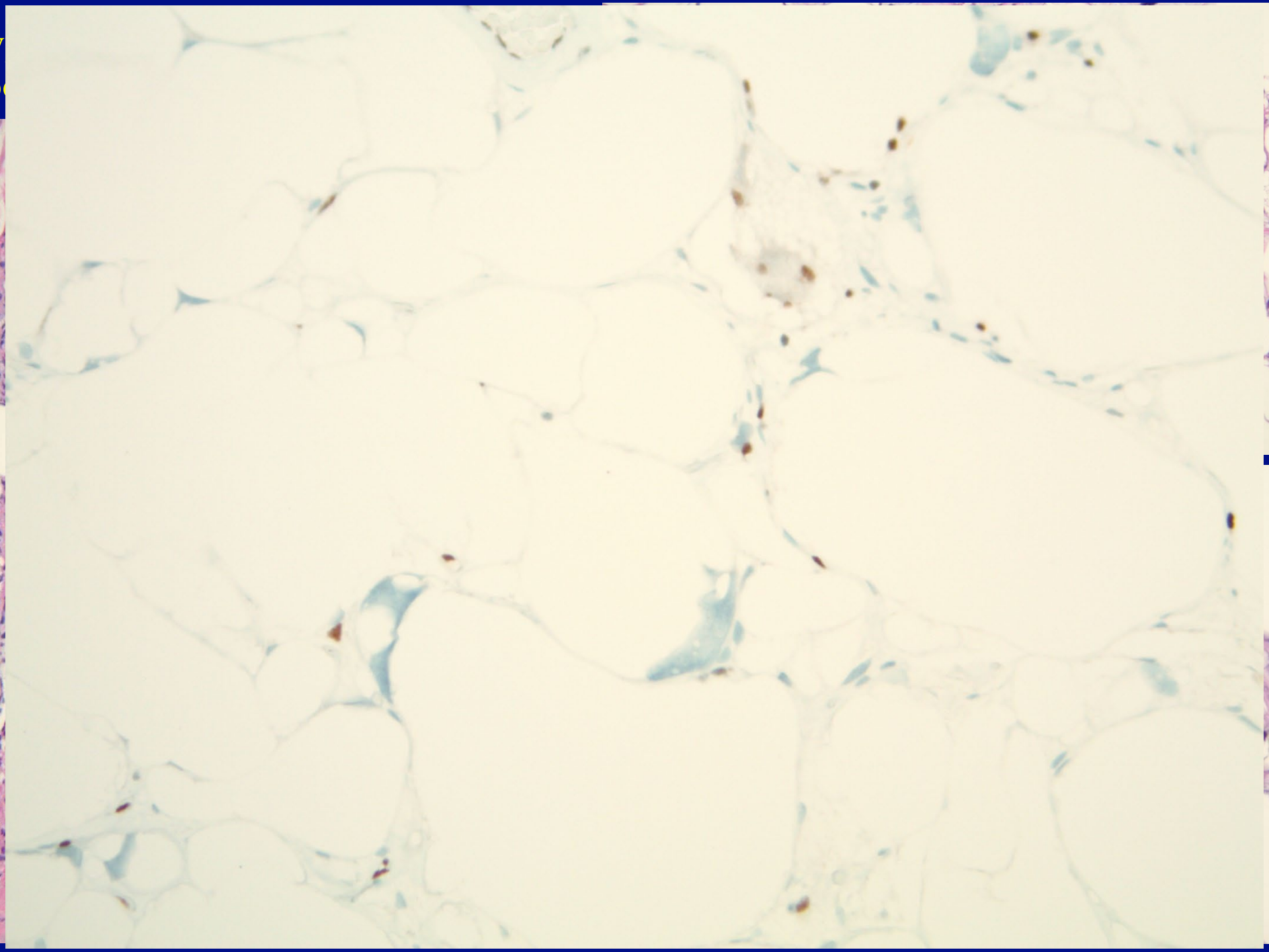
Atypical Spindle Cell / Pleomorphic Lipomatous Tumor

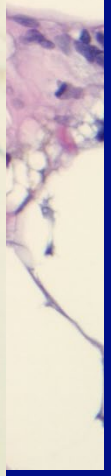
- Predominantly middle aged to older adults (6th decade)
- Subcutis > Subfacial, predominantly extremities, esp. hand, foot, and thigh
- Unencapsulated, less defined margins, mildly atypical spindled cells, admixed with adipocytes, in a fibrous to myxoid stroma, lipoblasts, range of cellularity.
- Usually +CD34, less commonly S100 and desmin. Loss of RB1 50-80% of cases. MDM2 and CDK4 -
- Deletions/losses RB1 and flanking genes
- Local recurrences <5% of cases

Marino-Enriquez A, et al. Atypical spindle cell lipomatous tumor: clinicopathologic characterization of 232 cases demonstrating a morphologic spectrum. *Am J Surg Pathol* 2017;41:234-44.
Anderson WJ. Atypical pleomorphic lipomatous tumor: expanding our current understanding in a clinicopathologic analysis of 64 cases. *Am J Surg Pathol* 2021;45:1282-1292.

Aty
Lip

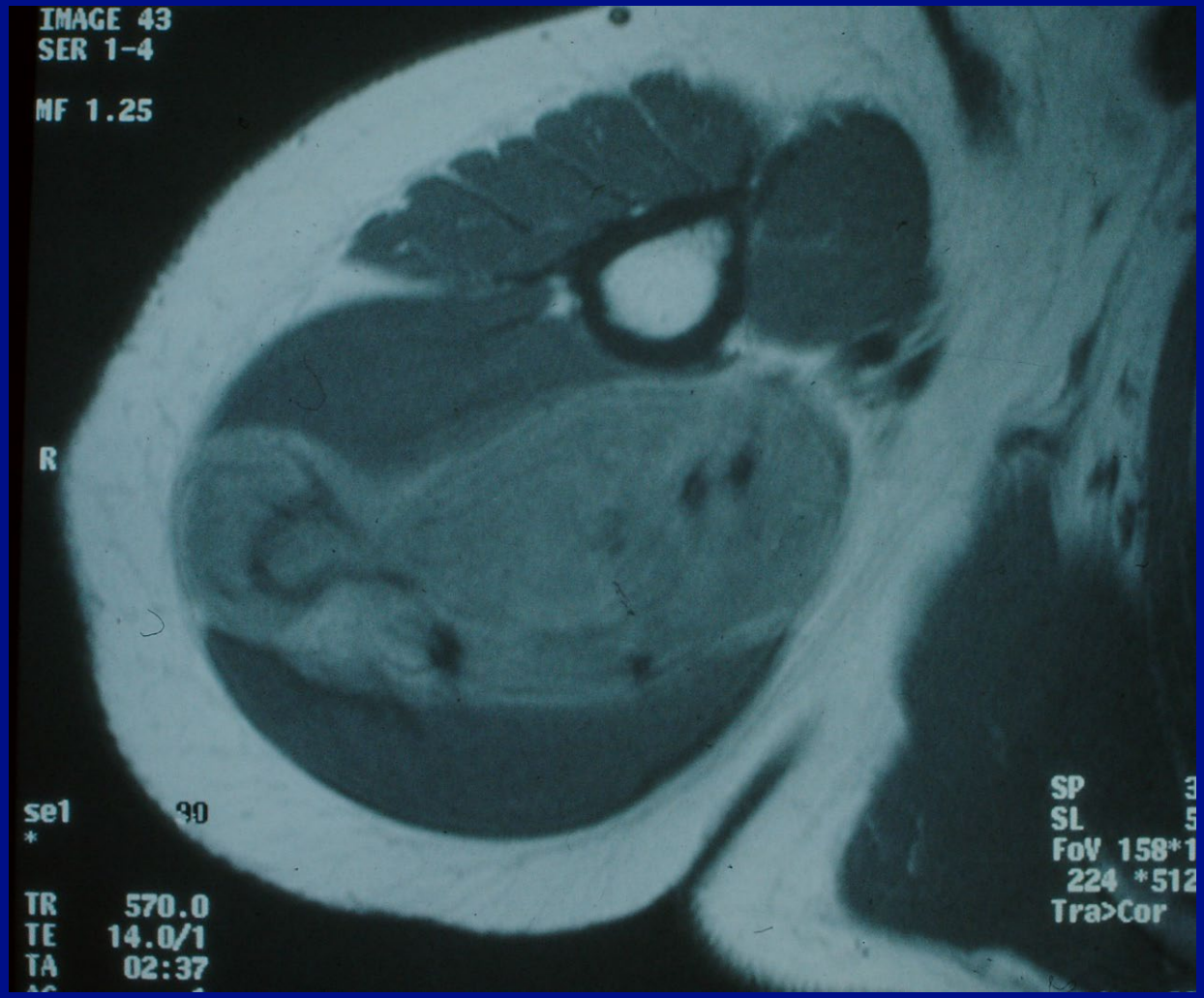






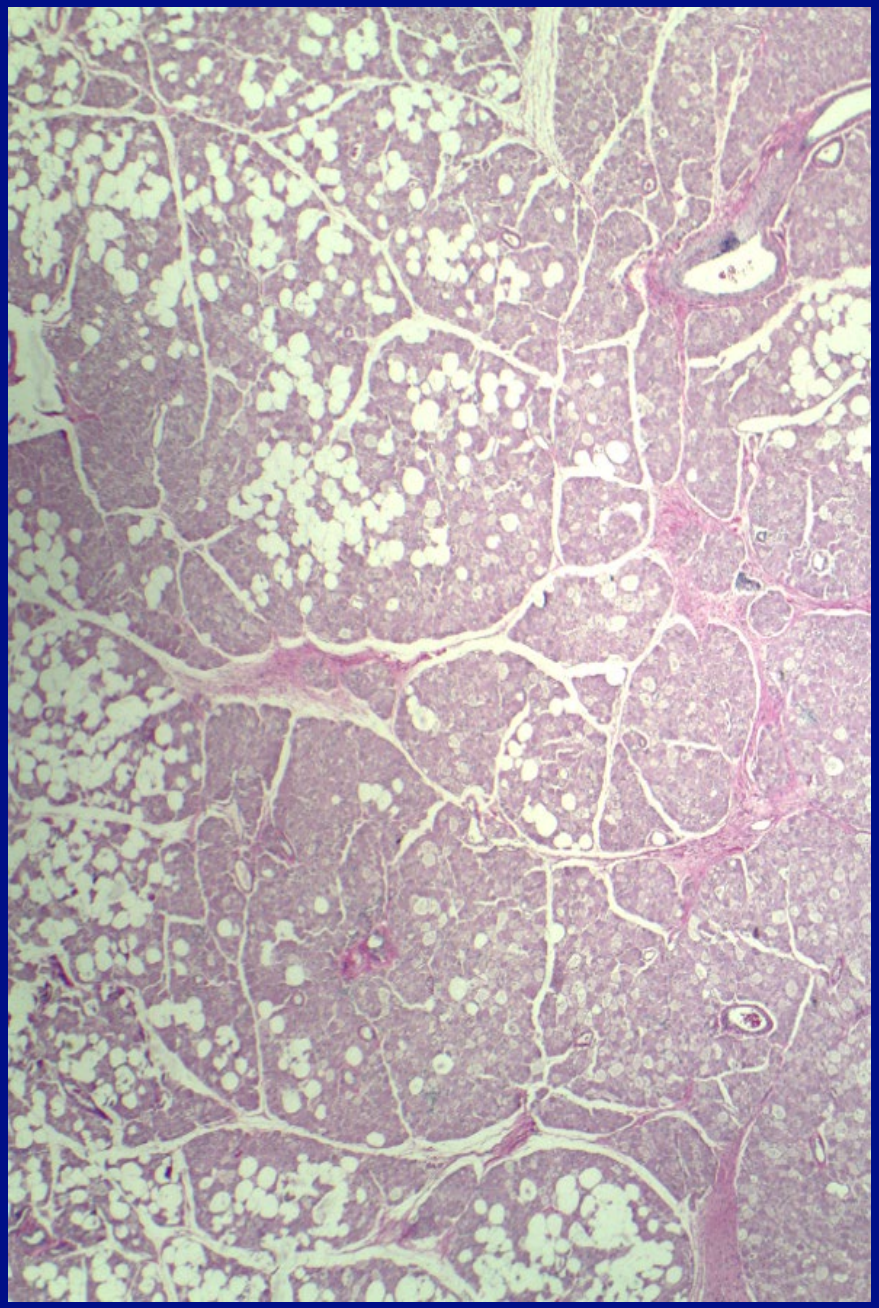
Hibernoma

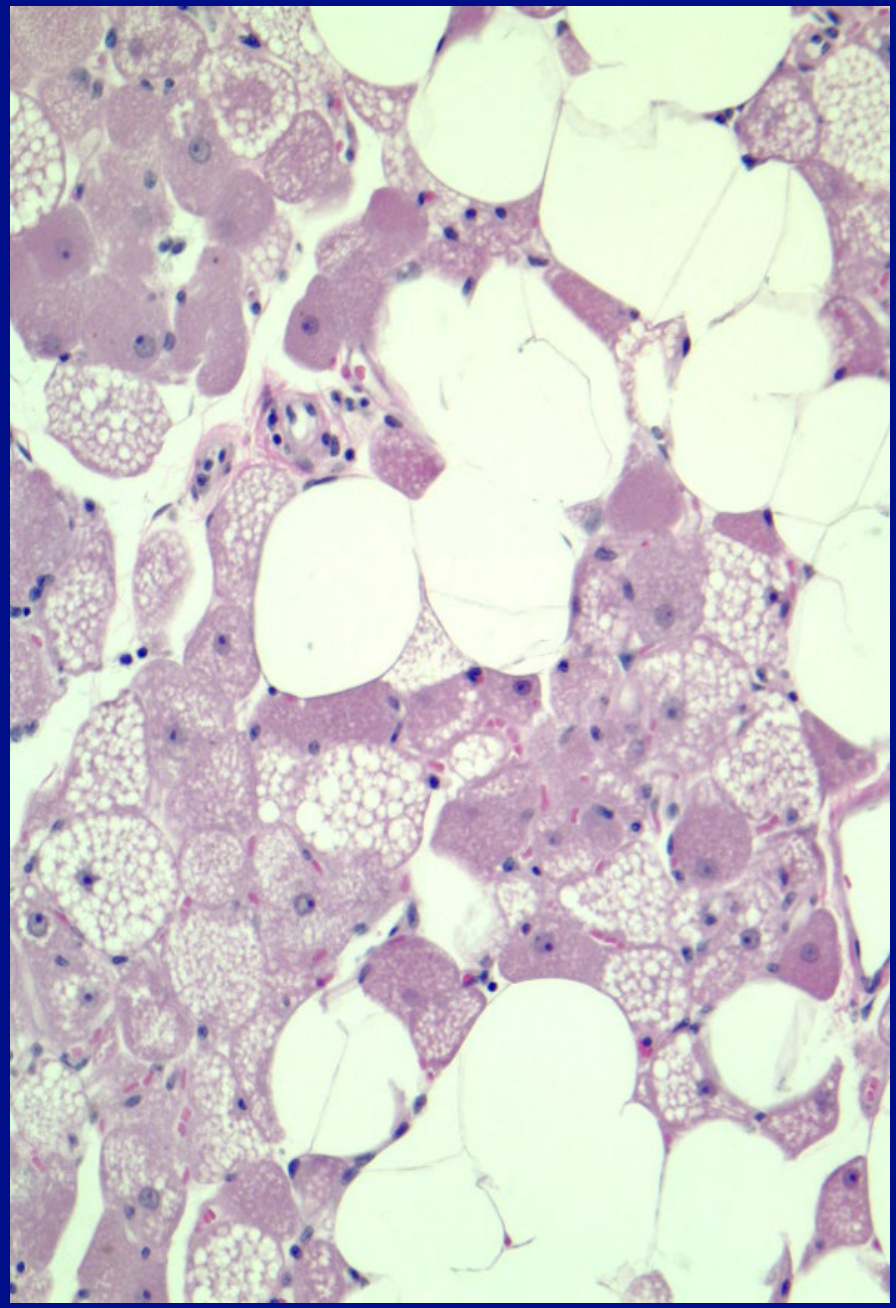
- Young to middle aged adults
- (20-40 yr).
- Thigh, trunk, and upper extremity.
- MRI signal intensity intermediate between mature adipose tissue and skeletal muscle.
- Varying proportions of white and brown fat.
- Rearrangements of 11q13-21 (MEN1 and AIP codeletion). Most common partners are 9q34 and 14q11.
- Negative MDM2 and CDK4



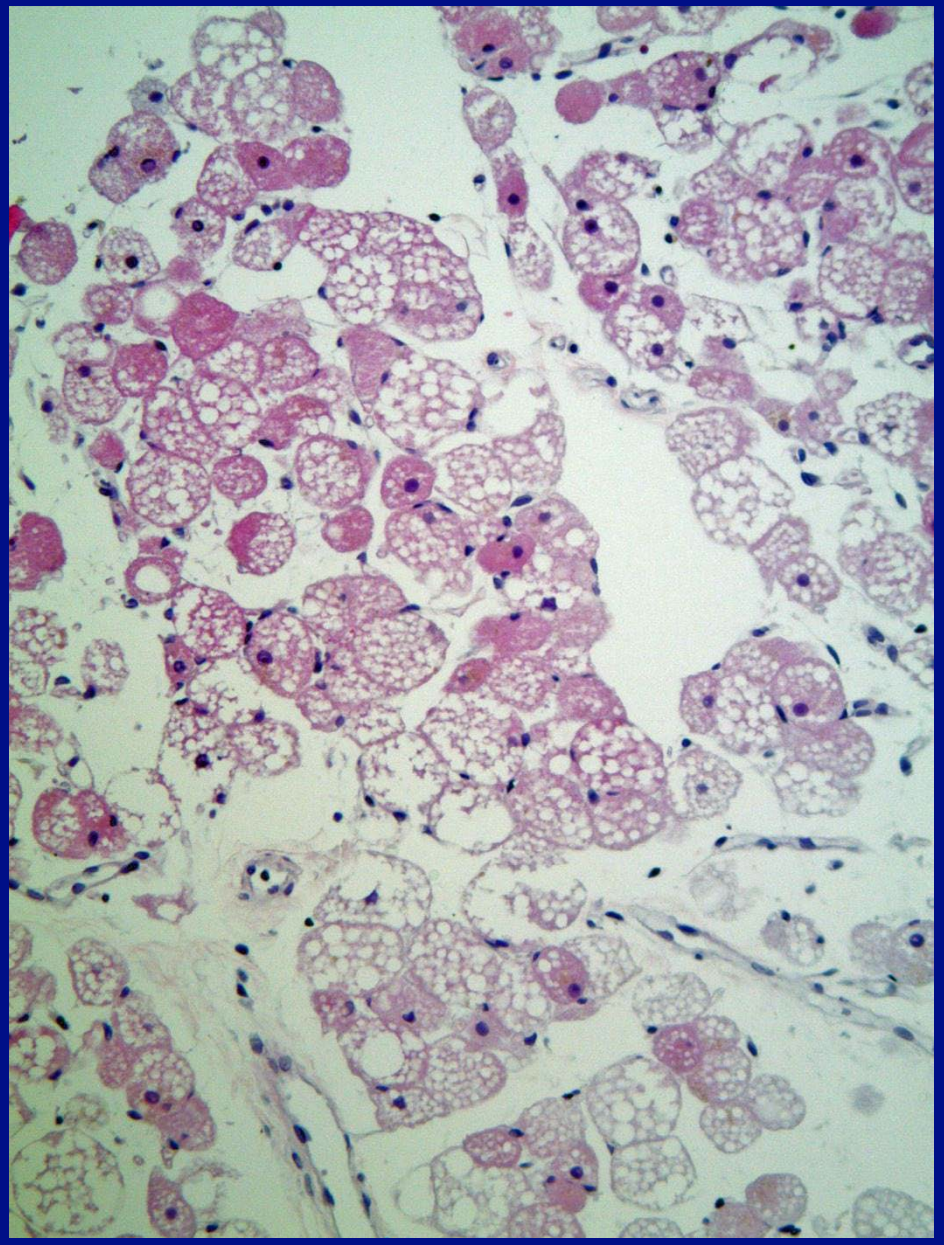
Al Hmada Y, et al. Hibernoma mimicking atypical lipomatous tumor: 64 cases of a morphologically distinct subset. *Am J Surg Pathol* 2018;42:951-7.

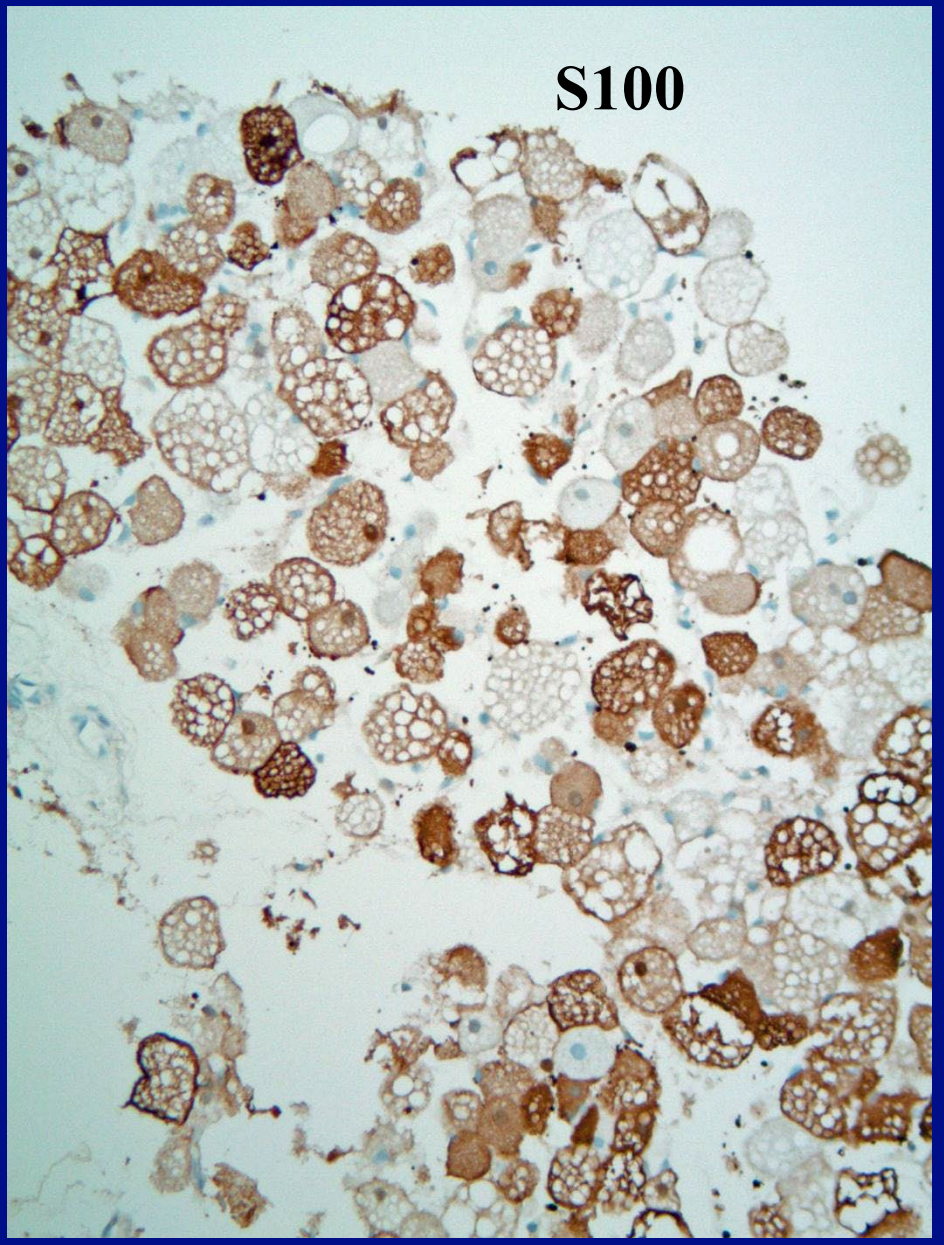
Hibernoma





Hibernoma





When to order molecular testing? All "funny lipomas"? Part 1

Zhang H, et al. Molecular testing for lipomatous tumors: critical analysis and test recommendations based on analysis of 405 extremity-based tumors. Am J Surg Pathol 2010;34:1304-1311.

- 405 tumors histologically and via FISH for *MDM2* at Mayo Clinic
- Histologic classification = ordinary lipoma (324), intramuscular lipoma (29), and ALT/WDL (52).
- Agreement between histologic dx and molecular testing 96%.
- Tendency of pathologists to overestimate cytologic atypia and thus ALT (precision 79%; accuracy 88%).
- FISH reclassified 4% (18).

1) 11 ALT/WDL → ordinary lipoma and IM lipoma. No recurrences.
2) 7 ordinary lipomas → ALT/WDL (6 were >15 cm and deeply located). 2 recurred.

Conclusions and recommendations:

1) Pathologists tend to overestimate atypia via morphology.
2) Molecular FISH testing for the following (extremity):
   a) Relapsing/recurrent tumors.
   b) Tumors with ?atypia.
   c) Large >15 cm tumors.

All Tumors Evaluated were Excisions with reported Negative Margins!

When to order molecular testing? All "funny lipomas"? Part 2

Clay MR, et al. MDM2 amplification in problematic lipomatous tumors: analysis of FISH testing criteria. *Am J Surg Pathol* 2015;34:1433-1439.

- Background: FISH analysis performed in the following "problematic" situations: 1) lipomas >10 cm, 2) equivocal atypia, 3) "recurrent" lipomas, 4) all retroperitoneal/pelvic/abdominal lipomas.
- 301 consecutive cases in which dx could not be established via morphology alone.
- 108 (36%) ALT/WDL.
- Incidence of features proven to be ALT: 68 (36%, 187) >10 cm in size. 72 (50%, 145) with equivocal atypia. 18 (55%, 33) recurrent tumors. 30 (35%, 86) retro/pelvis/abdominal.
- ALTs consistently in patients >50 years of age, 1 superficial, none in the hands and feet.

Conclusions and recommendations:

1) Most ALT/WDL can be diagnosed by histologic criteria, which "include mature fat punctuated with large atypical hyperchromatic cells".
2) Molecular FISH testing recommended for the following:

a) Recurrent lesions.

b) Deep extremity lesions >10 cm in patients >50 years of age.

c) Cases with equivocal atypia.

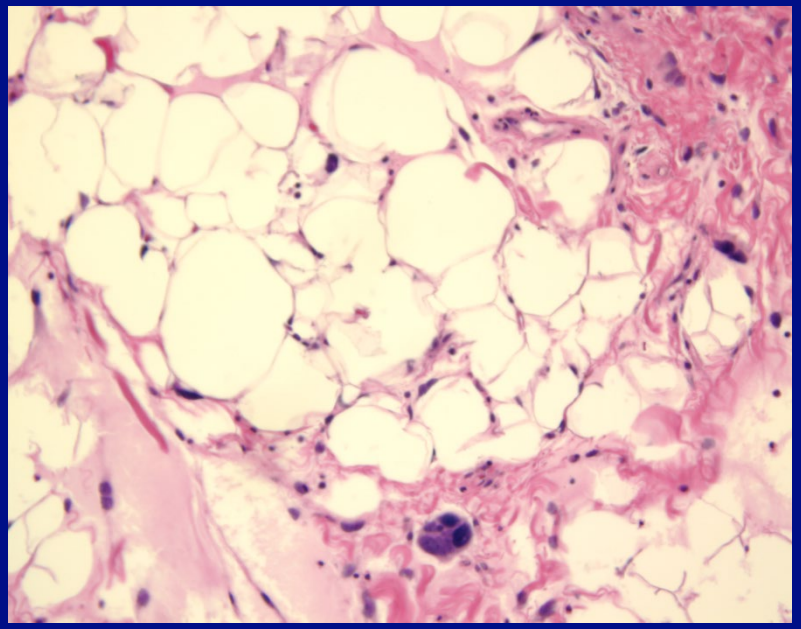
d) Lesions in the retroperitoneum and pelvis and abdomen.

270 Excisions and 31 Core Needle Bx's

Personal Practice

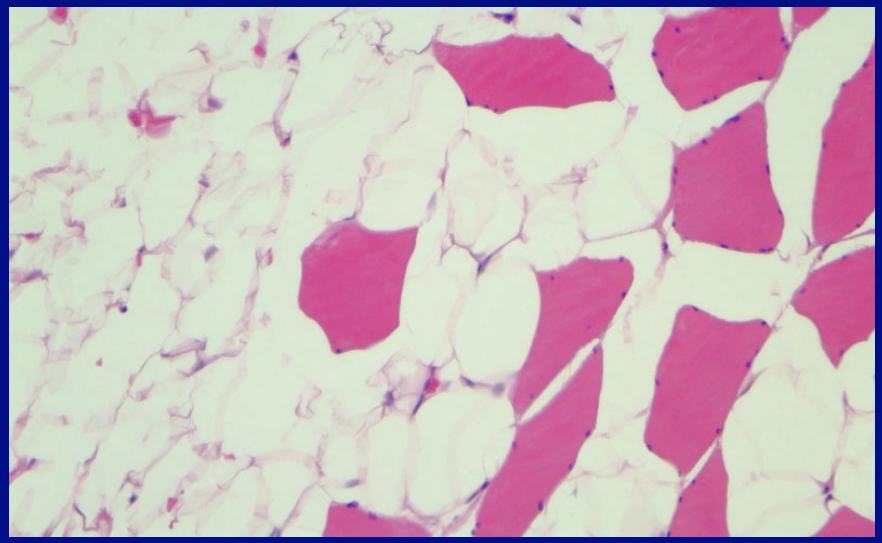
H&E DIAGNOSTIC

- Outside of the subcutis of the head and neck, I render a diagnosis of ALT, no FISH or IHC.
- Exception: the differential of SCL, I use CD34 and MDM2 IHC.



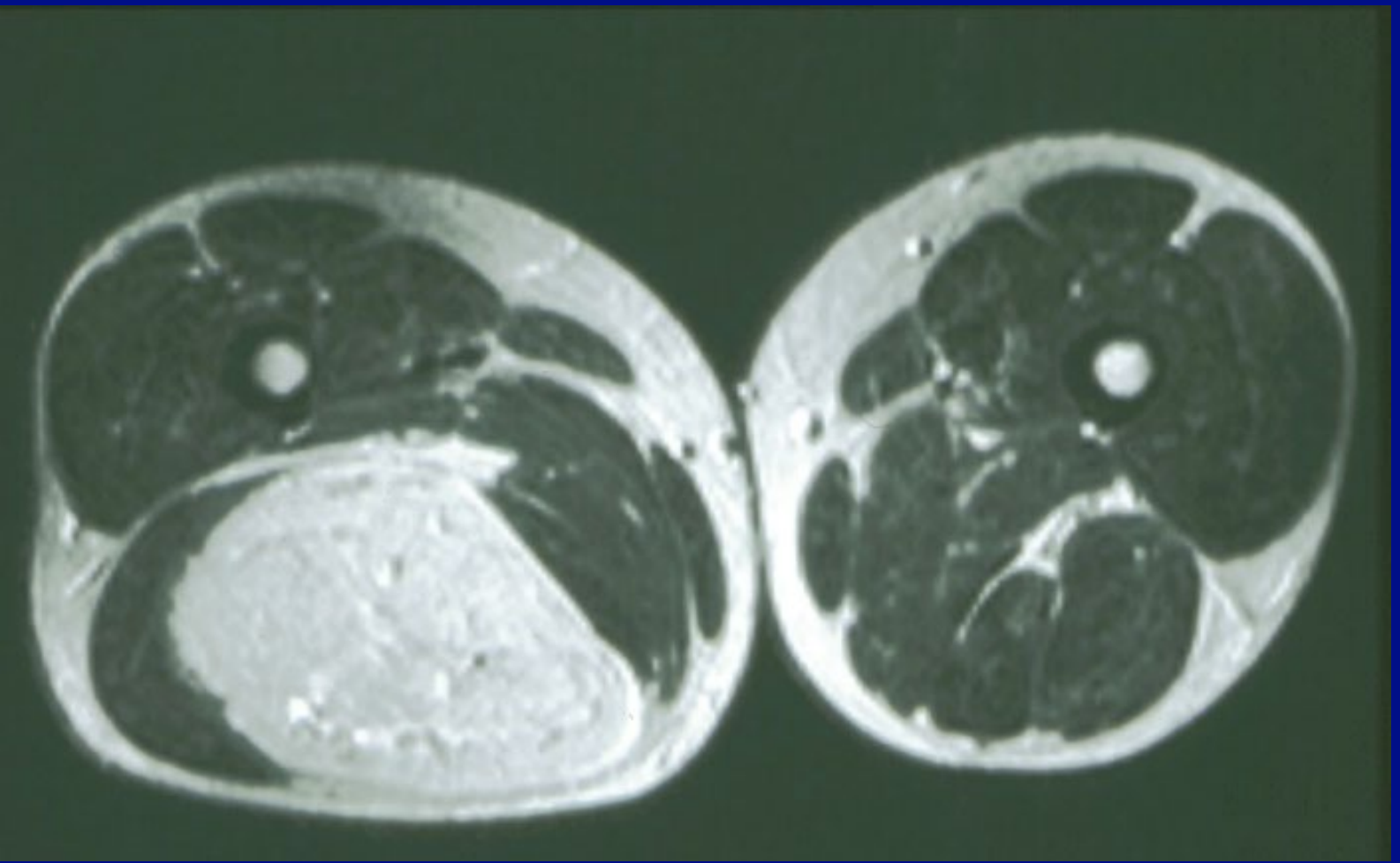
H&E NOT DIAGNOSTIC

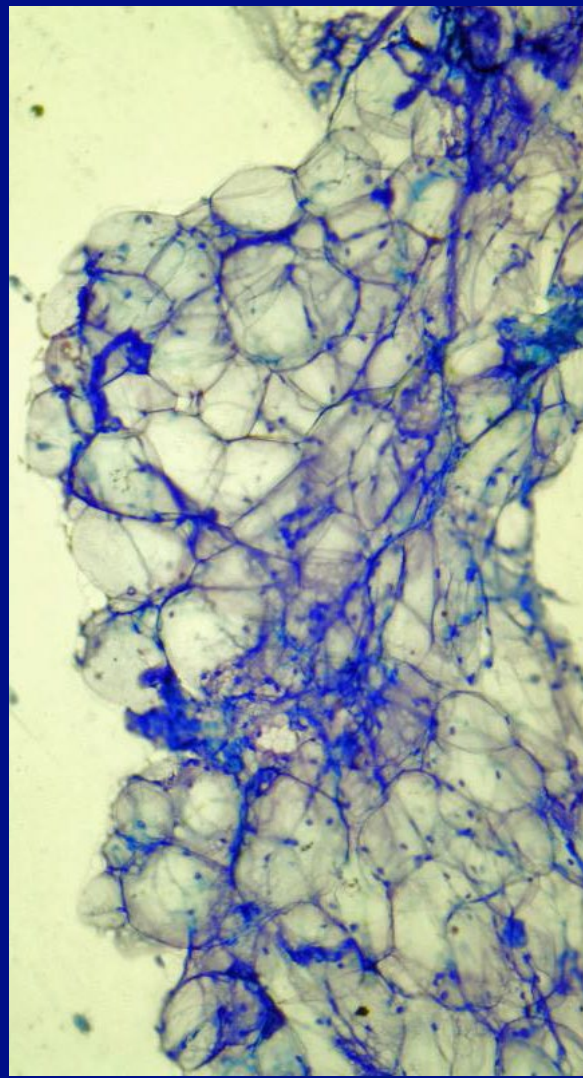
- >50 yr, deep, and large size >10 cm, ext, FISH MDM2.
- Retroperitoneal, thoracic, abdominal/retro, FISH MDM2.
- Equivocal atypia or difficult to classify, FISH MDM2.



What about small biopsies? FNA or CNB?

Molecular via FISH MDM2 has made all small biopsies a viable option!





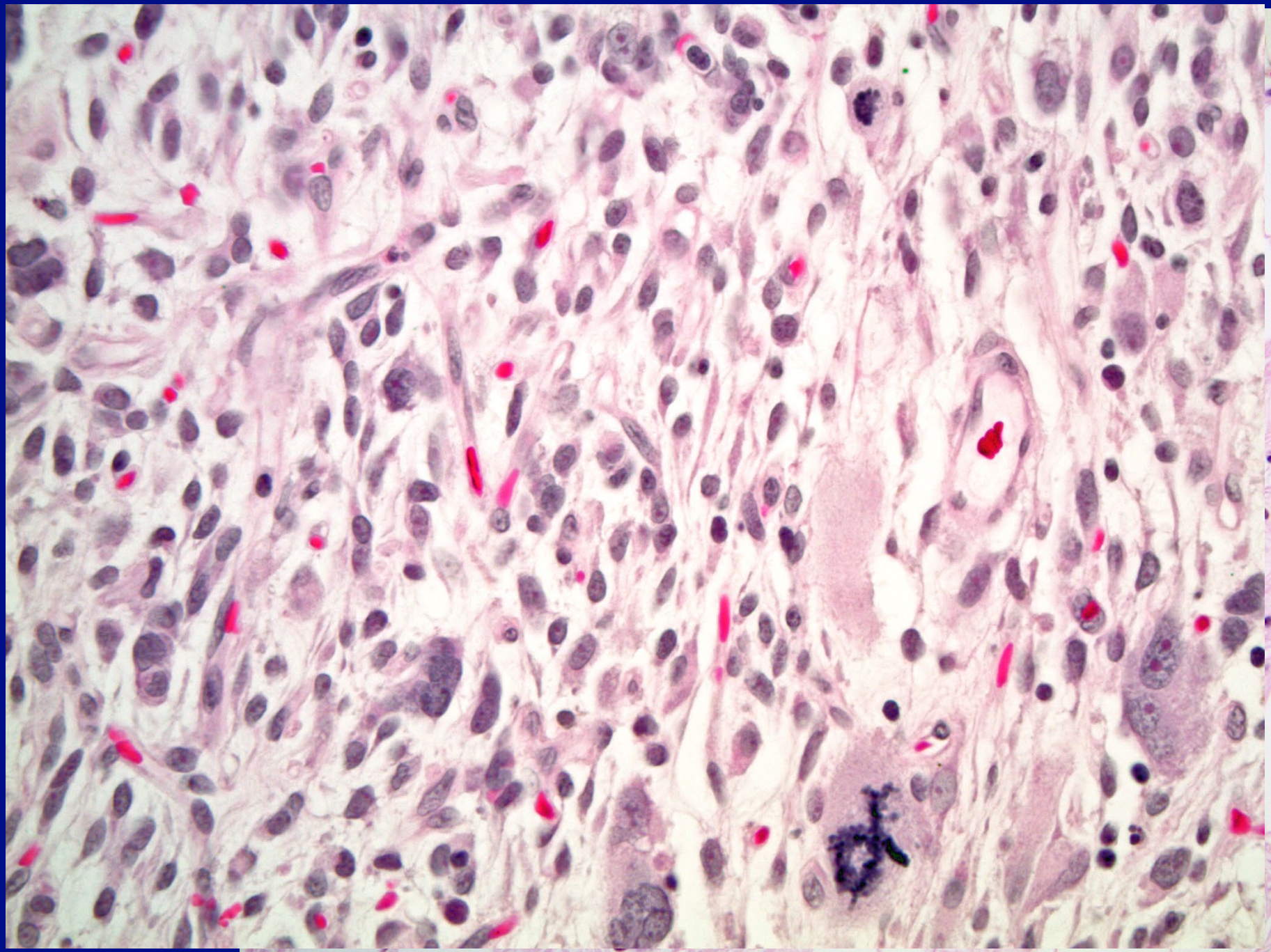
Dedifferentiated Liposarcoma

- Implies transformation to a high grade “most often” non-liposarcomatous sarcoma. Updated definition includes the fact that the non-liposarcomatous component may represent “pleomorphic liposarcoma”.

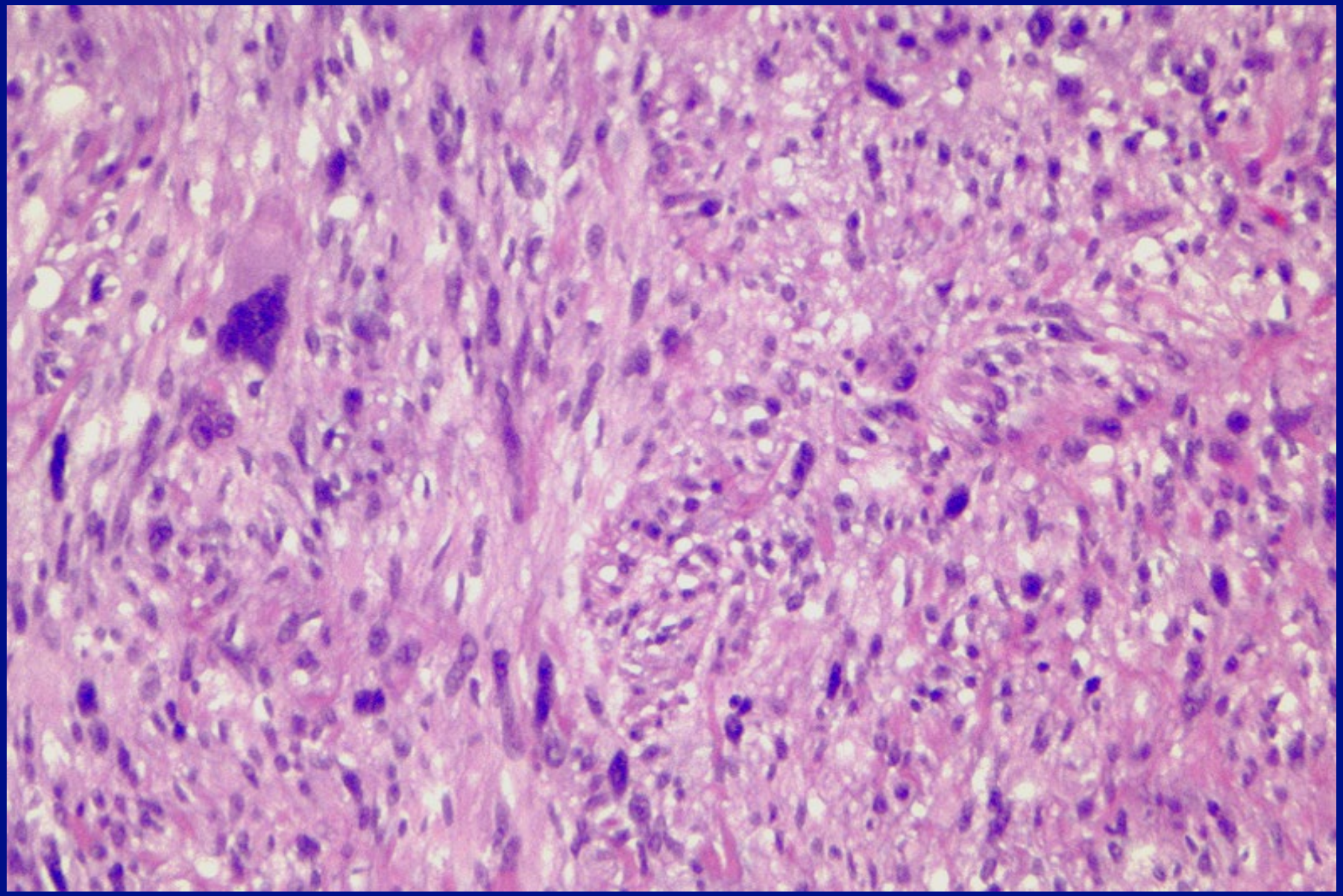
- Classical definition is 2 settings: juxtaposed to low grade liposarcoma (most common) vs. arising in the region of a previously excised low grade liposarcoma.

- Molecular age allows a 3rd setting: dedifferentiated liposarcoma in the absence of the above = MDM2+

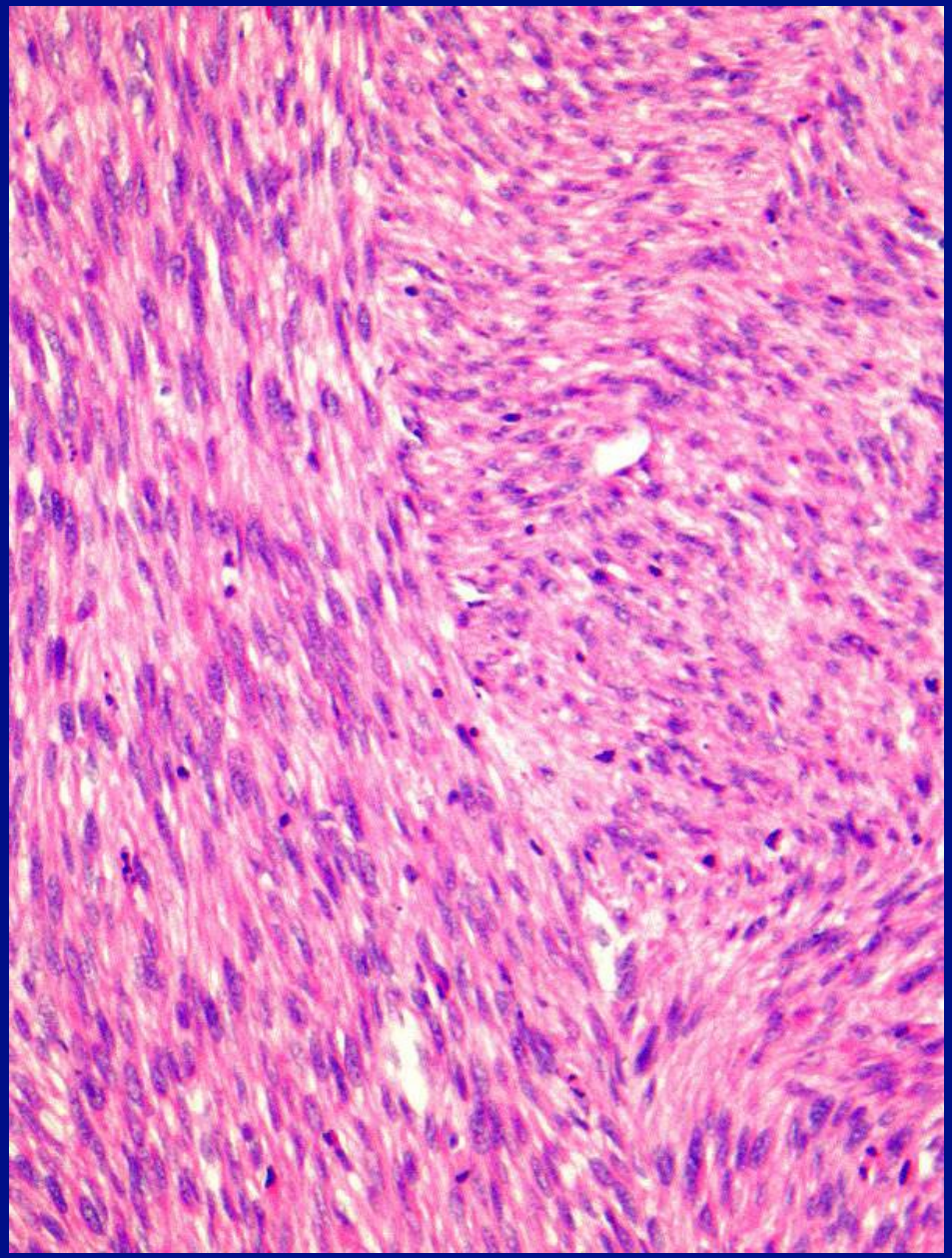
- Why is important to separate from other pleomorphic sarcomas? Surgical margins and prognosis.

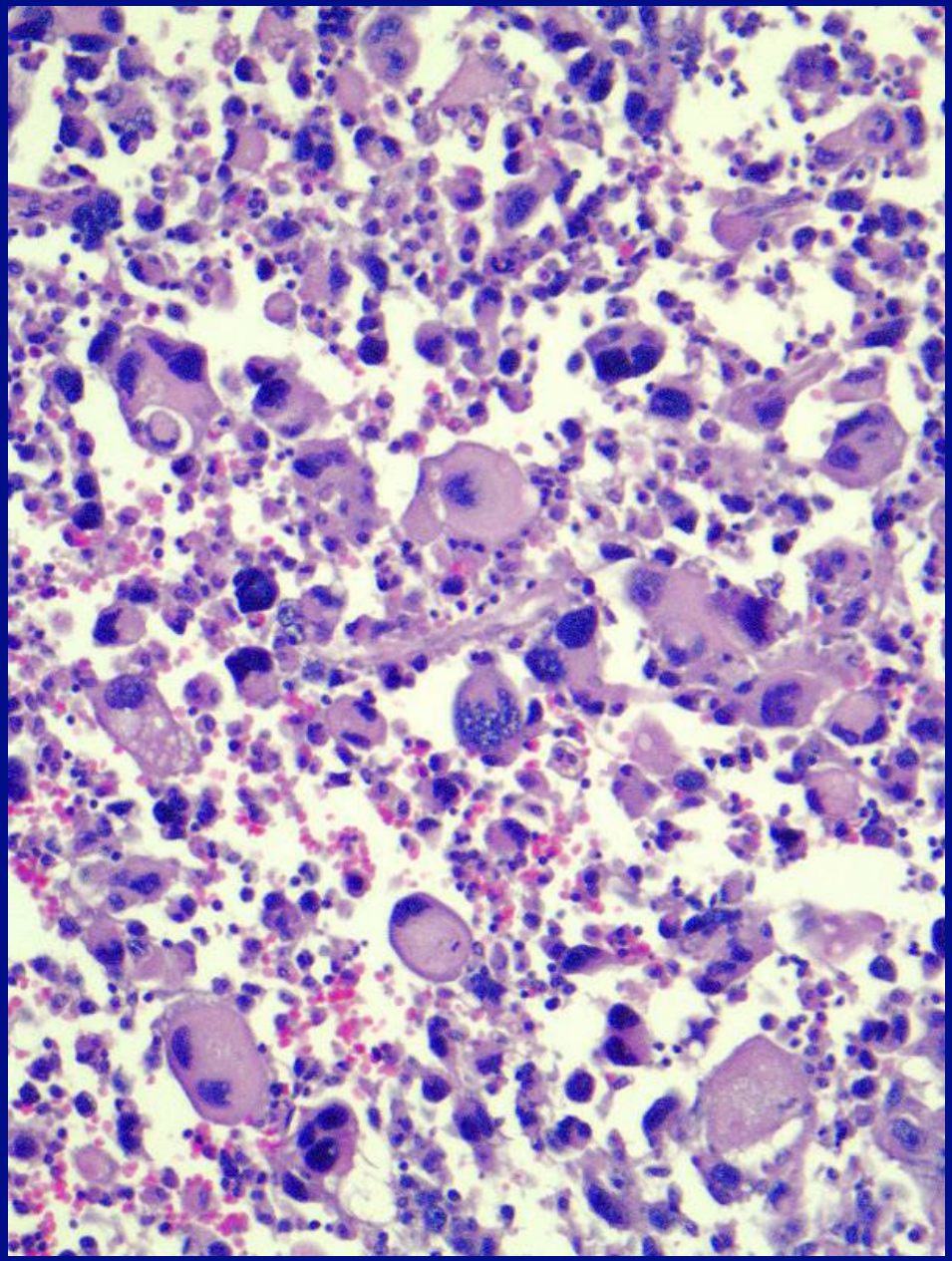


Remember UPS is a diagnosis of exclusion…exclude dediff LPS

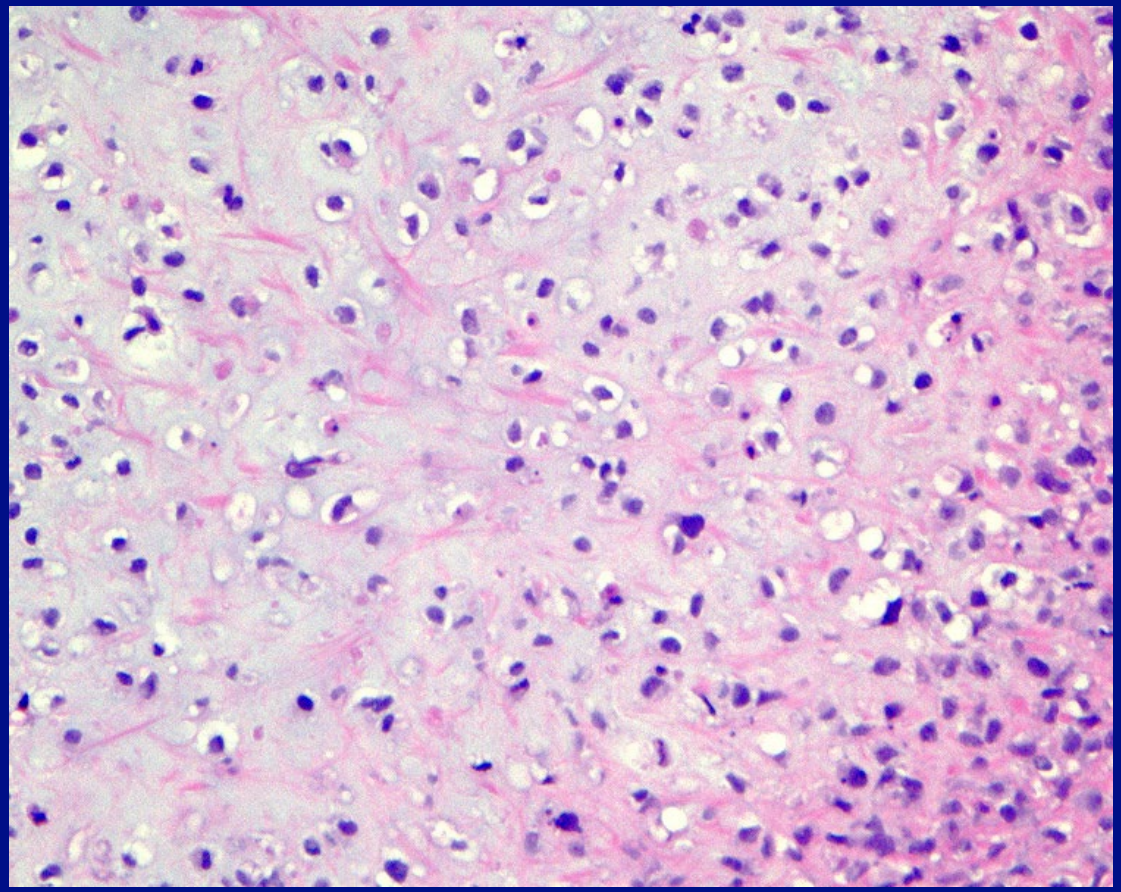


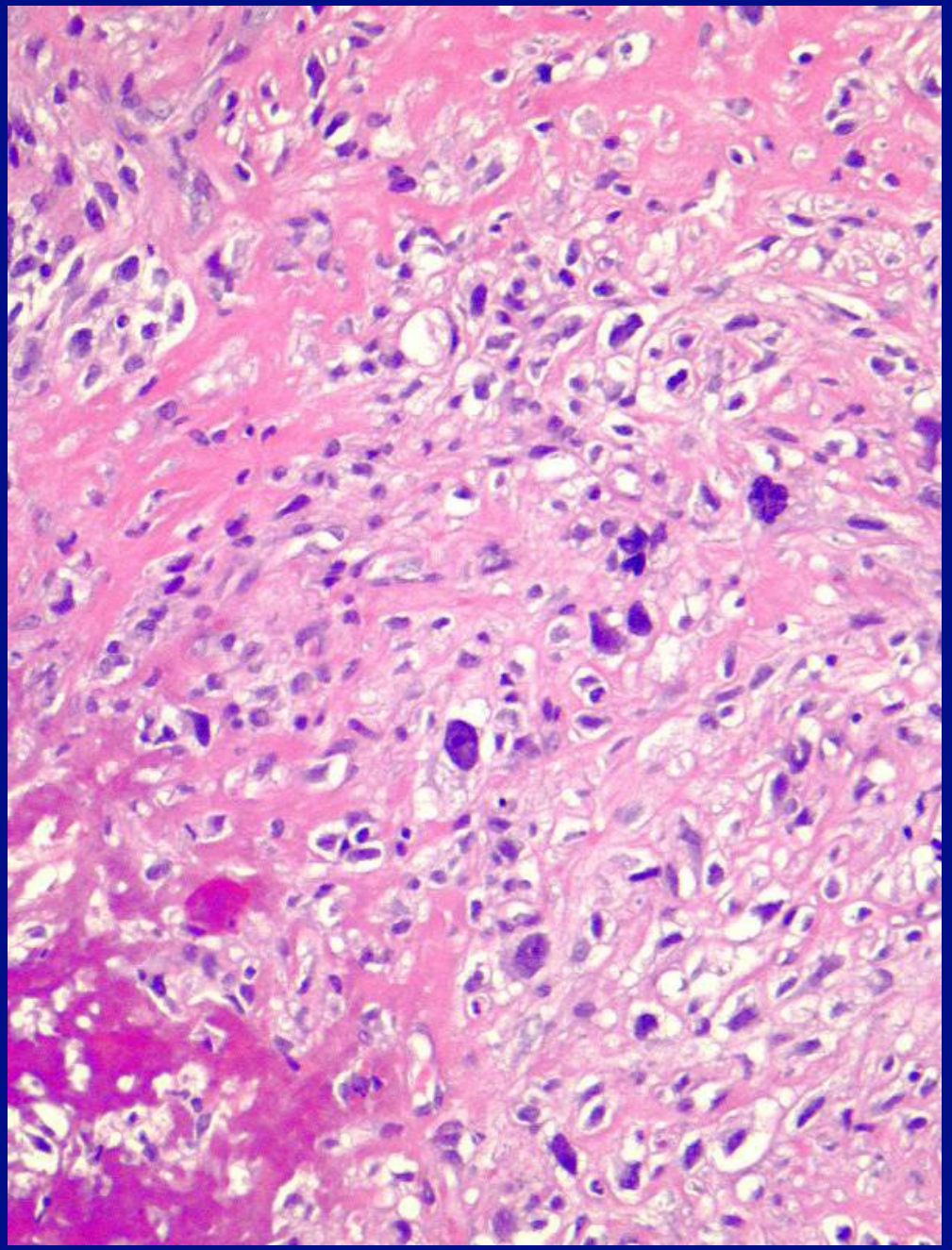
Dedifferentiated liposarcoma with myoid differentiation



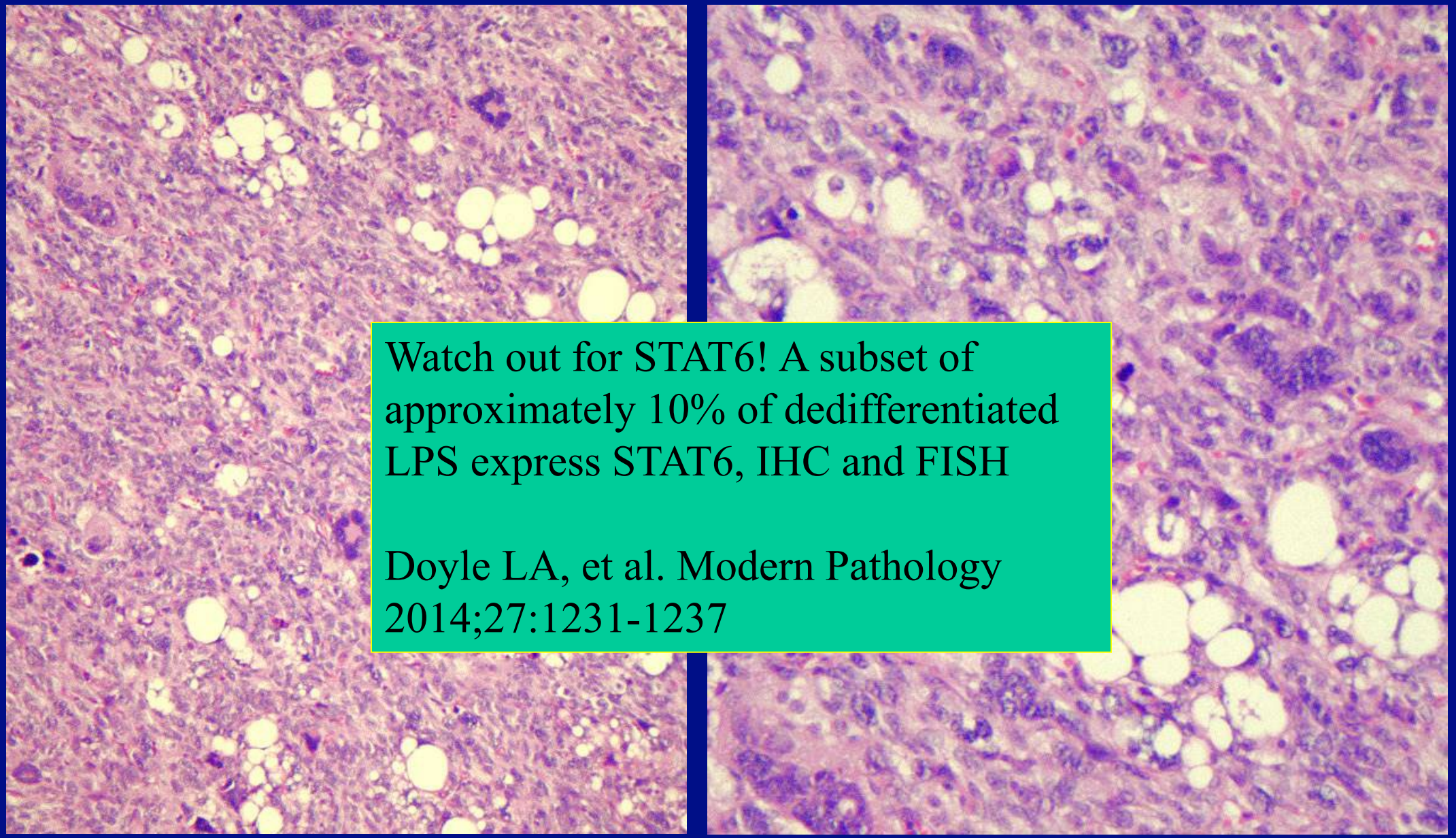


Dedifferentiated Liposarcoma with osteosarcomatous and/or chondrosarcomatous differentiation





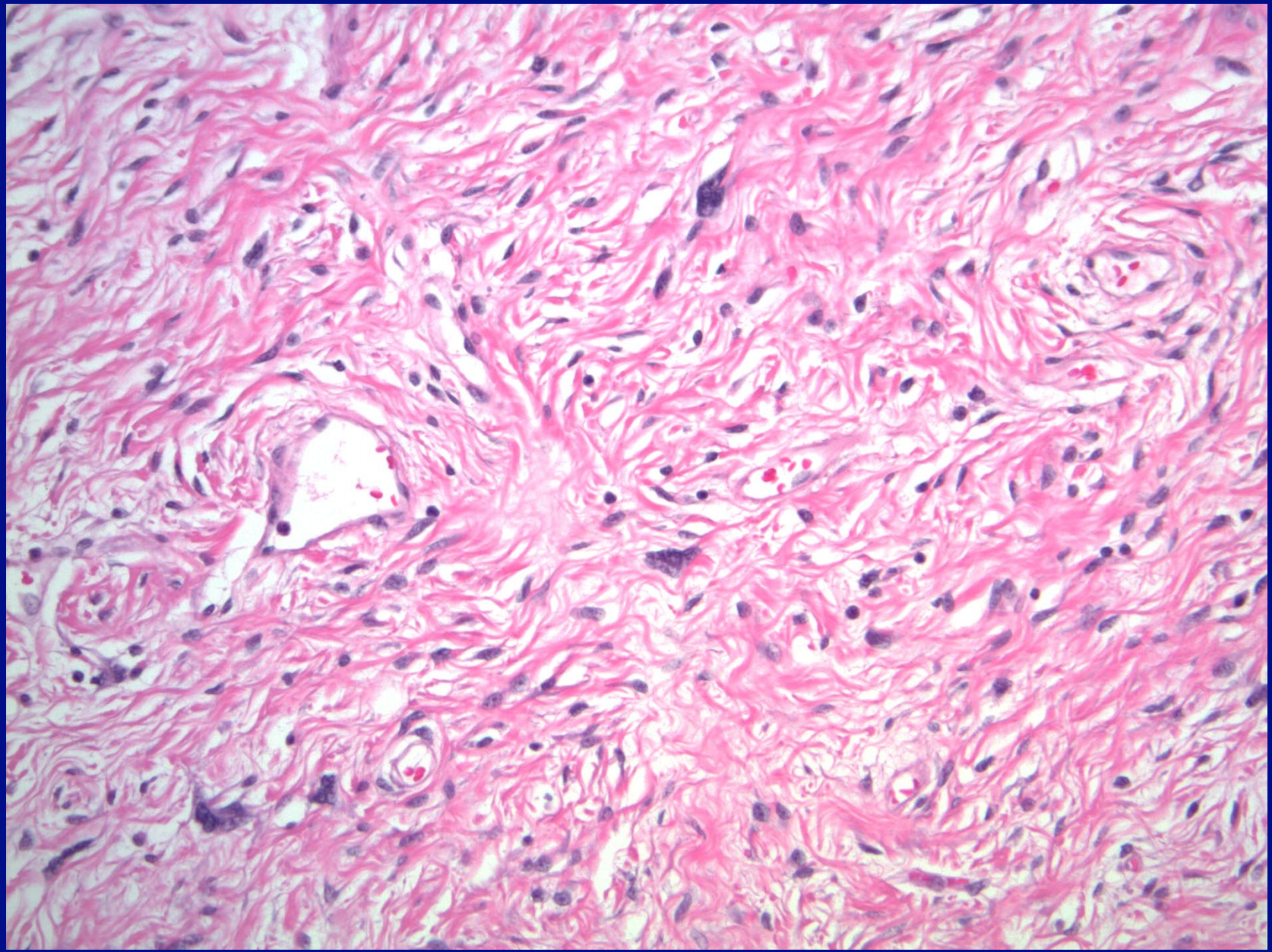
“Homologous” dedifferentiated liposarcoma with a pleomorphic LPS component. Marino-Enriquez A, et al. Am J Surg Pathol 2010;34:1122-31



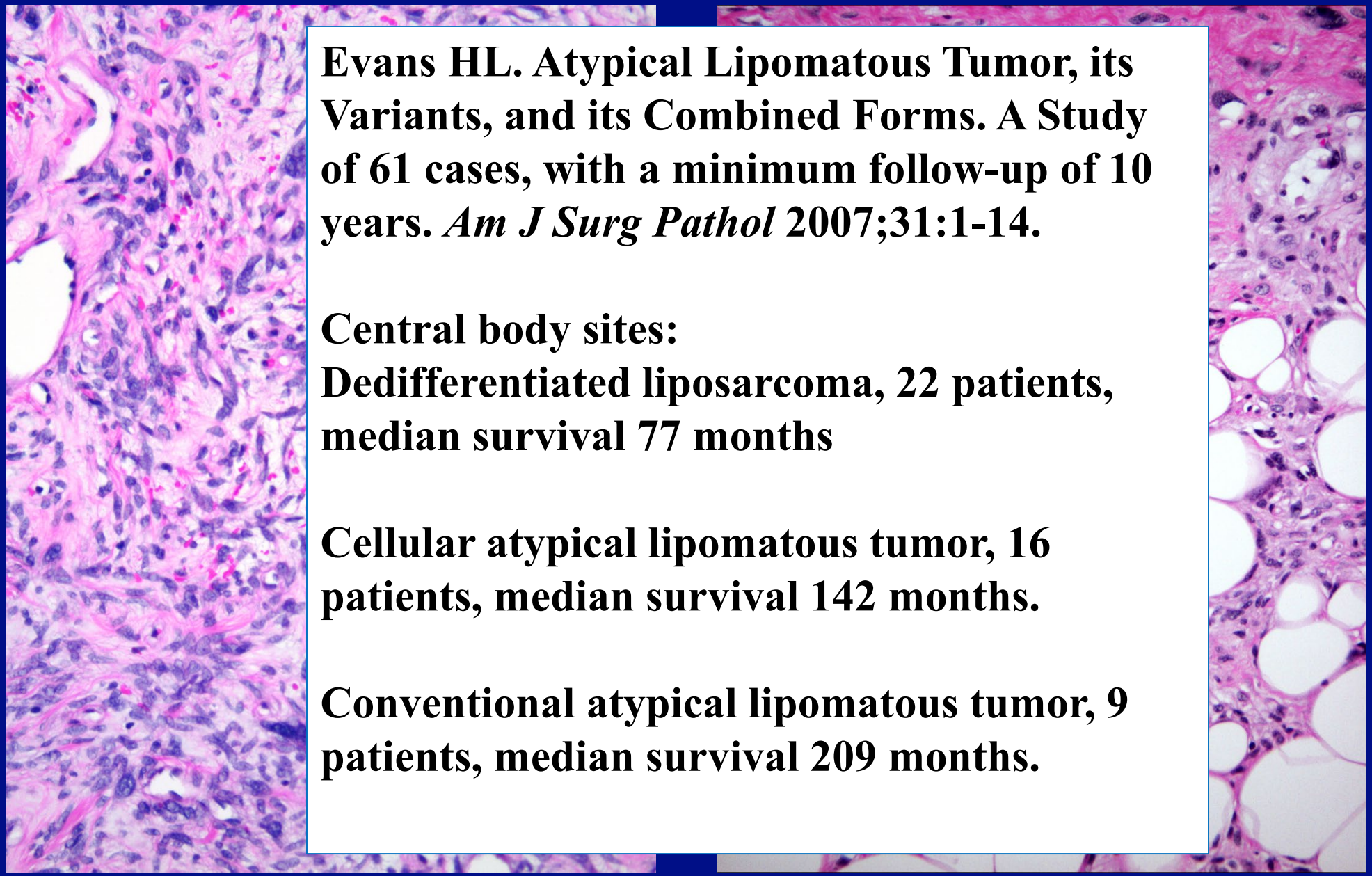
Watch out for STAT6! A subset of approximately 10% of dedifferentiated LPS express STAT6, IHC and FISH

Doyle LA, et al. Modern Pathology 2014;27:1231-1237

Does low grade dedifferentiated LPS exist?



How do we differentiated cellular ALT from dedifferentiated liposarcoma?



Evans HL. Atypical Lipomatous Tumor, its Variants, and its Combined Forms. A Study of 61 cases, with a minimum follow-up of 10 years. *Am J Surg Pathol* 2007;31:1-14.

Central body sites:
Dedifferentiated liposarcoma, 22 patients, median survival 77 months

Cellular atypical lipomatous tumor, 16 patients, median survival 142 months.

Conventional atypical lipomatous tumor, 9 patients, median survival 209 months.

TABLE 1. Evidence-based Definition for DL

An epithelioid to spindle cell sarcoma, with at least 5 MF/10 HPF focally, which may exhibit heterologous (eg, rhabdomyosarcomatous, osteosarcomatous) or homologous (eg, pleomorphic liposarcoma) elements, occurring in the following scenarios:

(1) Arising concomitantly with ALT/WDL, as an abrupt or less commonly gradual transition (primary or de novo DL)

(2) Arising as a local recurrence from the same anatomic site of a previously documented ALT/WDL (secondary DL)

(3) In the absence of a concomitant (1) or prior (2) ALT/WDL, confirmed molecularly (eg, *MDM2* gene amplification)

ALT/WDL indicates atypical lipomatous tumor/well-differentiated liposarcoma; DL, dedifferentiated liposarcoma; MF, mitotic figures.

cellularity in DL. Instead, the reader is left to make their own judgments regarding distinguishing features.

We all need to learn from our dogs!

Focus on the present and relationships.