

# IRAP

January 25, 2010

Presented by  
The University of Chicago Residents



## Case 1

**Presenter:** Nicole A Cipriani, MD

**Attending:** Aliya N Husain, MD

**Diagnosis:** Pulmonary capillary hemangiomatosis

### **Key Morphologic Features**

| <b>Feature</b>                 | <b>Pulmonary arterial hypertension</b> | <b>Pulmonary veno-occlusive disease</b> | <b>Pulmonary capillary hemangiomatosis</b>  |
|--------------------------------|--|---|---|
| <b>Hypertrophic Arterioles</b> | <b>+++<br/>plexiform lesions</b>       | <b>+</b>                                | <b>+</b>                                    |
| <b>Occluded Veins</b>          | <b>-</b>                               | <b>+++</b>                              | <b>+ secondary to capillary compression</b> |
| <b>Capillary Proliferation</b> | <b>+ dilation</b>                      | <b>+ dilation</b>                       | <b>+++</b>                                  |

### **Pulmonary capillary hemangiomatosis:**

- **Gross:** reddish spongiform nodules diffusely throughout pulmonary parenchyma
- **Histologic:**
  - Airways normal
  - Arteries with mild changes of pulmonary hypertension including intimal fibrosis & medial hypertrophy
  - Veins with mild intimal fibrosis
  - Septa not edematous with lack of lymphatic dilation
  - Nodules of capillaries in alveolar walls with regular distribution, not correlating to anatomic structures
  - Higher density of capillaries in center of nodule, with thinning out at periphery (highlighted by CD31, CD34)

### **Discussion**

- Pulmonary Capillary Hemangiomatosis (PCH) and Pulmonary Veno-Occlusive Disease (PVOD) clinically resemble Idiopathic (Primary) Pulmonary Arterial Hypertension (PAH):
  - Dyspnea, lower extremity edema
  - Increased pulmonary arterial pressures
  - Cor pulmonale
- Radiographic findings may help differentiate:
  - Micronodular opacities are seen on CT scan in PCH
- Diagnosis in surgical pathology (VATS lung biopsy) is important because of different response to treatment:
  - PAH responds well to continuous infusion of vasodilators (such as prostacyclin)
  - PCH and PVOD do not respond well to vasodilators; Instead, fatal pulmonary edema may ensue
- Definitive treatment of PCH and PVOD is lung transplant
- Pathogenesis of PCH and PVOD is unclear, but may be related to PAH

- Bone Morphogenetic Protein Receptor type 2 (BMPR-II) is mutated in cases of idiopathic and familial pulmonary arterial hypertension
- BMPR-II has been shown to be mutated in rare cases of pulmonary veno-occlusive disease
- BMPR-II mutation in PAH causes endothelial and smooth muscle proliferation, resulting in plexiform lesions and concentric arteriolar hypertrophy, respectively
- Markers of endothelial proliferation (VEGF, PDGF & PDGFR, Ki67) are increased in both PAH and PCH
  - Case reports document symptomatic improvement with PDGFR inhibitors (imatinib) in PAH patients
  - Studies document improvement of pulmonary hypertension in mouse models
- Some markers (PPAR- $\gamma$ , caveolin-1) are divergent: decreased in PAH but increased in PCH; May relate to histologic differences

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### Case 2

**Presenter:** Maria Tretiakova, M.D., Ph.D.

**Attending:** Aliya Husain, M.D. and Jerome Taxy, M.D.

**Clinical history:** 60 y.o. Caucasian female with pre-B cell ALL diagnosed in 12/2007, who was on maintenance chemotherapy. Her last bone marrow biopsy showed no residual precursor B-lymphoblastic leukemia. She presented with high-grade fever (103.2 F), SOB and tachycardia, requiring ventilation and circulatory support. CT showed bilateral opacities and lung infiltrates. Her blood culture was repeatedly negative, however her bronchial culture was positive for parainfluenza virus, for which she was started on Ribovirin. The patient was persistently febrile and died of multi-organ failure on day 4 after presentation. Representative section of lung is submitted.

**Diagnosis:** Disseminated toxoplasmosis.

**Key Clinical and Morphologic Features:** The autopsy findings included serosanguinous pleural effusions with 900 cc on the right and 800 cc on the left. The right and left lungs were severely enlarged (1127 and 1268 gm, respectively, congested with underinflated dark red parenchyma with patchy areas of brownish discoloration. Microscopically there was bilateral diffuse alveolar damage (DAD) in organizing phase with disseminated *Toxoplasma gondii* bradyzoites in alveolar spaces, vascular and alveolar walls, and intracellular tachyzoites. The heart was also significantly enlarged (weight 504 gm) with left ventricular hypertrophy (left ventricle 1.6 cm).

Microscopically, the myocardium contained disseminated *Toxoplasma gondii* bradyzoites and tachyzoites with focal destruction of myocardial fibers. This histopathology was consistent with the early stage of destructive toxoplasmic myocarditis in a background of intramural and perivascular fibrosis, patchy hypertrophy and fatty infiltration. The brain showed parasitic infestation with *Toxoplasma gondii* throughout the cerebral cortex and in the basal ganglia. Presence of parasite *Toxoplasma gondii* in lungs, heart and brain was confirmed by positive immunostaining.

**Discussion:** *Toxoplasma gondii* is a protozoan parasite that infects up to a third of the world's population, but is relatively uncommon in the US with 22.5% prevalence. Infection is mainly acquired by ingestion of food or water that is contaminated with oocysts shed by cats or by eating undercooked or raw meat containing tissue cysts. Most individuals are infected inadvertently, thus the specific route of transmission cannot usually be established. *T gondii* primary infection in children and adults (including pregnant women) is asymptomatic in most patients. In about 10%, it causes a self-limited and non-specific illness with isolated cervical or occipital lymphadenopathy that rarely needs treatment.

In immunocompromised patients, reactivation of latent disease can cause life-threatening opportunistic disease, primarily in the central nervous system with subacute gradual process evolving over weeks to an acute confusional state, with or without focal neurological deficits, evolving over days. Toxoplasmosis has been frequently described in patients with the acquired immunodeficiency syndrome (AIDS), but more rarely could be found in patients with cancer, chemotherapy or after transplantation. Reactivation and subsequent pathology is usually confined to a single organ system; disseminated disease is quite rare but usually fatal in the absence of specific treatment. Israelski DM and Remington JS review of 128 cases of cancer-associated toxoplasmosis showed that most cases occur during progressive neoplastic disease with only 10% in stable remission. There was involvement of nearly every organ system, with encephalitis, chorioretinitis, pneumonitis, clinical acute respiratory failure and hemodynamic abnormalities similar to septic shock.

Pulmonary toxoplasmosis, once considered a rare complication of human immunodeficiency, has been reported with increasing frequency in the 1990's. However, published descriptions of the pathologic changes have been scant, involve mainly single cases, and for which the conclusions are not always in agreement. Four cases of pulmonary toxoplasmosis observed at autopsy in patients with AIDS included *Toxoplasma gondii* pneumonia in two cases and interstitial pneumonitis with diffuse alveolar damage in another two cases. Histopathologic diagnosis of the infection required careful search for the organisms even when they were plentiful. Immunohistochemistry identified far more organisms than could be appreciated with routine H & E stains and confirmed the diagnosis.

This case illustrates that toxoplasmosis should be suspected in patients with neoplastic disease such as lymphomas and leukemias, who present with unexplained neurologic, pulmonary, or febrile symptoms during or after chemotherapy.

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### **Case 3**

**Presenter:** Ling Gao, M.D.

**Attending:** Anthony Montag, M.D. and Thomas Krausz, M.D.

**Diagnosis:** Inflammatory well-differentiated liposarcoma (WDLPS)

#### **Differential Diagnosis**

- Undifferentiated pleomorphic sarcoma with prominent inflammation (Inflammatory MFH)
- Pleomorphic liposarcoma
- Dedifferentiated liposarcoma

#### **Key morphologic features**

- Inflammatory background rich in lymphocytes, plasma cells, and foamy histiocytes
- Bizarre multinucleated tumor cells
- Focal conventional adipocytic WDLPS with scattered lipoblasts

#### **Discussion**

- Inflammatory liposarcoma is a rare subtype of WDLPS and occurs almost exclusively in the retroperitoneum
- Retroperitoneal WDLPS has a poor prognosis because of its location, and the local recurrence rate is high, almost 100%
- The risk of dedifferentiation is time dependent and is probably more than 20%
- The WDLPS and dedifferentiated liposarcoma (DDLPS) are characterized by a 12q14-15 amplification involving MDM2, CDK4 as well as HMGA2 genes. The cytogenetic features include supernumerary rings or giant rod chromosomes that contain the 12 q14-15 region
- MDM2 is an important negative regulator of the p53 tumor suppressor gene and therefore decreases apoptosis. Retinoblastoma protein (Rb) functions as a tumor suppressor by binding to transcription factor E2F and inhibiting its cell cycle promoting function. CDK4 can relieve E2F from the inhibitory effect of Rb by dissociating E2F/Rb complex through hyperphosphorylating Rb.
- It is important to differentiate the WDLPS/DDLPS from pleomorphic liposarcoma and undifferentiated pleomorphic sarcoma (MFH), because DDLPS has much better prognosis with a relatively low metastatic potential (15-20%)

- IHC for MDM2 and CDK4 is a useful screening method in the diagnosis of WDLPS/DDLPS, but FISH is the most sensitive and specific diagnostic tool

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#### Case 4

**Presenter:** Xuefeng Zhang, MD

**Attending:** Jerome B Taxy, MD

**Diagnosis:** Dedifferentiated adenoid cystic carcinoma with sarcomatous changes/Adenoid cystic carcinoma with high-grade transformation.

#### Differential diagnosis

- Analogous to Ca ex pleomorphic adenoma (malignant transformation of a benign neoplasm).
- Collision tumor (ACC with another primary tumor).
- Variant of ACC.
  - Grade III/Solid variant ACC (high grade, but maintaining same lineage of differentiation as conventional ACC).

#### Key Morphologic features

- Grossly, the lesion occupied right maxillary sinus and extensively invaded surround tissue.
- Microscopically, three components:
  - Conventional ACC.
  - Poorly differentiated carcinoma.
  - Undifferentiated, sarcomatoid component.
- Part of the neoplasm totally lost the original lineage of differentiation.

## Discussion

- Dedifferentiated adenoid cystic carcinoma is a rare entity first described in 1999.
- Besides the presence of conventional ACC, the histological hallmarks of dedifferentiated component include:
  - Necrosis.
  - High mitotic rate.
  - The loss of the biphasic ductal-myoepithelial differentiation.
  - Unique patterns: squamoid and micropapillary.
  - The most common morphology: poorly differentiated cribriform adenocarcinoma, and solid undifferentiated carcinoma.
  - Sarcomatoid changes are rare but can be present (1 case).
- Summary of 25 cases reported in the literature:
  - Age: 32-74, Median 57.
  - Gender: M:F = 1.5:1.
  - Location: Sinonasal (40%), submandibular (28%).
  - Local recurrence: 53%.
  - Metastasis:
    - Lymph node: 58%, (versus conventional ACC 5-25% lymph node metastasis). Extranodal extension common.
    - Distant: 53%, lung most common.
  - Survival: 1-135 (median 36) months.

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## Case 5

**Presenter:** Jenny Pogoriler, MD PhD

**Attending:** Elizabeth Hyjeck, MD

**Clinical history:** The patient is a 61 year old male who presented to an outside hospital with pancytopenia, splenomegaly and liver failure. His bone marrow demonstrated hemophagocytosis, and an extensive infectious disease workup was negative. A PET scan showed uptake in the right testicle, and a testicular ultrasound showed multiple ill-defined masses.

**Diagnosis:** Hematopoietic neoplasm most consistent with anaplastic large cell lymphoma (CD30+, ALK-, LCA +, CD2+, CD7+, CD56+, CD43+, EMA+, TIA1+, granzyme B+, perforin +, CD3-, CD5-, CD4-, CD8-, TCRβ-, CD15-, EBV-), associated with Hemophagocytic Lymphohistiocytosis.

#### **Key Diagnostic Features of Anaplastic Large Cell Lymphoma, ALK-**

- Morphology:
  - Hallmark cells
    - Eccentric, horseshoe shaped nucleus
    - Eosinophilic golgi region
  - Cohesive growth in sinuses
- Immunohistochemistry:
  - Strong, uniform CD30 positive staining in membrane and golgi region of all tumor cells
  - ALK –
  - Usually expresses some T cell markers
  - Often expresses cytotoxic markers
  - May be EMA+
- Usually has T cell receptor rearrangements (80%)

#### **Discussion**

- Lymphoma-associated hemophagocytic lymphohistiocytosis is most frequently associated with NK and T cell lymphomas, but can be associated with B cell lymphomas and Hodgkin's lymphoma.
- ALK- ALCL is a new provisional entity in the 2008 WHO
- ALK- ALCL is distinct from ALK+ALCL
  - It occurs more frequently in adults
  - It is less likely to be extranodal
  - It is less likely to have a "null" cell phenotype
  - It has a worse prognosis
- CD56+ ALCLs (either ALK+ or ALK-) have a worse prognosis
- TCR rearrangements are detected less frequently in ALCL than in other types of T cell malignancies
- ALK-ALCL is clinically and immunophenotypically distinct from Peripheral T cell lymphoma, NOS
  - ALK- ALCL has a better overall and failure free survival
  - ALK-ALCL is more likely to express EMA and cytotoxic markers
  - ALK-ALCL is more likely to lose expression of T cell markers including CD3, CD2, CD4 and CD43
  - PTCL, NOS can be CD30 positive
    - Expression is usually variable, with strongest expression in the largest cells
  - This is a controversial entity, and experts may disagree on the diagnosis

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## **Case 6**

**Presenter:** Jocelyn Moore, MD

**Attending:** Lucia Schuger, MD and Aliya Husain, MD

**Diagnosis:** Pulmonary Lymphangiomyomatosis (LAM)

### **Differential Diagnosis**

- Hamartoma
- Leiomyoma/leiomyosarcoma
- Smooth muscle hyperplasia in association with interstitial lung disease
- Kaposi sarcoma
- Emphysema

### **Key Morphologic Features**

- Cystic lung lesions
- Nodules of smooth muscle (SM) like cells with focal vacuolization of cytoplasm and oval nuclei
- Non-concentric arrangement of SM like cells
- Lymphatic channels within nodules of SM like cells
- Strong positivity for SM markers
- Focal positivity for melanocytic markers, ER, PR, and VEGF-R3

### **Discussion**

- LAM is a rare lung disease effecting predominantly women of childbearing age, though is now being diagnosed in post-menopausal women as well.
- LAM is a member of the PEComa family.
- LAM occurs both sporadically and in association with tuberous sclerosis complex. Mutations of *TSC2* have been implicated in the pathogenesis LAM.
- There is evidence supporting the benign metastasis theory of renal AML/LAM.
- Lung transplant is the only curative therapy, though recurrence in graft is not uncommon.
- Pregnancy and estrogen administration exacerbates disease progression, while oophorectomy sometimes slows progression of pulmonary dysfunction. Hormonal therapy has not been proven to be beneficial.
- Estrogen has been shown to facilitate metastasis of tuberin-null cells in mice.
- Blockage of the mTOR pathway with rapamycin shows promising initial results; the MILES clinical trail is ongoing.

- Vascular endothelial growth factors from nearby lymphatic endothelial cells may increase proliferation of LAM cells via upregulation of mTOR pathway.

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## Case 7

**Presenter:** Rebecca Buell-Gutbrod, MD

**Attending:** Katja Gwin, MD, PhD

**Clinical History:** This is a 43 year old G4P2 female with a history of a pelvic mass resected at an outside hospital four years ago. The patient presents with abdominal pain. CT shows a 7 cm hepatic dome mass and multiple omental soft tissue masses. Surgical debulking is performed.

**Diagnosis:** Metastasizing Ovarian Sex Cord Tumor with Annular Tubules (SCTAT)

**Key Morphologic Features:** The predominant, classic, pattern consists of what Scully described as simple and complex annular tubules. The simple tubules being ring shaped, with the nuclei oriented peripherally and around a central hyaline body of basement membrane material, with an anuclear cytoplasmic zone which forms the major component of the ring. The more numerous complex tubules are made up of intercommunicating rings revolving around multiple hyaline bodies. Other sections show

small nests of cells with nuclei oriented peripherally and surrounded by basement membrane material, extensive hyalinization of the tubules and stroma and reactive spindled stroma that nearly obscures the tumor cells in some areas.

**Discussion:** SCTAT is associated with Peutz Jeghers syndrome in 30% of cases. The tumor is usually incidentally discovered in these patients, appears at a young age (mean 27 years), is often bilateral, calcified, and small. It is considered benign, with only three malignant cases reported in the literature. Sporadic SCTAT occurs in a very different clinical setting.

While patients are generally young (mean 34 years), the lesion is usually unilateral, and is malignant in up to 30% of cases with spread along the lymphatics.

The lineage of differentiation of these tumors has long been debated, with histological overlap and simultaneous occurrence with both Sertoli and granulosa cell tumors. Ultrastructurally Charcot-Böttcher filaments have been demonstrated in some, but not all, examined cases. The current WHO classification acknowledges this and proposes that these tumors are variants of Sertoli cell tumors.

We applied a novel marker of granulosa cell differentiation, FOXL2, which we previously tested on normal ovarian follicles and granulosa cell tumors, to two cases of sporadic SCTAT. Both revealed strong nuclear staining. A Sertoli cell adenoma, from a patient with XY testicular feminization, did not express FOXL2. These findings suggest that SCTAT is differentiating along the granulosa cell lineage.

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