#### Disclosures November 2, 2015

David Levin, MD has disclosed that he is a stockholder with Ekso Bionics. The activity planners have determined that this financial relationship is not relevant to the case being presented. The following planners and faculty have no financial relationships with commercial interests to disclose:

Presenters: Christine Louie, MD Teri Longacre, MD Peyman Samghabadi, MD Hannes Vogel, MD Jarish Cohen, MD, PhD Andrew Horvai, MD, PhD Sarah Cherny, MD Linlin Wang, MD Kurt Schaberg, MD Ankur Sangoi, MD Activity Planners: Kristin Jensen, MD Ankur Sangoi, MD William Rogers, MD

#### SB 5991

80-year-old man with CLL, now presenting with diarrhea. Small/large bowel biopsies.

Christine Louie/Teri Longacre; Stanford











### DIAGNOSIS?



#### **Idelalisib-associated Enterocolitis**

## Idelalisib

Approved by FDA last year for:

- Relapsed CLL
- Accelerated approval also granted for relapsed follicular lymphoma and relapsed SLL



# Idelalisib

Adverse reactions include:

- Diarrhea
- Hepatotoxicity
- Pneumonitis
- Intestinal perforation



## Small bowel histology

- Apoptosis present in all cases
- Intraepithelial lymphocytes and villous blunting also commonly seen
- Main diagnostic differential includes GVHD, celiac disease





## Colon – histologic features

| Morphologic feature                      | Ν           |
|--|-------------|
| Cryptitis                                | 11/11       |
| Neutrophilic crypt abscess               | 7/11        |
| Increased crypt epithelial apoptosis     | 11/11       |
| Exudate/erosion                          | 1/11        |
| Increased intraepithelial<br>lymphocytes | 8/11        |
| Crypt architectural distortion           | 7/11 (mild) |

## Colon – histologic features

- Most cases resembled GVHD or IBD/infectious colitis
- A few cases showed prominent intraepithelial lymphocytes – resembling lymphocytic colitis







## Take Home Points

- Apoptosis and cryptitis are the most common features
- Only mild architectural distortion in the colon
- Differential diagnosis/mimics may include GVHD, IBD, infection (CMV), and celiac disease

### AJSP- Epub August 2015

#### Idelalisib-associated Enterocolitis Clinicopathologic Features and Distinction From Other Enterocolitides

Christine Y. Louie, MD,\* Michael A. DiMaio, MD,\* Karen E. Matsukuma, MD, PhD,† Steven E. Coutre, MD,‡ Gerald J. Berry, MD,\* and Teri A. Longacre, MD\*

#### Idelalisib-associated Colitis

Histologic Findings in 14 Patients

Anna-Sophie Weidner, MD,\* Nicole C. Panarelli, MD,\* Julia T. Geyer, MD,\* Erica B. Bhavsar, BS,† Richard R. Furman, MD,† John P. Leonard, MD,† Jose Jessurun, MD,\* and Rhonda K. Yantiss, MD\*

#### SB 5992

82-year-old man with a 2.1 cm sellar and suprasellar mass abutting the optic chiasm and contacting the left internal carotid artery with possible sinus infiltration. The radiologist's impression is that the lesion was most consistent with pituitary macroadenoma. Intraoperative diagnosis was adenoma by cytologic preparation. Initial immunohistochemical work up reveals a synaptophysin negative neoplasm.

Peyman Samghabadi/Hannes Vogel/Donald Born; Stanford

















### DIAGNOSIS?



## **Clinical History**

82 year old man with a multi week history of worsening double vision

Left frontal headache and a left droopy eye.

Decrease energy level in the last several months.

Low libido and sexual function for 25 years.

Denies heat/cold intolerance, weight loss/gain, change in shoe or hand size

## T1 FLAIR



### T1 with contrast



## T1 with contrast














BRAF (V600E)







#### **ADDITIONAL NEGATIVE STUDIES**

- GFAP Transthyretin S100 SOX-10 PAX8 TTF1
- (CK20) (Synaptophysin)



# ?

## ?

?





## DIAGNOSIS PITUITARY, SELLAR TUMOR, RESECTION -- METASTATIC PROSTATE ADENOCARCINOMA



# Pituitary Metastases

Usually present at late stage disease, e.g. known primary diagnosis

to pituitary gland

~1% of all intracranial metastases

```
Primary sites:
Breast (37.2%)
Lung (24.2%)
Prostate (5.2%)
Kidney (4.9%)
```

Table 1 425 reported cases of N N Primary site Percentage Primary site Percentage primary malignancies metastatic 158 37.2 Multiple myeloma 3 Breast 0.7 103 24.2 Lang Paranasal sinus 3 0.7 22 5.2 Prostate Oral cavity 3 0.7 Renal 21 4.9 Lymphoma 2 0.5 13 2 Melanoma/Skin 3.1 Larynx 0.5 13 2 Thyroid 3.1 Germ cell tumor 0.5 Colon 12 2 2.8 Ovary 0.5 Unknown 12 2.8 Ilcum 0.2 Stomach 0 2.1 Retroperitoneum 0.2 Pancreas 7 1.6 Bile duct 0.2 Liver 6 1.4 Lymphosarcoma 0.2 5 1.2 0.2 Pharynx Penis Endometrium 5 1.2 Thymus 0.2 Leukemia 5 1.2 Nasal cavities 0.2 Urinary/bladder 0.9 Salivary glands 0.2 References from [6, 17, 26, 29, Uterine/cervix 0.9 Merkel cell carcinoma 0.2

He W, Chen F, Dalm B,. Kirby P,. Greenlee J. Metastatic involvement of the pituitary gland: a systematic review with pooled individual patient data analysis. Pituitary (2015) 18:159–168

41, 46, 47, 48-63]

# Clinical Presentation Of Pituitary Metastases

Diabetes Insipidus (most common and specific)

Anterior Pituitary Insufficiency

Cranial Nerve Palsy

Headaches

Visual Disturbances

He W, Chen F, Dalm B,. Kirby P,. Greenlee J. Metastatic involvement of the pituitary gland: a systematic review with pooled individual patient data analysis. Pituitary (2015) 18:159–168

# **Imaging-Pituitary Metastases**

Neurohypophysis

# (Breast has an affinity for the adenohypophysis)

Invasion of the cavernous sinus Sclerosis in the surround sella turcica *Thickening of the pituitary stalk* 

Fassett DR, Cauldwell WT. Metastases to the pituitary gland. Neurosurg Focus. 2004 Apr 15;16(4):E8.

### SB 5993

59-year-old man with a history of thin melanoma and a feeling of fullness as his presenting symptom. Imaging showed a circumscribed 24 cm solid, centrally necrotic mass in the right retroperitoneum. He underwent resection of the mass. Grossly the tumor was a 23.5 cm largely solid, multinodular, tan/orange, hemorrhagic, and necrotic mass.

#### Jarish Cohen/Andrew Horvai; UCSF















# DIAGNOSIS?



# Imaging





**Coronal BTFE MRI** 

Axial CT

# **Gross Pathology**





0,0







#### Synaptophysin

# IHC results table

| Positive      | Negative         |
|---------------|------------------|
| Inhibin       | Keratin cocktail |
| Synaptophysin | EMA              |
| Melan-A       | SOX10            |
|               | Chromogranin A   |
|               | SMA              |
# Diagnosis

• Adrenal cortical carcinoma, pT3

| CAP Approved  | Endocrine • Adrenal Gland<br>AdrenalGland 3.2.0.0          |
|---|--|
| Primary Tumor (pT)<br>pTX: Cannot be determined<br>pT0: No evidence of primary tumor<br>pT1: Tumor 5 cm or less in greatest dimension, no extra<br>pT2: Tumor greater than 5 cm, no extra-adrenal invas<br>pT3: Tumor of any size with local invasion, but not invo<br>pT4: Tumor of any size with invasion of adjacent organ | a-adrenal invasion<br>ion<br>ading adjacent organs#<br>ns# |
| * Adjacent organs include kidney, diaphragm, great vessels, po<br>Note: There is no category of carcinoma in situ (pTis) relative to  | ancreas, and liver.<br>carcinomas of the adrenal gland.    |

## Discussion

#### **Modified Weiss Criteria**

- Mitotic rate >5/ HPF (2)
- Cytoplasm (clear cells comprise ≤ 25% of tumor) (2)
- Abnormal mitoses (1)
- Necrosis (1)
- Capsular invasion (1)
- Score of ≥ 3 is suggestive of malignancy



### Discussion

100% 80% % Positive 60% Adrenal cortical hyperplasia . Adrenal cortical adenoma 40% Adrenal cortical carcinoma 20% Primary CC-RCC 0% Metastatic CC-RCC calretinin CAM5.2 D2-40 nidirlni RCC S 100 AE1/AE3 CD10 MelanA EMA PAX2 SF-1 Vimentin AE1 pankeratin 34BE12 Antibody (minimum 4 cases)

FIGURE 1. Review of previously reported immunohistochemical findings in adrenal cortical lesions and CC-RCC 2-6,9-12,16,25,27,33,34,36,41,42,44,45,50,53,54

Am J Surg Pathol • Volume 35, Number 5, May 2011

## References

- Aubert S, Wacrenier A, Leroy X, et al. Weiss system revised: A clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. Am J Surg Pathol 2002; 26(12):1612-1619.
- DeLellis RA, Lloyd RV, Heitz PU, Eng C, ed. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Endocrine Organs. Lyon, France: IARC Press; 2004:136.
- Sangoi AR, Fujiwara M, West RB, et al. Immunohistochemical distinction of primary adrenal cortical lesions from metastatic clear cell renal cell carcinoma: a study of 248 cases. Am J Surg Pathol 2011; 35(5):678-86.



#### SB 5994

60-year-old man with right orbital mass, displacing right superior and medial rectus.

Andrew Horvai; UCSF











## DIAGNOSIS?



## Imaging



Axial FS T1













## IHC results summary

| Positive | Negative |
|----------|----------|
| CD34     | MUC4     |
| STAT6    | Keratin  |
|          | Desmin   |
|          | S100     |

# Diagnosis

Solitary fibrous tumor (SFT) with giant cells
– so-called "giant cell angiofibroma"

## Discussion: SFT with giant cells

- Predilection for head and neck, esp. orbit
- Usually cured with simple excision
  SFT can metastasize, unpredictable
- Inv12(q13q13)  $\rightarrow$  NAB2-STAT6 fusion
  - Requires RT-PCR (7+ probe pairs due to variants)
  - Most common variant (ex4 to ex2/4)  $\rightarrow$  thoracic
  - Results in STAT6 *nuclear* expression, regardless of exact fusion variant

### SFT with giant cells (GC angiofibroma)

#### Why does this antibody work so well?



## STAT6



## GC *fibroblastoma* (pediatric DFSP)





## References

- Dei Tos AP et al. Giant cell angiofibroma. A distinctive orbital tumor in adults. Am J Surg Pathol 1995;19:1286-93
- Kao YC et al. Clinicopathological and genetic heterogeneity of the head and neck solitary fibrous tumours: a comparative histological, immunohistochemical, and molecular study of 36 cases. Histopathology Epub 2015
- Tai HC et al. NAB2-STAT6 fusion types account for clinicopathological variations in solitary fibrous tumors. Mod Pathol 2015;28:1324-35

### SB 5995

#### 58-year-old man with 2 day history of gross hematuria.

#### Sarah Cherny; Kaiser San Francisco











## DIAGNOSIS?



- Benign myofibroblastic proliferation of the urinary bladder
  - Inflammatory myofibroblastic tumor
  - Inflammatory pseudotumor
  - Postoperative spindle cell tumor
  - Pseudosarcomatous myofibroblastic proliferation
  - Pseudosarcomatous fibromyxoid tumor

- Clinical
  - Rare
  - Usually 2<sup>nd</sup> to 4<sup>th</sup> decade; may also occur in children
  - Gross hematuria > abdominal pain, irritative or obstructive voiding symptoms
  - Polypoid or submucosal nodule, ranging from 1.5 to 13 cm
Left anterolateral fungating bladder mass measuring 3.0 x 2.0 x 2.4 cm (AP x TR x CC) with invasion through the bladder wall, but not to nearby organs or abdominal wall.

- Histology
  - Variably cellular proliferation of myofibroblasts
    - Fine, evenly distributed nuclear chromatin
    - Tapered elongate cytoplasmic processes
    - Marked variation in nuclear size
    - Scattered macronucleoli
    - Loose fascicular architecture
    - Mitotic activity may be brisk
  - Invasion of muscularis propria is common
    - Does not denote increased risk for aggressive behavior
  - Admixed inflammatory cells, including eos and plasma cells

- Ancillary tests:
  - Commonly co-express actin-SM and low molecular weight keratins
    - Nonreactive for HMWK
  - ALK1 expression by IHC varies widely: 8-89%
  - Desmin reactivity variable

- Ddx:
  - Rhabdomyosarcoma
  - Sarcomatoid urothelial carcinoma
  - Leiomyosarcoma
  - Fibromyxoid nephrogenic adenoma
  - Urothelial carcinoma with myxoid stroma

- Prognosis
  - Risk of local recurrence after transurethral resection varies between studies, but approaches 20% in one series
  - No metastases have been reported to date

# SB 5996 Heart transplant patient, nasal septum mass biopsied.

**David Levin; Washington Hospital** 











# DIAGNOSIS?





#### **DISSEMINATED ACANTHAMOEBIASIS**

- 60 yo female with NICM s/p OHT dec 2014 c/b post op tamponade and ESRD
- onset of sx april 2015, bx dx rhinosinusitis amoebiasis june2015 rapidly followed by skin and bone bx confirmation of DA.
- Acanthamoeba confirmed by CDC using ipox and pcr
- This patient was treated with fluconazole, miltefosine (only available from CDC), flucytosine
- Transferred to USCF, continued on antibiotics and had immunosuppressant medication meds adjusted (d/c valcyte and monitored tac) discharged 2 weeks later on 7/3/15. Condition on discharge "fair"

#### ACANTHAMOEBA

- Free-living amoebas are environmental protozoan parasites with worldwide distribution.
- Four genera cause disease in humans: Naegleria (only N. fowleri), Acanthamoeba (several species), Balamuthia (only B. mandrillaris), and Sappinia (only S. pedata)
- All of these species cause central nervous system (CNS) infections,
- 2 types of CNS infections-- "primary amebic meningoencephalitis" N. Fowleri and "granulomatous amebic encephalitis" Acanthamoeba species, Balamuthia and Sappinia
- Acanthamoeba and Balamuthia and may also cause localized non-CNS infections (eg. acanthamoebiasis keratitis) and disseminated infections
- Exposure is through lungs, olfactory neuroepithelium and ulcerated/broken skin
- People with AIDS, diabetes, pregnancy, liver disease, alcoholism, steroids xs antibiotics, lupus, cancer and organ ransplant are at increased risk
- In the United States, Balamuthia infection might be more common among Hispanic Americans
- Balamuthia and Acanthamoeba can infect anyone, but immunosuppressed are at increased risk

Acanthamoeba spp. have been found in soil; fresh, brackish, and sea water; sewage; swimming pools; contact lens equipment; medicinal pools; dental treatment units; dialysis machines; heating, ventilating, and air conditioning systems; mammalian cell cultures; vegetables; human nostrils and throats; and human and animal brain, skin, and lung tissues.

#### REFERENCES

- CDC
- UP TO DATE
- Stéphane Barete, et. al. "Fatal Disseminated Acanthamoeba lenticulata Infection in a Heart Transplant Patient," Emerging Infectious Diseases • www.cdc.gov/eid
  Vol. 13, No. 5, May 2007
- Rivera MA<sup>1</sup>, Padhya TA. "Acanthamoeba: a rare primary cause of rhinosinusitis." Laryngoscope. 2002 Jul;112(7 Pt 1):1201-3.



### SB 5997

73-year-old man with a left liver tumor concerning for cholangiocarcinoma on imaging study. Left liver FNA biopsy of tumor called mixed HCC-cholangiocarcinoma. Left hepatic lobectomy submitted.

Linlin Wang; UCSF











# DIAGNOSIS?





Mucicarmine

S.

0

CK7

5

СК19

10

6.5

J

20

## Combined Hepatocellular-Cholangiocarcinoma (HCC-CC)?

- Combined HCC-CC is rare tumor with both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) features.
- Distinction of cHCC-CC from HCC and CC may be challenging, but has prognostic and therapeutic implications.
- Cholangiocarcinoma component in cHCC-CC Morphology: Glandular formation in fibrotic stroma Intracellular mucin
   IHC: Loss of hepatocellular markers Expression of CK7/CK19



## Mucin ≠ Biliary Differentiation

#### Primary Hepatic Tumors With Myxoid Change Morphologically Unique Hepatic Adenomas and Hepatocellular Carcinomas

Safia N. Salaria, MD,\* Rondell P. Graham, MBBS,† Shinichi Aishima, MD,‡ Taofic Mounajjed, MD,† Matthew M. Yeh, MD, PhD,§ and Michael S. Torbenson, MD† Am J Surg Pathol 2015;39:318–324





## **CK7 and CK19 Expression in HCC**

Table 1. Expression of cytokeratins 7 and 19 in hepatocellular carcinoma

| Expression<br>levels of CK19 | Expression levels of CK7 |    |    |     |       |
|------------------------------|--------------------------|----|----|-----|-------|
|                              |                          | +  | ++ | +++ | Total |
|                              | 93                       | 25 | 21 | 3   | 142   |
| +                            | 1                        | 7  | 1  | 0   | 9     |
| ++                           | 0                        | 2  | 4  | 0   | 6     |
| +++                          | 0                        | 0  | 0  | 0   | 0     |
| Total                        | 94                       | 34 | 26 | 3   | 157   |

CK7, cytokeratin 7; CK 19, cytokeratin 19.



Uenishi et al. Cancer Sci. 2003 Oct;94(10):851-7.

# Take Home Messages

- 1. The diagnosis of cHCC-CC may be challenging, especially in limited biopsies.
- 2. Myxoid changes can be seen in HCC.
- 3. CK7 and CK19 can be expressed in HCC.

# SB 5998 76-year-old woman with a distal pancreas mass.

Kurt Schaber/Teri Longacre; Stanford








## DIAGNOSIS?

















## Pancreatic Acinar Cell Carcinoma

**Clinical Features** 

- Rare, <2% of all pancreatic carcinomas
- Presenting symptoms are usually non-specific
  - Jaundice is rare
  - Sometimes elevated lipase levels may lead to subcutaneous or intraosseous fat necrosis
- Metastases usually occur early in disease
- Long-term survival is poor
  - Few patients live to 5 years

## Pancreatic Acinar Cell Carcinoma

Pathologic features

- Grossly, usually large, solid, circumscribed tumors
- Cellular tumor nodules with little or no stroma
- Monotonous sheets and nests
- Cells show basal nuclear polarization and eosinophilic granular cytoplasm
- Often single prominent nucleolus

## Pancreatic Acinar Cell Carcinoma

- Documentation of enzyme production important for diagnosis.
  - Zymogens stain with PASd
    - Must exclude cytoplasmic mucin
  - Immunohistochemistry for trypsin, lipase, or chymotrypsin, which is more sensitive and specific

# **Differential diagnosis**

- Primary differential diagnosis is PanNET
  - May be histologically very similar
  - Stain with Synaptophysin or Chromogranin
- Pancreatoblastoma
  - Primarily pediatric tumor
  - Contain squamoid nests
- Solid Pseudopapilary Neoplasm
  - Pseudopapillae
  - Nuclear staining with  $\beta$ -catenin

### SB 5999

## 67-year-old man underwent TURP. Pathologic stage of this urothelial cancer?

Ankur Sangoi; El Camino Hospital















## DIAGNOSIS?



# AJCC 7<sup>th</sup> ed Urinary Bladder

#### Primary Tumor (pT)

- \_\_\_ pTX: Primary tumor cannot be assessed
- No evidence of primary tumor
- \_\_\_ pT0: \_\_\_ pTa: Noninvasive papillary carcinoma
- Carcinoma in situ: "flat tumor" pTis:
- :ITq Tumor invades subepithelial connective tissue (lamina propria)
- pT2: Tumor invades muscularis propria (detrusor muscle)
- pT2a: Tumor invades superficial muscularis propria (inner half)
- Tumor invades deep muscularis propria (outer half) pT2b:
- pT3: Tumor invades perivesical tissue
- pT3a: Microscopically
- pT3b: Macroscopically (extravesicular mass)
- pT4: Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
  - pT4a: Tumor invades prostatic stroma or uterus or vagina
  - TUMOLINVAGES DEIVIC WAIL OLABAOMINAL WAIL

## AJCC 7<sup>th</sup> ed Urethra

| <u>Primary Tumor (pT)</u> (urothelial [transitional cell] carcinoma of the prostate) |          |  |
|--|----------|--|
|  | pTX:     | Cannot be assessed   |
|  | pT0:     | No evidence of primary tumor   |
|  | pTa:     | Noninvasive papillary, polypoid, or verrucous carcinoma  |
|  | pTis pu: | Carcinoma in situ, involvement of prostatic urethra  |
|  | pTis pd: | Carcinoma in situ, involvement of prostatic ducts  |
|  | pT1:     | Tumor invades subepithelial connective tissue (only applied to tumors invading from the urethral lumen)#                 |
|  | pT2:     | Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral<br>muscle                          |
|  | pT3:     | Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension) |
|  | pT4:     | Tumor invades other adjacent organs (invasion of the bladder)  |











## DIAGNOSIS

- Urinary bladder, TUR:
  - High grade urothelial carcinoma
    - Invading prostatic stroma
    - pT4a (clinically bladder mass invading prostate)

## SB 6000

# 64-year-old man underwent radical prostatectomy. Pathologic stage of this prostate cancer?

Ankur Sangoi; El Camino Hospital













## DIAGNOSIS?



# AJCC 7<sup>th</sup> ed Prostate

#### Primary Tumor (pT)

- \_\_\_ Not identified
- \_\_\_ pT2: Organ confined
- + \_\_\_\_ pT2a: Unilateral, involving one-half of 1 side or less
- + \_\_\_\_ pT2b: Unilateral, involving more than one-half of 1 side but not both sides
- + \_\_\_\_ pT2c: Bilateral disease
- pT3: Extraprostatic extension
- \_\_\_\_pT3a: Extraprostatic extension or microscopic invasion of bladder neck
- \_\_\_\_ pT3b: Seminal vesicle invasion
- \_\_\_\_pT4: Invasion of rectum, levator muscles and/or pelvic wall (Note J)
#### anterior fibromuscular stroma

peripheral tone

prostatic urethra

ejaculatory ducts peripheral 20ne

utricle







#### DIAGNOSIS

- Prostate, radical prostatectomy:
  - Prostatic adenocarcinoma, Gleason grade
    4+3 with tertiary pattern 5
  - Bilateral involvement
  - -pT2c

#### International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 4: seminal vesicles and lymph nodes

Daniel M Berney<sup>1</sup>, Thomas M Wheeler<sup>2</sup>, David J Grignon<sup>3</sup>, Jonathan I Epstein<sup>4</sup>, David F Griffiths<sup>5</sup>, Peter A Humphrey<sup>6</sup>, Theo van der Kwast<sup>7</sup>, Rodolfo Montironi<sup>8</sup>, Brett Delahunt<sup>9</sup>, Lars Egevad<sup>10</sup>, John R Srigley<sup>11</sup> and the ISUP Prostate Cancer Group\*

**MODERN PATHOLOGY** (2011) 24, 39-47

## **SV Grossing**

SV sampling

- Selective (consensus) vs complete

Direction of SV sampling (no consensus)

- Transverse vs longitudinal vs combination

Junction of SV/prostate taken

- Consensus  $\rightarrow$  YES

# SV pT3b Staging (all consensus)

- SVI defined as muscular wall invasion
- Only extraprostatic SVI
- Ejaculatory duct not pT3b
- Method of SVI not recorded

### SV pT3b Staging (no consensus)

Vascular invasion of SV only as pT3b