



Soft Tissue Pathology: Common Diagnostic Dilemmas

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Disclosures

Relevant financial relationships:

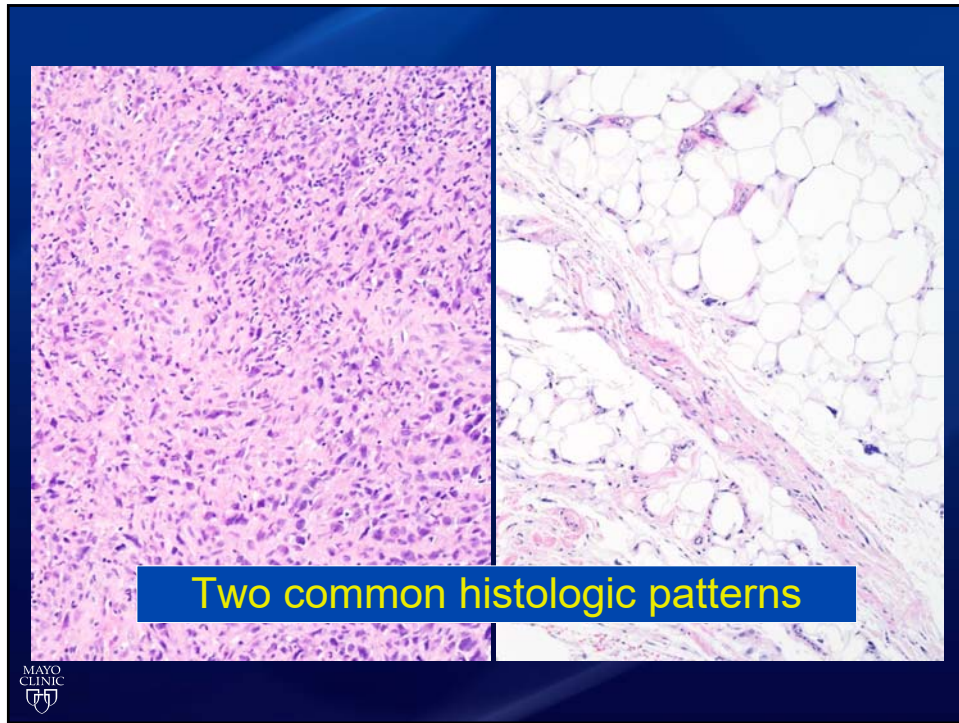
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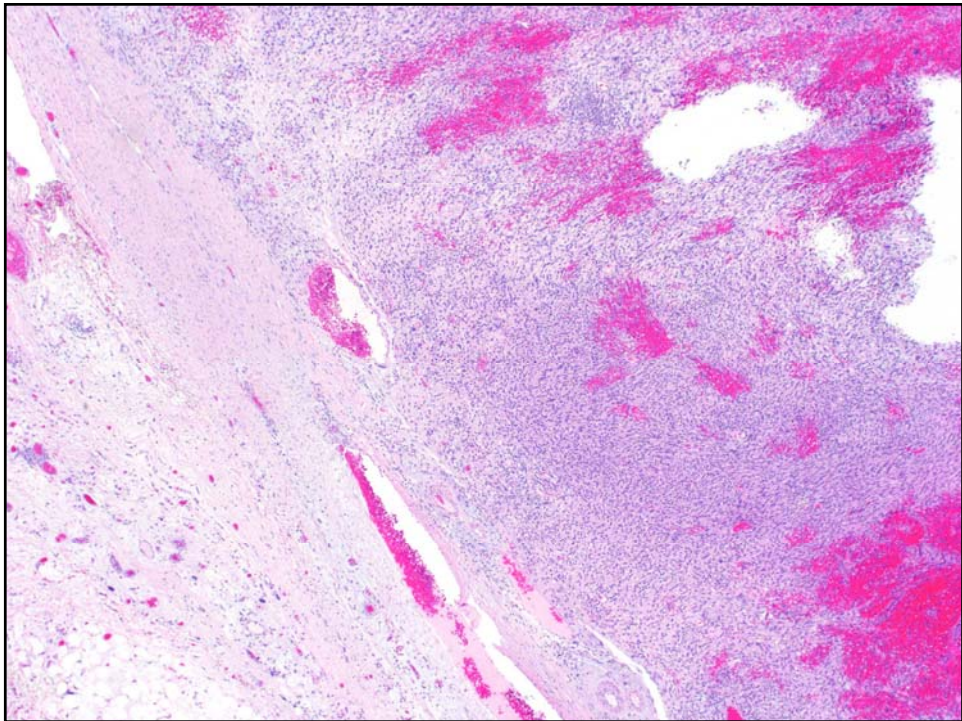
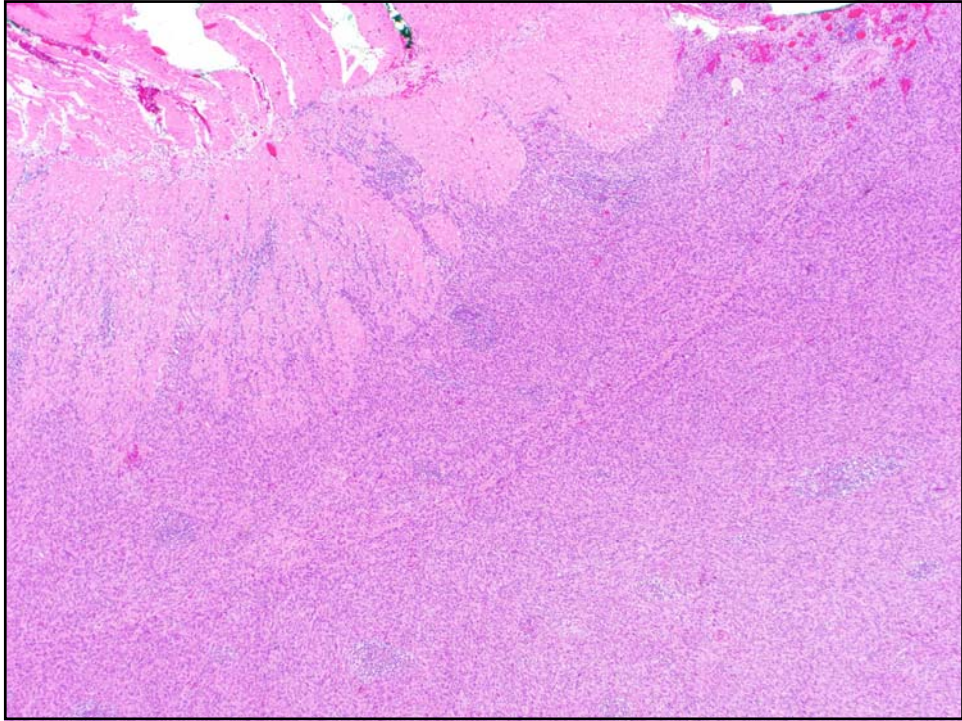


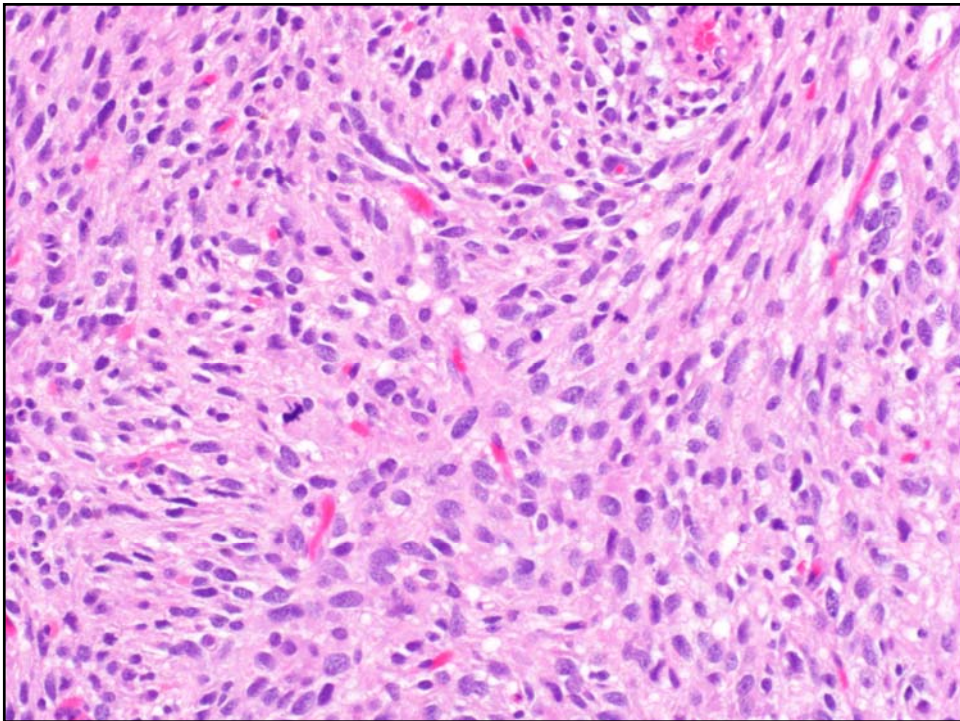
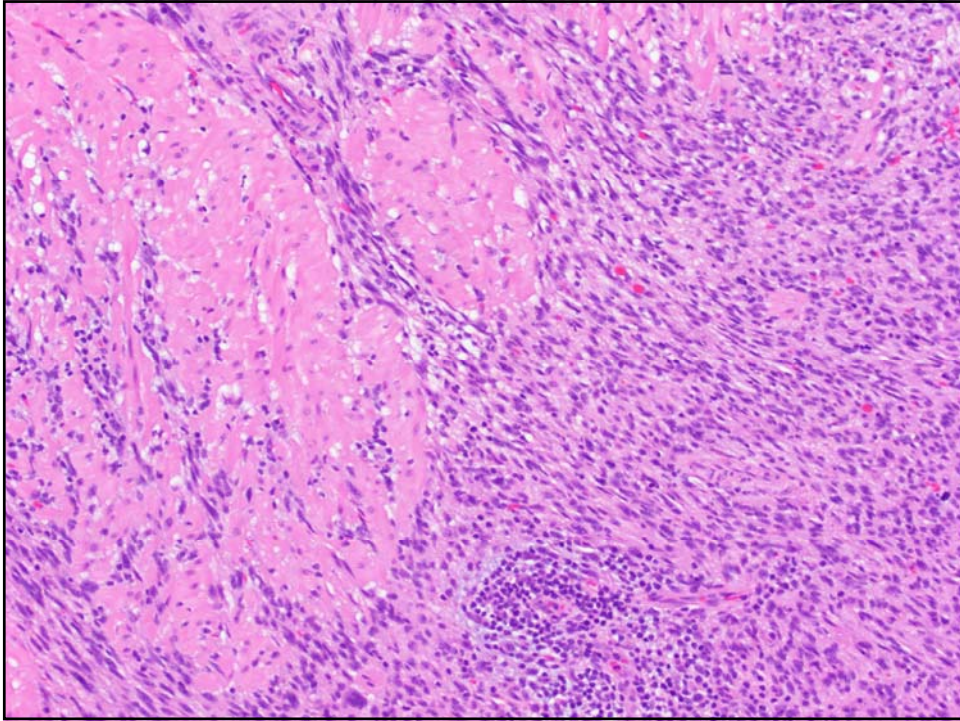
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Case 1

53-year-old man presenting with a 15 cm intraabdominal mass, adherent to ileum and large bowel

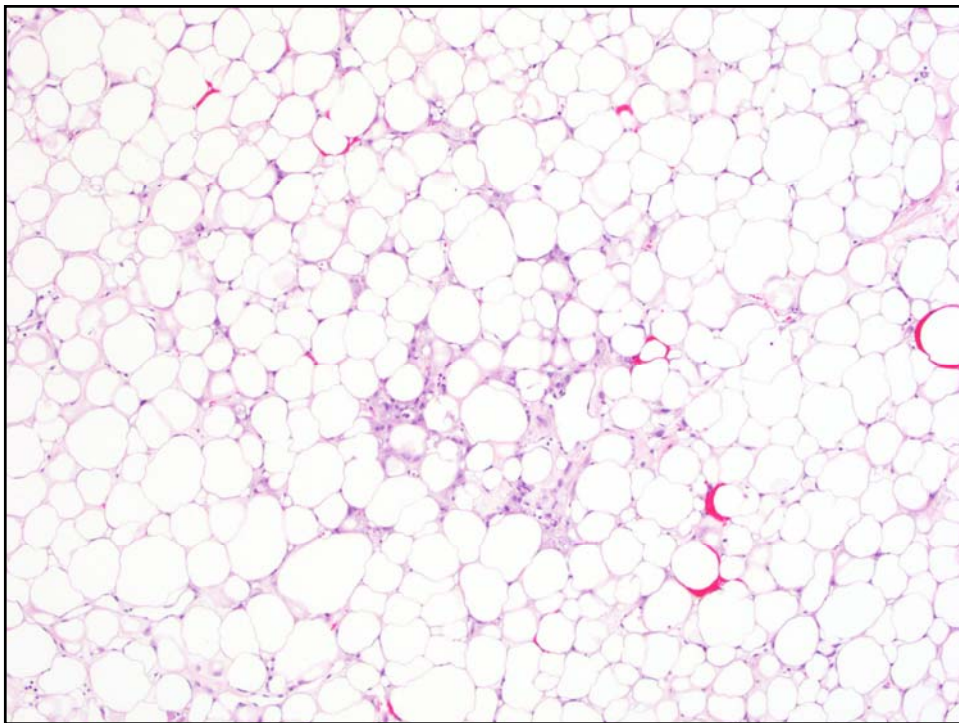
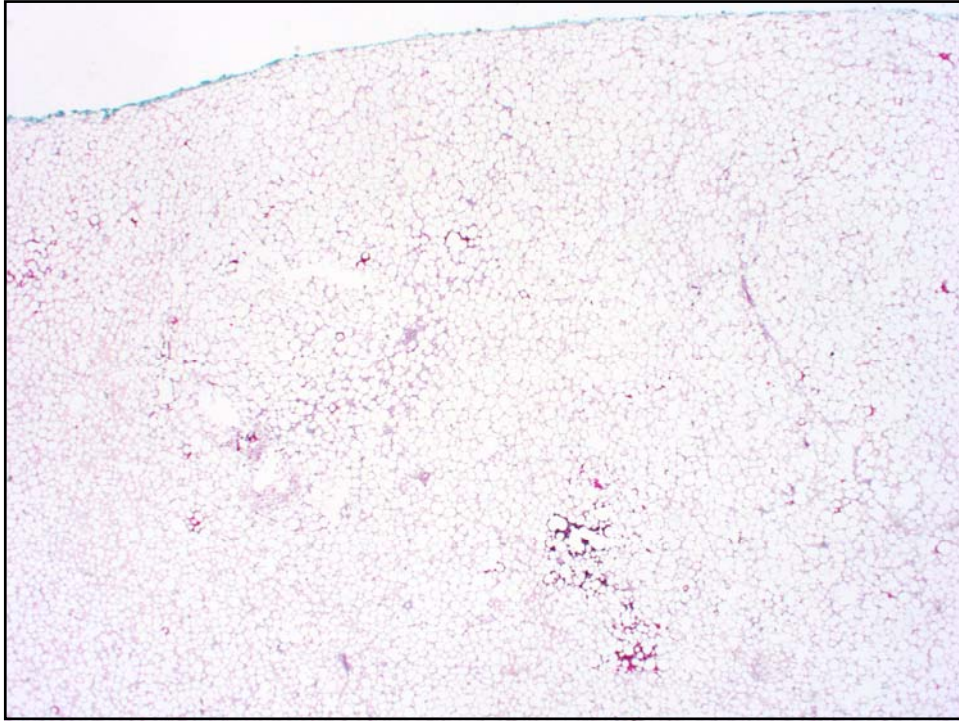


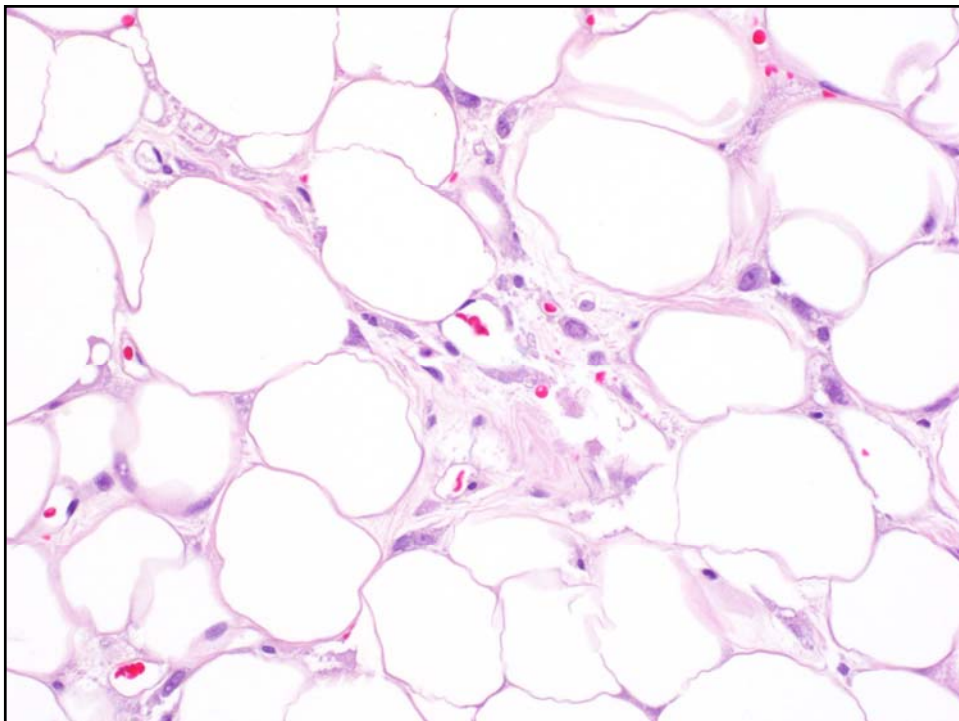
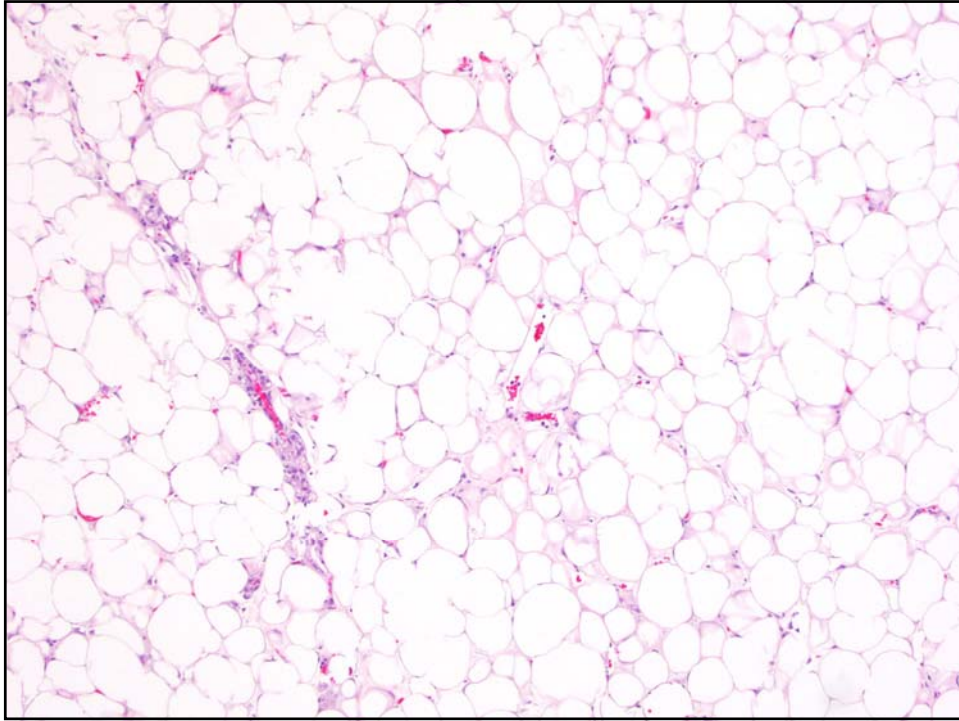


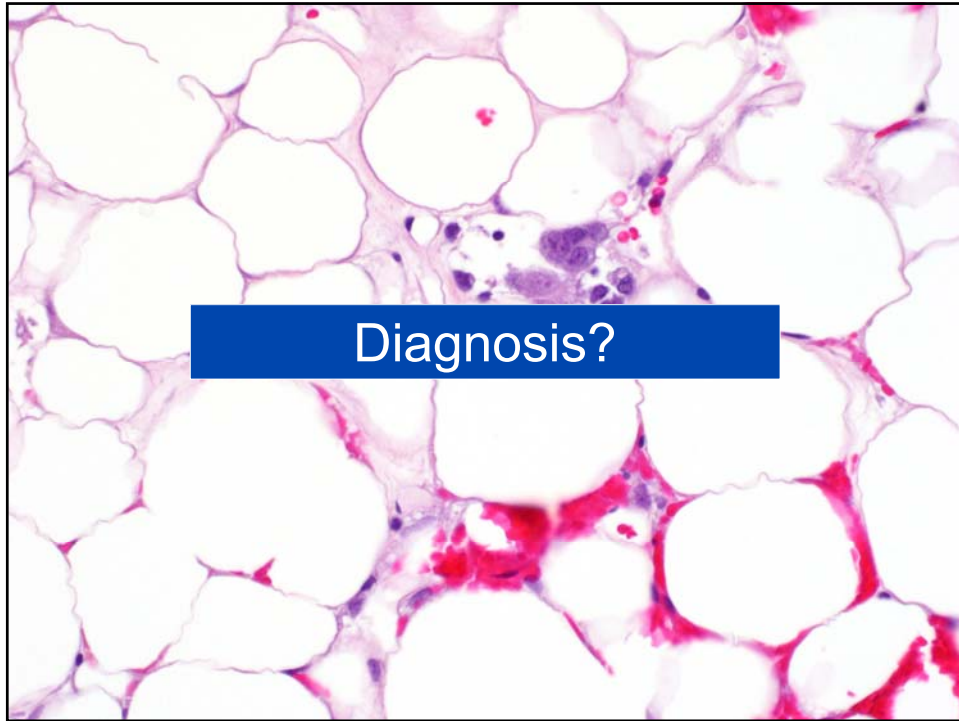


Case 2

49-year-old woman presenting with a 4.7 cm retroperitoneal mass, surgically excised







Learning Objectives

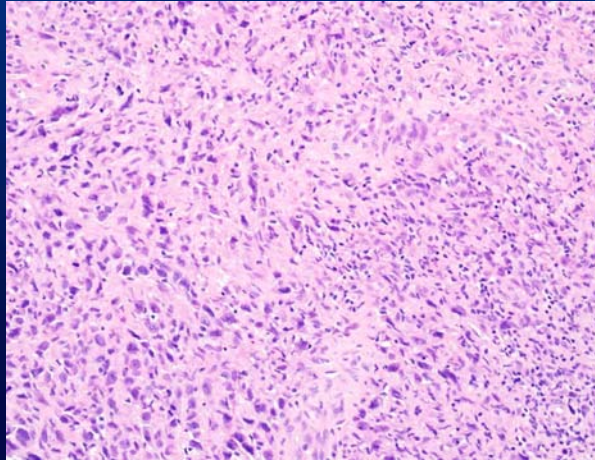
Pleomorphic sarcomatoid neoplasms:

1. Review diagnostic approach
2. Understand importance of sub-classification

Well-differentiated lipomatous neoplasms:

1. Review diagnostic approach
2. Understand utility and indications for *MDM2* FISH

Pleomorphic Sarcomatoid Neoplasms



Where do I start?



Main Diagnostic Issues

1. Exclude non-sarcomatous tumors



Cancer statistics

	New cases	Deaths
All sites	1,660,290	580,350
GI tract	290,200	144,570
Lung	246,210	163,890
Breast	234,580	40,030
Melanoma	76,690	9,480
Lymphoma	79,030	20,200
Soft tissue	11,410	4,390



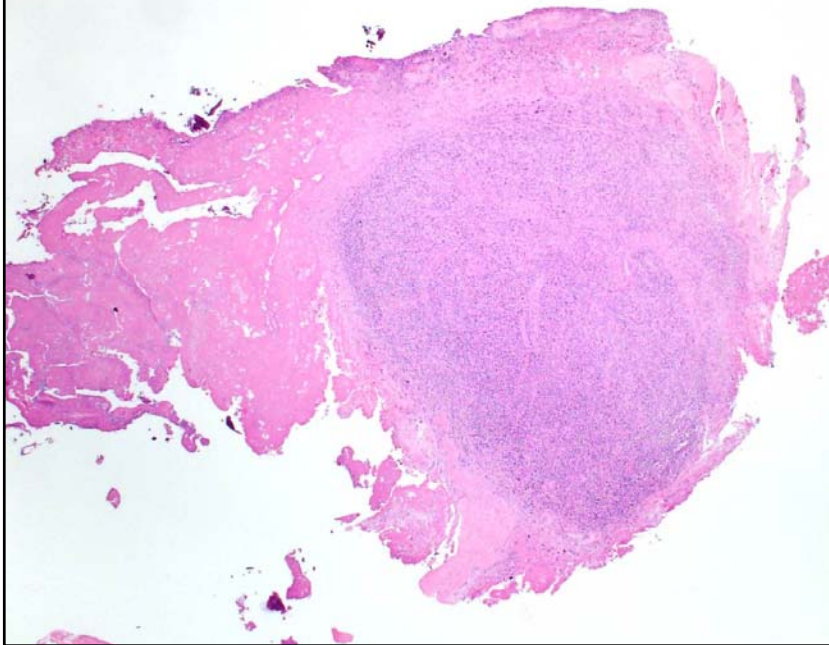
American Cancer Society, 2013

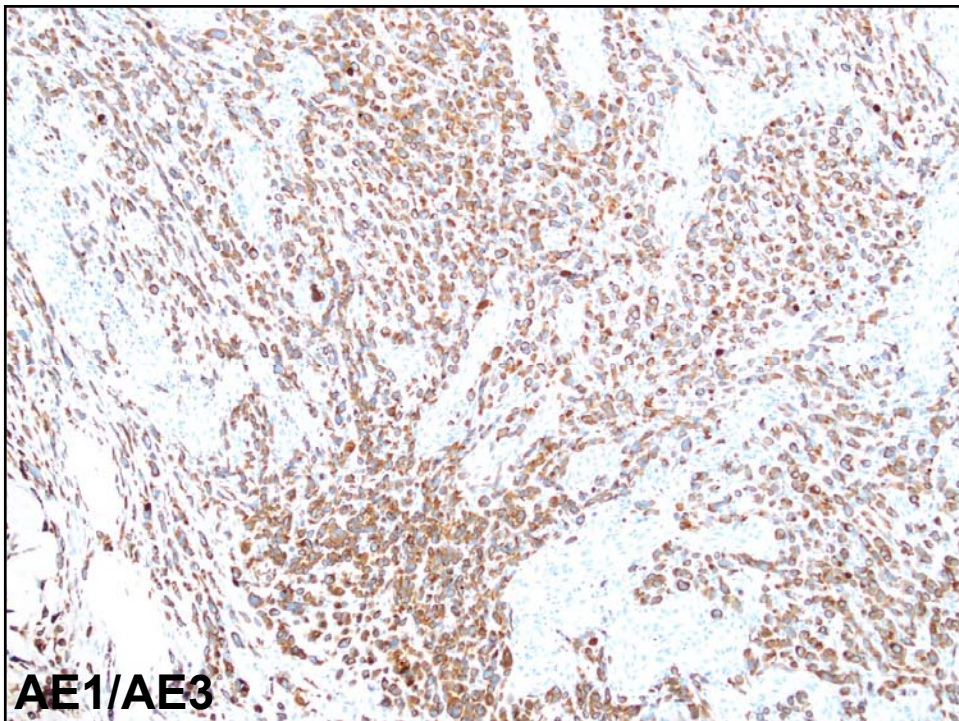
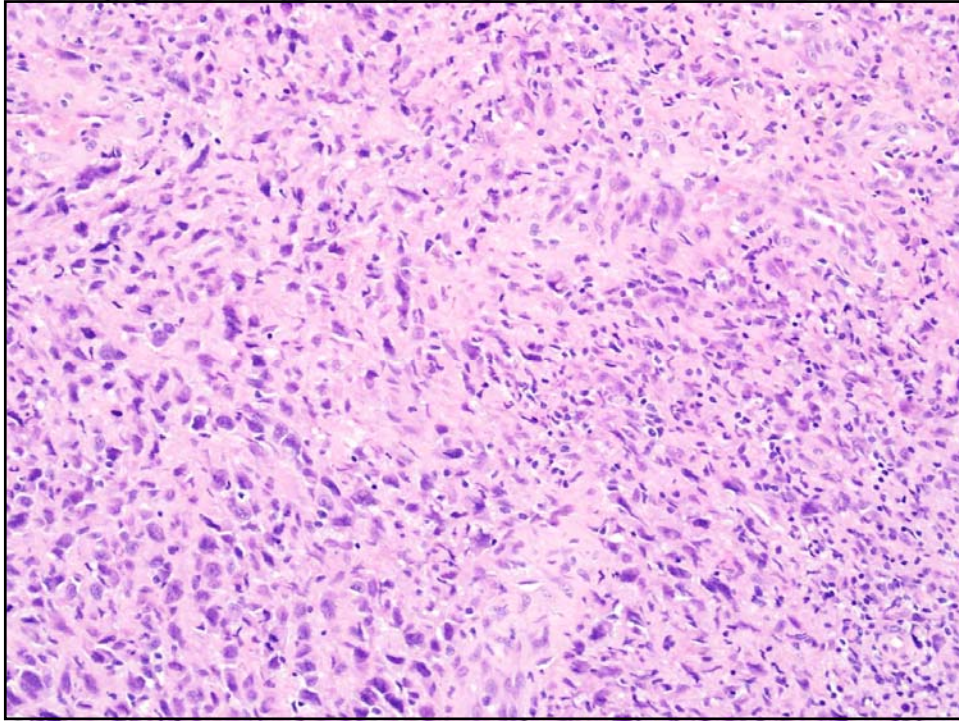
Step 1: Exclude carcinoma, melanoma, lymphoma

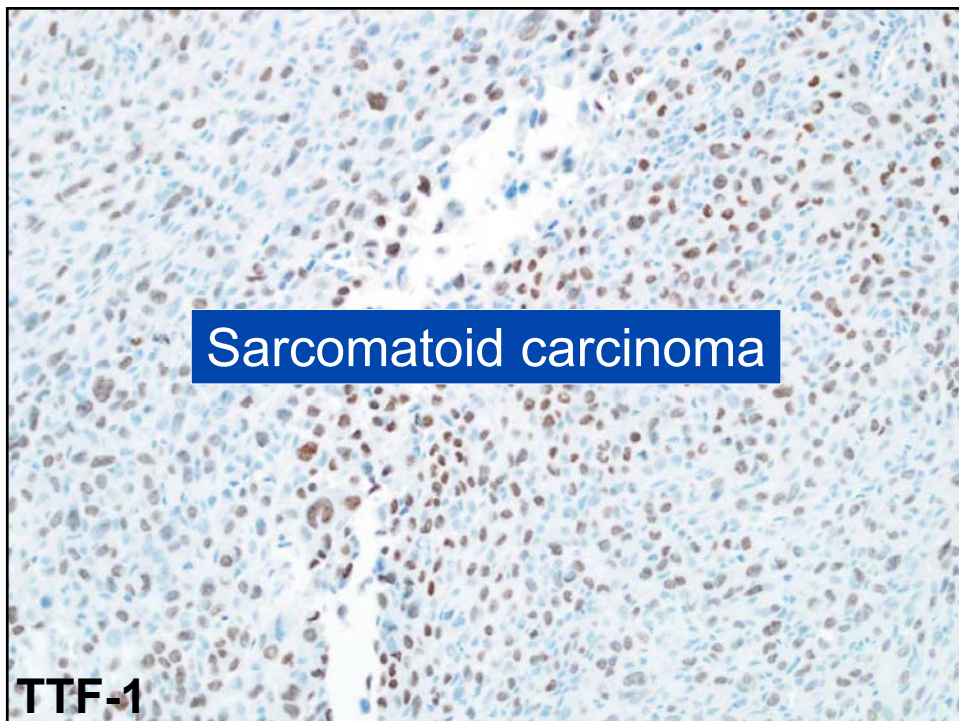
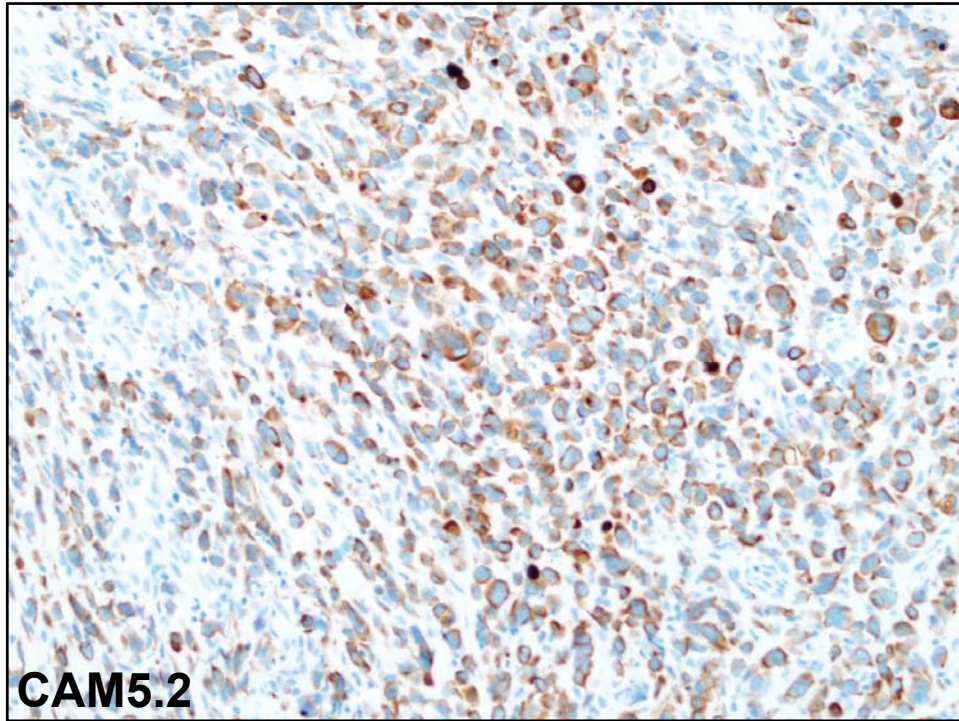
- Clinical history
- Histologic clues
- Immunohistochemistry
 - Keratins (AE1/AE3, CAM5.2, CK5/6)
 - S-100 +/- HMB45, melanA, tyrosinase
 - Hematolymphoid markers



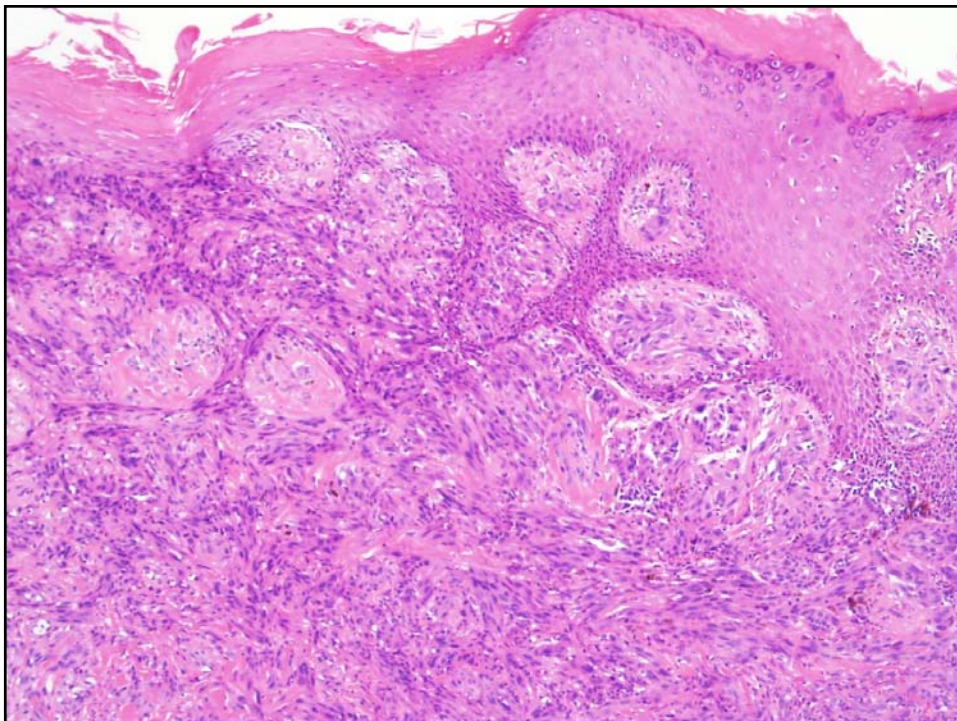
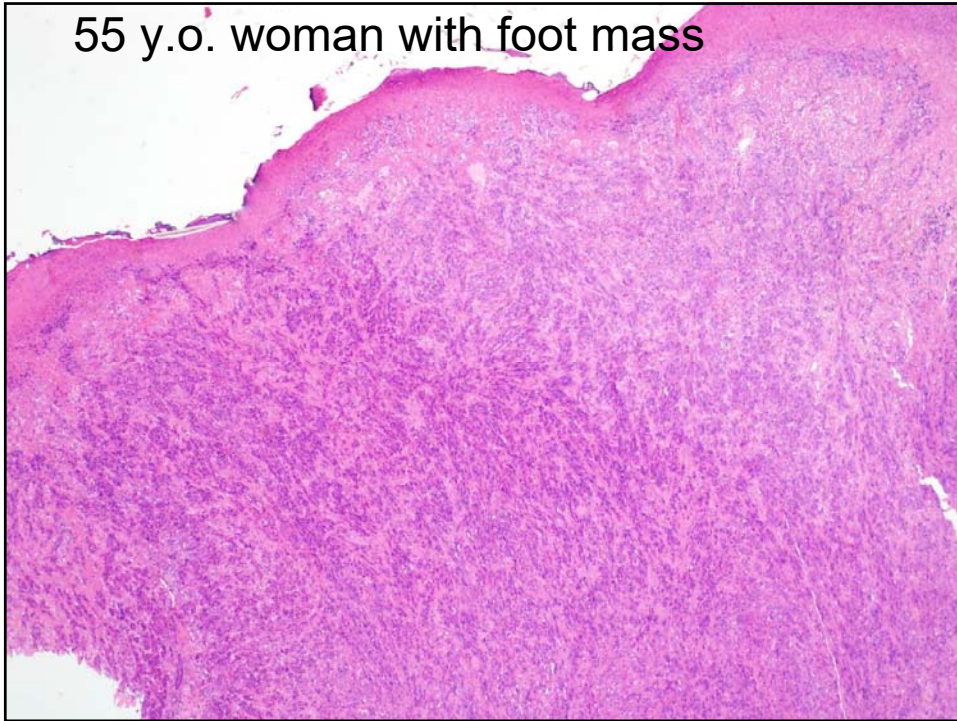
80 y.o. man with thigh mass

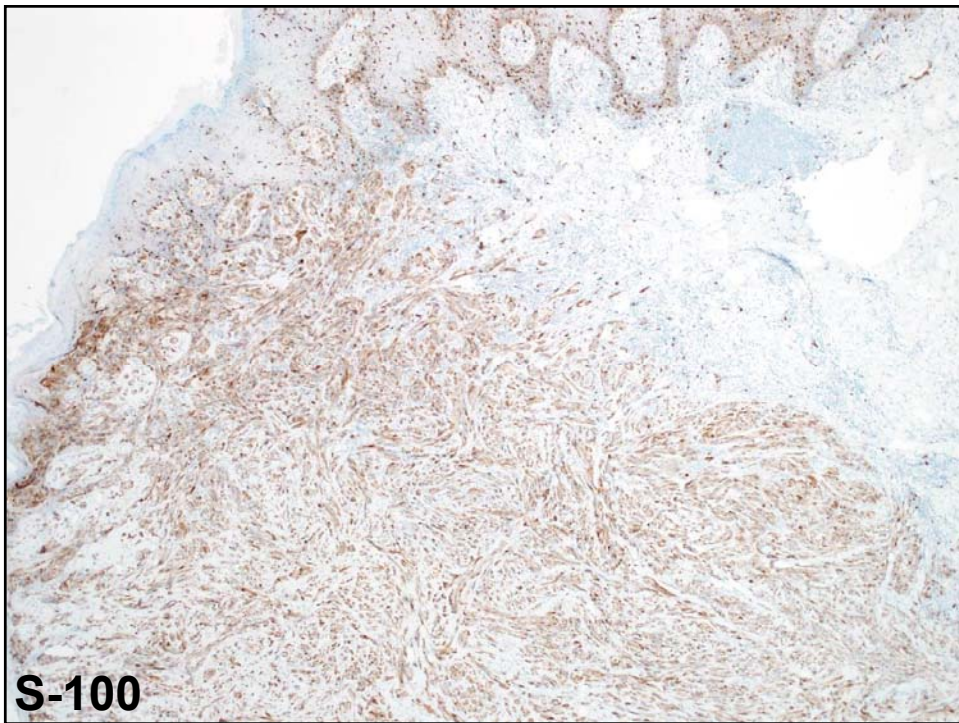
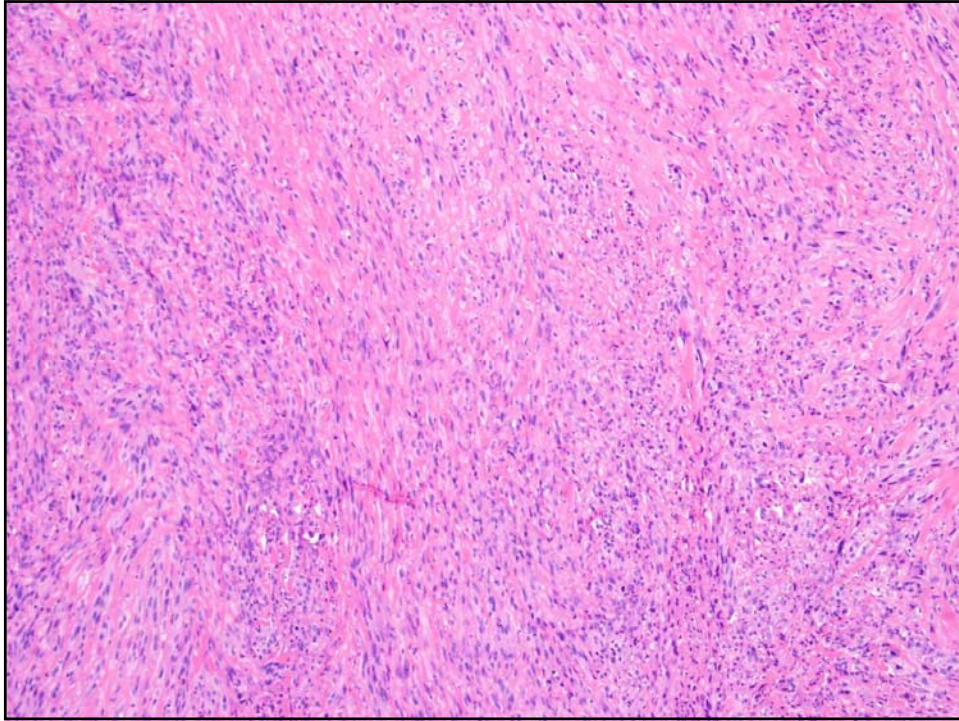




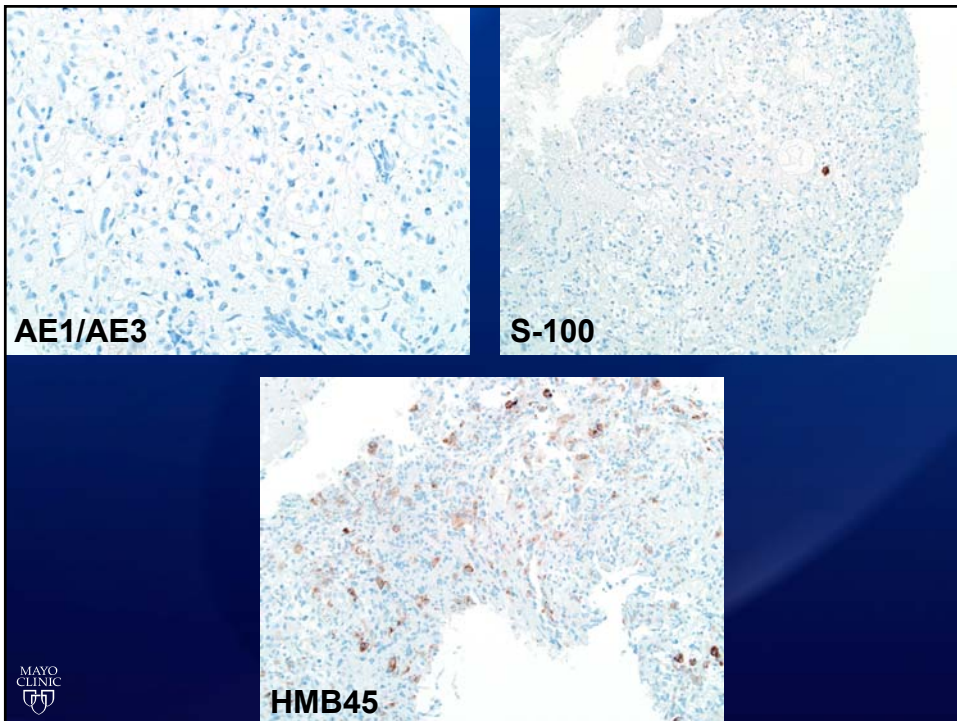
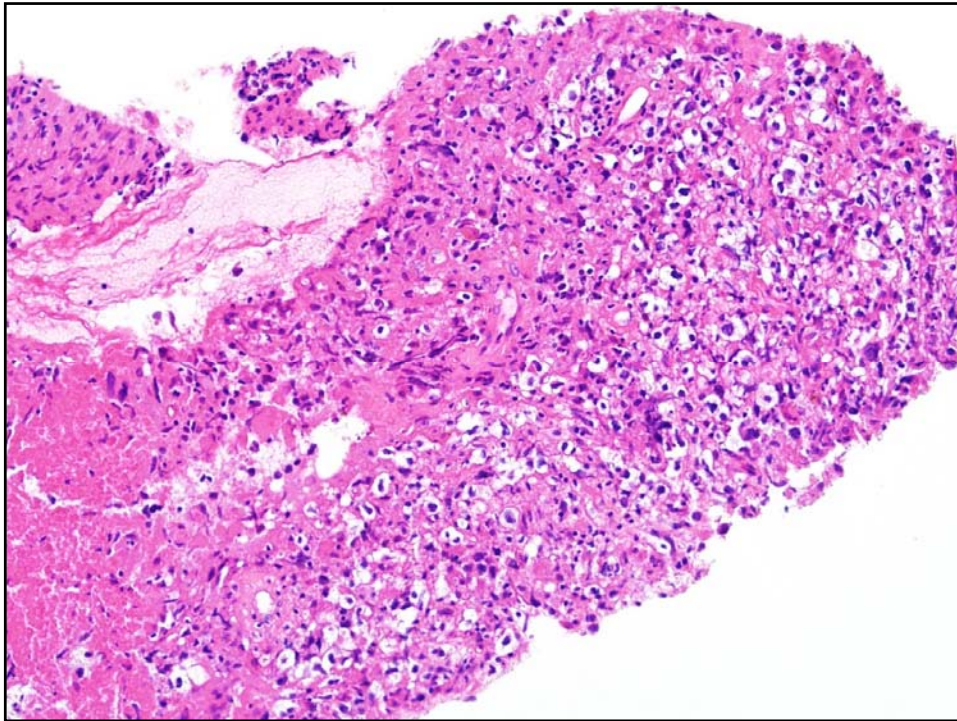


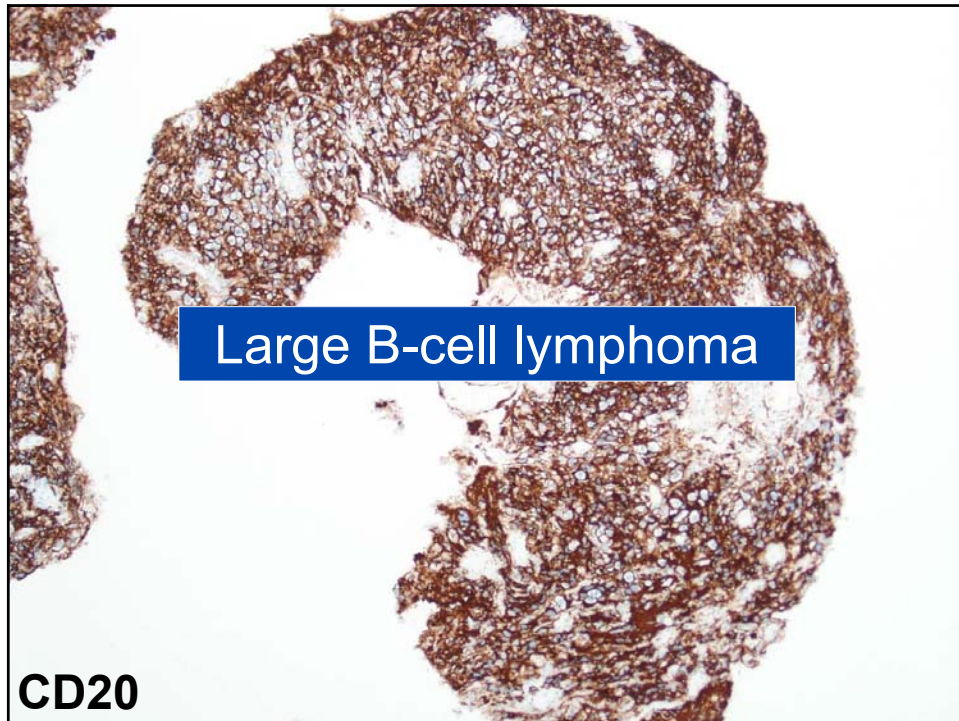
55 y.o. woman with foot mass







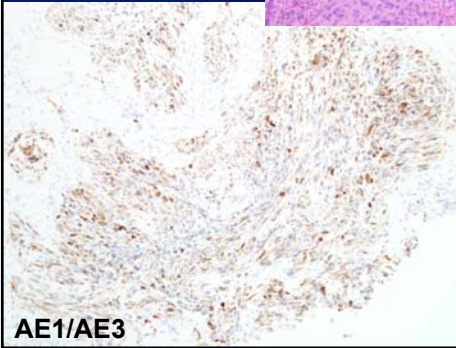
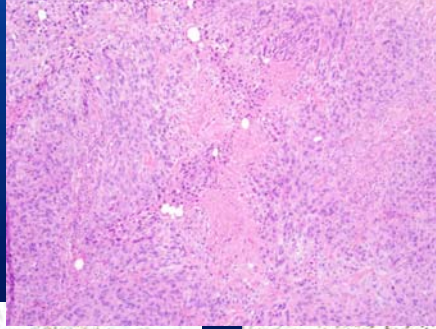




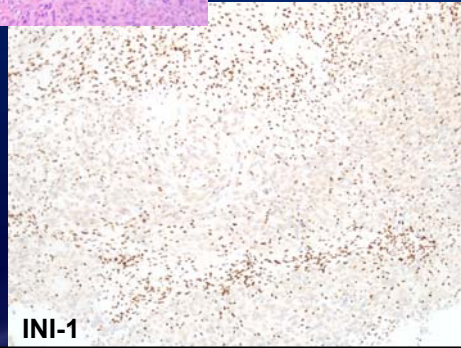
Pitfalls

- Epithelioid sarcoma
- Aberrant keratin expression in sarcoma
- S-100 positive dendritic cells
- Clear cell sarcoma

Epithelioid sarcoma

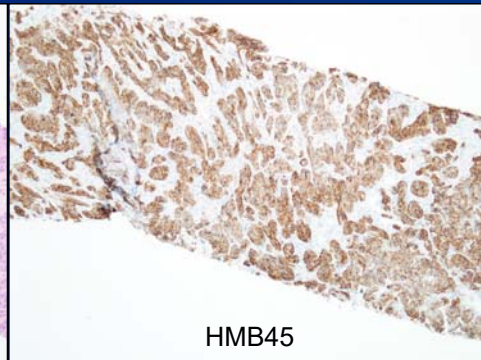
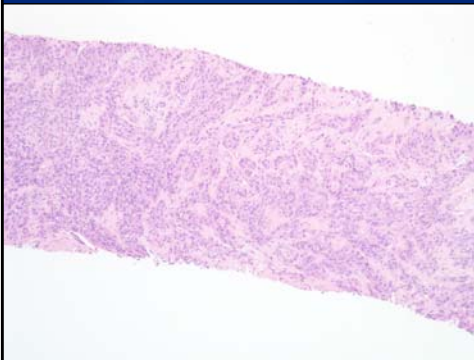


AE1/AE3



INI-1

Clear cell sarcoma



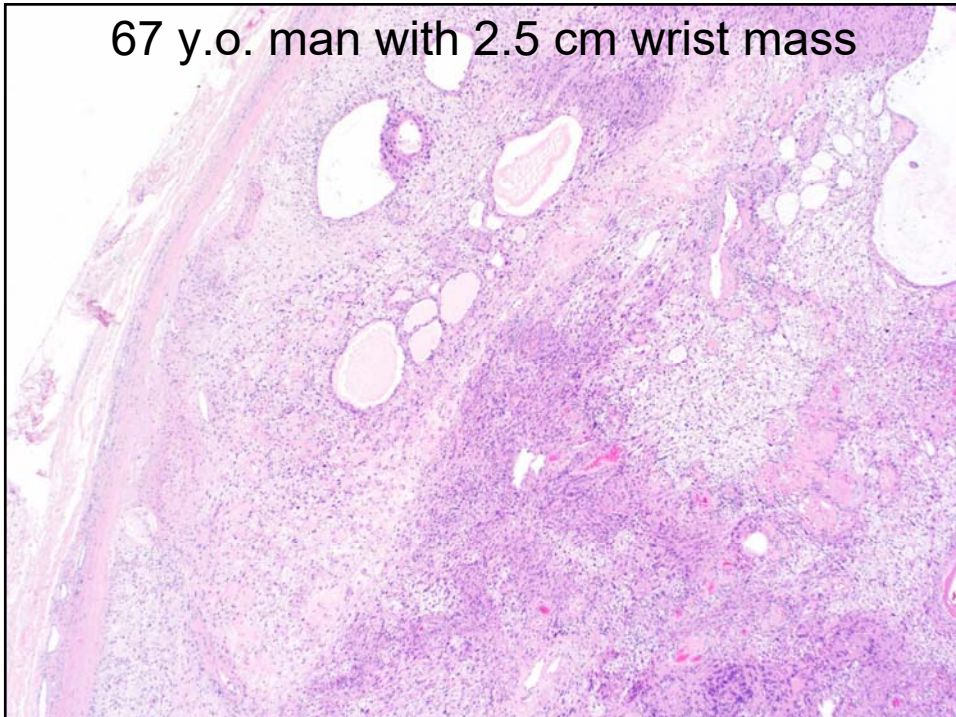
HMB45

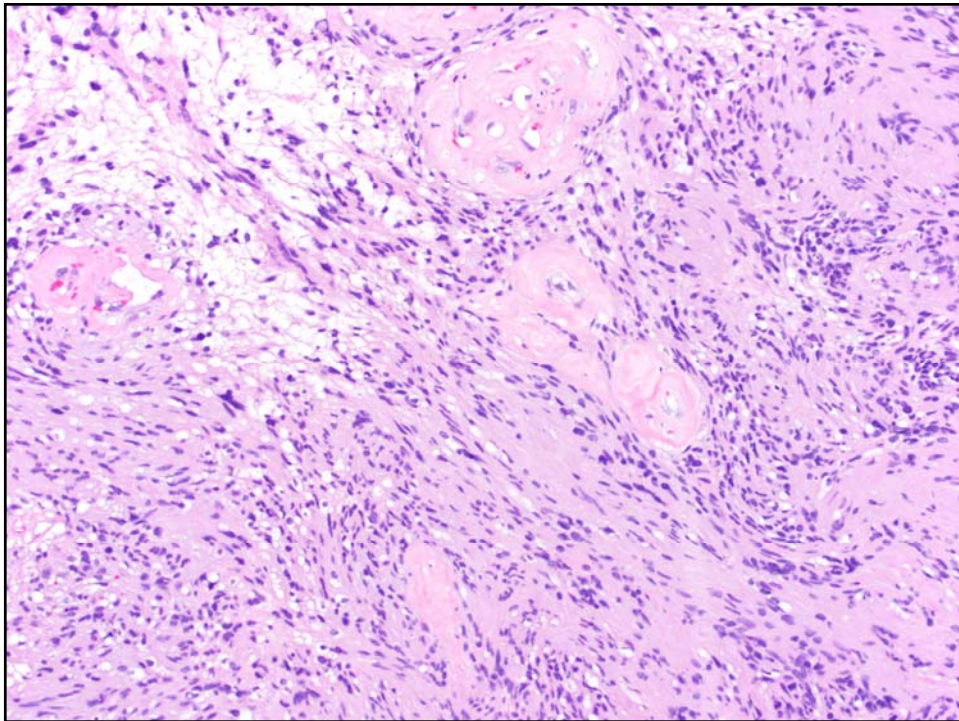
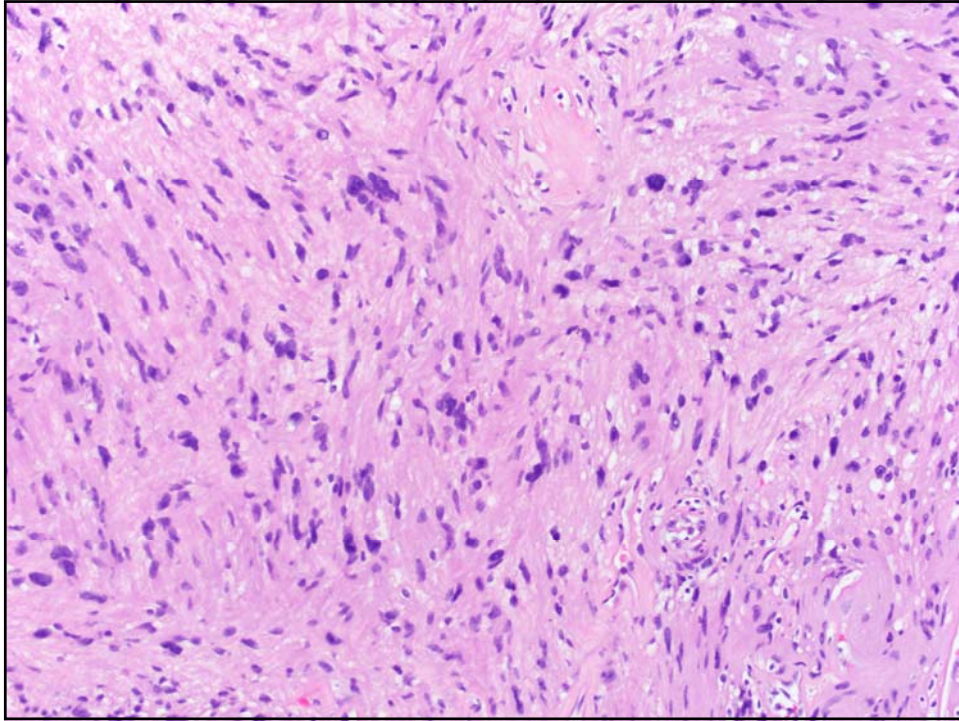
Main Diagnostic Issues

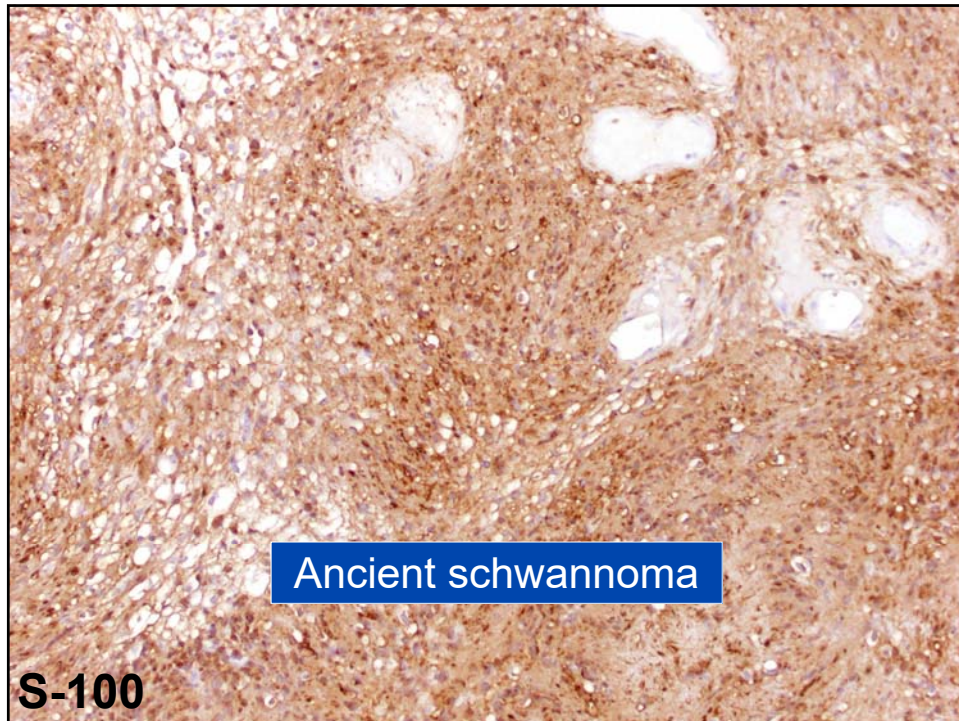
1. Exclude non-sarcomatous tumors
2. Consider benign mimics



67 y.o. man with 2.5 cm wrist mass







Step 2: Exclude benign mimics

- Atypical fibroxanthoma (AFX)
- Pleomorphic lipoma
- Pleomorphic fibroma of skin
- “Ancient” schwannoma
- “Symplastic” leiomyoma of uterus
- Pleomorphic hyalinizing angiectatic tumor (PHAT)

Main Diagnostic Issues

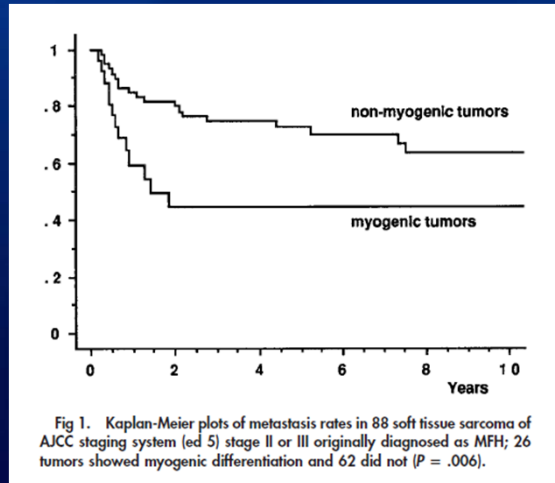
1. Exclude non-sarcomatous tumors
2. Consider benign mimics
3. Maximize efforts to subclassify, and avoid using “UPS” whenever possible



Why subclassify pleomorphic sarcomas?

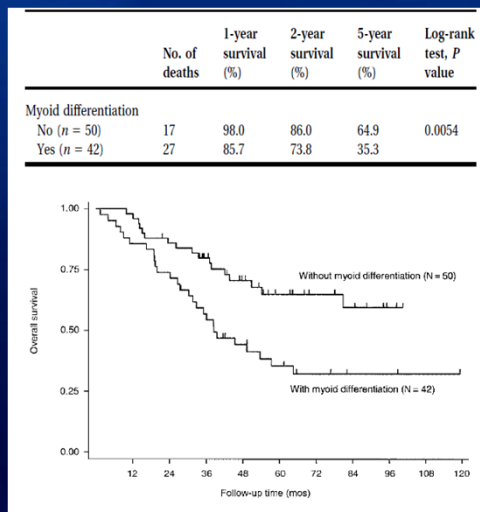


Not all pleomorphic sarcomas are created equal

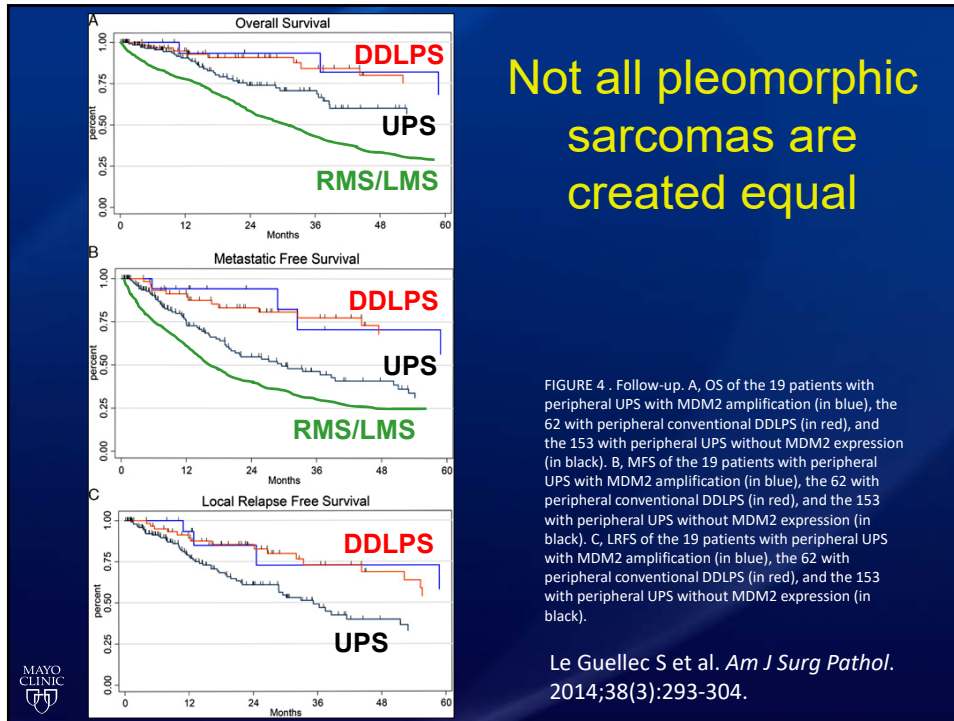


Fletcher CD, et al. *J Clin Oncol.* 2001;19:3045-50.

Not all pleomorphic sarcomas are created equal



Deyrup AT, et al. *Cancer* 2003;98:805-13.



Subtype-Specific Treatments

- GIST – imatinib
- Rhabdomyosarcoma – VAC
- DFSP, desmoids, TGCT – imatinib
- Myxoid/round cell liposarcoma -- trabectedin
- PEComas – sirolimus
- ASPS, malignant SFT, clear cell sarcoma -- sunitinib, pazopanib
- Liposarcoma – MDM2 inhibitors (trials)
- Leiomyosarcoma, liposarcoma – eribulin (trials)

Step 3: Subclassifying Pleomorphic Sarcomas

- Myogenic differentiation?
 - Pleomorphic leiomyosarcoma
 - Pleomorphic rhabdomyosarcoma
- Features of myxofibrosarcoma?
 - Myxofibrosarcoma (high grade)
- Atypical fat next to it?
 - Dedifferentiated liposarcoma
- Lipoblasts *within* it?
 - Pleomorphic liposarcoma
- Malignant osteoid?
 - Extraskeletal osteosarcoma
- No identifiable line(s) of differentiation?
 - Undifferentiated pleomorphic sarcoma

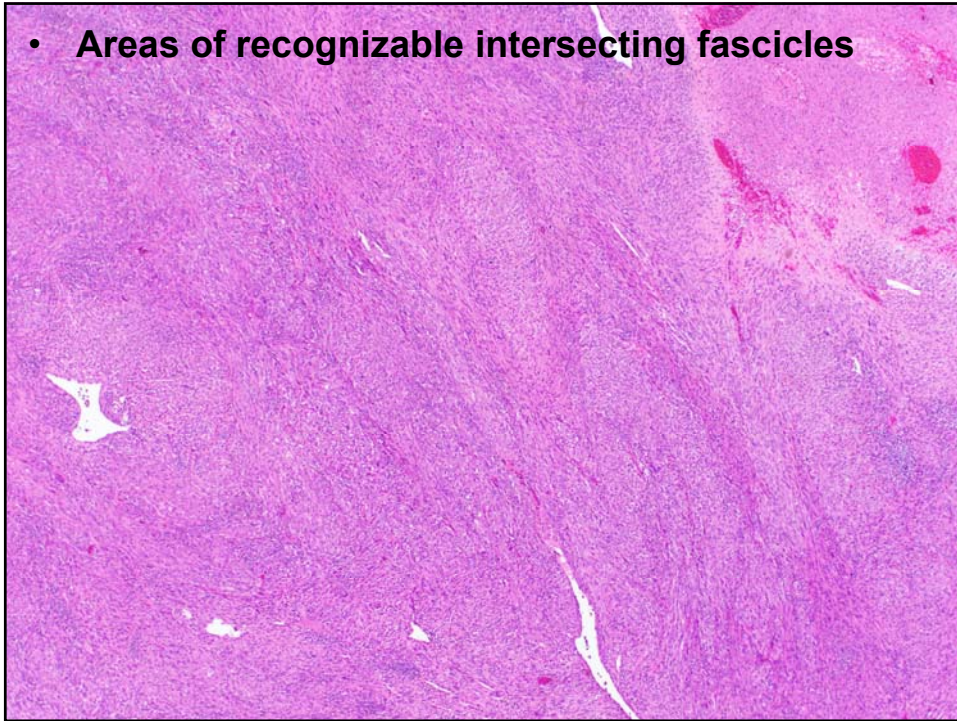


Pleomorphic Leiomyosarcoma

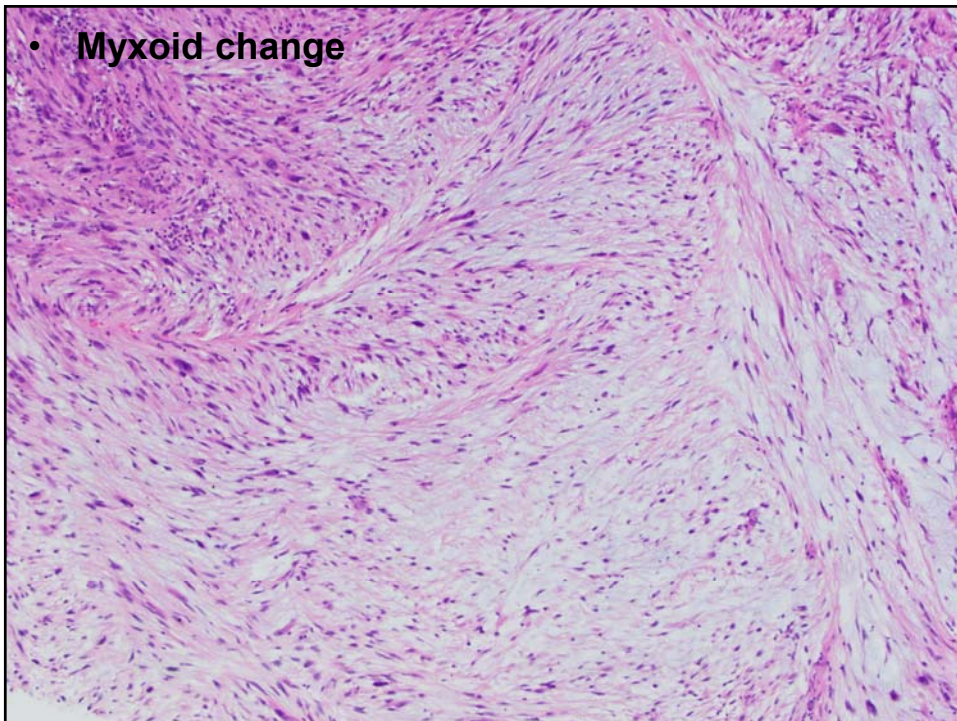
- Older adults
- M:F ratio – 1:2
- Retroperitoneum > abdominal cavity >> extremities
- 5-year metastasis: >60%
- 5-year survival: 50%



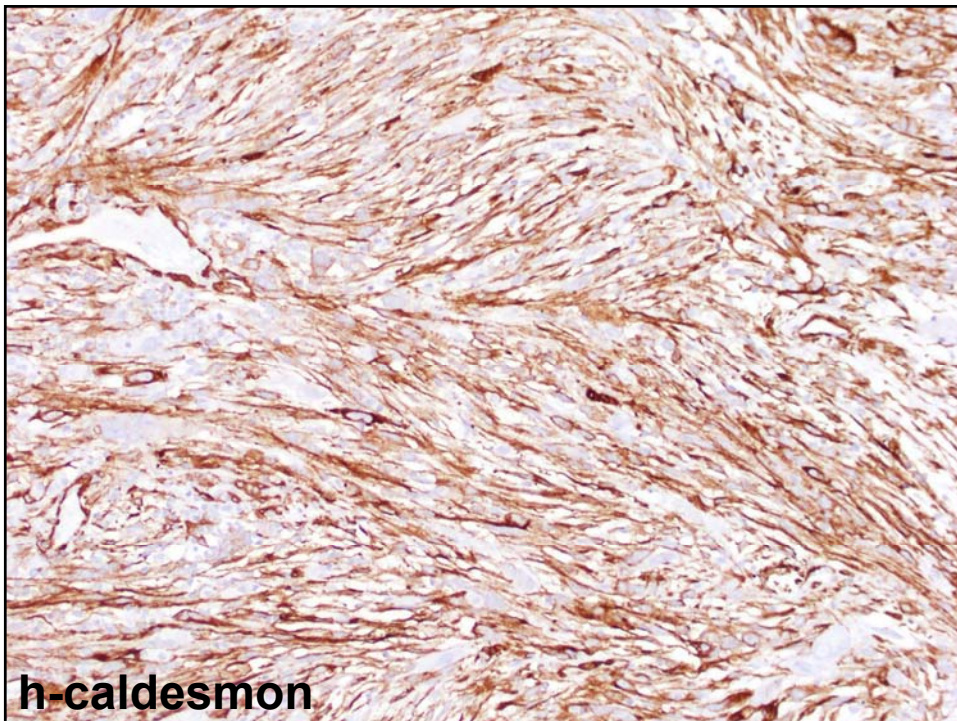
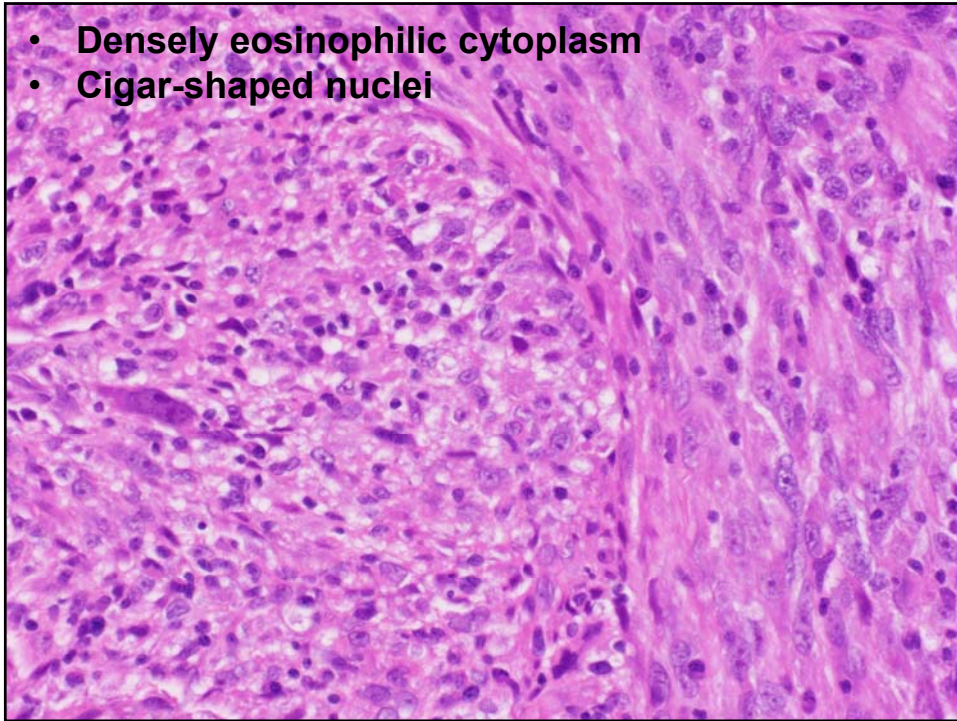
- **Areas of recognizable intersecting fascicles**



- **Myxoid change**



- **Densely eosinophilic cytoplasm**
- **Cigar-shaped nuclei**



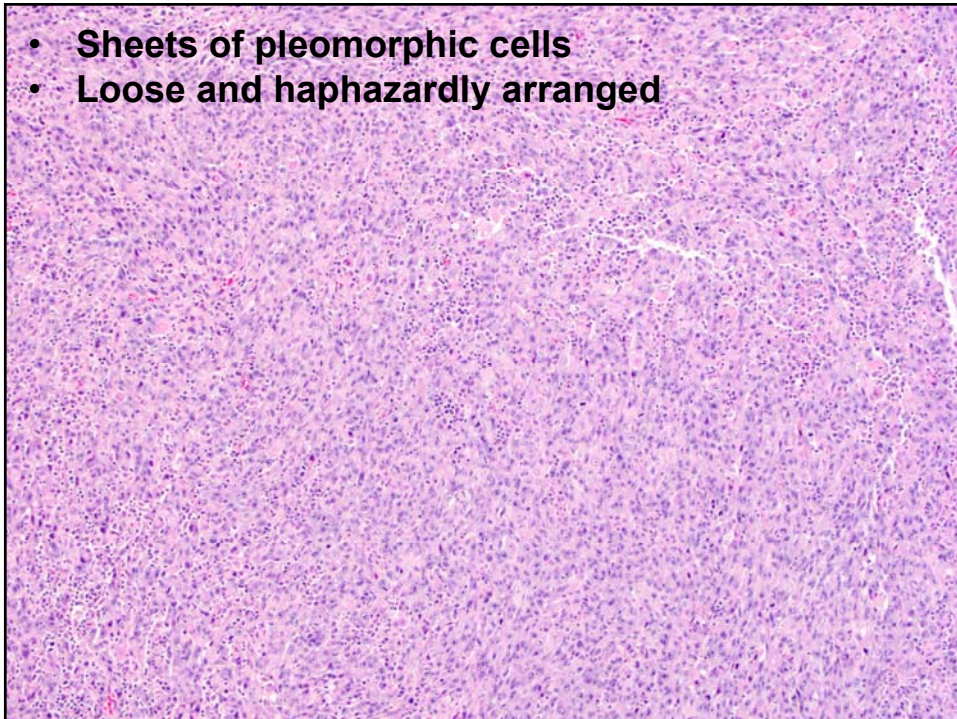
h-caldesmon

Pleomorphic Rhabdomyosarcoma

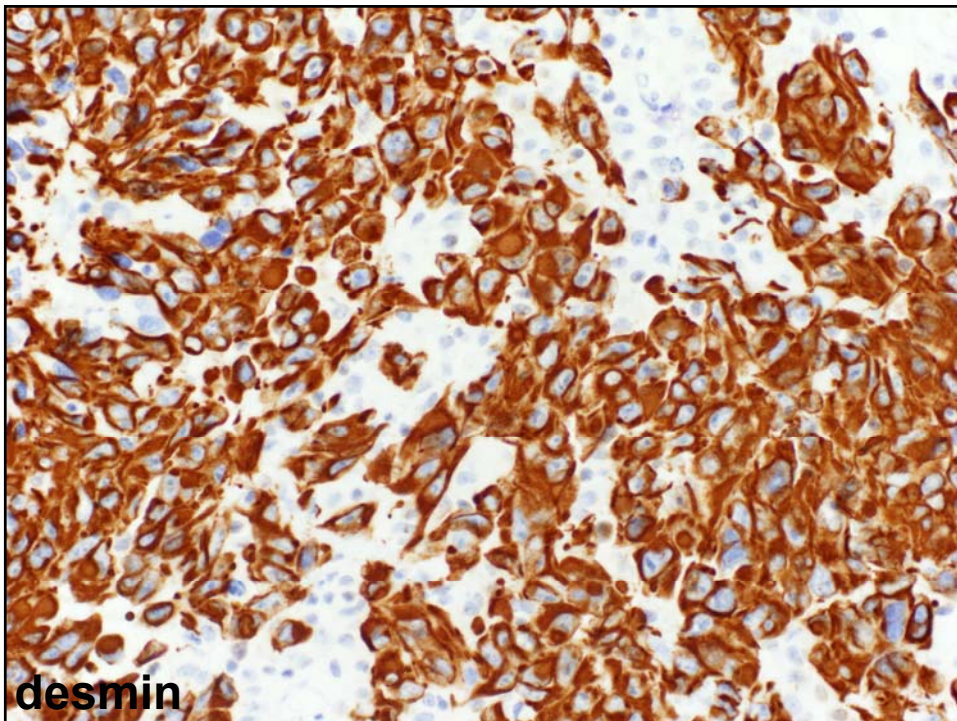
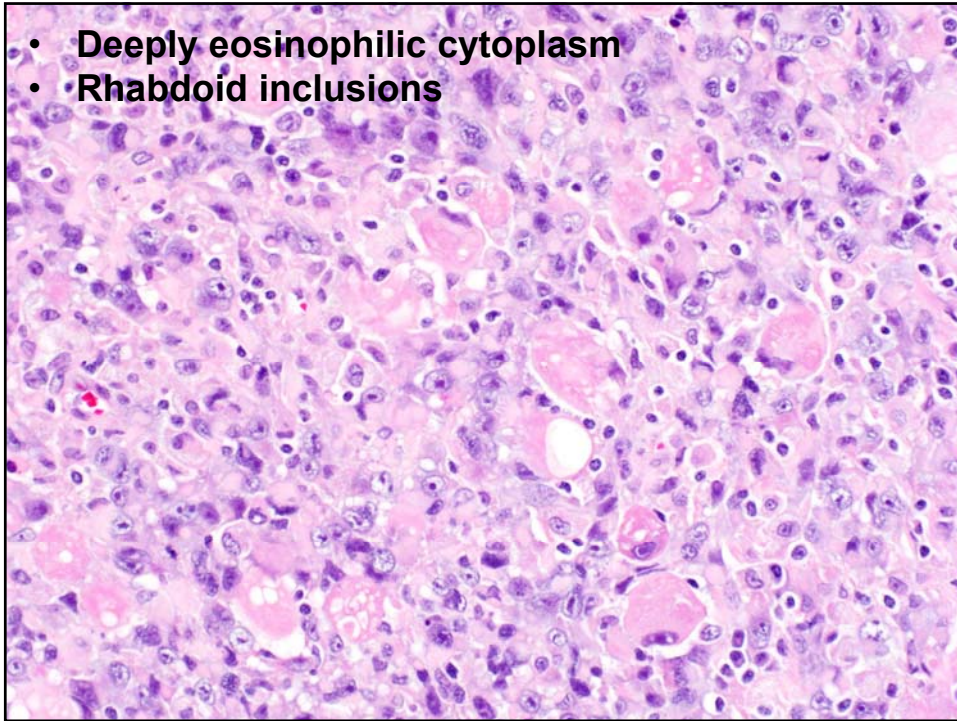
- Almost exclusively in older adults
- More common in men
- Deep soft tissues of extremities (especially thigh)
- 5-year metastasis: >80%
- 5-year survival: 10-15%

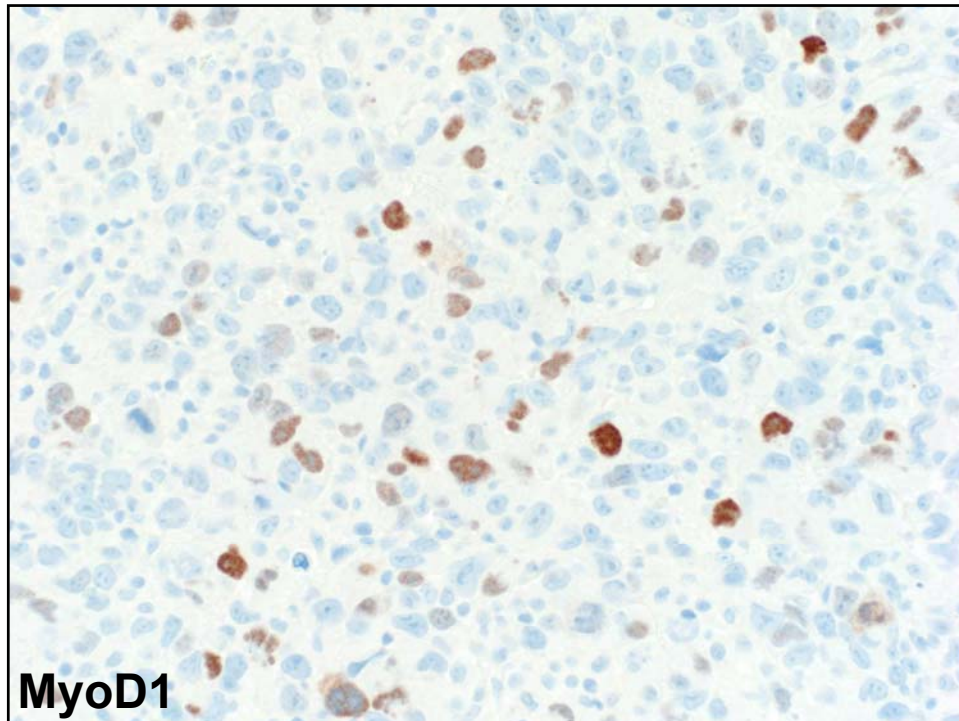


- **Sheets of pleomorphic cells**
- **Loose and haphazardly arranged**



- Deeply eosinophilic cytoplasm
- Rhabdoid inclusions





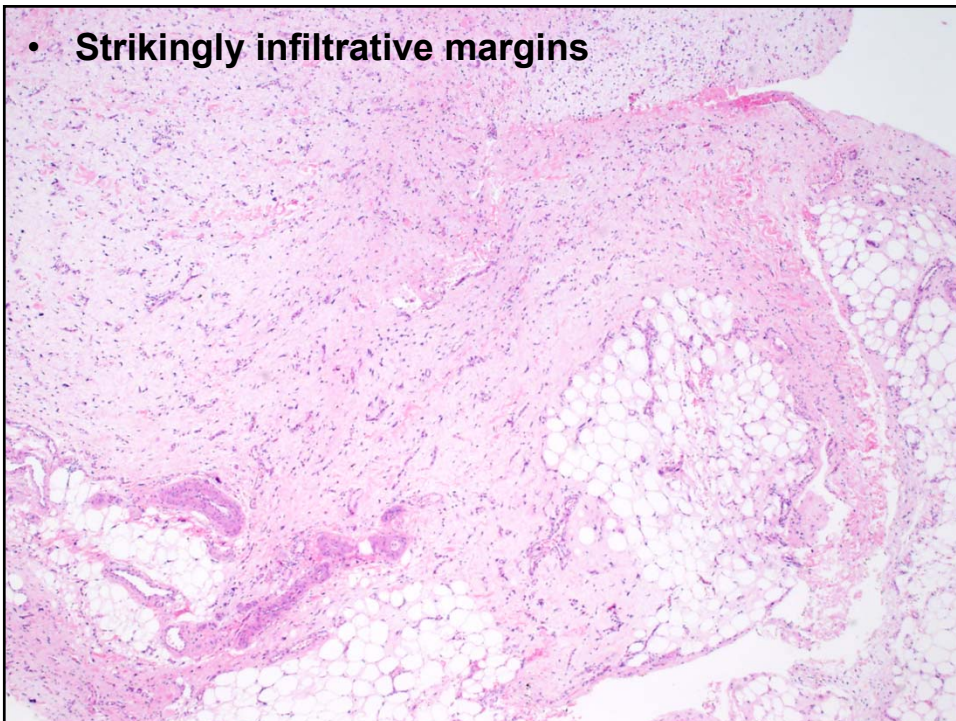
Myxofibrosarcoma

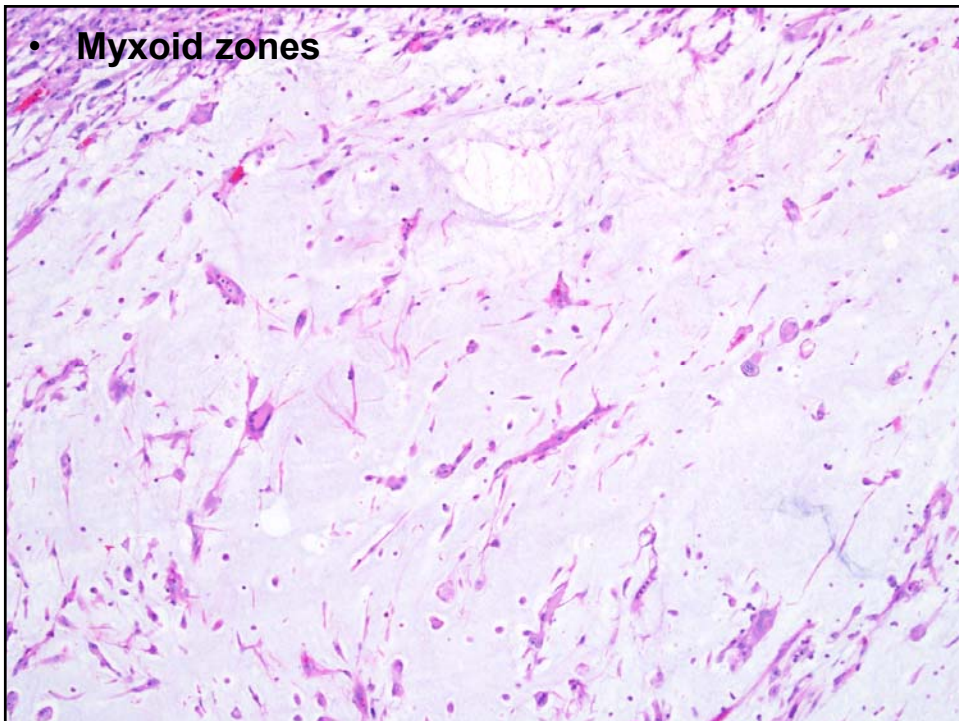
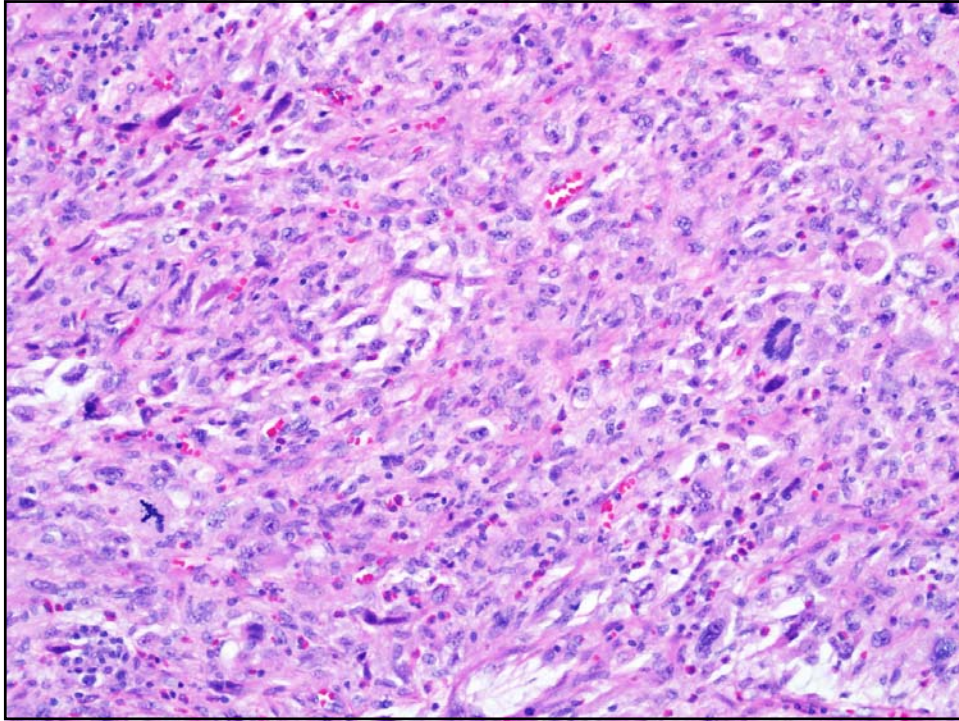
- Old term: “Myxoid MFH”
- Elderly (6th-8th decades)
- Limbs (lower ext > upper ext)
- ~2/3 arise in subcutaneous location
- Atypia and myxoid stroma vary
- 5-year metastasis: 30-35%
- 5-year survival: 50-70%

- **Subcutaneous**
- **Lobulated**

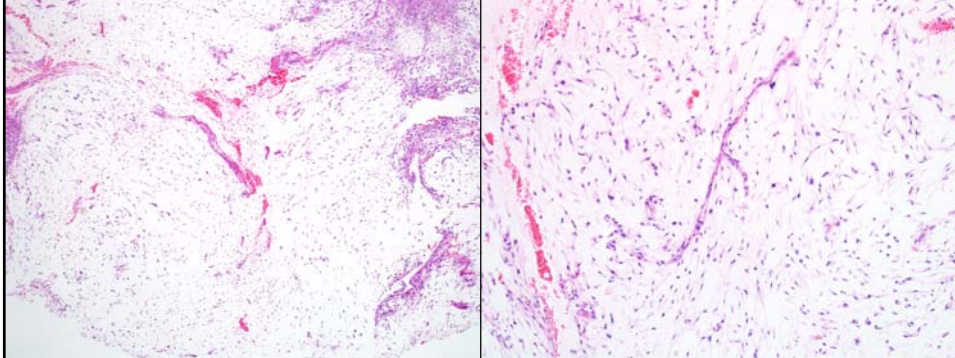


- **Strikingly infiltrative margins**





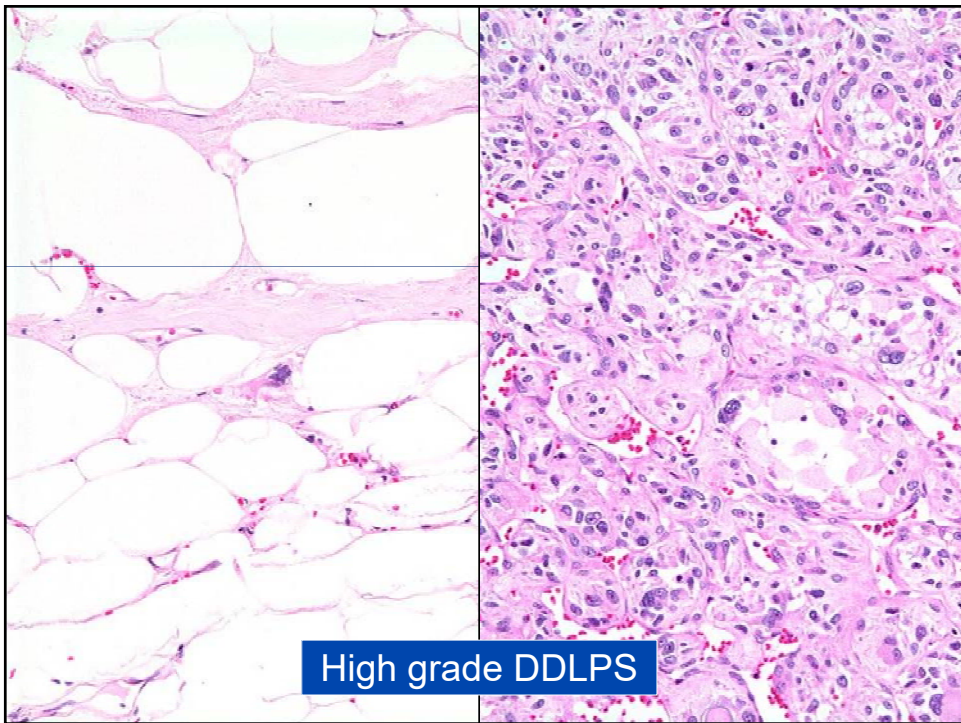
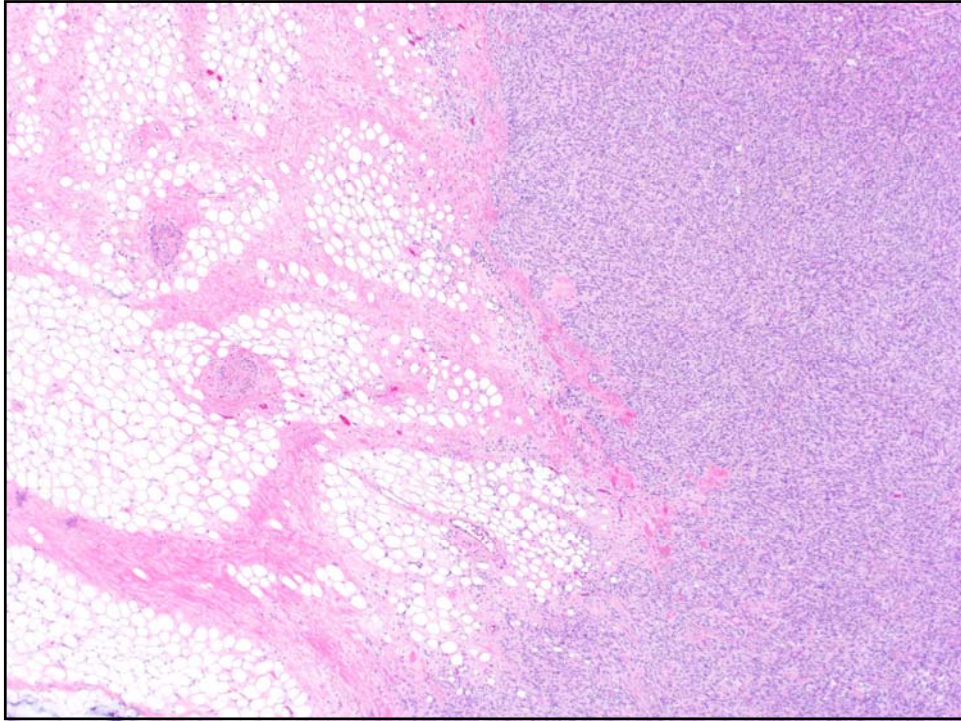
- Delicate curvilinear vessels

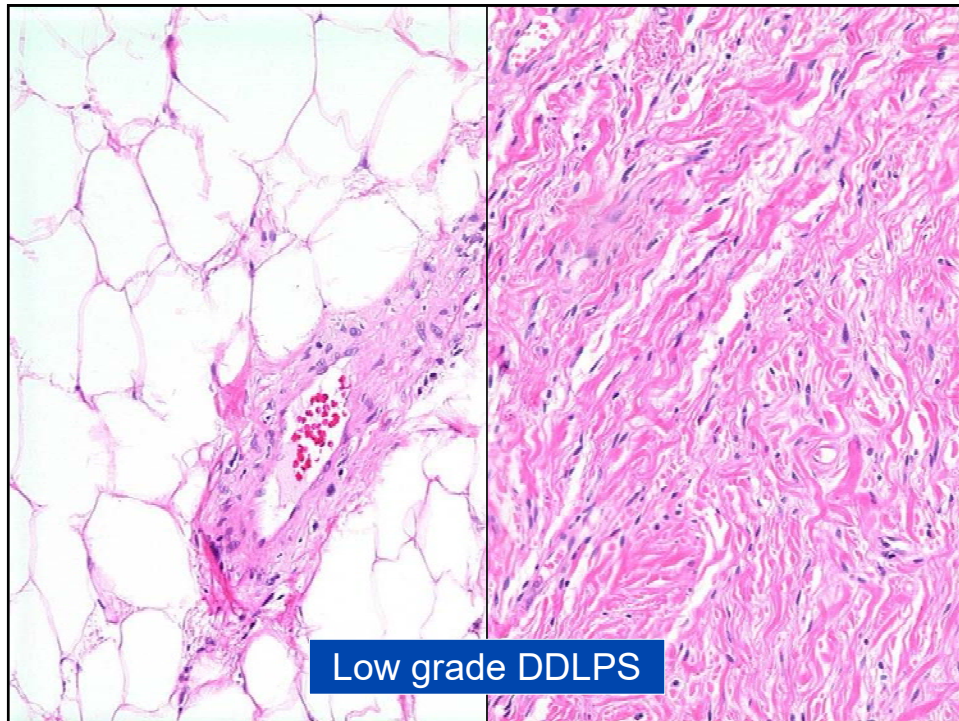


Dedifferentiated Liposarcoma

- Definition: Development of (usually) high grade, non-lipogenic sarcoma in setting of pre-existing well-diff. LPS
- Older adults (M:F ratio -- 3:1)
- Retroperitoneum > groin >>> extremities
- 5-year metastasis: 15-20%
- 5-year survival: 70%
- >90% amplification of 12q13-15 (*MDM2*)
- Pleomorphic sarcoma in retroperitoneum = DDLPS until proven otherwise



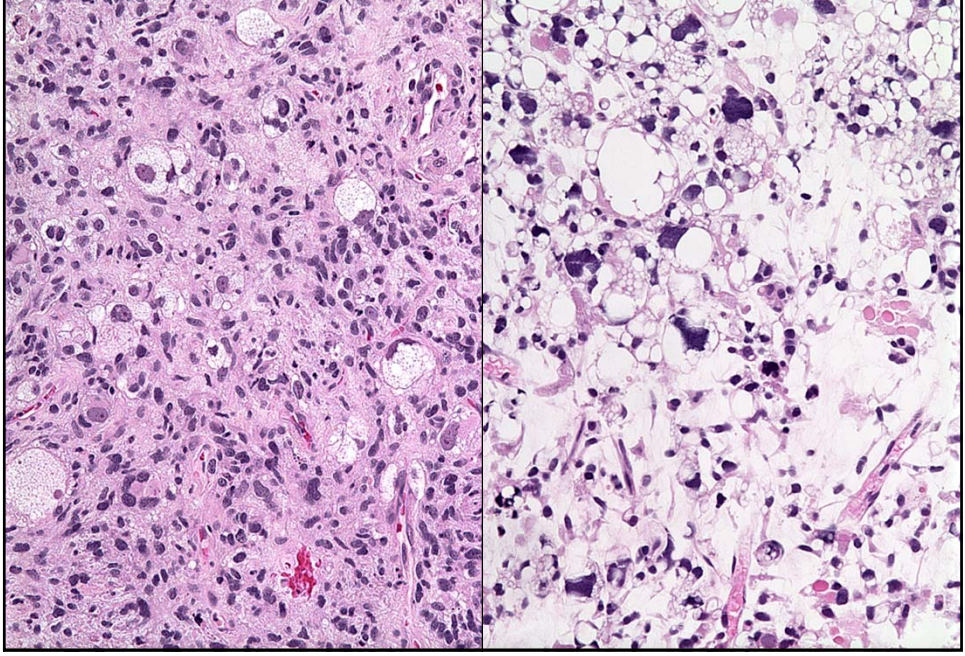




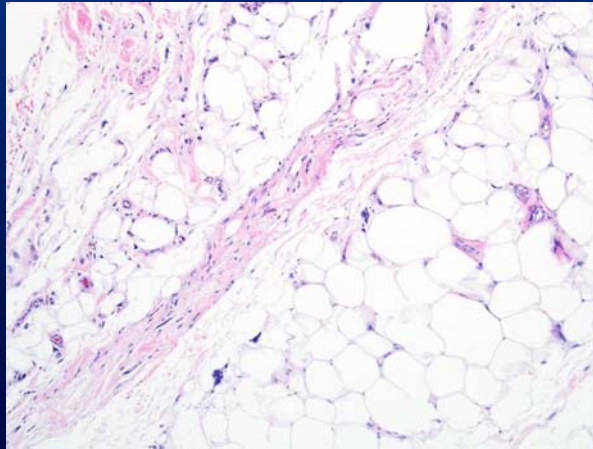
Pleomorphic Liposarcoma

- Older adults (> 50 years)
- Deep soft tissues of extremities
- 5-year metastasis: 30-50%
- 5-year survival: 20%

- **Unequivocal lipoblasts within pleomorphic tumor**



Well-Differentiated Lipomatous Neoplasms



MAYO
CLINIC

Diagnostic Challenges

- Morphologic overlap
- IHC usually unhelpful
- Rarity of some entities
- Inconsistent application of terminology
- Recent advances in cytogenetics and molecular diagnostics

MAYO
CLINIC

Rules of fatty tumors



Well-differentiated fatty tumors

Rules:

1. Location:

- Lipomas occur in superficial soft tissue
- Liposarcomas occur in deep soft tissue

2. Do not look for lipoblasts

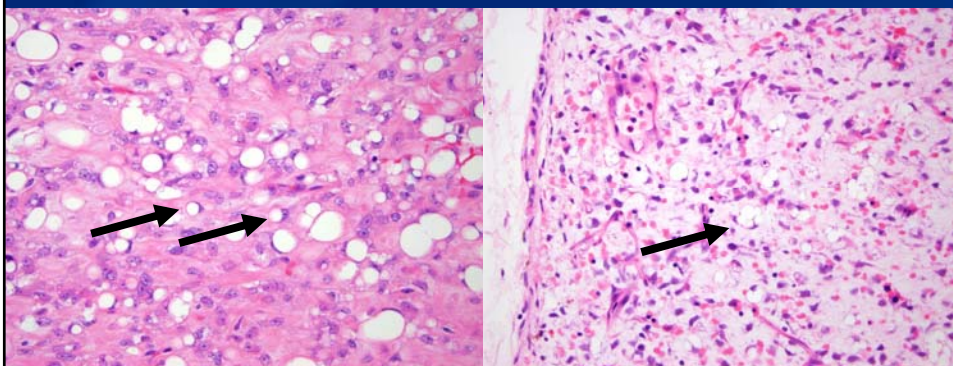
3. Cytogenetics can be helpful



Important (and not important) cells in fatty lesions



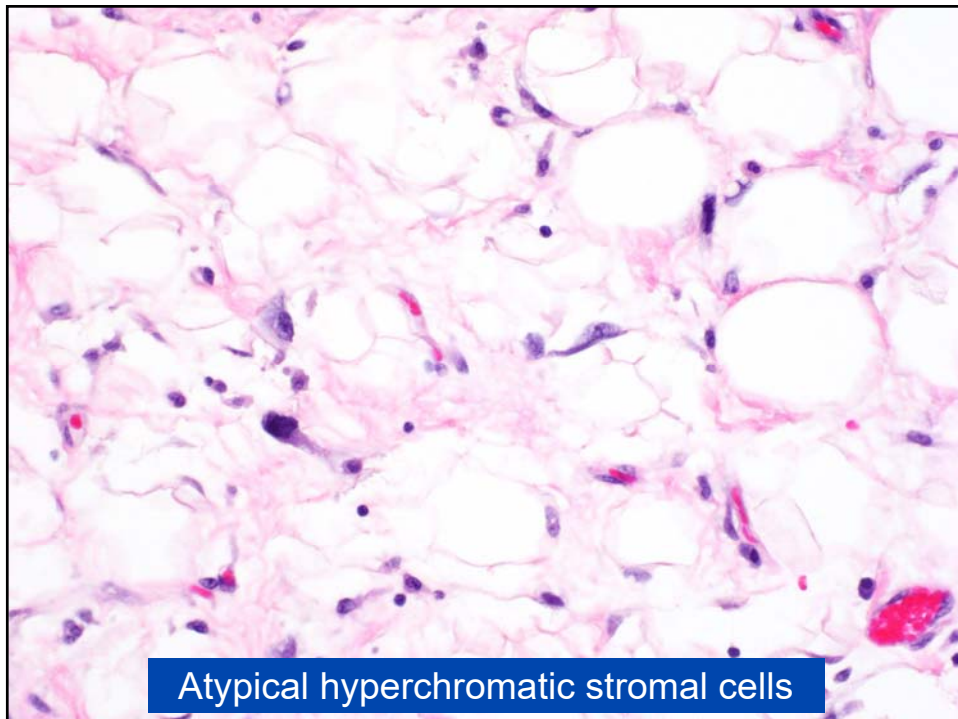
Lipoblasts

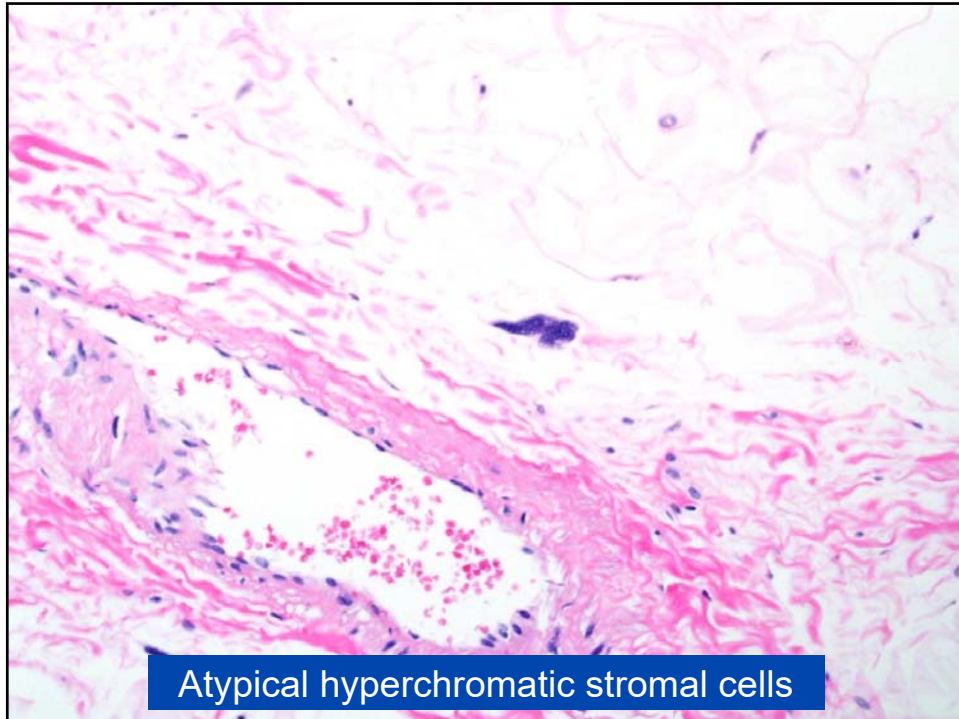


Lipoblasts in well-differentiated fatty tumors?

1. They may be seen in benign lesions (e.g. lipoblastoma, spindle cell/pleomorphic lipoma, chondroid lipoma)
2. Most liposarcomas do not have them

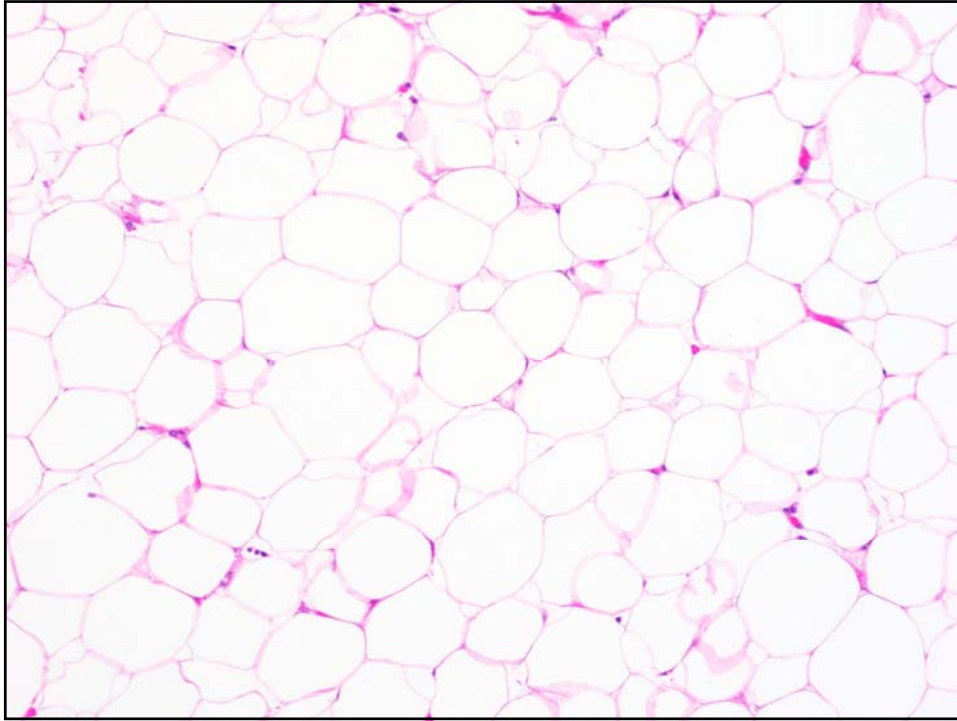
I never look for them.





Lipoma

- Age: 40-60
- Mobile, painless
- No fibrous or solid areas; <10 cm
- No atypical hyperchromatic stromal cells
- 2/3 have 12q13-15 aberrations



Atypical Lipomatous Tumor / Well-Differentiated Liposarcoma

- Terminology is confusing!!!
- ALT and WDLPS are the same entity

Atypical Lipomatous Tumor / Well-Differentiated Liposarcoma

- 6th and 7th decades of life
- M=F
- Deep soft tissue sites
- Non-metastasizing
- Local recurrence (rate related to site)
- May dedifferentiate (rate related to site)
- Characteristic cytogenetic abnormalities in almost all cases



Why “Atypical Lipomatous Tumor”?

TABLE 16-3 BEHAVIOR OF 83 ALN/WDLs

Site	Recurrence (%)	Died of disease (%)	Dedifferentiation (%)	Years of follow-up range and median
Extremity	43	0	6	2-25 (9)
Retroperitoneum	91	33	17	1-35 (10)
Groin	79	14	28	2-25 (8)
<i>Total</i>	63	11	13	

From Weiss SW, Rao VK. ALN/WDL (atypical lipoma) of deep soft tissue of the extremities, retroperitoneum and miscellaneous sites: a follow-up study of 92 cases with analysis of the incidence of "dedifferentiation." *Am J Surg Pathol* 1992; 16:1051.

© Elsevier, Inc. 2008 Weiss and Goldblum. *Enzinger and Weiss's Soft Tissue Tumors*, 5th edition.

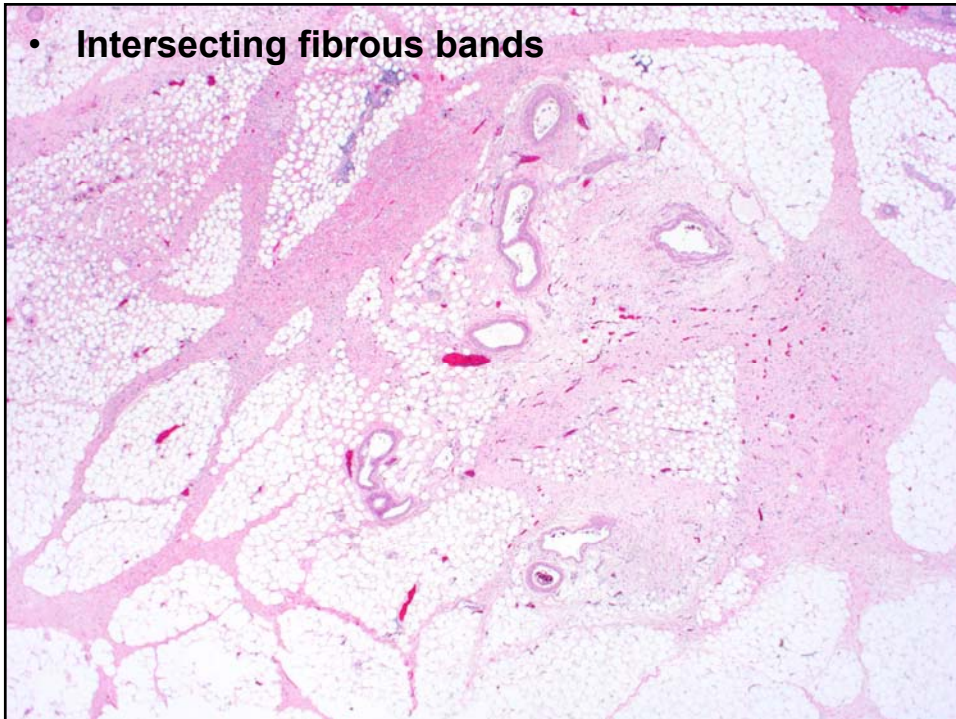


Why “Atypical Lipomatous Tumor”?

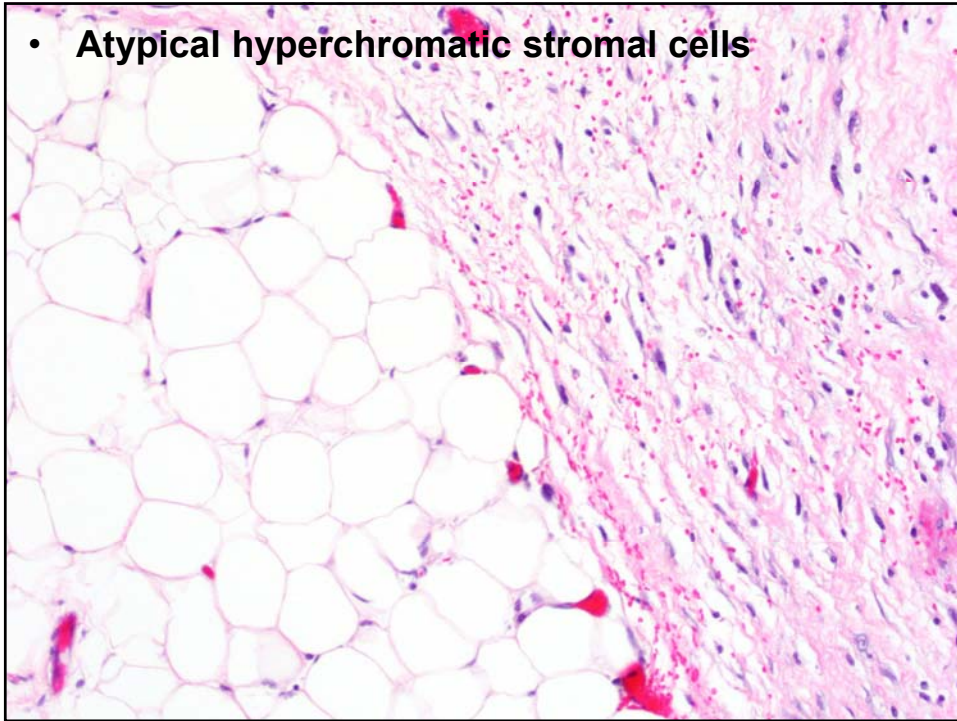
- “ALT” was introduced to avoid labeling pts with tumor in extremity with “sarcoma”
- In the retroperitoneum / groin, only use “WDPLS”



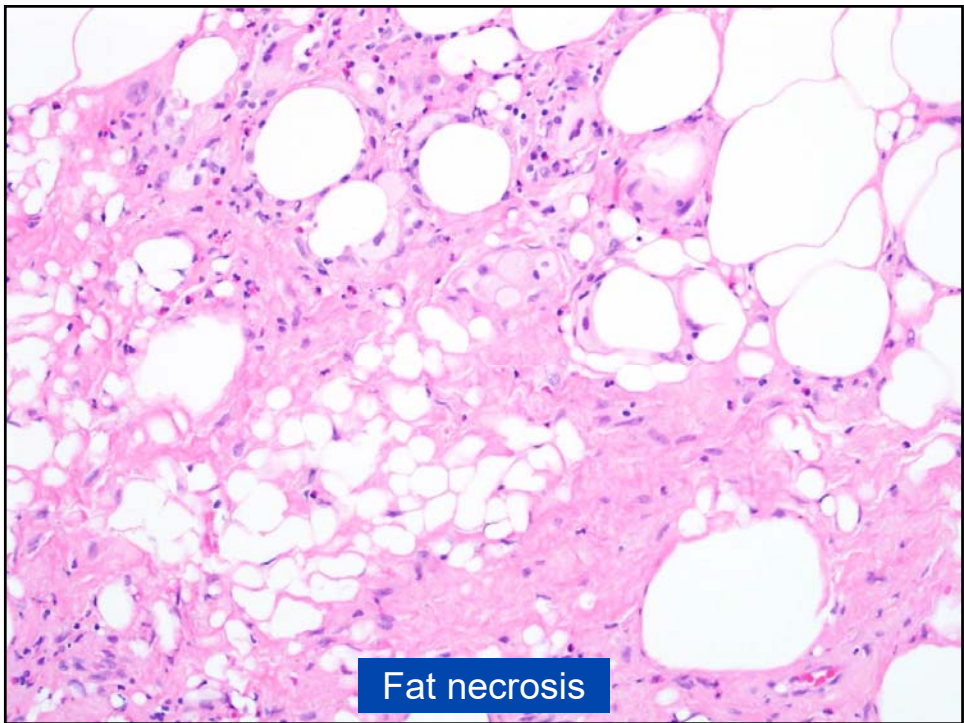
- **Intersecting fibrous bands**

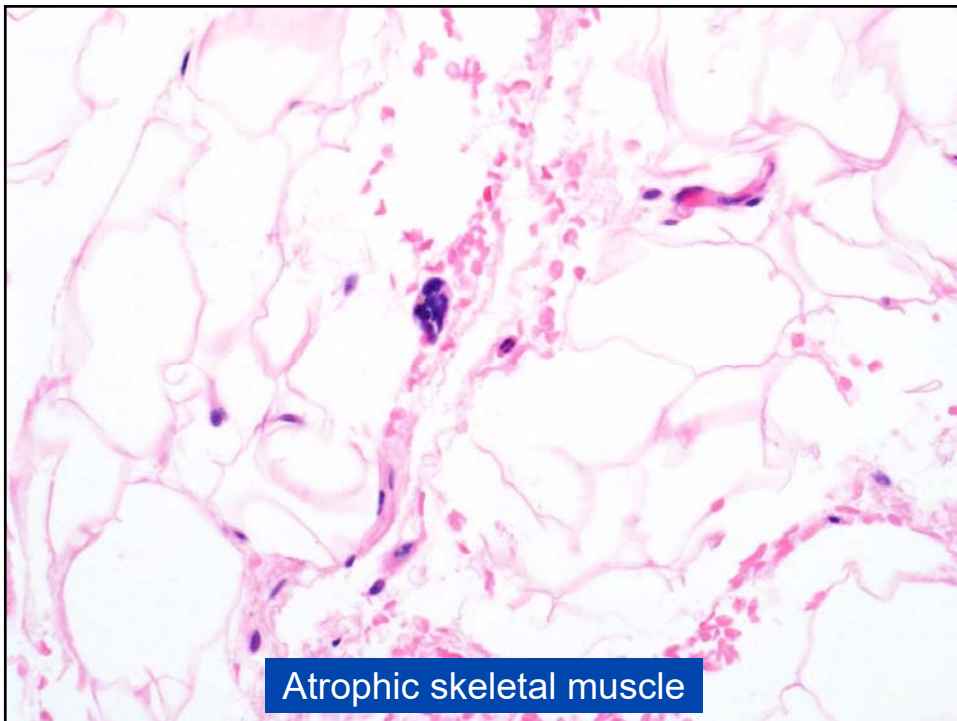
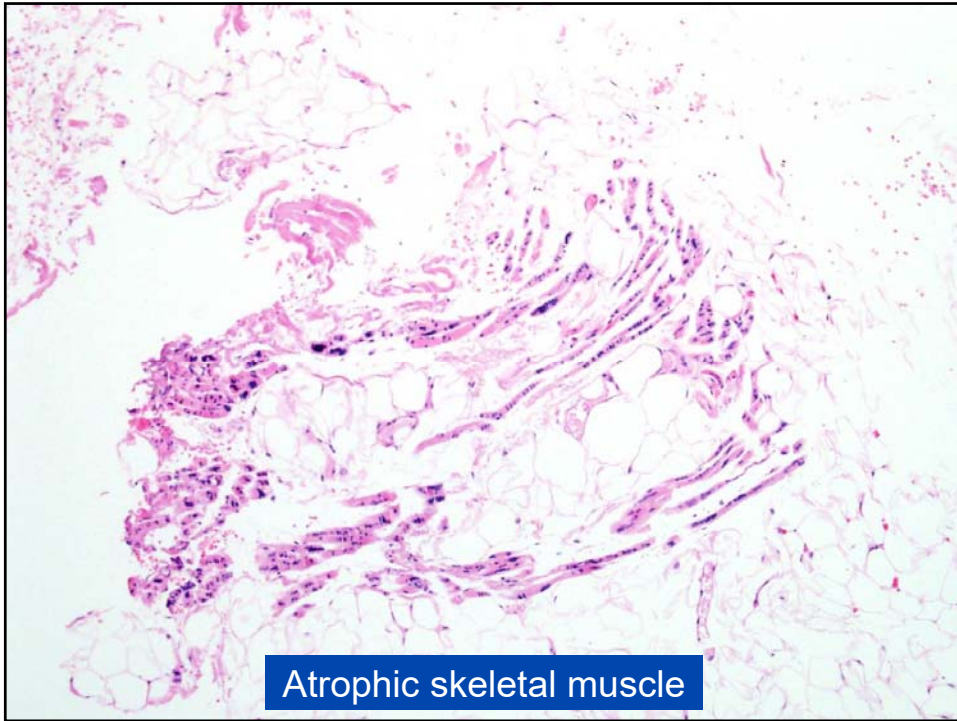


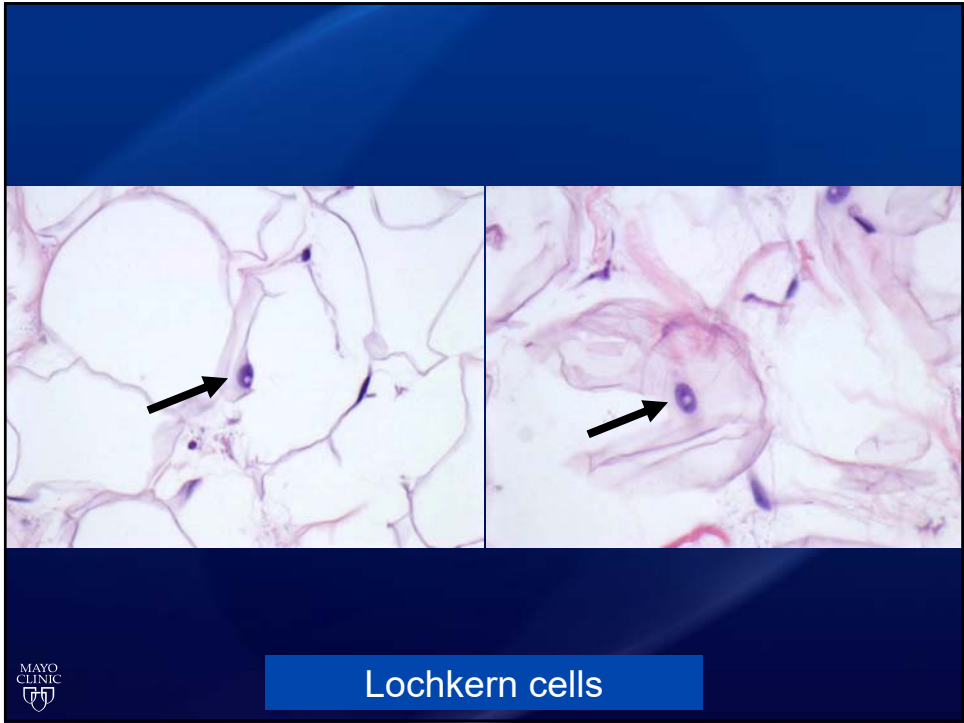
- **Atypical hyperchromatic stromal cells**



Potential mimics of atypical
hyperchromatic stromal cells







Lochkern cells

Cytogenetics of fatty tumors

Tumor	Chromosomal aberration
Lipoma (ordinary)	Translocations involving 12q13-15 Interstitial deletions of 13q Rearrangements involving 6p21-23
Angiolipoma	None
Spindle cell/pleomorphic lipoma	Loss of 16q13 Unbalanced 13q alterations
Lipoblastoma/lipoblastomatosis	Translocations involving 8q11-13
Hibernoma	Translocations involving 11q13 Translocations involving 10q22

© Elsevier, Inc. 2008 Weiss and Goldblum. *Enzinger and Weiss's Soft Tissue Tumors*, 5th edition

[CANCER RESEARCH 55, 24-27, January 1, 1995]
Advances in Brief

Translocation t(12;16)(q13;p11) in Myxoid Liposarcoma and Round Cell Liposarcoma: Molecular and Cytogenetic Analysis¹

Jennifer C. Knight,² Pamela J. Renwick, Paola Dal Cin, Herman Van Den Berghe, and Christopher D. M. Fletcher
Soft Tissue Tumor Unit, Department of Histopathology, U.M.D.S. St. Thomas' Hospital, London SE1 7EH, United Kingdom [J. C. K., P. J. R., C. D. M. F.], and Center for Human Genetics, University of Leuven, B-3000 Leuven, Belgium [P. D. C., H. V. D. B.]



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 Study Group).

Rosal J, Akerman M, Dal Cin P, DeWever I, Fletcher CD, Mandahl N, Mertens F, Mifelman F, Rydholm A, Sciort R, Tallini G, Van den Berghe H, Van de Ven W, Vanni R, Willen H.

Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.



Am J Surg Pathol, 1996 Oct;20(10):1182-9

Genetics of ALT / WDLPS

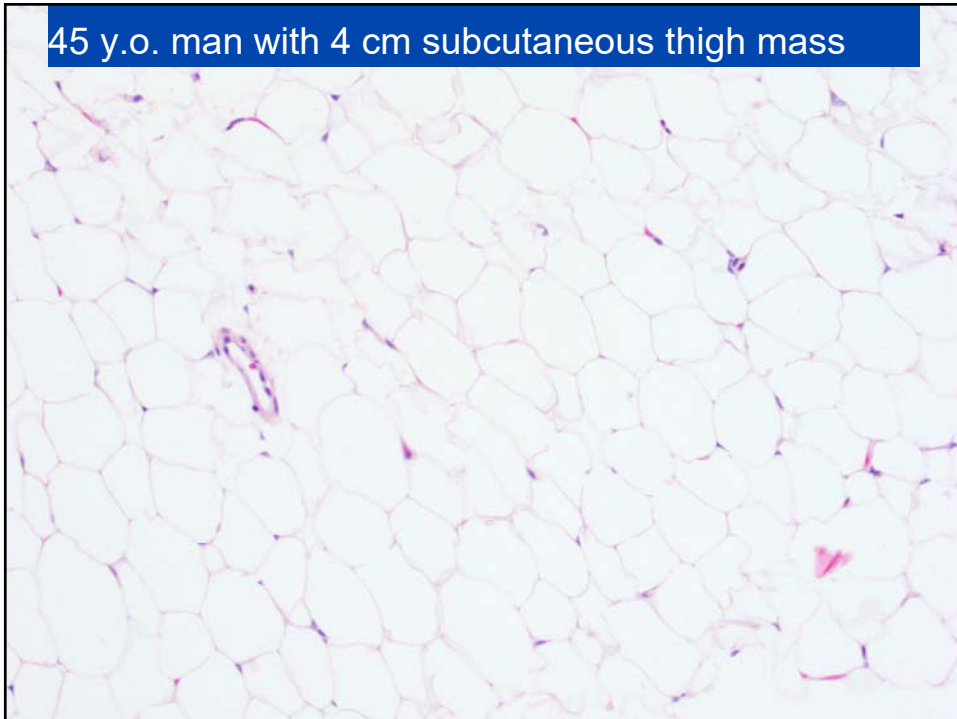
- Giant ring and marker chromosomes
- Amplification of 12q14-15, including *MDM2*, *CDK4*, *SAS*, and *HMGIC*
- Amplification and overexpression of *MDM2* and *CDK4*
- IHC, FISH, CISH testing

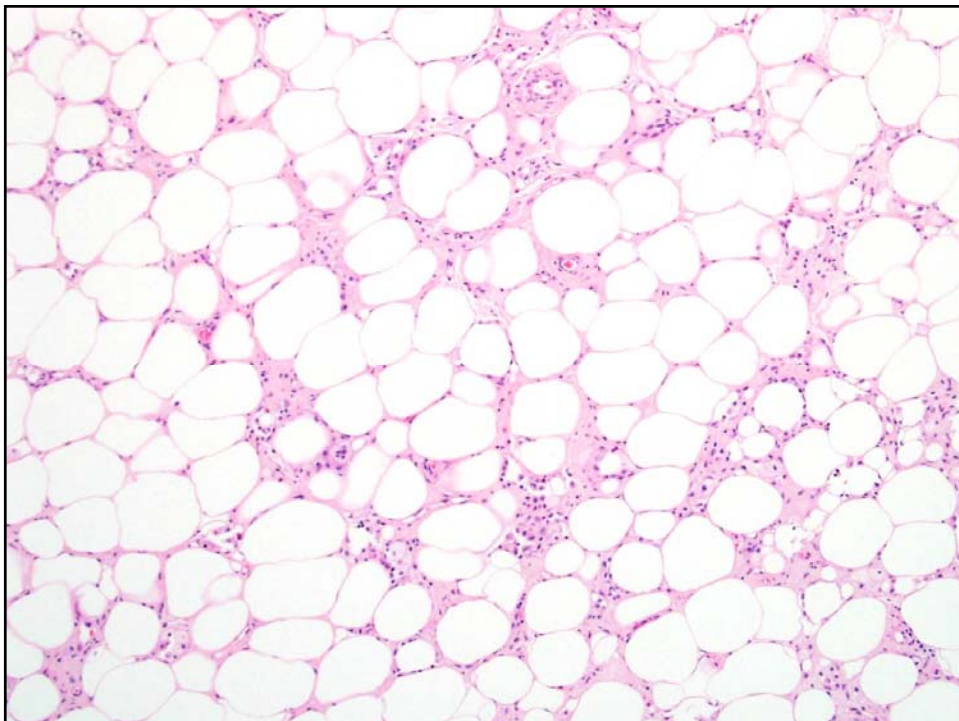
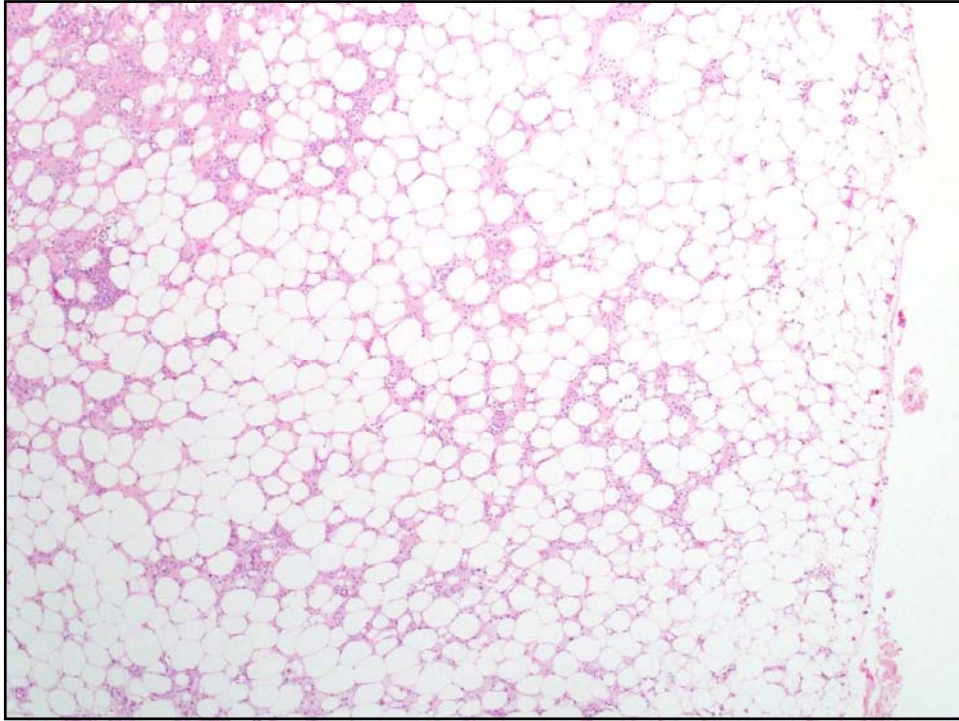


Case examples

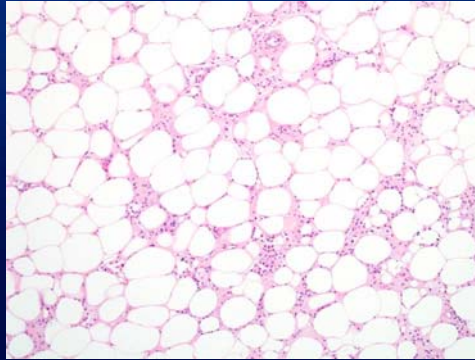


45 y.o. man with 4 cm subcutaneous thigh mass





- Is this an atypical lipomatous tumor?
 - Location: Superficial
 - Atypical hyperchromatic stromal cells? No

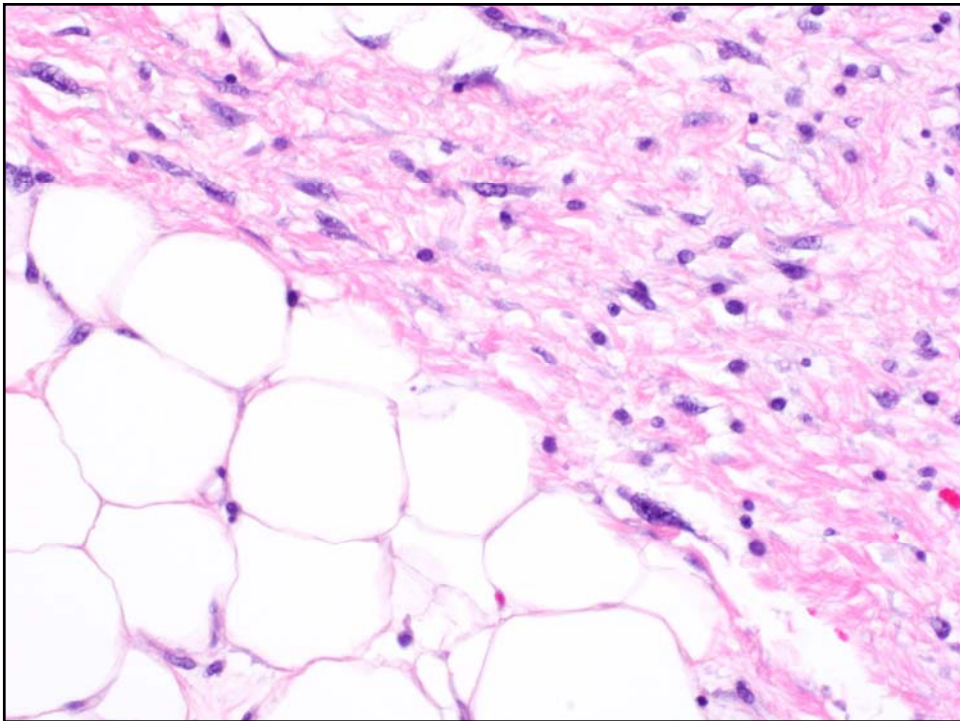
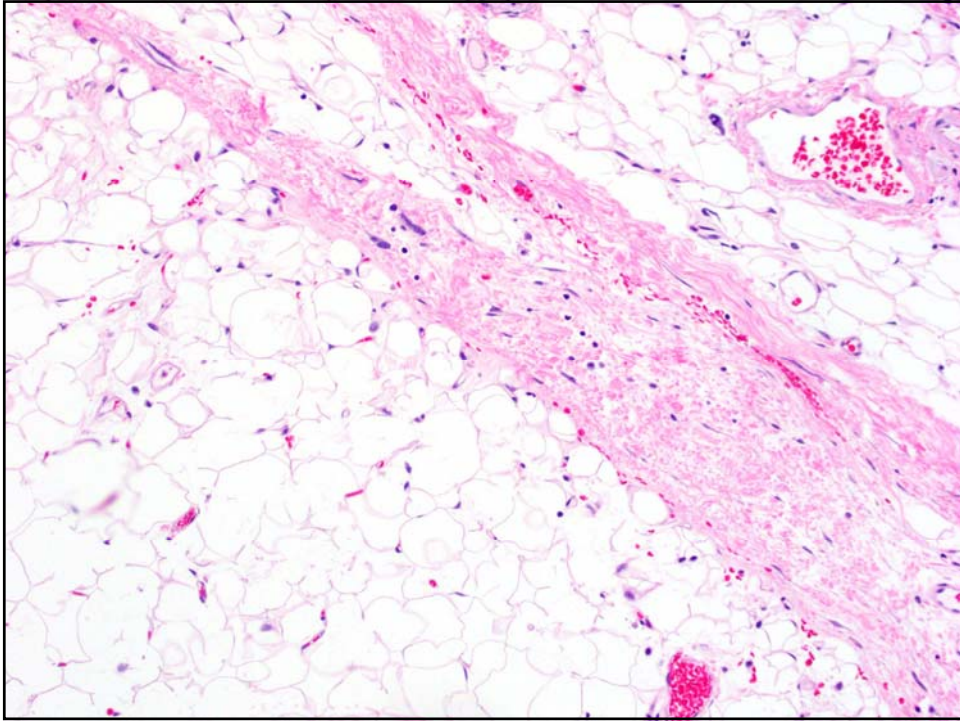


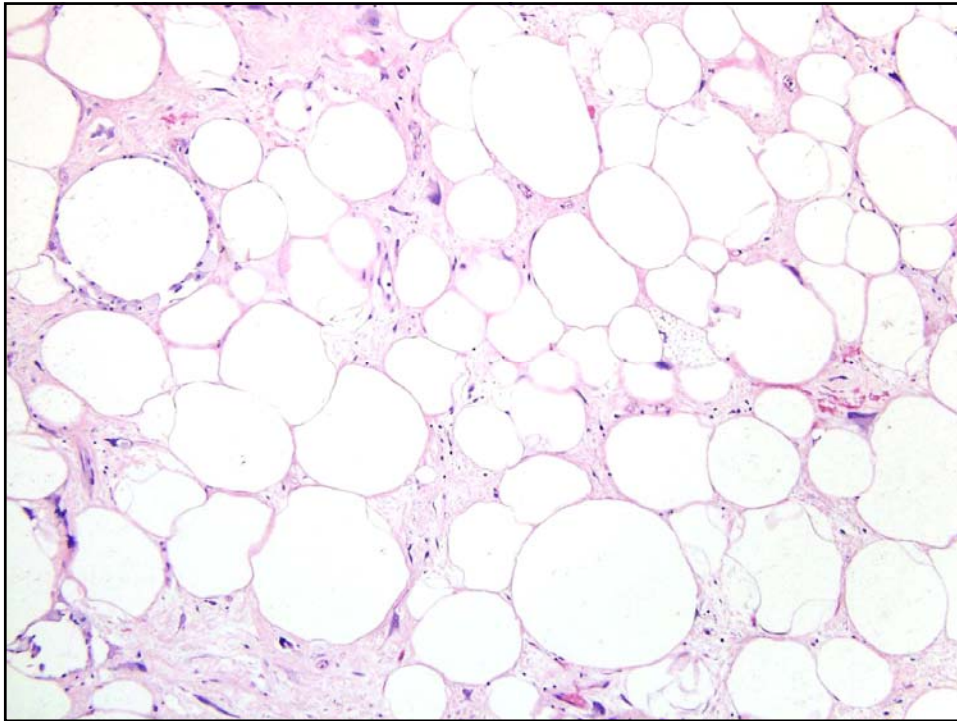
Lipoma with fat necrosis



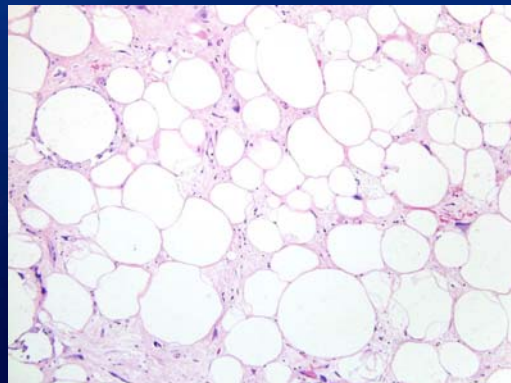
52 y.o. man with 14 cm intramuscular thigh mass





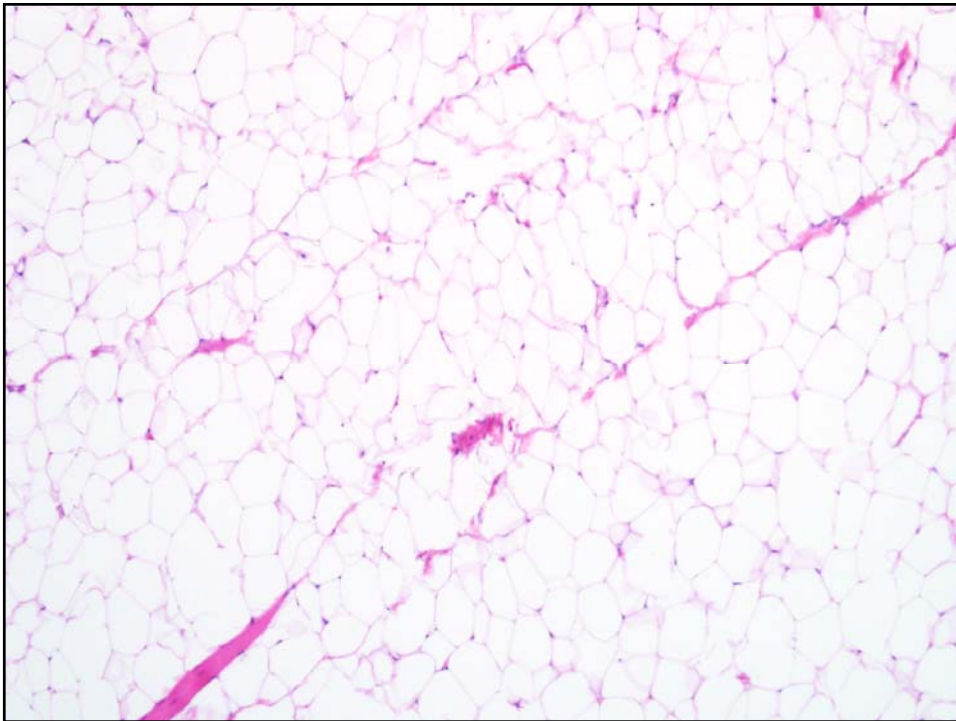
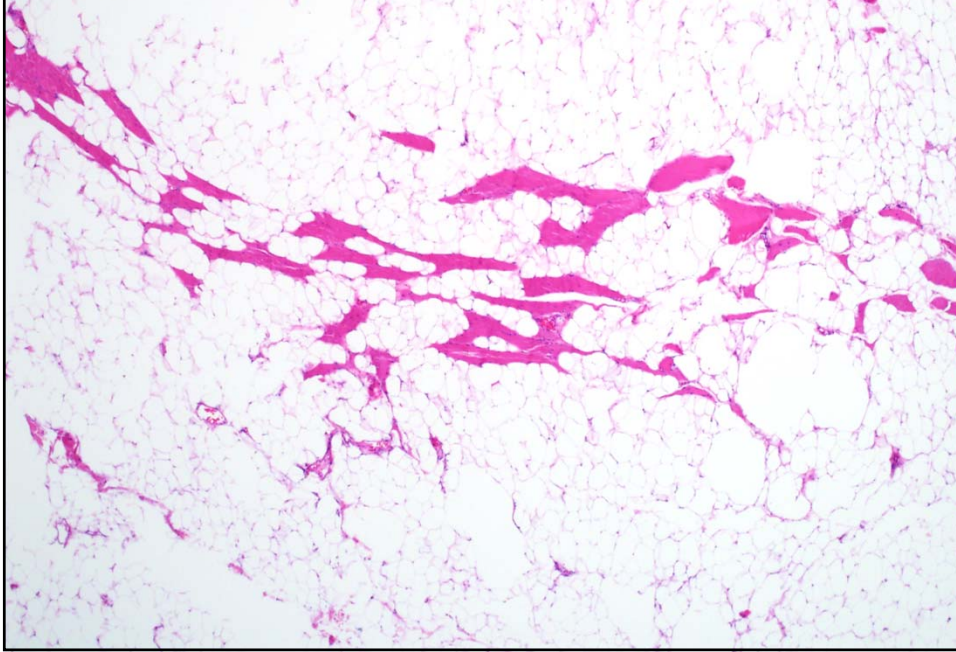


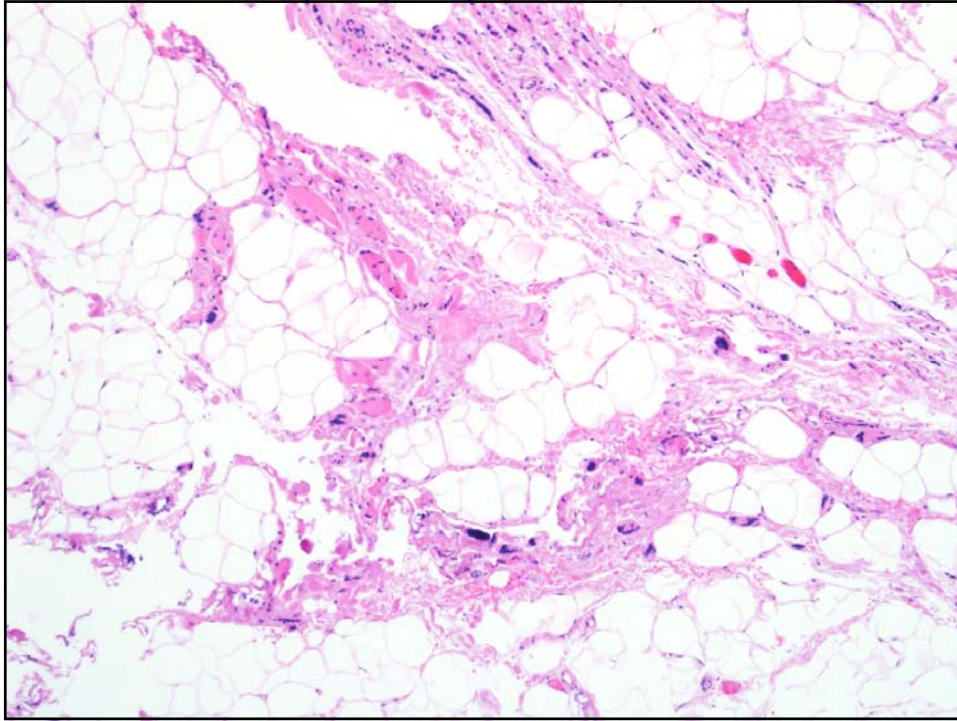
- Is this an atypical lipomatous tumor?
 - Location: Deep, in extremity
 - Atypical hyperchromatic stromal cells: YES



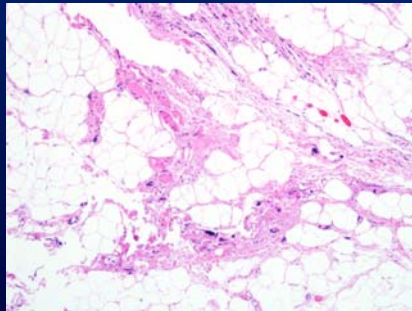
Atypical lipomatous tumor
(with fat necrosis)

47 y.o. man with 18 cm intramuscular thigh mass

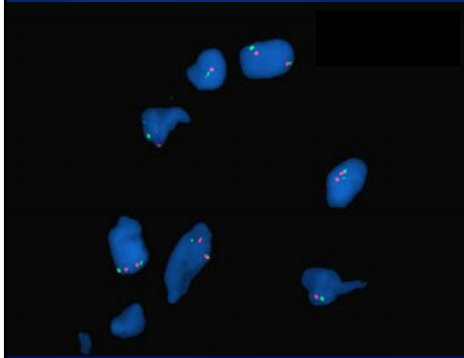




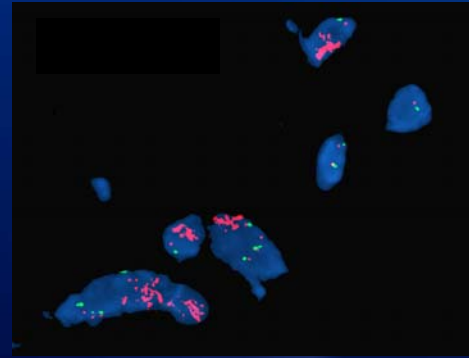
- Is this an atypical lipomatous tumor?
 - Location: Deep
 - Large (18 cm)
 - Atypical hyperchromatic stromal cells: No
 - What next?



MDM2 FISH



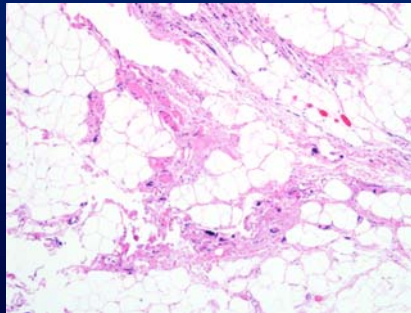
Our case



Control with *MDM2* amplified



- Is this an atypical lipomatous tumor?
 - Deep
 - Large (18 cm)
 - No atypical hyperchromatic stromal cells
 - *MDM2* is not amplified



Intramuscular lipoma



- When do I do FISH studies for *MDM2* amplification?



ORIGINAL ARTICLE

Molecular Testing for Lipomatous Tumors: Critical Analysis and Test Recommendations Based on the Analysis of 405 Extremity-based Tumors

Hongying Zhang, MD, PhD,* Michele Erickson-Johnson, MS,† Xiaoke Wang, MS,†
 Jennifer L. Oliveira, MD,† Antonio G. Nascimento, MD,† Frank H. Sim, MD,‡
 Doris E. Wenger, MD,§ Renata Q. Zamolyi, MD,|| Vera L. Pannain, MD,||
 and Andre M. Oliveira, MD†

TABLE 3. Indications for Molecular Analysis for Lipomatous Tumors

Lipomatous tumors with equivocal cytologic atypia
 Recurrent “lipomas”
 Deep seated lipomatous tumors without cytologic atypia larger than 15 cm
 Retroperitoneal (or intra-abdominal) lipomatous tumors without cytologic atypia*

*See Ref. 23.



(*Am J Surg Pathol* 2010;34:1304–1311)

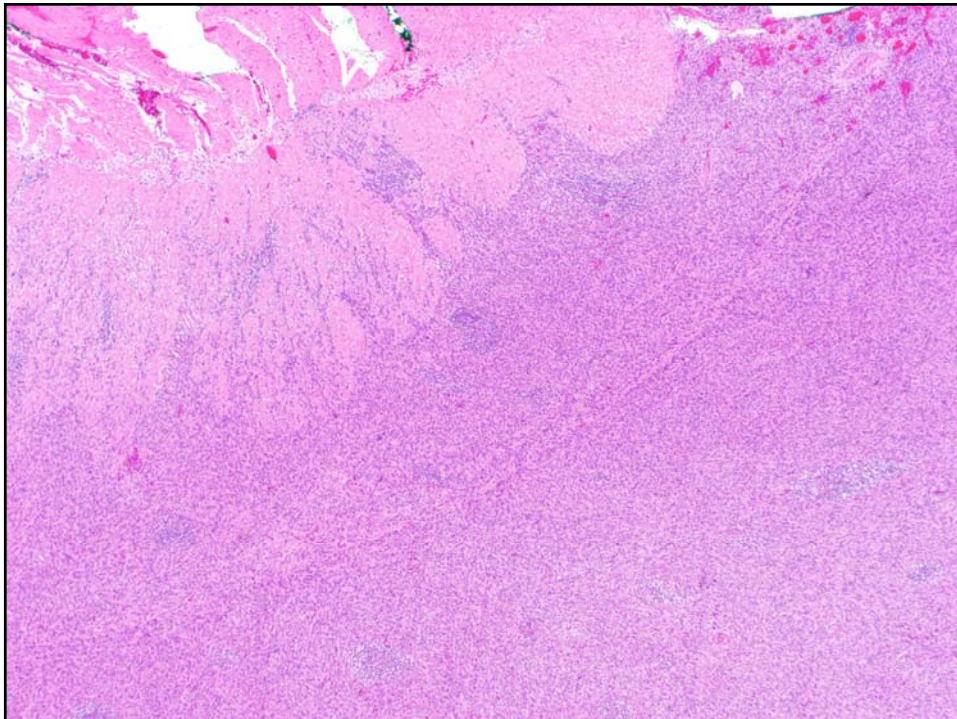
Other well-differentiated fatty tumors

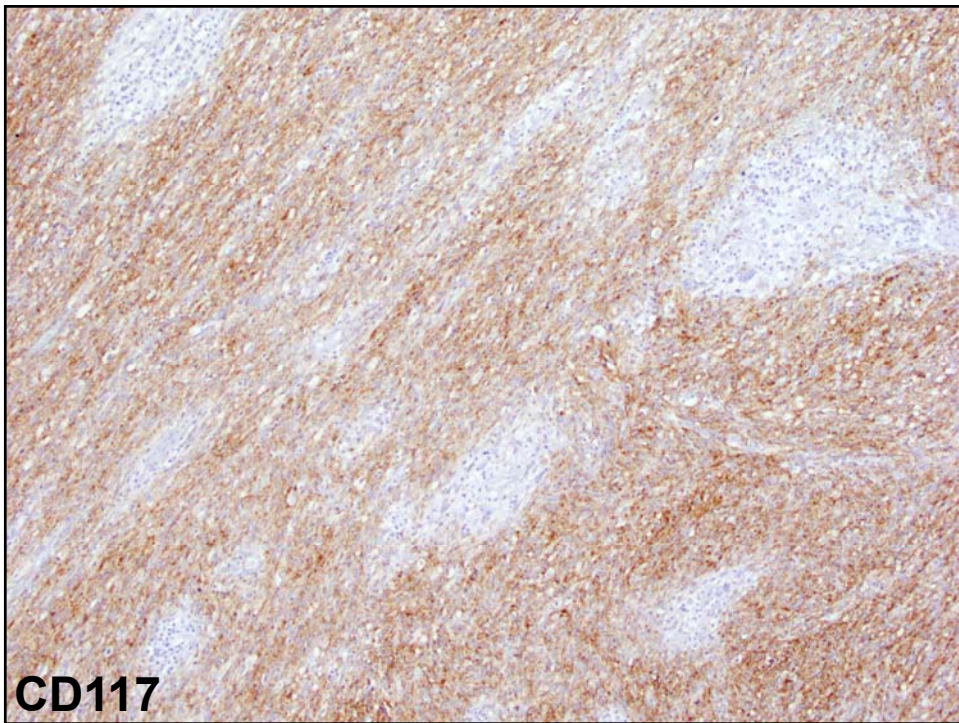
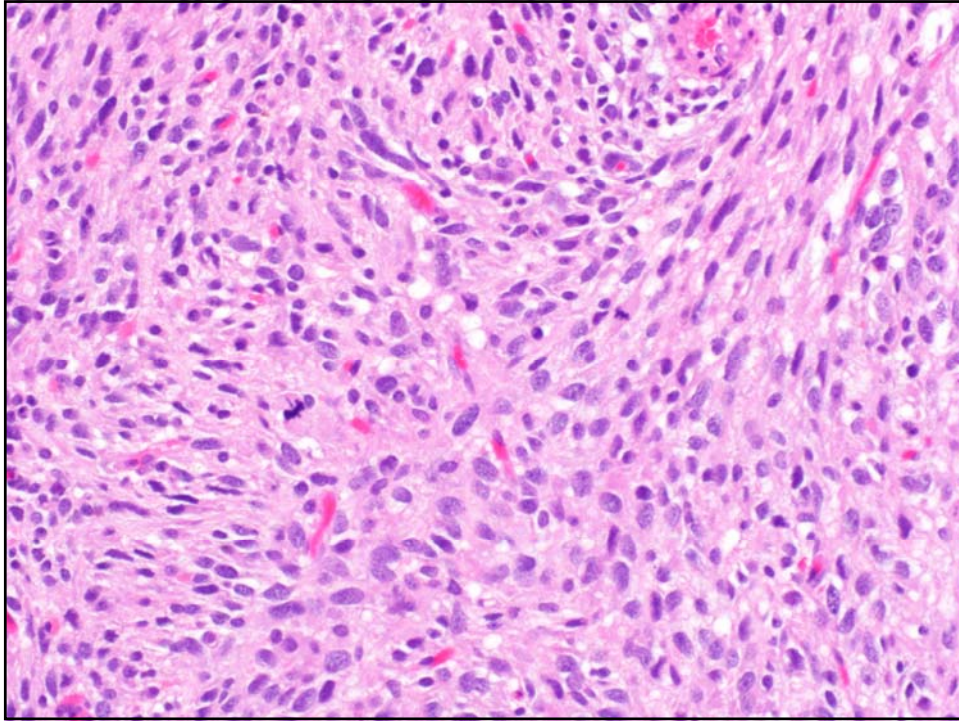
- Spindle cell / pleomorphic lipoma
- Lipomatous SFT
- Fat-predominant AML
- Silicone reaction
- Massive localized lymphedema

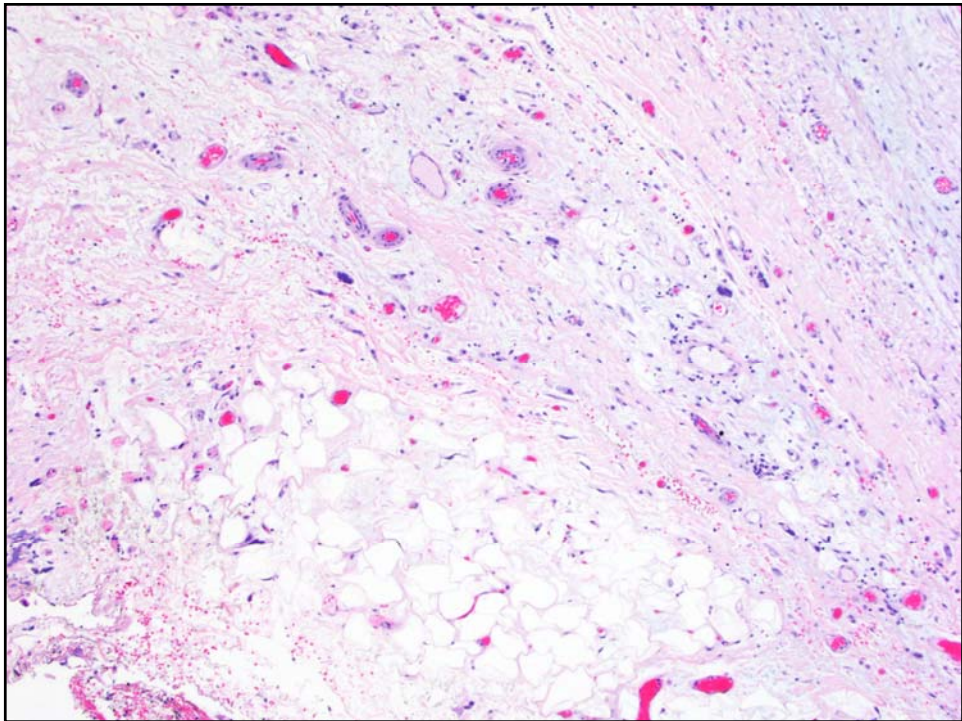
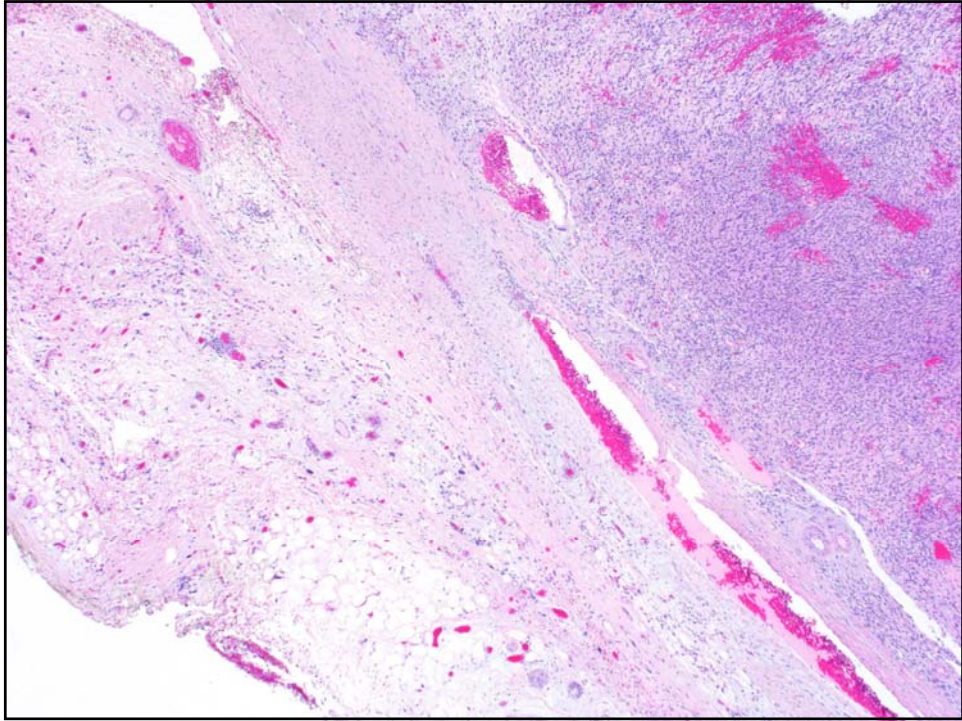


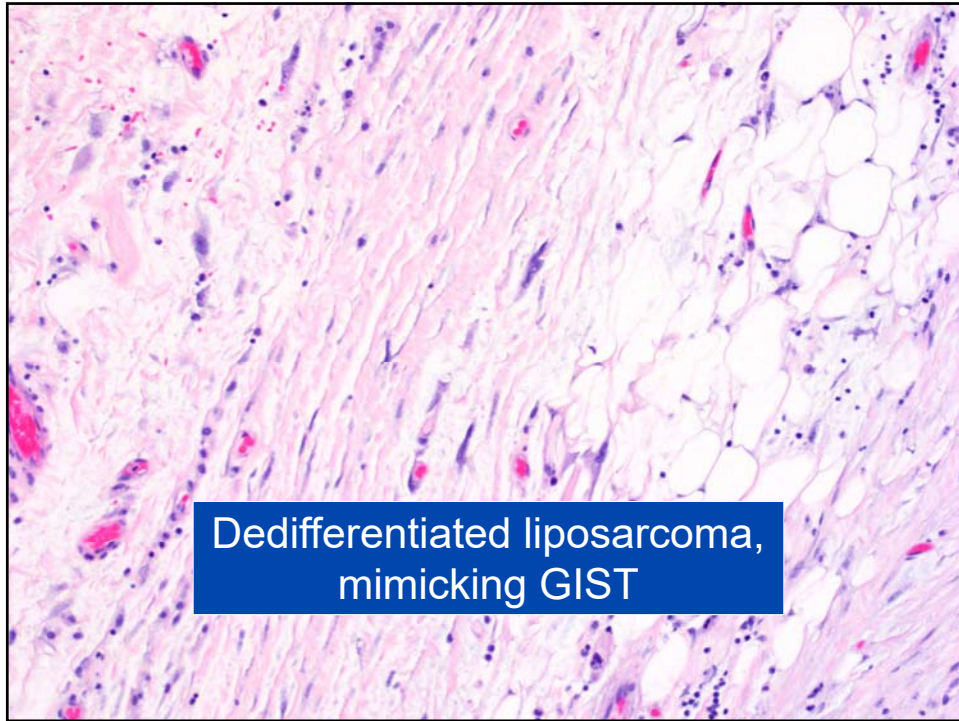
Case 1

53-year-old man presenting with a 15 cm intraabdominal mass, adherent to the ileum and a segment of large bowel



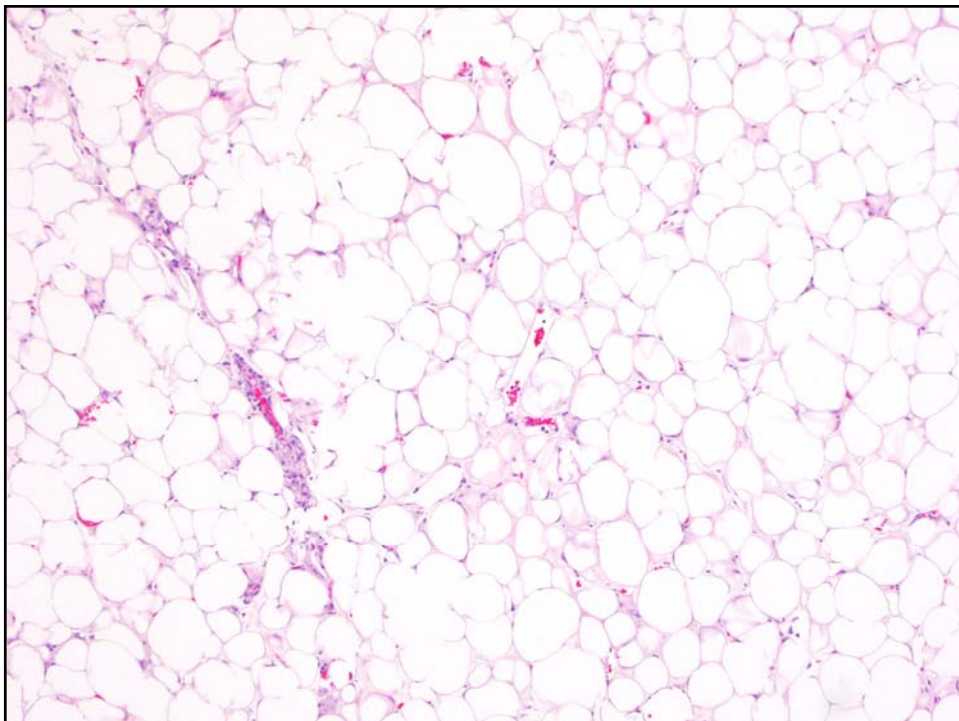
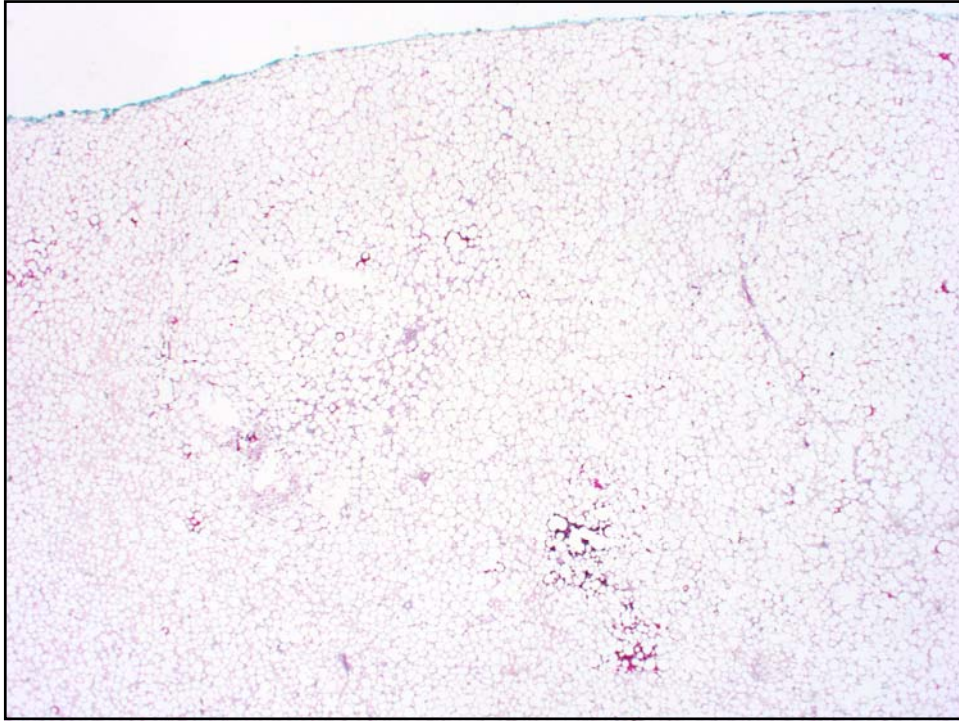


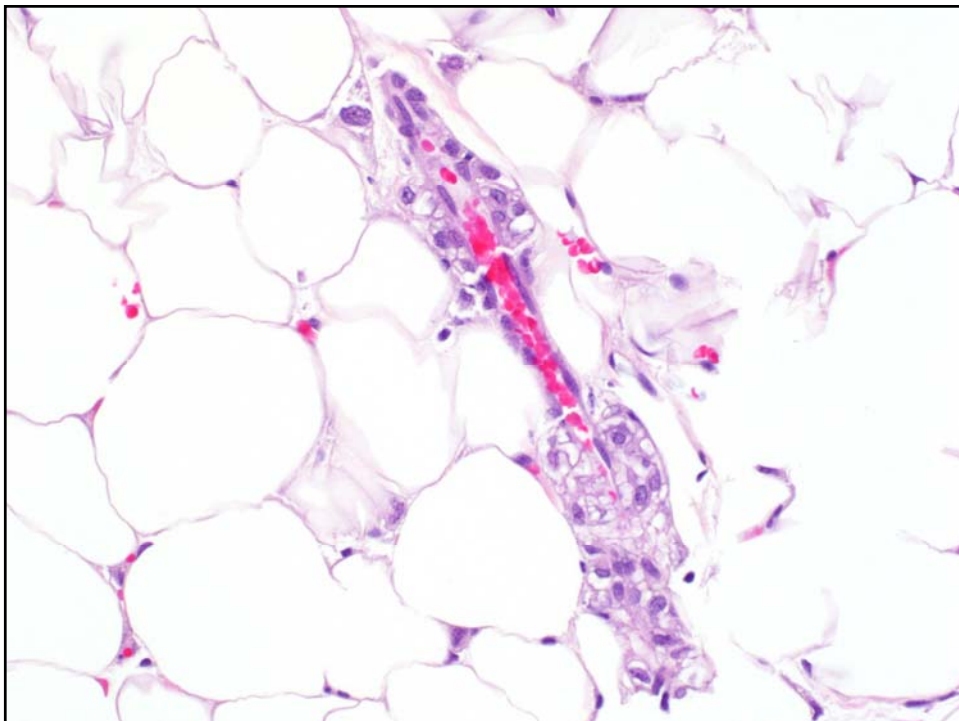
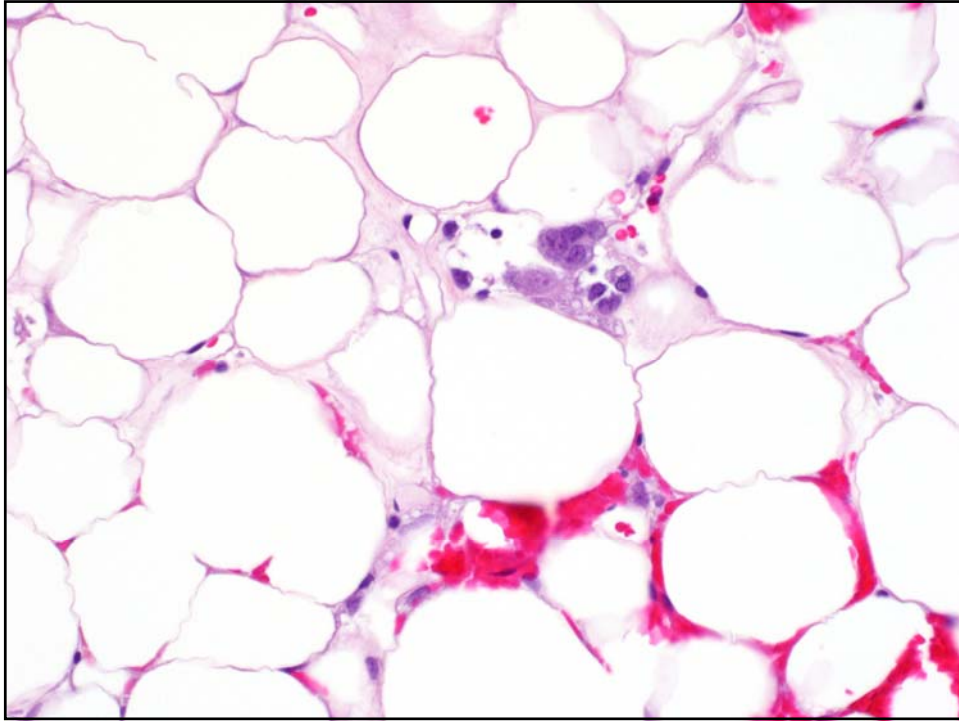


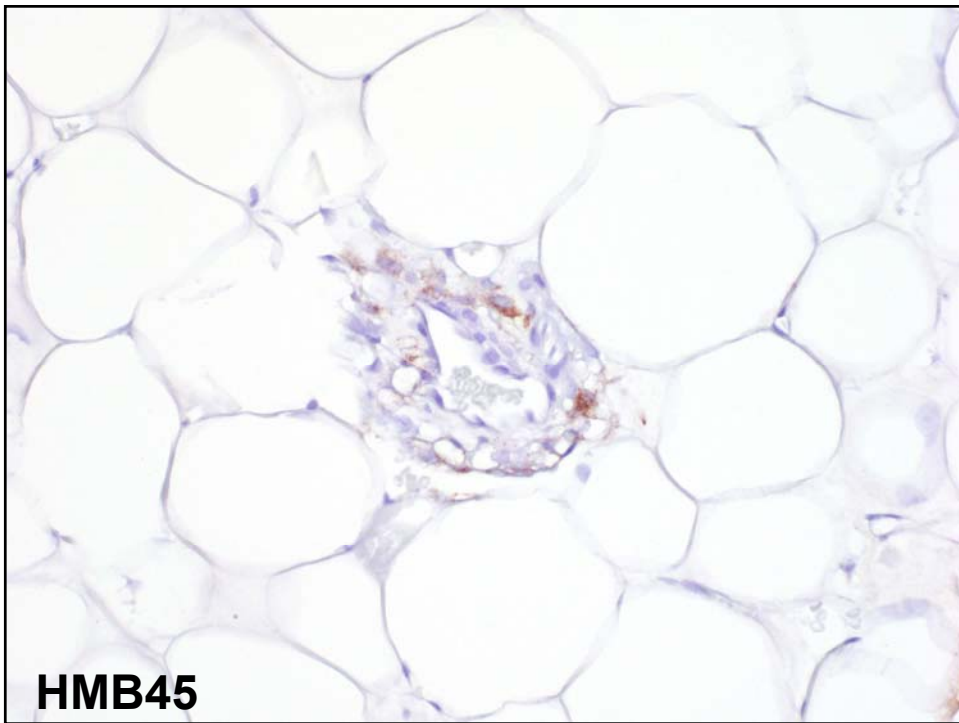
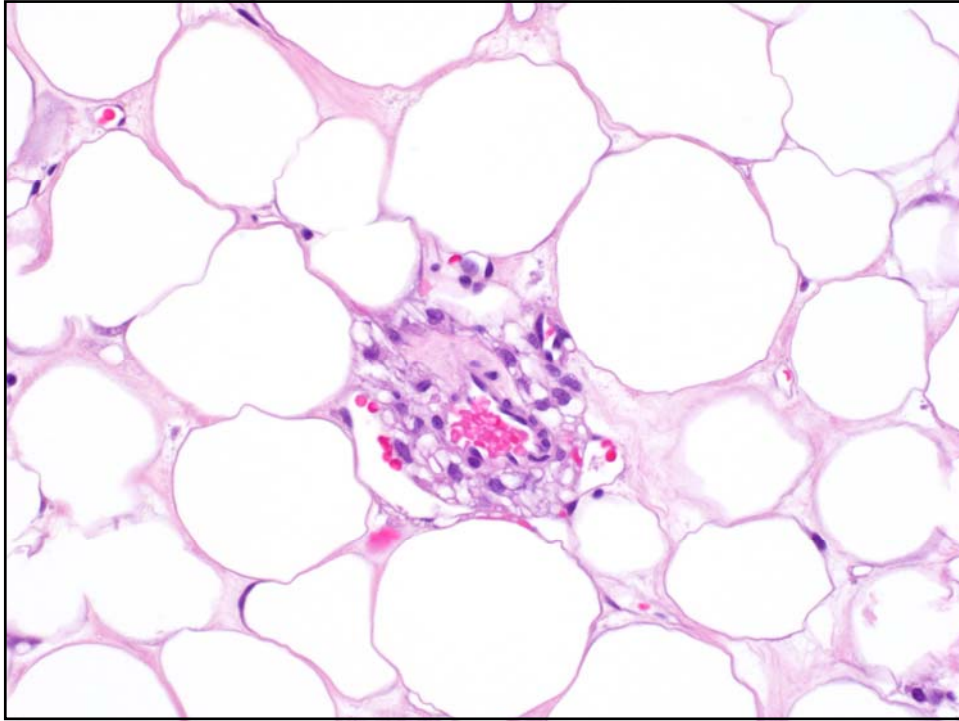


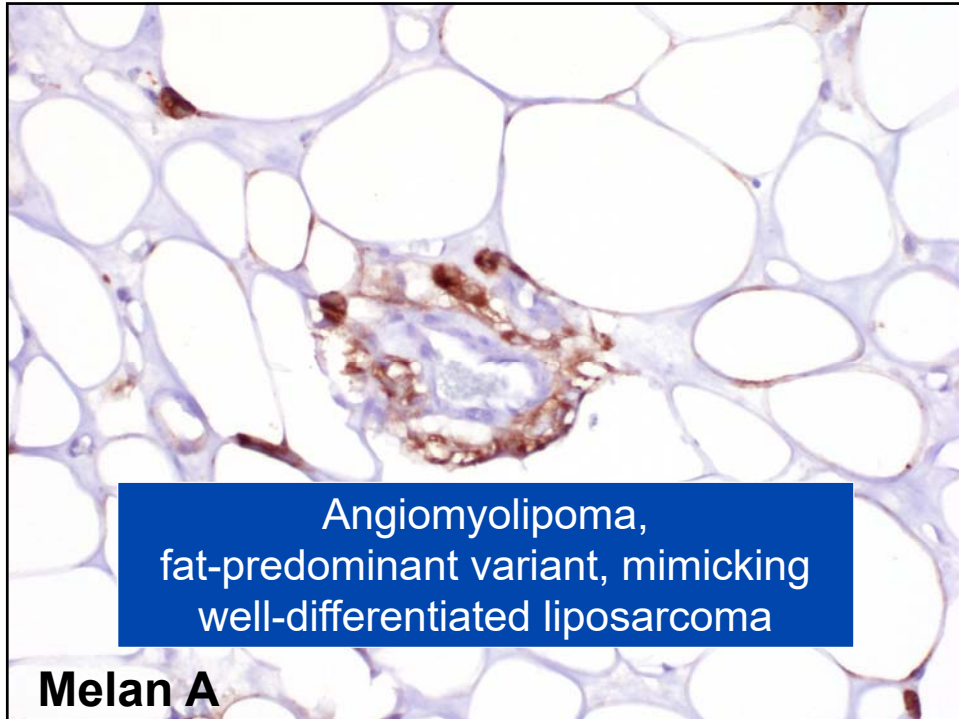
Case 2

49-year-old woman presenting with a 4.7 cm retroperitoneal mass, surgically excised









Take-Home Points

- Consider carcinoma / melanoma / lymphoma first
- Don't forget benign mimics
- Subclassify pleomorphic sarcomas if possible
- Avoid "UPS" diagnosis if possible
- Any pleomorphic sarcoma in retroperitoneum = DDLPS (until proven otherwise)

Take-Home Points

- For ALT / WDLPS:
 - Use “WDLPS” – retroperitoneum, groin, mediastinum
 - Use “ALT” – deep soft tissue of extremities
- Consider *MDM2* FISH if:
 1. Cytologic atypia equivocal
 2. Recurrent “lipoma”
 3. Large, deep extremity tumors without atypia
 4. Retroperitoneal, intraabdominal, groin tumors without atypia



QUESTIONS?

