**RUSH UNIVERSITY MEDICAL CENTER**

**ILLINOIS**

**REGISTRY OF**

**ANATOMIC PATHOLOGY**

**CASE HISTORIES AND DIAGNOSES**

**MARCH 30, 2015**

**Case #1**

**PRESENTER:** Jorge Novo, MD

**ATTENDING:** Leonidas Arvanitis, MD

**CASE HISTORY:** A 55-year-old woman with a history of morning headaches, nausea and lethargy presents to the emergency department after a new onset-seizure. CT scan shows multiple cystic lesions with scattered calcifications in the cerebral hemispheres, basal ganglia, pons, and cerebellum. MRI shows multiple cysts with contrast enhancement, and white matter edema. After a stereotactic biopsy is performed, the patient undergoes resection of the lesion.

**DIAGNOSIS:** Leukoencephalopathy, Cerebral calcifications and Cysts (LCC).

**DISCUSSION:**

* LCC is a very rare leukoencephalopathy, with only 19 adult cases reported in the English literature, and only 13 with histopathologic examination. (range = 18-69, mean age = 34).
* Clinical presentation may present with acute neurologic symptoms simulating a stroke, or present with symptoms of mass effect mimicking a neoplasm.
* Initially characterized in 1996 by Labrune et. al. with the radiologic triad of:
  + Progressive cerebral and cerebellar calcifications.
  + Diffuse abnormal white matter signaling.
  + Space-occupying cysts with mass effect.
* Kleinschmidt-DeMasters et. al. performed the most detailed histopathologic characterization of LCC in 2009. H&E examination shows:
  + Gliosis.
  + Rosenthal fibers.
  + Angiomatous changes with fibrin thrombi and surrounding microinfarction.
  + Calcifications.
* Current pathogenesis is unknown, although it is thought to be related to other small vessel disorders (CADASIL, CARASIL, HERNS, cerebral amyloid angiopathy). No genetic alterations have been currently identified.
* Prognosis is variable due to cyst expansion.
* Approximately 40% of patients undergo surgery for symptom management.
  + If resectable, excision of the cysts is recommended.
  + Shunting procedures (LP,VP, CVP, Ommaya) have been demonstrated to manage symptoms in patients with LCC.
* Differential diagnosis includes:
  + Neoplastic prcesses (glioma, glioneuronal).
  + Infectious (Toxoplasmosis, chronic neurocysticersosis).
  + Vascular (thromboembolic, cerebral amyloid angiopathy, CADASIL).
  + Metabolic (Fahr disease).
  + Leukoencephalopathy (Coat’s plus syndrome)
    - Infancy or early childhood onset. Rare adult cases.
    - Similar radiologic triad + retinal telangiectasis or exudates.
    - Physical abnormalities, including skin and hair changes, lytic and sclerotic metaphyseal lesions, and vascular ectasias in stomach, small intestine and liver.
    - Characterized by CTC1 mutations.

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**Case # 2**

**PRESENTER:** Smita Patel, MD, PGY-2

**ATTENDING:** David Cimbaluk, MD

**DIAGNOSIS:** Collagenofibrotic Glomerulopathy (aka; collagen type-III glomerulopathy)

**IMPORTANT DIFFERENTIAL DIAGNOSIS BASED ON LIGHT MICROSCOPY, SPECIAL STAINS AND IMMUNOFLUORESCENCE:**

* Membranoproliferative Glomerulonephritis type I
* Diabetic Glomerulosclerosis
* Light chain deposition disease
* Amyloidosis
* Immunotactoid glomerulopathy

**IMPORTANT DIFFERENTIAL DIAGNOSIS BASED ULTRASTRUCTURAL FEATURES:**

* Fibronectin Glomerulopathy:
  + Inherited disease with non-organized deposits of fibronectin in fine granular pattern in mesangium
* Nail-patella syndrome:
  + Inherited disease with characteristic physical abnormalities
  + The atypical collagen type-III accumulates in lamina densa of glomerular basement membrane (GBM) causing an irregular thickening of GBM

**KEY MORPHOLOGICAL FEATURES:**

**1) LIGHT MICROSCOPY:**

* Global expansion of the glomerular tufts by eosinophilic amorphous material
* Marked thickening of capillary walls causing narrowing of capillary lumens
* Mesangial expansion with or without mild cellularity

**2) SPECIAL STAINS:**

**PAS:** Weakly positive

**Jones:** Thickened capillary walls without splits, spikes or holes

**Immunofluorescence:** Negative or shows focal non-specific deposits of immunoglobulins (most commonly IgM) and complement components

**Congo-red:** Negative

**Immunohistochemistry:** Mesangial and peripheral capillary loop staining with anti-type III collagen

**3) HALLMARK/DEFINITIVE TEST:**

**Electron Microscopy:**

* **Low power:** Massive and global accumulation of fibrillar material of collagen type-III within the mesangial matrix and along the subendothelial aspect of a GBM. The lamina densa of GBM is not involved
* **High power**: Transverse band structure of fibrils, with a distinct periodicity of 60 nm. The fibrils form irregularly arranged bundles on longitudinal section and flower-like appearance on cross section.

**DISCUSSION:**

* Collagenofibrotic glomerulopathy (CFG) is a glomerular disease characterized by massive accumulation of congo red negative, non-immunologic derived deposits of atypical type III collagen fibrils within the mesangial matrix and sub-endothelial space
* There are 44 reported cases of CFG in the English language literature (33 adult cases and 13 pediatric cases)
* 9 of 13 pediatric cases shown to have a family history suggestive of autosomal recessive inheritance pattern
* Common clinical presentation: Proteinuria and edema with or without in adults and additionally hematuria is seen more frequently in pediatric cases. The characteristic physical abnormalities seen in Nail-patella syndrome are not seen in cases of CFG
* Majority of the patients reported to have high serum levels of procollagen peptide type III and suggests that being a useful and non-invasive marker of disease activity
* Disease course is more progressive and severe in pediatric-onset cases
* Native locations of collagen type-III are fetal skin, blood vessels, interstitium of the kidney however, should not be in the structures of glomeruli
* Cause and pathogenesis: Controversial in regards to nature of the disease being sporadic versus inherited and primary versus secondary
* Treatment: No specific treatment available. Main treatment consists of control of hypertension, edema, dialysis and transplant in ESKD. Role of systemic glucocorticoids still needs further clinical trials.

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**Case # 3**

**PRESENTER:** Diana Murro, MD, PGY-2

**ATTENDING:** Paolo Gattuso, MD

**DIAGNOSIS:** Secondary poorly differentiated synovial sarcoma of the thyroid

**IMPORTANT DIFFERENTIAL DIAGNOSIS OF:**

* Medullary thyroid carcinoma
* Spindle epithelial tumor with thymus-like differentiation (SETTLE)
* Undifferentiated/anaplastic thyroid carcinoma
* Spindle-cell melanoma

**KEY CYTOLOGIC FEATURES:**

* Spindle cells with oval nuclei, delicate cytoplasm, granular chromatin and indistinct nucleoli.
* Epithelioid cells with round nuclei and ample pink cytoplasm.
* Conspicuous mitotic figures.
* Occasional cells with round to oval nuclei and prominent nucleoli.
* Some nuclei with longitudinal folds.
* Nuclear pleomorphism.
* Extracellular hyaline globules.

**DISCUSSION:**

Secondary thyroid malignancies:

* Patients are usually older than patients with primary thyroid malignancies (age >50 years) without female predominance.
* Presentation is either clinically occult or similar to primary thyroid tumor presentation (dysphagia, dysphonia).
* Most common primaries are breast, lung, and renal carcinoma, head and neck squamous cell carcinoma, melanoma and lymphoma.
* Time to metastases can be years (latency period 8 months-17 years).
* Metastatic sarcoma to the thyroid is very rare and has been described only in case reports.
* Although sarcomas may be confused with medullary thyroid carcinoma, pure spindle cell pattern medullary carcinoma is very rare.

Synovial sarcoma (SS) of the thyroid:

* Fewer than 10 cases have been reported likely due to the fact that only about 5% of synovial sarcomas occur anywhere in the head and neck region.
* Three cases of primary thyroid sarcoma sampled by FNA have been described and all were diagnosed as primary thyroid neoplasms (anaplastic thyroid carcinoma, follicular neoplasm and medullary thyroid carcinoma).
* One metastatic SS was reported from a patient with elbow SS and prior lung metastases. However, confirmatory FISH studies were not performed on the thyroid sample.

Fine needle aspiration (FNA) diagnosis of secondary thyroid malignancies

* Secondary malignancies represent 0.1% of thyroid FNAs.
* Occult primaries have been reported in 20-76% of cases, leading to a possible misdiagnosis of a primary thyroid neoplasm.
* FNA sensitivity for diagnosing a primary malignant lesion ranges from 64-100%.
* Focal tumor necrosis is found in 1/3 of secondary thyroid malignancies.
* Special studies for TTF-1 and thyroglobulin can rule out a thyroid primary. Pax-8 can be used to rule out undifferentiated/anaplastic thyroid carcinoma.
* FNA is most helpful when clinical history is known and can guide surgical decisions.
  + Lobectomy for single metastasis
  + Total thyroidectomy for multiple metastases
  + No surgical treatment if patient has aggressive primary with poor survival

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**Case # 4**

**PRESENTER:** Jamie Macagba Slade, M.D.

**ATTENDING:** Ritu Ghai, M.D.

**DIAGNOSIS:** Benign neural neoplasm of nerve sheath origin with a ganglion cell component and foci of heterologous epithelial differentiation (possible composite ganglioneuroma-paraganglioma with glandular component)

**IMPORTANT DIFFERENTIAL DIAGNOSIS:**

* Teratoma with neural overgrowth
* Ganglioneuroma with glandular differentiation
* Benign epithelioid schwannoma
* Benign glandular schwannoma
* Composite ganglioneuroma-paraganglioma with glandular component

**KEY MORPHOLOGICAL FEATURES:**

* Tumor composed of heterogenous morphology including:
  + A major component consisting of a bland spindle cell proliferation (neural differentiation) with foci of ganglion-like cells
  + A minor component consisting of large, epithelioid cells with abundant eosinophilic and granular cytoplasm
  + Rare microscopic foci of glandular structures lined by cuboidal to columnar ciliated epithelium (epithelial differentiation)
* Electron microscopy findings of the spindle cell component consistent with peripheral nerve sheath differentiation. The epithelioid cell component contained mitochondria and lacked dense-core neurosecretory granules.

**DISCUSSION:**

* Neurogenic tumors are most commonly located in the posterior mediastinum and include schwannomas, neurofibromas, malignant peripheral nerve sheath tumors, ganglioneuroma, ganglioneuroblastoma, neuroblastoma, and paragangliomas.
* Neurogenic tumors, although rare, can be located in the anterior mediastinum.
* We presented an unusual tumor in the anterior mediastinum with predominant neurogenic differentiation with a ganglioniccomponent and focal heterologous glandular differentiation.

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**Case #5**

**PRESENTER:**  Alaa Alsadi, MD.

**ATTENDING:**  Ira Miller, MD, Ph.D.

**CASE HISTORY:** This patient is a 30 year-old male with a past medical history of diabetes type 1, hypertension, chronic kidney disease, and renal-pancreatic transplantation 10 years ago. He presented with a 20 lb weight loss over 10 months along with mild fever and night sweats. Physical exam showed diffuse lymphadenopathy. Initial blood workup was significant for a Hb of 5 g/dL. An enlarged inguinal lymph node was excised.

**KEY DIAGNOSTIC FEATURES OF OUR CASE**

* Intact reactive, secondary lymphoid follicle
* Expanded interfollicular zones with mature appearing, quiescent plasma cells and hyalinized vessels
* Plasma cells show lambda light chain isotype predominance by in situ hybridization
* No plasmablasts are identified in the mantle zone
* HHV8 immunostain is negative
* Flow cytometry showed monotypic lambda+ plasma cells without an associated monotypic B cell population
* Plasma immunoglobulins show IgG of 2478 mg/dl, which is 85% IgG lambda on immunoelectrophoresis, with no decrease in levels of IgA or IgM. Electrophoresis histogram is consistent with the presence of an IgG lambda paraprotein, possibly with diffuse background IgG lambda increase. Molecular studies for clonality were technically unsuccessful

**DIAGNOSIS:** Post-transplant lymphoproliferative disease with features of multicentric Castleman disease, plasma cell variant (HHV8-negative), with associated autoimmune hemolytic anemia.

**DIFFERENTIAL DIAGNOSIS:**

* PTLD, monomorphic, plasmacytoma-like:

Can be nodal or extranodal. Can be EBV+. More destructive appearing than our case.

* PTLD, early changes, plasmacytic hyperplasia:

Localized to tonsils or lymph node.

* Reactive lymphadenopathy with plasma cell hyperplasia:

Occurs outside of transplant setting. Nodal architecture (sinuses, etc.) is more preserved than in our case.

* Lymphoplasmacytic lymphoma:

Presents as a systemic neoplasm with marrow involvement in nearly all cases

Lymph nodes may be involved

Paraprotein is nearly always IgM (Waldenstrom macroglobulinemia)

Plasma cells are admixed with variable proportions of mature lymphocytes and plasmacytoid lymphocytes

* Marginal zone lymphoma with extensive plasmacytic differentiation:

Variant of marginal zone B cell lymphoma where clonal B cells cannot be identified (plasmacytoma)

Presents similar to MALT lymphoma, with localized disease

Can be histologically identical to our case.

* Multicentric Castleman Disease, Plasma cell variant:

1. Half of cases are associated with HIV and show mantle zone IgM lambda restricted plasmablasts infected with HHV8.
   * + - Viral IL6 and human IL6 are pathogenic
       - May evolve to “micro lymphomas” and overt plasmablastic lymphoma
       - Poor prognosis
2. Other cases occur in settings of immunocompromise or immune dysregulation.
   * + - Usually polytypic. It is uncertain if monotypia has been reported in this entity.
       - Few cases have been well described in the literature
       - Human IL6 considered to be important in pathogenesis

**MANAGEMENT AND FOLLOW UP:**

The patient’s dose of cyclosporin was reduced. His anemia completely resolved. Follow up serum studies showed no detectible paraproteins and normalization of all quantitative immunoglobulin studies.

**DISCUSSION:**

The discussed case shows partial clinical and morphological characteristics of two different pathological groups:

* First group is the post-transplant lymphoproliferative diseases (PTLD);  of this group, our case is most morphologically similar to plasmacytic hyperplasia, however, this entity is not typically a systemic process, is polytypic, and usually occurs early post-transplant.
* Second group is the low grade lymphoproliferative diseases; of this group, our case is most morphologically similar to marginal zone B cell lymphoma with extensive plasmacytic differentiation, however, this entity is not typically a systemic process and is not (by the WHO definition ) a recognized subtype of PTLD.

The rapid clinical response to reducing immune suppression in our case (in a non-clonal PTLD-fashion) as well as the striking morphological similarity to Castleman’ disease (a systemic non clonal entity) lead to our hybrid diagnosis of a post-transplant lymphoproliferative disease with features of Castleman disease. A few cases of post-transplant lymphoproliferative disease are reported in the literature.

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**Case #6**

**PRESENTER:** Aparna Harbhajanka, MD

**ATTENDING:** Paolo Gattuso, MD

**CASE HISTORY:** A 55-year-old female presented with history of recurrent tumor. A computed tomography (CT) scan of the primary tumor showed well-defined punched out defect with sharply demarcated margins involving the mandible in the region of teeth numbers 19 and 20 with nonenhancing soft tissue. She had a segmental resection of the left mandible with neck dissection. After 4 years she presented with an enlarging mass of the left side of the jaw over months and shifting of the left jaw inferiorly and open mouth deformity. Radiological examination showed approximately 2.9 x 3.0 cm enhancing lesion in the left buccal space most likely representing recurrent tumor.

**DIAGNOSIS:** Clear cell odontogenic carcinoma

**IMPORTANT DIFFERENTIAL DIAGNOSES:**

* Clear cell salivary gland carcinoma
* Clear cell Ameloblastoma
* Metastatic Clear cell renal cell carcinoma

**DISCUSSION:**

* Rare neoplasm with histological features and immunophenotype of clear cell salivary gland carcinoma
* Hansen et al (1985) described the first case
* Odontogenic tumor of the jaw
* Mandible > maxilla
* Posterior > anterior site
* Fifth to seventh decades
* Etiology of tumor is unknown
  + Origin from odontogenic epithelium
* Histology:
  + Solid sheets and nests of clear cells
  + Three patterns
    - Biphasic -clear cell component intermixed with eosinophilic cell component
    - Monophasic pattern - clear cells
    - Ameloblastomatous - clear cell nests with peripheral nuclear palisading (least common).
* IHC: CK8/18 and CK19 positive, EMA and S100 ocassionally positive.
* Molecular: EWSR1-ATF1 translocation
* Treatment:
  + Best disease free survival is radical surgical resection
  + Adjuvant therapy post surgery unclear
* Key points:
  + Clear cell odontogenic carcinoma RARE
  + Can share microscopic features with Clear cell salivary gland carcinoma
  + Need to rule out metastatic RCC
  + Molecular: EWSR1-ATF1 translocation
  + No standardized treatment
    - Surgical resection yields best results
    - Chemo and radiation may be helpful for recurrent disease

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