

Illinois Registry of Anatomic Pathology  
November 16, 2015  
Rush University Medical Center

**Case #1**

**PRESENTER:** Arlen Brickman, MD

**ATTENDING:** Ritu Ghai, MD

**CASE HISTORY:** 45 year old obese African American female, G5P5 presents to an outside institution with irregular vaginal bleeding. She has a self-reported history of fibroids in 2008. Her physical exam was unremarkable and she reported her last menstrual period was two months prior to her presentation. Beta HCG on presentation showed a level <1000 mIU/ml and an endometrial curettage was performed. Based on these results, imaging including ultrasound and full body CT was performed. A low density lesion 4.2 x 3.3 cm emanating from the posterior body of the lower uterine segment was identified. A total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy was performed.

**DIAGNOSIS:** Epithelioid Trophoblastic Tumor (ETT)

**DISCUSSION:**

- A rare and unusual type of trophoblastic tumor ~100 reported cases, resembling a carcinoma.
- First reported by Shih and Kurman in a case series in 1998 of 14 cases. “Epithelioid Trophoblastic Tumor: A Neoplasm Distinct From Choriocarcinoma and Placental Site Trophoblastic Tumor Simulating Carcinoma”
- Originally termed “atypical choriocarcinoma” and was described in the lungs of patients with antecedent choriocarcinoma.
- Patients present with; abnormal vaginal bleeding (>60%), antecedent molar pregnancy (~36%), metastases (~35%), mean age at diagnosis is 38 years, mean interval between a preceding gestation and the diagnosis of ETT is 76 months, the range from 1-18 years.  $\beta$ -HCG levels are usually low (<2500 mIU/mL), rarely  $\beta$ -HCG negative (only a few cases described), and rarely highly elevated levels  $\beta$ -HCG (>100 000 mIU/mL) , usually high levels are associated in conjunction with a choriocarcinoma. ETT can be seen in association with choriocarcinoma as well as Placental site trophoblastic tumor.
- The tumors are well-circumscribed, solitary, discrete and expansile, largely necrotic, hemorrhagic, tan/ brown in color and can involve the surface epithelium.
- They are the only gestational trophoblastic tumors that morphologically have calcifications and can re-epithelize endometrium and cervix.
- Recurrence and metastasis are common.
- So few cases have been reported that the treatment options are still experimental and mostly involve resection and chemotherapy.
- Differential diagnosis includes:
  - o Poorly differentiated carcinoma of the female reproductive tract primary or metastatic.
  - o Exaggerated placental site(EPS)
  - o Placental site trophoblastic tumor (PSTT)
  - o Epithelioid trophoblastic tumor (ETT)
  - o Choriocarcinoma
- With such a wide spectrum of presentation it is important to consider an ETT in the differential diagnosis to optimize the treatment and management outcomes of these patients.

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**Case #2**

**PRESENTER:** Aparna Harbhajanka, MD

**ATTENDING:** Jerome Loew, MD

**CASE HISTORY:** A 64-year old male with a history of alcoholic cirrhosis s/p orthotopic liver transplantation in 2004, on immunosuppression with chronic kidney disease, congestive heart failure, COPD and hypertension presented with neck and left arm pain for 2 months that gradually worsened. Subsequently he developed sudden lower extremity weakness that quickly progressed to paraplegia, followed by upper extremity weakness. On physical examination, he had bilateral lower extremity weakness, sensory level ~T4, Deep tendon reflexes 4+, upgoing toes, + Hoffman's sign Right>Left. MRI showed abnormal increased T2 signal and associated enhancement involving the C6 and C7 vertebral bodies, minimal fluid in the C6-7 disc space, severe spinal canal stenosis at C5-6 and C6-7 and cord compression at C5 and C6 vertebral levels with cord edema. The lesion was excised. A section of the lesion is provided for review.

**DIAGNOSIS:** Monomorphic B-cell Post-transplant lymphoproliferative disorder

**DISCUSSION:**

- The term 'post-transplant lymphoproliferative disorder' (PTLD) was first introduced in 1984 by Starzl.
- PTLD is a heterogeneous group of lymphoid and/or plasmacytic proliferations occurring in the setting of solid organ transplant and hematopoietic stem cell transplant patients following immunosuppression. The PTLD spectrum includes entities ranging from reactive hyperplasia to malignant lymphoma.
- The incidence of PTLD ranges from 1-10% in solid organ transplant recipients and <1% in stem cell transplant recipients.
- Risk factors for developing PTLD include the type of allograft, type and duration of immunosuppression, age, race, genetic predisposition and infection.
- PTLD can present in any organ system at any time. Central nervous system involvement varies with organ transplanted and predominantly involves the brain. There is only one case report of thoracic epidural spinal cord compression secondary to PTLD.
- According to the latest WHO classification in 2008, PTLD is classified into four basic histological types: (1) early lesions; (2) polymorphic (P-PTLD); (3) monomorphic (M-PTLD); and (4) classical Hodgkin lymphoma. PTLDs can be defined as early- or late-onset if the diagnosis is made within or after 12 months from transplantation, respectively.
- EBV-positive PTLD generally arise earlier after transplantation than EBV-negative ones.
- Early lesions consist of benign polyclonal lymphoproliferations, which may regress with reduction of the immunosuppressive regimen.
- P-PTLD is composed of a mixed population of immunoblasts, plasma cells and intermediate-sized lymphoid cells. Most P-PTLDs are EBV-positive and arise within one year of transplantation.
- M-PTLDs are mainly of B-cell origin. Most are Diffuse Large B-cell lymphoma. Other subtypes are Burkitt's lymphoma, plasmacytoma-like and plasma cell myeloma.
- 5 year survival rates of 30 to 60% have been reported.
- No standard treatment

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**Case #3**

**PRESENTER:** Lei Yan, BM, PhD

**ATTENDING:** Ira J. Miller, MD, PhD

**CASE HISTORY:** A 32-year-old female with a history of papillary thyroid carcinoma s/p total thyroidectomy and iodine ablation therapy presented to the ED with heavy vaginal bleeding. On physical examination, the patient was noted to have significant vaginal bleeding, softball sized vaginal clots, a large bulky uterus and a 4.0cm exophytic friable cervical mass. Trans-abdominal ultrasound showed a 2.8 x 2.5 x 2.4 cm cervical mass with an epicenter at the anterior cervix concerning for malignancy. She underwent cervical biopsy and D&C, and eventually received radical hysterectomy with bilateral salpingectomy.

**DIAGNOSIS:** Malignant peripheral nerve sheath tumor of the endocervix

**DISCUSSION:**

- Malignant peripheral nerve sheath tumor (MPNST) of the endocervix is rare. To date, at least 9 cases of cervical MPNST have been reported, all of which showed unequivocal histologic features of malignancy.
- Endocervical MPNST seems to have a predilection for young women with a mean age of 44 (range= 21-73 years). The tumors usually present as a cervical polyp or mass lesion with an average size of 3.8 cm (range= 1.2-8.0 cm). Vaginal bleeding is the most common initial presentation.
- Histopathologic features include:
  - o Compact proliferation of spindled-to-epithelioid cells with eosinophilic cytoplasm
  - o Monomorphic or mildly pleomorphic
  - o Herringbone, loose fascicular, or ill-defined storiform patterns typical of "fibrosarcoma"
  - o No or minimal nuclear atypia
  - o No necrosis
  - o The tumor is mitotically active.
- In most cases, assignment of peripheral nerve sheath lineage was based on reactivity for S100 protein and no evidence of other specific lineage differentiation by morphology and immunohistochemistry.
- Pathogenesis is currently unknown, although a possible relationship with the endocervical CD34 positive stromal fibrocyte has been postulated.
- Approximately 2/3 of patients underwent total abdominal hysterectomy. One-third of patients were treated with polypectomy with a high local recurrence rate.
- Differential diagnosis includes:
  - o Carcinosarcoma
  - o Melanoma
  - o Clear cell sarcoma
  - o Leiomyosarcoma
  - o Synovial sarcoma
  - o Endometrial stromal sarcoma
  - o Spindle cell variant of embryonal rhabdomyosarcoma

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**Case #4**

**PRESENTER:** Hussein Alnajar, MD

**ATTENDING:** Leonidas Arvanitis, MD

**CASE HISTORY:** A 69 year old male with a history of chronic unexplained headache for 5 years and associated memory loss for 6 months. He presented with an episode of verbal unresponsiveness 5 days prior to admission. MRI showed diffuse dural thickening and enhancement involving the tentorium, posterior aspects of the falx, left parieto-occipital convexity and posterior fossa. There was also associated leptomeningeal involvement and significant vasogenic edema in the left parietal lobe.

**DIAGNOSIS:**

- Chronic pachymeningitis with focal meningotheial proliferation and increased IgG4-positive plasma cells
- Leptomeningeal involvement
- May represent IgG4 related disease

**DISCUSSION:**

- Inflammatory meningeal disease is characterized by thickened dura and symptoms due to compression of adjacent structures, mainly headache.
- The differential diagnosis of diffuse meningeal thickening:
  - o Inflammatory/Autoimmune lesions
    - Sarcoidosis
    - Collagen vascular disease
    - Idiopathic hypertrophic pachymeningitis
  - o Infection
    - Tuberculosis
    - Fungal
  - o Neoplastic process
    - Lymphomatosis
    - Carcinomatosis
- Idiopathic hypertrophic pachymeningitis (IHP) is a rare disease of unknown origin with chronic clinical course. It is characterized by marked inflammatory hypertrophy and fibrosis of the dura mater. The thickened dura causes progressive neurological deficit. Chronic headache and multiple cranial neuropathies are the most common clinical manifestation. By neuroimaging it is characterized by diffuse or localized thickening of the dura. Other causes of inflammatory meningeal disease must be ruled out before the diagnosis of IHP can be made.
- Recent studies proposed that a proportion of IHP cases may be a part of the IgG4-related disease spectrum.
- IgG4-related pachy- and leptomeningeal disease is a newly described condition associated with the IgG4-RD spectrum.
- Lindstrom et. al. performed the most detailed clinicopathologic characterization of IgG4-RD in 2010. They retrospectively analyzed ten cases with unexplained meningeal inflammation determine whether or not IgG4-RD represent a distinct subtype of IHP.
  - o They stated that it is important to consider IgG4-RD in the differential diagnosis of meningeal thickening and/or enhancement.
  - o In addition, they recommended that cases that contained greater than ten IgG4-positive cells/HPF with the classical histological features of IgG4-related disease including lymphoplasmacytic inflammation, fibrosis and phlebitis to be considered IgG4-related.
- Carruthers et. al . suggested the following criteria to diagnose IgG4-RD:
  - o A dense lymphoplasmacytic infiltrate



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- Storiform pattern of fibrosis
  - Obliterative phlebitis
  - Absolute number of IgG4+ plasma cells >10 PER HPF
  - Ratio of IgG4/IgG plasma cells >40%
- The combination of at least two of the H&E features and the immunohistochemical cutoffs makes the diagnosis

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**Case #5**

**PRESENTER:** Sara Javidiparsijani, MD

**ATTENDING:** David Cimbaluk, MD

**CASE HISTORY:** A 42 y/o female with past medical history of SLE for 7 years was referred to renal clinic for persistent hematuria and proteinuria. The patient did not recall being treated for lupus nephritis. She had no family history of renal disease. Her physical exam was unremarkable except for alopecia, and lab data were unremarkable except for 50 mg/day proteinuria and 3+ hematuria. Imaging studies were normal. Renal biopsy was performed for further investigation.

**DIAGNOSIS:** Fabry Disease

**DISCUSSION:**

- Fabry disease is an X-linked lysosomal storage disease due to  $\alpha$ -galactosidase A deficiency. The deficiency results in accumulation of globotriaosylceramide (GL3) in different organs and tissues including renal glomeruli, endothelial cells, myocardial cells, cornea and skin which results in end organ damage. The affected patients will have higher morbidity and mortality due to end stage renal disease, cardiac complications and early onset cerebrovascular diseases.
- Female patients may also suffer from the disease although the exact mechanisms of female disease are not fully understood.
- Skewed X inactivation may explain the symptomatic disease in some females, but most recently it has been discovered that most females with Fabry disease have random X inactivation and the hypothetical mechanism of disease in these patients is inefficient cross-correction between healthy and affected cells.  
In male patients, the clinical diagnosis can be made by measuring the blood or urine level of the enzyme  $\alpha$ -galactosidase A enzyme.  
In female patients the diagnosis is made by genetic studies for DNA mutations associated with Fabry disease.
- The renal biopsy of the patient shows enlargement of a subset of podocytes. The cytoplasm of affected podocytes is filled with bubbly material. Immunofluorescence microscopy is negative for complement of Ig deposits. EM shows the characteristic intracytoplasmic myelin bodies (zebra bodies) which are concentric electron dense lamellated round inclusions.
- Differential diagnosis includes:
  - o Gaucher disease.
  - o Niemann Pick disease.
  - o Hydroxychloroquine deposits
  - o Aminoglycosides deposits
  - o Amiodarone deposits

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**Case #6**

**PRESENTER:** Smita Patel, MD, PGY-3

**ATTENDING:** Ira J. Miller, MD, PhD

**CASE HISTORY:** A 25-year old woman with no significant past medical or family history presented with very painful lesion involving her left distal femur. On initial imaging, the lesion was lytic and blastic with no associated major soft tissue mass. Initial blood work-up was significant for IgG of 2007 mg/dl and IgM of 225 mg/dl. A biopsy of the lesion was performed and sent for intraoperative consultation.

**DIAGNOSIS:** Extranodal Marginal Zone Lymphoma with Plasmacytic Differentiation

**DISCUSSION:**

- On the basis of morphological features, distinguishing mature B-cell lymphomas with plasmacytic differentiation is very challenging.
- The differential diagnosis of bone tumors containing plasma cells includes
  - o Plasma cell neoplasm
  - o Solitary plasmacytoma
  - o Low-grade lymphoma with plasmacytic differentiation
  - o Lymphoplasmacytic lymphoma
  - o Marginal zone lymphoma
  - o IgG4-related disease of bone
- Correlation with clinical, serological, immunophenotypical features along with staging work-up is required for definitive diagnosis. Plasmacytomas/ multiple myeloma do not have a separate B cell component. LPL usually has systemic involvement, and IgM paraprotein.
- The distinction is not always clear-cut and some cases may need to be diagnosed as a “small B-cell lymphoma with plasmacytic differentiation” with a differential diagnosis provided.
  - o The utility of MYD88 mutation as a possible diagnostic marker has received widespread attention recently in distinguishing LPL from other B cell lymphomas.
    - Swerdlow et al. reviewed the cases contributed to 2014 SH workshop. There is a very strong association between MyD88 mutation and LPL, but MyD88 mutation is also present in cases of MZLs including cases with plasmacytic differentiation, and CLL/SLL. MyD88 mutation is also known to be present in Non-GC DLBCL (30%), especially those of leg-type and immune privileged sites such as CNS and testis. So, the presence of a MyD88 mutation does not necessitate the diagnosis of LPL.
  - o The diagnosis of transformation to DLBCL is reserved for cases in which large cells are present in sheets or make up over 50% of population (Molina T, Swerdlow S et al., AJCP 2011, Stanford criteria)
- Primary lymphoma of bone was first described by Oberling in 1928. Parker and Jackson reported a series in 1939 under the designation “reticulum cell sarcoma of bone”. They are rare and account for <1% of all lymphoma, 7% of malignant bone tumors, and 4-5% of extra-nodal lymphomas
  - o Predominant subtype is DLBCL, followed in frequency by FL. B lymphoblastic lymphoma, ALCL and HL may also present as bone tumors. At Rush, there were 2 cases of marginal zone B cell lymphoma in about 10 years, so they are rare.
  - o Neither the WHO handbook of 2008 nor Ishii et al mention bone as a specific site for involvement by extranodal marginal zone B cell lymphoma.
  - o IgG4-Related disease of the bone has been reported, has similar histologic features to IgG4 disease of other sites, and typically has a diffuse polytypic lymphoplasmacytic infiltrate storiform fibrosis, obliterative fibrosis, and increased IgG4 immunoglobulin isotype-producing plasma cells.
- Take home point:

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- Not every neoplasm in bone that has plasma cells is in the myeloma spectrum of tumors. But, in practice, nearly all tumors of bone that have many plasma cells are plasmacytomas.

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