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

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Activity Planners/Moderator: Kristin Jensen, MD Ankur Sangoi, MD

SB 6211 Allison Zemek/Sunny Kao; Stanford

53-year-old man with left periurethral obstructing mass noted on urethroscopy, with bladder outlet obstruction and prostatic enlargement.













Pos: CK7, cam5.2, AE1/3

Neg: PSA, NKX3.1, CK20, GATA3, p63



chromo

Well-differentiated neuroendocrine tumor

Clinical features:

- Rare <1% (6 in 25 years, Epstein 2011)
- Age range: 45-60 yrs
- Smooth, polypoid nodules
- Bladder neck, trigone, urethra

Pathogenesis:

Unclear: perhaps chronic inflammation/reactive

Well-differentiated neuroendocrine tumor

Histopathologic features:

- Uniform cuboidal or columnar cells
- Pseudoglandular pattern with acinar and cribriform structures
- Inconspicuous nucleoli*
- Paneth cell-like eosinophilic granules*
- Confined to lamina propria, associated with cystitis cystica et glandularis*

Immunohistochemical features: Synapto/chromo+ CK7+ CK20- PSA-

Table 1 2016 WHOClassification of neuroendocrinetumors of the urinary bladder

Neuroendocrine tumors of the urinary tract	Synonym(s)			
Small cell neuroendocrine carcinoma	Neuroendocrine carcinoma			
	Oat cell carcinoma (obsolete)			
Large cell neuroendocrine carcinoma	None			
Well-differentiated neuroendocrine tumor	Carcinoid tumor			
Paraganglioma	Extraadrenal pheochromocytoma			

Endocr Pathol (2016) 27:188-199

Reported ranges of positive IHC (%)	CK7	CK20	S100	GATA3
Small cell NEC	50-64	0	40	32
Large cell NEC	-	-	0	-
Well-differentiated neuroendocrine tumor (carcinoid)	75	0	-	-
Paraganglioma	0	0	100	83-100

Well-differentiated neuroendocrine tumor

Treatment:

- Complete excision

Prognosis:

- Seems to be good if primary and well-differentiated, need more follow up studies

- Need to exclude metastatic neuroendocrine tumor (as in this case)

Take home point:

- neuroendocrine tumors are everywhere...

References

- Chen YB, Epstein JI. Primary carcinoid tumors of the urinary bladder and prostatic urethra: a clinicopathologic study of 6 cases. Am J Surg Pathol. 2011 Mar;35(3):442-6. PMID: 21317716
- Kouba E, Cheng L. Neuroendocrine Tumors of the Urinary Bladder According to the 2016 World Health Organization Classification: Molecular and Clinical Characteristics. Endocr Pathol. 2016 Sep;27(3):188-99. PubMed PMID: 27334654

SB 6212 Jonathan Lavezo/Eduardo Zambrano; Stanford

32-year-old woman European descent with a 5 cm hypervascular right periaortic mass found on CT scan just inferior to the 3rd portion of the duodenum.











Southbay Presentation

Jonathan Lavezo MD, AP/NP Eduardo Zambrano MD





(1)







Family History

- Father diagnosed with an abdominal paraganglioma at age 56, he underwent chemotherapy and radiation therapy. History of multiple strokes and radiation exposure on his job site. He died at age 56
- Paternal aunt diagnosed with a hormone secreting periaortic paraganglioma at age 57. She underwent genetic testing at the University of Michigan Cancer Genetics clinic and was found to carry an SDHB mutation (c.79C>T, p.Arg27X)



Genetic Results

- Familial Pathogenic SDHB Variant: PRESENT
 - Gene = *SDHB*
 - Variant = c.79C>T (p.Arg27X)
 - Zygosity = heterozygous

SDH-B RELATED HEREDITARY PARAGANGLIOM-PHEOCHROMOCYTOMA SYNDROME

- Autosomal Dominant condition characterized by the growth of paragangliomas/pheochromocytomas
- Frequently diagnosed in 3rd decade of life
 - Adrenal = pheochromocytoma
 - Extra-adrenal = paraganglioma
 - Sympathetic (abdomen) or parasympathetic (head and neck)
- Five types of hereditary paragangliomapheochromocytoma (types 1 - 5)
 - Type-4 = usually develop extra-adrenal paragangliomas in the abdomen and are at higher risk of malignant/metastatic disease



Syndrome	Gene	PC	TAPGL	HNPGL	Multifocal	Malignant	RCC	Other
PGL1	SDHD ^a	~10-25%	20-25%	85%	55-60%	~4%	~ 8%	GIST and PA
PGL2	SDHAF2 ^a	0	0	100%	0	0	0	-
PGL3	SDHC	0	Rare	? ^b	15-20%	0%	Rare	GIST
PGL4	SDHB	20-25%	50%	20-30%	20-25%	~30%	~ 14%	GIST and PA
PGL5	SDHA	Rare	Rare	Rare	Rare	Rare	0	GIST and PA

Table 1 Clinical features (penetrance) of PGL syndromes 1–5

PC, phaeochromocytoma; TAPGL, thoracoabdominal PGL; HNPGL, head and neck PGL; RCC, renai ceii carcinoma, PA, pituitary adenoma; GIST, gastrointestinal stromal tumour. Neumann et al. (2002), Amar et al. (2005), Schiavi et al. (2005), Benn et al. (2006), Cascón et al. (2009), Hao et al. (2009), Mannelli et al. (2009), Burnichon et al. (2009), Ricketts et al. (2010), Welander et al. (2011) and Gimenez-Roqueplo et al. (2012). "Paternally inherited.

^bLifetime prevalence not yet determined.

Reference

 Fifteen Years of Paraganglioma: Clinical Manifestations of paraganglioma syndromes types 1-5. *Endocr Relat Cancer*. 2015 Aug; 22(4): T91-T103.

SB 6213 Sanjay Kakar; UCSF

35-year-old woman w/history of IV drug use died in car accident. 4cm liver mass noted while evaluating for liver transplant and sent for frozen section.




Frozen section

- Diagnosis: Hepatocellular adenoma
- Liver, both kidneys, heart and lung were used for transplant

Permanent sections

10











Reticulin

0.00 200

10 - 1

-

Liver fatty acid binding protein (LFABP)

Glutamine synthetase

HCA classification: WHO 2010

	HNF1α- inactivated	β-catenin activated	Inflammatory
Histology	Steatosis	Atypical features	Sinusoidal dilatation
Association with HCC	Rare	40%	Uncommon
IHC	Loss of LFABP	Nuclear β- catenin Diffuse GS	SAA CRP

Zucman-Rossi, Hepatology, 2006 WHO blue book, 2010

Liver fatty acid binding protein (LFABP)

Glutamine synthetase GS)



IHC: subtyping adenoma

- IHC for subtyping adenoma, not for diagnosis
- Establish diagnosis of adenoma before subtyping
- Pitfalls

-LFABP loss can occur in HCC -SAA, CRP staining can be seen in HCC -Diffuse GS staining in HCC



FZ dx: Hepatocellular adenoma Concerning features

- Necrosis
- Mitotic activity
- Reticulin-poor stroma
- Diffuse GS staining

Additional stains

- Arginase-1, Hep Par 1: negative
- Keratin: negative



Diagnosis

Hepatic angiomyolipoma

Hepatic AML

- Most are sporadic; 5-15% TSC
- Predominantly epithelioid
- Radiologic features like HCC

Wang, AJCP 2006 Agaimy, Int J Clin Exp Pathol 2012 Aydin, AJSP 2009 Wang, Medicine (Baltimore) 2014

Helpful features: spindling, indistinct outlines



AML: Foamy macrophages



Questions

- Diffuse GS staining
- Benign or malignant





Diffuse GS staining

5 AML cases

- No beta-catenin mutation
- TSC2 mutation in all cases

Diffuse GS

- Activation of Wnt pathway by TSC2 mutation
- Vascular flow

AML: benign or malignant

High risk histologic features

- Size >5 cm
- Marked cytologic atypia
- Hypercellularity
- Necrosis
- Mitoses >1 in 50 HPF
- Infiltrative border
- Vascular invasion

Malignant: 2 or more high risk features Uncertain: Size >5 cm or marked atypia without other features

Folpe, AJSP 2005

Hepatic AML series, n=16

	Benign (n=14)	Malignant (n=2)
Size >10 cm	3 (21%)	1
Marked atypia	3 (21%)	2
Mitoses (>1 in 50 HPF)	3 (21%)	1
Necrosis	4 (29%)	2
Vascular invasion	2 (14%)	1
Metastasis	None	2

Zhen/Kakar, USCAP 2017

'Malignant' Hepatic AML

- **Current case: high risk features**
- Necrosis
- Mitoses: 2 in 50 HPF

SB 6214 Jonathan Lavezo/Hannes Vogel; Stanford

36-year-old man who presents with a 4 day history of severe bilateral frontal headache. He has a history of headaches 6 months prior to the recent increase in severity. MRI revealed a 3.0 x 2.8 x 2.5 cm solid and cystic mass associated with coarse calcifications arising from the margin of the left lateral ventricle frontal horn. There is enhancement of the solid component.




















Subependymal Giant Cell Astrocytoma

- Most common CNS neoplasm in patients with tuberous sclerosis
- Occur in 1st two decades of life
- Often present with epilepsy or symptoms of increase ICP
 - Acute presentation can be massive intraventricular hemorrhage

Molecular Results

- Stanford Solid Tumor Actionable Mutation Panel (STAMP) (2.2.1)Testing

 POSITIVE FOR *TSC1* Q654X MUTATION
- Biallelic inactivation of TSC1 or TSC2 and activation of mTOR
- Neoplasms demonstrate glial, neuronal and mixed neuroglial features

– Neuroglial progenitor cell of origin

• No germline testing to date

SB 6215 Sarah Cherny; Kaiser San Francisco

67-year-old man with 2 month h/o of abdominal pain/bloating. No improvement with Omeprazole. Weight loss of 5 lbs, but patient admits to being afraid to eat b/c worsens symptoms. Upper endoscopy performed, gastroenterologist noted "duodenitis", biopsied.













- Diagnosis: metastatic prostate carcinoma
- 2009: At age 59, PSA = 4.2; PNBX x6
 - Gleason grade 5 + 4 = score 9 / Grade group 5, involving 80-100% of all 6 prostate cores
- Follow up bone scan and bone biopsy (2009) confirmed multiple bony metastases at time of diagnosis
 - Increasing pelvic lymphadenopathy over subsequent years
- Successfully managed with non-surgical, non-radiation treatment options, with minimal symptoms until 2017
 - PSA currently = 18

• Typical sites of metastases:

– Bone, lymph nodes, lung, liver, brain

- Tjarks BJ, Muirhead D. "Metastatic Adenocarcinoma of the Prostate Diagnosed in a Colon Polyp: A Unique Clinicopathologic Scenario." SD Med. 2016 Jul;69(7):309-311.
 - Diagnosed with prostate CA 4 years earlier
 - Unclear grade / stage from abstract

SB 6216 Sarah Cherny; Kaiser San Francisco

73-year-old man, FIT+, referred for colonoscopy. Gastroenterologist identified 2mm rectal hyperplastic polyp as well as patch of "abnormal appearing mucosa" in the rectum, biopsied.











- Diagnosis: metastatic prostate carcinoma
- 2004: At age 61, PSA = 13.8, PNBX x6
 - Single core involved by 2 mm of Gleason grade 3 + 3 = score 6 / Grade group 1
- EBXRT, with PSA <1 through 2007
 - Lupron initiated in 2007, with PSA rise
 - Imaging shows disease recurrence limited to prostate and associated lymph nodes
 - Patient is asymptomatic

- Vaghefi H, Magi-Galluzzi C, Klein EA. "Local recurrence of prostate cancer in rectal submucosa after transrectal needle biopsy and radical prostatectomy." Urology. 2005 Oct;66(4):881.
- Blight EM Jr. "Seeding of prostate adenocarcinoma following transrectal needle biopsy." Urology. 1992 Mar;39(3):297-8.

Common Types of Cancer	Estimated New Cases 2017	Estimated Deaths 2017	
1. Breast Cancer (Female)	252,710	40,610	Prostate cancer represe 9.6% of all new cancer ca in the U.S.
2. Lung and Bronchus Cancer	222,500	155,870	
3. Prostate Cancer	161,360	26,730	
4. Colon and Rectum Cancer	135,430	50,260	
5. Melanoma of the Skin	87,110	9,730	
6. Bladder Cancer	79,030	16,870	
7. Non-Hodgkin Lymphoma	72,240	20,140	
8. Kidney and Renal Pelvis Cancer	63,990	14,400	
9. Leukemia	62,130	24,500	
10. Endometrial Cancer	61,380	10,920	

In 2017, it is estimated that there will be 161,360 new cases of prostate cancer and an estimated 26,730 people will die of this disease.

Age distribution of prostate CA diagnosis



Average age of diagnosis = 66

New cases by Race/Ethnicity



Prostate cancer deaths by Race/Ethnicity

Number of Deaths per 100,000 Persons by Race/Ethnicity: Prostate Cancer



Age distribution of prostate cancer deaths



Average age of death due to prostate CA = 80

SB 6217 (scanned slide available) Mahendra Ranchod; Good Samaritan Hospital

54-year-old woman developed skin rash after radiation/chemotherapy for anaplastic oligodendroglioma. Routine coloscopy 2 years after chemo showed mild colitis involving entire colon, resembling treated UC.














Clinical History

- 54 yr old woman with anaplastic oligo and skin rash
- Underwent routine colonoscopy
- No GI symptoms
- Diffuse mild colitis, with nodularity and friability, resembling treated U.C.

Additional history

Patient has history systemic mastocytosis

- Skin rash 4 years earlier; bx showed mastocytosis
- B.M. bx showed mastocytosis
 - CD25 positive
 - D816V KIT mutation
- Splenomegaly

Indolent systemic mastocytosis.

Cutaneous symptoms managed with Allegra

Systemic Mastocytosis

- Bone Marrow: almost always involved
- Skin: 80%
- GI Tract : 60-80%
- Spleen, Liver, lymph nodes, other

GIT in Systemic Mastocytosis

- May be asymptomatic
- Abdominal pain, vomiting, bloating, wt. loss etc.
- Endoscopy: nodularity, erosions, erythema, sometimes mimicing Crohn's disease

GI biopsy findings in Mastocytosis

- First, you have to consider this diagnosis
 - Confirm with CD117 and mast cell tryptase
- Challenges:
 - Occasionally, GI is first presentation
 - Cells may have clear cytoplasm resembling histiocytes
 - Mast cells obscured by heavy infiltrate of eosinophils
 - Crypt distortion mimics Crohn's or U.C.
 - How many mast cells are enough?

 >100/HPF (controls have up to 30/HPF)
 CD2, CD25 and D816V KIT mutation

SB 6218 (scanned slide available) Keith Duncan; Mills-Peninsula Hospital

58-year-old woman with lobulated breast mass.



















BENIGN FIBROEPITHEIAL PROLIFERATION WITH PROMINENT DIGITAL FIBROMATOSIS-LIKE INCLUSIONS





Dr. Fletcher consult

Rare lesions Fletcher reported 1st example: Am J. Surg Pathol. 1994: 18: 296-301 Inclusions are unusual finding of no known biological significance Subsequent bx basically negative

SB 6219 (scanned slide available) Jenny Hoffmann/Megan Troxell; Stanford

36-year-old woman with history of renal transplant presenting with 1 week of left upper breast tenderness, warmth, and bilateral nipple inversion.













Differential diagnosis

- Hematolymphoid (PTLD)
 - PTCL (e.g ALCL)
 - DLBCL
- Poorly differentiated carcinoma







Posttransplant lymphoproliferative disorders (PTLD) Plasmacytic hyperplasia PTLD Infectious mononucleosis PTLD Florid follicular hyperplasia PTLD* Polymorphic PTLD Monomorphic PTLD (B- and T-/NK-cell types) Classical Hodgkin lymphoma PTLD

Number	Age	Histology	Initial symptoms	Onset of PTLD after transplant (years)	Treatment	Clinical outcome
1	20	EBV-associated, extranodal NK-cell lymphoma of nasal type	Left breast mass and axillary lymphadenopathy	5	Reduction of immunosuppression and chemotherapy	Refractory to treatment and died 1 month after diagnosis
2	28	EBV-associated polymorphic PTLD	Fever and palpable masses at both breasts	13	Reduction of immunosuppressive therapy	Patient died due to Escherischia coli septicaemia
3	18	EBV-positive marginal zone B cell lymphoma	Tender right breast mass	5	Reduction of immunosuppressive therapy	Resolution of breast mass
4	22	Peripheral T cell lymphoma, EBV negative	Cough and right breast mass	3	Chemotherapy for treatment of concomitant relapse of AML	Died of disseminated fungal infection after 6 months of chemotherapy
5	55	Burkitt-like lymphoma, EBV negative	Left breast mass	8	Reduction of immunosuppressive therapy and chemotherapy	Resolution of breast mass and no relapse of lymphoma for 4 years

Table 1 Summary of PTLD cases involving the breast

EBV Epstein-Barr virus, PTLD post-transplant lymphoproliferative disorders, NK cell natural killer cell, AML acute myeloid leukaemia

References

- Swerdlow SH, Webber SA, Chadburn A, Ferry JA et al (2008) Posttransplant lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris N (eds) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed. International Agency for Research on Cancer, Lyon, France, pp 343–349
- Swerdlow SH, Campo Elias, Pileri S, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.
- Tsao L, Draoua HY, Mansukhani M, Bhagat G, Alobeid B. EBV-associated, extranodal NK-cell lymphoma, nasal type of the breast, after heart transplantation. Mod Pathol. 2004;17:125–130
- Uslu N, Eserdag S. Breast involvement with post-transplant lymphoproliferative disease in a renal transplant recipient. Transplant Proc. 2013;45:2822–2824
- Nassif S, Ozdemirli M. EBV-positive low-grade marginal zone lymphoma in the breast with massive amyloid deposition arising in a heart transplant patient: a report of an unusual case. Pediatr Transplant 2013;17:E141–E145
- Hwang JY, Cha ES, Lee JE, Sung SH. Isolated posttransplantation lymphoproliferative disease involving the breast and axilla as peripheral T-cell lymphoma. Korean J Radiol. 2013;14:718–722
- Law MF, Chan HN, et al. Burkitt-like post-transplant lymphoproliferative disorder (PTLD) presenting with breast mass in a renal transplant recipient: a report of a rare case. Ann Hematol. 2014;93:2083-2085.
- Jeppesen BM, Pommier RF, Troxell ML. Post-transplant lymphoproliferative disorder at the site of recurrent breast abscesses. Breast J. 2011 Sep-Oct;17(5):529-31.

SB 6220 (scanned slide available) Kelly Mooney/Dean Fong; Stanford

70-year-old man with hypertrophic cardiomyopathy and cardiac arrest. Section of autopsy heart submitted.
















Hydrophilic polymer emboli: an under-recognized iatrogenic cause of ischemia and infarct





MODERN PATHOLOGY (2010) 23, 921-930

Hydrophilic polymer: coating on common devices







Interventional catheters, aneurysm occlusion, stents

Lung



Right occipital cortex

Lung

MODERN PATHOLOGY (2010) 23, 921-930

Temporal cortex



Lung

Left foot

Lung

MODERN PATHOLOGY (2010) 23, 921-930

Frequency of clinical literature reports related to polymer coating embolism



A.M. Chopra et al. / Cardiovascular Pathology 30 (2017) 45-54

Our case

- Emboli confined to heart sections
- Patient also with: CLL, severe atherosclerotic calcification, and myocardium with dense fibrosis, prominent myocyte hypertrophy
- Cause of death: cardiac arrest
- No definite link between emboli and death

Issues with many reported cases

- Very ill patients, underwent interventions using various coated medical devices

 Patient in our case had pacemaker and stents
- Causative device(s) cannot definitively be identified
- Even in fatal cases, histologic findings subtle, involving scattered vascular channels <1 mm

- Below conventional imaging spatial resolution

FDA Safety Communication

Intravascular Medical Devices: FDA Safety Communication - Lubricious Coating Separation



Including medical devices such as intravascular catheters, guidewires, balloon angioplasty catheters, delivery sheaths, and implant delivery systems

[Posted 11/23/2015]

AUDIENCE: Risk Manager, Cardiology, Surgery, Radiology, Pathology

ISSUE: The FDA wants to make health care providers aware of the possibility that hydrophilic and/or hydrophobic coatings may separate (e.g., peel, flake, shed, delaminate, slough off) from medical devices and potentially cause serious injuries to patients. Coating separation can be caused by a number of factors, ranging from the difficulty of the procedure and the patient's anatomy to practitioner technique or using the wrong device for the procedure, to improper preconditioning of the device and improper storage conditions as well as issues with device design or manufacturing processes. Based on current information, the FDA believes the overall benefits of these devices continue to outweigh the risks. However, health care providers should be aware of potential problems and consider certain actions prior to use.

Possible solution

- Using lower-particulate-release lubricious coatings on intravascular devices
- 0% emboli rate in swine myocardium with low-particulate version of hydrophilic coating

Babcock DE, Hergenrother RW, Craig DA, Kolodgie FD, Virmani R. In vivo distribution of particulate matter from coated angioplasty balloon catheters. Biomaterials 2013; 34(13):3196–205.