**Case 1: Congenital Rhabdomyosarcoma**

*Presenter: Lily Marsden, MD*

**History:** The patient is a 4-day-old female who was transferred on day of life 1 from an outside hospital because of a large facial mass and numerous, variably-sized, red-purple nodules covering the body. The mass was identified prenatally and fetal MRI suggested that the mass was arising from the left frontal lobe through a defect in the cribriform plate. No other fetal anomalies were identified. She was born to a G1P0 mother without any known medical comorbidities, and other than continuous growth of the mass in utero, the pregnancy was unremarkable with regular prenatal care. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Upon admission, repeat imaging with brain MRI showed a mass measuring 10.3 x 7.0 x 4.5 cm with peripheral enhancement arising from the subcutaneous soft tissues of the midline face with no calvarial defect or intracranial extension. Imaging also showed innumerable subcutaneous masses throughout the body, within the paraspinal musculature, throughout the retroperitoneum and replacing the pancreas. A skin biopsy was performed.

**Diagnosis:** Congenital rhabdomyosarcoma, favor alveolar subtype

**Differential Diagnosis:**

* Neuroblastoma
* Lymphoma/leukemia
* PNET/Ewing’s sarcoma family of tumors
* Transplacental metastasis
	+ Melanoma
	+ Lymphoma/leukemia

**Key Microscopic Features:**

* Non-cohesive, large, predominantly uniform, hyperchromatic tumor cells, most with prominent nucleoli
* Usually scant cytoplasm but can see some cells with moderate to abundant eosinophilic cytoplasm
* Solid pattern of growth
* Rare pleomorphic cells can be seen
* Brisk mitotic activity with atypical forms

**Immunohistochemical stains:**

* Positive: Desmin, myogenin, myoD1
* Negative: Tyrosine hydroxylase, synaptophysin, CD3, CD20, TdT, CD34, MPO, S100, Melan-A, retained BAF-47

**Ancillary Studies:**

* Transcripts for t(2;13) and t(1;13) can be negative in cases of congenital alveolar RMS

**Discussion:**

* Neonatal/congenital RMS, defined as neoplasm presenting at less than 1 month of age, is extremely rare
	+ It represent ~1% of all childhood RMS
* Less than 50 cases have been reported in the literature
	+ In larger studies, the majority are categorized as embryonal
	+ Most case reports discuss the alveolar subtype
* Alveolar subtype is distinct from alveolar RMS in older children
	+ >50% of cases present as cutaneous/subcutaneous primary lesions
		- Must be on the differential diagnosis in “blueberry muffin baby” with:
			* Extramedullary hematopoiesis due to infection (TORCH organisms)
			* Hemolytic disease of the newborn
			* Hereditary spherocytosis
			* Congenital vascular malformations
			* Langerhans cell histiocytosis
			* Neuroblastoma
			* Leukemia/lymphoma manifesting as leukemia cutis
	+ Many reported cases in the literature do not have t(1;13) or t(2;13) translocations characteristic of alveolar RMS in older patients
* Congenital alveolar RMS is a highly malignant tumor
	+ The longest survival that has been reported is 27 months of age

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**Case #2**

Presenter: Shunyou Gong, MD, PhD

Clinical history: 3 year-old boy presented with a firm subcutaneous nodule on the right side of his neck, measuring 4 cm in greatest dimension. Mom noted this nodule approximately 6 weeks ago and it was slowly growing. He was otherwise asymptomatic and CBC was normal. A biopsy was performed.

Diagnosis: B-lymphoblastic lymphoma/leukemia.

Histology: H&E stained sections reveal skin with dense dermal lymphocytic infiltrate extending to subcutaneous fat. There is no significant epidermotropism. The infiltrate is composed of predominantly medium-sized atypical cells with oval nuclei, fine chromatin and small nucleoli. Rare residual follicles and scattered small mature lymphocytes are seen in the background. Frequent mitotic figures are noted.

Immunohistochemical stains for CD20, CD3, CD79a, PAX-5, CD34, TdT, BCL-2, BCL-6, CD10, CD21, MPO, and Ki-67 were performed. The malignant cell are uniformly strongly positive for TdT and CD10, positive for PAX-5, CD79a, BCL-2, and weakly positive for CD20, negative for CD34, CD3, MPO, and BCL-6. A few
residual follicles are composed of CD20-strongly positive B cells and with follicular dendritic cell meshwork highlighted by CD21. The diffuse areas with leukemic infiltrate have no FDC meshwork. CD3 shows scattered background small T cells.Ki-67 shows a high proliferation index (approximately 80% of lymphoma cells are positive).

Differential diagnosis for the case:

1. Lymphoblastic lymphomas (B or T)
2. Primary cutaneous T-cell lymphomas (Mycosis fungoides, primary cutaneous CD30+ T-cell LPD, etc.)
3. Myeloid sarcoma (acute myeloid leukemia involving skin)
4. Blastic plasmacytoid dendritic cell neoplasm
5. Cutaneous low grade B-cell lymphomas (cutaneous marginal zone lymphoma or primary cutaneous follicle center cell lymphoma)

Discussion:

B-lymphoblastic lymphoma/leukemia (B-ALL) is a neoplasm of immature B cells which is postulated to arise from precursor B cells in the bone marrow. About 80% of precursor B-cell neoplasms present as acute leukemias, with bone marrow and peripheral blood involvement. By definition, the term “lymphoma” is used in cases exhibiting a bulky lesion in tissue, with no or minimal evidence of peripheral blood and bone marrow involvement, with a threshold of <25% blasts in the bone marrow.

Cases exceeding this number of blasts in the bone marrow or with significant peripheral blood involvement are designated leukaemia, but there is a significant biological and clinical overlap between neoplasms diagnosed as lymphoblastic lymphoma and acute lymphoblastic leukaemia. The most up-to-date WHO tumor classification now names this neoplasm as B-lymphoblastic leukemia/lymphoma.

Although very rare, skin may be the primary presenting site of B-ALL, particularly in children. In reality, B-lymphoblastic lymphoma/leukemia is the third most common cutaneous lymphoproliferative disease in children, after mycosis fungoides (MF) and CD30+ lymphoproliferative disorder (LPD). The most common anatomic site is head and neck region, involved in 80% of cases. Cutaneous involvement by B-lymphoblastic lymphoma/leukemia occurs twice as common in girls as in boys, with a median age at diagnosis of 5 years. About 20% of patients present with multiple cutaneous lesions. In half of the patients, extracutaneous disease is evident at presentation. Histologically, the tumor cells often display artificial changes due to high fragility, making histopathological diagnosis difficult. A large battery of immunohistochemical stains may be necessary to render an accurate diagnosis.

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**CASE # 3**

Nicoleta Arva, MD/PhD

Pediatric pathologist, Ann & Robert H. Lurie Children’s Hospital of Chicago

Assistant Professor of Pathology, Feinberg School of Medicine, Northwestern University

**Clinical history:** The patient is a previously healthy 13 year old male who presented with left leg pain for the past two months.

**Physical Exam:** No palpable mass; left leg with intact sensation and motor function; adequate circulation.

**Radiology:** MRI of the pelvis revealed a large (9.7 cm), lobular left pelvic mass which appeared to be centered at the left sacrum with extension across the sacroiliac joint and into the adjacent soft tissues.

**Pathology:** Patient underwent an open biopsy of the lesion. Sections revealed a malignant neoplasm composed of oval/spindle cells with a storiform/fascicular arrangement. The cells were uniform, with oval nuclei, fine chromatin pattern and fair amount of eosinophilic cytoplasm. Nucleoli were inconspicuous. No osteoid or chondroid material was appreciated. Numerous small, thin-walled, compressed vascular channels were seen between the tumor cells. Immunohistochemical studies revealed positivity for vimentin, CD99 (both cytoplasmic and membranous pattern), Bcl-2 (cytoplasmic); lesional cells were negative for S-100, SMA, EMA, desmin, CD68 and CD31.

Molecular studies were performed and demonstrated negative EWSR1-FLI1, EWSR1-ERG, SYT-SSX, CIC-DUX4 fusion transcripts (by RT-PCR). EWSR1 and FUS FISH studies did not reveal rearrangements of these genes.

RT-PCR for BCOR- CCNB3 was positive.

**FINAL DIAGNOSIS: UNDIFFERENTIATED SARCOMA WITH BCOR-CCNB3 TRANSLOCATION.**

**UNDIFFERENTIATED SARCOMA WITH BCOR-CCNB3 TRANSLOCATION**

* Clinical characteristics:
	+ Localized to bone, preferentially long bones, the spine, and pelvis
	+ Occurs in adolescents or young adults, ranging from 6 to 26 years with a median age of 13 years
	+ Male to female ratio of 2:1
* Histopathology:

A review by Peters TL et al. (Peters TL et al. *BCOR-CCNB3 fusions are frequent in undifferentiated sarcomas of male children.* Mod Pathol. 2015 Apr;28(4):575-86) of the pre-treatment diagnostic biopsy specimens from the six BCOR-CCNB3 positive cases showed tumors of variable cellularity. The tumors were comprised of areas with high cellularity alternating with less cellular areas in which discohesive neoplastic cells were embedded, often in an edematous and myxoid stroma containing occasionally angulated thin-walled vessels. Tumor cells had scant to moderate amounts of eosinophilic cytoplasm, and irregular nuclear contours. Nuclei were vesicular with finely dispersed chromatin and occasional indistinct to small nucleoli. None of the tumors showed bizarre nuclear pleomorphism that would be more compatible with a diagnosis of undifferentiated pleomorphic sarcoma. Areas of necrosis were seen in three tumors, ranging from focal to 50% of the tumor area. Mitotic activity was often brisk in the pre-treatment tumors, with a median of 30 mitoses per 10 high-power fields (ranging from 1 to 40).

Immunohistochemistry can show expression of CCNB3 (100%), bcl2 (90%), CD99 (60%), and CD117 (60%).

* The tumor is characterized by paracentric inversion on chromosome X resulting in a BCOR-CCNB3 fusion gene. The pathogenic role of BCOR-CCNB3 fusions in sarcomas remains to be determined. Whereas CCNB3 is thought to be a meiotic cyclin restricted to spermatocytes, the BCOR gene, originally discovered to encode a nuclear corepressor of BCL6, regulates mesenchymal stem cell function through epigenetic modification of histone methylation. The expression of the BCOR-CCNB3 fusion gene in undifferentiated unclassified sarcomas is therefore consistent with the presumed activity of the BCOR promoter in putative mesenchymal progenitor cells.
* The clinical outcomes for patients with BCOR-CCNB3 are currently unclear, given the small number of such patients reported to date and the heterogeneity of treatment regimens administered. In a study by Puls F. et al. (Puls F. et al*. BCOR-CCNB3 (Ewing-like) sarcoma: a clinicopathologic analysis of 10 cases, in comparison with conventional Ewing sarcoma.* Am J Surg Pathol. 2014 Oct;38(10):1307-18) the overall survival of BCOR-CCNB3 sarcoma (75% at 5 y) was not statistically different from a large series of classic Ewing sarcoma (54% at 5 y).
* Differential diagnosis:
	1. Ewing sarcoma
		+ Can have similar clinical features
		+ Histologic features can be comparable, although Ewing sarcoma may exhibit peri-vascular or Homer-Wright pseudorosettes; CD99 has a characteristic membranous staining pattern
		+ Classical fusion transcripts; gene re-arrangement can be demonstrated by EWSR1 or FUS FISH studies using break-apart probes

* 1. Small cell osteosarcoma
		+ Comprises approximately 1.5% of all osteosarcoma
		+ More commonly seen in the second decade of life (slightly later than conventional osteosarcoma)
		+ Usually involved metaphysis of the long bones
		+ Radiologically, it has mixed lytic and blastic pattern and can destroy the cortex often extending into the soft tissue; mineralized matrix is present in most of the tumors
		+ Composed of hyperchromatic cells with round to oval nuclei and scanty cytoplasm
		+ Nucleoli are rarely seen
		+ The diagnosis requires the presence of osteoid/bone matrix production
		+ No specific immunophenotype; tumor cells may variably express CD99
		+ No recurrent molecular genetic abnormalities have been detected
	2. Synovial sarcoma
		+ Malignant mesenchymal neoplasm with partial epithelial differentiation
		+ Accounts for 5% to 10% of all soft tissue sarcomas
		+ Encountered predominantly in older children and young adults
		+ Occurs at almost any anatomic site
		+ 2 major histologic subtypes (biphasic and monophasic)
		+ Defined by the presence of the t(X;18)(p11.2;q11.2) translocation, involving the SS18 gene on chromosome 18 and one of several synovial sarcoma X (SSX) genes on chromosome X
	3. Mesenchymal chondroscracoma
		+ Rare but highly malignant tumor, accounting for <3% of all primary chondrosarcomas
		+ May occur at any age, with a peak incidence in the second and third decades of life
		+ Shows a widespread skeletal distribution but more commonly arises in the axial skeleton, including craniofacial bones, ribs, ilium, and vertebrae
		+ Radiologically, presents as lytic and destructive lesions; calcified matrix, poor margination, and cortical destruction with an accompanying soft-tissue mass are frequently seen
		+ Histology:
			- Biphasic appearance with sheets of primitive small, round, blue cells admixed with variable amount of well-differentiated hyaline cartilage islands
			- A hemangiopericytoma-like vascular pattern is common in the hypercellular, small cell zones
			- The small cell component is variably positive for CD99
			- SOX9 is positive in both small cell and cartilaginous components
		+ Molecular studies:
			- A recurrent HEY1-NCOA2 fusion has recently been identified
			- IDH1/2 mutations were not detected
	4. Rhabdomyosarcoma
		+ Accounts for 4%–5% of all childhood malignancies and nearly half of pediatric soft tissue sarcomas
		+ WHO 2013 classification:
			- Embryonal (ERMS)
			- Alveolar (ARMS)
			- Spindle cell sclerosing
			- Pleomorphic
		+ ERMS
			- Represents 80% of all RMS
			- Composed of cells resembling fetal skeletal muscle
			- Most frequently in the 1st decade of life
			- Most commonly seen in the head and neck area and GU tract
			- Genetically heterogeneous
			- Intermediate prognosis
		+ ARMS
			- Comprises 15%–20% of all RMS
			- More common in the extremities
			- Occurs in older children and teenagers
			- About 75% of ARMSs harbor the gene fusion between PAX3/PAX7 and FOXO1
			- Worse prognosis
	5. Undifferentiated sarcoma with CIC-DUX4 translocation
		+ In 2006, 2 cases of “Ewing-like sarcoma” were found to harbor a recurrent chromosomal translocation t(4;19)(q35;q13), which resulted in fusion between CIC, a human homolog of Drosophila capicua, which encodes a high mobility group box transcription factor, and DUX4, a double homeodomain gene
		+ 34 cases are reported to date: the age distribution ranges from 5 to 62 years, with an equal sex distribution; all reported cases are soft tissue based, except 1 with peritonsillar and mandible involvement and another involving bone by direct extension
		+ Histology:
			- Comprised of small, blue, round cells
			- Variable degree of geographic necrosis
			- Mild nuclear pleomorphism, coarse chromatin, prominent nucleoli
			- Clear cytoplasm
			- Focal extracellular myxoid matrix
			- The vast majority of cases show CD99 immunoreactivity, ranging from focal and/or weak to diffuse and/or strong; most tumors are focally positive for S-100 protein; desmin, myogenin, cytokeratin, and EMA reactivity was found in rare cases

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**Case 4: Acute Villitis**

*Presenter: Lily Marsden, MD*

History: The patient is a 23 year-old G1P0 female at 40 and 3/7 weeks gestation who presented to Labor and Delivery with spontaneous contractions. Six days before admission she presented to clinic with vaginal burning with vesicles and was prescribed acyclovir for presumed herpes simplex virus. Upon admission she was afebrile but had a fever to 100.4 F during delivery. The infant had Apgars of 8 and 9 a 1 and 5 minutes, respectively. Amniotic fluid was slightly meconium stained. The infant appeared healthy until day 2 of life when he began experiencing fevers, poor feeding and increased irritability. Placental examination was performed.

Diagnosis: Acute villitis secondary to Listeria infection

**Differential Diagnosis:**

* Herpes Simplex Virus
* Varicella Zoster Virus
* Mycobacterium tuberculosis
* Normal enteric/vaginal flora:
	+ Group B Streptococcus
	+ Escherichia coli

**Key Microscopic Features:**

* Acute villitis with micro and macroabscesses
	+ Predominantly neutrophils and histiocytes
* Chorionamnionitis with large numbers of organisms

**Special/immunohistochemical stains:**

* Gram stain will highlights numerous gram positive coccobacilli
* Negative immunohistochemistry for HSV, VZV
* Negative special stains for AFB

**Ancillary Studies:**

* Blood cultures often taken from neonate

**Discussion:**

* There are a limited number of organisms that result in an acute villitis
* Listeria is the most well-known because of its characteristic micro- and macroabscesses
* Mother infected through consumption of contaminated food products (unpasteurized milk products, deli meats, vegetables)
* Infection is 20X more common in pregnant women that in the general population
* Diagnosis is difficult to make unless suspected
	+ Mother will often only have mild flu-like symptoms
* Neonatal infection can result in intrauterine fetal demise, pneumonia, sepsis and meningitis
* If infant presents with sepsis symptoms soon after birth, clinicians should be advised to perform bacterial cultures as well as viral cultures and possibly cultures for M. tuberculosis based on maternal risk factors
* Placental examination is important and can provide answers before cultures come back
* Can often distinguish bacteria by Gram stain
	+ Listeria: Gram positive coccobacilli
	+ GBS: Gram positive cocci in pairs and chains
	+ E. coli: Gram negative bacilli
* Immunohistochemistry can be used if HSV or VZV suspected based on patient history
* Mycobacterium tuberculosis is a rare entity that is often forgotten
	+ Usually placenta will be heavily colonized and special stains can be used

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**Case 5**

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

**Clinical History:** This is an infant male born at 39 and 2/7 weeks' gestational age via cesarean for failure to progress at a hospital across the state lines. Past medical history is remarkable for an abnormal prenatal ultrasound for which the patient underwent an MRI after he was delivered. Physical exam was remarkable for cleft lip and palate. The MRI is below.



There is a large cyst in the extra-axial space of the left anterior cranial fossa, extending slightly across midline, with associated cerebral compression and displacement of the left frontal and temporal lobes. There is also a solid mass with apparent lateral dural base near the displaced left frontal and temporal lobes, with slight peripheral enhancement. Sections from the solid mass are submitted for your review.

**Diagnosis: *Intracranial Extracerebral Glioneuronal Heterotopia (IEGH)***

**Differential Diagnosis:** Teratoma, DIGG.

**Key Features/Discussion:** Heterotopic brain tissue can occur anywhere in the CNS. The earliest reports were of tissue located in the dura and occipital scalp, but IEGH can also be seen in the face, spine, and thoracic cavity. It will anchor to normally developed cortical tissue or the dura. Components of the telencephalon most likely will resemble normal developing cortical tissue and should be called Intracranial Extracerebral Glioneuronal Heterotopia. Anomalies occurring earlier than 28 days gestation can occur and may contain more portions of the neural tube resulting in variations of what we are seeing. For example cerebrum, brainstem, cerebellum (call it Intracranial Extracerebral Brain Heterotopia).

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