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

Abbas Agaimy, MD
Erlangen, Germany
abbas.agaimy@uk-erlangen.de
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.
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 phenotype 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 retroperitoneal 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-Enriquez, MD, and Christopher D.M. Fletcher, MD, FRCPath

no case originated in the retroperitoneum

desmin

FIGURE 2. Focally prominent cytoplasmic rhabdoid inclusions were seen in 3 cases (case 14).
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.
EMA was requested to exclude CK-neg rhabdoid undifferentiated carcinoma.
Frankly rhabdoid phenotype but intact INI1: always think of melanoma


Fortunately, rhabdoid MM retains specific melanoma markers

- HMB45 in rhabdoid MM
- SMARCB1
Histological patterns of PD lower GI carcinomas

- **Monomorphobic 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

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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
  - Spindle sarcomatoid

- Combined
Mammalian SWI/SNF chromatin remodelling complex

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 interdependent 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).
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 affected.
- 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.
Phenotypic homology among some INI1-deficient neoplasms

Soft tissue

GI

INI1
Phenotypic homology among some INI1-deficient neoplasms

proximal epithelioid sarcoma

MSI CRC with SMARCB1 loss
MLH1 loss/V600E

Genetics dictates phenotypes
Phenotypes predict genetics

INI1
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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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 encompassing 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
WHO molecular grading needs to 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.
Sunrise, Nile province, Sudan (images within 5min)

Pathol. Institute, Erlangen

Thank you for your attention