

## NOTES ON CASES:

### **IRAP case #1: Pedram Pouryazdanparast, M.D.**

#### **Case History**

A 52 year-old Caucasian woman presented with blue discoloration of the left periorbital skin and eye that was present since age 2. The lesion grew proportionally during development but became more pigmented with age. Biopsies at age 5, 32 and 42 showed changes consistent with nevus of Ota. Three months prior to presentation, she developed rapidly progressive loss of vision in the left eye. Imaging revealed a large retro-orbital mass involving the optic nerve, eyelids, skin, subcutaneous tissue, bony walls of sinus and intra-orbital contents. The patient underwent exenteration and resection of the lesion around the eye.

#### **Histopathology**

The histopathology of the sections showed a predominately dermal-based melanocytic proliferation that varied in cellularity and cytological features from area to area. In the superficial dermis, a nevus of Ota, characterized by a paucicellular proliferation of bland dendritic and pigmented melanocytes and associated melanophages dispersed haphazardly among the collagen bundles, was identified. In deeper areas, single cells and thin fascicles of bland, pigmented dendritic melanocytes resembling common blue nevus were observed coursing through sclerotic dermal collagen. Additionally, a component with features of cellular blue nevus characterized by the presence of larger, cellular fascicles of spindled, oval, and epithelioid melanocytes with pale to eosinophilic cytoplasm, vesicular chromatin, inconspicuous nucleoli, but lacking mitotic activity, was found. The fascicles of the cellular blue nevus were typically intermixed with more heavily pigmented dendritic melanocytes and melanophages. Most important to the diagnosis was the finding of deeply located expansile and infiltrative nodules composed of confluent fascicles of large epithelioid and spindled shaped cells with prominent nucleoli, high mitotic activity, and exhibiting tumoral necrosis (features key in distinguishing a melanoma from a cellular blue nevus!!). Sections from the orbit showed melanosis but no involvement of the uvea by melanoma.

#### **Molecular Studies**

Mutational analysis performed by PCR of common oncogenes, including GNAQ, BRAF, NRAS and KIT did not show any mutations in regions frequently found in these genes in melanocytic neoplasia. Comparative genomic hybridization (CGH) identified gains involving chromosomes 1q, 6p, 8q, 9q, and loss of 6q in the melanoma areas, while no aberrations were detected in the blue nevus areas. All aberrations, with the exception of the gain of chromosome 9q, are common DNA copy number changes in melanoma. Fluorescence in situ hybridization (FISH) studies with probes targeting 6p25, 6q23, Cep6

and 11q13 were also performed from multiple sections and concordantly showed gains in 6p25 and losses in 6q23. The 6p25 copy numbers varied in the morphologically malignant areas with the atypical expansile nodular areas showing the highest number of signals (between 3 and 7 copy numbers per cell) while less overtly atypical areas showed lower levels of gains in 6p25. By contrast, FISH did not detect chromosomal aberrations in the blue nevus areas of the lesion. These molecular findings support the microscopic interpretation of a melanocytic process that ranged from a benign congenital lesion to melanoma with presence of intermediate lesions having features of common/cellular blue nevus.

### **Diagnosis**

Nevus of Ota Showing Progressive Evolution to Melanoma with Intermediate Stages Resembling Cellular Blue Nevus

### **References**

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2. Van Raamsdonk CD, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature.* 2009;457:599-602
3. Qian Y, et al. Iris melanoma arising in iris nevus in oculo-dermal melanocytosis. *Surv Ophthalmol.* 2008;53:411-415
4. Barnhill RL, et al. Atypical cellular blue nevi (cellular blue nevi with atypical features): lack of consensus for diagnosis and distinction from cellular blue nevi and malignant melanoma ("malignant blue nevus"). *Am J Surg Pathol.* 2008;32:36-44
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### **IRAP case #2: Xianzhong Ding, M.D., Ph.D.**

**Clinical history:** The patient is a 54 year-old female with persistent menorrhagia and anemia for several months. Her past medical and family histories are non-contributory. She was initially diagnosed with submucosal fibroid. In an attempt to minimize her bleeding, the patient was treated with Lupron. A repeat ultrasound revealed that the "myoma" had not only not shrunk, but actually had enlarged. Given the ultrasound findings and failure of medical therapy, the patient underwent laparoscopic hysterectomy. The surgical specimen was received and designated as "uterus and cervix". Grossly the endometrium and myometrium were distorted well circumscribed mass lesions (1-5 cm). Serial sectioning of the lesions revealed tan, whorled cut surfaces with no necrosis or hemorrhage. The lesions were well-circumscribed but not encapsulated.

**Diagnosis:** Uterine tumor resembling Ovarian Sex Cord Tumor, type II.

**Key morphological features:**

- Grossly, the tumor is often well-circumscribed with a pushing border and located mostly in myometrium but occasionally may project in a polypoid fashion into the uterine cavity.

- Microscopically, the process is lobulated with smooth muscle bundles forming septa partitioning lesional tissue. Tumor cells form single-layered cords, anastomosing trabeculae, small and large nests, and occasionally hollow tubular structures and are embedded within a predominantly myxocollagenous stromal matrix.

- Cytologically, the key proliferating element is a cuboidal to polygonal-shaped epithelioid cell with a vesicular, occasionally grooved, nucleus and moderate to abundant eosinophilic cytoplasm. Mitotic activity is typically negligible.

### **Discussion**

- Uterine tumor resembling Ovarian Sex Cord Tumor was first described by Clement and Scully in 1976 and divided in 2 subtypes. The type I is a typical endometrial stromal tumor with minor sex-cord stromal element (< 50%) while the type II variant is composed predominantly of ovarian sex-cord elements (> 50%).
- Clinically, the patient is often a middle aged woman, presenting with abnormal uterine bleeding and an enlarged uterus or palpable uterine mass.
- The lesion can mimic several pathological entities including endometrioid carcinoma, endometrial stromal tumor, epithelioid leiomyoma/leiomyosarcoma, PECome (perivascular epithelioid cell tumor) and metastatic carcinoma.
- Immunostains are particularly helpful for differential diagnosis. The tumor is often immunoexpress inhibin, CD99, calretinin, CD56 (sensitive sex-cord stromal markers) and variably express Melan A (MART-1), vimentin, ER, PR, keratins, actins, desmin, WT-1, S-100 protein, and CD117.
- EMA stain is always negative (unlike carcinoma).
- Unlike the type I variant that acts like a low-grade endometrial stromal sarcoma, the tumor has the potential to behave in a low-grade malignant fashion. A 15% recurrence rate has been documented after resection. Additionally, the type II variant does not possess the *JAZF1-JJAZ1* (7;17) translocation that occurs in over 60% of typical endometrial stromal sarcomas (*AJSP* 33:1206, 2009)

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Czernobilsky B. Uterine tumors resembling ovarian sex cord tumors: an update. *Int J Gynecol Pathol.* 2008 Apr;27(2):229-35.

Biermann K, Heukamp LC, Büttner R, Zhou H. Uterine tumor resembling an ovarian sex cord tumor associated with metastasis. *Int J Gynecol Pathol.* 2008 Jan;27(1):58-60.

### **IRAP case #3 :Natasha Berg, M.D. and Beverly Nelson, M.D.**

**Clinical History:** 63 year-old man with a nine year history of CLL/SLL status-post failed mini-allogeneic stem cell transplant two years ago presented to the hospital with fatigue, abdominal distension, cough and dyspnea and was noted to have significantly increased lymphadenopathy.

#### **Differential Diagnosis:**

Hodgkin Lymphoma arising in a background of CLL/SLL (about 15% of Richter's syndrome cases).

Prolymphocytic transformation of CLL/SLL

**Diagnosis:** Diffuse Large B-Cell Lymphoma arising in a background of CLL/SLL (Richter Syndrome)

**Key Histologic Features:** Lymph node with typical features of CLL/SLL including proliferation centers with para-immunoblasts. Key diagnostic finding is the presence of diffuse infiltrate of cells with large round to irregular nuclei with prominent nucleoli. Immunophenotypic profile by flow cytometry is similar to original CLL profile:

#### **Discussion:**

- Richter Syndrome is rare, occurring in 3-10% of CLL/SLL cases (may be under-reported) and the frequency of the disorder is increasing probably on account of increased immune suppression and/or emergence of therapy-resistant clones.
- p53 mutations or deletions and EBV involved in pathogenesis.
- A small subset of cases is unrelated to the CLL clone.
- Symptoms occur suddenly and include fever, night sweats, abdominal pain or rapid swelling of lymph nodes baseline.
- Histologic diagnosis, biopsy should target largest lesion. Along with lymph nodes, the process may involve the gastrointestinal tract, skin, liver, tonsils, and bone marrow.
- Predictors of Richter Syndrome development include: CD38 expression, absence of del 13q14, IGHV4-39 mutational status and lymph node size  $\geq 3$ cm
- Numerous therapies have been purported to induce remission, but the overall prognosis is poor with a median survival of less than 12 months

#### **References:**

Döhner et al. Genomic aberrations and survival in chronic lymphocytic leukemia, *New England Journal of Medicine* 2000; 343: 1910-6.

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Rossi, D, Gaidano, G, Richter syndrome: molecular insights and clinical perspectives. *Hematological Oncology* 2009; 27: 1-10.

Rossi et al. Biological and clinical risk factors of chronic lymphocytic leukaemia transformation to Richter Syndrome. *British Journal of Haematology*, 2008. 142: 202.

Tsimberidou et al. Clinical outcomes and prognostic factors in patients with Richter's Syndrome treated with chemotherapy or chemoimmunotherapy with or without stem cell transplantation. *Journal of Clinical Oncology* 2008. 24:2343-2351.

#### **IRAP case #4 : Josette William M.D, Ph.D**

**Clinical history:** 47-year-old male presented with a one-year history of shortness of breath on exertion. Patient was diagnosed with pneumonia by chest x-ray and treated with antibiotics, but his initial symptoms failed to completely resolve. CT scan performed at NMH demonstrated a left lung mass occupying the lower lobe and extending into the left hilum. Flexible fiberoptic bronchoscopy was performed and showed that the tumor was nearly occluding the entire left lower lobe bronchus. Left pneumonectomy was performed.

**Diagnosis:** High-Grade Intimal Sarcoma of the Pulmonary Artery with Rhabdomyosarcomatous Differentiation

#### **Discussion:**

- Pulmonary artery intimal sarcoma (PAIS) was first reported by Mandelstamm in 1923.
- Presents in 5th & 6th decades of life with no sex predilection.
- Rare tumor whose true incidence is underestimated as many are not discovered until death. However, compared with other major sarcomas affecting the great vessels, it is much less common than inferior vena cava leiomyosarcoma, and also less common than sarcomas arising in the aorta.

#### **Clinical presentation:**

- Dyspnea, chest pain, hemoptysis, and syncope.
- Clinical suspicion of pulmonary embolism in approximately 40% of patients often delays diagnosis and proper treatment. (Tavora et al., 2008).
- 3-4% of patients carrying a diagnosis of thromboembolic pulmonary hypertension found to have PAIS (Anderson et al., 1995).
- Imaging features, including vascular distension, inhomogeneous attenuation and enhancement after gadolinium separates PAIS from PE.  
**Site of origin:** pulmonary trunk (80%), less often from LPA, RPA, both pulmonary arteries, and rarely from pulmonary valve.

#### **Histogenesis:**

- PAIS is purported to arise from a pleuripotential intimal cell.

- 80% of tumors exhibit myofibroblastic differentiation with variable actin and desmin expression or demonstrate ultrastructural features of myofibroblasts.

### **Histologic subtypes (Tavora et al., 2008)**

- 1.) Pleomorphic-fascicular with features of:
  - -High-grade myxofibrosarcoma
  - -MFH
  - -Epithelioid differentiation
  - -HPC
- 2.) Myogenic (leiomyosarcoma and rhabdomyosarcoma)
- 3.) Matrix-producing sarcomas (osteosarcoma and myxoid chondrosarcoma)
- 4.) Low-grade myofibroblastic sarcoma.

### **Clinicopathologic features associated with prolonged survival (Tavora et al, 2008)**

- Age < 40 y.
- Intra-arterial low-grade myofibroblastic sarcoma.

### **Treatment:**

- Curative surgery (complete local or radical excision).
- The role of radiotherapy and chemotherapy is currently uncertain. However improved survival with combined postoperative chemoradiation has been reported.

### **Prognosis:**

- Slightly better prognosis than intimal aortic sarcomas but worse than primary lung parenchymal sarcomas. Survival over 3 years is rare (except for intra-arterial myofibroblastic sarcoma).

### **References:**

1-Sebenik M, et al. Undifferentiated Intimal Sarcoma of Large Systemic Blood Vessels. The American Journal of Surgical Pathology. 2005; 70: 1184-1193

2-Tavora F, et al. Pulmonary Artery Sarcoma: A Histologic and Follow-up Study With Emphasis on a Subset of Low-grade Myofibroblastic Sarcomas With a Good Long-term Follow-up. The American Journal of Surgical Pathology. 2008 ; 12: 1751-1761.

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4. Gaumann A, et al. Exploration of the APC/beta-catenin (WNT) pathway and a histologic classification system for pulmonary artery intimal sarcoma. A study of 18 cases. Virchow Arch. 2008; 453: 473-484.

**IRAP case #5 : Kyle M. Annen, D.O.**

Diagnosis: Sclerosing Polycystic Adenosis of the Salivary Gland

Differential Diagnosis:

1. Acinic Cell Carcinoma
2. Low-Grade Salivary Duct Carcinoma
3. Sclerosing Sialadenitis
4. Polycystic (Dysgenetic) Disease

Key Clinical Features

- Mostly affects females; peak incidence in the 4<sup>th</sup> and 5<sup>th</sup> decades of life.
- Most often presents as an asymptomatic mass; parotid gland most common salivary gland involved (>85% of cases).

Key Pathologic Features

- Well-circumscribed, partially encapsulated gray to yellow-tan multinodular lesion found macroscopically.
- Microscopically, the process is characterized by the presence of lobules of densely sclerotic, hyalinized collagen in which an epithelial component of microcysts, duct-like and acinar structures (resembling fibrocystic disease and/or sclerosing adenosis of the breast) is embedded.
- Cellular element includes sebaceous-like, vacuolated, apocrine, acinic (with large PAS-positive zymogen granules), mucin-secreting, and squamous cells.
- Focal lymphocytic infiltrate common
- Ductal epithelial cellularity and cytological atypia present in 40%-75% of cases
- Myoepithelial cells surround each epithelial structure.

Immunohistochemistry:

Positive

Cytokeratin

Vimentin (+/-)

S-100

Antimitochondrial Antibody

Gross cystic disease fluid protein (BRST-2)

80% of epithelial cells express PR and 20% express ER

(Myoepithelial markers decorate myoepithelial cells)

Negative

CEA

C-erbB2

Pathogenesis:

- Although initially considered a reactive, inflammatory process, the finding of monoclonality by evaluation of polymorphism in the androgen receptor locus indicates the possibility of a true neoplasm (*AJSP* 30:939, 2006).

Outcome/ Prognosis and Treatment:

- Recurrences, sometimes multiple, reported in <1/3 of cases, but no metastases documented to date.
- Surgical excision with clear margins and preservation of facial nerve function recommended management for this disorder.

References:

1. D.R. Gnepp. Sclerosing Polycystic Adenosis of the Salivary Gland: A Lesion That May Be Associated With Dysplasia and Carcinoma In Situ. *Advances in Anatomic Pathology* 2003;10: 218-222
2. D.R. Gnepp, et al. Sclerosing Polycystic Adenosis of the Salivary Gland, a report of 16 cases. *Am J Surg Pathol.* 2006;30 (2) 154-164.
3. W Cheuk, JKC Chan. *Advances in Salivary Gland Pathology. Histopathology* 2007;51: 1-20

**IRAP case #6 : Bevan Tandon, M.D.**

**Clinical History:** The patient is a 28 year old primigravida Caucasian female who presented to the Northwestern Memorial Hospital Labor and Delivery unit for a scheduled induction of labor at 40.6 weeks. Prenatal course was uncomplicated and surgical history is remarkable for dermoid cyst excision performed in 1996. At Cesarean section, diffuse nodularity involving the vesicouterine peritoneum and omentum was noted. The nodules were all less than 2cm in greatest dimension and a partial omentectomy was performed.

**Differential Diagnosis:** Ovarian teratoma related gliomatosis peritonei, Lymphangi leiomyomas, Stromal cell leutenization, Disseminated peritoneal carcinomatosis

**Diagnosis:** Leiomyomatosis Peritonealis Disseminata

**Key Histologic features:** Nodules of spindled smooth muscle cells ranging from microscopic to over 2 cm. and exhibiting fascicular growth pattern typically occurring within a fibroadipose background. Cells have bland cytological features similar to conventional leiomyoma and lack significant mitotic activity. Lesional cells immunopositive for hormonal markers ER/PR, and smooth muscle markers, e.g. SMA, desmin, actin.

**Discussion:**

- Leiomyomatosis peritonealis disseminata (LPD) is a rare disease that presents as multiple peritoneal or subperitoneal leiomyomatous nodules that may mimic peritoneal carcinomatosis. - LPD nodules are typically incidentally noted, and are usually <2cm in greatest dimension.
- Fewer than 100 cases have been reported in the literature and no ethnic group predominance has been identified.
- LPD histogenesis in premenopausal females is still unknown. LPD is typically observed in association with altered hormonal states, e.g. pregnancy, hormonal therapy, and steroid producing ovarian tumors.
- Animal studies have revealed that prolonged, elevated estrogen exposure can induce metaplasia of mesenchymal stem cells into fibroblasts and leiomyocytes, and can induce development of disseminated peritoneal nodules similar to that seen in LPD.
- Clonal studies have demonstrated each nodule is clonal and all nodules have the same pattern of X chromosome inactivation .
- LPD usually pursues a benign course, although 2-5% of cases reported have shown malignant transformation with progression to leiomyosarcoma
- Surgical excision is usually curative however hormonal therapy may also induce regression without relapse

**References:**

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