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RETROPERITONEUM:
 spindle cell lesions

MOUNT SINAI HOSPITAL
 Joseph and Wolf Lebovic Health Complex
 Bright Minds. Big Hearts. The Best Medicine.



DISCLOSURE

I have no actual, or potential, conflict of interest in relation to this presentation to disclose




OUTLINE

Goal
 • Offer approach to ‘common’ retroperitoneal soft tissue tumours (and their mimics)

Definitions

Patients (x3)
 • Case presentation
 • Diagnosis – audience participation
 • Discussion of differential diagnosis

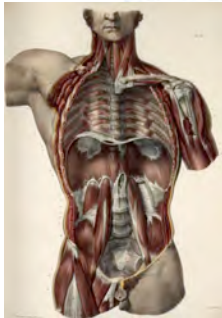
Summary




DEFINITIONS

Retroperitoneum

- Space between the parietal peritoneum and the posterior abdominal wall




"retroperitoneum, n." OED Online. 2014. Oxford University Press; web. (accessed November 1, 2014).
 Bourguery MJ. *Traité complet de l'anatomie de l'homme comprenant la médecine opératoire*. 1831-1854. C. Delaunay; Paris.
 (<http://link.library.utoronto.ca/anatomia/application/index.cfm>)




DEFINITIONS (2)

Boundaries

- Anterior: peritoneum
- Posterior: abdominal wall
- Lateral: quadratus lumborum
- Superior: 12th rib and vertebra
- Inferior: sacrum and iliac crest




Van Roggen JF, Hogendoorn PC. *Sarcoma*. 2000;4(1-2):17-26.
 Quain J. *The muscles of the human body*. 1836. London : Taylor and Walton.
 (<http://link.library.utoronto.ca/anatomia/application/index.cfm>)



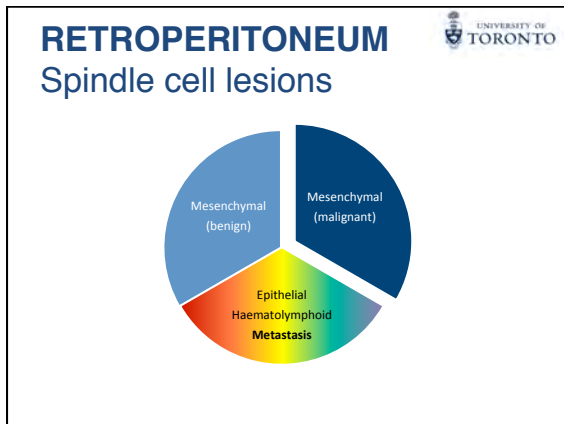
DEFINITIONS (3)

Contents

- Adrenal glands
- Colon (ascending and descending; rectum)
- Connective tissue
- Duodenum
- Esophagus
- Kidneys and ureters
- Lymph nodes
- Nerve branches
- Pancreas
- Vessels (e.g., aorta and inferior vena cava)



Van Roggen JF, Hogendoorn PC. *Sarcoma*. 2000;4(1-2):17-26.
 MacLise J. *Surgical anatomy*. 1856. London: J. Churchill. (<http://link.library.utoronto.ca/anatomia/application/index.cfm>)



CASE 1

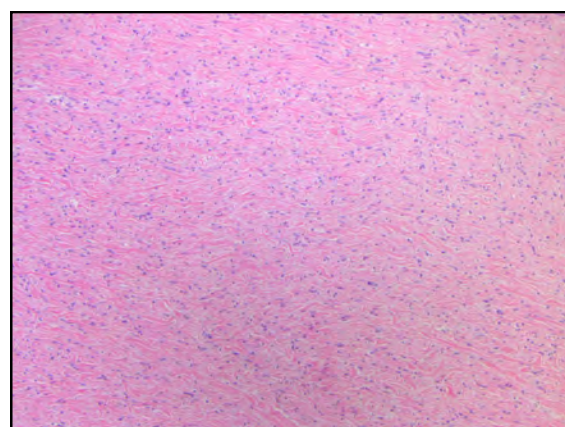
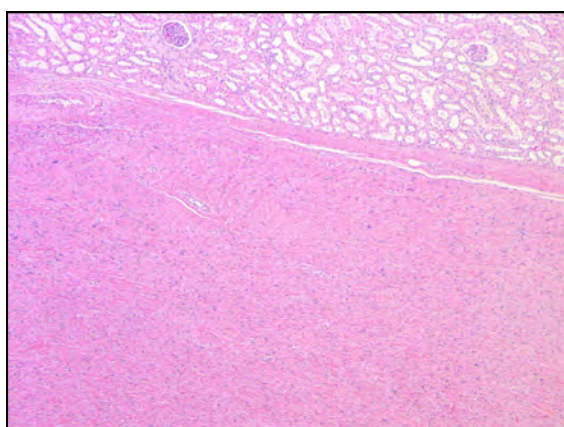
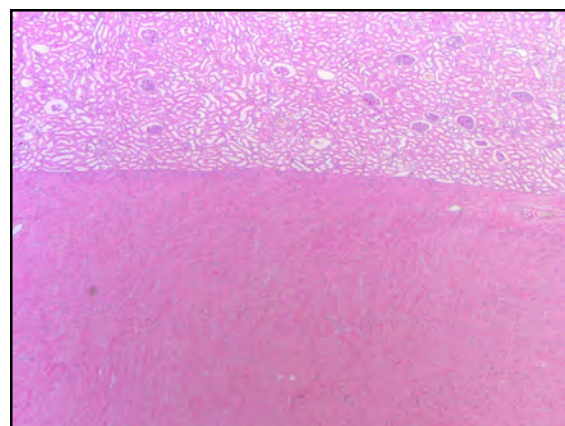
- 54 M. Presented to family physician with symptoms of early satiety
- Past medical history significant for hypertension and DM type II
- On examination the patient was obese, with abdominal “fullness”

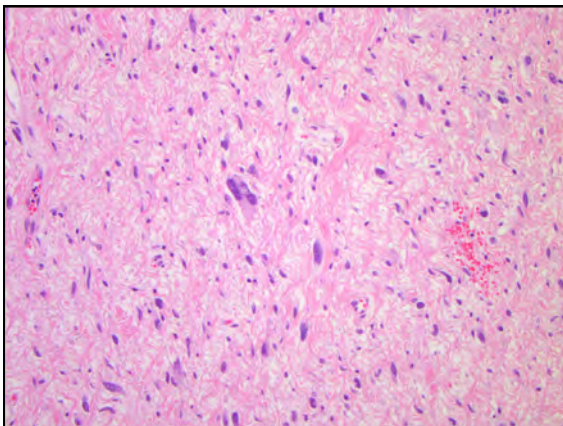
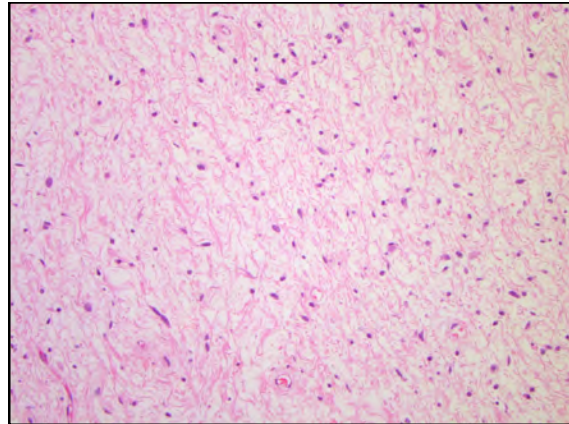
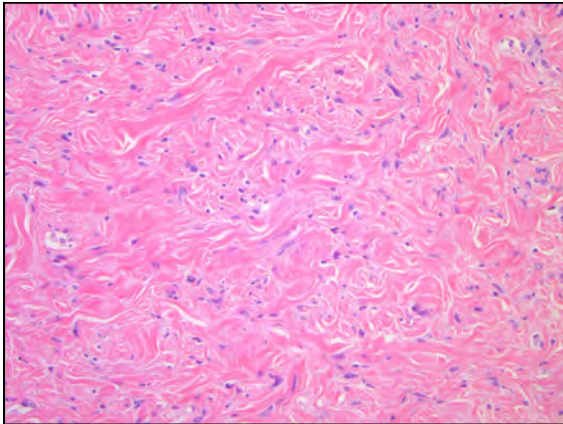
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CASE 1 (2)

- MRI revealed a large mass intimately associated with the right kidney
- Patient referred to community urologist, with resection of putative renal cell carcinoma

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CASE 1 (3)

Differential diagnosis

- a) Sarcomatoid renal cell carcinoma
- b) Dedifferentiated liposarcoma
- c) Nerve sheath tumour (e.g., neurofibroma, MPNST)
- d) Retroperitoneal fibrosis (Ormond's disease)
- e) I do not know – need immunohistochemistry

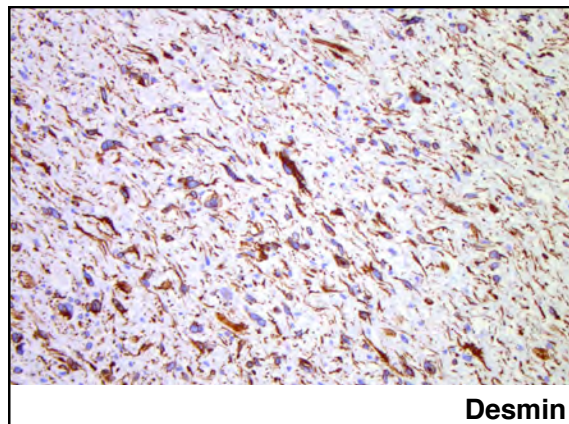
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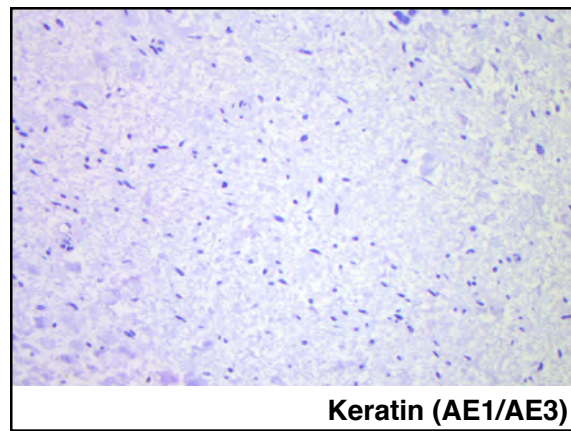
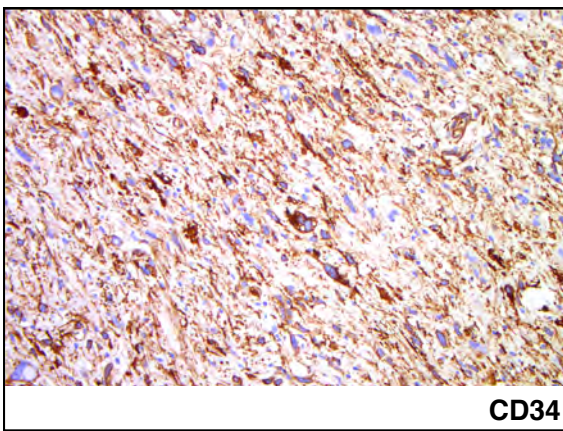
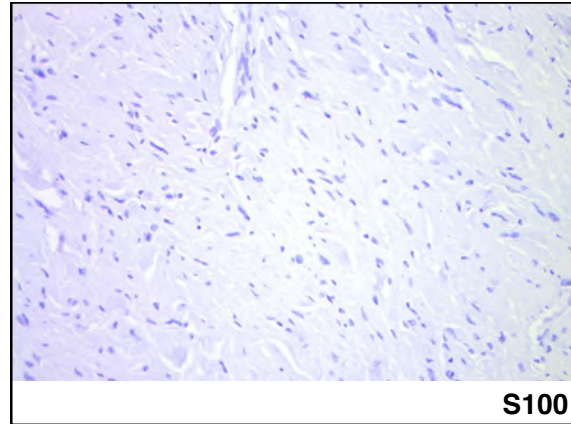
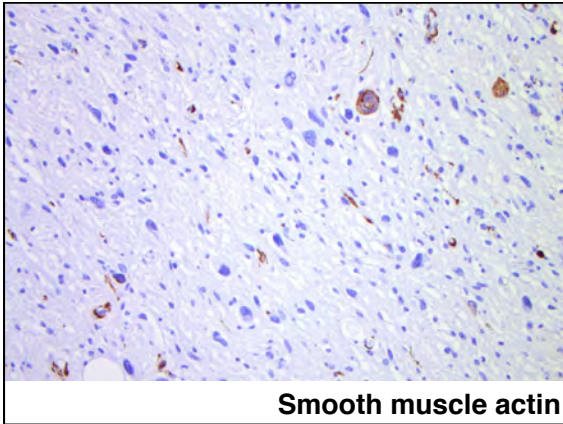
CASE 1 (4)


Immunohistochemistry

Screening Panel (spindle cell neoplasms)

- Desmin
- Smooth muscle actin
- S100
- CD34
- Keratin (AE1/AE3) / epithelial membrane antigen






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CASE 1 (5)

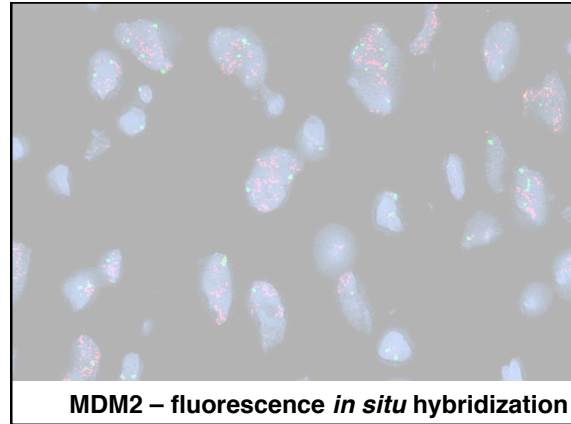
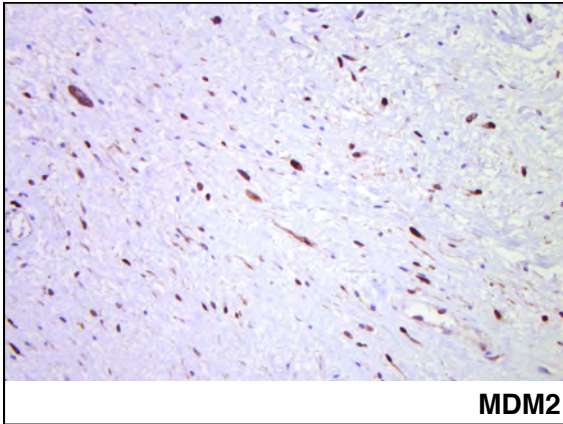
Diagnosis

- a) Sarcomatoid renal cell carcinoma
- b) Dedifferentiated liposarcoma
- c) Nerve sheath tumour (e.g., neurofibroma, MPNST)
- d) Retroperitoneal fibrosis (Ormond's disease)
- e) I *still* do not know

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CASE 1 (6)
Immunohistochemistry

Screening Panel	Confirmatory Panel
<ul style="list-style-type: none"> • Desmin • Smooth muscle actin • S100 • CD34 • Keratin (AE1/AE3) / epithelial membrane antigen 	<ul style="list-style-type: none"> • PAX8 • MDM2 / CDK4 / p16 • Neurofilament / CD56 / PGP9.5 • IgG / IgG4

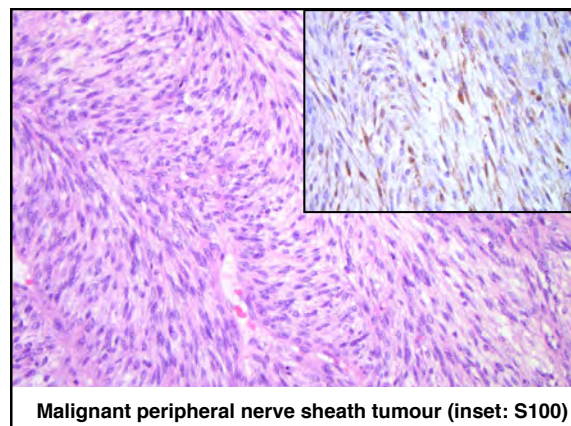
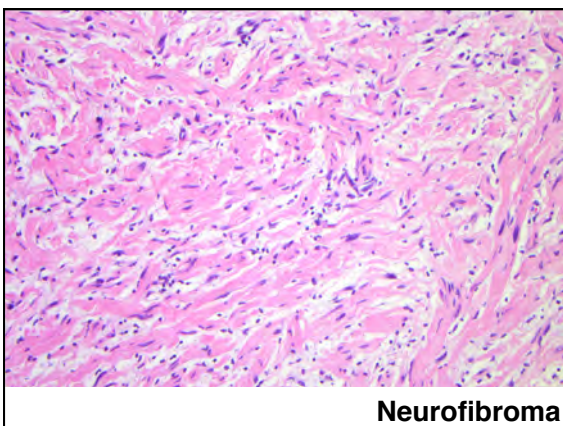
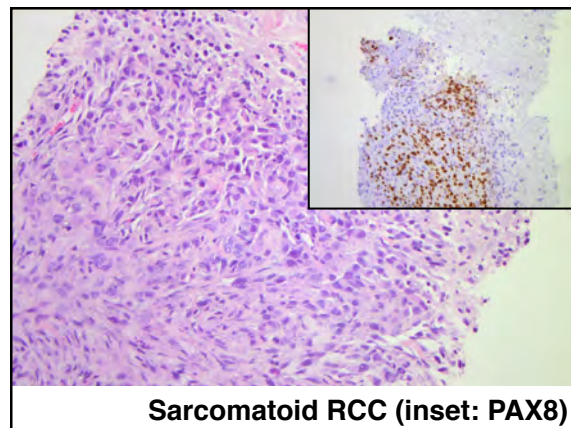


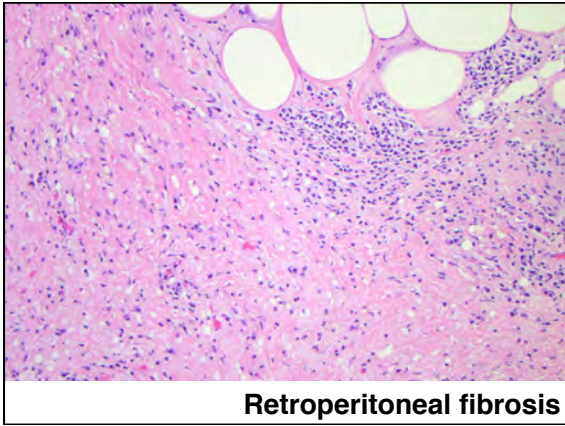
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CASE 1 (7)

Diagnosis

- a) Sarcomatoid renal cell carcinoma
- b) **Dedifferentiated liposarcoma**
- c) Nerve sheath tumour (e.g., neurofibroma, MPNST)
- d) Retroperitoneal fibrosis (Ormond's disease)
- e) *I still do not know*






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LIPOSARCOMA

World Health Organization (2013)
 Well differentiated liposarcoma (atypical lipomatous tumour *)
 Dedifferentiated liposarcoma
 Myxoid / round cell liposarcoma
 Pleomorphic liposarcoma




Fletcher CDM et al. WHO Classification of Tumours of Soft Tissue and Bone, 2013;1-242.

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LIPOSARCOMA

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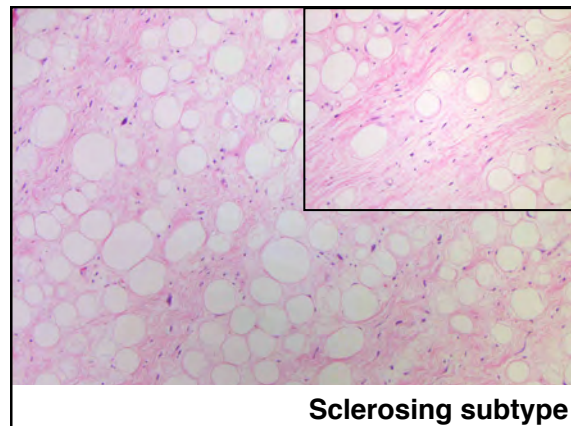
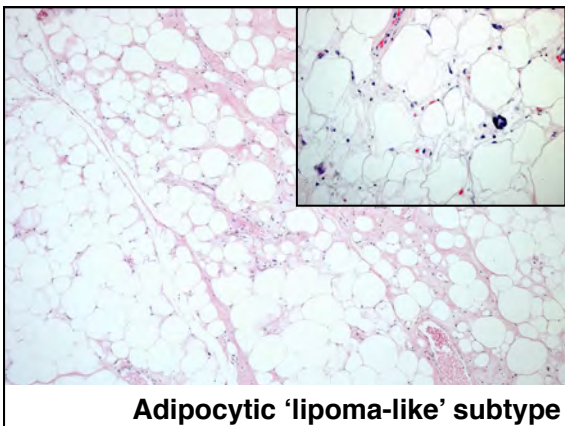


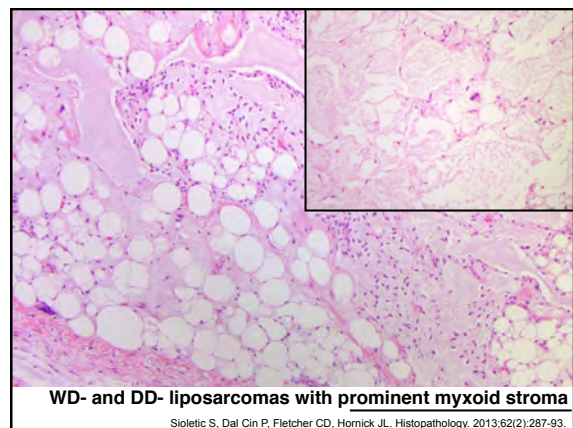
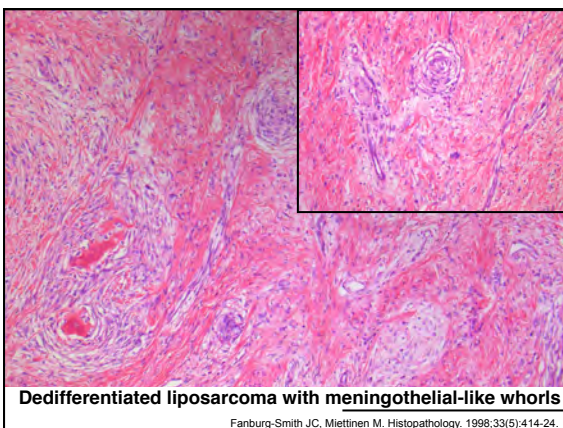
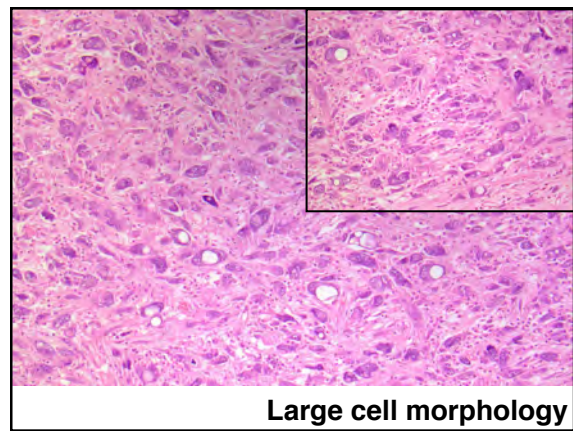
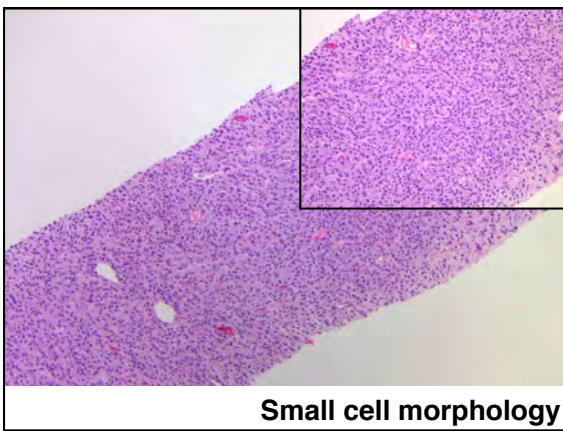
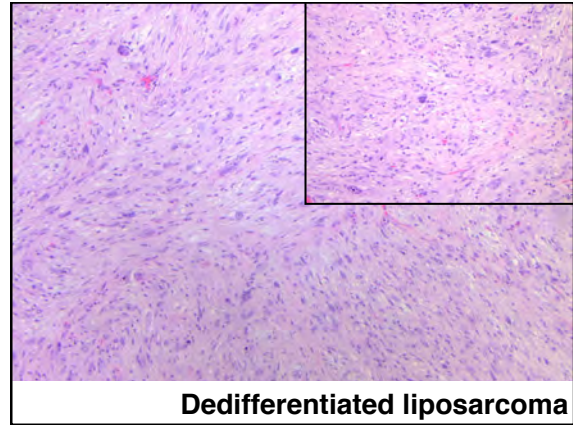
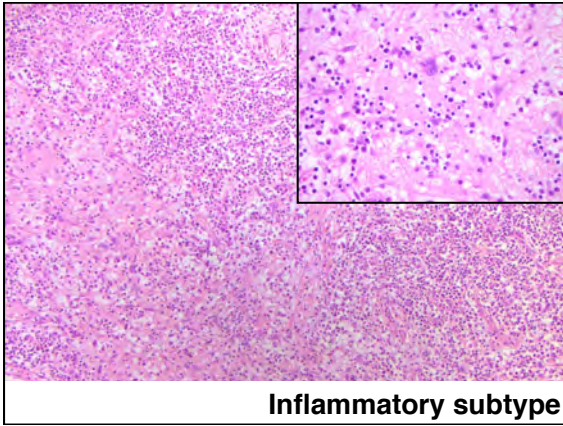
Fletcher CDM et al. WHO Classification of Tumours of Soft Tissue and Bone, 2013;1-242.

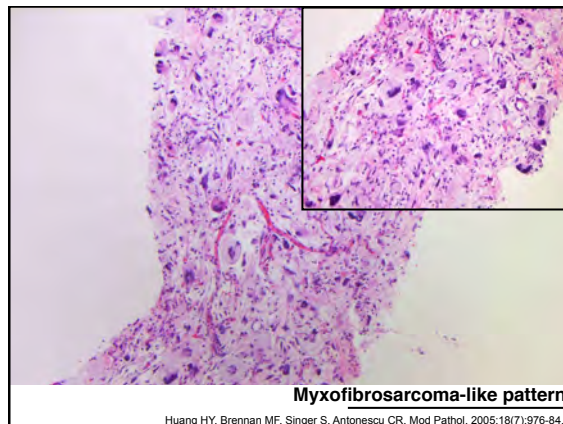
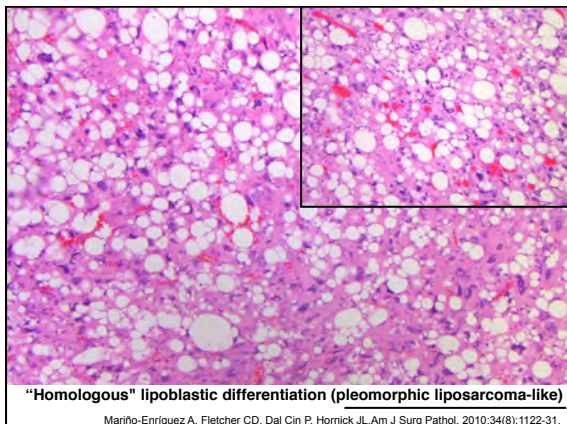
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LIPOSARCOMA (2)

DIFFERENTIATION







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LIPOSARCOMA (3)

Definition

- Malignant neoplasm with adipocytic derivation

Epidemiology

- Most common sarcoma of retroperitoneum
- 90% of dedifferentiated cases arise *de novo*, with 10% occurring on recurrence

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LIPOSARCOMA (4)

Histology

- Well-differentiated and/or dedifferentiated
- Plethora of histomorphologies

Immunohistochemistry

- Routine stains typically non-diagnostic (+/- CD34, +/- desmin, +/- SMA, +/- S100, +/- EMA)
- MDM2 and CDK4 helpful, particularly with dedifferentiation

Molecular

- Characterized by MDM2 amplification

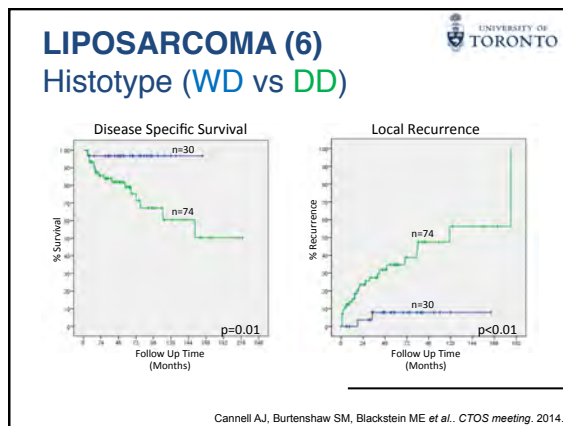
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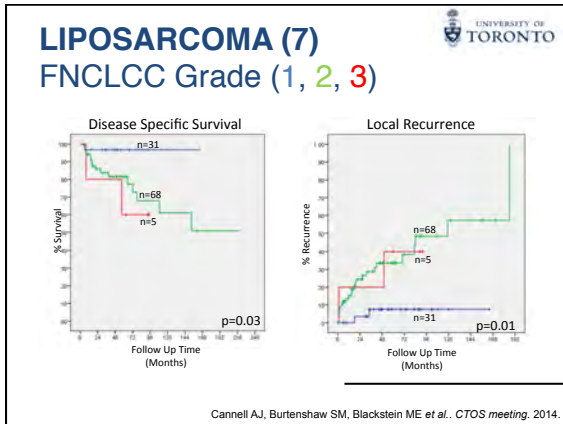
LIPOSARCOMA (5)

Prognosis

- Clinical
 - Completeness of resection
- Pathologic
 - Histotype (well differentiated vs dedifferentiated)
 - FNCLCC grade

Cannell AJ, Burtenshaw SM, Blackstein ME et al. CTOS meeting. 2014.
 Mussi C, Collini P, Miceli R et al. *Cancer.* 2008;113(7):1657-65.
 Singer S, Antonescu CR, Riedel E et al. *Ann Surg.* 2003;238(3):358-70.



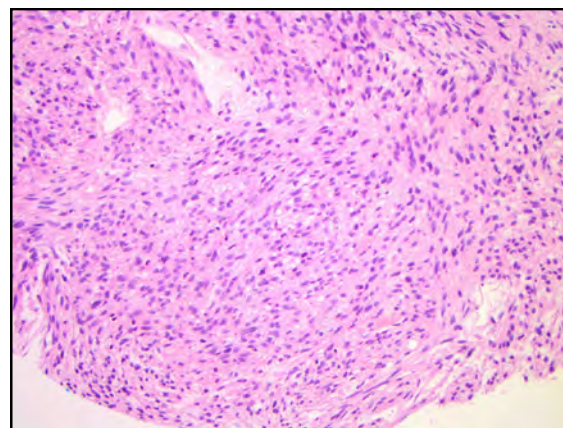
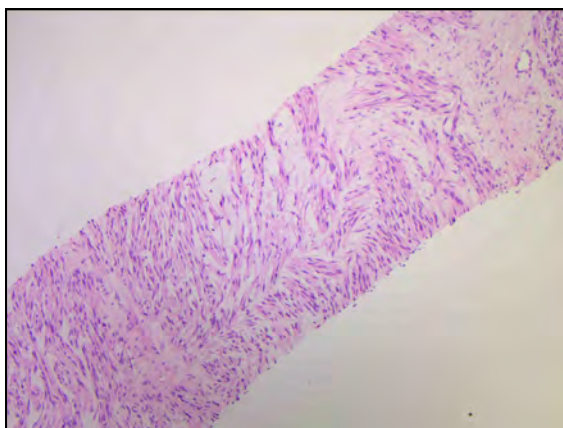


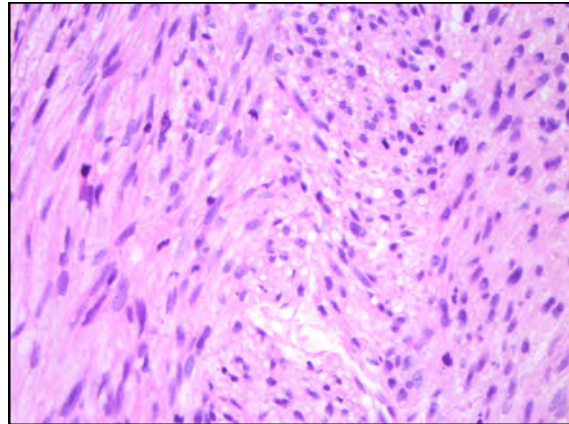
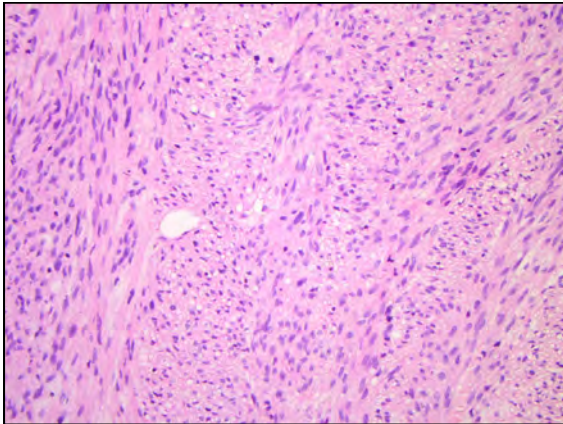
CASE 2


- 64 F. Presented to family physician with abdominal pain
- Past medical history is significant for leiomyomata. Hysterectomy after 4th child
- On examination palpable LUQ mass

CASE 2 (2)

- MRI reveals a large mass abutting the IVC, stomach and head of pancreas
- Biopsy performed






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CASE 2 (3)

Differential Diagnosis

- a) Gastrointestinal stromal tumour
- b) Angiomyolipoma (fat-poor)
- c) Leiomyosarcoma
- d) 'Benign' metastasizing uterine leiomyoma
- e) I do not know – need immunohistochemistry

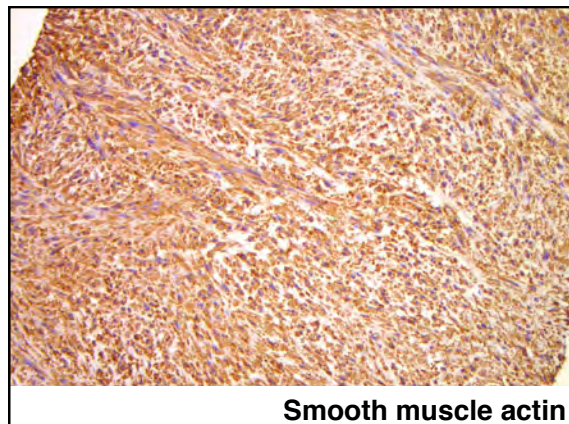
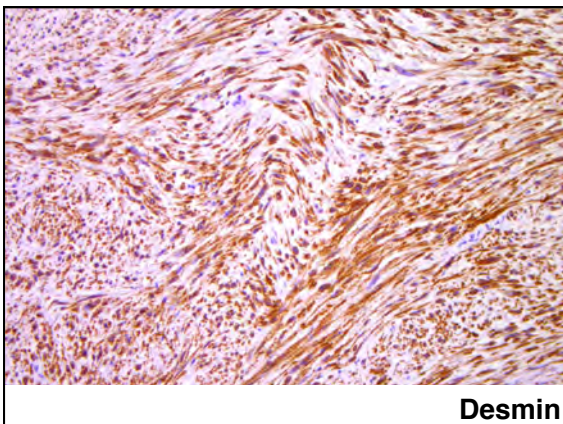
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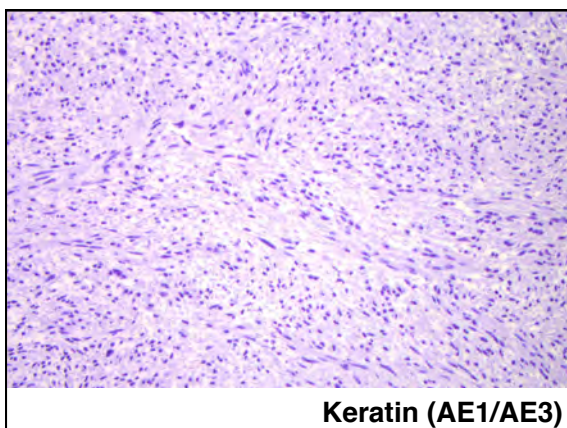
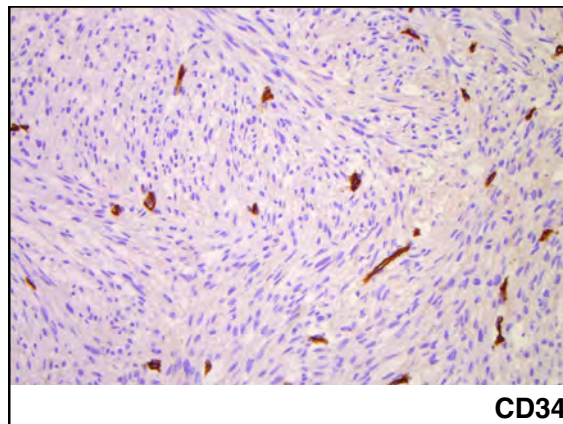
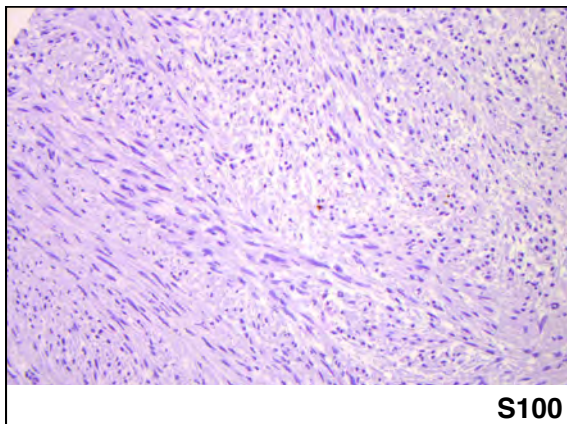
CASE 2 (4)


Immunohistochemistry

Screening Panel (spindle cell neoplasms)

- Desmin
- Smooth muscle actin
- S100
- CD34
- Keratin (AE1/AE3) / epithelial membrane antigen






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CASE 2 (5)

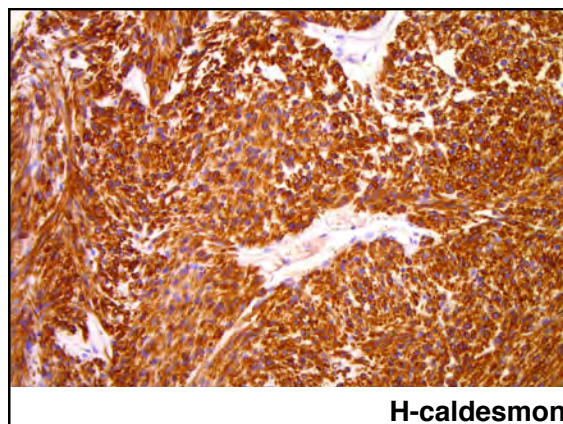
Diagnosis

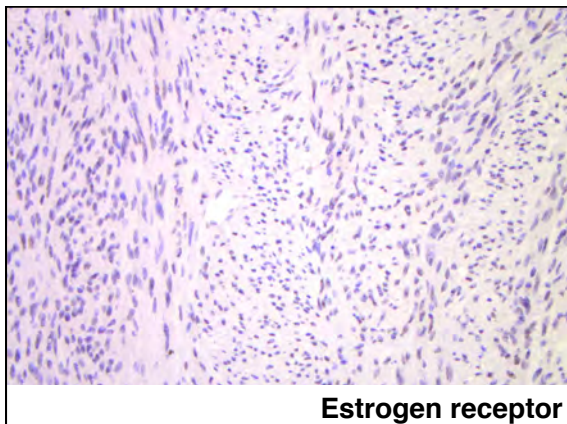
- a) Gastrointestinal stromal tumour
- b) Angiomyolipoma (fat-poor)
- c) Leiomyosarcoma
- d) 'Benign' metastasizing uterine leiomyoma
- e) *still* do not know


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CASE 2 (6)
Immunohistochemistry

<p>Screening Panel</p> <ul style="list-style-type: none"> • Desmin • Smooth muscle actin • S100 • CD34 • Keratin (AE1/AE3) / epithelial membrane antigen 	<p>Confirmatory Panel</p> <ul style="list-style-type: none"> • CD117/ DOG1 • HMB45 / MART1 • H-caldesmon • ER/ PgR
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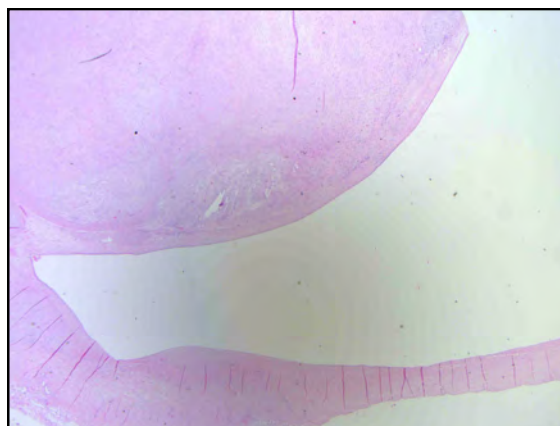
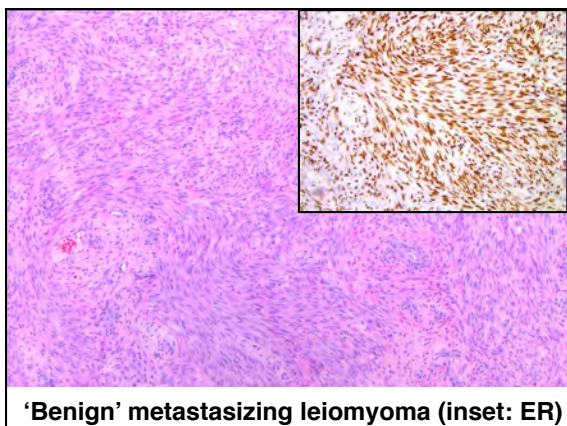
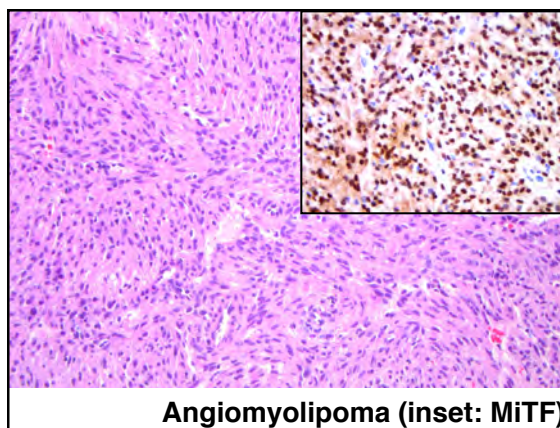
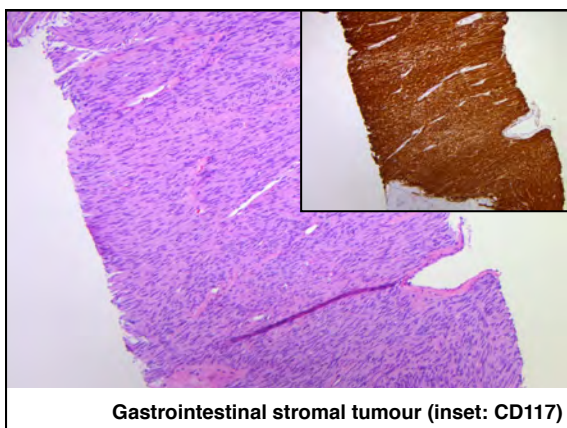


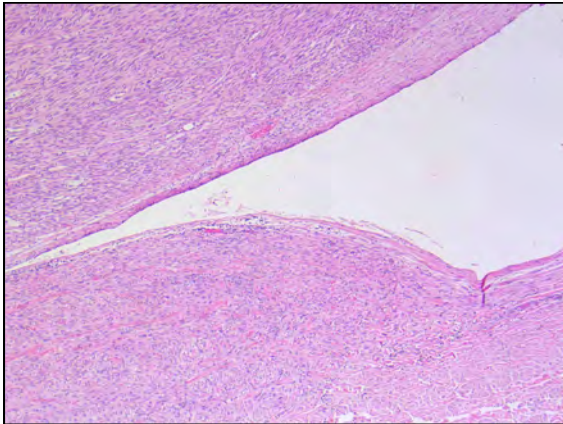
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CASE 2 (7)

Diagnosis

- a) Gastrointestinal stromal tumour
- b) Angiomyolipoma (fat-poor)
- c) **Leiomyosarcoma**
- d) 'Benign' metastasizing uterine leiomyoma
- e) *still* do not know





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LEIOMYOSARCOMA

Definition

- Malignant neoplasm showing 'pure' smooth muscle differentiation

Epidemiology


- Second most common sarcoma arising in retroperitoneum
- Predominant sarcoma arising from large blood vessels (esp. IVC)
- F > M

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LEIOMYOSARCOMA (2)


Histology

- Intersecting fascicles of spindle-epithelioid cells
- Eosinophilic cytoplasm
- May have perinuclear vacuole
- Cigar-shaped nucleus with hyperchromasia
- Mitotic activity (1 or more per 50 HPFs)*
- +/- Necrosis


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LEIOMYOSARCOMA (3)

<p>Leiomyoma</p> <ul style="list-style-type: none"> • No 'significant' atypia • At most, very low mitotic activity* <ul style="list-style-type: none"> – M (< 1 per 50 HPFs) – F (≤ 5 per 50 if ER / PR positive) • May see degenerative changes but <i>not</i> necrosis 	<p>Leiomyosarcoma</p> <ul style="list-style-type: none"> • At least focal atypia • Mitotic activity • May see necrosis
--	--



Fletcher CDM et al. WHO Classification of Tumours of Soft Tissue and Bone. 2013;1:242.

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LEIOMYOSARCOMA (4)


Immunohistochemistry

- (+) smooth muscle actin, desmin, H-caldesmon
- (+/- focal) keratin, CD34, CD117, S100

May have loss of desmin, SMA, H-caldesmon with dedifferentiation

Molecular Analysis

- Complex genetic aberrations (*MED12*, other mutations)
- Not diagnostically relevant

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LEIOMYOSARCOMA (5)

Prognosis

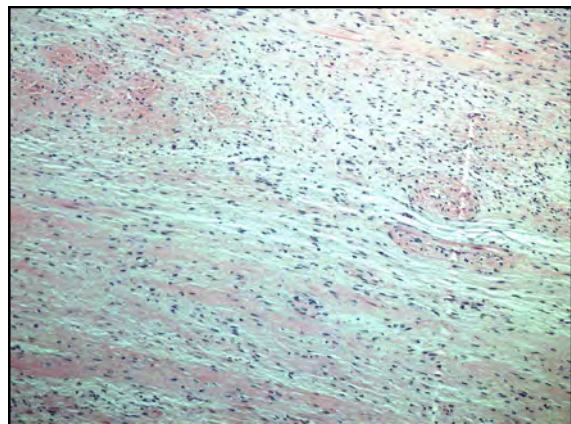
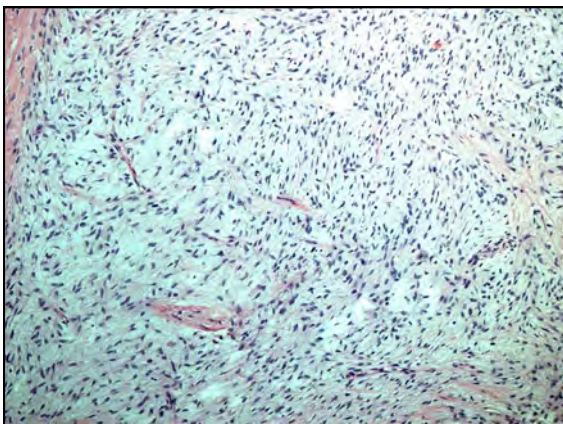
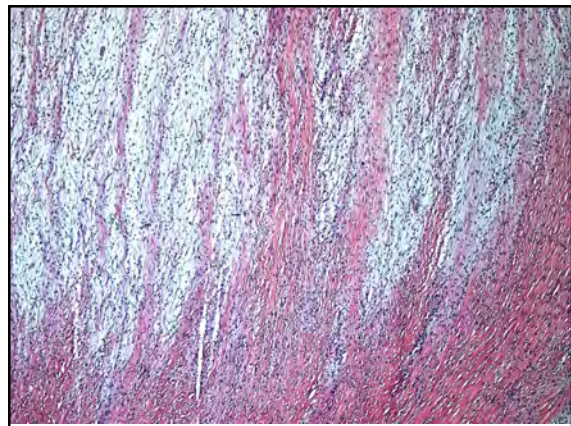
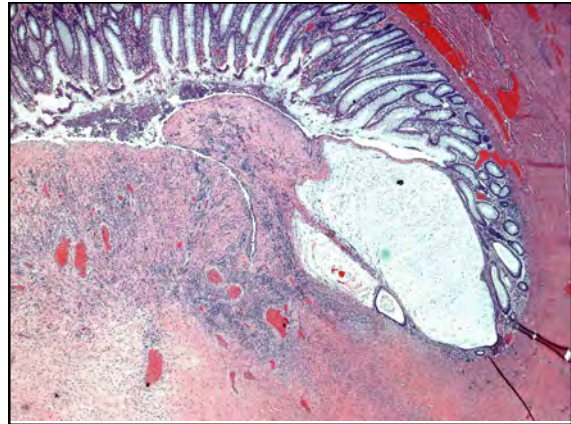
- Retroperitoneal cases frequently fatal:
 - Attain large size prior to detection
 - Intimate with vital organs and vessels, making it difficult to attain clear margins
 - Grade important for predicting risk of metastasis

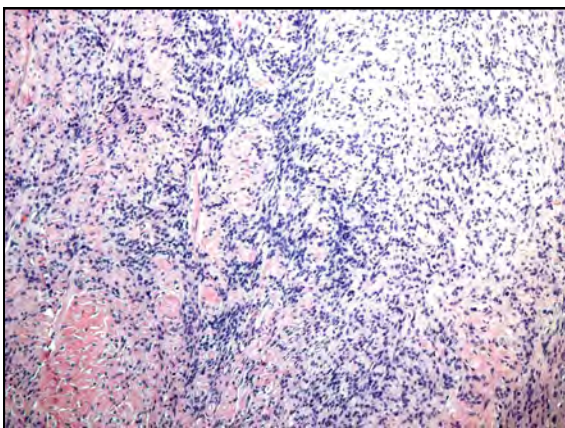
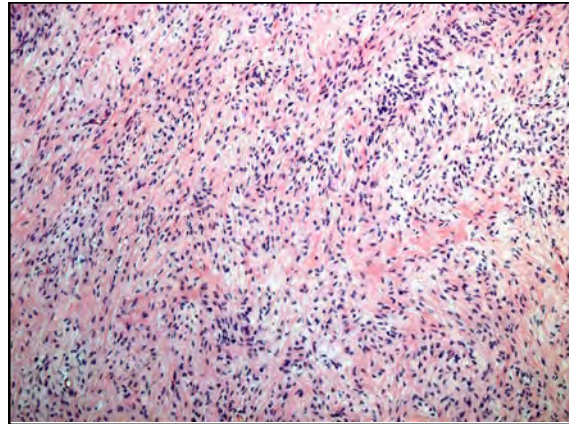
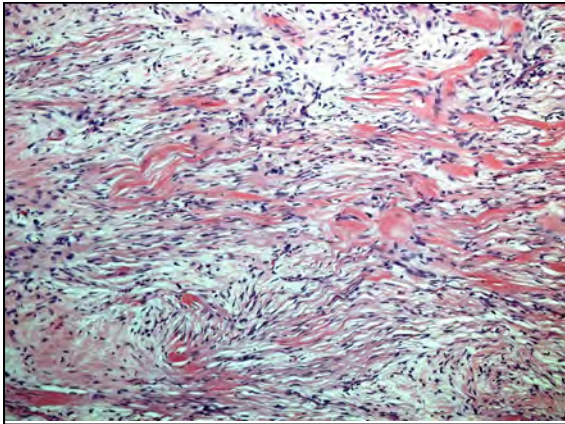
Gladdy RA, Qin LX, Moraco N et al. Ann Surg Oncol. 2013;20(6):1851-7.


CASE 3



- 22 F. Presented to family physician with constipation and rectal bleeding
- No significant past medical history
- Diagnostic imaging demonstrates a 5 cm rectosigmoid mass
- Resected by general surgeon






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CASE 3 (2)

Differential Diagnosis

- a) Inflammatory myofibroblastic tumour
- b) Desmoid-type fibromatosis
- c) Solitary fibrous tumour
- d) Low-grade fibromyxoid sarcoma
- e) I do not know – need immunohistochemistry


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CASE 3 (3)

Immunohistochemistry provided with case

- Negative for desmin, smooth muscle actin, S100, CD34, CD117, HMB45

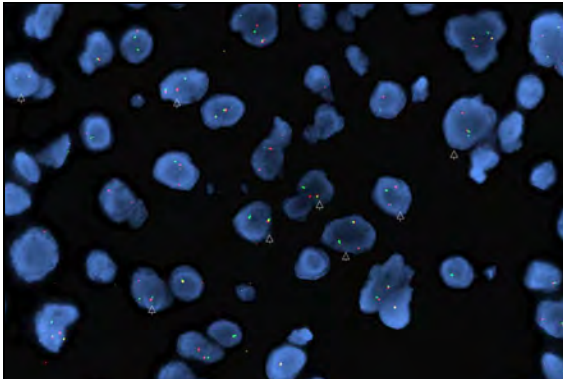
(On-slide positive controls stained appropriately)

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CASE 3 (4)

Diagnosis

- a) Inflammatory myofibroblastic tumour
- b) Desmoid-type fibromatosis
- c) Solitary fibrous tumour
- d) Low-grade fibromyxoid sarcoma
- e) I *still* do not know



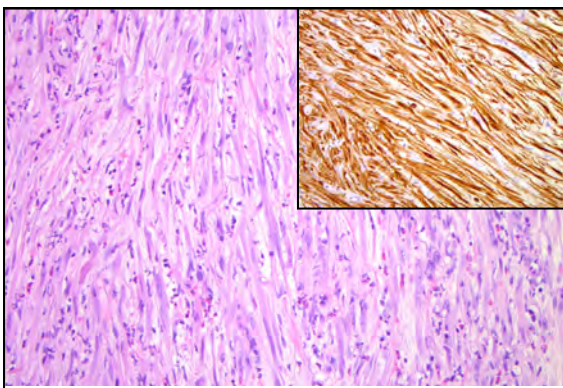
FUS – fluorescence *in situ* hybridization

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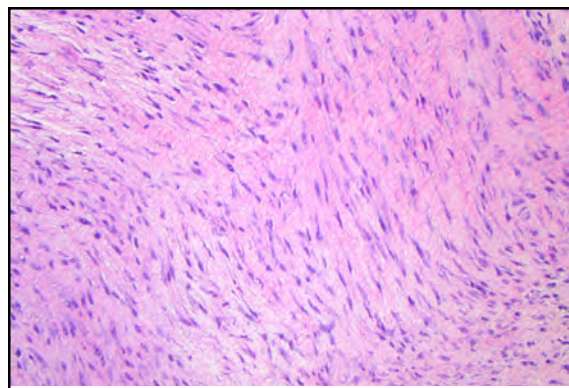
CASE 3 (5)

Diagnosis

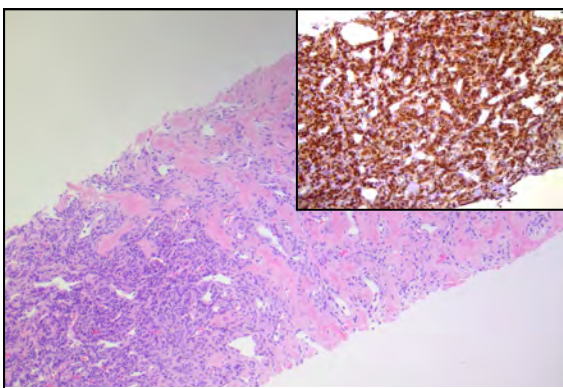
- a) Inflammatory myofibroblastic tumour
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- c) Solitary fibrous tumour
- d) Low-grade fibromyxoid sarcoma**
- e) I *still* do not know




Inflammatory myofibroblastic tumour (inset: ALK1)



Desmoid-type fibromatosis



Solitary fibrous tumour (inset: STAT6)

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FIBROSARCOMA


Low-grade fibromyxoid sarcoma

Definition

- Malignant fibroblastic neoplasm

Epidemiology

- Part of a heterogenous group of fibroblastic sarcomas
- Uncommon; may be under recognized
- Young adults; F = M

FIBROSARCOMA (2) 


Low-grade fibromyxoid sarcoma

Morphology

- Admixture of collagenous and myxoid regions.
- Morphologically bland
- Mitotic activity generally inconspicuous
- Curvilinear vasculature
- +/- giant collagen rosettes

Immunohistochemistry


- EMA at least focally positive in ~ 80% of cases
- MUC4 positive

FIBROSARCOMA (3) 

Low-grade fibromyxoid sarcoma

Molecular

- Majority:
 - Cytogenetics: t(7;16)(q33;p11)
 - Fusion product: FUS-CREB3L2
- Minority:
 - Cytogenetics: t(11;16)(p11;p11)
 - Fusion product: FUS-CREB3L1
- Others

FIBROSARCOMA (4) 


Low-grade fibromyxoid sarcoma

Prognosis

- 10% risk of local recurrence in first 5 years
- Late risk of local recurrence and metastasis
(depends on subtype of fibrosarcoma)

Others types occurring in retroperitoneum


- Sclerosing epithelioid fibrosarcoma
- Inflammatory myofibroblastic tumour / sarcoma
- Malignant subtype of solitary fibrous tumor

SUMMARY 

Retroperitoneal sarcoma

- Sarcoma is rare (< 1% of cancers)
- National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program:
 - 1973-1987: 19,684 cases
 - > 50% in soft tissue
 - M>F; median M= 54.8, F= 55.3


Landis SH et al. 1999. CA Cancer J Clin. 1999;49(1):8-31.
Mack TM. Cancer. 1995;75(1Suppl):211-44.

SUMMARY (2) 

Retroperitoneal sarcoma

- SEER
 - Liposarcoma (21.7%)
 - Malignant mesothelioma (19.6%)
 - Leiomyosarcoma (19.2%)
 - Malignant fibrous histiocytoma (10.9%)
 - Sarcoma, NOS (9.8%)
 - Neuroblastoma (8.2%)
 - Fibrosarcoma (3.3%)
 - MPNST (2.0%)
 - Rhabdomyosarcoma (1.9%)
 - Others (3.4%)

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SUMMARY (2) 

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SUMMARY (3)
Retroperitoneal sarcoma

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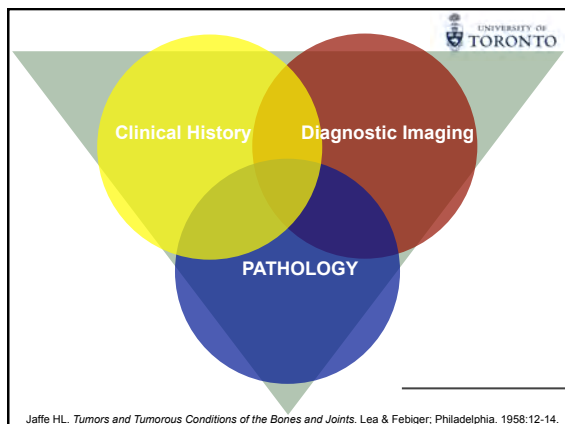
- May encounter on needle core biopsy, or inadvertently on excision
- Important to recognize based on risk of local recurrence and death
- When faced with an unusual morphology and/or immunophenotype consider possibility of **dedifferentiated liposarcoma**

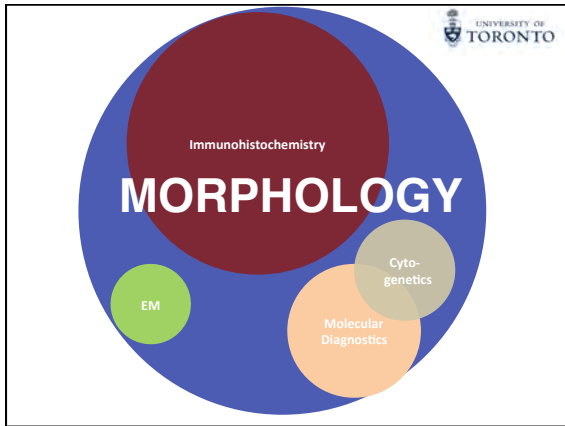
SUMMARY (4)
Retroperitoneal sarcoma

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- Should have a low threshold to refer cases (subspecialty expertise, availability of ancillary techniques, QA)
- *Imperative* primary resections be performed at designated sarcoma centre
- Multidisciplinary setting: Radiology, Pathology, Surgical oncology, Radiation oncology, Medical oncology

ESMO/European Sarcoma Network Working Group. *Ann Oncol*. 2014;25(Suppl 3): iii102-12.





QUESTIONS

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