Beyond the H&E: Where morphology meets molecular maladies

Case Objectives

- Recognizing a site-specific tumor entity.
- Recognizing specific cell phenotypes.
- Linking this cell phenotype to a genotype.
- Phenotype-genotype correlation: pathways vs single genes.
- Recognizing phenotypic variation within same entity
- 35 yo female with right ethmoidal/ frontal sinus mass
- Resection followed by adj chemoradiation (2008)

Initial histology: monotonous basaloid appearance

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Pan-CK

Diagnosis 2008: basaloid SCC

- 2013: lung, pericardial, liver + pleural mets.
- Resection of a bleeding lung met.
Resected lung mets: in part similarly basaloid

Resected lung MTS: Focal prominent rhabdoid cells

What is a rhabdoid cell?

- Medium to large rounded/oval cells
- Hyaline cytoplasmic paranuclear inclusion (intermediate filaments)
- Eccentric vesicular nucleus with eosinophilic macronucleolus
- Frequent bi/multinucleation (Hodgkin-like)

Likened to rhabdomyoblasts

Intermediate filaments in eosinophilic cells of epithelioid sarcoma.

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The rhabdoid phenotype and molecular pathways

- The rhabdoid phenotype in pediatric AT/RT and malignant rhabdoid tumors was specifically associated with deletion of the BAF47 (SMARCB1/INI1) gene locus.
  (Biegel et al, 1992)

Back to our case: metastasis 2013

SMARCB1/INI-1

Back to the original sinonasal tumor from 2008

In addition to basaloid SCC-like features anaplastic areas but very few rhabdoid cells

Back to the original sinonasal tumor from 2008

Complete loss of SMARCB1 in the whole tumor
SMARCB1 FISH: biallelic deletion of SMARCB1/INI1 gene locus.

Normal cells

SMARCB1-deficient sinonasal carcinomas

Wider histopathologic spectrum than initially thought

- >70% basaloid (prototype).
- Uncommon subtypes:
  - Large cell rhabdoid
  - Epithelioid sarcoma-like multinodular.
  - Oncocytoid.
  - Squamoid.
  - Small cell NE-like
  - Many seem to respond dramatically to chemoradiation

Agaimy & Bishop, unpublished

Rhabdoid features in tumors with intact SMARCB1: non-specific phenotype?

IN1 expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas

Agaimy & Bishop, unpublished

IN1 expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas
To explain a "rhabdoid phenotype" in a given neoplasm consider not only SMARCB1 but other members of the SMARC family of chromatin remodellers, the SWI/SNF complex.

- SWI/SNF-related Matrix-associated Actin-dependent
  Regulators of Chromatin, subfamilies B (SMARCB1), A (SMARCA2, SMARCA4), C (SMARCC1, SMARCC2), SMARCD, SMARCE, SMARCF & others
  (ARID1A, B, etc.).

SWI/SNF chromatin remodelling 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 function mutations).

Common Features of SWI/SNF-deficient neoplasms

- Any age (0-80yrs), but > in children & adolescent.
- Disease course: mostly highly aggressive.
- Site: can affect nearly any body site.
- Histology:
  - Monotonous or anaplastic but usually no bizarre smudge nuclei.
  - Variable rhabdoid cells (0-100%).
  - Small blue cell (basaloid or Ewing-like) in some cases.
  - In adults/elderly, frequently composite.
  - Frequent coexpression of vimentin & pankeratin.

- Loss of function mutations = loss of the protein (deficiency).
- Protein loss is limited to the neoplastic cells.
- IHC markers are becoming available for most of subunits.
- SMARCB1 (INI1) most extensively studied subunit.
- SWI/SNF-related neoplasms arise either:
  - de novo (AT/RT; single gene diseases).
  - via dedifferentiation (double or triple hit, e.g. GI & GU)
Some of „pleomorphic (giant cell) carcinomas” are probably SWI/SNF-related

PLEOMORPHIC CARCINOMA OF THE PANCREAS
An Analysis of 15 Cases
Tam-Pu Teoheng, MD,* Ram Garg,Garcia, MS, and John M. Kiely, MD
Cancer 30:2114-2120, 1977

Phenotypic homology among some SWI/SNF-deficient neoplasms

proximal epithelioid sarcoma
MSI CRC with SMARCB1 loss

The rhabdoid cell, the hallmark of alterations in the SWI/SNF chromatin remodeling complex, varies from <1% to 100%

SWI/SNF Complex-deficient Undifferentiated/Rhabdoid Carcinomas of the Gastrointestinal Tract
A Series of 13 Cases Highlighting Mutually Exclusive Loss of SMARCA4 and SMARCA2 and Frequent Co-inactivation of SMARCB1 and SMARCA2
Athan Agalos, MD,* Doris Deum, MD,† Bruno Mork, MD,‡ Jonas Lidmalmsson, MD,‡ Michael Michal, MD,§ and Anna Hartmann, MD

Concomitant loss of SMARCA2 and SMARCA4 expression in small cell carcinoma of the ovary, hypercalcemic type

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

SMARCA4-deficient gastric carcinoma

Vimentin

Pankeratin

Site-specific morphology of SWI/SNF-deficient neoplasia
Renal medullary carcinoma

SMARCB1-deficient esophagogastric junction adenocarcinoma

Amin et al, Am J Surg Pathol • Volume 38, Number 7, July 2014
So-called composite rhabdoid tumors are SWI/SNF-linked dedifferentiated neoplasms with distinctive components.

Secondary SWI/SNF alteration (mutation) in the differentiated neoplasm causes a shift to undiff “rhabdoid” phenotype.

Secondary INI1-mutation in endometrioid CA associated with dedifferentiation=composite morphology.

Image: Donner et al, Hum Pathol, 2007

In the gyn-tract, SMARCA4 loss is not limited to SCCOH.

SMARCB1 was intact but SMARCA4 was lost in the undiff component of this dedifferentiated endometrioid adenocarcinoma.
Prognostic impact of the rhabdoid cell component

The more rhabdoid = the worst is prognosis

Renal medullary carcinoma: rhabdoid features and the absence of INIT expression as markers of aggressive behavior

GI & pancreatic cases (Agaimy et al): median & mean survival: 4 months

Sinonasal cases: usually less rhabdoid = better outcome

SWI/SNF deficiency:
The hope for a specific effective therapy is growing

A rationale to target the SWI/SNF complex for cancer therapy

Frankly rhabdoid phenotype but intact SWI/SNF markers: always think of melanoma

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

and do not forget the name-giving „mother“ of the rhabdoid phenotype

FIGURE 2: Focally prominent cytoplasmic rhabdoid inclusions were seen in 3 cases (case 1).

Thank you for your attention