What is new in epithelioid soft tissue tumors?
Polygonal cells with copious cytoplasm mimicking carcinoma
Epithelioid cells may range from large cell pattern to smaller cells = large cell & small round cell variant
Epithelioid cell morphology:
Epithelial differentiation common (CK+ or ultrastructural)
Epithelioid cells may display variable rhabdoid cell features = rhabdoid variant
Every thing can be rhabdoid
= rhabdoid can be every thing
Major subclasses of epithelioid soft tissue neoplasms

❖ Neoplasms driven by SWI/SNF inactivation
  o Epithelioid sarcoma, rhabdoid tumors, SCCOHT, etc.

❖ Neoplasms associated with specific gene fusions or ampl.
  o Sclerosing epi fibrosarcoma, NUT sarcoma, GLI1-related

❖ Epithelioid variants related to specific genotypes
  o Epithelioid IMT with ALK-RANBP2 or ALK-RRBP1 fusions

❖ Non-specific epithelioid variants of every thing
  o Epithelioid RMS, pleo liposarcoma, dediff LS, MFS, etc.
The rhabdoid phenotype in pediatric malignant rhabdoid tumors is specifically associated with deletion of the BAF47 (SMARCB1/INI1) gene locus.

(Biegel et al, 1992)
The rhabdoid cell (likened to rhabdomyoblasts)

- Hyaline cytoplasmic paranuclear inclusion (intermediate filaments).
- Eccentric vesicular nucleus with eosinophilic macronucleolus.
- Frequent bi/multinucleation (may be Hodgkin-like).
Rhabdoid features in tumors with intact SMARCB1: non-specific phenotype?
Rhabdoid features in tumors with intact SMARCB1: non-specific phenotype?

SWI/SNF pathway taught us to think in a sense of "functional gene group" instead of the old "single gene concept" (same concept as for MMR deficiency in CRC)
To explain a „rhabdoid phenotype“ in a given neoplasm consider not only SMARCB1 but also other members of the SMARC family of chromatin remodellers, the SWI/SNF complex

✓ > 20 closely related genes.
✓ Regulates gene transcription, cell differentiation & proliferation.
✓ Mutated in >20% of all cancers (almost same frequency as TP53).
✓ Tumor suppressor function = loss of the protein (deficiency).

**SWI/SNF Chromatin Remodeling and Human Malignancies**

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**Figure 1**

Scheme of the BAF and PBAF SWI/SNF complexes based on the model proposed by Kadoch et al. (5). The different subunits are labeled with their protein names. For correspondence with gene names, see Table 1.
Common Features of SWI/SNF-deficient neoplasms

- Any age (0-80yrs), but > in children & adolescent.
- Disease course: mostly aggressive.
- Site: can affect nearly any body site.
- **Histology:**
  - Monotonous epithelioid/anaplastic cells
  - Usually no bizarre nuclei.
  - Variable rhabdoid cells (0-100%).
  - Small blue cell (basaloid or Ewing-like) in some cases.
  - Frequent coexpression of vimentin & pankeratin.
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
Phenotypic homology among some SWI/SNF-deficient neoplasms
Genetic diktates phenotype & phenotype predicts genetic
proximal epithelioid sarcoma
MSI CRC with SMARCB1 loss
With exceptions, the vast majority of SWI/SNF-deficient neoplasms coexpress pankeratins and vimentin, irrespective of different lines.
The large cell spectrum

- Proximal-type ES
- SCCOHT, large cell pattern
- SMARCA4-related mediastinal sarcoma
- Dediff endometrial or GI carcinoma
- Etc.
SMARCA4-deficient thoracic (mediastino-pulmonary) sarcoma

✓ Reported in 2015 by French group (n=19 + recent follow-up series)
✓ Males 30-35 yo.
✓ Compressive mediastino-pulmonary masses.
✓ All smokers.
✓ Median survival 7 months.
✓ Expression profiles similar to rhabdoid tumors & SCCOHT.
Long DDx:
- Epithelioid mesothelioma
- Epithelioid melanoma
- Epithelioid angiosarcoma
- Epithelioid MPNST
- Large cell carcinoma
- Hematolymphoid
✓ All CK+/EMA+/SOX2+
✓ Mainly mediastinal
✓ Less common pleura & lung
✓ CD34+ in >50%.
✓ Others +: SALL4 & claudin-4
✓ Neg: p63 & NUT

Are these really sarcomas????
Undiff carcinomas????
OR
Epithelioid „I don´t-know-ma“?
Epithelioid variants of every thing

➢ Collectively not uncommon.
➢ Diagnosis difficult on limited biopsy (sampling!).
➢ Specific pheno- or genotypic markers depend on entity.
➢ **Diagnosis by:**
  - Immunophenotype: MM & epithelioid rhabdomyosarcoma.
  - Immunophenotype + genotype: epithelioid IMT (EIMS).
  - Genotype: epithelioid dedifferentiated liposarcoma.
  - HE only (resampling): e.g. epithelioid pleomorphic liposarcoma.
  - Clinical history + genotype: dedifferentiated melanoma.
Frankly rhabdoid phenotype but intact SWI/SNF markers: always think of melanoma

HMB45 in rhabdoid MM
Except for its rhabdoid features this variant shows typical markers of RMS

Very rare (2/15 cases)

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

- Rare aggressive IMT variant (<50 cases reported).
- Striking male predilection (> 5: 1).
- Median age: 39 yrs.
- All intra-abdominal (mesentery & omentum)
- Median size: 15 cm.
- Mets: (liver, lung, nodes).
- 7/19 patients DOD; 7 AWD, only 6 alive with NED.
- Responsive to ALK inhibitors (crizotinib).
Epithelioid inflammatory myofibroblastic sarcoma

Histopathological features

✓ Sheets of **large rounded epithelioid cells**.
✓ Abundant **myxoid stroma**.
✓ **Prominent neutrophils** but scanty plasma cells.
✓ Minor **spindle cell (IMT) component**.
✓ IHC +: **perinuclear ALK, desmin, SMA, CD30**+
✓ IHC negative: keratins, EMA, S100, MYF4, caldesmon.
extensive permeation of the muscularis propria
brisk mitotic activity
myxoid/chordoid pattern seen focally
Minor conventional IMT-like area
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Epithelioid dedifferentiated liposarcoma

- Rare
- Same demographics as dediff liposarcoma
- Retorperitoneal/psoas muscle
- Mainly elderly males
- Very high metastatic rare
- Frequent expression of keratins
- Focal well diff or sclerosing component
- MDM2/CDK4+/ amplified
- Exclude others if no well diff component
Sclerosing and lipogenic areas helpful
Keratin dots are frequent
MDM2/CDK4 amplified
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  • **HE only (resampling):** e.g. epithelioid pleo liposarcoma.
  • Clinical history + genotype: dedifferentiated melanoma.
Young adult male, deep thigh mass
Extensive sampling revealed numerous pleomorphic lipoblasts = epithelioid pleomorphic liposarcoma

Resampling is the only immunomarker to verify pleomorphic liposarcoma
Think of the great mimicker in any unclassified epithelioid malignancy
68 yo male, large inguinal mass, every thing negative
TST15 gene panel: V600E BRAF mutation detected.

History in retrospect:
Skin melanoma excised 9 yrs ago from ipsilateral leg.
The list of epithelioid soft tissue entities is growing
Epithelioid soft tissue neoplasms associated with specific gene fusions/ or amplifications

A Distinct Malignant Epithelioid Neoplasm With GLI1 Gene Rearrangements, Frequent S100 Protein Expression, and Metastatic Potential

Expanding the Spectrum of Pathologic Entities With ACTB/MALAT1/PTCH1-GLI1 Fusions

Cristina R. Antonescu, MD, Narasimhan P. Agaram, MD, Yun-Shao Sung, MSc, Lei Zhang, MD, David Swanson, BSc, and Brendan C. Dickson, MD

GLI1-amplifications expand the spectrum of soft tissue neoplasms defined by GLI1 gene fusions

Narasimhan P. Agaram, Lei Zhang, Yun-Shao Sung, Samuel Singer, Todd Stevens, Carlos N. Prieto-Granada, Justin A. Bishop, Benjamin A. Wood, David Swanson, Brendan C. Dickson, Cristina R. Antonescu