BDIAP/ BSG Symposium on Lower GI Pathology, 23-24th November 2018, London

The differential diagnosis of poorly differentiated tumors of the lower GI tract

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Speaker Declarations

Name of Speaker: Abbas Agaimy, MD

This presenter has the following declarations of relationship with industry

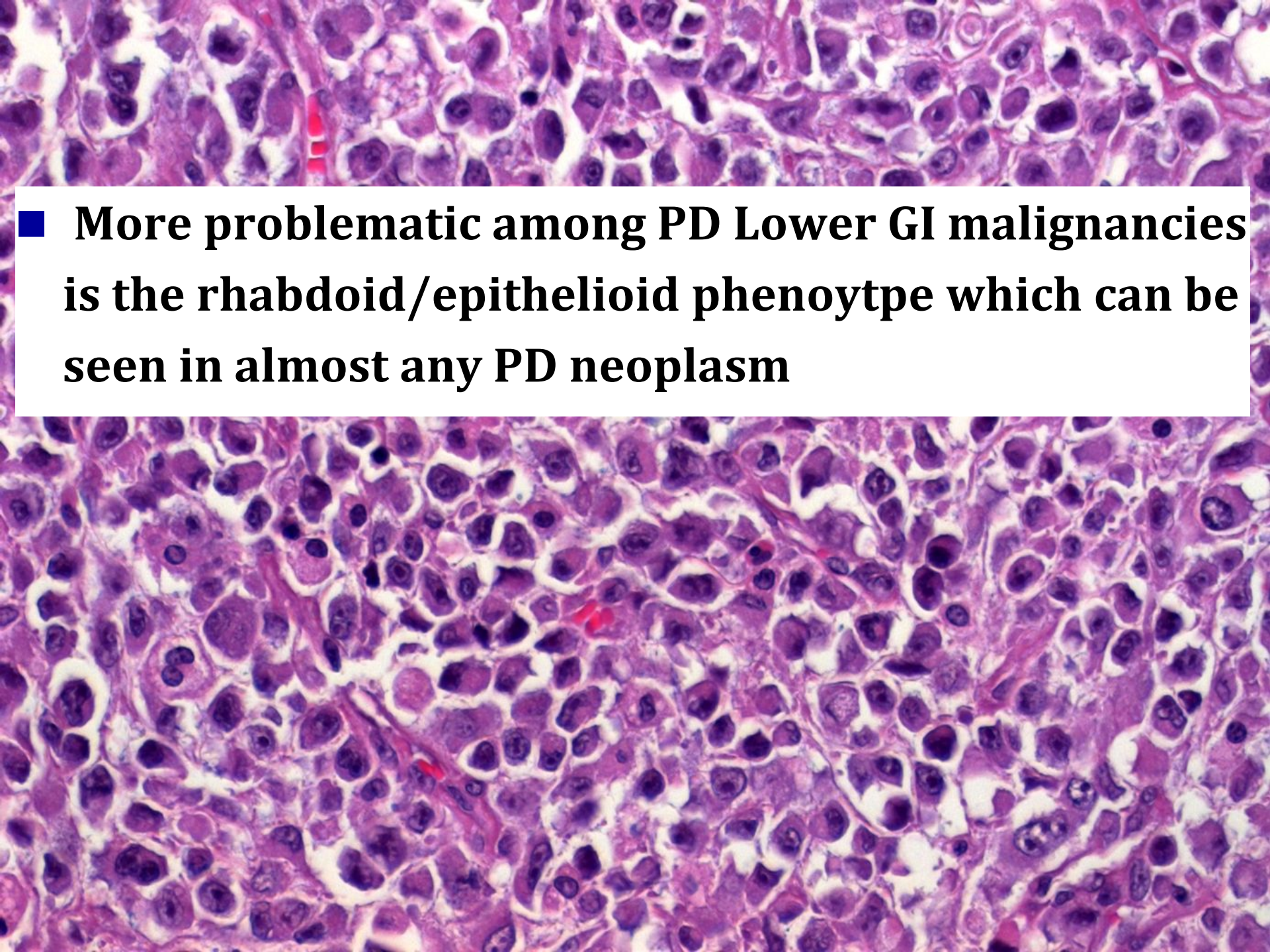
- NONE

Outlines

- **Major DDx of PD lower GI malignancies.**
- **Histological patterns of PD lower GI carcinomas.**

PD lower GI malignancies
major DDx considerations

- **Neoplasms composed of monotonous epithelioid, rhabdoid anaplastic-looking or pleomorphic and spindled sarcomatoid cells may represent:**
  - **Carcinomas: primary or metastatic**
  - **Lymphomas**
  - **Melanoma**
  - **(rarely) sarcomas (mets more common than primary)**



- **More problematic among PD Lower GI malignancies is the rhabdoid/epithelioid phenoytpe which can be seen in almost any PD neoplasm**

PD sarcomas in the lower GI tract

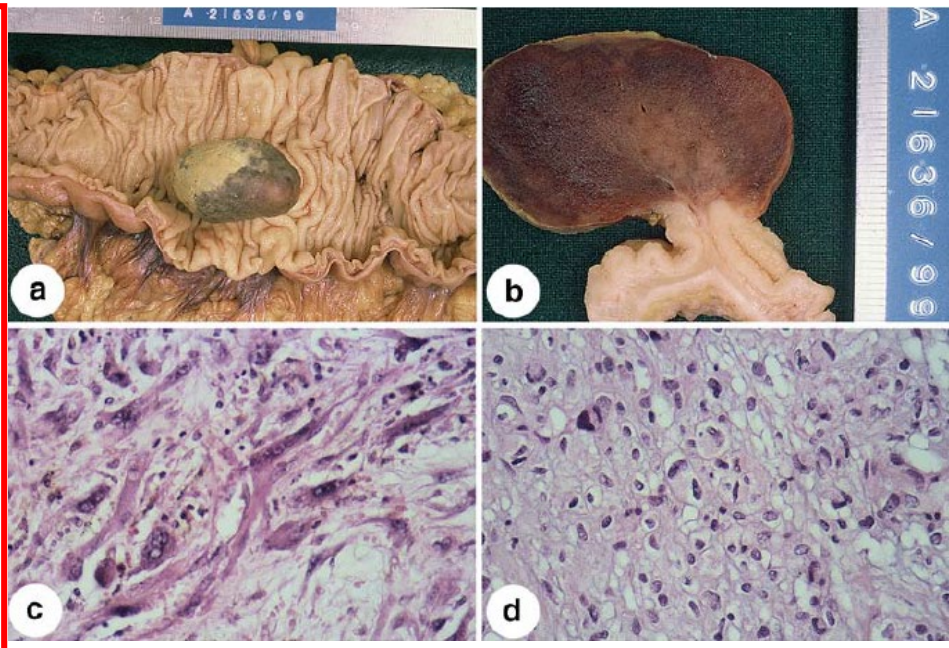
Primary vanishingly rare.

Mets uncommon.

Usually extensive transmural.

Think of mets if

- **Prominent polypoid growth**
- **(Bleeding sarcomatous polyp)**
- **Multifocal disease**



Sigmoid mets 5 yrs after „UPS“, thigh

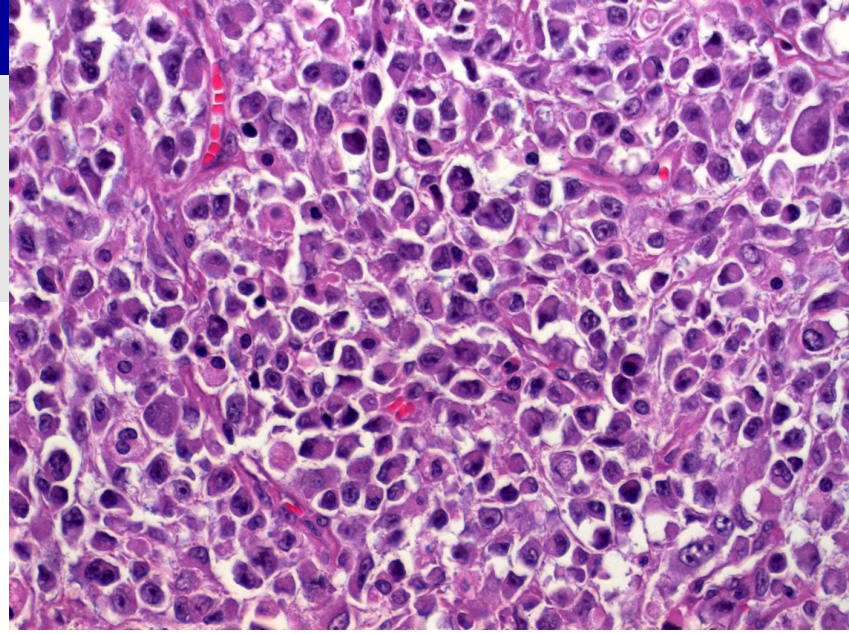
Agaimy et al, Virchows Arch, 2007

PD lower GI malignancies
DDx: sarcoma metastasis to GI tract

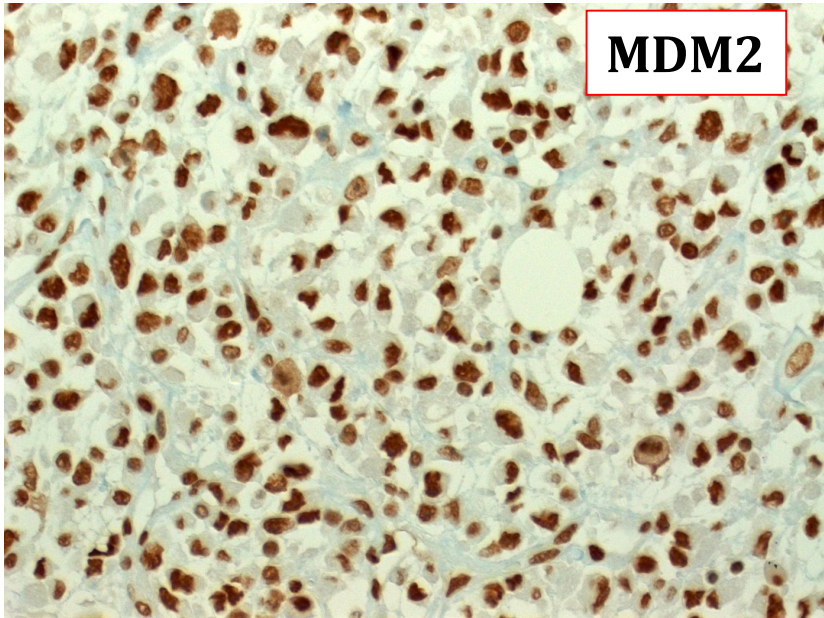
- **Undifferentiated pleomorphic sarcoma, leiomyosarcoma & angiosarcoma are main sources.**

- **Extension from dediff liposarcoma and other retroperitoneal sarcomas should be ruled out.**

Dediff liposarcoma with rhabdoid & epithelioid pattern



- Mainly elderly males.
- highly aggressive.
- Large retoperitoneal masses.
- GI involvement direct or mets.
- Frequent CK expression (pitfall).
- Huge mass, retroperit. Bulk
- Well diff component (imaging!)
- MDM2/CDK4 alterations



Makise et al, AJSP, 2017
Agaimy et al, Hum Pathol, 2017

Epithelioid Rhabdomyosarcoma: Clinicopathologic Analysis of 16 Cases of a Morphologically Distinct Variant of Rhabdomyosarcoma

Vickie Y. Jo, MD, Adrián Mariño-Enríquez, MD, and Christopher D.M. Fletcher, MD, FRCPath

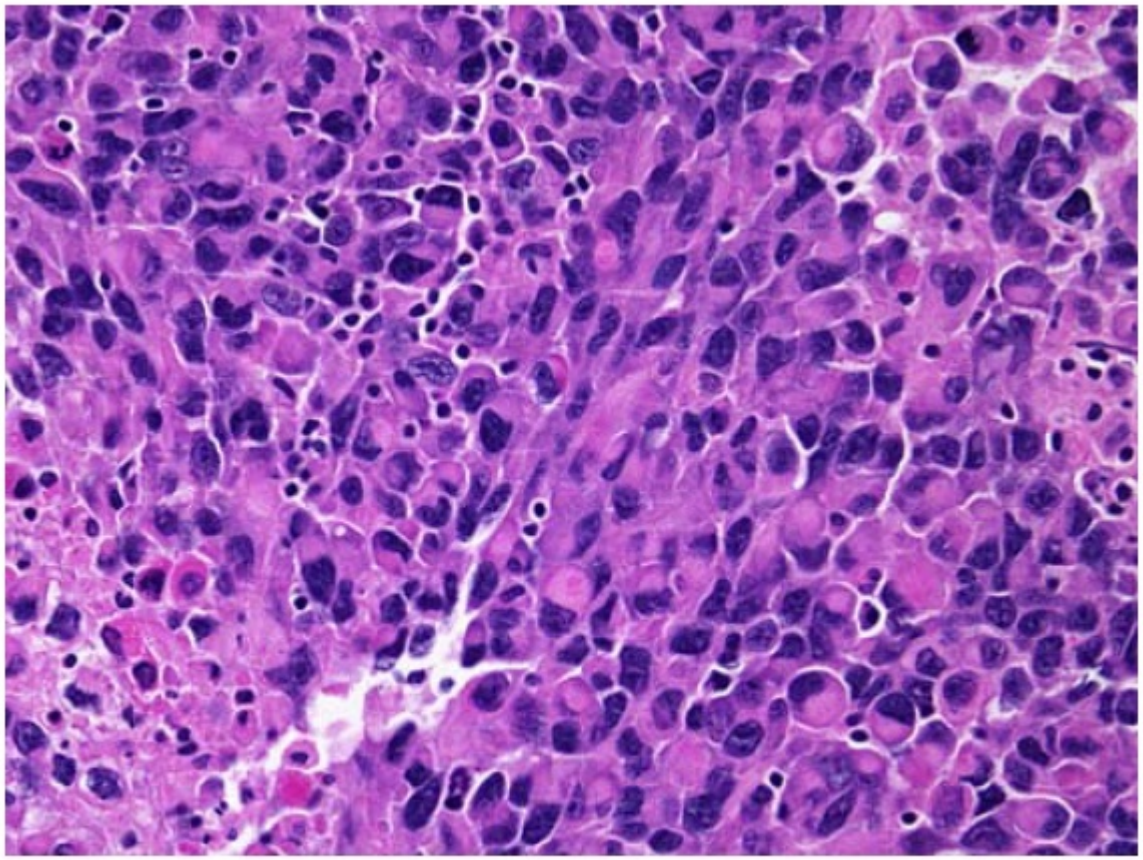
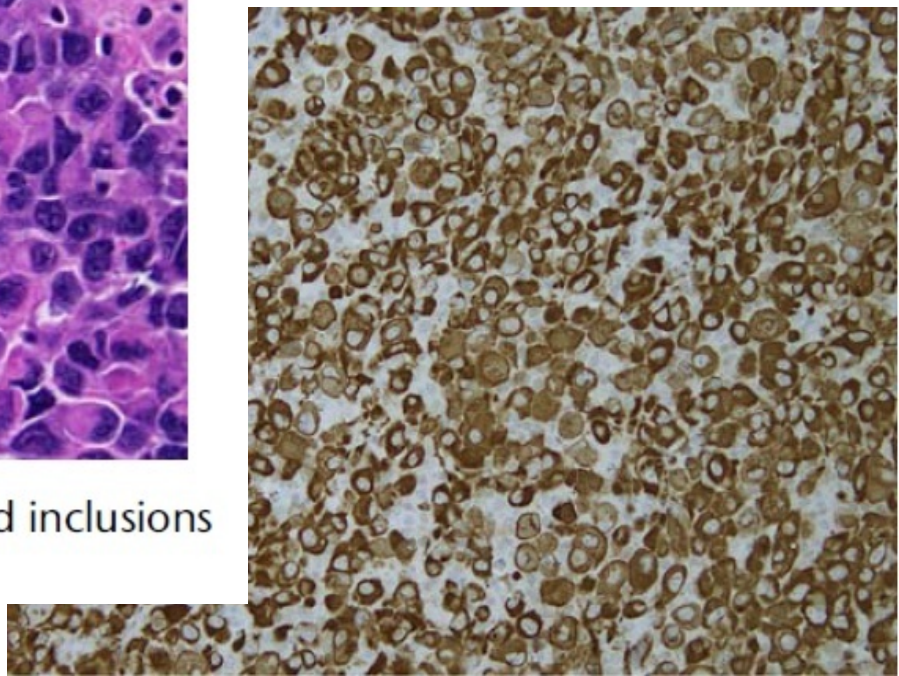


FIGURE 2. Focally prominent cytoplasmic rhabdoid inclusions were seen in 3 cases (case 14).

no case originated in the retroperitoneum

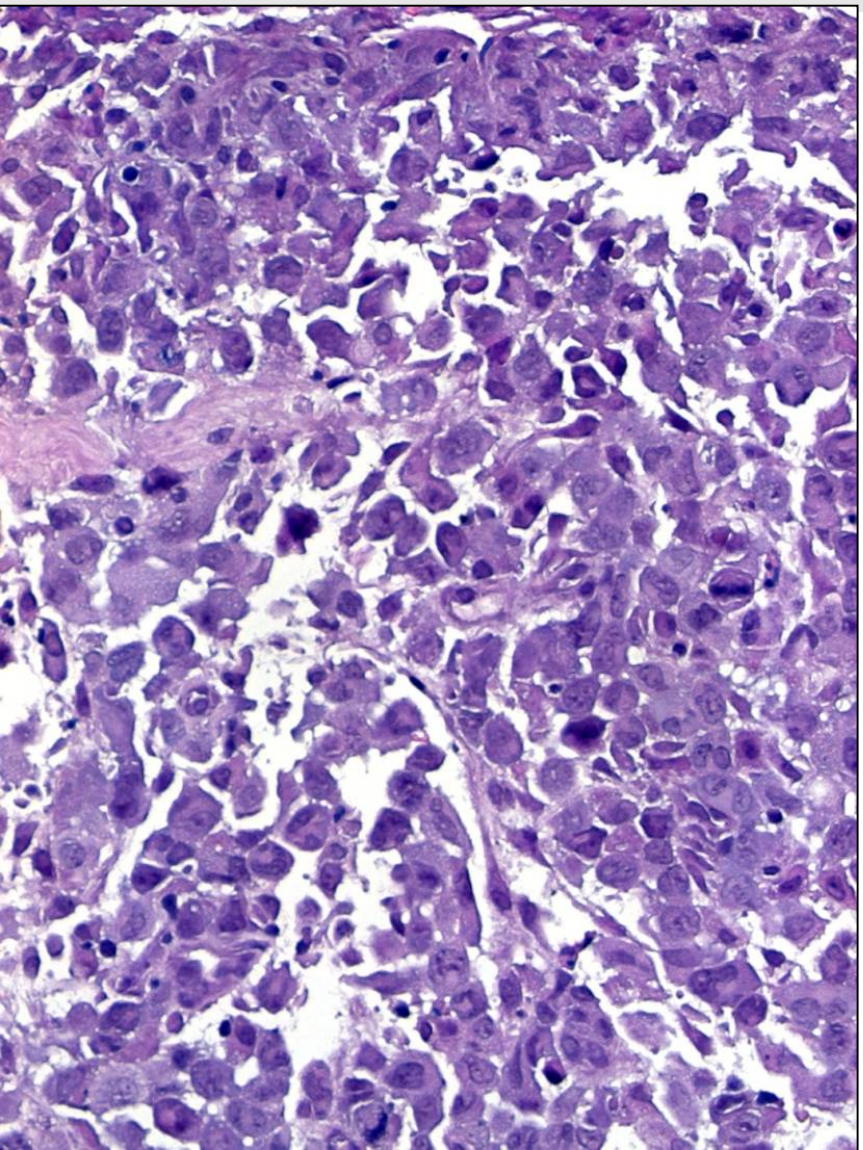
desmin



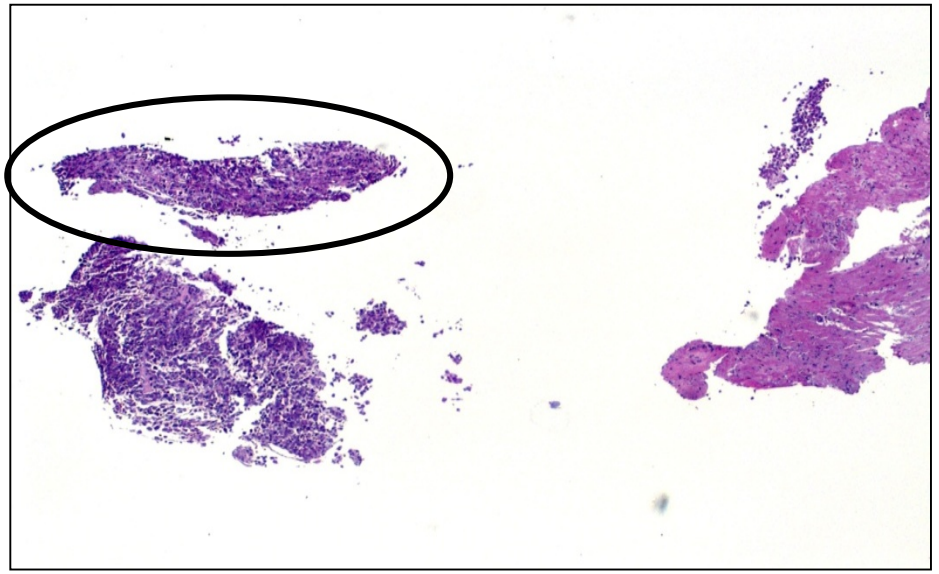
Lymphomas

- Mainly in the small intestine but rare in the lower GI tract.
- Anaplastic large cell lymphoma at particular risk to be missed if appropriate markers not included.
- CD45 and T-cell markers frequently negative in ALCL.

47 yo female with NF1, multiple GISTs and large abdominal mass (cores obtained intra-op)



Suggestive of undiff rhabdoid carcinoma but CK neg.



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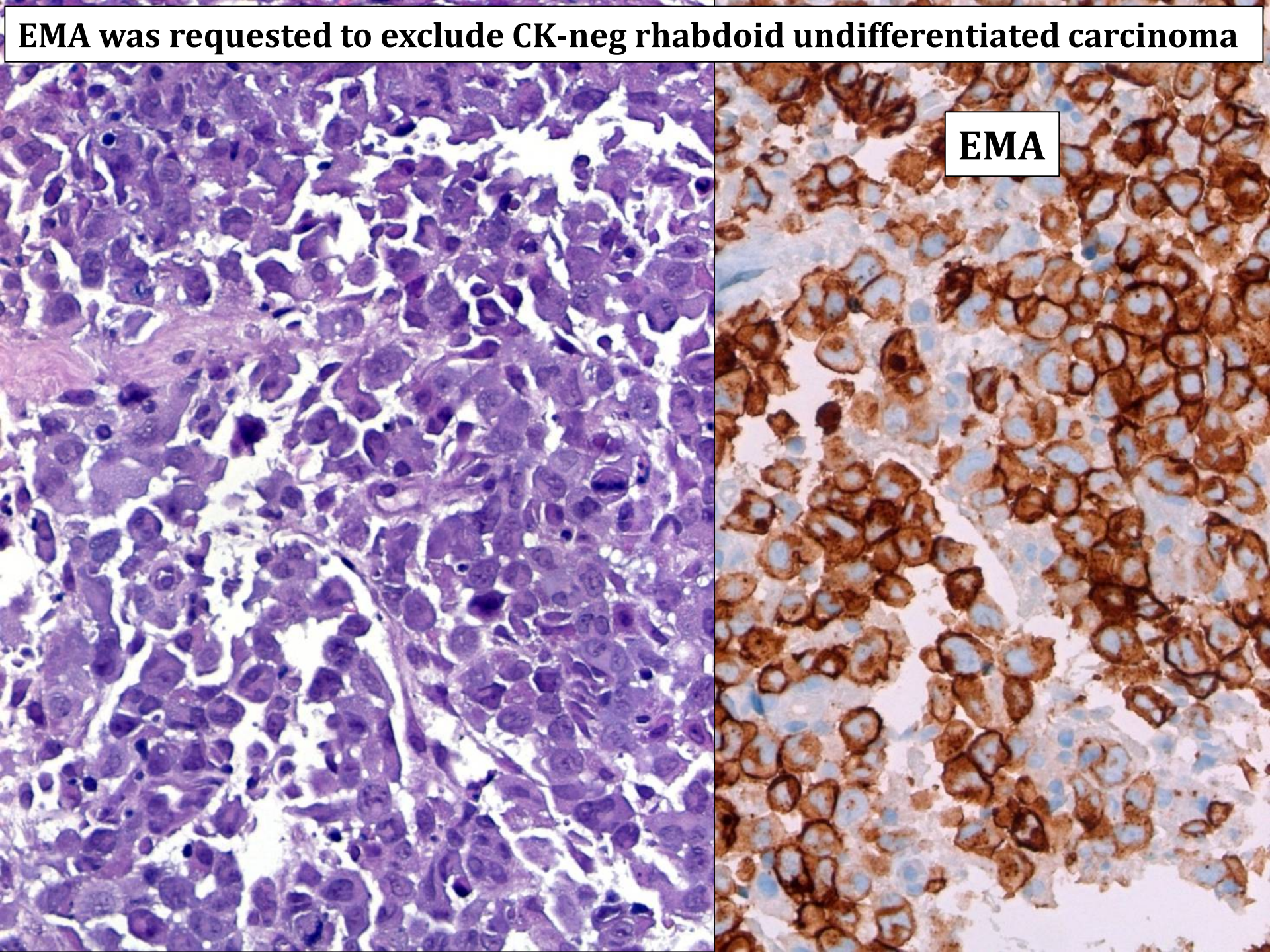
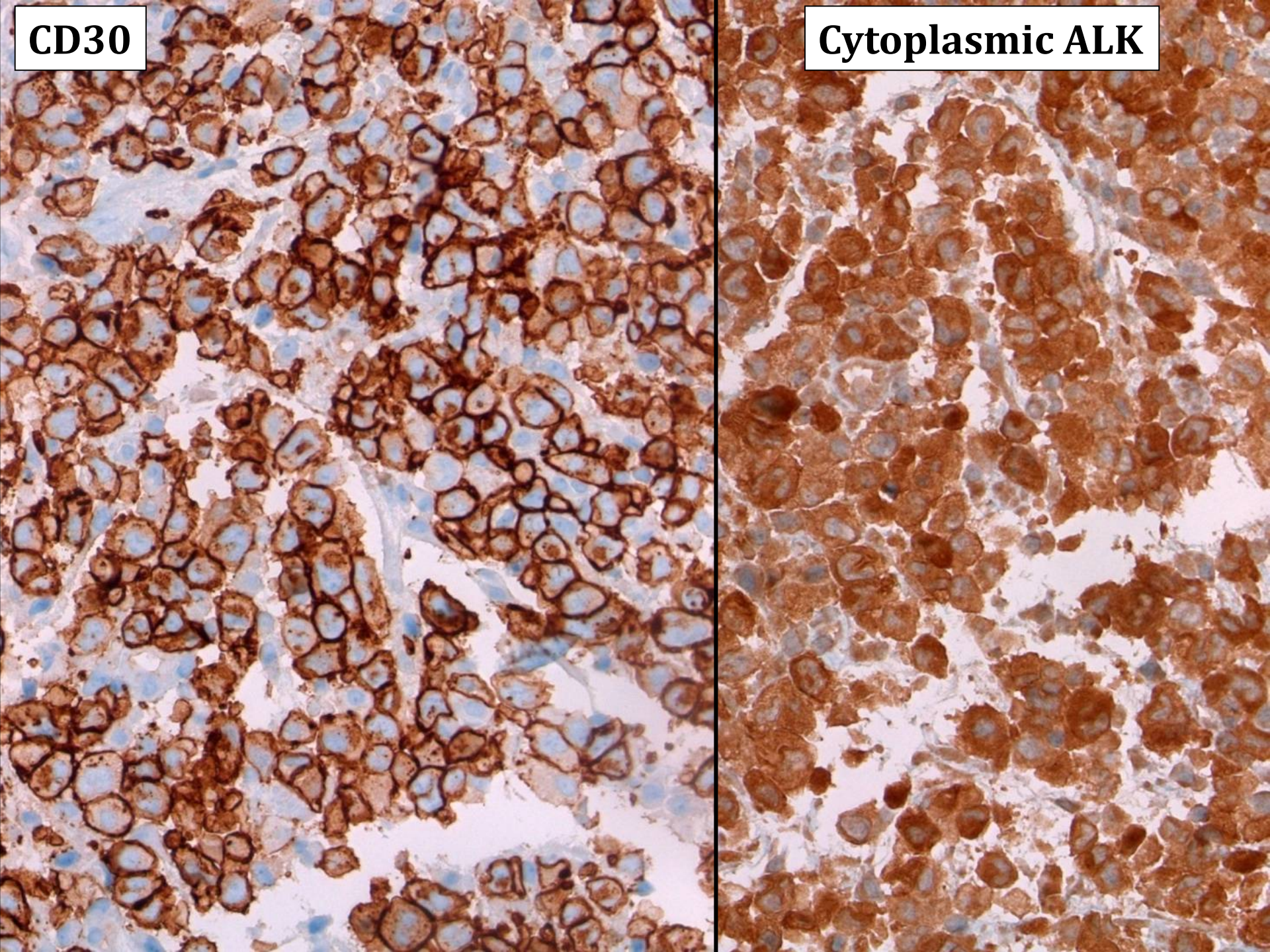
EMA was requested to exclude CK-neg rhabdoid undifferentiated carcinoma




CD30
Cytoplasmic ALK

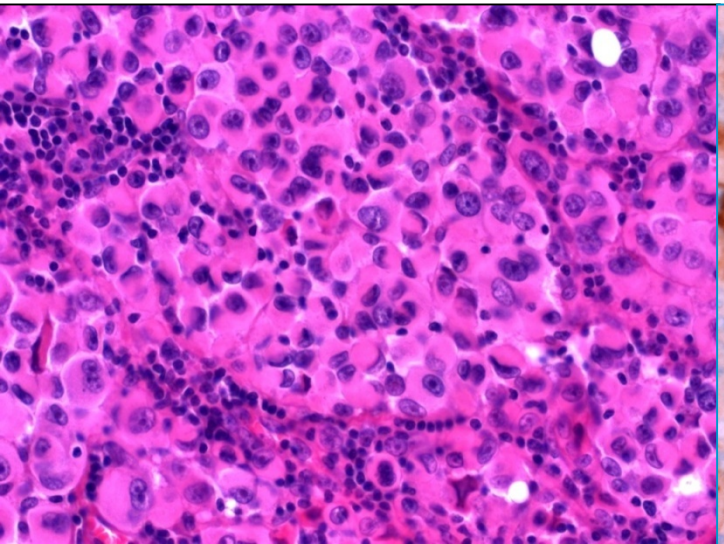
Frankly rhabdoid phenotype but intact INI1: always think of melanoma

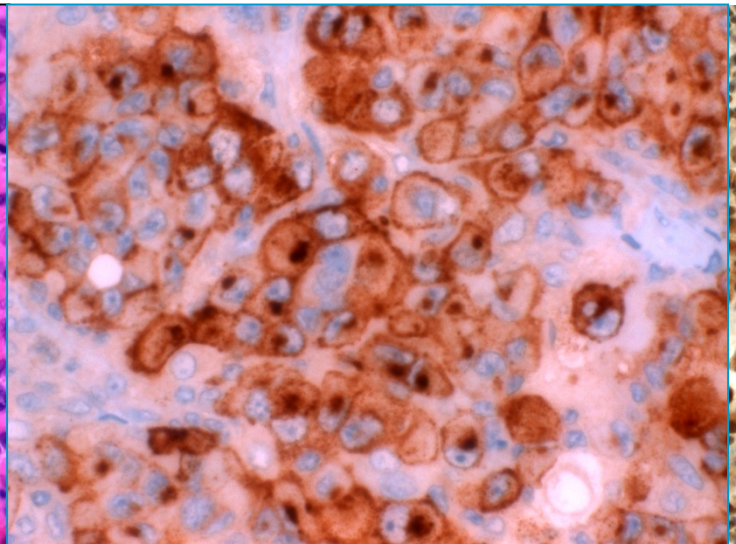
Metastatic malignant melanoma showing a rhabdoid phenotype: further evidence of a non-specific histological pattern. Bittesini L, Dei Tos AP, Fletcher CD. Histopathology. 1992 Feb;20(2):167-70.

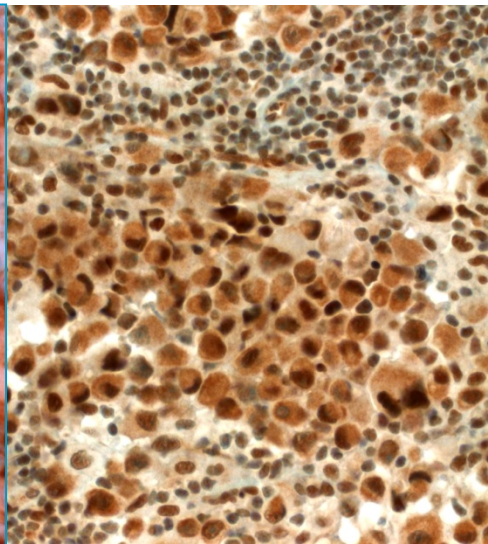
Fortunately, rhabdoid MM retains specific melanoma markers

HMB45 in rhabdoid MM

SMARCB1







Histological patterns of PD lower GI carcinomas

- **Monomorphic cells:**
  - **Medullary**
  - **Rhabdoid (indistinguishable from pediatric rhabdoid tumors)**
  - **Large anaplastic cells (indistinguishable from proximal ES)**
  - **Small round cell sarcoma-like or lymphoma-like**
  - **Mixed**
- **Bizarre pleomorphic cells**
- **Spindled sarcomatoid**
- **Combined**

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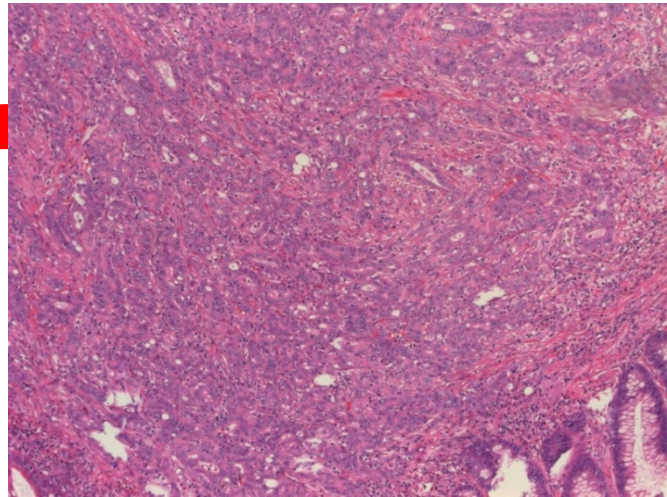
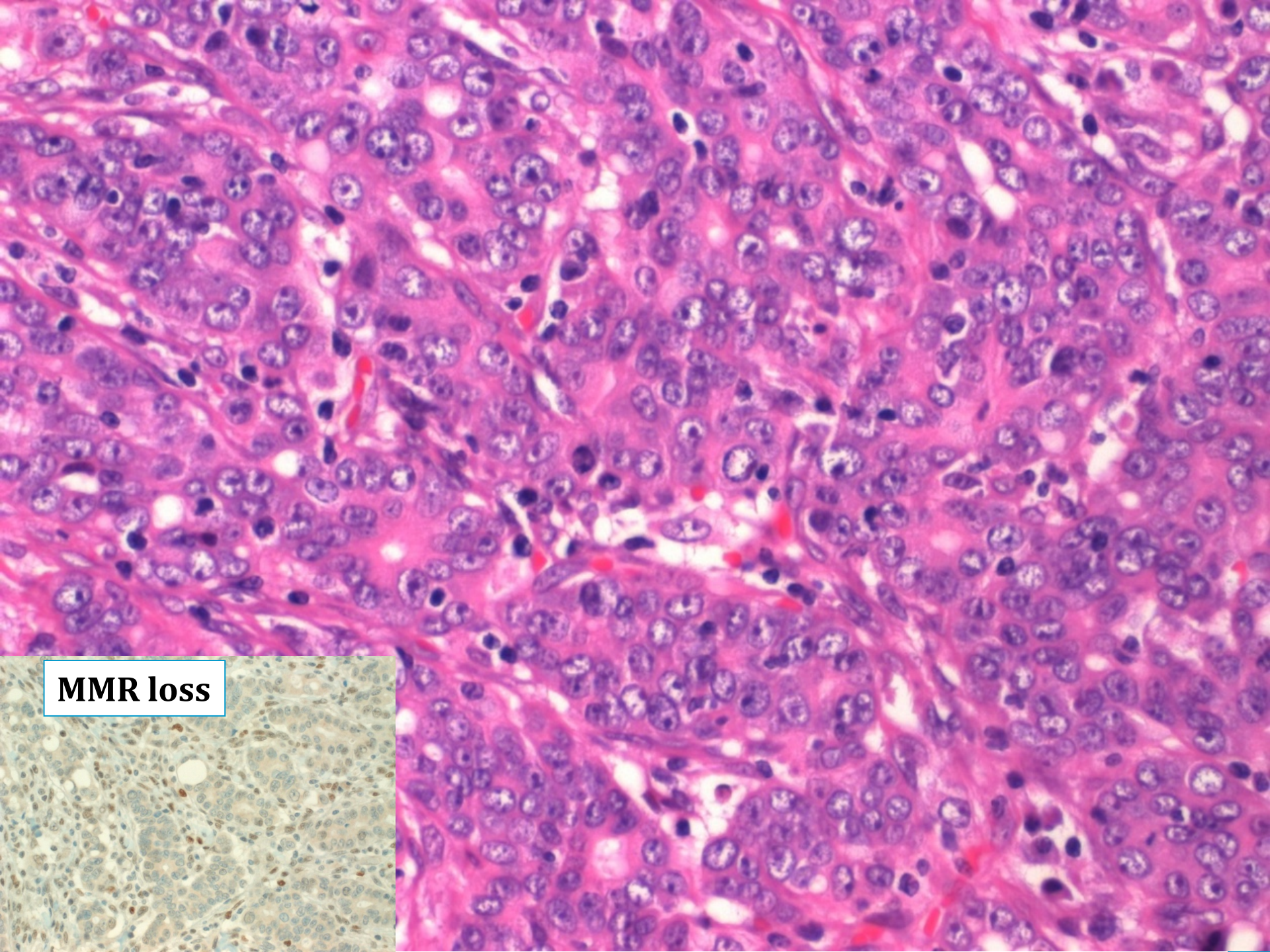
Any of these patterns may suggest a specific genotype

- Bizarre pleomorphic cells
- Spindled sarcomatoid
- Combined

Medullary carcinoma

- The prototype of MMR deficient MSI CRC.
- Prominent tumor-infiltrating lymphocytes (TILs).
- Usually indolent behavior, therefore „WHO: low-grade“.
- May be sporadic or Lynch-related.
- Mucinous or signet ring component may be present.
- Crohn-like inflammation.
- **A subset highly aggressive (unexplained**




MMR loss

Histological patterns of PD lower GI carcinomas

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- **Majority of neoplasms with undiff monotonous pattern Have SWI/SNF chromatin remodelling complex defects**
- Spindled sarcomatoid
- Combined

Mammalian SWI/SNF chromatin remodelling complex

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 2905–2908, April 1994
Biochemistry

Five *SWI/SNF* gene products are components of a large multisubunit complex required for transcriptional enhancement

CRAIG L. PETERSON*†, ANDREW DINGWALL‡, AND MATTHEW P. SCOTT‡

- ✓ A complex of **> 20 closely interdependant genes**.
- ✓ Regulates gene transcription, cell differentiation & proliferation.
- ✓ Highly conserved (expressed in all normal cells).
- ✓ **Mutated in >20% of all cancers.**
- ✓ Has a tumor suppressor function (**loss of function mutations**).

Table 1 Subunits of the SWI/SNF complexes

Subunit	Gene (alias)	Predicted molecular weight (kDa)	Type of SWI/SNF complex	Domain	Function
BRG1	*SMARCA4*	184.5	Core subunit	ATPase/bromo	ATPase and helicase catalytic subunit
BRM	*SMARCA2*	181	BAF-specific core subunit	ATPase/bromo	ATPase and helicase catalytic subunit
BAF47	*SMARCB1* (*hSNF5*, *INI1*)	44	Core subunit	SNF5	Unknown
BAF155	*SMARCC1* (*SWI3*)	123	Core subunit	Chromo/SANT/BRCT	Unknown
BAF170	*SMARCC2*	133	Core subunit	Chromo/SANT/BRCT	Unknown
BAF250a	*ARID1A* (*SMARCF1*)	242			
BAF250b	*ARID1B*	236			
BAF200	*ARID2*	197	PBAF-specific core subunit	ARID	DNA binding
BAF57	*SMARCE1*	47	BAF/PBAF	HMG	Unknown
BAF45a	*PHF10*	56	BAF/PBAF	Zinc finger_RING	Unknown
BAF45b/c/d	*DPF1/3/2*	42.5/43/44	BAF/PBAF	Zinc finger_RING	Unknown
BAF53a/b	*ACTL6A/B*	47.5/47	BAF/PBAF	Actin	Chromatin/nuclear matrix association Enhance ATPase activity
β-actin	*ACTB*	41.5	BAF/PBAF	Actin	Unknown
BAF60a/b/c	*SMARCD1/2/3*	58/59/55	BAF/PBAF	SWIB/MDM2	Unknown
BCL7A/B/C	*BCL7A/B/C*	23/23/23.5	BAF	Unknown	Unknown
BCL11A/B	*BCL11A/B*	91/95.5	BAF	Zinc finger_C2H2	Unknown
BRD9	*BRD9*	67	BAF	Bromo	Bind acetylated H3
SYT	*SS18*	46	BAF	Unknown	Transcriptional coactivator
BAF180	*PBRM1*	193	PBAF	BAH/HMG/Bromo	Unknown
BRD7	*BRD7*	74	PBAF	Bromo	Unknown

Loss of any of these component genes may result in similar phenotype

Common Features of SWI/SNF-deficient neoplasms

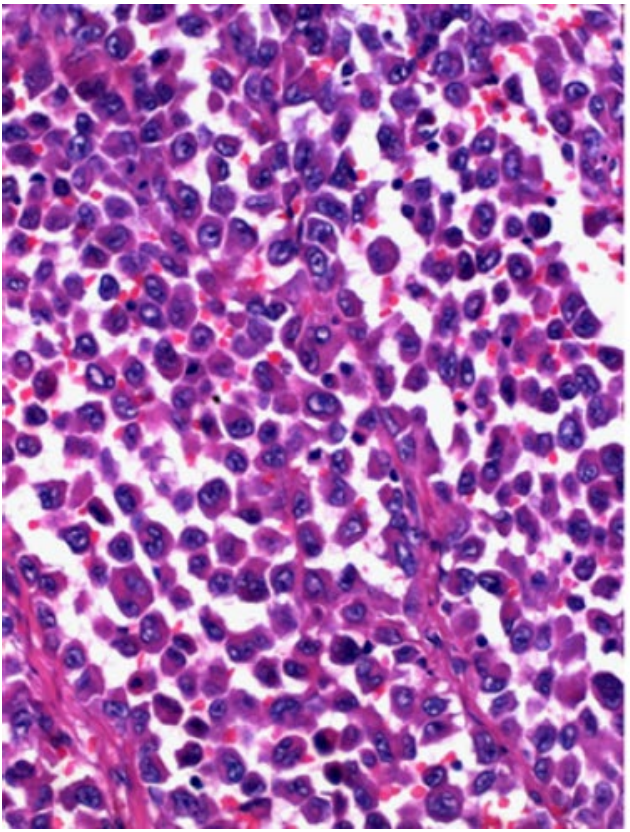
- **Any age & any body site can be affcted.**
- **Disease course: mostly highly aggressive.**
- **Histology:**
  - Monotonous or anaplastic with little pleomorphism.
  - Variable rhabdoid cell population (0-100%).
  - Small blue cell (basaloid) appearance in some cases.
  - Can be composite (+ other differentiated histology).
  - IHC: loss of affected SWI/SNF member
  - Frequent coexpression of vimentin & pan-CK.

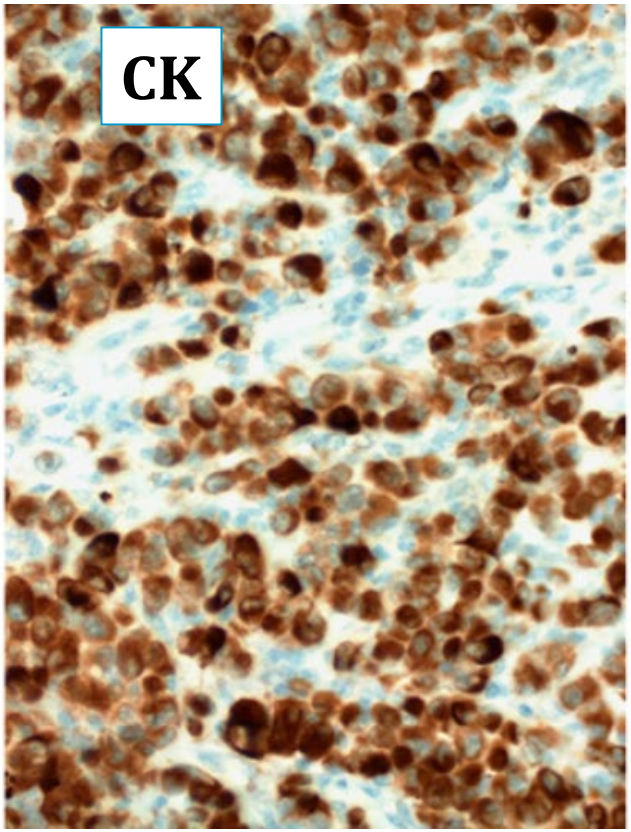
SWI/SNF-deficient CRC

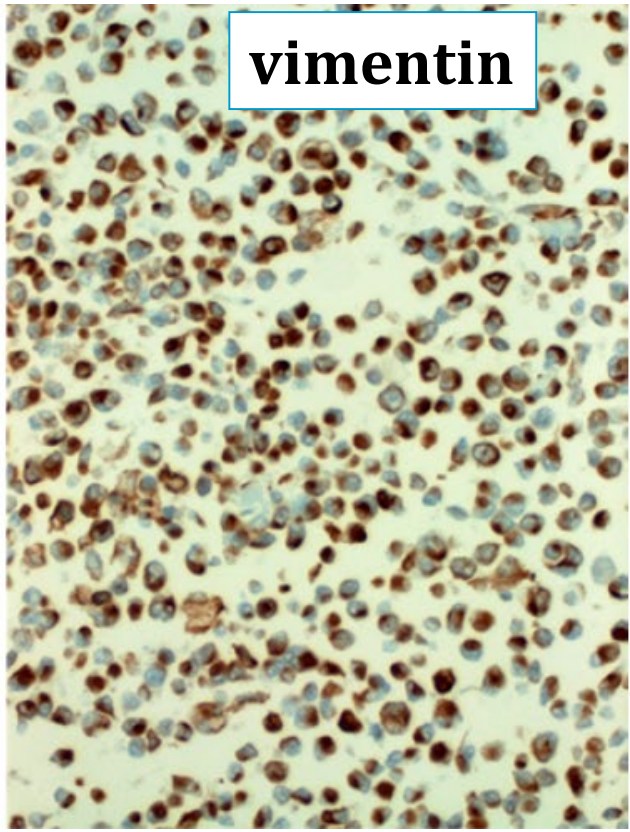
- Variable component are lost in up to 25% of MSI-H cases.
- Undiff/rhabdoid histology (may be MMR-deficient as well).
- Associated with aggressive course (death 1-6 mo post-op).
- Distributed all over colorectum.
- Median age 57 ys, males >>>> females.
- WHO Molecular grading not valid for those MSI-H cases!

Many reported as malignant rhabdoid tumors of GI in the elderly (obsolete)

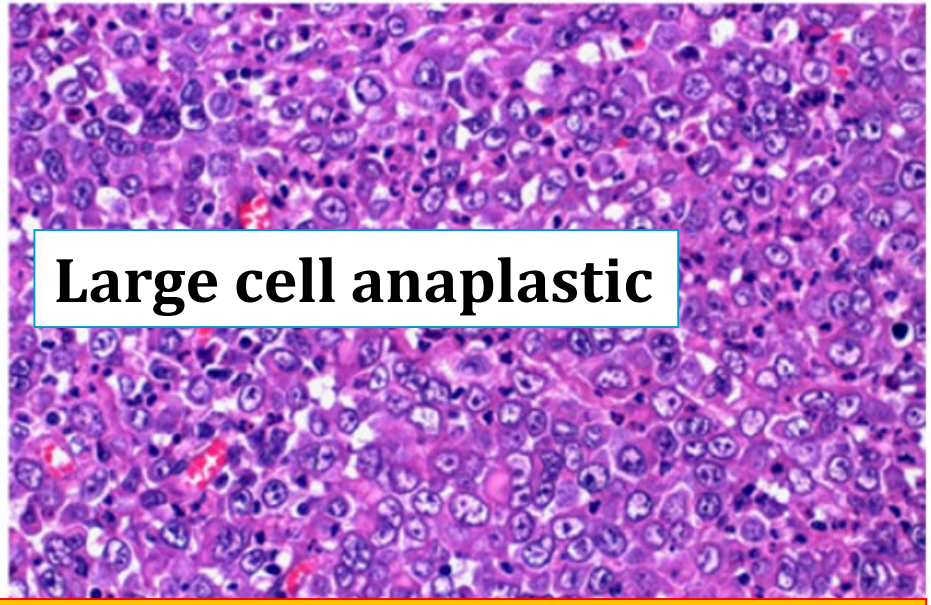
A subset of PD lower GI carcinomas show pure rhabdoid morphology



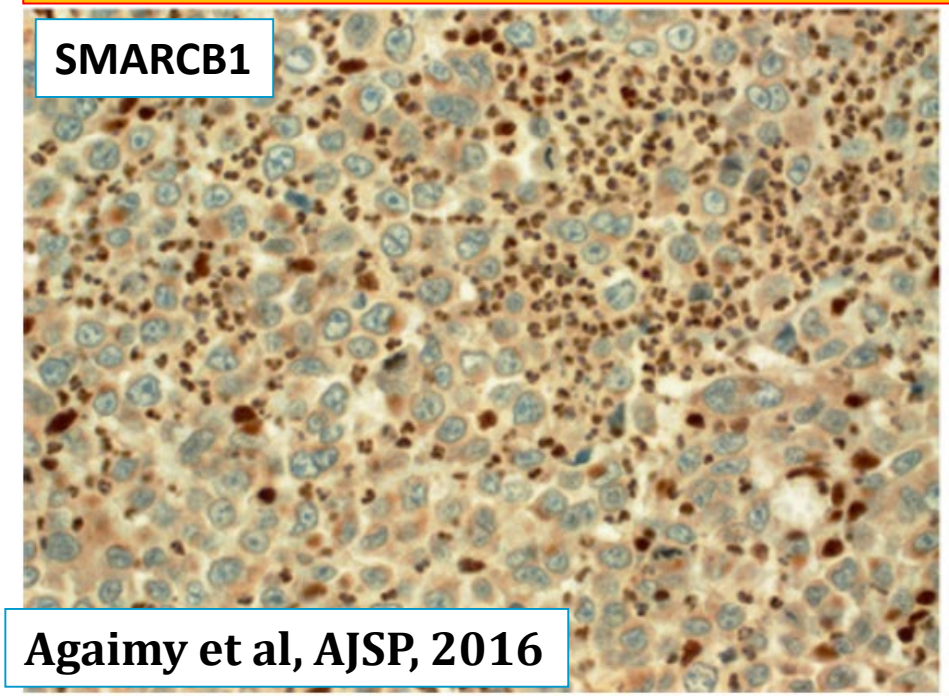


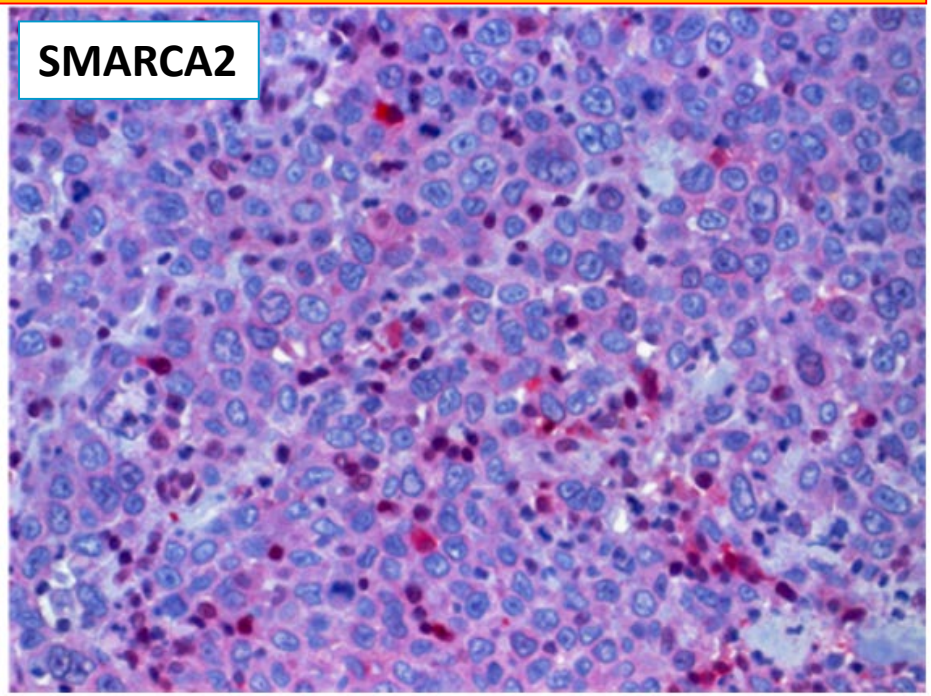


With exceptions, the majority of SWI/SNF-deficient neoplasms coexpress pankeratins and vimentin, irrespective of diff line



Prominent frequently neutrophilic background inflammation may be associated with severe peripheral neutrophilia & paraneoplasia



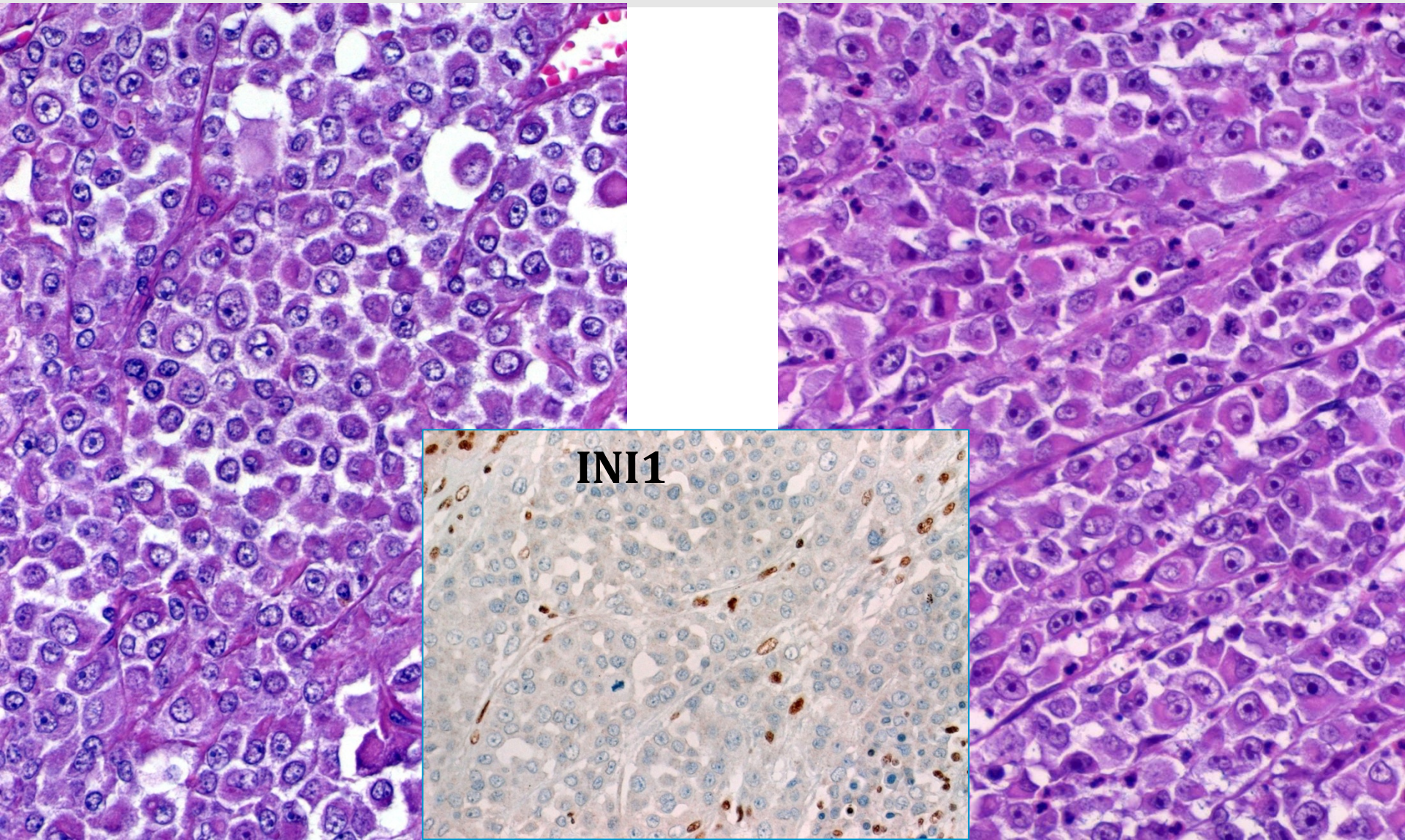


Agaimy et al, AJSP, 2016

Phenotypic homology among some INI1-deficient neoplasms

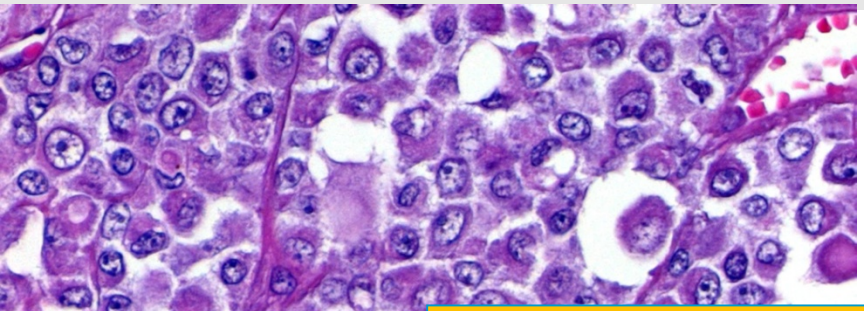
Soft tissue

GI

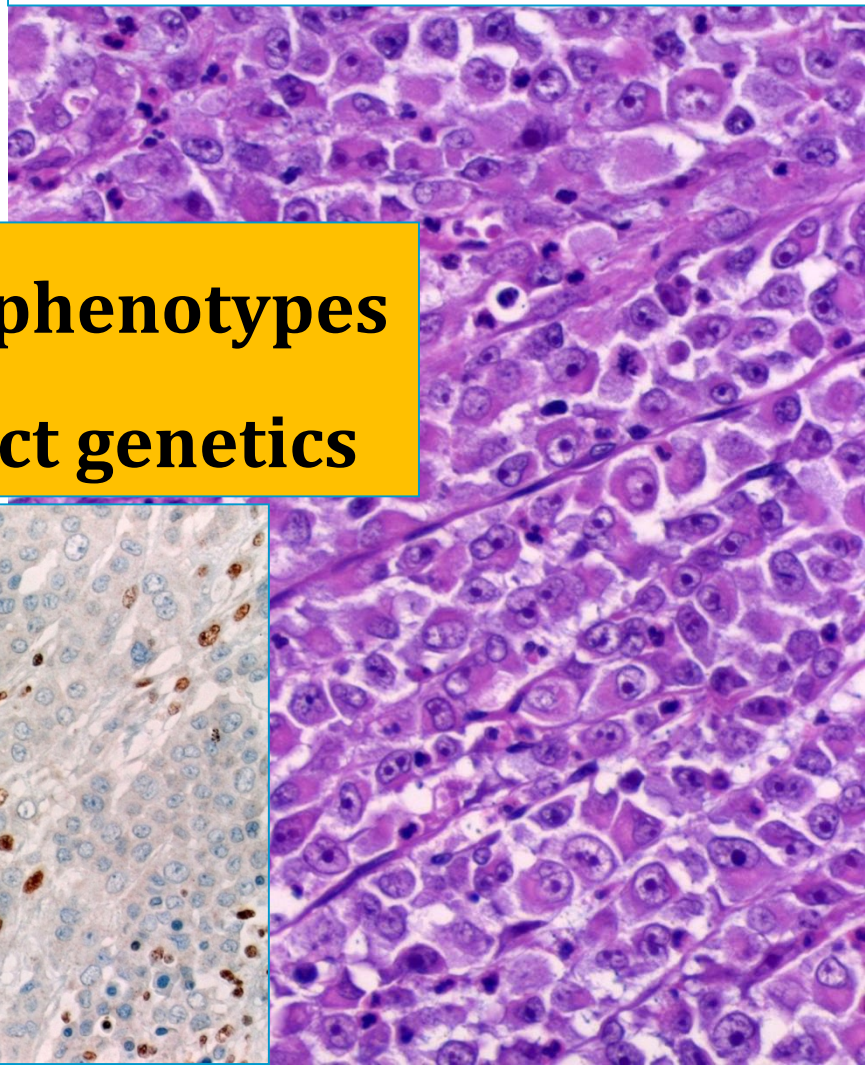


Phenotypic homology among some INI1-deficient neoplasms

proximal epithelioid sarcoma

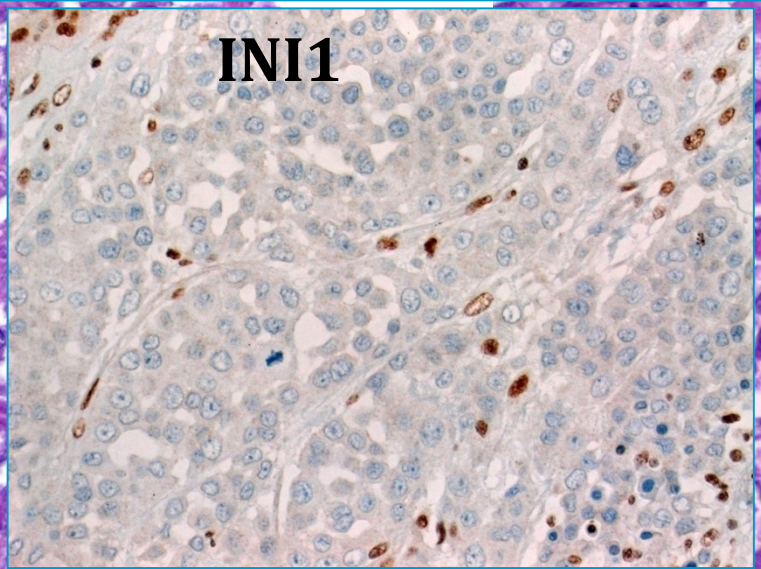


MSI CRC with SMARCB1 loss
MLH1 loss/V600E

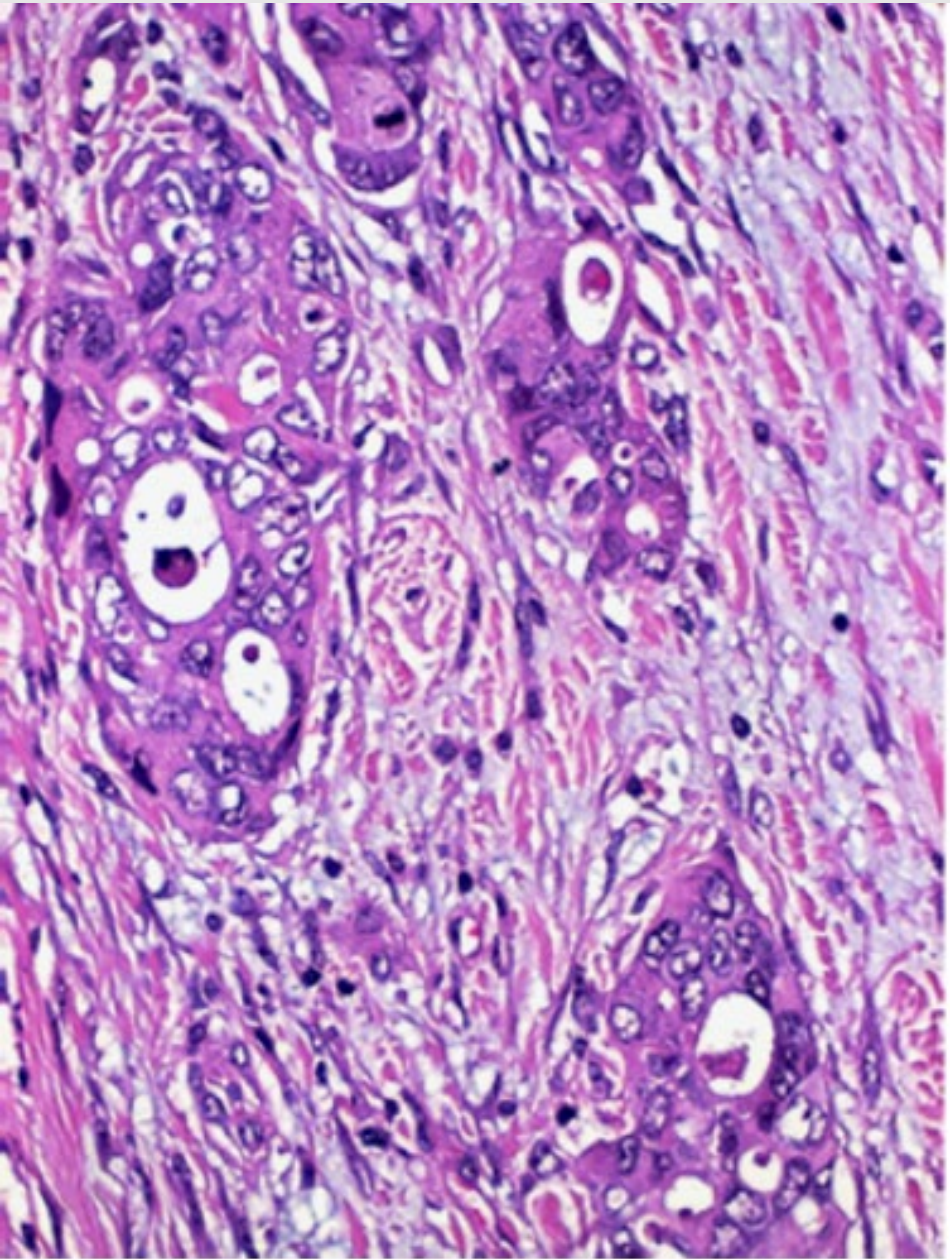


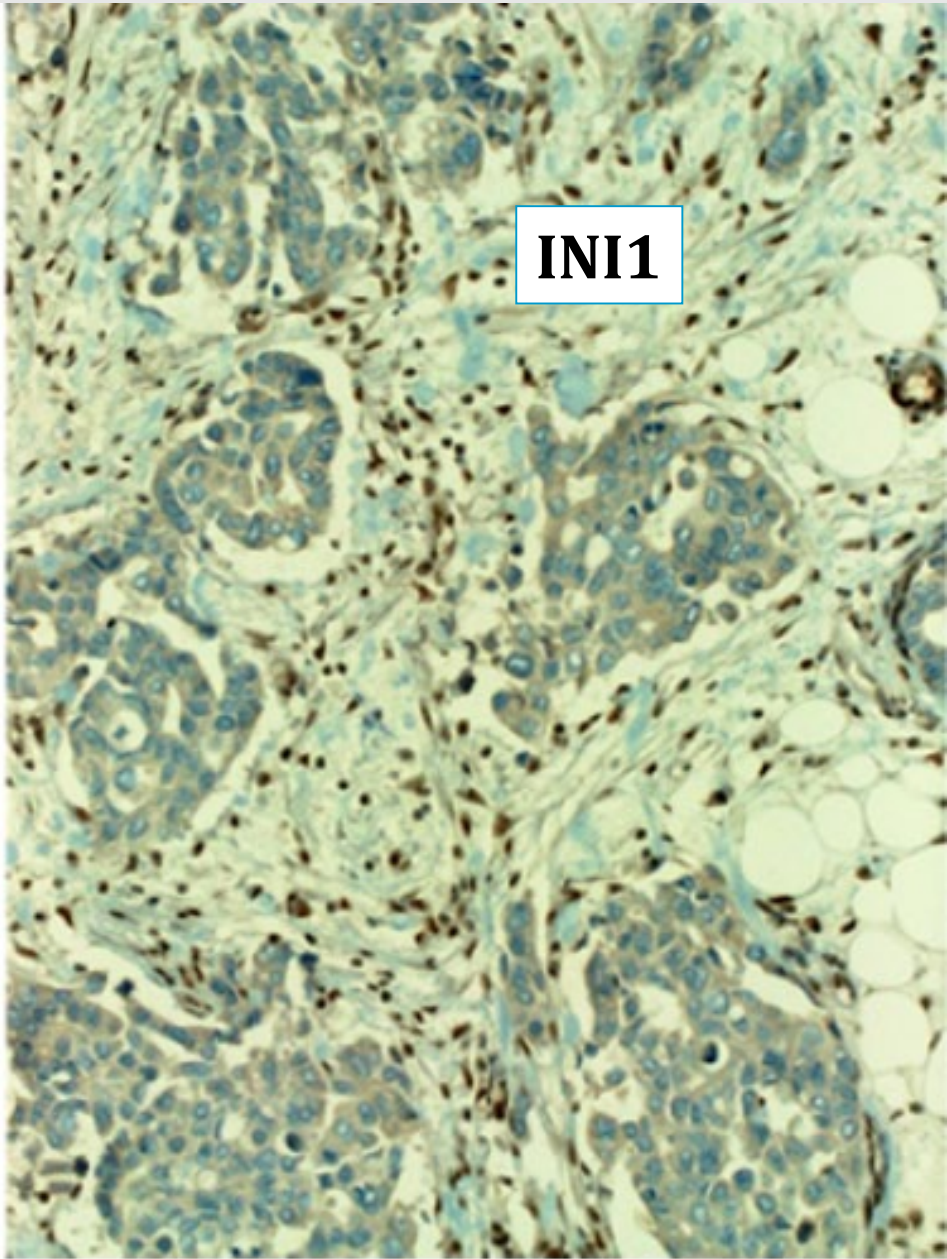
Genetics dictates phenotypes

Phenotypes predict genetics



Differentiated foci (=epithelial origin) seen in 15-20%





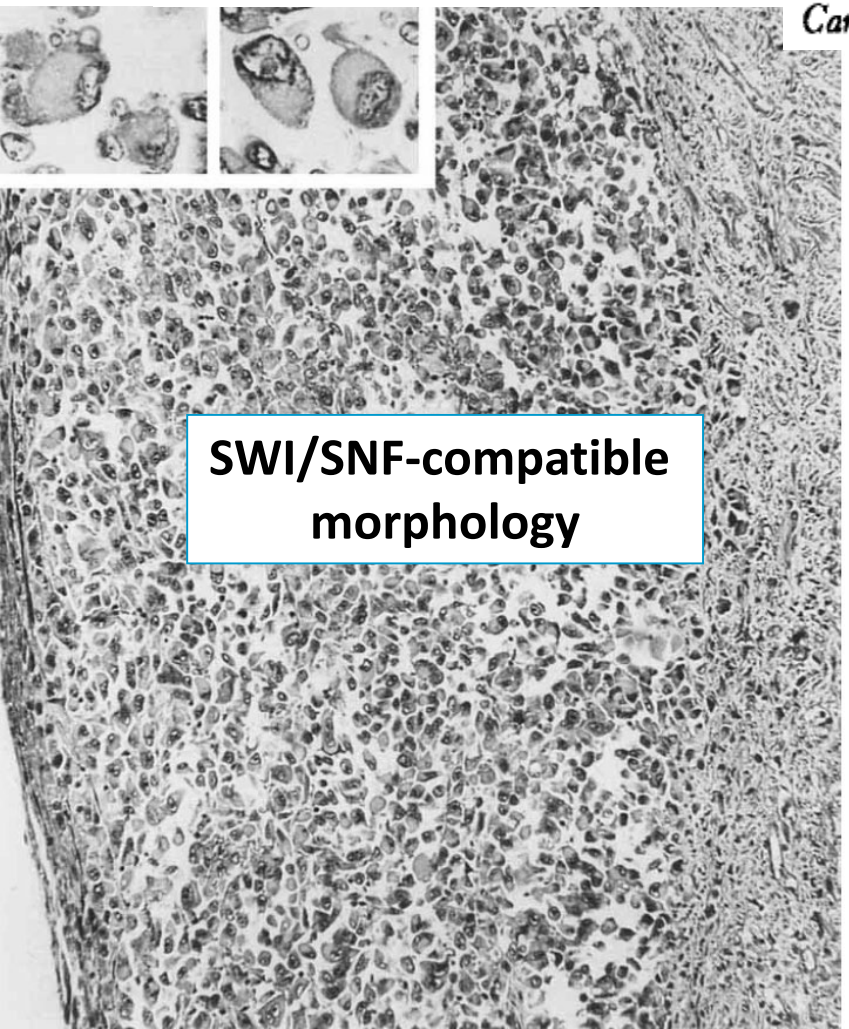
Pleomorphic (giant cell) carcinomas“ of GI & pancreas are probably in part SWI/SNF-related

PLEOMORPHIC CARCINOMA OF THE PANCREAS

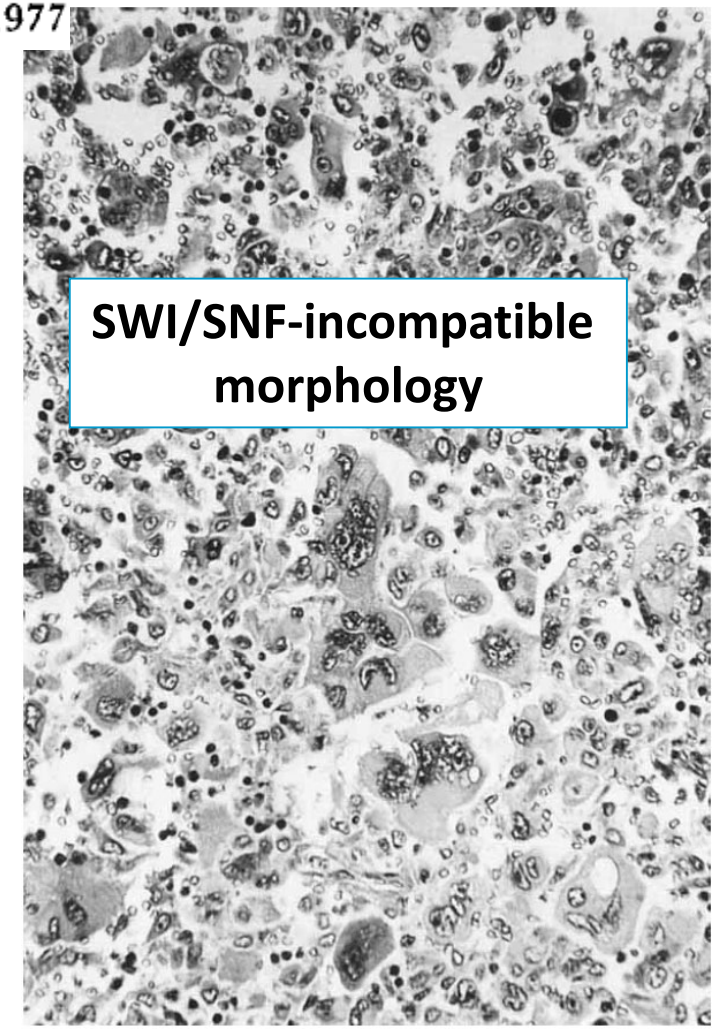
An Analysis of 15 Cases

TAI-PO TSCHANG, MD,* RAUL GARZA-GARZA, MD AND JOHN M. KISSANE, MD

Cancer 39:2114–2126, 1977



SWI/SNF-compatible morphology



SWI/SNF-incompatible morphology

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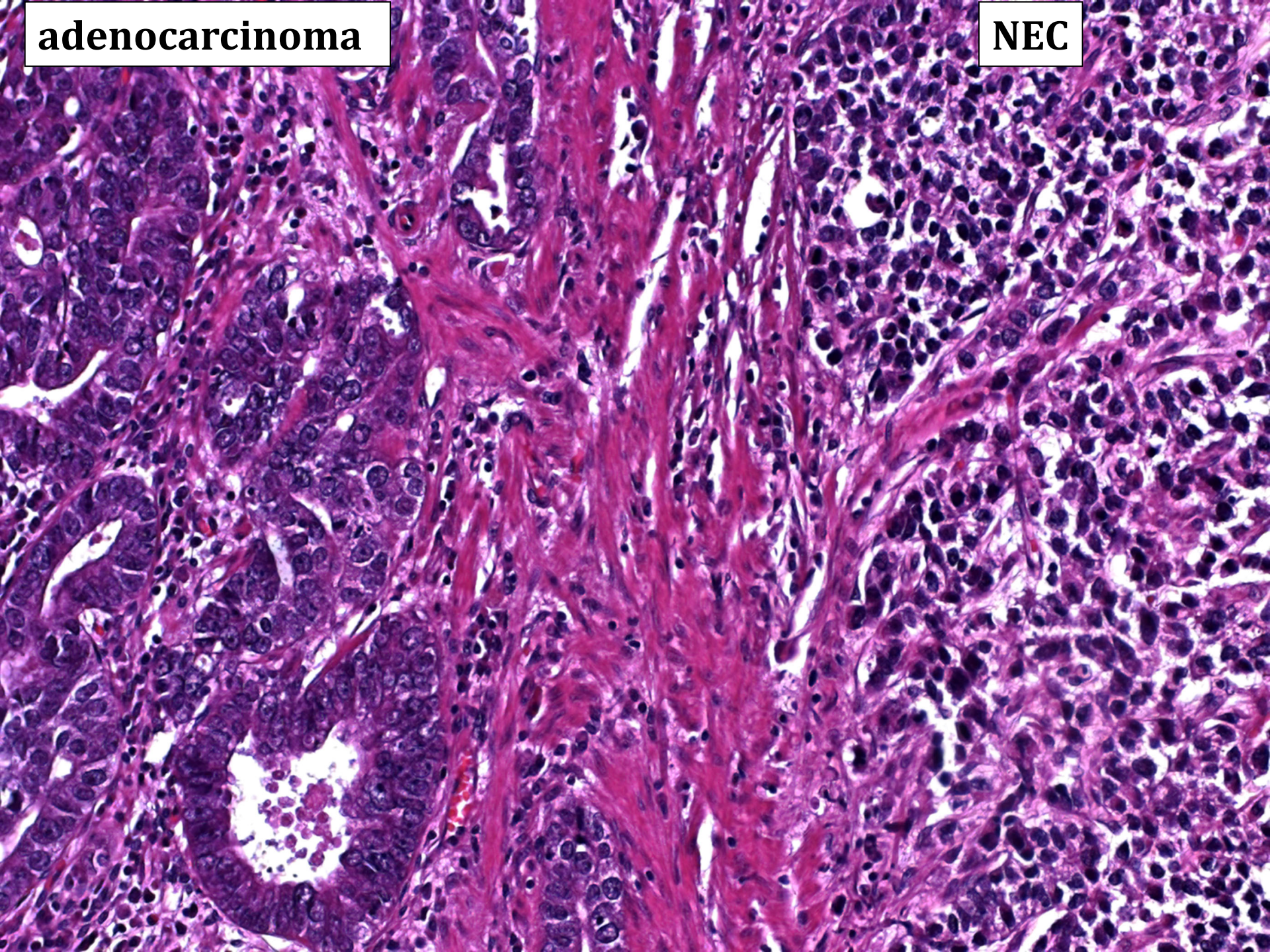
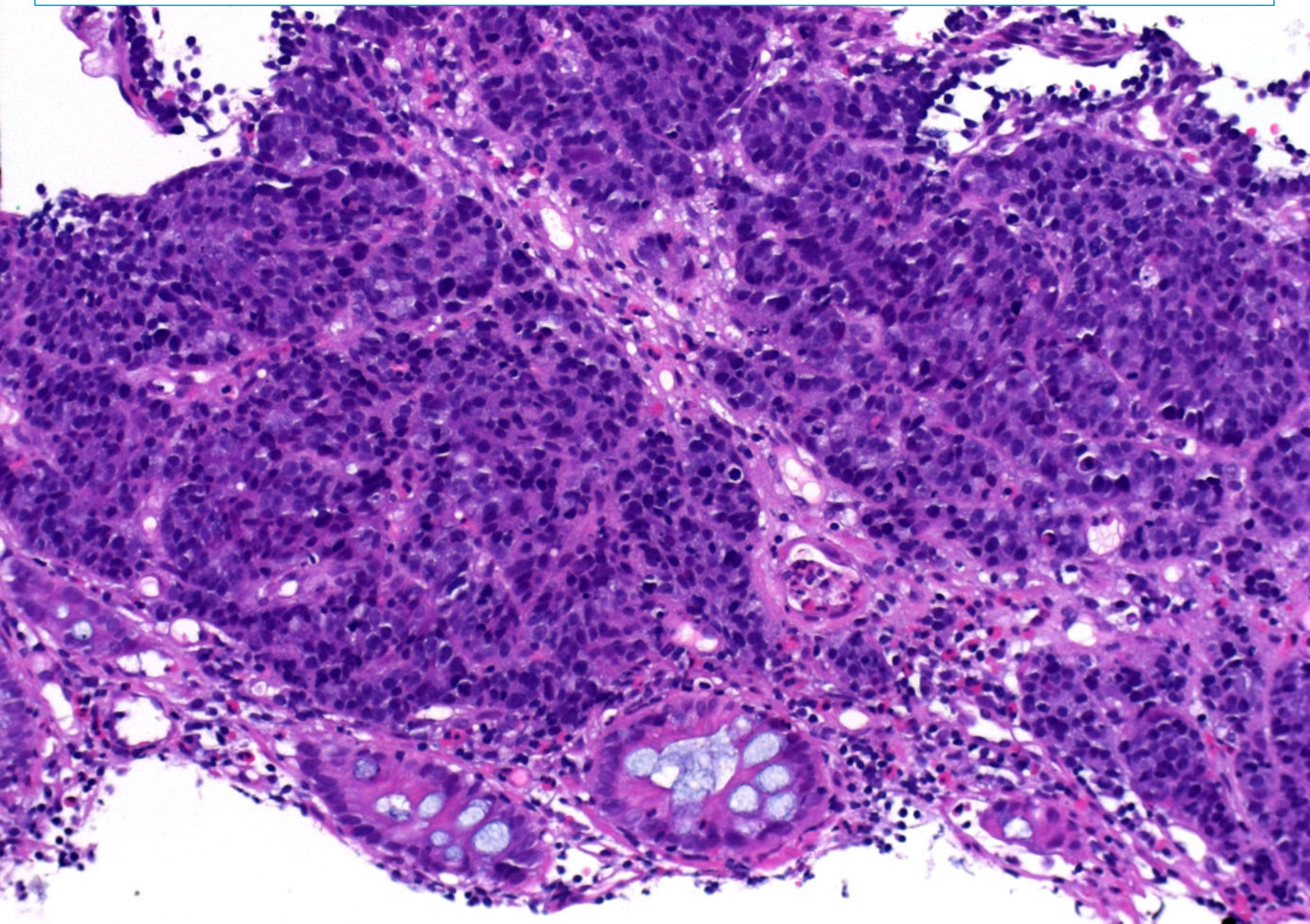
  - Mixed
- Bizarre pleomorphic cells
- Spindled sarcomatoid
- **Combined**

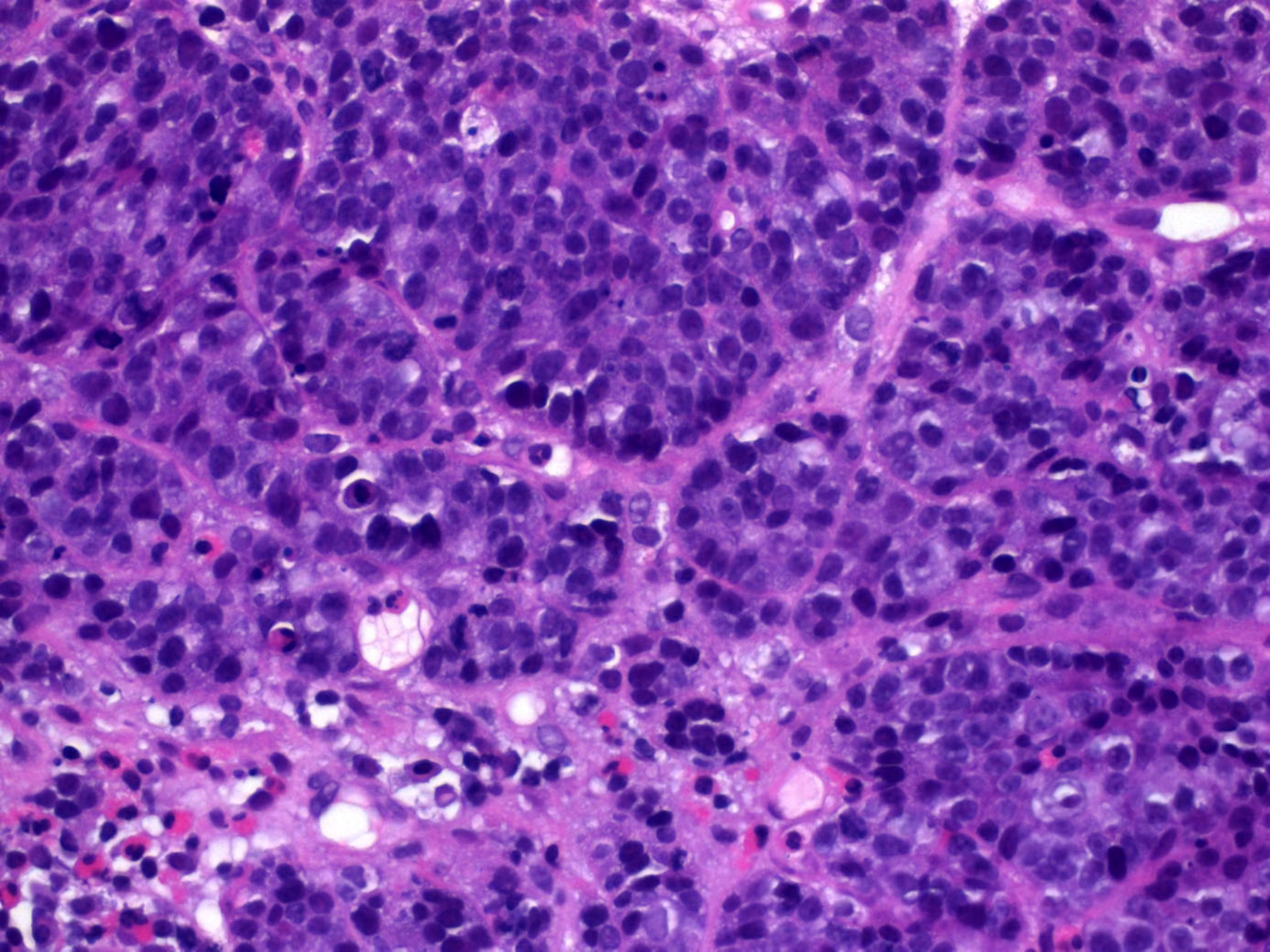
Combined diff/dediff pattern in PD lower GI carcinoma

- Characteristic of mixed adenoneuroendocrine neoplasms.
- NE component usually PD (large or small cell NEC).
- Mets usually of the NE component.
- Frequent aberrant TP53 signature, RB1 loss.
- Occassional loss of SMARCA4, ARID1A, etc.

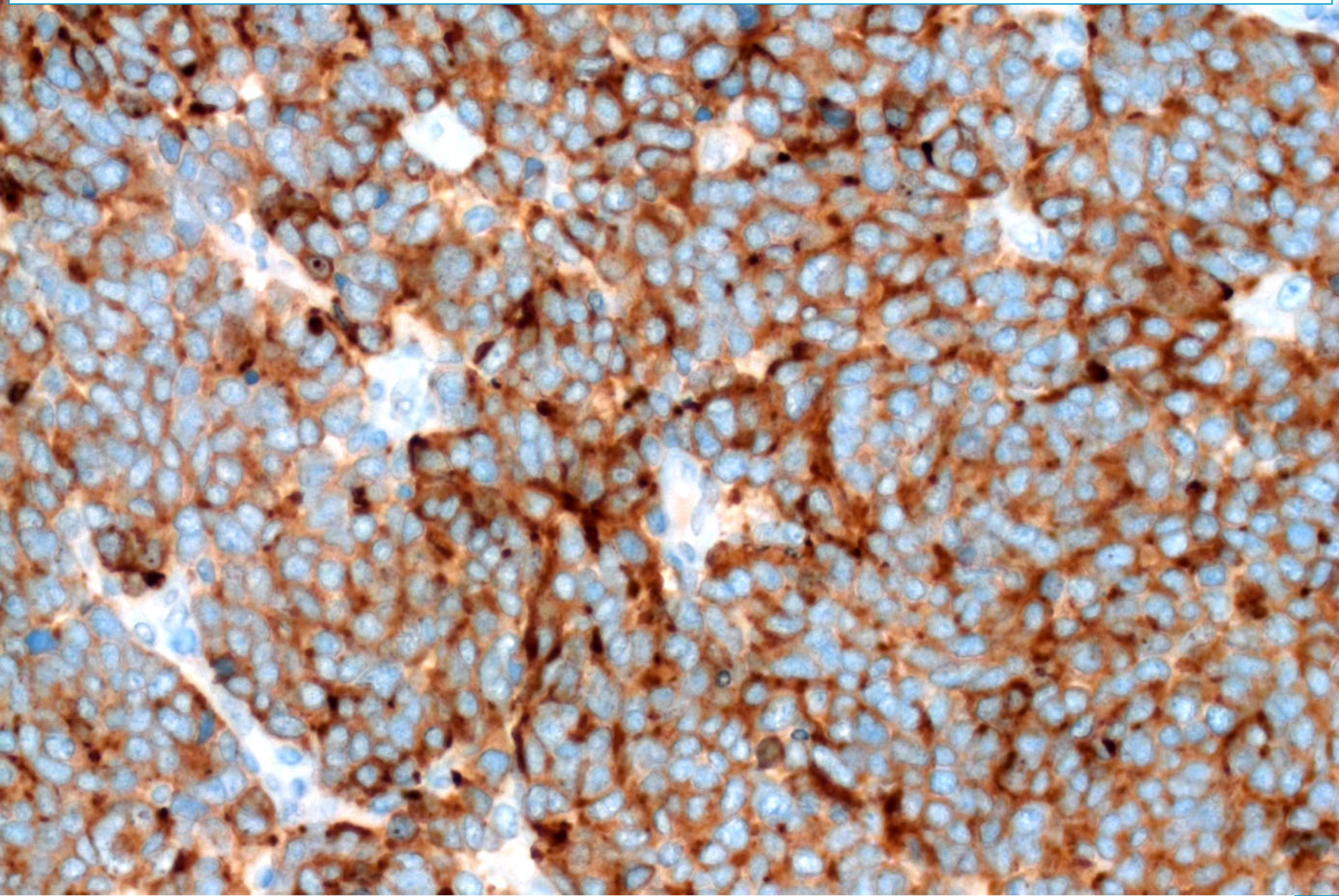

adenocarcinoma
NEC

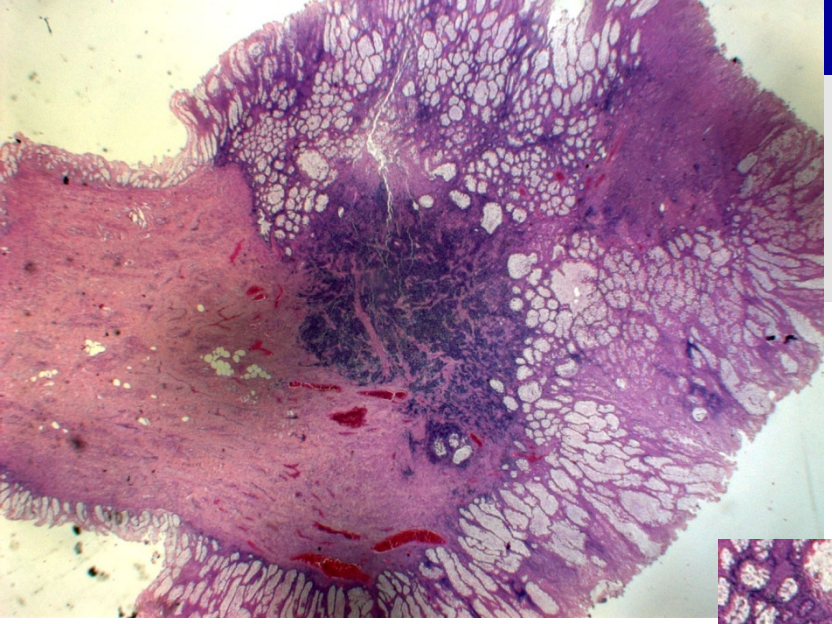
Fused glands mimicking cribriform carcinoma: frequent in large cell NEC



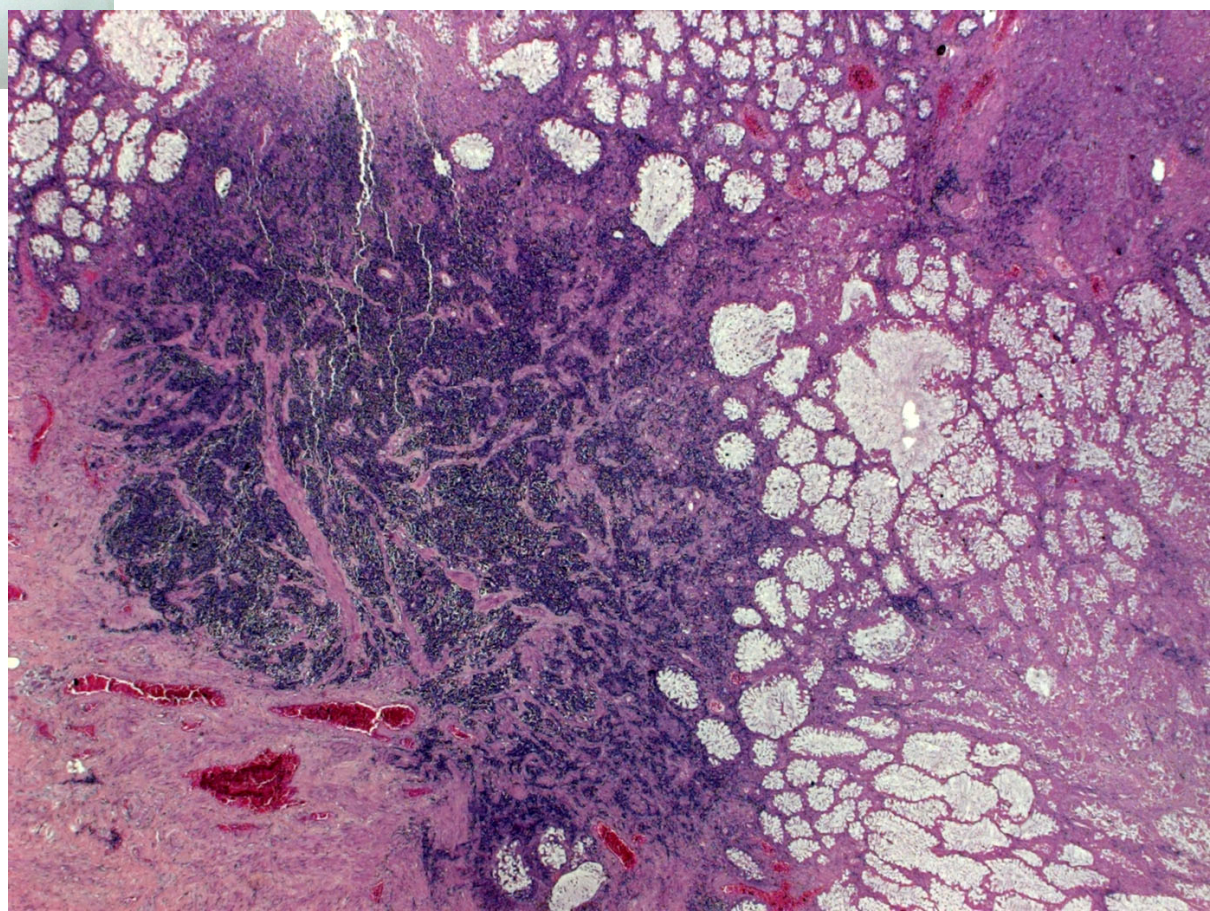


Diffuse synaptophysin (stains synaptic junctions): diffuse cytoplasmic or neuroaxon-like

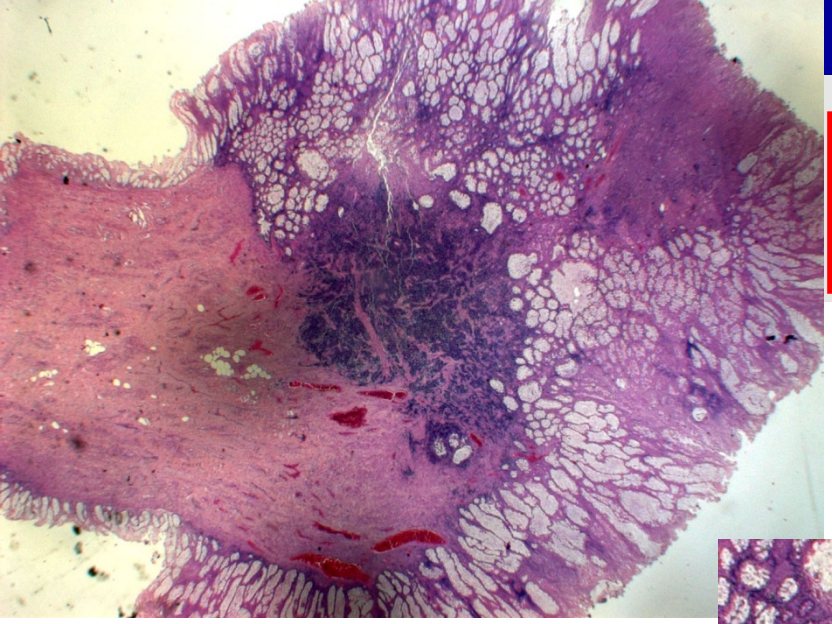


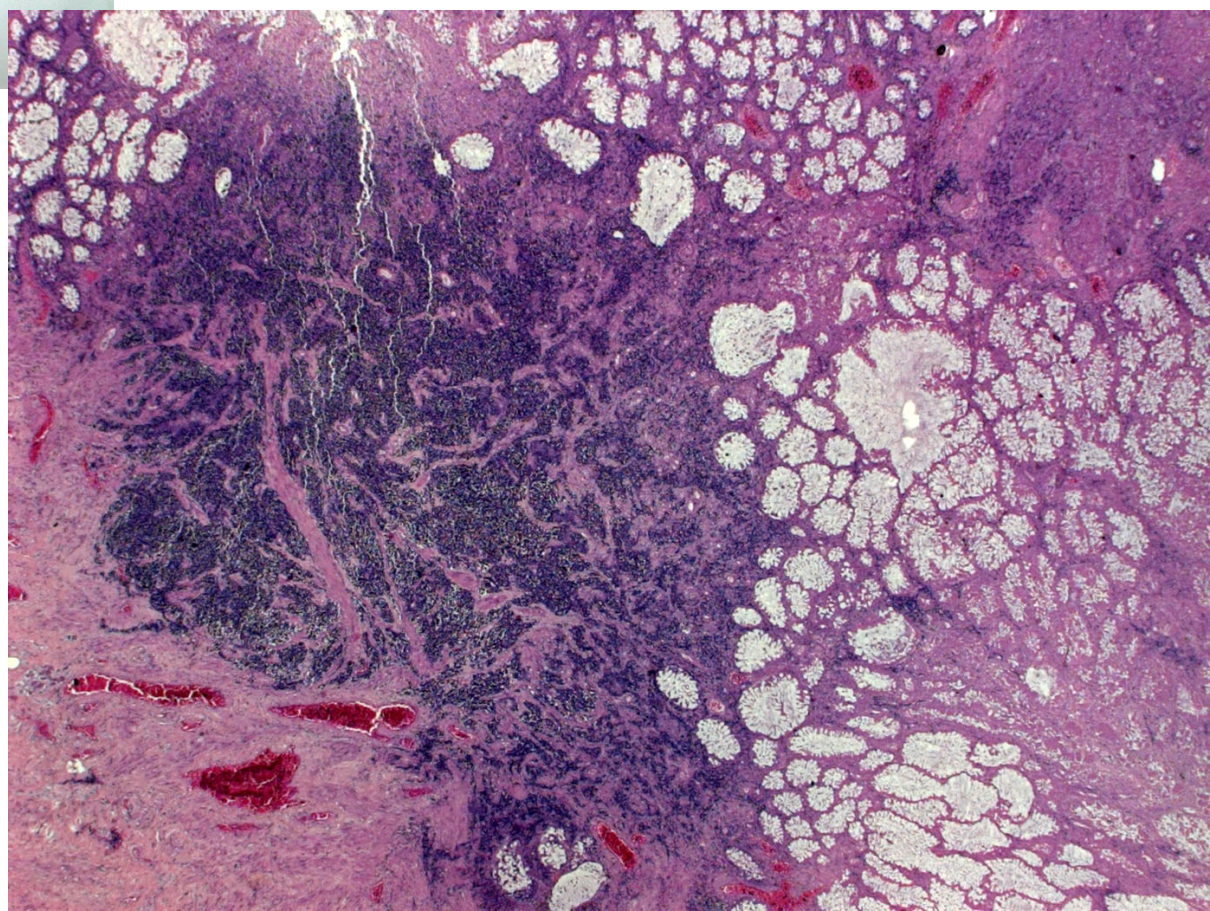


PD (small or large cell) carcinoma beneath adenoma (autopsy):
usually= MANEC



MANEC mimics: SCLC metastatic to colorectal adenoma (autopsy)





Conclusion

- **PD lower GI malignancies represent a highly heterogeneous group of aggressive neoplasms encompasing CRC, melanoma, lymphoma and sarcoma.**
- **Their morphology can be highly overlapping.**
- **Every thing can go rhabdoid (bad sign).**
- **High suspicion index + well selected IHC panel mandatory**

Conclusion, cont.

- **WHO molecular grading needs be revised for those cases with poor differentiation and SWI/SNF loss.**
- **Recognition of possible MMR deficiency (immune therapy?).**
- **Other therapeutic strategies emerging for SWI/SNF-deficient cases.**

Thank you for your attention

Sunrise, Nile province, Sudan (images within 5min)

Pathol. Institute, Erlangen