**Illinois Registry of Anatomic**

**Pathology**

**Northwestern Memorial Hospital**

**22 October 2012**

Case Number 1 (Celina Villa, MD**): Diffuse large B cell lymphoma of the brain with bizarre morphology in an immunocompetent woman.**

**Histology**

Representative sections show a hypercellular lesion composed of large, poorly cohesive, pleomorphic cells with moderate amount of pale, eosinophilic cytoplasm. A striking population of larger cells with enormous nuclei containing many prominent nucleoli is noted. Mitotic activity is brisk and numerous apoptotic bodies and foci necrosis are identified.

**Differential diagnosis**

Primary brain lesions:

Glioblastoma multiforme

Giant cell variant

Gliosarcoma variant

Metastatic lesions:

Melanoma

Poorly differentiated carcinoma

Hematopoietic malignancy

**Immunohistochemical studies**

Positive stains:

CD45, CD20, CD79a, PAX-5: Supports B cell origin

Bcl-6 and MUM-1: Supports a non-germinal center lymphoma

Negative stains:

Germinal center cell marker: CD10

T cell markers: CD3, CD5

Glial marker: GFAP

Epithelial markers: CAM 5.2, CK7, CK20, Mammaglobin, TTF-1, p63

Melanoma marker: HMB45

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Case Number 2 (Dr. Emily Rostlund, M.D**.): Intrauterine fetal demise secondary to congenital parvovirus B19 infection**

**GROSS AND HISTOLOGIC FINDINGS:**

Autopsy revealed a non-dysmorphic male fetus with organ weights and measurements overall consistent with 13-14 weeks gestation. The majority of the organs showed significant maceration changes with maximal or near maximal loss of nuclear basophilia. The presence of maximal loss of basophilia in the adrenal glands was consistent with intrauterine fetal demise at least one week prior to delivery. The fetal lungs, kidneys, liver and many other organs contained innumerable erythroid cells containing large, glassy, pink viral-type intranuclear inclusions, most of which were seen in the vessels. Rare inclusions were seen in the vessels within the placental villi.

**DIFFERENTIAL DIAGNOSIS:**

- Cytomegalovirus

- Herpes Simplex Virus

- Parvovirus B19

- Varicella Zoster virus

**IMMUNOHISTOCHEMISTRY:**

- Parvovirus immunostain: innumerable positive erythroid cells in fetal and placental tissue

- CMV immunostains: negative

- HSV immunostains: negative

**SUMMARY:**

Parvovirus 19 is a single-stranded DNA virus that most commonly presents as the self-limited “fifth disease” or erythema infectiosum in children. Infants infected via maternal transmission may present with fetal hydrops detectable by ultrasound. This complication results from the proclivity for the virus to infect rapidly proliferating erythroid progenitor cells causing anemia. The virus also infects myocardial cells and can cause congestive heart failure. Direct injury to the liver and extramedullary hematopoiesis within the liver reduce the organ’s capacity to produce albumen and colloid osmotic pressure decreases. Hydrops occurs in approximately 10% of infants infected before 20 weeks. With in-utero transfusion, most infants appear to recover from the infection even if severely anemic prior to the procedure.

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Case Number 3 (Dr. E. Gersbach, M.D.): **Extranodal Rosai-Dorfman Disease with Cutaneous Manifestations**

**HISTOLOGY:** Low-power magnification shows a relatively well-circumscribed intradermal nodule composed of large cells with abundant pale cytoplasm and scattered lymphocytes and plasma cells. Higher magnification reveals a sheet-like growth pattern of large, polygonal cells with pale eosinophilic cytoplasm and nuclei with small but conspicuous nucleoli. The cytoplasm of the large cells contains intact lymphocytes and occasional plasma cells (emperiopolesis). The background contains many lymphocytes and plasma cells. Dilated lymphatics are present and some contain the large pale cells exhibiting emperiopolesis.

**DIFFERENTIAL DIAGNOSIS**: (All of these histiocytic/dendritic cell tumors express hemosiderin scavenger receptor, CD163, and lack convincing emperiopolesis)

-Histiocytic pseudotumor-Spindle cell histiocytic proliferation containing numerous (usually mycobacterial and less often bacterial) organisms and acute inflammatory cells.

-Langerhans Cell Histiocytosis- Histiocytes with “coffee bean” nuclei and a heavy eosinophilic infiltrate. Immunohistochemically, lesion is positive for Langerin (most specific) and CD1a. Approximately 40% of tested examples show *BRAF* mutations.

-Juvenile Xanthogranuloma (and clinical variants, progressive nodular histiocytosis, eruptive histiocytosis, and xanthoma disseminata)- Non-Langerhans cell histiocytic lesion with Touton-type giant cells and smaller xanthomatous cells (in the well-developed stage of the process). Immunohistochemically, lesional cells are negative for S100-protein.

-Erdheim-Chester Disease-Disseminated form of non-Langerhans cell histiocytosis characterized clinically by radiologic evidence of diaphyseal and metaphyseal sclerosis of long bone along with extraskeletal manifestations including lung and cutaneous lesions. Immunohistochemically, lesional cells are negative for S100-protein. Approximately 50% of tested examples show *BRAF* mutations.

Reticulohistiocytosis- histiocytes with PAS-(+) eosinophilic cytoplasm and characteristically 2-10 nuclei per cell. Multifocal lesions predilect to face and digits and are associated with internal malignancy (30%) and arthritis and demonstrate less multinucleation.

**SPECIAL STAINS:**

-S100: Positive in large lesional cells

-CD68: Positive in large lesional cells

-CD163: Positive in large lesional cells

-CD1a: Negative

-p16: Focally positive

-SV40: Negative

-CMV: Negative

**Etiology:**

Etiology of lesion probably abnormal histiocytic reaction to unknown antigen. Possible inciting agents include CMV, HHV6 and 8, and SV40 (but molecular proof is lacking).

**Summary:**

Extra-nodal Rosai-Dorfman occurs in up to 40% of patients with or without nodal disease. Skin, head and neck, and bone are the three most commonly affected sites. Cutaneous lesions often times demonstrate more spindling and fibrosis than non-cutaneous lesions. Etiology is presently a conundrum. Our patient fits this category as he was not found to have lymphadenopathy but did manifest extensive involvement of the nasal mucosa with lesions having clinical features of Rosai-Dorfman.

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Case Number 4 (Dr. Elizabeth Bertsch, M.D.): **Sessile Serrated Polyposis**

**Clinical History:** The patient is a 66-year-old male with no significant past medical, surgical, or family history who presented for a routine screening colonoscopy. Biopsies of the polyps were consistent with tubular adenomas and sessile serrated polyps with and without dysplasia. Due to polyp burden, the patient subsequently underwent an open total proctocolectomy with loop ileostomy which revealed approximately 50-60 polyps predominately in the left colon ranging in size from 0.4 to 2.4 cm in greatest dimension. A majority of the polyps were grossly sessile.

**Diagnosis: Sessile Serrated Polyposis**

**Differential Diagnosis:**

• Familial adenomatous polyposis

• Juvenile polyposis

• Peutz-Jeghers syndrome

• PTEN hamartoma tumor syndrome

• Hyperplastic/serrated polyposis syndrome

**WHO Criteria:**

• At least 5 serrated polyps proximal to the sigmoid colon (with most in the right colon) which include 2 polyps that > 1 cm

• > 20 serrated polyps of any size distributed throughout the colon

• Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis syndrome

**Key Microscopic Features of Serrated Adenoma:**

• Architectural distortion including crypt dilatation, horizontal orientation of deep crypts, serrations of crypt epithelium extending to the crypt bases, and inverted crypts

• Abnormal proliferation including mitoses in upper crypts, and cells within the mid and upper portion of the crypt that exhibit nuclear atypia and prominent nucleoli.

**Immunohistochemical stains:**

• Loss of hMLH1 can be demonstrated in regions of conventional epithelial dysplasia or carcinoma

**Discussion:**

• Serrated polyposis syndrome is a newly described entity that differs from the above mentioned colorectal cancer syndromes by lacking a distinct genetic abnormality.

• Serrated polyposis syndrome is likely underrecognized by clinicians and pathologist, but is associated with an increased risk of colorectal carcinoma.

• The syndrome is associated with an increase number of serrated polyps (mostly microvesicular hyperplastic polyps and serrated adenomas with and without conventional dysplasia).

• Recent studies have shown that the serrated polyps in the syndrome are associated with *BRAF* mutations and the serrated pathway of colorectal carcinogenesis, while the conventional adenomas in these patients more often harbor *KRAS* mutations.

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Case Number 5 (Dr. Adam Beattie, M.D.): **Mammary Analogue Secretory Carcinoma.**

**HISTOLOGICAL AND IMMUNOHISTOCHEMICAL FINDINGS:**

Representative section of the tumor reveals a lobular architecture with cells arranged in microcystic, tubular, papillary and solid patterns. At low power, the microcystic and tubular spaces contain eosinophilic secretory material that stain positive for PAS. At higher power, the cells have large vesicular nuclei with distinctive centrally located nucleoli and pale eosinophilic granular or vacuolated cytoplasm3. PAS staining, however, fails to identify intracytoplasmic zymogen granules. Tumor cells demonstrate strong and diffuse Immunoexpression of S100 protein and mammoglobin, but negativity for smooth muscle markers3.

**DIFFERENTIAL DIAGNOSES:**

1. **Acinic Cell Carcinoma**: This tumor has the potential to show histologic overlap with the mammary analogue secretory carcinoma. Characteristically, well-differentiated acinic cell carcinoma features polygonal cells with vesicular nuclei, prominent nucleoli and lightly basophilic cytoplasm harboring coarse eosinophilic zymogen granules that are located apically within the cell. Less differentiated examples demonstrate cytologic and architectural features that simulate those of the mammary analogue secretory carcinoma. Clinicopathologic features distinguishing the latter from acinic cell carcinoma include male predominance, cytoplasmic zymogen-type secretory granules which are PAS-diastase( +), and stronger S100-protein, mammaglobin immunoexpression, weak or absent DOG-1 expression, and presence of the characteristic t(12;15)(p13;q25).
2. **Low Grade Cystadenocarcinoma:** Low-grade ductal carcinoma that is usually non-invasive (intraductal) as evidenced by tumor nests invested by myoepithelial cells. The tumor shows histologic overlap with mammary analogue secretory carcinoma. This tumor demonstrates cribriform and micropapillary growth patterns resembling atypical hyperplasia or low-grade intraductal carcinoma of the breast. Tumors may express S100-protein (+), but lack mammaglobin expression and are not associated with t(12;15) ETV6-NTRK3.
3. **Adenoid Cystic Carcinoma**: Distinct dual population of ductal and myoepithelial cells with high nucleocytoplasmic ratios and hyperchromatic, angulated nuclei. Immunohistochemically, cells of adenoid cystic carcinoma express myoepithelial markers, S100-protein, smooth muscle markers, c-kit (CD117), and p63(peripheral pattern of expression); and also CD43.
4. **Mucoepidermoid Carcinoma**: Composed of variable proportions of mucous, epidermoid, and intermediate (most common) cells; associated with t(11;19), MECT-MAML2.

**Summary:**

Mammary analogue secretory carcinoma (MASC) is a recently described low-grade malignancy of salivary glands that predilects the parotid gland. Histologically, the tumor shows histological features of mammary secretory carcinoma of the breast1. Over one-half of salivary gland tumors initially categorized as “zymogen granule-poor” acinic cell carcinomas and some S100-positive low-grade ductal carcinomas of the salivary gland (low-grade cystadenocarcinoma) have been reclassified as MASC based primarily on the presence of t(12;15)1. The tumor shows a low-power lobular architecture with macrocystic, microcystic, tubular, and solid growth patterns1. Cytologically, the cells show low-grade vesicular nuclei and pale, PAS-(-) eosinophilic granular or vacuolated cytoplasm3. One feature that is helpful in differentiating MASC from acinic cell carcinoma is the absence of zymogen (PAS-positive)3 Intracytoplasmic granules. Immunohistochemistry is also helpful as MASC shows strong positivity for S100-protein, high-molecular weight keratin, MUC1, MUC4, and mammoglobin, and negativity for basal cell/myoepithelial markers p63, calponin, and smooth muscle actin3. Additionally, MASC demonstrates a distinct translocation, t(12;15)(p13;q25) which has not been identified in other salivary gland tumors3. This translocation results in the ETV6-NTRK3 fusion3. The translocation is confirmed by FISH using the ETV6 (TEL) (12p13) Dual Color, Break Apart Rearrangement Probe (VYSIS/Abbott)3. The ETV6-NTRK3 translocation is not specific to MASC and is also found in infantile fibrosarcoma, secretory carcinoma of the breast, acute myelogenous leukemias, and cellular mesoblastic nephroma3. The survival rate for MASC is slightly worse than that of classical acinic cell carcinoma.

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Case Number 6 (Dr. Alexandra Larson, MD): **Inflammatory Myofibroblastic Tumor of the Bladder**

**HISTOLOGIC AND IMMUNOHISTOCHEMICAL FINDINGS:**

Microscopic examination reveals a variably cellular submucosal spindle cell tumor that infiltrates the muscularis propria but does not appear to arise from it. In the superficial hypocellular areas, the background is myxoid and a granulation tissue-like proliferation of capillaries and prominent acute inflammatory infiltrate are observed. In the deeper, more cellular areas, the spindle cells form fascicles. The cells in both areas are cytologically uniform with abundant bipolar eosinophilic fibrillar cytoplasm, which lacks cross-striations. The nuclei are vesicular with finely dispersed chromatin and a conspicuous nucleolus. No cytological atypia, atypical mitotic figures, or deep tumoral necrosis are identified. Immunohistochemically, the cells express keratin AE1/AE3 and smooth muscle actin in a “tram-track” or perimembranous pattern, but are negative for desmin. They display cytoplasmic positivity for anti-ALK-1.

**DIFFERENTIAL DIAGNOSES:**

Postoperative spindle cell nodule: History of recent instrumentation/surgery; diffusely hypercellular; less myxoid and inflamed, and show many mitoses.

Pseudosarcomatous stromal reaction: Spindle cell reaction to urothelial carcinoma; nodular-fasciitis-like pattern of reactive-appearing spindled cells with a similar immunoprofile as IMT, including ALK positivity.

Leiomyosarcoma : Intimately associated with muscularis propria; cellular with conspicuous nuclear pleomorphism/atypia; mitoses (including atypical forms), thick-walled vessels, less of a myxoid stroma, a lesser number of plasma cells, and/or deep tumor necrosis are present.

Sarcomatoid carcinoma: variant of urothelial carcinoma with frank sarcomatous cytology around invading carcinoma

**SUMMARY:**

Inflammatory myofibroblastic tumor of the bladder is a neoplastic entity with the potential for misdiagnosis as leiomyosarcoma (smooth muscle appearance of the cells and infiltration of muscularis in nearly 50% of cases) or sarcomatoid carcinoma (due to keratin immunoexpression). Attention to the uniform cytologic appearance of the myoid cells, the thin-walled granulation tissue-like vascular component, plasma cell infiltrate, and perimembranous immunoexpression of smooth muscle actin (characteristic of myofibroblasts) and ALK-1 expression in the majority of cases will lead to the correct diagnosis.

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