IRAP – February 28, 2022
Presented by University of Illinois Hospital & Health Sciences System
and John H. Stroger, Jr. Hospital of Cook County

CASE #1
Presenter: Batool Huzaifa, MBBS, MD
Attending: Ree Nicholas, DO
Diagnosis: Mesonephric Carcinoma vs Mesonephric-Like Carcinoma

Clinical History:
66 year old G3 postmenopausal woman with abnormal uterine bleeding for 10 months. On CT, the uterus was lobulated and heterogeneous with fibroids. Malignancy was identified on dilatation and curettage. The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and peritonectomy. On hysterectomy, the tumor occupied the majority of the endometrial cavity with extensive involvement of lower uterine segment, anterior lateral serosal surface, and full-thickness stromal invasion with positive paracervical soft tissue margin. Multiple leiomyomas were identified. The tumor was microsatellite instability (MSI) proficient by immunohistochemistry and HER2 fluorescence in situ hybridization was not amplified. Her course was complicated by benign jejunal perforation treated by resection and antibiotics. After the patient's status improved, carbotaxol every 3 weeks for a plan of 6 cycles was initiated. Representative section of the slide from the mass is sent for your review (Scanned slides)

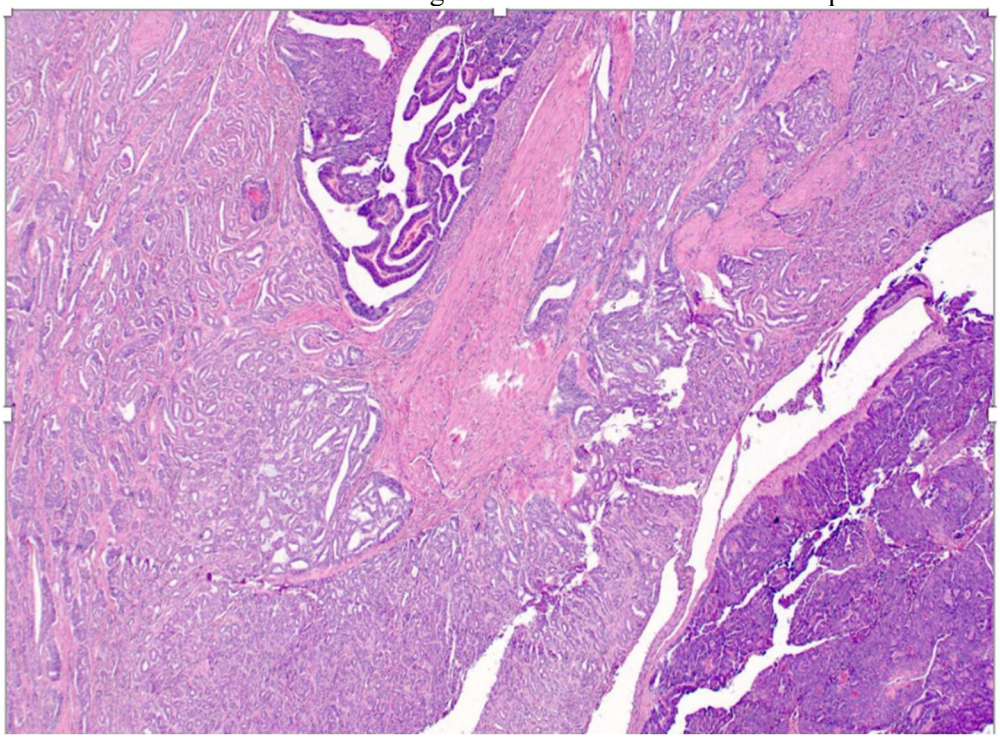
Differential Diagnosis:
- Dedifferentiated endometrioid carcinoma
- Carcinosarcoma (MMMT)
- Endometrioid carcinoma with prominent non-sarcomatous spindled component
- Mesonephric carcinoma/ Mesonephric-like carcinoma

Key Features:
- Variable histologic patterns, and may have areas of glandular, solid, and spindled morphology, with the spindled areas lacking overt features of sarcoma.
- Negative ER, PR with GATA3 positivity

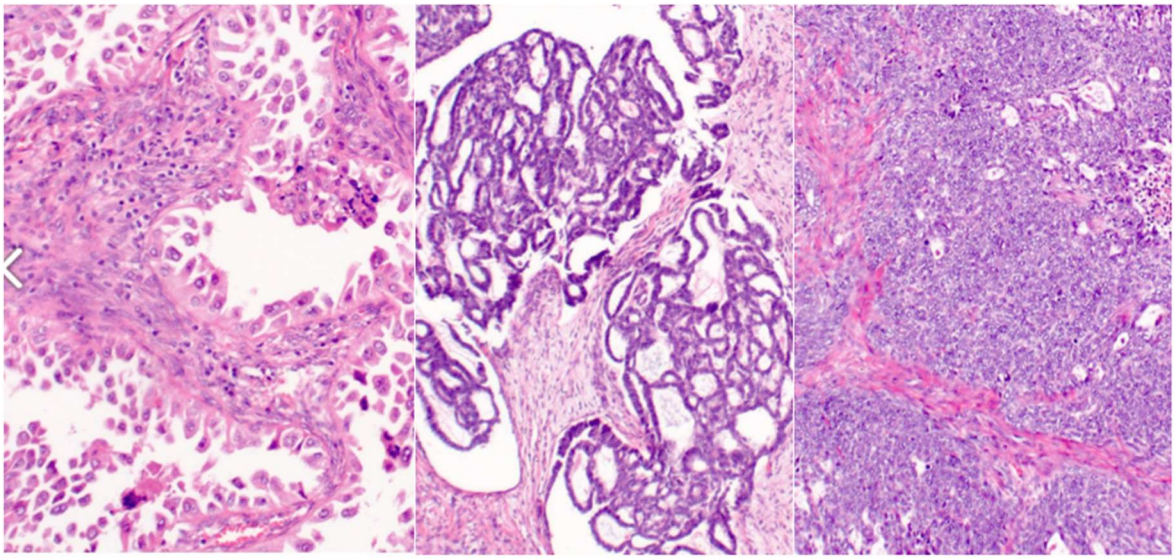
Ancillary Studies:
- IHC: Typical IHC finding in these tumors is GATA 3 nuclear positivity. PAX8 and HNFB-1 may also show nuclear positivity. CD10 may show luminal staining. Calretinin may show nuclear and cytoplasmic staining. Androgen receptor can be variably positive. TTF1 may or may not show nuclear positivity

Discussion:
MC and MLC are rare tumors, overall representing about 1% of all endometrial carcinomas and < 1% of all cervical adenocarcinomas. Conventionally, these tumors can be differentiated by primary location, with MC arising within the usual distribution of mesonephric duct remnants (classically walls of the cervix and vagina), and MLC arising outside this distribution, such as in the uterine corpus, ovaries, or outside the Gynecologic tract. The mean age of diagnosis for these tumors is 52 in one literature review. Both tumors can have variable histologic patterns, and may have areas of glandular, solid, and spindled morphology, with the spindled areas lacking overt features of sarcoma. The leading symptom for both is abnormal vaginal bleeding.
Typical gross findings are a gray-tan mass in the uterine cavity with or without infiltration of the adjacent myometrium if it is MLC, whereas MC are typically centered in the walls of vagina or cervix. These

tumors can exhibit many histologic patterns, often varying between tumors and between different microscopic fields of the same tumor. This image shows ductal tubular and solid patterns.



Most commonly these tumors have a tubular pattern; consisting of small back to back tubules lined by cuboidal cells, sometimes containing intraluminal colloid-like secretions that stain positive for PAS-D and mucicarmine. Shown below are some other histologic patterns seen in these tumors. The papillary pattern mimics clear cell carcinoma, the middle image is of the sieve-like pattern. And rightmost is the solid pattern which lacks significant pleomorphism.



Other histologic patterns observed are retiform, sex cord-like, hobnail, glomeruloid. Tumor cells usually have mild to moderately pleomorphic nuclei with inconspicuous to prominent nucleoli. Mitotic figures can be rare or readily apparent. These tumors are often deeply infiltrative but may show little desmoplasia. Mesonephric carcinomas are often associated with peripheral mesonephric remnants or mesonephric hyperplasia.

A paper published in 2018 by Pors et al showed that GATA3 had the highest sensitivity and specificity (91% and 94%) compared with TTF1 (45% and 99%), CD10 (73% and 83%), and calretinin (36% and 89%). GATA3, however, also stained a substantial number of uterine carcinosarcomas (23/113, 20%). Even then, GATA3 was the best overall marker for mesonephric and mesonephric-like carcinomas.
A useful and practical observation from the same study was the inverse staining pattern between GATA3 and TTF1. It was therefore recommended by the authors that in small biopsy samples where a mesonephric neoplasm is suspected, GATA3 staining should be performed first because of its higher sensitivity. If negative, due to the inverse staining pattern between GATA3 and TTF1, TTF1 staining should then be performed.

Summary:
The main histologic clue for both tumors is that they have a mixture of different histologic patterns. The presence of mesonephric remnants and the epicenter of the tumor benign located in the cervix or vagina may help to differentiate between the two. However, with extensive involvement, it may not be possible to differentiate between these two entities, as in our case.

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CASE #2:
Presenter: Bartlomiej Radzik, MD
Attending: Manuel F. Utset, MD, PhD
Diagnosis: NF1-Mutant Pilocytic Astrocytoma

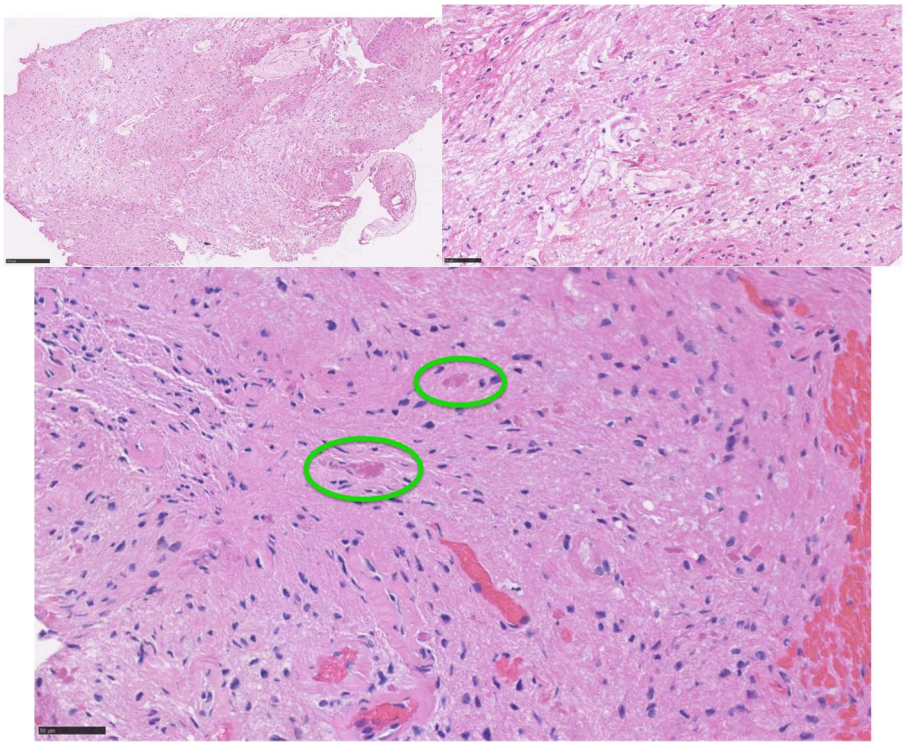
Clinical History:
73-year-old woman presented with difficulty in walking, recent onset, associated with a tingling sensation in her right leg and left foot as well as lower abdomen and back. Per report, imaging studies demonstrated diffuse increased T2 signal within the spinal cord, the majority of which was in the thoracic spine, associated with peripheral enhancement. The patient was also noted to have a homogeneously enhancing lesion in the anterior skull base, showing expansion into the Sella. Intraoperatively, the spinal mass was noted to have an intramedullary component, with regions showing no discernable plane of dissection from the spinal cord parenchyma. (Scanned Slides)

Differential Diagnosis:

- Diffuse midline glioma (H3K27M mut)
- IDH mutant astrocytoma
- Spinal cord ependymoma
- Piloid gliosis
- Pilocytic astrocytoma

Key Features:

On frozen section the "extramedullary mass" looked like an intramedullary glial proliferation. There was also a clinical question of tuberculosis; however, examination of the frozen section showed no evidence of granuloma. The frozen section was signed out as "Atypical glial cell proliferation with Rosenthal fibers. Negative for granuloma." On higher magnification, a glial proliferation associated with numerous Rosenthal fibers can be seen. The glial cells display a haphazard arrangement and nuclear pleomorphism, most consistent with a neoplastic process. The Rosenthal Fibers can also be seen on the formalin-fixed H/E stain. Mitotic figures are not identified. Focally, the glial cell nuclei are arranged in linear chains that may represent subtle perivascular rosettes.



Ancillary Studies:

- IHC: Immunohistochemical stains showed diffuse positivity of GFAP, negative for P53, with a low Ki67 (<1%) and rare axons highlighted on neurofilament staining. Additional stains performed at the Mayo Clinic were reported as negative for Histone H3 K27M, BRAF V600E, and IDH1 R132H and showed retained expression of ATRX.
- Molecular: Next-Generation Sequencing studies performed at the Mayo Clinic using a Neuro-Oncology Targeted Next Generation Sequencing Panel identified a mutation in the NF1 gene (p.W336*), as well as variants of uncertain significance in the LRP1B, TET1, and WRN genes.

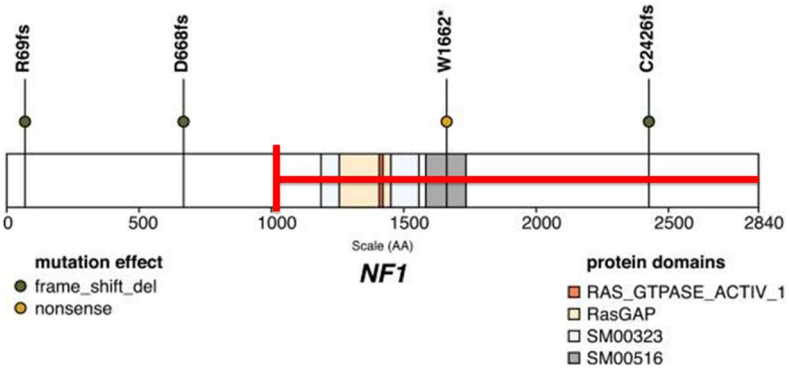
Discussion:

The most frequent variants of intramedullary spinal cord tumors are ependymomas and astrocytomas, which in total comprise about 60% and 30% respectively, of all IMSCT cases diagnosed, while the remaining 10% include hemangioblastomas and metastatic tumors. In adults, the relative incidence of pilocytic astrocytomas is approximately 0.8%.

Pilocytic astrocytomas are histologically characterized by their biphasic appearance; namely, compact fibrillar portions (elongated nuclei and Rosenthal fibers) and loose microcystic portions (round to oval nuclei, cobweb-like processes, and eosinophilic granular bodies) as well as GFAP-staining in the cell cytoplasm. They may show great histological variability, sometimes making definite characterization difficult.

The most common mutations seen in spinal cord pilocytic astrocytomas are BRAF V600E and BRAF KIAA1549 mutations, with mutations in the NF1 gene only comprising 15-20% of these tumors. There is a strong association between the development of pilocytic astrocytomas in patients with germline mutations in the NF1 gene, however, pilocytic astrocytomas with sporadic NF1 mutations occur less frequently.

The Neurofibromin protein, from the NF1 gene, stimulates the GTPase activity of Ras, and is currently believed to be a regulator of RAS activity. Further, a paper by Morcos et. al showed that various mutations in the NF1 gene showed increased affinity for the GTPase domain of the Ras protein. Our tumor's nonsense mutation was found at amino acid 1007, knocking out the critical domain for function. Therefore, the activated form of RAS runs unopposed, leading to proliferation and differentiation.



Piloid gliosis can be difficult to distinguish from a pilocytic astrocytoma, which is a very rare diagnosis in this location and this age group. A potential pitfall arises when the biopsy specimen comes not from the spinal cord tumor, but the adjacent spinal cord parenchyma showing piloid gliosis. Piloid gliosis often occurs secondary to multiple tumors including craniopharyngioma, hemangioblastoma, or an ependymoma. The periphery of the tumor often shows piloid gliosis and numerous Rosenthal fibers as seen on the right, as well as low cellularity and a variable amount of inflammatory cells and hemosiderin, especially around an ependymoma. A biopsy taken from this region may lead to the mistaken diagnosis of a pilocytic astrocytoma. However piloid gliosis should not show any genetic changes characteristic of pilocytic astrocytoma or any other neoplasm.

However, additional Next-Generation Sequencing studies performed at the Mayo Clinic using a Neuro-Oncology Targeted Next Generation Sequencing Panel identified a mutation in the NF1 gene (p.W336*), as well as variants of uncertain significance in the LRP1B, TET1, and WRN genes, which solidifies the diagnosis of pilocytic astrocytoma.

Summary:

The important points to remember are that the most common spinal tumor in adults is an ependymoma, and the surrounding gliosis can easily be mistaken for an astrocytoma. Additionally, astrocytomas in adults must be stained with Histone H3K27M mutant and IHD1, as these entities will change the WHO grading based on their presence or absence. Finally, NF1 mutations can cause pilocytic astrocytomas as a result of the disinhibition of the RAS signaling pathway.

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Case #3:
Presenter: Ujalla Sheikh MBBS, MS
Attending: Elizabeth Wiley, MD
Diagnosis: AV node cystic tumor (intracardiac endodermal heterotopia)

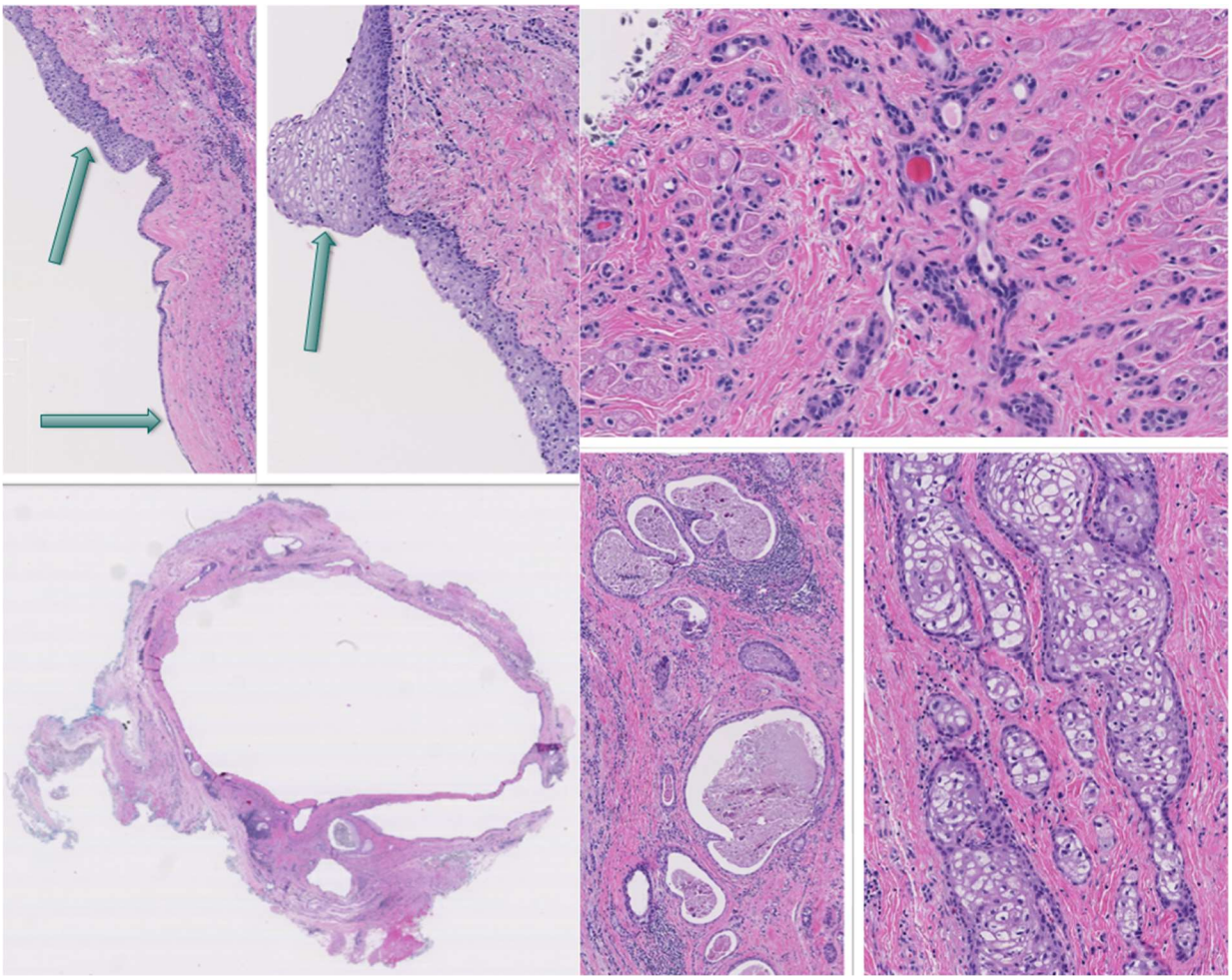
Clinical History:
a 46-year-old female with past medical history of asthma and past surgical history of abdominoplasty, hysterectomy, appendectomy and oophorectomy for ovarian cyst, presented to the emergency department with worsening shortness of breath and generalized weakness for past 3 weeks. As part of extensive work up, she underwent a CT chest which revealed 2 cm oval hyper-density mass within the atrial septum. Follow-up with echocardiogram showed, approximately 1.8 x 2.1 cm mass in the right atrium, appears fixed in nature, at the inferior portion of the interatrial septum very close to the base of the tricuspid valve. Further, the patient developed acute dyspnea and hypoxia, with lightheadedness and vision changes. ECG demonstrated sinus rhythm with 1st degree AV block. Given the risk of cardiac arrhythmia, the patient underwent median sternotomy with intra-atrial mass resection and permanent pacemaker placement. A representative section of this specimen is submitted for review. (Scanned slides)

Differential Diagnosis:

- Cardiac teratoma
- Mesothelial cyst
- Intracardiac bronchogenic cyst
- AV node cystic tumor
- Cardiac myxoma.

Key Features:
Gross examination showed a 2.2 cm cystic mass with tan-brown grumous contents encircled by a thin smooth cyst wall.

Microscopic examination showed a cyst that contained a surrounding fibrous and cystic area. The cyst was lined by various epithelial cells - from flattened cuboidal cells to transitional to squamous epithelium. Surrounding the main cyst were multiple cysts of variable sizes filled with proteinaceous and keratin debris and nests of cells filled with squamoid clear cells with centrally located small compact nuclei or sebaceous like differentiation. Minor components of cells showed glands with corpora amylacea in glandular lumens. The background consists of dense fibrosis and chronic inflammatory cells.



Ancillary Studies:

Since rarity of this tumor, immunohistochemical analysis was done based on literature review, showing strong diffuse expression of CKAE1/AE3, positive expression of EMA, as reported in these lesions. GATA3 was performed to see breast or urothelial differentiation, and showed positivity in lesional cells, this has not been reported in literature. Lesional cells were negative for calretinin. CK20, TTF, PAX8 and s100., It's been reported that these lesions contain neuroendocrine cells and stains positive with calcitonin. In our case calcitonin was performed and was negative in lesional cells.

Discussion:

Cystic tumor of the atrioventricular nodal region was first described in 1911, is a rare and congenital primary cardiac tumor, usually identified at autopsy. It comprises 2.7% of cardiac tumors. It's located at the base of the interatrial septum. CTAV is considered the smallest tumor capable of causing sudden and unexpected death, typically due to severe AV block or ventricular arrhythmia. It has been diagnosed mostly in the third to fourth decades, with a wide age range, between (11 months to 89 years). It occurs primarily in women, with a 3:1 female-to-male ratio.

The etiology is still an area of controversy. It is believed that these lesions are endodermal in origin arises from foregut endodermal rests, which become enfolded into the heart during embryogenesis. Studies have indicated that 10% of individuals with cystic tumor of the AV node also have midline developmental defects and other congenital lesions with possible familial occurrence. Associated lesions includes complex congenital heart disease, thyroglossal duct cysts, cysts in the ovaries, breasts, ventricular septal defect, encephalocele and has also been reported in association with Emery-Dreifuss muscular dystrophy, an X-linked recessive disease.

The gross findings show a cyst-like structure containing a brown paste-like material, rim of surrounding tissue. The tumor size varies, as the majority are between 0.2 and 2 cm in diameter. On microscopic examination, cystic areas are lined by flattened cuboidal or squamous epithelium. The cell nests are composed of epithelial cells, which may be squamous, sebaceous, cuboidal, or transitional. Dense fibrosis is often seen surrounding the cysts of cell nests with a lymphocytic reaction. Smooth muscle, mitotic figures or atypia which would be suggestive of malignancy have been reported. Immunohistochemically, the cells of this lesion stains positive for cytokeratin and carcinoembryonic antigen, demonstrating epithelial differentiation.

In reviewing the literature, to the best of our knowledge, approximately 70 cases of TAV have been published in the literature since 1911, with most of them diagnosed at autopsy. Balasundaram et al in 1992, was the first authors to report on a case of CTAV, which was successfully resected. A review by Cina et al. found 120 cases of sudden death attributed to primary cardiac tumors in the (published) literature. From which 103 of these lesions were histologically benign (86%), their intracardiac locations precipitated conductive and hemodynamic abnormalities that resulted in sudden death. The most common intracardiac lesion causing sudden death, was cystic tumor of the AV node, also called endodermal heterotopia of the AV node.

Summary:

In summary, the cystic tumor of the AV node is the most common primary cardiac tumor that can cause sudden cardiac death. Antemortem diagnosis requires special attention to echocardiography, CT scan and MR with a focus on the AV node especially at the base of interatrial septum. Despite its rarity, cystic AV node tumor should be considered in the differential diagnosis of heart block in children and young adults. Microscopically, these lesions are composed of multiple cysts, ducts and solid nests of cells in dense fibrous stroma. Immunohistochemistry supports an epithelial endodermal origin of the tumors (CK and EMA). Surgical intervention and close follow-up should be considered.

References:

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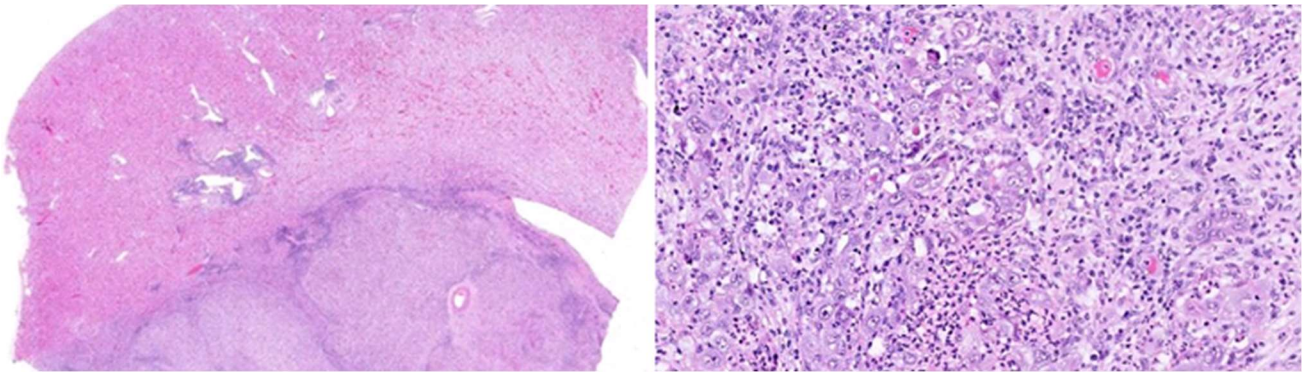
Case #4:
Presenter: Pouyan Kheirkhah, MD
Attending: Vikas Mehta, MBBS, MD
Diagnosis: Renal cell carcinoma with ALK gene rearrangement

Clinical History:
Our patient was a 22-year-old African American male with no significant past medical history who presented to the emergency room after a motor vehicle accident. A pelvic CT scan demonstrated a 14 x 13 x 12 cm heterogeneous mass arising in the right renal sinus. Radical nephrectomy was performed. Representative section of the slide from the mass was sent for review (Scanned slides).

Key Features:
Grossly there was a yellow and tan, well circumscribed lesion, centered in medulla near the upper pole of the kidney. Microscopically, the tumor was located in the medulla overlying cortex. There were sheets of tumor cells with vesicular, pleomorphic nuclei, abundant cytoplasm and intracytoplasmic lumina with a background of inflammatory cells, especially neutrophils. There was an extensive lymphovascular invasion as well as metastatic tumor to multiple lymph nodes. Sickle red blood cells were present under the microscope.



Differential Diagnosis:

- Renal Medullary Cell Carcinoma (RMC)
- Collecting Duct Carcinoma (CDC)
- TFE Translocation-Associated Renal Cell Carcinoma
- SDHB-Related Renal Cell Carcinoma
- Clear Cell Carcinoma, High Grade
- Urothelial Carcinoma

Ancillary Studies:

- IHC: positive for ALK, INI-1, TFE3, SDHB, CA9, SMARCA4 and negative for GATA3 and P63
- Molecular: VCL/ALK dual fusion probe FISH showed VCL-ALK in >95% nuclei

Discussion:

In the past decade, the world was introduced through a variety of papers, to a new entity called renal cell carcinoma with novel VCL-ALK fusion. Now we have enough evidence to show that ALK-RCC represents a novel and genetically distinct entity. ALK can fuse with various partner genes leading to aberrant ALK activation and the formation of oncogenic chimeric proteins. It can be identified either by IHC, FISH or by sequencing methods. Since the first reports in 2011, about 40 cases have been documented. There is an availability for targeted ALK inhibitor therapies with documented response to therapy. A majority of the cases are indolent, but they may exhibit malignant behavior, including metastatic disease and death, documented in about 25% of the reported cases.

We have two main subtypes for this tumor. In pediatric subtype, patients are usually African-American with sickle cell trait and tumors typically occur in the renal medulla and exhibitVCL-ALK and TPM3-ALK fusions and morphologic similarities to adult renal medullary carcinoma and collecting duct carcinoma. The adult subtypes of ALK-RCC are usually cortical and show a heterogeneous morphology. Microscopically we can have a mucinous background. Solid, tubulocystic growth, focal signet-ring cells or metanephric adenoma-like morphology can also be seen. There are sheets of spindled to polygonal discohesive cells with abundant cytoplasm, large vesicular nuclei with variable prominent nucleoli and occasional nuclear grooves, conspicuous intracytoplasmic vacuoles and diffuse inflammatory infiltrate.

Summary:

ALK rearrangement renal cell carcinomas are now considered a distinct entity. They are centered in the medulla and they have heterogeneous morphology. There are two subtypes (pediatric and adult), ALK is diffusely positive, they retain the INI1, and TFE3 is often expressed in the nuclei of tumor cells. One should always try to differentiate this entity from collecting duct carcinoma, medullary carcinoma and others, especially as there is targeted therapy available for this tumor.

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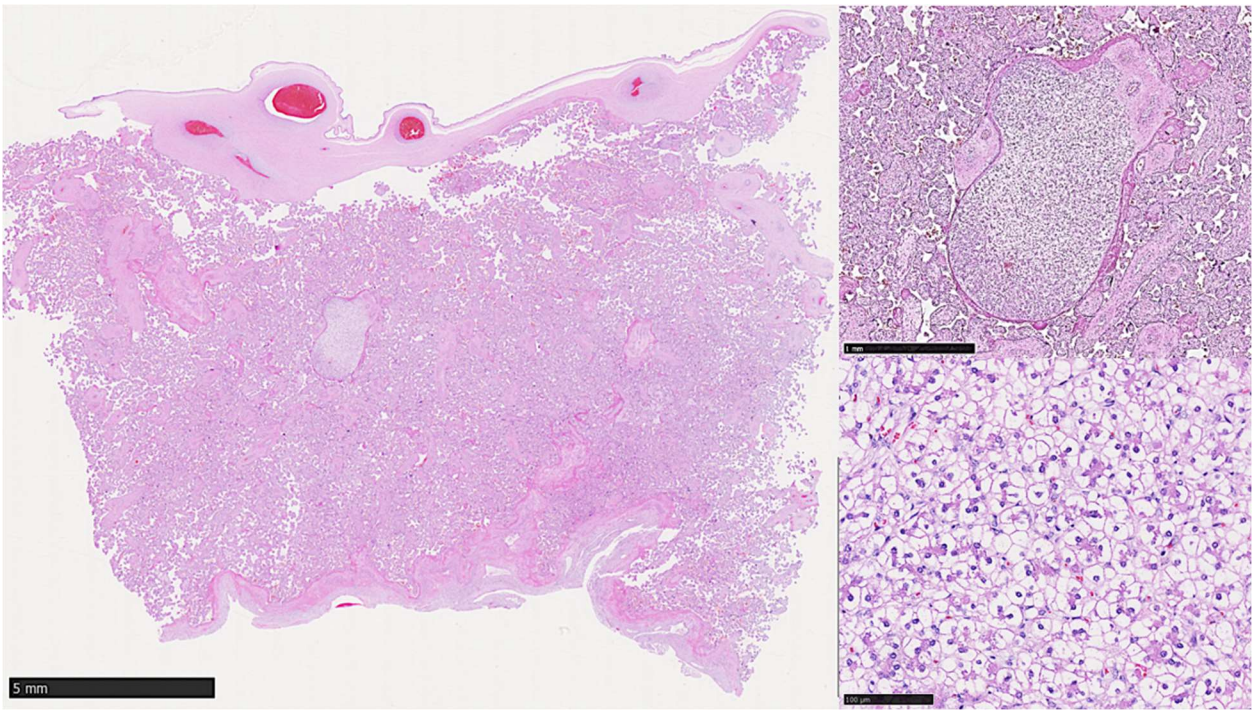
Case #5:
Presenter: Saman Karimi, MD, MS
Attending: Attending: Steven Garzon, MD
Diagnosis: Intraplacental hepatic heterotopia

Clinical History:
A 27-year-old female (G3P0202) with a history of premature delivery, irregular menses, leiomyomata, and current pregnancy complicated by anemia, had a spontaneous vaginal delivery, giving birth to a premature female infant at 31+5 weeks gestational age. The patient had no known history of malignancies and social and family history were noncontributory. The placenta was submitted to surgical pathology for histopathological evaluation and a whole slide imaging of the full thickness section of the placenta is submitted for your review (Scanned Slides).

Differential Diagnosis:
- Adrenal Heterotopia
- Melanoma with Clear Cell Changes
- Clear Cell Variant of Hepatocellular Carcinoma
- Clear Cell Renal Cell Carcinoma
- Intraplacental Hepatic Heterotopia

Key Features:
Our gross examination did not reveal a grossly identifiable lesion. Microscopic examination of the placental full thickness section shows an incidental finding of a foci of a well-circumscribed, pale lesion admixed with the chorionic villi. On intermediate magnification, we see a well-demarcated, encapsulated cohesive sheet of pale and clear cells with associated vasculature surrounding the lesion. On high magnification, we can appreciate monotonous, polygonal cells with uniform nuclei, abundant clear cytoplasm. No abnormal mitoses or areas of necrosis are seen on inspection of the lesion.



Ancillary Studies:

- HepPar1 +, CAM 5.2 +, AFP +, Glypican 3+
- Reticulin (show appropriate reticulin network)
- CD34+ (endothelial cells/sinusoidal spaces)
-

IHC Stain	Result
Cam 5.2	+
Inhibin	-
S100	-
CD10	-
HepPar-1	+
Glypican-3	+
CD34	+ (sinusoidal spaces/Endothelial cells)
AFP	+
B-Catenin	-
Reticulin	show appropriate reticulin network
PLAP	-
GATA-3	-
B-HCG	-

Discussion:

Intraplacental hepatic heterotopia is a benign and extremely rare lesion with only 15 cases reported in the literature. The pathophysiology remains unknown and currently there are several hypotheses regarding the pathogenesis of this entity, including the possibility that these are specialized monodermal teratoma, and others suggest that intraplacental hepatic heterotopia occur due to aberrant migration or displacement of cells from the developing hepatic buds. Grossly, intraplacental hepatic heterotopia are usually small, ranging from 0.3-1 cm, well circumscribed, tan to dark brown nodule mixed with the chorionic villi and

occasionally found on the surface of the umbilical cord. They can be encapsulated, and occasionally not grossly visible as was the case with our specimen. Microscopically, these lesions are well-circumscribed, composed of sheets and nests of polygonal epithelial cells with moderate amounts of eosinophilic to clear cytoplasm. Typically, no associated portal tracts are present in these lesions, although they can be surrounded by vasculature as was the case with our lesion. The lesional cells are monotonous, bland with no nuclear atypia and have a low mitotic activity.

The immunophenotype of the lesion includes HepPar-1 +, Glypican-3 +, CD34 + (sinusoidal capillarization pattern), AE1/AE3 +, Cam 5.2 +, Beta-Catenin -, Reticulin shows appropriate reticulin network.Glypican-3 is an oncoprotein that serves as a sensitive marker in hepatocellular carcinoma and several other malignancies. It belongs to the heparan sulfate proteoglycans family, 60-70 kD in size. However, all glypican proteins are highly expressed during embryonic development and therefore, expression of Glypican-3 in embryonic and fetal development is expected and consistent with normal fetal development.

Thus far, 15 cases (including our case) of intraplacental hepatic heterotopia have been reported in the literature. Thirteen of the reported cases were associated with premature labor, as was the case with our patient. Further studies are needed to evaluate the significance of this observed association, but the rarity of the lesion poses a significant investigative challenge. Currently, there is no consensus on naming this lesion and they have been reported in the literature as placental hepatocellular adenoma, intraplacental hepatic heterotopia and hepatocellular adenoma-like lesion of the placenta.

Summary:
Hepatic heterotopia of the placenta is a rare lesion occurring ectopically. Clinical history is key in guiding clinicopathological investigation of this entity. Accurate diagnosis of intraplacental hepatic heterotopia and its distinction from metastatic malignancies is imperative for guiding clinical decisions and patient management. And finally, there is a possible association with premature labor and further research is needed.

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