Disclosures
February 6, 2017

Dr. Benjamin Buelow has disclosed that he is now an employee of TeneoBio, Inc., a commercial interest as defined by ACCME. He submitted his case prior to his employment of TeneoBio, Inc. and the case itself is not relevant to his employment and will be presented on his behalf by Dr. Julieann Lee of UCSF. Dr. Buelow has recused himself from any control in the content of the presentation.

The following planners and faculty had no financial relationships with commercial interests to disclose:

**Presenters:**
- Kerri Rieger, MD
- Charles Lombard, MD
- Alana Shain, MD
- Sunny Kao, MD
- Mahendra Ranchod, MD
- Malti Kshirsagar, MD
- Seth Lummus, MD
- Don Born, MD
- Julieann Lee, MD
- Ankur Sangoi, MD

**Activity Planners/Moderator:**
- Kristin Jensen, MD
- Ankur Sangoi, MD
62-year-old male with one month history of cough and shortness of breath and one week history of widespread rash and mucosal erosions
PMH: retroperitoneal Castleman disease Clinical ddx: EM/SJS, lichenoid drug eruption, r/o paraneoplastic pemphigus.
Paraneoplastic Pemphigus (PNP)

- Autoimmune blistering disorder that occurs in the setting of lymphoproliferative disorders and other malignancies
- Clinical presentation typically begins with painful, severe stomatitis
- Cutaneous lesions are polymorphic and can resemble erythema multiforme, lichen planus, pemphigus vulgaris and bullous pemphigoid

Frew and Murrell, Dermatol Clin 2011
Paraneoplastic Pemphigus (PNP)

• Mortality is high (up to 90%) and can be partly attributed to pulmonary involvement, usually in the form of bronchiolitis obliterans

• Disease results from autoantibodies that target a number of antigens, the most important of which are thought to be the plakin proteins

• Management:
  – Treatment of the underlying malignancy
  – Suppression of disease activity (systemic steroids and other immunosuppressants)
PNP: histopathology

- Lichenoid/interface dermatitis with dyskeratosis, acantholysis
- +/- subepidermal bullae
PNP: immunofluorescence

- **Direct IF** shows IgG and C3 on epidermal cell surfaces and at BMZ
  - 41% sensitivity; 87% specificity

- **Indirect IF** on transitional epithelial tissue (typically rat bladder)
  - 86% sensitivity; 98% specificity
43-year-old male with hematuria. CT shows a partially calcified cystic urachal lesion.
SB 6132
(scanned slide available)

Charles Lombard; El Camino Hospital

27-year-old female with 13cm ovarian mass.
27 yo F with Ovarian mass and Hypercalcemia

Small cell carcinoma of the ovary
Hypercalcemic type
SCCO-HT
Clinical features

• Age: 23 (1-71)

• Presentation
  – Pain 68%
  – Mass 55%
  – Hypercalcemia 68%

• Familial cases
  – Autosomal dominant pattern
  – SMARCA4 mutation
SCCO-HT
Histology

• Diffuse sheets of small undifferentiated cells
  – Nests, cords, clusters, follicle like spaces
  – Spindled areas, clear cell areas, hyaline globules
  – Rhabdoid features can be seen
  – Can have admixed large cell areas with enlarged nucleoli (Large cell variant– these predominate)
  – High mitotic rate

• Misdiagnosis rate in published series
  – 19-30%
SCCO-HT

“Polyimmunophenotypic”

- WT1 95%
- P53 85%
- CD10: 95%
- Keratin variable 60-90%
- EMA variable 30-90%
- Calretinin variable 70%
- Synapto variable 15%
- But wait... there is a new kid on the block!!!
BRG1/(SMARCA4 encoded protein)
IHC for BRG1 protein

• BRG1 is encoded by SMARCA4
  – Mutation leads to loss of BRG1 expression by IHC

• Although some other tumors also lose this
  – Ovarian clear cell ca 4%; ESS 8%; EMCA rare
  – Most tumors in DDX lack this expression
    • SCC ovary pulmonary type, GCT, S-L tumor, Germ cell tumors, rhabomyosarc, DSRCT, Ewings sarcoma, synovial sarcoma, lymphoma, melanoma

• In this case patient had loss of BRG1 and BRM by IHC
  – BRM loss thought to be 2° to epigenetic silencing not mutation to SMARC B2

• 92% of cases have SMARCA4 mutation; 86% have loss of BRG1 by IHC
  – One study: 43% of SCCO-HT mutations were GERMLINE mutations
SCCO-HT
What kind of tumor is this???

• ?? Carcinoma
  – EM: desmosomes, tight junctions, ...
  – IHC: some keratin, EMA, NE markers
• ?? Germ cell origin
  – EM: X-cellular BM-like material
  – LM: PAS+ globules
• ?? Sex cord stromal tumor
  – Follicle-like structures, calretinin positivity,…

• **Variant of malignant rhabdoid tumor**
  – Histologic similarity to
    • Renal rhabdoid tumor
    • CNS atypical teratoid rhabdoid tumor
  – Mutations in SW1/SNF pathway
    • SMARCB2 in rhabdoid tumors
    • SMARCA4 in SCCO-HT
SCCO-HT
Familial Cases

• Germline SMARCA4 mutations found in as many as 43% of cases of SCCO-HT.
  – But incidence of familial cases is low
    • Tumor of young females (esp germline cases)
    • Father may carry “silent” mutation
  – Recommend testing in all for germline mutation
    • Female Carriers are at risk for SCCO-HT
      – Prophylactic Oophorectomy??
      – Close follow up with U/S screening??
    • M/F children(< 4-5 y) may be at risk for RT’s
SCCO-HT Treatment

- Most are treated with primary surgery followed by chemotherapy
- 5 y survival rate for stage I disease: 50%
- Debatable role for RT

REFERENCE:

Patient received VPCBAE Chemotherapy and is currently NED at 13 months.
SB 6133
Mucinous Cystic Tumor of Low Malignant Potential

Case courtesy Dr. Peter Ames, Renown Health, Reno, NV

Alana Shain/Sunny Kao Stanford
Urachal Epithelial Neoplasms

• Glandular (the majority)
  – Noncystic invasive adenocarcinoma, 83%
  – Cystic tumors, 17%

• Non-glandular (rare!)
  – urothelial, squamous cell, neuroendocrine, mixed type
Mucinous cystic tumors

- Classification analogous to ovarian tumors
- Cystic lumina (usually unilocular), copious mucin
- Presentation incidental or related to mass lesion (vs. hematuria for noncystic invasive adenocarcinoma)
- Reports of pseudomyxoma peritonei

Immunoprofile similar to primary ovarian tumors
CK7+ (60%), CK20+, CDX2+
Nuclear beta catenin negative, ER/PR negative

Amin et al. 2014
Mucinous Cystic Tumors

- Mucinous Cystadenoma
- MCT of LMP
- MCT of LMP with Intraepithelial carcinoma (<2 mm, <5% overall)
- Mucinous cystadenocarcinoma (microinvasion or frank invasion)

Amin et al. 2014
Mucinous Cystic Tumors

Mucinous Cystadenoma

MCT of LMP

MCT of LMP with Intraepithelial carcinoma (<2 mm, <5% overall)

Mucinous cystadenocarcinoma (microinvasion or frank invasion)

Amin et al. 2014
Mucinous Cystic Tumors

- Mucinous Cystadenoma
- MCT of LMP
- MCT of LMP with Intraepithelial carcinoma (<2 mm, <5% overall)
- Mucinous cystadenocarcinoma (microinvasion or frank invasion)

Amin et al. 2014
Mucinous Cystic Tumors

- Mucinous Cystadenoma
- MCT of LMP
- MCT of LMP with Intraepithelial carcinoma (<2 mm, <5% overall)
- Mucinous cystadenocarcinoma (microinvasion or frank invasion)

Amin et al. 2014
Outcome Urachal Epithelial Neoplasms

Survival of noninvasive mucinous cystic tumors is significantly better than noncystic adenocarcinomas.

Amin et al. 2014
Is it urachal?

WHO Criteria for diagnosis of urachal adenocarcinoma
(WHO 2016, page 113)

1. Location of the tumor in the bladder dome and/or anterior wall
2. Epicenter of carcinoma in the bladder wall
3. Absence of widespread cystitis cystica and/or cystitis glandularis beyond the dome or anterior wall
4. Absence of known primary elsewhere

- Urachal vs. non-urachal adenocarcinoma prognosis controversial, but tumors confined to urachus and bladder wall have better outcomes
- Other prognostic factors: grade, lymph nodes, metastasis
- Partial cystectomy, urachectomy, umbillectomy
References

• The WHO, 2016


SB 6134

Mahendra Ranchod; Good Samaritan Hospital

56-year-old female, routine annual Pap smear submitted.
Metastatic Lobular Carcinoma: Uncommon sites

Gastrointestinal Tract
Peritoneum
Retroperitoneum
Meninges (carcinomatous meningitis)
Uterus
SB 6135
(scanned slide available)

Malti Kshirsagar; El Camino Hospital
52-year-old male with “right spermatic granuloma” excisional specimen submitted.
Differential diagnosis:

1. Vasitis nodosa

2. Metastatic adenocarcinoma

3. Adenomatoid tumor – arising in spermatic cord or adjacent epididymis

4. Malignant mesothelioma
Vas deferens and adventitia
Vas deferens with “tubular proliferation”
Complex tubular proliferation
Perineural involvement
Spermatozoa within tubules
Extravasated spermatozoa
Histiocytic reaction with chronic inflammation
Diagnosis: Vasitis nodosa

Per patient’s wife:
“Oh yeah, he had a vasectomy years ago”
Term “Vasitis nodosa” coined in 1943 by JA Benjamin et al


Subsequent reports (1954-1967) referred to these lesions as:
1. “Unusual vas deferens tumor”
2. “Spermatic cord tumor”
3. Vas deferens lesion “simulating salpingitis isthmica nodosa”
4. “Mesonephric hamartoma”

Vasitis Nodosa
ALBERT L. OLSON, M.D.
Department of Pathology, Loma Linda University Hospital, Loma Linda, California 92354

ABSTRACT

 Olson, Albert L.: Vasitis nodosa. Amer. J. Clin. Path. 55: 364-368, 1971. Three cases in which extravasation of spermatozoa in the wall of the vas deferens occurred, accompanied by formation of epithelial-lined spaces within the wall, are reported. All of the patients previously had undergone vasectomies. Review of the literature reveals several cases with similar lesions but different names. The author suggests that the lesions be designated “vasitis nodosa,” partly because what apparently was the first case reported was described by that name and partly because of the resemblance to salpingitis isthmica nodosa. Obstruction may be the most significant factor in pathogenesis.

DURING THE PAST TWO DECADES there have been several reports of nodules of the vas deferens which contained intramural epithelial structures. However, because of different etiologic concepts various names have been applied to these lesions. This paper will present three similar cases, with suggestions as to pathogenesis and nomenclature.

Report of Cases

Case 1. A 51-year-old man had a repeat vasectomy because of failure of a vasectomy done 19 months earlier. One of the segments from the second operation appeared normal grossly, but the other was a firm, triangular specimen measuring 2.5 by 1.8 by 0.7 cm.

Case 2. A 56-year-old man underwent a transurethral resection of the prostate accompanied by a bilateral vasectomy, although the history recorded a previous bilateral vasectomy in 1951. The surgeon noted that the left vas was enlarged and contained yellow mucoid fluid. The larger of the two segments excised was 0.3 cm. in diameter.

Case 3. A 38-year-old man had pain in his groin for 5 or 6 days. Past history disclosed a vasectomy 10 years previously. A tender, firm nodule was palpated in the region of the right globus major, resulting in surgical exploration which revealed a nodule in the vas deferens. The submitted specimen was 3 cm. long and had an oval cross section measuring 1.4 by 0.5 cm.

Microscopic Findings

Case 1. There was loss of the normal muscle pattern except in one eccentrically located region where a circular zone of smooth muscle surrounded a group of epithelial-lined spaces interpreted as remnants of the original lumen (Fig. 1). Elsewhere there was a mixture of fibrous connective tissue, smooth muscle fibers, numerous spermatozoa, histiocytes, and epithelial cells with pale-staining nuclei and cytoplasm. These epithelial cells occurred in randomly situated groups of small nests, acini, and ducts (Fig. 2). Spermatozoa were present in the lumina of a few of these
Vasitis Nodosa & Epididymis Nodosa

1. Occur most commonly as late post-vasectomy changes (in up to 50% of men) – usually an incidental finding

2. May also occur following trauma, herniorrhaphy, and prostatectomy

3. Lesions typically small (less than 1 cm)

4. Most lesions asymptomatic, though patients may present with scrotal swelling/pain/tenderness

5. Most cases require no treatment. In patients who are symptomatic, surgical resection is generally curative
Why does it happen?

- Tubular obstruction
- Increased luminal pressure
- “Blow out” injury with leakage of spermatozoa
- Inflammatory reaction with excessive regeneration of the epithelial lining
Vasitis Nodosa & Epididymitis nodosa- Histology

1. Proliferation of small ducts and gland-like structures in walls of vas deferens (and epididymis) – may not communicate with lumen of vas deferens

2. Glands/tubules lined by bland cuboidal or low columnar cells

3. May see perineural and possibly vascular invasion

4. Intraluminal spermatozoa are a reassuring finding

5. Extravasation of sperm with inflammatory response

6. 70% cases show associated sperm granulomas
References:
2-year-old 11 month female, previously healthy, who fell backwards from her high chair and struck her head on the wooden floor. An X-ray demonstrated a skull fracture, and a subsequent neuroimaging showed a large heterogenous mass in the left parietal, occipital, and frontal lobes.
Initial CT
CNS Ganglioneuroblastoma

- One of the “other” embryonal tumors
- WHO grade IV
- Very rare (~10 cases reported)
- Surgery/chemo/radiation
- Survivals were reported in three of the 10 previously reported patients with the range of survival after initial symptoms was 0.7–36 months (median 11 months), which is substantially less than the 60% 3 year survival in pediatric patients with cerebral neuroblastomas

Key Diagnostic Points

• An embryonal tumor with divergent morphologies and varying degrees of neuronal differentiation – poorly differentiated neuroepithelial cells, groups of neurocytic cells, and ganglion cells

• Dysplastic ganglion cells are a prominent element in small groups rather than dispersed
New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs

Graphical Abstract

Central Nervous System Primitive Neuroectodermal Tumors (CNS-PNET)

DNA Methylation Profiling

Known CNS Tumor Entities

Genetic Characterization

New Molecular CNS Tumor Entities

Authors
Dominik Sturm, Brent A. Orr, Umut H. Toprak, ..., David W. Ellison, Andrey Korshunov, Marcel Kool

Correspondence
m.kool@dkfz.de

In Brief
Highly malignant primitive neuroectodermal tumors of the CNS (CNS-PNETs) have been challenging to diagnose and distinguish from other kinds of brain tumors, but molecular profiling now reveals that these cancers can be readily classified into some known tumor types and four new entities with distinct histopathological and clinical features, paving the way for meaningful clinical trials.
Clinical follow-up

Post-op 9/10

12/5
Clinical follow-up

• Doing well overall
• CSF from an LP on 9/19/16 was negative for metastatic disease. Post operatively Valeria had right facial paresis and right hemiparesis, which improved over the last few months.
• Enrolled on St. Jude study SJYC07 and began induction therapy on 9/23/16 and completed therapy on 1/3/17.
• Second resection last week
SB 6137
(scanned slide available)

Ben Buelow/Julieann Lee; UCSF

16-year-old female who presented with an abdominal mass. Intraoperatively she had an 18cm smooth ovarian mass composed of homogenous tan-white focally hemorrhagic tissue. The patient’s AFP and B-HCG were markedly elevated. Frozen section of the main mass showed sheets of monotonous large moderately cohesive polygonal cells with nucleomegaly, coarse chromatin, and variably prominent nucleoli. A brisk lymphocytic infiltrate was present. A periaortric LN submitted for frozen section was negative. A second peripancreatic LN was submitted for permanent section and is shown here.
16-year-old female with a 16 cm right ovarian mass, and “peripancreatic lymphadenopathy”

Julieann Lee & Ben Buelow
UCSF
South Bay Pathology Society
February 6, 2017
Solid Pseudopapillary Neoplasm

Abundant Hyaline Globules and Pseudopapillae
Solid Pseudopapillary Neoplasm

CD10

B-catenin
SALL4 Negative

Pan-keratin Negative

HMB45 Negative

Chromogranin Negative
60% Dysgerminoma

15% Embryonal Carcinoma

25% Yolk sac tumor, AFP positive
Solid Pseudopapillary Neoplasm of the Pancreas

- Occur predominantly in young women
- Usually discovered incidentally
- Rare: ~2% of all exocrine pancreatic neoplasms
- Metastasis in ~10% of cases
- Rarely can directly extend into stomach, duodenum, and spleen
- 85% cases cured with complete surgical resection
- Origin outside of the pancreas is uncommon, has been reported in retropancreatic tissue
Solid Pseudopapillary Neoplasm of the Pancreas

- Solid to cystic, often mixed
- Poorly cohesive monomorphic cells
- Pseudopapillae
- Eosinophilic hyaline globules
- Often have nuclear grooves
- No morphologic predictors of outcome

- Nuclear/cytoplasmic B-catenin, and CD10 positive
Ankur Sangoi; El Camino Hospital
DIAGNOSIS?
DDx of splenic cysts

- Echinococcal cyst
- epithelial cyst
- dermoid cyst
- mesothelial cyst
- pseudocyst
- Vascular lesion (lymphangioma)
DX: SPLENIC EPITHELIAL CYST
(“splenic epidermoid cyst”)

• Uncommon
• Etiology unknown
  – May arise from metaplasia in mesothelial cysts
• Usually children/young adults
• Solitary or multiple
  – May be associated with accessory spleen
• Often large and require splenectomy
• Can be associated with elevated serum CEA and CA19-9 levels
SB 6139
(scanned slide available)

Ankur Sangoi; El Camino Hospital
73-year-old male with BPH. TURP performed.
DIAGNOSIS

• Prostate, TURP:
  – Nodular prostatic hyperplasia
  – Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
  – Malakoplakia
• From 4381 prostate specimens
  – 29 lymphomas (<1%) in prostate specimens or pelvic LNs
    • 18 incidental cases
    • 11 with concurrent known lymphoma
    • Subtype: mostly CLL/SLL; less often marginal zone lymphoma, mantle cell lymphoma, follicular lymphoma, DLBCL
Malakoplakia

- Rare histiocytic disease that occurs in all organs
  - Common in GU tract, particularly bladder
- Caused by defects in phagocytic or degradative functions of histiocytes in response to gram negative coliforms (*E. coli* or *Proteus*) that results in chronic inflammatory state, followed by intracellular deposition of iron and calcium (known as Michaelis-Gutmann bodies)
- Often misdiagnosed clinically as a malignant condition
Ankur Sangoi; El Camino Hospital

37-year-old male with reported history of stage II mixed nonseminomatous germ cell tumor (80% embryonal carcinoma/15% teratoma/5% yolk sac tumor) status post radical orchietomy and chemotherapy with residual teratomatous elements on retroperitoneal lymph node dissection in 2013.

He now presents with an 11.5 cm abdominal mass and bulky paratracheal lymphadenopathy with elevated serum AFP, beta-HCG, and LDH.
IHC SUMMARY

- AE1/AE3: positive
- Glypican3: positive
- SALL4: positive
- OCT3/4: negative
- CD30: negative
- Desmin: negative
- SOX11: negative
- CD43: negative
DIAGNOSIS

• Yolk sac tumor
  – Predominantly sarcomatoid variant
  – Focal microcystic variant

• No evidence of somatic malignancy (no transformation to frank sarcoma)
Malignant “transformation” of testicular GCTs

- Uncommon overall
- Usually sarcomatoid transformation
  - Less often: carcinomatous transformation
  - Occurs in late recurrences
  - Subtype frequency: rhabdomyosarcoma, angiosarcoma, leiomyosarcoma, chondrosarcoma
- Can also be sarcoma NOS subtype
Many Postchemotherapy Sarcomatous Tumors in Patients With Testicular Germ Cell Tumors Are Sarcomatoid Yolk Sac Tumors

A Study of 33 Cases

Brooke E. Howitt, MD,* Martin J. Magers, MD,† Kevin R. Rice, MD,‡ Cristina D. Cole, MD,† and Thomas M. Ulbright, MD†
Postchemotherapy sarcomatous tumors in testicular GCTs

- 33 sarcomatoid tumors lacking specific sarcoma subtype (NOS)
- Yolk sac tumor criteria:
  - Moderate intensity and >10% staining with both AE1/AE3 and glypican3
  - 22 of 33 (67%) tumors met this criteria
    - 50% cases desmin positive but myogenin negative
    - 68% SALL4 positive; all MUC4 negative
  → Sarcomatoid yolk sac tumors
- Typically occur several years after initial Dx with normal to mildly elevated AFP
- Behave aggressively when high grade