

NORTHWESTERN

UNIVERSITY

Illinois Registry of Anatomic Pathology

27 October 2014

**CASE 1 (Dr. Kirstin Howell, M.D.):** **Soft Tissue Hemangioblastoma**

**Clinical history:** The patient is a 36 year-old female with a history of multiple neoplasms in various anatomical sites that have required resection. She is undergoing resection of an enlarging right perirectal/pelvic mass which measures 4.2 cm in greatest dimension at time of surgery.

**Gross and histologic finding and immunohistochemical profile**:

Grossly, the specimen is yellow gray and well-circumscribed, with a cut surface notable for multiple cystic spaces and areas of hemorrhage. On low-power magnification, an intricate, arborizing vascular pattern is noted that includes large, staghorn vessels and smaller, irregularly shaped, and compressed capillary channels. On higher power, we see that the vessels are intimately associated with sheets of epithelioid tumor cells with eosinophilic, foamy and vacuolated cytoplasm and ill-defined cell borders. The nuclei have hyperchromatic, condensed chromatin, and are slightly variable in size and shape with inconspicuous nucleoli. There are very rare mitotic figures and no necrosis is observed. Immunohistochemically, the tumor cells are diffusely inhibin and S-100 protein positive and show focal membranous expression of CA-IX. CD34 and CD31 highlight the rich vascularity of the tumor.

**Differential Diagnosis**

1. **Renal cell carcinoma**: Classic renal cell carcinoma (RCC) is the most common renal cancer and consists of 60-70% of all renal tumors. Nests of tumor cells with abundant, clear to lightly eosinophilic cytoplasm and delicate cell borders are surrounded by a rich vascular network. RCC can metastasize widely and to unusual places, and given the patient’s history, this was a real concern. Unlike the patient’s tumor, however, RCC has more of a nested architecture with its cells more uniformly oriented with respect to vessels walls, and the cells typically have defined cell borders. The vasculature of RCC is less arborizing and usually lacks hemangiopericytomatous vessels. Immunohistochemical expression for RCC is positive for CD10, PAX8 and EMA and negative for inhibin and S-100 protein.
2. **Solitary fibrous tumor**: Solitary fibrous tumors are slow-growing, painless tumors that develop from submesothelial fibroblasts on the pleural and serosal surfaces such as the pericardium, peritoneum and liver surface in addition to a multitude of non-serosal areas including (but not restricted to ) the mediastinum, orbit, thyroid, nasal cavity, meninges, and soft tissue. Grossly, the lesion is well-circumscribed with a nodular and firm cut surface. The tumors possess at least focally a hemangiopercytomatous vascular component, which is reminiscent of the vasculature seen in hemangioblastoma. However, solitary fibrous tumor has a less monomorphic growth pattern than hemangioblastoma, and the lesional element consists of cytologically bland spindle cells that are interspersed among long, thin collagen bundles and are unlike the plump vacuolated cells in hemangioblastoma. The tumors are positive for CD34, CD99, STAT6 and often Bcl-2.
3. **Lipomatous solitary fibrous tumor**: The overall architecture is that of a solitary fibrous tumor and differs from the latter only by the presence of distinct mature adipocytes. Therefore, the same histological features and immunoprofile used to differentiate classic SFT from hemangioblastoma applies.

**4. Perivascular epithelioid cell tumor (PEComa)**: The presence of epithelioid cells with partially cleared cytoplasm typical of some PEComas could potential lead to a misdiagnosis of hemangioblastoma. The PEComa has an intricate vascular network in which epithelioid tumor cells are arranged radially around the vessel wall and the more spindle component is often times located away from the vessels. PEComas usually have a more nested pattern than hemangioblastoma and the cells are typically less vacuolated. PEComas show expression of commonly used melanocytic markers, HMB-45 and melan-A, and smooth muscle markers, smooth muscle actin and desmin, as well as CD1a and cathepsin K.

**Summary**:

Hemangioblastoma is a rare, benign tumor that typically arises in the cerebellum and upper spinal cord, and may be sporadic or associated with Von Hippel-Lindau (VHL) syndrome. Twenty-five percent of hemangioblastomas of the central nervous system are associated with VHL, and up to 80% of patients with VHL develop hemangioblastoma, which are often times multiple. Tumors that arise outside of the central nervous system (CNS) are very rare, with only a few case studies and small series published. Non-CNS tumors are usually associated with peripheral nerves, but have been identified in the liver, lung, skin, adrenals, bladder, pancreas, maxillary bone, kidney, nasal skin and retroperitoneum. CNS hemangioblastoma have a male predominance, with a mean age of onset of 30 years in patients with VHL and 40-50 years in patients with sporadic tumors. The tumors are well-circumscribed with solid and cystic components and are composed of sheets of epithelioid cells with variably vacuolated cytoplasm intimately associated with an intricate vascular network. The cells show have little mitotic activity or cellular atypia. Peripheral (non-CNS) tumors have an equal male:female ratio and an older median age of onset (6th. decade). Compared with the much more common CNS hemangioblastomas, those arising in peripheral soft tissue have a more solid growth pattern, have a more collagenous and hyalinized stroma, and often show a greater degree of cytological atypia. Hemangioblastoma expresses inhibin, S-100 protein, and neuron specific enolase. GLUT1 and brachyury have been found in CNS hemangioblastoma. Hemangioblastoma are negative for keratin, HMB-45, melan-A, GFAP and PAX8.

Tumor growth is believed caused by alterations in the VHL gene at 3p25-26, leading to activation of the hypoxia inducible factor pathway. In normoxic conditions, pVHL binds to hydroxylated HIF-1α and targets the complex for proteasomal degradation. In hypoxic conditions, HIF-1α is not hydroxylated and pVHL is unable to bind the protein. HIF-1α translocates to the nucleus where it complexes with HIF-1β and binds to the hypoxia response element promoters, causing generation of proangiogenic and proliferative growth factors including as vascular endothelial growth factor, erythropoietin, platelet derived growth factor, and transforming growth factor. Mutated pVHL fails to bind HIF-1α and the protein accumulates in the cytoplasm and translocates to the nucleus upregulating the genes of the hypoxia pathway (“pseudohypoxia” pathway). Recent studies using cultured retinal pigment epithelial cells subjected to hypoxic conditions report production of stem cell factors, including Wnt pathway markers, hematopoietic/endothelial progenitor cell factor CD133, CD34, NANOG and NOTCH1. These results suggest origin of the tumor from a vasoformative progenitor cell (angioblast).

References

1. Ceballos KM et al. Lipomatous hemangiopericytoma, a morphologically distinct soft tissue tumor. Arch Pathol Lab Medicine. 1999; 123:941-945.
2. Doyle LA and Fletcher CDM. Peripheral hemangioblastoma clinicopathologic characterization in a series of 22 cases. Am J Surg Pathol. 2014; 38:119-127.
3. Fanburg-Smith J et al. Retroperitoneal peripheral hemagioblastoma: a case report and review of the literature. Annals of Diagnostic Pathology. 200; 4:81-87.
4. Michal M et al. Primary capillary hemangioblastoma of peripheral soft tissues. Am J Surg Pathol. 2004; 28:962-965.
5. Liapis G et al. Lipomatous hemangiopericytoma-solitary fibrous tumour of low malignant potential. OA Case Reports. 2013; 2:72.
6. Nonaka D, Rodriguez J and Rosai J. Extraneural hemangioblastoma: a report of 5 cases. Am J Surg Pathol. 2007; 31:1545-51.
7. Patton KT, Satcher RL and Laskin WB. Capillary hemangioblastoma of soft tissue, a case and review of the literature. Human Pathology. 2005; 36:1135-1139.
8. Ratcliffe PJ, Pugh CW and Maxwell PH. Targeting tumors through the HIF system. Nature Medicine. 2000; 6:1315-16.
9. Yoshida A et al. Soft tissue hemangioblastoma of the retroperitoneum A case study and review of the literature. Appl Immunohistochem Mol Morphol. 2010; 18:479-482.
10. Ponnaluri VKC, Vavilala DT, Parkash S, et al. Hypoxia mediated expression of stem cell markers in VHL-associated hemangioblastomas. Biochem. Biophys. Res. Commun. 2013;438:71-78.
11. Chan CC, Chew EY, Shen J, et al. Expression of stem cell markers in ocular hemangioblastoma associated with vonHippel-Lindau (VHL) disease. Mol. Vis. 2005;11:697-704.

**Case Number 2 (Dr. Missia Kohler, M.D.): Adult Onset Leukodystrophy with Spheroids (AOLD)**

**Clinical history:** The patient was a 58 year-old male with progressive word finding difficulties. As his disease progressed, he developed deficiencies in calculating and writing. Near the time of his death, he was dependent on others for his activities of daily living and had no speech output. The patient ultimately died secondary to dehydration.

**Gross findings:**

The brain weight was significantly decreased from the expected normal range. There was asymmetric atrophy of the frontal, temporal and parietal lobes, and there was asymmetric white matter degeneration of the frontal and parietal lobes.

**Histologic findings:**

Representative sections show severe rarefaction of the white matter in the frontal and temporal lobes. In areas of white matter damage, axonal spheroids are present that stained positive for neurofilament. Pigmented glial cells are also seen in white matter, and these cells autofluoresce. There are many GFAP positive reactive astrocytes, and macrophages are seen in areas of white matter degeneration that are positive for CD68.

**Differential Diagnosis**

* **Frontotemporal Lobar Dementia**
	+ Progressive Supranuclear Palsy
	+ Corticobasal Degeneration
	+ Frontotemporal Lobar Dementia with TAR DNA binding protein-43 (FTLD-TDP)
* **Creutzfeldt-Jakob Disease**
* **Metachromatic Leukodystrophy**
* **Multiple Sclerosis**

**Summary**

Adult Onset Leukodystrophy with Spheroids (AOLD) is a progressive neurodegenerative disorder that is characterized by the presence of axonal spheroids in areas of white matter loss. The age of onset ranges from 15-78 years with a mean age of diagnosis of 42 years. Life expectancy ranges from 2 months to 34 years with a mean age of death at 48 years. Clinically, patients present with dementia, apraxia, ataxia, urinary incontinence and extrapyramidal symptoms. MRI shows patchy abnormalities in cerebral white matter that are initially asymmetrical but as the disease progresses, the lesions become more confluent. Grossly, there is frontal and temporal lobe atrophy along with atrophy of the corticospinal tracts and basis pontis. Some cases also show thinning of the corpus callosum and cerebellar degeneration. Microscopic features white matter rarefication due to widespread loss of myelin sheaths and axonal destruction. An important finding is the presence of axonal spheroids in the areas of white matter degeneration. Axonal spheroids are usually found in areas of recent white matter degeneration while older lesions usually do not contain as many spheroids. Axonal spheroids are contractions of axons into spherical structures. They are associated with axonal injury and can be seen in neurodegenerative disorders along with traumatic brain injury. Additional microscopic features include gliosis, lipid and pigment-laden macrophages. Immunohistochemistry supports the diagnosis and aids in highlighting the features seen on H&E. Neurofilament and a silver Bodian histochemical staining mark the axonal spheroids and the polyubiquitinated protein binding and shuttling component, p62, highlights the ballooned neurons. The macrophages stain positive with CD68. Genetically, AOLD is usually autosomal dominant but sporadic cases have been reported. AOLD is associated with a mutation in *CSR1R* (Colony Stimulating Factor 1 Receptor) gene. This gene codes for a cell surface receptor that regulates survival, proliferation, differentiation and function of microglia. The receptor has three parts: an extracellular ligand binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. The mutation causes disruption of the kinase domain that affects phosphorylation of downstream targets. This mutation links two once thought distinct entities of Pigmented Orthochromatic Leukodystrophy (POLD) and Hereditary Diffuse Leukoencephalopathy with Axonal Spheroids (HLDS) into one disease and AOLD is synonymous with the aforementioned diseases.

References

1. Bigio, E. Making the Diagnosis of Frontotemporal Lobar Degeneration. Archives of Pathology & Laboratory Medicine2013;137: 314-325.

2. Freeman, S., Hyman, B., Sims, K. et al. Adult Onset Leukodystrophy with Neuroaxonal Spheroids: Clinical, Neuroimaging and Neuropathologic Observations. Brain Pathology2009;19: 39-47.

3. Ironside, J., Mccardle, L., Horsburgh, A. et al. Pathological diagnosis of variant Creutzfeldt-Jakob. disease. APMIS2002;110: 79-87.

4. Marotti, J., Tobias, S., Fratkin, J. et al. Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia: Report of a family, historical perspective, and review of the literature. Acta Neuropathologica2004;107: 481-488.

5. Nicholson, A., Baker, M., Finch, N. et al. CSF1R mutations link POLD and HDLS as a single disease entity. Neurology2013;80: 1033-1040.

6. Pressman, P., Bigio, E., & Gittleman, D. Clinical Reasoning: A woman with rapidly progressive apraxia. Neurology2013; 80, 162-165.

7. Rohan, Z., & Matej, R. (2014). Current Concepts in the Classification and Diagnosis of Frontotemporal Lobar Degenerations: A Practical Approach. Archives of Pathology & Laboratory Medicine2014;138:132-138.

8. Seltman, R., Matthews, B. Frontotemporal Lobar Degeneration: epidemiology, pathology, diagnosis and management. CNS Drugs2012;26: 841-870.

9. Wong, J., Chow, T., Hazrati, L. Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia Can Present as Frontotemporal Dementia Syndrome. Dementia and Geriatric Cognitive Disorders2011;32: 150-158.

 **Case Number 3 (Dr. Julianne Ubago, M.D.): Invasive Lobular Carcinoma, pleomorphic variant, with CDH1 mutation**

**Clincal history:**  65 year-old female presented with bloody nipple discharge and a 2.5 cm palpable breast mass.

**Histologic findings:**

Representative breast core sections show discohesive tumor cells infiltrating breast stroma in a single-file architectural pattern. The tumor cells have high-grade morphological features including nuclear pleomorphism, prominent nucleoli, and a high mitotic rate. Evaluation of tumor markers shows that the tumor cells exhibit high expression of estrogen receptor (90%) and progesterone receptor (90%) and are negative for HER2. They also exhibit high Ki-67 proliferation index of 40%, but are negative for p53.

**Differential Diagnosis**

* **Invasive lobular carcinoma, pleomorphic variant**
* **Invasive ductal carcinoma, high grade**
* **Invasive lobular carcinoma, other variants**

 -Classic type

 -Signet-ring variant

* **Metastatic lesion**

**Summary**

Invasive lobular carcinoma (ILC) accounts for approximately 10% of all breast carcinomas and is important to differentiate from ductal carcinomas due to its propensity to metastasize to unique sites including the gastrointestinal and genitourinary tracts, meninges, bone marrow, eyelids, and serosal surfaces. The pleomorphic variant of ILC is a more aggressive variant and accounts for approximately 1% of all breast carcinomas. Microscopically, pleomorphic lobular carcinoma shows plasmacytoid, histiocytic, signet-ring, and/or apocrine features. Pleomorphic lobular carcinoma cells differ from those of conventional lobular carcinoma by their larger size and more abundant eosinophilic cytoplasm, marked nuclear shape variation including the presence of multinucleation, prominent nucleoli, irregular chromatin distribution, and higher mitotic activity. Pleomorphic lobular carcinoma typically conforms to histologic grade 3 invasive carcinoma. Unlike classic ILC that is usually ER/PR positive and HER2 negative, pleomorphic ILC less commonly shows ER/PR expression and is more commonly HER2 positive.

Some ILC are familial cancers associated with specific genetic mutations; our patient carried the CDH1 mutation which alters e-cadherin expression. It is part of the Hereditary Diffuse Gastric Cancer Syndrome (HDGCS) and shows autosomal dominant inheritance. The mutation is most commonly associated with gastric carcinoma, diffuse-type, but 30% of families with this mutation also have ILC history. The CDH1 gene encodes the Epithelial-cadherin protein. E-cadherin is a transmembrane glycoprotein that establishes calcium-dependent, homophilic adhesion complexes between epithelial cells. The protein anchors to actin filaments via intracellular p120, and alpha- and beta-catenin molecules. E-cadherin has an extracellular, transmembrane, and intracellular domain. Hereditary CDH1 mutations involved in HDGCS create premature stop codons which cause e-cadherin to lose all or part of its intracellular domain. This leads to complete loss of function of E-cadherin. This is in contrast to sporadic CDH1 mutations that are usually caused by promoter methylation which downregulates E-cadherin, but do not entirely lose its function or immunoexpression within affected cells. Mutation in the CDH1 gene confers a high risk for the development of breast carcinomas, similar to the risk associated with mutations in the BRCA1 and the BRCA2 genes. Guidelines are currently under development that will guide testing for this mutation as well as specific treatment options for patients with CDH1 mutations.

**References**

1. Benusiglio PR et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet. 2013; 50: 486-489.
2. Bulter D and M Rosa. Pleomorphic Lobular Carcinoma of the Breast. Arch Pathol Lab Med. 2013; 137: 1688-1692.
3. Contreras A and H Sattar. Lobular Neoplasia of the Breast: An Update. Arch Pathol Lab Med. 2009; 133: 1116-1120.
4. Dabbs DJ et al. Lobular neoplasia of the breast revisited with emphasis on the role of e-cadherin immunohistochemistry. Am J Surg Pathol. 2013; 37 (7): e1-e11.
5. Droufaou S et al. Multiple ways of silencing e-cadherin gene expression in Lobular Carcinoma of the breast. Int J Cancer. 2001; 92: 404-408.
6. Foulkes, WD. Inherited Susceptibility to Common Cancers. New England Journal of Medicine. 2008; 359:2143-2153
7. Petridis C et al. Germilne CDH1 mutations in bilateral lobular carcinoma in situ. Br J Cancer. 2014; 110: 1053-7.
8. Xie ZM et al. Germline mutations of the E-cadherin gene in families with inherited invasive lobular breast carcinoma but no diffuse gastric cancer. Cancer. 2011; 117:3112-7.

**Case Number 4 (Dr. Rebecca Linn, M.D.): Diffuse Placental Mesenchymal Dysplasia of one placenta in a diamniotic dichorionic twin gestation without an associated fetus**

**Clinical history:**  A 40 year-old G2P1 woman who conceived via in-vitro fertilization delivered an infant with a known complex heart defect (unbalanced atrioventriular canal) at 39.5 weeks. The 401 gram placenta delivered spontaneously and was followed by the expulsion of a separate 144 gram ovoid, well-circumscribed, white-tan mass measuring 11.5 x 9.1 x 3.2 cm.

**Gross and histologic findings and immunohistochemical profile:** The main placental disc was small for gestational age, but was otherwise unremarkable, with a spongy red cut surface without gross lesions. The well-circumscribed, separate 144 gram ovoid mass had a smooth to lobulated, firm, white-tan to pink cut surface with the appearance of multiple compressed cysts and focal myxoid change, and lacked a defined chorionic plate, basal plate, umbilical cord, fetus, or normal appearing placental parenchyma. Representative sections revealed a compact arrangement of large, bulbous stem villi-like structures without terminal villi. The villi-like structures contained partially sclerosed thick-walled vessels without circulating erythrocytes. These vessels were surrounded by a paucicellular stroma with edematous changes and occasional cistern formation. The outer surfaces of these villous structures were lined by trophoblasts with occasional tufting, but no overt trophoblastic hyperplasia was identified. CD31 immunohistochemical stain highlighted the endothelium lining the large intravillous vessels. Staining for p57/KIP2, a maternally expressed, paternally imprinted/silenced gene product, showed linear nuclear staining of the cytotrophoblast layer lining the enlarged villi; however, the stromal cells were negative.

**Molecular findings**: Short Tandem Repeat (STR) analysis was performed on the abnormal nodule and “normal” placenta. The ratio of maternal to paternal alleles was quantified at each STR. It revealed that the allelic ratios of the abnormal nodule were all outside the normal range indicating pan-genomic allelic imbalance, but no allelic imbalance was detected in the “normal placenta”. These results support the diagnosis of Androgenetic-Biparental Mosaicism (ABM) of the separate abnormal nodule consistent with placental mesenchymal dysplasia (PMD). STR analysis also failed to detect a shared Y chromosome-specific STR locus between the abnormal and normal placenta suggesting that they derived independently from different gametes. Therefore, this gestation likely represents a diamniotic dichorionic twin pregnancy consisting of one normal biparental diploid placenta (46, XY) and viable male fetus and one separate placenta with diffuse PMD (46,XX) and no associated fetus or umbilical cord.

**Differential diagnosis:**

1. **Complete hydatidiform mole (CHM) in a twin gestation with co-existing normal fetus:** Cases of twin gestations, predominantly dizygotic, consisting of one normal placenta with fetus and one CHM are reported in the literature. The molar twin has overall increased amounts of villous tissue for gestational age, with diffuse “grape-like” vesicles. As the CHM out grows its blood supply, it can occasionally infarct resulting in microscopic features reminiscent of PMD. This mimicry is perpetuated by the absence of a chorionic plate or gestational sac. In contrast to PMD, however, abundant circumferential trophoblastic proliferation is present histologically. The villi are also enlarged, edematous with central cisterns, but unlike PMD, often have abundant karyorrhectic villous stromal cells within these cisterns. Immunohistochemically, nuclear staining for p57/KIP2 is absent in both the stromal and cytotrophoblastic cells unlike PMD. Molecular genetic analysis typically reveals complete androgenetic diploidy (46, XX) without a biparental component. A majority of twin gestations affected by CHM are associated with in-vitro fertilization procedures and those affected by CHM with co-twin have a 33-55% risk of developing persistent gestational trophoblastic disease (GTD) as compared to singleton CHM gestations which only have a 15-25% risk.
2. **Partial hydatidiform mole (PHM):**  Similar to the classic cases of PMD, PHM consists of intermixed hydropic villi with vesicles and normal appearing villous tissue and a fetus; however, ectatic, tortuous chorionic vessels with thrombi are not typically present in cases of PHM. Also, in contrast to PMD, the fetus in PHM is usually abnormal, with symmetric intrauterine growth restriction, syndactyly of 3rd/4th digits and a triploid karyotype. Histologically, both have a dimorphic population of edematous/hydropic and normal-appearing villi; however, PHM has focal trophoblast proliferation around the abnormal villi and pseudoinclusions. Immunohistochemical nuclear staining for p57/KIP2 is positive in both the stromal and cytotrophoblastic cells, as there is a maternal component in each cell. Molecular genetic analysis will reveal diandric triploidy with the most common karyotype, 69, XXY. PHM a 1-5% risk of persistent GTD, much lower than CHM.
3. **Accessory lobe with infarction:** Accessory or succenturiate lobe occurs in 5-6% of routinely examined placentas. They typically have membranous vascular connections with the main placental disk, which were completely lacking in our case. Placentas with accessory lobes are at increased risk of infarction (up to 1/3 of cases), which is believed secondary to poor perfusion of maternal blood into the intervillous space. This leads to collapse and eventually fibrin deposition between pale, villi which show coagulative necrosis. These lesions can be patchy with areas of infarct next to viable villi. However, the entire accessory lobe can infarct and grossly these lesions have pale-tan, firm to granular cut surface without the cystic edematous changes that would be more typical of PMD. Molecular genetic analysis will also reveal biparental diploidy.
4. **Involuted or infarct placenta of an absorbed twin:** At delivery, this lesion can look very similar to the separate nodule seen in our case. A vascular accident or fetal abnormality can lead to the death of one twin relatively early in gestation. This intrauterine death leads to involution of the placenta, where the villi progressively become avascular with diffuse loss of basophilia and subsequent fibrin deposition in the intervillous space. Unlike in PMD, this process is not characterized by thick walled, cystically enlarge vessels or edematous, hydropic villi, and is nearly always associated with a fetus papyraceous.
5. **Chorangioma:** Typically presents as an intraparenchymal nodule(s) located along the periphery or subchorionic areas, similar to a classic case of PMD. However, unlike PMD, chorangioma is a well-circumscribed mass lesion composed of a reactive capillary proliferation microscopically reminiscent of a lobulated capillary hemangioma formed in response to hypoxia. Histologically, there is expansion of the stem villi, like in PMD. However, they are non-edematous and instead, have a proliferation of small capillaries embedded in a dense fiber-rich stroma covered by a single layer of trophoblasts. Occasionally, degenerative features including dystrophic calcification, necrosis, infarction, and hemosiderin deposition are evident. Immunohistochemical staining with CD31 will show positive staining of the endothelial lining of the small capillaries. Molecular genetic analysis will reveal biparental diploidy.

**Summary:**

 PMD is a rare, poorly understood placental lesion, initially described by Moscoso et. al. in 1991 as “diffuse mesenchymal stem villous hyperplasia”. Grossly, this lesion is characterized by placentomegaly with dilated, tortuous chorionic vessels and stem-villous hydropic cyst formation, often mimicking a molar gestation. Because of its similar gross appearance, it has previously been called “pseudo-partial mole”, “pseudo-mole” or “partly partial mole”. However, this lesion lacks the classic histologic findings of trophoblast proliferation around the abnormal villi seen in these molar specimens. Hiistologically, PMD reveals intermixed clusters of normal and abnormal villi with enlarged markedly ectatic, thick-walled vessels that predominantly involve stem villi. The chorionic plate demonstrates cistern formation. Distal villi have increased number of peripherally located small, thick-walled vessels and occasionally show hydropic degeneration. The hallmark molecular genetic finding of PMD is the presence of androgenetic-biparental mosaicism (ABM) or the mixture of two embryo-derived cell populations: a normal biparental diploid cell population and a completely androgenetic diploid cell population. The androgenetic cells preferentially distribute to the stroma of the villi, while the cytotrophoblasts are composed of the biparental cell population. The p57/KIP2 staining reflects this zonation within individual villi, with positive nuclear staining of the cytotrophoblasts as they have a maternal allelic component and negative staining of the stroma. The pathogenesis of ABM is incompletely understood, but is thought to be secondary to abnormal mitotic division after fertilization by one or two spermatozoa or fusion of two fertilized oocytes leading to a chimera.

 Unlike the typical case of PMD, our case had no chorionic plate, umbilical cord or fetus. To our knowledge, no cases have been reported with these findings, and in the past may have been mis-diagnosed as molar gestations if evaluated in its early form. Our case may represent a PMD with early loss of the fetus and subsequent involution of the normal villous tissue. Alternatively, it may actually be a link in the spectrum between classic ABM/PMD and complete androgenetic diploidy or CHM. The presence of ABM without the development of a fetus suggests that the phenotype of a gestation with excess androgenetic material greatly depends on the quantity and distribution of these cells within the tissue. Our case may represent a placenta in which a greater proportion of the villi had ABM than is seen in the typical case of PMD.

**References:**

1. Faye-Petersen OM, Kapur R, Placental Mesenchymal Dysplasia in Baergen, RN Ed. Surgical Pathology Clinics: Placental Pathology, Elsevier, Vol. 6, Issue 1, Pages 127-151, March 2013.
2. Heerema-Mckenney A, De Paepe ME, Popek EJ, et al. Diagnostic Pathology: Placenta. Amirsys:Elsevier 2015.
3. Ernst LM, Chou D, Parry S. Fetal thrombotic vasculopathy in twin placentas with complete hydatidiform mole. Pediatric and Developmental Pathology 2009;12:63-67.
4. Lewis GH, DeScipio C, Murphy KM. Characterization of androgenetic/biparental mosaic/chimeric conceptions, including those with a molar component: morphology, p57 immunohistochemistry, molecular genotyping, and risk of persistent gestational trophoblastic disease. International Journal of Gynecological Pathology. 2013;23:199-214.
5. Seckl MH, Sebire NJ, Berkowitz, RS. Gestational trophoblastic disease. Lancet 2010;376,717-719.
6. Pham T, Steele J, Stayboldt C et al. Placental Mesenchymal Dysplasia is Associated with high rates of intrauterine growth restriction and fetal demise. AM J Clin Pathol 2006;126:67-78.
7. Kaiser-Rogers KA, McFadden DE, Livasy CA et al. Androgenetic/biparental mosaicism causes placental mesenchymal dysplasia. J Med Genet 2006; 43:187-192.
8. Zhang P, McGinniss MJ, Sawai S, Benirschke K. Diploid/Triploid mosiac placenta with fetus towards a better understanding of ‘’partial moles’. Early Human Development. 2000;60, 1-11.
9. Suzuki S, Igarashi M. Clinical significance of pregnancies with succenturiate lobes of placenta. Arch Gynecol Obstet. 2008 Apr;277(4):299-301.

**Case Number 5 (Dr. Joseph Peevey, M.D.): Metastatic melanoma of gallbladder mucosa as primary site of recurrence.**

**Clinical history:** A 59-year-old male presented with a 3-day history of episodic right upper quadrant pain accompanied by nausea. CT revealed a thickened gallbladder consistent with cholecystitis. An attempt at cholecystectomy was terminated by obscuring inflammation and the patient was started on a 10-day course of antibiotics. Five months later, the patient returned again with symptoms of cholecystitis and a laparoscopic cholecystectomy was successfully performed.

**Gross and histologic findings and immunohistochemical profile:**

Laparoscopic cholecystectomy revealed an 8.6 x 3.8 x 3.5 cm gallbladder with roughened, hemorrhagic serosa and a thickened (1.5cm) wall. The gallbladder lumen contained friable pink-tan tissue which was adherent to the mucosa of the neck, body, fundus, and cystic duct. Histologic sections revealed infiltration of the gallbladder mucosa by a poorly differentiated neoplasm. The cells are large and epithelioid, and exhibit marked pleomorphism with abundant eosinophilic cytoplasm, and vesicular, often times multiple, nuclei harboring prominent centrally located nucleoli. Numerous mitosis including atypical mitotic figures were identified. Scattered small lymphocytes and plasma cells are noted throughout the lesion. There are no areas of invasion into the muscularis propria and no lymphovascular invasion is identified. Immunohistochemically, the tumor cells are diffusely and strongly positive for S-100 protein and SOX-10, but were negative stains for keratin AE 1/3, HMB-45, Melan-A, and EBER.

**Differential Diagnosis:**

**1. Gallbladder Carcinoma**: Highly fatal, but a rather uncommon malignancy. Vast majority are adenocarcinoma, however other subtypes do exist. Undifferentiated subtypes which would enter the differential diagnosis, lack glandular structures and include a variety of morphotypes, including spindle and giant cell carcinomas; carcinomas with osteoclast-like giant cells; small cell carcinoma; and a nodular or lobular type. Absence of a precursor lesion and the immunoprofile precludes this diagnosis.

**2. Metastatic adenocarcinoma:** Rarely reported intra-biliary growth ofmetastatic adenocarcinoma involving the liver, often colonic primary, can involve the gall bladder. Notably, metastatic tumors can spread along epithelial surfaces of biliary tree without disruption of basement membraneleading to a mucosal-restricted pattern of growth. Within the bile ducts this pattern can be confused with cholangiocarcinoma. Considered amongst possible carcinomas known to metastasize to gastrointestinal mucosa, were lobularbreast and gastric. The absence of a differentiated carcinoma elsewhere, and the immunoprofile preclude these diagnoses.

**3. High-grade, large cell lymphoma:** Secondary involvement of the gall bladder by systemic lymphoma is the most common presentation for lymphoma. AlthoughMALT is reportedly the most common primary lymphoma of gallbladder, primary large cell lymphoma occasionally arises in the gall bladder. This entity often presents with symptoms including lymphadenopathy and B-symptoms. Immunohistochemically, large cell lymphoma generally is a “B” cell neoplasm. Anaplastic large cell lymphoma can display multinucleate large cells, but is characterized by a cell with a reniform nucleus and paranuclear hof (“hallmark” cell). This lymphoma typically demonstrates expression of CD30, “T” cell markers, and often EMA. The immunoprofile in our case precludes these diagnoses.

**4. Follicular dendritic cell sarcoma:** A rare neoplasm that more commonly presents in head and neck region as lymphadenopathy, but can also present in gastrointestinal tract and soft tissue. Low-grade tumors display storiform growth of monomorphic spindled cells exhibiting vesicular nuclei and conspicuous nucleoli. High-grade variants more closely resemble our case as they display pleomorphic epithelioid cells with prominent nucleoli. Both subtypes have a prominent lymphoplasmacytic component. Tumors of purported follicular dendritic cell origin involving liver and spleen are often EBV-driven. Malignant follicular dendritic cells convincely express vimentin, CD21, CD35, and clusterin, but only weakly express S-100 protein. Interdigitating reticulum cell sarcoma, a tumor virtually restricted to lymph nodes (with rare examples occurring extranodally) and showing histologic overlap with follicular dendritic cell tumor, is more convincingly S-100 positive. With strong S100 and SOX10 positivity in our case, these diagnoses are excluded.

**Summary:**

Reports of malignant melanoma metastasizing to virtually any organ of the body and to bizarre sites years after diagnosis are legion, and the phenomenon carries a very poor prognosis with a survival period of 8.5 months from time of first metastasis. Gastrointestinal melanoma metastases do occur not infrequently. However, isolated metastasis to the gallbladder is a rarely reported phenomenon (5 cases in the English language literature; PUBMED). More commonly, the gallbladder is one of a multitude of sites involved by metastatic disease. Patients with isolated, resectable gallbladder metastasis generally live longer with survival up to 9 years reported in the literature. Microscopically, the lesion in our case was restricted to the mucosa without lymphovascular invasion or invasion into muscularis propria. Additional resection of surrounding tissue and lymph nodes was also negative for additional tumor. Indefinite and frequent disease surveillance via imaging and physical exam screening is needed for this patient, however 10-month post cholecystectomy the patient remains disease free. This case emphasizes the need for effective communication between clinician and pathologist. Without knowledge of a prior malignancy, the potential for misdiagnosis of an undifferentiated neoplasm is high.

**References:**

1. Vernadakis S, Rallis G, Danias N, et al. Metastatic melanoma of the gallbladder: An unusual clinical presentation of acute cholecystitis. World Journal of Gastroenterology.2009; 15: 3434-3436
2. Marone U, Caraco C, Losito S, et al. Laparoscopic cholecystectomy for melanoma metastatic to the gallbladder: is it an adequate surgical procedure? Report of a case and review of the literature. World Journal of Surgical Oncology 2007; 5: 141.
3. Samplaski M, Rosato E, Witkieqicz, et al. Malignant melanoma of the gallbladder: A report of two cases and review of the literature. Journal of Gastrointestinal Surgery 2008;12:1123-1126.
4. Gogas J, Mantas D, Gogas H, et al. Metastati melanoma in the gallbladder: Report of a case. Surgery Today 2003;33: 135-137.
5. Hundal R. and Shaffer E. Gallbladder cancer: epidemiology and outcome. Clinical Epidemiology. 2014;6: 99-109
6. Inui K, Yoshino J. Diagnosis of gallbladder tumors. Internal Medicine. 2011;50: 1133-1136.
7. Riopel M, Klimstra D, Godellas C, et al. Intrabiliary growth of metastatic colonic adenocarcinoma: A pattern of intrahepatic spread easily confused with primary neoplasia of the biliary tract. The American Journal of Surgical Pathology. 1997;21: 1030-1036.
8. Ghittoni G, Caturelli E, Viera F. Intrabile duct metastasis from colonic adenocarcinoma without liver parenchyma involvement: contrast enhanced ultrasonography detection. Abdominal Imaging. 2010;35: 346-348.
9. Li L, Shi Y, Gou Z, et al. Clinicopathological features and prognosis assessment of extranodal follicular dendritic cell sarcoma. World Journal of Gastroenterology. 2010;20: 2504-2519.
10. Kang T, Lee S, Song H. Follicular dendritic cell sarcoma of the abdomen: the imaging findings. Korean Journal of Radiology. 2011;11: 239-243.
11. Mitropoulos F. Primary Non-Hodgkins lymphoma of the gallbladder. Leukemia & Lymphoma. 2000;40: 123-31.

**Case Number 6 (Dr. Andrew Bandy, M.D.); Uterine smooth muscle tumor with HMB-45 expression**

**Clinical history:** The patient is a 50-year-old female who underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy for a 17 cm uterine mass.

**Gross and histologic findings and immunohistochemical profile**: The specimen is a 17.0 cm well-circumscribed myometrial mass with a white-tan, whorled cut surface showing yellow-tan areas and foci of hemorrhage. Representative sections demonstrate a lesion composed of a heterogeneous population of large spindled cells with eosinophilic, fibrillar cytoplasm and blunt-ended nuclei with vesicular chromatin, along with scattered epithelioid cells with atypical enlarged hyperchromatic nuclei harboring an occasional enlarged nucleolus, and abundant clear to foamy cytoplasm. Additionally, foamy histiocytes are encountered throughout the lesion. Mitoses are infrequent (up to 2 mitoses per 10 high power fields), but rare atypical mitotic figures are identified. Necrosis is not observed in any of the sections examined. Lesional cells immunoexpress ER, PR, WT-1, desmin and caldesmon, with weak and diffuse reactivity with smooth muscle actin and scattered positivity for HMB-45 in the large, atypical foamy cells. Lesional cells fail to express Melan A, MITF, PAX-8 and CD1a.

**Differential Diagnosis**:

1. **Perivascular Epithelioid Cell Neoplasm (PEComa)**: Although uterine PEComa is an infrequently encountered lesion, the female genital tract is a common site for this tumor with most cases reported in the uterus, and rarely in adnexa, cervix, or vagina. In the uterus, the lesion presents as a solitary mass with gray–white, tan to yellow, whorled to fleshy cut surface. The process presents as a well-circumscribed mass occasionally growing up to 16.0 cm in size or as ill-defined cords and nests growing in a manner reminiscent of low-grade endometrial stromal sarcoma. Histologically, the lesion differs from USMT by its composition of epithelioid and spindled cells with clear, vacuolated to granular eosinophilic cytoplasm lacking the fibrillar quality of a smooth muscle tumor, and an accentuated vascular network which separates groups of cells into nests. Features associated with malignancy include size >5cm, hypercellularity, high nuclear grade, mitotic activity >1/50 HPF, tumoral necrosis, vascular invasion, and infiltrative growth. Lesional cells immunoexpress HMB-45, but unlike USMT, also express additional melanocytic markers including melan A and MITF. TFE3/TFEb/MiTf upregulation of Cathepsin K results in its overexpression in PEComa. PEComa is also positive for at least one muscle marker including smooth muscle actin, desmin and caldesmon, and may express ER and PR. A subset of tumors occurring in younger-aged patients and exhibiting features overlapping with alveolar soft part sarcoma also express TFE-3 with reduction of smooth muscle marker expression. Some reports found positivity for CD1a in PEComa, which also assists in excluding a smooth muscle tumor. The lesion is negative for keratins and PAX-8.
2. **Endometrial Stromal Tumor:** An umbrella group which includes endometrial stromal nodule, low- and high-grade endometrial stromal sarcomas (ESS), and undifferentiated uterine sarcomas (UUS), are relatively uncommon uterine tumors. Grossly, all but the stromal nodule are usually poorly circumscribed. The endometrial stromal nodule is typically located in the myometrium, whereas endometrial stromal sarcomas are endometrial with extension into the myometrium. Endometrial stromal sarcomas are soft, fleshy, polypoid masses which grow and fill the endometrial cavity. Associated abundant hemorrhage and tumor necrosis may be present. The smooth muscle histologic features of the spindle component in our tumor do not resemble the spindle cells of endometrial stroma, thereby excluding endometrial stromal nodule and low-grade ESS. The cytologic atypia witnessed in our case most closely resembles the pleomorphism expected of UUS (in contrast to the more monomorphic atypia of high-grade ESS) with large cells exhibiting considerable variation in nuclear size and shape. Unlike our tumor, UUS exhibits true pleomorphism of anaplasia with nuclei exhibiting abnormal chromatin distribution, irregular nuclear membranes, and prominent nucleoli. Numerous mitotic figures are often evident in UUS. UUS, unlike low-grade endometrial stromal tumors, demonstrates only weak CD10 expression, and, in contrast to USMT, could potentially show weak expression of myoid markers.

**Summary:**

Uterine smooth muscle tumors (USMT) are extremely common. Many women with USMTs remain asymptomatic while others can have a varied clinical presentation which may warrant treatment. Generally, the leiomyoma presents as a sharply circumscribed, round, firm, gray-white mass with a whorled cut surface which often “shells out” of the surrounding myometrium, while leiomyosarcomas are more likely to have a fleshy cut surface with hemorrhage, necrosis, and a more infiltrative border. USMTs are generally spindle cell neoplasms, however epithelioid and clear cell features are occasionally encountered. The most commonly used microscopic predictors of clinical behavior of USMT are the number of mitotic figures, cytological atypia and tumor cell necrosis. The latter two parameters are readily appreciated at low-power magnification. Using these standardized criteria, the marked atypia, absence of necrosis and low mitotic count (2/10hpf) despite atypical mitotic figures identified in this case stratify this tumor into a “smooth muscle tumor of undetermined malignant potential (STUMP)” category. This designation is used when a smooth muscle tumor exhibits histological features equivocal for a definitive diagnosis of malignancy. Categories of STUMP (Kurman RJ. *Blaustein’s Pathology of the Female Genital Tract*; 6th. edition) include tumors exhibiting: 1.) mitotic index less than 10 mitoses per 10 HPF, mild atypia, and tumoral necrosis; 2.) 5-9 mitoses per 10 HPF (or atypical mitotic figures), diffuse moderate to severe atypia, but no tumoral necrosis, or 3.) >4 mitoses per 10 HPF, focal moderate to severe atypia, but no tumoral necrosis. One recent study found that 4-27% of STUMPs recur or metastasize.

Immunohistochemically, USMTs express combinations of smooth muscle markers (smooth muscle actin, calponin, desmin, and caldesmon) and Mullerian-related markers (ER, PR, WT-1). USMTs may occasionally express keratins 8 & 18. Leiomyosarcomas often demonstrate loss of PR, and diffuse expression of both p16 and p53. Tumors histologically conforming to STUMP but showing diffuse p16 and/or p53 have a high-risk for recurrence and/or metastasis. One study claims Ki-67 and/or p53 expression in over 15% of cells in all leiomyosarcomas, but not in any of the STUMPs tested.

Leiomyosarcomas of the uterus, including conventional and epithelioid clear cell morphotypes, occasionally express HMB-45. The majority of HMB-45-expressing leiomyosarcomas are poorly differentiated. HMB-45 expression has also been noted in a minority of leiomyomata and in somewhat less than 25% of endometrial stromal sarcomas. The reason for expression of HMB-45 in these tumors is currently a conundrum. In the absence of additional melanocytic marker positivity, as would be expected in uterine PEComa, it is recommended that tumors with morphologic features of smooth muscle tumors be diagnosed as such regardless of HMB-45 expression.

**References**:

1. Abeler VM, Nenodovic M. Diagnostic Immunohistochemistry in Uterine Sarcomas: A Study of 397 Cases. Int J Gynecol Pathol. 2011;30:236-243.
2. Conklin, CM, Longacre TA. Endometrial Stromal Tumors: The New WHO Classification. Adv Anat Pathol. 2014;21:383-393.
3. Fadare O, Liang SX. Epithelioid smooth muscle tumors of the uterus do not express CD1a:a potential immunohistochemical adjunct in their distinction from uterine perivascular epithelioid cell tumors. Annals of Diagnostic Pathology. 2008;12:401-405.
4. Folpe AL, Mentzel T, Lehr HA, et al. Perivascular Epithelioid Cell Neoplasms of Soft Tissue and Gynecologic Origin, A Clinicopathologic Study of 26 Cases and Review of the Literature. Am J Surg Pathol. 2005;29:1558-1575.
5. Ip PP, Cheung AN et al. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): a clinicopathologic analysis of 16 cases. Am J Surg Pathol. 2009;33:992-1005.
6. Saavedra JA, Heredia RD, Montero FC, et al. Endometrial Stromal Sarcomas, Immunoprofile with Emphasis on HMB45 Reactivity. Am J Clin Pathol. 2014;141:850-855.
7. Schoolmeester JK, Howitt BE, Hirsch MS, et al. Perivascular Epitheloid Cell Neoplasm (PEComa) of the Gynecologic Tract, Clinicopathologic and Immunohistochemical Characterization of 16 cases. Am J Surg Pathol 2014;38:176-188.
8. Silva EG, Bodurka DC, Scouros MA,et al. A uterine leiomyosarcoma that became positive for HMB45 in the metastasis. Annals of Diagnostic Pathology. 2005;9:43-45.
9. Silva EG, Deavers MT, Bodurka DC, et al. Uterine Epithelioid Leiomyosarcomas with Clear Cells, Reactivity with HMB-45 and the Concept of PEComa. Am J Surg Pathol. 2004;28:244-249.
10. Simpson KW, Albores-Saavedra J. HMB-45 Reactivity in Conventional Uterine Leiomyosarcomas. Am J Surg Pathol 2007;31:95-98.
11. Mittal K, Levine R et al. MIB-1 (Ki-67), p53, estrogen receptor, and progesterone receptor expression in uterine smooth muscle tumors. Hum Pathol. 2001;32:984-987.