Case #1

PRESENTER: Kritika Prasai, MBBS
ATTENDING: Hussein Alnajar, MD; Nicole Cipriani, MD

CASE HISTORY:
The patient is a 43-year-old female with a past medical history of Hashimoto thyroiditis. She presented with a self-palpable lump in her neck for the last 1 month with no associated pain. Ultrasound of the neck showed a lobulated, hypoechoic mass measuring 2.4 cm in the left lower thyroid. Patient underwent fine needle biopsy followed by near-total thyroidectomy and central neck dissection

Final diagnosis: Secretory carcinoma of Thyroid gland

Discussion:
Secretory carcinoma of thyroid gland (SCT) is a relatively new and a rare entity with only 12 cases reported in literature. It was first reported by Dogan et al, in 2016 in a case series. The name itself is based on the histomorphology and immunophenotype of the tumor that strongly resemble the well-established secretory carcinoma of the breast and the salivary gland. Moreover, SCT has been exclusively linked to ETV6-NTRK3 fusion, making this mutation a pathognomonic feature for this entity.

Histomorphology of SCT include variable architectural pattern with microcystic, papillary, solid and cribriform growth. The infiltrative tumor is surrounded by dense collagenous stroma. Other features include intraluminal and/or intracytoplasmic eosinophilic secretion that stain for PAS, MUC1, MUC4 and mammaglobin. Along with, abundant eosinophilic, vacuolated cytoplasm and round to elongated nucleus with nuclear grooving, membrane irregularities and prominent nucleolus. Features of papillary growth pattern along with nuclear features that often times resemble papillary thyroid carcinoma (PTC) makes it very difficult to differentiate SCT from PTC. Few key differentiating features include the characteristic cytoplasm of SCT, the inverse staining pattern of TTF-1 and Thyroglobulin with PTC being positive for both immunostains and SCT staining negative while staining positive for Mammaglobin, GCDFP-15 and GATA 3.

PTC has also been linked to NTRK fusion. This has made the identification even more complicated, since NTRK-rearranged PTC as well as SCT will share the same mutation related common features like mixed multinodular tumor pattern, extensive lymphvascular invasion and cervical lymph node metastasis. Overall NTRK fusion related thyroid cancers (NRTC) tend to be more aggressive with high metastatic rate. NRTC represent about 2.3% of total thyroid carcinoma. It has been reported in both radiation exposed as well as radiation naïve patients. Although, PTC is the most commonly reported NRTC, there are reports of PTC combined with poorly differentiated thyroid carcinoma as well as anaplastic thyroid carcinoma with NTRK1 fusion.

The recent FDA approval of tumor agnostic therapy with Larotrectinib (2018) and Entrectinib (2019) in patients with NTRK gene fusion-positive solid tumors has been of great significance. Larotretinib which is a TRKA, TRK B and C ATP-competitive inhibitor, Entrectinib small molecule inhibitor of TRKA, TRKB, TRKC, ROS1, ALK, JAK2, and ACK1 kinases are highly selective agents that have shown promising results with significant disease burden reduction and few case with no evidence of disease post therapy.

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Case #2

PRESENTER: Josh Wodskow, DO
ATTENDING: Ajit Paintal, MD

CASE HISTORY:

The patient is a 45-year-old female with a past medical history of hypertension and hyperlipidemia. She presented to her OB/GYN with vague intermittent left upper quadrant pain felt over the course of 4 months with bloating and early satiety. CT scan of abdomen and pelvis showed an 18.0 cm solid and cystic mass in the tail of the pancreas. A distal pancreatectomy was performed.

FINAL DIAGNOSIS:

- Pancreatoblastoma with extensive necrosis

DIFFERENTIAL DIAGNOSIS:

- Solid pseudopapillary tumor
- Mixed neuroendocrine carcinoma
- Acinar cell carcinoma

DISCUSSION: Pancreatoblastoma (PB) is a rare malignant pancreatic neoplasm that is primarily diagnosed in pediatric patients. PB has a bipolar distribution with a mean age of 5 and 40 years of age, however, only about 1/3 of cases are diagnosed in adults and in fact less than 100 case reports of adult PB have been described. Patients will present after vague abdominal pain, jaundice, or palpable mass. Grossly, PB is generally a large well-circumscribed solid to cystic mass that arises in any portion of the pancreas. Approximately 35% of patients will present with distant metastasis and 17% will have tumors that infiltrate adjacent local structures. Microscopically, PB displays embryonal morphology with sheets of flat epithelioid to spindled cells. Multiple lineages of differentiation can be found in PB including acinar, neuroendocrine, and rarely ductal differentiation with acinar differentiation being the predominant pattern. The main differentials of this unusual tumor are other neoplasms that display acinar cell differentiation including acinar cell carcinoma and mixed acinar-neuroendocrine carcinomas. Acinar cell differentiation can be identified with PAS-D positive granular staining, trypsin, amylase, lipase, and BCL10 positivity. BCL10 is the preferred method as the enzymatic expression of trypsin, amylase, and/or lipase within the tumor may lead to false negative staining. Acinar cell carcinoma (ACC) is a rare malignant neoplasm that presents as a well-circumscribed solid mass of the pancreas, however, ACC is primarily seen in the 7^{th} decade. Mixed acinar-neuroendocrine carcinomas have at least 25% of both neuroendocrine elements and acinar differentiation and behave in a manner similar to ACC. The question of mixed acinar-neuroendocrine carcinoma and PB can usually be solved with neuroendocrine markers as PB should have <25% positivity. However, the true morphologic difference between these acinar cell neoplasms are the characteristic squamoid morules present in PB. These morules can be highlighted through immunohistochemistry: SATB2 and CDX2 will be positive while BCL10 will be notably negative in the morular foci. Molecularly, ACC and PB have some overlap with 20% of ACC and almost all PB having *CTNNB1* or *APC* mutations. It has recently been shown that ACC will also have *BRAF*, *RAF1*, *RET* gene fusions and chromosomal instability while typically PB will not. For staging purposes all of the acinar cell differentiated carcinomas are staged using pancreatic ductal cell adenocarcinoma criteria.

Treatment relies almost entirely on complete surgical excision with limited knowledge on the effectiveness of other therapy modalities.

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Case #3
PRESENTER: Robert Tolke, MD
ATTENDING: Kruti Maniar, MD

CASE HISTORY:

A 75-year-old female with no relevant past medical history presented for the evaluation of post-menopausal bleeding. Ultrasonography showed a thickened endometrium. Endometrial biopsy was taken, and based on the results, a hysterectomy was performed. A 5.5 cm polypoid lesion was present within the uterine corpus

Presenter: Robert Toelke

Attending: Kruti Maniar, MD

Case History: A 75-year-old female with no relevant past medical history presented for evaluation of post-menopausal bleeding. An ultrasound was performed, showing a thickened endometrium. Endometrial biopsy was performed, and based on the results, a hysterectomy was performed. A 5.5 cm polypoid lesion was present within the uterine corpus.

Final Diagnosis: Carcinosarcoma with high grade neuroendocrine carcinoma component.

Differential Diagnosis: Carcinosarcoma + one of:

- Undifferentiated sarcoma
- Ewing sarcoma
- Neuroendocrine carcinoma
- Undifferentiated endometrial carcinoma

Discussion:

Neuroendocrine carcinoma is a rare malignancy, representing fewer than 1% of all cases of endometrial carcinoma. Most often, this tumor is diagnosed as a component of a mixed endometrial carcinoma, with reported admixed components including endometrioid carcinoma, serous carcinoma, and carcinosarcoma. Neuroendocrine carcinomas of the gynecologic tract can demonstrate a small cell morphology, similar to its lung counterpart, or a large cell morphology, in which the tumor cells demonstrate more cytoplasm and prominent nucleoli.

Correctly diagnosing a neuroendocrine carcinoma is important, as this diagnosis will change the treatment for the patient. Typical high-grade endometrial carcinomas are treated with carboplatin and paclitaxel. When a diagnosis includes a neuroendocrine carcinoma or even a component of neuroendocrine carcinoma, the treatment is switched to cisplatin and etoposide.

Our current recommendations for diagnosing neuroendocrine carcinoma of the gyn tract are based on a study in which 25 cases of endometrial neuroendocrine carcinoma were evaluated for neuroendocrine marker expression. In this study, all of these cases demonstrated positive staining for one of synaptophysin, chromogranin, and/or CD56, in at least 10% of the tumor cells. This 10% rule has been used as a cutoff for diagnosing endometrial neuroendocrine carcinomas; however, this 10% figure is somewhat arbitrary.

One of the challenges of using neuroendocrine markers to make this diagnosis is that undifferentiated endometrial carcinomas also can show focal neuroendocrine marker expression. One study evaluated 44 cases of undifferentiated endometrial carcinoma, and found that 33/44 showed positivity for at least one marker. While staining was typically only focal, in some cases it exceeded the arbitrarily defined cutoff of 10%, meaning that these cases met criteria for a neuroendocrine carcinoma. In this context, morphology is important. An undifferentiated carcinoma can show some focal neuroendocrine marker positivity, but its morphology will not be typical for a neuroendocrine carcinoma. Instead, these neoplasms tend to grow in solid or sheet-like patterns, whereas neuroendocrine tumors may have trabecular, pseudo-glandular, and/or rosette-like formations. Histologically, the cells of an undifferentiated carcinoma show coarse nuclear chromatin, in contrast to the classic "salt and pepper", or finely granular neuroendocrine nuclear features.

Looking at small cell carcinomas of the lung can provide some insight into the molecular patterns of these tumors. A typical molecular profile for a small cell carcinoma of the lung demonstrates a mutation of *TP53* and deletion of *RB1*. A deviation from this pattern should call into question the diagnosis of small cell carcinoma, as the tumor will likely not behave as a true neuroendocrine carcinoma. In cases of SCLC in which RB was not lost, tumors tended to resemble non-small cell carcinomas, and also tended to be refractory to traditional neuroendocrine carcinoma chemotherapy.

A study was performed looking at the molecular patterns of neuroendocrine endometrial carcinomas. In this study, 14 endometrial neuroendocrine carcinomas were evaluated. Of note, only two of these cases demonstrated a molecular profile typical of a small cell neuroendocrine carcinoma (*RB1* deletion and *TP53* mutation). These cases demonstrated a pure small cell morphology. The remainder of the cases showed a variety of molecular profiles, and most were associated with either mixed or large-cell morphologies. These findings, in the context of the lung literature, raise the question of what constitutes a true neuroendocrine carcinoma of the gyn tract, and whether those which lack RB loss will be less responsive to traditional neuroendocrine carcinoma chemotherapy regimens.

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Case #4

PRESENTER: Omar Abdelsadek MD
ATTENDING: Ajit Paintal MD, Curtis Hall MD, Yelena Kalugina MD

CASE HISTORY:

The patient is a 53-year-old male with past medical history of testicular germ cell tumor who presented with dizziness and bloody stools. CT scan of abdomen and pelvis revealed a 10.5 x 7.7 cm large complex cystic and solid mass in the right lower quadrant adjacent to cecum and terminal ileum. An excision of the mass was performed.

FINAL DIAGNOSIS: *ACTB – GLI*-1 gene fusion small bowel mesenteric tumor

DIFFERENTIAL DIAGNOSIS:

- Gastrointestinal stromal tumor (GIST)
- Solitary fibrous tumor (SFT)
- Sarcomatoid yolk sac tumor
- Dedifferentiated liposarcoma
- Schwannoma
- Myopericytoma
- Perivascular epithelioid cell tumor (PEComa)

DISCUSSION:

Activation of the *GLI* (glioma-associated oncogene homologue 1) oncogene is an important step in the sonic hedgehog signaling pathway, and leads to tissue-specific cell proliferation during embryogenesis. *GLI* activity in adult tissues is restricted, but has been identified in various neoplasms, as a result of mutations in the *PTCH* (patched) or *SMOH* (smoothened) genes, encoding components of the sonic hedgehog pathway, or by amplification of *GLI*. The B-actin (*ACTB)* gene, encoding an important cytoskeletal component, is under the control of a conserved, strong, and complex promoter that assures a high level of expression in non-muscle cells. *ACTB-GLI*1 gene fusions have been reported as the pathognomonic genetic abnormality defining an unusual subset of actin-positive, perivascular tumors with t (7;12) translocation.

Neoplasms with recurrent *ACTB-GLI*1 gene fusion were first reported by *Dahlen at al*. as likely benign lesions occurring in young adults; often arise in the tongue, and occasionally the stomach and soft tissue. Histologically, each tumor showed remarkably similar morphology composed of uniform spindle-shaped cells with small amount of pale eosinophilic cytoplasm and ovoid-to-spindle nuclei with vesicular chromatin. These spindle cells were consistently arranged around numerous blood vessels. *MALAT*-1-*GLI*1 gene fusion related tumors have been recently reported in gastric tumors, namely plexiform fibromyxoma and gastroblastoma. Histologically, these tumors demonstrate myxoid stroma contains numerous vessels and bland spindle cells. These spindle cells express alpha smooth muscle actin by IHC. Gastroblastomas additionally contain an epithelial component. An additional cohort study included 6 cases (4 females and 2 males) with age range 16–79, mean 36, median 32, five of these tumors were located within soft tissue; thigh, foot, retroperitoneum, chest wall and head and neck (submandibular area) and only one in bone (C2 vertebral body). Histologically, these tumors display a

morphologic spectrum, often with a nested growth pattern, typically separated by a rich capillary network, with either scant or more abundant clear cytoplasm. One case showed large cystic spaces, including malformed blood vessels. Other case showed a reticular or cord-like arrangement with conspicuous myxoid stroma. These cases are showing variability in morphology from ovoid to spindle shaped to small round blue cells, with variability in IHC staining pattern as well. The behavior of these *GLI*1 gene fusion related tumors can vary from benign to malignant behavior with metastatic potential.

In summary, the previously reported data in addition to our case support the existence of a newly identified, seemingly discrete group of soft tissue tumors at different locations of the body. The morphologic entity is somewhat variable between these tumors in different locations of the body which makes the identification and diagnosis of these tumors more challenging. In addition to morphological variance, the diagnosis of these tumors in unusual locations is not uncommon with some variations in IHC staining patterns as well. Identifying the molecular pattern of these tumor and the biological mechanism will facilitate more effective treatment options for patients including targeted therapy.

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Case #5
PRESENTER: Marika Forsythe, MD
ATTENDING: Mir B. Alikhan, MD

CASE HISTORY:

The patient is a 39-year-old female with a past medical history of alopecia and endometriosis. She presented to the emergency department with severe right shoulder and left hip pain, which had been worsening over several weeks with accompanying low-grade fever. Imaging was remarkable for cortical-based osseous lesions in the shoulder and pelvic girdle. Needle core biopsies were taken from each area.

FINAL DIAGNOSIS:

- Myeloid/Lymphoid neoplasm with *ETV6::ABL1* fusion, presenting as acute undifferentiated leukemia (myeloid sarcoma)

DISCUSSION: Acute undifferentiated leukemia (AUL) is a rare diagnosis and is defined by clonal proliferation of primitive hematopoietic cells and the absence of myeloid or lymphoid markers. Patients diagnosed with AUL have a higher median age than those with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), averaging 74 years vs. 65 and 12 years, respectively. A case study examined 1,444 cases of AUL diagnosed between years 2000-2016 to determine overall survival. Overall, the median overall survival for patients with AUL was roughly 9 months, in comparison to 27 months among those with ALL and 13 months with AML. This illustrates the poor prognosis associated with the disease.

ETV6::ABL1 is a tyrosine kinase fusion gene. It is a rare genetic aberration seen in hematologic malignancies with differing histopathologic features. Cases may appear similar to myeloproliferative neoplasms including chronic myeloid leukemia or they may appear as an acute leukemia after blastic transformation. Within the 2016 WHO there is no category encompassing malignancies with *ETV6::ABL1* fusion. Recently, a group of experts formulated a revised sub-classification called "Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions" (M/LN-eo) which has included entities with *ETV6::ABL1* fusion as a member. Although peripheral eosinophilia was absent from this particular case, eosinophilia is not a required element in the inclusion criteria of this category.

Studies have shown that *ETV6::ABL1* leukemias, though considerably rare, are similar to *BCR::ABL1* leukemias in many capacities, including gene expression profiling. Neoplasms with *ETV6::ABL1* fusions reportedly have excellent response to the second generation tyrosine kinase inhibitors such as nilotinib and dasatinib, and less so with first generation TKIs such as imatinib. Early initiation of TKI therapy allows for long-term survival without disease progression, increasing the importance of early identification to optimize patient care. As genetic testing becomes more ubiquitous, novel fusions are increasingly being discovered. This highlights the need for precise classification schemes to guide therapy and prognosis based on a combination of morphologic and genetic features.

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Case #6

PRESENTER: Payu Raval, MBBS.
ATTENDING: Ajit Paintal, MD; Igor Jovanovic, MD

CASE HISTORY:

The patient is a 68-year-old G8 female who presented with postmenopausal bleeding. Ultrasonography showed an 18 mm thick heterogeneous endometrium and a large 7.0 cm mass in the uterine cavity with a single enlarged lymph node in the left internal iliac chain. Her CA125 was elevated. She was scheduled for laparoscopic hysterectomy with BSO; on laparoscopic visualization, multiple tumor nodules were seen involving the peritoneal and pelvic cavities. Due to the high disease burden and multiple co-morbidities, the procedure was aborted, and only a peritoneal biopsy was taken

FINAL DIAGNOSIS:

YWHAE rearranged high-grade endometrial stromal sarcoma (HGESS)

DIFFERENTIAL DIAGNOSIS:

- Undifferentiated carcinoma
- Dedifferentiated carcinoma
- Carcinosarcoma with homologous stroma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Uterine tumors resembling ovarian sex cord tumors (UTROSCT)
- Low-grade endometrial stromal sarcoma, epithelioid (LGESS)
- Adenosarcoma with stromal overgrowth
- High-grade endometrial stromal sarcoma (HGESS)
- Undifferentiated uterine sarcoma (UUS)
- GIST

DISCUSSION:

High-grade endometrial stromal sarcoma (HGESS) is a malignant uterine mesenchymal tumor originating from the endometrial stroma, mainly occurring in the uterine corpus and rarely in the vagina. The age of presentation varies from 14-74 years (mean age 42-54 years) depending on the type of HGESS. The risk factors include tamoxifen use and pelvic irradiation. HGESS is rarely diagnosed on endometrial biopsy, and a hysterectomy is usually required for a definitive diagnosis.

The evolution and classification of endometrial stromal tumors are alluring and are becoming more nuanced with the recognition of recurrent genetic alterations in many cases. Initially, endometrial stromal sarcoma was classified as per mitotic activity, endometrial stromal differentiation, and cytologic atypia. In the 2003 WHO classification, they were divided into low-grade endometrial stromal sarcoma (LGESS) and undifferentiated uterine sarcoma (UUS) based on nuclear pleomorphism & necrosis (not mitosis). In the 2003 classification, HGESS was not given a separate category. Interestingly in 2008, Kurihara et al. defined another group with uniform cells, high-grade cytology, permeative myometrial invasion & clinical behavior between low-grade endometrial stromal sarcoma and undifferentiated uterine sarcoma based on IHC and molecular studies of 31 stromal sarcoma cases. Later in 2014, WHO added the HGESS into the classification and molecular features into various categories. LGESS has

translocations involving the polycomb gene family members, including *JAZF1-SUZ12* fusion and *EPC1-PHF1* rearrangement. HGESS has *YWHAE-FAM22* fusion; t(10;17), and UUS has Complex chromosomal changes. In 2019, Cotzia et al. classified 7/10 UUS into HGESS with BCOR IHC, FISH and next-generation targeted RNA sequencing. They detected *YWHAE* and *BCOR* rearrangements, *BCOR ITD* and *BRD8-PHF1* fusion. Some cases were not detected by FISH in the first place but were detected on RNA sequencing. Recently in the 2020 WHO classification, more molecular variants were added. In LGESS, 2/3 cases have fusions involving polycomb family genes, and HGESS includes *YWHAE* and *BCOR* rearrangements, *BCOR ITD* and other fusions.

Recently, *NTRK* fusion-positive uterine sarcoma has been described in young women. As more molecular variants are getting detected, the UUS category is shrinking. Now UUS is a diagnosis of exclusion, and high-grade tumors should be ruled out by extensive sampling and molecular studies.

HGESS has various types based on genetic alterations, but morphology and IHC can also help differentiate between various types. *YWHAE* rearranged type classically has two cell components- Round to epithelioid cell and spindle cell components. The spindle cell component is less cellular with fibrous stroma and without necrosis; the cells are cytologically bland without high mitotic activity. The round cell component is more cellular with a round to angulated nuclei and eosinophilic cytoplasm; nuclei have vesicular to granular chromatin and indistinct nucleoli; brisk mitosis and necrosis are usually present. Another type is *BCOR* fusion, which has a destructive pattern of myometrial invasion, and the tumor is composed of spindle cells with an abundant myxoid matrix. *BCOR* Internal tandem duplication (ITD) HGESS has a small round cell component, but occasional spindle cell components with the myxoid matrix can be seen too. HGESS NOS is associated with the LGESS areas.

LGESS is diffusely positive for CD10, ER, PR, and SMA. In *YWHAE* rearranged cases, the low-grade component is diffusely positive for CD10, ER, and PR and negative or focally positive for cyclin D1 and BCOR. Conversely, the high-grade component is diffusely positive for cyclin D1 and BCOR and negative for CD10, ER, and PR. *BCOR* rearranged cases are CD10 and cyclin D1 positive, but BCOR IHC may be negative, focal, or diffuse positive. *BCOR ITD* cases are CD10 and cyclin D1 positive and ER, PR negative. BCOR expression on IHC is more consistently seen in *YWHAE* rearranged cases than *BCOR* rearranged cases; *ZC3H7B-BCOR* fusion can have negative BCOR IHC because of low levels of BCOR mRNA expression.

Treatment options include cytoreductive surgery; and anthracycline-based chemotherapy in *YWHAE-NUTM2A/B* sarcomas. In addition, MDM2 or CDK4 inhibitors showed potential in *BCOR-rearranged* sarcomas. However, antihormonal therapy has a limited role because of the absence or limited expression of ER and PR.

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