**Case #1**

**Presenter: Dr. Jessica Gulliver**

**Attending: Dr. Pauline M. Chou**

**Clinical History:**

The patient is a 16 year old female with no significant past medical history who presented with fever, headache, shortness of breath, upper abdominal discomfort, nausea, and diarrhea. Ultrasound of the abdomen showed an enlarged liver with multiple lobulated hyperechoic masses with the largest measuring 15.2 cm. Biopsy was performed. Due to the extent of disease, the liver was explanted. A representative section of the liver mass is provided for review.

**Final Diagnosis**: Hepatocellular malignant neoplasm, not otherwise specified

**Differential Diagnosis:**

• Hepatocellular carcinoma

• Hepatoblastoma

• Hepatocellular malignant neoplasm-not otherwise specified

**Key Features**

• Clinical

o Usually presents in children older than 8 years of age

• Morphology

o Tumor heterogeneity

o Intermediate sized cells between hepatocellular carcinoma and fetal hepatoblastoma may be present

o Subset may have both hepatocellular carcinoma and hepatoblastoma-like areas

• Immunophenotype

o β-catenin staining heterogenous containing areas with nuclear, cytoplasmic, and membranous positivity

Discussion: In children, primary malignant liver tumors represent approximately 1% of all malignancies. The majority of malignant liver tumors in children are hepatoblastoma. Hepatoblastoma is more common under the age of 8 or earlier. Hepatocellular carcinomas occur more often in older children and adolescents. Hepatocellular malignant neoplasm-not otherwise specified occurs in children typically over the age of 8. Often, the background liver is normal. Morphologically, the tumor is heterogenous with some characterized by intermediate sized cells between hepatoblastoma and hepatocellular carcinoma and others containing both hepatocellular carcinoma-like and hepatoblastoma-like areas. β-catenin staining is also heterogenous. Some areas show β-catenin nuclear positivity and others show β-catenin cytoplasmic or membranous positivity. Molecularly, hepatocellular malignant neoplasm-not otherwise specified commonly contains CTNNB1 mutations similar to hepatoblastoma, as well as additional mutations typical of hepatocellular carcinoma. The molecular characteristics, like the tumor morphology and immunohistochemical staining pattern are heterogenous and show overlap between hepatoblastoma and hepatocellular carcinoma. The recognition of hepatocellular malignant neoplasm-not otherwise specified is important because in the current Pediatric Hepatic International Tumor Trial, they are treated as high-risk hepatoblastoma. Although evidence is continually being gathered, the tumors appear to behave more aggressively compared to hepatoblastoma.

**Learning Points:**

• Hepatocellular malignant neoplasm-not otherwise specified is difficult to recognize on biopsies due to sampling error and often limited tissue availability.

• It is an important differential to consider in older children when there is heterogenous tumor morphology.

• The tumor may behave more aggressively compared to hepatoblastoma.

• The diagnosis requires a constellation of clinical, morphologic, and immunohistochemical findings.

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**Case # 2.**

**Presenter: Shunyou (Shawn) Gong, MD**

**Attending: Shunyou (Shawn) Gong, MD**

**Clinical History:**

A 11-year-old female with history of refractory hemophagocytic lymphohistiocytosis (HLH) of unknown etiology (post treatment), presented with marked pancytopenia and splenomegaly. All through her illness she had never had lymphadenopathy or extranodal mass by physical examination and CT Scan. Splenectomy was performed for severe refractory cytopenia.

**Final Diagnosis:** Classic Hodgkin lymphoma, probably splenic primary, presenting with secondary HLH, with marked treatment effects

**Differential Diagnosis:**

• Classic Hodgkin lymphoma, presenting with secondary HLH

• Anaplastic large cell lymphoma, ALK-negative, presenting with secondary HLH

• Diffuse large B-cell lymphoma, CD20-negative, presenting with secondary HLH

**Key Features**

• Microscopically the sections of the spleen showed extensive necrosis and viable splenic parenchyma with foci of small nodules and clusters of atypical cells which were predominantly mononuclear, with convoluted nuclei, vesicular chromatin and prominent nucleoli. Rare cells resemble Reed-Sternberg cells. In the tumor nodules, the lymphoma cells were rich, with only few background small lymphocytes, plasma cells and histiocytes.

• Large cells were strongly positive for CD30, variably positive for PAX-5, focally positive for CD20, CD79a, CD15 and MUM-1. These cells were negative for CD3, CD2, CD5, CD7, CD4, CD8, TIA-1, OCT-2, EMA, ALK-1, AE1/AE3, adenovirus and EBER. CD20 and CD3 stained background small B-cells and T-cells but primarily outside the lymphoma cell nodules and clusters.

• PCR for T-cell receptor gene rearrangement showed a polyclonal pattern. PCR for immunoglobulin heavy chain gene rearrangements revealed suspicious B-cell clone for framework 3.

**Discussion:** Primary splenic classic Hodgkin lymphoma is a rare diagnostic entity among all cases of lymphomatous involvement of spleen. These cases are very challenging to diagnose, and misdiagnosis is common. The unusual feature of our case included depleted background inflammatory cells and challenging immunophenotype which might be due to previous immunochemical therapy given for HLH (particularly Etoposide and Campath). Along with that, another diagnostic challenge was due to extensive necrosis and only few tumor nodules. Overall, morphological and immunohistochemical findings supported diagnosis of classic Hodgkin lymphoma. These findings were further supported by a suspicious B-cell peak detected by PCR. Recognition of this entity in depleted background inflammatory cells and challenging immunophenotype is very important as it can be easily missed or misdiagnosed as splenic infarction due to treatment or other causes.

**Learning Points:**

• Never assume a diagnosis of familial HLH unless a mutation is identified

• Primary splenic Hodgkin lymphoma is extremely rare and difficult to diagnose.

• Partially treated Hodgkin lymphoma may show depleted inflammatory background and altered/atypical immunophenotype.

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**Case #3 : Diagnosis**

*Presenter: Robert Byrd*

*Attending: Robert Byrd*

**History:** The patient is an otherwise healthy 2-year-old boy who had a right-sided heartbeat first discovered by his father and confirmed by the pediatrician who noted abnormal heart sounds. Subsequent chest x-ray identified hyperinflation of the left lung, and follow-up chest CT described a large cystic space in the region of the left upper lobe with numerous thin septations, no normal pulmonary architecture, and associated rightward shift of the mediastinal structures. Left upper lobectomy was performed.

**Diagnosis:** Pleuropulmonary blastoma, regressed (PPB Type 1r)

**Differential Diagnosis:**

* Congenital pulmonary airway malformation
* Intralobar pulmonary sequestration
* Congenital lobar emphysema
* Bronchogenic cyst
* Pneumatocele
* Bullae

**Clinical Features of PPB:**

* Multilocular cyst (Type 1), mixed cystic and solid (Type 2), or solid mass (Type 3) on imaging
* Respiratory distress, tension pneumothorax (40% of cystic/Type 1), or asymptomatic/incidental
* Infants and toddlers, 94% diagnosed before age 6
* Have been detected in utero
* Peripheral, subpleural, may be exophytic

**Microscopic Features of cystic PPB (Type I):**

* Large multilocular cyst with delicate fibrous septa lined by flattened or cuboidal pneumocytes
* Fibrotic wall with prominent vasculature
* Absence of mucinous epithelium in the cyst lining
* Hypercellular collections of primitive mesenchyme +/- rhabdomyoblasts (cambium) and immature cartilage; can be extensive or widely scattered small subepithelial nodules
* Regressed PPB (Type 1r)
  + No hypercellular foci or immature mesenchyme
  + Fibrosis, necrosis, dystrophic calcification possible
  + Sample extensively to exclude focal cambium or cartilage
  + Desmin IHC may be helpful to help identify rhadomyoblasts

**Ancillary Studies:**

DICER1 mutation

* germline in 66%

**Discussion:**

* PPB is the most common primary malignancy of lung in childhood
* Arises from primitive immature mesenchyme of the lung (NOT malignant transformation of preexisting benign lung malformation)
* Purely cystic lesions must be sampled extensively to distinguish PPB Type I from CPAM
* Germline mutations associated with familial DICER1 syndrome (multiple bilateral lung cysts, cystic nephroma, small bowel polyps, ovarian sex-cord stromal tumors, thyroid carcinoma, nasal chondromesenchymal hamartoma and others)
* Purely cystic tumors that lack primitive cell component are classified as Type Ir/regressed
* No metastatic potential for Type I but complete resection essential due to risk of progression to Type II/III (occurs in 10%)

***Select References:***

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**Case # 4.**

**Presenter: Melissa Alejandra Mejia Bautista, MD, PGY3**

**Attending: Jeffrey Goldstein, MD, PhD.**

History: The patient is a 35-year-old G2P1001 with intrauterine fetal demise undergoing vaginal delivery at 21.5 weeks gestation. 1st trimester ultrasound showed a thickened nuchal fold, however cell free DNA was risk reducing. Of note, the patient received her 2nd dose of an mRNA vaccine against SARS-CoV-2 five days prior to presentation.

**Diagnosis:** Fetal Transient Abnormal Myelopoiesis vs. Acute Megakaryoblastic Leukemia

**Differential diagnosis:**

• Erythroblastosis fetalis

• Congenital Acute Leukemia

• Fetal Transient Abnormal Myelopoiesis (TAM)

• Metastatic disease to the placenta (fetal solid tumors)

**Key Clinical, Morphologic and Immunohistochemical features**

Clinical

• TAM is a clonal myeloproliferative condition that occurs in up to 10% of neonates with Down syndrome

• Presents with clinical and morphological findings indistinguishable from those of acute myeloid leukemia

• Usually diagnosed at the age of 3–7 day and resolves spontaneously over a period of several weeks to 3 months

• TAM carries a fetal and neonatal mortality rate of 20%

• In 20−30% of cases, non-remitting acute megakaryoblastic leukemia subsequently develops within 1–3 years

• Placental examination could be one of the earliest, if not the only, diagnostic clue of this condition, particularly in stillbirths, premature infants, and a subset of asymptomatic neonates

Morphologic

• Blasts have morphological and immunological features of megakaryocytic lineage

• In the placenta: Intravascular accumulation of immature blood cells, including megakaryoblasts and precursor cells of granulopoiesis

Immunohistochemical

• Positive for CD34, KIT (CD117), CD13, CD33, HLA-DR, CD4 (dim), CD41, CD42, IL3R, CD36, CD61, and CD71, often with aberrant expression of CD7 and CD56

• Negative for MPO, CD15, CD14, CD11a, and glycophorin A

**Discussion**

• TAM is a clonal disorder that requires trisomy 21 and somatic mutation in GATA1

• GATA1 gene is located on the short arm of the X chromosome, it encodes a transcription factor essential for normal erythropoiesis and particularly megakaryopoiesis

• Most TAM cases will undergo spontaneous resolution without need for treatment

• In 20−30% of cases, non-remitting acute megakaryoblastic leukemia subsequently develops within 1–3 years

• The cfDNA test provides excellent performance (at least 99 percent of trisomy 21 pregnancies). However, it is still considered a screening test due to infrequent false-positive and false-negative results.

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Additional resources

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**Case # 5.**

***Presenter: Aida Richardson, MD PhD***

***Attending: Aida Richardson, MD, PhD***

**History:** 5-year-old female with history of atypical teratoid rhabdoid tumor (ATRT), diagnosed in February 2019 and s/p chemotherapy (included intrathecal methotrexate, intra-theval hydrocortisone, intra-thecal cytarabine, vincristine, cisplatin, doxorubicin, and cytoxan; completed in June 2020) and radiation treatment (completed in August 2020). Post-treatment patient has developed anemia and thrombocytopenia. In December 2020 absolute monocytosis was noted. Her bone marrow from December 2020 was mildly hypocellular and show increase in mature monocytes (25-30%). Flow cytometry was negative for acute leukemia. Cytogenetic analysis of bone marrow from December, 2020 revealed abnormal mosaic female karyotype with t(1;10)(p10;p10),t(4;6)(q12;p25) in 2 cells and t(6;12)(p21.1;p13) in 1 cell (30 cells were analyzed in total). In March bone marrow procedure was performed again due to persistence of anemia, thrombocytopenia and monocytosis.

**IRAP Specimen submitted for your review**: Digital images from peripheral blood, bone marrow aspirate and core biopsy

**Diagnosis:**

Myelodysplastic/myeloproliferative neoplasm

**Differential Diagnosis:**

* Therapy-related myeloid neoplasm
* Acute myeloid leukemia
* Myelodysplastic syndrome
* Myelodysplastic/myeloproliferative neoplasm

**Key Clinical, Morphologic and Immunohistochemical Features**

* Clinical
  + H/o ATRT and s/p chemotherapy (include cyclophosphamide, cisplatin, vincristine, doxorubicin) and radiation treatment
  + Post-treatment (about 1 year) anemia and thrombocytopenia
  + Progressive leukocytosis with persistent absolute monocities
* Morphologic
  + Marked monocytosis with mostly mature monocytes
  + Blasts/promonocytes <20%
  + PB with increase in hypogranular neutrophils, few nRBC’s
  + Ancillary studies:
    - NGS revealed variant of potential clinical significance (Tier II) in KRAS and 2 variants of unknown clinical significance (Tier III) in ASXL1 and RUNX1. KRAS and RUNX1 variants were not detected in fibroblast culture specimen indicating somatic origin, while ASXL1 variant was detected in fibroblast culture indicating germline origin
    - Flow cytometry: 51% of non-erythroid cells are monocytes, partially expressing CD56 and left shifted
    - Abdominal ultrasound: no splenomegaly
    - Hb electrophoresis: increased HbF (14%)

**Discussion**

* Alkylating agent/radiation-related or topoisomerase II inhibitor-related
  + Many patients have received multiple types of therapy making the boundaries between these two categories not always clear
* Acute myeloid leukemia
  + The peripheral blood or bone marrow has ≥ 20% blasts (including promonocytes)
* Myelodysplastic syndrome
  + While granulocytic dysplasia is present patient also has persistent (≥3 months) peripheral blood monocytosis; absolute monocyte count >1000/microL and >10 percent of the entire white blood cell differential
* Myelodysplastic/myeloproliferative neoplasm
  + Chronic myelomonocytic leukemia
    - Usually occur at older age, KRAS mutations are less common in CMML, not many data in pediatric patients
  + Juvenile myelomonocytic leukemia
    - 7-10% cases do not have splenomegaly, late age onset of JMML has been reported but there is not much information in relation to the eventual therapy-relatedness
* Incidence of pediatric therapy related neoplasm is 0.5-1% with RAS pathway mutation being most common (KRAS, NF1)

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**Case # 6: Pleomorphic Xanthoastrocytoma**

***Presenter and Attending: Nitin Wadhwani, MD***

**Clinical history:**  This is a 10 year old right handed female who was found by her mother in bed with altered mental status and labored breathing. She was taken to the local emergency room by ambulance. She was GCS 9 upon arrival. A head CT showed a left sided tumor with intracranial hemorrhage. She was transferred to Lurie Children’s pediatric intensive care unit and was taken to the OR for a left frontal-parietal-temporal craniotomy. An evacuation of the hematoma and a sub-total resection of the intraventricular tumor was performed. Her tumor was stable for 2 years and then recurred in the resection cavity. Electronic images are provided for your review (Whole slide H&E and Olig2 immunostain; H&E of the recurrent tumor).

**Differential diagnosis:**

1. **Ependymoma**
2. **Astroblastoma**
3. **Pleomorphic Xanthoastrocytoma**
4. **High Grade Glioma/High Grade Neuroepithelial Tumor**

**Key points:**

1. Astroblastomatous rosettes can be seen in tumors other than Astroblastoma
2. The 2021 WHO recognizes Astroblastoma with MN1 alteration
3. Next generation sequencing may not be sufficient to resolve the differential diagnosis
4. DNA methylation is recommended for neuroepithelial tumors with a heterogenous appearance

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