Northwestern University Post IRAP Discussion
April 25, 2022

Case 1: (Dr. Megan Kinn): Lipoblastoma-like Tumor of the Vulva

Clinical History: The patient is a 40-year-old female with a history of endometriosis who presented with recurrent pelvic pain. CT abdomen/pelvis from an outside hospital revealed "something on the bladder." She was treated for interstitial cystitis and referred for pelvic floor physical therapy. Her pain persisted, and repeat CT abdomen/pelvis revealed an incidental tubular serpiginous fluid density lesion within the right labia majora. Follow-up MRI of the pelvis demonstrated a mildly enhancing 7.9 x 2.5 x 2.7 cm T2 hyperintense tubular lesion in the right labia majora, with an apparent small tract extending to a small caliber vessel at the anterior aspect of the vagina. She underwent left pudendal nerve block for pain control, followed by embolization for suspected AV malformation. The mass persisted, and she underwent surgical excision.

Gross and microscopic findings: Grossly, the lesion is yellow-tan and lobulated. Microscopically, the lesion is composed of lobules of adipocytes of varying sizes separated by thin and thick fibrous septae. The background is myxoid to collagenous, with areas of ropy collagen. Delicate, thin-walled vasculature is also seen. The tumor cells consist of short, bland spindled cells, as well as numerous uni- and bivacuolate lipoblasts. Intermixed mature adipocytes are also present.

Differential Diagnosis:
- Lipoblastoma
- Myxoid liposarcoma
- Spindle cell lipoma
- Lipoblastoma-like tumor of the vulva

Ancillary Studies:
- **IHC:** CD34 is positive in a subset of tumor cells, desmin is negative in tumor cells, and Rb1 shows patchy weak to negative staining in tumor cells
- **Molecular:** MDM2 FISH is negative

Discussion: Lipoblastoma-like tumor of the vulva (LLTV) is a benign mesenchymal neoplasm with adipocytic differentiation that was first reported in 2002. Overall, fewer than 20 cases have been reported in the literature. This entity occurs in reproductive age women, with a median age of 27 years. Patients typically present with an enlarging vulvar or groin mass that can be painful, and clinically can be mistaken as a Bartholin gland abnormality.

Grossly, the tumor is yellow-tan and lobulated with a myxoid or gelatinous cut surface, and ranges from 2-15 cm, with a median size of 5.6 cm. Histologic evaluation reveals a relatively well-delineated lesion composed of large lobules separated by thin to thick septae. The lobules are composed of variable proportions of mature adipocytes, bland uni- and bivacuolated lipoblasts, and bland spindle cells with short, stubby nuclei and eosinophilic fibrillary cytoplasm. The background is myxoid with variable stromal collagenization, and there is

prominent arborizing, thin-walled vasculature. There should be no necrosis, and no significant cytologic atypia or mitoses.

Morphologically, lipoblastoma-like tumor of the vulva has features of lipoblastoma, myxoid liposarcoma, and spindle cell lipoma, all of which should be considered in the differential diagnosis. Ancillary studies can be very helpful in ruling out these entities. LLTV lacks *PLAG1* and *HMGA2* alterations by FISH and microarray, which are commonly seen in lipoblastoma. LLTV also lacks *DDIT3 (CHOP)* rearrangements by FISH and microarray, which are seen in nearly all myxoid liposarcomas. Spindle cell lipomas are typically diffusely CD34 positive, and show loss of nuclear retinoblastoma (Rb1) expression by immunohistochemistry. FISH and microarray studies in spindle cell lipomas show 13q deletion, corresponding to loss of the *Rb1* gene. LLTV, on the other hand, lacks 13q structural abnormalities by FISH and microarray, and shows a mosaic pattern of weak and negative nuclear expression of Rb1 by immunohistochemistry.

LLTV is managed with surgical excision. Local recurrence has been reported in a few cases, typically associated with tumor involvement of the resection margin. Metastasis has not yet been reported.

In summary, LLTV is a rare benign mesenchymal neoplasm with adipocytic differentiation that occurs in reproductive age females. The lesion has morphologic features of lipoblastoma, myxoid liposarcoma, and spindle cell lipoma, but it is genetically distinct. It is important to recognize this benign entity in order to avoid misclassification and overtreatment.

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4. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 3)

Questions:

1. Which of the following describes the staining pattern of Rb1 in lipoblastoma-like tumor of the vulva?
    a. Cytoplasmic positivity
    b. Nuclear positivity

c. Mosaic pattern of weak to negative nuclear staining
d. Complete loss of nuclear staining
e. None of the above

2. Which of the following molecular alterations can be seen in lipoblastoma-like tumor of the vulva?

a. *FUS::DDIT3 (CHOP)*
b. *PLAG1* rearrangements
c. Deletion 13q
d. A and C
e. None of the above

3. Which of the following statements is true regarding lipoblastoma-like tumors of the vulva?

a. LLTV are usually < 2 cm in greatest dimension.
b. LLTV can occur in females of all ages, but is more common in women > 50 years of age.
c. The spindle cells in LLTV are reactive (non-neoplastic).
d. LLTV is composed of neoplastic spindle cells and lipoblasts.
e. LLTV is an infiltrative lesion with areas of necrosis and elevated mitotic activity.

<u>Case 2 (Sam Weinberg):</u> Burkitt-like lymphoma with 11q aberration

Clinical History:
The patient is a 21-year-old male who noticed intermittent swelling in the left groin for a few months. Imaging performed at that time showed a possible enlarged lymph node that was 3.05 x 1.8 cm. Repeat imaging ~6 months later revealed increasing lymph node enlargement (5 cm x 5cm) with new mediastinal, hilar and cervical lymphadenopathy. Ultra-sounded guided biopsy of the enlarged inguinal lymph node was performed to evaluate for a possible malignancy.

Microscopic Findings:
Sheets of medium to large, atypical lymphocytes with large nuclei and a moderate amount of cytoplasm. Frequent apoptotic bodies and mitotic figures are seen, and scattered tingible body macrophages are also present, resulting in a "Starry-sky" appearance.

Initial Immunohistochemical Staining:

Stain	**Result**
CD3	Scattered positive T cells
CD20	Positive in large, atypical lymphocytes
CD10	Positive in large, atypical lymphocytes
BCL6	Positive in large, atypical lymphocytes
BCL2	Negative in large, atypical lymphocytes. Positive in T cells
Ki67	Positive in virtually all large, atypical lymphocytes.

Differential Diagnosis:
- Burkitt lymphoma
- Diffuse Large B cell lymphoma, NOS
- High-grade B cell lymphoma with Myc, BCL2 and/or BCL6 rearrangements
- Burkitt-like lymphoma with 11q aberration

Ancillary Studies:

Test	**Result**
Myc IHC	Variably positive in large, atypical lymphocytes. ~40-50% overall
Eber ISH	Negative
FISH for t(8,14)	Negative
FISH for MYC rearrangements	Negative
Microarray	Positive for aberration on chromosome 11q with proximal amplification and distal (telomeric) deletion.

Discussion:
The patient in the case presented with initial morphologic and immunophenotypic findings consistent with Burkitt lymphoma, including a morphologic "starry-sky" appearance and an immunophenotype of a CD10+, BCL6+, BCL2- B cell lymphoma with virtually every cell

showing Ki67 positivity. Further workup, however, revealed atypical features, including variable Myc positivity and lack of an identifiable MYC rearrangement. Importantly, this is a relatively common clinical scenario as ~10% of morphologically defined Burkitt lymphoma's lack an identifiable MYC rearrangement. The lack of identifiable MYC rearrangements is partly due to the lack of a diagnostic test that can identify all MYC rearrangements and because multiple B cell lymphomas can present with Burkitt-like morphology. Historically, this group included high-grade B cell lymphoma with morphology between Burkitt and diffuse large B cell lymphoma (DLBCL) and DLBCL (Gray zone), NOS. There is no grey zone lymphoma in the current WHO guidelines; instead, this entity has been replaced with high grade B cell lymphoma, which is further defined by the presence of MYC, BCL2 and/or BCL6 rearrangement. Further testing was performed in this case, and whole genome microarray profiling revealed an aberration in chromosome 11q. This finding allowed for a diagnosis of the provisional WHO entity Burkitt-like Lymphoma with 11q aberration. This entity is defined by Burkitt-like morphology and immunophenotype in the absence of an identifiable MYC rearrangement, which instead shows alterations to 11q with proximal gain and distal (telomeric) loss. Recent work has suggested that in MYC-rearrangement negative lymphomas with Burkitt-like morphology, this 11q aberration may be identified in up to 50% of the cases. Thus, microarray is an essential test for all cases of Burkitt-like morphology that lack classic immunohistochemical or FISH-based findings. At this juncture, the clinical features of Burkitt-like lymphoma with 11q aberration are relatively unclear. However, early studies suggest that these behave more similarly to classic Burkitt Lymphoma than DLBCL and are currently treated similarly to classic Burkitt lymphoma at our institution.

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Questions:

1) A 21-year-old patient presents with a rapidly increasing cervical lymph node. Biopsy reveals a high-grade B cell lymphoma that is CD10+, BCL-6+, BCL-2-, MYC-, >95% Ki-67+, and Eber-. Cytogenetic studies are negative for MYC, BCL2 and BCL6 rearrangements. What additional testing should be ordered in this case?

a) Next Generation Sequencing
b) BCR Clonality Assessment
c) Microarray genotyping
d) Cytogenic analysis
e) No further testing is needed.

2. Which of the following translocations is classically associated with Burkitt Lymphoma?

a. t(8;14)(q24;q32)
b. t(11;14)(q13;q32)
c. t(14;18)(q32;q21)
d. t(9;22)(q34;q11)

3. Which of the following clinical features is commonly seen in Burkitt-like lymphoma with 11q aberration?

a. Indolent Course
b. Multiple cytogenetic abnormalities
c. Occurs predominantly in older patients
d. Typically presents with diffuse lymphadenopathy

Case 3: (Dr. Yevgen Chornenkyy): High grade/undifferentiated carcinoma with dominant rhabdoid/ plasmacytoid feature (INI1/SMARCB1-deficient carcinoma)

Clinical History: The patient is a 25-year-old male with no past medical history presenting with severe anemia (Hb 3.5) and severe fatigue. Endoscopy demonstrated an oozing duodenal ulcer. The patient underwent a CT Abdomen Pelvis demonstrating a 7.1 x 4.3 cm partially necrotic pancreatic head-neck mass, eroding the stomach and duodenum. The mass was encasing main portal vein, celiac trunk, and proximal celiac arterial branches. He underwent a biopsy to characterize the lesion

Microscopic findings: On low power the biopsy demonstrated solid sheets of cells with monotonous plasmacytoid / rhabdoid morphology. On higher power the cells contain eosinophilic cytoplasm, irregular nuclear contours, and prominent nucleolus. There is a vague vascular / luminal architecture.

Differential Diagnosis:

- Pancreatic ductal adenocarcinoma, undifferentiated
    - SMARCB1/INI1-deficient undifferentiated carcinoma
- Metastatic adenocarcinoma and melanoma
- Acinar cell carcinoma, solid pattern
- Angiosarcoma
- Gastrointestional stromal tumor
- Epithelioid sarcoma, proximal type
- Alveolar rhabdomyosarcoma

Ancillary Studies:

- **IHC:** Tumor cells are diffusely positive for AE1/AE3, CK19, SMAD4, Cam5.2, Vimentin, and demonstrate nuclear and cytoplasmic loss of INI1/SMARCB1
- **Molecular:** PTEN deletion, MSH2 p.(R214I), SETD2 p.(T592K)

Discussion: SMARCB1 is the core subunit of the SWI/sucrose non-fermenting (SNF) ATP-dependent chromatin remodeling complex located on the long arm of chromosome 22 (22q11.2). The SWI/SNF ATPase subunit genes are frequently mutated and specific types of human cancers. For example, SMARCB1 mutations are found in rhabdoid tumors, while SMARCA4/2 mutations are found in pancreatic cancer, medulloblastoma, lung adenocarcinoma, and Burkitt's lymphoma. The list of reported SMARCB1-deficient neoplasms is growing and includes cancers from various organ sites, including undifferentiated pancreatic rhabdoid carcinoma, that contains prominent rhabdoid features. Approximately, 28% of these cases have SMARCB1 loss and 25% have KRAS alterations.

The undifferentiated gastrointestinal carcinomas (UGCs), is a recently recognized group of carcinomas demonstrating a morphological spectrum that ranges from pure rhabdoid to poorly differentiated (solid-pattern) adenocarcinoma appearance. These tumors show loss of SMARCB1 and are frequently associated with microsatellite instability and loss of mismatch-repair proteins as a background genotype. This suggests that SMARCB1 loss is a secondary molecular

event. In cases with intact SMARCB1, other genes in the SWI/SNF complex, including SMARCA4 and SMARCA2, play a role in pathogenesis.

Supporting this, recently published paper by Agaimy et al, evaluated 13 cases of SWI/SNF complex-deficient undifferentiated/rhabdoid carcinomas of the gastrointestinal tract. They found that these neoplasms contain mutually exclusive loss of SMARCA4 and SMARCA2 and frequent co-inactivation of SMARCB1 and SMARCA2. The histology of these neoplasms consists of anaplastic large cells and rhabdoid cells, but could also include spindle cells, and most cases were Pan-CK was positive, with absent CK7, CK20, CDX2, p63 staining.

The UGCs includes the undifferentiated rhabdoid carcinoma of the pancreas (which are SMARCB1/INI1 deficient), is a very rare neoplasm with fewer than 100 cases reported. According to the WHO classification system, these tumors fall within the broad category of sarcomatoid undifferentiated carcinoma. Agaimy et al further subtype undifferentiated rhabdoid carcinomas into 2 groups. The pleomorphic variant tends to have KRAS alterations, while the monomorphic variant tends to be SMARCB1/INI1 deficient.

There is a lack of data informing optimal management of these neoplasms. Surgery is the treatment of choice and chemotherapy is generally chosen based on extrapolation for pancreatic ductal adenocarcinoma. FOLFIRINOX being 1st line, and nab-paclitaxel or gemcitabine-capecitabine being second line. Reported overall survival ranges from 1 to 9 months.

Key Learning Points:

- Rhabdoid Tumors can develop secondary to dysregulation of SWI/SNF chromatin remodeling complex – of which SMARCB1, SMARC4 and SMARC2 are components
- In the GI Tract these are putatively classified "SWI/SNF Complex-deficient Undifferentiated/Rhabdoid Carcinomas of the Gastrointestinal Tract"
- IHC for SMARCB1/INI1 Loss and molecular analysis is helpful for ruling in/out this neoplasm
- Treatment and outcomes are poorly characterized – as the neoplasm is very rare

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7. WHO classification of Tumors: Digestive System Tumors

Questions:

1. What is the most common SWI/SNF subunit mutated in the undifferentiated gastrointestinal carcinomas?
   A. SMARCA2
   B. SMARCA3
   C. SMARCA4
   D. SMARCB1
   E. SMARCD1
2. What is the most common morphology of undifferentiated gastrointestinal carcinomas?
   A. Papillary, anaplastic, with nuclear inclusions and grooves
   B. Vascular lesion with anaplastic and hobnailed cells
   C. Three components, intermediate cells, epidermoid cells, and mucocytes
   D. Patternless pattern with long sweeping fascicles
   E. Monotonous rhaboid/monocytoid morphology with prominent nucleoli

3. In undifferentiated gastrointestinal carcinomas, the association of microsatellite instability and loss of mismatch-repair proteins with SMARCB1 most likely suggests which of the following conclusions?
   A. SMARCB1 loss is a primary event
   B. SMARCB1 loss is a secondary event
   C. SMARCA4 and SMARCA2 are lost when SMARCB1 is intact
   D. These cancers lose INI1/SMARCB1 nuclear and cytoplasmic staining by IHC
   E. Pancreatic ductal adenocarcinomas are more aggressive than undifferentiated gastrointestinal carcinomas

<u>Case 4 (Dr. Erik Pearson)</u>: Intracranial Solitary Fibrous Tumor

Clinical History: The patient is a 65-year-old woman with history of medial sphenoid wing meningioma removed 12 years ago. In 2015, she noted diplopia, lid lag, and paresthesia of the right face.
MRI revealed an apparent recurrence of her meningioma. She underwent surgical resection of the mass.

Imaging and microscopic findings: The 2015 MRI showed surgical changes from the previous surgery and an extra-axial mass with presumed enhancement, centered at the right greater wing of the sphenoid bone with involvement of the right orbital apex and extension into the orbit. The mass also had a small nodular protrusion seen within the right sphenoid sinus which had increased in size. Microscopically, the mass is hypercellular consisting of ovoid to spindle cells arranged haphazardly. The background is collagenous with extravasation of erythrocytes. Medium and high power views show hyalinized vessels and prominent branching of vessels ("staghorn vessels"). The cells are monomorphic with vesicular chromatin. There are 9 mitoses per 10 high power fields.

Differential Diagnosis:
- Mesenchymal chondrosarcoma
- Monophasic synovial sarcoma
- Atypical meningioma
- Solitary fibrous tumor

Ancillary Studies:
- CD99 positive
- Reticulin envelops individual cells
- EMA negative
- CD34 negative

Discussion: Intracranial solitary fibrous tumor accounts for less then 1% of all primary CNS neoplasms. Atypical meningioma was the obvious consideration given the patient's history of meningioma; however, the morphology and IHC staining were only compatible with solitary fibrous tumor. IHC in particular confirmed the diagnosis. CD99 staining, negativity for EMA, and individual envelopment of tumor cells with reticulin are inconsistent with meningioma. CD34 is expected to be diffusely positive in SFT; however, the CNS WHO explicitly states that CD34 is often lost in higher grade tumors. The diagnosis in 2015 was made substantially more difficult by lack of IHC for STAT6, which is highly sensitive and specific for SFT, and by lack of IHC for somatostatin receptor (SSTR2A), which is highly sensitive and specific for meningioma. Another interesting feature of this case was the wording of the 2015 diagnosis: "anaplastic hemangiopericytoma, WHO grade 3." The terminology has since changed to "solitary fibrous tumor" and would now be considered grade 2.

After resection, the patient had radiation therapy. Surveillance MRI in Feb 2020 showed an extra-axial mass centered in the right inferior orbital fissure. She received 2 rounds of radiation to this area. In Jan 2022, she was discovered to have a new left pleural mass that was biopsied.

The new mass showed very similar morphology to the 2015 resection including a similar mitotic count. Additionally, the new lesion stained with IHC for STAT6 and was a 100% match for solitary fibrous tumor using DNA methylation profiling, leading to a diagnosis of metastatic solitary fibrous tumor.

Intracranial solitary fibrous tumors were called hemangiopericytoma prior to 2016 when the CNS WHO introduced the term "solitary fibrous tumor/hemangiopericytoma (SFT/HPC)." Currently, the 2021 CNS WHO prefers the term "solitary fibrous tumor". Most are dural-based and often supratentorial although about 10% are spinal. Uncommon locations include the cerebellopontine angle, the pineal gland, and the sellar region. The cell of origin and histogenesis are still unknown; however, the fibroblastic nature and characteristic NAB2-STAT6 fusion which is formed by paracentric inversion of 12q13 suggest that intracranial and extracranial SFT should be grouped together. Multiple fusions of NAB2 and STAT6 are possible, but the STAT6 protein is almost always expressed. This creates a rare situation in which IHC is more specific than FISH. The current research regarding intracranial SFT centers on prognosis. Two large studies have recently shown that a combination of mitotic count and presence of necrosis are the most predictive of outcomes; thus, the current grading is grade 1: < 5 mitoses/10 hpf; grade 2: > or equal to 5 mitoses/10 hpf without necrosis; grade 3: > or equal to 5 mitoses/10 hpf with necrosis. The soft tissue CNS does not yet have consensus on a single grading scheme and suggests the use of one of several risk calculators.

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Questions:

1. Which of the following is correct regarding the current WHO terminology for SFT?
    a. The WHO CNS preferred terminology is "solitary fibrous tumor/hemangiopericytoma (SFT/HPC)".
    b. The WHO CNS recommends distinguishing solitary fibrous tumor and hemangiopericytoma based on morphology.
    c. The WHO CNS prefers "hemangiopericytoma", while the WHO soft tissue prefers "solitary fibrous tumor".
    d. Both the WHO CNS and WHO soft tissue prefer "solitary fibrous tumor".

2. Which IHC markers are currently considered most useful in diagnosis of solitary fibrous tumor and meningioma?
    a. SFT – CD34; meningioma – EMA
    b. SFT – STAT6; meningioma – EMA
    c. SFT – STAT6; meningioma – SSTR2A
    d. SFT – CD34; meningioma – SSTR2A

3. Which of the following is true regarding grading of SFT?
    a. WHO CNS and WHO soft tissue use the same grading system.
    b. WHO CNS grading is based on mitoses and necrosis.
    c. WHO CNS and WHO soft tissue grading are only based on mitoses.
    d. WHO CNS grading is only based on mitoses but WHO soft tissue grading is based on mitoses and necrosis.

<u>Case 5 (Dr. Taylor Zak):</u> Ossifying fibromyxoid tumor

Clinical History: 43 year old male with slowly enlarging right foot mass. MRI of the foot showed a 7 cm lobulated mass located in the lateral plantar aspect of the foot with appearance worrisome for sarcoma. The patient underwent surgical excision of the mass.

Gross and microscopic findings: Grossly the tumor was a multi-lobulated relatively well circumscribed mass with a relatively homogeneous cut surface. Microscopically, the tumor showed variably cellular nests and cords of bland epithelioid spindle cells embedded in a predominantly fibrous matrix. Other areas showed vague myxoid matrix. Increased mitotic figures of 9-19 per 10 high power fields were observed. Necrosis was not identified.

Differential diagnosis:

- Myoepithelioma
- Ossifying fibromyxoid tumor
- Sclerosing epithelioid fibrosarcoma
- Epithelioid malignant peripheral nerve sheath tumor
- Epithelioid schwannoma
- Extraskeletal myxoid chondrosarcoma

Ancillary Studies:

- **IHC:** Tumor cells were focal positive for Keratin AE1/AE3, Desmin, EMA, CD34, and SMA, diffusely positive for CD10, and negative for HMB45, S100, STAT6, MyoD1, and MUC4, and INI1 was retained.
- **Sarcoma targeted gene fusion panel**: *MEAF6::PHF1* fusion identified

Discussion: Ossifying fibromyxoid tumor (OFMT) is a rare tumor of uncertain differentiation. These tumors most frequently arise in deep tissues of the extremities, with more than 40% of cases occurring in the lower extremity. OFMT was a wide range of ages at presentation, with cases reported between 5 and 88 years old with a median age of 50 years. Tumors usually present as a painless slow growing mass. Imaging may show a peripheral rim of bone or calcification. Microscopically, tumors show a well circumscribed lobulated architecture with nests, cords, and sheets of epithelioid spindle cells embedded in a variably fibrous or myxoid stroma. Typically, mitotic count is low, but may be elevated in malignant cases. OFMT can show a relatively unique immunohistochemical profile including S100, Desmin, and CD10 co-positivity. INI1 expression is lost in the majority of cases. 85% of OMFT exhibit a gene fusion, with *PHF1* being the most commonly involved gene. A malignant subtype has been proposed with the criteria for malignancy including high nuclear grade or >2 mitosis per 10 HPF. Treatment is with surgical excision and recurrence rates are between 10 and 20%.

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Questions:

1. What gene is most commonly rearranged in Ossifying fibromyxoid tumor?
    a. *NTRK*
    b. *PHF1*
    c. *EWSR1*
    d. ETV6
2. A patient is diagnosed with ossifying fibromyxoid tumor based on morphologic, immunohistochemical, and molecular studies. Which of the following would classify this tumor as malignant subtype.
    a. Tumor necrosis
    b. presence heterologous elements including bone
    c. Loss of INI1 expression
    d. >2 mitosis per 10 HPF
3. Which of the following immunohistochemical profiles is most consistent with ossifying fibromyxoid tumor?
    a. S100+, Desmin +, INI1 lost
    b. S100-, Desmin -, INI1 lost
    c. S100+, Desmin -, INI1 retained
    d. S100-, Desmin -, INI1 retained

Case 6: (Dr. Zachary Coty-Fattal): High grade renal cell carcinoma, most consistent with papillary RCC, with admixed extramedullary hematopoesis

Clinical History: The patient is a 63-year-old man with a past history of HIV on HAART with a detectable viral load and acute myeloid leukemia (IDH1, SRSF2, RUNX1, TET2, PHF6, and CEBPA mutant). His AML was originally diagnosed 6 months ago. He was treated with 7+3 chemotherapy regimen. A follow-up bone marrow biopsy one month later revealed AML with 81% blasts. He was then treated with Ivosidenib. While undergoing a workup for a stem cell transplant, a 1.6 cm right renal mass was noted on MRI. The renal mass had a small area of enhancement concerning for a neoplastic process.

Microscopic findings: The tumor was comprised of small clusters of gland forming cells with a separate non-epithelial component. The epithelial component was composed of cells with medium to large nuclei with relatively smooth nuclear contours, dispersed chromatin, variably prominent nucleoli, and moderate to ample pale to eosinophilic cytoplasm. The non-epithelial component consists of a variety of cells with myeloid, erythroid, and megakaryocytic differentiation without mitoses or necrosis.

Differential Diagnosis:

- Epithelial component:
    - Clear cell renal cell carcinoma
    - Clear cell papillary renal cell tumor
    - Papillary renal cell carcinoma
- Non-epithelial component
    - Myeloid sarcoma
    - Extramedullary hematopoesis

Ancillary Studies:

IHC: The epithelial cells were diffusely positive for AMACR, CK7, and CD10, and negative for CA-IX, TFE3, C-and KIT/CD117. The non-epithelial component was negative for C-KIT/CD117 and CD34. There were scattered cells positive for myeloperoxidase, CD3, and CD20.

Molecular: Sanger sequencing was negative for IDH1/IDH2 mutations.

Discussion: Epithelial renal neoplasms can be fairly easily differentiated by their expression of various immunohistochemical stains. Clear cell renal cell carcinoma is positive for CD10, and CA-IX (box-like) and is negative for expression of CK7 with variable AMACR expression. Papillary renal cell carcinoma is positive for CD10, AMACR, and CK7 with variable expression of CA-IX. Clear cell papillary renal cell tumor is positive for CK7 and CA-IX (cup-like), and is negative for CD10 and AMACR.

Immunohistochemically, myeloid sarcomas are a very heterogenous group of tumors. They frequently show positivity for CD68 KP1, CD33, and CD43. They also occasionally show positivity for CD45, MPO, and CD117. The remaining immunohistochemical profile varies greatly from case to case. They also will frequently show molecular alterations that are classical for acute myeloid leukemia. Importantly, myeloid sarcomas will almost always have overlapping molecular alterations when associated with an acute myeloid leukemia.

There have been several recent changes to the WHO classification of renal neoplasms. Firstly, the diagnosis of clear cell papillary renal cell carcinoma has been changed to clear cell papillary renal cell tumor. This is due to the low-grade nature of the lesion, without reported metastases and with a relatively indolent clinical course. The second important change was to the classification of papillary renal cell carcinoma. In the previous editions of the WHO classification of tumors, papillary renal cell carcinoma was divided into type 1 and type 2 based on morphologic and molecular features. Type 1 showed a single layer of small eosinophilic cells with scant cytoplasm, and showed frequent trisomies with occasional loss of X and Y chromosomes. Type 2 is composed of pseudostratified cells with more ample cytoplasm and more cytologic atypia. These tumors had a more heterogenous mutational profile. In the most recent WHO update, many of these tumors were shown to be TFE3 mutant, and thus were classified into the new grouping of "molecularly defined renal cell neoplasms."

In summary, renal epithelial neoplasms can be fairly easily distinguished based on their immunohistochemical profile. There were several important changes in the 2020 WHO classification of renal neoplasms. These included the change of clear cell papillary renal cell carcinoma to clear cell papillary renal cell tumor, and the removal of the type 1 and type 2 division in papillary renal cell carcinoma, as well as the reclassification of many renal cell neoplasms into the "molecularly defined renal cell neoplasms."

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Questions:

1. An epithelial renal cell neoplasms shows cup-like staining with CA-IX. What is the most appropriate diagnosis for this tumor?
    a. Clear cell renal cell carcinoma
    b. Clear cell papillary renal cell carcinoma
    c. Clear cell papillary renal cell tumor
    d. Papillary renal cell carcinoma

2. A patient has a renal neoplasms composed of pseudostratified epithelial cells with ample cytoplasm and cytologic atypia. A sample of the tumor is sent for next generation sequencing, and shows no mutations. Karyotyping shows a gain of chromosome 7, 17 and 20. What is the most appropriate diagnosis?
    a. *TFE3*-associated renal cell carcinoma
    b. Clear cell renal cell carcinoma
    c. Papillary renal cell carcinoma, type 2
    d. Papillary renal cell carcinoma

3. A patient has a past history of IDH1 mutant acute myeloid leukemia. They present with a mass in the retroperitoneum that is composed of large atypical cells with scant cytoplasms and nuclear atypia. A sample is available for next generation sequencing. What molecular alteration is most likely present?
    a. *TP53*
    b. *NPM1*
    c. *KMT2A*
    d. *ASXL1*
    e. *IDH1*

Answer Key

Case 1:
1)C
2)E
3)D

Case 2:
1) C
2) A
3) B

Case 3:
1)D
2)E
3)B

Case 4:
1)D
2)C
3)B

Case 5:
1)B
2)D
3)A

Case 6:
1)C
2)D
3)E