CASE #1
Presenter: Brittany Cody, DO
Attending: Mark Pool, MD

CASE HISTORY: The patient is a 59-year old female who presented with a mass of the roof of her mouth for many years and reports 1 year maxillary pain, and only recent bleeding with clots and facial swelling. She initially presented to a dentist who performed an incisional biopsy which was reviewed at an outside institution. The patient was subsequently referred to an ENT at Rush. The patient denied significant past medical and social histories.

Physical exam was notable for a soft reddish 3x3cm mass which appeared to arise from the left palate and extend to the buccal and intrasinus regions.

CT scan was obtained and showed an enhancing mass measuring 6cm and involving the left nasal cavity, hard and soft palate, and eroding into the bone around the left premolar teeth as well as enlarged but subcentimeter left level II and IB region lymph nodes and a single 1.3cm right level IIA lymph node.

The patient underwent left nasal endoscopy for repeat biopsy.

After the diagnosis based on endoscopic biopsy was rendered, a left maxillectomy and left neck dissection was performed.

DIAGNOSIS: Invasive carcinoma with squamous and adenoid cystic features, likely representing a variant of squamous cell carcinoma

DIFFERENTIAL DIAGNOSIS:
- HPV-related multiphenotypic sinonasal carcinoma (previously known as HPV-associated adenoid cystic-like carcinoma)
- Adenoid cystic carcinoma
- Sinonasal nonkeratinizing squamous cell carcinoma
- Polymorphous low-grade adenocarcinoma
- SMARCB1-deficient carcinoma

DISCUSSION:
- p16 is seen in a variety of sinonasal tumors
  - Diffuse expression can aid in differentiation in some cases
- Many tumors of the sinonasal tract can have an adenoid cystic-like component
- Carcinomas of sinonasal tract are very heterogeneous and may have overlapping histology

- In the majority of cases, a definitive diagnosis can be rendered based on the morphology, IHC and molecular studies. However, there are selective cases where this is not possible. In cases such as these, we can offer a descriptive diagnosis and offer our best categorization of the disease.

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QUESTIONS:

1) Which of the following provides the best evidence for a diagnosis of HPV-related multiphenotypic sinonasal carcinoma?
   A. An adenoid cystic-like pattern
   B. Squamous differentiation
   C. Widely infiltrative lesion with rapid clinical course
   D. Diffuse p16 positivity
   E. Positive in situ hybridization for HR-HPV

2) Which entity would be most likely to have nests/sheets of basaloid cells showing strong CD117 positivity?

A. HPV-related multiphenotypic sinonasal carcinoma
B. Adenoid cystic carcinoma, solid type
C. Sinonasal nonkeratinizing squamous cell carcinoma
D. Polymorphous low-grade adenocarcinoma
E. SMARCB1-deficient carcinoma

ANSWERS: 1) E., 2) B.

CASE #2
Presenter: Waqas Mahmud, MBBS
Attending: Paolo Gattuso, MD

CASE HISTORY: A 62-year old Caucasian male was referred for bilateral femoral neck fractures. History of fall from a low lying chair 1 month ago resulted in groin and buttock pain that has been getting worse since onset, with severe pain limiting weight bearing. Patient also complains of right deep posterior buttock pain for 1.5 years worsening over same period. Pain radiates distally and thought it was associated with sciatica. MRI shows stress fracture of bilateral femur necks and a lobulated complex mass (2.7 x 3.4 x 6.9cm) medial to gluteus maximus muscle and deep to adductor magnus.

DIAGNOSIS: Phosphaturic mesenchymal tumor with prominent adipocytic component

DIFFERENTIAL DIAGNOSIS:
- Giant cell tumor of soft tissue
- Tenosynovial giant cell tumor

DISCUSSION:
- Exceptionally rare
- Paraneoplastic syndrome; Tumor induced osteomalacia (TIO) in most affected patients
- Produce fibroblast growth factor 23 (FGF-23) causing phosphaturia
- Can be found in any soft tissue or bone location (extremities common)
- Histologic features
  - Bland spindle to stellate cells
  - Hyalinized smudgy matrix
  - Well-developed capillary network
  - 'Grungy' calcifications in the matrix
  - Multinucleated giant cells, hemosiderin and hemorrhage
  - Immunohistochemistry is non-specific. Documented expression of FGF-23 by IHC and mRNA.

- FN1-FGFR1 Translocation in 46% patients
- Cured with complete excision

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QUESTIONS:

1) Due to the presence of large ‘ectatic’ vessels, phosphaturic mesenchymal tumors can be confused with?
   A. Pleomorphic angiectatic tumor
   B. Angiosarcoma
   C. Glomangiopericytoma
   D. Hemangiopericytoma
   E. Giant cell tumor

2) Occurrence of malignant phosphaturic mesenchymal tumor is associated with which of the following?
   A. Gender
   B. Size

C. Location
D. History of radiation
E. Recurrence

ANSWERS: 1) D., 2) E.

CASE #3
Presenter: Prih Rohra, MD
Attending: David Cimbaluk, MD

CASE HISTORY: A 44-year old female with a past medical history significant for hypothyroidism and gout presented with decreased urine output and acute renal failure. She described her urine as foamy with no hematuria. No prior history of kidney disease. Serological workup showed monoclonal IgA lambda in the urine. On admission the patient's serum creatinine level was 3.8 and continued to rise. Bone marrow biopsy showed plasma cell neoplasm involving 7% of marrow cells. A percutaneous kidney biopsy was performed to determine the etiology for the renal failure.

DIAGNOSIS: Crystalglobulinemia

DIFFERENTIAL DIAGNOSIS:
- Amyloidosis
- Fibrillary glomerulonephritis
- Monoclonal immunoglobulin deposition disease
- Cryoglobulinemia
- Lupus nephritis

DISCUSSION:
<u>Background</u>
- First described in 1938 in association with multiple myeloma and is one of the rarest manifestations of monoclonal gammopathy. True incidence of the disease is unknown.
- No clear risk factors have been identified.
- Has features of Type 1 and Type 2 cryoglobulinemia.
- Characterized by reversible crystallization of monoclonal immunoglobulins composed of both light and heavy chains below 37 C.

<u>Crystalglobulinemia</u>
- It is suggested that it occurs due to Fc-Fc interactions of IgG-type (in our case IgA) monoclonal protein, possibly due to abnormal glycosylation of the light chain portion of monoclonal protein or through interactions with albumin. These interactions are

enhanced by cooling and stasis in the systemic microvasculature, leading to crystal formation. The crystals formed lead to vascular endothelial damage and activation of coagulation cascade predisposing the patient to thrombosis, occlusive changes and subsequent ischemic injury.

Clinical Presentation

- Ulcerated and purpuric lesions, commonly in distal extremities
- Renal and intestinal small vessel involvement
- Peripheral neuropathy and polyarthropathy
- Corneal and bone marrow deposition

Renal Biopsy Findings

- Glomeruli with intracapillary eosinophilic thrombi occluding the glomerular capillary lumens, with mesangial expansion and hypercellularity. The thrombi are strongly positive for PAS stain. Electron microscopy shows these deposits have crystalline structure with an organized substructure forming lattice like pattern and periodicity of 20-30 nm.

Treatment

- No standard therapy.
- Steroids and thalidomide have been used for ulcers and renal dysfunction.
- Plasma exchange has shown symptomatic improvement.

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QUESTIONS:

1) A 53-year old man with a history of chronic obstructive pulmonary disease and alcoholism presented to a community hospital with a purpuric rash and anuria. In the last 7 months, the patient had multiple admissions for episodic acute respiratory distress and kidney failure requiring hemodialysis. His hospital course had been complicated by deep venous thrombosis, basal ganglia hemorrhagic stroke, sepsis, and monoclonal gammopathy of undetermined significance (MGUS). Approximately 1 week before admission, the patient developed obtundation, mucosal petechiae, and a diffuse nonpalpable purpuric rash extensively involving his scalp, face, trunk, and all extremities. A skin biopsy showed thrombotic vasculopathy with minimal neutrophilic inflammation and kidney biopsy showed glomeruli with intraluminal capillary thrombi which are strongly positive for PAS stain and EM showed a cluster of intratubular crystals with organized sub-structure. What is the diagnosis?
   A. Lupus nephritis
   B. Henoch-Schönlein Purpura
   C. Crystalglobulinemia
   D. Cryoglobulinemia
   E. Amyloidosis

2) Which of the following statements is correct?
   A. Crystalgobulinemia has better prognosis when associated with MM
   B. Crystalglobulinemia is one of the most common complication of MM
   C. Crystalglobulinemia has worse prognosis with MGRS
   D. Crystalglobulinemia has features of both Type1 and Type2 cryglobulinemia

ANSWERS: 1) C., 2) D.

CASE #4
Presenter: Karina Furlan, MD
Attending: Ira Miller, MD

CASE HISTORY: This is a 63-year old female with a chief complaint of erythema in the lateral aspect of her right breast. PMH: High cholesterol, essential hypertension, carcinoma with medullary features in the left breast 10 years ago; s/p bilateral mastectomies with placement of saline implants due to personal and family history of BRCA1 mutation (Deleterious mutation, W182X). Physical exam: Erythema in the lateral aspect right breast, no lymphadenopathy, no additional findings or symptoms. Core needle biopsy was performed showing sheets of large cells with necrosis in the background. Additional workup: PET scan showed disseminated disease. Resection of tumor, implant and capsule was performed, showing tumor in the outer surface of fibrous capsule. A section of the excision specimen is provided for review.

DIAGNOSIS: Breast implant-associated anaplastic large cell lymphoma

DIFFERENTIAL DIAGNOSIS:
- **Carcinomas**
  - Recurrent Carcinoma with Medullary Features, Poorly Differentiated Carcinoma
- **High grade round cell tumors**
  - Metastatic Melanoma, Pleomorphic Undifferentiated Sarcoma, Ewing sarcoma, Ewing-like sarcomas (CIC, B-COR and BAF mutations)
- **Aggressive Lymphomas**
  - B-cell lymphomas: Diffuse Large B-Cell Lymphoma, Pleomorphic Mantle Cell, Lymphoma, Lymphoblastic Lymphoma
  - T-cell lymphomas: Anaplastic Large Cell Lymphoma, PTCL NOS, EBV+, NK/T cell Lymphoma, Subcutaneous panniculitis-like T-cell Lymphoma

DISCUSSION:
- Anaplastic Large Cell Lymphomas are CD30+ T-cell lymphomas subdivided in ALK+ or ALK- lymphomas, depending on the expression of Anaplastic Lymphoma Kinase

- The initial clinical presentation is usually lymphadenopathy, however dissemination to different organs is not uncommon (systemic disease)
- A purely cutaneous form is described, usually ALK+. Microscopy shows sheets of large discohesive cells with variable amount of necrosis
- Abundant cytoplasm and pleomorphic horseshoe-shaped nuclei are commonly seen

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)

Background

- 4.93% of women in the US have breast implants. Possible complications: Contracture, Bacterial biofilm formation, Gram negative contaminants (Ralstonia spp)

Epidemiology

- Very rare disease, close to 500 cases have been reported in the literature so far. The great majority of the cases are localized; rarely disseminated disease can occur

Clinical presentation

- Median interval of 9 years between surgery and clinical findings, late "seroma" in seen in 2/3 of patients, tumor mass in 1/3 of patients.

Diagnosis

- Cytology
  - Large cells with pleomorphic and enlarged nuclei, prominent nucleoli with variable amount of cytoplasmic vacuoles
  - Since effusion (seroma) is the most common finding, cytology is an easy method of triage.
- Histology:
  - Large sheets of pleomorphic, discohesive cells with variable amount of necrosis in the background
  - Cells show abundant cytoplasm with increased N:C ratio and prominent nucleoli
  - Horseshoe-shaped nuclei is described (Hallmark cells)

Staging system

Tumor (T)	T1	Effusion confined to a layer on luminal side of capsule
	T2	Early capsule infiltration
	T3	Cell aggregates or sheets infiltrating the capsule
	T4	Lymphoma infiltrates beyond the capsule
Lymph node (N)	N0	No lymph node involvement
	N1	1 regional node involvement
	N2	>1 regional node involved
Metastasis (M)	M0	No distant spread
	M1	Spread to other organs/distant sites

Immunohistochemical stains

- Positive: CD30 (100%), CD43 (80%), CD4 (80%), CD3 (33%)
- Negative: ALK (100%)

Pathogenesis

- Bacterial biofilm infection in the surface of textured breast implants (Gram negative contaminant bacteria Ralstonia spp) was identified in BIA-ALCL cases
- When compared with negative controls, there was a significant difference in the cultured bacteria
- Smooth surface of breast implants is prone to infection by gram positive bacteria as Staphylococcus epidermidis

Genetics

- Recently it was demonstrated by IHC that STAT3 protein is expressed in BIA-ALCL
- The mechanism of activation seems to be associated with the chronic inflammation in response to the bacteria biofilm infection
- BIA-ALCL is known as a triple negative lymphoma since ALK, p63 or DUSP22 translocations have not been identified so far

Treatment

- Surgical removal of breast implant and capsule (curative in localized disease)
- Disseminated disease: Chemotherapy (Anthracycline-based) and radiotherapy
- Future directions: Antibody conjugate Brentuximab-vendotin and strategies to inhibit STAT3 pathway.

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QUESTIONS:

1) Which of the following loci is translocated in BIA-ALCL?
   A. ALK1,
   B. DUSP22,
   C. P63,
   D. BCL2,
   E. None of the above.

2) Which of the following is associated with breast implant associated anaplastic large cell lymphoma?
   A. A breast implant with a smooth surface
   B. A biofilm containing Staph aureus
   C. A biofilm containing mycobacterium marinum
   D. A biofilm containing Ralstonia species
   E. A high fat diet

ANSWERS: 1) E., 2) D.

CASE #5
Presenter: Jayjay Blanco, MD
Attending: Ritu Ghai, MD

CASE HISTORY: The patient is a 32-year old male with a significant past medical history of familial adenomatous polyposis status post total colectomy and J-pouch creation who presented to RUMC Emergency Department on September 28, 2018 with a chief complaint of shortness of breath over a period of 3 weeks. He has been treated with walking pneumonia with azithromycin with some improvement. In early October 2018, he reported to have increasing shortness of breath with associated substernal pressure/pain and intermittent feelings of lightheadedness. He was also noted to have minimal productive cough with clear sputum as well as 5-6 pounds of unintentional weight loss. He is currently a non-smoker but has a remote smoking history (<1 pack/day x 2 years).

In our emergency department, initial evaluation with a chest x-ray revealed a complete left lung white-out picture with right to left tracheal deviation and a chest CT scan demonstrating a large subcarinal mass with endobronchial extension causing a complete left main stem bronchus obstruction, most consistent with malignancy along with evidence of multiple right pulmonary nodules, small left pleural effusion with nodular opacities, and subacute and acute rib fractures.

On physical examination, a left testicular mass was noted. A testicular ultrasound was done as well as an abdominal/pelvis CT scan showed a heterogeneous mass lesion in the left testis concerning for testicular malignancy. Testicular markers were sent and showed an elevated LDH with normal AFP and beta HCG.

An inguinal orchiectomy was subsequently performed. Also, the patient underwent bronchoscopy with tumor de-bulking and stent placement. He also started bleomycin and cisplatin/etoposide chemotherapy.

DIAGNOSIS:
- Subcarinal/endobronchial mass: Poorly differentiated basaloid squamous cell carcinoma
- Left testicular mass: Collision tumor of metastatic poorly differentiated basaloid squamous cell carcinoma with primary Sertoli cell tumor

DIFFERENTIAL DIAGNOSIS:
- Primary squamous cell carcinoma of the testis arising from an epidermal cyst
- Secondary somatic-type malignancy arising from a teratoma
- Malignant mixed germ cell tumor
- Metastatic squamous cell carcinoma + minor component of a primary testicular tumor (Collision tumor)

DISCUSSION:

Testicular neoplasms

- 1% of all cancers
- Germ cell tumors (>90%); gonadal stromal tumors (~5%)
- 20 - 40 years old
- Majority of testicular neoplasms are primary tumors
- 6 - 7% of testicular neoplasms present as mass

Metastatic tumors of testis

Clinical Features

- Metastasis to the testis is extremely rare
- Majority > 40 years old
- Most frequent primary site → prostate (excluding lymphoma and leukemia) followed by lung, kidney and the GI tract
- Typically, presents as a complication of progressive/known disease or as a primary sign of malignancy
- Primary sign of occult disease → difficult to distinguish primary from secondary carcinoma of the testis
- Serum tumor markers (AFP, B-HCG) within normal limits provide useful information for differential diagnosis

Gross and Histology

- Localized mass, multiple nodules or diffuse enlargement of testis
- Usually unilateral and solitary (> 90%)
- Histologic and cytologic features recapitulate their site of origin; has an expansile growth pattern; prominent lymphovascular invasion

Additional discussion

- Testicular metastases from SCC of the lung have rarely been reported in literature
- Patel et al in 1989 □ > 200 cases from autopsies or orchiectomy specimens for treatment of prostate cancer
- 13 (6.2%) presented with testicular tumors, and had no lung cancer
- Most common primary: prostate (34.6%), lungs (17.3%)
- The reason why testicular metastases are so rare is unknown
- Smallman and Odedra: relatively low temperature of the scrotum □ unacceptable condition for the establishment of metastatic tumor cells
- Several metastasis routes have been postulated for the testes:
  - direct invasion from the adjacent lesions
  - retrograde venous embolism
  - arterial embolization
  - retrograde lymphatic extension from para-aortic lymph nodes
  - transperitoneal seeding
  - retrograde extension from the vas deferens

- Although testicular metastasis with widely disseminated disease may be not of much clinical significance
- Important that testicular metastasis be distinguished from a primary testicular tumor since management/therapy can differ

Treatment and Prognosis

- Surgical resection for palliative pain control
- Adjuvant therapy based on primary site and histology
- Generally has a poor prognosis

Sertoli cell tumor

- Pure sex cord-stromal tumor composed of Sertoli cells
- < 1%; most are sporadic
- Average 45 years old
- Gross: Small, well-circumscribed, homogeneous gray-white to yellow, firm mass
- Histology: Tubules, microcystic, solid cords and nests, and rarely spindled (sarcomatoid); Uniform cuboidal or columnar cells with moderate pale to lightly eosinophilic cytoplasm, often prominent cytoplasmic vacuoles; Bland round to ovoid nuclei, occasional centrally located nucleoli, and rare mitoses; May have paucicellular, hyalinized, vascular fibrous stroma, or lymphoid aggregates
- 12% of cases are malignant
- Features associated with malignancy are large size (> 5 cm) (range 2 - 18 cm), vascular invasion, marked nuclear pleomorphism, tumor necrosis, mitotic index > 5/10HPF
- Associated with Peutz-Jeghers, androgen insensitivity or Carney syndromes (Large cell calcifying type)
- Beta-catenin immunohistochemical stain is performed to confirm the Sertoli cell tumor component and shows both nuclear and cytoplasmic expression. The squamous cell carcinoma also displays nuclear and cytoplasmic positivity for beta-catenin, supporting a role for disruption of the canonical Wnt-signaling pathway, as occurs in colonic adenocarcinomas in FAP patients, in the pathogenesis/progression of the squamous cell carcinoma.

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QUESTIONS:

1) A 75-year old man presents with a 4.0 cm right testicular mass. Histologically, you suspect this to be an embryonal carcinoma, but your initial panel of immunohistochemical stains demonstrates the following results: PLAP-, OCT3/4-, CD30-, AE1/AE3+. After discussion with the clinical team, you learn the patient has a history of malignancy at another anatomic site. You therefore decide your second round of stains to include the following:
   A. S100, Melan-A
   B. CD45, CD20, CD3
   C. PSA, PSAP
   D. Hep-Par1, arginase-1
   E. WT-1, calretinin

2) A 25-year old man presents with a 2.3 cm right testicular mass. You review his prior surgical pathology specimen history of a previous excision of a cutaneous myxoma. The current testicular mass specimen is diagnosed as LCCSCT (Large Cell Calcifying Sertoli Cell Tumor). When writing the final report for the orchiectomy specimen, it is important to mention the possibility of which syndrome in the diagnostic comment?
   A. Carney complex
   B. Carney triad
   C. Mazabraud syndrome
   D. Von Hippel-Lindau disease
   E. Muir-Torre syndrome

ANSWERS: 1) C., 2) A.

CASE #6
Presenter: Josean Ramos, MD
Attending: Lin Cheng, MD, PhD

CASE HISTORY: A 78-year old female presented with abnormal chest CT scan during cancer surveillance. The patient had a significant past medical history including breast cancer at age 56 (s/p lumpectomy, then ipsilateral recurrence and mastectomy in 2002), colon adenocarcinoma (s/p right hemicolectomy in 2012), high-grade papillary urothelial carcinoma of the right renal pelvis (s/p right nephroureterectomy in 2016), desmoid tumor (followed conservatively), NASH cirrhosis, ITP, HTN, DM, thyroid nodules and hyperthyroidism. Her abnormal chest CT showed multiple small nodules in right middle and right lower lobes of lung,

highly suspicious for malignancy. The patient then received stereotactic body radiation therapy (SBRT) without histological diagnosis of the nodules. PET-CT upon completion of radiation therapy showed no significant hypermetabolic activity in the nodules. However, subsequent imaging studies showed that the size of one of the right lower lobe nodules had increased gradually. Therefore, the patient underwent a right lower lobe wedge resection by video-assisted thoracoscopic surgery (VATS). The H&E stained section of the nodule is provided for your review.

DIAGNOSIS: Papillary adenocarcinoma with prominent morule-like component

DIFFERENTIAL DIAGNOSIS:

- Metastatic tumors
  - High-grade papillary urothelial carcinoma
  - Colon adenocarcinoma
  - Breast cancer
  - Papillary thyroid carcinoma (with variants)
- Primary tumors
  - Pulmonary blastoma
  - Fetal adenocarcinoma of lung
  - Sclerosing pneumocytoma

DISCUSSION:

- Morule-like components appear as tight clusters of monomorphic bland-looking spindle cells within the adenocarcinoma component
- Differential diagnosis with squamoid morule-forming lesions should be considered
- Molecular studies should be performed for possible target therapy but should not rely on them for diagnosis.

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QUESTIONS:

1) What is the most common mutation seen in pulmonary adenocarcinoma with morule-like components?
   A. KRAS
   B. EGFR
   C. ALK
   D. BRAF
   E. ROS1

2) In which of the following entity beta-catenin immunohistochemical stain commonly shows membranous staining pattern?
   A. Pancreatoblastoma
   B. Pulmonary blastoma
   C. Fetal adenocarcinoma of lung
   D. Pulmonary papillary adenocarcinoma with morule-like component

ANSWERS: 1) B., 2) D.